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M Buxton,[1] N Caine,[2] D Chase,[3] D Connelly,[4] A Grace,[5] C Jackson,[6] J Parkes[7] and L Sharples[8*]

[1] Health Economics Research Group (HERG), Brunel University, Uxbridge, UK
[2] Department of Health, London, UK
[3] National Coordinating Centre for Health Technology Assessment, Wessex Institute for Health Research and Development, University of Southampton, UK
[4] Department of Medical Cardiology, Glasgow Royal Infirmary, UK
[5] Cardiology Department, Papworth Hospital NHS Foundation Trust, Cambridge, UK
[6] Department of Epidemiology and Public Health, Imperial College, London, UK
[7] Public Health Sciences and Medical Statistics, Southampton General Hospital, UK
[8] MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK

* Corresponding author

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The research reported in this monograph was commissioned by the HTA Programme as project number 99/23/04. The contractual start date was in July 2001. The draft report began editorial review in May 2004 and was accepted for publication in January 2006. 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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Abstract

A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context

M Buxton,[1] N Caine,[2] D Chase,[3] D Connelly,[4] A Grace,[5] C Jackson,[6] J Parkes[7] and L Sharples[8*]

[1] Health Economics Research Group (HERG), Brunel University, Uxbridge, UK
[2] Department of Health, London, UK
[3] National Coordinating Centre for Health Technology Assessment, Wessex Institute for Health Research and Development, University of Southampton, UK
[4] Department of Medical Cardiology, Glasgow Royal Infirmary, UK
[5] Cardiology Department, Papworth Hospital NHS Foundation Trust, Cambridge, UK
[6] Department of Epidemiology and Public Health, Imperial College, London, UK
[7] Public Health Sciences and Medical Statistics, Southampton General Hospital, UK
[8] MRC Biostatistics Unit, Institute of Public Health, Cambridge, UK
* Corresponding author

Objectives: To update the systematic review evidence on the effectiveness, health-related quality of life (HRQoL) and cost-effectiveness of implantable cardioverter defibrillators (ICDs); compilation of new data on the service provision in the UK; and on the clinical characteristics, survival, quality of life and costs of ICD patients in the UK, and a new cost-effectiveness model using both international RCT and UK-specific data.

Data sources: Electronic databases searched from November 1999 to March 2003, this was supplemented by a systematic review of research published during 2003–5. Survey data.

Review methods: Studies were selected and assessed. A survey of ICD centres was carried out. Basic data were obtained from two major implanting centres including 535 patients (approximately 10% of overall UK activity) implanted between 1991 and 2002, and retrieval of fuller data, on patient characteristics, management and resource use, from patient notes for a sample of 426 patients was attempted. A cross-sectional survey collected HRQoL data (using the Nottingham Health Profile, Short Form 36, Hospital Anxiety and Depression questionnaire, EuroQoL 5 Dimensions and disease-specific questions) on a sample of 229 patients. A Markov model combined UK patient data with data from published randomised controlled trials (RCTs) to estimate incremental costs per life-year or quality-adjusted life-year (QALY) gained.

Results: None of the economic analyses in the studies found could be directly applied to the UK. The multiple sources of routine data available (including the national ICD database) provide an imperfect picture of the need for and use of ICDs. Implantation rates have been rising to a rate of around 20 per million population. Mean age is increasing and most ICDs are implanted into men aged 45–74 years. There is significant geographical variation. A survey of 41 UK centres provided additional evidence, particularly of variation in level of activity and resourcing. Most detailed data were obtained for 380 patients (89%). The postal survey produced a 73% response rate. Demographic characteristics of these patients were similar to ICD recipients in the UK as a whole and patients included in secondary prevention RCTs. Mean actuarial survival at 1, 3 and 5 years was 92%, 86% and 71%, respectively. Patient age at implantation and functional status significantly affected survival. Levels of most of the HRQoL measures were lower than for a UK general population There was no evidence of a change with time from implantation. Patients who had suffered ICD shocks had significantly poorer HRQoL. Most patients

nevertheless expressed a high level of satisfaction with ICD therapy. Mean initial costs of implantation showed little variation between centres (£23,300 versus £22,100) or between earlier and more recent implants. There appeared to be greater variation between patients presenting along different pathways. Postdischarge costs (tests, medications and follow-up consultations) and costs of additional hospitalisations were also calculated. Using the Markov model it was found that over a 20-year horizon, mean discounted incremental costs were £70,900 (£35,000–142,400). Mean discounted gain was 1.24 years (0.29–2.32) or 0.93 QALYs. Cost-effectiveness was most favourable for men aged over 70 years with a left ventricular ejection fraction (LVEF) below 35%. If the treatment effect were to continue, then the cost per life-year over a lifetime might fall to around £32,000. Five RCTs of ICDs, a meta-analysis and, a cost-effectiveness analysis of ICDs used in primary prevention, and a meta-analysis of ICDs in patients with non-ischaemic cardiomyopathy have been published recently. These trials provide confirmation of survival benefit of ICDs used in primary prevention in both ischaemic and non-ischaemic cardiomyopathy patients. Costs per QALY ranged from US$34,000 in older trials to controls being both less expensive and more effective (CABG Patch, DINAMIT). More recent trials estimated cost per QALY between $50,300 and $70,200. The inconsistency in evidence for a HRQoL benefit has not been resolved and further work on risk stratification is necessary.

Conclusions: The evidence of short- to medium-term patient benefit from ICDs is strong but cost-effectiveness modelling indicates that the extent of that benefit is probably not sufficient to make the technology cost-effective as used currently in the UK. One reason is the high rates of postimplantation hospitalisation. Better patient targeting and efforts to reduce the need for such hospitalisation may improve cost-effectiveness. Further cost-effectiveness modelling, underpinned by an improved ICD database with reliable long-term follow-up, is required. The absence of a robust measure of the incidence of sudden cardiac death is noted and this may be an area where further organisational changes with improved data collection would help.

Contents

List of abbreviations

AAD	antiarrhythmic drug
ACE	angiotensin-converting enzyme
AMI	acute myocardial infarction
AMIOVIRT	Amiodarone versus Implantable Cardioverter-Defibrillator Trial
ARR	absolute risk reduction
ARVD	arrhythmogenic right ventricular dysplasia
ATP	antitachycardia pacing
AVID	Antiarrhythmic Versus Implantable Defibrillator
BNF	British National Formulary
BPEG	British Pacing and Electrophysiology Group
CABG	coronary artery bypass graft
CASH	Cardiac Arrest Study Hamburg
CAT	Cardiomyopathy Trial
CEAC	cost-effectiveness acceptability curve
CHD	coronary heart disease
CI	confidence interval
CIDS	Canadian Implantable Defibrillator Study
COMPANION	Comparison of Medical Therapy Pacing and Defibrillation Trial
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effectiveness
DEFINITE	Defibrillator in Non-Ischaemic Dilated Cardiomyopathy Treatment Evaluation
DGH	district general hospital
DHA	district health authority
DINAMIT	ICD in Acute Myocardial Infarction Trial
EP	electrophysiological testing
EQ-5D	EuroQoL 5 Dimension
ETT	exercise tolerance test
FDA	Food and Drug Administration
HAD	Hospital Anxiety and Depression (scale)
HR	hazard ratio
HRQoL	health-related quality of life
ICD	implantable cardioverter defibrillator
ICD-10	International Classification of Diseases 10
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IHD	ischaemic heart disease
ITU	intensive therapy unit
LOS	length of stay
LVEF	left ventricular ejection fraction
LYG	life-year gained
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MCS	mental component score
MHI	Mental Health Inventory
MI	myocardial infarction
MM	medical management
MRI	magnetic resonance imaging
MUSTT	Multicenter Unsustained Tachycardia Trial
NA	not applicable

continued

List of abbreviations *continued*

NHP	Nottingham Health Profile
NHS EED	NHS Economic Evaluations Database
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
NYHA	New York Heart Association
OHE HEED	Office of Health Economics Health Economic Evaluations Database
ONS	Office for National Statistics
PCC	Patient Concerns Checklist
PCS	physical component score
PSSRU HCHS	Personal Social Services Research Unit Hospital and Community Health Services
QALY	quality-adjusted life-year
R&D	research and development
RCT	randomised controlled trial
RHA	regional health authority
RR	relative risk
RRR	relative risk reduction
SCD	sudden cardiac death
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
SD	standard deviation
SE	standard error
SF-36	Short Form 36
SHA	strategic health authority
SMR	standardised mortality ratio
SPR	specialist registrar
VF	ventricular fibrillation
VT	ventricular tachycardia
WTE	whole-time equivalent

