Health Technology Assessment 2005; Vol. 9: No. 30

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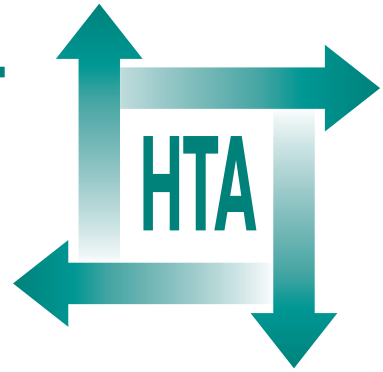
August 2005

Health Technology Assessment
NHS R&D HTA Programme



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Systematic review on urine albumin testing for early detection of diabetic complications

DJ Newman,[1] MB Mattock,[1*] ABS Dawnay,[2] S Kerry,[3] A McGuire,[4] M Yaqoob,[5] GA Hitman[6] and C Hawke[7]

[1] South-West Thames Institute for Renal Research, St Helier Hospital, Carshalton, UK
[2] Department of Clinical Biochemistry, University College London Hospitals, London, UK
[3] Department of Community Health Sciences, St George's, University of London, UK
[4] Department of Health Economics, London School of Economics, UK
[5] Department of Nephrology, Barts & The London, Queen Mary's School of Medicine and Dentistry, University of London, UK
[6] Department of Diabetes and Metabolic Medicine, Barts & The London, Queen Mary's School of Medicine and Dentistry, University of London, UK
[7] Formerly at Public Health Department, Hastings and St Leonard's Primary Care Trust, Hastings, UK

* Corresponding author

Declared competing interests of authors: GA Hitman has served as a consultant to and received travel expenses and payment for speaking at meetings and funding for research from pharmaceutical companies marketing lipid- and glucose-lowering drugs, including AstraZeneca, Pfizer and GSK.

Published August 2005

This report should be referenced as follows:

Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, *et al*. Systematic review on urine albumin testing for early detection of diabetic complications. *Health Technol Assess* 2005;**9**(30).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

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The research reported in this monograph was commissioned by the HTA Programme as project number 96/33/02. The contractual start date was in June 1998. The draft report began editorial review in May 2002 and was accepted for publication in March 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

Abstract

Systematic review on urine albumin testing for early detection of diabetic complications

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[1] South-West Thames Institute for Renal Research, St Helier Hospital, Carshalton, UK
[2] Department of Clinical Biochemistry, University College London Hospitals, London, UK
[3] Department of Community Health Sciences, St George's, University of London, UK
[4] Department of Health Economics, London School of Economics, UK
[5] Department of Nephrology, Barts & The London, Queen Mary's School of Medicine and Dentistry, University of London, UK
[6] Department of Diabetes and Metabolic Medicine, Barts & The London, Queen Mary's School of Medicine and Dentistry, University of London, UK
[7] Formerly at Public Health Department, Hastings and St Leonard's Primary Care Trust, Hastings, UK
* Corresponding author

Objectives: To determine whether microalbuminuria is an independent prognostic factor for the development of diabetic complications and whether improved glycaemic or blood pressure control has a greater influence on the development of diabetic complications in those with microalbuminuria than in those with normoalbuminuria.
Data sources: Electronic databases up until January 2002.
Review methods: A protocol for peer review by an external expert panel was prepared that included selection criteria for data extraction and required two independent reviewers to undertake article selection and review. Completeness was assessed using hand-searching of major journals. Random effects meta-analysis was used to obtain combined estimates of relative risk (RR). Funnel plots, trim and fill methods and meta-regression were used to assess publication bias and sources of heterogeneity.
Results: In patients with type 1 or type 2 DM and microalbuminuria there is a RR of all-cause mortality of 1.8 [95% confidence interval (CI) 1.5 to 2.1] and 1.9 (95% CI 1.7 to 2.1) respectively. Similar RRs were found for other mortality end-points, with age of cohort being inversely related to the RR in type 2 DM. In patients with type 1 DM, there is evidence that microalbuminuria or raised albumin excretion rate has only weak, if any, independent prognostic significance for the incidence of retinopathy and no evidence that it predicts progression of retinopathy, although strong evidence exists for the independent prognostic significance of microalbuminuria or raised albumin excretion rate for the development of proliferative retinopathy (crude RR of 4.1, 95% CI 1.8 to 9.4). For type 2 DM, there is no evidence of any independent prognostic significance for the incidence of retinopathy and little, if any, prognostic relationship between microalbuminuria and the progression of retinopathy or development of proliferative retinopathy. In patients with type 1 DM and microalbuminuria there is an RR of developing end-stage renal disease (ESRD) of 4.8 (95% CI 3.0 to 7.5) and a higher RR (7.5, 95% CI 5.4 to 10.5) of developing clinical proteinuria, with a significantly greater fall in glomerular filtration rate (GFR) in patients with microalbuminuria. In patients with type 2 DM, similar RRs were observed: 3.6 (95% CI 1.6 to 8.4) for developing ESRD and 7.5 (95% CI 5.2 to 10.9) for developing clinical proteinuria, with a significantly greater decline in GFR in the microalbuminuria group of 1.7 (95% CI 0.1 to 3.2) ml per minute per year compared with those who were normoalbuminuric. In adults with type 1 or type 2 DM and microalbuminuria at baseline, the numbers progressing to clinical proteinuria (19% and 24%, respectively) and those regressing to normoalbuminuria (26% and 18%, respectively) did not differ significantly. In children with type 1 DM, regression (44%) was significantly more frequent than progression (15%). In

patients with type 1 or type 2 DM and microalbuminuria, there is scarce evidence as to whether improved glycaemic control has any effect on the incidence of cardiovascular disease (CVD), the incidence or progression of retinopathy, or the development of renal complications. However, among patients not stratified by albuminuria, improved glycaemic control benefits retinal and renal complications and may benefit CVD. In the effects of angiotensin-converting enzyme (ACE) inhibitors on GFR in normotensive microalbuminuric patients with type 1 DM, there was no evidence of a consistent treatment effect. There is strong evidence from 11 trials in normotensive type 1 patients with microalbuminuria of a beneficial effect of ACE inhibitor treatment on the risk of developing clinical proteinuria and on the risk of regression to normoalbuminuria. Patients with type 2 DM and microalbuminuria, whether hypertensive or not, may obtain additional cardiovascular benefit from an ACE inhibitor and there may be a beneficial effect on the development of retinopathy in normotensive patients irrespective of albuminuria. There is limited evidence that treatment of hypertensive microalbuminuric type 2 diabetic patients with blockers of the renin–angiotensin system is associated with preserved GFR, but also evidence of no differences in GFR in comparisons with other antihypertensive agents. The data on GFR in normotensive cohorts are inconclusive. In normotensive type 2 patients with microalbuminuria there is evidence from three trials (all enalapril) of a reduction in risk of developing clinical proteinuria; in hypertensive patients there is evidence from one placebo-controlled trial (irbesartan) of a reduction in this risk. Intensive compared with moderate blood pressure control did not affect the rate of progression of microalbuminuria to clinical proteinuria in the one available study. There is inconclusive evidence from four trials of any difference in the proportions of hypertensive patients progressing from microalbuminuria to clinical proteinuria when ACE inhibitors are compared with other antihypertensive agents, and in one trial regression was two-fold higher with lisinopril than with nifedipine.

Conclusions: The most pronounced benefits of glycaemic control identified in this review are on retinal and renal complications in both normoalbuminuric and microalbuminuric patients considered together, with little or no evidence of any greater benefit in those with microalbuminuria. Hence, microalbuminuric status may be a false boundary when considering the benefits of glycaemic control. Classification of a person as normoalbuminuric must not serve to suggest that they will derive less benefit from optimal glycaemic control than a person who is microalbuminuric. All hypertensive patients benefit from blood pressure lowering and there is little evidence of additional benefit in those with microalbuminuria. Antihypertensive therapy with an ACE inhibitor in normotensive patients with microalbuminuria is beneficial. Monitoring microalbuminuria does not have a proven role in modulating antihypertensive therapy while the patient remains hypertensive. Recommendations for microalbuminuria research include: determining rate and predictors of development and factors involved in regression; carrying out economic evaluations of different screening strategies; investigating the effects of screening on patients; standardising screening tests to enable use of common reference ranges; evaluating the effects of lipid-lowering therapy; and using to modulate antihypertensive therapy.

Dedication

Dr David J Newman, the leader of this project, tragically died after a mountaineering accident in March 2003. David was a greatly respected colleague and a good friend.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Albumin creatinine ratio Used to define microalbuminuria.

Angiotensin-converting enzyme inhibitor An anti-hypertensive treatment.

Clinical proteinuria Urine albumin excretion greater than 300 mg in 24 hours, or as defined by authors: referred to as macroalbuminuria by some authors.

Cardiovascular disease Any abnormal condition characterised by dysfunction of the heart and blood vessels.

Cardiovascular disease mortality Death where there is clear evidence of cardiovascular cause.

Coronary heart disease An abnormal condition that may affect the arteries of the heart and produce pathological affects, e.g. arteriosclerosis.

Diabetic retinopathy Although the development of blindness is the most rigorous end-point, this was only considered very rarely in the literature. Proliferative retinopathy was accepted as a surrogate end-point. The definition as used by an author has been accepted. Diabetic retinopathy can be graded according to its severity. This can be from minor capillary exudates to proliferative retinopathy with reduced vision and eventually blindness.

End-stage renal disease Glomerular filtration rate <10 ml per minute; requirement for renal replacement therapy or death from renal failure.

Glomerular filtration rate Measurement of this provides robust evidence for changes in kidney function.

Glycosylated haemoglobin The best assessment of the quality of glycaemic control in patients with diabetes.

Heterogeneity In systematic reviews this refers to variability or differences between studies in the estimates of effect. This can be caused by differences in study design or differences in key patient characteristics, e.g. duration of diabetes and age.

Hypertension Blood pressure targets for patients with diabetes have been falling: this review took the authors' definition of hypertension and recorded it in the appropriate table.

Intensive insulin therapy A form of therapy that uses multiple injections or continuous insulin infusions to improve glycaemic control for patients with diabetes.

Intention to treat An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not. This form of analysis is favoured as it mirrors the non-compliance and treatment changes that are likely to occur in clinical practice.

Microalbuminuria There is a range of consensus guidelines: this review took the different study authors' definition of microalbuminuria in the first instance; in each case this definition was extracted, as were the number of measurements and the analytical technique used to establish the diagnosis. Microalbuminuria can be measured as albumin excretion rate, albumin/creatinine ratio or as a concentration of albumin in urine.

continued

Glossary *continued*

Medical Subject Headings (MeSH) A standard set of keyboarding terms used by the US National Library of Medicine to index articles in Index Medicus and MEDLINE.

Meta-analysis The use of statistical techniques in a systematic review to integrate the results of included studies.

Myocardial infarction A heart attack.

Normoalbuminuria Normal albumin levels as defined by the authors.

Number needed to treat The number of patients who need to be treated to achieve one additional favourable outcome, calculated as 1/Absolute risk reduction.

Odds ratio The ratio of the odds of an event, usually the ratio of the odds of an event in the microalbuminuria group to the normoalbuminuria group. The odds is the ratio of the probability of an event to the probability that it does not happen.

Relative risk For event data such as mortality, this is the ratio of the event rate in the study group to the control group. In this review it is usually the event rate in the microalbuminuria group compared with the normoalbuminuria group. Crude relative risk is used to refer to relative risk calculated without adjustment for any confounders.

Renal replacement therapy Any form of dialysis therapy or a functioning renal transplant.

Type 1 diabetes mellitus Previously known as insulin-dependent diabetes mellitus. Patients diagnosed with diabetes of acute onset due to absolute insulin deficiency and requiring insulin replacement therapy; more likely to occur in younger people.

Type 2 diabetes mellitus Previously known as non-insulin-dependent diabetes mellitus. It has complex causes, including reduced sensitivity to circulating insulin; more likely to occur in older people.

List of abbreviations

ABCD	Appropriate Blood pressure Control in Diabetes
ACCR	albumin/creatinine clearance ratio
ACE	angiotensin-converting enzyme
ACE-I	angiotensin-converting enzyme inhibitor
ACR	albumin/creatinine ratio
AER	albumin excretion rate
AHT	antihypertensive treatment
AT1	angiotensin II type 1
ATLANTIS	ACE-inhibitor Trial to Lower Albuminuria in Normotensive Insulin-dependent Subjects
BHS	British Hypertension Society
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass graft
CAD	coronary artery disease
CHD	coronary heart disease
CI	confidence interval
CIT	conventional insulin therapy
CP	clinical proteinuria
CRD	Centre for Reviews and Dissemination
CRF	chronic renal failure
CSII	continuous subcutaneous insulin infusion
CVD	cardiovascular disease

continued

List of abbreviations *continued*

DBP	diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
df	degrees of freedom
DIGAMI	Diabetes and Insulin in Acute Myocardial Infarction
DM	diabetes mellitus
DR	diabetic retinopathy
EDC	Epidemiology of Diabetes Complications
EDIC	Epidemiology of Diabetes Interventions and Complications
EMCSG	European Microalbuminuria Captopril Study Group
ESPRIT	European Study for the Prevention of Renal Disease in Type 1 DM
ESRD	end-stage renal disease
ESRF	end-stage renal failure
F	family-based
FACET	Fosinopril versus Amlodipine Cardiovascular Events Randomised Trial
FU	follow-up period
G	general practice-based
GFR	glomerular filtration rate
H	hospital-based
HbA_{1c}	glycosylated haemoglobin
HDL	high-density lipoprotein
HOPE	Heart Outcomes Prevention Evaluation
HOT	Hypertension Optimal Treatment
IGC	intensive glycaemic control
IIT	intensive insulin therapy
IMSG	Italian Microalbuminuria Study Group in IDDM
LDL	low-density lipoprotein
LFT	liver function tests
MA	microalbuminuria
MAP	mean arterial pressure
MCS	Microalbuminuria Collaborative Study
MCSG	Microalbuminuria Captopril Study Group
MDI	multiple daily injections
MDNSG	Melbourne Diabetic Nephropathy Study Group
MI	myocardial infarction
MRFIT	Multiple Risk Factor Intervention Trial
NA	normoalbuminuria
NAMSG	North American Microalbuminuria Study Group
NC	not calculable
ND	newly diagnosed
NE	not extractable
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
NR	not reported
ns	not significant
NSC	National Screening Committee
OR	odds ratio
P	population-based
PCS	Prospective Complications Study
PDR	proliferative diabetic retinopathy
RCPEDRG	Royal College of Physicians of Edinburgh Diabetes Register Group
RCT	randomised controlled trial
RR	relative risk
RRT	renal replacement therapy
SBP	systolic blood pressure
SCI	Science Citation Index

continued

List of abbreviations *continued*

SD	standard deviation
SDIS	Stockholm Diabetes Intervention Study
SEM	standard error of the mean
SMR	standardised mortality ratio
UAC	urinary albumin concentration
UAE	urinary albumin excretion
UGDP	University Group Diabetes Program
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
vWF	von Willebrand factor
WESDR	Wisconsin Epidemiological Study of Diabetic Retinopathy
WHR	waist/hip ratio
WMD	weighted mean difference

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Microalbuminuria is predictive of adverse events in patients with type 1 and type 2 diabetes mellitus (DM) and might be a useful screening tool to help to target treatment more effectively. There is evidence of decreasing prevalence of diabetic complications, particularly nephropathy and retinopathy, probably due to improved treatment of all patients with diabetes irrespective of urine albumin status. Hence, there is uncertainty about the value of a national screening programme for microalbuminuria, which would be justified only if patients identified with microalbuminuria are at greater risk, cannot be otherwise currently identified and derive greater treatment benefit than patients with normoalbuminuria. This systematic review has sought evidence to support screening for microalbuminuria by evaluating end-points in patients with DM who are microalbuminuric compared with those patients who are normoalbuminuric.

Research questions

Question 1: In patients with type 1 or type 2 DM, what is the evidence that microalbuminuria is an independent prognostic factor for the development of diabetic complications? The following complications were assessed: mortality (Review 1), the development and progression of retinopathy (Review 2) and the development of renal failure (Review 3).

Question 2: In subjects with type 1 or type 2 DM and microalbuminuria, what is the evidence that improved glycaemic control (Review 4) or improved blood pressure control, including the use of angiotensin-converting enzyme (ACE) inhibitors in normotensive patients (Review 5) has influenced the development of diabetic complications more than in those without microalbuminuria?

Methods

The steering group prepared a protocol for peer review by an external expert panel: it included selection criteria for data extraction and required two independent reviewers to undertake article selection and review. The literature was explored electronically up until January 2002. Completeness was assessed using hand-searching of major journals. Lead authors were contacted when data extraction was not possible or when a study was unpublished. Random effects meta-analysis was used to obtain combined estimates of relative risk (RR). Funnel plots, trim and fill methods and meta-regression were used to assess publication bias and sources of heterogeneity.

Results

In patients with type 1 or type 2 DM, is there a prognostic relationship between the presence of microalbuminuria and mortality?

In patients with type 1 DM and microalbuminuria there is an RR of all-cause mortality of 1.8 [95% confidence interval (CI) 1.5 to 2.1] that is unaffected by adjustment for confounders. Similar RRs were found for other mortality end-points: cardiovascular disease (CVD) mortality 1.9 (95% CI 1.3 to 2.9), coronary heart disease (CHD) mortality 2.1 (95% CI 1.2 to 3.5) and aggregate CVD morbidity and mortality 2.0 (95% CI 1.5 to 2.6). After adjusting for confounders, the data sets supporting the relationship of microalbuminuria with these last three end-points were small and/or lacked consensus, and further studies are required with adjustments for covariates to confirm a relationship.

Similar results were observed for type 2 DM: an RR of 1.9 (95% CI 1.7 to 2.1) for all-cause mortality, 2.0 (95% CI 1.7 to 2.3) for CVD mortality and 2.3 (95% CI 1.7 to 3.1) for CHD mortality. Adjustment for confounders only very slightly reduced these values. For all-cause mortality, age of cohort was inversely related to the RR. It was not possible to calculate a combined RR for aggregate CVD morbidity and mortality, although it was evident that no consensus exists.

In patients with type 1 or type 2 DM, is there a prognostic relationship between the presence of microalbuminuria and the development and progression of retinopathy?

In patients with type 1 DM, there is evidence that microalbuminuria or raised albumin excretion

rate has only weak, if any, independent prognostic significance for the incidence of retinopathy and no evidence that it predicts progression of retinopathy. There is strong evidence for the independent prognostic significance of microalbuminuria or raised albumin excretion rate for the development of proliferative retinopathy (crude RR of 4.1, 95% CI 1.8 to 9.4).

In patients with type 2 DM, there is no evidence that microalbuminuria or raised albumin excretion rate has any independent prognostic significance for the incidence of retinopathy. The limited evidence indicates little if any prognostic relationship between microalbuminuria and the progression of retinopathy or development of proliferative retinopathy.

In patients with type 1 or type 2 DM, is there a prognostic relationship between the presence of microalbuminuria and the development of renal failure?

In patients with type 1 DM and microalbuminuria there is an RR of developing end-stage renal disease (ESRD) of 4.8 (95% CI 3.0 to 7.5) and a higher relative risk (7.5, 95% CI 5.4 to 10.5) of developing clinical proteinuria. The two studies that reported change in glomerular filtration rate (GFR) both reported a significantly greater fall in GFR in patients with microalbuminuria.

In patients with type 2 DM, similar RRs were observed: 3.6 (95% CI 1.6 to 8.4) for developing ESRD and 7.5 (95% CI 5.2 to 10.9) for developing clinical proteinuria. In addition, a significantly greater decline in GFR was seen in the microalbuminuria group of 1.7 (95% CI 0.1 to 3.2) ml per minute per year compared with those who were normoalbuminuric.

In adults with type 1 or type 2 DM and microalbuminuria at baseline, the numbers progressing to clinical proteinuria (19% and 24%, respectively) and those regressing to normoalbuminuria (26% and 18%, respectively) did not differ significantly. In children with type 1 DM, regression (44%) was significantly more frequent than progression (15%).

In patients with type 1 or type 2 DM and microalbuminuria, does improved glycaemic control reduce the rate of development of secondary diabetic complications?

In patients with type 1 DM and microalbuminuria, there is no evidence as to whether improved glycaemic control has any effect on the incidence of CVD, the incidence or progression of retinopathy, the development of proliferative retinopathy, the development of ESRD or the decline in GFR; there is inconclusive evidence as to whether there is any effect on the development of clinical proteinuria (RR 0.6, 95% CI 0.3 to 1.2). Among patients not stratified by albuminuria, improved glycaemic control might be beneficial with respect to CVD and is beneficial in reducing both the incidence and progression of retinopathy and the development of proliferative retinopathy. There are no data with respect to developing ESRD and limited evidence showing little effect on GFR decline. The Diabetes Control and Complications Trial (DCCT) provides convincing evidence of a beneficial effect in reducing the development of clinical proteinuria in a predominantly normoalbuminuric cohort and also of preventing the development of microalbuminuria.

In patients with type 2 DM and microalbuminuria, there is no evidence as to whether improved glycaemic control has any effect on the incidence of CVD, the incidence or progression of retinopathy or the development of ESRD. There is evidence from one trial that improved glycaemic control in this group has little if any effect on the decline in GFR and data on the progression to clinical proteinuria are inconclusive. Among patients not stratified by albuminuria, there is little evidence of improved glycaemic control reducing CVD, but good evidence of a beneficial effect on the incidence and progression of retinopathy. There is inconclusive evidence of any effect on the development of ESRD, but one trial showed a lesser decline in GFR with improved glycaemic control and there was some evidence for slowing the development of clinical proteinuria. There was also strong evidence that improved glycaemic control prevented or slowed progression from normoalbuminuria to microalbuminuria, although this was not the focus of this analysis.

In patients with type 1 or type 2 DM and microalbuminuria, does treatment with antihypertensive drugs reduce the rate of development of secondary diabetic complications?

Trials in patients with type 1 DM and microalbuminuria have mostly included normotensive subjects and focused on the effect of antihypertensive agents, particularly ACE inhibitors, for their possible renoprotective benefits. There were no trials with CVD as an end-

point. There is evidence from one large trial that normotensive patients with type 1 DM treated with an ACE inhibitor show a reduced risk of progression of retinopathy, but there was no evidence of added benefit for patients with microalbuminuria. There were no trials with ESRD as an end-point. In the eight trials evaluating the effects of ACE inhibitors on GFR in normotensive microalbuminuric patients, there was no evidence of a consistent treatment effect. There is strong evidence from 11 trials in normotensive patients with microalbuminuria of a beneficial effect of ACE inhibitor treatment on the risk of developing clinical proteinuria (RR = 0.36, 95% CI 0.22 to 0.58) and on the risk of regression to normoalbuminuria (RR = 5.3, 95% CI 2.5 to 11.5). There were no trials in hypertensive subjects with microalbuminuria comparing different antihypertensive regimes.

In patients with type 2 DM and microalbuminuria, whether hypertensive or not, there is evidence from one trial that patients with microalbuminuria obtain additional cardiovascular benefit from an ACE inhibitor. Evidence from one trial also showed a beneficial effect on the development of retinopathy in normotensive type 2 patients, but no difference in the treatment effect between normoalbuminuric and microalbuminuric patients. In hypertensive subjects, neither of the two trials examining progression of retinopathy in relation to intensive blood pressure control, or the two trials comparing the effects of different antihypertensive agents, examined this in the microalbuminuric subgroup. There were no relevant trials with ESRD as an end-point in hypertensive or normotensive microalbuminuric patients. There is limited evidence that treatment of hypertensive microalbuminuric type 2 diabetic patients with blockers of the renin–angiotensin system is associated with preserved GFR, but also evidence of no differences in GFR in comparisons with other antihypertensive agents. The data on GFR in normotensive cohorts are inconclusive. In normotensive type 2 patients with microalbuminuria there is evidence from three trials (all enalapril) of a reduction in risk of developing clinical proteinuria (RR 0.28, 95% CI 0.15 to 0.53); in hypertensive patients there is evidence from one placebo-controlled trial (irbesartan) of a reduction in this risk. Intensive compared with moderate blood pressure control did not affect the rate of progression of microalbuminuria to clinical proteinuria in the one available study. There is inconclusive evidence from four trials of any difference in the proportions of hypertensive patients progressing from microalbuminuria to clinical proteinuria when ACE inhibitors are compared with other antihypertensive agents (RR 0.74, 95% CI 0.44 to 1.24), and in one trial regression was two-fold higher with lisinopril (26%) than with nifedipine (14%).

Implications for healthcare

Patients with diabetes at highest risk of developing major complications can predominantly be identified through determination of risk factors such as glycosylated haemoglobin (HbA_{1c}), blood pressure and lipid profile. Glycaemic control is the first aim of diabetic therapy. The most pronounced benefits of glycaemic control identified in this review are on retinal and renal complications in both normoalbuminuric and microalbuminuric patients considered together, with little or no evidence of any greater benefit in those with microalbuminuria. Hence, microalbuminuric status may be a false boundary when considering the benefits of glycaemic control. Classification of a person as normoalbuminuric must not serve to suggest that they will derive less benefit from optimal glycaemic control than a person who is microalbuminuric.

When considering the value of urine albumin in identifying patients with diabetes who require the introduction of antihypertensive medication (which is currently the only optional medical therapy to reduce albumin excretion), the following conclusions can be drawn:

- With regard to hypertension, there was very little evidence from this systematic review that identifying those patients who also had microalbuminuria was of any additional benefit, since all patients with diabetes and hypertension benefit from improved blood pressure control.
- This review provides evidence that microalbuminuria surveillance of patients with type 1 or type 2 diabetes who are normotensive (and not on antihypertensive therapy) may be effective, since antihypertensive therapy with an ACE-inhibitor substantially reduces their risk of progressing to clinical proteinuria and confers cardiovascular benefits, and these patients cannot be otherwise identified. It is likely that patients who are normotensive on antihypertensive treatment but who remain

microalbuminuric would derive similar benefit, although they are highly likely to be on ACE inhibitor treatment already. All patients with microalbuminuria are also at increased mortality risk, even after adjustment for confounding factors, and patients with type 2 DM are also at increased risk of CVD and CHD mortality. Hence, assessment of cardiovascular risk and implementation of ACE inhibitor therapy should be considered in normotensive patients with microalbuminuria. Preliminary economic evaluation was inconclusive and further work in this area is required.
- In the authors' opinion, there is insufficient evidence to state that universal screening for microalbuminuria is of benefit to all patients with either type 1 or type 2 diabetes at present and indeed, if negative, it may provide false reassurance in the presence of suboptimal glycaemic and blood pressure control.
- Urine albumin measurement may be a useful indicator of the response to antihypertensive therapy, but does not have a proven role within the microalbuminuric range in modulating therapy over and above the measurement of blood pressure while the patient remains hypertensive, and this is not an indication for its use as a screening test.

Recommendations for research

The recommendations that follow are those that, in the authors' opinion, are the most important.

- What is the annual rate of development of microalbuminuria in patients with type 1 and type 2 DM who initially screen normoalbuminuric, and which risk factors predict the development of microalbuminuria? A systematic review of the literature is suggested.
- What are the factors that determine regression of microalbuminuria in adults and children with DM? Is this accompanied by reduction of risk of complications and why is regression rate apparently higher in children?
- There is a need for further economic evaluation of screening for microalbuminuria in type 1 and type 2 DM considering different strategies such as those used in a preliminary study considering blood pressure control (Appendix 2) and also incorporating glycaemic control.
- How variable is the analytical classification of patients as microalbuminuric and which analytical performance criteria (especially with regard to bias at low concentration) are required to standardise urine screening tests for detecting microalbuminuria?
- What is the effect of lipid-lowering therapy on urine albumin excretion in patients with microalbuminuria and normoalbuminuria?
- Does patient knowledge of their urine albumin status increase their compliance with medication and lifestyle advice over and above any effect on compliance derived from knowledge of their HbA_{1c} and blood pressure? Is any gain at the expense of increased emotional stress?
- Can antihypertensive therapy in hypertensive patients with microalbuminuria be better tailored to the individual patient and improve outcomes by using urine albumin measurements in conjunction with blood pressure to adjust treatment compared with blood pressure targets alone?

Chapter 1

Introduction and rationale

Diabetes mellitus

Diabetes mellitus (DM) is a complex condition in which the body is unable to control the amount of glucose in the blood, either because there is an absence of insulin or because the insulin that is produced is not fully effective. Uncontrolled diabetes can lead to metabolic disturbances that increase the risk of long-term complications affecting a number of the body's systems.

In type 1 DM, the pancreas produces insufficient insulin. It usually presents with symptoms of extreme tiredness and excessive thirst, and onset may be very rapid and result in acute emergency admission. Uncontrolled hyperglycaemia (raised blood glucose) can lead to ketoacidosis, a serious condition that can cause multiple system failure and death. Type 2 DM has complex causes, including reduced sensitivity to circulating insulin. It is more common and represents more than 80% of cases of diabetes, with over 1 million people diagnosed in the UK. Onset is usually much slower than type 1 DM, and patients may be asymptomatic for many years, only presenting when complications occur.

Diabetes is a serious, lifelong disease that accounts for about 9% of hospital costs, although total costs are much larger. It affects at least 3% of the population, although many more are undiagnosed, and numbers are rising rapidly. The prevalence of diabetes increases with age and is three to four times more common in people of Asian and African–Caribbean origin. The number of people with diabetes in the UK is expected to increase from 1.4 million to 3 million by the year 2010 because of the ageing population and increasing levels of obesity. There is no cure for diabetes and much of the burden of care falls on individuals who have to manage the disease themselves day to day.

Most patients with either type 1 or type 2 DM eventually develop one or more of a range of secondary complications predominantly resulting from microvascular and macrovascular injury. These include retinopathy, nephropathy and neuropathy, but also an increased mortality particularly associated with cardiovascular events.[1,2] These complications arise as a result of the metabolic disturbances associated with hyperglycaemia. Current guidelines suggest that patients should be screened for signs of retinopathy, nephropathy and peripheral vascular disease, as well as routine monitoring of their glycaemic and blood pressure control and other cardiovascular risk factors. There is thus a wide variety of tools available for the assessment of the current health status of a patient with diabetes, and many studies have looked at both the potential prognostic significance of these measurements and the ability to modify those risks by various interventions.

Screening programmes

The introduction of a screening programme is somewhat different to the routine monitoring of patients in that it implies a rigorous programme with national or at least local audit programmes. For biochemical screening, it also implies a consensus on the analytical method and biological sample to use and that a national external quality assessment programme is available. It also fundamentally requires that there is strong evidence of a therapeutic intervention that will benefit patients in the defined population who screen positive more than the remainder of the population. When considering a new screening programme it also behoves the proposers of that programme to identify the added benefit of the new risk marker. This can be considered in two ways: by assuming that existing programmes are universally accepted and assessing what can be added by the new marker, or by considering whether the new marker can replace any or all of the existing programmes.

Application of the National Screening Committee recommendations to microalbuminuria screening

The National Screening Committee (NSC) has suggested that the following definition should be considered when evaluating a new screening process:

> Screening is a public health service in which members of a defined population, who do not necessarily perceive they are at risk of, or are already affected by a disease or its complications, are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatment to reduce the risk of a disease or its complications.

Screening has important ethical differences from clinical practice as the health service may be targeting apparently healthy people, offering to help individuals to make better informed choices about their health. However, there are risks involved and it is important that people have realistic expectations of what a screening programme can deliver. Although screening has the potential to save lives or improve quality of life through early diagnosis of serious conditions, it is not a foolproof process. Screening can reduce the risk of developing a condition or its complications, but it cannot offer a guarantee of protection. In any screening programme, there is an irreducible minimum of false-positive results (wrongly reported as having the condition) and false-negative results (wrongly reported as not having the condition). The NSC is increasingly presenting screening as risk reduction to emphasise this point.[3]

To justify screening for microalbuminuria, there should be evidence that identifying patients with microalbuminuria provides a benefit in terms of an enhanced response to therapeutic interventions of improved glycaemic and blood pressure control when compared with treating the population of people with diabetes as a whole, particularly those whose urine albumin excretion is normal.

Urine albumin excretion as a screening test

Increased excretion of albumin into the urine is thought to occur as a result of increased systemic capillary leakiness in the kidney resulting in increased passage of albumin through the glomerulus. This is believed to occur as a result of endothelial cell injury, but there is also the possibility that increased urinary excretion of albumin occurs owing to decreased reabsorption by the renal proximal tubular epithelial cells. Whichever is the primary mechanism it is now accepted beyond doubt that increased excretion of albumin into the urine carries with it a significantly increased risk of progressive renal disease, whether associated with diabetes or not.[4–6] As there are potentially different mechanisms associated with the development of increased albumin excretion it is feasible that the development of microalbuminuria in patients with diabetes may be an aggregate of other risk factors or markers and show little independent association with significant clinical outcomes when these other risk factors are adjusted for.

The measurement of urinary albumin for the screening and monitoring of the development of diabetic nephropathy has been the focus of considerable clinical and analytical research since the 1970s. A consensus has developed that an increase in albumin excretion is predictive of the development of nephropathy, and there are now internationally agreed cut-offs (Appendix 1) defining the level above which urine albumin is classified as increased, albeit with some variation when expressed as a ratio to creatinine.[2,7–9] However, many of these studies demonstrate that a proportion of patients with increased urinary albumin excretion according to these consensus recommendations do not go on to develop nephropathy, indicating that its prognostic specificity is not 100%. In fact, the diagnostic sensitivity, specificity and positive predictive value of increased albumin excretion have not been systematically studied owing to the very long time-course of the disease.[10] There has been much discussion about which urine collection method to use (24-hour, overnight, 4-hour timed or random) and the units to be used to express these results (μg per minute, mg per 24 hours, mg l^{-1} or mg $mmol^{-1}$ creatinine).

Many studies have looked at sensitivity and specificity of semi-quantitative versus quantitative analytical methods. However, at the time of this review there was only one publication of note pointing out the difficulty of applying any defined cut-off point. There has also been an absence of an agreed international calibrant for urinary albumin assay and little discussion as to how the wide variety of different analytical methods, which do not give identical results as shown by national quality assessment returns, may affect the ability to reach a defined consensus concentration.[11] These confounding or unanswered questions, along with the wide biological variations in urinary albumin excretion (30–50% variation from day to day), have left a residual suspicion concerning the merits of urine albumin screening in diabetes when blood pressure and glycaemic control remain the overriding clinical concern of most diabetologists.

Immunoassays for the measurement of urinary albumin were developed in the early 1960s.[12] Specific antibodies were relatively easily generated

and the high sensitivity of this analytical technology facilitated the measurement of the mg l^{-1} concentrations that were excreted in the urine of healthy individuals. Early studies in patients with type 2 DM by Keen and colleagues[13] and in type 1 by Mogensen and Christensen[14] showed that a proportion of diabetic patients manifested an increase in urinary albumin that was above the normal range but below the level associated with clinical proteinuria. This subclinical increase in urinary albumin came to be called microalbuminuria. These patients showed a gradual increase in the excretion of urine albumin that pre-dated any detectable increase in urine total protein, increase in serum creatinine or decrease in glomerular filtration rate (GFR). Further studies in patients with type I DM from Viberti and colleagues in London[15] and from other independent groups in Denmark[14,17] showed that the subgroup of patients who developed microalbuminuria almost invariably went on to develop established nephropathy (clinical proteinuria), which progressed inexorably to end-stage renal failure (ESRF) requiring renal replacement therapy. The natural history of this relatively common secondary complication became established, with approximately 30% of all patients with type 1 DM eventually succumbing, and models were developed to describe its progress. Several studies have established that nephropathy may develop in a similar way in patients with type 2 DM. Because the diagnosis of type 2 DM is less acute, the timing of the onset of microalbuminuria and nephropathy is less well defined. Further studies established that a common confounding factor was the development of hypertension, and patients with microalbuminuria and increased systemic blood pressure progressed more rapidly to overt nephropathy. Diabetic subjects of Asian ethnic origin have a significantly higher risk of developing microalbuminuria and nephropathy and it appears probable that they reach ESRF more rapidly than other ethnic groupings.

There is also growing interest in the utility of urine albumin as a prognostic factor in the development of other diabetic complications, particularly cardiovascular disease (CVD), with some evidence that microalbuminuria may be a risk factor for cardiovascular morbidity and mortality.[18] There is a growing school of thought that now considers microalbuminuria to be of little importance to nephropathy, but more an important indicator of a generally poor prognosis. This is taken as indicating which patients should be focused on for intensive interventions, irrespective of which secondary complications they were actually most at risk of developing. The evidence to support this contention has not, however, been considered in a systematic manner.

Available interventions

There are three main interventions available to reduce the risk of patients with diabetes developing secondary complications. These are improved control of glycaemia, blood pressure and plasma lipids; of these three, most work has been focused on the first two in relation to the microvascular complications peculiar to diabetes, whereas all three have been studied in relation to the macrovascular complications.

Improved glycaemic control

The results of the Diabetes Control and Complications Trial (DCCT) demonstrated the effectiveness of improved glycaemic control in significantly reducing the rate of progression of diabetic nephropathy and retinopathy[19] and, to a lesser degree, macrovascular disease, in patients with type 1 DM.[16] Similar benefits have been found in patients with type 2 DM, as in the UK Prospective Diabetes Study (UKPDS),[20] but others have suggested that the benefits are not so clear.[21]

Antihypertensive medication

The introduction of different varieties of antihypertensive drugs offered improvements in blood pressure regulation and one class, the angiotensin-converting enzyme (ACE) inhibitors, was shown in several studies to have a better antiproteinuric effect in addition to the antihypertensive effect.[22] ACE inhibitors have now been shown in several international randomised and placebo-controlled trials to reduce urine albumin excretion and, perhaps more importantly, reduce the rate of fall in GFR. This has led to the suggestion that prolonged treatment with ACE inhibitors will slow the rate of progression of diabetic nephropathy and thus keep patients off expensive renal replacement programmes for many years.[23] By costing renal replacement therapy (RRT), urine albumin screening programmes and ACE inhibitor therapy, several cost-effectiveness studies have suggested that, theoretically, many millions of pounds per annum could be saved from the healthcare budget if all patients identified with microalbuminuria were treated thereafter with an ACE inhibitor.[24–26]

The consideration in a discussion on screening is that several potential interventions are available; the problem is that they may be considered to be so effective that an additional risk marker such as development of microalbuminuria may not be

required to introduce the treatments in the patient population. A separate question is whether the development of an additional risk marker may have an educative role and improve patient compliance with the intervention(s).

Residual uncertainty about the effectiveness of urine albumin screening

It is an attractive hypothesis from the viewpoints of patient welfare and health economics that a cost-effective and non-invasive screening programme combined with effective treatment can reduce the incidence of secondary complications. However, several unresolved problems prevent this attractive hypothesis being widely accepted into clinical practice. First and most importantly, there has been no published comprehensive meta-analysis of the available studies looking at the prognostic significance of microalbuminuria. The only available overview focused on microalbuminuria and mortality in patients with type 2 DM.[18] Most of the published studies look either at relatively small numbers of patients or across relatively short periods, and although risk assessments were performed using objective clinical outcomes, such as death and entry to renal replacement programmes, others used surrogate end-points such as the doubling of serum creatinine concentrations.

One of the further problems with assessing the effectiveness of urine albumin measurement in identifying secondary complications has been the lack of a gold-standard diagnostic test. Although the development of ESRF is a reliable outcome measure, this can take several decades to develop. A renal biopsy could provide a more immediate reference point, but this is not a procedure amenable to population studies.

To the practising clinician there are other more direct issues. The main clinical focus in diabetes is the regulation of glucose homeostasis, followed by that of blood pressure; the relevance of microalbuminuria can appear secondary as these are themselves a significant challenge, being clear risk factors for the development of nephropathy and other diabetic complications in their own right. This has led to poor cooperation between diabetologists and other specialists, which is only recently being overcome in the practical form, for instance, of joint diabetic and renal clinics. The question that needs to be resolved in the minds of the wider medical and scientific community is whether screening for microalbuminuria is a useful aid with which to focus on patients who would benefit from improved glycaemic control and/or prescription of an ACE inhibitor. Is it, for instance, more sensitive than the measurement of blood pressure (with the well-known problems of 'whitecoat' hypertension) in assessing the risk of nephropathy, and can prescription of an ACE inhibitor be reliably made on this basis alone (i.e. in potentially normotensive individuals)?

During the course of the review process, while seeking peer review of the protocol and during early discussion of the evidence, it became clear that for most diabetologists the value of identifying a subject as having microalbuminuria was also to be viewed in the context of managing their own time and expectations. There was a general acceptance of the overall value of reducing blood pressure and improving glycaemic control, but it was believed that the added value of microalbuminuria lay not in whether this is an independent risk marker for the development of secondary complications, but in that it was a surrogate or more properly an aggregate risk marker that would identify a smaller number of patients on whom the diabetologist needed to focus their limited resources. Although all patients with diabetes would potentially benefit from the therapeutic interventions, it was accepted that it was not possible to do this. The numbers with microalbuminuria were smaller and could be perceived to be in a worse condition, even if the added risk component was negligible according to the available evidence. The overriding issue is that if all patients with diabetes can be shown to benefit from the two therapeutic interventions, then what is the added benefit 'for the patient' of being identified as having microalbuminuria?

At the start of this review there was one published systematic review considering the association of microalbuminuria with any secondary complication or type of diabetes.[18] Indeed, the St Vincent's Group report of 1996[27] still recommended that further work was required on the "Validation of the positive cost/benefit ratio of screening, monitoring and treatment of microalbuminuria based on clinical data". The purpose of this new systematic review was to be an authoritative review of the literature with regard to the value of microalbuminuria as a risk marker for the development of the major secondary complications of diabetes in patients with either type 1 or type 2 DM; then further, to look at the value of improved glycaemic and blood pressure control in reducing the development of each of

these complications. In all, this theoretically required 42 different systematic reviews to be undertaken.

Research questions

- Question 1: In patients with type 1 or type 2 DM, what is the evidence that microalbuminuria is an independent prognostic factor for the development of diabetic complications?
- Question 2: In patients with type 1 or type 2 DM and microalbuminuria, what is the evidence that improved glycaemic control or improved blood pressure control (including the use of ACE inhibitors in normotensive patients) has influenced the development of diabetic complications more than in those without microalbuminuria?

Chapter 2
Review methods

Protocol development

The starting point for this systematic review was that a series of clinical, analytical and economic questions should be addressed. At the first meeting of the steering group it was apparent that these could not all be addressed and that the review needed to be redefined and the main questions had to be reconsidered.

Secondary complications of diabetes

Initially the aim of the review was first to address the value of urine albumin screening in identifying patients with either type 1 or type 2 DM who were at risk of developing any of the secondary complications of those diseases. These secondary complications included increased mortality that can be subdivided into CVD and coronary heart disease (CHD) or aggregated into all-cause mortality, nephropathy, retinopathy, neuropathy and peripheral vascular disease. This was considered to be an unrealistic task, especially when nephropathy and retinopathy each has different stages in its development that have to be validated. This is required as there is little evidence connecting the presence of microalbuminuria and the development of primary outcome measures such as requirement for RRT or development of blindness owing to the long-term follow-up required. An early decision of the steering group, later validated by the external peer-review panel, was to restrict the secondary complications to mortality (all-cause, CVD and CHD related), nephropathy and retinopathy.

Definition of a screening test

During the development of the review protocol it became clear that a precise semantic definition of a screening test was required. Thus, this review considered the added value of identifying an increased excretion of urine albumin, independent of any changes in glycaemic or blood pressure control. This added value should identify an increased risk of developing a secondary complication for which there is an intervention that has a greater benefit in the identified high-risk or microalbuminuric group of patients than in those who are normoalbuminuric.

Clinical interventions

A wide range of risk-modifying interventions is available to clinical staff caring for patients with diabetes. This review has considered that there are two main interventions that predominate and has focused first on improvements in glycaemic control and second on improvement in blood pressure control, by whatever approach. This is not to suggest that lipid-lowering therapies, use of aspirin, dietary modification, and so on, have no place in the care of a patient with diabetes, but to render a review possible.

Health economic analysis

There have been a few studies looking at the health economic aspects of the care and treatment of patients with both types of diabetes. The major costs are associated with the larger number of people who have type 2 DM and thus it was felt that any modelling should be focused on this group of patients. However, there were inadequate resources to allow a comprehensive economic analysis and a preliminary evaluation is given in Appendix 2.

Analytical techniques

Part of the original aim of this review was to advise on the appropriateness of different analytical techniques and urine samples. This element of the review was not undertaken.

Having redefined the nature and scope of the review, the protocol for exploring the literature was devised according to the Centre for Reviews and Dissemination (CRD) Guidelines.[28]

An external review panel was selected from experts in diabetes, nephrology, clinical biochemistry, public health and general practice. The members of this group are listed in the Acknowledgements. The review panel was asked to validate the review protocol for conformity with the questions addressed, selection of analytical methods, sampling protocols, patients and outcome measures.

Inclusion criteria

For research question 1, articles were initially selected for review if they: (1) were reports of primary research studies; (2) were cohort studies or from the placebo arms of randomised controlled trials (RCTs); (3) were of at least 1 year's duration; (4) included subjects with adequately defined DM; and (5) reported baseline quantitative or semi-quantitative measurements of urinary albumin concentration, excretion rate or ratio of urinary albumin to creatinine. Duplicate publications or articles where all patients were either normoalbuminuric or had overt nephropathy were excluded. Articles where all patients were microalbuminuric were only included in the review of the regression of microalbuminuria to normoalbuminuria, otherwise such articles were excluded.

For each review within research question 1 the article should have examined urinary albumin excretion in relation to the following outcomes: all-cause mortality, cardiovascular mortality, CHD mortality or CHD morbidity and mortality (mortality review), development or progression of retinopathy (retinopathy review), end-stage renal disease (ESRD), decline in GFR or progression to clinical proteinuria (nephropathy review).

For research question 2, articles were included if they: (1) were reports of primary research studies; (2) were RCTs that had examined the effects of either improved glycaemic control or antihypertensive therapy; (3) were of at least 1 year's duration; (4) included subjects with adequately defined DM; and (5) had reported baseline quantitative or semi-quantitative measurements of urinary albumin concentration, excretion rate or ratio of urinary albumin to creatinine. The articles should also have reported the effect of the intervention on at least one of the following end-points: CVD (i.e. any of the end-points used in the mortality review as described above), development or progression of retinopathy, development of ESRD, change in GFR or development of clinical proteinuria in patients with microalbuminuria.

Following review the inclusion criteria were checked; relevant data could not be extracted from all articles. The reasons why these articles were excluded are described in the text. When several articles were found to relate to the same cohort of patients, one article was selected for the extraction of the outcomes, although additional information may have been obtained from the other articles. In general, the article selected was the one with the longest follow-up, unless the data could be extracted more easily from an earlier report. Other exclusions applied at this stage were losses to follow-up of greater than 50%, focus on pregnancy or no patients with normoalbuminuria. Abstracts were only included if additional information was available from the authors or from other publications from that group.

Search strategy

Databases searched and algorithms used are described in detail in Appendix 3. In general, the following databases were used: MEDLINE (1966 to January 2002), EMBASE (1980 to January 2002) (both with no language restrictions) and SCISEARCH (until January 2002). The latter was used to find articles citing the first three reports in this area. A review of reference lists from major articles was undertaken and an attempt to identify unpublished work was limited to asking researchers interested in the field to identify other references and to searching the SIGLE database of unpublished work. The journals *Diabetes*, *Diabetes Care*, *Diabetologia*, *Diabetic Medicine*, *Kidney International* and *Journal of the American Society of Nephrology* were hand-searched from January 1995 to January 2002 to validate the electronic searching.

Data extraction

Data were extracted from the valid studies by two independent members of the steering group and any disagreements resolved in conjunction with a third reviewer. Separate criteria forms were drawn up for each research question and end-point. The detailed forms used for each step are included in Appendix 4 and cover Eligibility criteria, Quality criteria and Data extraction. Any studies selected and important studies excluded are noted within each separate review, with justifications.

Extracted data from selected studies were entered into tables and additional information with regard to urine samples collected, analytical methods used, definitions of outcome measure, hypertension or microalbuminuria were recorded along with demographic information such as mean age, gender distribution and duration of diabetes. Where raw outcome data could not be extracted from a paper the authors were contacted, but this was not always successful. As the aim was to extract authors' adjusted risk

estimates and these were more commonly calculated as adjusted relative risks, relative risk was used throughout.

Statistical analyses

The relationship between outcome and predictor variables was estimated using relative risk. Meta-analysis was performed using the DerSimonian and Laird random effects model.[29] Heterogeneity between studies was tested using the χ^2 test. Egger's test was used to assess potential publication bias by a funnel plot.[30] Sensitivity of the estimate of publication bias was assessed by the trim and fill method.[31] Authors' adjusted risk estimates were analysed where available and meta-analysis was carried out using a random effects model based on the relative risks and 95% confidence intervals.

Prevalence of microalbuminuria was estimated from cross-sectional surveys. The combined prevalence was calculated as a weighted (for sample size) mean of the prevalence from each individual study with the 95% confidence interval. The same method was used for analysis of regression to normoalbuminuria of those with microalbuminuria at baseline. Sources of heterogeneity were assessed using a random effect regression analysis, with mean age at recruitment, known duration of diabetes at recruitment, duration of follow-up and publication date as independent variables. All analysis was carried out using Stata (Release 6.0; StataCorp, College Station, TX, USA).

Chapter 3

Systematic review 1: In patients with type 1 or type 2 diabetes, is there a prognostic relationship between the presence of microalbuminuria and mortality?

Introduction

Mortality can be due to any cause, including deaths due to non-diabetes-related factors. The advantage of this as an end-point is that it only requires a death certificate to be available to validate the event. As diabetes is most commonly associated with vascular disease it is important to study the association with CVD (disease of any part of the vascular bed) and CHD (disease of the coronary arteries) and the mortality associated with them. The definitions of these end-points are complex and a variety of internationally recognised disease codes is available. Nonetheless, the accuracy of the use of definitions and their recording on death certificates varies widely.

General eligibility of studies

Studies considered eligible were of adults and children with adequately defined type 1 DM or adults with type 2 DM from all settings and available ethnic groups, where quantitative or semi-quantitative measurements of urinary albumin concentration, excretion rate or ratio of urinary albumin to creatinine were reported (see eligibility criteria, Appendix 4).

More specifically, for questions of prognosis, an article was deemed relevant if:

- it was a primary research study
- subjects with diabetes mellitus were included
- it was a cohort (prospective) study or placebo arm of an RCT
- urinary albumin had been measured at baseline
- the article reported on the relation of baseline microalbuminuria to a defined outcome.

Any of the following end-points were specified and recorded:

- all-cause (total) mortality
- CVD mortality
- CVD morbidity and mortality
- CHD mortality
- CHD morbidity and mortality.

Selection of studies

Searches were focused on the prognostic ability of microalbuminuria for any of the above end-points, in either type 1 or type 2 DM. Since it is not uncommon for an article to report on more than one end-point in relation to baseline microalbuminuria, some articles are used for more than one research question. All peer-reviewed publications (without language restriction) were eligible for inclusion in the study. Searches of the MEDLINE (1966–2002) and EMBASE (1980–2002) databases were carried out at intervals until January 2002. The search strategy is detailed in Appendix 3. In addition, Science Citation Index (SCI) was used to identify all articles until January 2002 citing the earliest reports of a relation between microalbuminuria and mortality in type 1 DM[15] and type 2 DM.[32,33] To complement and validate the electronic searches, six major journals publishing work relevant to the research questions were hand-searched for the 7 years from 1995 to January 2002. Data from abstracts were used only when further information was available from authors or additional published work. The bibliographies of all retrieved articles were searched for additional reports.

Relationship between microalbuminuria and all-cause (total) mortality in patients with type 1 DM

Search results

The MEDLINE and EMBASE searches yielded a total of 845 articles of potential relevance to microalbuminuria and mortality in type 1 or type 2 DM (Appendix 3). Reasons for exclusion of articles were: no end-point of relevance, cross-

TABLE 1 *Relationship between microalbuminuria and total mortality in patients with Type 1 DM: characteristics of included studies*

Source	Setting	End-points	FU (y)	*n*	Gender (% male)	Mean age (y)	Mean duration of diabetes (y)	MA prevalence (%)	CP prevalence (%)
Forsblom *et al.*, 1992[40]	Helsinki, Finland (H)	TM, CP	10	71	39	36	26	28	31
Messent *et al.*, 1992[42]	London, UK (H)	TM, CVD, CRF, CP	23	63	65	40	10	13	NC
Pedersen *et al.*, 1992[44]	Aarhus, Denmark (H)	TM, CRF, CP	18	44	100	25	12	32	NC
Torffvit and Agardh, 1993[38]	Lund, Sweden (H)	TM, CVD morbidity	5	476	47	35	20	25	14
Beatty *et al.*, 1994[41]	Belfast, UK (H)	TM, CP	8	86	NE	49	20	NC	NC
Rossing *et al.*, 1996[35]	Glostrup, Denmark (H)	TM, CVD	10	939	53	40	20	19	18
EURODIAB, 1999[46]	Europe (H)	TM, CHD morbidity, CP	8	2659	51	33	15	22	9
Muhlhauser *et al.*, 2000[45]	Düsseldorf, Germany (H)	TM	10	3453	50	28	11	36	5
Weis *et al.*, 2001[43]	Portsmouth, UK (H)	TM, CVD	14	147	56	32	17	35	NC
Summary			**9**	**7938**	**51**	**32**	**14**	**28**	**9**

CP, clinical proteinuria; CRF, chronic renal failure; FU, follow-up period; H, hospital-based; *n*, total number with known albuminuria status; NC, not calculable; NE, not extractable; MA, microalbuminuria; TM, total mortality.

sectional study, studied type 2 DM only, review, all subjects normoalbuminuric, microalbuminuric or with overt nephropathy at baseline, duplicate publication in national journal, letter or comment. After these exclusions, ten papers on type 1 DM were initially selected.[34–43] Three additional reports[15,44,45] were found in the ten bibliographies and one in meeting abstracts.[46] Thus, 14 articles were initially selected. No further relevant articles on type 1 DM were identified among the 1045 articles found using SCI or by journal hand-searching.

Among these 14 articles there were three paired reports;[15,35,36,38,39,42] one article was excluded from each pair, with exclusions based on a shorter follow-up,[15] a less complete report[39] or a less relevant focus.[36] Klein and colleagues was not selected as no mortality data were reported.[34] Two of the articles were in abstract form,[44,46] but were selected as additional data were available, either from an earlier article[14] or from the study authors.[46] Further information was also sought from three studies where mortality[35,43] or CVD morbidity and mortality[37] were end-points; Weiss[43] and Rossing[35] provided all requested data, but no additional information was obtainable from the third study and it was not selected.[37] Although Muhlhauser and colleagues[45] used a non-specific method to define 'microproteinuria' (microalbuminuria) the article was selected, as the method had been previously validated against an immunological reference technique.[47] Total mortality data were therefore available from nine studies.

Characteristics of included studies

The main characteristics of these nine studies are shown in *Tables 1* and *2*. Data were reported from 7938 patients with known urinary albumin status: normoalbuminuria, microalbuminuria or clinical proteinuria. Fifty-one per cent were male. Patients were followed up for a mean of 9 years (range 5–23 years), and had a mean age of 32 years (range 25–49 years) and mean duration of diabetes of 14 years (range 10–26 years). Six of the

TABLE 2 *Relationship between microalbuminuria and total mortality in patients with Type 1 DM: events and risk estimates*

Source	Urine collection	Definition of MA	MA deaths/ total	NA deaths/ total	Crude RR (95% CI)	Authors' adjusted RR (95% CI)
Forsblom *et al.*, 1992[40]	2 × overnight, 1 × 24 h	20–200 μg per minute	2/18[a]	2/26[b]	1.4 (0.2 to 9.3)	NR
Messent *et al.*, 1992[42]	1 × timed overnight	30–140 μg per minute	5/8	17/53[b]	1.9 (1.0 to 3.8)	NR
Pedersen *et al.*, 1992[44]	3 × 1 h	15–150 μg per minute	5/14	1/26[b]	9.3 (1.2 to 72)	NR
Torffvit and Agardh, 1993[38]	1 × morning	31–299 mg l^{-1}	5/118	6/289	2.0 (0.6 to 6.6)	NR
Beatty *et al.*, 1994[41]	1 × morning	35–300 mg l^{-1}	10/43	6/43	1.7 (0.7 to 4.2)	1.7 (0.7 to 4.2)
Rossing *et al.*, 1996[35a]	3 × 24 h	30–300 mg l^{-1}	45/181	90/593	1.6 (1.2 to 2.2)	2.0 (1.4 to 2.8)
EURODIAB, 1999[46a]	1 × 24 h	20–200 μg per minute	24/573	40/1859	1.9 (1.2 to 3.2)	1.5 (0.9 to 2.7)
Muhlhauser *et al.*, 2000[45]	1 × 24 h	51–499 mg l^{-1} protein	66/1257	58/1829	1.7 (1.2 to 2.3)	NR
Weis *et al.*, 2001[43a]	1 × early morning	ACR > 2.1 mg $mmol^{-1}$	15/51	13/96	2.2 (1.1 to 4.2)	1.2 (0.2 to 7.3)
Meta-analysis, 2002			**177/2263**	**233/4814**	**1.8 (1.5 to 2.1)**	**1.8 (1.4 to 2.4)**

[a] Personal communication with author.
[b] Numbers differ from *Table 1* owing to subtraction of patients lost to follow-up but albuminuria status known.
ACR, albumin/creatinine ratio; NR, not reported; RR, relative risk.

studies used a single urine collection (three were timed collections and three were morning spot samples), while in the other three studies three timed urine collections were made (*Table 2*). Eight different definitions of microalbuminuria were used in the nine studies. The overall prevalence of microalbuminuria was 28% [95% confidence interval (CI) 22 to 35] from the eight studies in which it was possible to calculate prevalence. The remaining study included an equal number of patients with microalbuminuria and normoalbuminuria by design.[41]

Study quality

The definition of type 1 DM was considered inadequate in three of the articles.[41–43] Three studies had collected some data historically[42,44,45] A blind assessment of outcomes was explicitly reported in only one study.[46] No study reported a mean follow-up of less than 5 years. Losses to follow-up were less than 15% in all studies and less than 5% in six. Five studies did not report adjustment for confounding factors.[38,40,42,44,45]

Mortality risk

In each of the nine studies reporting on total mortality, a positive association was found between microalbuminuria and death (*Table 2*). A meta-analysis of the crude relative risks from these studies yielded an overall relative risk of 1.8 (95% CI 1.5 to 2.1) with no significant heterogeneity between studies ($p = 0.89$) (*Figure 1*).

Adjusted risk estimates

Three studies explicitly adjusted for the confounding effects of other factors. Rossing and colleagues[35] adjusted for age, gender, short stature, low social class and diastolic blood pressure, while the EURODIAB study adjusted for age, gender, glycosylated haemoglobin (HbA_{1c}), diastolic blood pressure (DBP), baseline CVD and serum cholesterol.[46] Weis and colleagues adjusted for age, gender, retinopathy, serum creatinine and serum urea.[43] In the study by Beatty and colleagues, equal-sized groups were matched for age and gender at baseline;[41] hence, the crude unadjusted relative risk (1.7, 95% CI 0.7 to 4.2)

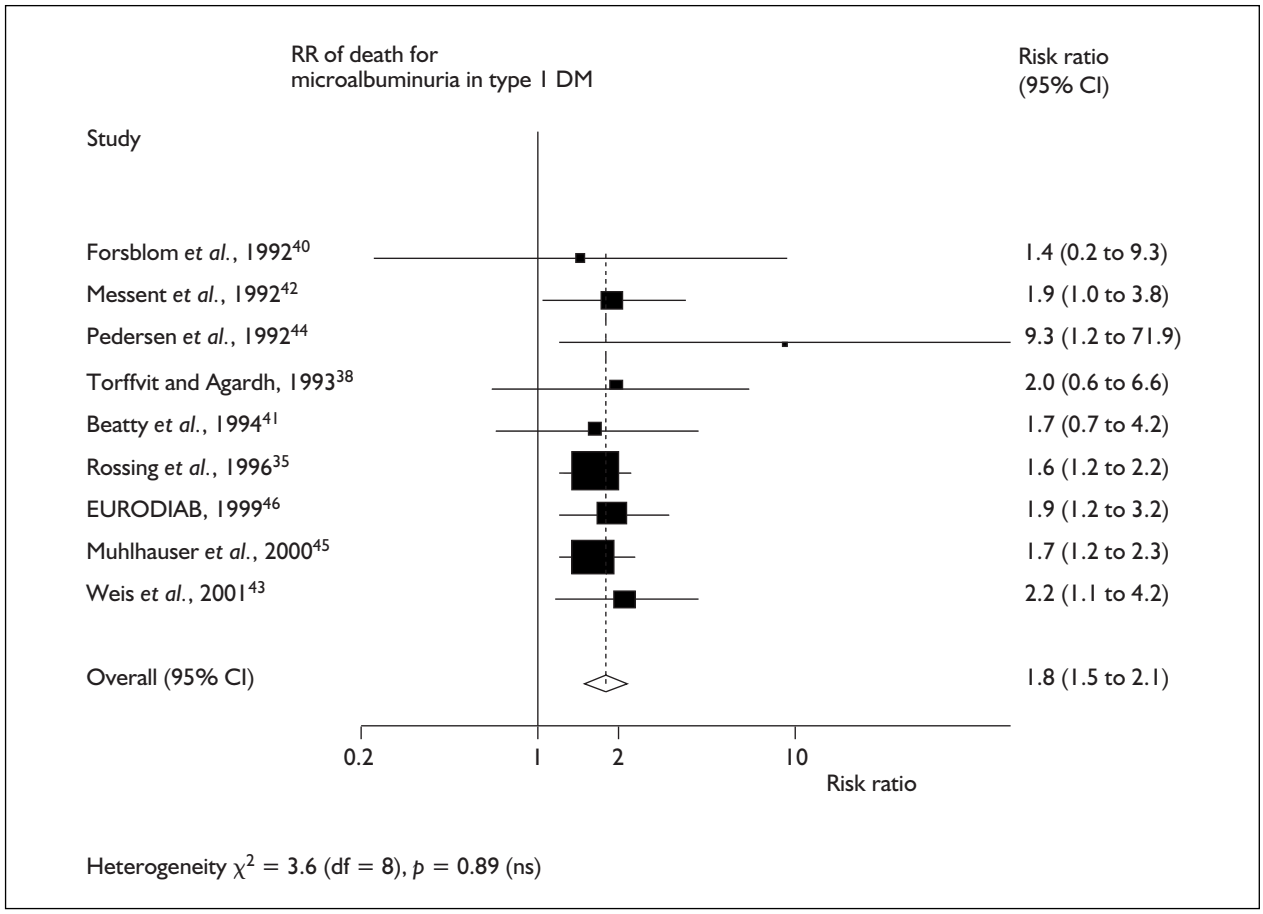

FIGURE 1 *Forest plot for relative risk of mortality with microalbuminuria in type 1 DM. df, degrees of freedom; ns, not significant.*

could therefore be regarded as if it were an adjusted relative risk. The relative risks for the largest studies (EURODIAB[46] and Rossing[35]) were not attenuated by adjustment for confounding factors. Overall, the relative risk from the meta-analysis for the four studies was 1.8 (95% CI 1.4 to 2.4), little changed from the unadjusted relative risk (*Figure 2*).

Conclusions

There have been relatively few studies, but the summary data include over 7000 microalbuminuric and normoalbuminuric patients followed for a mean of 9 years, during which period there were some 410 deaths. There was no significant heterogeneity between the studies ($p > 0.5$). Those patients with microalbuminuria have a mean relative risk of dying of 1.8 times (95% CI 1.5 to 2.1) those with normoalbuminuria. Only four of these studies adjusted for the confounding effects of other risk factors, but the overall relative risk remained unchanged.

Relationship between microalbuminuria and CVD mortality in patients with type 1 DM

Only four of the studies in type 1 DM have reported on microalbuminuria in relation to future CVD mortality[35,42,43,46] (*Table 3*). A meta-analysis of crude relative risks from these studies gives an overall relative risk of 1.9 (95% CI 1.3 to 2.9) (*Figure 3*).

Adjusted risk estimates

Three of these studies adjusted their risk estimates for the confounding effect of other variables,[35,42,47] but only two reported the actual adjusted estimates[35,46] (*Table 3*). Messent and colleagues found that microalbuminuria remained a significant independent predictor of cardiovascular mortality after adjustment for age and duration of diabetes.[42] In the EURODIAB

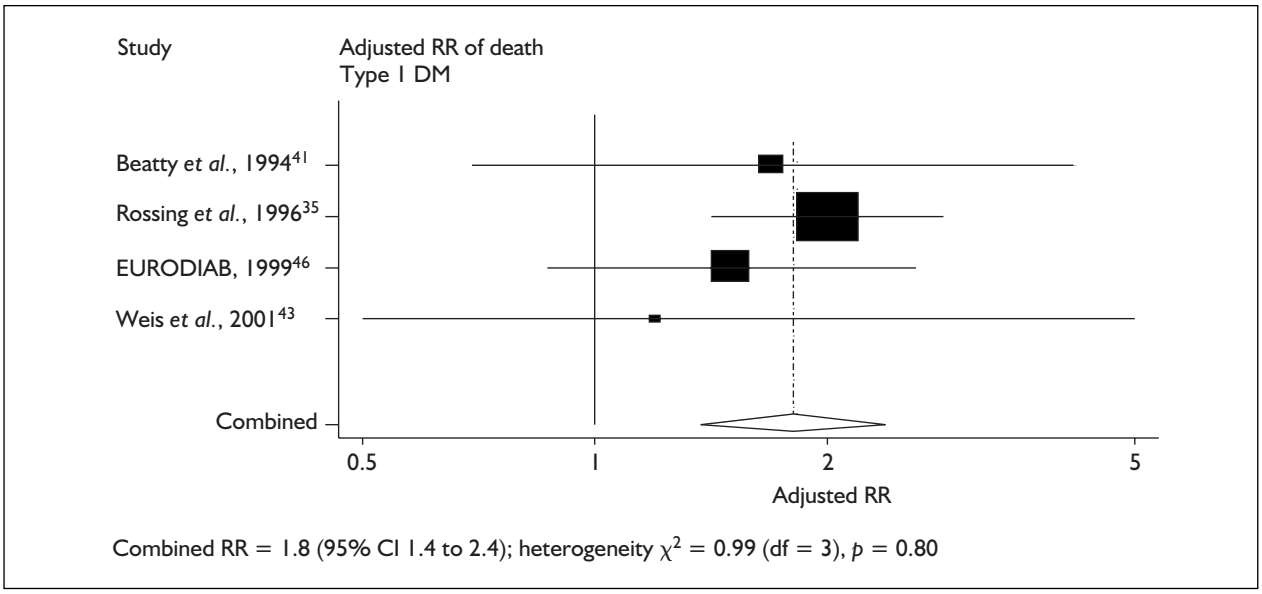

FIGURE 2 *Forest plot for adjusted relative risk of mortality with microalbuminuria in type 1 DM*

TABLE 3 *Relationship between microalbuminuria and CVD mortality in patients with type 1 DM*

Source	Setting	Age (y)	Mean duration of diabetes (y)	FU (y)	MA deaths/ total	NA deaths/ total	Crude RR (95% CI)	Authors' adjusted RR (95% CI)
Messent *et al.*, 1992[42]	London, UK (H)	40	10	23	4/8	9/53	2.9 (1.2 to 7.3)	p = 0.047
Rossing *et al.*, 1996[35]	Glostrup, Denmark (H)	40	20	10	18/181	33/593	1.8 (1.0 to 3.1)	2.2 (1.2 to 3.8)
EURODIAB, 1999[46]	Europe (H)	33	15	8	5/573	9/1859	1.8 (0.6 to 5.4)	1.4 (0.4 to 4.4)
Weis *et al.*, 2001[43]	Portsmouth, UK (H)	32	17	14	4/51	6/96	1.3 (0.4 to 4.2)	NR
Meta-analysis, 2002		**34**	**17**	**9**	**31/813**	**57/2601**	**1.9 (1.3 to 2.9)**	

Prospective Complications Study[46] there were very few cardiovascular mortality events, so although microalbuminuria had a similar increased risk as other studies it was not significant. The risk was attenuated after adjustment for age, gender, HbA_{1c}, diastolic blood pressure and baseline CVD. Rossing and colleagues found that age, gender, microalbuminuria or overt nephropathy, social class, systolic blood pressure (SBP) and DBP, HbA_{1c} and presence of retinopathy were univariate predictors of death.[35] In backward stepwise Cox regression analysis, age, smoking, hypertension, overt nephropathy and microalbuminuria (RR = 2.2 95% CI 1.2 to 3.8) entered the final model. By censoring those who developed overt nephropathy during the 10-year study, irrespective of whether they suffered the outcome subsequently, the authors showed that the excess CVD mortality associated with microalbuminuria was independent of the development of overt nephropathy.

Relationship between microalbuminuria and CHD mortality in patients with type 1 DM

Only three of the studies in patients with type 1 DM reported on microalbuminuria in relation to future CHD mortality[35,41,46] (*Table 4*). A meta-analysis of crude relative risks from these studies is shown in *Figure 4*. The overall risk was 2.1 (95% CI 1.2 to 3.5). In the EURODIAB study, after

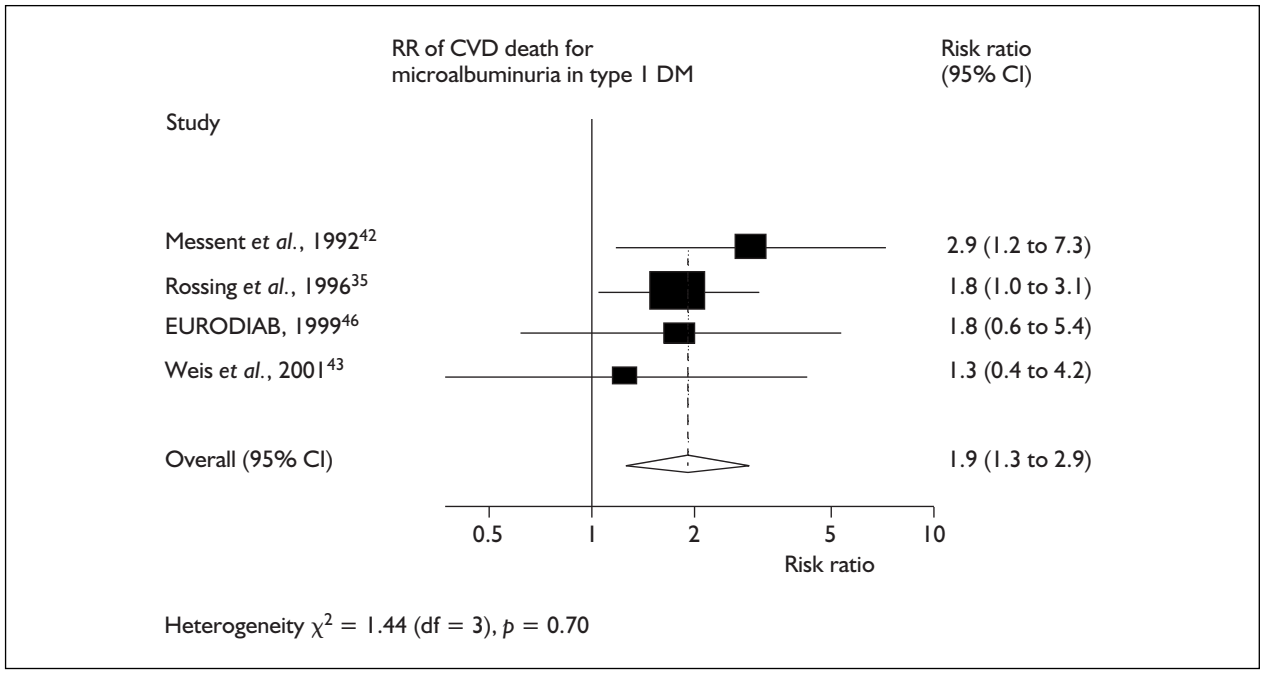

FIGURE 3 *Forest plot for relative risk of CVD mortality with microalbuminuria in type 1 DM*

TABLE 4 *Relationship between microalbuminuria and CHD mortality in patients with type 1 DM*

Source	Setting	Age (y)	Mean duration of diabetes (y)	FU (y)	MA deaths/ total	NA deaths/ total	Crude RR (95% CI)	Authors' adjusted RR (95% CI)
Beatty *et al.*, 1994[41]	Belfast, UK (H)	49	20	8	6/43	4/43	1.5 (0.5 to 4.9)	NR
Rossing *et al.*, 1996[35]	Glostrup, Denmark (H)	40	20	10	13/181	17/593	2.5 (1.2 to 5.1)	NR
EURODIAB, 1999[46]	Europe (H)	33	15	8	4/573	8/1859	1.6 (0.5 to 5.4)	1.3 (0.4 to 4.5)
Meta-analysis, 2002		**45**	**16**	**8**	**23/797**	**29/2495**	**2.1 (1.2 to 3.5)**	

adjusting for age, gender, HbA_{1c}, DBP and baseline CVD, the relative risk of microalbuminuria for CHD mortality was 1.3 (95% CI 0.4 to 4.5).[46]

Relationship between microalbuminuria and CVD morbidity and mortality in patients with type 1 DM

Four studies in patients with type 1 DM have examined the predictive power of microalbuminuria for CVD morbidity and mortality (*Table 5*). All studies showed an increased event rate in patients with microalbuminuria and the overall combined relative risk was 2.0 (95% CI 1.5 to 2.6) (*Figure 5*) with no heterogeneity between studies in spite of the different end-points (*Table 5*). Three studies adjusted for the effect of confounding factors. Deckert and colleagues[37] showed that urinary albumin excretion rate (AER) was a significant predictor of the outcome ($p < 0.002$) and remained significant after adjustment for other risk factors including age, gender, smoking, blood pressure, plasma cholesterol and duration of diabetes ($p = 0.03$). EURODIAB[46] found that the relative risk was 1.8 (95% CI 1.2 to 2.8) after adjustment for age and gender; after further adjustment for SBP, plasma cholesterol and CVD at baseline there was no further change in risk (RR = 1.8, 95% CI 1.2 to 2.8). Allowance was made for the development of overt nephropathy in the Deckert study[37] but not

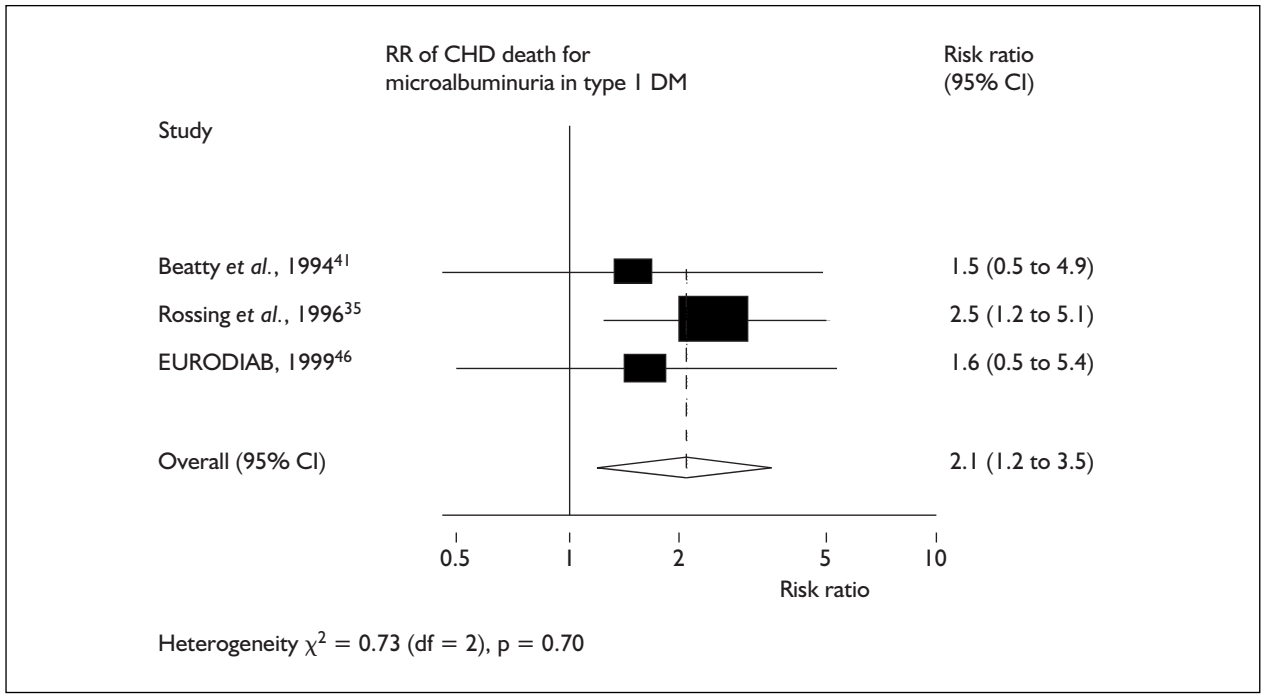

FIGURE 4 *Forest plot for relative risk of CHD mortality with microalbuminuria in Type 1 DM*

TABLE 5 *Relationship between microalbuminuria and CVD morbidity and mortality in patients with type 1 DM*

Source	Setting	Definition of CVD morbidity and mortality	MA events/ total	NA events/ total	Crude RR (95% CI)	Authors' adjusted RR (95% CI)
Torffvit and Agardh, 1993[38]	Lund, Sweden (H)	Death or MI or cerebrovascular disease or amputation or renal insufficiency (serum creatinine > 200 mmol l^{-1} or kidney transplant or dialysis)	10/118	10/289	2.5 (1.1 to 5.7)	NR
Deckert *et al.*, 1996[37a]	Gentofte, Denmark (H)	CVD death or atherosclerotic disease defined from Rose questionnaire	NE	NE	2.5 (1.0 to 5.9)	1.0 (1.0 to 1.2) for UAE
EURODIAB, 1999[46]	Europe (H)	Heart attack or MI or CABG or angina (participant reported) and/or ECG indicating possible or probable CHD or death from CHD	45/448	83/1481	1.8 (1.3 to 2.5)	1.8 (1.2 to 2.8)
Weis *et al.*, 2001[43]	Portsmouth, UK (H)	Rose questionnaire and/or ECG-defined CAD, or death from coronary artery disease	13/44	12/91	2.2 (0.9 to 5.4)	2.3 (0.8 to 6.5)
Meta-analysis, 2002					**2.0 (1.5 to 2.6)**	

[a] Mean age 35 years, duration of DM 18 years, follow-up 10 years. For other studies see *Table 1*.
CABG, coronary artery bypass graft; MI, myocardial infarction.

