

A randomised trial of the effect and cost-effectiveness of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with screen-detected type 2 diabetes: the Anglo–Danish–Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION-Europe) study

Rebecca K Simmons,¹ Knut Borch-Johnsen,^{2,3}
Torsten Lauritzen,³ Guy EHM Rutten,⁴
Anelli Sandbæk,³ Maureen van den Donk,⁴
James A Black,¹ Libo Tao,¹ Edward CF Wilson,⁵
Melanie J Davies,⁶ Kamlesh Khunti,⁶ Stephen J Sharp,¹
Nicholas J Wareham¹ and Simon J Griffin^{1*}

¹Medical Research Council Epidemiology Unit, School of Clinical Medicine, University of Cambridge, Cambridge, UK

²Holbæk Hospital, Holbæk, Denmark

³School of Public Health, Department of General Practice, University of Aarhus, Aarhus, Denmark

⁴Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

⁵Department of Public Health and Primary Care, Cambridge Centre for Health Services Research, University of Cambridge, School of Clinical Medicine, Cambridge, UK

⁶Diabetes Research Centre, Leicester Diabetes Centre, University of Leicester, Leicester General Hospital, Leicester, UK

*Corresponding author

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Scientific summary

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Scientific summary

Background

Type 2 diabetes represents a major global public health challenge. The UK NHS spends £7.7B per year on the complications of diabetes, mainly attributable to macrovascular disease. Intensive treatment (IT) of multiple cardiovascular risk factors can halve the rates of cardiovascular disease (CVD) and mortality among people with established type 2 diabetes. The effect of intensive multifactorial treatment earlier in the course of the disease is unknown. Resolving this uncertainty is important in assessing the costs and benefits of screening for diabetes.

Objectives

We aimed to examine the effectiveness of intensive multifactorial treatment among patients with type 2 diabetes detected by screening for 5-year macrovascular, microvascular and patient-reported outcomes. We also aimed to estimate the short- and long-term cost-effectiveness of IT compared with routine care (RC) in terms of mean costs and quality-adjusted life-years (QALYs) accrued.

Methods

We undertook a pragmatic, multicentre, cluster-randomised, parallel-group trial with a concurrent economic evaluation of intensive multifactorial treatment among individuals with screen-detected diabetes. A total of 343 general practices in Denmark, the Netherlands, and Cambridge and Leicester, UK, were independently randomised to screening plus RC of diabetes according to national guidelines or screening and promotion of target-driven IT of multiple risk factors. We undertook population-based stepwise screening among people aged 40–69 years (50–69 years in the Netherlands) without known diabetes between April 2001 and December 2006. Individuals were diagnosed with diabetes according to 1999 World Health Organization criteria. General practitioners (GPs) assessed patients against exclusion criteria: having an illness with a life expectancy of < 12 months; being housebound; being pregnant or lactating; or having psychological or psychiatric problems that might invalidate informed consent.

In IT practices, GPs, practice nurses and participants were educated in target-driven management (using medication and promotion of a healthy lifestyle) of hyperglycaemia, blood pressure and cholesterol. The intervention delivered was practice based, except in Leicester, where patients also had access to individualised community clinics every 2 months. Treatment targets and algorithms were based on trial data demonstrating the benefits of IT of CVD risk factors among those with type 2 diabetes. Practitioners were advised to treat to the following targets: glycated haemoglobin (HbA_{1c}) of < 53 mmol/l (7.0%) if HbA_{1c} > 6.5%; blood pressure of ≤ 135/85 mmHg if ≥ 120/80 mmHg; cholesterol of < 5 mmol/l without ischaemic heart disease or < 4.5 mmol/l with ischaemic heart disease; and prescription of aspirin to those treated with antihypertensive medication. The treatment algorithm included a recommendation to prescribe a statin to all patients with a cholesterol level of ≥ 3.5 mmol/l following results from the Heart Protection Study. Individuals in the RC group received the standard pattern of diabetes care according to current recommendations in each centre. Group allocation was concealed from those assessing and adjudicating outcomes.

The primary end point was a composite of first cardiovascular event, including cardiovascular mortality, cardiovascular morbidity (non-fatal myocardial infarction and non-fatal stroke), revascularisation and non-traumatic amputation during a mean [standard deviation (SD)] follow-up of 5.3 (1.6) years. In each centre participants' medical records or national registers were searched for potential end points. For each possible end point, packs containing relevant clinical information were prepared and sent to two members of the expert committees, who were unaware of group allocation, for independent adjudication according to an agreed protocol using standardised case report forms.

Secondary end points were (1) all-cause mortality; (2) microvascular outcomes, including kidney function [microalbuminuria, macroalbuminuria and estimated glomerular filtration rate (eGFR)], retinopathy (retinal photos) and peripheral neuropathy (questionnaire data) at 5 years; and (3) patient-reported outcomes, including health status (European Quality of Life-5 Dimensions) at baseline and 5 years and health status [Short Form questionnaire-36 items (SF-36), European Quality of Life visual analogue scale (EQ-VAS)], well-being (12-item short form of the Well-Being Questionnaire), diabetes-specific quality of life (Audit of Diabetes-Dependent Quality of Life) and satisfaction with diabetes treatment (Diabetes Treatment Satisfaction Questionnaire) at 5 years.