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

In September 2000, the National Institute for Health and Clinical Excellence (NICE) published guidance on the use of implantable cardioverter defibrillators (ICDs) for arrhythmias. That guidance relied heavily on a small number of relatively large-scale randomised controlled trials (RCTs) of ICDs compared with conventional management conducted principally in North America. Questions remain about the generalisability of their results to the UK, particularly the associated analyses of cost-effectiveness. This study was designed not simply to update the existing systematic review of published literature, but also to collect original data relating to the UK to use with international trial data to model the cost-effectiveness of ICDs in a UK context. Thus, this report contains a combination of an updating of the systematic review evidence on the effectiveness, health-related quality of life (HRQoL) and cost-effectiveness of ICDs; compilation of new data on the service provision in the UK; and on the clinical characteristics, survival, quality of life and costs of ICD patients in the UK, and a new cost-effectiveness model using both international RCT and UK-specific data.

Updated systematic reviews of studies of effectiveness, quality of life and cost-effectiveness

Objectives

To update the earlier review on clinical effectiveness and cost-effectiveness of ICDs compared with conventional therapy of patients at risk of sudden cardiac death (SCD) due to arrhythmias.

Methods

Electronic databases and reference lists were searched from November 1999 to March 2003 for RCTs, systematic reviews and meta-analyses following recognised principles. Cost-effectiveness studies pre-dating the availability of RCT data were excluded.

Results

Five original clinical studies meeting these criteria were identified that had been published since the previous review: three RCTs of effectiveness (CASH, MADIT II and CAT) and two RCT-based studies of HRQoL (based on the AVID and CIDS trials). In addition, there was one systematic review and one meta-analysis of secondary prevention trials. Eight economic studies were appraised, of which four were directly based on an RCT, two on specific registries/databases and two models used multiple sources. None of the economic analyses could be directly applied to the UK.

Conclusions

There is increasingly strong RCT evidence for the survival benefits of ICDs compared with medical management of ventricular arrhythmias following survival of cardiac arrest and in preventing SCD in those at high risk. The evidence on impact on HRQoL is conflicting and relatively weak. The estimates of cost-effectiveness vary considerably, not least because of the different time-horizons considered and the need to make assumptions on long-term relative effectiveness.

Data on service provision in the UK

Objectives

To review the current use of, and service provision for, ICDs in the UK.

Methods

Multiple published data sources were used and a survey of ICD centres was conducted.

Results

The multiple sources of routine data available (including the national ICD database) provide an imperfect picture of the need for and use of ICDs. Implantation rates have been rising to a rate of around 20 per million population. Mean age is increasing and most ICDs are implanted into men aged 45–74 years. There is significant geographical variation. A survey of 41 UK centres provided additional evidence, particularly of variation in level of activity and resourcing.

Conclusions
Rates of implantation of ICDs in 2000 were less than half of the target suggested by the NICE guidelines, and capacity to increase these rates is constrained by a variety of factors.

Data on clinical characteristics, survival, quality of life and costs of ICD patients in the UK

Objective
To describe the clinical characteristics, survival, quality of life and resource use/costs in a sample of UK patients.

Methods
Basic data were obtained from two major implanting centres including 535 patients (about 10% of overall UK activity) implanted between 1991 and 2002, and retrieval of fuller data, on patient characteristics, management and resource use, from patient notes for a sample of 426 patients was attempted. A cross-sectional survey collected HRQoL data (using the Nottingham Health Profile, Short Form 36, Hospital Anxiety and Depression questionnaire, EuroQoL 5 Dimensions and disease-specific questions) on a sample of 229 patients.

Results
Most detailed data were obtained for 380 patients (89%). The postal survey produced a 73% response rate. Demographic characteristics of these patients were similar to ICD recipients in the UK as a whole and patients included in secondary prevention RCTs. Mean actuarial survival at 1, 3 and 5 years was 92%, 86% and 71%, respectively. Patient age at implantation and functional status significantly affected survival.

Levels of most of the HRQoL measures were lower than for a UK general population There was no evidence of a change with time from implantation. Patients who had suffered ICD shocks had significantly poorer HRQoL. Most patients nevertheless expressed a high level of satisfaction with ICD therapy.

Mean initial costs of implantation showed little variation between centres (£23,300 versus £22,100) or between earlier and more recent implants. There appeared to be greater variation between patients presenting along different pathways. Postdischarge costs (tests, medications and follow-up consultations) and costs of additional hospitalisations were also calculated.

Conclusions
These data showed the degree of similarity of the UK ICD recipients to those in the secondary prevention trials, and identified the main characteristics that appear to be systematically related to survival [age at implant and left ventricular ejection fraction (LVEF)], to HRQoL (number of shocks) and to costs of implantation (patient pathways). These data provide key parameter values for the UK relevant model of cost-effectiveness.

Cost-effectiveness model for the UK

Objective
To estimate the cost-effectiveness of ICDs compared with antiarrhythmic drug treatment in the UK, in secondary prevention patients at risk of SCD.

Methods
A Markov model combined UK patient data with data from published RCTs to estimate incremental costs per life-year or quality-adjusted life-year (QALY) gained.

Results
Over a 20-year horizon, mean discounted incremental costs were £70,900 (£35,000–142,400). Mean discounted gain was 1.24 years (0.29–2.32) or 0.93 QALYs. Cost-effectiveness was most favourable for men aged over 70 years with an LVEF below 35%. If the treatment effect were to continue, then the cost per life-year over a lifetime might fall to around £32,000.

Conclusions
Although there is considerable uncertainty involved in modelling beyond the experience of the trials, the results suggest that ICDs, as currently applied in the UK, are not cost-effective by conventional standards.

Addendum

Objective
To summarise and discuss new primary and secondary research published while the main study was under review.

Methods
A systematic review of published work during 2003–2005 was undertaken.

Results

Five RCTs of ICDs, a meta-analysis and, a cost-effectiveness analysis of ICDs used in primary prevention, and a meta-analysis of ICDs in patients with non-ischaemic cardiomyopathy have been published recently. These trials provide confirmation of survival benefit of ICDs used in primary prevention in both ischaemic and non-ischaemic cardiomyopathy patients. Costs per QALY ranged from US$34,000 in older trials (MADIT, MUSTT) to controls being both less expensive and more effective (CABG Patch, DINAMIT). More recent trials estimated cost per QALY between $50,300 and $70,200. The inconsistency in evidence for a HRQoL benefit has not been resolved and further work on risk stratification is necessary.

Conclusions

Overall, the survival benefit and cost-effectiveness estimates for primary prevention patients are similar to those for secondary prevention patients in the UK.

Overall conclusions

The evidence of short- to medium-term patient benefit from ICDs is strong but cost-effectiveness modelling indicates that the extent of that benefit is probably not sufficient to make the technology cost-effective as used currently in the UK. One reason is the high rates of postimplantation hospitalisation. Better patient targeting and efforts to reduce the need for such hospitalisation may improve cost-effectiveness.

Recommendations for further research

Further cost-effectiveness modelling, underpinned by an improved ICD database with reliable long-term follow-up, is required. This can now begin fully to address the cost-effectiveness of primary prevention, particularly as the results from other primary prevention trials are added to those from MADIT II.

The absence of a robust measure of the incidence of SCDs is noted. This may be an area where further organisational changes with improved data collection would help. However, to be effective this will require the co-ordination of information from a wide range of sources, including the records of pathology services and coroners' offices.