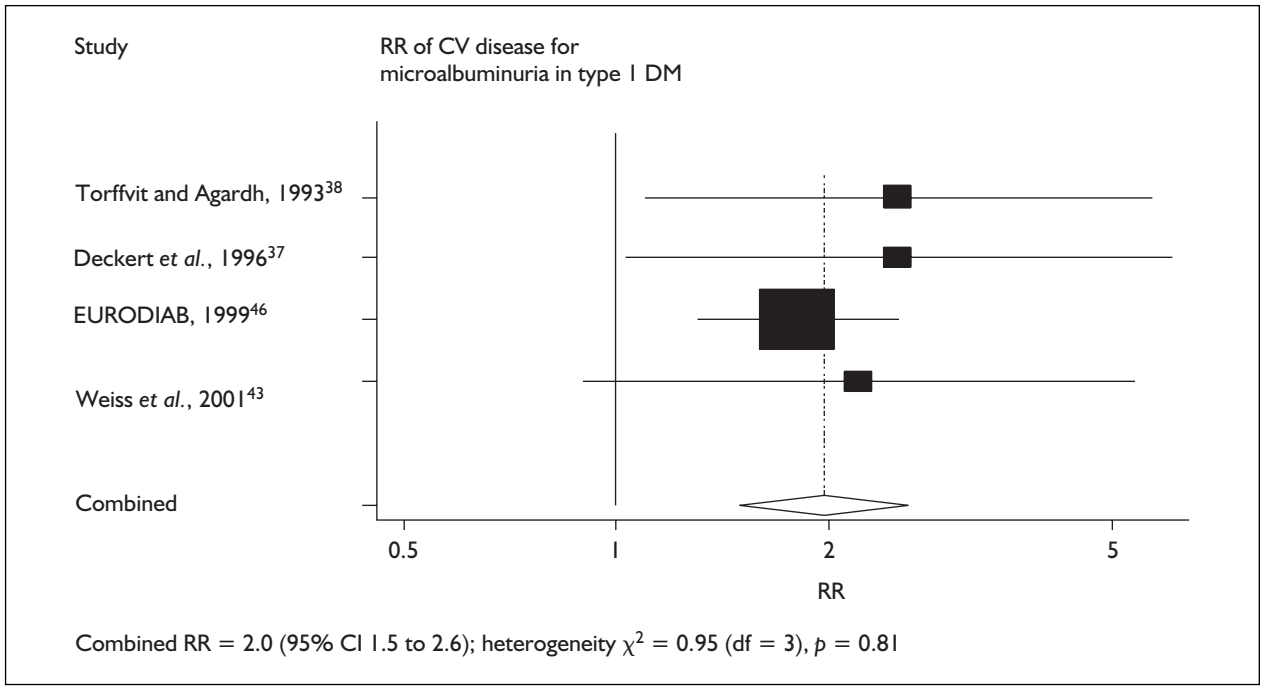

FIGURE 5 *Forest plot for relative risk of CVD morbidity and mortality with microalbuminuria in type 1 DM*

in EURODIAB.[46] Weis and colleagues[43] adjusted for age and gender, but the relative risk remained essentially unchanged after adjustment (2.3, 95% CI 0.8 to 6.5).

Relationship between microalbuminuria and mortality in patients with type 1 DM: conclusions

For patients with type 1 DM, nine studies were identified with respect to all-cause mortality, four with respect to CVD mortality, three with respect to CHD mortality and four for combined CVD mortality and morbidity end-points. Compared with normoalbuminuria there is an increased relative risk associated with microalbuminuria of 1.8 (95% CI 1.5 to 2.1) for all-cause mortality that is unaffected (1.8, 95% CI 1.4 to 2.4) when adjusted for important covariates such as age, gender and duration of diabetes in the four studies that did this. There was also an increased relative risk associated with microalbuminuria for CVD mortality (1.9, 95% CI 1.3 to 2.9), for CHD mortality (2.1, 95% CI 1.2 to 3.5) and for the aggregate end-point of CVD morbidity and mortality (2.0, 95% CI 1.5 to 2.6). After adjusting for confounders, the data sets supporting the relationship of microalbuminuria with CVD (three studies) and CHD mortality (one study) and with CVD morbidity and mortality (three studies) are small and/or lack consensus, hence further studies are required with adjustments for covariates to confirm whether a relationship remains between these end-points and microalbuminuria.

Relationship between microalbuminuria and all-cause (total) mortality in patients with type 2 DM

Search results

After initial exclusions as described above from the database of 845 articles [see section 'Relationship between microalbuminuria and all-cause (total) mortality in patients with type 1 DM, Search results', p. 11], the MEDLINE and EMBASE searches yielded 44 articles potentially relevant to microalbuminuria and total, CVD or CHD mortality, and to morbidity and mortality, in type 2 DM.[20,32,33,48–88] Three additional articles were found in SCI.[89–91] The bibliographies of these papers yielded a further four relevant articles.[92–95] One study was located among meeting abstracts;[96] the authors provided detailed further information on request and the study was included. Another study[97] was identified from a personal list of references (MM). No additional articles were found by journal hand-searching. Therefore, 53 articles were initially identified.

There were several multiple reports detailing different lengths of follow-up of the same cohort. Nine groups had published at least two follow-up reports of their study cohorts.[33,48–59,81,86–88,92,93,96] In five of these paired articles the studies with longer follow-up were selected.[49,52,58,88,96] The longer follow-up study from Torffvit and Agardh[87] was also selected. Although the article by Agardh and colleagues[81] was not selected for the mortality review, it was used in the morbidity and mortality section. Similarly, Gall[50] was not selected for the mortality overview but was used in the CHD mortality section. In three other paired articles, selection was based on relevant data being more readily extractable[33,53] or more complete,[56] irrespective of follow-up time. Articles by Schmitz and colleagues[89] and Araki and colleagues[59] were excluded because it was unclear whether the patients had been included in other reports from the groups.[33,55,58,59] Weitgasser[74] was not selected as relevant data could not be extracted. Forty articles remained. The authors of nine of these studies were contacted with requests for further unpublished information. Six authors provided all requested data.[67,70,76,88,91,96] The authors of the three other studies were unable to locate data,[97] reluctant to perform subgroup analysis[20] (and not used for the mortality overview but used for the morbidity and mortality section) or did not reply.[49] Allawi[97] and Standl[49] were, however, included as partial information on mortality was available. This left 39 articles.

In 11 of these articles[75,77–80,82–85,94,95] the main focus was CVD or CHD mortality or aggregate morbidity and mortality, and total mortality data either were unavailable or had been taken from a different article from the group. Jager[75] was more relevant to the CVD question than other articles from this group.[82,83,95] For one of these cohorts[79] there had been, under the same or different authorship, six reports.[78–80,84,85,94] One of the latter 10-year follow-up reports presented data on CVD mortality[79] and another on CHD morbidity and mortality,[80] and both were selected for those respective sections. Thus, seven of these articles were selected for subsequent sections of this chapter. This left 28 articles for the review of microalbuminuria and total mortality.

Articles excluded from mortality review

After review a total of 25 articles was excluded.[20,48,50,51,54,55,57,59,74,75,77–86,89,92–95]

Characteristics of the individual studies

Tables 6 and *7* give the main characteristics of the 28 studies included in the mortality overview. Beatty and colleagues[63] and MacLeod and colleagues[64] described the follow-up of equal-sized groups with microalbuminuria and normoalbuminuria matched on certain baseline characteristics. In total, data were reported on 10,298 patients followed for a mean of 7 years. There was considerable variation in length of follow-up (2–14 years) and study size (42–1769 patients). Mean known duration of diabetes was 10 years, ranging from 5 to 15 years. Mean age of patients ranged from 52 to 68 years in individual studies.

Definition of microalbuminuria

Only eight of 28 studies (32%) used the consensus definition of 20–200 μg per minute (or 30–300 mg per 24 hours).[98] Each of the remaining 20 studies had a slightly different definition of microalbuminuria.

Number of urine collections

Of the 27 studies where the number of urine collections was specified, 21 (75%) used a single urine collection at baseline. One of these studies, however, mentioned "one sample or more"[32] and another "percentages of 31 with one collection and 68 with more".[33] Of the six remaining studies, three with two or three collections were in Japanese, Chinese or Asian Indian groups. Only three studies among Caucasians explicitly used multiple urine collections.[60,68,72]

Type of urine collection

Various types of urine collection were used in these studies. Among timed collections with results expressed as albumin excretion rate, eight were overnight (in one of these studies some collections were overnight and others during a 2-hour oral glucose tolerance test), six were for 24 hours and two others for 1-hour and 4-hour periods. Untimed (spot) samples were collected in the morning in nine studies and at random in three studies, with albumin results expressed as concentration in ten studies and as a ratio to creatinine in the remaining two.

Methods for measurement of urinary albumin

Radioimmunoassay was the most frequently used analytical method in these studies (19, 68%). Three further studies used nephelometry, two used immunoturbidimetry and one an enzyme-linked immunosorbent assay. Torffvit and Agardh[86] used electroimmunoassay for the first part of their study and immunoturbidimetry for the second part. The two largest studies used a specific but semi-quantitative agglutination–inhibition-based method[71] and either radioimmunoassay

TABLE 6 *Relationship between microalbuminuria and total mortality in patients with Type 2 DM: characteristics of included studies*

Source	Setting	End-points	FU (y)	*n*	Gender (% male)	Mean age (y)	Mean duration of diabetes (y)	MA prevalence (%)	CP prevalence (%)
Jarrett *et al.*, 1984[32]	London, UK (H)	TM	14	42	NE	52	6	17	NC
Mogensen, 1984[33]	Aarhus, Denmark (H)	TM	10	232	55	66	9	NC	NC
Damsgaard *et al.*, 1992[53]	Fredericia, Denmark (P)	TM	9	211	NE	68	NE	NC	NC
Stehouwer *et al.*, 1992[60]	Rotterdam, Netherlands (H)	TM, CVD	3	95	44	63	13	NC	NC
Neil *et al.*, 1993[56]	Oxford, UK (P)	TM, CHD	6	236	52	68	7	15	4
John *et al.*, 1994[90]	Vellore, India (H)	TM	5	481	47	55	9	19	8
Beatty *et al.*, 1995[63]	Belfast, UK (H)	TM, CHD	8	94	NE	63	8	NC	NC
Chan *et al.*, 1995[61]	Hong Kong China (H)	TM	2	403	37	54	6	22	23
MacLeod *et al.*, 1995[64]	Newcastle upon Tyne, UK (H)	TM, CVD	8	306	NE	67	8	NC	NC
Beilin *et al.*, 1996[65]	Perth, Australia (H)	TM, CVD, CHD	5	666	47	63	13	32	10
Standl *et al.*, 1996[49]	Munich, Germany (G)	TM, CVD	10	290	36	65	8	NC	NC
Agewall *et al.*, 1997[62]	Göteborg, Sweden (H)	TM, CVD	6	94	100	67	NE	38	14
Allawi *et al.*, 1997[97]	London, UK (H)	TM, CVD	9	85	65	57	NE	NC	NC
Araki *et al.*, 1997[58]	Shiga, Japan (H)	TM, CVD	6	297	55	58	9	32	NC
Friis and Pedersen, 1997[66]	Frederiksberg, Denmark (H)	TM	3	46	65	62	NE	35	NC
Wirta *et al.*, 1997[67]	Tampere, Finland (P)	TM, SCM	9	145	NE	61	11	27	7
Forsblom *et al.*, 1998[68]	Helsinki, Finland (P)	TM, CVD	9	134	51	58	9	17	2
Gall *et al.*, 1998[96]	Steno, Denmark (H)	TM, CVD	10	549	54	59	9	28	14
Mattock *et al.*, 1998[52]	London, UK (H)	TM, CHD	7	150	57	59	5	25	3
Hänninen *et al.*, 1999[69]	Mikkeli, Finland (P)	TM	5	237	53	58	6	29	4
Biderman *et al.*, 2000[91]	Beer-Sheva, Israel (P)	TM	8	498	47	62	9	NC	NC
Casiglia *et al.*, 2000[70]	Padova, Italy (H)	TM, CVD	6	683	NE	63	NE	24	3
Valmadrid *et al.*, 2000[71]	Wisconsin USA (P)	TM, CVD/CHD	12	840	45	68	15	25	21

continued

TABLE 6 *Relationship between microalbuminuria and total mortality in patients with Type 2 DM: characteristics of included studies (cont'd)*

Source	Setting	End-points	FU (y)	*n*	Gender (% male)	Mean age (y)	Mean duration of diabetes (y)	MA prevalence (%)	CP prevalence (%)
de Grauw *et al.*, 2001[72]	Nijmegen, Netherlands (G)	TM, CVD	6	262	39	66	5	19	0
Florkowski *et al.*, 2001[88]	Christchurch, New Zealand (H)	TM, CHD	10	447	47	62	10	NC	NC
Gerstein, 2001[73]	Europe, North and South America (RCT)	TM, CVD, CHF	5	1769	63	65	11	32	NC
Isomaa *et al.*, 2001[76]	Finland and Sweden (F)	TM, CVD	7	621	47	59	NE	17	2
Torffvit and Agardh, 2002[87]	Lund, Sweden (H)	TM, CVD	10	385	65	54	NE	27	8
Summary			**7**	**10298**	**51**	**62**	**10**	**26**	**10**

CHF, congestive heart-failure; F, family-based; G, general practice-based; N, number of patients; P, population-based; RCT, placebo arm of RCT; SCM, sudden cardiac mortality.

(European and North American recruits to the study) or immunoturbidimetry (South American recruits).[73]

Prevalence of microalbuminuria

Despite this marked heterogeneity in methodology, the mean prevalence of microalbuminuria was quite similar, 26% (95% CI 23 to 29; range 15–38%), in the 19 studies in which it was possible to calculate baseline prevalence.

Ethnic origin

The majority (20, 71%) of the included studies were carried out in Europe. In addition, one study in each case was carried out in the USA, Israel, Japan, China (Hong Kong), India, Australia, New Zealand and a multinational setting (patients from centres in North America, South America and Europe).

Study quality

The definition of type 2 DM was considered inadequate in seven of the 28 articles.[32,58,61,65,72,90,97] Two studies had collected some data historically.[32,33] A blind assessment of outcomes was explicitly reported in only three studies.[60,62,73] Only three studies reported a mean follow-up of 3 years or less.[60,61,66] Losses to follow-up exceeded 5% in only four studies.[49,61,88,90] There was no reported adjustment for confounding factors in five articles.[33,60,66,87,90]

Risk of total mortality

Twenty-eight studies reported total mortality data. In 22 of these, raw data for the calculation of crude relative risks were extractable from the article. In a further four studies the raw data were provided by the authors in response to a written request,[67,70,76] including full details from a study published in abstract form only.[96] Relevant method details were also provided by Florkowski and colleagues.[88] In two other studies raw data were not extractable from the article and were unavailable from study authors.[49,97] The article by Wirta and co-workers[67] included data on separate cohorts of both newly diagnosed and established type 2 diabetic patients; only the established diabetic cohort was included in the meta-analysis of 26 studies below. In total, data were reported on 9244 patients with type 2 DM.

In each of these studies a positive association was noted between microalbuminuria and death (*Figure 6*). The meta-analysis gave an overall relative risk of 1.9 (95% CI 1.7 to 2.1), but with highly significant heterogeneity between the studies (*Figure 6*).

TABLE 7 *Relationship between microalbuminuria and total mortality in patients with Type 2 DM: events and risk estimates*

Source	Urine collection	Definition of MA	MA deaths/ total	NA deaths/total	Crude RR (95% CI)
Jarrett *et al.*, 1984[32]	1 × overnight	30–140 μg per minute	6/7	11/35	2.7 (1.5 to 4.8)
Mogensen, 1984[33]	1 × morning spot	30–140 mg l^{-1}	59/76	63/128	1.6 (1.3 to 2.0)
Damsgaard *et al.*, 1992[53]	1 × 1 h	>17.4 μg per minute	63/107	39/104	1.6 (1.2 to 2.1)
Stehouwer *et al.*, 1992[60]	3 × 4 h	15–200 μg per minute	5/28	1/67	12 (1.5 to 98)
Neil *et al.*, 1993[56]	1 × random spot	40–200 mg l^{-1}	21/36	44/145	1.9 (1.3 to 2.8)
John *et al.*, 1994[90]	2 × 24 h	20-200 μg per minute	7/93	12/349	2.2 (0.9 to 5.4)
Beatty *et al.*, 1995[63]	1 × morning spot	35–300 mg l^{-1}	22/47	10/47	2.2 (1.2 to 4.1)
Chan *et al.*, 1995[61]	2 × random spot	ACR 5.6–38 mg $mmol^{-1}$	7/94	4/208	3.9 (1.2 to 12.9)
MacLeod *et al.*, 1995[64]	1 × overnight	>10.5 μg per minute	90/153	63/153	1.4 (1.1 to 1.8)
Beilin *et al.*, 1996[65]	1 × morning	30–300 mg l^{-1}	68/211	67/390	1.9 (1.4 to 2.5)
Standl *et al.*, 1996[49]	1 × first morning	30–200 mg l^{-1}	NE	NE	NC
Agewall *et al.*, 1997[62]	1 × overnight	20–200 μg per minute	15/36	11/45	1.7 (0.9 to 3.2)
Allawi *et al.*, 1997[97]	1 × overnight	>10 μg per minute	NE	NE	NC
Araki *et al.*, 1997[58]	3 × 24 h	15–200 μg per minute	14/96	14/201	2.1 (1.0 to 4.2)
Friis and Pedersen, 1997[66]	1 × overnight	20–200 μg per minute	6/16	3/30	3.8 (1.1 to 13.0)
Wirta *et al.*, 1997[67]	1 × 24 h	30–300 mg per 24 h	13/39	16/96	2.0 (1.1 to 3.8)
Forsblom *et al.*, 1998[68]	3 × 24 h	20–200 μg per minute	17/23	21/108	3.8 (2.4 to 6.0)
Gall *et al.*, 1998[96]	1 × 24 h	30–299 mg per 24 h	89/151	111/323	1.7 (1.4 to 2.1)
Mattock *et al.*, 1998[52]	1 × overnight	20–200 mg per minute	18/37	18/109	2.9 (1.7 to 5.0)
Hänninen *et al.*, 1999[69]	1 × overnight	20–200 μg per minute	9/68	6/159	3.5 (1.3 to 9.5)
Biderman *et al.*, 2000[91]	1 × morning spot	>30 mg per l^{-1}	68/118	86/380	2.5 (2.0 to 3.2)
Casiglia *et al.*, 2000[70]	24 h (number unknown)	30–300 mg per 24 h	44/164	78/497	1.7 (1.2 to 2.4)
Valmadrid *et al.*, 2000[71]	1 × random spot	>30 mg per l^{-1}	154/208	228/460	1.5 (1.3 to 1.7)
de Grauw *et al.*, 2001[72]	3 × morning spot	20–200 mg per l^{-1}	13/50	44/202	1.2 (0.7 to 2.0)
Florkowski *et al.*, 2001[88]	1 × morning spot	≥ 50 mg/l^{-1}	49/81	138/338	1.5 (1.2 to 1.8)
Gerstein, 2001[73]	1 × morning spot	ACR ≥ 2.0 mg $mmol^{-1}$	122/587	125/1182	2.0 (1.6 to 2.5)
Isomaa *et al.*, 2001[76]	1 × timed[a]	>20 μg per minute	31/81	107/526	1.9 (1.4 to 2.6)
Torffvit and Agardh, 2002[87]	1 × morning spot	31–299 mg/l^{-1}	34/103	53/252	1.6 (1.1–2.3)
Meta-analysis, 2002			**1044/2710**	**1373/6534**	**1.9 (1.7 to 2.1)**

[a] During oral glucose tolerance test or overnight.

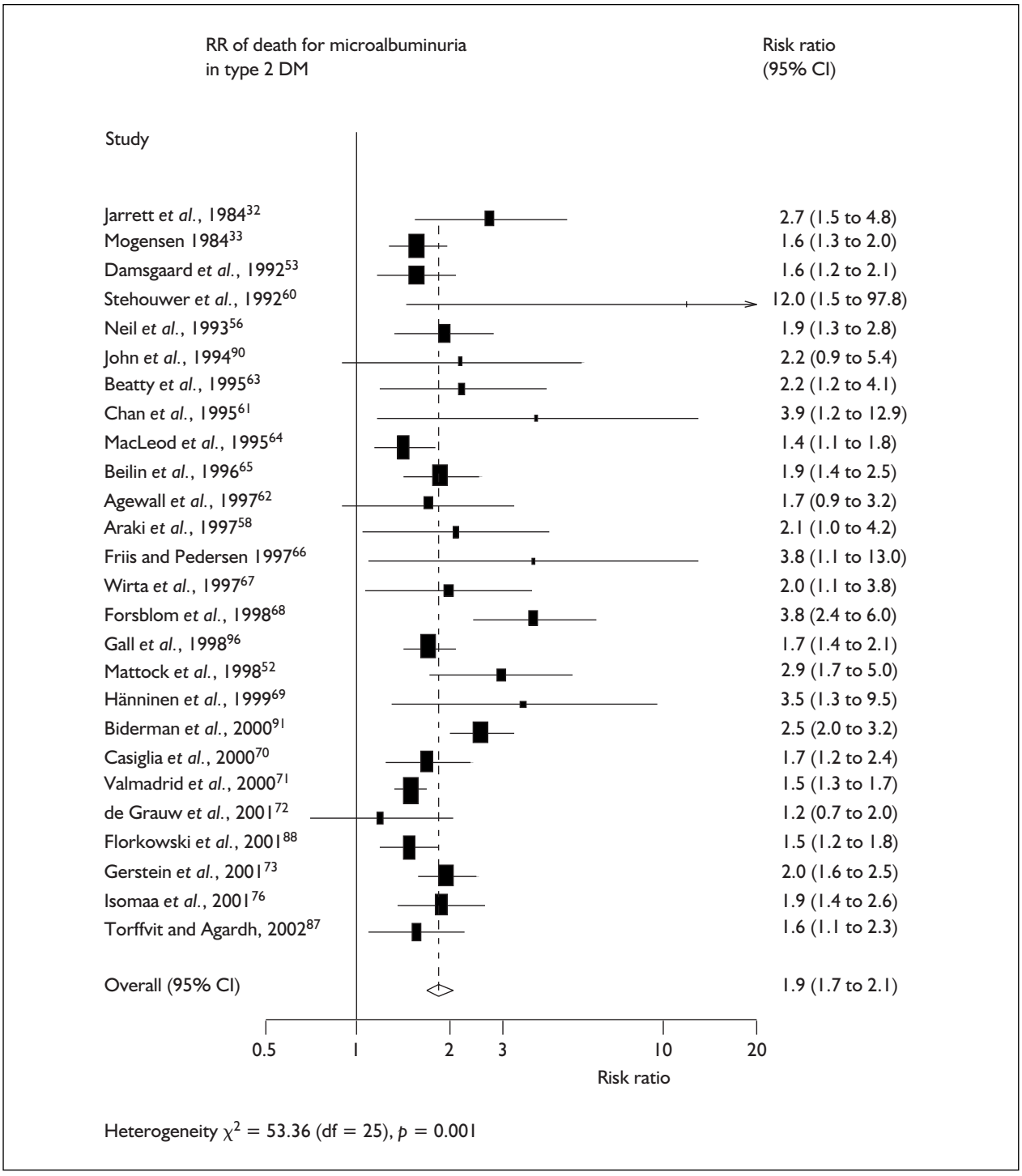

FIGURE 6 *Forest plot for relative risk of mortality with microalbuminuria in type 2 DM*

Publication bias

The funnel plot (*Figure 7*) indicates asymmetry. Those studies with large relative risks tend to have low precision. Egger's test for publication bias gives $p < 0.001$. The trim and fill method estimated ten missing studies and gave an adjusted risk of 1.6 (95% CI 1.5 to 1.9).

Meta-regression

Meta-regression was used to investigate whether age or gender of patients at recruitment, known duration of diabetes at recruitment, duration of follow-up or publication date was related to the reported relative risk.

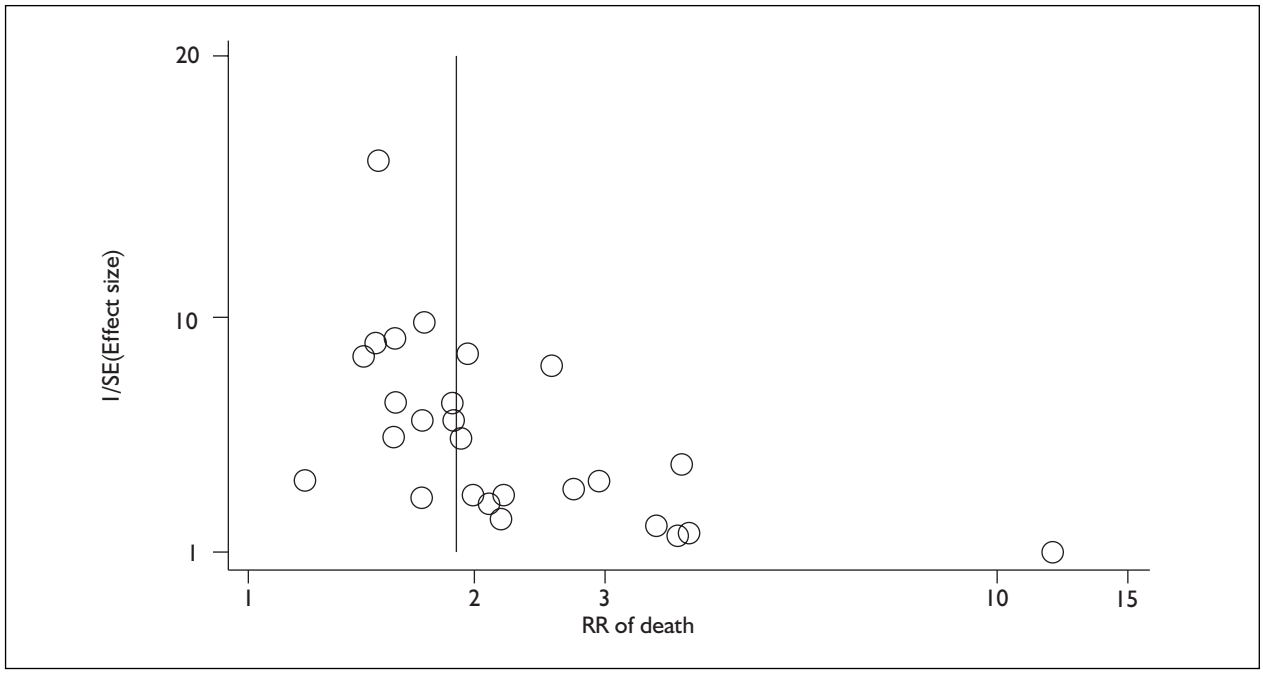

FIGURE 7 *Funnel plot for relative risk of mortality with microalbuminuria in type 2 DM*

Only age was significantly related to the relative risk, with younger patients showing a greater effect (*Figure 8* and *Table 8*). Thus, the estimated relative risk of mortality at the age of 55 years is 2.3, reducing to 1.7 at 65 years of age.

Inclusion of patients with clinical proteinuria

The studies by Damsgaard,[53] Stehouwer,[60] MacLeod,[64] Biderman[91] and Florkowski and colleagues[88] include some patients with clinical proteinuria in their microalbuminuric groups. As the relative risk might be higher than would otherwise be expected, the meta-analysis was repeated without these five studies but gave the same relative risk of 1.9 (95% CI 1.7 to 2.1). Heterogeneity was slightly reduced, but was still highly significant: heterogeneity $\chi^2 = 35.54$ (df = 20), $p = 0.017$.

Adjusted risk estimates

Among the 28 mortality reports, only five did not report any results from adjusted analyses.[33,60,66,87,90] *Table 9* shows the crude unadjusted relative risk (where available) together with the adjusted estimate and the particular variables considered. In the studies by MacLeod[64] and Beatty and colleagues,[63] equal-sized groups were matched for some factors at baseline. These two studies were therefore included (using the crude unadjusted relative risks and 95% confidence intervals as if they were adjusted risks). The risk estimate from Agewall was not included as it was uncertain whether this was an adjusted estimate.[62] A crude relative risk was not extractable from Allawi, although an adjusted risk estimate was reported.[97] Jarrett and colleagues[32] reported an adjusted relative risk of 3.3 ($p < 0.01$), but did not report the confidence interval or standard error. The confidence interval was estimated assuming $p = 0.01$.[32] Two studies without an adjusted relative risk available for synthesis reported that urinary albumin excretion or microalbuminuria was a significant predictor of mortality in adjusted models[49,58] and two reported that it was not significant.[61,67] Thus, there were 18 estimates of adjusted relative risk available. The combined relative risk was 1.8 (95% CI 1.6 to 1.9), and the heterogeneity was no longer significant ($p = 0.53$) (*Figure 9*).

Six of these 18 studies included some patients with clinical proteinuria when calculating adjusted relative risks.[53,64,69,76,88,91] This may have the effect of making the relative risk too high. The six studies were therefore removed and the meta-analysis was repeated. The overall relative risk was the same 1.8 (95% CI 1.6 to 2.0), heterogeneity χ^2 $p = 0.75$.

Evidence for mortality prediction of microalbuminuria below conventional cut-off points

There is a persisting debate as to which level of urinary albumin excretion should be accepted as

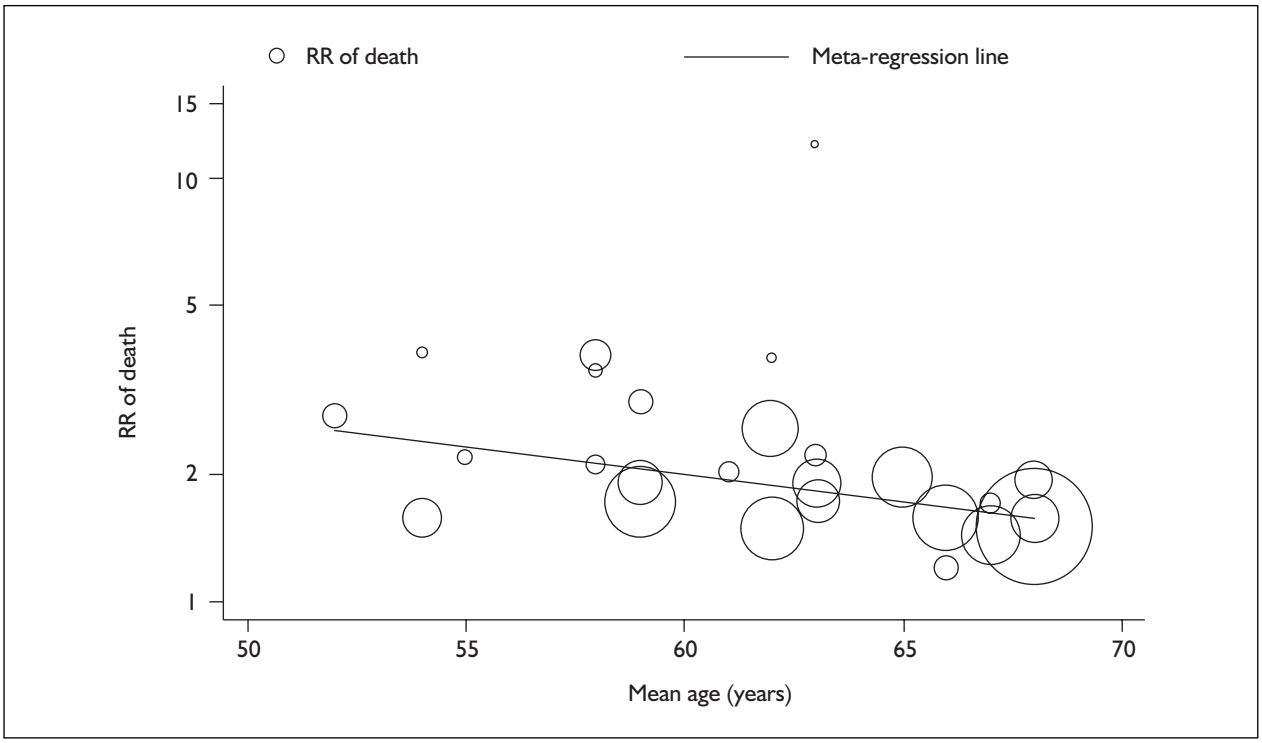

FIGURE 8 *Meta regression for relative risk of mortality against age in type 2 DM*

TABLE 8 *Meta-regression coefficients for mortality in patients with type 2 DM*

Variable	Regression coefficient	95% CI	*p*-Value
Age	–0.029	–0.051 to –0.008	0.007
% Male	0.000	–0.012 to 0.012	0.98
Duration of diabetes	–0.029	–0.078 to 0.021	0.25
Length of follow-up	–0.032	–0.072 to 0.008	0.12
Publication date	–0.002	–0.023 to 0.020	0.88

conferring additional risk of mortality in patients with type 2 DM. Any cut-off point is arbitrary when applied to a continuous biological variable such as urinary AER. The AER range of 20–200 μg per minute or 30–300 mg per day defining microalbuminuria was chosen on the basis of existing evidence at the time (1986). Cut-off levels were taken from those predictive of the development of nephropathy in patients with type 1 DM, but these have since been widely used in type 2 DM also. Even in the earliest two studies in this field[32,33] evidence was presented suggesting that the predictive power of raised AER for mortality in patients with type 2 DM extended below the levels defining microalbuminuria. The 53 initially selected articles (see section 'Search results' p. 18) were re-examined for any further evidence relating to this and seven relevant papers were found.[32,33,50,56,64,69,73]

Jarrett and colleagues[32] found that both age-adjusted AER above 30 μg per minute and age-adjusted AER above 10 μg per minute predicted subsequent mortality over a 14-year follow-up in type 2 DM, with relative risks of 3.3 ($p < 0.01$) and 4.0 ($p < 0.001$) respectively. However, the study was small, with AER being available in only 42 patients at baseline. Mogensen[33] examined the 9.5-year mortality rates of microalbuminuric type 2 diabetic patients in comparison with patients matched for age, gender and type of treatment, but with both lower and higher albumin concentrations. Comparisons were made between the mortality among these 232 patients and that found in the general Danish population of similar age and same gender during the same period. There was a 37% increase in mortality in patients with albumin concentration below 15 mg l^{-1} ($p = 0.03$), a 76% increase for the range 16–29 mg l^{-1} ($p < 0.001$),

TABLE 9 *Authors' adjusted risk estimates of the relationship between microalbuminuria and mortality in patients with type 2 DM*

Source	Crude RR (95% CI)	Authors' adjusted RR (95% CI)	Factors allowed for
Jarrett *et al.*, 1984[32]	2.7 (1.5 to 4.8)	3.3 (1.3 to 8.2)[a]	Age, gender, BP
Mogensen, 1984[33]	1.6 (1.3 to 2.0)	NE	No adjustments
Damsgaard *et al.*, 1992[53]	1.6 (1.2 to 2.1)	2.1 (1.6 to 2.8)	Age, gender, glucose lipids, CHD, hypertension, smoking
Stehouwer *et al.*, 1992[60]	12 (1.5 to 98)	NE	No adjustments
Neil *et al.*, 1993[56]	1.9 (1.3 to 2.8)	2.2 (1.3 to 3.7)	Age, duration, retinopathy, lens opacity, claudication
John *et al.*, 1994[90]	2.2 (0.9 to 5.4)	NE	No adjustments
Beatty *et al.*, 1995[63]	2.2 (1.2 to 4.1)	2.2 (1.2 to 4.1)	Age and gender matched with controls
Chan *et al.*, 1995[61]	4.1 (1.2 to 13.8)	ns in model	Age, glucose, creatinine
MacLeod *et al.*, 1995[64]	1.4 (1.1 to 1.8)	1.4 (1.1 to 1.8)	Age, gender and duration matched with controls
Beilin *et al.*, 1996[65]	1.9 (1.4 to 2.5)	1.8 (1.2 to 2.6)	Age, gender, duration, BMI, BP, HbA_{1c}, lipids, CHD, retinopathy
Standl *et al.*, 1996[49]	NE[b]	UAC. Significant in models	Age, fasting glucose, carotid artery disease, vWF
Agewall *et al.*, 1997[62]	1.7 (0.9 to 3.2)	2.3 (1.1 to 5.0) for UAE	Unclear whether this is an adjusted estimate
Allawi *et al.*, 1997[97]	NE	2.6 (0.95 to 7.0)	Age, WHR, lipids, urate, urea
Araki *et al.*, 1997[58]	2.1 (1.0 to 4.2)	NE. Significant in model	Age, gender
Friis and Pedersen, 1997[66]	3.8 (1.1 to 13.0)	NE	No adjustments
Wirta *et al.*, 1997[67]	2.0 (1.1 to 3.8)	NE. ns in model	Age, gender, CHD, lipids
Forsblom *et al.*, 1998[68]	3.8 (2.4 to 6.0)	2.9 (1.2 to 7.0)	Age, gender, macroangiopathy, lipids, HbA_{1c}, retinopathy
Gall *et al.*, 1998[96]	1.7 (1.4 to 2.1)	1.8 (1.4 to 2.4)	Age, gender, CHD, cholesterol
Mattock *et al.*, 1998[52]	2.9 (1.7 to 5.0)	1.2 (0.5 to 2.8)	Age, gender, CHD, HbA_{1c}, cholesterol
Hänninen *et al.*, 1999[69]	3.5 (1.3 to 9.5)	1.1 (0.5 to 2.5)[c]	Age, gender, CHD
Biderman *et al.*, 2000[91]	2.5 (2.0 to 3.2)	2.3 (1.4 to 4.0)	Age, HbA_{1c}, triglycerides, self-reported CHD
Casiglia *et al.*, 2000[70]	1.7 (1.2 to 2.4)	1.6 (1.1 to 2.2)	Age, gender, CHD, lipids, HbA_{1c}, retinopathy
Valmadrid *et al.*, 2000[71]	1.5 (1.3 to 1.7)	1.7 (1.4 to 2.1)	Age, gender, glycaemic control, CVD, retinopathy
de Grauw *et al.*, 2001[72]	1.2 (0.7 to 2.0)	1.2 (0.6 to 2.2)	Age, gender, duration
Florkowski *et al.*, 2001[88]	1.5 (1.2 to 1.8)	1.6 (1.1 to 2.3)	Age, BMI, lipids, HbA_{1c}, CAD, smoking, hypertension
Gerstein, 2001[73]	2.0 (1.6 to 2.5)	1.9 (1.4 to 2.4)	Age, gender, smoking, lipids HbA_{1c}, hypertension
Isomaa *et al.*, 2001[76]	1.9 (1.4 to 2.6)	2.3 (1.3 to 4.1)	Age, male gender, hypertension, smoking, lipids
Torffvit and Agardh, 2002[87]	1.6 (1.1 to 2.3)	NE	No adjustments

[a] $p < 0.01$ reported in paper; confidence interval estimated from $p = 0.01$.
[b] 40–200 vs <15 mg l^{-1}.
[c] Includes patients with clinical proteinuria.
BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; UAC, urinary albumin concentration; UAE, urinary albumin excretion; vWF, von Willebrand factor.

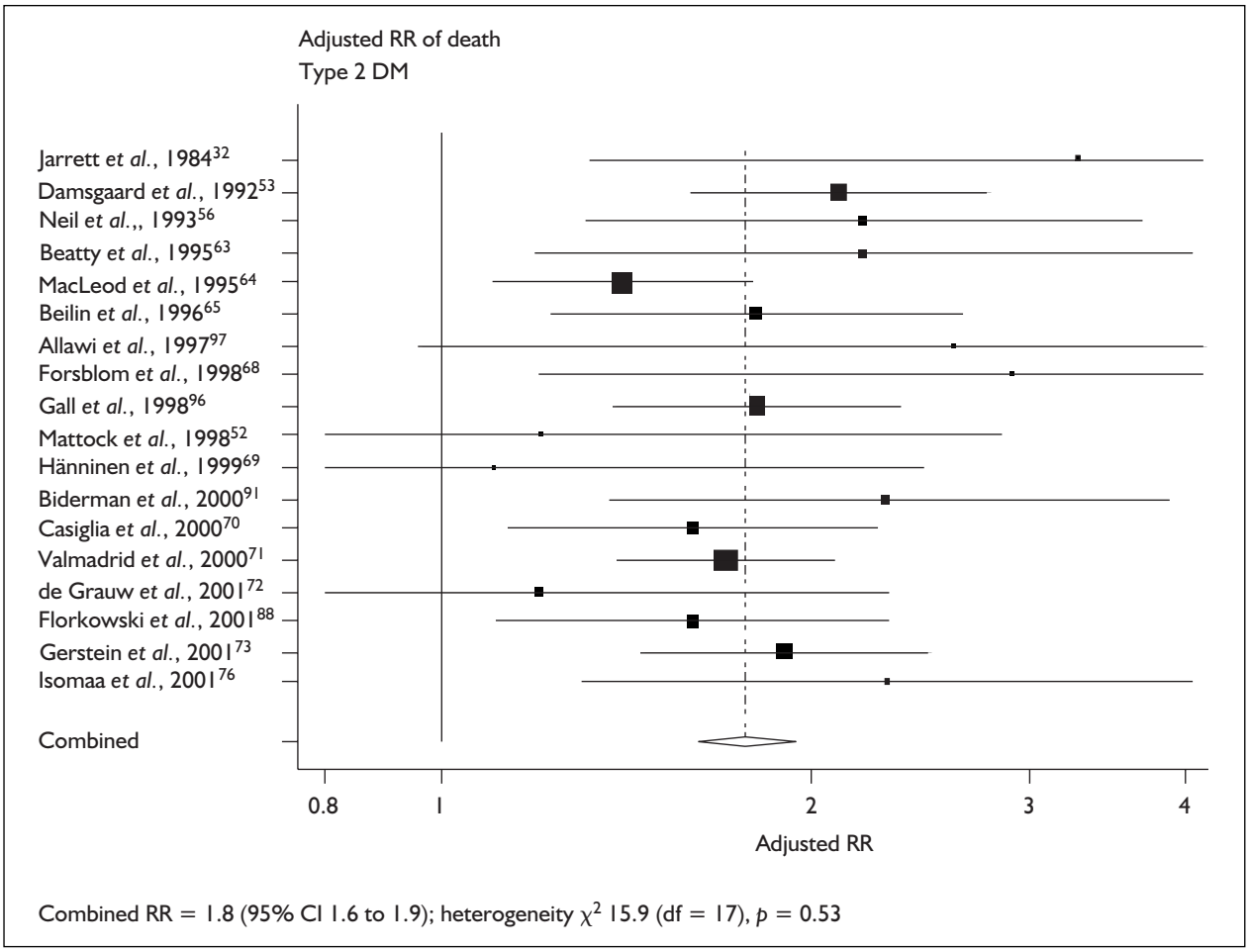

FIGURE 9 *Forest plot for adjusted risk of mortality with microalbuminuria in type 2 DM*

148% for those in the microalbuminuric range of 30–140 mg l^{-1} ($p < 0.001$) and 105% for those in the macroalbuminuric range of greater than 140 mg l^{-1} ($p < 0.001$). These earlier studies suggested that excess risk of mortality might be present at AER levels well below those defining microalbuminuria.

MacLeod and colleagues[64] examined this question further in a cohort of 306 type 2 patients followed for 8 years (overnight AER had been measured at baseline). The mortality rate in the borderline group (AER 10.6–29.9 μg per minute) was significantly higher than in controls (AER < 10.5 μg per minute): 104 versus 61 per 1000 person-years (OR = 2.27, 95% CI 1.08 to 5.12). Comparing those patients with AER greater than or equal to 30 μg per minute with controls, there was a similar increase in mortality (OR = 2.18, 95% CI 1.03 to 4.93). The authors concluded that even a minor elevation in AER above the normal non-diabetic range was associated with excess mortality. Neil and colleagues[56] carried out a population-based prospective study of microalbuminuria as a predictor of mortality with a 6-year follow-up of 236 patients with type 2 DM. Baseline urinary albumin concentrations were divided into four categories: below 15 mg l^{-1} (control), 15–39 mg l^{-1} (borderline), 40–200 mg l^{-1} (microalbuminuria) and above 200 mg l^{-1} (clinical proteinuria). The standardised mortality ratio (SMR) was 116 (95% CI 84 to 156) for the control group (not significant), 156 (95% CI 91 to 250) for the borderline group (not significant) and 238 (95% CI 148 to 365) for the microalbuminuric group ($p < 0.001$), giving some evidence for a dose–response relationship.

In a 5-year prospective study of 328 Danish type 2 diabetic patients, Gall and colleagues[50] found a relative risk of death in univariate Cox regression analysis of 2.5 (95% CI 1.3 to 5.0) for microalbuminuria versus normoalbuminuria (AER 30–300 versus AER <30 mg per 24 hours). In the subgroup of 191 patients with normoalbuminuria, AER above the median value of 8 mg per 24 hours was associated with a relative risk of death of 2.7 (95% CI 0.9 to 7.7) compared with patients who

had AER less than or equal to the median. This suggested that risk of mortality extended to levels of AER well below those defining microalbuminuria. A 5-year prospective study of 252 Finnish type 2 diabetic patients reported by Hänninen and colleagues[69] found an increased crude relative risk of microalbuminuria (AER 20–200 μg per minute) for mortality of 3.5 (95% CI 1.3 to 9.5), but in the normoalbuminuric group (AER <20 μg per minute) the mortality rates were equal among those under and above median AER.

The Heart Outcomes Prevention Evaluation (HOPE) study was a large cohort study with a median 4.5 years of follow-up, based on nearly 3500 patients with type 2 DM from community and academic practices in North and South America and Europe.[73] Patients had a baseline measurement of urine ACR (mg $mmol^{-1}$) and dipstick-positive proteinuria was an exclusion criterion. Mortality outcome was analysed according to the level of albuminuria (expressed in quartiles of ACR) and a graded relationship was found between baseline ACR and risk of mortality. Thus, compared with ACR in the first quartile (ACR <0.22), the relative risk of all-cause death was 0.9 (95% CI 0.6 to 1.1) in the second quartile (ACR 0.22–0.57), 1.4 (1.0 to 2.0) in the third quartile (ACR 0.58–1.62) and 2.4 (1.8 to 3.2) in the fourth quartile (ACR > 1.62) [test for trend after controlling for age, gender, blood pressure, waist/hip ratio (WHR) and HbA_{1c}, $p < 0.001$]. The fourth quartile includes participants with microalbuminuria (defined by an ACR of ≥ 2 mg $mmol^{-1}$ for both men and women). The results indicate that the relationship between ACR and mortality extends to as low as 0.5 mg $mmol^{-1}$, well below currently accepted screening thresholds for a diagnosis of microalbuminuria.

In conclusion, the majority of studies that have investigated the relationship between submicroalbuminuric urinary albumin excretion and death rate have found a significant positive association. Moreover, Rachmani and colleagues[99] have found that this may also apply to other outcomes, such as rate of progression to microalbuminuria and rate of decline in GFR. The implication of these findings is that the currently accepted threshold value for the definition of microalbuminuria may no longer be relevant in patients with type 2 DM.

Conclusions

Compared with type 1 DM, there are more studies ($n = 28$) available in those with type 2 DM, but they show considerable heterogeneity ($p < 0.001$). The unadjusted overall relative risk of death among patients with type 2 DM and microalbuminuria is 1.9 (95% CI 1.7 to 2.1), which is very similar to that found in patients with type 1 DM (1.8, 95% CI 1.5 to 2.1). Age was significantly and inversely related to relative risk, which was 2.3 at the age of 55, reducing to 1.7 at 65. Authors' adjusted risk estimates from the 18 available studies reduce the relative risk to 1.8 (95% CI 1.6 to 1.9) and heterogeneity is no longer evident, but it must be noted that each author has not considered the same risk factors. Removal of the few studies that included a minority of patients with clinical proteinuria was without effect on the calculated relative risk. There has been a previous systematic review of the associations of microalbuminuria and mortality among patients with type 2 DM[18] that comprised only eight studies. However, the overall risk estimates (1.8, 95% CI 1.4 to 2.5) were similar to those found in the present analysis.

Relationship between microalbuminuria and CVD mortality in patients with type 2 DM

Characteristics of the individual studies

From the 53 articles originally identified (see section 'Search results', p. 18) 15 studies were selected for inclusion[49,58,61,62,64,65,70–72,75–77,79,96,97] and some of their basic characteristics are shown in *Table 10*. The majority of these studies also report on the relation of microalbuminuria to total mortality and thus some information is repeated. Raw data for the calculation of crude relative risk were available for 4687 patients from 13 studies.

CVD mortality risk

All but one study showed a positive association between microalbuminuria and CVD death (*Figure 10*). The meta-analysis gave an overall relative risk of 2.0 (95% CI 1.7 to 2.3) with no significant heterogeneity.

Publication bias

The funnel plot (*Figure 11*) shows some asymmetry indicating publication bias, although Egger's test gives $p = 0.09$. Trim and fill sensitivity analysis gave a random effects relative risk of 1.9 (95% CI 1.6 to 2.3).

Meta-regression

Meta-regression was carried out on age at recruitment, known duration of diabetes at recruitment, duration of follow-up and publication

TABLE 10 *Relationship between microalbuminuria and CVD mortality in patients with type 2 DM*

Source	Setting	Age (y)	Mean duration of diabetes (y)	FU (y)	MA deaths/total	NA deaths/total	Crude RR (95% CI)
Chan *et al.*, 1995[61]	Hong Kong, China (H)	54	6	2	6/94	3/208	4.4 (1.1 to 17.3)
MacLeod *et al.*, 1995[64]	Newcastle upon Tyne, UK (H)	67	8	8	65/153	39/153	1.7 (1.2 to 2.3)
Beilin *et al.*, 1996[65]	Perth, Australia (H)	63	13	5	36/211	30/390	2.2 (1.4 to 3.5)
Niskanen *et al.*, 1996[79]	Kuopio, Finland (P)	56	NE	10	9/28	19/105	1.8 (0.9 to 3.5)
Standl *et al.*, 1996[49]	Munich, Germany (G)	65	8	10	NE	NE	NC
Agewall *et al.*, 1997[62]	Göteborg, Sweden (H)	67	NE	6	11/36	5/45	2.8 (1.1 to 7.2)
Allawi *et al.*, 1997[97]	London, UK (H)	57	NE	9	NE	NE	NC
Araki *et al.*, 1997[58]	Shiga, Japan (H)	58	9	6	4/96	6/201	1.4 (0.4 to 4.8)
Gall *et al.*, 1998[96]	Gentofte, Denmark (H)	59	9	10	54/151	52/323	2.2 (1.6 to 3.1)
Vanzetto *et al.*, 1999[77]	Grenoble, France (H)	63	14	2	7/51	1/107	14.7 (1.9 to 116)
Casiglia *et al.*, 2000[70]	Padova, Italy (H)	63	NE	6	25/164	37/497	2.0 (1.3 to 3.3)
Valmadrid *et al.*, 2000[71]	Wisconsin USA (P)	68	15	12	113/208	146/460	1.7 (1.4 to 2.1)
de Grauw *et al.*, 2001[72]	Nijmegen, Netherlands (G)	66	5	6	7/50	29/202	1.0 (0.5 to 2.1)
Isomaa *et al.*, 2001[76]	Finland and Sweden (F)	59	NE	7	24/81	68/526	2.3 (1.5 to 3.4)
Jager *et al.*, 2001[75]	Amsterdam, Netherlands (P)	66	NE	7	8/28	9/119	3.8 (1.6 to 8.9)
Meta-analysis, 2002		**62**	**11**	**7**	**369/1351**	**444/3336**	**2.0 (1.7 to 2.3)**

date (*Table 11*). None of the factors was significant in the regression models, although there was a negative relationship with age as found with total mortality. However, fewer studies were available, thus reducing the power of the analysis.

Inclusion of patients with clinical proteinuria

There are three studies where the raw data may be affected by the presence of clinically proteinuric patients in the group.[64,77,79] The meta-analysis was therefore repeated with these three studies removed, but the estimate of relative risk remained unchanged at 2.0 (95% CI 1.7 to 2.4).

Adjusted risk estimates

Of the 15 selected studies, two did not adjust for other factors.[61,77] Thus, there were 13 studies available to address this question[49,58,62,64,65,70–72,75,76,79,96,97] (*Table 12*). Standl[49] and Allawi and colleagues[97] reported only that urinary albumin excretion or microalbuminuria, respectively, was not significant in adjusted models for CVD prediction. Niskanen and colleagues[79] found that the adjusted odds ratio of microalbuminuria for CVD mortality was just significant in an adjusted model, but it was not possible to combine this estimate with adjusted relative risks. In the study by MacLeod and co-workers, equal-sized groups were matched for some factors at baseline.[64] This study was therefore included (using the crude unadjusted relative risk and 95% confidence intervals as if it was an adjusted risk estimate). Therefore, there were ten studies available for meta-analysis. The

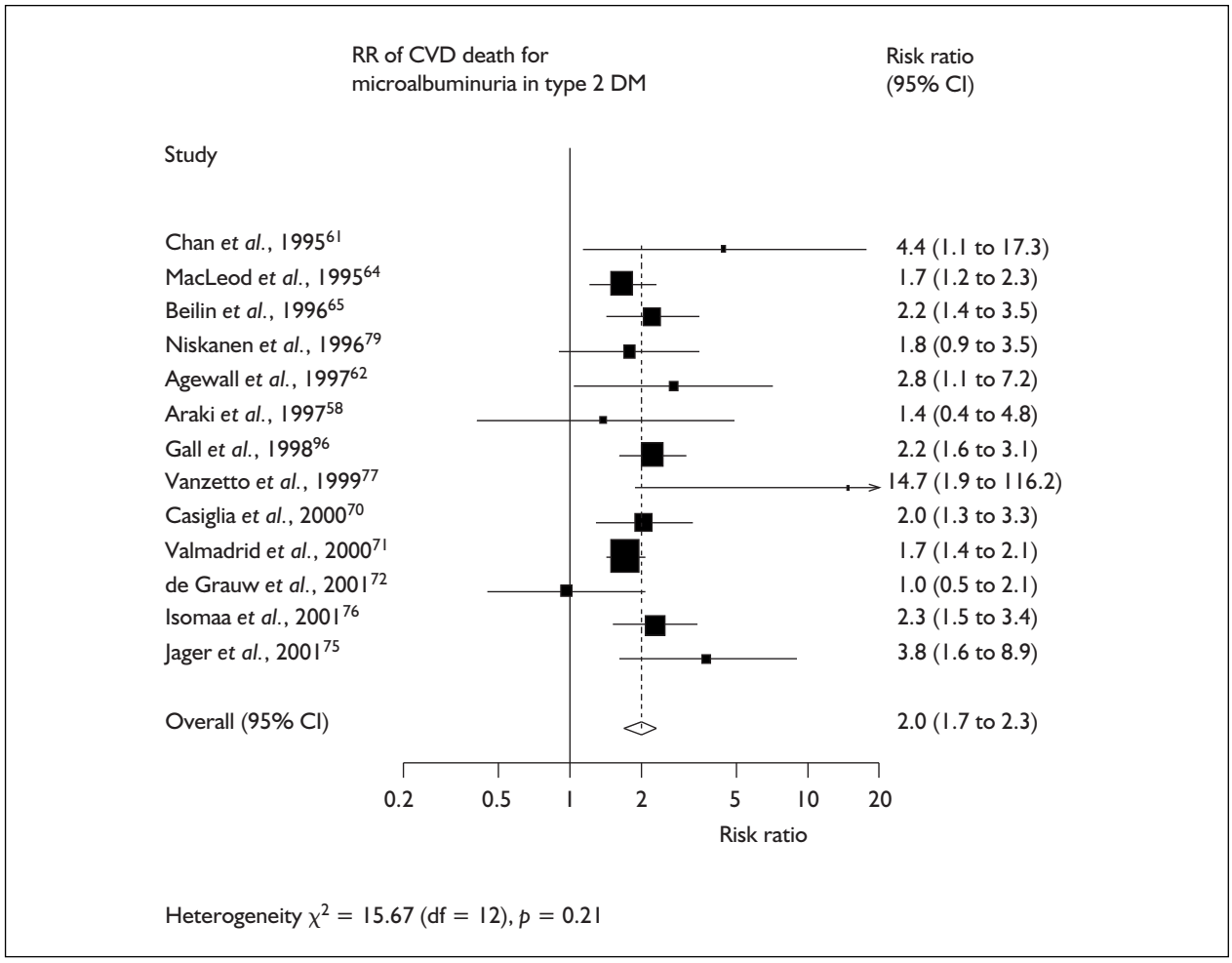

FIGURE 10 *Forest plot for relative risk of CVD mortality with microalbuminuria in Type 2 DM*

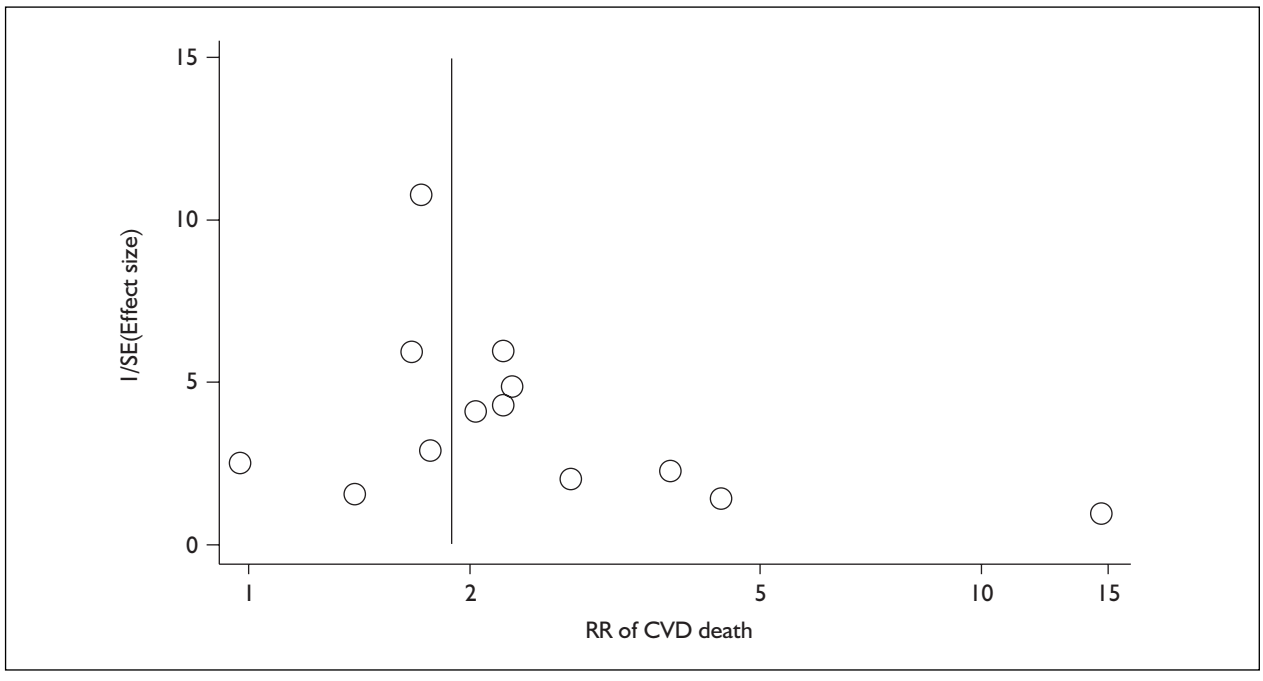

FIGURE 11 *Funnel plot for relative risk of CVD mortality with microalbuminuria in type 2 DM*

TABLE 11 *Meta-regression coefficients for CVD mortality in type 2 DM*

Variable	Regression coefficient	95% CI	*p*-Value
Age	–0.027	–0.057 to 0.001	0.065
Duration of diabetes	–0.001	–0.042 to 0.039	0.96
Length of follow-up	–0.038	–0.083 to 0.007	0.10
Publication date	–0.002	–0.064 to 0.059	0.94

TABLE 12 *Authors' adjusted risk estimates of microalbuminuria for CVD mortality in patients with type 2 DM*

Source	Crude RR (95% CI)	Adjusted RR (95% CI)	Factors allowed for
MacLeod *et al.*, 1995[64]	1.7 (1.2 to 2.3)	1.7 (1.2 to 2.3)	Matching at baseline for age, gender, duration
Beilin *et al.*, 1996[65]	2.2 (1.4 to 3.5)	2.3 (1.4 to 4.0)	Age, gender, duration, BMI, BP, HbA_{1c}, lipids, CHD, retinopathy
Niskanen *et al.*, 1996[79]	1.8 (0.9 to 3.5)	Adjusted OR 4.0 (1.0 to 15)	Age, gender, lipids, ECG, glucose, hypertension
Standl *et al.*, 1996[49]	NE	UAE ns in models	Age, HbA_{1c}, CHD, BP, lipids
Agewall *et al.*, 1997[62]	2.8 (1.1 to 7.2)	1.9 (1.0 to 3.6)	Age, triglycerides, creatinine, glucose, smoking, CVD, HbA_{1c}
Allawi *et al.*, 1997[97]	NE	NS in models	Age, CVD, BMI, lipids, hypertension
Araki *et al.*, 1997[58]	1.4 (0.4 to 4.8)	0.9 (0.4 to 1.2)	Age, gender, duration, lipids, HbA_{1c}, BP
Gall *et al.*, 1998[96]	2.2 (1.6 to 3.1)	2.8 (1.9 to 4.1)	Age, gender, CHD, cholesterol
Casiglia *et al.*, 2000[70]	2.1 (1.3 to 3.3)	2.0 (1.2 to 3.7)	Age, gender, lipids, CHD
Valmadrid *et al.*, 2000[71]	1.8 (1.4 to 2.4)	1.9 (1.4 to 2.4)	Age, gender, glycaemic control, CVD, retinopathy
de Grauw *et al.*, 2001[72]	1.0 (0.5 to 2.1)	1.2 (0.5 to 2.8)	Age
Isomaa *et al.*, 2001[76]	2.3 (1.5 to 3.4)	3.2 (1.7 to 5.9)	Age, gender, LDL-cholesterol, smoking
Jager *et al.*, 2001[75]	3.8 (1.6 to 8.9)	2.8 (1.0 to 8.1)	Age, gender, HbA_{1c}, duration, hypertension

LDL, low-density lipoprotein.

overall estimate obtained from adjusted relative risks from individual studies was 1.9 (95% CI 1.6 to 2.4) (*Figure 12*), which is similar to the overall unadjusted risk of 2.0 (95% CI 1.7 to 2.3), and there was no significant heterogeneity.

Relationship between microalbuminuria and CHD mortality in patients with type 2 DM

From the 53 articles originally identified [see section 'Search results', p. 18] there were eight studies that reported the relationship between CHD deaths and microalbuminuria[50,52,56,58,64,65,67,71] (*Table 13*). The meta-analysis gave an overall relative risk of 2.3 (95% CI 1.7 to 3.1), with no significant heterogeneity between the studies (*Figure 13*).

Publication bias

There was little evidence of publication bias in the funnel plot (*Figure 14*) and Egger's test for publication bias was not significant ($p = 0.18$). However, trim and fill analysis estimated two missing studies and gave a relative risk of 2.0 (95% CI 1.4 to 2.8).

Adjusted risk estimates

Only three of these studies reported adjusted risk estimates of microalbuminuria for CHD mortality[52,65,71] (*Table 14*). However, in the study by MacLeod and colleagues equal-sized groups were matched for some factors at baseline.[64] This

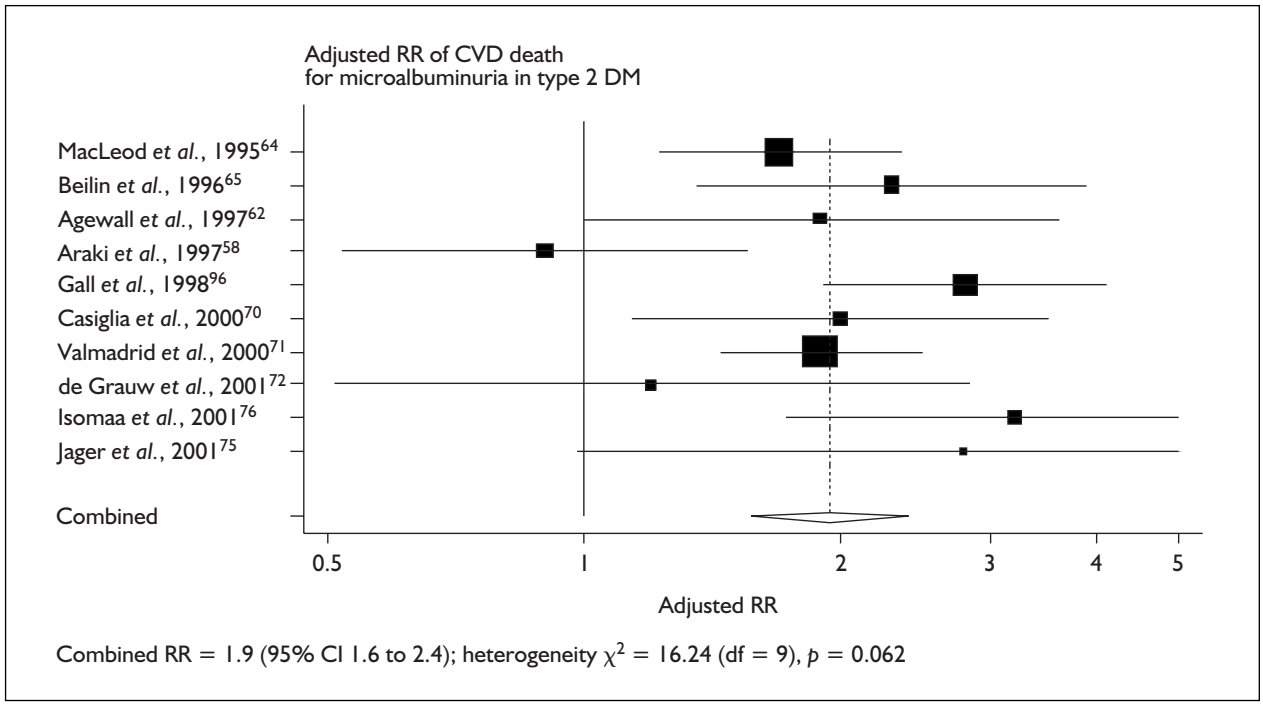

FIGURE 12 *Forest plot for adjusted relative risk of CVD mortality with microalbuminuria in type 2 DM*

TABLE 13 *Relationship between microalbuminuria and CHD mortality in patients with type 2 DM*

Source	Setting	Age (y)	Mean duration of diabetes (y)	FU (y)	MA deaths/total	NA deaths/total	Crude RR (95% CI)
Neil *et al.*, 1993[56]	Oxford, UK (P)	68	7	6	10/36	14/190	3.8 (1.8 to 7.8)
Gall *et al.*, 1995[50]	Gentofte, Denmark (H)	54	6	5	7/86	3/191	5.2 (1.4 to 20)
MacLeod *et al.*, 1995[64]	Newcastle upon Type, UK (H)	67	8	8	49/153	29/153	1.7 (1.1 to 2.5)
Beilin *et al.*, 1996[65]	Perth, Australia (H)	63	13	5	26/211	26/390	1.8 (1.1 to 3.1)
Araki *et al.*, 1997[58]	Shiga, Japan (H)	58	9	6	2/96	5/201	0.8 (0.2 to 4.2)
Wirta *et a1.*, 1997[67]	Tampere, Finland (P)	61	11	9	6/39	5/96	3.0 (1.0 to 9.1)
Mattock *et al.*, 1998[52]	London, UK (H)	59	5	7	13/37	7/109	5.5 (2.4 to 12.7)
Valmadrid *et al.*, 2000[71]	Wisconsin, USA (P)	68	15	12	77/208	92/460	1.9 (1.4 to 2.4)
Meta-analysis, 2002		**63**	**11**	**8**	**190/866**	**181/1790**	**2.3 (1.7 to 3.1)**

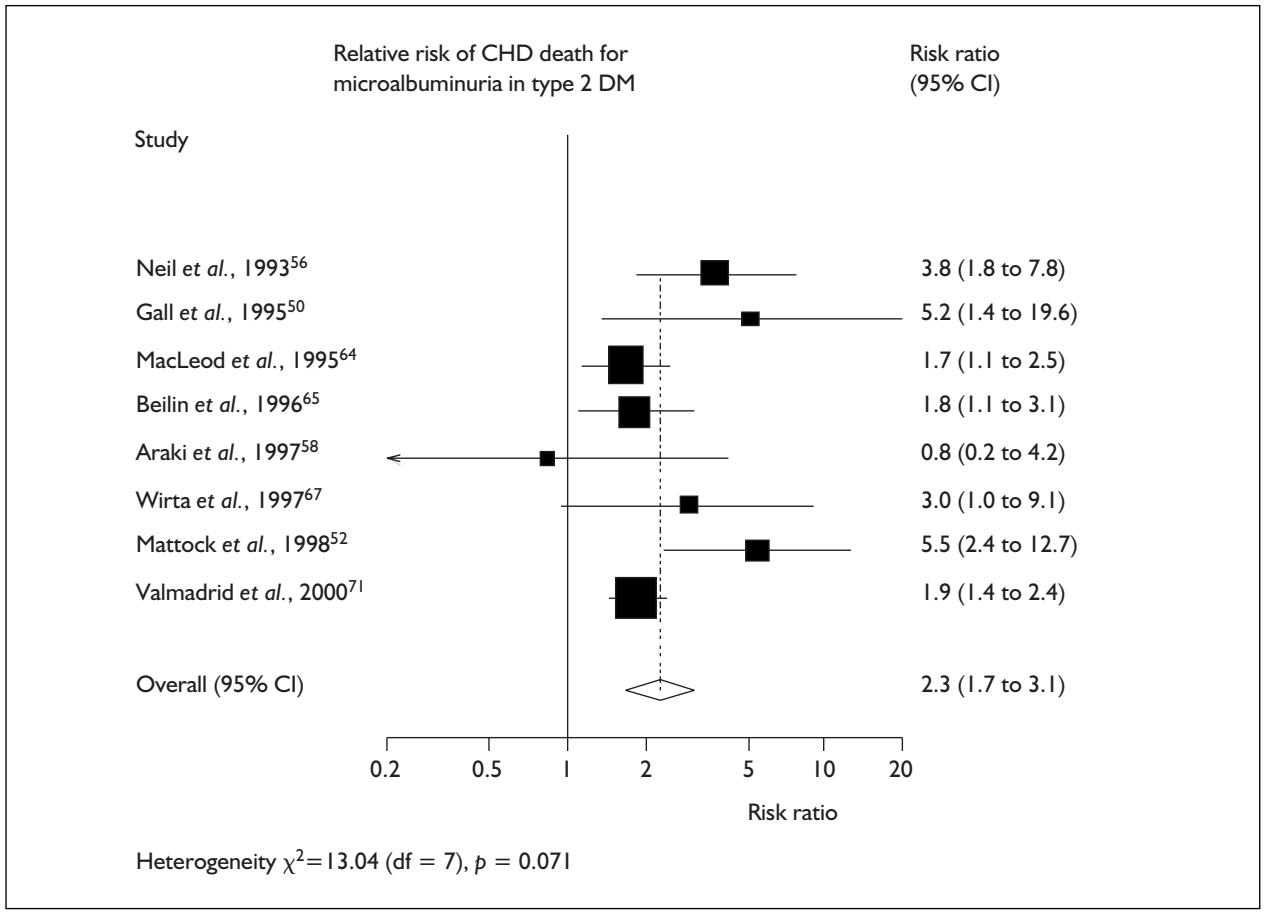

FIGURE 13 *Forest plot for relative risk of CHD mortality with microalbuminuria in type 2 DM*

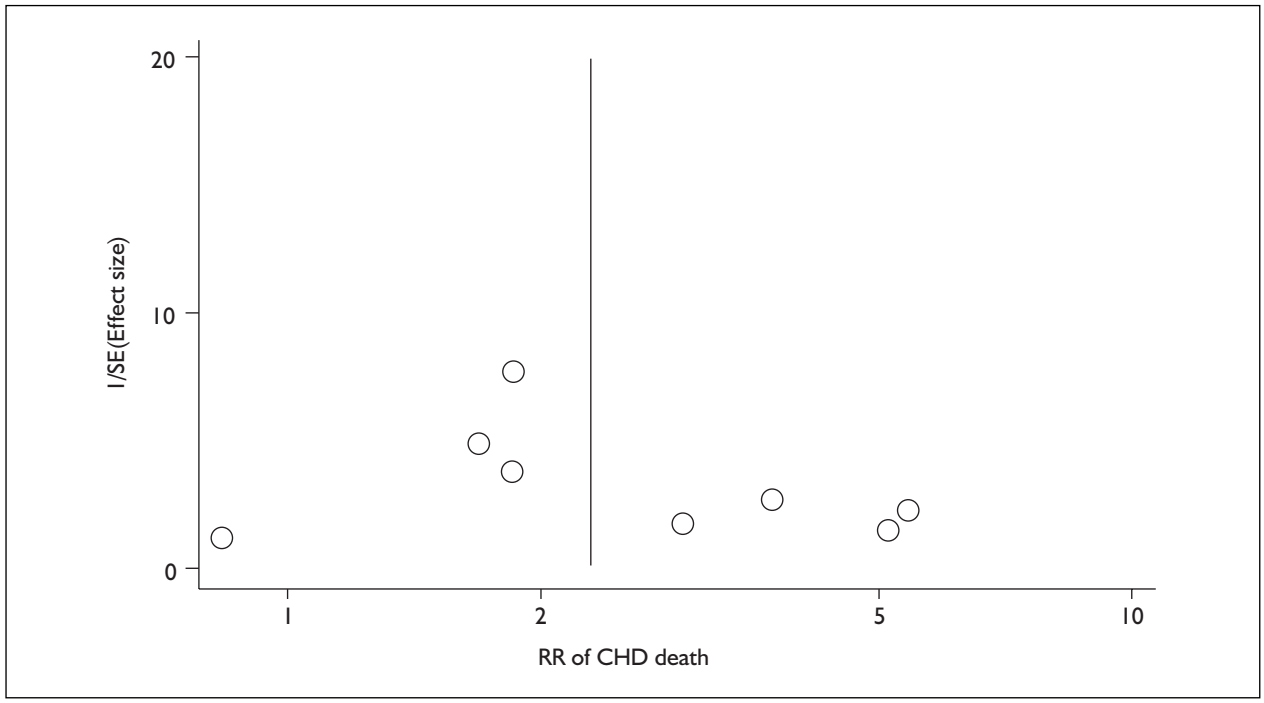

FIGURE 14 *Funnel plot for the relative risk of CHD mortality with microalbuminuria in type 2 DM*

TABLE 14 *Authors' adjusted risk estimates of microalbuminuria for CHD mortality in patients with type 2 DM*

Source	Crude RR (95% CI)	Adjusted RR (95% CI)	Factors allowed for
MacLeod *et al.*, 1995[64]	1.7 (1.1 to 2.5)	1.7 (1.1 to 2.5)	Matching at baseline for age, gender and duration
Beilin *et al.*, 1996[64]	1.8 (1.1 to 3.1)	1.8 (1.0 to 3.3)	Age, duration, CHD, HbA_{1c}, blood pressure, etc.
Mattock *et al.*, 1998[52]	5.5 (2.4 to 12.7)	1.8 (0.6 to 6.0)	Age, sex, CHD, HbA_1, cholesterol
Valmadrid *et al.*, 2000[71]	1.9 (1.4 to 2.4)	2.0 (1.4 to 2.7)	Age, gender, glycaemic control, CVD, retinopathy, etc.