An individually randomised trial would have required a total of 2700 individuals (1350 per group) to detect a 30% reduction in cumulative risk of the primary end point at a 5% significance level and with 90% power, allowing for 10% loss to follow-up and assuming an event rate in the RC group of 3% per year [based on results from the UK Prospective Diabetes Study (UKPDS)]. We expected a minimal effect of clustering within general practices, with an estimated intracluster correlation coefficient of 0.01; assuming an average of 10 participants per general practice, the design effect was 1.09 and thus we inflated the estimated sample size for this cluster trial to 3000.

An economic evaluation of the intervention in the UK was undertaken from a UK payer (NHS) perspective using trial data to estimate the mean costs and QALYs gained per patient for the IT and RC interventions. We report short-term (within-trial) and long-term (10–30 years based on decision modelling) incremental cost-effectiveness ratios (ICERs) and associated decision uncertainty.

Results

We recruited 3057 (RC, $n = 1379$; IT, $n = 1678$) participants between 2001 and 2006. Two participants from the RC group withdrew consent in the first few months of the study and hence data were included for 1377 RC participants. Prescription of glucose-lowering, antihypertensive and lipid-lowering medication increased in both groups, with more patients in the IT group than in the RC group prescribed cardioprotective medication at follow-up. Clinically important improvements in cardiovascular risk factors and modelled cardiovascular risk were observed in both study groups between baseline and 5 years' follow-up. Modest differences between groups in the reduction in levels of HbA_{1c}, blood pressure, cholesterol and modelled cardiovascular risk favoured the IT group. In the whole trial cohort, 10-year modelled CVD risk was 27.3% (SD 13.9%) at baseline and 21.3% (SD 13.8%) at 5 years' follow-up. The incidence of first cardiovascular event [IT 7.2%, 13.5 per 1000 person-years; RC 8.5%, 15.9 per 1000 person-years; hazard ratio 0.83, 95% confidence interval (CI) 0.65 to 1.05] and all-cause mortality (IT 6.2%, 11.6 per 1000 person-years; RC 6.7%, 12.5 per 1000 person-years; hazard ratio 0.91, 95% CI 0.69 to 1.21) did not differ significantly between groups.

Five years after diagnosis any kind of albuminuria was present in 22.7% of participants in the IT group and 24.4% of participants in the RC group [odds ratio (OR) 0.88, 95% CI 0.72 to 1.07]. Retinopathy was present in 10.2% of the IT group and 12.1% of the RC group (OR 0.84, 95% CI 0.64 to 1.10); eight patients had severe retinopathy ($n = 1$ IT; $n = 7$ RC). Neuropathy was present in 4.9% and 5.9% of the IT and RC groups, respectively (OR 0.95, 95% CI 0.68 to 1.34). The eGFR increased between baseline and follow-up in both groups (IT 4.31 ml/minute; RC 6.44 ml/minute).

Health status, well-being, diabetes-specific quality of life and treatment satisfaction did not differ significantly between the IT group and the RC group after 5 years' follow-up. There was some heterogeneity between centres [I^2 between 13% (SF-36 physical functioning) and 73% (EQ-VAS)].

The incremental cost to the NHS of the IT intervention was £285, £935, £1190 and £1745 over a 1-, 5-, 10- and 30-year time horizon, respectively (discounted at 3.5%). Incremental QALYs were 0.0000, -0.0040, 0.0140 and 0.0465 over the same time horizons. Point estimate ICERs suggested that the intervention was not cost-effective although the ratio improved over time: the ICER over 10 years was £82,250, falling to £37,500 over 30 years. The ICER fell below £30,000 only when the intervention cost was below £631 per patient; we estimated the cost of the intervention at £981.

Conclusions

Compared with RC, IT was associated with modest increases in prescribed treatment and reduced levels of cardiovascular risk factors, but reductions in the incidence of cardiovascular events, microvascular complications and death over 5 years were not statistically significant. Despite increasing age and diabetes duration there was a decline in modelled CVD risk in the whole trial cohort in the 5 years following diagnosis. The IT intervention did not adversely affect patient-reported outcomes. Given conventional thresholds for cost-effectiveness, the IT intervention was not cost-effective compared with RC for screen-detected diabetes patients in the UK. The intervention may be cost-effective if it can be delivered at a reduced cost.

The lower than expected CVD event rate means that the 5-year duration of follow-up may be insufficient to detect a potential difference between groups. The apparent divergence of event rates from 4 years suggests that further follow-up of this trial is justified to test whether or not IT reduces cardiovascular risk in the long term as seen in the UKPDS.

Intensive treatment by lifestyle intervention and prescription of cardioprotective medication led to clinically important reductions in CVD risk factors and modelled CVD risk in the trial cohort. Furthermore, IT was not associated with adverse patient-reported outcomes. As such, health practitioners might consider treating multiple cardiovascular risk factors early and intensively in the diabetes disease trajectory, when the rate of CVD risk progression may be slowed.

Trial registration

This trial is registered as NCT00237549.

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Editorial contact: nhredit@southampton.ac.uk

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