Chapter 1

Sudden cardiac death

Introduction

In September 2000, the National Institute for Health and Clinical Excellence (NICE) published guidance on the use of implantable cardioverter defibrillators (ICDs) for arrhythmias,[1] and in November 2000 the rapid review, produced to inform that process, was published by the NHS HTA Programme.[2] That review emphasised the importance of a small number of relatively large-scale trials conducted principally in North America. Although these potentially provide a relatively strong evidence base, there are inevitably questions about the generalisability of their results to the UK, particularly the generalisability of the cost-effectiveness analyses. Nevertheless, it is unlikely that large-scale trials will be undertaken in the UK to provide UK-specific trial evidence. This study was designed not simply to update the systematic review of published literature but also, perhaps more importantly, to collect original data relating to the UK to use with international trial data to model cost-effectiveness of ICDs in the UK context. Thus, this report contains a combination of systematic review evidence (Chapters 2 and 3), new descriptive data relating to the UK (Chapters 4–7) and new cost-effectiveness modelling (Chapter 8). The final part of the report (Chapter 9) summarises the conclusions from, and considers the implications of, the new evidence. The information provided in this report was accurate at the time of the study. As might be expected in this rapidly changing field, a number of new trials and cost-effectiveness studies appeared while this manuscript was under review. A summary of these studies and their implications for further research has been provided as an addendum.

Causes of sudden cardiac death

Sudden cardiac death (SCD) is defined as an abrupt loss of consciousness and unexpected death due to cardiac causes, which occurs within 1 hour of onset of symptoms. About 80% of SCD events are caused by ventricular tachyarrhythmias, that is, ventricular tachycardia (VT) and ventricular fibrillation (VF). The remaining 20% consists of a number of conditions, including bradycardia (slow heartbeats).

As part of the background to this study the authors sought to obtain estimates of the incidence and prognosis of life-threatening ventricular arrhythmias. More specifically, they sought to estimate numbers relevant to the groups of patients on which this focuses, that is, patients who suffer:

- sudden cardiac death
- out-of-hospital cardiac arrest
- symptomatic sustained VT
- inducible VT on electrophysiological testing (EP) after acute myocardial infarction (AMI).

The relationship between these groups, and pathways through which these patients become known to the health service, is shown in *Figure 1*.

This review does not include studies specifically assessing incidence and prognosis for patients with familial conditions with a high risk of SCD, studies of patients with non-life-threatening ventricular arrhythmias (i.e. non-sustained VT), and studies including patients experiencing ventricular arrhythmias during or shortly after acute ischaemia (i.e. with potentially transient and reversible arrhythmias).

A search of the electronic databases MEDLINE and EMBASE was undertaken. Studies published between January 1989 and January 2003 were considered for inclusion. The search strategies used are shown in Appendix 1. Reference lists of recent reviews and included studies were also checked. Two reviewers independently assessed the eligibility of each paper and the quality and content of included studies.

Only systematic reviews, the largest international or UK studies for each presenting indication were considered for eligibility in this review. Types of studies were prospective and retrospective population-based observational studies of the incidence and/or prognosis of ventricular arrhythmia and prospective and retrospective prognostic studies with a representative, well-defined sample of patients with newly diagnosed ventricular arrhythmias. The review only included incidence studies that had results (or at least allowed calculation) of the incidence rate (and

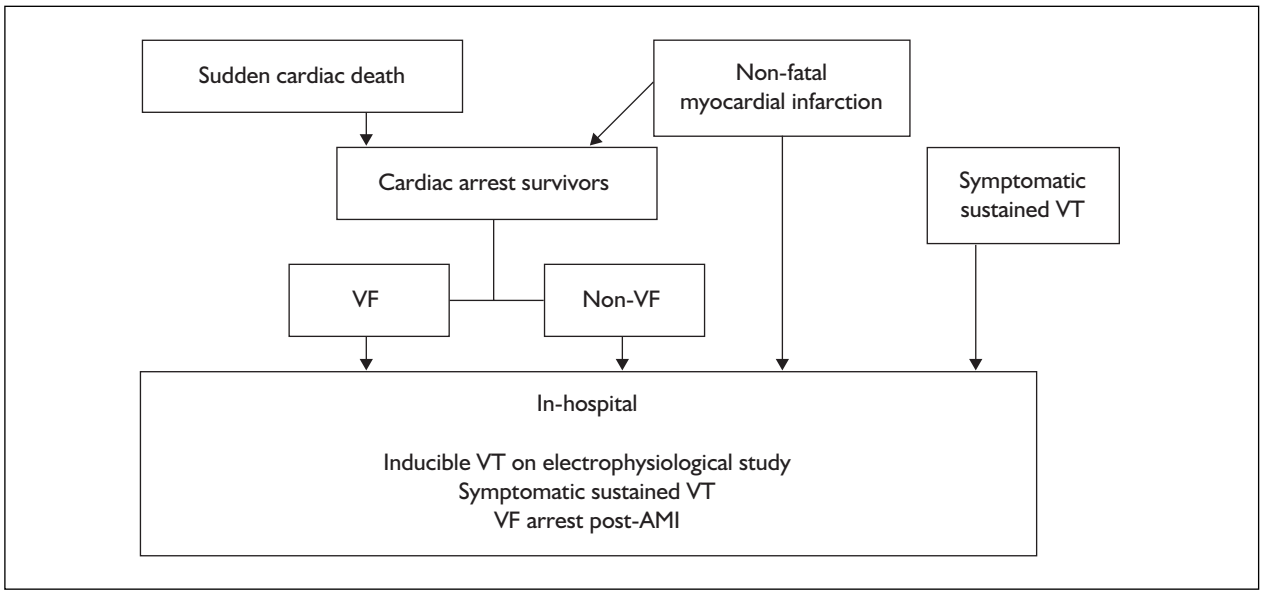

FIGURE 1 *How patients with life-threatening arrhythmias could enter the health service*

95% confidence intervals). As these studies were all published between 1989 and 2003, the prognostic studies do not provide the natural history of ventricular arrhythmias, but estimate prognosis using management strategies used in the 1990s.

The MEDLINE search generated 3426 hits, of which 63 papers were considered for possible inclusion in this review. The EMBASE search generated 5071 hits (about 3300 of these had already been identified in MEDLINE), of which 57 extra papers were considered for possible inclusion. Data from these 120 papers identified are currently being extracted for a PhD thesis and will be published subsequently. This contextual study uses data only from the largest international study, the largest UK study (if a UK study has been undertaken) and any systematic reviews for each presenting symptom or presenting known aetiology; that is, the six most relevant of these 120 studies identified.

Ventricular arrhythmias

Studies of life-threatening ventricular arrhythmias can include patients who have suffered a cardiac arrest, where the presenting rhythm is VF. Therefore, there is an overlap with cardiac arrest studies. However, studies on ventricular arrhythmias may also include patients who have suffered sustained VT, had inducible VT or may have suffered a ventricular arrhythmia post-myocardial infarction (MI).

There are no published UK-based incidence and prognostic studies of life-threatening ventricular arrhythmias. The largest international study of life-threatening ventricular arrhythmias was a US retrospective cohort study of patients with primary diagnoses of VT or VF using routine data.[3] This study used data files of the California Office of Statewide Planning and Development to identify all patients discharged from all Californian hospitals. Patients with a prior admission of VT or VF in 1991 were excluded in an attempt to create a cohort of patients with new-onset ventricular arrhythmias. In total, 5798 males and 2915 females with ventricular arrhythmias were identified during the study period. Of these patients, 82% were white, 7% black, 7% Latino and 4% Asian; 18% were aged less than 55 years, 18% aged 55–64 years, 33% aged 65–74 years and 31% aged 75 years or more. Age-adjusted hospitalisation rates were broken down by ethnicity and no overall rate was presented. For men, whites had a rate of 24.5 per 100,000, blacks 14.2 per 100,000, Asians 7.4 per 100,000 and Latinos 4.3 per 100,000. For women, rates per 100,000 were 11 for blacks and whites, 3.8 for Asians and 3.1 for Latinos. For patients who survived the index admission, ICDs were implanted for 10% of black patients, 15% of Latinos, 16% of Asians and 22% of white patients. During the initial hospital admission, the mortality rate for black patients was 13%, Latinos 11%, Asians 11% and white patients 10%. Among patients discharged alive from initial hospitalisation, 1-year mortality rates were 20% for blacks, 15% for Latinos, 13% for Asians and 15% for white patients.