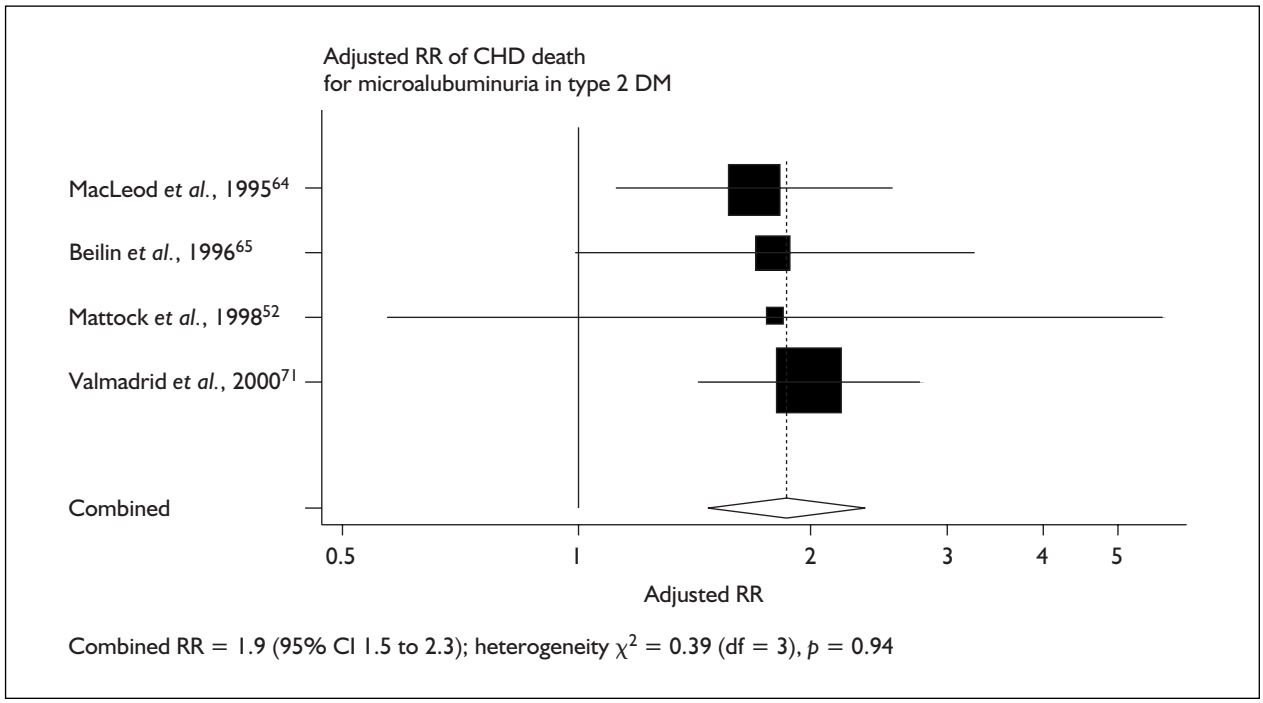

FIGURE 15 *Forest plot for adjusted relative risk of CHD mortality with microalbuminuria in type 2 DM*

study was therefore included (using the crude unadjusted relative risk and 95% confidence intervals as if it was an adjusted risk estimate). Adjustment attenuated the relative risk, but it was still highly significant at 1.9 (95% CI 1.5 to 2.3) with no evidence of heterogeneity (*Figure 15*).

Relationship between microalbuminuria and CVD morbidity and mortality in patients with type 2 DM

From the 53 articles originally identified (see section 'Search results', p. 18) there were nine with potential relevance to the question of the predictive power of microalbuminuria for CVD morbidity and mortality in type 2 DM.[20,52,60,62,68,72,73,80,81] Stehouwer and colleagues[60] reported on the relationship of baseline AER to new CVD events by comparing percentages of patients free of CVD events by category of AER. Raised baseline AER was associated with an increased risk of new CVD events only in patients with von Willebrand factor (vWF) concentrations above the median (RR 3.7, 95% CI 1.3 to 11.9) and not in patients with lower vWF (RR = 0.2, 95% CI 0.01 to 1.3). The overall relative risk, however, was not indicated and the subgroup with raised AER included patients with clinical albuminuria; the study was therefore not included. Agewall and colleagues[62] reported on total and CVD mortality in type 2 patients with hypertension. Both fatal and non-fatal events were tabulated, but no analysis was carried out on the

TABLE 15 *Relationship between microalbuminuria and CVD morbidity and mortality in patients with type 2 DM*

Source	Setting	Definition of cardiovascular morbidity and mortality	*n*	MA event rate	NA event rate	Crude RR (95% CI)	Authors' adjusted RR (95% CI)
Agardh *et al.*, 1996[81]	Lund, Sweden (H)	Death or non-fatal MI, cerebrovascular disease or amputation	451	NE	NE	NE	OR = 1.6 (0.9 to 3.0)
Forsblom *et al.*, 1998[68]	Helsinki, Finland (H)	Non-fatal CHD (medical history and ECG), peripheral vascular disease or stroke, or fatal MI, heart failure or stroke	134	NE	NE	NE	AER ns in multivariate model
Mattock *et al.*, 1998[52]	London, UK (H)	Death from CHD (death certificate), or angina or MI (Rose questionnaire) and/or ECG abnormalities	146	NE	NE	NE	OR = 10.0 (1.6 to 61) in multivariate model in men
UKPDS, 1998[20]	Multicentre, UK (H)	Angina with confirmatory ECG or fatal or non-fatal MI	3055	NE	NE	NE	MA ns in multivariate model
de Grauw *et al.*, 2001[72]	Nijmegen, Netherlands (P)	CVD morbidity and causes of death recorded by GP at least one of MI, angina, heart failure, stroke, transient ischaemic attack or peripheral vascular disease	262	NE	NE	NE	1.4 (0.8 to 2.3)
Gerstein, 2001[73]	Multinational study North and South America and Europe	MI, stroke or CVD death	3498	28.6%	15.3%	1.9 (1.6 to 2.5)	1.8 (1.5 to 2.3)

n, total number with known albuminuria status; OR, odds ratio.

predictive power of microalbuminuria for CVD morbidity and mortality. It was not considered possible to distinguish between the frequency of CVD at baseline and follow-up and the study was not included. In the study by Uusitupa and colleagues,[80] the focus was on the relationship of serum lipoprotein abnormalities to CVD morbidity and mortality and the study was not selected. This left six studies for inclusion and some of their basic characteristics are shown in *Table 15*.

Because of the differing methods of statistical analysis, a meta-analysis of these studies is not possible. Study authors adjusted their results for a variety of possibly confounding factors. Agardh and colleagues[81] adjusted for age, duration of diabetes, serum creatinine, HbA_{1c}, SBP and DBP; Forsblom and colleagues[68] for age, HbA_{1c}, lipids, creatinine clearance, retinopathy, smoking and neuropathy; Mattock and colleagues[52] for age, smoking, diastolic blood pressure and serum cholesterol; while de Grauw and colleagues[72] adjusted for age only. It is notable that the two largest studies, the UKPDS (results adjusted for age, gender, blood pressure, HbA_{1c} and serum lipids)[20] and the HOPE study (adjusted for age, gender, blood pressure, WHR and HbA_{1c})[73] which are both based on RCTs and included some 3000 diabetic patients each, are not in agreement regarding the predictive power of microalbuminuria for CVD morbidity and mortality. The results from further large, ongoing studies are needed to resolve this uncertainty.

Conclusions

There was a positive relationship between baseline microalbuminuria and incident CHD or CVD morbidity and mortality in some studies, but the evidence is so far inconsistent. The results of further studies are required.

Relationship between microalbuminuria and mortality in type 2 DM: conclusions

For patients with type 2 DM, 53 articles were initially identified. This reduced after applying the protocol requirements to 28 with respect to all-cause mortality, 13 with respect to CVD mortality, eight with respect to CHD mortality, and six for combined CVD mortality and morbidity end-points. Compared with normoalbuminuria there was an increased relative risk associated with microalbuminuria of 1.9 (95% 1.7 to 2.1) for all-cause mortality that was related to mean age of cohort on meta-regression (RR 2.3 at the age of 55, reducing to 1.7 at 65), but was little changed (1.8, 95% CI 1.6 to 1.9) when adjusted for important covariates such as age, gender and duration of diabetes in the 18 studies that did this. There was also an increased relative risk associated with microalbuminuria for CVD mortality (2.0, 95% CI 1.7 to 2.3) that remained similar (1.9, 95% CI 1.6 to 2.4) after adjustment for confounders (ten studies). A minority of studies examining all-cause and CVD mortality included some few patients with clinical proteinuria, but removal of these studies had no effect on the calculated relative risk. Microalbuminuria increased the relative risk for CHD mortality (2.3, 95% CI 1.7 to 3.1), but this was slightly attenuated (1.9, 95% CI 1.5 to 2.3) after adjustment (four studies). Because of differing methods of statistical analysis, a meta-analysis for the aggregate end-point of CVD morbidity and mortality was not possible. However, it is evident that no consensus exists in published studies with respect to this end-point and the results from large ongoing studies are awaited.

Chapter 4

Systematic review 2: In patients with type 1 or type 2 diabetes, is there a prognostic relationship between the presence of microalbuminuria and the development and progression of retinopathy?

Relationship between microalbuminuria and retinopathy in patients with type 1 DM

Retinopathy is the most common complication of type 1 DM which, after 20 years, may come to affect 70–100% of patients.[100–102] However, the more severe proliferative retinopathy ultimately develops in only 40–60% of patients.[103] Retinopathy is a leading cause of blindness in Europe and the USA.[104,105] In a 10-year follow-up of a population-based cohort of people with type 1 DM, baseline HbA_{1c} level was strongly related to the incidence or the progression of diabetic retinopathy and this was independent of other baseline covariates.[106] Baseline systolic blood pressure was also significantly associated with incidence of retinopathy.[107] The only intervention that has been shown to prevent development and slow progression of retinopathy is tight glycaemic control,[19] although this approach is not wholly effective.

Overt nephropathy is less common than retinopathy, developing in 25–40% of patients,[108] but is almost invariably associated with some retinopathic change. It is well known that patients with type 1 DM and clinical proteinuria have a prevalence of proliferative retinopathy and/or macular oedema several times higher than that of similar patients without proteinuria.[109] Furthermore, clinical proteinuria is a risk factor for the incidence of proliferative diabetic retinopathy (PDR) in type 1 DM, although this was only of borderline statistical significance after controlling for glycaemic control, hypertension and duration of diabetes.[110] Both concordance and discordance have been reported for retinopathy (assessed by seven-field colour stereophotography) and nephropathy (kidney biopsy structural studies and AER).[111] There is a cross-sectional association between retinopathy (either any retinopathy or proliferative retinopathy) and the earliest manifestation of nephropathy, microalbuminuria, in type 1 DM,[112] not explained by the confounding effects of glycaemia, hypertension and duration of diabetes. Is there a prognostic relationship between the presence of microalbuminuria and the development and progression of retinopathy?

Search results

The MEDLINE and EMBASE searches yielded a total of 295 articles of potential relevance to the prognostic significance of microalbuminuria for development or progression of retinopathy in type 1 or type 2 DM (Appendix 3). Reasons for initial exclusion of articles included: cross-sectional study, review, studied type 2 DM only, no examination of microalbuminuria or AER in relation to development or progression of retinopathy, duplicate publication or overt nephropathy at baseline. This left 25 articles in type 1 DM for further examination.[39,113–136] The bibliographies of these articles were examined and another potentially relevant article was found.[137] Of the 26 articles initially selected, some focused on incidence of retinopathy and others on progression of existing retinopathy.

Development of retinopathy in those free of retinopathy at baseline

Castillo and colleagues[122] examined factors relating to development of retinopathy, but microalbuminuria was only assessed at the 4-year follow-up examination and the article was therefore not selected. Gomes and colleagues[133] reported data relevant to the question and the study was selected. In a 4-year follow-up study, Janka and colleagues[137] recruited type 1 diabetic patients with minimal or no diabetic retinopathy and evaluated determinants of the development of more severe forms of retinopathy, but microalbuminuria was not assessed and the article was not selected. Danne and colleagues[119] assessed the influence of long-term glycaemic control and microalbuminuria on the development of

background retinopathy; the study was selected. D'Annunzio and colleagues[125] carried out a 3–19-year follow-up of 100 children and adolescents diagnosed in childhood. However, all subjects were normoalbuminuric at baseline and the study was not selected. In a 6-year follow-up of patients with type 1 DM and no retinopathy, Skrha and co-workers[114] found a rise in ACR in those patients developing new retinopathy. However, microalbuminuria was not defined and the study was not selected.

In a 6-year follow-up of young people with type 1 DM, Olsen and colleagues[132] found that the risk markers for development and progression of retinopathy were HbA_{1c}, age and duration of diabetes, but neither baseline AER nor microalbuminuria was examined in relation to the retinopathy end-point and losses to follow-up were particularly heavy, hence the study was not selected. In a 3-year retrospective study, Kordonouri and colleagues[123] noted that patients with early background retinopathy had an increased HbA_{1c} and lower high-density lipoprotein (HDL)-cholesterol in the 3 years prior to this. However, the relationship between baseline AER or microalbuminuria and development of retinopathy was not examined and the article was not selected. Villar and colleagues[129] focused on the development of microalbuminuria in type 1 and type 2 DM, and the study was not selected. The EURODIAB Prospective Complications Study (PCS)[135] examined the relative importance of risk factors for incident retinopathy in a 7-year follow-up study of a large cohort of people with type 1 DM; as baseline AER was included among these factors the study was selected.

Development of PDR

Vigstrup and Mogensen,[113] Gilbert and colleagues,[128] The Royal College of Physicians of Edinburgh Diabetes Register Group (RCPEDRG)[131] and Krolewski and colleagues[115] all reported data directly relevant to the question and were selected. In a 10-year follow-up study, Rossing and co-workers[127] found a significant, independent relationship between baseline degree of retinopathy and albuminuria (normoalbuminuria, microalbuminuria or macroalbuminuria) and the subsequent development of PDR. As there was no separate assessment of the predictive ability of microalbuminuria, however, the study was not selected. In Mathiesen,[121] patients were normoalbuminuric at the start of a 10-year prospective study, but a proportion developed microalbuminuria during the study and the effect of this on development of PDR was assessed: the study was therefore selected. Almdal[118] was a 5-year study of the predictive ability of microalbuminuria in type 1 DM with PDR as a secondary end-point; the study was selected. Kullberg and colleagues[116] showed that poor glycaemic control for some years preceded the diagnosis of PDR and nephropathy (clinical proteinuria), but microalbuminuria was not considered and the study was not selected.

In a 14-year follow-up study, Kalter-Leibovici and colleagues[126] found that mean HbA_{1c} values and non-Ashkenazi Jewish origin were significantly and independently related to progression of retinopathy, but microalbuminuria was not assessed and the study was not selected. The EURODIAB PCS also examined the risk factors for progression to PDR over 7 years of follow-up among people with type 1 DM who had mild, moderate or severe non-proliferative retinopathy at baseline;[136] since AER was measured at baseline the study was included.

Incidence and progression of retinopathy

In the Pittsburgh Epidemiology of Diabetes Complications (EDC) study, Lloyd and colleagues[120] examined the relationship between incidence and progression of retinopathy over 2 years and microalbuminuria: the study was selected. Another report from the EDC group summarised the incidence of complications over 4 years,[124] but since less detail on retinopathy was provided the article was not selected. The development and progression of retinopathy and loss of visual acuity were examined in relation to risk indicators, including urine albumin, in a 10-year follow-up of type 1 diabetic patients by Lovestam-Adrian and colleagues,[134] and the study was selected. Descriptions of the 5-year follow-up of the same cohort reported by Agardh and colleagues[39,117] and a 15-year follow-up of a subset of the same cohort reported by Lovestam-Adrian and colleagues[130] were not selected as they were less complete.

Articles not selected

Fourteen articles were excluded.[39,114,116,117,122–127,129,130,132,137]

Characteristics of included studies

The main characteristics of these 11 studies (12 articles) are shown in *Table 16*. Data were reported from 4672 patients, 50% of whom were male. Patients were followed up for a mean of 7 years (range 4–18 years), and had a mean age of 31 years (range 20–35 years) and mean

TABLE 16 *Relationship between microalbuminuria and retinopathy in patients with type 1 DM; characteristics of included studies*

Source	Setting	Design	End-point	Retinal screening method	*n*	FU (y)	Mean age (y)	Mean duration of diabetes (y)	Gender (% male)
Vigstrup and Mogensen, 1985[113]	Denmark (H)	Retrospective	PDR	Ophthalmoscopy: dilated pupils	43	10	24	13	100
Krolewski *et al.*, 1992[115]	USA (H)	Case-control	PDR	Stereo-photographs, Airlie House	162	18	29	18	52
Almdal *et al.*, 1994[118]	Denmark (H)	Prospective	PDR or blindness	Ophthalmoscopy: dilated pupils	230	5	35	20	50
Danne *et al.*, 1994[119]	Germany (H)	Prospective	Incidence of DR	Ophthalmoscopy and fluorescein angiography	104	16	20	10	55
EDC (Lloyd *et al.*), 1995[120]	USA (H)	Prospective	Incidence of DR; progression of DR and progression to PDR	Stereo fundus photographs, Airlie House	322	2	28	19	53
Mathiesen *et al.*, 1995[121]	Denmark (H)	Prospective	PDR	Ophthalmoscopy	200	4	34	17	57
Gilbert *et al.*, 1998[128]	Australia (H)	Prospective	PDR or CME	Ophthalmoscopy	80	11	29	19	58
Gomes *et al.*, 2000[133]	Brazil (H)	Prospective	Incidence of DR	Ophthalmoscopy	36	4.5	22	7	42
RCPEDRG, 2000[131]	Scotland (H)	Prospective	Maculopathy or PDR	Ophthalmoscopy	1223	4	30	10	53
Lovestam-Adrian *et al.*, 2001[134]	Sweden (H)	Prospective	Incidence or progression of DR and progression to PDR	Retinal photography	259	10	34	19	
EURODIAB PCS (Chaturvedi *et al.*), 2001[135]	Europe (H)	Prospective	Incidence of DR	Retinal photography, centrally graded	764	7	30	10	51
EURODIAB PCS (Porta *et al.*), 2001[136]	Europe (H)	Prospective	Progression to PDR	Retinal photography, centrally graded	1249	7	32	13	52
Summary					**4672**	**7**	**31**	**13**	**50**

CME, clinically significant macular oedema; DR, diabetic retinopathy.

duration of diabetes of 13 years (range 7–20 years). Several different retinal screening methods were used.

Meta-analysis

Tables 17 and *18*, respectively, show the relationship between AER or microalbuminuria and incidence of retinopathy, or overall progression of retinopathy. The number of events in groups defined by microalbuminuria or normoalbuminuria was only extractable for one study. Where available, baseline AER values are shown from the groups developing or not developing new retinopathy.

TABLE 17 *Relationship between AER and incidence of retinopathy in patients with Type 1 DM and without retinopathy at baseline*

Source	MA events/total	NA events/total	Crude RR (95% CI)	Patients developing retinopathy		Patients not developing retinopathy		Difference in AER	Factors associated with progression	AER or MA in multivariate model
				n	AER	*n*	AER			
Danne *et al.*, 1994[119]	NE	NE	NE	NE	NE	NE	NE	NE	HbA_{1c}* Duration* MA*	MA ($p = 0.02$)
EDC (Lloyd *et al.*), 1995[120]	NE	NE	NE	23	NE	46	NE	NE	DBP*	AER ns
Gomes *et al.*, 2000[133]	NE	NE	NE	10	11.5 (2.7 to 53)[a] μg per minute	26	6.3 (3 to 26)[a] μg per minute	$p = 0.06$	Age Duration AER	NE
Lovestam–Adrian, *et al.*, 2001[134]	NE	NE	NE	71	NE	47	NE	ns	HbA_{1c}*	AER ns
EURODIAB PCS (Chaturvedi *et al.*), 2001[135]	86/135	317/595	1.2 (1.0 to 1.4)	429	12 (6, 19)[b] μg per minute	335	10 (6, 14)[b] μg per minute	$p < 0.001$	Age Duration HbA_{1c}* AER MA Cholesterol Triglycerides* Fibrinogen GGT WHR* Insulin dose	AER ns MA NR

[a] Median (range).
[b] Mean (25th, 75th percentiles) for log-transformed data.
GGT, γ-glutamyl transferase.
* Significant in multivariate model.

TABLE 18 *Relationship between AER and overall progression of retinopathy in patients with type 1 DM*

Source	Patients with progression		Patients without progression		Differences in AER	Factors associated with progression	MA or AER in multivariate model
	n	AER	*n*	AER			
EDC (Lloyd *et al.*), 1995[120]	74	4.3 (3.8 to 4.1)[a] μg per minute	248	3.6 (3.0 to 3.3)[a] μg per minute	1.2 (1.0 to 1.4)[b] μg per minute	FU LDL-cholesterol Fibrinogen HbA_{1c}* Triglycerides AER Baseline DR*	ns
Lovestam-Adrian *et al.*, 2001[134]	150	NE	109	NE	ns	Higher mean HbA_{1c}*	ns

[a] Geometric mean (95% CI).
[b] Ratio of geometric means (95% CI).
* Significant in multivariate model.

In the five studies that examined incidence of retinopathy in type 1 DM (*Table 17*), there was some evidence that AER was higher or microalbuminuria more prevalent at baseline in patients who subsequently developed retinopathy, compared with those who did not. In three of the studies, AER or microalbuminuria was a univariate predictor of retinopathy, as were also such factors as glycaemic control and duration of diabetes. However, among the four studies that used multivariate analysis to allow for confounding interactions, microalbuminuria remained significant in one study, but AER was not significant in the other three.

In the two studies that reported on overall progression of retinopathy in relation to baseline AER (*Table 18*), AER was not a significant predictor of the end-point in multivariate analysis after allowing for the effect of glycaemic control.

Four of the seven studies that examined predictors of the development of proliferative retinopathy included microalbuminuria measurements (*Table 19*). A meta-analysis of crude relative risks gave a relative risk of 4.1 (95% CI 1.8 to 9.4) (*Figure 16*). Four studies examined the predictive power of AER or microalbuminuria in multivariate models allowing for other important factors, such as glycaemic control, duration of diabetes and blood pressure. In three of these four studies, including the two largest, raised AER remained a significant independent risk factor for the development of proliferative retinopathy.

Moreover, among groups of type 1 DM patients with normoalbuminuria or microalbuminuria, those who progressed to microalbuminuria or macroalbuminuria (compared with those remaining persistently normoalbuminuric),[128] or showed an increased rate of progression of AER,[118] developed proliferative retinopathy more frequently.

Conclusions

For patients with type 1 and type 2 DM, 295 articles were initially identified that were potentially relevant to the question of the prognostic significance of microalbuminuria for incidence or progression of retinopathy. After applying the protocol criteria, 12 articles from 11 studies were selected for type 1 DM.

There is only weak evidence that microalbuminuria or raised AER has any independent prognostic significance for the incidence of retinopathy in type 1 DM. There is weak evidence that AER does not predict progression of retinopathy. Poor glycaemic control appears to be the strongest risk factor for retinopathy and is also a risk factor for the development of microalbuminuria.[138] There is strong evidence, however, for the independent prognostic significance of microalbuminuria or raised AER for the development of proliferative retinopathy (RR = 4.1, 95% CI 1.8 to 9.4). Nonetheless, it must be remembered that the presence of retinopathy is an equally strong predictor for the development of microalbuminuria.[129,138]

TABLE 19 *Relationship between microalbuminuria and development of proliferative retinopathy in patients with Type 1 DM: events and risk estimates*

Source	MA events/total	NA events/total	Crude RR (95% CI)	Patients with progression		Patients without progression		Difference in AER	Factors associated with progression	AER or MA in multivariate model
				n	AER	*n*	AER			
Vigstrup and Mogensen, 1985[113]	9/14	1/29	18.6 (2.6 to 133.0)	10	NE	33	NE	NE	SBP MA	NR
Krolewski *et al.*, 1992[115]	21/36	18/73	OR[a] 5.1 (2.2 to 11.8)	NE	NE	NE	NE	NE	MA	MA $p < 0.05$
EDC (Lloyd *et al.*), 1995[120]	NE	NE	NE	33	5.5 (3.9 to 7.7)[a] μg per minute	289	3.3 (3.1 to 3.6)[a] μg per minute	1.6 (1.3 to 2.1)[b] μg per minute	AER, FU LDL-cholesterol Fibrinogen HbA_{1c}* Triglycerides	AER ns
Mathiesen *et al.*, 1995[121]	6/27	9/166	4.1 (1.6 to 10.6)	15	NE	185	NE	NE	NR	NR
RCPEDRG, 2000[131]	26/207	72/1016	1.8 (1.2 to 2.7)	98	NE	1125	NE	NE	AER* Duration* HbA_{1c}* BP*	AER $p < 0.05$ (highest quintile) RR = 1.22 (95% CI 0.50 to 2.94)
Lovestam-Adrian *et al.*, 2001[134]	NE	NE	NE	98	NE	161	NE	NE	HbA_{1c}	NR
EURODIAB PCS (Porta *et al.*), 2001[136]	59/135	71/896	5.5 (4.1 to 7.4)	157	29 (8, 66)[d] μg per minute	1092	12 (7, 10)[d] μg per minute	$p < 0.0001$	AER* Duration HbA_{1c}* DBP Cholesterol Triglycerides LDL-cholesterol WHR Age Baseline DR*	AER $p < 0.05$
Meta-analysis	**121/419**	**171/2180**	**4.1 (1.8 to 9.4)**							

[a] Results from case–control study so OR calculated but not entered in meta-analysis although included in column totals.
[b] Geometric mean (95% CI).
[c] Ratio of geometric means (95% CI).
[d] Mean (25th, 75th percentiles) for log-transformed data.
* Significant in multivariate model.

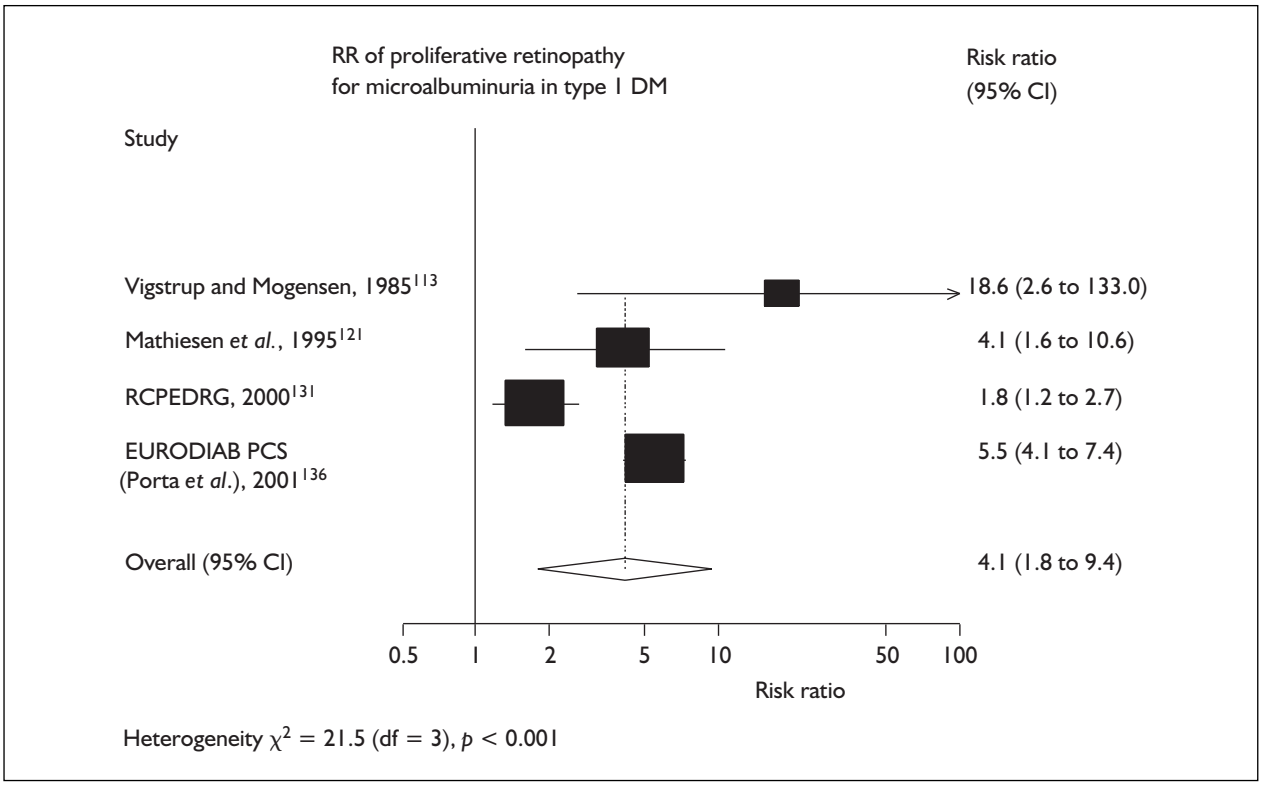

FIGURE 16 *Forest plot for relative risk of proliferative retinopathy with microalbuminuria in type 1 DM*

Relationship between microalbuminuria and retinopathy in patients with type 2 DM

As in type 1 DM, diabetic retinopathy is a common complication of type 2 DM and carries with it the threat of blindness. Also, as in type 1 DM, Klein and colleagues[106] found that, in a population-based 10-year prospective study of people with type 2 DM, HbA_{1c} level at baseline was strongly related to the incidence or progression of diabetic retinopathy. In the UKPDS,[139] an intensive blood glucose control policy with an 11% reduction in median HbA_{1c} over the first 10 years was associated with a 25% reduction in the risk of microvascular end-points, most of which was due to fewer patients requiring photocoagulation (laser therapy for advanced diabetic retinopathy). There was also a significant reduction in progression of retinopathy when intensive therapy was compared with conventional therapy. Patients in the UKPDS were followed from the diagnosis of type 2 DM and the fact that nearly 40% had retinopathy at presentation suggests there had been a considerable time between onset of disease and diagnosis. Klein and colleagues[107] found that, in contrast to type 1 DM, there was no consistent association between blood pressure and retinopathy in a 10-year prospective study of people with type 2 DM. Nonetheless, the results of an embedded study of the UKPDS showed that, over a 9-year follow-up, tighter blood pressure control led to a decrease in the need for photocoagulation.[140]

Similarly to type 1 DM, although concordance between retinopathy and microalbuminuria is relatively common, some discordance is present.[141] There is, as in type 1 DM, a cross-sectional relationship between microalbuminuria and diabetic retinopathy in type 2 DM,[142,143] although it seems weaker in type 2 DM and explained by other factors.[144]

Search results

After initial exclusions as described above from the database of 295 articles (see section 'Search results', p. 37), the MEDLINE and EMBASE searches yielded 15 articles potentially relevant to microalbuminuria and development or progression of retinopathy in type 2 DM.[81,84,129,145–156] The bibliographies of these papers identified four further articles.[110,157–159] Of the 19 articles initially selected, some focused on incidence of retinopathy and others on progression of existing retinopathy.

Incidence or progression of diabetic retinopathy

West[158] was a cross-sectional study and was not selected. Molyneaux and colleagues[152] found that both the development of diabetic retinopathy and, to a lesser extent, the development of microalbuminuria were related to mean HbA_{1c} during a follow-up period of several years. The authors did not, however, examine microalbuminuria in relation to the development of retinopathy and the study was not selected. In the UKPDS 6-year follow-up from diagnosis of type 2 DM, Stratton and colleagues[155] found that development of retinopathy was strongly associated with baseline glycaemia, glycaemic exposure over 6 years, higher blood pressure and with not smoking. In those who already had retinopathy, progression was associated with older age, male gender, hyperglycaemia and not smoking. Although urinary albumin levels were measured, they were not used as a covariate in the analysis and the study was not selected. In another article from the UKDPS, Davis and colleagues[146] found that subsequent risk of retinopathy over 6 years increased with age at diagnosis, but urinary albumin was not used as a covariate and the article was not selected. Florkowski and colleagues[151] reported predictors of the development of retinopathy, including "albuminuria" (defined as albumin concentration >50 mg l^{-1} and with a baseline prevalence of 19%) and the study was selected.

Kim and colleagues[148] examined the development and progression of diabetic retinopathy in relation to baseline prognostic variables in a 5-year follow-up study of Koreans with type 2 DM. Since the relationship of baseline AER to development and progression was also assessed, the study was selected. Rachmani and colleagues[154] randomised 250 patients with type 2 DM, with normal blood pressure and either normoalbuminuria or microalbuminuria, to receive the ACE inhibitor enalapril or placebo for 5 years. It was found that, in comparison with placebo, enalapril reduced the incidence of retinopathy. The placebo group of this RCT was included in the present study. Both Park and colleagues[149] and Villar and colleagues[129] focused on the development of microalbuminuria in initially normoalbuminuric type 2 DM patients and the articles were not selected. Niskanen[84] and Voutilainen-Kaunisto[156] were, respectively, 5- and 10-year follow-up reports on a cohort of newly diagnosed type 2 DM patients in Finland. The 10-year follow-up report was selected as it included information on the relationship of microalbuminuria to development of retinopathy. The 5-year incidence of retinopathy was examined in a study of 451 type 2 diabetic patients by Agardh and colleagues.[81] Since the relationship of baseline urinary albumin concentration with incident retinopathy was examined, the study was included. In a study of French type 2 DM patients initially free of retinopathy, Guillausseau and co-workers[147] examined factors predicting the 7-year development of retinopathy; as urinary albumin was included the study was selected.

Development of PDR

In a 13-year follow-up study of Native Americans in Oklahoma, by Lee and colleagues,[145] the significant predictors of PDR included background retinopathy, an increased fasting plasma glucose, long duration of diabetes and elevated SBP, but neither AER nor microalbuminuria was considered and the study was not selected. Klein and colleagues[110] found that gross proteinuria (measured by reagent strip) was not a significant risk factor for the 4-year incidence of PDR in a population-based study of older-onset diabetic subjects in Wisconsin, but AER was not measured and the study was not selected. Nelson and co-workers[157] found that the 4-year incidence of PDR in Pima Indians was associated with hypertension, proteinuria and other factors after controlling for age, gender and duration of diabetes; neither AER nor microalbuminuria was considered, however. In a 4-year follow-up study of type 2 diabetic patients in Taiwan, Chen and colleagues[159] found that the progression of retinopathy was correlated with mean fasting blood glucose and proteinuria (reagent strip method), but urinary AER was not measured and the study was not selected. A 6-year retrospective study of Japanese type 2 patients by Tanaka and colleagues[150] focused on the role of glycaemic control and blood pressure in the development and progression of nephropathy; the study was not selected. In a study of type 2 DM in Chile, Durruty and co-workers[153] followed the 2-year progression of retinopathy in patients with either normoalbuminuria or microalbuminuria at baseline; the study was selected. Seven articles were selected.

Articles excluded

Twelve articles were excluded.[84,110,129,145,146,149,150,152,155,157–159]

Characteristics of included studies

The main characteristics of these seven articles are shown in *Table 20*. Data were reported from 866 patients of whom 54% were male. Patients were followed up for a mean of 7 years (range 2–10 years), and had a mean age of 55 years (range 52–60 years) and mean duration of

TABLE 20 *Relationship between microalbuminuria and retinopathy in patients with type 2 DM: characteristics of included studies*

Source	Setting	Design	End-point	Retinal screening method	*N*	FU (y)	Mean age (y)	Mean duration of diabetes (y)	Gender (% male)
Agardh *et al.*, 1996[81]	Sweden (H)	Prospective	Incidence of DR, progression of DR	Fundus photography	240	5	54	9	65
Florkowski *et al.*, 1998[151]	New Zealand (H)	Prospective	Incidence of DR	Not stated	153	6	60	9	47
Guillausseau *et al.*, 1998[147]	France (H)	Retrospective	Incidence of DR	Fluorescein angiography	64	7	55	8	55
Kim *et al.*, 1998[148]	Korea (H)	Prospective	Incidence of DR and PDR	Ophthalmoscopy	130	5	NE	NE	NE
Rachmani *et al.*, 2000[154]	Israel (H)	RCT	Incidence of DR	Fundoscopy	124	5	52	6	47
Durruty *et al.*, 2000[153]	Chile (H)	Prospective	Progression of DR	Fundoscopy and retinal photography	75	2	55	10	48
Voutilainen-Kaunisto *et al.*, 2001[156]	Finland (P)	Prospective	Incidence of DR	Fundus photography	80	10	56	0	53
Summary					**866**	**7**	**55**	**8**	**54**

diabetes of 8 years (range 0–10 years). Various retinal screening methods were used.

Meta-analysis

Among the six studies that examined incidence of retinopathy in type 2 DM (*Table 21*), there are three studies where it was possible to calculate relative risk. The combined relative risk was 1.0 (95% CI 0.6 to 1.6), with no evidence of heterogeneity (*Figure 17*). Similarly, in the other three studies there was no evidence that AER was higher or microalbuminuria more prevalent at baseline in patients who subsequently developed retinopathy, compared with those who did not.

For overall progression of retinopathy in type 2 DM there is very little available information (*Table 22*) regarding the prognostic significance of microalbuminuria or AER. One of the two studies found an excess development of retinopathy in patients with microalbuminuria, but there was no allowance for the confounding effects of glycaemic control or blood pressure.

Only one study was located that examined the prognostic significance of AER for the development of proliferative retinopathy in type 2 DM (*Table 23*). Raised AER was a univariate predictor of the end-point, but AER was no longer significant after allowing for the confounding effects of glycaemic control and BMI.

Conclusions

For patients with type 1 or type 2 DM, 295 articles were initially identified that were potentially relevant to the question of the prognostic significance of microalbuminuria for incidence or progression of retinopathy. After applying the protocol criteria seven studies on type 2 DM were selected.

There is less information available on type 2 than on type 1 DM, but the available data provide no evidence that microalbuminuria or raised AER has any independent prognostic significance for the incidence of diabetic retinopathy in type 2 DM, and more information is needed. The limited

TABLE 21 *Relationship between microalbuminuria and incidence of retinopathy in patients with type 2 DM: events and risk estimates*

Source	MA events/total	NA events/total	Crude RR (95% CI)	Patients developing retinopathy		Patients not developing retinopathy		Difference in AER	Factors associated with progression	AER or MA in multivariate model
				N	AER Mean (95% CI)	*N*	AER Mean (95% CI)			
Agardh *et al.*, 1996[81]	NE	NE	NE	74	NE	166	NE	NE	Duration HbA_{1c} SBP	AER ns
Florkowski *et al.*, 1998[151]	NE	NE	NE	51	NE	102	NE	NE	HbA_{1c} Hypertension Duration	AER ns
Guillausseau *et al.*, 1998[147]	1/3	13/61	1.6 (0.3 to 8.3)	14	NE	50	NE	NE	HbA_{1c}*	AER ns
Kim *et al.*, 1998[148]	NE	NE	NE	30	14 (5 to 23) μg per minute	100	17 (10 to 24) μg per minute	−3 (−14 to 8) μg per minute	Age Duration HbA_{1c}*	AER ns
Rachmani *et al.*, 2000[154]	8/45	13/79	1.1 (0.5 to 2.4)	21	NE	103	NE	NE	NR	NR
Voutilainen-Kaunisto *et al.*, 2001[156]	9/16	31/64	0.9 (0.5 to 1.7)	40	NE	40	NE	NE	Fasting plasma glucose	NR
Meta-analysis	**18/64**	**57/204**	**1.0 (0.6 to 1.6)**							

* Factor remained significant in multivariate model.

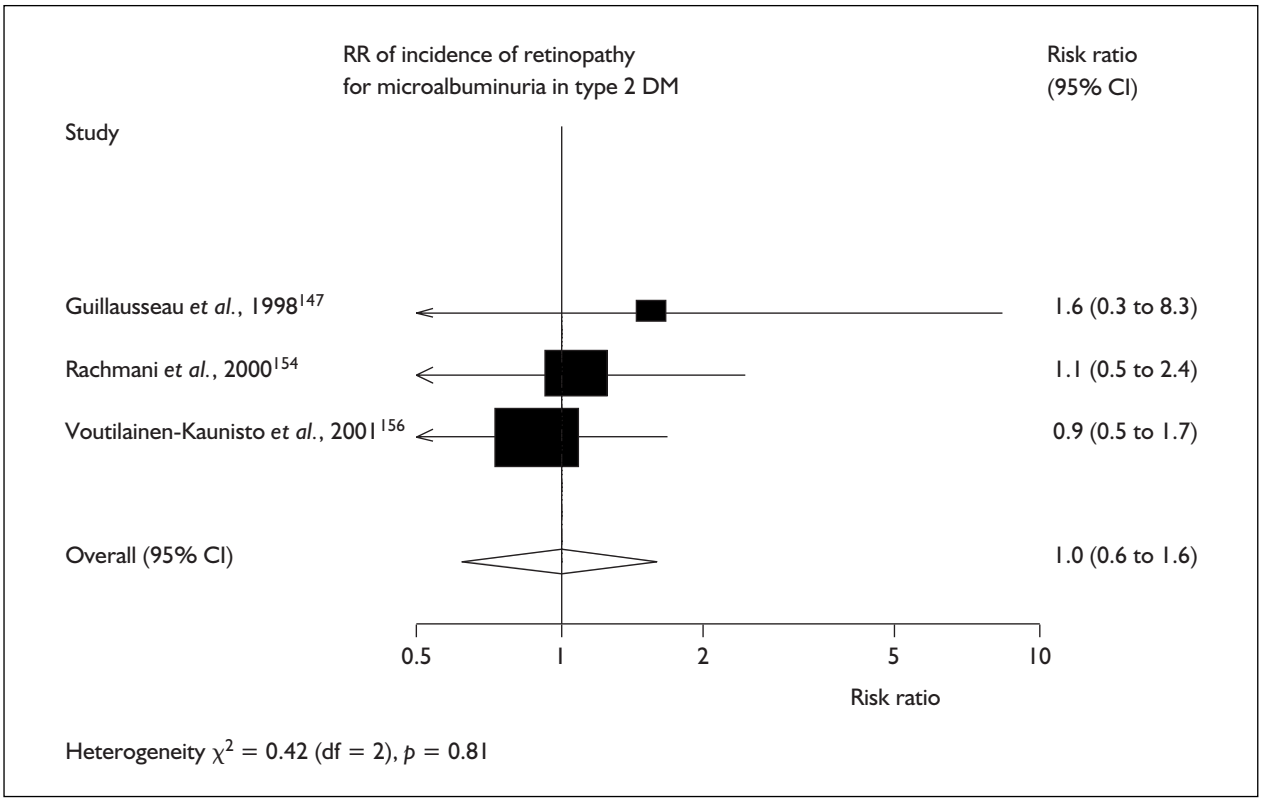

FIGURE 17 *Forest plot for relative risk of incidence of retinopathy with microalbuminuria in type 2 DM*

TABLE 22 *Relationship between microalbuminuria and overall progression of retinopathy in type 2 DM: events and risk estimates*

Source	*N*	Number progressing	MA events/total	NA events/total	Crude RR (95% CI)	Factors associated with progression	AER or MA in multivariate model
Agardh *et al.*, 1996[81]	77	26	NE	NE	NE	SBP	AER ns
Durruty *et al.*, 2000[153]	75	10	7/32	3/57	4.2 (1.2 to 15.0)	NR	NR

TABLE 23 *Relationship between AER and development of proliferative retinopathy in patients with type 2 DM*

Source	Patients with progression		Patients without progression		Differences in AER	Factors associated with progression	AER or MA in multivariate model
	N	AER Mean (95% CI)	*N*	AER Mean (95% CI)			
Kim *et al.*, 1998[148]	11	67 (31 to 103) μg per minute	45	23 (15 to 31) μg per minute	44 (2 to 86) μg per minute	Change in BMI HbA_{1c}[a] AER	AER ns

[a] Factor remained significant in multivariate model.

evidence indicates little if any prognostic relationship between microalbuminuria and the progression of retinopathy or development of proliferative retinopathy. Poor glycaemic control appears to be the strongest risk factor for retinopathy in type 2 DM and is also a risk factor for the development of microalbuminuria.[160] Moreover, as in type 1 DM, it must be remembered that the presence of retinopathy is a strong predictor for the development of microalbuminuria in type 2 DM.[129,149,160]

Chapter 5

Systematic review 3: In patients with type 1 or type 2 diabetes, is there a prognostic relationship between the presence of microalbuminuria and the development of renal failure?

Relationship between microalbuminuria and the development of ESRD in patients with type 1 DM

The ESRD end-point has been defined as death due to renal failure (death certificate) or requirement for RRT (renal transplant or dialysis) or by a composite end-point that included either of these and/or an abnormally high serum creatinine. This latter end-point indicates significant renal impairment rather than ESRD, but was included owing to the paucity of studies that used only the hard end-points, since many have used a composite.

Search results

The MEDLINE and EMBASE searches yielded a total of 272 articles of potential relevance to the prognostic significance of microalbuminuria for ESRD in type 1 DM (Appendix 3). Reasons for initial exclusion of articles were: no end-point of relevance, cross-sectional study, review, all subjects either normoalbuminuric, microalbuminuric (with no reference group) or with overt nephropathy at baseline, duplicate publication, economic evaluation, RCT, letter or comment. After these exclusions, 11 papers on type 1 DM were initially selected for further examination.[14,34,35,38–42,118,161,162] Examination of the bibliographies of these papers gave two further potentially relevant articles,[15,17] making a total of 13 articles.

Renal disease mortality may be a minor contributor to all-cause mortality and any reference to it not necessarily prominent. This means that the electronic database index terms for that article may not include renal disease. Therefore, all nine articles selected for the relationship of microalbuminuria to all-cause mortality in type 1 DM [see section 'Relationship between microalbuminuria and all-cause (total) mortality in patients with type 1 DM', p. 11] were examined for any reference to either renal disease mortality or renal failure as an outcome. Five of these had already been found and initially selected from the renal search mentioned above.[35,38,40–42] Of the remaining four articles, two had ESRD as one of the end-points,[44,45] while the authors of the other two articles provided unpublished data on ESRD on written request.[43,46] Therefore, a total of 17 studies was initially selected.

In the 5-year follow-up study by Torffvit and Agardh,[38] a total of 476 patients with differing albuminuria status were included. Thirteen patients developed renal insufficiency (defined by either a serum creatinine of >200 mmol l^{-1} or the need for dialysis), but it was unclear from which albuminuria group these cases arose. Since the mean and range of baseline albumin excretion of these 13 patients was 1615 (116–5020) mg l^{-1}, the majority were likely to have been initially clinically proteinuric; neither this study nor another less relevant report on the same cohort[39] was selected. Parving[17] and Almdal[118] were excluded as these articles did not mention ESRD.

Although Pedersen[44] was an abstract it was included since previously published supporting data were available.[14] Viberti[15] and Messent[42] were two follow-up reports on the same cohort; the study with longer follow-up was selected.[42] Of the two articles by Rossing and colleagues[35,161] the more relevant one was selected.[35] Forsblom[40] and Beatty[41] both recorded lack of development of ESRD in their microalbuminuric or normoalbuminuric groups and the two articles were therefore included. In total, ten studies were included in the review[34,35,40–46,162] and their main characteristics are shown in *Table 24*.

Articles excluded

Of the 17 articles initially selected, seven were excluded.[14,15,17,38,39,118,161]

TABLE 24 *Microalbuminuria and development of ESRD in patients with type 1 DM: characteristics of included studies, events and risk estimates*

Source	Setting	Mean age (y)	Mean duration of diabetes (y)	FU (y)	MA deaths/ total	NA deaths/ total	Definition of end-point	Crude RR (95% CI)
Forsblom *et al.*, 1992[40]	Finland (H)	36	24	10	0/20	0/29	ESRF	NC
Messent *et al.*, 1992[42]	London, UK (H)	39	12	23	2/8	4/53	If reported in death certificate or if living when serum creatinine ≥ 150 μmol l^{-1} and AER ≥ 30 μg per minute	3.3 (0.7 to 15.2)
Pedersen *et al.*, 1992[44]	Aarhus, Denmark (H)	24	12	18	4/14	0/30	Death from renal failure	18.6 (1.1 to 323)
Beatty *et al.*, 1994[41]	Ireland (H)	49	20	8	0/43	0/43	Death from chronic renal failure	NC
Rossing *et al.*, 1996[35]	Gentofte, Denmark (H)	40	20	10	6/181	2/593	ESRD on death certificate or serum creatinine >500 μmol l^{-1} in year before death	9.8 (2.0 to 48.3)
Klein *et al.*, 1999[34]	Wisconsin, USA	31	16	10	24/120	7/298	Serum creatinine ≥ 177 μmol l^{-1} or dialysis or transplant	8.5 (3.8 to 19.2)
EURODIAB, 1999[46]	Europe (H)	33	15	8	2/399	3/1267	Dialysis or transplant at follow-up	2.1 (0.4 to 12.6)
Muhlhauser, *et al.*, 2000[45]	Germany (H)	28	11	10	19/1257	10/1829	RRT	2.8 (1.3 to 5.9)
Hadjadj *et al.*, 2001[162]	Angers, France	33	16	6	1/35	1/251	Serum creatinine >150 μmol l^{-1}	7.2 (0.5 to 112)
Weis *et al.*, 2001[43]	Portsmouth, UK (H)	32	17	14	2/51	1/96	Death from ESRF (death certificates, hospital notes, post-mortem examinations)	3.8 (0.3 to 40.5)
Meta analysis, 2002		**32**	**14**	**10**	**60/2128**	**28/4489**		**4.8 (3.0 to 7.5)**

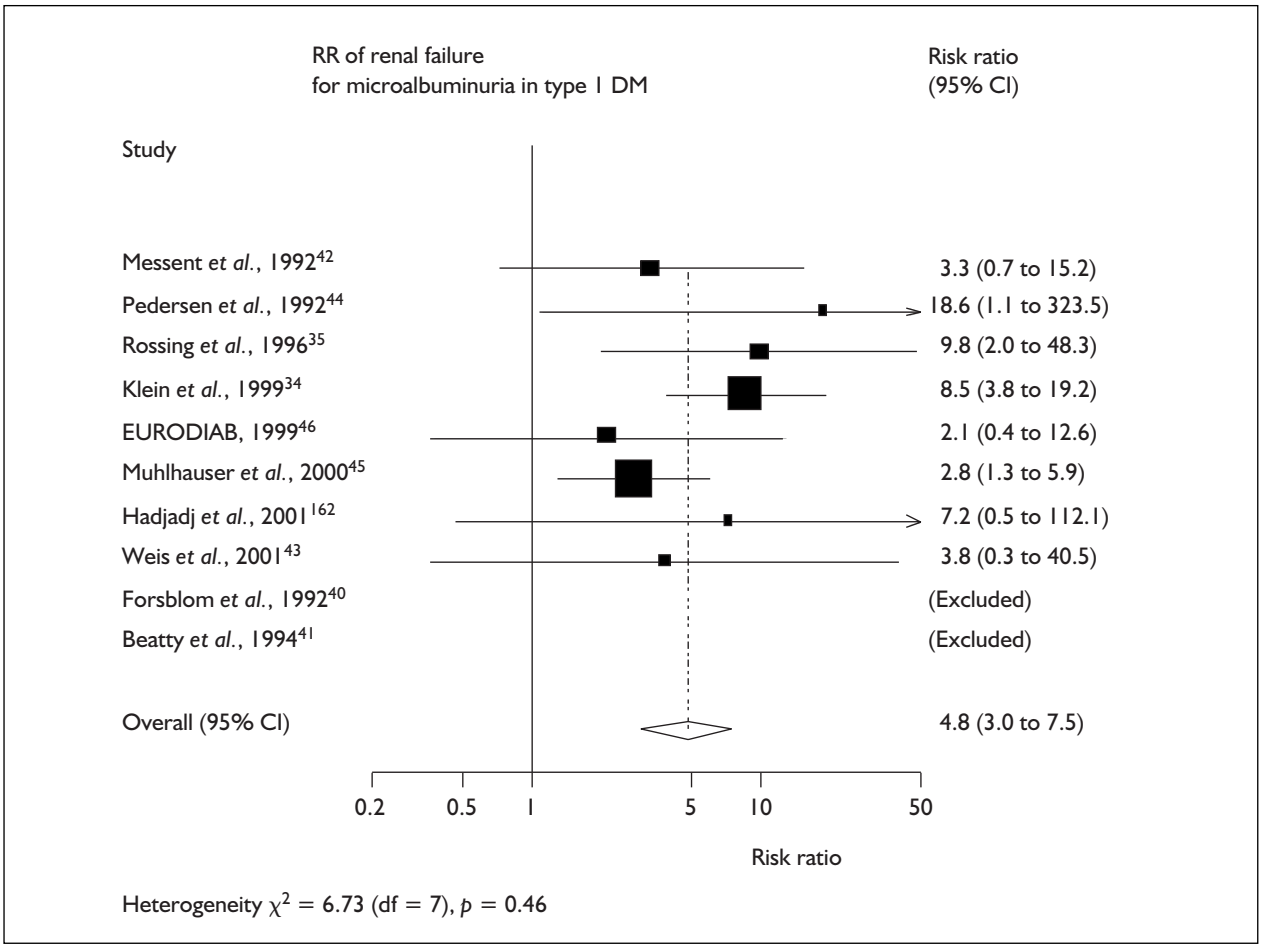

FIGURE 18 *Forest plot for relative risk of ESRD with microalbuminuria in patients with type 1 DM*

Meta-analysis

Two studies[40,41] were excluded from the meta-analysis as they had no events in either the microalbuminuric or normoalbuminuric groups. The overall relative risk of ESRD was 4.8 (95% CI 3.0 to 7.5) (*Figure 18*). There was no significant heterogeneity between studies. In two studies,[42,162] the only specified end-point of a serum creatinine above 150 μmol l^{-1} was weak as a definition of ESRD and the precise severity of renal failure was not clear. However, exclusion of these studies had no significant effect on the overall relative risk (5.0, 95% CI 2.7 to 9.2).

Relationship between microalbuminuria and the fall in GFR in patients with type 1 DM

This end-point was considered to include GFR, measured directly using a renal or plasma clearance technique, or indirectly using either creatinine clearance or a calculation based on the Cockcroft and Gault algorithm from the measured serum creatinine.

Search results

The MEDLINE and EMBASE searches yielded a total of 270 articles of potential relevance to the prognostic significance of microalbuminuria for a decline in GFR in type 1 DM (Appendix 3). Reasons for initial exclusion of articles were: review, no end-point of relevance, cross-sectional study, all subjects either normoalbuminuric, microalbuminuric (with no reference group) or with overt nephropathy at baseline, duplicate publication, RCT with no end-point of relevance, letter or comment, focus on pregnancy or focus on kidney structure. Only five articles[14,34,163–165] were initially selected as relevant to the question and they were examined in detail. Three of these reports focused on different aspects of the same cohort (Mogensen and Christensen,[14,163] Christensen and Mogensen;[164] the first of these reports was selected as the most relevant.[14] Mathiesen[165] was not selected since there was no

control group with normoalbuminuria. In a large, population-based study of people with type 1 DM, Klein and colleagues[34] reported on the 10-year incidence of creatinine clearance decline according to the presence or absence of microalbuminuria at baseline; the study was selected. Thus, only two studies were selected.[14,34] Details of these studies are given in *Table 24*; Mogensen and Christensen[14] use the same cohort as Pedersen et al.[44]

Articles excluded

Three articles were excluded.[163–165]

Meta-analysis

Mogensen and Christensen[14] showed that the annual fall in GFR in patients with microalbuminuria was 5.3 ml per minute compared with 0.2 ml per minute in the normoalbuminuria group ($p < 0.001$). Klein and colleagues[34] showed a relative risk of 1.45 (95% CI 1.1 to 1.88) for a fall in creatinine clearance of at least 3 ml per minute 1.73 m^{-2} per year among patients with microalbuminuria compared with normoalbuminuria. Although both studies showed a significantly greater fall in GFR per year in the microalbuminuria group, no meta-analysis was possible since there were only two studies and the end-point was analysed differently in each study.

Relationship between microalbuminuria and the development of clinical proteinuria in patients with type 1 DM

The term clinical proteinuria is synonymous with clinical albuminuria and is used here to define an AER in excess of microalbuminuria. The articles selected include observational studies following the development of clinical proteinuria in cohorts that included both subjects with microalbuminuria and those with normoalbuminuria, thus allowing the calculation of relative risk of the outcome. The control arms of RCTs may also allow calculation of relative risk of this outcome if they contain both subjects with microalbuminuria and normoalbuminuria. While collecting these data any information was noted on proportions of subjects with microalbuminuria who regressed to normoalbuminuria. Articles were also selected where cohorts comprised only subjects with microalbuminuria (i.e. with no control group) since they may also provide information on the proportions of subjects with microalbuminuria who regress to normoalbuminuria.

Search results

The MEDLINE and EMBASE searches yielded a total of 597 references potentially relevant in examining the development of clinical proteinuria among subjects with microalbuminuria and either type 1 or type 2 DM (Appendix 3). Reasons for initial exclusion of articles included: no end-point of relevance, review, editorial, comment or letter, normoalbuminuric at baseline, addressing renal structure only, overt nephropathy at baseline, cross-sectional study, focusing on pregnancy, methodological study, economic evaluation, development of microalbuminuria, dietary study or duplicate publication. This left 62 articles in subjects with type 1 DM and 55 in those with type 2 DM.

Further examination of the 62 articles in people with type 1 DM resulted in a number of exclusions. Two articles were further follow-up reports of the same cohort; the reports with longer follow-up were included. Messent[42] is a 23-year follow-up of the cohort originally reported by Viberti and colleagues[15] (which was a 14-year follow-up study). Pedersen[44] is an 18-year follow-up report (the earlier report was a 10-year study by Mogensen and Christensen[14]) and although it is in abstract form it was included as background information was available from the earlier report. Five reports of the 7-year follow-up of patients with type 1 and type 2 DM by Jerums and co-authors were retrieved.[166–170] The article by Cooper and colleagues[167] was selected as relevant data were more readily extractable than from the other reports. Gilbert[169] contained relevant and extractable data, but was a subset of patients from the group reported by Cooper and colleagues.[167]

Mathiesen 1984[171] was not considered an independent study and was not included since a significant proportion of patients were common to Parving,[17] which was selected. Mathiesen 1995[121] was not selected as the focus was on development of microalbuminuria, while Mathiesen 1989[172] was a shorter follow-up report of the same cohort. Mathiesen 1997[165] was not selected since the focus was on type 1 patients with microalbuminuria and change in GFR, there was no control group and nearly half of the patients came from the group earlier described by Feldt-Rasmussen and colleagues[173] (see RCTs, below). The findings of Salardi and colleagues were reported in both abstract[174] and letter form,[175] and data from the letter were included. Torffvit and Agardh[38] and

Agardh and colleagues[39,117] each describe different aspects of the 5-year follow-up of a cohort of type 1 diabetic patients. Torffvit and Agardh[38] was chosen as the data we required were most readily extracted from the article.

The 7-year follow-up of the EURODIAB IDDM Complications Study had been reported in abstract form only.[176] On written request, further, unpublished, information was provided by the study coordinators. Wilson[177] was not included as the main focus was on prorenin. Of a series of retrieved articles from Rudberg and co-workers,[178–182] relevant data were most readily extracted from Rudberg and colleagues 1992.[178] Two reports from the EDC study were relevant,[124,183] and the article with data that were extractable and also had the longer follow-up was chosen.[183] Kalter-Leibovici [184] did not address the particular study question and data were not extractable to do so. Other studies included were Watts,[185] Forsblom,[40] Beatty,[41] Almdal,[118] Shield,[186] Bojestig,[187] Gorman,[188] Warram,[189] Hadjadj[162] and an article from the RCPEDRG.[131] Tabaei,[190] Twyman[191] and Olsen[132] were not included as losses to follow-up exceeded 50% in these studies. There were other, clearly reported, studies where losses to follow-up (the highest of which was 39% overall) gave cause for concern. Characteristics of the included observational studies are given in *Table 25*.

The placebo or conventional treatment groups of RCTs were also considered and the included studies are shown in *Table 26*. Of the five RCTs examining the effect of improved glycaemic control, two included groups of subjects with normoalbuminuria and microalbuminuria, Reichard[192] and DCCT,[193] and could be used for estimates of relative risk. The Stockholm Diabetes Intervention Study (SDIS) has been the subject of numerous reports, with differing lengths of follow-up of the original cohorts.[194–197] The 5-year follow-up report by Reichard and colleagues[192] was used since data could be most readily extracted from that article. The 7.5-year follow-up report was, however, used for extraction of the proportions of subjects remaining in each albuminuria category (see *Table 28*).[197] The RCTs of Bangstad,[198] Feldt-Rasmussen[173] and the Microalbuminuria Collaborative Study (MCS) Group[199] included only subjects with microalbuminuria. Information on the fate of these subjects at the end of the study was available either from the study itself or from the review by Parving.[200]

Nine further RCTs examined the blood pressure-lowering and renoprotective effects of ACE inhibition in patients with type 1 DM with microalbuminuria. Two of these trials (Viberti[201] and Laffel[202]) have strong similarities in protocol and have been been analysed and reported in combination [Microalbuminuria Captopril Study Group (MCSG)[203]]; the latter combined paper was chosen as it reported relevant regression data. The 4-year follow-up report from Mathiesen and colleagues[204] was selected rather than the subsequent 8-year follow-up report[205] because it was a more complete report that included regression data. Other trials selected were Marre,[206] Chase,[207] Bakris,[208] Crepaldi[209] and the ACE inhibitor Trial to Lower Albuminuria in Normotensive Insulin-dependent Subjects (ATLANTIS) study.[210] The EUCLID study[211] did not report progression to clinical proteinuria among patients with normoalbuminuria or whether there was any regression to normoalbuminuria among patients with microalbuminuria, so the study was excluded.

Articles excluded

Observational studies

Twenty-three articles were excluded.[14,15,39,117,121,124,132,165,166,168–172,174,177,179–182,184,190,191]

RCTs

Seven articles were excluded.[194–196,201,202,205,211]

Meta-analysis of the development of clinical proteinuria

There were 19 studies with data on the development of clinical proteinuria in both patients with microalbuminuria and those with normoalbuminuria (*Table 27*). One study[186] was excluded from the meta-analysis as there were no events in either group. The overall relative risk was 7.5 (95% CI 5.4 to 10.5) with no significant heterogeneity between the studies (*Figure 19*). The funnel plot is fairly symmetric (*Figure 20*), indicating little evidence of publication bias, and Egger's test was not significant ($p = 0.71$).

Removing the three studies that included a majority of adolescents, [Gorman (mean age 14 years),[188] Bojestig (mean age 16 years)[187] and Rudberg (mean age 17 years)[178]] gave a relative risk of 8.0 (95% CI 5.7 to 11.2), while the relative risk for these three studies combined was 3.9 (95% CI 1.1 to 13.2); the difference between these was not significant.

Meta-analysis of the regression of microalbuminuria to normoalbuminuria

All studies of adults with microalbuminuria that reported both whether patients had progressed to clinical proteinuria and whether patients had regressed to normoalbuminuria are shown in

TABLE 25 *Microalbuminuria and development of clinical proteinuria in type 1 DM: characteristics of included observational studies*

Source	Setting	Total no. (NA/MA/CP)	Gender (% male)	Mean age (y)	Mean duration of diabetes (y)	Urine collection	Definition of MA	FU (y)
Parving *et al.*, 1982[17]	Gentofte, Denmark (H)	25 (17/8/0)	36	32	19	1 × 24 h	40–300 mg per 24 h	6
Cooper *et al.*, 1988[167]	Melbourne, Australia(H)	52 (50/2/0)	67	30	7	3 × albumin clearance	30–150 μg per minute	7
Watts *et al.*, 1991[185]	Portsmouth, UK (H)	172 (127/45/0)	56	30	16	Early morning spot	ACR >3.5 mg mmol^{-1}	4
Forsblom *et al.*, 1992[40]	Helsinki, Finland (H)	71 (29/20/22)	39	36	18	1 × 24 h and 2× overnight	20–200 μg per minute	10
Messent *et al.*, 1992[42]	London, UK (H)	63 (55/8/0)	65	40	12	1× overnight	30–140 μg per minute	23
Pedersen *et al.*, 1992[44]	Aarhus, Denmark (H)	44 (30/14/0)	100	24	13	3 × 1 h	15–150 μg per minute	18
Rudberg *et al.*, 1992[178]	Stockholm, Sweden (H)	64 (53/11/0)	52	17	12	2 × overnight per annum	20–200 μg per minute	8
Torffvit and Agardh, 1993[38]	Lund, Sweden, (H)	476 (289/118/69)	53	35	20	1 × early morning	31–299 mg l^{-1}	5
Almdal *et al.*, 1994[118]	Gentofte, Denmark (H)	230 (112/118/0)	50	36	20	1 × 24 h	30–299 mg per 24 h	5
Beatty *et al.*, 1994[41]	Belfast, UK (H)	86 (43/43/0)	50	49	20	1 × random spot	35–300 mg l^{-1}	8
Shield *et al.*, 1995[186]	Bristol, UK (H)	75 (66/9/0)	43	16	NE	94% at least 2 × overnight	20–200 μg per minute	3
Salardi *et al.*, 1996[175]	Bologna, Italy (H)	14 with MA	NE	15	6	NE	30–300 μg per day	6
Bojestig *et al.*, 1996[187]	Linkoping and Eksjo, Sweden (H)	109 (81/27/1)	46	16	8	2 × 24 h	20–200 μg per minute	10
EDC, 1996[183]	Pittsburgh, USA (P)	294 (205/89/0)	50	29	19	3 × timed samples	20–200 μg per minute	6
Gorman *et al.*, 1999[188]	Ontario, Canada (H)	75 (47/28/0)	55	14	5	1 x 24 h	15–200 μg per minute	6
RCPEDRG, 2000[131]	Scotland, UK (H)	1201 (973/228/0)	53	33	13	2 x morning spot	19.2–200 mg l^{-1}	4
Warram *et al.*, 2000[189]	Boston, USA (H)	279 (279 with MA)	49	30	18	Majority >3 spot samples	ACR 1.9–28 (M) 2.8–40 (F) mg mmol^{-1}	4
EURODIAB, 1999[176]	Europe (H)	1622 (1134/352/136)	51	32	14	1 × 24 h	20–200 μg per minute	7
Hadjadj *et al.*, 2001[162]	Angers, France (H)	310 (251/35/24)	58	34	15	2 or more spot samples	20–200 mg l^{-1}	6
Summary		**5262 (3562/1448/252)**	**52**	**31**	**14**			**6**

TABLE 26 *Microalbuminuria and development of clinical proteinuria in patients with type 1 DM: characteristics of included RCTs*

Source	Setting	Total no. in placebo arm (NA/MA/CP)	Gender (% male)	Mean age (y)	Mean duration of diabetes (y)	Urine collection	Definition of MA	FU (y)
Feldt-Rasmussen *et al.*, 1986[173]	Gentofte, Denmark (H) RCT (IGC)	18 (0/18/0)	56	29	15	3 × 24 h	30–300 mg per 24 h	2
Marre *et al.*, 1988[206]	Paris, France RCT (ACE)	10 (0/10/0)	60	39	17	2–3 × 24 h	30–300 mg 24 h	1
Mathiesen *et al.*, 1991[204]	Copenhagen, Denmark (H) RCT (ACE)	23 (0/23/0)	48	27	17	3 × 24 h	30–300 mg l^{-1}	4
SDIS, 1991[192]	Stockholm, Sweden (H) RCT (IGC)	51 (35/13/3)	52	32	16	24 h	20–200 μg per minute	5
Chase *et al.*, 1993[207]	Colorado, USA RCT (ACE)	9 (0/9/0)	56	20	12	2 ×overnight	20–200 μg per minute	2
Bakris *et al.*, 1994[208]	USA RCT (ACE)	7 (0/7/0)	57	25	7	24 h	NE	3
Bangstad *et al.*, 1994[198]	Oslo, Norway (H) RCT (IGC)	9 (0/9/0)	NE	20	11	1 × overnight per minute	15–200 μg	2
DCCT, 1995[193]	USA RCT (IGC)	357 (322/35/0)[a]	54	27	9	1 × 4 h	28–139 μg per minute	7
MCS, 1995[199]	UK (H) RCT (IGC)	34 (0/34/0)	71	37	18	Timed overnight	30–200 μg per minute	5
MCSG, 1996[203]	Europe and North America RCT (ACE)	119 (0/119/0)	50	32.5	18	3 × overnight	20–200 μg	2
Crepaldi *et al.*, 1998[209]	Italy RCT (ACE)	68 (0/34/34)	68	37	19	3 × overnight	20–200 μg per minute	3
ATLANTIS, 2000[210]	UK and Ireland (H) RCT (ACE)	46 (0/46/0)	NE	40	23	NR	20–200 μg per minute	2
Summary		**751 (357/357/37)**	**55**	**30**	**14**			**5**

[a] Secondary prevention.
RCT, conventional treatment arm of RCT; RCT (ACE), RCT examining hypotensive/renal effects of ACE inhibition; RCT (IGC), RCT examining intensified glycaemic control.

Table 28. Of patients with microalbuminuria at baseline, 19% progressed to clinical proteinuria while a greater number, 26%, regressed to normoalbuminuria. However, this difference was not statistically significant (difference 6%, 95% CI –6 to 19).

Among adolescents with a similar length of follow-up, there was a more marked rate of regression (44%) and a lower rate of progression (15%) and this difference was highly significant (difference 29%, 95% CI 8 to 51, $p = 0.009$ (*Table 29*).

TABLE 27 *Microalbuminuria and development of clinical proteinuria in patients with type 1 DM: events and risk estimates*

Source	Lost to follow-up (%)	Death rate (%)	CP/total MA	CP/total NA	Crude RR (95% CI)	Factors associated with progression
Parving *et al.*, 1982[17]	8	4	5/8	1/15	9.4 (1.3 to 67)	None mentioned
Cooper *et al.*, 1988[167]	19	NE	2/2	4/50	12.5 (4.9 to 32)	No change in blood pressure or glycaemic control
SDIS, 1991[192]	8	6	4/13	4/33	2.5 (0.7 to 8.7)	Glycaemic control
Watts *et al.*, 1991[185]	7	2	9/45[a]	2/127	12.7 (2.9 to 57)	HbA_{1c}, retinopathy
Forsblom *et al.*, 1992[40]	10	9	5/18	2/26	3.6 (0.8 to 16.6)	Raised BMI
Messent *et al.*, 1992[42]	3	31	6/8	3/53	13.3 (4.1 to 42.7)	None mentioned
Pedersen *et al.*, 1992[44]	9	15	10/14	1/26	18.6 (2.6 to 131)	None mentioned
Rudberg *et al.*, 1992[178]	14	1	2/11	3/53	3.2 (0.6 to 17.0)	Increased GFR, independent of glycaemic control
Torffvit and Agardh, 1993[38]	7	4[b]	16/118	3/289	13.1 (3.9 to 44.0)	HbA_{1c}, blood pressure
Almdal *et al.*, 1994[118]	26	NE	22/118	2/112	10.4 (2.5 to 43.4)	HbA_{1c}, blood pressure
Beatty *et al.*, 1994[41]	14	19	5/27	0/33	13.4 (0.8 to 231)	None found
DCCT, 1995[193]	1	0.7	8/35[c]	23/322[c]	3.2 (1.5 to 6.7)	Glycaemic control
Shield *et al.*, 1995[186]	7	0	0/9	0/66	NC	Glycaemic control
Bojestig *et al.*, 1996[187]	9	2	5/26	0/69	28.5 (1.6 to 498)	Glycaemic control
EDC, 1996[183]	NE[d]	NE	23/89	11/205	4.8 (2.5 to 9.5)	Age, glycaemic control, blood pressure, lipids
Gorman *et al.*, 1999[188]	Retrospective		4/28	3/47	2.2 (0.5 to 9.3)	HbA_{1c}
RCPEDRG, 2000[131]	21	NE	36/228	10/973	15.4 (7.7 to 30.5)	Duration >15 y, HbA_{1c}
EURODIAB, 1999[176]	39	3	49/352	19/1134	8.3 (5.0 to 13.9)	HbA_{1c}, weight
Hadjadj *et al.*, 2001[162]	8	3	4/35	2/251	14.3 (2.7 to 75.4)	HbA_{1c}, SBP, D allele of the ACE I/D
Meta-analysis, 2002			**215/1184**	**93/3890**	**7.5 (5.4 to 10.5)**	

[a] Estimated from figure in article.
[b] Death rate includes patients with CP.
[c] These figures are for the incidence of CP over the period of the study, as prevalence of CP at the end of the study was not extractable for the NA group. Prevalence of CP at the end of the study is used in *Tables 28* and *29*.
[d] Unclear but may be substantial.

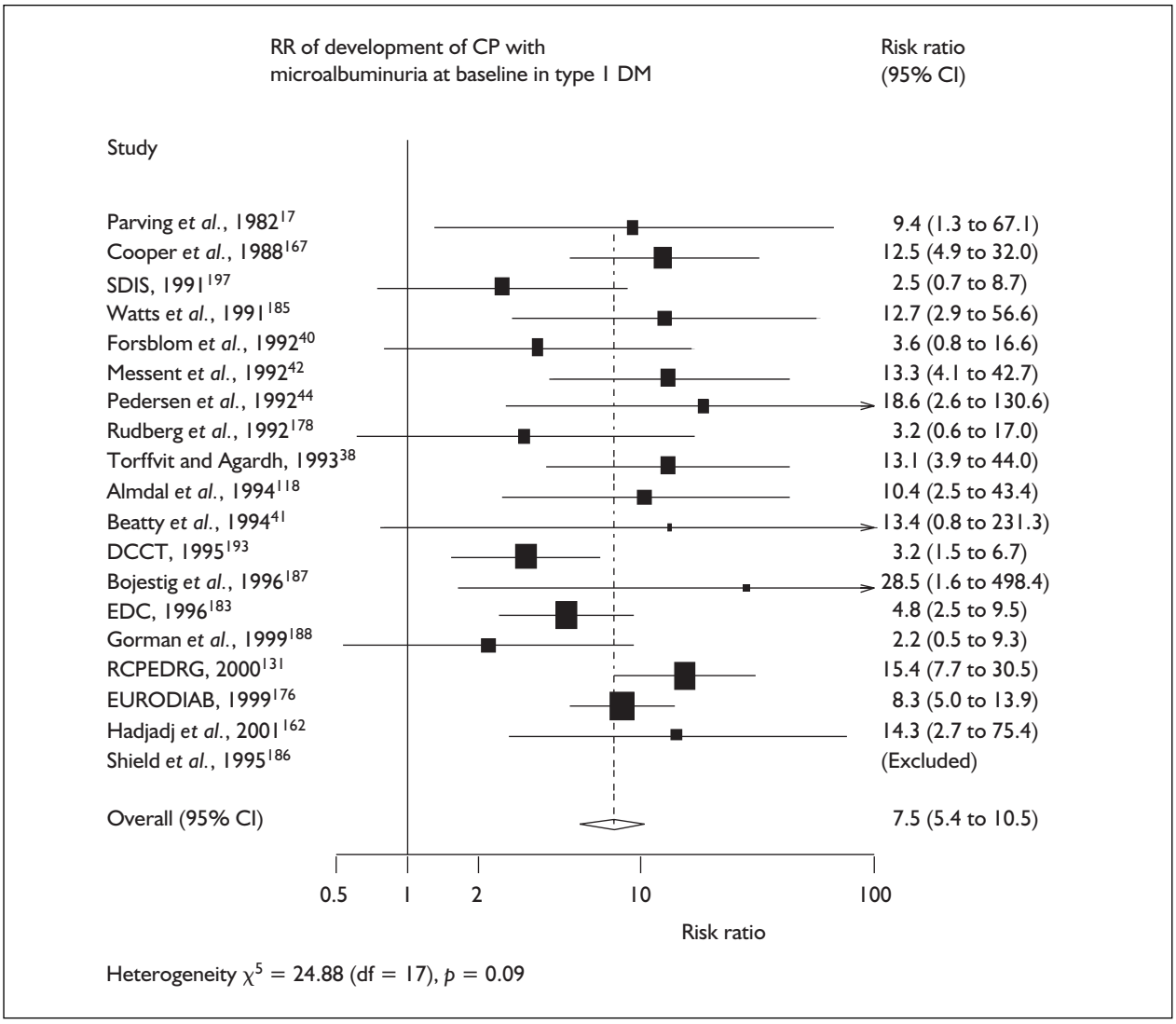

FIGURE 19 *Forest plot for relative risk of developing clinical proteinuria with microalbuminuria in patients with type 1 DM*

Relationship between microalbuminuria and the development of ESRD in patients with type 2 DM

The ESRD end-point was defined in the first section of this chapter.

Search results

The MEDLINE and EMBASE searches gave a total of 176 articles of potential relevance to the prognostic significance of microalbuminuria for ESRD in type 2 DM (Appendix 3). Reasons for initial exclusion of articles were: review, cross-sectional study, no end-point of relevance, RCT of no relevance, methodological study, economic evaluation, proposed trial, duplicate publication or overt nephropathy at baseline. After these exclusions, only four articles were selected for further examination; by Mogensen,[33] Chan and colleagues,[61] Valmadrid and colleagues[71] and Torffvit and Agardh.[86]

As noted for type 1 DM (see first section of this chapter), renal disease mortality may be a minor contributor to all-cause mortality in type 2 DM and any reference to it is not necessarily prominent. Thus, the electronic database index terms may not include renal disease and the article may not be retrieved. Therefore, all 28 papers selected for examination of the relationship between microalbuminuria and all-cause mortality in type 2 DM, the additional three articles selected for CVD mortality and a further two selected for CVD morbidity and mortality were studied for any references to renal disease mortality or renal failure as an outcome (see the

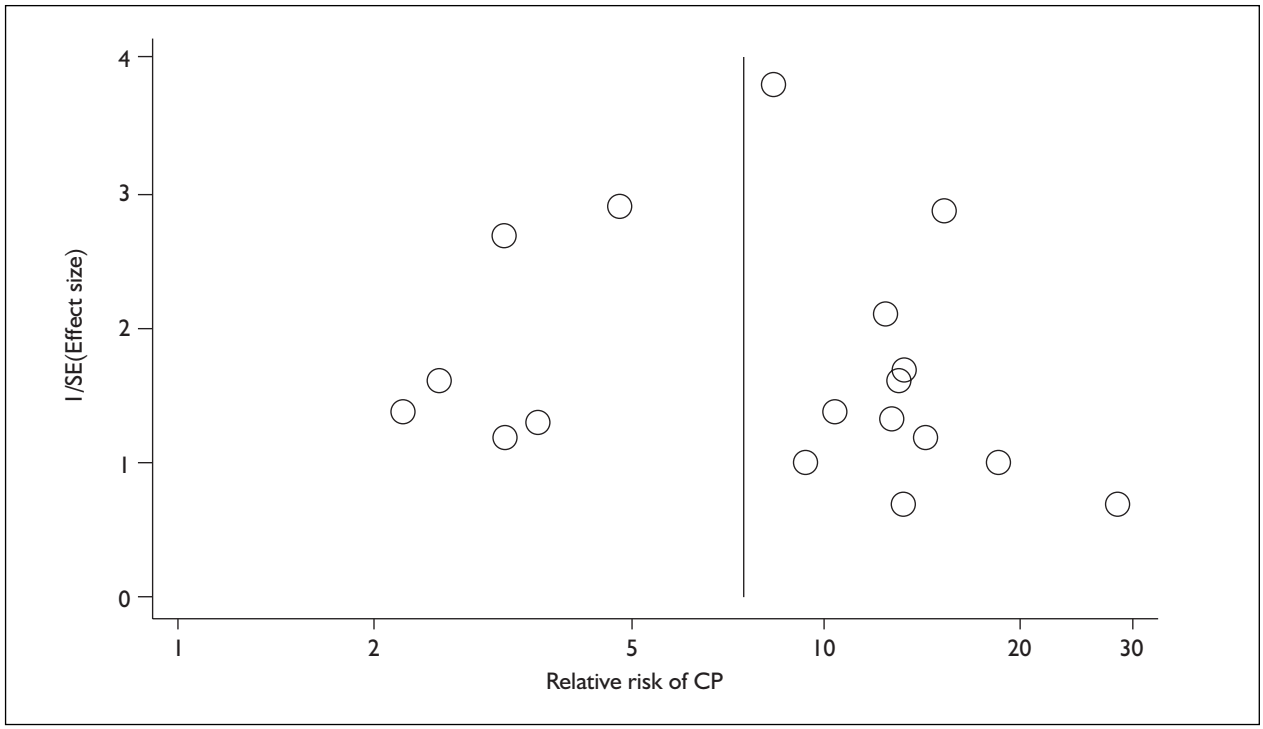

FIGURE 20 *Funnel plot for relative risk of developing clinical proteinuria with microalbuminuria in patients with type 1 DM*

TABLE 28 *Category of albuminuria at follow-up of adults with type 1 DM who initially had microalbuminuria: studies reporting both progression and regression*

Study	No. with MA at baseline	FU (y)	Category of albumin status at follow-up of those with MA at baseline (*n*)		
			NA	MA	CP
Parving *et al.*, 1982[17]	8	6	2	1	5
Feldt-Rasmussen *et al.*, 1986[173]	18	2	5	8	5
Marre *et al.*, 1988[206]	10	1	0	7	3
Mathiesen *et al.*, 1991[204]	23	4	2	14	7
SDIS, 1991[a]	13	8	4	5	4
Forsblom *et al.*, 1992[40]	20	10	0	14	6
Messent *et al.*, 1992[42]	8	23	0	1	7
Pedersen *et al.*, 1992[44]	13	18	1	2	10
Chase *et al.*, 1993[207]	9	2	0	8	1
Torffvit and Agardh, 1993[38]	118	5	46	54	18
Almdal *et al.*, 1994[118]	118	5	39	57	22
Bakris *et al.*, 1994[208]	7	2	0	5	2[b]
Bangstad *et al.*, 1994[198]	9	2	1	7	1
Beatty *et al.*, 1994[41]	27	8	12	10	5
DCCT, 1995[193]	35	7	18	11	6
MCS, 1995[199]	34	5	12	16	6
MCSG, 1996[203]	114	2	8	85	21
Crepaldi *et al.*, 1998[209]	34	1	1	26	7
EURODIAB, 1999[176]	352	7	178	125	49
ATLANTIS, 2000[210]	46	2	2	39	5
Warram *et al.*, 2000[189]	279	4	4	214	61
Summary	**1295**	**6**	**335 (26%)**	**709 (55%)**	**251 (19%)**

[a] Reichard *et al.* (1993)[197] was used for this analysis.
[b] Personal communication from author.

TABLE 29 *Category of albuminuria at follow-up of children and adolescents with type 1 DM who initially had microalbuminuria: studies reporting both progression and regression*

Study	No. with MA at baseline	FU (y)	Category of albumin status at follow-up of those with MA at baseline (*n*)		
			NA	MA	CP
Rudberg *et al.*, 1992[178]	11	8	4	5	2
Salardi *et al.*, 1995[174]	14	6	7	5	2
Shield *et al.*, 1995[186]	9	3	5	4	0
Bojestig *et al.*, 1996[187]	27	10	16	6	5
Gorman *et al.*, 1999[188]	28	6	7	17	4
Summary	**89**	**7**	**39 (44%)**	**37 (42%)**	**13 (15%)**

three relevant sections in Chapter 3). Four of the 33 articles had already been located and initially selected from the renal search mentioned above.[33,61,71,86] For Torffvit and Agardh,[86] another 10-year follow-up report on the same cohort but with a slightly different focus, from Torffvit and Agardh,[87] was found in a search on the first author's name; it was used to provide supplementary information on the earlier article. A total of 34 articles was therefore considered.

Four of these 34 articles included specific information on microalbuminuria in relation to renal disease outcome and recorded at least one renal event.[33,58,61,86] An article by Gall and colleagues[96] was in abstract form, but the authors provided substantial additional information on written request, including details on deaths from uraemia. A further seven studies specifically reported no renal disease mortality in their normoalbuminuric or microalbuminuric groups over the period of follow-up.[32,52,63,64,67,72,97] Characteristics of the 12 included studies are shown in *Table 30*.

Articles excluded

Of the 34 articles initially selected, 22 were excluded. Five studies reported deaths from renal disease but did not report the patient's albuminuria status at baseline.[20,56,66,68,79] Sixteen studies did not report whether patients died from renal causes.[49,53,60,62,65,69–71,73,75–77,81,88,90,91] One article was used for supplementary information.[87]

Meta-analysis

Risk estimates for the development of ESRD are shown in *Table 30* and *Figure 21*. Seven studies were excluded from the analysis as there were no deaths from renal disease in either group. Among the other studies the relative risk of ESRD was 3.6 (95% CI 1.6 to 8.4) with no evidence of heterogeneity between studies.

Relationship between microalbuminuria and the fall in GFR in patients with type 2 DM

This end-point was considered to include GFR measured either directly using a renal or plasma clearance technique, or indirectly using creatinine clearance or a calculation based on the Cockcroft and Gault algorithm from the measured serum creatinine.

Search results

The MEDLINE and EMBASE searches yielded a total of 197 articles of potential relevance to the question of the prognostic significance of microalbuminuria for a decline in GFR in type 2 DM (Appendix 3). Reasons for initial exclusions of articles were: review, cross-sectional study, normoalbuminuria at baseline, overt nephropathy at baseline, no end-point of relevance, RCT with no end-point of relevance, focused on hyperfiltration, duplicate publication, methodological study. After these exclusions ten articles were initially selected as relevant.

The articles by Nielsen and colleagues[212,213] were, respectively, 3.4-year and 5.5-year follow-up reports of the same cohort, and the longer follow-up report was selected. Lemley[214] was found to be a subgroup of the cohort studied by Nelson and colleagues[215] and was not included. Rachmani[99] was selected as relevant, even though the authors' definition of microalbuminuria was below the conventional cut-off point for microalbuminuria. Nosadini[216] was not selected as no normoalbuminuric control group was included in the article. Miyauchi,[217] Nelson,[215]

TABLE 30 *Microalbuminuria and development of ESRD in patients with Type 2 DM: characteristics of included studies, events and risk estimates*

Source	Setting	*n*	Mean age (y)	Mean duration of diabetes (y)	FU (y)	MA events/ total	NA events/ total	Definition of renal event	Crude RR (95% CI)
Jarrett *et al.*, 1984[32]	London, UK (H)	42	52	6	14	0/7	0/35	Death from renal disease	NC
Mogensen, 1984[33]	Aarhus, Denmark (H)	232	68	9	9	3/76	1/128	Death from uraemia	5.1 (0.5 to 48)
Beatty *et al.*, 1995[63]	Belfast, UK (H)	94	63	8	8	0/47	0/47	Death from CRF	NC
Chan *et al.*, 1995[61]	Hong Kong, China (H)	403	58	6	2	1/94	0/208	Death from renal failure	6.7 (0.3 to 164)
MacLeod *et al.*, 1995[64]	Newcastle upon Tyne, UK (H)	306	67	8	8	0/153	0/153	Death from renal failure	NC
Allawi *et al.*, 1997[97]	London, UK (H)	85	57	NE	9	0/NE	0/NE	Death from renal disease	NC
Araki *et al.*, 1997[58]	Shiga, Japan (H)	297	57	10	6.4	1/96	0/201	Death from renal failure	6.2 (0.3 to 152)
Wirta *et al.*, 1997[67]	Tampere, Finland (P)	135	61	11	9	0/39	0/96	Death from renal disease	NC
Gall *et al.*, 1998[96]	Gentofte, Denmark (H)	549	59	9	10	2/151	3/323	Death from uraemia	1.4 (0.2 to 8.4)
Mattock *et al.*, 1998[52]	London, UK (H)	146	59	5	7	0/37	0/109	Death from renal disease	NC
de Grauw *et al.*, 2001[72]	Nijmegen, Netherlands (G)	252	66	5	6	0/50	0/202	Death from renal disease	NC
Torffvit and Agardh, 2001[86]	Lund, Sweden (H)	385	54	NE	10	7/103	4/252	Serum creatinine >200 μmol l^{-1} or dialysis or renal transplantation	4.3 (1.3 to 14.3)
Meta-analysis, 2002		**2926**	**61**	**8**	**8**	**14/853**	**8/1754**		**3.6 (1.6 to 8.4)**

Wirta,[218] Friis and Pedersen[66] and Berrut[219] were also selected. Features of the seven selected studies are shown in *Table 31*.

Articles excluded

Of the ten articles initially selected, three were subsequently excluded.[212,214,216]

Meta-analysis

Only six studies reported sufficient information to be able to calculate the fall in GFR in each of the two groups (*Table 31*). In five of these studies, the fall in GFR was greater among patients who had microalbuminuria at baseline, the difference being 1.7 (95% CI 0.1 to 3.2) ml per minute per year. There was no significant heterogeneity between studies (*Figure 22*). In the remaining study[218] data were not retrievable in a format to allow inclusion in the meta-analysis. The authors reported no change in GFR over time in either the normoalbuminuric or microalbuminuric subjects. Patients in different studies were either normotensive or mostly hypertensive or on antihypertensive treatment, but this did not appear to relate to the outcome and there were too few studies for separate analysis.

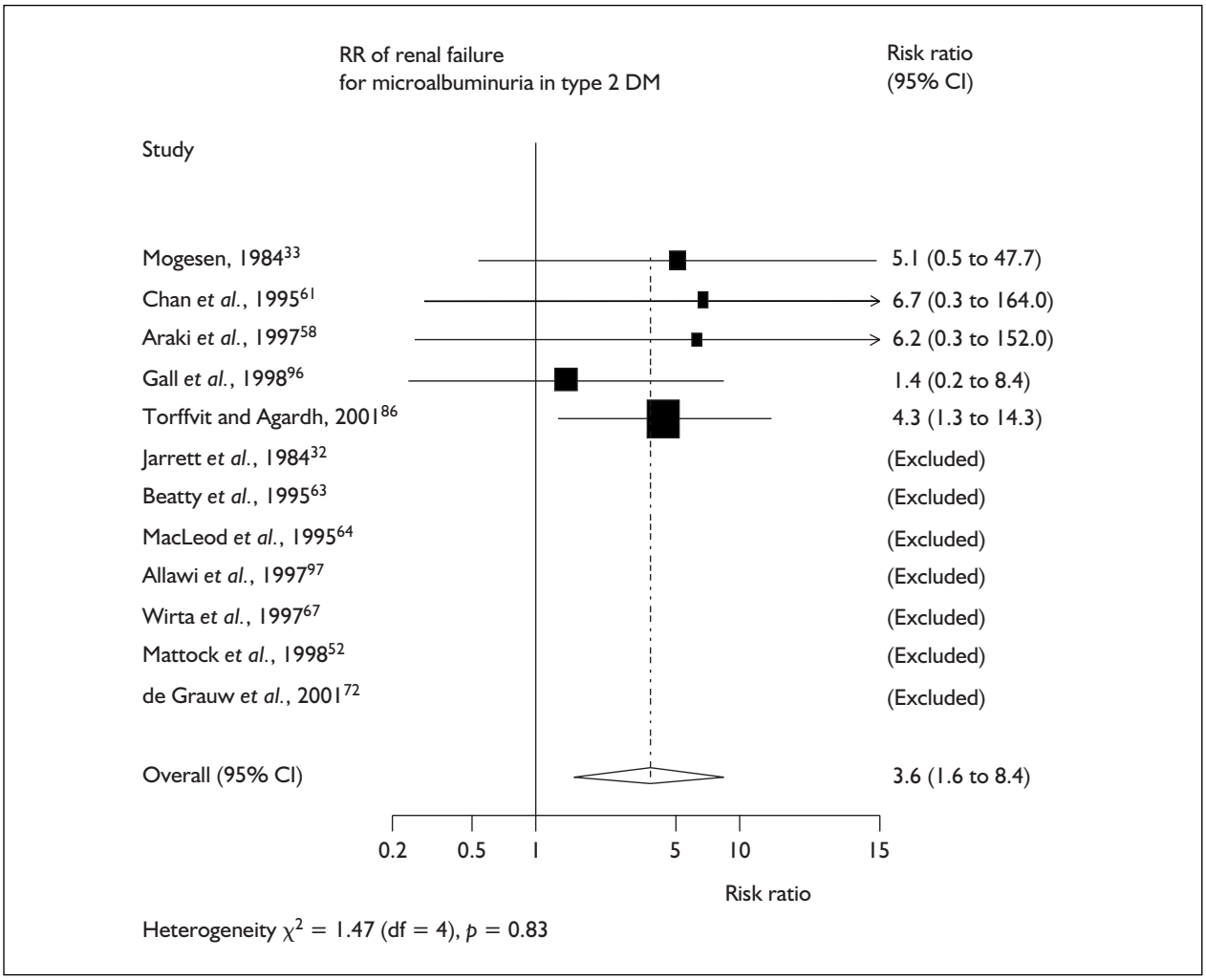

FIGURE 21 *Forest plot for relative risk of ESRD with microalbuminuria in type 2 DM*

Relationship between microalbuminuria and the development of clinical proteinuria in patients with type 2 DM

The articles selected include observational studies and the control arms of RCTs, as described in the section 'Relationship between microalbuminuria and the development of clinical proteinuria in patients with type 1 DM', p. 52).

Search results

There were 55 articles initially selected for further examination (see section 'Search results', p. 52). Five reports of the 7-year follow-up of type 1 and type 2 DM patients by Jerums and co-authors were retrieved.[166–170] Cooper[167]was selected as relevant data were more readily extractable. Gilbert[169] contained relevant and extractable data but was a subset of patients from the group reported by Cooper and colleagues.[167] Both Mogensen[33] and Mogensen and Christensen[163] contained relevant data, but Mogensen[33] was selected as more complete. Three Japanese papers report 3-year,[220] 5-year[92] and 10-year[59] studies of the same cohort. The study with the longest follow-up was selected.[59] A fourth article, by Araki and colleagues[58] dealt only with follow-up for mortality and was not selected for this section of the review. The articles by Nielsen and colleagues[212,213] are 3.4-year and 5.5-year follow-up reports, respectively. The article with the shorter follow-up[212] was selected since, in the second article,[213] data were not readily extractable and losses to follow-up were more than 45%. Data for the relative risk of microalbuminuria for clinical proteinuria could not be extracted from Stiegler,[48] but data on the progression and regression of

TABLE 31 *Microalbuminuria and decline in GFR in patients with type 2 DM: characteristics of included studies and analysis of decline in GFR*

Source	Setting	Definition of MA	Mean age (y)	Duration (y)	FU (y)	MA (*n*)	NA (*n*)	Blood pressure	GFR method	MA GFR fall ml per minute per year ± SD (range)	NA GFR fall ml per minute per year ± SD (range)	Difference in fall (MA-NA) ml per minute per year (95% CI)
Miyauchi, *et al.*, 1995[217]	Ishikawa, Japan (H)	30–300 mg per 24 h	58	8	5	15	16	Normotensive (< 140/90)	Sodium thiosulphate	93 (70–115) to 84 (63–103)[c]	87 (65–136) to 85 (61–123)[c]	1.4 (–2.7 to 5.5)[d]
Nelson *et al.*, 1996[215]	Arizona, USA (P)	ACR 3.4–34 mg $mmol^{-1}$[a]	44	13	5	46	16	5% of NA and 10% of MA on AHT	Iothalamate clearance	1 ± 12.5[e]	–0.6 ± 10.2[e]	1.6 (–4.6 to 7.8)
Wirta *et al.*, 1996[218]	Tampere, Finland (P)	>30 mg per 24 h[b]	55	0	6	29	80	42% on AHT, 63% >160/95	^{51}Cr-EDTA clearance	No change	No change	ns
Berrut *et al.*, 1997[219]	Angers, France (H)	30–300 mg per 24 h	60	10	2	21	51	All 160/95 or AHT	^{51}Cr-EDTA clearance, single injection	5.0 ± 9.5[e]	–2.0 ± 8.5[e]	7.0 (2.3 to 11.7)
Friis and Pedersen, 1997[66]	Fredericksberg, Denmark (H)	20–200 μg per minute	62	8	1	16	30	43% 160/95 or AHT	^{51}Cr-EDTA clearance, single injection	5.0 87 (54–125) to 82 (50–132)[c]	2.0 97 (58–143) to 95 (63–135)[c]	3.0 (0.0 to 6.0)[f]
Nielson *et al.*, 1997[213]	Aarhus, Denmark (H)	20–200 μg per minute	63	8	6	11	20	50% >160/95	51 Cr-EDTA clearance, single injection	1.0 ± 2.3[e]	1.2 ± 2.2[e]	–0.2 (–1.9 to 1.5)
Rachmani *et al.*, 2000[99]	Tel-Aviv, Israel (H)	20–30 mg l^{-1}	48	2	8	109	359	<140/90	Calculated from Levy formula	2.5 ± 5.1[e]	1.2 ± 3.5[e]	1.3 (0.3 to 2.3)
Meta-analysis			**51**	**4**	**6**	**247**	**572**					**1.7 (0.1 to 3.2)**

[a] Converted from mg g^{-1}.
[b] ????
[c] Initial vs follow-up.
[d] Confidence interval is calculated using the standard deviation for the change in GFR calculated as the average standard deviation in the other five studies.
[e] Calculated from data in paper.
[f] $p < 0.05$; confidence interval estimated from $p = 0.05$.
AHT, antihypertensive treatment.

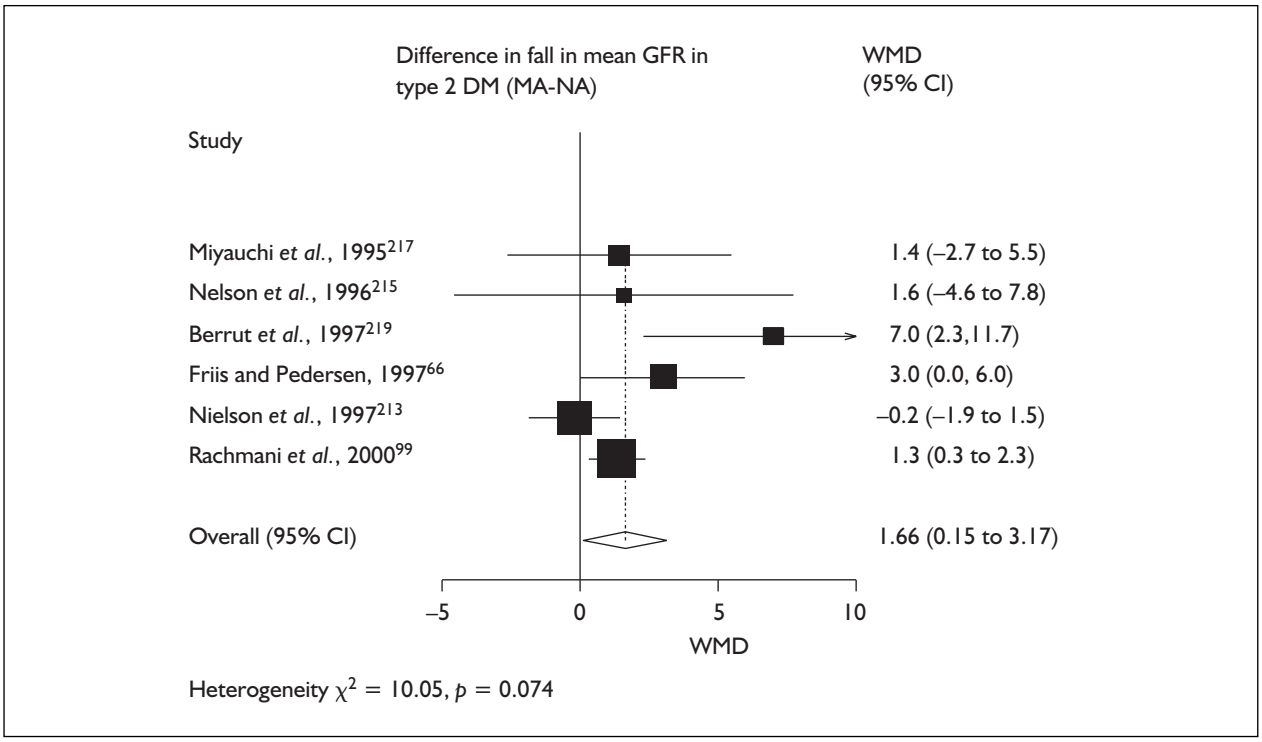

FIGURE 22 *Forest plot comparing the fall in GFR between normoalbuminuric and microalbuminuric patients with type 2 DM*

microalbuminuria were extractable and the article was selected.

Huang[221] was a further follow-up report of the cohort described by Wirta and colleagues,[218] but had a less relevant focus, and the latter article[218] was selected. Niskanen[79] was relevant, but data were not extractable and the authors did not respond to letters seeking clarification. Neither Hoy[222] nor Oue[223] was selected as the data were not analysed by baseline microalbuminuria. In Friis and Pedersen,[66] there was a particularly high rate of development of clinical proteinuria in a follow-up period of only 30 months, but it was unclear how many of these patients initially had normoalbuminuria or microalbuminuria. Lunt[224] included mostly clinically proteinuric patients at baseline. In Schmitz and Vaeth[55] there were insufficient data available to determine the baseline albuminuria category of re-examined survivors, but another article by Schmitz and colleagues was selected.[89] Shoji [225] only included 11 patients with normoalbuminuria or microalbuminuria, was retrospective in design and focused on kidney biopsy findings. Yoshida[226] was not selected as the end-point was not clinical proteinuria. Torffvit and Agardh[86] is a 10-year follow-up report and the 5-year follow-up of this cohort[81] has also been published; the report with longer follow-up was selected. Hadjadj[227] followed 351 type 2 DM patients with defined stages of nephropathy for a mean of 32 months, defining progression as movement from one stage to another (e.g. normoalbuminuria to microalbuminuria, microalbuminuria to clinical proteinuria). Forty per cent of patients progressed by at least one stage of nephropathy, but as there was no description of the initial and final albuminuria category of progressors the article was not selected. Three articles from the same group reported different aspects of the rate of progression of microalbuminuria.[228–230] The focus was, however, on mean yearly change in the ACR (rather than categorical change from microalbuminuria to clinical proteinuria), with no control group; none of the three articles was therefore selected.

Other articles selected were Nelson,[231] John,[90] Beatty,[63] Kawazu,[232] Chan,[61] Miyauchi,[217] Berrut,[219] Song,[233] Tanaka,[150] Nosadini[216] and de Grauw.[72] (*Table 32*). Tabei[190] was not included as losses to follow-up (52%) were heavy and disproportionate between the normoalbuminuric and microalbuminuric groups. There were other clearly reported studies (see *Table 34*) where losses to follow-up (the highest of which was 32% overall) gave cause for concern.

TABLE 32 *Microalbuminuria and development of clinical proteinuria in patients with type 2 DM: characteristics of included observational studies*

Source	Setting	Total no. (NA/MA/CP)	Gender (% male)	Mean age (y)	Mean duration of diabetes (y)	Urine collection	Definition of MA	FU (y)
Mogensen, 1984[33]	Aarhus, Denmark (H)	232 (128/76/28)	55	67	9	1 or more morning spot	30–140 mg l^{-1}	9
Cooper *et al.*, 1988[167]	Melbourne, Australia (H)	61 (51/3/7)	57 (NA and MA)	58	13	24 h 3-monthly	30–150 μg per minute	7
Nelson *et al.*, 1991[231]	Pima Indians, USA (P)	439 (299/140/0)	31	49	0–18	1 × spot morning	ACR 3.4–34 mg $mmol^{-1}$[a]	4
Stiegler *et al.*, 1992[48]	Munich, Germany (G)	290 (NE)	34	65	7	1 × first morning	30–200 mg l^{-1}	3
Nielsen *et al.*, 1993[212]	Aarhus, Denmark (H)	37 (24/13/0)	62	63	7	2 × 24 h	20–200 μg per minute	3
John *et al.*, 1994[90]	Southern India (H)	481 (349/93/39)	47	53	10	2 x 24 h	20–200 μg per minute	5
Kawazu *et al.*, 1994[232]	Gunma, Japan (H)	48 (33/15/0)	73	55	11	1 × spot morning	ACR 1.7–23 mg $mmol^{-1}$[a]	8
Schmitz *et al.*, 1994[89]	Aarhus, Denmark (H)	278 (206/52/20)	54	64	9	1 × spot morning	15–200 mg l^{-1}	6
Araki *et al.*, 1995[59]	Shiga, Japan (H)	47 (30/17/0)	40	59	10	3 × 24 h	15–200 μg per minute	10
Beatty *et al.*, 1995[63]	Belfast, UK (H)	94 (47/47/0)	50	64	8	1 × spot morning	35–300 mg l^{-1}	8
Chan *et al.*, 1995[61]	Hong Kong, China (H)	374 (208/94/72)	38	54	6	1 × spot random	ACR 5.6–38 mg $mmol^{-1}$	2
Miyauchi *et al.*, 1995[217]	Ishikawa, Japan (H)	38 (16/15/7)	42	58	8	2 x 24 h	30–300 mg per 24 h	5
Wirta *et al.*, 1996[218]	Tampere, Finland (H)	109 (78/26/4)	52	56	0 (ND)	1 x 24 h	30–300 mg per 24 h	6
Berrut *et al.*, 1997[219]	Angers, France (H)	205 (151/54/0)	51	60	10	3 × 24 h	30–300 mg per 24 h	2
Song *et al.*, 1998[233]	Seoul, South Korea (H)	46 (0/46/0)	39	58	11	2 x 24 h	20–200 μg per minute	5
Tanaka *et al.*, 1998[150]	Tokyo, Japan (H)	123 (74/49/0)	70	67	15	1 × 24 h	<20 μg per minute	6
Nosadini *et al.*, 2000[216]	Padova, Italy	108 (0/74/34)	53 (MA)	58	11	3 x 24 h	20–199 μg per minute	4
de Grauw *et al.*, 2001[72]	Nijmegen, Netherlands (G)	262 (202/50/0)	39	66	5	3 × spot morning	20–200 mg l^{-1}	6
Torffvit and Agardh, 2001[86]	Lund, Sweden (H)	385 (251/103/30)	65	54	8	3 × spot morning	0.01–0.1 × 10^3 ACCR	10

[a] Converted from mg g^{-1}.
ND, newly diagnosed; ACCR, albumin and creatinine clearance ratio.

TABLE 33 *Microalbuminuria and development of clinical proteinuria in patients with type 2 DM: characteristics of included RCTs*

Source	Setting	Placebo group (*n*)	Gender (% male)	Mean age (y)	Mean duration of diabetes (y)	Urine collection	Definition of MA	FU (y)
Sano *et al.*, 1996[240]	Nagoya, Japan (RCT)	28	NE	64	12	3 × 24 h at baseline, 1 × 24 h subsequently	20–300 mg per 24 h	4
Parving *et al.*, 2001[241]	96 centres worldwide RCT (ACE)	201 with MA	69	58	10	3 x overnight	20–200 μg per minute	2

RCT (ACE), RCT examining hypotensive/renal effects of ACE inhibition.

The placebo or conventional treatment groups of RCTs were also considered. Several RCTs examined intensified compared with conventional glycaemic control in type 2 DM: UKPDS,[234] the Kumamoto study at 6- and 8-year follow-up[235,236] and the Veterans Affairs Cooperative Study.[21] However, data on the progression of microalbuminuria to clinical proteinuria in the conventional treatment groups were not extractable from any of these studies. RCTs of ACE inhibitor versus placebo included three articles from Ravid and colleagues.[237–239] In Ravid,[239] the follow-up period had been extended but as an open study. All subjects were microalbuminuric, no data on regression of microalbuminuria were reported and none of the studies were selected; for the same reasons Ahmad[22] was not selected. Sano[240] was selected as data on the progression and regression of microalbuminuria in the control group could be extracted from an included figure. A placebo-controlled angiotensin II receptor blocker trial reported by Parving and colleagues[241] gave clear information on both the progression and regression of microalbuminuria in the placebo group, and the study was selected (*Table 33*). A smaller placebo-controlled trial using angiotensin II receptor blockers reported by Muirhead and colleagues[242] gave no information on regression and was not selected.

Articles excluded

Cohort studies

Twenty-four articles were excluded.[55,58,66,79,81,92,163,166,168–170,190,213,220–230]

RCT's

Nine articles were excluded.[21,22,234–239,242]

Meta-analysis of the development of clinical proteinuria

There were 16 studies with data on the development of clinical proteinuria in both patients with microalbuminuria and with normoalbuminuria (*Table 34*). The overall relative risk was 7.5 (95% CI 5.2 to 10.9) (*Figure 23*). Although the heterogeneity test was not significant there was still evidence of publication bias from the funnel plot (*Figure 24*) and Egger's test for publication bias was significant ($p = 0.014$). The trim and fill method estimated seven missing studies and gave an estimated relative risk of 5.5 (95% CI 3.8 to 8.1).

The studies used for the meta-analysis are quite heterogeneous in terms of ethnicity, and renal failure is believed to be a less frequent outcome in white subjects than in other ethnic groups. In general accord with this, the pooled relative risk for clinical proteinuria in the nine studies reporting on mainly white subjects was slightly less than in the seven studies reporting on Japanese, Korean, Chinese, Indian Asian and Pima Indian subjects, 6.6 (95% CI 4.0 to 10.8) compared with 8.6 (95% CI 5.1 to 14.5), respectively, but not significantly different.

Meta-analysis of the regression of microalbuminuria to normoalbuminuria

All studies that reported both whether patients had progressed to clinical proteinuria and whether patients had regressed to normoalbuminuria are shown in *Table 35*. Of patients with microalbuminuria at baseline, 24% progressed to clinical proteinuria while 18% regressed to normoalbuminuria. This difference is not statistically significant (difference 7%, 95% CI –6 to 19).

TABLE 34 *Microalbuminuria and development of clinical proteinuria in patients with Type 2 DM; events and risk estimates*

Source	Lost to follow-up (%)	Death rate (%)	CP/total MA	CP/total NA	Crude RR (95% CI)	Factors associated with progression
Mogensen, 1984[33]	NE	63	17/76	7/128	4.1 (1.8 to 9.4)	NE
Cooper *et al.*, 1988[167]	19	0	3/3	5/51	10.2 (4.4 to 23.4)	No relation with glucose control or BP
Nelson *et al.*, 1991[231]	0	NE	47/140	12/299	8.4 (4.6 to 15)	Glycaemic control, duration of diabetes and baseline ACR
Nielsen *et al.*, 1993[212]	24	11	3/13	0/24	12.5 (0.7 to 225)	SBP
John *et al.*, 1994[90]	27	4	23/61	10/241	9.1 (4.6 to 18.1)	Initial AER
Kawazu *et al.*, 1994[232]	Retrospective		5/15	0/33	23.4 (1.4 to 397)	Overall glycaemic control
Schmitz *et al.*, 1994[89]	32	29	11/34	1/135	43.7 (5.8 to 326)	SBP, HbA_{1c} and level of albuminuria
Araki *et al.*, 1995[59]	19	11	7/11	4/23	3.7 (1.4 to 9.9)	AER
Beatty *et al.*, 1995[63]	19	34	5/19	0/31	17.6 (1.0 to 301)	None found
Chan *et al.*, 1995[61]	12	4	17/94	2/208	18.8 (4.4 to 80)	Baseline ACR
Miyauchi *et al.*, 1995[217]	0	0	4/15	1/16	4.3 (0.5 to 34)	None found
Wirta *et al.*, 1996[218]	18	11	5/26	2/78	7.5 (1.6 to 36)	Fasting serum insulin and HbA_{1c}, but not BP
Berrut *et al.*, 1997[219]	27	5	4/21	1/51	9.7 (1.2 to 82)	Hypertension
Tanaka *et al.*, 1998[150]	30	NE	26/49	0/74	80 (5.0 to 1274)	Hypertension
de Grauw *et al.*, 2001[72]	28	22	3/25	2/138	8.3 (1.5 to 47)	Duration of diabetes
Torffvit and Agardh, 2001[86]	4	NE	38/103	26/252	3.6 (2.3 to 5.6)	HbA_{1c} and BP
Meta-analysis, 2002			**218/705**	**73/1782**	**7.5 (5.2 to 10.9)**	

Relationship between microalbuminuria and the development of renal failure: conclusions

Summary of review findings

Type 1 DM

For the development of ESRD 272 articles were initially identified, which reduced after applying the protocol requirements to ten studies; for GFR, 270 articles of potential relevance reduced to two studies. From among 597 articles for either type 1 or type 2 DM, 19 relevant studies were retrieved for the development of clinical proteinuria in type 1 DM; for regression of microalbuminuria there were 21 studies in adults and five in children. For patients with microalbuminuria, there is a significantly increased risk of developing ESRD (RR 4.8, 95% CI 3.0 to 7.5) and clinical proteinuria, (RR 7.5, 95% CI 5.4 to 10.5); the latter remained significant when adults and children were analysed separately. There were only two studies reporting on GFR and they used different outcomes, but both showed a significantly greater decline among patients with microalbuminuria. Examination of the category of albuminuria at follow-up of adult patients with microalbuminuria at baseline showed no significant difference between the numbers progressing to clinical proteinuria (19%) and those regressing to normoalbuminuria (26%). However, among adolescents with a similar length of follow-up, significantly more regressed to normoalbuminuria (44%) than progressed to clinical proteinuria (15%).

Type 2 DM

For the development of ESRD 176 articles were initially identified, which reduced after applying the protocol requirements to 12 studies; for GFR, 197 articles of potential relevance reduced to seven studies. From among 597 articles for either type 1 or type 2 DM, 16 relevant studies were

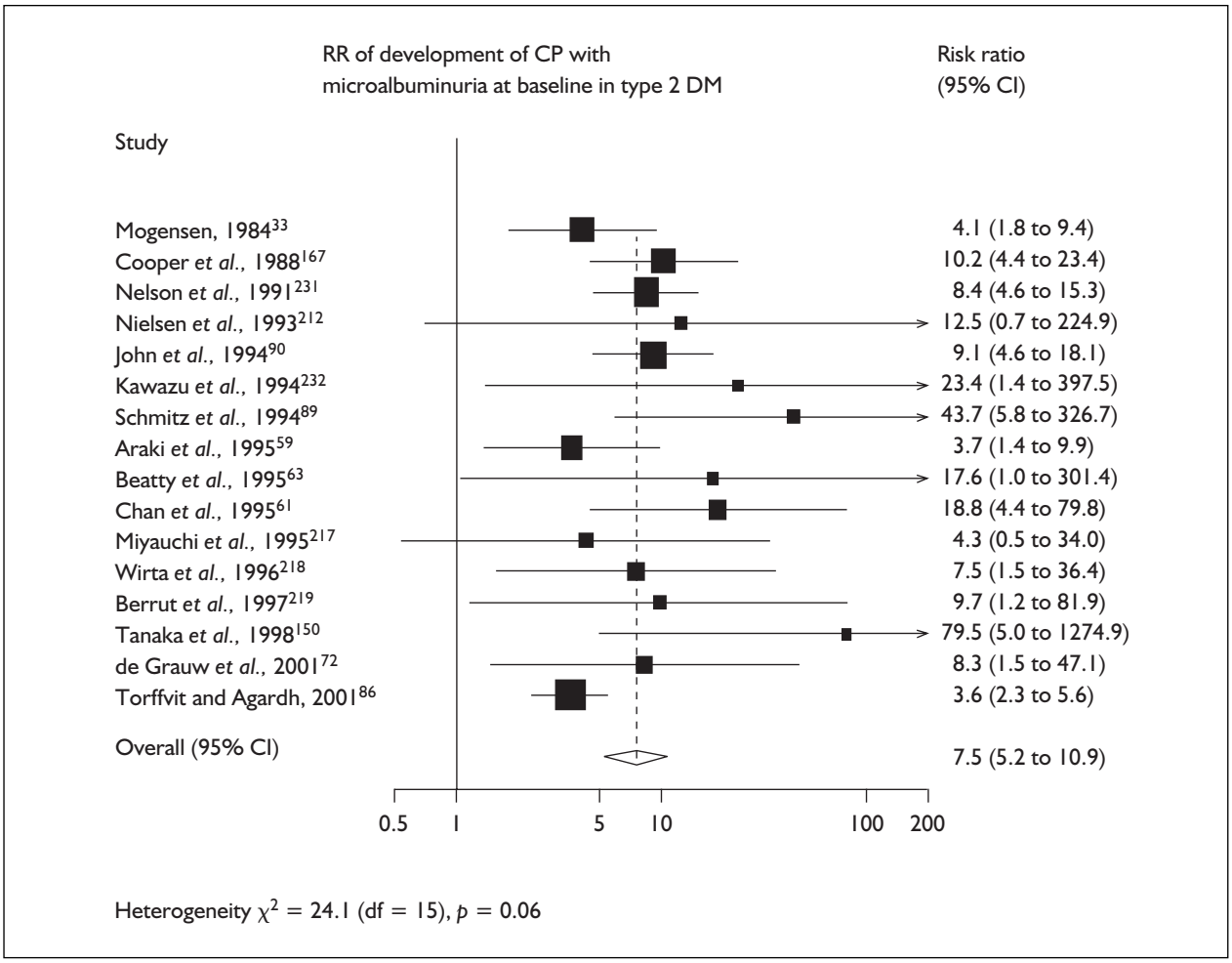

FIGURE 23 *Forest plot for relative risk of the development of clinical proteinuria with microalbuminuria at baseline in type 2 DM*

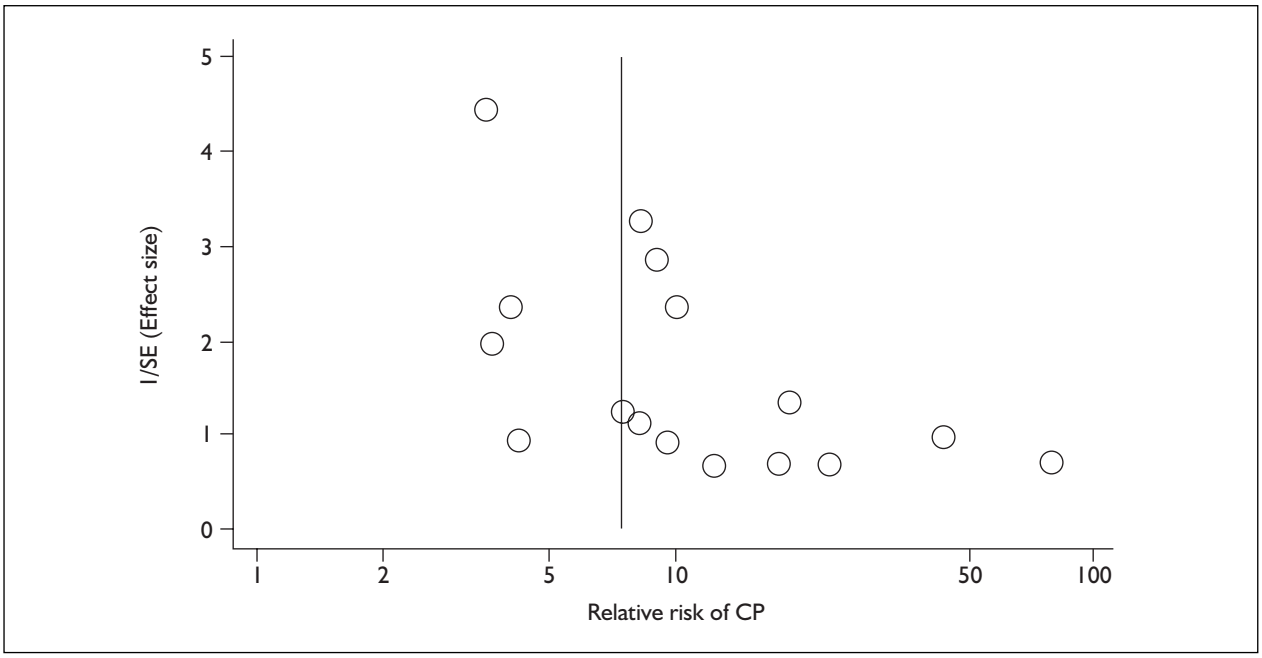

FIGURE 24 *Funnel plot for relative risk of the development of clinical proteinuria with microalbuminuria at baseline in type 2 DM*

TABLE 35 *Category of albuminuria at follow-up of adults with type 2 DM who initially had microalbuminuria: studies reporting both progression and regression*

Study	No. with MA at baseline	FU (y)	Category of albumin status at follow-up of those with MA at baseline, (*n*) (%)		
			NA	MA	CP
Stiegler *et al.*, 1992[48]	56	3	15 (27)	29 (52)	12 (21)
John *et al.*, 1994[90]	61	5	9 (15)	29 (47)	23 (38)
Schmitz *et al.*, 1994[89]	34	4	3 (9)	20 (59)	11 (32)
Araki *et al.*, 1995[59]	11	10	2 (18)	2 (18)	7 (64)
Beatty *et al.*, 1995[63]	19	8	6 (32)	8 (42)	5 (26)
Chan *et al.*, 1995[61]	94	2	29 (31)	48 (51)	17 (18)
Sano *et al.*, 1996[240]	28	4	3 (11)	19 (68)	6 (21)
Wirta *et al.*, 1996[218]	26	6	9 (35)	12 (46)	5 (19)
Berrut *et al.*, 1997[219]	21	2	7 (33)	10 (48)	4 (19)
Song *et al.*, 1998[233]	46	5	0 (0)	23 (50)	23 (50)
Nosadini *et al.*, 2000[216]	74	4	8 (11)	55 (74)	11 (15)
de Grauw *et al.*, 2001[72]	25	6	10 (40)	12 (48)	3 (12)
Torffvit and Agardh, 2001[72]	103	10	0 (0)	65 (63)	38 (37)
Parving *et al.*, 2001[241]	201	2	42 (21)	129 (64)	30 (15)
Summary	**799**		**143 (18)**	**461 (58)**	**195 (24)**

retrieved for the development of clinical proteinuria in type 2 DM; for regression of microalbuminuria there were 14 studies. For patients with microalbuminuria, there is a significantly increased risk of developing ESRD, (RR 3.6, 95% CI 1.6 to 8.4) and clinical proteinuria (RR 7.5, 95% CI 5.2 to 10.9), and a significantly greater decline in GFR of 1.7 (95% CI 0.1 to 3.2) ml per minute per year compared with those who were normoalbuminuric. The risk of developing clinical proteinuria was not significantly different between non-white and white populations. Examination of the category of albuminuria at follow-up of adult patients with microalbuminuria at baseline showed no significant difference between the numbers progressing to clinical proteinuria (24%) and those regressing to normoalbuminuria (18%).

Chapter 6

Systematic review 4: In patients with type 1 or type 2 diabetes and microalbuminuria, does improved glycaemic control reduce the rate of development of secondary diabetic complications?

Introduction to studies of glycaemic control in patients with type 1 DM

Since the 1970s, a substantial body of animal experimental studies, human observational studies and clinical trials has directly linked hyperglycaemia with the development of diabetic complications.[243] Several studies have now clearly shown that, compared with conventional insulin treatment (CIT) intensive insulin therapy (IIT) reduces the risk of developing the microvascular complications of type 1 DM, namely retinopathy, nephropathy and neuropathy. These studies include a series of small RCTs, which have been reviewed and meta-analysed by Wang and colleagues,[244] and a subsequent large long-term RCT, the DCCT.[19]

The DCCT studied two cohorts of type 1 patients, to answer two distinct questions. First, would intensive treatment prevent or delay the development of complications in those who had no complications at baseline? Second, would intensive treatment prevent or slow the progression of complications in those who had early complications at baseline? These were, respectively, primary and secondary intervention trials.

The primary prevention cohort consisted of 726 subjects with duration of diabetes of 1–5 years, mean (SD) age 26 (7) years, no visible retinopathy and normoalbuminuria (AER < 28 μg per minute). The median AER was 8 μg per minute. The secondary intervention cohort consisted of 715 subjects with duration of diabetes of 1–15 years and mean age 27 (7) years. They had minimal or moderate retinopathy and an AER below 139 μg per minute. The median AER was 9.7 μg per minute. Seventy-three of these secondary intervention subjects had microalbuminuria (AER 28–139 μg per minute). The mean duration of follow-up for the full cohort was 6.5 years (range 3–9 years). Losses to follow-up did not exceed 1%. At baseline, mean HbA_{1c} levels were similar in both treatment groups. By 3 months after randomisation, mean HbA_{1c} was approximately two percentage points lower in the intensive treatment than in the conventional treatment group and this difference was maintained throughout the entire study.

In both cohorts, microalbuminuria developed in fewer patients in the intensive therapy group than in the conventional therapy group. The mean adjusted risk of microalbuminuria was reduced by 34% ($p = 0.04$) in the primary prevention cohort and by 43% ($p = 0.001$) in the secondary prevention cohort.

At the close of the DCCT, patients in the conventional therapy group were offered intensive therapy. Most patients in the DCCT (96%) were subsequently enrolled in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a post-trial long-term (10-year) observational study.[245] By the end of the study the mean age will approximate 43 years and mean duration of diabetes will exceed 20 years. This planned long-term prospective observational study has a number of objectives that will shed light on many of the questions posed here, as discussed below.

General search strategy

MEDLINE and EMBASE were searched for RCTs carried out among patients with either type 1 or type 2 DM and microalbuminuria that examined the effects of improved glycaemic control on any of the following end-points: CVD, development or progression of retinopathy, ESRD, decline in GFR or development of clinical proteinuria (Appendix 3). An initial complexity is that the microvascular complications, nephropathy, retinopathy and neuropathy, have been assessed either alone or in different combinations in reports from particular trials, thereby increasing

the number of articles to be examined. Moreover, because of a paucity of end-points in the smaller trials, some trials have been extended for longer than originally planned, with multiple follow-up reports from individual trials. As stated in the study protocol, the intention was generally to choose the report with the longest follow-up. The extended follow-up periods, however, were often at the expense of losing the original treatment assignments, for example because of the crossing over of patients from CIT to IIT with reduction of average glycaemic difference with time. Thus, only those trial reports where the original random allocation was maintained were included. It was also specified that the trial should include at least a proportion of patients with microalbuminuria and that the duration of the study was at least 1 year.

Search results

For type 1 DM, the MEDLINE and EMBASE searches yielded a total of 295 potentially relevant articles. Reasons for initial exclusion of articles were: cross-sectional study, review, comment or meeting report, RCT with no treatment or endpoint of relevance, longitudinal study, focus on pregnancy, duplicate publication, economic evaluation and report of trial design. The bibliographies of retrieved articles were also searched. Thirty-three potentially relevant trial reports were initially selected.[16,19,173,192–199,245–266]

This chapter also comments on two relevant meta-analyses.[244,267] These studies were considered for each of the five sections that follow.

Improved glycaemic control and CVD in patients with type 1 DM and microalbuminuria

The large vessel complications of diabetes (cardiovascular, cerebrovascular and peripheral-vascular) contribute most to the excess morbidity and mortality associated with type 1 DM.[268,269] Cohort studies have found that, in people with type 1 DM, higher average levels of blood glucose are associated with higher incidence of CVD.[270] Indeed, a recent meta-regression analysis of data from 20 published studies strongly suggests that the progressive relationship between glucose levels and cardiovascular risk extends to below the diabetic threshold.[271] As discussed in Systematic review 1 (Chapter 3), there is some evidence that microalbuminuria has an independent predictive ability for CVD morbidity and mortality in type 1 DM. Moreover, it has long been known that improved glycaemic control will reduce urinary AER.[272] Does improved glycaemic control reduce CVD risk in people with type 1 DM and microalbuminuria?

Search results

There is no trial evidence that is directly relevant to the research question. A series of early RCTs examined the relationship between metabolic control and the complications of type 1 DM (Holman,[248] the Steno study,[264] the Steno 2 study,[266] the Oslo study[259] and SDIS.[273] The later results of the Steno 1 and 2 studies were reported in one article.[266] These trials were not designed to have the power to detect changes in the risk of developing macrovascular complications. The DCCT[19] was larger than all of the previous and subsequently reported trials together. Again, however, its major focus was on microvascular complications and, like the smaller trials, it was not powered to detect changes in macrovascular risk. A recent systematic review and meta-analysis examined the effects of IIT on the risk of macrovascular disease in patients with type 1 DM.[267] This publication included all known RCTs of IIT in type 1 DM, to estimate the effect on macrovascular disease risk (the five trials mentioned above). There was no significant effect of intensified treatment on the number of patients having one or more macrovascular events, or on overall macrovascular mortality, but these studies do not allow analysis by albuminuria status. Since the DCCT has established IIT as the goal of care for most people with type 1 DM,[274] further randomised trials are unlikely on ethical grounds.

Comments

There are some limitations to the meta-analysis of Lawson and colleagues.[267] Different types of events within the same class (e.g. angina and MI) were counted as separate events (as done in the DCCT), even though events within the same class are not independent. In addition, the large DCCT study made an inordinate contribution to the meta-analysis. The findings were interpreted as suggesting that IIT may stabilise macrovascular disease or prevent progression in those already at risk. Some support for this view comes from a study using high-frequency ultrasound to assess early atherosclerosis in type 1 diabetic patients.[275] Twelve years after randomisation to IIT or CIT, the authors found that IIT was associated with benefit in terms of better endothelial function and less stiff arteries. However, these ultrasound findings could not be linked to clinical events, as there were only three such events among the 59 included patients. Detailed analysis of the DCCT results[16] showed that the number of combined

macrovascular events in the conventionally treated group was almost twice as high as in the intensively treated group, although this was not statistically significant. The participants were young (average age at entry 27 years) and those with hypertension or known CAD had been excluded. The consequent low incidence of macrovascular events limited the power of the study to detect an effect of treatment on macrovascular disease. It is notable that only 73 of the 1441 subjects had microalbuminuria at baseline and the effect of improved glycaemic control on macrovascular events in this subgroup was not analysed separately. The numbers of CVD events are likely to increase substantially over the follow-up period of the EDIC study, which may provide conclusive data in future.

Conclusions

Taken together, the RCTs provide modest support for a beneficial effect of glucose lowering with insulin on the incidence of CVD in patients with type 1 DM. There is no evidence of adverse CVD outcomes, although IIT is associated with an increased frequency of severe adverse effects, notably hypoglycaemic episodes and weight gain.[30] The question of differential effects in the microalbuminuric subset of patients remains unanswered. Since microalbuminuric patients with type 1 DM are at higher risk of all-cause and CVD mortality (Systematic review 1, Chapter 3) it would be expected that these patients would show the greatest treatment benefit. Further light may be thrown on this question by continued follow-up of the EDIC cohort.[245]

Improved glycaemic control and retinopathy in patients with type 1 DM and microalbuminuria

As reviewed by Genuth,[243] numerous studies have demonstrated an association between glycaemic control and the presence of retinopathy in type 1 DM. The Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) is the largest population-based study that has examined this relationship prospectively.[106] After controlling for confounding factors, baseline HbA_{1c} was found to be the most important risk factor for the incidence and progression of retinopathy in people with type 1 DM. Such studies suggest that improved glycaemic control will affect the incidence of retinopathy. However, only RCTs can definitively test whether control of glycaemia will reduce the incidence and progression of retinopathy. Such studies have now clearly shown that, compared with CIT, IIT reduces the risks for development or progression of retinopathy. The studies include a series of small RCTs, which have been reviewed and meta-analysed by Wang and colleagues,[244] and a subsequent large long-term RCT, the DCCT.[19]

Search results

In the meta-analysis by Wang and colleagues,[244] most patients had background or non-proliferative retinopathy. After 2–5 years of intensive treatment the risk of retinopathy progression was significantly reduced (OR = 0.49, 95% CI 0.28 to 0.85, $p = 0.011$) and there was no significant heterogeneity. However, the impact of intensive treatment on retinopathy in patients with microalbuminuria was not separately analysed.

In the DCCT primary prevention cohort, over the 6-year follow-up, retinopathy developed in 23 patients receiving IIT and in 91 receiving CIT. IIT reduced the adjusted mean risk of retinopathy by 76% (95% CI 62 to 85). In the secondary prevention cohort, 77 patients in the IIT group and 143 patients in the CIT group showed progression of retinopathy. IIT reduced the mean adjusted risk of progression by 54% (95% CI 39 to 66). The risks of developing proliferative or severe non-proliferative retinopathy or requiring treatment by photocoagulation were also markedly reduced by intensive therapy. The effect of IIT on retinopathy progression in the subgroup with microalbuminuria was not presented.[19] However, the consistency of the retinopathy results was examined by analysing the cumulative incidence of a sustained progression of retinopathy by three steps among subgroups. The subgroups were defined by baseline covariates such as age (adults versus adolescents), mean blood pressure and albuminuria. A consistent reduction in the risk of retinopathy was found in all subgroups, in both the primary and secondary intervention cohorts.

Data are presented below (see section 'Improved glycaemic control and development of clinical proteinuria in patients with type 1 DM and microalbuminuria', p. 75) on the five RCTs that analysed the effect of intensive treatment on progression from microalbuminuria to clinical proteinuria. One of these studies was the microalbuminuric subgroup reported on by the DCCT and discussed above. Evidence on progression of retinopathy was sought from the remaining four studies. In Bangstad,[198] retinopathy was not one of the study end-points. The MCS[199] was not designed to investigate the effect of intensive therapy on the progression of retinopathy. Changes in retinopathy, however,

were stated to be similar in the two treatment groups. Retinopathy was assessed in the 2-year Steno 2 study reported by Feldt-Rasmussen and colleagues,[173] but the only reported finding was that two patients in each treatment group developed proliferative changes requiring laser therapy. The nephropathy outcome in the microalbuminuric subset of patients studied by Reichard and Rosenqvist (SDIS) could be extracted from the article.[195] Over the 3-year intervention period, however, and in the full set of patients, there was no significant difference in retinopathy progression between treatment groups.

Conclusions

Examination of the effect of IIT on the incidence or progression of retinopathy in people with type 1 DM and microalbuminuria has not been a primary objective in any trial so far reported. Studies that have provided some secondary information on this aspect have lacked the power to provide a definitive result. The DCCT results, however, particularly with regard to progression of retinopathy in the secondary intervention cohort, are important and reassuring. Taken with the subgroup analysis of important baseline covariates (including albuminuria), they suggest that people with type 1 DM and microalbuminuria will experience as much benefit from intensive treatment as the majority of the cohort.

Improved glycaemic control and development of ESRD in patients with type 1 DM and microalbuminuria

As discussed in Systematic review 3 (Chapter 5), there is some evidence from observational studies that patients with type 1 DM and microalbuminuria have a significant excess risk of developing ESRD. At present, however, there is no direct evidence from RCTs that improving glycaemic control in patients with type 1 DM has any effect on the development of ESRD.

In the DCCT,[19] IIT delayed the onset and slowed the progression of retinopathy, nephropathy and neuropathy, as judged by effects on mostly surrogate end-points. The development of microalbuminuria was reduced by 39% and clinical proteinuria by 56%. The study included only 73 patients (5%) with baseline microalbuminuria. Following this trial, IIT has become the treatment of choice in type 1 DM and it is considered that any further trial addressing similar questions would be unethical. The published 3–4-year follow-up of the cohort enrolled in the EDIC study has shown that, despite the narrowing glycaemic separation, the benefits of intensive treatment persisted long after the actual period of such therapy.[245] Whether these findings will translate to a decrease in the development of ESRD will only be known after long-term follow-up of the EDIC cohort.

Improved glycaemic control and change in GFR in patients with type 1 DM and microalbuminuria

As discussed in Chapter 5 (see section 'Relationship between microalbuminuria and the fall in GFR in patients with type 1 DM', p. 51), patients with microalbuminuria appear to have a significantly greater fall in GFR, with time, than those with normoalbuminuria. In the paper by Klein and colleagues[34] the relative risk of a creatinine clearance decline of at least 3 ml per minute 1.73 m^{-2} per year in subjects with baseline microalbuminuria was 1.45 (95% CI 1.11 to 1.88). The confounding influence of other factors, such as age, duration of diabetes, HbA_{1c}, arterial blood pressure and smoking was allowed for in logistic regression models. The odds ratio for a 1% increase in glycated haemoglobin remained highly significant (1.22, 95% CI 1.12 to 1.34, $p < 0.0001$). Such studies suggest that controlling glycaemia may reduce the rate of decline of renal function in patients with type 1 DM. However, only RCTs can truly test this question.

Search results

The searches found 33 trial reports. Trials of at least 1 year's duration were sought, where GFR or creatinine clearance had been measured at the start and at the end of the study, and which included patients with microalbuminuria.

The earliest trials[246,247] did not include measures of urinary albumin or creatinine clearance and were therefore not relevant to the question. The Oxford study[248] measured creatinine clearance in a 2-year trial, but not urinary AER, and the study was not included. Bell[249] was a 30-week study only. Helve[251] was a cross-over study with only 6-month periods on continuous subcutaneous insulin infusion (CSII) and no urinary albumin data were reported. Neither study was selected. Christensen and colleagues[250] measured GFR, but all patients were normoalbuminuric. The Kroc Study Group[252,253] used CSII for IIT during only 8 months of treatment comparison. Although the majority of patients were studied again after

2 years, some had crossed over to the opposite treatment and thus neither article was included. In the Aarhus study,[254–256] patients were normoalbuminuric at entry and the study was not included. The first Steno study[262–264] was not included since no information on the microalbuminuric subset was provided in early publications. Although the microalbuminuric patients were described in a later combined analysis with Steno study 2,[266] this was after the randomisation had been broken.

This left 19 reports for consideration in either the review of change in GFR or the development of clinical proteinuria. There were multiple reports from the SDIS, reporting continuing follow-up at 18 months,[194] 3 years,[195,196] 5 years[192] and 7.5 years.[197] Since GFR and AER had been measured at the beginning and end of the study, one of the 3-year reports was selected.[195] This report was chosen because randomisation was modified after this time-point. None of the multiple reports from the Oslo study[257–261] was selected, as GFR had not been measured at baseline in the conventional treatment group (although it had in the two experimental groups). The Steno study 2 is relevant, as it included only microalbuminuric patients and GFR was measured. Of the multiple reports from this study,[173,265,266] a 2-year report[173] was selected, as randomisation was broken after this point. Of four reports from the DCCT and EDIC,[16,19,193,245] the nephropathy subgroup analysis was most relevant to the question.[193] Trial reports from Bangstad and colleagues[198] and MCS[199] were directly relevant and were selected.

Selected studies

Five articles were selected.[173,193,195,198,199] (*Table 36*).

Articles excluded

Twenty-eight articles were excluded.[16,19,192,194,196,197,245–266]

In the small study by Bangstad and colleagues,[198] patients with microalbuminuria were randomised to either intensive treatment by CSII ($n = 9$) or conventional therapy (multiple injections or two or three injections of insulin per day) ($n = 9$). Patients on CSII significantly ($p < 0.014$) improved their HbA_{1c} (mean decrease of 1.1 in $\%HbA_{1c}$), whereas no significant reduction was found in the CIT group. AER showed a slight increase in both groups. The GFR showed no significant change in either of the groups, but data were not shown in the article. In the SDIS,[195] GFR decreased significantly in both groups. In the CIT group five patients with normal GFR at entry had reduced GFR (<90 ml per minute) and microalbuminuria or clinical proteinuria after 3 years. This did not occur in the IIT patients. There was no correlation between reduction in GFR and changes in AER. However, although GFR was measured in the groups as a whole it was not reported separately in the microalbuminuric subset. In the much larger DCCT,[19] creatinine clearance was measured in both the primary prevention cohort (with normoalbuminuria and no retinopathy at baseline) and the secondary prevention cohort (early retinopathy at baseline and 10% of patients with microalbuminuria). For the primary, secondary or combined cohorts, there were no significant differences in creatinine clearance between treatment groups during the study. There were a few cases in which subjects experienced development of clinical proteinuria and a reduced creatinine clearance of below 70 ml per minute 1.73 m^{-2}. In the secondary prevention group there were two of these events in the intensive and four in the conventional treatment groups. In the primary prevention group there were no events in the IIT group and one event in the CIT group. Although AER data are presented separately for the microalbuminuric subgroup of the DCCT,[193] there was no subgroup analysis of the change in creatinine clearance in patients stratified by AER. Five years after initiation of the DCCT, ^{125}I-iothalamate clearance studies were carried out on all new patients at entry, as an additional measurement of GFR. In the smaller number measured, there were no significant differences in iothalamate clearance in the intensive versus the conventionally treated groups, in either the secondary prevention or primary prevention cohort, but patients stratified by AER were not separately analysed. Only the Steno 2 study[173] and the MCS[199] have sufficient data to examine intervention effects on GFR in patients with microalbuminuria, and they are shown in *Table 37*.

In the Steno 2 study, GFR fell significantly during intensive therapy ($p < 0.01$), but remained unchanged in the conventional treatment group. In the MCS, GFR was significantly higher in the intensive therapy group at baseline, and fell significantly. In each of these two studies, there was no significant difference between end of study GFR when comparing intensive and conventional therapy.

Conclusions

It is thus not clear whether GFR, characteristically increased in young individuals with type 1 DM, is

TABLE 36 *Improved glycaemic control and change in GFR in patients with type 1 DM and microalbuminuria at baseline: characteristics of included studies*

Study	Setting	Total no. (MA)	Gender (% male)	Mean age (y)	Mean duration of diabetes (y)	GFR method	Urine collection	Definition of MA	FU (y)
Steno 2 (Feldt-Rasmussen *et al.*, 1986)[173]	Steno Hospital, Denmark	36 (36)	58	31	15	^{51}Cr-EDTA clearance	2 of 3 24 h	20–200 μg per minute	2
SDIS (Reichard and Rosenqvist, 1989)[195]	Stockholm, Sweden	95 (21)[a]	53	30	17	^{51}Cr-EDTA clearance	1 × 24 h	20–200 μg per minute	3
Bangstad *et al.*, 1994[198]	Oslo, Norway	18 (18)	NE	20	11	Inulin clearance	2 of 3 overnight samples	15–200 μg per minute	2–3
DCCT, 1995[193]	29 centres, USA and Canada	1441 (73)[a]	54	27	9 (secondary intervention cohort)	Creatinine clearance, iothalamate clearance	1 × 4 h	28–139 μg per minute	7
MCS, 1995[199]	Nine hospital clinics, UK	70 (70)	73	37	20	^{51}Cr-EDTA clearance	1 of 2 overnight samples	30–200 μg per minute	5

[a] Subgroup analysis.

TABLE 37 *Changes in GFR during improved glycaemic control in patients with type 1 DM and microalbuminuria*

Study	IIT		CIT		IIT vs CIT	
	Entry	End	Entry	End	End of study	Intervention effect (95% CI)
Steno 2 (Feldt-Rasmussen *et al.*, 1986)[173]	109 (4)[a]	99 (5)[a]	116 (5)[a]	114 (6)[a]	$p = 0.06$	8 (–14 to 28)[b]
MCS, 1995[199]	125[c] (112 to 138)	100[c] (90 to 110)	108[c] (99 to 118)	108[c] (98 to 118)	ns	1.25 (1.03 to 1.5)[d]

[a] Mean (SEM).
[b] Intervention effect is fall in GFR with IIT – fall with CIT.
[c] Geometric mean (95% CI).
[d] Intervention effect is % fall in GFR with IIT/% fall in GFR with CIT calculated from the geometric means and 95% CI.

reduced by long-term improvement in glycaemic control.[254,276] There is an acute effect that can be seen in the intensive therapy arms of two of the five RCTs selected.[173,199] However, GFR was generally quite stable in the conventional treatment groups of these trials and the absence of GFR decline may not have allowed detection of any beneficial effect of intensive treatment. Nonetheless, there was no significant difference between end of study GFR in intensive versus conventional groups among type 1 diabetic patients. The limited available evidence suggests that improved glycaemic control has little effect on GFR decline among type 1 diabetic patients whether or not they have microalbuminuria. Given the length of time required to see a decline in GFR, the generally short follow-up time probably accounts for the lack of conclusive evidence.

Improved glycaemic control and development of clinical proteinuria in patients with type 1 DM and microalbuminuria

The development of clinical proteinuria has long been held to herald the development of overt diabetic nephropathy. The paucity of data regarding the effect of improved glycaemic control on GFR decline and the development of ESRD is a reflection of the long follow-up period required to detect a significant change. Hence, more studies have sought evidence of an effect on the surrogate end-point, the development of clinical proteinuria.

Search results

Thirty-three trial reports were initially considered for inclusion in this review. The reasons for not selecting 14 of these articles are common to the previous section and to this section and will not be repeated. This left 19 articles for consideration.

In the Oslo study,[257] 45 patients with type 1 DM were randomised to treatment with CSII, multiple daily insulin injections (five or six daily, MDI) or conventional twice-daily insulin injections, CIT) for 2 years. Eleven of the 45 patients had above normal AER (>27 mg per 24 hours) and this did not change regardless of treatment group. No patient developed clinical proteinuria. However, the study was not included as the numbers of patients with microalbuminuria in the CIT arm could not be extracted. Reports with longer follow-up[258–261] could not be included as data were obtained well after randomisation had ended.

Steno 2[173,265,266] was a second and independent study, which focused on nephropathy in 36 type 1 diabetic patients randomised to CSII or CIT. All patients had microalbuminuria at baseline. At 2 years' follow-up,[173] HbA_{1c} on CSII was 7.2% compared with 8.6% on CIT ($p < 0.001$) and clinical diabetic nephropathy had developed in five patients on conventional treatment but in none of the CSII group ($p < 0.05$). This report was selected.

Among these pioneering trials, the largest was the SDIS.[194] Ninety-five patients with type 1 DM were randomised to either IIT with MDIs, a structured educational programme and home blood glucose monitoring, or to CIT. A significant proportion of the patients (21/95) were microalbuminuric at entry to the study. Multiple articles from the SDIS group reported continuing follow-up at 18 months,[194] 3 years,[195,196] 5 years[192] and nearly 8 years.[197] One of the 3-year reports was selected.[195] The AER increased significantly in the CIT group ($p = 0.033$), but not in the IIT group, with a significant difference between the groups after 3 years ($p = 0.031$). This report was chosen because randomisation was modified after this time-point and because data on the outcome of the microalbuminuric subset were presented.

In the DCCT,[19] the risk of clinical proteinuria (AER >200 μg per minute) was reduced by 56% ($p = 0.01$) in the secondary intervention cohort. A more detailed description of the effects of intensive treatment on nephropathy was subsequently published in 1995.[193] Among the 73 secondary intervention cohort subjects with microalbuminuria (AER 28–139 μg per minute) at baseline, the development of clinical proteinuria did not differ significantly between the two treatment groups. It was notable that in the secondary intervention cohort, the 6.5% rate of change of AER per year in the CIT group significantly exceeded that in the IIT group ($p < 0.001$). Results from this subgroup analysis were selected for the present review. The DCCT article on macrovascular events gives no further information on nephropathy outcome[16] and the EDIC study[245] was reported 4 years after randomisation ended.

The MCS group[199] examined the effect of intensive versus conventional therapy among patients with type 1 DM and microalbuminuria. Patients allocated to intensive therapy received insulin by CSII or MDI, while the majority of patients allocated to CIT received two daily injections of insulin. Six patients in each treatment

group progressed to clinical proteinuria. After 6 months of intensive treatment, HbA_{1c} fell from 10.3% to 8.9% ($p < 0.001$), while in the CIT group HbA_{1c} levels remained unchanged throughout. The glycaemic separation grew progressively less with time and a significant difference between treatment groups could not be sustained after 3 years. In part, this may be explained by cross-over to different therapy arms. However, as patients received their assigned therapy for 92% of the time they were in the study and losses to follow-up were acceptably low, this study was selected for the present overview.

Bangstad[198] was a small RCT (18 patients were randomised) in type 1 DM patients with microalbuminuria. The primary objective of the study was the investigation of progression of kidney morphological changes and AER was a secondary end-point. Patients on CSII improved their mean HbA_{1c} from 10.1% to 8.6% ($p = 0.01$), while there was no significant reduction in the CIT group (10.1% versus 9.7%). The increment in basement membrane thickness and matrix expansion was significantly larger in the group randomised to CIT during a period of 2–3 years and was positively correlated with HbA_{1c}; this study was selected. DCCT[193] was also selected as the microalbuminuric subgroup was described separately.

Selected studies

Five articles were selected.[173,193,195,198,199]

Articles excluded

Twenty-eight articles were excluded.[16,19,192,194,196,197,245–266]

Baseline characteristics of the five included studies are shown in *Table 36* as the studies selected are the same as those for change in GFR. *Table 38* shows the effects of improved glycaemic control on development of clinical proteinuria in type 1 DM patients with microalbuminuria. Losses to follow-up were very low in general, but reached 14% in the intensive treatment group of the MCS. Meta-analysis (*Figure 25*) gave an overall relative risk of 0.6 (95% CI 0.3 to 1.2) with no significant heterogeneity.