TABLE 1 *Largest international and largest national study of the incidence and prognosis of cardiac arrests where resuscitation was attempted*

Study	Geographical location and population	Date and study duration	Case definition	Case finding methods	Number of cases and baseline characteristics
Cobb *et al.*, 2002[5]	Seattle, USA About 560,000 people	1980–2000	Consecutive patients suffering a cardiac arrest who received advanced life support by paramedics. Patients whose arrest was not due to cardiac causes were excluded	Cases were primarily identified via the medical incident report submitted by paramedics for all patients attended. Any missing data were obtained from death certificates or hospital admission forms	There were 1072 treated cardiac arrests in 1979–1980. In 1989–1990 there were 870 and in 1999–2000 there were 744 cardiac arrests. The total number of cardiac arrest cases per year decreased by 31% over the decade
Sedgwick *et al.*, 2000[6]	Scotland, UK 5.1 million people	May 1990 to April 1991	Presumed cardiac arrests. Data on the cause of the arrest were not collected. However, discharge summaries of survivors suggested a cardiac cause for 92% of cases	Cases reported by the ambulance service. Patients felt unsuitable for resuscitation by the ambulance crew were not reported	1700 cardiac arrests

Cardiac arrests

There is a wealth of literature on the incidence and prognosis of out-of-hospital cardiac arrests from communities worldwide. This literature distinguished itself from literature on SCD because it focuses on cases where advanced life support was attempted, usually by paramedics. As with SCD, incidence and prognosis vary widely. Comparison of rates between studies is difficult. It is highly plausible that great variation exists both within and between services on who received advanced life support.

A systematic review of the incidence of cardiac arrest was published in 1993.[4] Studies reporting incidence and survival rates from peer-reviewed journals identified through automated searching (methods not reported) from 1970 to 1989 were considered. Studies including cardiac arrests due to non-cardiac causes were excluded. If more than one study for a given community fulfilled the criteria, Becker and colleagues used the one conducted for the longest duration and/or largest population. Studies of 20 communities met the inclusion criteria. Incidence rates varied from 35.7 to 128.3 per 100,000. Survival rates ranged from 1.6 to 20.7 per 100 cases. The authors found that incidence rates in the communities were related negatively to survival rates; as the incidence rate increased, the survival rate to discharge decreased. Unfortunately, this review[4] provided no information on the case definitions, case identification methods or calculation of survival for each of the individual studies. It is unclear whether these studies are comparable enough in their methods to examine this relationship. The authors comment that inconsistencies existed and could have resulted in the under- and over-reporting of cases, with the effect of reducing or increasing the survival rate.

Uniform reporting of cardiac arrest studies, using a standardised format known as the Utstein template, was initiated in the early 1990s. Later studies should therefore be more comparable.

More recent studies have provided data on the first rhythm recorded by emergency personnel (i.e. VF, asystole and pulseless electrical activity), and presented prognostic data by this important predictor of survival. Cardiac arrest survivors identified as experiencing VF are candidates for ICDs. The largest international study (from the USA)[5] and the largest UK study[6] are described in *Table 1*.

Age-adjusted incidence rates per 1000 for those aged 20 years and over, from Cobb and colleagues,[5] are shown in *Table 2*. The prognosis of

TABLE 2 *Age-adjusted incidence rates per 1000 treated cardiac arrest patients with presumed cardiac aetiology during three periods*

	1979–1980	1989–1990	1999–2000
All treated cardiac arrests	1072	870	744
Adjusted incidence rate (95% CI)	1.39 (1.28 to 1.51)	1.10 (1.01 to 1.21)	0.91 (0.83 to 1.01)
Adjusted incidence rate for men (95% CI)	2.15 (1.95 to 2.37)	1.59 (1.42 to 1.77)	1.24 (1.10 to 1.39)
Adjusted incidence rate for women (95% CI)	0.68 (0.58 to 0.81)	0.65 (0.55 to 0.77)	0.61 (0.52 to 0.72)
VF first recorded rhythm	652	410	303
Adjusted incidence rate (95% CI)	0.85 (0.77 to 0.95)	0.54 (0.47 to 0.61)	0.38 (0.32 to 0.44)
Adjusted incidence rate for men (95% CI)	1.39 (1.23 to 1.57)	0.85 (0.73 to 0.98)	0.60 (0.51 to 0.71)
Adjusted incidence rate for women (95% CI)	0.35 (0.28 to 0.44)	0.25 (0.20 to 0.33)	0.17 (0.13 to 0.24)

CI, confidence interval.

cardiac arrest was reported by first recorded rhythm. In 1979–1980, 33% (217) of people identified as suffering a cardiac arrest with VF as first recorded rhythm were discharged alive. The proportion of patients discharged alive did not change significantly through the periods. These data provide optimistic survival estimates. Seattle is widely recognised as providing a gold standard on paramedic response times and cardiac arrest survival.

The Heartstart Scotland project has published results using this template. Study methods are shown in *Table 1*.[6] The population-based rate was 33 patients suffering cardiac arrest per 100,000 per year. The authors noted that this figure is likely to be an underestimate, probably due to under-reporting. Of 1676 cases for which medical records could be identified, 1383 (83%) were declared dead on arrival at hospital or in the emergency department, 119 (7%) died in a hospital ward, 174 (10%) were discharged alive and 148 (9%) were alive at 1 year. For 1197 cases (71%), VF was the recorded rhythm. The survival rate was 11% (136 of 1197) at 1 year for these patients, as opposed to 3% for patients in asystole or pulseless rhythm (12 of 479 patients).

Incidence of sudden cardiac death

The Task Force on Sudden Cardiac Death of the European Society of Cardiology define SCD as "natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms; pre-existing heart disease may have been known to be present, but the time and mode of death are unexpected".[7] (European Society of Cardiology Guidelines on Sudden Cardiac Death have recently been updated.[8]) However, the definition can include an element of time and estimates may or may not include unwitnessed deaths. Rates vary considerably within the literature, probably owing to both differences in case definitions and true variations between populations and time.

The largest international study on SCD and the largest national study identified through searching are described in *Table 3*. The international study was a retrospective national surveillance study of SCDs in all people in the USA.[9] The age-adjusted SCD rate was 206.5 per 100,000 in men and 140.7 per 100,000 in women. Rates varied by ethnic origin: the rate was 253.6 for black men per 100,000 and 204.5 per 100,000 for white men. However, the rates were similar when comparing black and white women. SCD rates varied by state, ranging from 114.2 per 100,000 in Hawaii to 212.2 per 100,000 in Mississippi. Rates for the years 1989 to 1998 are published by Zheng and colleagues.[9]

Several UK studies have assessed out-of-hospital case fatality from acute coronary events. The largest of these studies was undertaken in Scotland. Study methods are shown in *Table 3*. All out-of-hospital deaths from first MI were identified from 1986 to 1995 using the Scottish record linked database.[10] Population-based rates of out-of-hospital cardiac deaths were presented graphically by gender and age group for the years 1986 and 1995. Rates increased with age: in 1986, the mortality rate for men aged 55–64 years was 420 per 100,000, compared with 2753 per 100,000 in men older than 85 years (142 versus 2064, respectively, in women). Between 1986 and 1995, mortality rates fell by one-quarter in women and by more than one-third in men. Mortality rate falls were much larger in younger age groups. There were also greater reductions in mortality rate in deprived socio-economic groups than in affluent groups.

TABLE 3 *Largest international and national study on SCD incidence rates*

Study	Type of study	Geographical location and population	Date and study duration	Case definition	Case finding methods	Number of cases and baseline characteristics
Centers for Disease Control and Prevention, 2001[9]	Retrospective national surveillance study	USA US Bureau of Census Data was used to estimate resident populations	1999	Sudden cardiac deaths were defined as a death occurring outside hospital or in the emergency room or as 'dead on arrival' with an underlying cause of death reported as cardiac disease	Cardiac deaths were identified using ICD-10 disease codes derived from death certificate data	462,340 SCDs of 728,743 cardiac deaths
Capewell *et al.*, 2001[10]	Retrospective cohort study	Scotland, UK population of 5.1 million	1986–95	Out-of-hospital cardiac deaths were defined as deaths from a first MI outside hospital (did not survive to reach hospital)	Scottish record linked database of NHS hospital admissions and deaths recorded by the General Register Office for Scotland	83,365 deaths. Number of deaths fell from 9484 in 1986 to 6712 in 1995. Mean age at death increased from 73 to 75.3 years. Proportion of persons older than 75 years increased from 35.8% to 42.8% of men and from 60.3% to 66.7% of women

ICD-10, International Classification of Diseases-10.