Conclusions

Whether considered individually or in combination, none of the five included studies showed a significant treatment effect on the progression from microalbuminuria to clinical proteinuria. Parving[200] examined the same trials and concluded that intensive treatment showed no statistically significant impact on the distribution of normoalbuminuria, microalbuminuria and clinical proteinuria, despite inclusion of the 5-year results of the SDIS,[192] which were recorded some years after randomisation had ended. A reduction of 40% was observed, but this was not significant because the studies were small. The DCCT[19] reported a 56% risk reduction in development of clinical proteinuria by intensive treatment in type 1 diabetic patients with predominantly normoalbuminuria, which was significant. There was also strong evidence for the prevention of microalbuminuria among patients with baseline normoalbuminuria in the DCCT.

The findings suggest that intensive treatment in type 1 patients with microalbuminuria is likely to have a limited effect on the prevention of clinical proteinuria. Other therapies, such as reduction of blood pressure, may be more effective at this point in the clinical course of diabetic nephropathy. This should not detract, however, from the strong likelihood that the clinical course of the more prevalent diabetic complications, early retinopathy and neuropathy, may improve with intensive treatment of hyperglycaemia.

Introduction to studies of glycaemic control in patients with type 2 DM

A number of studies identified a strong independent association between hyperglycaemia and rate of development of microvascular complications in patients with type 2 DM, after controlling for such factors as duration of diabetes, blood pressure and body weight.[277] One of the largest and most comprehensive prospective observational studies was the WESDR.[106] It followed up a population-based sample of patients with adult-onset diabetes, stratified by insulin use or non-use, for 10 years. Results revealed an exponential relationship between worsening glycaemic control (as indicated by increasing HbA_{1c}) and the incidence of retinopathy, nephropathy and neuropathy.[106,107] In the WESDR study, HbA_{1c} was also associated with mortality from diabetes, ischaemic heart disease and stroke.[270] However, only RCTs can test whether lowering blood glucose reduces the incidence of diabetic complications in type 2 DM, and there are five trials that make a major contribution to answering this question in relation to several end-points studied here.

UGDP

In the University Group Diabetes Program (UGDP) study,[278] 823 patients with type 2 DM

TABLE 38 *Improved glycaemic control and development of clinical proteinuria in patients with type 1 DM and microalbuminuria: glycaemic separation achieved and events and risk estimates*

Study	IIT HbA_{1c} (%)	CIT HbA_{1c} (%)	IIT CP/total	CIT CP/total	Crude RR (95% CI)
Steno 2, (Feldt-Rasmussen *et al.*, 1986)[173]	7.2	8.6	0/18	5/18	0.09 (0.01 to 1.53)
SDIS (Reichard and Rosenquist, 1989)[195]	7.4	9.0	1/8	5/13	0.32 (0.05 to 2.30)
Bangstad *et al.*, 1994[198]	8.6	9.7	1/9	1/9	1.00 (0.07 to 13.64)
DCCT, 1995[193]	7.2	9.1	4/38	6/35	0.61 (0.19 to 2.00)
MCS, 1995[199]	8.9[a]	9.8	6/36	6/34	0.94 (0.34 to 2.65

[a] This was the nadir after 6 months of treatment; a significant difference in total HbA_{1c} between intensive and conventionally treated groups was not maintained beyond 3 years.

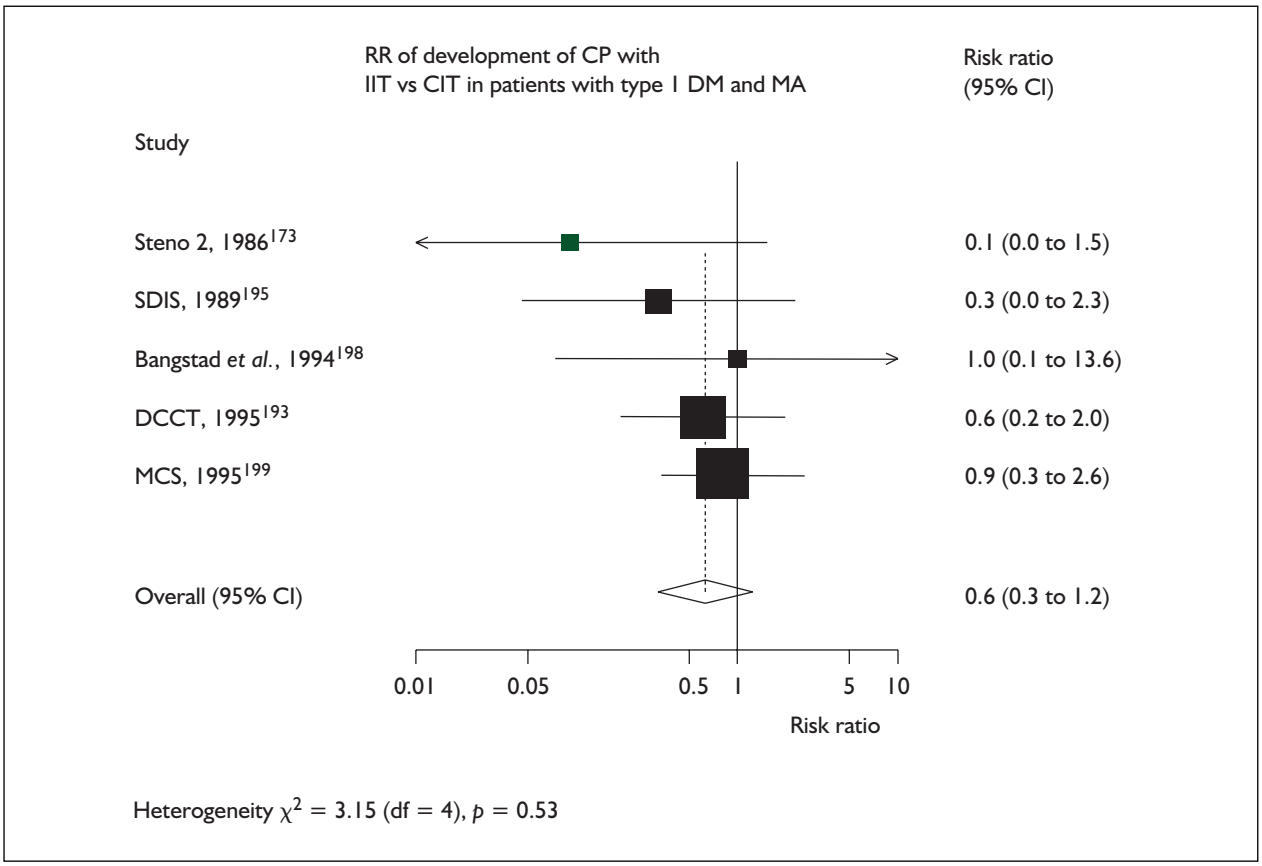

FIGURE 25 *Forest plot for relative risk of developing clinical proteinuria with IIT versus CIT in patients with microalbuminuria at baseline and type 1 DM*

were randomly assigned to placebo, tolbutamide and fixed-dose insulin or variable-dose insulin, and there were 200 subjects in each treatment group. At the time, HbA_{1c} was not available as a method for measurement of chronic hyperglycaemia and the difference in glucose control was, at most, 1.7 mmol l^{-1}. However, urine albumin was not measured in this study.

Kumamoto

The second controlled trial in patients with type 2 DM was the Kumamoto study.[235] Although much smaller, the Kumamoto study was similar in design to the DCCT. One-hundred and ten lean Japanese subjects were randomly assigned to either IIT (multiple insulin injections) or CIT. The mean HbA_{1c} values over 6 years were significantly lower

in the IIT group than in the CIT group (7.1% versus 9.4%, $p < 0.001$). Fifty-five patients with no retinopathy and normoalbuminuria (AER <30 mg per 24 hours) formed the primary prevention cohort. The mean (SD) AER was 14 (13) mg per 24 hours. The other 55 patients showed early retinopathy, had AER < 300 mg per 24 hours and formed the secondary prevention cohort. Mean (SD) AER was 43 (78) mg per 24 hours. The proportion of patients with baseline microalbuminuria (30–300 mg per 24 hours) in the secondary prevention cohort is not stated, but was not high given the mean AER. The HbA_{1c} separation between treatment groups was close to 2% and there was a significant reduction in the incidence of the microvascular complications of diabetes. Thereby, there was evidence that the findings of the DCCT also extended to patients with type 2 DM.

VA Cooperative Study
In the feasibility trial of the Veterans Affairs Cooperative Study,[279] 153 male patients with type 2 DM were randomly assigned to either intensive or standard treatment for 3 years. Losses to follow-up did not exceed 9%. In total, 38% of patients had microalbuminuria at entry and they were evenly assigned to both treatment groups. A 2% separation in HbA_{1c} between study groups was maintained for the mean follow-up period of 27 months, but the study was limited by its size and relatively short duration. The full Veterans Administration Diabetes Trial (VADT) is now proceeding, and will include 1700 men and women with established type 2 DM.[280]

DIGAMI
In the Diabetes and Insulin in Acute Myocardial Infarction (DIGAMI) trial, 620 patients (84% with type 2 DM) were randomised within 24 hours of an acute MI to either IIT or standard treatment.[281] HbA_{1c} fell significantly with intensive insulin treatment (fall of 1.1% on intensive treatment versus 0.4% on standard treatment at 3 months and 0.9% versus 0.4% at 1 year).

UKPDS
Initiated in 1977, the UKPDS[139] was designed to establish whether intensive blood glucose control would reduce the risk of microvascular or macrovascular complications in people with type 2 DM. It included 3867 people, median age 54 years, newly diagnosed with type 2 DM and inadequately controlled by diet alone. Patients were randomised to conventional treatment (diet alone) or intensive treatment with either a sulphonylurea or insulin. Obese patients were randomised to conventional treatment, metformin, sulphonylurea or insulin. Intensive treatment designed to achieve near normal glycaemia was compared with conventional therapy. Over a 10-year period, the median HbA_{1c} achieved on intensive therapy was 7.0%, compared with 7.9% on conventional therapy. A random urine albumin concentration >50 mg l^{-1} was used to define microalbuminuria. Clinical-grade proteinuria was defined as a urine albumin concentration greater than 300 mg l^{-1}. Unlike the DCCT, which focused primarily on surrogate end-points, the UKPDS used mostly 'hard' end-points. Three aggregate end-points were used to assess differences between conventional and intensive treatment: any diabetes-related end-point, diabetes-related death and all-cause mortality. Compared with the conventional group, the risk in the intensive group was 12% lower (95% CI 1 to 21, $p = 0.029$) for any diabetes-related end-point. It was 10% lower (95% CI –11 to 27, $p = 0.34$) for any diabetes-related death and 6% lower (95% CI –10 to 20, $p = 0.44$) for all-cause mortality. Most of the risk reduction in the any diabetes-related aggregate end-point was due to a 25% risk reduction (95% CI 7 to 40, $p = 0.009$) in microvascular end-points, most of which was due to fewer cases of retinal photocoagulation. The UKPDS results establish that lowering blood glucose benefits retinopathy, nephropathy, and perhaps neuropathy.

General search strategy
This is described in detail in the first section of this chapter (p. 69).

Search results
For type 2 DM, the MEDLINE and EMBASE searches yielded a total of 406 potentially relevant articles (Appendix 3). After initial exclusions as previously described (first section of this chapter), only five potentially relevant RCTs were located: UGDP,[278] Kumamoto Study,[235] VA Cooperative Study,[282] DIGAMI[281,283] and UKPDS.[140]

Improved glycaemic control and CVD in patients with type 2 DM and microalbuminuria

A recent systematic review by Groeneveld and colleagues[284] has examined the relationship between blood glucose level and mortality in type 2 DM. Of the 27 eligible articles (mostly prospective observational studies), 23 showed a positive relationship. It was concluded that there is

a positive but rather weak relationship between measures of blood glucose control and the risk of mortality among patients with type 2 DM. However, only RCTs can test whether lowering blood glucose reduces the incidence of mortality or macrovascular disease.

Search results

The question of the effect of improved glycaemic control on CVD incidence has been addressed in two recent evidence-based reviews.[277,285] The searches found five RCTs that include data relevant to this question: UGDP,[278] Kumamoto Study,[235] VA Cooperative Study,[282] DIGAMI[281,283] and UKPDS.[140]

UGDP[278]

UGDP was the first major prospective trial to examine the effect of glycaemic control on CVD events.[278] No treatment group had lower mortality than the placebo group. Glucose lowering with insulin did not reduce CVD events and there was no significant difference in the rate of MI between intensive and conventional treatment groups. The observation was made, however, that use of tolbutamide (a sulphonylurea) was associated with significant excess mortality. The suspicion that glucose lowering with oral agents among patients with type 2 DM may be harmful has persisted for many years after this trial. Urine albumin was not measured in this study.

Kumamoto[235]

Patients with hypertension, hypercholesterolaemia or obesity were excluded. In consequence, there were only six patients with major cardiovascular, cerebrovascular and peripheral vascular events. Although the event rate in the intensive treatment group was half that of the conventional treatment group (0.6 versus 1.3 events per 100 person-years), this was not statistically significant.

VA Cooperative Study[282]

Many of the patients had prevalent CVD. There was a non-significant trend towards more major CHD events in the intensive than the standard treatment group. A further analysis of the results by the presence of microalbuminuria has been reported by Levin and colleagues.[21] Among patients with microalbuminuria at entry, the number of new macrovascular events did not differ between those treated by intensive compared with standard therapy. Unexpectedly, intensive therapy was associated with significantly more macrovascular events among patients entering without microalbuminuria. However, the study was limited by its size and short duration and a clearer picture should emerge from the ongoing full study which will include 1700 men and women with established type 2 DM.[280]

DIGAMI

IIT lowered mortality significantly over the first year and after a mean 3.5-year period of follow-up.[281,283] Two limitations to the generalisability of this study are the use of an initial insulin infusion in those patients randomised to improved glycaemic control, and the highly specific clinical setting. Urine albumin was not measured in this study.

UKPDS

There was no effect of better control by sulphonylureas or insulin on total CVD events over 10 years of follow-up. There was a trend towards a reduction in non-fatal MI ($p = 0.052$). Obese patients treated with metformin had a significant reduction in MI ($p < 0.01$), but the addition of metformin to sulphonylureas was associated with an increase in MI ($p < 0.039$). The relatively small improvement in glycaemic control and the complexity of the protocol limit clear interpretation of the data on CVD. Epidemiological analysis of the UKPDS data showed a continuous association between risk of cardiovascular (and microvascular) complications and glycaemia.[286] Such studies do not prove, however, that high blood glucose causes these complications, or that treatment to lower blood glucose would reduce the risk. There is no available information on the microalbuminuric subgroup.

Adverse effects

The treatment-specific adverse effects of intensive treatment include an increased frequency of hypoglycaemic episodes, weight gain and early worsening of angiopathy. The general adverse effects include greater patient inconvenience, increased cost and medical resource use.

Conclusions

The evidence on the effect of improved glycaemic control on CVD in patients with type 2 DM is limited and equivocal. Nonetheless, aggressive control of raised blood glucose with insulin and oral agents or both does not increase the risk of CVD, and may decrease this risk. There is no evidence as to whether or not the subset of diabetic patients with microalbuminuria shows any more or less benefit from this treatment.

Improved glycaemic control and retinopathy in patients with type 2 DM and microalbuminuria

The large population-based WESDR prospective observational study included 1780 people with type 2 DM, in whom the 10-year incidence and progression of retinopathy were assessed.[106] After controlling for other baseline covariates, HbA_{1c} was the most important risk factor for the incidence and progression of retinopathy. Such findings suggest that improvement of glycaemic control may reduce the incidence of retinopathy, but randomised clinical trials are required to test this.

Search results

Only two trials were located that addressed this question, the Kumamoto study[235] and the UKPDS.[139]

Kumamoto

All patients had direct ophthalmoscopy with pupil dilation, colour fundus photography and fluorescein angiography.[235] The degree of retinopathy was determined by two examiners, on a scale of 19 stages for both eyes. A change of at least two stages was used for incidence and progression. In the primary prevention cohort during the 6-year period, retinopathy appeared in two patients in the IIT group and eight patients in the CIT group. The cumulative percentage in the IIT group was significantly lower than in the CIT group (7.7% versus 32.0%, $p = 0.039$). In the secondary prevention cohort over the 6-year period, progression of retinopathy was found in five patients in the IIT group and 11 patients in the CIT group. The cumulative percentage of patients with progression was lower in the IIT group than the CIT group (19.2% versus 44.0%, $p = 0.049$). No subgroup analysis of retinopathy progression was carried out in the group of patients with microalbuminuria in the secondary intervention cohort.

UKPDS

Retinopathy was assessed by ophthalmoscopy with pupil dilation and by retinal colour photographs.[139] These were graded by external assessors using a standard scale; a two-step increase was defined as progression. The UKPDS used mostly 'hard' end-points. Of the three aggregate end-points used to assess differences between conventional and intensive treatment (any diabetes-related end-point, diabetes-related death or all-cause mortality), only one (any diabetes-related end-point) is considered here. Compared with the conventional group, the risk in the intensive group was 12% lower (95% CI 1 to 21, $p = 0.029$) for any diabetes-related end-point. Most of the risk reduction in the any diabetes-related end-point was due to a 25% risk reduction ($p = 0.009$) in microvascular end-points, most of which was due to fewer cases of retinal photocoagulation.

Surrogate end-points were also assessed every 3 years in the UKPDS. After 6 years of follow-up (and subsequently), a smaller proportion of patients in the intensive group than in the conventional group had a two-step deterioration in retinopathy (RR = 0.83, 95% CI 0.67 to 1.01, $p = 0.017$). Only 18% of the cohort was microalbuminuric at baseline, however, and there was no information available on retinopathy outcome in the microalbuminuric subgroup.

Conclusions

No RCT has specifically examined the effect of intensified glycaemic control on the incidence or progression of retinopathy in people with type 2 DM and microalbuminuria. Moreover, there is no available subgroup analysis from the large UKPDS. Both the Kumamoto study and UKPDS showed significant beneficial effects of improved glycaemic control on the incidence and progression of diabetic retinopathy in predominantly normoalbuminuric cohorts. There seems little reason to believe that people with type 2 DM and microalbuminuria would benefit any less from intensified treatment than the normoalbuminuric majority.

Improved glycaemic control and development of ESRD in patients with type 2 DM and microalbuminuria

As noted previously for patients with type 1 DM (see section 'Improved glycaemic control and development of ESRD in patients with type 1 DM and microalbuminuria', p. 72), there is no evidence from RCTs that improved glycaemic control in patients with type 2 DM and microalbuminuria has any effect on the development of ESRD. The largest trial examining the effect of improved glycaemic control on the risk of developing the complications of type 2 DM was the UKPDS.[139] Eighteen per cent of the cohort had microalbuminuria at entry. Less than 1% of all patients developed renal failure. The relative risk (of intensive treatment versus

conventional treatment) for death from renal disease was 1.63 (95% CI 0.21 to 12.49) and for renal failure 0.73 (95% CI 0.25 to 2.14), both being non-significant. There is no information available on the microalbuminuric subgroup. Further information may come from long-term follow-up of this cohort and from the ongoing VADT, a randomised trial of intensified insulin treatment in 1700 established type 2 diabetic patients.[280]

Improved glycaemic control and change in GFR in patients with type 2 DM and microalbuminuria

Five randomised trials have examined the effects of improved glycaemic control on the incidence of complications in patients with type 2 DM, and they are briefly described above (see section 'Improved glycaemic control and CVD in patients with type 2 DM and microalbuminuria', p. 78). UGDP,[278] the DIGAMI study[281,283] and the Kumamoto study[235] did not measure GFR and were not considered here.

UKPDS

The UKPDS[139] mainly focused on 'hard' end-points rather than surrogates. Nonetheless, a series of surrogate end-points was assessed, including a two-fold increase in serum creatinine. Intensive versus conventional therapy was associated with a significant reduction in the relative risk of a two-fold serum creatinine increase over 12 years (0.26, 95% CI 0.07 to 0.91, $p = 0.0028$). This was the treatment effect in the group as a whole and there is no subgroup analysis available in those with microalbuminuria at entry. There are no reports of creatinine clearance from the UKPDS.

VA Cooperative Study[21,282]

Creatinine clearance was calculated according to the method of Cockcroft and Gault.[287] In the groups with no microalbuminuria there was no significant reduction in creatinine clearance, regardless of treatment group. Only the group entering with microalbuminuria had a significant reduction in creatinine clearance at 2 years, averaging 17% in the IIT group ($p = 0.0001$) and 12% in the CIT group ($p = 0.009$). The decline in the microalbuminuria group approximated 12 ml per minute during the 2 years and was greater than that due to ageing during a 2-year period. In this study, the apparent benefit of improved glycaemic control on progression of microalbuminuria (see next section) did not extend to creatinine clearance, which deteriorated regardless of whether microalbuminuria was retarded.

Conclusions

There is evidence from one RCT[21,282] that intensified glycaemic control has little if any effect on GFR decline in type 2 diabetic patients with microalbuminuria. There is, therefore, a need for more evidence on the effect of glycaemic control on GFR in type 2 DM. The VA Cooperative Studies Program has recently initiated a trial on the effect of intensive glucose control on cardiovascular complications among patients with type 2 DM. Nephropathy will be a secondary end-point.

Improved glycaemic control and development of clinical proteinuria in patients with type 2 DM and microalbuminuria

Prospective observational studies show that people with type 2 DM and microalbuminuria are at increased risk for the development of clinical proteinuria (see section 'Relationship between microalbuminuria and the development of clinical proteinuria in patients with type 2 DM', p. 61). In some of the studies, poor glycaemic control was shown to promote progression. This is clearly demonstrated in the largest and most recent of these prospective studies.[86] Only RCTs, however, can definitively test whether improved glycaemic control will reduce the incidence of clinical proteinuria. Until recently, the lack of proof in type 2 DM meant that it was only possible to conclude that cautious application of the results of the DCCT seemed to be warranted.[243]

Search results

Only five RCTs have examined the benefit of lowering blood glucose on the incidence of diabetic complications in type 2 DM. One of these trials, UGDP,[278] took place before the prognostic significance of microalbuminuria was recognised and before measurements of HbA_{1c} became available. The DIGAMI study[281,283] focused on mortality as the end-point and did not report measurements of urinary albumin excretion. These two studies are described in more detail above (see section 'Introduction to studies of glycaemic control in patients with type 2 DM', p. 76). Three other trials, the Kumamoto Study[235] the UKPD study[139] and the VA Cooperative Study,[288] reported data of some relevance to the question and were included. The 6-year Kumamoto study

TABLE 39 *VA Cooperative Study: albuminuria status of patients at follow-up with and without microalbuminuria at entry*

Treatment group	NA at entry		MA at entry		
	n	MA at FU, *n* (%)	*n*	NA at FU, *n* (%)	CP at FU, *n* (%)
IIT	42	7 (17)	24	7 (29)	3 (12)
CIT	46	30 (65)	28	10 (36)	10 (36)
RR (IIT vs CIT)		0.26 (0.13 to 0.52)		0.82 (0.37 to 1.81)	0.35 (0.11 to 1.13)

has also been extended to 8 years of follow-up.[236] Since this was beyond the original planned randomisation period and there had been some cross-overs to alternative therapy, the 6-year follow-up study was selected.

Kumamoto[235]

During the 6-year follow-up of the primary prevention cohort, five patients in the CIT group and two in the IIT group developed microalbuminuria. Two patients in the CIT group and none in the IIT group developed clinical proteinuria. The cumulative percentage of patients showing progression of nephropathy (as defined) was significantly lower in the IIT group than in the CIT group (8% versus 28%, $p = 0.032$). In the secondary prevention cohort (which included a proportion of microalbuminuric patients), six patients in the CIT group and three in the IIT group developed microalbuminuria. Two patients in the CIT group but none in the IIT group developed clinical proteinuria. The cumulative percentage of patients showing progression of nephropathy was, again, significantly lower in the IIT group than in the CIT group (12% versus 32%, $p = 0.044$). In the combined cohort, intensive glycaemic control by IIT reduced the average risk of worsening in nephropathy by 70% (95% CI 14 to 89%). This study supports the hypothesis that glycaemic control will impact on the progression of nephropathy in patients with type 2 DM, but those with microalbuminuria were not separately analysed. However, patients were lean and insulin sensitive, and those with hypertension and abnormal plasma lipids were excluded. There was some concern, therefore, as to how far these findings apply to Caucasian type 2 diabetic patients, who are commonly obese and insulin resistant.

UKPDS[139]

Surrogate end-points were also assessed every 3 years in the UKPDS. Over a 12-year period, the relative risk (for intensive treatment) of progression to microalbuminuria was 0.67 (95% CI 0.53 to 0.86, $p = 0.00005$). For progression to clinical proteinuria the relative risk was 0.66 (95% CI 0.39 to 1.10, $p = 0.036$). Only 18% of the cohort was microalbuminuric at baseline, however, and there was no information available on outcomes in the microalbuminuric subgroup.

VA Cooperative Study

A further analysis of the results by the presence of microalbuminuria has been reported.[288] ACR was measured in 3-hour morning collections. Microalbuminuria was defined as an ACR between 0.03 and 0.30 mg g^{-1} (equivalent to 3.4 to 34 mg $mmol^{-1}$), while over 0.30 was classified as overt nephropathy (clinical proteinuria). The increase in the ACR from baseline to 24 months was significantly higher in the CIT group (difference 0.141) than in the IIT group (difference 0.040, $p = 0.043$). This suggests that intensive treatment was slowing, although not eliminating, the progression of urinary albumin excretion. The authors also examined the effects of treatment in subgroups defined by the presence or absence of microalbuminuria (*Table 39*).

In the normoalbuminuric group, intensive treatment for 24 months significantly reduced the rate of progression to microalbuminuria by nearly 75% (RR = 0.26, 95% CI 0.13 to 0.52, $p = 0.05$). However, while in the microalbuminuria group a reduction of 65% in the progression to clinical proteinuria was observed, this was not significant owing to the small number of patients with microalbuminuria at baseline.

Conclusions

These three studies provide some evidence that intensive treatment of hyperglycaemia in normoalbuminuric type 2 DM patients will, at least in a proportion, prevent the development of microalbuminuria. There is also some evidence that this treatment will reduce the rate of development of clinical proteinuria. Each study, however, only included a proportion of patients with microalbuminuria. Only one of these studies,

the VA Cooperative Study, specifically examined the effect of glycaemic control in those with microalbuminuria and this was in a subgroup analysis. That study was also limited by its size and short duration. There is, therefore, a need for more evidence on the effect of glycaemic control on the development of clinical proteinuria in patients with type 2 DM and microalbuminuria.

Improved glycaemic control and the development of complications in type 1 and type 2 DM: conclusions

Type 1 DM

In patients with type 1 DM and microalbuminuria there is no evidence as to whether or not improved glycaemic control has any effect on the incidence of CVD, the incidence or progression of retinopathy, the development of proliferative retinopathy, the development of ESRD or the decline in GFR. The results from trials carried out to date have failed to show conclusively that improving glycaemic control reduces the development of clinical proteinuria (RR = 0.6, 95% CI 0.3 to 1.2).

However in patients with type 1 DM not stratified by albuminuria status, improved glycaemic control may be beneficial with respect to CVD and is beneficial in reducing both the incidence and progression of retinopathy and the development of proliferative retinopathy. There are no data with respect to the development of ESRD and limited evidence showing little significant effect on GFR decline. DCCT provides convincing evidence of a beneficial effect in reducing the development of clinical proteinuria in a predominantly normoalbuminuric cohort and also of preventing the development of microalbuminuria.

Further evidence of the effect of improved glycaemic control should be available in future from the EDIC study. Evidence to date suggests that any benefit is irrespective of whether or not the patients have microalbuminuria.

Type 2 DM

In patients with type 2 DM and microalbuminuria, there is no evidence as to whether or not improved glycaemic control has any effect on the incidence of CVD, the incidence or progression of retinopathy or the development of ESRD. There is evidence from one trial that improved glycaemic control in this group has little if any effect on the decline in GFR and data on the progression to clinical proteinuria are inconclusive.

However, in patients with type 2 DM not stratified by albuminuria status, there is little evidence of improved glycaemic control reducing CVD, but good evidence of a beneficial effect on the incidence and progression of retinopathy. There is inconclusive evidence of any effect on the development of ESRD, but one trial showed a lesser decline in GFR with improved glycaemic control and there was some evidence for slowing the development of clinical proteinuria. In the studies included here there was strong evidence that improved glycaemic control prevented or slowed progression from normoalbuminuria to microalbuminuria, although this was not the focus of the analysis.

Chapter 7

Systematic review 5: In subjects with type 1 or type 2 diabetes and microalbuminuria, does treatment with antihypertensive drugs reduce the rate of development of secondary complications?

Introduction

There have been many studies looking at the benefits of treating hypertension among patients with type 1 or type 2 DM. Most have used very small numbers of patients and short follow-up periods, and very few indeed have studied the benefits of treating patients with microalbuminuria alone rather than in combination with patients who have clinical proteinuria. While the benefits of treating hypertension effectively are beyond doubt, the nature of this review was to identify whether targeting those patients with microalbuminuria gave any added benefit over treating hypertension per se in all patients with diabetes and to determine whether the use of antihypertensive agents in normotensive patients with microalbuminuria was beneficial. The situation is further complicated as treatment targets for hypertension in diabetes are reducing, thus diminishing the value of earlier studies. Some commentators have recently argued that treatment of hypertension among patients with diabetes should focus on normalising albumin excretion. These changing targets make interpretation of literature findings difficult.

Antihypertensive therapy and CVD in patients with type 1 DM and microalbuminuria

Search strategy

The search strategy for this section was to focus on the RCTs that have been carried out in patients with type 1 DM and microalbuminuria (Appendix 3). Hypertension in type 1 DM is intimately linked to the development of diabetic renal disease, and the onset of clinical proteinuria frequently occurs before hypertension.[289] As discussed in detail below (see section 'Antihypertensive therapy and development of clinical proteinuria in patients with type 1 DM and microalbuminuria', p. 88), this means that the majority of type 1 diabetic patients with microalbuminuria are still normotensive. Because of this, the focus of most trials has been in evaluating the renoprotective properties of ACE inhibitors and other antihypertensive agents in normotensive type 1 diabetic patients with microalbuminuria. Rather than seeking trials with a given end-point, all trials were sought that had been carried out in the above group of patients with type 1 DM and the study examined which end-points had been recorded that fell into the categories.

Search results

Search results are detailed below (see section 'Antihypertensive therapy and development of clinical proteinuria in patients with type 1 DM and microalbuminuria', p. 88). A number of studies examined the effect of antihypertensive therapy, particularly with ACE inhibitors, in patients with type 1 DM, but their main focus has been the effect on development or progression of nephropathy. The studies in microalbuminuric patients with type 1 DM have either not been large enough or were of insufficient duration to record changes in the more distant hard end-points of cardiovascular or renal disease. The only trials recording an effect of anti-hypertensive therapy on hard end-points in patients with type 1 DM are in high-risk patients with overt nephropathy,[290] who were predominantly hypertensive. Large intervention studies with the power to examine hard end-points have included mostly older patients with type 2 DM.

Conclusions

There are no data in either hypertensive or normotensive type 1 diabetic patients as to whether identifying those with microalbuminuria is of any added benefit with regard to the effect of antihypertensive therapy on CVD. It is reasonable to assume that hypertensive patients with microalbuminuria will derive as much benefit as other hypertensive patients with diabetes,

irrespective of urine albumin status. Whether there is any cardiovascular benefit for normotensive patients with microalbuminuria is unknown.

Antihypertensive therapy and retinopathy in patients with type 1 DM and microalbuminuria

Search results

Although it is known that increased blood pressure is an important risk factor for the development of retinopathy,[291] very few RCTs have examined the effect of antihypertensive therapy on the development and progression of retinopathy in normotensive and/or hypertensive patients with type 1 DM and microalbuminuria. The largest of these trials was the EUCLID study.[292] This study found that the ACE inhibitor lisinopril may decrease retinopathy progression in normotensive patients with type 1 DM. Only 15% of these patients were microalbuminuric at baseline, however, and progression of retinopathy was unrelated to albuminuria status. This article included a meta-analysis of four studies (including the EUCLID study); the overall odds ratio was 0.49 (95% CI 0.30 to 0.79) with no significant heterogeneity. The meta-analysis, however, included patients with both type 1 and type 2 DM with predominantly normoalbuminuria (since EUCLID was by far the largest study), as well as microalbuminuria and clinical proteinuria. Further large studies are in progress.

Conclusions

There are no data on whether or not identifying those patients with type 1 DM and microalbuminuria is of any added benefit with regard to the effect of antihypertensive therapy on the development or progression of retinopathy. The ongoing Diabetic Retinopathy Candesartan Trials (DIRECT) programme plans to recruit 4500 patients with type 1 or type 2 DM, to examine whether the angiotensin-2-receptor blocker candesartan will reduce the incidence and progression of diabetic retinopathy.[293]

Antihypertensive therapy and development of ESRD in patients with type 1 DM and microalbuminuria

Search results

No trials could be found that included this end-point.

Conclusions

There are no trial data on whether or not antihypertensive therapy in patients with type 1 DM and microalbuminuria, whether normotensive or hypertensive, is of any benefit with regard to the development of ESRD.

Antihypertensive therapy and change in GFR in patients with type 1 DM and microalbuminuria

Search results

Twelve studies were identified; Bakris[208] was excluded as the treatment was titrated using GFR as an end-point. Three papers reported on the MCSG study, of which two were excluded as incomplete.[201,202] The third article was a combined analysis of the two latter trials[203] and was selected. The EUCLID study[294] did not report GFR measurements and was not selected.

The eight included trials that enrolled normotensive microalbuminuric patients with type 1 DM and examined the effect of ACE inhibitors on GFR decline are shown in *Table 40*: Marre,[206] Mathiesen,[204] Chase,[207] MCSG,[203] Crepaldi, for the Italian Microalbuminuria Study Group (IMSG) in IDDM,[209] ATLANTIS,[295] Jerums [Melbourne Diabetic Nephropathy Study Group (MDNSG)][296] and Bojestig.[297] No trials were found that examined this end-point in hypertensive microalbuminuric patients with type 1 DM.

Meta-analysis

There was considerable baseline imbalance in GFR in some of the studies, leading to an overestimate of the treatment effect if only follow-up data are used. Allowance for this can be made by calculating the annual fall from baseline. These data were available directly for three studies and were estimated from the means and standard deviations from another two studies. The standard deviation of the fall for the estimated studies is likely to be an overestimate as it could not be calculated within each patient. However, the estimates of fall will be unbiased. The average difference in annual fall in GFR was –0.03 ml per minute (95% CI –1.65 to 1.60) (*Figure 26*), indicating no consistent treatment effect. There was no significant heterogeneity between the studies.

GFR in subjects developing clinical proteinuria during these studies

Mathiesen and colleagues[204] noted an increased annual rate of decline of GFR, measured by an

TABLE 40 *GFR in normotensive patients with type 1 DM and microalbuminuria: effect of ACE inhibitors*

	FU (y)	GFR in ACE-I group (ml per minute 1.73 m^{-2})				GFR in placebo group (ml per minute 1.73 m^{-2})			
		n	Initial mean (SD)	Final mean (SD)	Annual fall (95% CI)	*n*	Initial mean (SD)	Final mean (SD)	Annual fall (95% CI)
Marre *et al.*, 1988[206a]	1	10	131 (90–158)[d]	124 (110–234)[d]	NS	10	129 (104–195)[d]	109 (80–192)[d]	$p < 0.05$
Mathiesen *et al.*, 1991[204a]	4	21	126 (24)	123 (NE)	1.4 (0 to 2)	23	129 (18)	127 (NE)	0.6 (–1 to 3)
Chase *et al.*, 1993[207bc]	2	7	92 (13)	85 (5)	–3.9 (–9.0 to 1.2)	9	90 (15)	90 (34)	0 (–24.5 to 24.5)
MCSG, 1996[203b]	2	116	95 (38)[e]	93 (43)[e]	1.4 (–2.6 to 5.3)	119	95 (35)[e]	84 (43)[e]	6.4 (–2.5 to 10.2)
IMSG (Crepaldi *et al.*, 1998[209ac])	3	32	113 (16)	109 (19)	1.3 (–1.6 to 4.2)	34	110 (15)	105 (15)	1.7 (–0.8 to 4.4)
ATLANTIS, 2000[295a]	2								
(5 mg dose)		32	109 (29)	NE	ns	37	100 (23)	NE	ns
(1.25 mg dose)		32	104 (26)	NE	ns				
MDNSG (Jerums *et al.*, 2001[296a])	5	9	95 (21)[e]	90 (27)[e]	1.0 (–1.4 to 3.4)	7	90 (19)[e]	82 (13)[e]	1.3 (–0.9 to 3.5)
Bojestig *et al.*, 2001[297a]	2								
16 (5 mg)		16	100 (69–134)[d]	104 (57–135)[d]	ns	16	108 (49–138)[d]	102 (60–173)[d]	ns
19 (1.25 mg)		19	100 (63–144)[d]	95 (61–132)[d]					

[a] GFR estimated with exogenous marker.
[b] GFR estimated with endogenous marker.
[c] Fall estimated from initial and final means and SD.
[d] Median and range.
[e] SD estimated from either the standard error or the confidence interval.
ACE-I, angiotensin-converting enzyme inhibitor.

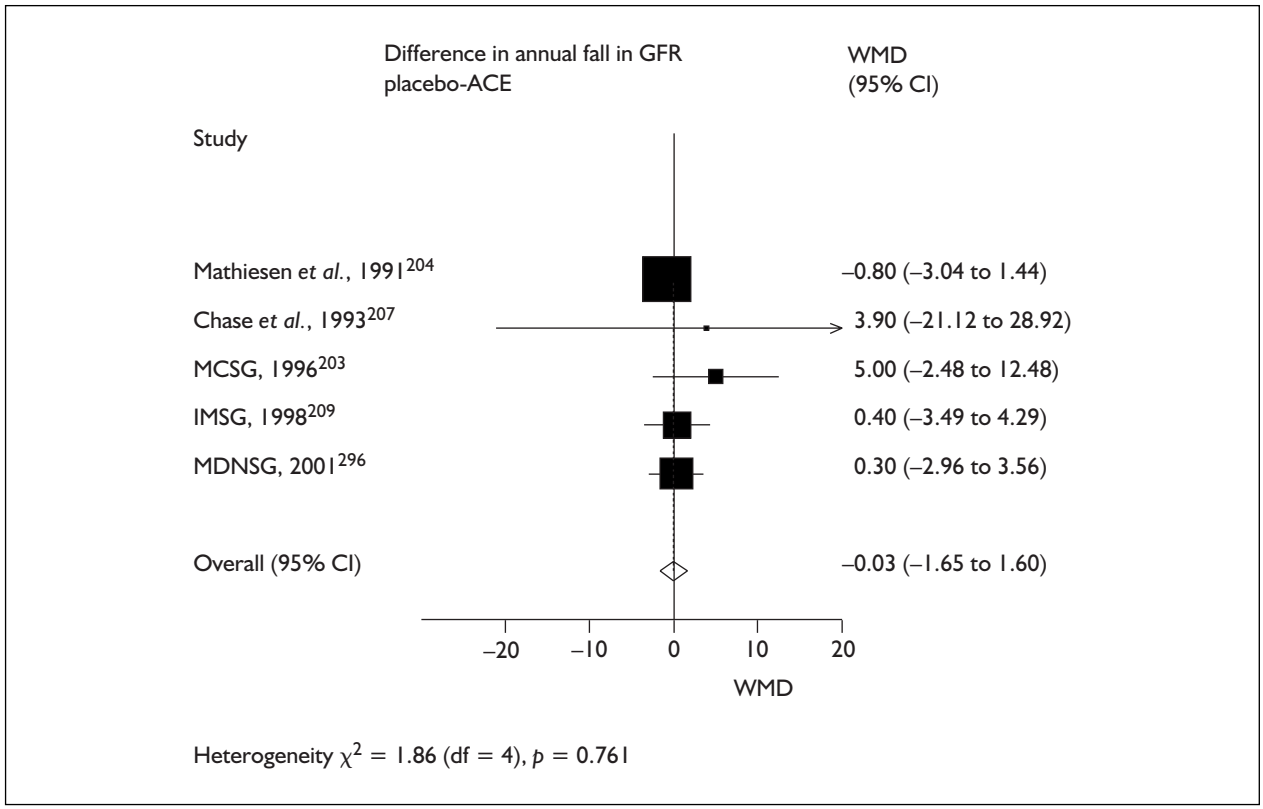

FIGURE 26 *Forest plot for difference in annual fall in GFR between ACE inhibitor and placebo in normotensive patients with type 1 DM and microalbuminuria*

isotopic method, in the group of patients who developed clinical proteinuria compared with those who did not progress. In contrast, Viberti and colleagues,[201] using creatinine clearance, found no significant fall in GFR among patients who, independently of treatment, progressed to clinical proteinuria. This question was not addressed in any of the other selected articles.

Conclusions

There is no evidence that the use of ACE inhibitors in normotensive patients with type 1 DM and microalbuminuria has any effect on GFR over and above that seen in the placebo group, although it may be that the follow-up period was too short.

Antihypertensive therapy and development of clinical proteinuria in patients with type 1 DM and microalbuminuria

Blood pressure is known to be slightly higher, although still within the normal range, in patients with type 1 DM when microalbuminuria develops.[298,299] In the early 1980s, Mogensen and colleagues[300] proposed a five-stage classification of the renal changes and lesions accompanying the development of nephropathy in type 1 DM. This classification has been recently updated by the author.[301] In stage 1, at the diagnosis of diabetes, there is an acute renal hypertrophy and hyperfunction with increased GFR; AER may be increased but this is reversible by insulin treatment and blood pressure is normal. In stage 2, patients are normoalbuminuric (AER <20 μg per minute) with blood pressure as in the background population, GFR remains increased, and on renal biopsy there is an increased basement membrane thickness. In stage 3, the stage of incipient diabetic nephropathy, AER is 20–200 μg per minute, typically after 6–15 years in around 35% of patients. GFR is still above normal and there is further basement membrane thickening and mesangial expansion. At this third stage, blood pressure may rise by around 3 mm per year if untreated. Stage 4, clinically overt diabetic nephropathy, develops in around 35% of patients after 15–25 years; there are clear structural renal abnormalities and GFR declines at around 10 ml per minute per year. Blood pressure may be high, increasing by around 5 mm per year unless treated. At stage 5, after 25–30 years the final outcome of ESRF is reached, GFR is below 10 ml

per minute, there are advanced renal structural changes and blood pressure is high if untreated.

It was originally shown by Mogensen[302] and by Parving and colleagues[303] that antihypertensive therapy could lower proteinuria and reduce the rate of decline of GFR in patients with type 1 DM with overt nephropathy. Subsequently, patients with type 1 DM and microalbuminuria and normal blood pressure were examined in early clinical trials, with patients acting as their own controls.[304] It was found that antihypertensive treatment with β-blockers could lead to regression of microalbuminuria. ACE inhibitors were also introduced in the 1980s. Theoretically, they have some particular advantages in diabetes; for example, they have no impact on glycaemia or plasma lipids. The concept of a specific renoprotective action of ACE inhibitors was introduced by Björck and colleagues.[305] They found that enalapril treatment of patients with type 1 DM and diabetic nephropathy for 2 years reduced AER and reduced the rate of decline of GFR when compared with doses of metoprolol (a β-blocking agent) that were equally effective in reducing systemic blood pressure. Initially, the concept of renoprotection included three facets: diminution of AER increase, prevention of GFR decline, and an effect that was over and above that derived from lowering of systemic blood pressure. Such effects are consistent with the experimental evidence for local inhibition of the renin–angiotensin system in the kidney.[306]

A subsequent large clinical trial by the Collaborative Study Group[290] further examined the question of whether the ACE inhibitor drug captopril has kidney-protecting properties independent of its effect on blood pressure in patients with type 1 DM and established diabetic nephropathy. Patients received antihypertensive therapy other than ACE inhibitors or calcium antagonists during the trial, as required clinically. Compared with placebo, captopril treatment was associated with a 50% reduction in the combined end-point of death, dialysis and renal transplantation, which was suggested to be independent of the small difference in blood pressure between the groups.

The benefit of ACE inhibitors in the earliest clinical manifestation of diabetic nephropathy, microalbuminuria, was demonstrated by Marre and colleagues[206] who showed that ACE inhibition with enalapril lowered AER in normotensive patients with type 1 DM and microalbuminuria. A subsequent series of RCTs largely confirmed these findings. The introduction of ACE inhibitors has been a major step forward in diabetes care and they are now recommended for the treatment of patients with type 1 DM and microalbuminuria, even if normotensive.[167] The question arises, what proportion of patients with type 1 DM and microalbuminuria is normotensive?

Perhaps the largest Europe-wide assessment of arterial blood pressure in patients with type 1 DM was carried out in the EURODIAB IDDM Complications Study.[307] This was a cross-sectional study examining 3250 randomly selected type 1 diabetic patients from 31 diabetes clinics in 16 European countries between 1989 and 1990. Hypertension was defined as SBP greater than or equal to 140 mmHg or DBP greater than or equal to 90 mmHg or the current taking of antihypertensive medication. Overall, 24% of patients had hypertension, with 10% of patients on blood pressure-lowering drugs. The crude prevalence of hypertension increased from 17% among those with normoalbuminuria to 29% in those with microalbuminuria and 69% of those with macroalbuminuria. Thus, the majority of people with type 1 DM and microalbuminuria were still normotensive by the criteria used in the study.

Search results

Patients with hypertension require treatment and this excludes the possibility of a placebo-controlled trial in the absence of other antihypertensive treatment. RCTs comparing different antihypertensive drugs in hypertensive patients with type 1 DM and microalbuminuria would be of significance, but no such trial met the criteria for selection. Previous meta-analyses examining the effect of antihypertensive treatment on proteinuria have often combined widely disparate studies, for example pooling studies in patients with type 1 and type 2 DM, non-diabetic subjects with diabetic patients, normotensive and hypertensive subjects, and patients with microalbuminuria and overt diabetic nephropathy.[308–313] Overall, these analyses concur in finding that ACE inhibitors may have particular advantages in the treatment of diabetic patients with increased urinary protein excretion. No evidence was found, however, for prevention of diabetic renal disease in these generally short-term studies. The use of ACE inhibitors in normotensive microalbuminuric subjects to prevent the development of overt diabetic nephropathy was not examined.

There were insufficient data available in long-term studies to enable review of the use of antihypertensive agents other than ACE inhibitors

in preventing progression of microalbuminuria to clinical proteinuria in normotensive patients with type 1 DM.

To be included, randomised trials of antihypertensive agents had to have enrolled initially normotensive, microalbuminuric patients with type 1 DM and have a duration of treatment of at least 1 year (to allow sufficient time for development of the end-point). The trial had to be placebo controlled or include a non-intervention group for comparison.

The searches identified a series of potentially relevant systematic reviews and meta-analyses and a series of reports of RCTs. The high-sensitivity, low-specificity MEDLINE search (Appendix 3) yielded 168 citations. The abstracts of these articles were examined and 145 articles were removed. The reasons for exclusion were as follows: short-term trial (42 articles), not an RCT (38), clinical proteinuria at baseline (19), cross-sectional study (19), duplicate in national journal or duplicate entry (5), normoalbuminuria at baseline (5), comparative study (2), other intervention (4), type 2 DM (4), review (3), cross-over trial (2), economic evaluation (1) and trial design (1). This left 23 articles for scrutiny.

The EMBASE search (Appendix 3) yielded 142 citations. Examination of the abstracts led to 123 articles being excluded. The reasons for exclusion were as follows: review (35 articles), short-term trial (33), clinical proteinuria at baseline (15), cross-sectional study (10), not an RCT (6), meeting report (5), no end-point of relevance (4), other intervention (3), renal structure (3), normoalbuminuria at baseline (3), trial design (2), animal study (1), cost-effectiveness (1), duplicate (1) and multifactorial intervention (1). Nineteen articles remained for scrutiny.

Of the 23 articles in MEDLINE and 19 in EMBASE, 18 were common to both. A search of the Cochrane Controlled Trials Register (Appendix 3) did not identify any additional articles: of the initial 86 citations the 13 selected were articles already identified on MEDLINE or EMBASE.

There were 23 articles where the full papers were examined. The reference lists of these papers were scrutinised and a further article was found.[324] The papers were: Laffel,[202] Viberti,[201] MCSG,[203] Bakris,[208] Chase,[207] Crepaldi,[209] Marre,[206,314] Mathiesen,[204,205] ATLANTIS,[295] O'Donnell,[315] Poulsen,[316,317] Bojestig,[297] ESPRIT,[318] MDNSG,[319] Jerums,[296] EUCLID,[320] Bilo,[321] Hallab,[322] Brichard,[323] Hansen[324] and Katayama.[325] A meta-analysis by the ACE Inhibitors in Diabetic Nephropathy Trialist Group 2001[326] was also retrieved.

The earliest trial was that reported in two publications on the same cohort by Marre and colleagues.[206,314] These studies were of 6 months' and 1-year's duration, respectively. There were four patients with type 2 DM, but the majority had type 1 DM. The 1-year study was selected.[206] Chase[207] and Bakris[208] were initially selected for review. The 4-year study by Mathiesen and colleagues[204] was selected rather than the 8-year follow-up of the same cohort[205] because of a more complete report. Brichard[323] was not an RCT. Hallab[322] was a comparison between two antihypertensive agents. Hansen[324] was a subset of patients included in the European Microalbuminuria Captopril Study Group (EMCSG),[201] and to avoid double counting was not selected. Bilo[321] was a very small study (six subjects on ACE inhibitor, five on placebo) with no extractable information on progression to overt nephropathy. Moreover, there were considerable imbalances at baseline: mean HbA_{1c} was much lower in the placebo group and AER much higher than in the ACE inhibitor treatment group. The study was not selected. Two relatively large trials of the effect of captopril on progression to clinical proteinuria have been reported, Viberti[201] for the EMCSG and Laffel[202] for the North American Microalbuminuria Study Group (NAMSG). As these two trials used a very similar design, a combined analysis of the two studies has also been reported.[203] The two individual trials were selected for review.

An article by Crepaldi and colleagues[209] for the Italian Microalbuminuria Study Group in IDDM (IMSG), comparing lisinopril or nifedipine with placebo, was also selected. For the purposes of the meta-analysis, only the ACE inhibitor group was compared with placebo. Two articles were available from the MDNSG.[296,319] Both articles compared the effects of the ACE inhibitor perindopril with nifedipine. The earlier article was not selected, however, as it included patients with both type 1 and type 2 DM and did not include a placebo control group. The later article[296] was a new study that included three treatment arms: perindopril, nifedipine and placebo. For the meta-analysis only the perindopril and placebo groups were compared. O'Donnell and colleagues[315] included normotensive microalbuminuric patients with type 1 and type 2 DM in their randomised double-

blind trial of lisinopril versus placebo. As results could not be separately assessed by type of diabetes, the article was not selected. The European Study for the Prevention of Renal Disease in Type 1 DM (ESPRIT)[318] included some patients with overt nephropathy (eligibility criterion was an AER between 30 and 1500 μg per minute) and was therefore not selected. The large, multicentre EUCLID study[294] was selected for review, although microalbuminuric patients only made up a subset and supporting information was limited.

Two other recent trials reported by the ATLANTIS Study Group[295] and Bojestig and colleagues[297] for the PRIMA Study Group were also selected, although the latter article reported no events in either treatment or placebo groups. Katayama and colleagues[325] examined the effects of two different ACE inhibitors in comparison with placebo in a randomised controlled study in Japanese patients with type 1 DM. Since both microalbuminuric and clinically proteinuric patients were enrolled (e.g. the mean ± SD baseline AER in the placebo group was 619 ± 750 μg per minute) and separate results for these groups were not presented, the article was not selected. Poulsen and colleagues[317] reported a post-hoc analysis of 58 patients with AER between 20 and 70 μg per minute treated for 2 years in two randomised, placebo-controlled, double-blind studies of the effects of lisinopril. One of these trials had already been selected,[209] and to avoid double counting the post-hoc analysis was not selected. The second of these trials was reported in another article by Poulsen and colleagues.[316] The focus of this article was exercise-induced albuminuria. Only the lower segment of the spectrum of microalbuminuria was examined and the pre-exercise results were presented in a figure, from which results could not reliably be extracted. The authors did not respond to a request for clarification and the study was therefore not selected. The meta-analysis by the ACE Inhibitors in Diabetic Nephropathy Trialist Group[326] was also selected for scrutiny.

Articles excluded

Thirteen articles were excluded.[203,205,314–319,321–325]

Meta-analysis

Tables 41–43 present some characteristics of the 11 trials that evaluated the development of clinical proteinuria among normotensive patients with type 1 DM and microalbuminuria treated with ACE inhibitor or placebo (or no intervention). In total, 671 patients were included. The average follow-up was 2 years (range 1–4 years). Four studies used captopril, three used lisinopril, two used ramipril and one study each enalapril or perindopril. In two trials, a low and a standard

TABLE 41 *ACE inhibitors and development of clinical proteinuria in normotensive patients with type 1 DM and microalbuminuria: interventions and blood pressure at entry*

Study	No. of subjects at entry to trial	FU (y)	ACE-I (daily treatment)	Blood pressure at entry (mmHg)
Marre *et al.*, 1988[206]	20	1	Enalapril 20 mg	<160/95
Mathiesen *et al.*, 1991[204]	44	4	Captopril 25 rising to 100 mg (Thiazide after 30 months)	<160/95
Chase *et al.*, 1993[207]	16	2	Captopril 100 mg	<140/90
Bakris *et al.*, 1994[208]	15	2	Lisinopril 100 mg	"Normotensive"
EMCSG (Viberti *et al.*, 1994)[201]	88	2	Captopril 100 mg	<145/90 if age <35 y <160/95 if age ≥ 35 y
NAMSG (Laffel *et al.*, 1995)[202]	137	2	Captopril 100 mg	<140/90
EUCLID, 1997[320]	73	2	Lisinopril 10 mg	SBP <156 DBP <90
IMSG (Crepaldi *et al.*, 1998)[209]	66	3	Lisinopril 10 mg	SBP ≥ 115 and ≤ 140 DBP ≥ 75 and ≤ 90
ATLANTIS, 2000[295]	134	2	Ramipril 1.25 mg (44) Ramipril 5 mg (44)	<150/90 if age <50 y <165/90 if age 50–65 y
MDNSG (Jerums *et al.*, 2001)[296]	23	3	Perindopril 8 mg	<140/90 if age <40 y <160/90 if age ≥ 40 y
Bojestig *et al.*, 2001[297]	55	2	Ramipril 1.25 (19) Ramipril 5 mg (18)	DBP <90

TABLE 42 *ACE inhibition and development of clinical proteinuria in normotensive patients with type 1 DM and microalbuminuria: characteristics of patients at baseline*

	Age (y)		Duration (y)		Gender (% male)		HbA_{1c}		AER (mg per 24 hours)	
Study	**ACE-I**	**Placebo**	**ACE-I**	**Placebo**	**ACE-I**	**Placebo**	**ACE-I**	**Placebo**	**ACE-I**	**Placebo**
Marre *et al.*, 1988[206]	39	39	17	18	60	60	8.4[a]	8.2	124	81
Mathiesen *et al.*, 1991[204]	31	27	19	17	52	48	8.4	8.3	82	105
Chase *et al.*, 1993[207]	22	20	14	12	100	56	8.8	8.0	135	159
Bakris *et al.*, 1994[208]	28	25	9	7	38	57	8.2	8.5	132	170
EMCSG (Viberti *et al.*, 1994)[201]	32	31	16	18	57	54	9.0	8.6	75	75
NAMSG (Laffel *et al.*, 1995)[202]	32	33	18	18	53	48	7.6	8.0	89	89
EUCLID, 1997[320]	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
IMSG (Crepaldi *et al.*, 1998)[209]	38	37	19	19	66	68	8.2	8.9	78	127
ATLANTIS, 2000[295]	40	40	19	23	63	87	12.1[b] 11.3[c]	10.7	72	85
MDNSG (Jerums *et al.*, 2001)[296]	35	28	21	15	31	70	8.5	9.2	95	95
Bojestig *et al.*, 2001[297]	39	38	22	21	78	78	7.2	7.4	99	148
Average	31	29	16	15	54	57	8.6	8.6	98	113

[a] Total HbA_1.
[b] Lower dose of Ramipril.
[c] Higher dose of Ramipril.

TABLE 43 *Effect of treatment with ACE inhibitor compared with placebo on MAP in normotensive patients with type 1 DM and microalbuminuria*

Study	**ACE-I baseline**	**ACE-I FU**	**ACE-I change**	**Placebo baseline**	**Placebo FU**	**Placebo change**	**Difference in change (Placebo – ACE-I)**
Marre *et al.*, 1988[206]	100	90	–10	99	98	–1	9
Mathiesen *et al.*, 1991[204]	95	89	–6	93	92	–1	5
Chase *et al.*, 1993[207]	91	95	+4	90	91	+1	–3
Bakris *et al.*, 1994[208]	96	86	–10	94	102	+8	18
EMCSG (Viberti *et al.*, 1994)[201]	93	90	–3	92	93	+1	4
NAMSG (Laffel *et al.*, 1995)[202]	92	88	–4	92	95	+3	7
EUCLID, 1997[320]	NE	NE	NE	NE	NE	NE	
IMSG (Crepaldi *et al.*, 1998)[209]	97	88	–9	98	93	–5	4
ATLANTIS, 2000[295]	95 (1.25 mg) 96 (5.0 mg)	92 94	–3 –2	94	97	+3	6 5
MDNSG (Jerums *et al.*, 2001)[296]	98	90	–8	95	98	+3	11
Bojestig *et al.*, 2001[297]	93 (1.25 mg) 93 (5.0mg)	95 94	+2 +1	93	96	+3	1 2

TABLE 44 *Relative risk of development of clinical proteinuria for normotensive patients with type 1 DM and microalbuminuria: ACE inhibitor versus placebo*

Study	ACE-I CP/total	Placebo CP/total	Crude RR (95% CI)
Marre *et al.*, 1988[206]	0/10	3/10	0.14 (0.01 to 2.45)
Mathiesen *et al.*, 1991[204]	0/21	7/23	0.07 (0.00 to 1.20)
Chase, 1993[207]	1/6	1/9	1.50 (0.11 to 19.64)
Bakris *et al.*, 1994[208]	0/8	2/7	0.18 (0.01 to 3.18)
EMCSG (Viberti *et al.*, 1994)[201]	4/46	12/46	0.33 (0.12 to 0.96)
NAMSG (Laffel *et al.*, 1995)[202]	4/70	13/73	0.32 (0.11 to 0.94)
EUCLID, 1997[320]	3/45	6/34	0.38 (0.10 to 1.40)
IMSG (Crepaldi *et al.*, 1998)[209]	2/32	7/34	0.30 (0.07 to 1.35)
ATLANTIS, 2000[295]	6/88	5/46	0.63 (0.20 to 1.95)
MDNSG (Jerums *et al.*, 2001)[296]	1/13	3/10	0.26 (0.03 to 2.11)
Bojestig *et al.*, 2001[297]	0/37	0/18	NC
Meta-analysis (2002), 11 studies	**21/376**	**59/310**	**0.36 (0.22 to 0.58)**

TABLE 45 *Relative risk of regression from microalbuminuria to normoalbuminuria in normotensive patients with type 1 DM: ACE inhibitor versus placebo*

Study	ACE-I NA/total	Placebo NA/total	RR (95% CI)
Marre *et al.*, 1988[206]	5/10	0/10	11.0 (0.7 to 176)
Mathiesen *et al.*, 1991[204]	5/21	2/23	2.7 (0.6 to 12.6)
Chase, 1993[207]	1/6	0/9	4.3 (0.2 to 91)
Bakris *et al.*, 1994[208]	6/8	0/7	11.6 (0.8 to 174)
IMSG (Crepaldi *et al.*, 1998)[209]	5/32	1/34	5.3 (0.7 to 43)
ATLANTIS, 2000[295]	14/88	2/46	3.7 (0.9 to 15.4)
MDNSG (Jerums *et al.*, 2001)[296]	7/13	0/10	11.8 (0.8 to 185)
Bojestig *et al.*, 2001[297]	0/37	0/18	NC
Meta-analysis (2002), 8 studies	**43/215**	**5/157**	**5.3 (2.5 to 11.5)**

dose of ramipril were separately compared with placebo.[295,297] There was an average of 54% men in the treatment groups and 57% in the placebo groups, with average baseline age, duration of diabetes, HbA_{1c} and AER being similar between groups. Mean arterial pressure (MAP) was calculated as DBP plus one-third of pulse pressure.

Of the 376 patients randomised to treatment with an ACE inhibitor in 11 trials, 21 (5.6%) developed clinical proteinuria. By comparison, of the 310 patients randomised to the placebo or no treatment arm of these studies, 59 (19.2%) developed clinical proteinuria (*Table 44*). The overall relative risk was 0.36 (95% CI 0.22 to 0.58), with no significant heterogeneity between studies (*Figure 27*). The funnel plot shows no evidence of publication bias (*Figure 28*).

Regression of microalbuminuria to normoalbuminuria

Data on the number of microalbuminuric patients who reverted to normoalbuminuria in the ACE inhibitor-treated groups compared with those treated with placebo or no intervention were available in eight of the 11 studies (*Table 45*). None of the eight trials, individually, showed a significant increase in relative risk for patients treated with ACE inhibitor. The overall relative risk, however, was significantly increased (5.3, 95% CI 2.5 to 11.5), with no significant heterogeneity between studies (*Figure 29*). The funnel plot showed no evidence of publication bias (*Figure 30*).

Adverse events

The data on side-effects were not always complete, making a formal analysis difficult. There was no

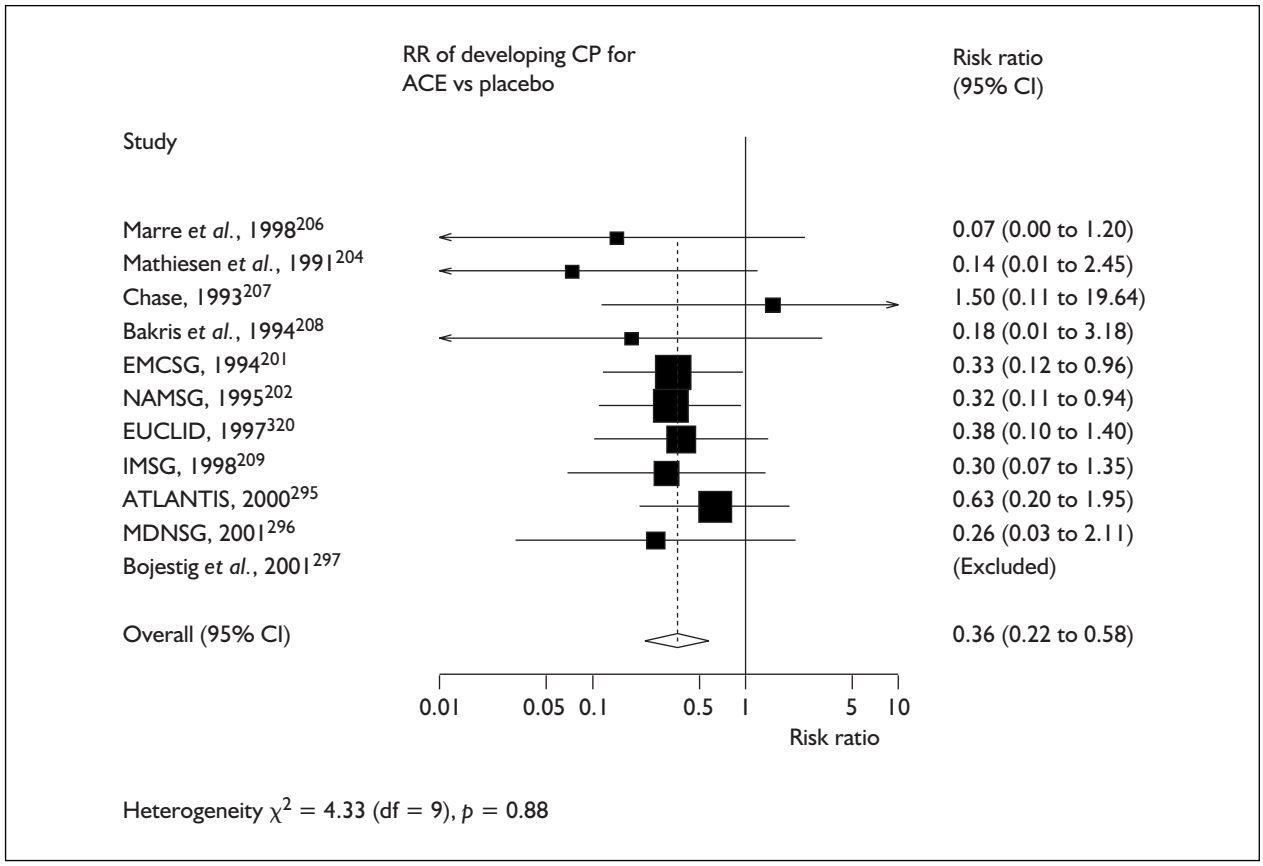

FIGURE 27 *Forest plot for relative risk of developing clinical proteinuria with ACE inhibitor compared with placebo in normotensive patients with type 1 DM and microalbuminuria*

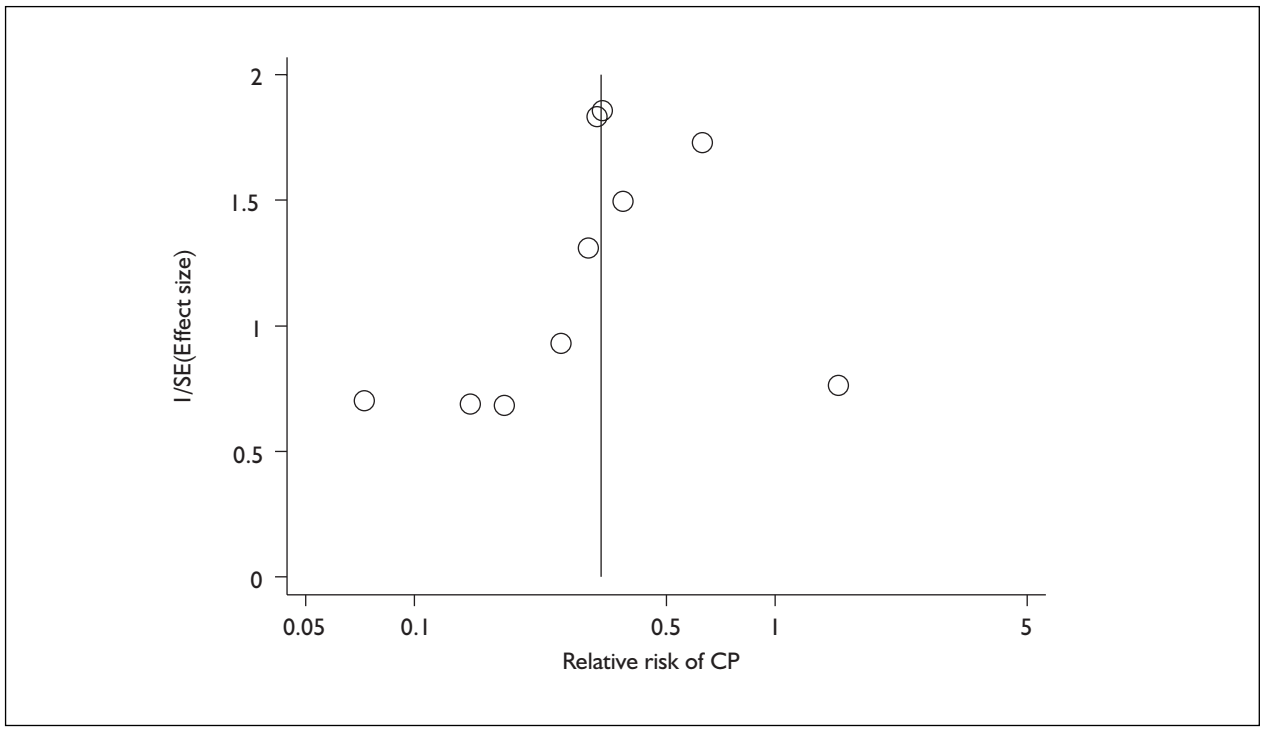

FIGURE 28 *Funnel plot for relative risk of developing clinical proteinuria with ACE inhibitor compared with placebo in normotensive patients with type 1 DM and microalbuminuria*

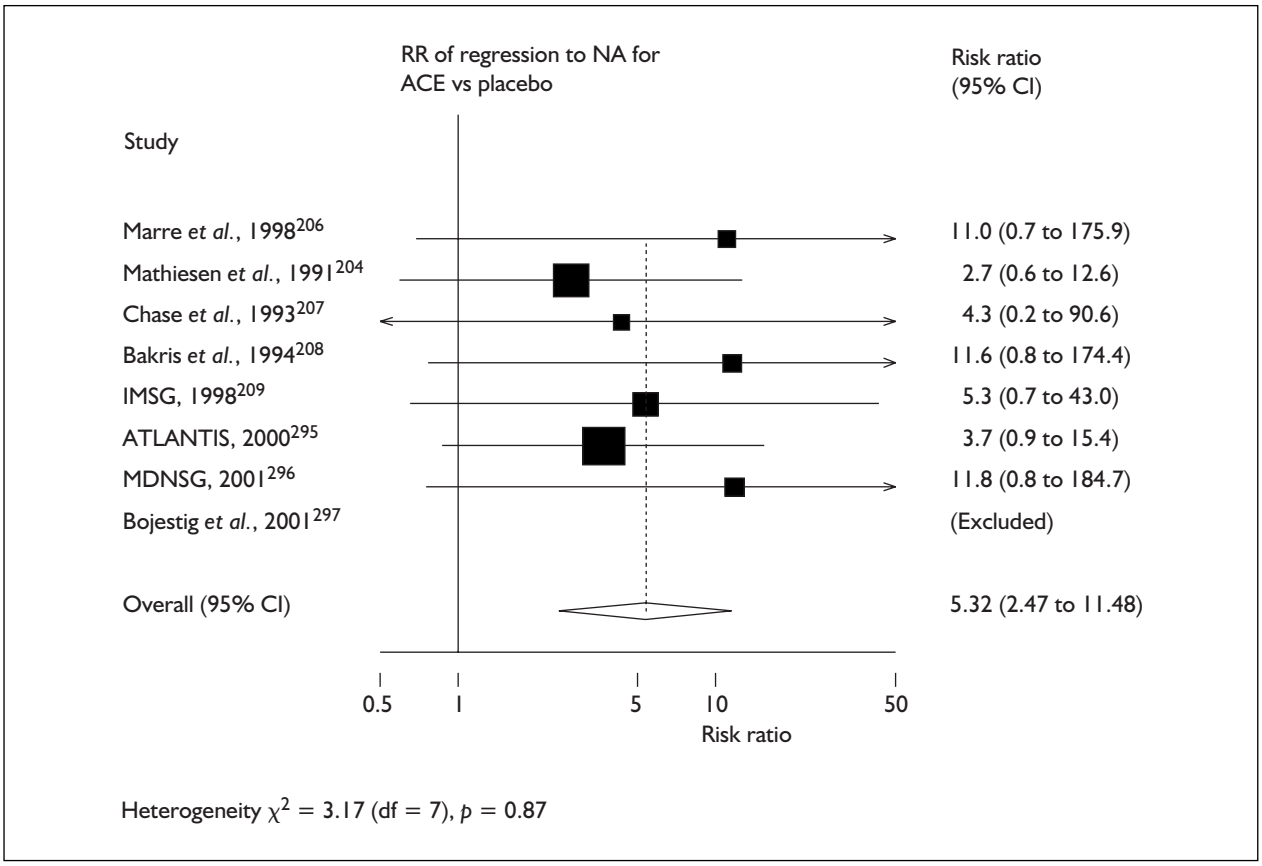

FIGURE 29 *Forest plot for relative risk of regression to normoalbuminuria with ACE inhibitor compared with placebo in normotensive patients with type 1 DM and microalbuminuria*

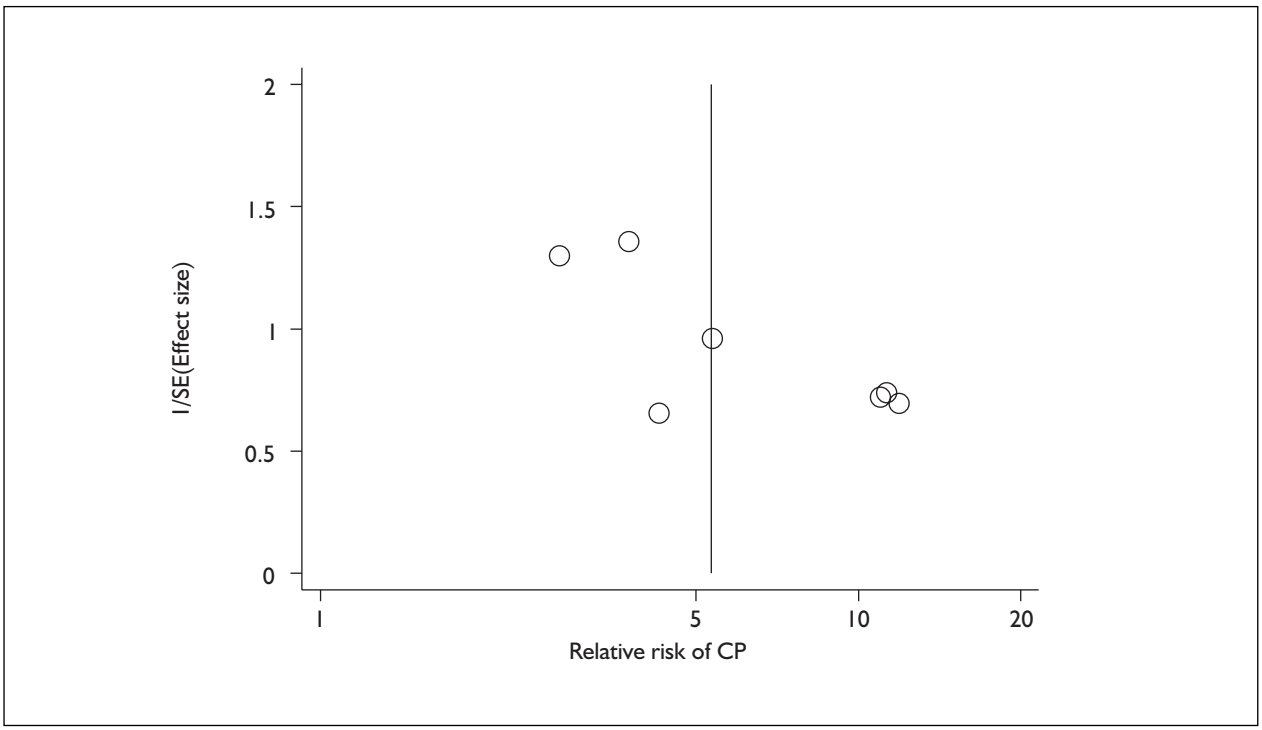

FIGURE 30 *Funnel plot for relative risk of showing regression with ACE inhibitor compared with placebo in normotensive patients with type 1 DM and microalbuminuria*

evidence of more serious events among patients treated with ACE inhibitors, although the ATLANTIS study reported five deaths in that group and none in the placebo group (*Table 46*). The deaths were not considered to be directly due to treatment. Intolerable dry cough is a known side-effect of ACE inhibitor treatment and this was reported in four trials. A meta-analysis of these four studies showed a slight, non-significant increase in cough compared with placebo: relative risk of cough of 1.2 (95% CI 0.8 to 1.9).

TABLE 46 *Adverse events reported in the included trials*

Study	Adverse events by group		Any other information on adverse events
	ACE-I	**Placebo (or non-intervention)**	
Marre *et al.*, 1988[206]	–	–	Not mentioned
Mathiesen *et al.*, 1991[204]	–	–	There were no side-effects
Chase., 1993[207]	–	–	Not mentioned
Bakris *et al.*, 1994[208]	–	–	One dropped out with dizziness and orthostasis (group not mentioned)
EMCSG, 1994[201]	Crescentic Glomerulonephritis (1) Mild skin rash (1)	Persistent cough (2)	
NAMCSG, 1995[202]	Neutropenia (1) Haemolytic anaemia (1) Orthostatic hypotension (1) Worsening of seizure control (1) Cough (20.5%)	Abnormal LFT (2) Vision disturbance (1) Hypotension (1) Hypertensive crisis (1) Cough (22.9%)	
EUCLID, 1997[320]	Serious adverse events (56) Cough (24 episodes in 21 individuals)	Serious adverse events (52) Cough (seven episodes in seven individuals)	
IMSG, 1998[209]	–	–	Lower limb oedema (2) and hyperkalaemia (1) were mentioned as withdrawals, but group not stated. No changes in serum potassium during follow-up for all patients
ATLANTIS, 2000[295]	Cardiovascular adverse events: 1.25 mg dose: 17% 5.0 mg dose: 18% MI: 1.25 mg (2) 5.0 mg (1) Chest pain: 1.25 mg (3) 5.0 mg (1) Deaths: (5)	Cardiovascular adverse events: 17% MI: (1) Chest pain: (5) Deaths (0)	No significant difference in reporting of adverse events between groups Deaths considered not directly due to treatment
MDNSG, 2001[296]	Lichen planus (1) Urticaria (1)	–	
Bojestig *et al.*, 2001[297]	1.25 mg dose: Arthralgia (1) 5.0 mg dose: Cough (1) Faintness (1)	No withdrawals from study	No significant difference between treatment groups in proportions of subjects reporting adverse events ($p = 0.80$)

LFT, liver function tests.

TABLE 47 *Absolute reduction in risk and numbers needed to treat (NNT) to prevent clinical proteinuria in normotensive patients with type 1 DM and microalbuminuria*

Study	FU (y)	Absolute risk reduction (95% CI)	NNT	Absolute annual risk reduction (95% CI)	NNT for 1 year
Marre *et al.*, 1988[206]	1	30 (2 to 58)	3	30 (2 to 58)	3
Mathiesen *et al.*, 1991[204]	4	30 (12 to 49)	3	8 (–3 to 180	12
Chase, 1993[207]	2	–6 (–42 to 31)	17 (to harm)	–3 (–29 to 24)	34 (to harm)
Bakris *et al.*, 1994[208]	1.5	29 (–5 to 62)	4	19 (–10 to 48)	5
EMCSG, 1994[201]	2	17 (2 to 32)	6	9 (–3 to 20)	12
NAMCSG, 1995[202]	2	12 (2 to 22)	8	6 (–2 to 14)	17
EUCLID, 1997[320]	2	11 (–4 to 26)	9	5 (–5 to 16)	18
IMSG, 1998[209]	3	14 (–2 to 30)	7	5 (–5 to 15)	21
ATLANTIS, 2000[295]	2	4 (–6 to 14)	25	2 (–6 to 10)	49
MDNSG, 2001[296]	3	22 (–10 to 54)	4	7 (–13 to 28)	13
Bojestig *et al.*, 2001[297]	2	0	NC	0 (–6 to 6)	NC
Meta-analysis (2002), 11 studies	**2.2**	**14 (8 to 20)**		**4 (1 to 7)**	**24 (14 to 91)**

Clinical impact: numbers needed to treat to prevent clinical proteinuria

Eleven studies were included in the meta-analysis of absolute risk reduction (*Table 47*). One study showed a negative effect of treatment and hence the entry in the NNT column is the number needed to harm. There was no significant heterogeneity for the annual risk reduction ($\chi^2 = 8.1$, $p = 0.62$) and overall absolute risk reduction was 4 (95% CI 1 to 7), giving an NNT of 24 patients for 1 year to prevent one case of overt nephropathy. Bojestig and colleagues,[297] reporting for the PRIMA Study Group, had no events in either intervention or control arms. While the estimate of difference is unambiguous the estimation of its standard error is difficult and may have been underestimated by the method of adding 0.5 to each cell. In the analysis, this study is given a large weight because of its small standard error. Omitting this study from the analysis gives a risk reduction of 6 (95% CI 2 to 9), leading to an NNT of 17.

Conclusions

In this meta-analysis of 11 RCTs carried out in normotensive patients with type 1 DM and microalbuminuria, treatment with ACE inhibitors reduced the incidence of progression to clinical proteinuria by 64% compared with placebo or no treatment. Consistency was high, as only one small trial suggested no benefit from ACE inhibitors. Several previous systematic reviews and meta-analyses have been carried out in this area. Only two of these, however, have provided risk estimates. The relative risk found in the present study and its precision, 0.36 (95% CI 0.22 to 0.58) compares closely with the relative risk of 0.35 (95% CI 0.24 to 0.53) found in a meta-analysis of nine trials by Kshirsagar and colleagues.[327] The latter review included patients with diabetes and microalbuminuria, but average baseline MAP was normal in only four trials. Seven of the trials were carried out in patients with type 1 DM and two trials in patients with type 2 DM. The other recent review, from the ACE Inhibitors in Diabetic Nephropathy Trialist Group,[328] was based on individual patient data from 12 trials and included, like the present review, only normotensive patients with type 1 DM and microalbuminuria. Such studies allow more reliable subgroup analyses. The odds ratio for risk of progression to clinical proteinuria was 0.38 (95% CI 0.25 to 0.57). The present findings were comparable when the results were expressed in the form of an overall odds ratio, 0.30 (95% CI 0.18 to 0.52).

As well as a reduced incidence of progression to clinical proteinuria, the present review found regression of microalbuminuria to normoalbuminuria to be over five times more likely in patients treated with ACE inhibitors (RR 5.3, 95% CI 2.5 to 11.5). Significantly higher regression to normoalbuminuria in normotensive patients with type 1 DM and microalbuminuria being treated with ACE inhibitors (OR 3.07, 95% CI 2.15 to 4.44) was also found in a previous meta-analysis.[328] Although two of the larger trials were excluded as there were no available data, there is no evidence of publication bias in the main analysis (clinical proteinuria). There may be

a small bias in the analysis of regression of microalbuminuria.

Neither of the two previous reviews providing overall risk estimates gave any estimate of the therapeutic effort needed to achieve the results. In the present meta-analysis it was estimated that 24 patients would have to be treated with ACE inhibitors for 1 year to prevent one additional case of clinical proteinuria.

Overall, unweighted MAP fell by about 4 mmHg in these mostly normotensive patients on ACE inhibitor therapy in comparison to a slight rise of 1 mmHg in the placebo or no treatment group. It seems unlikely, although it cannot be ruled out, that a 64% decrease in the incidence of clinical proteinuria could be caused by such a change in arterial pressure. It seems much more likely that ACE inhibitors have a specific renal effect beyond their antihypertensive effect. In the ACE Inhibitors in Diabetic Nephropathy Trialist Group report,[328] the AER was 50.5% (29.2 to 65.5%) lower in treated patients than in those receiving placebo. Adjustment for the small change in blood pressure only attenuated the treatment difference in albumin excretion rate to 45.1% (18.6 to 63.1%). That study also noted that treatment effect varied with baseline AER, being 74.1% and 17.8% among patients with AER levels of 200 and 20 μg per minute, respectively.

Antihypertensive therapy and CVD in patients with type 2 DM and microalbuminuria

Hypertension was identified as a strong risk factor for CVD in diabetic and non-diabetic patients in the Whitehall Study,[329] the Framingham Study[330] and the Multiple Risk Factor Intervention Trial (MRFIT).[331] The purpose of lowering blood pressure is to reduce cardiovascular events. Among patients with diabetes, there is the potential added benefit of reducing the burden of microvascular disease (retinopathy and nephropathy). Several large trials have addressed the question of the primary or secondary prevention of CVD by treatment of hypertension. Among the different classes of agents used, the ACE inhibitors are believed to be particularly effective in reducing the progression of nephropathy in diabetes, with effects that seem unexplained by blood pressure lowering alone. The benefits of controlling blood pressure have been well documented in large trials in general hypertensive populations, but less well documented in diabetic patients, who have often comprised only subgroups within the large trials.[332]

Search results

The search strategy for these sections is shown in Appendix 3. To be included, randomised trials of antihypertensive agents had to have enrolled initially normotensive, microalbuminuric patients with type 2 DM and have duration of treatment of at least 1 year (to allow sufficient time for development of the end-point). The trial had to be placebo controlled or include a non-intervention group for comparison. Randomised trials were also sought in hypertensive, microalbuminuric patients with type 2 DM that compared a particular antihypertensive agent with placebo, compared intensive versus moderate blood pressure control or compared two antihypertensive agents, in trials where treatment was for at least 1 year. Rather than seeking trials with a given end-point, all the trials were sought that had been carried out in the above groups of patients with type 2 DM, and the study examined which end-points had been recorded that fell into the categories that were sought (see the final section in this chapter, p. 103).

The searches identified only a limited number of large trials of potential relevance: Hypertension Optimal Treatment (HOT),[332] Fosinopril versus Amlodipine Cardiovascular Events Randomised Trial (FACET),[333] UKPDS,[334,335] Appropriate Blood Pressure Control in Diabetes (ABCD)[336] and the HOPE and MICRO-HOPE substudy.[337]

The HOT trial[332] reported a secondary analysis of the 1501 type 2 diabetic patients included in the study. There was a 51% reduction in major cardiovascular events in patients whose DBP target was below 80 mmHg compared with those whose target was below 90 mmHg. There is no available information on albuminuria status in these patients.

FACET[333] was not selected, as one of the exclusion criteria in that trial was an AER above 40 μg per minute, effectively removing many patients with microalbuminuria at baseline.

In the UKPDS,[334] 1148 patients with type 2 DM and hypertension were allocated to either tight blood pressure control (aiming at a BP of <150/85 mmHg) or less tight control (aiming at a BP of <180/105 mmHg) with a median follow-up of 8.4 years. There was a clinically important reduction in the risk of deaths related to diabetes and stroke as well as in microvascular end-points.

The baseline prevalence of microalbuminuria was 17% and no subgroup analysis of the microalbuminuric subset is available. A further UKPDS article examined the efficacy of captopril and atenolol in the group allocated to tight blood pressure control[335] and found that captopril and atenolol were equally effective in reducing the risk of macrovascular end-points. There was no subgroup analysis in the microalbuminuric subset.

In the ABCD trial,[336] 470 patients with type 2 DM and hypertension were randomised to intensive blood pressure control versus moderate control and followed for 5 years. Intensive therapy was associated with a lower incidence of deaths (5.5 versus 10%, $p = 0.037$), but no difference with regard to the progression of diabetic complications. The primary end-point was creatinine clearance and this was analysed according to the presence or absence of microalbuminuria. However, there was no subgroup analysis examining the relationship of microalbuminuria to cardiovascular end-points. The incidence of cardiovascular complications was also examined in those ABCD participants who were randomised to the calcium channel blocker nisoldipine or the ACE inhibitor enalapril.[338] A higher incidence of fatal and non-fatal MI was found with nisoldipine. There was no subgroup analysis examining the effect in microalbuminuric patients.

The HOPE study[337] included a substantial proportion of diabetic patients with hypertension (57%) and microalbuminuria (32%). The study examined whether the ACE inhibitor ramipril could lower the risk of cardiovascular and renal disease in diabetes. The study included 3577 people with diabetes (97% type 2) aged over 55 years (mean 65 years). Subjects had either a previous cardiovascular event or at least one cardiovascular risk factor. The study was therefore a mix of primary and secondary prevention. Patients were randomly assigned to ramipril 10 mg per day or placebo for an average of 4.5 years. Some results of the study are shown in *Table 48*.

The benefit of ramipril was apparent irrespective of whether subjects had a history of cardiovascular events, hypertension or microalbuminuria. The cardiovascular benefit was greater than that attributable to the small decrease in blood pressure. There has been a further analysis, by the presence of microalbuminuria, of the patients with and without diabetes in the HOPE study.[73] After controlling for randomisation to receive ramipril, the adjusted relative risk for microalbuminuria compared with normoalbuminuria was 1.97 (95% CI 1.68 to 2.31) for a combined end-point of MI, stroke or cardiovascular death, 2.15 (95% CI 1.78 to 2.60) for all-cause mortality and 3.70 (95% CI 2.64 to 5.17) for hospitalisation for congestive heart failure. The close association between microalbuminuria and these outcomes remained after controlling for other risk cardiovascular risk factors in the placebo and ramipril groups.

Conclusions

In people with diabetes, antihypertensive treatment reduces cardiovascular events. Aggressive control of blood pressure with target DBP below 80 mmHg reduces cardiovascular morbidity and mortality compared with less tight control. One trial separately analysed the effects of treatment with an ACE inhibitor in patients with type 2 DM and microalbuminuria, and concluded that patients with microalbuminuria will obtain additional cardiovascular benefit from this therapy. Since the completion of data gathering for this review, another large RCT, DIABHYCAR, comparing low-dose ramipril (1.25 mg per day) with placebo (on top of usual treatment) for at least 3 years in patients with type 2 DM and persistent microalbuminuria or proteinuria, has been completed.[339] Despite a slight decrease in blood pressure and AER, this regimen had no effect on cardiovascular outcome. High doses of ramipril (and perhaps other blockers of the renin–angiotensin system) thus appear preferable to low doses in the prevention of cardiovascular events in high-risk patients.

TABLE 48 *Mixed primary and secondary prevention of cardiovascular events in patients with type 2 DM: the HOPE study*[337]

Intervention	Study type (duration)	Outcome	Events/sample size (%)		NNT (95% CI)
			Intervention	Control	
Ramipril 10 mg per day	RCT (4.5 y)	Total mortality	196/1808 (11%)	240/1769 (14%)	32 (19 to 83)
Ramipril 10 mg per day	RCT (4.5 y)	MI, stroke or CVD death	277/1808 (15%)	351/1769 (20%)	22 (14 to 49)

Antihypertensive therapy and retinopathy in patients with type 2 DM and microalbuminuria

Placebo-controlled trials in normotensive patients with type 2 DM and microalbuminuria

Full details of the three potentially relevant RCTs located[22,237,240] are described in the last section of this chapter.

Only one of these trials had any information on retinopathy in relation to treatment[237] and, using information from a further trial from the group,[340] was subsequently published by Rachmani and colleagues.[154] Two-hundred and fifty normotensive patients with type 2 DM and either normoalbuminuria or microalbuminuria were randomised to receive enalapril (10 mg per day) or placebo. New cases of retinopathy were recorded by annual fundoscopy for 5–6 years. The proportion of patients who developed retinopathy was significantly lower among those allocated to enalapril (9/126, 7.1%) than to placebo (23/124, 18.5%; $p = 0.024$). There was no significant difference in mean blood pressure between groups. There was no significant difference in the treatment effects when examined separately in normoalbuminuric and microalbuminuric patients.

Conclusions

The one available trial suggests that enalapril may have a beneficial effect on the development of retinopathy in normotensive type 2 DM patients with either normoalbuminuria or microalbuminuria. This was apparently independent of any blood pressure-lowering effect of enalapril. The methodology for evaluation of retinopathy was not objective, however, and further large studies using objective methods are in progress.

Trials comparing different antihypertensive agents and intensive versus moderate blood pressure control in normotensive patients with type 2 DM and microalbuminuria

No trials were found.

Conclusions

No appropriate trials were located within the search period (ending January 2002). Later in 2002, however, the ABCD trial[341] published results of intensive versus moderate DBP control in 480 normotensive (BP < 140/90 mmHg) type 2 diabetic patients. As described in the final section of this chapter, a proportion of patients had microalbuminuria. The intensive blood pressure control group showed significantly less progression of diabetic retinopathy ($p = 0.019$). The results were the same whether enalapril or nisoldipine was used as the initial antihypertensive agent.

Placebo-controlled trials in hypertensive patients with type 2 DM and microalbuminuria

Two trials were potentially relevant[241,342] and are described in detail in the last two sections of this chapter. Neither trial, however, assessed retinopathy in relation to treatment.

Conclusions

There is no available information from this trial category.

Trials comparing intensive versus moderate blood pressure control in hypertensive patients with type 2 DM and microalbuminuria

Two large trials were initially selected as having potentially relevant information: UKPDS[334] and ABCD[336]; they are described in detail in the last section of this chapter (p. 103).

In the ABCD trial,[336] retinopathy was assessed by objective methods. During the 5-year follow-up period 30% of patients randomised to intensive therapy versus 34% of those randomised to moderate therapy progressed by three or more steps, a non-significant difference ($p = 0.42$). The microalbuminuric subset was not separately analysed. In the larger UKPDS trial,[334] during 8 years of follow-up, and using objective methods for assessment of retinopathy, tight blood pressure control compared with less tight control was associated with a significant 34% reduction in risk of deterioration of retinopathy by two or more steps ($p = 0.004$); there was no subgroup analysis in those with microalbuminuria.

Conclusions

Two trials examining progression of retinopathy in relation to intensive blood pressure control disagreed regarding its effect, and neither study examined this in the microalbuminuric subset.

Trials comparing different antihypertensive agents in hypertensive patients with type 2 DM and microalbuminuria

Five potentially relevant RCTs were located.[335,336,343–345] They are described in detail in the last section of this chapter (p. 103).

Chan and colleagues[343] did not assess retinopathy in relation to treatment in their 1-year study. In the 3-year study from Lacourciere and colleagues[344] there was no assessment of retinopathy. Similarly, retinopathy was not an end-point in the large, multicentre 1-year trial reported by Agardh and colleagues.[345] The UKPDS[335] compared the effects of tight blood pressure control with captopril and atenolol in 1148 hypertensive patients with type 2 DM. Captopril and atenolol were similarly effective in reducing the progression of retinopathy over 9 years of follow-up. However, there was no analysis in the microalbuminuric subset. In the ABCD trial,[336] intensive blood pressure control (compared with moderate control) was less effective in reducing the risk of retinopathy progression, perhaps because of poorer glycaemic control. There was no significant difference in progression when comparing enalapril and nisoldipine as antihypertensive agents. Although subgroup analyses were performed in the normoalbuminuric and microalbuminuric subsets with some end-points, retinopathy was not included.

Conclusions

Two trials that have compared the effects of different antihypertensive agents on the progression of retinopathy showed no difference in outcome by agent used, but disagreed regarding the effect of treatment; there was no available information on any differential effects in the microalbuminuric subset.

Antihypertensive therapy and development of ESRD in patients with type 2 DM and microalbuminuria

Of all the RCTs examined in this review, only three (ABCD, UKPDS and HOPE) have the potential, in terms of size of study and length of follow-up, to provide information on development of the ESRD end-point in relation to microalbuminuria.

In the 5-year ABCD trial,[336] ESRD was not an end-point in any report from the study. In the UKPDS,[334] tight blood pressure control was compared with less tight control over a median period of 8.4 years. There were eight cases of renal failure in the 758 patient tight control group and seven cases in the 390 patients allocated to less tight control. The relative risk for tight control was 0.58 (95% CI 0.15 to 2.21). Similar results were recorded for death from renal failure. There was no subgroup analysis.

In the 4.5-year trial of ramipril versus placebo (on top of usual therapy) carried out in more than 3500 patients with DM (97% had type 2 DM and 56% had hypertension) in the HOPE study,[337] one of the outcomes was a requirement for renal dialysis. Dialysis was required in ten (0.5%) of the ramipril-treated patients and in eight (0.5%) of those on placebo. The relative risk reduction was not significant ($p = 0.70$). The benefit of ramipril in the HOPE study was noted irrespective of whether patients had hypertension or microalbuminuria.

Conclusions

There is no evidence of a beneficial effect of antihypertensive therapy on the development of ESRD and no available information on this end-point for the microalbuminuric subset.

Antihypertensive therapy and change in GFR in patients with type 2 DM and microalbuminuria

Placebo-controlled trials in normotensive patients with type 2 DM and microalbuminuria

The three trials selected[22,237,240] are described in detail in the next section (p. 103). Blood pressure was equivalent in both groups in these studies.

In a randomised, double-blind, placebo-controlled trial carried out in Israel, Ravid and colleagues[237] allocated 94 normotensive type 2 diabetic patients with microalbuminuria to receive enalapril 10 mg per day or placebo for 5 years. Reciprocal creatinine decreased by 1% (ns) of the initial value during 5 years in the enalapril group, but by 13% ($p < 0.05$) in the placebo group. The difference between the mean rate of decline in reciprocal creatinine differed between the two groups ($p < 0.02$).

In a study by Sano and colleagues,[240] 62 normotensive Japanese type 2 diabetic patients with microalbuminuria were randomised to receive either enalapril 5 mg per day or no treatment for 4 years. There were no significant changes in creatinine clearance in either group over the study period.

In a single-blind trial from India, Ahmad and colleagues[22] randomised 103 normotensive patients with type 2 DM and microalbuminuria to enalapril 10 mg per day or placebo for 5 years. As measured by inulin clearance, GFR remained unchanged in both groups over the study period.

Conclusions

The data are inconclusive as to whether treatment of normotensive, microalbuminuric type 2 diabetic patients with the ACE inhibitor enalapril was associated with better preservation of GFR.

Trials comparing different antihypertensive agents and intensive versus moderate blood pressure control in normotensive patients with type 2 DM and microalbuminuria

No trials were found.

Conclusions

No appropriate trials were located within the search period (ending January 2002). Later in 2002, however, the ABCD trial[341] published results of intensive versus moderate diastolic blood pressure control in 480 normotensive (BP < 140/90 mmHg) type 2 diabetic patients. As described in the next section, a proportion of patients had microalbuminuria. There was a significant effect ($p = 0.028$) of intensive therapy on progression from microalbuminuria to clinical proteinuria, but there was no change in creatinine clearance. The results did not differ when either the ACE inhibitor enalapril or the calcium channel blocker nisoldipine was used for intensive therapy.

Placebo-controlled trials in hypertensive patients with type 2 DM and microalbuminuria

Two trials were located.[241,342]

Lebovitz and colleagues[342] carried out a 3-year prospective, double-blind, placebo-controlled trial of enalapril (10–40 mg per day for a target DBP of 65–80 mmHg) in 165 hypertensive type 2 DM patients with normoalbuminuria, microalbuminuria or clinical proteinuria. Effects were assessed in relation to baseline albuminuria status. Enalapril decreased the rate of progression from microalbuminuria to clinical proteinuria (8/38 placebo-treated versus 2/30 enalapril-treated patients), even though blood pressure was equalised between groups. Among patients with microalbuminuria the rate of loss of GFR with time (measured by iothalamate clearance) in the placebo group ($n = 21$) was –0.416 ml per minute (SEM 0.192) compared with –0.003 (0.179) ($n = 17$) in patients treated with enalapril. This did not differ significantly, however, from the values in patients with normoalbuminuria, where the rate of GFR loss in the placebo group ($n = 19$) was –0.235 (SEM 0.15) compared with 0.386 (0.178) ($n = 18$) in the enalapril group. Baseline GFR was similar in the two groups. Thus, enalapril treatment had a significant effect in preserving GFR in both normoalbuminuric and microalbuminuric type 2 diabetic patients with hypertension.

The large (590-patient), multinational, randomised, double-blind, placebo-controlled, 2-year study of the angiotensin II receptor antagonist irbesartan, carried out by Parving and colleagues[241] is described in the next section p. 10. Creatinine clearance was a secondary end-point. There was a significant reduction in the rate of progression to clinical proteinuria in the irbesartan-treated groups (at both dose levels), but this was associated with no significant decline in creatinine clearance in either the irbesartan or placebo-treated groups, in whom blood pressure was nearly identical.

Conclusions

According to the limited available evidence, renal function remains stable in hypertensive type 2 diabetic patients with microalbuminuria treated with ACE-inhibitors (compared with a decline in placebo) or angiotensin II receptor blockers (also stable in the placebo group). The one study comparing treatment effects of an ACE inhibitor in normoalbuminuric and microalbuminuric subsets found equivalent benefit.

Trials comparing intensive versus moderate blood pressure control in hypertensive patients with type 2 DM and microalbuminuria

The two relevant trials located were the UKPDS[334] and ABCD[336] studies, described in detail in the following section.

In the UKPDS (17% had baseline microalbuminuria) there was no difference between 'tight' and 'less tight' blood pressure control on progression to clinical proteinuria during an 8-year follow-up. GFR was not assessed, but there was no change in plasma creatinine concentration between the two groups. It is unknown whether there was a differential effect in the normoalbuminuric and microalbuminuric subgroups, and the study was not selected.

In the 5-year ABCD trial, after the initial 1 year of antihypertensive treatment, creatinine clearance stabilised in both the intensive and moderate blood pressure control groups with either baseline normoalbuminuria or microalbuminuria (in contrast to the group with baseline clinical proteinuria, where creatinine clearance steadily declined on either therapy).

Conclusions

In one large RCT, when intensive blood pressure therapy was compared with moderate therapy in hypertensive type 2 patients for 5 years, no differences in creatinine clearance were found in either the normoalbuminuric or microalbuminuric subsets.

Trials comparing different antihypertensive agents in hypertensive patients with type 2 DM and microalbuminuria

The five RCTs located are described in detail in the next section.[335,336,343–345] They include normoalbuminuric, microalbuminuric and clinically proteinuric patients, or microalbuminuric patients alone. The UKPDS was not selected as there was no subgroup analysis of the microalbuminuric subset.

Chan and colleagues,[343] in a 1-year comparison of enalapril with the calcium channel blocker nifedipine in 89 hypertensive type 2 diabetic patients, found a significantly greater fall in AER in the microalbuminuric group randomised to enalapril compared with the group randomised to nifedipine. However, there was no difference in change in creatinine clearance between groups.

Lacourciere and colleagues[344] compared 3-year therapy with captopril with metoprolol (either with or without hydrochlorothiazide) in 74 hypertensive type 2 diabetic patients. In patients with microalbuminuria, AER fell significantly more on captopril than on metoprolol, despite similar changes in blood pressure. There was, however, no significant difference in GFR (estimated by plasma disappearance of labelled EDTA) between the two treatment groups.

In a multicentre study of the effects of 12 months of therapy with lisinopril or nifedipine in 335 type 2 diabetic patients with hypertension and microalbuminuria, Agardh and colleagues[345] found a significantly more beneficial effect of lisinopril on AER than nifedipine, despite similar effects on blood pressure. However, creatinine clearance did not change significantly on either treatment.

Within the ABCD trial,[336] 470 hypertensive type 2 diabetic patients had been randomised to intensive or moderate blood pressure control. Patients were further randomised to receive either enalapril or nisoldipine as the primary antihypertensive medication. Over the 5-year study, there were no significant differences in creatinine clearance in patients in either the normoalbuminuric or microalbuminuric subgroups, when comparing treatment with enalapril versus nisoldipine.

Conclusions

Four RCTs were located where ACE inhibitors have been compared with other antihypertensive agents in hypertensive, microalbuminuric patients with type 2 DM, three of these being subgroup analyses. There were no significant differences in GFR or creatinine clearance in these comparisons.

Antihypertensive therapy and development of clinical proteinuria in patients with type 2 DM and microalbuminuria

Hypertension is very common in people with type 2 DM and is often part of the metabolic syndrome.[346] Compared with normoglycaemic individuals, about twice as many people with type 2 DM are hypertensive (around 50%).[347] In the UKPDS, 4054 newly diagnosed patients with type 2 DM were considered for the Hypertension in Diabetes Study.[140] Of these patients, 38% had hypertension (defined by SBP ≥ 160 mmHg and/or DBP ≥ 90 mmHg or ≥ 150/85 mmHg in patients receiving antihypertensive treatment). When nephropathy develops, almost 70% of patients may have high blood pressure.[301] In contrast to patients with type 1 DM with microalbuminuria, patients with type 2 DM and microalbuminuria are often hypertensive. Therefore, studies evaluating the effects of ACE inhibitors in microalbuminuric patients with type 2 DM have often included a much higher proportion of patients with hypertension.[348] Clinical trials of the renoprotective properties of ACE inhibitors, or of other antihypertensive agents, have included normoalbuminuric, microalbuminuric or clinically proteinuric patients with type 2 DM with or without hypertension. This study focused on trials in patients with type 2 DM who were normotensive and microalbuminuric, or hypertensive and microalbuminuric.

Search results

To be included, randomised trials of antihypertensive agents had to have enrolled initially normotensive, microalbuminuric patients with type 2 DM and have duration of treatment of at least 1 year (to allow sufficient time for development of the end-point). The trial had to be placebo controlled or include a non-

intervention group for comparison. Randomised trials were also sought in hypertensive, microalbuminuric patients with type 2 DM, that compared a particular antihypertensive agent with placebo or compared two antihypertensive agents, in trials where treatment was for at least 1 year.

The searches identified a series of reports of potentially relevant RCTs or systematic reviews and meta-analyses. The systematic reviews were referred to earlier in this chapter (section 'Antihypertensive therapy and development of clinical proteinuria in patients with type 1 DM and microalbuminuria', p. 88). The MEDLINE search (Appendix 3) yielded 196 citations. The abstracts of these articles were examined and 168 articles were removed. The reasons for exclusion were as follows: short-term trial (44 articles), not an RCT (40), cross-sectional study (22), review (21), other interventions (15), clinical proteinuria at baseline (12), trial description (9), letter or comment (2), duplicate entry or duplicate in national journal (2) and economic evaluation (1). This left 28 trial reports for scrutiny.

The EMBASE search (see Appendix 3) yielded 199 citations. Examination of the abstracts led to 165 articles being removed. Reasons for exclusion were as follows: review (49), short-term trial (44), other interventions (16), clinical proteinuria at baseline (12), cross-sectional study (11), not an RCT (10), letter or comment (8), meeting report (6), trial description (5), duplicate (1), type 1 DM (1), multifactorial intervention (1) and economic evaluation (1). Thirty-four trial reports remained. Nineteen articles in the MEDLINE search were also among the 34 found in the EMBASE search. Therefore, from these two searches 43 articles were retrieved for further scrutiny (and from which all studies in the following sections were selected).

Placebo-controlled trials in normotensive patients with type 2 DM and microalbuminuria

Seventeen of the 43 articles were of potential relevance to the first part of the question (i.e. they focused on normotensive patients with type 2 DM and microalbuminuria) and were examined in detail. Five of the 17 articles were from Ravid and co-authors, in Israel.[237–239,349,350] In Ravid[349] the focus was on the effects of an ACE inhibitor, enalapril, on plasma lipids in a placebo-controlled trial. Ravid[350] examined the effects of enalapril versus placebo in normoalbuminuric, normotensive patients with type 2 DM. Three other articles from the Ravid group report the long-term effects of ACE inhibition on development of nephropathy in normotensive, microalbuminuric patients with type 2 DM. The study was continued from its 5-year double-blind first phase into a further 2 years (second phase) of an open study. Patients were given the choice to receive enalapril or no treatment; thereby, four groups of patients were now formed for the 7-year study.[239] The earliest paper was selected, Ravid (1993),[237] as it was a randomised, double-blind, placebo-controlled trial for the entire follow-up period and was more complete than the subsequently published shorter report. Rachmani (2000)[99] reported on the incidence of retinopathy in the same group of patients as Ravid (1993)[237] and was therefore not selected for this question.

Ahmad and colleagues,[22] in a study from India, reported a 5-year randomised, single-blind, placebo-controlled trial of enalapril in normotensive patients with type 2 DM and microalbuminuria and this study was also selected. Two studies from Sano and colleagues in Japan reported randomised studies of enalapril treatment in type 2 diabetic patients with persistent microalbuminuria.[240,351] The earlier study included both normotensive and hypertensive patients. The later study was larger and focused on normotensive patients, and was selected.[240] A 48-week placebo-controlled trial of the ACE inhibitor drug lisinopril in normotensive diabetic patients with microalbuminuria was reported by O'Donnell and colleagues.[315] The trial, however, included patients with type 1 DM (the majority) and type 2 DM and as it was not possible to separate results for the two groups the study was not selected. A small, randomised, placebo-controlled trial of another ACE inhibitor drug, captopril, was reported by Capek and colleagues.[352] Ten patients were assigned to captopril and ten to placebo. Twenty-five per cent of patients, however, were lost to follow-up, 26% of the remaining patients were hypertensive and there was no development of the end-point, clinical proteinuria, in either group. The study was not selected.

Cheung and colleagues[353] and Muirhead and colleagues[242] reported different aspects of a 52-week study of the effects of valsartan (an angiotensin II receptor-blocking agent) and captopril on reducing microalbuminuria in patients with type 2 DM. This was a placebo-controlled trial yet it not only enrolled normotensive patients but also treated hypertensive patients, including those previously treated with ACE inhibitors. Neither study was selected. Nankervis and colleagues[354] reported a 3-year randomised,

placebo-controlled trial of perindopril, focusing on renal morphometry, but also considering renal function and albuminuria. The study was not selected as type 1 and type 2 DM patients without baseline hypertension were included and the study was too small to allow examination of subgroups. Ishida[355] included both normotensive and mildly hypertensive patients with type 2 DM and was not selected.

The two articles by Durruty and colleagues[153,356] described different aspects of the same cohort. The earlier article[356] focused on the effect of ACE inhibition on urinary albumin excretion in an 18-month study. The majority of the patients, however, were normoalbuminuric at baseline and the study was not selected. This left three randomised trials for review.

Articles excluded

Fourteen articles were excluded.[154,155,238,239,242,315,349–356]

Meta-analysis

Some characteristics of the three trials that evaluated the development of clinical proteinuria among normotensive patients with type 2 DM and microalbuminuria treated with anti-hypertensive agents (all ACE inhibitors) or placebo are shown in *Tables 49* and *50*. In the trial reported by Sano and colleagues[240] the control group was untreated. In total, 253 patients were included. The average follow-up was 4.7 years (range 4–5 years). All three studies used enalapril. There was an average of 66% men in the treatment groups and 73% in the placebo groups; the number of men and women taking part was not stated in one study. Average baseline age, known duration of diabetes, HbA_{1c} and AER (standardised to mg per 24 hour) were similar between groups. MAP was calculated as DBP plus one-third of pulse pressure (*Table 51*).

Of the 129 patients randomised to treatment with an ACE inhibitor in three trials, ten (7.8%) developed clinical proteinuria. By comparison, of the 124 patients randomised to the placebo or no-treatment arm of these studies, 37 (29.8%) developed clinical proteinuria (*Table 52*). The overall relative risk was 0.28 (95% CI 0.15 to 0.53), with no significant heterogeneity between studies (*Figure 31*).

Regression of microalbuminuria to normoalbuminuria

No information on regression of microalbuminuria was given in these three articles.

TABLE 49 *ACE inhibition and development of clinical proteinuria in normotensive patients with type 2 DM and microalbuminuria: interventions and blood pressure at entry*

Study	No. of subjects at entry to trial	FU (y)	ACE-I (daily treatment)	BP at entry (mmHg)
Ravid *et al.*, 1993[237]	94	5	Enalapril 10 mg	≤140/90
Sano *et al.*, 1996[240]	56	4	Enalapril 5 mg	<150/90
Ahmad *et al.*, 1997[22]	103	5	Enalapril 10 mg	≤140/90

TABLE 50 *ACE inhibition and development of clinical proteinuria in normotensive patients with type 2 DM and microalbuminuria: characteristics of patients at baseline*

	Age (y)		Known duration of DM (y)		Gender (% male)		HbA_{1c}		AER (mg per 24 hours)	
Study	ACE-I	Placebo	ACE-I	Placebo	ACE-I	Placebo	ACE-I	Placebo	ACE-I	Placebo
Ravid *et al.*, 1993[237]	44	45	7	7	75	87	10.4[a]	10.4	143	123
Sano *et al.*, 1996[240]	62	64	12	12	NA	NA	8.1	8.0	115	94
Ahmad *et al.*, 1997[22]	50	50	9	9	57	58	8.0	8.1	79	76
Average	52	53	9	9	66	73	8.8	8.8	112	98

[a] Total HbA_1.

TABLE 51 *Effect on MAP of treatment with ACE inhibitor or placebo in normotensive patients with type 2 DM and microalbuminuria*

Study	ACE-I baseline	ACE-I FU	ACE-I change	Placebo baseline	Placebo FU	Placebo change	Difference in change (Placebo – ACE-I)
Ravid *et al.*, 1993[237]	99	100	+1	97	102	+5	+4
Sano *et al.*, 1996[240]	93	NR	–	93	NR	–	–
Ahmad *et al.*, 1997[22]	98	98	0	99	100	+1	+1

–, No change reported by authors.

TABLE 52 *Relative risk of development of clinical proteinuria for normotensive patients with type 2 DM and microalbuminuria: ACE inhibitor versus placebo*

Study	ACE-I CP/total	Placebo CP/total	Crude RR (95% CI)
Ravid *et al.*, 1993[237]	6/49	19/45	0.29 (0.13 to 0.66)
Sano *et al.*, 1996[240]	0/28	6/28	0.08 (0.00 to 1.30)
Ahmad *et al.*, 1997[22]	4/52	12/51	0.33 (0.11 to 0.95)
Meta-analysis, 2002	**10/129**	**37/124**	**0.28 (0.15 to 0.53)**

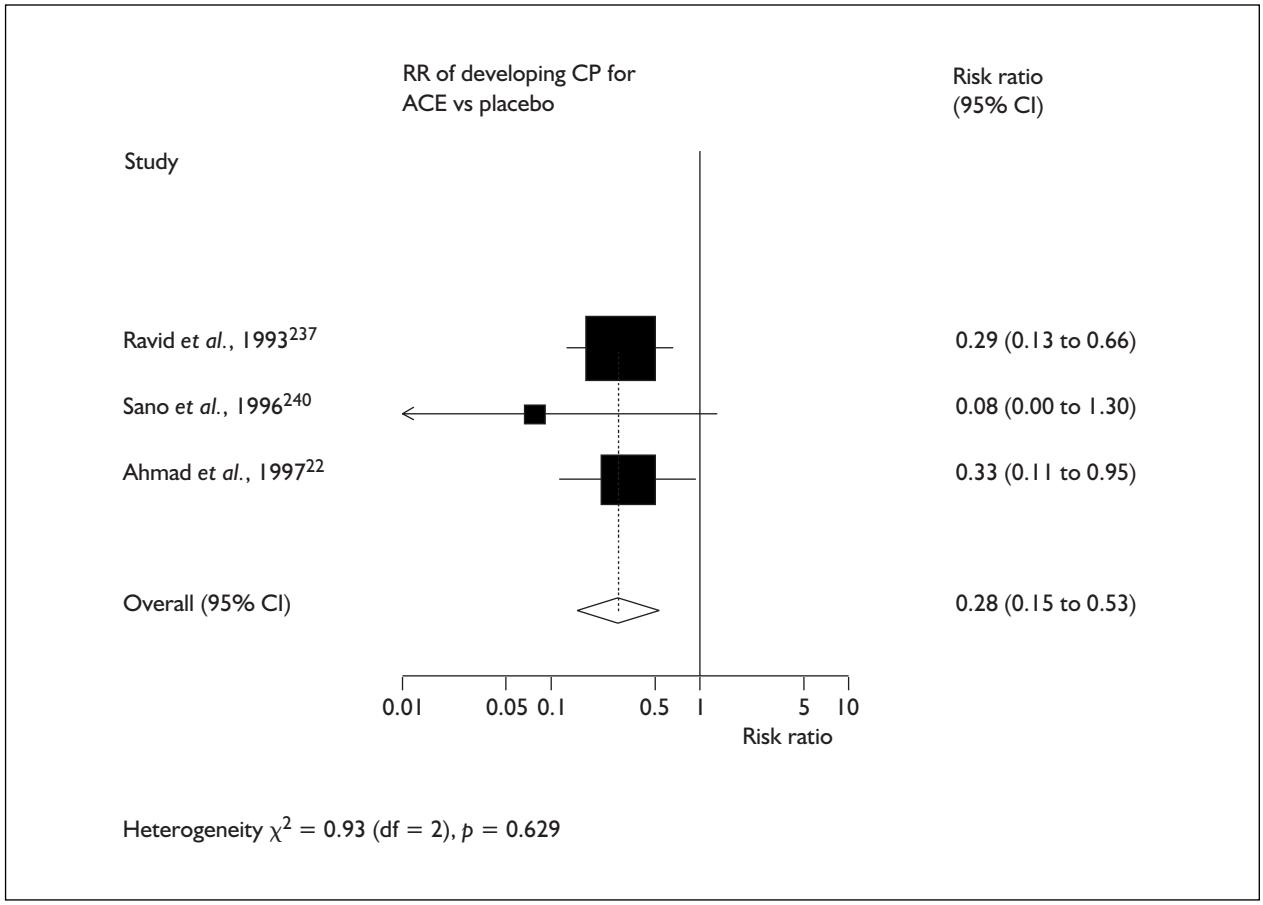

FIGURE 31 *Forest plot for relative risk of developing clinical proteinuria with ACE inhibitor compared with placebo in normotensive patients with type 2 DM and microalbuminuria*

TABLE 53 *Adverse events reported in included trials in patients with type 2 DM*

Study	Adverse events by group		Any other information on adverse events
	ACE-I	Placebo (or non-intervention)	
Ravid *et al.*, 1993[237]	Disturbing cough (4)	Disturbing cough (2)	Three patients (one on enalapril) lost to follow-up
Sano *et al.*, 1996[240]	–	–	No side-effects (cough, hyperkalaemia or anaemia) reported during the study period
Ahmad *et al.*, 1997[22]	–	Eight of 12 placebo treated patients developing clinical proteinuria had evidence of CHD	Serum potassium increased significantly in the enalapril group (from 3.69 ± SD 0.17 to 4.20 ± 0.14 mmol l^{-1})

TABLE 54 *Absolute reduction in risk and NNT to prevent clinical proteinuria in normotensive patients with type 2 DM and microalbuminuria*

Study	FU (y)	Absolute risk reduction (95% CI)	NNT	Absolute annual risk reduction (95% CI)	NNT for 1 year
Ravid *et al.*, 1993[237]	5	30 (13 to 47)	3.3	6 (–3 to 15)	17
Sano *et al.*, 1996[240]	4	21 (6 to 37)	4.8	5 (–3 to 14)	19
Ahmad *et al.*, 1997[22]	5	16 (2 to 30)	6.3	3 (–4 to 10)	31
Meta-analysis, 2002 (3 studies)	**4.7**	**21 (13 to 30)**		**4.5 (0 to 9)**	**22 (10 and over)**

Adverse events

There was no evidence of more serious events among patients treated with the ACE inhibitor enalapril (*Table 53*), but the data on side-effects may be incompletely reported.

Clinical impact: NNT to prevent clinical proteinuria

Three studies were included in the meta-analysis of absolute risk reduction. The overall absolute annual risk reduction was 4.5%, giving an NNT of 22 patients per year to prevent one case of clinical proteinuria (*Table 54*).

Conclusions

In this meta-analysis of three RCTs carried out in normotensive patients with type 2 DM and microalbuminuria, treatment with the ACE inhibitor enalapril reduced the incidence of progression to clinical proteinuria by 72% compared with placebo or no treatment. Consistency was high since benefit from enalapril was suggested in all three trials. There was considerably less trial information available in patients with type 2 DM than in patients with type 1 DM and the subjects studied were mostly from non-European ethnic groups.

A previously published evidence-based review and meta-analysis is directly relevant.[357] The work originally included a meta-analysis of three trials in patients with type 1 DM and two with type 2 DM.[358] Three estimates of overall odds ratio for progression from microalbuminuria to clinical proteinuria were calculated: the combined estimate from trials in both types of diabetes and separate estimates for trials in patients with type 1 and type 2 DM. For patients with type 2 DM (two trials) the odds ratio was 0.14 (95% CI 0.05 to 0.40). This compares closely with the calculated odds ratio of 0.20 (95% CI 0.09 to 0.43) from the present meta-analysis of three trials. This is not surprising since two of the trials,[237,240] are common to both meta-analyses. In their subsequent evidence-based review, Haider and colleagues also included a third trial.[22] A meta-analysis of the three trials was not carried out, but risk reductions and NNT were calculated from the individual trials. There was no consideration of adverse events.

Overall, unweighted MAP rose slightly, but only by 1 mmHg or less in the normotensive patients on ACE inhibitor therapy, compared with a slightly greater rise, of 1–4 mmHg, in the placebo or no-treatment group. However, data on post-treatment

blood pressure were not available from one of the trials, although it was reported as unchanged. As also concluded from the trials in normotensive patients with type 1 DM and microalbuminuria, it seems improbable that a 72% decrease in incidence of clinical proteinuria could be caused by such a change in arterial pressure. It seems more likely that ACE inhibitors have a specific renoprotective effect beyond their antihypertensive action.

In the present meta-analysis it was estimated that 22 patients would have to be treated with ACE inhibitors for 1 year to prevent one additional case of clinical proteinuria. There was no evidence of more serious events among patients treated with the ACE inhibitor enalapril, but the data on side-effects may be incompletely reported.

The available evidence therefore shows that in normotensive subjects with type 2 DM the ACE inhibitor drug enalapril slows the progression of microalbuminuria to clinical proteinuria.

Trials comparing different antihypertensive agents and intensive versus moderate blood pressure control in normotensive patients with type 2 DM and microalbuminuria

Search results

Among the remaining 26 trials identified as described above, only one study appeared relevant. Tutuncu and colleagues[359] randomly assigned 32 normotensive patients with type 2 DM and microalbuminuria to 1 year's therapy with enalapril, the angiotensin II type 1 (AT_1) receptor blocker losartan, or both agents. No patient developed clinical proteinuria. The amount of reduction in AER did not differ significantly among the three groups, with no indication that the combination of both agents gave additional benefit. There was no indication that this was a blinded study, however, and it was not selected. No trial was located that compared intensive versus moderate blood pressure control in normotensive patients with type 2 DM and microalbuminuria.

Article excluded

Tutuncu *et al.*, 2001.[359]

Conclusions

No appropriate trials were located within the search period (ending January 2002). Soon after wards, however, the ABCD trial[341] examined the effect of intensive versus moderate DBP pressure control in 480 normotensive (BP < 140/90) type 2 diabetic patients. Subjects were randomised to intensive (10 mmHg below baseline DBP) versus moderate (80–89 mmHg) DBP control for 5 years. Patients on moderate therapy received placebo, while intensive therapy patients received enalapril or nisoldipine in a blinded manner. With intensive therapy a lower percentage of patients progressed from normoalbuminuria to microalbuminuria ($p = 0.012$) and microalbuminuria to clinical proteinuria ($p = 0.028$). The results were the same whether enalapril or nisoldipine was used.

Placebo-controlled trials in hypertensive patients with type 2 DM and microalbuminuria

Search results

Lebovitz and colleagues carried out a 3-year, prospective, randomised double-blind placebo-controlled trial of enalapril in hypertensive patients with type 2 DM, but the study was published in abstract form only.[360] The authors subsequently published a full report, but the focus was on GFR, with incomplete data available on patient characteristics in the microalbuminuric subgroup and a 27% loss to follow-up.[342] The study was selected for the previous section, but not for the present section. Overlack[361] was a large, multicentre, double-blind, randomised, placebo-controlled trial with perindopril, but the treatment was for 6 weeks only and the study was not selected. Parving[241] was a large, multicentre, multinational, randomised, double-blind, placebo-controlled trial of the AT_1 antagonist irbesartan in hypertensive patients with type 2 DM and microalbuminuria. The study was selected. The HOPE study[337] was a 4.5-year placebo-controlled trial of the ACE inhibitor ramipril in people with or without type 2 DM and one additional CVD risk factor. The study was not selected for this part of the review because only 56% of patients had hypertension and only 32% had microalbuminuria. An analysis of the microalbuminuric subset in relation to the development of clinical proteinuria has not yet been published.

Articles excluded

Four studies were excluded.[337,342,360,361]

Meta-analysis

No meta-analysis was possible since only one study was found.[241] This large, multinational, double-blind, randomised study evaluated the effectiveness of the AT_1 receptor antagonist irbesartan in delaying or preventing the development of clinical proteinuria in hypertensive patients with type 2 DM and microalbuminuria. Two dose levels of

TABLE 55 *AT_1 antagonist treatment compared with placebo in patients with type 2 DM, hypertension and microalbuminuria: interventions and blood pressure at entry*

Study	Study design	Total *n*	MA *n*	AT_1 antagonist	Comparator	BP entry criteria (mmHg)
Parving *et al.*, 2001[241]	Randomised, double-blind, placebo-controlled, multicentre	590	590	Irbesartan 150 mg per day (*n* = 195) Irbesartan 300 mg per day (*n* = 194)	Placebo (*n* = 201)	SBP >135 and/or DBP <85

TABLE 56 *Relative risk of development of clinical proteinuria for hypertensive patients with type 2 DM and microalbuminuria: AT_1 antagonist versus placebo*

Study	CP/total MA AT_1 antagonist	CP/total MA placebo	Crude RR (95% CI)
Parving *et al.*, 2001[241]	29/389	30/201	0.50 (0.31 to 0.81)

irbesartan were examined in comparison with placebo treatment over a 2-year period of treatment. Additional antihypertensive drugs, but not ACE inhibitors, were used to achieve the blood pressure goals. Some characteristics of the trial are shown in *Table 55*.

The unadjusted relative risk for the development of clinical proteinuria was 0.61 (95% CI 0.34 to 1.08) for the 150-mg group and 0.30 (95% CI 0.14 to 0.61) for the 300-mg group. The relative risk of clinical proteinuria for the combined irbesartan groups is shown in *Table 56*.

Adverse events

Serious adverse events were recorded in 22.8% of patients in the placebo group and in 15.4% of those in the combined irbesartan groups ($p = 0.02$).

Conclusions

Treatment with irbesartan significantly reduced the rate of progression to clinical proteinuria. This was considered independent of SBP, as average blood pressure during the study was only minimally lower in the irbesartan groups than in the placebo group. However, outcomes may have been biased since patients were allowed to use only non-dihydropyridine calcium channel antagonists and not verapamil or diltiazem (reported to have the same antiproteinuric effect as ACE inhibitors).

Similar findings were reported from the HOPE study and MICRO-HOPE substudy,[337] in which 3577 people with diabetes (almost all type 2 DM) and one other risk factor were randomly assigned to ramipril or placebo: 56% had a history of hypertension and 32% had microalbuminuria. The study lasted for 4.5 years. Ramipril treatment was associated with a significant reduction in the risk of development of clinical proteinuria (from normoalbuminuric and microalbuminuric groups combined), although blood pressure fell only minimally on ramipril compared with placebo. However, there was some imbalance in CVD at baseline in the randomised groups in the HOPE study, biasing outcomes to be more favourable with ramipril.

Trials comparing intensive versus moderate blood pressure control in hypertensive patients with type 2 DM and microalbuminuria

Search results

There are two large trials in this category where microalbuminuria was assessed at baseline. The Hypertension in Diabetes Study was a multicentre, randomised, controlled trial embedded within the UKPDS (UKPDS 38).[140] This trial was designed to determine whether tight blood pressure control (aiming for BP <150/85 mmHg), compared with less tight control (aiming for BP <180/105 mmHg), prevents macrovascular and microvascular complications. Newly diagnosed patients with type 2 DM and hypertension were enrolled into the study. Hypertension was defined as SBP greater than or equal to 160 mmHg and/or DBP greater than or equal to 90 mmHg (727 patients) or, in 421 patients receiving antihypertensive medication, as SBP greater or equal to 150 mmHg and/or DBP greater than or equal to 85 mmHg. Those

randomly allocated to tight blood pressure control received either captopril or atenolol to maximal doses. Other agents were added if targets were not met (in the sequence frusemide, slow-release nifedipine, methyldopa and prazosin). In those patients assigned less tight control of blood pressure, ACE inhibitors or β-blockers were avoided. In total, 1148 patients (55% men) were followed for a median period of 8.4 years. The prevalence of microalbuminuria at baseline was 17%. Mean blood pressure in patients over 9 years of follow-up was 144/82 in those under tight control and 154/87 in those under less tight control ($p < 0.0001$). There was no difference over the study period in mean HbA_{1c} between the groups assigned to tight and less tight control.

The UKPDS mostly focused on hard end-points, but also assessed a range of surrogate endpoints. By 6 years, there was a non-significant 39% reduction in risk for clinical proteinuria (defined by UAC >300 mg l^{-1}). Relative risks for tight control were 0.57 (95% CI 0.25 to 1.29) at 3 years, 0.61 (95% CI 0.31 to 1.21) at 6 years and 1.06 (95% CI 0.42 to 2.67) at 9 years. No analysis of progression to clinical proteinuria in the microalbuminuric subset has been published. Despite personal contacts and discussion, the UKPDS could not provide any raw data that could be used in a meta-analysis. Hence, although there was no difference between tight and less tight blood pressure control on progression to clinical proteinuria, it is unknown whether there was a differential effect in the normoalbuminuric and microalbuminuric subgroups.

The ABCD trial, referred to in the previous section, also examined the development of clinical proteinuria in hypertensive patients with type 2 DM.[336] Patients were randomised to intensive or moderate blood pressure control. Information on progression to clinical proteinuria in the microalbuminuric subset was included and the article was therefore selected for review.

Meta-analysis

No meta-analysis was possible since only one study was found.[336] The ABCD study examined the effect of blood pressure control on the development of diabetic complications in the 470 hypertensive patients with type 2 DM recruited to the trial. Hypertensive subjects (baseline DBP ≥90 mmHg) were randomised to intensive blood pressure control (DBP goal of 75 mmHg) versus moderate blood pressure control (DBP goal of 80–89 mmHg). Patients were further randomised to either nisoldipine (a long-acting calcium channel antagonist) or to the ACE inhibitor enalapril and followed for a mean of 5.3 years. The mean blood pressure achieved (last 4 years of study) was 132/78 in the intensive group and 138/86 in the moderate control group ($p < 0.001$). The subgroup of patients with microalbuminuria was separately examined. The percentage of patients who progressed from microalbuminuria (AER 20–200 μg per minute) to clinical proteinuria (AER ≥200 μg per minute) was 16% in the intensive therapy group versus 23% in the moderate therapy group ($p = 0.28$).

Conclusions

Compared with moderate blood pressure control, intensive blood pressure control did not affect the rate of progression of microalbuminuria to clinical proteinuria in the one study from which data were available. This suggests that a level of blood pressure may have been reached in the moderate group whereby a further reduction exerts no additional benefit in respect of nephropathy progression. It remains possible, however, that a larger group of patients with longer follow-up might demonstrate a more beneficial effect of intensive therapy. However, the results do support the observations of the UKPDS, where progression to clinical proteinuria of a combined cohort of normoalbuminuric and microalbuminuric patients was unaffected by tight or less tight control.

Trials comparing different antihypertensive agents in hypertensive patients with type 2 DM and microalbuminuria

Search results

The UKPDS trial mentioned above used either captopril or the β-blocker atenolol as main treatment. A further article from the UKPDS[335] examined the efficacy of atenolol and captopril in 758 patients from the tight blood pressure control group in reducing the risk of macrovascular and microvascular complications, including progression to clinical proteinuria. Over 9 years, those allocated to captopril or atenolol had similarly reduced blood pressures (144/83 and 143/81 mmHg, respectively). The progression to clinical proteinuria over 9 years did not differ significantly in those allocated to captopril (7/153) versus atenolol (14/146) ($p = 0.09$), but analysis of the microalbuminuric subgroup separately from the normoalbuminuric group was not possible, as discussed above. Although it was not possible to include the UKPDS trial in the meta-analysis, comparative data are tabulated alongside the included studies.

Within the ABCD trial, described above,[336] patients were further randomised to receive either enalapril or nisoldipine as the primary antihypertensive medication. Information on progression to clinical proteinuria was available for the microalbuminuric subset and the study was selected for this section of the review. FACET[333] was not selected as one of the exclusion criteria in that trial was an AER above 40 μg per minute, effectively removing many patients with microalbuminuria at baseline.

Rachmani[362] was a cross-over trial of 4-month phases and was not selected. Bretzel[363] was not an RCT. Chan[343] was a 1-year, randomised, double-blind comparison of enalapril with nifedipine. At the end of the trial, patients remained on their assigned therapy and were followed for a total of 5.5 years.[364] The 1-year trial was selected. Agardh[345] was a double-blind randomised, parallel-group, multicentre and multinational study that compared the effect of 12 months of treatment with lisinopril with slow-release nifedipine. Progression of albuminuria was given by albuminuria status at baseline and the study was selected. Ruggenenti[365] and Mosconi[366] report, respectively, the 12-month and 27-month follow-up of a trial comparing the renal effects of enalapril and nitrendipine in hypertensive patients with type 2 DM. The initial 3 months of the trial were double blind and the following 2 years single blind. The trial was small, with only eight patients randomised to each therapy arm, and the focus was on GFR measurements. No patient developed clinical proteinuria over the full 27 months. The study was not selected.

Velussi[367] was a 3-year, randomised, double-blind trial comparing antihypertensive treatment with cilazapril to amlodipine in hypertensive patients with type 2 DM and normoalbuminuria or microalbuminuria. Two of the 21 microalbuminuric patients developed clinical proteinuria during the study, but the treatment arm from which they originated was not specified. The study was therefore not selected. There were three articles from Lacourciere and colleagues. The first[368] was a 9-month study and was not selected. The next study[344] was a prospective, double-blind, randomised investigation of captopril compared with conventional therapy in hypertensive patients with type 2 DM and microalbuminuria, and was selected for review. The third study from Lacourciere[369] was a 1-year, prospective, double-blind trial comparing an ACE inhibitor drug, enalapril, with an angiotensin II type 1 receptor antagonist (AT_1 antagonist). Clinical proteinuria did not develop in any patients from either group and the study was therefore not selected. There were two trials reported by Fogari and colleagues. The first[370] was a 1-year randomised, double-blind study examining the effects of amlodipine and enalapril on urinary albumin excretion in hypertensive patients with type 2 DM and microalbuminuria. No patient in either group developed clinical proteinuria and the study was therefore not selected. The second study by Fogari[371] was a 2-year double-blind, randomised trial that compared the long-term effects of fosinopril with amlodipine in elderly patients with type 2 DM along with hypertension and microalbuminuria. There was a 50% loss to follow-up in the trial and no patient developed clinical proteinuria in either group; the study was not selected.

The Japan Multicentre Investigation of Antihypertensive treatment for Nephropathy in Diabetics (J-MIND)[372] was an open-label, randomised, prospective trial comparing enalapril with long-acting nifedipine. Normoalbuminuric and microalbuminuric patients with type 2 DM and hypertension were enrolled and results are given by baseline albuminuria status. In view of the open-label design, the study was not included. Schnack[373] was an open-label, randomised, prospective trial of 1 year's treatment with either ramipril or atenolol in hypertensive patients with type 2 DM; the study was not selected.

Articles excluded

Thirteen articles were excluded.[333,362,363,365–374]

Meta-analysis

Some characteristics of the four trials that evaluated the development of clinical proteinuria among patients with hypertension, type 2 DM and microalbuminuria treated with ACE inhibitors in comparison with other antihypertensive therapies are shown in *Tables 57–59*, alongside comparative data from the UKPDS. In total, 1774 patients were randomised to treatment with either an ACE inhibitor as primary medication (two studies used captopril, two enalapril and one lisinopril) or other antihypertensive therapies. These included nifedipine in two studies, nisoldipine, atenolol or conventional therapy (which included metoprolol and hydrochlorothiazide). The UKPDS includes the 758 patients randomly allocated tight control of blood pressure with either captopril or atenolol. This design of the ABCD study differed from the UKPDS as 'intensively' treated patients could be on enalapril or nisoldipine as primary medication, as could those patients allocated to 'moderate'

TABLE 57 *ACE inhibitor treatment compared with other antihypertensive therapies in hypertensive patients with type 2 DM and microalbuminuria: interventions and blood pressure at entry*

Author	Total no.	No. with MA	Follow-up (y)	ACE-I	Other therapies	BP entry criteria (mmHg)	BP goal (mmHg)
Chan *et al.*, 1992[343]	102	36	1	Enalapril (21)	Nifedipine (modified release) (15)	SBP 150–220 and/or DBP >100	SBP ≤ 140
Lacourciere *et al.*, 1993[344]	109	21	3	Captopril (9)	Conventional (12)	DBP 92–110	DBP ≤ 85
Agardh *et al.*, 1996[345]	335	335	1	Lisinopril (168)	Nifedipine (167)	DBP 90–110	DBP < 90
UKPDS, 1998[140]	758	18%	9	Captopril (400)	Atenolol (358)	SBP ≥160 and/or DBP ≥ 90 SBP ≥150 and/or DBP ≥ 85 (AHT)	SBP < 150, DBP < 85
ABCD (Estacio *et al.*, 2000)[335]	470	150	5	Enalapril (67)	Nisoldipine (83)	DBP ≥ 90	DBP = 75 (intensive) DBP 80–89 (moderate)

TABLE 58 *ACE inhibitor treatment compared with other antihypertensive therapies in hypertensive patients with type 2 DM and microalbuminuria: characteristics of patients at baseline*

	Age (y)		Gender (% male)		Duration (y)		HbA_{1c} (%)		AER (mg per 24 hours)	
Study	ACE-I	Other	ACE-I	Other	ACE-I	Other	ACE-I	Other	ACE-I	Other
Chan *et al.*, 1992[343]	60	56	40	40	6	6	10.4[a]	9.8	65	70
Lacourciere *et al.*, 1993[344]	58	56	65	50	6	8	9.2[a] SG	9.3 SG	86 SG	66 SG
Agardh *et al.*, 1996[345]	59	58	70	73	NE	NE	7.5	7.6	94	91
UKPDS, 1998[140]	56	56	51	57	ND	ND	6.9	7.0	16% ≥ 50 mg l^{-1}	20% ≥ 50 mg l^{-1}
ABCD, 2000[336]	58	58	67	68	8	8	11.5[a]	11.7	NE	NE

[a] Total HbA_1.
SG, values from the microalbuminuric subgroup (value in total group not given in article).

blood pressure control. The blood pressure goals in each study are shown in *Table 57*. Age, gender, HbA_{1c} and AER (standardised to mg per 24 hours) were similar between treatment arms at baseline (*Table 58*). Blood pressures achieved on these therapies are shown in *Table 59*. In four of these trials, information on progression of microalbuminuria to clinical proteinuria was available. It was not available for the UKPDS. One trial included only patients with microalbuminuria, but in the other three trials microalbuminuric patients formed a subgroup. In total, 542 microalbuminuric patients were included in these four trials. The average follow-up was 2.5 years (range 1–5 years).

Of the 257 patients randomised to treatment with an ACE-inhibitor in four trials, 19 (7.4%) developed clinical proteinuria. By comparison, of the 276 patients randomised to other therapies, 32 (11.6%) developed clinical proteinuria (*Table 60*). The overall relative risk was 0.74 (95%

TABLE 59 *Effect on blood pressure of treatment with an ACE inhibitor compared with other antihypertensive therapy in hypertensive patients with type 2 DM and microalbuminuria*

Author	BP at randomisation (ACE-I)	BP at end of study (ACE-I)	BP at randomisation (non-ACE-I)	BP at end of study (non-ACE)	Difference at end of study (95% CI)
Chan *et al.*, 1992[343]	174/92 (17/13)	NE	166/91 (16/9)	NE	–21.2 (–24.8 to –16.3) (enalapril) –20.1 (–24.1 to –18.4) (nifedipine)
Lacourciere *et al.*, 1993[344]	161/97(3/2)[a]	148/85 (7/3)	168/100 (4/3)	159/87 (3/3)	No significant difference between therapies
Agardh *et al.*, 1996[345]	163/98 (17/6)	147/88 (18/10)	161/97 (18/5)	150/88 (18/9)	2 (–5.5 to 1.6)/1 (–1.2 to 2.6)
UKPDS, 1998[140]	159/94 (20/10)	144/83 (14/8)	159/93 (19/10)	143/81 (14/7)	1(–1 to 3)/1 (0 to 2)
ABCD (Estacio *et al.*, 2000)[336]	NE	NE	NE	NE	No significant difference between therapies

[a] SEM.

TABLE 60 *Relative risk of development of clinical proteinuria in hypertensive patients with type 2 DM and microalbuminuria: ACE inhibitor versus other antihypertensive therapy*

Study	CP/total MA (ACE-I)	CP/total MA (Other treatment)	Crude RR (95% CI)
Chan *et al.*, 1992[343]	0/13	2/14	0.21 (0.01 to 4.08)
Lacourciere *et al.*, 1993[344]	0/9	2/12	0.26 (0.01 to 4.83)
Agardh *et al.*, 1996[345]	6/168	11/167	0.54 (0.21 to 1.43)
UKPDS, 1998[140]	NE	NE	
ABCD, 2000[336]	13/67	17/83	0.95 (0.50 to 1.81)
Meta-analysis, 2002 (4 studies)	**19/257**	**32/276**	**0.74 (0.44 to 1.24)**

CI 0.44 to 1.24), with no significant heterogeneity between studies (*Figure 32*). There is clear asymmetry in the Forrest plot indicating publication bias. However, a trim and fill analysis did not alter the estimate of relative risk.

Regression of microalbuminuria to normoalbuminuria

Regression from microalbuminuria to normoalbuminuria was referred to in only one of these articles.[345] Among patients treated with lisinopril for 1 year, regression to normoalbuminuria (AER <20 μg per minute) occurred in 44/168 (26.2%) compared with 23/167 (13.8%) in those treated with nifedipine.

Adverse events

Adverse events were thoroughly reported in some studies but incompletely in others (*Table 61*). In the largest of these studies, UKPDS, there was a significant excess of cough in the captopril-treated group ($p < 0.0001$). In the proportion of patients who suffer this distressing side-effect, it has been suggested that an angiotensin-receptor blocker (with a much lower incidence of cough reported as a side-effect) should be used instead. Intermittent claudication or cold feet and bronchospasm was much more commonly reported on atenolol than on captopril ($p < 0.0001$).

Conclusions

In this meta-analysis of four RCTs among hypertensive type 2 diabetic patients with microalbuminuria, treatment with ACE inhibitors as the primary medication reduced arterial blood pressure as effectively as other antihypertensive therapies that did not include an ACE inhibitor. Monotherapy was effective in achieving blood

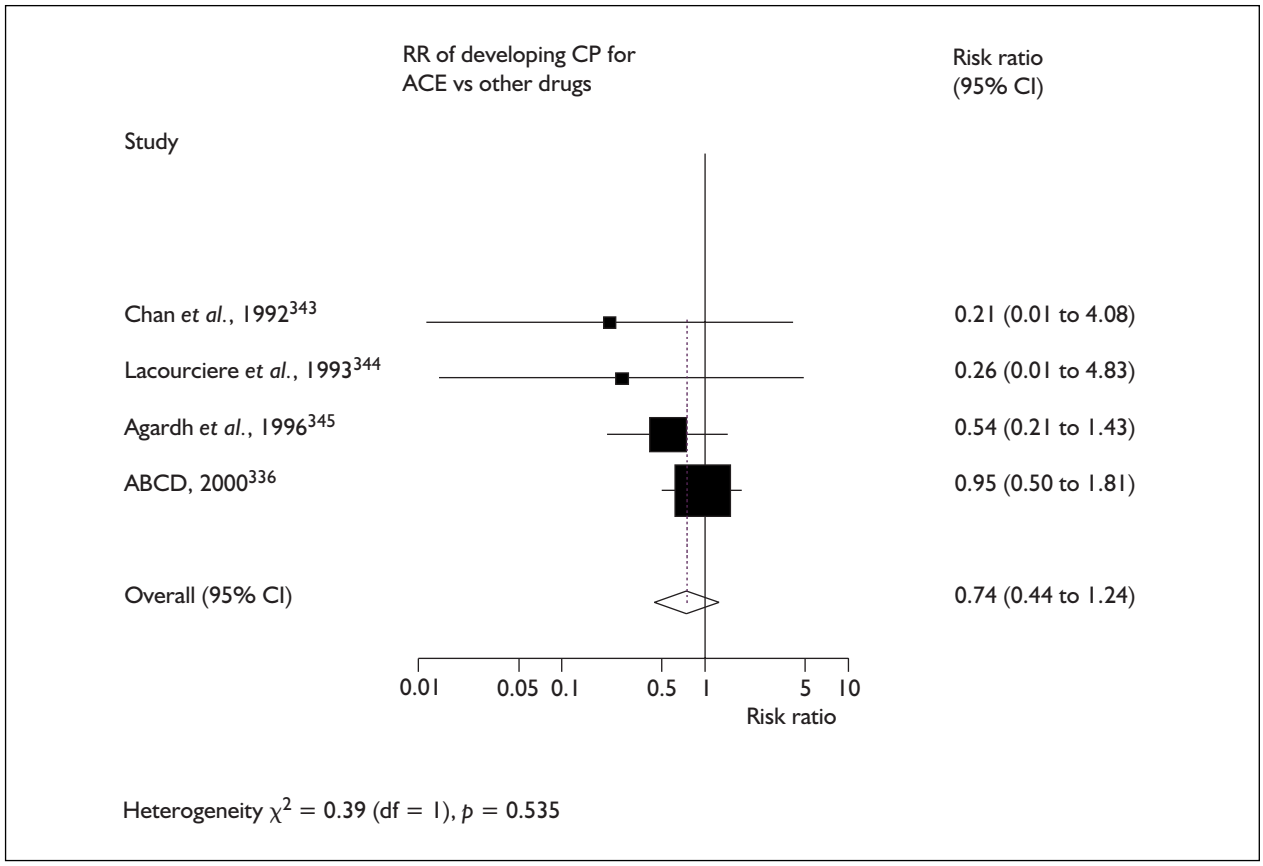

FIGURE 32 *Forest plot for relative risk of developing clinical proteinuria with ACE inhibitor compared with other drugs in hypertensive patients with type 2 DM and microalbuminuria*

pressure goals in only a minority of patients, with the majority requiring combination therapy. There was no significant difference in the proportions of patients progressing from microalbuminuria to clinical proteinuria between the two modes of therapy. Although the largest study of this kind, UKPDS,[335] could not be included in the meta-analysis, the findings are comparable. In that study, captopril was compared with atenolol over a 9-year follow-up period. The proportion of patients who had clinical proteinuria (starting with either normoalbuminuria or microalbuminuria) did not differ significantly at the end of the study. Taken with important findings on other end-points, the results of these studies suggest that blood pressure reduction in itself may be more important than the treatment used and no specific renoprotective effect of ACE inhibition was demonstrable.

TABLE 61 *Adverse events reported in the reviewed trials*

Study	Adverse events by group		Any other information on adverse events
	ACE-I	**Other therapies**	
Chan *et al.*, 1992[343]	Of nine patients taking enalapril who did not complete 1 year, three were withdrawn because of cough, three because of inadequate control of blood pressure, one died of MI and one developed angina	Of three patients who received nifedipine, one had inadequate BP control, one had angina and one had tuberculous lymphadenitis	–
Lacourciere *et al.*, 1993[344]	16 patients withdrawn during 3 years. Four died, three from MI and one from colon cancer	19 patients withdrawn. No information on reasons for withdrawal	–
Agardh *et al.*, 1996[345]	21 patients on lisinopril were withdrawn because of adverse events. Over the 12-month treatment period, one or more adverse events were reported by 71% of patients receiving lisinopril	28 patients on nifedipine were withdrawn because of adverse events. Over the treatment period, adverse events were reported by 73% receiving nifedipine	Headache, vasodilatory effects and peripheral oedema were reported more frequently on nifedipine. Cough and bronchitis were more frequently reported on lisinopril
UKPDS, 1998[140]	Main reasons for non-compliance: cough (16), increased creatinine (5), claudication or cold feet (0), bronchospasm (0), impotence (1), other (36)	Main reasons for non-compliance: cough (0), increased creatinine (5), claudication or cold feet (15), bronchospasm (22), impotence (6), other (36)	More patients in the atenolol group than in the captopril group stopped taking their allocated treatment
ABCD, 2000[336]	There were 41 adverse events. In addition, there were 41 deaths or cardiovascular events	There were 54 adverse events. In addition, there were 50 deaths or cardiovascular events	There was no significant difference in the number of patients discontinuing study medication between those randomised to nisoldipine and enalapril

Chapter 8

Discussion and conclusions

The focus of this review was first to establish the evidence for the prognostic significance of microalbuminuria in people with diabetes for the development of defined complications – namely cardiovascular, retinal and renal disease – as well as mortality. The second aim was to address whether, by separately identifying those with microalbuminuria from those with normoalbuminuria, there were added benefits for the people in this subgroup over and above the benefits in the normoalbuminuric majority with regard to improved control of glycaemia and hypertension, including the use of antihypertensive agents in normotensive people, which would lead to a greater reduction in complications. This review has not considered those patients with diabetic nephropathy (those with clinical proteinuria and/or a reduced GFR) who have already progressed beyond the stage of microalbuminuria and in whom there is already overwhelming evidence for aggressive treatment at least to slow further deterioration. The authors are not aware of any publications since the searches were completed that would have significantly altered the results of the meta-analyses, apart from a strengthening of the prognostic significance of microalbuminuria for CVD mortality, after adjustment for confounders, in patients with type 1 DM.

The most pronounced benefits of glycaemic control identified in this review are on retinal and renal complications in both normoalbuminuric and microalbuminuric patients considered together with little or no evidence of any greater benefit in those with microalbuminuria. Hence microalbuminuric status may be a false boundary when considering the benefits of glycaemic control for these end-points. Classification of a person as normoalbuminuric must not serve to suggest that they will derive less benefit from optimal glycaemic control than a person who is microalbuminuric. The National Institute for Health and Clinical Excellence (NICE) guidelines for glycaemic control, published since the inception of this study,[375,376] recommend a target DCCT-harmonised HbA_{1c} of 7.5% or lower for all patients with a target of 6.5% or lower for those at significant risk of macrovascular complications, citing epidemiological evidence from DCCT and UKPDS that "microvascular risk was low once average HbA_{1c} was around 7.0–8.0% while arterial risk continued to fall down to 6.0 to 7.0% (DCCT standardised)". A raised AER is cited as the most important arterial risk factor in type 1 DM[375] and would, even in the absence of other evidence of arterial risk, alter the target, but not until an HbA_{1c} of 7.5% had been achieved. Given the continuum of risk associated with any elevation of HbA_{1c} irrespective of whether the patient is normoalbuminuric or microalbuminuric, support to achieve optimal glycaemic control for all should be provided. However, only about 20% of patients with type 1 DM achieve levels of HbA_{1c} below 7.5%.[375]

This review finds that microalbuminuria predicts an increased risk of mortality in both type 1 and type 2 DM and also, in type 2 DM, an increased risk of CVD and CHD mortality. The present meta-analysis found some evidence that improved glycaemic control may be beneficial with regard to CVD in type 1 DM, but little evidence for type 2 DM and no evidence favouring additional benefit in the subgroup of patients with microalbuminuria. It may be that improved glycaemic control must be sustained for much longer periods than have been studied in these trials to see an effect on CVD. There was also a cardiovascular benefit of ACE inhibitor therapy in patients with type 2 DM and microalbuminuria irrespective of the presence of hypertension, but no trials in type 1 DM.