TABLE 4 *Summary of rates relating to SCD*

Presenting symptom/aetiology	Study	Population-based rate in men	Population-based rate in women
Sudden cardiac death incidence	US national surveillance study 1999 data	206.5 per 100,000	140.7 per 100,000
	Scottish record linkage study, 1995 data	Age 55–64 years: 210 per 100,000 Age 65–74 years: 620 per 100,000 Age ≥ 85 years: 2147 per 100,000	Age 55–64 years: 68 per 100,000 Age 65–74 years: 322 per 100,000 Age ≥ 85 years: 1609 per 100,000
Cardiac arrests with VF as first recorded rhythm incidence	Seattle study, 1999–2000 data	60 per 100,000	17 per 100,000
	Heartstart Scotland 1990–1991	Calculated as 24 per 100,000 (given that 71% had VF as first recorded rhythm)	
Cardiac arrest prognosis	Seattle study, 1999–2000 data	32% of patients included in this study were discharged alive (approximate rate of 12 per 100,000)	
	Heartstart Scotland, 1990–1991	10% of patients included in this study were discharged alive (approximate rate of 2.4 per 100,000)	
Life-threatening ventricular arrhythmias incidence	Californian study, 1991	White people: 24.5 per 100,000	White people: 11 per 100,000
Life-threatening ventricular arrhythmias prognosis	Californian study, 1991	White people: 10% to hospital discharge (approximate rate of 1.8 per 100,000)	

The case definitions in the two previously described studies are different. The Scottish study of out-of-hospital cardiac deaths only included deaths from first MI. Studies on cardiac arrest survivors suggest that these deaths may represent only about one-fifth of SCDs.[11] The US data better reflect the SCD rate. From these studies, it is possible to begin to estimate population-based rates of SCD and life-threatening ventricular arrhythmias. *Table 4* summarises the rates estimated in these studies. It is important to acknowledge that rates vary between studies owing to differences in case definitions, speed of emergency service, underlying risk, time and place.

Trends in these studies show that the incidence of SCD is declining, especially for men. (A recent report on SCD temporal trends from the Framingham Heart Study also identified a decline in SCD risk. This trend was evident for people with and without heart disease.[12]) Older people are at much higher risk of SCD than younger people, but the decline in incidence rate with time is much greater for younger than for older people. As would be expected, age-adjusted incidence rates in cardiac arrest (with VF as the first recorded rhythm) are also declining. However, prognosis to hospital discharge has not changed.

The incidence rate for life-threatening ventricular arrhythmias appears to be low, given the incidence and prognostic estimate for cardiac arrest. However, the cardiac arrest data include patients who died while in the care of the emergency services, whereas the incidence data for ventricular arrhythmias are for all patients admitted.

Sudden cardiac death: survival

The survival rates for SCD are less than 5% in most industrialised countries. Survival rates for out-of-hospital sudden cardiac episodes in the UK are about 2%. SCD accounts for some 25–30% of all cardiovascular deaths, claiming an estimated 70,000–90,000 lives each year in the UK.

About 15% of sudden cardiac episode survivors will experience another SCD event within 1 year. Untreated, the recurrence is usually fatal. However, some survivors live for many years without treatment.

Risk factors for SCD include:

- a previous SCD episode
- previous VT

- a prior MI
- coronary artery disease
- family history of SCD and familial cardiac conditions, e.g. long QT syndrome
- poor cardiac function, quantified as low left ventricular ejection fraction (LVEF)
- heart failure.

Treatments

Treatments are aimed at either suppressing or terminating the arrhythmia. The main treatments are:

- antiarrhythmic drug (AAD) therapy, which may be guided by Holter monitoring (ambulatory 24-hour ECG tape-recording) or EP. AADs are divided into classes I–IV. Class III drugs, which include amiodarone, are the most commonly used for long-term management of ventricular arrhythmias. Chronic prophylactic AAD therapy is aimed at suppressing the development of arrhythmias, and not at terminating an arrhythmia once it is initiated.
- ICDs, which actively sense and can terminate life-threatening ventricular tachyarrhythmias.

The use of ICDs in patients who have had a previous SCD episode or previous VT is referred to as secondary prevention. In cases with perceived high risk but who have not suffered a previous SCD event or ventricular arrhythmia, the use is referred to as primary prevention.

The technology

An ICD is a battery-powered, fully implantable device that monitors heart rhythm and has the capacity to deliver an electrical shock to restore normal sinus rhythm when potentially life-threatening ventricular arrhythmias are detected. An ICD system consists of the device and one or more leads which are implanted into the patient's body. The original devices simply offered defibrillation shocks. With improvements in sensing, the latest devices offer graded therapeutic responses to a sensed ventricular arrhythmia. Antitachycardia pacing (ATP), low-energy synchronised cardioversion and high-energy defibrillation shocks can be given via a single transvenous lead. Such devices can be programmed to detect and treat episodes of VT and VF, the precise programmed values being governed by the patient's clinical history, maximum sinus rate, and rates of any documented ventricular (and supraventricular) arrhythmias. Separate 'zones' can be programmed for detection of VF (e.g. rate > 200–220 per minute) and VT, and some devices allow for two separate VT detection zones. Additional discriminatory features, such as sudden onset, beat-to-beat variability, QRS width and/or morphology, and (if available) atrial rate can also be programmed to help to discriminate between atrial and ventricular arrhythmias. Even if the patient has a history of only VF, it is customary to programme the device for detection and treatment of VT, as many patients will present with new-onset VT after the implant. VF is usually treated with shocks at the maximum energy of the device, but the ICD can be programmed to treat ventricular tachycardia by a variety of modalities of antitachycardia pacing, or if necessary by low-energy cardioversion shocks.

When first introduced in the early 1980s, transthoracic procedures were involved: the generator was normally implanted beneath the skin of the abdomen (under the rectus abdominis muscle) and thoracotomy under general anaesthetic was required to attach three or four electrode patches to the epicardial surface of the heart. Newer models are much smaller, similar in size to older modes of pacemaker (30–40 cm^3), can be placed beneath the skin and tissues of the chest, and usually require one or two leads which can be inserted via a vein (transvenous) under local anaesthesia and sedation.

Current guidance

In September 2000, NICE completed an appraisal[1] that recommended that the use of ICDs should be routinely considered for the following circumstances:

- As 'secondary prevention' for patients who present with:
  - cardiac arrest due to either VT or VF
  - spontaneous sustained VT causing syncope or significant haemodynamic compromise
  - sustained VT without syncope/cardiac arrest, and who have an associated reduction in LVEF (less than 35%) but are no worse than class III of the New York Heart Association (NYHA) functional classification of heart failure.
- As 'primary prevention' for patients with:
  - a history of previous MI and all of the following:
    - non-sustained VT on Holter monitoring
    - inducible VT on EP
    - left ventricular dysfunction with LVEF less than 35% and no worse than class III NYHA

– a familial cardiac condition with a high risk of SCD, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular dysplasia (ARVD) and following repair of tetralogy of Fallot.

They also recommended that ICDs should not be used routinely for the following patients:

- those with spontaneous sustained VT associated with minimal symptoms and good cardiac function (LVEF > 35%).
- those who present with syncope of unknown cause (with no previous history of MI) and who have inducible VT on EP in the presence of normal cardiac function (LVEF >35%).

NICE considered that the evidence for patients with syncope of unknown origin, with haemodynamically significant sustained VT or VF induced at EP and in the presence of impaired cardiac function [i.e. ejection fraction (LVEF) <35%] was insufficient to recommend the use of ICDs. They did, however, recommend that a detailed cost-effectiveness study should be undertaken in at least two of the larger implantation centres, building on data from the National Pacemaker Database Registry of ICDs. This recommendation provided the starting point for the current report.