Good blood pressure control is key to cardiovascular and renal protection in people with diabetes and hypertension, and almost all patients will require a combination of blood pressure-lowering drugs, probably including at least a combination of a thiazide/thiazide-like diuretic and an ACE inhibitor or angiotensin receptor blocker to confer cardiorenal protection according to the latest guidelines from the British Hypertension Society (BHS).[377] Treatment should be initiated at a sustained SBP greater than or equal to 140 mmHg and/or DBP greater than or equal to 90 mmHg, with targets of below 130 and below 80 mmHg respectively, levels noted to be difficult to achieve in some patients. The targets are for all people with diabetes and especially those with microalbuminuria or diabetic nephropathy.

This systematic review finds strong evidence of a benefit of ACE inhibitor therapy in preventing progression to clinical proteinuria in normotensive microalbuminuric patients with type 1 or type 2 DM and for regression to normoalbuminuria in type 1, but no data on the use of other antihypertensive agents in these groups. In hypertensive type 2 DM patients with microalbuminuria the data were inconclusive as to whether ACE inhibition was more effective than other antihypertensive therapy (not involving blockade of the renin–angiotensin system) in preventing progression to clinical proteinuria, although regression to normoalbuminuria was higher; however, in one trial the angiotension receptor blocker irbesartan was more effective than non-renin–angiotensin system antihypertensive therapy and induced greater regression. There were no data in similar patients with type 1 DM. Thus, in hypertension, reduction of blood pressure appears to be the dominant factor in preventing progression of microalbuminuria to clinical proteinuria, while therapy with ACE inhibitors is of proven benefit in reducing progression in normotensive individuals. However, given the renoprotective effects of renin–angiotensin system blockade in patients with clinical proteinuria, as reviewed by Strippoli and colleagues,[378] and given recent evidence[379] of primary prevention of microalbuminuria in patients with type 2 diabetes, hypertension and normoalbuminuria treated with an ACE inhibitor, it would appear that renin–angiotensin system blockade should be the norm for any hypertensive diabetic regardless of urine albumin and for normotensive patients with microalbuminuria. Although ACE inhibitors have been more widely studied than angiotensin receptor blockers, the available evidence suggests that the latter offer effective renoprotection. However, ACE inhibitors appear superior in reducing mortality risk[378] (due to evidence largely from the MICRO-HOPE study), whereas angiotensin receptor blockers were without effect on mortality. In several trials angiotensin receptor blockers appear to have increased the risk of MI.[380]

NICE guidelines for the management of renal disease in type 2 DM[381] state that all patients with type 2 diabetes should have an annual measurement of urine albumin to creatinine ratio or albumin concentration on a first morning urine where practicable, and using a laboratory or near patient test specifically for microalbuminuria. If positive for microalbuminuria (Appendix 1), the test should be repeated twice within 1 month. If confirmed and in the absence of retinopathy, non-diabetic causes of renal disease should be sought. Otherwise, patients should commence on ACE inhibitor therapy to maintain blood pressure below 135/75 mmHg and tighten glycaemic control to maintain HbA_{1c} below 6.5–7.5%, and cardiovascular risk factors should be managed aggressively. Urine albumin and serum creatinine are then to be measured at every clinic visit. There is no guidance concerning subsequent modulation of therapy in response to changes in urine albumin.

The more recently published NICE guidelines for people with type 1 DM[375] stipulate annual measurement of urine albumin, preferably on a first pass urine and with calculation of an ACR. If positive for microalbuminuria in the absence of a urinary infection, the test should be repeated at each clinic visit or every 3–4 months. If microalbuminuria is confirmed and retinopathy present, treatment should be commenced with an ACE inhibitor (or angiotensin receptor blocker if necessary) in combination with other therapy to reduce blood pressure to below 130/80 mmHg. Adults with microalbuminuria or two or more features of the metabolic syndrome should be treated as the highest risk category (as though they had type 2 diabetes or declared arterial disease) and should commence on 75 mg aspirin daily and a standard dose of a statin. However, if microalbuminuria regresses to normal as a result of ACE inhibition and in the absence of other risk factors it is not clear whether this treatment should be continued lifelong. In the absence of microalbuminuria, patients who are hypertensive should commence antihypertensive therapy at a threshold of 135/85 mmHg, lower than that recommended by the current BHS guidelines.[377]

Patients who are hypertensive, irrespective of urine albumin excretion, should already be on antihypertensive therapy (likely to be at least a combination of a thiazide and an ACE inhibitor), aspirin (if aged over 50 years, BP controlled to <150/90 mmHg and 10-year CVD risk >20%) and a statin in line with the Coronary Heart Disease National Service Framework guidelines[382] and BHS guidelines,[377] and reduction of blood pressure per se appears to be the key factor in preventing worsening albuminuria, as evidenced by this review. Monitoring urine albumin thereafter would only appear justified if there were any benefit from using the results to titrate medication separately from any medication adjustment based on blood pressure. There are no RCTs for any outcome that compare the use of urine albumin measurements in addition to blood

pressure versus blood pressure alone as a guide to adjusting therapy in hypertensive patients with microalbuminuria.

Regular surveillance of urine albumin is the only means of identifying those patients who are normotensive yet microalbuminuric and who will benefit from treatment, commonly but not exclusively with an ACE inhibitor, as evidenced by this systematic review not only for patients with type 2 DM but also for those with type 1 DM.

The relative risk of progressing to renal failure of patients with microalbuminuria compared with those who had a normal AER provided evidence to support the predictive value of microalbuminuria for the development of ESRD, an increased rate of fall in GFR and the development of clinical proteinuria in patients with either type 1 or type 2 DM. For the development of clinical proteinuria in type 1 DM there were sufficient studies to allow separate analysis of adult and adolescent patients. This showed the relative risk in adolescents to be half of that in adults, although statistically not significant since the few adolescent studies resulted in a wide confidence interval. However, a contributory factor to this observation may be the significantly higher rate of regression (by three-fold) to normoalbuminuria than of progression to clinical proteinuria among adolescent microalbuminuric patients, whereas in microalbuminuric adults with type 1 or type 2 DM the rates of regression and progression were not different.

Some regression may be due to misclassification as microalbuminuric at baseline, since not all studies followed currently accepted guidelines of screen positive in at least two of three samples. However, the present findings concur with other recently published large studies in microalbuminuric patients with type 1 DM,[383,384] where misclassification was unlikely owing to stringent conditions to categorise albumin excretion. Among an inception cohort of patients, one study also demonstrated that similar numbers of patients with microalbuminuria progressed to clinical proteinuria (34%) as regressed to normoalbuminuria (35%), although regression only persisted in half of the patients.[383] Although both adults and children were included they were not separately analysed, but those patients who regressed tended towards a younger mean age, and had significantly lower arterial pressure, a lower albumin excretion rate and lower serum cholesterol at onset of microalbuminuria. In a prevalence cohort of 386 patients with persistent microalbuminuria followed up for 6 years, 19% progressed to clinical proteinuria, whereas 58% regressed to normoalbuminuria.[384] Regression was associated with younger age, HbA_{1c} below 8%, low SBP (<115 mmHg), but not the use of ACE inhibitors, microalbuminuria of short duration and low total serum cholesterol (<5.12 mmol l^{-1}) and triglycerides (<1.64 mmol l^{-1}).

The effect of lipid-lowering therapies on urine albumin excretion has not been systematically reviewed, although small relatively short-term clinical studies report that statins reduce AER,[385] whereas *in vitro* studies indicate a statin-mediated reduced tubular uptake of albumin that would be predicted to increase urine albumin.[386] Analysis of AERs in the large and longer term Collaborative Atorvastatin Diabetes Study (CARDS) trial[387] is ongoing (Colhoun H: personal communication, 2005) and should provide a definitive answer. Of the other two therapeutic interventions studied in the present review there were only sufficient studies for a meta-analysis of regression in relation to ACE inhibitor versus placebo in normotensive patients with type 1 DM and microalbuminuria. This showed a five-fold higher rate of regression with the ACE inhibitor, in line with a recently published systematic review of ACE inhibitor-induced regression in patients with type 1 and type 2 DM.[378] Hence, established therapeutic interventions in widespread use should reduce the prevalence of microalbuminuria. Whether this will always equate to reduced target organ damage remains to be established.

Central to the assignment of microalbuminuria status is the numerical definition of this term. Whereas identical (or nearly so) cut-offs have been generally adopted, they take no account of variations in bias between laboratories, which external quality assessment schemes show to be significant especially at the lower concentrations that may be critical in determining the boundary between normoalbuminuria and microalbuminuria. The extent of 'postcode' microalbuminuria (or normoalbuminuria) should be determined to inform better guidelines on key analytical assay performance criteria that should be provided as part of any national screening programme.[11] Such guidelines already exist for the measurement of HbA_{1c} and were specified for prostate-specific antigen as part of the national Prostate Cancer Risk Management Programme.

The prognostic value of microalbuminuria is dependent on the validity of baseline assignment of patients to category of albuminuria. This fell short of current recommendation in many studies.

Some used only one baseline measurement, defined microalbuminuria by urinary albumin concentration rather than by excretion rate or ratio to creatinine, changed assay method during the course of the study or did not explicitly state that other possible causes of microalbuminuria (e.g. exercise, urinary tract infection, blood contamination) had been sought and excluded. Also, increasing recognition of the importance of improved glycaemic control and the use of antihypertensive treatment may have lessened the prognostic value of microalbuminuria during the course of studies. The category of microalbuminuria embraces a ten-fold range of AER, and those patients with higher rates will progress to renal failure more rapidly than those with lower rates. Differences between studies in the distribution of AER within the microalbuminuric range at baseline, the rate of progression through the microalbuminuric range,[230] length of follow-up and duration of diabetes may all contribute to heterogeneity of outcome.

The association of regression with a lower AER and shorter duration of microalbuminuria is not surprising and emphasises the need for confirmation of screen-positive tests. According to NICE guidelines for type 2 DM,[381] ACE inhibitor therapy can be initiated when all results have been derived from a near patient test (that may be only semi-quantitative) and on the basis of a random urine albumin concentration alone, with no correction for creatinine, an approach to classification far less rigorous than in the majority of studies reporting in the literature.

Targets for glycaemic and blood pressure control can only be achieved with the compliance of the patient. Knowing and understanding the meaning of the numerical values for HbA_{1c} and blood pressure provides patients with a focus and incentive to achieve targets. Nonetheless, compliance remains a problem. If it were known that patient knowledge of their urine albumin status provided an additional motivational factor sufficient to increase compliance without causing additional undue stress then regular surveillance may be indicated, but studies are lacking. The converse is that a 'normal' test result may be interpreted as meaning that lack of optimal treatment does not matter, leading to a greater likelihood of developing complications, since the prognostic significance of AER for CVD is apparent even within the reference range.[73]

The authors are mindful of the fact that in a resource-limited healthcare system, people at high risk of a treatable disorder will require more clinical attention to management and will draw the limited clinical resources away from those at lower risk. However, if movement from a lower risk to a higher risk category is preventable rather than preordained, the consequence of this divergence of clinical attention is a constant or an increasing incidence of those progressing to high risk. One must therefore be careful to ensure that the line drawn between high and low risk is clearly defined and evidence based, both to protect those at low risk from unnecessary interventions and to optimise interventions for those at high risk. The introduction of a test to define this line more clearly has to be considered against current objective measurements that define on which side of the line a person will fall and current treatment strategies that are already implemented and whether they will be modified by knowledge from the new test.

A strategy that pursues optimal control of glycaemia and particularly of hypertension before microalbuminuria surveillance would reduce the number of patients defined as microalbuminuric and permit clinical attention to focus on this smaller group, in which further intensification of glycaemic and blood pressure control may be required to achieve clinical benefit. From the economic perspective, preliminary analysis suggests that selective screening for microalbuminuria in normotensive patients with type 2 DM and treatment with an ACE inhibitor of those who screen positive may be an effective strategy (Appendix 2). Advice on cessation of smoking (which is associated with microalbuminuria), diet and exercise, and implementation of lipid-lowering therapy are applicable to all patients irrespective of their urine albumin status. Testing for microalbuminuria is a target in the recently implemented General Medical Services Quality and Outcomes Framework. Laboratory requests for microalbuminuria have risen only steadily over recent years, but with an increase of over 100% in the first 3 months of 2004 alone,[388] a rise that is set to continue with increasing compliance with the Contract. With the consequences for patient treatment of a positive result even in the absence of other risk factors according to NICE guidelines, it is essential that national guidelines for key analytical performance criteria are devised and implemented to ensure the validity of standardised reference ranges.

The prognostic significance of microalbuminuria for the complications addressed in this review

needs to be considered against the enormous changes in therapy that have been recommended, many for over a decade, and yet are still not implemented in and/or complied with by many patients, namely optimisation of glycaemic control, antihypertensive and lipid-lowering therapies, as well as lifestyle changes. However, in patients in whom such implementation has occurred, does testing for microalbuminuria still carry the same prognostic significance? If so, then research can be focused to develop other additional treatment strategies. It is notable that regression of microalbuminuria to normoalbuminuria is substantial and most likely to be due to improved blood pressure control or an aggregate of improved treatments. In the face of regression, guidance is required concerning the continuation of concomitant treatment that was not the cause of regression but was instituted as a result of the now absent risk marker.

Implications for healthcare

Patients with diabetes at highest risk of developing major complications can predominantly be identified through determination of risk factors such as HbA_{1c}, blood pressure and lipid profile. Glycaemic control is the first aim of diabetic therapy. The most pronounced benefits of glycaemic control identified in this review are on retinal and renal complications in both normoalbuminuric and microalbuminuric patients considered together with little or no evidence of any greater benefit in those with microalbuminuria. Hence, microalbuminuric status may be a false boundary when considering the benefits of glycaemic control. Classification of a person as normoalbuminuric must not serve to suggest that they will derive less benefit from optimal glycaemic control than a person who is microalbuminuric.

When considering the value of urine albumin in identifying patients with diabetes who require the introduction of antihypertensive medication (which is currently the only optional medical therapy to reduce albumin excretion), the following conclusions can be drawn.

- With regard to hypertension, there was very little evidence from this systematic review that identifying those patients who also had microalbuminuria was of any additional benefit, since all patients with diabetes and hypertension benefit from improved blood pressure control.
- This review provides evidence that microalbuminuria surveillance of patients with type 1 or type 2 diabetes who are normotensive (and not on antihypertensive therapy) may be effective, since antihypertensive therapy with an ACE inhibitor substantially reduces their risk of progressing to clinical proteinuria and confers cardiovascular benefits, and these patients cannot be otherwise identified. It is likely that patients who are normotensive on antihypertensive treatment but who remain microalbuminuric would derive similar benefit, although they are highly likely to be on ACE inhibitor treatment already. All patients with microalbuminuria are also at increased mortality risk, even after adjustment for confounding factors, and patients with type 2 DM are also at increased risk of CVD and CHD mortality. Hence, assessment of cardiovascular risk and implementation of ACE inhibitor therapy should be considered in normotensive patients with microalbuminuria. Preliminary economic evaluation was inconclusive and further work in this area is required.
- In the authors' opinion, there is insufficient evidence to state that universal screening for microalbuminuria is of benefit to all patients with either type 1 or type 2 diabetes at present and indeed, if negative, it may provide false reassurance in the presence of suboptimal glycaemic and blood pressure control.
- Urine albumin measurement may be a useful indicator of the response to antihypertensive therapy, but does not have a proven role within the microalbuminuric range in modulating therapy over and above the measurement of blood pressure while the patient remains hypertensive, and this is not an indication for its use as a screening test.

Recommendations for research

There remain numerous areas of continuing uncertainty and many research recommendations could be made on the basis of these systematic reviews. The research recommendations made are those that the authors consider most important.

- What is the annual rate of development of microalbuminuria in patients with type 1 and type 2 DM who initially screen normoalbuminuric, and which risk factors predict the development of microalbuminuria? A systematic review of the literature is suggested.
- What are the factors that determine regression of microalbuminuria in adults and children with DM; is this accompanied by reduction of risk of

complications and why is the regression rate apparently higher in children?
- There is a need for further economic evaluation of screening for microalbuminuria in type 1 and type 2 DM, considering different strategies such as those used in the preliminary study considering blood pressure control (Appendix 2) and also incorporating glycaemic control.
- How variable is the analytical classification of patients as microalbuminuric, and which analytical performance criteria (especially with regard to bias at low concentration) are required to standardise urine screening tests for detecting microalbuminuria?
- What is the effect of lipid-lowering therapy on urine albumin excretion in patients with microalbuminuria and normoalbuminuria?
- Does patient knowledge of their urine albumin status increase their compliance with medication and lifestyle advice over and above any effect on compliance derived from knowledge of their HbA_{1c} and blood pressure? Is any gain at the expense of increased emotional stress?
- Can antihypertensive therapy in hypertensive patients with microalbuminuria be better tailored to the individual patient and improve outcomes by using urine albumin measurements in conjunction with blood pressure to adjust treatment compared with blood pressure targets alone?

Acknowledgements

South West Thames Kidney Fund, Epsom and St Helier Hospital NHS Trust Support For Science Programme, British Diabetic Association (now Diabetes UK) and Bayer USA Inc. are acknowledged for continuing support costs to extend the initial one-year grant from the Health Technology Assessment Programme. Many other individuals have contributed to the development of the review protocol and in informal discussions and their help was invaluable. However, the conclusions of the review necessarily represent the views of its authors and may not represent those of the experts mentioned below.

Members of the external review panel: Professor Gene Feder (Professor of General Practice and Primary Care, St Bartholomew's and Royal London Medical School), Professor Terry Feest (Professor of Clinical Nephrology, University of Bristol), Professor Sally Marshall (Professor of Medicine, The Medical School, Newcastle upon Tyne), Dr Mary Pierce (Senior Lecturer in General Practice, Imperial College School of Medicine, London), Dr David Rowe (Consultant Clinical Biochemist, Southampton General Hospital) and Professor Ken Shaw (Consultant Physician and Endocrinologist, Queen Alexandra Hospital, Portsmouth).

For preparing a first draft of the economic evaluation: Mrs Brenda Armstrong.

Colleagues who generously spared time for informal discussions: Professor RR Holman, Professor Sir KGMM Alberti, Professor H Keen, Professor GC Viberti, Professor JH Fuller, Professor Nicholas Wald, Professor Deborah Ashby, Mrs Mary MacKinnon, Dr Susan Manley, Dr Margaret McGeown and Dr Louise Parsons.

Authors or co-authors of studies quoted in this review who have kindly provided us with additional data: John Fuller, David Webb, Lynda Stevens, Nish Chaturvedi, R John Jarrett and Ute Weis (UK), Gerald Watts and Valerie Burke (Australia), Chris Florkowski (New Zealand), Peter Rossing (Denmark), Mari-Anne Gall (Denmark), Ole Wirta (Finland), Bo Isomaa (Finland), George Bakris (USA), S Weitzman and A Biderman (Israel) and E Casiglia (Italy).

For generous help in St Helier Hospital Library: Edward George and Marco Isetta.

For secretarial assistance at the Institute for Renal Research, St Helier Hospital: Mrs Enid Ford.

Contribution of authors

Dr David Newman (Consultant Clinical Biochemist) led the project; obtained original funding and subsequent financial support; coordinated the project; contributed to the intellectual development of the project; helped develop the study protocol and design standard forms; participated in assessing study eligibility, quality and data extraction; prepared the tables; co-authored the first draft of the report.

Dr Martin Mattock (Senior Research Fellow) coordinated the project; contributed to the intellectual development of the project; helped develop the study protocol and design standard forms; carried out the searches; participated in assessing study eligibility, quality and data extraction; prepared the tables; co-authored the first draft of the report; collaborated on the extensive rewriting of the first draft after peer-review to produce the final report.

Dr Anne Dawnay (Senior Lecturer and Consultant Biochemist) obtained original funding; contributed to the intellectual development of the project; helped develop the study protocol and design standard forms; participated in assessing study eligibility, quality and data extraction; wrote and revised sections of the first draft of the report; collaborated on the extensive rewriting of the first draft after peer-review to produce the final report.

Ms Sally Kerry (Senior Lecturer in Medical Statistics) participated in assessing study eligibility, quality and data extraction; carried out the statistical analysis and interpretation; prepared the figures; contributed to revising the first draft of the report; collaborated on the extensive rewriting of the first draft after peer-review to produce the final report.

Dr Alistair McGuire (Professor of Health Economics) obtained original funding; was responsible for the economic analysis described in Appendix 2.

Dr Magdi Yaqoob (Professor of Nephrology and Consultant Nephrologist) obtained original funding; contributed to the intellectual development of the project; helped develop the study protocol and design standard forms; participated in assessing study eligibility, quality and data extraction; commented on the first and final drafts of the report.

Dr Graham Hitman (Professor of Molecular Medicine and Consultant Diabetologist) obtained original funding; contributed to the intellectual development of the project; helped develop the study protocol and design standard forms; participated in assessing study eligibility, quality and data extraction; commented on the first and final drafts of the report.

Dr Catherine Hawke (Consultant in Public Health Medicine) obtained original funding; contributed to the intellectual development of the project; helped develop the study protocol and design standard forms; participated in assessing study eligibility, quality and data extraction; commented on the first and final drafts of the report.

References

1. Roper NA, Bilous RW, Kelly WF, Unwin NC, Connolly VM. Excess mortality in a population with diabetes and the impact of material deprivation; longitudinal, population based study. *BMJ* 2001;**322**:1389–93.
2. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, *et al*. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation* 1999;**100**:1134–46.
3. UK National Screening Committee. *The NSC handbook of population screening programmes*. Department of Health, London; 1998.
4. Ruggenenti P, Perna A, Mosconi L, Matalone M, Pisoni R, Gaspari F, *et al*. Proteinuria predicts end-stage renal failure in non-diabetic chronic nephropathies. *Kidney Int Suppl* 1997;**63**(7):S54–7.
5. Keane WF. Proteinuria: its clinical importance and role in progressive renal disease. *Am J Kidney Dis* 2000;**35**(4 Suppl 1):S97–105.
6. McGuire DK. Influence of proteinuria on long-term outcome among patients with diabetes: the evidence continues to accumulate. *Am Heart J* 2000;**139**:934–5.
7. Bennett PH, Haffner S, Kasiske BL, Keane WF, Mogensen CE, Parving HH, *et al*. Screening and management of microalbuminuria in patients with diabetes mellitus: recommendations to the Scientific Advisory Board of the National Kidney Foundation from an ad hoc committee of the Council on Diabetes Mellitus of the National Kidney Foundation. *Am J Kidney Dis* 1995; **25**:107–12.
8. American Diabetes Association and the National Kidney Foundation. Consensus development conference on the diagnosis and management of nephropathy in patients with diabetes mellitus. *Diabetes Care* 1994;**17**:1357–61.
9. Mogyorosi A, Ziyadeh FN. Diabetes and hypertension. Australian Diabetes Society position statement. *Med J Aust* 1996;**164**:571–2.
10. Zelmanovitz T, Gross JL, Oliveira JR, Paggi A, Tatsch MA, Azevedo, MJ. The receiver operating characteristics curve in the evaluation of a random urine specimen as a screening test for diabetic nephropathy. *Diabetes Care* 1997;**20**:516–19.
11. Rowe DJF, Dawnay A, Watts GF. Microalbuminuria in diabetes mellitus: review and recommendations for the measurement of albumin in urine. *Ann Clin Biochem* 1990;**27**:297–312.
12. Keen H, Chlouverakis C. An immunoassay method for urinary albumin at low concentrations. *Lancet* 1963;**ii**:913–16.
13. Keen H, Chlouverakis C, Fuller J, Jarrett RJ. The concomitants of raised blood sugar: studies in newly-detected hyperglycaemics. II. Urinary albumin excretion, blood pressure and their relation to blood sugar levels. *Guys Hospital Reports* 1969;**118**:247–54.
14. Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin-dependent patients. *N Engl J Med* 1984;**311**:89–93.
15. Viberti GC, Jarrett RJ, Mahmud U, Hill RD, Argyropoulos A, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* 1982;**i**:1430–2.
16. Diabetes Control and Complications Trial Group. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. *Am J Cardiol* 1995;**75**:894–903.
17. Parving HH, Oxenboll B, Svendsen PA, Christiansen JS, Andersen AR. Early detection of patients at risk of developing diabetic nephropathy. A longitudinal study of urinary albumin excretion. *Acta Endocrinologica* 1982; **100**:550–5.
18. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. *Arch Intern Med* 1997;**157**:1413–18.
19. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977–86.
20. Turner RC, Millns H, Neil HAW, Stratton IM, Manley SE, Mathews DR, *et al*. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: UKPDS:23. *BMJ* 1998;**316**:823–8.
21. Levin SR, Coburn JW, Abraira C, Henderson WG, Colwell JA, Emanuele NV, *et al*. Effect of intensive glycemic control on microalbuminuria in type 2 diabetes. Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial Investigators. *Diabetes Care* 2000;**23**:1478–85.
22. Ahmad J, Siddiqui MA, Ahmad H. Effective postponement of diabetic nephropathy with

enalapril in normotensive type 2 diabetic patients with microalbuminuria. *Diabetes Care* 1997; **20**:1576–81.

23. Golan L, Birkmeyer J, Welch G. The cost effectiveness of treating all patients with Type 2 diabetes with angiotensin-coverting enzyme inhibitors. *Ann Intern Med* 1999;**131**:660–7.

24. Borch-Johnsen K, Wenzel H, Viberti GC, Mogensen CE. Is screening and intervention for microalbuminuria worthwhile in patients with insulin-dependent diabetes? *BMJ* 1993;**306**:1722–3.

25. Borch-Johnsen K. ACE inhibitors in patients with diabetes-mellitus – clinical and economic considerations. *Pharmacoeconomics* 1996;**9**:392–8.

26. Siegel J, Krolewski A, Warram J, Weinstein M. Cost-effectiveness of screening and early treatment of nephropathy in patients with insulin-dependent diabetes mellitus. *J Am Soc Nephrol* 1992; **3**:S111–19.

27. Viberti GC, Marshall S, Beech R, Brown V, Derben P, Higson N, *et al*. Report on renal disease in diabetes. *Diabet Med* 1996;**13**(Suppl 4):S6–12.

28. NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness*. CRD guidelines for those carrying out or commissioning reviews. CRD Report 4. York: CRD, University of York; 1996.

29. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88.

30. Egger M, Davey Smith G, Stettler C, Diem P. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta analysis. *Diabet Med* 1997;**14**:919–28.

31. Sutton AJ, Abrams KR, Jones DR, Sheldon T, Song F. *Methods for meta-analysis in medical research*. Chichester: Wiley; 2000.

32. Jarrett RJ, Viberti GC, Argyropoulos A, Hill RD, Mahmud U, Murrells TJ. Microalbuminuria predicts mortality in non-insulin-dependent diabetics. *Diabet Med* 1984;**1**:17–19.

33. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. *N Engl J Med* 1984;**310**:356–60.

34. Klein R, Klein BEK, Moss SE, Cruickshanks KJ, Brazy PC. The 10-year incidence of renal insufficiency in people with type 1 diabetes. *Diabetes Care* 1999;**22**:743–51.

35. Rossing P, Hougaard P, Borch-Johnsen K, Parving HH. Predictors of mortality in insulin dependent diabetes; 10 year observational follow up study. *BMJ* 1996;**313**:779–84.

36. Rossing P, Breum L, Major-Pedersen A, Sato A, Winding H, Pietersen A, *et al*. Prolonged QTc interval predicts mortality in patients with type 1 diabetes mellitus. *Diabet Med* 2001;**18**:199–205.

37. Deckert T, Yokoyama H, Mathiesen E, Ronn B, Jensen T, Feldt-Rasmussen B, *et al*. Cohort study of predictive value of urinary albumin excretion for atherosclerotic vascular disease in patients with insulin dependent diabetes. *BMJ* 1996;**312**:871–4.

38. Torffvit O, Agardh CD. The predictive value of albuminuria for cardiovascular and renal disease. A 5-year follow-up study of 476 patients with type I diabetes mellitus. *J Diabetes Complications* 1993; **7**:49–56.

39. Agardh CD, Agardh E, Torffvit O. The association between retinopathy, nephropathy, cardiovascular disease and long-term metabolic control in type 1 diabetes mellitus: a 5 year follow-up study of 442 adult patients in routine care. *Diabetes Res Clin Pract* 1997;**35**:113–21.

40. Forsblom CM, Groop PH, Ekstrand A, Groop LC. Predictive value of microalbuminuria in patients with insulin-dependent diabetes of long duration [see comments]. *BMJ* 1992;**305**:1051–3.

41. Beatty OL, Ritchie CM, Hadden DR, Kennedy L, Bell PM, Atkinson AB. Is a random urinary albumin concentration a useful screening test in insulin-treated diabetic patients? *Ir J Med Sci* 1994; **163**:406–9.

42. Messent JW, Elliott TG, Hill RD, Jarrett RJ, Keen H, Viberti GC. Prognostic significance of microalbuminuria in insulin-dependent diabetes mellitus: a twenty-three year follow-up study. *Kidney Int* 1992;**41**:836–9.

43. Weis U, Turner B, Gibney J, Watts GF, Burke GL, Shaw KM, *et al*. Long-term predictors of coronary artery disease and mortality in type 1 diabetes. *Q JM* 2001;**94**:623–30.

44. Pedersen M, Christensen CK, Mogensen CE. Long-term (18 year) prognosis for normo- and microalbuminuric type 1 (insulin-dependent) diabetic patients. *Diabetologia* 1992;**35**:A60.

45. Muhlhauser I, Overmann H, Bender R, Jorgens V, Berger M. Predictors of mortality and end-stage diabetic complications in patients with type 1 diabetes mellitus on intensified insulin therapy. *Diabet Med* 2000;**17**:727–34.

46. The EURODIAB Prospective Complications Study (PCS) Group. Risk factors for coronary heart disease morbidity and mortality differ in men and women with type 1 diabetes [abstract]. *Diabetologia* 1999;**42**(Suppl 1):A48.

47. Sawicki PT, Heinemann L, Berger M. Comparison of methods for determination of microalbuminuria in diabetic patients. *Diabet Med* 1989;**6**:412–15.

48. Stiegler H, Standl E, Schulz K, Roth R, Lehmacher W. Morbidity, mortality, and albuminuria in type 2 diabetic patients: a three-year prospective study of a random cohort in general practice. *Diabet Med* 1992;**9**:646–53.

49. Standl E, Balletshofer B, Dahl B, Weichenhain B, Stiegler H, Hormann A, *et al*. Predictors of 10–year macrovascular and overall mortality in patients with NIDDM: the Munich General Practitioner Project. *Diabetologia* 1996;**39**:1540–5.

50. Gall M-A, Borch-Johnsen K, Hougaard P, Nielsen FS, Parving H-H. Albuminuria and poor glycemic control predict mortality in NIDDM. *Diabetes* 1995;**11**:1303–9.

51. Mattock MB, Morrish NJ, Viberti G, Keen H, Fitzgerald AP, Jackson G. Prospective study of microalbuminuria as predictor of mortality in NIDDM. *Diabetes* 1992;**41**:736–41.

52. Mattock MB, Barnes DJ, Viberti G, Keen H, Burt D, Hughes JM, *et al*. Microalbuminuria and coronary heart disease in NIDDM: an incidence study. *Diabetes* 1998;**47**:1786–92.

53. Damsgaard EM, Froland A, Jorgensen OD, Mogensen CE. Eight to nine year mortality in known non-insulin dependent diabetics and controls. *Kidney Int* 1992;**41**:731–5.

54. Damsgaard EM, Froland A, Jorgensen OD, Mogensen CE. Prognostic value of urinary albumin excretion rate and other risk factors in elderly diabetic patients and non-diabetic control subjects surviving the first 5 years after assessment. *Diabetologia* 1993;**36**:1030–6.

55. Schmitz A, Vaeth M. Microalbuminuria: A major risk factor in non-insulin-dependent diabetes. A 10-year follow-up study of 503 patients. *Diabet Med* 1988;**5**:126–34.

56. Neil HAW, Hawkins M, Potok M, Thorogood M, Cohen D, Mann J. A prospective population-based study of microalbuminuria as a predictor of mortality in NIDDM. *Diabetes Care* 1993; **16**:996–1003.

57. Neil HAW, Hawkins MM, Potock MHN, Mann JI. Prognostic value of urinary albumin concentration in diabetic patients surviving the first 5 years after assessment. *Diabetologia* 1994;**37**:1287–8.

58. Araki S, Haneda M, Togawa M, Sugimoto T, Shikano T, Nakagawa T, *et al*. Microalbuminuria is not associated with cardiovascular death in Japanese NIDDM. *Diabetes Res Clin Pract* 1997; **35**:35–40.

59. Araki SI, Kikkawa R, Haneda M, Koya D, Togawa M, Liang PM, *et al*. Microalbuminuria cannot predict cardiovascular death in Japanese subjects with non-insulin-dependent diabetes mellitus. *J Diabetes Complications* 1995;**9**:323–5.

60. Stehouwer CD, Nauta JJ, Zeldenrust GC, Hackeng WH, Donker AJ, Den Ottolander GJ. Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin-dependent diabetes mellitus. *Lancet* 1992; **340**:319–23.

61. Chan JCN, Cheung CK, Cheung MYF, Swaminathan R, Critchley J, Cockram CS. Abnormal albuminuria as a predictor of mortality and renal impairment in Chinese patients with NIDDM. *Diabetes Care* 1995;**18**:1013–16.

62. Agewall S, Wikstrand J, Ljungman S, Fagerberg B. Usefulness of microalbuminuria in predicting cardiovascular mortality in treated hypertensive men with and without diabetes mellitus. *Am J Cardiol* 1997;**80**:164–9.

63. Beatty OL, Ritchie CM, Bell PM, Hadden DR, Kennedy L, Atkinson AB. Microalbuminuria as identified by a spot morning urine specimen in non-insulin-treated diabetes: an eight-year follow-up study. *Diabet Med* 1995;**12**:261–6.

64. MacLeod JM, Lutale J, Marshall SM. Albumin excretion and vascular deaths in NIDDM. *Diabetologia* 1995;**38**:610–16.

65. Beilin J, Stanton KG, McCann VJ, Knuiman MW, Divitini ML. Microalbuminuria in type 2 diabetes: an independent predictor of cardiovascular mortality. *Australian and New Zealand Journal of Medicine* 1996;**26**:519–25.

66. Friis T, Pedersen LR. Microalbuminuria in type 2 diabetic patients: a prospective follow-up study. *Ann Clin Biochem* 1997;**34**:247–51.

67. Wirta O, Pasternack A, Mustonen J, Laippala P. Renal and cardiovascular predictors of 9-year total and sudden cardiac mortality in non-insulin-dependent diabetic subjects. *Nephrol Dial Transplant* 1997;**12**:2612–17.

68. Forsblom CM, Sane T, Groop P-H, Totterman KJ, Kallio M, Saloranta C, *et al*. Risk factors for mortality in type II (non-insulin-dependent) diabetes: evidence of a role for neuropathy and a protective effect of HLA-DR4. *Diabetologia* 1998; **41**:1253–62.

69. Hänninen J, Takala J, Keinanen-Kiukaanniemi S. Albuminuria and other risk factors for mortality in patients with non-insulin-dependent diabetes mellitus aged under 65 years: a population-based prospective 5–year study. *Diabetes Res Clin Pract* 1999;**43**:121–6.

70. Casiglia E, Zanette G, Mazza A, Donadon V, Donada C, Pizziol A, *et al*. Cardiovascular mortality in non-insulin-dependent diabetes mellitus. A controlled study among 683 diabetics and 683 age- and sex-matched normal subjects. *Eur J Epidemiol* 2000;**16**:677–84.

71. Valmadrid CT, Klein R, Moss SE, Klein BE. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. *Arch Intern Med* 2000;**160**:1093–100.

72. de Grauw WJC, van de Lisdonk EH, van Gerwen WHEM, Verstappen M, van den Hoogen HJM, Willems JL, *et al*. Microalbuminuria in patients

with type 2 diabetes mellitus from general practice: course and predictive value. *Diabet Med* 2001;**18**:139–43.

73. Gerstein HC. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; **286**:421–6.

74. Weitgasser R, Schnoell F, Gappmayer B, Kartnig I. Prospective evaluation of urinary *N*-acetyl-β-D-glucosaminidase with respect to macrovascular disease in elderly type 2 diabetic patients. *Diabetes Care* 1999;**22**:1882–6.

75. Jager A, van Hinsbergh VW, Kostense P, Emeis JJ, Nijpels G, Dekker JM, *et al*. Prognostic implications of retinopathy and a high plasma von Willebrand factor concentration in type 2 diabetic subjects with microalbuminuria. *Nephrol Dial Transplant* 2001;**16**:529–36.

76. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, *et al*. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;**24**:683–9.

77. Vanzetto G, Halimi S, Hammoud T, Fagret D, Benhamou PY, Cordonnier D, *et al*. Prediction of cardiovascular events in clinically selected high-risk NIDDM patients. *Diabetes Care* 1999;**22**:19–26.

78. Niskanen L, Sitonen O, Suhonen M, Uusitupa M. Medial arterial calcification predicts cardiovascular mortality in patients with NIDDM. *Diabetes Care* 1994;**17**:1252–6.

79. Niskanen LK, Penttila I, Parviainen M, Uusitupa MIJ. Evolution, risk factors, and prognostic implications of albuminuria in NIDDM. *Diabetes Care* 1996;**19**:486–93.

80. Uusitupa MIJ, Niskanen LK, Siitonen O, Voutilainen E, Pyorala K. Ten-year cardiovascular mortality in relation to risk factors and abnormalities in lipoprotein composition in type 2 (non-insulin-dependent) diabetic and non-diabetic subjects. *Diabetologia* 1993;**36**:1175–84.

81. Agardh CD, Agardh E, Torffvit O. The prognostic value of albuminuria for the development of cardiovascular disease and retinopathy: a 5-year follow-up of 451 patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 1996;**32**:35–44.

82. Jager A, Van Hinsbergh VWM, Kostense PJ, Emeis JJ, Nijpels G, Dekker JM, *et al*. Increased levels of soluble vascular cell adhesion molecule 1 are associated with risk of cardiovascular mortality in type 2: The Hoorn study. *Diabetes* 2000; **49**:485–91.

83. Stehouwer CD, Gall MA, Hougaard P, Jakobs C, Parving HH. Plasma homocysteine concentration predicts mortality in non-insulin-dependent diabetic patients with and without albuminuria. *Kidney Int* 1999;**55**:308–14.

84. Niskanen L, Voutilainen R, Terasvirta M, Lehtinen J, Teppo AM, Groop L, *et al*. A prospective study of clinical and metabolic associates of proteinuria in patients with type 2 diabetes mellitus. *Diabet Med* 1993;**10**:543–9.

85. Niskanen L, Turpeinen A, Penttila I, Uusitupa MIJ. Hyperglycemia and compositional lipoprotein abnormalities as predictors of cardiovascular mortality in type 2 diabetes. *Diabetes Care* 1998; **21**:1861–9.

86. Torffvit O, Agardh CD. The impact of metabolic and blood pressure control on incidence and progression of nephropathy. A 10-year study of 385 type 2 diabetic patients. *J Diabetes Complications* 2001;**15**:307–13.

87. Torffvit O, Agardh CD. A blood pressure cut-off level identified for renal failure, but not for macrovascular complications in type 2 diabetes: a 10-year observation study. *Horm Metab Res* 2002; **34**:32–5.

88. Florkowski CM, Scott RS, Coope PA, Moir CL. Predictors of mortality from type 2 diabetes mellitus in Canterbury, New Zealand; a ten-year cohort study. *Diabetes Res Clin Pract* 2001; **53**:113–20.

89. Schmitz A, Vaeth M, Mogensen CE. Systolic blood pressure relates to the rate of progression of albuminuria in NIDDM. *Diabetologia* 1994; **37**:1251–8.

90. John L, Rao PS, Kanagasabapathy AS. Rate of progression of albuminuria in type II diabetes. Five-year prospective study from south India. *Diabetes Care* 1994;**17**:888–90.

91. Biderman A, Rosenblatt I, Rosen S, Zangwill LM, Shalev R, Friger M, *et al*. Sex differentials in predictors of mortality for patients with adult-onset diabetes. *Diabetes Care* 2000;**23**:602–5.

92. Haneda M, Kikkawa R, Togawa M, Koya D, Kajiwara N, Uzu T, *et al*. High blood pressure is a risk factor for the development of microalbuminuria in Japanese subjects with non-insulin-dependent diabetes mellitus. *J Diabetes Complications* 1992;**6**:181–5.

93. Florkowski CM, Scott RS, Moir CL, Graham PJ. Lipids but not glycaemic parameters predict total mortality from type 2 diabetes mellitus in Canterbury, New Zealand. *Diabet Med* 1998; **15**:386–92.

94. Uusitupa M, Niskanen L, Siitonen O, Voutilainen E, Pyorala K. 5-Year incidence of atherosclerotic vascular disease in relation to general risk factors, insulin level, and abnormalities in lipoprotein composition in non-insulin-dependent diabetic and nondiabetic subjects. *Circulation* 1990;**82**:27–36.

95. Jager A, Van Hinsbergh VWM, Kostense PJ, Emeis JJ, Yudkin JS, Nijpels G, *et al*. Von

Willebrand factor, C-reactive protein and five year mortality in diabetic and non-diabetic subjects: the Hoorn study. *Diabetes* 1999;**49**:485–91.

96. Gall M-A, Knudsen E, Hougaard P, Borch-Johnsen K, Parving H-H. Predictors of 10-year mortality in patients with non-insulin-dependent (NIDDM) diabetes mellitus. *J Am Soc Nephrol* 1998;**9**:115A.

97. Allawi J, Fitzgerald AP, Lee M, Burakowska A, Jarrett RJ. Increased albumin excretion, fat distribution and other risk factors for all-causes and cardiovascular mortality in a selected population of type 2 diabetic subjects not treated with insulin. *Diabetes Res* 1997;**32**:1–9.

98. Mogensen C, Chachati A, Christensen CK, Close CF, Deckert T, Hommel E, *et al*. Microalbuminuria: an early marker of renal involvement in diabetes. *Uraemia Investigation* 1986;**9**:85–95.

99. Rachmani R, Levi Z, Lidar M, Slavachevski I, Half-Onn E, Ravid M. Considerations about the threshold value of microalbuminuria in patients with diabetes mellitus: lessons from an 8-year follow-up study of 599 patients. *Diabetes Res Clin Pract* 2000;**49**:187–94.

100. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. 2. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 1984;**102**:520–6.

101. Orchard TJ, Dorman JS, Maser RE, Becker DJ, Drash AL, Ellis D, *et al*. Prevalence of complications in IDDM by sex and duration. Pittsburgh Epidemiology of Diabetes Complications Study-2. *Diabetes* 1990;**39**:1116–24.

102. Sjoelie AK, Stephenson J, Aldington S, Kohner E, Janka H, Stevens L, *et al*. Retinopathy and vision loss in insulin-dependent diabetes in Europe. The EURODIAB IDDM Complications Study. *Ophthalmology* 1997;**104**:252–60.

103. Krolewski AS, Warram JH, Rand LI, Christlieb AR, Busick EJ, Kahn CR. Risk of proliferative diabetic retinopathy in juvenile-onset type 1 diabetes: a 40-yr follow-up study. *Diabetes Care* 1986;**9**:443–52.

104. Dwyer MS, Melton LJ, Ballard DJ, Palumbo PJ, Trautman JC, Chu CP. Incidence of diabetic retinopathy and blindness: a population-based study in Rochester, Minnesota. *Diabetes Care* 1985; **8**:316–22.

105. Trautner C, Haastert B, Giani G, Berger M. Incidence of blindness in southern Germany between 1990 and 1998. *Diabetologia* 2001; **44**:147–50.

106. Klein R, Klein BE, Moss SE. Relation of glycemic control to diabetic microvascular complications in diabetes mellitus. *Ann Intern Med* 1996;**124**:90–6.

107. Klein BE, Klein R, Moss SE, Palta M. A cohort study of the relationship of diabetic retinopathy to blood pressure. *Arch Ophthalmol* 1995;**113**:601–6.

108. Knowles HCL, Guest GM, Lampe J, Kessler M, Skilman TG. The course of juvenile diabetes treated with unmeasured diet. *Diabetes* 1965; **14**:239–73.

109. Kofoed-Enevoldsen A, Jensen T, Borch-Johnsen K, Deckert T. Incidence of retinopathy in type 1 (insulin-dependent) diabetes: association with clinical nephropathy. *J Diabetes Complications* 1987; **1**:96–9.

110. Klein R, Moss SE, Klein BE. Is gross proteinuria a risk factor for the incidence of proliferative diabetic retinopathy? *Ophthalmology* 1993; **100**:1140–6.

111. Chavers BM, Mauer MS, Ramsay RS, Steffes MW. Relationship between retinal and glomerular lesions in IDDM patients. *Diabetes* 1994;**43**:441–6.

112. Cruickshanks KJ, Ritter LA, Klein R, Moss SE. The association of microalbuminuria with diabetic retinopathy. *Ophthalmology* 1993;**100**:862–7.

113. Vigstrup J, Mogensen CE. Proliferative diabetic retinopathy: at risk patients identified by early detection of microalbuminuria. *Acta Ophthalmol* 1985;**63**:530–4.

114. Skrha J, Haas T, Sperl M, Stibor V, Stolba P. A six-year follow-up of the relationship between *N*-acetyl-β-glucosaminidase and albuminuria in relation to retinopathy. *Diabet Med* 1991;**8**:817–21.

115. Krolewski AS, Barzilay J, Warram JH, Martin BC, Pfeifer M, Rand LI. Risk of early-onset proliferative retinopathy in IDDM is closely related to cardiovascular autonomic neuropathy. *Diabetes* 1992;**41**:430–7.

116. Kullberg CE, Arnqvist HJ. Elevated long-term glycated haemoglobin precedes proliferative retinopathy and nephropathy in type 1 (insulin-dependent) diabetic patients. *Diabetologia* 1993; **36**:961–5.

117. Agardh E, Agardh CD, Torffvit O. A 5-year follow-up study on the incidence of retinopathy in type 1 diabetes mellitus in relation to medical risk indicators. *J Intern Med* 1994;**235**:353–8.

118. Almdal T, Norgaard K, Feldt-Rasmussen B, Deckert T. The predictive value of microalbuminuria in IDDM: a five-year follow-up study. *Diabetes Care* 1994;**17**:120–5.

119. Danne T, Weber B, Hartmann R, Enders I, Burger W, Hovener G. Long-term glycemic control has a nonlinear association to the frequency of background retinopathy in adolescents with diabetes. Follow-up of the Berlin Retinopathy Study. *Diabetes Care* 1994;**17**:1390–6.

120. Lloyd CE, Klein R, Maser RE, Kuller LH, Becker DJ, Orchard TJ. The progression of

retinopathy over 2 years: the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study. *J Diabetes Complications* 1995;**9**:140–8.

121. Mathiesen ER, Ronn B, Storm B, Foght H, Deckert T. The natural course of microalbuminuria in insulin-dependent diabetes: a 10-year prospective study. *Diabet Med* 1995;**12**:482–7.

122. Castillo A, Del Castillo J, Diaz D, Sayagues O, Ruibal J, Garcia-Sanchez J. Analysis of the blood–retinal barrier: its relation to clinical and metabolic factors and progression to retinopathy in juvenile diabetics. A 4-year follow-up study. *Graefe's Arch Clin Exp Ophthalmol* 1996; **234**:246–50.

123. Kordonouri O, Danne T, Hopfenmuller W, Enders I, Hovener G, Weber B. Lipid profiles and blood pressure: are they risk factors for the development of early background retinopathy and incipient nephropathy in children with insulin-dependent diabetes mellitus? *Acta Paediatr* 1996; **85**:43–8.

124. Lloyd CE, Becker D, Ellis D, Orchard TJ. Incidence of complications in insulin-dependent diabetes mellitus: a survival analysis. *Am J Epidemiol* 1996;**143**:431–41.

125. D'Annunzio G, Malvezzi F, Vitali L, Barone C, Giacchero R, Klersy C, *et al*. A 3–19-year follow-up study on diabetic retinopathy in patients diagnosed in childhood and treated with conventional therapy. *Diabet Med* 1997;**14**:951–8.

126. Kalter-Leibovici O, Leibovici L, Loya N, Kremer I, Axer-Siegel R, Karp M, *et al*. The development and progression of diabetic retinopathy in type 1 diabetic patients: a cohort study. *Diabet Med* 1997; **14**:856–66.

127. Rossing K, Jacobsen P, Rossing P, Lauritzen E, Lund-Andersen H, Parving H-H. Improved visual function in IDDM patients with unchanged cumulative incidence of sight-threatening diabetic retinopathy. *Diabetes Care* 1998;**21**:2007–15.

128. Gilbert RE, Tsalamandris C, Allen TJ, Colville D, Jerums G. Early nephropathy predicts vision-threatening retinal disease in patients with type I diabetes mellitus. *J Am Soc Nephrol* 1998;**9**:85–9.

129. Villar G, Garcia Y, Goicolea I, Vazquez JA. Determinants of development of microalbuminuria in normotensive patients with type 1 and type 2 diabetes. *Diabetes Metabolism* 1999;**25**:246–54.

130. Lovestam-Adrian M, Agardh E, Agardh CD. The temporal development of retinopathy and nephropathy in type 1 diabetes mellitus during 15 years diabetes duration. *Diabetes Res Clin Pract* 1999;**45**:15–23.

131. RCPEDRG. Near-normal urinary albumin concentrations predict progression to diabetic nephropathy in type 1 diabetes mellitus. *Diabet Med* 2000;**17**:782–91.

132. Olsen BS, Sjolie A-K, Hougaard P, Johannesen J, Borch-Johnsen K, Marinelli K, *et al*. 6-year nationwide cohort study of glycaemic control in young people with type 1 diabetes: risk markers for the development of retinopathy, nephropathy and neuropathy. *J Diabetes Complications* 2000; **14**:295–300.

133. Gomes MB, Dorigo D, Da Silva GR, Goncalves MF, Neves R. Prospective study of development of microalbuminuria and retinopathy in Brazilian IDDM patients. *Acta Diabetol* 2000;**37**:19–25.

134. Lovestam-Adrian M, Agardh CD, Torffvit O, Agardh E. Diabetic retinopathy, visual acuity, and medical risk indicators. A continuous 10-year follow-up study in type 1 diabetic patients under routine care. *J Diabetes Complications* 2001; **15**:287–94.

135. Chaturvedi N, Sjoelie A-K, Porta M, Aldington SJ, Fuller JH, Songini M, *et al*. Markers of insulin resistance are strong risk factors for retinopathy incidence in type 1 diabetes. *Diabetes Care* 2001; **24**:284–9.

136. Porta M, Sjoelie A-K, Chaturvedi N, Stevens L, Rottiers R, Veglio M, *et al*. Risk factors for progression to proliferative diabetic retinopathy in the EURODIAB Prospective Complications Study. *Diabetologia* 2001;**44**:2203–9.

137. Janka HU, Warram JH, Rand LI, Krolewski AS. Risk factors for progression of background retinopathy in long-standing IDDM. *Diabetes* 1989; **38**:460–4.

138. Chaturvedi N, Bandinelli S, Mangili R, Penno G, Rottiers RE, Fuller JH. Microalbuminuria in type 1 diabetes: rates, risk factors and glycemic threshold. *Kidney Int* 2001;**60**:219–27.

139. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonyureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**:837–53.

140. Turner R, Holman R, Stratton I, Cull C, Frighi V, Manley S, *et al*. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;**317**:703–13.

141. Kanauchi M, Kawano T, Uyama H, Shiiki H, Dohi K. Discordance between retinopathy and nephropathy in type 2 diabetes. *Nephron* 1998; **80**:171–4.

142. Gall M-A, Rossing P, Skott P, Damsbo P, Vaag A, Bech K, *et al*. Prevalence of micro- and macroalbuminuria, arterial hypertension, retinopathy and large vessel disease in European type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 1991;**34**:655–61.

143. Wirta O, Pasternack A, Mustonen J, Laioppala P, Lahde Y. Retinopathy is independently related to microalbuminuria in type 2 diabetes mellitus. *Clin Nephrol* 1999;**51**:329–34.

144. Savage S, Estacio RO, Jeffers B, Schrier RW. Urinary albumin excretion as a predictor of diabetic retinopathy, neuropathy, and cardiovascular disease in NIDDM. *Diabetes Care* 1996;**19i**:1243–8.

145. Lee ET, Lee VS, Lu M, Russell D. Development of proliferative retinopathy in NIDDM. A follow-up study of American Indians in Oklahoma. *Diabetes* 1992;**41**:359–67.

146. Davis TME, Stratton IM, Fox CJ, Holman RR, Turner RC. UK Prospective Diabetes Study 22. Effect of age at diagnosis on diabetic tissue damage during the first 6 years of NIDDM. *Diabetes Care* 1997;**20**:1435–41.

147. Guillausseau PJ, Massin P, Charles MA, Allaguy H, Guvenli Z, Virally M, *et al*. Glycaemic control and development of retinopathy in type 2 diabetes mellitus: a longitudinal study. *Diabet Med* 1998; **15**:151–5.

148. Kim HK, Kim CH, Kim SW, Park JY, Hong SK, Yoon YH, *et al*. Development and progression of diabetic retinopathy in Koreans with NIDDM. *Diabetes Care* 1998;**21**:134–8.

149. Park J-Y, Kim H-K, Chung YE, Kim SW, Hong SK, Lee K-U. Incidence and determinants of microalbuminuria in Koreans with type 2 diabetes. *Diabetes Care* 1998;**21**:530–4.

150. Tanaka Y, Atsumi Y, Matsuoka K, Onuma T, Tohjima T, Kawamori R. Role of glycemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. *Diabetes Care* 1998;**21**:116–20.

151. Florkowski CM, Scott RS, Moir CL, Graham PJ. Clinical and biochemical outcomes of Type 2 diabetes mellitus in Canterbury, New Zealand: a 6-year cohort study. *Diabetes Res Clin Pract* 1998; **40**:167–73.

152. Molyneaux LM, Constantino MI, McGill M, Zilkens R, Yue DK. Better glycaemic control and risk reduction of diabetic complications in type 2 diabetes: comparison with the DCCT. *Diabetes Res Clin Pract* 1998;**42**:77–83.

153. Durruty A, Carpentier C, Krause I, Garcia de los Rios A. Retinal involvement in type 2 diabetics with microalbuminuria. *Rev Med Chil* 2000; **128**:1085–92.

154. Rachmani R, Lidar M, Levy Z, Ravid M. Effect of enalapril on the incidence of retinopathy in normotensive patients with type 2 diabetes. *European Journal of Internal Medicine* 2000; **11**:48–50.

155. Stratton I, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE, *et al*. UKPDS 50: risk factors for incidence and progression of retinopathy in type 2 diabetes over 6 years from diagnosis. *Diabetologia* 2001;**44**:156–63.

156. Voutilainen-Kaunisto RM, Terasvirta ME, Uusitupa MIJ, Niskanen LK. Occurrence and predictors of retinopathy and visual acuity in type 2 diabetic patients and control subjects: 10-year follow-up from the diagnosis. *J Diabetes Complications* 2001; **15**:24–33.

157. Nelson RG, Wolfe JA, Horton MB, Pettitt DJ, Bennett PH, Knowler WC. Proliferative retinopathy in NIDDM: incidence and risk factors in Pima Indians. *Diabetes* 1989;**38**:435–40.

158. West KM, Erdreich LJ, Stober JA. A detailed study of risk factors for retinopathy and nephropathy in diabetes. *Diabetes* 1980;**29**:501–8.

159. Chen M-S, Kao C-S, Fu C-C, Chen C-J, Tai T-Y. Incidence and progression of diabetic retinopathy among non-insulin-dependent diabetic subjects: a 4-year follow-up. *Int J Epidemiol* 1995;**24**:787–95.

160. Gall MA, Hougaard P, Borch-Johnsen K, Parving HH. Risk factors for development of incipient and overt diabetic nephropathy in patients with non-insulin dependent diabetes mellitus: prospective, observational study. *BMJ* 1997;**314**:783–8.

161. Rossing P, Rossing K, Jacobsen P, Parving HH. Unchanged incidence of diabetic nephropathy in IDDM patients. *Diabetes* 1995;**44**:739–43.

162. Hadjadj S, Belloum R, Bouhanick B, Gallois Y, Guilloteau G, Chatellier G, *et al*. Progostic value of angiotensin-1 converting enzyme I/D polymorphism for nephropathy in type 1 diabetes mellitus: a prospective study. *J Am Soc Nephrol* 2001;**12**:541–9.

163. Mogensen CE, Christensen CK. Blood pressure changes and renal function in incipient and overt diabetic nephropathy. *Hypertension* 1985;**7**:II-64–73.

164. Christensen CK, Mogensen CE. The course of incipient diabetic nephropathy: studies of albumin excretion and blood pressure. *Diabet Med* 1985; **2**:97–102.

165. Mathiesen ER, Feldt-Rasmussen B, Hommel E, Deckert T, Parving HH. Stable glomerular filtration rate in normotensive IDDM patients with stable microalbuminuria. A 5-year prospective study. *Diabetes Care* 1997;**20**:286–9.

166. Jerums G, Murray RM, Seeman E, Cooper ME, Edgley S, Marwick K, *et al*. Lack of effect of gliclazide on early diabetic nephropathy and retinopathy: a two-year controlled study. *Diabetes Res Clin Pract* 1987;**3**:71–80.

167. Cooper ME, Frauman A, O'Brien RC, Seeman E, Murray RM, Jerums G. Progression of proteinuria in type 1 and type 2 diabetes. *Diabet Med* 1988; **5**:361–8.

168. Jerums G, Allen TJ, Cooper ME. Triphasic changes in selectivity with increasing proteinuria in type 1 and type 2 diabetes. *Diabet Med* 1989; **6**:772–9.

169. Gilbert RE, Tsalamandris C, Bach LA, Panagiotopoulos S, O'Brien RC, Allen TJ, *et al*. Long-term glycemic control and the rate of progression of early kidney disease. *Kidney Int* 1993;**44**:855–9.

170. Tsalamandris C, Allen TJ, Gilbert RE, Sinha A, Panagiotopoulos S, Cooper ME, *et al*. Progressive decline in renal function in diabetic patients with and without albuminuria. *Diabetes* 1994;**43**:649–55.

171. Mathiesen ER, Oxenboll B, Johansen K, Svendsen PA, Deckert T. Incipient nephropathy in type 1 (insulin-dependent) diabetes. *Diabetologia* 1984; **26**:406–10.

172. Mathiesen ER. Time relationship between blood pressure rise and the development of diabetic nephropathy. *Diabete Metab* 1989;**15**:318–19.

173. Feldt-Rasmussen B, Mathiesen ER, Deckert T. Effect of two years of strict metabolic control on progression of incipient nephropathy in insulin-dependent diabetes. *Lancet* 1986;**ii**:1300–4.

174. Salardi S, Tacconi M, Zucchini S, Steri L, Mazzanti L, Cacciari E. Evolution of microalbuminuria in diabetic patients treated or not with enalapril. *J Pediatr Endocrinol Metab* 1995; **8**:230.

175. Salardi S, Cacciari E, Shield JPH. Is microalbuminuria progressive? [letter] *Arch Dis Child* 1996;**75**:266.

176. The EURODIAB Prospective Complications Study (PCS) Group. Risk factors for progression of nephropathy in type 1 diabetic subjects in Europe [abstract]. *Diabetologia* 1999;**42**(Suppl 1):A71.

177. Wilson DM, Luetscher JA. Plasma prorenin activity and complications in children with insulin-dependent diabetes mellitus. *N Engl J Med* 1990; **323**:1101–6.

178. Rudberg S, Persson B, Dahlquist G. Increased glomerular filtration rate as a predictor of diabetic nephropathy – an 8-year prospective study. *Kidney Int* 1992;**41**:822–8.

179. Rudberg S, Ullman E, Dahlquist G. Relationship between early metabolic control and the development of microalbuminuria – a longitudinal study in children with type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 1993;**36**:1309–14.

180. Rudberg S, Dahlquist G. Determinants of progression of microalbuminuria in adolescents with IDDM. *Diabetes Care* 1996;**19**:369–71.

181. Rudberg S, Rasmussen LM, Bangstad HJ, Osterby R. Influence of insertion/deletion polymorphism in the ACE-I gene on the progression of diabetic glomerulopathy in type 1 diabetic patients with microalbuminuria. *Diabetes Care* 2000;**23**:544–8.

182. Dahlquist G, Stattin E-L, Rudberg S. Urinary albumin excretion rate and glomerular filtration rate in the prediction of diabetic nephropathy; a long-term follow-up study of childhood onset type-1 diabetic patients. *Nephrol Dial Transplant* 2001;**16**:1382–6.

183. Nowalk MP, Stuhldreher WL, Becker D, Ellis D, Caggiula AW, Orchard TJ. The relationship of protein intake to changes in renal function in an adult population with insulin-dependent diabetes mellitus. The Epidemiology of Diabetes Complications Study. *Diabetes Nutr Metab* 1996; **9**:247–57.

184. Kalter-Leibovici O, Van Dyk DJ, Leibovici L, Loya N, Erman A, Kremer I, *et al*. Risk factors for development of diabetic nephropathy and retinopathy in Jewish IDDM patients. *Diabetes* 1991;**40**:204–10.

185. Watts GF, Harris R, Shaw KM. The determinants of early nephropathy in insulin-dependent diabetes mellitus: a prospective study based on the urinary excretion of albumin. *Q JM* 1991;**79**:365–78.

186. Shield JP, Hunt LP, Karachaliou F, Karavanaki K, Baum JD. Is microalbuminuria progressive? *Arch Dis Child* 1995;**73**:512–14.

187. Bojestig M, Arnqvist HJ, Karlberg BE, Ludvigsson J. Glycemic control and prognosis in type I diabetic patients with microalbuminuria. *Diabetes Care* 1996;**19**:313–17.

188. Gorman D, Sochett E, Daneman D. The natural history of microalbuminuria in adolescents with type 1 diabetes. *J Pediatr* 1999;**134**:333–7.

189. Warram JH, Scott LJ, Hanna LS, Wantman M, Cohen SE, Laffel LMB, *et al*. Progression of microalbuminuria to proteinuria in type 1 diabetes: nonlinear relationship with hyperglycemia. *Diabetes* 2000;**49**:94–100.

190. Tabei BP, Al-Kassab AS, Ilag LL, Zawicki CM, Herman WH. Does microalbuminuria predict diabetic nephropathy? *Diabetes Care* 2001; **24**:1560–6.

191. Twyman S, Rowe D, Mansell P, Schapira D, Betts P, Leatherdale B. Longitudinal study of urinary albumin excretion in young diabetic patients – Wessex Diabetic Nephropathy Project. *Diabet Med* 2001;**18**:402–8.

192. Reichard P, Berglund B, Britz A, Cars I, Nilsson BY, Rosenqvist U. Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM): the Stockholm Diabetes Intervention Study (SDIS) after 5 years. *J Intern Med* 1991;**230**:101–8.

193. Diabetes Control and Complications (DCCT) Research Group. Effect of intensive therapy on the

development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. *Kidney Int* 1995;**47**:1703–20.

194. Reichard P, Britz A, Cars I, Nilsson BY, Sobocinsky-Olsson B, Rosenqvist U. The Stockholm Diabetes Intervention Study (SDIS): 18 months' results. *Acta Med Scand* 1988; **224**:115–22.

195. Reichard P, Rosenqvist U. Nephropathy is delayed by intensified insulin treatment in patients with insulin-dependent diabetes mellitus and retinopathy. *J Intern Med* 1989;**226**:81–7.

196. Reichard P, Britz A, Carlsson P, Cars I, Lindblad L, Nilsson BY, *et al*. Metabolic control and complications over 3 years in patients with insulin dependent diabetes (IDDM): the Stockholm Diabetes Intervention Study (SDIS). *J Intern Med* 1990;**228**:511–17.

197. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 1993;**329**:304–9.

198. Bangstad HJ, Osterby R, Dahl-Jorgensen K, Berg KJ, Hartmann A, Hanssen KF. Improvement of blood glucose control in IDDM patients retards the progression of morphological changes in early diabetic nephropathy. *Diabetologia* 1994;**37**:483–90.

199. Microalbuminuria Collaborative Study Group, United Kingdom. Intensive therapy and progression to clinical albuminuria in patients with insulin dependent diabetes mellitus and microalbuminuria. *BMJ* 1995;**311**:973–7.

200. Parving H-H. Renoprotection in diabetes: genetic and non-genetic risk factors and treatment. *Diabetologia* 1998;**41**:745–59.

201. Viberti G, Mogensen CE, Groop LC, Pauls JF. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. European Microalbuminuria Captopril Study Group [see comments]. *JAMA* 1994;**271**:275–9.

202. Laffel LMB, McGill JB, Gans DJ. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. *Am J Med* 1995;**99**:497–504.

203. Microalbuminuria Captopril Study Group. Captopril reduces the risk of nephropathy in IDDM patients with microalbuminuria. *Diabetologia* 1996;**39**:587–93.

204. Mathiesen ER, Hommel E, Giese J, Parving H-H. Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. *BMJ* 1991;**303**:81–7.

205. Mathiesen ER, Hommel E, Hansen HP, Smidt UM, Parving HH. Randomised controlled trial of long term efficacy of captopril on preservation of kidney function in normotensive patients with insulin dependent diabetes and microalbuminuria. *BMJ* 1999;**319**:24–5.

206. Marre M, Chatellier G, Leblanc H, Guyene TT, Menard J, Passa P. Prevention of diabetic nephropathy with enalapril in normotensive diabetics with microalbuminuria. *BMJ* 1988; **297**:1092–5.

207. Chase HP. Angiotensin-converting enzyme inhibitor treatment in young normotensive diabetic subjects: a two-year trial. *Annals of Ophthalmology* 1993;**25**:284–9.

208. Bakris GL, Slataper R, Vicknair N, Sadler R. ACE inhibitor mediated reductions in renal size and microalbuminuria in normotensive, diabetic subjects. *J Diabetes Complications* 1994;**8**:2–6.

209. Crepaldi G, Carta Q, Deferrari G, Mangili R, Navalesi R, Santeusanio F, *et al*. Effects of lisinopril and nifedipine on the progression to overt albuminuria in IDDM patients with incipient nephropathy and normal blood pressure. *Diabetes Care* 1998;**21**:104–10.

210. O'Hare JP, Bilous R, Mitchell T, O'Callaghan CJ, Viberti GC, Willoughby R, *et al*. Low-dose ramipril reduces microalbuminuria in type 1 diabetic patients without hypertension: Results of a randomized controlled trial. *Diabetes Care* 2000; **23**:1823–9.

211. EUCLID Study Group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. *Lancet* 1997;**349**:1787–92.

212. Nielsen S, Schmitz A, Rehling M, Mogensen CE. Systolic blood pressure relates to the rate of decline of glomerular filtration rate in type II diabetes. *Diabetes Care* 1993;**16**:1427–32.

213. Nielsen S, Schmitz A, Rehling M, Mogensen CE. The clinical course of renal function in NIDDM patients with normo- and microalbuminuria. *J Intern Med* 1997;**241**:133–41.

214. Lemley KV, Abdullah I, Myers BD, Meyer TW, Blouch K, Smith WE, *et al*. Evolution of incipient nephropathy in type 2 diabetes mellitus. *Kidney Int* 2000;**58**:1228–37.

215. Nelson RG, Bennett PH, Beck GJ, Tan M, Knowler WC, Mitch WE, *et al*. Diabetic Renal Disease Study Group. Development and progression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1996;**335**:1636–42.

216. Nosadini R, Velussi M, Brocco E, Bruseghin M, Abaterusso C, Saller A, *et al*. Course of renal function in type 2 diabetic patients with abnormalities of albumin excretion rate. *Diabetes* 2000;**49**:476–84.

217. Miyauchi E, Hosojima J, Morimoto S. Urinary angiotensin-converting enzyme activity in type 2 diabetes mellitus: its relationship to diabetic nephropathy. *Acta Diabetol* 1995;**32**:193–7.

218. Wirta OR, Pasternack AI, Mustonen JT, Koivula TA, Harmoinen A. Urinary albumin excretion rate and its determinants after 6 years in non-insulin-dependent diabetic patients. *Nephrol Dial Transplant* 1996;**11**:449–56.

219. Berrut G, Bouhanick B, Fabbri P, Guilloteau G, Bled F, Le Jeune JJ, *et al*. Microalbuminuria as a predictor of a drop in glomerular filtration rate in subjects with non-insulin-dependent diabetes mellitus and hypertension. *Clin Nephrol* 1997; **48**:92–7.

220. Shigeta Y, Haneda M, Kikkawa R. Clinical significance of microalbuminuria in Japanese subjects with non-insulin-dependent diabetes. *J Diabetes Complications* 1991;**5**:84–6.

221. Huang XH, Rantalaiho V, Wirta O, Pasternack A, Koivula T, Hiltunen TP, *et al*. Angiotensin-converting enzyme gene polymorphism is associated with coronary heart disease in non-insulin-dependent diabetic patients evaluated for 9 years. *Metabolism* 1998;**47**:1258–62.

222. Hoy WE, Wang Z, VanBuynder P, Baker PR, Mathews JD. The natural history of renal disease in Australian Aborigines. Part 1. Changes in albuminuria and glomerular filtration rate over time. *Kidney Int* 2001;**60**:243–8.

223. Oue T, Namba M, Nakajima H, Ono A, Horikawa Y, Yamamoto K, *et al*. Risk factors for the progression of microalbuminuria in Japanese type 2 diabetic patients – a 10 year follow-up study. *Diabetes Res Clin Pract* 1999;**46**:47–55.

224. Lunt H, Graham PJ, Jury DR, Lim CW, Crooke MJ, Smith RB, *et al*. The prognostic significance of urinary albumin in Polynesians with non-insulin-dependent diabetes. *Diabetes Res Clin Pract* 1994; **25**:141–5.

225. Shoji T, Kanda T, Nakamura H, Hayashi T, Okada N, Nakanishi I, *et al*. Are glomerular lesions alternatives to microalbuminuria in predicting later progression of diabetic nephropathy? *Clin Nephrol* 1996;**45**:367–71.

226. Yoshida H, Kuriyama S, Atsumi Y, Tomonari H, Mitarai T, Hamaguchi A, *et al*. Angiotensin I converting enzyme gene polymorphism in non-insulin dependent diabetes mellitus. *Kidney Int* 1996;**50**:657–64.

227. Hadjadj S, Fanelli A, Torremocha F, Marechaud R. Prospective follow-up study of the renal function in type 2 diabetic patients. *Arch Mal Coeur* 2001; **94**:928–32.

228. Smulders YM, Rakic M, Stehouwer CD, Weijers RN, Slaats EH, Silberbusch J. Determinants of progression of microalbuminuria in patients with NIDDM. A prospective study. *Diabetes Care* 1997; **20**:999–1005.

229. Smulders YM, van Eeden AE, Stehouwer CD, Weijers RN, Slaats EH, Silberbusch J. Can reduction in hypertriglyceridaemia slow progression of microalbuminuria in patients with non-insulin-dependent diabetes mellitus? *Eur J Clin Invest* 1997;**27**:997–1002.

230. Spoelstra-de Man AME, Brouwer CB, Stehouwer CDA, Smulders YM. Rapid progression of albumin excretion is an independent predictor of cardiovascular mortality in patients with type 2 diabetes and microalbuminuria. *Diabetes Care* 2001; **24**:2097–101.

231. Nelson RG, Knowler WC, Pettitt DJ, Saad MF, Charles MA, Bennett PH. Assessment of risk of overt nephropathy in diabetic patients from albumin excretion in untimed urine specimens. *Arch Intern Med* 1991;**151**:1761–5.

232. Kawazu S, Tomono S, Shimizu M, Kato N, Ohno T, Ishii C, *et al*. The relationship between early diabetic nephropathy and control of plasma glucose in non-insulin-dependent diabetes mellitus. The effect of glycemic control on the development and progression of diabetic nephropathy in an 8-year follow-up study. *J Diabetes Complications* 1994;**8**:13–17.

233. Song KH, Yoon KH, Kang MI, Cha BY, Lee KW, Son HY, *et al*. Progression to overt proteinuria in microalbuminuric Koreans with non-insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract* 1998;**42**:117–21.

234. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**:837–53.

235. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, *et al*. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995;**28**:103–17.

236. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care* 2000;**23**(Suppl 2):B21–9.

237. Ravid M, Savin H, Jutrin I, Bental T, Katz B, Lishner M. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. *Ann Intern Med* 1993;**118**:577–81.

238. Ravid M, Savin H, Jutrin I, Bental T, Lang R, Lishner M. Long-term effect of ACE inhibition on

development of nephropathy in diabetes mellitus type II. *Kidney Int Suppl* 1994;**45**:S161–4.

239. Ravid M, Lang R, Rachmani R, Lishner M. Long-term renoprotective effect of angiotensin-converting enzyme inhibition in non-insulin-dependent diabetes mellitus. A 7-year follow-up study. *Arch Intern Med* 1996;**156**:286–9.

240. Sano T, Hotta N, Kawamura T, Matsumae H, Chaya S, Sasaki H, *et al*. Effects of long-term enalapril treatment on persistent microalbuminuria in normotensive type 2 diabetic patients: results of a 4–year, prospective, randomized study. *Diabet Med* 1996;**13**:120–4.

241. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P, *et al*. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;**345**:870–8.

242. Muirhead N, Feagan BF, Mahon J, Lewanczuk RZ, Rodger NW, Botteri F, *et al*. The effects of valsartan and captopril on reducing microalbuminuria in patients with type 2 diabetes mellitus: a placebo-controlled trial. *Current Therapeutic Research, Clinical and Experimental* 1999;**60**:650–60.

243. Genuth SM. The case for blood glucose control. *Advances in Internal Medicine* 1995;**40**:573–623.

244. Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type 1 diabetes. *Lancet* 1993; **341**:1306–9.

245. Epidemiology of Diabetes Interventions and Complications Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med* 2000;**342**:381–9.

246. Job D, Eschwege E, Guyot-Argenton C. Effect of multiple daily insulin injections on the course of diabetic retinopathy. *Diabetes* 1976;**25**:463–9.

247. Eschwege E, Job D, Guyot-Argenton C, Aubry JP, Tchobroutsky G. Delayed progression of diabetic retinopathy by divided insulin administration: a further follow-up. *Diabetologia* 1979;**16**:13–15.

248. Holman RR, Dornan TL, Mayon-White V, Howard-Williams J, Orde-Peckar C, Jenkins L, *et al*. Prevention of deterioration of renal and sensory-nerve function by more intensive management of insulin-dependent diabetic patients. A two-year randomised prospective study. *Lancet* 1983;**i**:204–8.

249. Bell PM, Hayes JR, Hadden DR, Archer DB. The effect of plasma glucose control by continuous subcutaneous insulin infusion or conventional therapy on retinal morphology and urinary albumin excretion. *Diabete Metab* 1985;**11**:254–61.

250. Christensen CK, Sandahl Cristiansen J, Schmitz A, Christensen T, Hermansen K, Mogensen CE. Effect of continuous subcutaneous insulin infusion on kidney fanction and size in IDDM patients: a 2 year controlled study. *J Diabetes Complications* 1987;**1**:91–5.

251. Helve E, Laatikainen L, Merenmies L, Koivisto V. Continuous insulin infusion therapy and retinopathy in patients with type 1 diabetes. *Acta Endocrinologica* 1987;**115**:313–19.

252. Kroc Study Group. Blood glucose control and the evolution of diabetic retinopathy and albuminuria: a preliminary multicenter trial. *N Engl J Med* 1984; **311**:365–72.

253. Kroc Study Group. Effect of diabetic control on retinopathy: follow-up report of the Kroc randomized clinical trial. *Invest Ophthalmol Vis Sci* 1985;**26**(Suppl 3):61–8.

254. Beck-Nielsen H, Richelsen B, Mogensen CE. Effect of insulin pump treatment for one year on renal function and retinal morphology in patients with IDDM. *Diabetes Care* 1985;**6**:585–9.