Summary

SCD is primarily caused by ventricular tachyarrhythmia or ventricular fibrillation. Annual SCD incidence rates in 1999 were 206.5 per 100,000 in men and 140.7 per 100,000 in women in a large US study. The largest UK study identified showed that SCD incidence increases markedly with age, from 210 per 100,000 in men aged 55–64 to 214.7 per 100,000 in men aged 85 and over. However, incidence of SCD is declining over time. The prognosis following cardiac arrest is poor, with survival after SCD less than 5% in most industrialised countries. About 15% of SCD survivors experience a second SCD event within 1 year. Treatment is either AADs, which suppress developments of events, or ICDs, which can stop life-threatening ventricular tachyarrhythmias. There is little UK-based evidence regarding the effectiveness or cost-effectiveness of ICDs.

Chapter 2

Systematic review of the effectiveness of implantable cardioverter defibrillators in management of arrhythmias

Background

A systematic review on the effectiveness of ICD therapy in the management of ventricular arrhythmias was published by the NHS HTA Programme in November 2000.[2] Seven randomised controlled trials (RCTs) were identified,[13–20] the majority of which were of good quality. The main results from that review of these studies are summarised in *Tables 5–7*, and these form the context of this updated review.

The key findings from the 2000 review are summarised below.

Six trials found a survival advantage for patients treated with ICD: two out of three primary prevention studies and all of the secondary prevention studies. The size of the effect in the secondary prevention trials ranged from an absolute risk reduction (ARR) for ICD therapy of 3.7 to 21% and relative risk reduction (RRR) of 19.7 to 37%. In two of the primary prevention trials the ARR for ICD therapy ranged from 22.8 to 24% (non-random evidence) and the RRR from 54 to 56%. Reduction in total mortality is mainly driven by reduction in arrhythmic deaths.

The Coronary Artery Bypass Graft (CABG) Patch Trial found no significant difference in mortality between ICD and usual therapies. There was a non-significant ARR in the usual therapy group of 1.7% and a relative risk in the ICD group of 1.07. Factors that may have influenced this difference are patients in this trial having a lower risk of SCD from arrhythmias preventable by ICD therapy compared with other trials, and the surgery itself, which may lead to a reduced risk of SCD.

Estimated benefits from RCT data were reported as 0.23–0.8 additional years of life over various periods with ICD therapy compared with AAD therapy.

This previous systematic review for NICE also assessed the effects of ICD therapy on the quality of life of the recipient. Quality of life data from three of the effectiveness RCTs were in the public domain, one published from the CABG Patch Trial[22] and two unpublished available as abstracts of conference proceedings. Namerow and colleagues,[22] in the CABG Patch Trial, showed that patients in the ICD group at 6 months had lower levels of psychological well-being, reported feeling less healthy, and had reduced physical and emotional role functioning compared with controls. For patients with ICD, shocks are a likely explanation for lower mental health scores. A published preliminary analysis from AVID had revealed difficulties in data collected before and after randomisation.[23] Unpublished data on quality of life from MADIT showed no difference in quality of life between ICD and controls, and quality of life scores correlated negatively with number of shocks received. Overall, the quality of life with ICD showed mild to moderate disability.

A literature review, which included qualitative studies, examined the psychosocial impact of ICDs and found five studies with preimplantation and postimplantation assessment of psychosocial adjustment in recipients of ICD, and 18 studies of postimplantation assessment.[24] This review concluded that ICD-specific fears (e.g. fear of shock, fear of death, fear of embarrassment) are commonly experienced by recipients, along with lifestyle changes (e.g. driving restrictions, concerns about sexual activity and social interactions). Symptoms of anxiety are widely reported by ICD recipients, with 13–38% of recipients reporting diagnosable levels of anxiety. Depressive symptoms are reported at the same rate as other cardiac populations. Patients reported feeling fearful and anxious before receiving the ICD and that the anxiety and depression persisted after implantation but generally diminished over time. In one study, one-third had clinical anxiety and depression, which persisted, with 40–63% of this group continuing to have difficulties after 1 year.[25] Anxiety about the ICD firing was closely linked to occurrence of depression, as was avoidance of activities. Psychosocial adjustment risk profiles indicate that younger ICD recipients (<50 years)

TABLE 5 *Summary of RCTs of ICD versus medication to reduce SCD: trial characteristics*

Study	No. of patients	Inclusion criteria	Age (years) mean ± SD	Gender (% male)	Intervention and type of ICD insertion	Comparator	Duration of follow-up (months)
Primary prevention of VT/VF							
MADIT Multicenter Automatic Defibrillator Implantation Trial, 1996[13]	196	MI ≥ 3 weeks before entry, with documented asymptomatic unsustained VT unrelated to MI, LVEF ≤ 0.35, with inducible VT not suppressed by procainamide, NYHA functional class I, II or III, no indications for CABG or angioplasty within 3 months	63 ± 9	92	Prophylactic ICD, 47% transthoracic devices, 53% transvenous devices	Conventional tiered therapy	27
MUSTT Multicenter Unsustained Tachycardia Trial, 1993,[14] 1999[15]	704	CHD, non-sustained VT. LVEF < 40% and EP-diagnosed inducible sustained VT	66.5 (58–72)[a]	90	EP-guided treatment (ACE inhibitor and/or β-blocker, and sequential AAD therapy supplemented with ICD if drug therapy failed to make VT no longer inducible), transvenous devices	Conservative (ACE inhibitor and/or β-blocker when tolerated and no AAD therapy)	39
CABG Patch Coronary Artery Bypass Patch Trial, 1997[16]	900	Patients having CABG with LVEF < 0.36 and abnormalities of signal-averaged ECG	63.5 ± 9	85.5	ICD, transvenous devices	Control (usual treatment)	Mean ± SD 32 ± 16
Secondary prevention (recurrent VT/VF)							
AVID Antiarrhythmic Versus Implantable Defibrillator, 1997[17]	1016	Cardiac arrest survivors (45%) or sustained VT with syncope, or symptomatic sustained VT (55%) with LVEF ≤ 40%	65 ± 11	79.5	ICD, transvenous devices	Amiodarone or sotalol	45, mean 27
CASH Cardiac Arrest Study Hamburg, 1993[18] (Preliminary results only published)	230	Survivors of cardiac arrest	57 ± 11	80	ICD, transthoracic devices pre-1991, transvenous devices post-1991	Amiodarone or metoprolol (propefenone arm deleted in 1992 owing to high mortality rate)	Minimum 24

continued

TABLE 5 *Summary of RCTs of ICD versus medication to reduce SCD: trial characteristics (cont'd)*

Study	No. of patients	Inclusion criteria	Age (years) mean ± SD	Gender (% male)	Intervention and type of ICD insertion	Comparator	Duration of follow-up (months)
CIDS Canadian Implantable Defibrillator Study, 2000, 1993[19,21]	600	Survivors of cardiac arrest, tachyarrhythmias with symptoms, with LVEF < 35%	63.5 ± 9	84	ICD, first 33 transthoracic devices, remaining 277 transvenous devices	Amiodarone	36–60
Wever *et al.*, 1995[20]	60	Survivors of cardiac arrest	57.0 ± 10	90	ICD, apart from three transvenous devices	Tiered drug therapy	27

[a] Median (range).
ACE, angiotensin-converting enzyme; CHD, coronary heart disease.

TABLE 6 *Summary of RCTs of ICD versus medication to reduce SCD: main results*

Study	Relative reduction in risk	Absolute results	NNT (95% CI)[a]
Primary prevention of VT/VF			
MADIT, 1996[13]	RR, ICD arm: 0.46 (95% CI 0.26 to 0.82, $p = 0.009$) RRR: 54%	Absolute mortality: ICD: 15.8% Conventional therapy: 38.6% ARR: 22.8%	5 (3 to 10)
MUSTT, 1993,[14] 1999[15]	Absolute all-cause mortality in randomised comparison: Conservative vs EP-guided RRR 13%	Absolute all-cause mortality in randomised comparison: Conservative: 48% EP-guided 42% ARR 6%	17
	EP arm (non-randomised comparison) ICD vs drug therapy RRR: 56%	EP arm (non-randomised comparison) ICD vs drug therapy Total mortality ICD: 24% Drug therapy 55% ARR 31%	3

continued

TABLE 6 *Summary of RCTs of ICD versus medication to reduce SCD: main results (cont'd)*

Study	Relative reduction in risk	Absolute results	NNT (95% CI)[a]
CABG Patch, 1997[16]	RR, ICD arm: 1.07 (95% CI 0.81 to 1.42, p =0.64) Adjusted RR 1.03 (95% CI 0.75 to 1.41)	Absolute mortality: ICD: 22.6% at 32 months Control: 20.9% at 32 months ARR in usual treatment group: 1.7%	58 (14 to infinity)
Secondary prevention (recurrent VT/VF)			9 (6 to 18)
AVID, 1997[17]	Relative reduction in total mortality (adjusted) in ICD arm: 37 ± 22% (1 year), 24 ± 22% (2 years), 29 ± 23% (3 years), ($p < 0.02$)	Absolute mortality: ICD: 10.7% (1 year), 18.4% (2 years), 24.6% (3 years) Amiodarone/sotalol: 17.7% (1 year), 25.3% (2 years), 35.9% (3 years) ARR: 7% (1 year), 6.9% (2 years), 11.3% (3 year)	
CASH, 1993[18]	At 2 years: RR: 0.63 RRR: 37% ($p = 0.081$)	Total mortality: ICD: 11.5% Propefenone: 29.3% Trial stopped At 2 years: Absolute total mortality ICD 19.6% Amiodarone/metoprolol 12.1% ARR: 7.5% % Reduction in mortality year 1–9: 41.9, 39.3, 28.4, 27.7, 22.8, 11.4, 9.1, 10.6, 24.7	14 (6 to infinity)
CIDS, 2000,[19] 1993[21]	RRR at 5 years: 19.7% with ICD ($p = 0.142$)	Absolute mortality at 5 years: ICD: 23% Amiodarone: 27% ARR: 3.7%	24 (10 to infinity)
Wever *et al.*, 1995[20]	RR of death in ICD arm: 0.27 (95% CI 0.09 to 0.85; $p = 0.02$)	Absolute mortality: Early ICD: 14% at 2 years Conventional group: 35% at 2 years ARR: 21% at 2 years	5 (3 to infinity)

[a] Calculated by the authors using Arcus software.
NNT, number needed to treat; RR, relative risk.

TABLE 7 *Unwanted effects of interventions in included trials*

Study	ICD therapy	AAD
Primary prevention of VT/VF		
MADIT, 1996[13]	Adverse events in 19/95 patients: 2 pneumothorax, 2 infection, 7 lead problems, 7 rhythm problems	Adverse events in 12/101 patients: 5 unexplained syncope, 7 VT/VF, amiodarone discontinued in 46%
MUSTT, 1993,[14] 1999[15]	EP-guided arm: complications occurred in 5 patients with inducible sustained VT (0.7%) non-fatal	
CABG Patch, 1997[16]	Significantly different complications in ICD: 12.3% infection, 8.5% pneumonia, 2.7% deep sternal wound infection	
Secondary prevention (recurrent VT/VF)		
AVID, 1997[17]	Adverse events in 19/507 patients: 6 bleeding, 13 haematoma, 10 infection, 8 pneumothorax, 1 cardiac perforation	5% pulmonary toxic, 16% required thyroid replacement medication
CASH, 1993[18]	5 patients (5.1%) died perioperatively: 3 epicardial device infection, 2 explantation, 6 haematoma, 1 pericardial effusion, 3 pleural effusion, 1 pneumothorax, 3 dislodgement/migration of leads, 2 device dysfunction	Propefenone: 12/56 side-effects, 61% higher total mortality: drug stopped
	Overall complication 23%, explantation rate 2.1%	Amiodarone: hyperthyroidism in 3 (3%), drug stopped in 9 (9%) Metoprolol: drug stopped in 10 (10%)
CIDS, 2000,[19] 1993[21]	At 3 years: 5.1% infection, 2.6% lead fracture, 11.9% pulmonary toxic, 0.9% hepatic, 1.8% thyroid, 8.5% CNS	At 3 years: amiodarone: 22% stopped, 19.6% pulmonary toxic, 5.1% hepatic, 8.8% thyroid, 26% CNS
Wever *et al.*, 1995[20]	Migration of lead in 1 patient, infection in 1 patient	16/31 late ICD (15 predischarge)

and those with high discharge rates may experience the most adjustment difficulties. In four of the included studies a reported 75–93% of patients with ICDs had a positive attitude towards the ICD, regarding it as a 'life extender' and very important to their life. In one study 62% of patients resumed employment, and these were more likely to be educated and less likely to have had a history of MI. Comparison of groups of patients with ICDs and a similar group with coronary artery disease found that the quality of life did not differ between the groups, but patients with ICDs were less anxious. However, with increasing number of shocks the percentage of psychologically distressed patients rose from 10% to over 50%, with patients having lower quality of life scores.[26]

There are several problems with many of these quality of life studies highlighted by the HTA systematic review, including:

- small sample sizes
- selection bias
- non-standardised assessment measures
- lack of baseline assessment
- lack of long-term follow-up data
- confounding by the patients' reactions to suffering major illness and near-death experiences.

Updated review (2003)

This report updates this earlier review based on searches of the literature from 2000 to 2003 and was accurate up to the end of 2003. Its aim is to update the systematic review conducted by HTA for NICE in 1999 on the effectiveness and cost-effectiveness of ICD therapy in the management of patients at risk of sudden cardiac death due to arrhythmias. Studies that were published after 2003, during the time this document was under review, have been summarised as an addendum.

Specific objectives were:

- to present the evidence on the clinical effectiveness that has been published since 1999 using the same methodology as in the HTA report[2] including identical inclusion criteria and search strategy

- to present the evidence on the effect on quality of life of patients receiving ICDs.

Methods for reviewing effectiveness

The review was conducted following the general principles outlined in the NHS Centre for Reviews and Dissemination (CRD) Report 4.[27] Sources of information, including databases searched and key search terms, are as follows.

A literature search was performed to ascertain the evidence of the effectiveness of ICD therapy.

Electronic databases searched from November 1999 to March 2003 were:

- Cochrane Library 2003 No. 1
- MEDLINE 1999–2003
- EMBASE 1999–2003
- BIDS Science Citation index 1999–2003
- National Research Register 1999–2003
- International Network of Agencies for Health Technology Assessment 1999–2003.

Search terms used are detailed in Appendix 1.

To identify RCTs, the Lefevre strategy was used (see Appendix 2).

The following searches were also conducted.

- Relevant websites (such as North American Society of Pacing and Electrophysiology, British Cardiac Society, British Heart Foundation) were searched for conference proceedings or abstracts.
- Reference lists were searched and relevant articles retrieved. Search terms were added following initial searches as appropriate.

Studies were graded according to the level of evidence. (Only those studies of higher level of evidence, systematic reviews, meta-analyses and RCTs, were located and appraised.) Authors of ongoing trials were contacted to seek further information and data.

Inclusion criteria

Studies were included if they were systematic reviews, meta-analyses or RCTs comparing ICDs with conventional therapy (such as AAD, catheter ablation or surgery) in people at high risk of SCD usually due to ventricular arrhythmia.

The three main patient outcomes measures that were included were:

- overall mortality
- arrhythmic deaths
- health-related quality of life (HRQoL)

Studies identified by the search strategy were assessed for inclusion by one reviewer (JP).

Data extraction strategy

Data extraction was undertaken by one reviewer (JP) and checked by a second reviewer (DCh), with any disagreements being resolved through discussion.

Quality assessment strategy

Included studies were assessed using standard critical appraisal criteria and checklists such as those developed by the Critical Appraisal Skills Programme and CRD.[28] Primary studies were scored using the Jadad scale (Jadad) and secondary studies were scored using the CRD Review Score scale (see Appendix 3). Although the Jadad score is low for non-blinded studies it was used here to be consistent with the previous systematic review[2] and the recent HTA review.[29] Quality assessment was undertaken by one reviewer (JP) and checked by a second reviewer (DCh), with any disagreements being resolved through discussion.