255. Olsen T, Ehlers N, Nielsen CB, Beck-Nielsen H. Diabetic retinopathy after one year of improved metabolic control obtained by continuous subcutaneous insulin infusion (CSII). *Acta Ophthalmol* 1985;**63**:315–19.

256. Beck-Nielsen H, Olesen T, Mogensen CE, Richelsen B, Olsen HW, Ehlers N, *et al*. Effect of near normoglycemia for 5 years on progression of early diabetic retinopathy and renal involvement. *Diabetes Res* 1990;**15**:185–90.

257. Dahl-Jorgensen K, Brinchmann-Hansen O, Hanssen KF, Ganes T, Kierulf P, Smeland E, *et al*. Effect of near normoglycaemia for two years on progression of early diabetic retinopathy, nephropathy, and neuropathy: the Oslo study. *BMJ* 1986;**293**:1195–9.

258. Dahl-Jorgensen K, Hanssen KF, Kierulf P, Bjoro T, Sandvik L, Aagenaes O. Reduction of urinary albumin excretion after 4 years of continuous subcutaneous insulin infusion in insulin-dependent diabetes mellitus. *Acta Endocrinologica* 1988;**117**:19–25.

259. Brinchmann-Hansen O, Dahl-Jorgensen K, Sandvik L, Hanssen KF. Blood glucose concentrations and progression of diabetic retinopathy: the seven year results of the Oslo study. *BMJ* 1992;**304**:19–22.

260. Brinchmann-Hansen O, Dahl-Jorgensen K, Hanssen KF, Sandvik L. The response of diabetic retinopathy to 41 months of multiple insulin injections, insulin pumps, and conventional insulin therapy. *Arch Ophthalmol* 1988;**106**:1242–6.

261. Dahl-Jorgensen K, Bjoro T, Kierulf P, Sandvik L, Bangstad HJ, Hanssen KF. Long-term glycemic

control and kidney function in insulin-dependent diabetes mellitus. *Kidney Int* 1992;**41**:920–3.

262. Steno Study Group. Effect of 6 months of strict metabolic control on eye and kidney function in insulin-dependent diabetics with background retinopathy. *Lancet* 1982;**i**:121–4.

263. Lauritzen T, Frost-Larsem K, Larsen H-W, Deckert T. Effect of 1 year of near-normal blood glucose levels on retinopathy in insulin-dependent diabetics. *Lancet* 1983;**i**:200–4.

264. Lauritzen T, Frost-Larsen K, Larsen H-W, Deckert T. Two-year experience with continuous subcutaneous insulin infusion in relation to retinopathy and neuropathy. *Diabetes* 1985; **34**(Suppl 3):74–9.

265. Feldt-Rasmussen B, Mathiesen ER, Hegedus L, Deckert T. Kidney function during 12 months of strict metabolic control in insulin-dependent diabetic patients with incipient nephropathy. *N Engl J Med* 1986;**314**:665–70.

266. Feldt-Rasmussen B, Mathiesen ER, Jensen T, Lauritzen T, Deckert T. Effect of improved metabolic control on loss of kidney function in type 1 (insulin-dependent) diabetic patients: an update of the Steno studies. *Diabetologia* 1991; **34**:164–70.

267. Lawson ML, Gerstein HC, Tsui E, Zinman B. Effect of intensive therapy on early macrovascular disease in young individuals with type 1 diabetes. *Diabetes Care* 1999;**22**(Suppl 2):B35–9.

268. Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes onset before the age of thirty-one: 1. Survival, causes of death and complications. *Diabetologia* 1978;**14**:363–70.

269. Krolewski AS, Kosinski EJ, Warram JH, Leland OS, Busick EJ, Asmal AC, *et al*. Magnitude and determinants of coronary heart disease in juvenile-onset, insulin-dependent diabetes mellitus. *Am J Cardiol* 1987;**59**:750–5.

270. Moss SE, Klein R, Klein BEK, Meuer SM. The association of glycaemia and cause-specific mortality in a diabetic population. *Arch Intern Med* 1994;**154**:2473–9.

271. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. *Diabetes Care* 1999; **22**:233–40.

272. Viberti GC, Pickup JC, Jarrett RJ, Keen H. Effect of control of blood glucose on urinary excretion of albumin and beta2 microglobulin in insulin-dependent diabetes. *N Engl J Med* 1979; **300**:638–41.

273. Reichard P, Pihl M. Mortality and treatment side-effects during long-term intensified conventional insulin treatment in the Stockholm Diabetes Intervention Study. *Diabetes* 1994;**43**:313–17.

274. American Diabetes Association. Implications of the Diabetes Control and Complications Trial. *Diabetes Care* 2002;**25**(Suppl 1):S25–7.

275. Jensen-Urstad KJ, Reichard PG, Rosfors JS, Lindblad LEL, Jensen-Urstad MT. Early atherosclerosis is retarded by improved long-term blood glucose control in patients with IDDM. *Diabetes* 1996;**45**:1253–8.

276. Wiseman MJ, Saunders AJ, Keen H, Viberti G. Effect of blood glucose control on increased glomerular filtration rate and kidney size in insulin-dependent diabetes. *N Engl J Med* 1985; **312**:617–21.

277. Gaster B, Hirsch IB. The effects of improved glycemic control on complications in type 2 diabetes. *Arch Intern Med* 1998;**158**:134–40.

278. University Group Diabetes Program. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. *Diabetes* 1970;**19**(Suppl 2):747–830.

279. Abraira C, Colwell JA, Nuttall FQ, Sawin CT, Nagel NJ, Comstock JP, *et al*. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. Veterans Affairs Cooperative Study in Type II Diabetes. *Diabetes Care* 1995;**18**:1113–23.

280. Duckworth WC, McCarren M, Abraira C. Glucose control and cardiovascular complications: the VA Diabetes Trial. *Diabetes Care* 2001;**24**:942–5.

281. Malmberg K, Ryden L, Efendic S, Herliz J, Nicol P, Walderstrom A, *et al*. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI Study). *J Am Coll Cardiol* 1995;**26**:57–65.

282. Abraira C, Colwell J, Nuttall F, Sawin CT, Henderson W, Comstock JP, *et al*. Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial: Veterans Affairs Cooperative Study on Glycemic Control and Comlications in type 2 diabetes. *Arch Intern Med* 1997;**157**:181–8.

283. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. *BMJ* 1997;**314**:1512–15.

284. Groeneveld Y, Petri H, Hermans J, Springer MP. Relationship between blood glucose level and mortality in type 2 diabetes mellitus: a systematic review. *Diabet Med* 1999;**16**:2–13.

285. O'Connor PJ, Spann SJ, Woolf SH. Care of adults with type 2 diabetes mellitus: a review of the evidence. *J Fam Pract* 1998;**47**(Suppl):S13–22.

286. Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, *et al*. Association of glycaemia

with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; **321**:405–12.

287. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**:31–41.

288. Levin SR, Coburn JW, Abraira C, Henderson WG, Colwell JA, Emanuele NV, *et al*. Effect of intensive glycemic control on microalbuminuria in type 2 diabetes. *Diabetes Care* 2000;**23**:1478–85.

289. Mathiesen ER. Time relationship between blood pressure rise and the development of diabetic nephropathy. *Diabete Metab* 1989;**15**:318–19.

290. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; **329**:1456–62.

291. Parving HH. Diabetic hypertensive patients – a group in need of particular care and attention? *Int J Clin Pract* 1997;**92**(Suppl):13–18.

292. Chaturvedi N, Sjolie AK, Stephenson JM, Abrahamian H, Keipes M, Castellarin A, *et al*. Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. *Lancet* 1998;**351**:28–31.

293. Sjolie A-K, Chaturvedi N. The retinal renin–angiotensin system: implications for therapy in diabetic retinopathy. *J Hum Hypertens* 2002; **16**:S42–6.

294. EUCLID Study Group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. *Lancet* 1997;**349**:1787–92.

295. ATLANTIS Study Group. Low-dose ramipril reduces microalbuminuria in type 1 diabetic patients without hypertension. *Diabetes Care* 2000; **23**:1823–9.

296. Jerums G, Allen TJ, Campbell DJ, Cooper ME, Gilbert RE, Hammond JJ, *et al*. Long-term comparison between perindopril and nifedipine in normotensive patients with type 1 diabetes and microalbuminuria. *Am J Kidney Dis* 2001;**37**:890–9.

297. Bojestig M, Karlberg BE, Lindstrom T, Nystrom FH. Reduction of ACE activity is insufficient to decrease microalbuminuria in normotensive patients with type 1 diabetes. *Diabetes Care* 2001;**24**:919–24.

298. Chase HP, Garg SK, Harris S, Hoops SL, Marshall G. High–normal blood pressure and early diabetic nephropathy. *Arch Intern Med* 1990; **150**:639–41.

299. Poulsen PL, Hansen KW, Mogensen CE. Ambulatory blood pressure in the transition from normo- to microalbuminuria. A longitudinal study in IDDM patients. *Diabetes* 1994;**43**:1248–53.

300. Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal disease. With emphasis on the stage of incipient diabetic nephropathy. *Diabetes* 1983;**32**(Suppl 2):64–78.

301. Mogensen CE. Microalbuminuria, blood pressure and diabetic renal disease: origin and development of ideas. *Diabetologia* 1999;**42**:263–85.

302. Mogensen CE. Long-term antihypertensive treatment inhibiting progression of diabetic nephropathy. *BMJ* 1982;**285**:685–8.

303. Parving HH, Andersen AR, Smidt UM, Svendsen PA. Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. *Lancet* 1983; **i**:1175–9.

304. Christensen CK, Mogensen CE. Antihypertensive treatment: long-term reversal of progression of albuminuria in incipient diabetic nephropathy. A longitudinal study of renal function. *J Diabetes Complications* 1987;**1**(2):45–52.

305. Björck S, Mulec H, Johnsen SA, Norden G, Aurell M. Renal protective effect of enalapril in diabetic nephropathy. *BMJ* 1992;**304**:339–43.

306. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM. Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 1986;**77**:1925–30.

307. Collado-Mesa F, Colhoun HM, Stevens LK, Boavida J, Ferriss JB, Karamanos B, *et al*. Prevalence and management of hypertension in type 1 diabetes mellitus in Europe: the EURODIAB IDDM Complications Study. *Diabet Med* 1999;**16**:41–8.

308. Weidmann P, Boehlen LM, de Courten M, Ferrari P. Antihypertensive therapy in diabetic patients. *J Hum Hypertens* 1992;**6**(Suppl 2):S23–36.

309. Bohlen L, de Courten M, Weidmann P. Comparative study of the effect of ACE-inhibitors and other antihypertensive agents on proteinuria in diabetic patients. *Am J Hypertens* 1994; **7**:84–92S.

310. Weidmann P, Schneider M, Bohlen L. Therapeutic efficacy of different antihypertensive drugs in human diabetic nephropathy: an updated meta-analysis. *Nephrol Dial Transplant* 1995; **10**(Suppl 9):39–45.

311. Kasiske BL, Kalil RS, Ma JZ, Liao M, Keane WF. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. *Ann Intern Med* 1993;**118**:129–38.

312. Maki DD, Ma JZ, Louis TA, Kasiske BL. Long-term effects of antihypertensive agents on

proteinuria and renal function. *Arch Intern Med* 1995;**155**:1073–80.

313. Gansevoort RT, Sluiter WJ, Hemmelder MH, de Zeeuw D, de Jong PE. Antiproteinuric effect of blood-pressure-lowering agents: a meta-analysis of comparative trials. *Nephrol Dial Transplant* 1995; **10**:1963–74.

314. Marre M, Leblanc H, Suarez L, Guyenne TT, Menard J, Passa P. Converting enzyme inhibition and kidney function in normotensive diabetic patients with persistent microalbuminuria. *BMJ* 1987;**294**:1448–52.

315. O'Donnell MJ, Rowe BR, Lawson N, Horton A, Gyde OH, Barnett AH. Placebo-controlled trial of lisinopril in normotensive diabetic patients with incipient nephropathy. *J Hum Hypertens* 1993; **7**:327–32.

316. Poulsen PL, Ebbehoj E, Mogensen CE. Lisinopril reduces albuminuria during exercise in low grade microalbuminuric type 1 diabetic patients: a double blind randomized study. *J Intern Med* 2001; **249**:433–40.

317. Poulsen PL, Ebbehoj E, Nosadini R, Fioretto P, Deferrari G, Crepaldi G, *et al*. Early ACE-I intervention in microalbuminuric patients with type 1 diabetes: effects on albumin excretion, 24 h ambulatory blood pressure, and renal function. *Diabetes Metab* 2001;**27**:123–8.

318. European Study for the Prevention of Renal Disease in Type 1 Diabetes (ESPRIT). Effect of 3 years of antihypertensive therapy on renal structure in type 1 diabetic patients with albuminuria. *Diabetes* 2001;**50**:843–50.

319. Melbourne Diabetic Nephropathy Study Group. Comparison between perindopril and nifedipine in hypertensive and normotensive diabetic patients with microalbuminuria. *BMJ* 1991; **302**:210–16.

320. EUCLID Study Group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. *Lancet* 1997;**349**:1787–92.

321. Bilo H, Kluitman E, van Ballegooie E, Potter van Loon BJ, Bakker K, Michels B, *et al*. Long term use of captopril or nifedipine in normotensive microalbuminuric patients with insulin-dependent diabetes mellitus. *Diabetes Res* 1993;**23**:115–22.

322. Hallab M, Gallois Y, Chatellier G, Rohmer V, Fressinaud P, Marre M. Comparison of reduction in microalbuminuria by enalapril and hydrochlorothiazide in normotensive patients with insulin dependent diabetes. *BMJ* 1993;**306**:175–82.

323. Brichard SM, Santoni JP, Thomas JR, van de Voorde K, Ketelslegers JM, Lambert AE. Long term reduction of microalbuminuria after 1 year of angiotensin converting enzyme inhibition by perindopril in hypertensive insulin-treated diabetic patients. *Diabete Metab* 1990;**16**:30–6.

324. Hansen KW, Klein F, Christensen PD, Sorensen K, Andersen PH, Moller J, *et al*. Effects of captopril on ambulatory blood pressure, renal and cardiac function in microalbuminuric type 1 diabetic patients. *Diabete Metab* 1994;**20**:485–93.

325. Katayama S, Kikkawa R, Isogai S, Sasaki N, Matsuura N, Tajima N, *et al*. Effect of captopril or imidapril on the progression of diabetic nephropathy in Japanese with type 1 diabetes mellitus: a randomized controlled study (JAPAN-IDDM). *Diabetes Res Clin Pract* 2002;**55**:113–21.

326. ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? *Ann Intern Med* 2001;**134**:370–9.

327. Kshirsagar AV, Joy MS, Hogan SL, Falk RJ, Colindres RE. Effect of ACE inhibitors in diabetic and nondiabetic chronic renal disease: a systematic overview of randomized placebo-controlled trials. *Am J Kidney Dis* 2000;**35**:695–707.

328. Barnett AH, Bilous R, Bojestig M, Crepaldi G, Nosadini R, Chaturvedi N, *et al*. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med* 2001;**134**:370–9.

329. Clarke R, Lewington S, Youngman L, Sherliker P, Peto R, Collins R. Underestimation of the importance of blood pressure and cholesterol for coronary heart disease mortality in old age. *Eur Heart J* 2002;**23**:286–93.

330. O'Donnell CJ, Kannel WB. Epidemiologic appraisal of hypertension as a coronary risk factor in the elderly. *Am J Geriatr Cardiol* 2002;**11**:86–92.

331. Domanski M, Mitchell G, Pfeffer M, Neaton JD, Norman J, Svendsen K, *et al*. Pulse pressure and cardiovascular disease-related mortality: follow-up study of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 2002;**287**:2677–83.

332. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfieldt D, Julius S, *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;**351**:1755–62.

333. Tatti P, Pahor M, Byington RP, Di Mauro P, Guarisco R, Strollo G, *et al*. Outcome results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998; **21**:597–603.

334. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;**317**:703–13.

335. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998;**317**:713–20.

336. Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000;**23**(Suppl 2):B54–64.

337. HOPE Study Group. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE and MICRO-HOPE sub study. *Lancet* 2000; **355**:253–9.

338. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Scrier RO. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998; **338**:645–52.

339. Marre M, Lievre M, Chatellier G, Mann J, Passa P, Menard J. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ* 2004;**328**:495–9.

340. Ravid M, Brosh D, Levi Z, Bar-Dayan Y, Ravid D, Rachmani R. Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. *Ann Intern Med* 1998;**128**:982–8.

341. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int* 2002;**61**:1086–97.

342. Lebovitz HE, Wiegmann TB, Cnaan A, Shahinfar S, Sica DA, Broadstone V, *et al*. Renal protective effects of enalapril in hypertensive NIDDM: role of baseline albuminuria. *Kidney Int Suppl* 1994; **45**:S150–5.

343. Chan JCN, Cockram CS, Nicholls MG, Cheung CK, Swaminathan R. Comparison of enalapril and nifedipine in treating non-insulin dependent diabetes associated with hypertension: one year analysis. *BMJ* 1992;**305**:981–5.

344. Lacourciere Y, Nadeau A, Poirier L, Tancrede G. Captopril or conventional therapy in hypertensive type II diabetics. Three-year analysis. *Hypertension* 1993;**21**:786–94.

345. Agardh CD, Garcia-Puig T, Charbonne B, Angelkort B, Barnett AH. Greater reduction of urinary albumin excretion in hypertensive type II diabetic patients with incipient nephropathy by lisinopril than by nifedipine. *J Hum Hypertens* 1996;**10**:185–92.

346. DeFronzo RA, Ferranini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. *Diabetes Care* 1991;**14**:173–94.

347. Kannel WB, Wilson PW, Zhang TJ. The epidemiology of impaired glucose tolerance and hypertension. *Am Heart J* 1991;**121**:1268–73.

348. Cooper ME. Renal protection and angiotensin converting enzyme inhibition in microalbuminuric type I and type II diabetic patients. *J Hypertens Suppl* 1996;**14**:S11–14.

349. Ravid M, Neumann L, Lishner M. Plasma lipids and the progression of nephropathy in diabetes mellitus type II: effect of ACE inhibitors. *Kidney Int* 1995;**47**:907–10.

350. Ravid M, Brosh D, Levi Z, Bar-Dayan Y, Ravid D, Rachmani R. Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus: a randomized, controlled trial. *Ann Intern Med* 1998;**128**:982–8.

351. Sano T, Kawamura T, Matsumae H, Sasaki H, Nakayama M, Hara T, *et al*. Effects of long-term enalapril treatment on persistent microalbuminuria in well-controlled hypertensive and normotensive NIDDM patients. *Diabetes Care* 1994;**17**:420–4.

352. Capek M, Schnack C, Ludvik B, Kautzky-Willer A, Banyai M, Prager R. Effects of captopril treatment versus placebo on renal function in type 2 diabetic patients with microalbuminuria: a long-term study. *Clin Invest* 1994;**72**:961–6.

353. Cheung R, Lewanczuk RZ, Rodger NW, Huff MW, Oddou-Stock P, Botteri F, *et al*. The effect of valsartan and captopril on lipid parameters in patients with type II diabetes mellitus and nephropathy. *Int J Clin Pract* 1999;**53**:584–6.

354. Nankervis A, Nicholls K, Kilmartin G, Allen P, Ratnaike S, Martin FIR. Effects of perindopril on renal histomorphometry in diabetic subjects with microalbuminuria: a 3-year placebo-controlled biopsy study. *Metabolism* 1998;**47**(12 Suppl 1):12–15.

355. Ishida S, Egusa G, Hara H, Yamakido M, Ishida K, Kubo K, *et al*. Efficacy of angiotensin-converting enzyme inhibitor on the urinary excretion of albumin in NIDDM patients. *Journal of the Japan Diabetes Society* 1995;**38**:163–71.

356. Durruty P, Tapia JC, Ugarte C, Perez E, Krause P, Soto N, *et al*. Urinary albumin excretion in non-insulin-dependent diabetic patients. Effects of an angiotensin-converting enzyme inhibitor. *Rev Med Chil* 1996;**124**:1036–44.

357. Haider A, Oh P, Peloso PM. An evidence-based review of ACE inhibitors in incipient diabetic nephropathy. *Can J Clin Pharmacol* 2000;**7**:115–19.

358. Haider AW, Chen L, Larson MG, Evans JC, Chen MH, Levy D. Antecedent hypertension confers increased risk for adverse outcomes after initial myocardial infarction. *Hypertension* 1997; **30**:1020–4.

359. Tutuncu NB, Gurlek A, Gedik O. Efficacy of ACE inhibitors and ATII receptor blockers in patients with microalbuminuria: a prospective study. *Acta Diabetol* 2001;**38**:157–61.

360. Lebovitz HE, Cnaan A, Wiegman T, Broadstone V, Schwartz S, Sica D, *et al*. Enalapril slows the progression of renal disease in non-insulin dependent diabetes mellitus (NIDDM): results of a 3 year multicenter, randomized, prospective, double-blinded study [abstract]. *J Am Soc Nephrol* 1992;**3**(suppl 3):335.

361. Overlack A, Adamczak M, Bachmann W, Bonner G, Bretzel RG, Derichs R, *et al*. ACE-inhibition with perindopril in essential hypertensive patients with concomitant diseases. *Am J Med* 1994;**97**:126–34.

362. Rachmani R, Levi Z, Slavachevsky I, Half-Onn E, Ravid M. Effect of an alpha-Adrenergic blocker, and ACE inhibitor and hydrochlorothiazide on blood pressure and on renal function in type 2 diabetic patients with hypertension and albuminuria. *Nephron* 1998;**80**:175–82.

363. Bretzel RG, Bollen CC, Maeser E, Federlin KF. Nephroprotective effects of nitrendipine in hypertensive type I and type II diabetic patients. *Am J Kidney Dis* 1993;**21**(6 Suppl 3):53–64.

364. Chan JC, Ko GT, Leung DH, Cheung RC, Cheung MY, So WY, *et al*. Long-term effects of angiotensin-converting enzyme inhibition and metabolic control in hypertensive type 2 diabetic patients. *Kidney Int* 2000;**57**:590–600.

365. Ruggenenti P, Mosconi L, Bianchi L, Cortesi L, Campana M, Pagani G, *et al*. Long-term treatment with either enalapril or nitrendipine stabilizes albuminuria and increases glomerular filtration rate in non-insulin-dependent diabetic patients. *Am J Kidney Dis* 1994;**24**:753–61.

366. Mosconi L, Ruggenenti P, Perna A, Mecca G, Remuzzi G. Nitrendipine and enalapril improve albuminuria and glomerular filtration rate in non-insulin dependent diabetes. *Kidney Int Suppl* 1996; **55**:S91–3.

367. Velussi M, Brocco E, Frigato F, Zolli M, Muollo B, Maioli M, *et al*. Effects of cilazapril and amlodipine on kidney function in hypertensive NIDDM patients. *Diabetes* 1996;**45**:216–22.

368. Lacourciere Y, Nadeau A, Poirier L, Tancrede G. Comparative effects of converting enzyme inhibition and conventional therapy in hypertensive non-insulin dependent diabetics with normal renal function. *Clin Invest Med* 1991; **14**:652–60.

369. Lacourciere Y, Belanger A, Godin C, Halle JE, Ross S, Wright N, *et al*. Long-term comparison of losartan and enalapril on kidney function in hypertensive type 2 diabetics with early nephropathy. *Kidney Int* 2000;**58**:762–9.

370. Fogari R, Zoppi A, Malamani GD, Lusardi P, Destro M, Corradi L. Effects of amlodipine vs enalapril on microalbuminuria in hypertensive patients with type II diabetes. *Clinical Drug Investigation* 1997;**13**(Suppl 1):42–9.

371. Fogari R, Zoppi A, Corradi L, Poletti L, Pasotti M, Fogari E, *et al*. Long-term effects of amlodipine versus fosinopril on microalbuminuria in elderly hypertensive patients with type 2 diabetes mellitus. *Current Therapeutic Research, Clinical and Experimental* 2000;**61**:163–73.

372. Baba S. Nifedipine and enalapril equally reduce the progression of nephropathy in hypertensive type 2 diabetics. *Diabetes Res Clin Pract* 2001; **54**:191–201.

373. Schnack C, Hoffmann W, Hopmeier P, Schernthaner G. Renal and metabolic effects of 1-year treatment with ramipril or atenolol in NIDDM patients with microalbuminuria. *Diabetologia* 1996;**39**:1611–16.

374. Chan JCN, Nicholls G, Cheung CK, Law LK, Swaminathan R, Cockram CS. Factors determining the blood pressure response to enalapril and nifedipine in hypertension associated with NIDDM. *Diabetes Care* 2000;**18**:1001–6.

375. National Institute for Clinical Excellence. *Type 1 diabetes in adults. National Clinical Guideline for diagnosis and management in primary and secondary care*. London: Royal College of Physicians; 2004.

376. National Institute for Clinical Excellence. *Management of type 2 diabetes. Management of blood glucose*. Clinical Guideline G. London: NICE; 2002.

377. Williams B, Poulter NR, Brown MJ, Davis MD, McInnes GT, Potter JF, *et al*. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004–BHS IV. *J Hum Hypertens* 2004;**18**:139–85.

378. Strippoli GFM, Deeks JJ, Schena FP, Craig JC. Effects of angiotensin converting enzyme inhibitors and angiotensin 2 receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. *BMJ* 2004; **329**(7470):828.

379. Ruggenenti P, Fassi A, IIieva AP, Bruno S, IIiev IP, Brusegan V, *et al*. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 2004;**351**:1941–51.

380. Verma S, Strauss M. Angiotensin receptor blockers and myocardial infarction. *BMJ* 2004;**329**:1248–9.

381. National Institute for Clinical Excellence. *Management of type 2 diabetes. Renal disease – prevention and early management*. Clinical Guideline F. London: NICE; 2002.

382. *National Service Framework for Coronary Heart Disease*. London: Department of Health; 2001.

383. Hovind P, Tarnow L, Rossing P, Jensen BR, Graae M, Torp I, *et al*. Predictors for the development of microalbuminuria and macroalbuminuria in patients with type 1 diabetes: inception cohort study. *BMJ* 2004;**325**:1105–8.

384. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. *N Engl J Med* 2003;**348**:2285–93.

385. Tonolo G, Ciccarese M, Brizzi P, Puddu L, Secchi G, Calvia P, *et al*. Reduction of albumin excretion rate in normotensive microalbuminuric type 2 diabetic patients during long-term simvastatin treatment. *Diabetes Care* 1997;**20**:1891–5.

386. Verhulst A, D'Haese PC, De Broe ME. Inhibitors of HMG-CoA reductase reduce receptor-mediated endocytosis in human kidney proximal tubular cells. *J Am Soc Nephrol* 2004;**15**:2249–57.

387. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, *et al*. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364**:685–96.

388. Beastall GH. The impact of the General Services contract-national evidence. *Bulletin of the Royal College of Pathologists* 2004;**128**:24–7.

389. Raikou M, McGuire A. The economics of screening and treatment in type 2 diabetes. *PharmacoEconomics* 2003;**21**:543–64.

390. Gray A, Raikou M, McGuire A, Fenn P, Stevens R, Cull C, *et al*. Cost-effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside randomised controlled trial (UKPDS 41). *BMJ* 2000;**320**:1373–8.

391. Gray A, Clarke P, Raikou M, Adler A, Stevens R, Neil A, *et al*. An economic evaluation of atenolol versus captopril in patients with type 2 diabetes (UKPDS 54). *Diabet Med* 2001;**18**:438–44.

392. Clarke P, Gray A, Adler A, Stevens R, Raikou M, Cull C, *et al*. Cost effectiveness analysis of intensive blood-glucose control with metformin in overweight patients with type 2 diabetes (UKPDS No. 51). *Diabetologia* 2001;**44**:298–304.

393. The cost-effectiveness of screening for type 2 diabetes. CDC Diabetes Cost-Effectiveness Study Group, Centers for Disease Control and Prevention. *JAMA* 1998;**280**:1757–63.

394. UK Prospective Diabetes Study Group. Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. *BMJ* 1998;**317**:720–5.

395. HOPE Study Group. Effects of an ACE inhibitor, Ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–53.

396. Berry J. Microalbuminuria testing in diabetes: is a dipstick as effective as laboratory tests. *British Journal of Community Nursing* 2003;**8**:267–73.

Appendix 1

Consensus guidelines for screening and monitoring the development of secondary complications in patients with either type 1 or type 2 diabetes

All recommendations are for use with two out of three samples testing positive if the first sample has tested positive. In addition, the St Vincent Declaration recommends that all patients with diabetes over 12 years of age with stabilised metabolic control are screened at least once per year, and timed collections are to be used for all those classified as microalbuminuric. NICE prefers a first morning sample where practicable and on at least an annual basis.

TABLE 62 *Upper limit of the reference range for healthy adults according to different sources*

Source	UAC (mg l^{-1})	Urine AER (mg per 24 hours)	Urine AER (μg per minute)	Urine ACR
ADA	Not stated	<30	<20	<30 mg mg^{-1} [a]
St Vincent Declaration				
Women	<20	<30	<20	<3.5 mg $mmol^{-1}$
Men	<20	<30	<20	<2.5 mg $mmol^{-1}$
National Kidney Foundation	Not stated	<30	<20	<30 mg g^{-1} [a]
SIGN				
Women	<20	<30	<20	<3.5 mg $mmol^{-1}$
Men	<20	<30	<20	<2.5 mg $mmol^{-1}$
NICE 2002				
Women	<20	Not stated	Not stated	<3.5 mg $mmol^{-1}$
Men	<20	Not stated	Not stated	<2.5 mg $mmol^{-1}$

[a] Equivalent to 3.4 mg $mmol^{-1}$.
ADA, American Diabetes Association; SIGN, Scottish Intercollegiate Guidelines Network.

Appendix 2

Economic evaluation of the value of urine albumin screening for secondary complications of diabetes in the type 2 diabetic population

Introduction

This appendix is supplemental to the other chapters in the report as it is not a systematic review of evidence, since there is no specific literature on this topic. Consequently, a basic model of the cost-effectiveness of urine albumin screening used to identify specific complications of microvascular damage in a population with type 2 DM is presented. The additional clinical treatment benefits gained from microalbuminuria screening have been considered in the main body of the report and found to be positive but small. Nevertheless, it may be that, given the costly nature of diabetic complications, there remains an economic justification for microalbuminuria screening, especially if this were targeted at the reduction in secondary complications arising from diabetes. Two problems present themselves with respect to undertaking a cost-effectiveness analysis of screening in this area. First, even if a urine albumin screening programme were set in place, the clinical outcome of a positive screen would merely suggest the implementation of treatment that should already be standard therapy in the majority of diabetic patients. On the assumption that glycaemic control, blood pressure and retinopathy are already adequately assessed and the resultant therapeutic responses are optimal, the value added of urine albumin screening is the identification of the additional patients at increased risk of developing secondary complications not already identified through existing monitoring of glycaemic control, retinal changes and high blood pressure. Second, the long-term clinical outcomes arising from microalbuminuria are known, but the timing of these events after identification of raised urine albumin is far from certain.

In identifying the appropriate population to be screened, several factors are considered. It would seem inappropriate to assess a new screening programme from an economics perspective without the assumption that current therapy is optimal as, if the current optimal therapy has been shown to be cost-effective, resources should in the first instance be moved to support this therapy, before further movement of resources to a new screening programme. The National Service Framework for Coronary Heart Disease is also relevant, as this recommends that patients at high risk of CVD should already be treated with antihypertensive medications, aspirin and statins. Given that diabetic patients have an equivalent risk of CVD to non-diabetic patients who have suffered a previous cardiovascular event, the existing guidelines state that diabetic patients without diagnosed CHD should have meticulous control of blood pressure and glucose. Hence, the value added of urine albumin screening would be limited to those diabetic patients who have optimal blood glucose control and normal blood pressure, but increased urine albumin excretion. Furthermore, given the progressive nature of diabetes, it is likely that value added would be greatest in the less overtly affected patient group. This may be identified as the non-insulin-dependent diabetic population and analysis is therefore restricted to the type 2 diabetic population.

In limiting analysis to consideration of type 2 DM, the general findings of a systematic review of the cost-effectiveness literature on type 2 DM undertaken by Raikou and McGuire[389] form useful background information. They searched the literature back to 1995 on the basis that recent epidemiological and clinical data have had a dramatic impact on the general knowledge concerning diabetes, and treatment patterns have subsequently been changing significantly. Moreover, the incidence and prevalence of diabetes, particularly type 2 DM, appear to have been increasing over recent years. Of a total of 384 articles identified through systematic search, only 23 were considered appropriately qualified as economic studies of type 2 DM, with a significant proportion confined to cost-of-illness studies rather than evaluations per se. There are then relatively few studies on the cost-effectiveness of treatments for type 2 DM generally. This partly

reflects the long observation time required to track disease progression and complications, the difficulties in establishing optimal standard therapies, the wide range of treatments applied to patients with type 2 DM and the relatively few long-term studies mapping follow-up to hard clinical end-points. The most extensive analysis, primarily concerned with intensive versus less intensive therapy, has been based on the longest running randomised trial in this area, the UKPDS.[139,334,390–392]

Within this general literature there is little on the cost-effectiveness of screening within the diabetic population for specific complications and nothing specific to testing urine albumin. The Centers for Disease Control and the Prevention Diabetes Cost-effectiveness Study Group ran a Monte Carlo simulation model to estimate the lifetime cost-effectiveness of a 1-year opportunistic screening programme for type 2 diabetes.[393] Cost-effectiveness was estimated for a cohort of individuals, aged 25 years and over, as compared with current screening guidelines that screening begin at 45 years of age. Earlier screening was assumed to reduce microvascular complications, and the health benefits were large in terms of life-years gained, but more than doubled when measured in terms of quality-adjusted life-years. The cost-effectiveness of screening was particularly beneficial with screening applied to the youngest age groups, as they had the most quality-adjusted life-years to gain, and ethnic minorities, as they have a high incidence of the disease. The results are sensitive to the many assumptions used and indeed the results might be taken as indicative rather than authoritative given the reliance on a wide range of assumptions.

Raikou and McGuire[389] also considered the literature on the cost-effectiveness of interventions aimed at specific complications in people with diabetes. In general, the literature covering the period of this review has not differentiated between type 1 and type 2 diabetic patients. A general broad conclusion is that the screening and treatment of diabetic complications are cost-effective, although this is tentative as it is based on little evidence. The general findings reached by their review suggested the following. That primary prevention of type 2 DM appeared cost-effective relative to other preventive measures, even at low levels of effectiveness, and represents a good return for specific high-risk groups. Opportunistic screening for type 2 DM also appears to be relatively cost-effective, and may indeed prove to have a lower cost-effectiveness ratio for younger age groups compared with existing tendencies to implement such programmes in those over 45 years of age. Such evidence is, nonetheless, thin and requires substantiation. The most extensive economic analysis of patients with type 2 DM with the further complication of hypertension was undertaken within the UKPDS trial and found intensive control and the use of ACE inhibitors to be cost-effective.[394]

The general findings, that even in the treatment of type 2 DM the cost-effectiveness evidence is not extensive and that the use of ACE inhibitors in the hypertensive diabetic population is highly cost-effective, are particularly important to the issue of screening for urine albumin excretion. This overall assessment of the literature is used to justify the adoption of the modelling methodology to assess the cost-effectiveness of a microalbuminuria screening programme as undertaken below.

Methods

With microalbuminuria, clinical complications are unlikely to manifest before 10 years and may take up to 20 years. Given this and the limited expected benefits from a urine albumin screen – since treatment options are the same as those implemented for all patients in this population, namely control of glycaemia and hypertension – a treatment standard that requires no screening based on urine albumin measurement is taken as the baseline option in the economic evaluation. Against this 'do nothing' baseline, incremental cost-effectiveness ratios are calculated for three different alternative strategies.

- *Option 1*: do not initiate a screening programme for urine albumin, but treat all known patients with type 2 DM with ACE inhibitors. This is the strategy implied by the National Service Framework for Coronary Heart Disease given the explicit recognition of the increased risk of CVD incurred by this population and an acknowledgement that poor glycaemic control is associated with the presence of hypertension. In this option, ACE inhibitors would be administered to all patients with type 2 DM, even if they had good glycaemic control, were normotensive and were not showing any evidence of microvascular damage.
- *Option 2*: annually screen all known patients with type 2 DM and only give ACE inhibitors to those with a positive microalbuminuria result. Some of those who screen positive for microalbuminuria will already be on

hypertensive medication and no new treatment intervention would be offered to these patients.
- *Option 3*: annually screen all known patients with type 2 DM who are not already on antihypertensive medication, and selectively give ACE inhibitors to those who screen positive.

Figure 33 sets out the general progression of disease in the type 2 DM population with respect to microalbuminuria as it manifests in terms of hypertension. This progression relates to a hypothetical cohort of incident patients where the proportion of patients affected by the different manifestations is also given. The health gains from the screening programme are particularly difficult to calculate as the annual rate of development of microalbuminuria in a previously screened and treated population is not known. Accordingly, the assumption is made below that a hypothetical incident cohort of 1000 patients per year is followed to a 10-year maximum, on the basis that this is the first year in which health benefits, measured in terms of changes in mortality arising from CVD, would be seen and therefore is the first year in which such a programme could be assessed. These mortality gains are based on the mortality rates for high-risk diabetes patients as derived from the HOPE study.[395] The health gain in HOPE was essentially a 2% reduction in cardiovascular deaths over a 5-year period. This converts to a reduction of 20 deaths per 1000 patients over a 5-year period. The health gain used in this calculation is set at half of this rate with manifestation after a 10-year period on the arbitrary assumption that, as with the manifestation of retinopathy, microalbuminuria will manifest clinical symptoms, in this case cardiovascular death, in 50% of the patients after 10 years. This gain is then applied to the relevant proportion of screened individuals. This is an extreme assumption made in the absence of any long-term mortality data directly related to microalbuminuria. Life-years gained are calculated through applying the life expectancy of a 55-year-old diabetic individual to these individuals; assumed to be 22.48 years. The HOPE results report the health gain in a high-risk population and reflect the total gain in health over a 5-year period. The gains in a general type 2 diabetic population may be more muted. Sensitivity analysis is used to consider this assumption.

Sensitivity analysis is also used to take account of the side-effects associated with ACE inhibitors or the dropout associated with these. The cost-effectiveness approach is therefore extremely simplistic in terms of modelling and assumption, reflecting the lack of long-term follow-up in microalbuminuric patients. The justification is that there is a lack of data for more dynamic modelling and that the systematic review is itself ambivalent with regards to clinical benefit of microalbuminuria screening. A more sophisticated and thorough estimation of the cost-effectiveness of such a screening programme is an area for further research.

A split between retinopathy, which results directly from microvascular damage, and microalbuminuria screening is retained, as there are additional treatments that would result from a positive screen for retinopathy, which is assumed to rely on a separate programme. Interest is confined here to microalbuminuria, and its implications with respect to CVD and retinopathy costs are subsequently ignored.

The perspective adopted for the analysis is that of the NHS provider. It is assumed the screening programme for urine albumin does not incur additional capital and infrastructure costs and these are subsequently ignored. Costs and health outcomes are discounted at 6%.

Several further assumptions were made to estimate the relevant patient populations for the three options. It is widely accepted that the majority of type 2 diabetic patients have higher than normal HbA_{1c} levels. The model is based on the assumption that 80% of type 2 diabetics have raised HbA_{1c} levels. Microalbuminuria estimates were based on the results of earlier chapters, where the prevalence was given as 8–34% in Caucasians and 26–57% in non-Caucasians, and the HOPE study, where the prevalence of microalbuminuria in a high-risk population was found to be 32%. Accordingly, for Option 2 the positive:negative population with microalbuminuria ratio was set at 32:68.

In Option 3 the at-risk population is also identified as having retinopathy or not. This is because it is known that the presence of microalbuminuria is known to be affected by the presence or absence of retinopathy. For those with retinopathy, the earlier chapters suggest a ratio of 85:15 of microalbuminuria to no microalbuminuria. In Option 2 the non-retinopathy to retinopathy ratio is 15:85 for normoalbuminuric patients with diabetes. A 43:57 non-retinopathy to retinopathy ratio in the raised HbA_{1c} arm is derived from information in UKPDS, with the converse ratio applying to the normal HbA_{1c} arm.

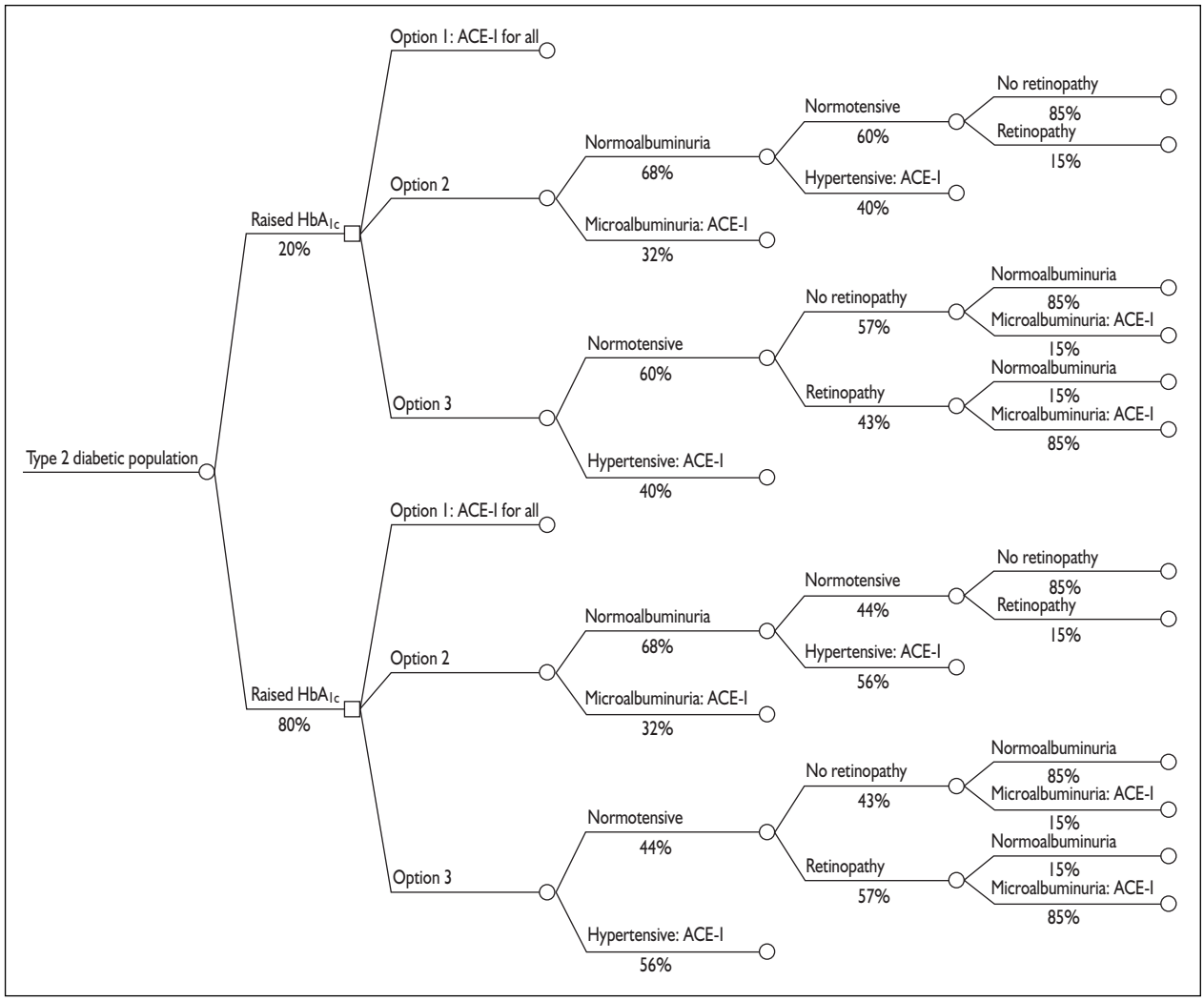

FIGURE 33 *Hypothetical options for microalbuminuria screening and ACE inhibitor treatment of incident patients with type 2 DM, split according to the degree of glycaemic control and the presence or absence of hypertension, microalbuminuria or retinopathy. See text for detailed explanations of assumptions.*

Estimates of the hypertensive population were taken from a range of sources. The HOPE study[395] considered diabetic populations who had suffered a previous cardiovascular event or had at least one other cardiovascular risk factor. In these studies the prevalence of hypertension was 56%. So, for the raised HbA_{1c} branch in the decision model the split between hypertensive and normotensive is accordingly given as 56:44. For the population with normal HbA_{1c} levels, data from earlier chapters suggest a ratio of 40:60 of hypertension to normotension.

The sensitivity and specificity of urine albumin testing are set at 95% and 93%, respectively, although these values vary with different cut-off values defined in the literature.[396] Urine albumin excretion is highly variable and repeat testing is recommended. A widely accepted procedure is to consider two positive tests out of three indicative of a diagnosis of microalbuminuria. Thus, the screening costs are calculated on the basis of a maximum of three tests per patient per year and the cost of the test, based on the use of test strips and additional time at the GP's, is set at £10 a test, giving an annual cost of £30 (all 2000 prices). For ACE inhibitor treatment only Zestril is licensed for use in treating the renal complications of diabetes, so Zestril® prices are used, with the mean annual drug cost based on a weighted average dosage and given as £113.06. This is a conservative estimate as it is known that ACE inhibitor treatment is associated with a degree of switching owing to minor side-effects, and these switching costs are ignored.

Results

The direct treatment costs for Option 1 are straightforward to estimate, as all patients with

type 2 DM would receive ACE inhibitors. The direct treatment costs for Option 2 are estimated on screening costs for all and a proportion of the type 2 diabetic population, identified as having raised microalbuminuria being treated, along with the existing hypertensive subjects, by ACE inhibitor. By selectively screening after the identification of the hypertensive population, Option 3 may be seen intuitively to achieve similar health gains, but more efficiently.

In terms of calculation, the basic annual costs of the screening programme for 1000 individuals per annum associated with the three options are given in *Table 63*. It is difficult to predict the clinical outcomes associated with identification of microalbuminuria. If the assumptions made above, based on the HOPE study and manifestation of clinical events in 50% of patients after a 10-year period, hold, ten deaths would be averted after screening ten incident cohorts of 1000 each year for 10 years. Given the lack of direct data on the long-term clinical manifestations arising from microalbuminuria, it is difficult to state whether or not these assumptions reflect reality. As noted above, the assumptions use data relating to evidence on high-risk diabetic patients, are based on manifestation of cardiovascular death alone and take no account of false-positive rates. They also amend the HOPE study ACE inhibitor effects by 50%, on the assumption that as with retinopathy only 50% of those identified with microalbuminuria will manifest clinical events and this will be after a 10-year period. Costs and benefits are discounted at 6%.

On this basis the incremental cost-effectiveness of the three screening programme options compared with a do-nothing baseline are given as £6629 per life-year gained for Option 1, £15,157 per life-year gained for Option 2 and £5745 per life-year gained for Option 3. As expected, Option 3, which is selective screening after the hypertensive population has been identified, is the preferred option. This is probably the most authoritative statement, that Option 3 with selective screening is the most cost-effective, that can be made given the data constraints and the simplicity of the modelling. That said, note that all options are based on comparison against a do-nothing option. Given the results, and that the implementation of ACE inhibitors for all and the selective screening give similar results, further work on the incremental cost-effectiveness of selective screening relative to ACE inhibitor treatment for all patients with type 2 DM appears warranted.

If the costs are increased by 50% to represent increased costs associated with side-effects arising from ACE inhibitor therapy, for example, or the higher costs associated with treating false negatives at a later date, and the health gains are halved, then the resultant incremental cost-effectiveness ratios are £19,987 per life-year gained for Option 1, £45,472 per life-year gained for Option 2 and £17,237 per life-year gained for Option 3. If only the health outcomes are halved, the resultant ratios are £13,258 per life-year gained for Option 1, £30,314 per life-year gained for Option 2 and £11,491 per life-year gained for Option 3. The volatility of the results to sensitivity analysis shows that due caution must be exercised in interpretation and no doubt results from the simplicity of the assumptions applied and the modelling itself.

Conclusions

This has been an extremely limited and basic exercise to assess the cost-effectiveness of a screening programme for microalbuminuria based on limited information concerning the appropriate treatment (as a positive screen merely indicates that individuals should be on the suggested therapy for the majority of patients with type 2 DM) as well as the lack of data on long-term health outcomes. The results are extremely sensitive to the crude assumptions made and an obvious recommendation before any such

TABLE 63 *Comparison of annual costs of a microalbuminuria screening and ACE inhibitor treatment programme for 1000 incident patients with type 2 DM according to the three options described in* Figure 33. *See text for detailed explanations of assumptions*

Option	% Screened	% Found with raised microalbuminuria	% Already on ACE-I owing to raised BP	Screening cost (£)	Total ACE-I cost (£)	Total cost (£)	Existing cost due to ACE-I (£)	Net cost of screening programme (£)
1						113,060		113,060
2	100	32	35.90	30,000	76,772	106,772	40,593	66,179
3	47.20	24.70	52.80	14,160	87,674	101,834	59,696	42,138

screening programme was initiated would be to have further investigation of the long-term impacts. Furthermore, a similar exercise should be applied to the total diabetic population. In particular, a detailed incremental cost-effectiveness analysis of initiating ACE inhibitor therapy in all type 2 diabetic patients versus selective screening for raised urine albumin in a normotensive type 2 diabetic population should be undertaken. An obvious extension is the consideration of the type 1 diabetic population. Finally, an important consideration that has not been discussed here is that the economic evaluation of an annual screening programme will depend on the rate of development of microalbuminuria in patients already screened, with the benefits of surveillance being different in the first and subsequent rounds. Further research is needed in this area.

Given that the long-term outcomes are not well defined, it is not, at this stage, recommended that the cost-effectiveness results be used to support any policy stance.

Appendix 3

Search strategies

Note on abbreviations: exp, explode; mp, text word; /, MeSH heading; $, unlimited truncation.

Review 1

Mortality

MEDLINE (1966–2002)

1. exp Diabetes mellitus/
2. Albuminuria/
3. "MICROALBUMIN$" mp
4. "URINARY ALBUMIN" mp.
5. "URINE ALBUMIN" mp.
6. "INCIPIENT DIABETIC NEPHROPATHY"
7. 2 or 3 or 4 or 5 or 6
8. exp Mortality/
9. exp Cardiovascular diseases/.
10. "MORTALITY" mp
11. 8 or 9 or 10
12. exp Cohort studies/
13. exp Prognosis/
14. 12 or 13
15. 1 and 7 and 11 and 14 **= 424 citations (type 1 and type 2)**

EMBASE (1980–2002)

1. exp Diabetes mellitus/
2. Microalbuminuria/
3. "URINARY ALBUMIN" mp.
4. "URINE ALBUMIN" mp.
5. "ALBUMINURIA" mp.
6. "INCIPIENT DIABETIC NEPHROPATHY" mp.
7. 2 or 3 or 4 or 5 or 6
8. exp Cardiovascular disease/
9. exp mortality/
10. 8 or 9
11. Prognosis/
12. Follow up/
13. Risk factor/
14. Prospective study/
15. Cohort analysis/
16. Longitudinal study/
17. 11 or 12 or 13 or 14 or 15 or 16
18. 1 and 7 and 10 and 17 **= 421 citations (type 1 and type 2)**

Review 2

Retinopathy

MEDLINE (1966–2002)

1. Diabetic retinopathy/
2. "MICROALBUMIN$" mp
3. "URINARY ALBUMIN" mp
4. Albuminuria/
5. 2 or 3 or 4
6. Exp Epidemiologic studies
7. 1 and 5 and 6 **= 204 citations (type 1 and type 2)**

EMBASE (1974–2002)

1. Diabetic retinopathy/
2. Proliferative retinopathy/
3. 1 or 2
4. Microalbuminuria/
5. "URINARY ALBUMIN" mp
6. Protein urine level/
7. 4 or 5 or 6
8. Prospective study/
9. Risk factor/
10. Longitudinal study/
11. Prognosis/
12. Cohort analysis/
13. 8 or 9 or 10 or 11 or 12
14. 3 and 7 and 13 **= 91 citations (type 1 and type 2)**

Review 3

Renal disease: renal failure

MEDLINE (1966–2002)

1. Diabetes Mellitus, Insulin-Dependent/
2. Diabetes Mellitus, Non-Insulin-Dependent/
3. "MICROALBUMIN$".mp.
4. "URINARY ALBUMIN".mp.
5. "INCIPIENT DIABETIC NEPHROPATHY".mp.
6. 3 or 4 or 5
7. Exp Kidney disease/
8. "RENAL FAILURE" .mp.
9. 7 or 8
10. Prognosis/
11. Exp Cohort Studies

12. 10 or 11
13. 1 and 6 and 9 and 12 **= 179 citations (type 1)**
14. 2 and 6 and 9 and 12 **= 120 citations (type 2)**

EMBASE (1980–2002)

1. Insulin dependent diabetes mellitus/
2. Non insulin dependent diabetes mellitus/
3. Microalbuminuria/
4. "MICROALBUMIN$".mp.
5. "URINARY ALBUMIN"
6. 3 or 4 or 5
7. Exp Kidney transplantation/
8. Chronic kidney disease/ or Glomerulopathy/ or Kidney disease/ or Kidney failure/
9. Exp hemodialysis/
10. Diabetic nephropathy/
11. 7 or 8 or 9 or 10
12. Follow up/
13. Chronic disease/ or Disease duration/ or Prognosis/ or Survival/ or Terminal disease/
14. Case control study/ or Longitudinal study/ or Prospective study/ or Retrospective study/
15. 12 or 13 or 14
16. 1 and 6 and 11 and 15 **= 93 citations (type 1)**
17. 2 and 6 and 11 and 15 **= 56 citations (type 2)**

Renal disease: fall in GFR

MEDLINE (1966–2002)

1. Diabetes Mellitus, Insulin-Dependent/
2. Diabetes Mellitus, Non-Insulin-Dependent/
3. Microalbumin$ .mp.
4. Urinary albumin .mp.
5. Incipient diabetic nephropathy .mp.
6. 3 or 4 or 5
7. Glomerular Filtration Rate/
8. Creatinine clearance .mp.
9. Serum creatinine .mp.
10. 7 or 8 or 9
11. PROGNOSIS/
12. Exp Cohort Studies/
13. 11 or 12
14. 1 and 6 and 10 and 13 (limit to human) **= 79 citations (type 1)**
15. 2 and 6 and 10 and 13 (limit to human) **= 65 citations (type 2)**

EMBASE (1980–2002)

1. Insulin dependent diabetes mellitus/
2. Non insulin dependent diabetes mellitus/
3. Microalbuminuria/
4. "URINARY ALBUMIN" .mp.
5. "URINE ALBUMIN" .mp.
6. "INCIPIENT DIABETIC NEPHROPATHY".mp.
7. Glomerulus filtration rate/
8. "GLOMERULAR FILTRATION RATE" .mp.
9. Creatinine clearance/
10. Exp Clinical study/
11. Prognosis/
12. 3 or 4 or 5 or 6
13. 7 or 8 or 9
14. 10 or 11
15. 1 and 12 and 13 and 14 (limit to human) **= 191 citations (type 1)**
16. 2 and 12 and 13 and 14 (limit to human) **= 132 citations (type 2)**

Renal disease: clinical proteinuria

MEDLINE (1966–2002)

1. Exp Diabetes mellitus/
2. "URINARY ALBUMIN".mp.
3. "URINE ALBUMIN".mp.
4. Albuminuria/
5. "MICROALBUMIN$". mp.
6. "INCIPIENT DIABETIC NEPHROPATHY".mp.
7. 2 or 3 or 4 or 5 or 6
8. Diabetic nephropathies/
9. Proteinuria/
10. "OVERT NEPHROPATHY".mp.
11. "MACROALBUMINURIA".mp.
12. "CLINICAL ALBUMINURIA".mp.
13. 8 or 9 or 10 or 11 or 12
14. exp Prognosis/
15. exp Longitudinal studies/
16. 14 or 15
17. 1 and 7 and 13 and 16
18. limit to review articles
19. 17 not 18
20. limit to animal studies
21. 19 not 20 **= 353 citations (type 1 and type 2)**

EMBASE (1980–2002)

1. Exp Diabetes mellitus/
2. Microalbuminuria/
3. "MICROALBUMIN$".mp.
4. "URINARY ALBUMIN".mp.
5. "URINE ALBUMIN".mp.
6. "INCIPIENT DIABETIC NEPHROPATHY".mp.
7. 2 or 3 or 4 or 5 or 6
8. Prognosis/ or Survival/
9. Follow up/
10. Prospective study/
11. Longitudinal study/
12. 8 or 9 or 10 or 11
13. 1 and 7 and 12
14. limit to reviews
15. 13 not 14 **= 244 citations (type 1 and type 2)**

Review 4

Intervention with improved glycaemic control

MEDLINE (1966–2002)

1. Diabetes Mellitus, Insulin-Dependent/
2. Diabetes Mellitus, Non-Insulin-Dependent/
3. Albuminuria/
4. MICROALBUMIN$.mp.
5. URINARY ALBUMIN. mp.
6. Glomerular Filtration Rate/
7. Diabetic Nephropathies/
8. Diabetic Retinopathy/
9. Diabetic Angiopathies/
10. Cardiovascular Diseases/
11. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. Blood Glucose/
13. Hypoglycemic Agents/
14. Blood Glucose Self-Monitoring/
15. Hemoglobin A, Glycosylated/
16. Insulin/ or Insulin Infusion Systems/
17. Injections, Subcutaneous/
18. 12 or 13 or 14 or 15 or 16 or 17
19. Randomized Controlled Trials/
20. Random Allocation/
21. RANDOM.mp.
22. Meta-Analysis/
23. Review Literature/
24. Exp Cohort Studies/
25. Exp Clinical Trials/
26. 19 or 20 or 21 or 22 or 23 or 24 or 25
27. 1 and 11 and 18 and 26 **= 195 citations (type 1)**
28. 2 and 11 and 18 and 26 **= 160 citations (type 2)**

EMBASE (1980–2002)

1. Diabetes Mellitus, Insulin-Dependent/
2. Diabetes Mellitus, Non-Insulin-Dependent/
3. Microalbuminuria/
4. URINARY ALBUMIN. mp.
5. Diabetic Nephropathy/
6. Glomerulus Filtration Rate/
7. Creatinine Clearance/
8. Diabetic Retinopathy/
9. Diabetic Angiopathy/
10. Cardiovascular Diseases/
11. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. Glucose Blood Level/ or Blood Glucose Monitoring/
13. Glycosylated Hemoglobin/ or Haemoglobin A1c/
14. Insulin/ or Insulin Infusion/
15. Antidiabetic Agent/
16. Sulfonyurea/
17. Biguanide-Derivative/
18. 12 or 13 or 14 or 15 or 16 or 17
19. Randomized Controlled Trial/
20. Randomization/
21. RANDOM. mp.
22. Meta-Analysis/
23. Systematic Review/
24. 19 or 20 or 21 or 22 or 23
25. 1 and 11 and 18 and 24 **= 100 citations (type 1)**
26. 2 and 11 and 18 and 24 **= 246 citations (type 2)**

Review 5

Intervention with antihypertensive agents

MEDLINE (1966–2002)

1. Diabetes Mellitus, Insulin-Dependent/
2. Diabetes Mellitus, Non-Insulin-Dependent/
3. microalbumin$.mp.
4. incipient diabetic nephropathy.mp.
5. urinary albumin.mp.
6. urine albumin.mp.
7. ALBUMINURIA/
8. 3 or 4 or 5 or 6 or 7
9. Randomized Controlled Trials/
10. randomized controlled trials.mp.
11. Random Allocation/
12. random allocation.mp.
13. Double-Blind Method/
14. Single-Blind Method/
15. exp Clinical Trials/
16. exp Longitudinal Studies/
17. PLACEBOS/
18. placebo.mp.
19. random$. mp.
20. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. HYPERTENSION/
22. Antihypertensive Agents/
23. Blood Pressure/pd, de [Pharmacology, Drug Effects]
24. Angiotensin-Converting Enzyme Inhibitors/
25. normotensive.mp.
26. 21 or 22 or 23 or 24 or 25
27. 1 and 8 and 20 and 26 **= 178 citations (type 1)**
28. 2 and 8 and 20 and 26 **= 168 citations (type 2)**

EMBASE (1980–2002)

1. Insulin Dependent Diabetes Mellitus/
2. Non Insulin Dependent Diabetes Mellitus/
3. MICROALBUMINURIA/
4. incipient diabetic nephropathy.mp.
5. urinary albumin.mp.
6. albuminuria.mp.

7. 3 or 4 or 5 or 6
8. Randomized Controlled Trial/
9. Randomization/
10. random$. mp.
11. Double Blind Procedure/
12. Single Blind Procedure/
13. PLACEBO/
14. exp Longitudinal Study/
15. Clinical Trial/
16. Prospective Study/
17. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. Antihypertensive Agent/ct, ad, cb, cm, dt [Clinical Trial, Drug Administration, Drug Combination, Drug Comparison, Drug Therapy]
19. HYPERTENSION/et, pc, dm, dt [Etiology, Prevention, Disease Management, Drug Therapy]
20. Blood Pressure/
21. normotens$.mp.
22. Dipeptidyl Carboxypeptidase/ or angiotensin converting enzyme.mp.
23. Dipeptidyl Carboxypeptidase Inhibitor/ or Angiotensin Receptor Antagonist/
24. 18 or 19 or 20 or 21 or 22 or 23
25. 1 and 7 and 17 and 24. **= 142 citations (type 1)**
26. 2 and 7 and 17 and 24. **= 199 citations (type 2)**

The Cochrane Library

The Cochrane Controlled Trials Register (CENTRAL/CCTR)

#1 DIABETES-MELLITUS-INSULIN-DEPENDENT: ME
#2 ALBUMINURIA: ME
#3 BLOOD-PRESSURE: ME
#4 #1 and #2 and #3 **= 86 citations (13 directly relevant)**

Systematic reviews and meta-analyses

Cochrane Database of Systematic Reviews

Search term-albuminuria **1 review found**

Database of Abstracts of Reviews of Effectiveness

Search term-albuminuria **4 reviews found**

MEDLINE (1966–2002)

1. exp Diabetes Mellitus/
2. Angiotensin-Converting Enzyme Inhibitors/
3. Hypertension/ or Antihypertensive Agents/
4. normotensive.mp.
5. Blood Pressure/pd, de [Pharmacology, Drug Effects]
6. 2 or 3 or 4 or 5
7. Meta-Analysis/
8. meta-analysis.mp.
9. systematic review.mp.
10. overview.mp.
11. data synthesis.mp.
12. Evidence-Based Medicine/
13. 7 or 8 or 9 or 10 or 11 or 12
14. 1 and 6 and 13 **= 121 citations**

Appendix 4

Eligibility, quality and data extraction forms

Research question 1: In patients with type 1 or type 2 DM, what is the evidence that microalbuminuria is an independent prognostic factor for the development of diabetic complications?

Research question 1: Eligibility criteria

Study code number Initials of reviewer

Please circle either Y (Yes) or N (No) for all questions

A1. Does this study include subjects with diabetes mellitus?	N	Y
A2. Is this a primary research study?	N	Y
A3. Is this a cohort (prospective or retrospective study) study?	N	Y
A4. Has urinary albumin been measured at baseline?	N	Y
A5. Are any of the following outcomes specified and recorded? (Please tick which) All-cause (total) mortality Cardiovascular mortality Cardiovascular morbidity & mortality Ischaemic heart disease (or coronary heart disease) mortality Ischaemic heart disease (or coronary heart disease morbidity & mortality Renal failure or need for dialysis Retinopathy or vision loss Surrogate end-points such as rate of decline of GFR, change in incidence of clinical albuminuria or change in serum creatinine	N	Y
A6. Does this article report only on the relation of clinical albuminuria (overt nephropathy) to the outcome?	N	Y

Decision to include

If the answer to A1 or A2 or A3 or A4 or A5 is No or if the answer to A6 is Yes then exclude, otherwise include.

Advice needed? N Y

Overall decision **Exclude** **Include** **Unclear**

Research question 1: Quality criteria

For all questions please circle either, Y (Yes), N (No) or U (Unclear) or comment, as appropriate.

Study code no: Initials of reviewer:

1.	Which study design has been used in this article?	Prospective Retrospective Other		
2.	Was the normoalbuminuric group selected from the same population as the microalbuminuric?	N	Y	U
3.	Were the cohorts comparable (other than albuminuria status) in the following baseline factors which may affect the outcome?			
	Age	N	Y	U
	Sex	N	Y	U
	Known duration of diabetes	N	Y	U
	Glycaemic control	N	Y	U
	Arterial blood pressure	N	Y	U
	Smoking habits	N	Y	U
	Serum cholesterol	N	Y	U
	Cardiovascular disease	N	Y	U
	Ethnic origin	N	Y	U
4.	Was there any adjustment for the effects of these confounding variables?	N	Y	U
5.	Was outcome assessment blind to albuminuria status?	N	Y	U
6.	What proportion of the cohort had complete follow-up?			
	Less than 50%	N	Y	U
	Between 50% and 80%	N	Y	U
	More than 80%	N	Y	U
7a.	What was the drop-out rate in the microalbuminuric group?			
7b.	What was the drop-out rate in the normoalbuminuric group?			

Research question 1: Data extraction

Please circle N (No), Y (Yes) or U (Unclear) or give relevant information, as appropriate.

Publication details

1.	Study (code number):	2.	Initials of reviewer:	
3.	Title:			
4.	Author and date of publication:			
5.	Country and City where study carried out:			
6.	In which language is this article?			
7.	If not in English, is translation necessary?	N	Y	U
8.	Is there more than one follow-up report from this study?	N	Y	U
9.	If yes, what are the code numbers of the other articles selected?			

10. What is the study setting?
    Hospital diabetes clinic
    General practice
    Population based
    Other

Patients

1.	Was this study carried out in type 1 (IDDM) subjects?	N	Y	U
2.	Was this study carried out in type 2 (NIDDM) subjects?	N	Y	U
3.	How many subjects are there in the cohort? All Men Women			
4.	What is the average age (and age range) of subjects in the cohort?			
5.	What is the average known duration of diabetes in this cohort? All Microalbuminuric Normoalbuminuric			
6.	What is the duration of follow-up?			
7.	When was the cohort assembled?			
8.	Is any information on social class provided?			
9.	If stated, what is the baseline prevalence of hypertension in the cohort?			
10.	What is the baseline prevalence of ischaemic heart disease or cardiovascular disease in the cohort?			
11.	Does the cohort comprise one ethnic group?	N	Y	U
12.	If yes to Q11, what is the ethnic group?			
13.	If no to Q11, were further ethnic groups analysed?	N	Y	U

If yes, data mentioned below will need to be collected for each ethnic group

Analysis & results

1. Which analytical method was used for measurement of urinary albumin?

2. How is microalbuminuria defined in this study?
   (And in how many urine samples at baseline?)

3. Was dipstick (e.g. Albustix)-positive proteinuria used as an exclusion criterion?

4. What is the baseline prevalence of microalbuminuria in this study, if calculable?

5.	Were urine samples stored frozen before assay? (If yes, at what temperature?)	N	Y	U
6.	Which outcomes were studied?			
7.	Is there an association between microalbuminuria and the outcome?	N	Y	U
8.	Does the "microalbuminuric" group include any subjects with clinical albuminuria? (i.e. with urinary albumin excretion rates >200 μg/min, >300 mg/day, or equivalent)	N	Y	U
9.	For which outcome is data now being extracted?			
10.	How is the outcome defined in this study?			
11.	Which statistical method was used to evaluate the prognostic significance of microalbuminuria for the outcome?			
	Cox survival analysis	N	Y	U
	Logistic regression analysis	N	Y	U
	Other			
12.	What proportion of patients was unavailable for follow-up?			
13.	Were their characteristics compared to those who completed the study?	N	Y	U
14.	If yes to Q13, are there any significant ($p < 0.05$) differences?	N	Y	U
15.	How many patients in the microalbuminuric group suffered the outcome?			
16.	What is the total number of patients in the microalbuminuric group at baseline?			
17.	How many patients in the normoalbuminuric group suffered the outcome?			
18.	What is the total number of patients on the normoalbuminuric group at baseline?			
19.	Are the baseline characteristics of patients with and without microalbuminuria shown?	N	Y	U
20.	If yes to Q19, are there significant ($p < 0.05$) differences between groups?	N	Y	U
21.	Was there adjustment for these differences or other important prognostic factors?	N	Y	U
22.	List the factors adjusted for in multivariate analysis			
23.	What is the value of the adjusted risk estimate (and 95% CI) of microalbuminuria for the outcome?			
24.	Any comments or queries?	N	Y	

Research question 2: In patients with type 1 or type 2 DM and microalbuminuria, what is the evidence that improved glycaemic control or improved blood pressure control (including the use of ACE inhibitors in normotensive patients) will influence the outcomes?

Research question 2: Eligibility criteria

Study (code number) Initials of reviewer

Please circle either Y (Yes) or N (No) for all questions

A1. Does this study include subjects with diabetes mellitus?	N	Y
A2. Is this a primary research study?	N	Y
A3. Is this a controlled clinical trial?	N	Y
A4. Are any of the interventions mentioned in research question 2 (improved glycaemic control or improved blood pressure control including use of ACE inhibitors in normotensive patients) used in this study?	N	Y
A5. Is the minimum follow-up period 12 months?	N	Y
A6. Has urinary albumin been measured at baseline?	N	Y
A7. Are any of the following outcomes specified and recorded? (Please tick which) All-cause (total) mortality Cardiovascular mortality Cardiovascular morbidity & mortality Ischaemic heart disease mortality Ischaemic heart disease morbidity & mortality Mortality from chronic renal failure Renal failure or need for dialysis Retinopathy or vision loss Surrogate end-points such as rate of decline of GFR, change in incidence of clinical albuminuria or change in serum creatinine.	N	Y
A8. Does this article report only on the relation of clinical albuminuria (overt nephropathy) to the outcome?	N	Y

Decision to include

If the answer to A1 or A2 or A3 or A4 or A5 or A6 or A7 is No or if the answer to A8 is Yes then exclude, otherwise include.

Advice needed? N Y

Overall decision **Exclude** **Include** **Unclear**

Research question 2: Quality criteria

Study (code number) Initials of reviewer

Please circle either Y (Yes) or N (No) or U (Unknown) for all questions, or whichever option A–D applies

Generation of allocation schedule

A1.	Was the trial described as "randomised"?		N	Y
A2.	Was allocation to groups truly random? (Random numbers, coin toss, etc.)			A
	Or			
	Was allocation pseudo-random? (Patient's number, date of birth, etc.)			B
	Or			
	Was allocation systematic? (i.e. non-random, e.g. alternate)			C
	Or			
	Was the method of randomisation not stated or unclear?			D

Concealment of treatment allocation

B1.	Was concealment adequate? (Central allocation at office or pharmacy, sequentially numbered or coded containers, or other methods where the trialist allocating treatment could not be aware of the treatment)			A
	or			
	Was concealment inadequate? (Allocation was alternate [by patient day of week, etc.] or based on information, e.g. date of birth, already known to the trialist)			B
	or			
	Was concealment unclear? (Inadequate information given)			C

Implementation of masking

C1.	Was the trial described as "double blind"?		N	Y
C2.	Was treatment allocation masked from participants? (Either stated explicitly, or an identical placebo is used)	U	N	Y
C3.	Was the treatment allocation masked from trialists?	U	N	Y
C4.	Was the treatment allocation masked at the outcome assessments?	U	N	Y

Completeness of the trial

D1.	Was the number of withdrawals in each group stated?	U	N	Y
D2.	Was an intention to treat analysis performed? (Analysis according to allocation)	U	N	Y

D3. What were the drop-out rates in each group of the trial for each of the main outcomes? (Or write unclear or not stated as appropriate)

Group	Outcome 1	Outcome 2	Outcome 3
1.			
2.			
3.			
4.			

D4. Are there substantial differences in completeness between the groups? U N Y

Research question 2: Data extraction

The present form, shown as an example, is designed for the end-point of clinical proteinuria

Please circle N (No), Y (Yes) or U (Unclear) or give relevant information, as appropriate.

Publication details

1. Study (code number):
2. Initials of reviewer:
3. Title (shortened):
4. Author and date of publication:
5. Country and City where study carried out:
6. In which language is this article?
7. If not in English, is translation necessary? N Y U
8. Is there more than one follow-up report from this study? N Y U
9. If yes, what is the code numbers of the other articles selected?
10. What is the study setting?
    Hospital diabetes clinic
    General practice
    Population based
    Other

Patients & interventions

1. Was this study carried out in type 1 (IDDM) subjects? N Y U
2. Was this study carried out in type 2 (NIDDM) subjects? N Y U
3. When was this study carried out?
4. What is the exact form and delivery of the intervention?
5. How many treatment groups are there in this study?
6. Is there a placebo-treated group (or a group who were untreated)? N Y U

7. Which comparisons between groups were made in this study?

8. What is the number of patients (men, women and all) in each group?

9. What is the average age (and age range) of patients in the study?

10. What is the average known duration of diabetes (and range) of patients in the study?

11. What is the mean level of HbA_{1c} among patients at study outset?

12. Were patients described as normotensive (if so, what was the definition used)?

13. Were patients described as hypertensive (if so, what was the definition used)?

14. From which ethnic group were patients recruited?

15. What is the duration of follow-up?

Analysis & results

1. Which analytical method was used for measurement of urinary albumin?

2. How is microalbuminuria defined in this study?

3. What type of urine sample was used (e.g. overnight, 24-hr, etc.)?

4. What is the frequency and number of urine collections in this study?

5. Were urine samples stored frozen before assay? (If yes, at what temperature?) N Y

6. Does the "microalbuminuric" group include any subjects with clinical albuminuria? (i.e. with urinary albumin excretion rates >200 μg/min, >300 mg/day, or equivalent) N Y U

7. Does the "microalbuminuric" group include any subjects with normal urinary albumin excretion? N Y U

8. What is the primary outcome variable in this study?

9. How is the outcome defined in this study?

10. Which other outcomes were studied?

11. How are they defined in this study?

12. For which outcome is data now being extracted (please use separate sheets for each outcome recorded)?

13. Was there recording of adverse events?

14. Which statistical methods were used in this study?

15. What proportion of patients was unavailable for follow-up in each group?

16. Were their characteristics compared to those who completed the study?	N	Y	U
17. If yes, are there any significant ($p < 0.05$) differences?	N	Y	U
18. What is the number and proportion of patients in the treatment group who developed clinical albuminuria?			
19. What is the number and proportion of patients in the placebo or control group who developed clinical albuminuria?			
20. Are these proportions significantly different?			
21. Are the times to progression significantly different?			
22. What is the risk reduction (and 95% CI) in progression from microalbuminuria to clinical albuminuria, if stated?			
23. Record the number needed to treat, if calculated			
24. What is the annual rate of progression of albumin excretion (%/yr and 95% CI) in the treatment group?			
25. What is the annual rate of progression of albumin excretion (%/yr and 95% CI) in the placebo group?			
26. What were the effects of this treatment on blood pressure?			
27. After adjustment for blood pressures, what is the risk reduction (and 95% CI), if stated, for progression from microalbuminuria to clinical albuminuria and is it statistically significant?			
28. Are other baseline factors, such as AER, adjusted for?			

If other comparisons have been made please fill out additional sheets for each

29. Are the baseline characteristics of patients with and without microalbuminuria shown?	N	Y	U
30. If yes, are there significant ($p < 0.05$) differences between groups?	N	Y	U
31. Was there any adjustment for these differences or other important prognostic factors?	N	Y	U
32. List the factors adjusted for in multivariate analysis			
33. Which baseline factors were independent predictors of progression to clinical albuminuria?			
34. Any comments or queries?	N	Y	

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We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278