Data analysis and synthesis

Data are presented as a narrative review with full tabulation of results of all included studies. A formal meta-analysis of the secondary prevention trials was not undertaken as a patient-based meta-analysis has been published of three trials, CASH, CIDS and AVID.[30] A meta-analysis of all included RCTs was not performed owing to the heterogeneity of the patient populations.[31]

Results

In total, 1049 titles and abstracts were screened for inclusion, then the full text of the five studies that met the criteria for inclusions were examined by the same reviewer.

There have been three published RCTs on the effectiveness of ICD therapy in the management of arrhythmias in the years 2000–2003[32–34] and there have been two studies assessing the quality of life of patients with ICDs derived from published randomised evidence.[35,36] In addition, there has been one systematic review on the efficacy of ICDs in people at increased risk of SCD,[37] and one meta-analysis of secondary prevention trials.[30]

Randomised controlled trials of effectiveness

The RCTs of the effectiveness of ICD therapy in the management of arrhythmias from 2000 to 2003 are the CASH trial,[32] MADIT II[33] and CAT.[34] (*Tables 8* and *9*)

MADIT II[33]

Jadad score = 3/5:

- reported randomised: yes
- described dropouts: yes
- method of randomisation: yes
- double blind: no.

This is an RCT assessing the prophylactic use of ICDs in 1232 patients with previous MI and heart failure with LVEF less than 30%. Patients were randomised to ICD or usual treatment. The results showed that patients with ICDs had a survival advantage (RRR 30%, ARR 6%) over those receiving usual treatment, and that this benefit was greater in those with a higher risk of mortality. The benefit appeared after 9 months after implantation, which contrasts with results from MADIT I, where survival rate improved in the first few months. This may be due to lower mortality in the conventional therapy arm in MADIT II, the lower LVEF cut-off used, the absence of risk stratification of arrhythmias as entry criteria, and the more intensive use of medical treatment. Subgroup analysis showed a similar benefit of ICDs regardless of age, gender, NYHA heart failure class and QRS duration. The increased hospitalisation of ICD patients with worsening heart failure is reported. This may be due to these patients living longer and so having time for their heart failure to deteriorate, or it may be associated with the devices. The life-years saved with MADIT II are moderate, but this may be affected by the follow-up being 20 months, so the full benefit of the ICD has not been seen yet.

This trial was stopped prematurely in November 2001 after an interim analysis showed a survival advantage for patients with ICDs that was statistically significant.

CAT[34]

Jadad score = 3/5:

- reported randomised: yes
- described dropouts: yes
- method of randomisation: yes
- double blind: no.

This was a pilot study to determine the effectiveness of ICDs in the management of patients with dilated cardiomyopathy of recent onset with impaired left ventricular function. Recruitment was undertaken over 6 years, and the primary outcome was all-cause mortality at 1 year. Power calculations assumed 30% mortality in 1 year, requiring 1348 patients to be recruited to detect a 6% difference in survival between groups at 1 year. An interim analysis was conducted after recruitment of 100 patients with at least 1 year of follow-up in 1997. This showed that overall mortality for all patients was 5.6%, with a difference in survival between the two groups of 2.6%. Further follow-up and survival analysis in 2000 showed no difference between the groups. The only predictor of total mortality was impaired LVEF. The authors conclude that ICDs did not confer any survival benefit in these patients, including those with lower LVEF and non-sustained VTs. The study was underpowered to detect differences because of the low event rate, which is likely to have led to the lack of survival benefit from ICDs.

CASH[32]

Jadad score = 3/5:

- reported randomised: yes
- described dropouts: yes
- method of randomisation: yes
- double blind: no.

The CASH Trial has been published in full since the last systematic review and is a trial in a secondary prevention setting. The propafenone arm was stopped prematurely owing to excess mortality. The 5-year results comparing ICDs with metopolol/amiodarone showed a continuing trend towards benefit from ICDs compared with drug therapy. Use of older devices and poorer perioperative risks may have led to an underestimate of the true effects of current devices. In CASH, the benefits of ICDs were more evident in the first 5 years after the index event and gradually declined, to an ARR of 10.6% at year 8. In addition, patients in CASH had higher LVEF and were healthier than in other trials, which may have led to lower benefits from ICD.

Meta-analysis[30]

CRD score = 6/6.

Results from three of the secondary prevention trials (AVID, CASH and CIDS) have been combined in a meta-analysis using individual patient data. The methods used to extract data

TABLE 8 *Effectiveness of ICD therapy: trial characteristics*

Study and country	No. of patients	Inclusion criteria	Age (years), mean ± SD	Gender (% male)	Intervention and type of ICD insertion	Comparator	Duration of follow-up
Primary prevention							
MADIT II Multicenter Automatic Defibrillator Implantation Trial II, 2002[33] 71 US centres, two in Israel, one in The Netherlands, two in Germany	1232	MI >1 month before and ejection fraction of <0.30 in 3 months before recruitment. Exclusion if FDA approved indication for ICD. First 6 months frequent ventricular ectopics on 24-hour Holter monitor		84	Transvenous ICD	Conventional medical therapy	Average 20 months (range 6 days to 53 months) trial terminated November 2001 as significant difference between groups
CAT Cardiomyopathy Trial, 2002[34] 15 German centres	104	Symptomatic idiopathic dilated cardiomyopathy ≤ 9 months and LVEF ≤ 0.30 and in NYHA class II or III. Excluded: coronary artery disease, symptomatic VT/VF	52 ± 11	80	Transvenous ICD	Usual treatment	22.8 ± 4.3 months, investigator follow-up, mean 5.5 ± 2.2 years
Secondary prevention							
CASH Cardiac Arrest Study Hamburg, 2000[32] Germany	288	Survivors of cardiac arrest	58 ± 11	80	Transthoracic devices pre-1991 (55%), transvenous devices post-1991 (44%)	Amiodarone or metoprolol (propafenone arm deleted in 1992 owing to high mortality rate)	Mean 57 ± 34 months, minimum of 2-year follow-up

FDA, Food and Drug Administration.

TABLE 9 *Effectiveness of ICD therapy: main results*

Study	Relative reduction in risk	Absolute results	NNT (95% CI)[a]	Unwanted side-effects of interventions
Primary prevention				
MADIT II, 2002[33]	RR: 0.69 (95% CI 0.51 to 0.93) $p = 0.016$ RRR: 31%	Total mortality: ICD: 14.3% Conventional: 19.8% ARR: 5.5%	18	Conventional therapy: 73 (14.9%) worsening heart failure ICD: 13 (1.8%) lead problems, 5 (0.7%) non-fatal infections, 148 (19.9%) worsening heart failure
CAT, 2002[34]		Total mortality: Long term (mean 5.5 ± 2.2 years) ICD: 13/50 26% Usual therapy: 17/54 (31%) Cumulative survival at 2, 4, 6 years ICD: 92%, 86%, 73% Usual therapy: 93%, 80%, 68% ($p = 0.554$)		ICD: 2 revisions due to dislocation and bleeding, 2 electrodes dislodged In following 24 months: 7 electrode dislodged, 2 infections requiring device replacement, 1 perforation
Secondary prevention				
CASH, 2000[32]	At 2 years: RR: 0.766 (upper 97.5% CI 1.112) RRR: 23.4% ($p = 0.081$)	Total mortality: ICD: 13.6% Propefenone: 29.3% Trial stopped At 2 years: Absolute total mortality: ICD: 36.4% (95% CI 26.9 to 46.6%) Amiodarone/metoprolol: 44.4% (95% CI 37.2 to 51.8%) ARR: 8.0% % Reduction in mortality year 1–9: 41.9, 39.3, 28.4, 27.7, 22.8, 11.4, 9.1, 10.6, 24.7	13 (6 to infinity)	Drug therapy: Propafenone: 12/56 side-effects, 61% higher total mortality: drug stopped Amiodarone: 3 (3%) hyperthyroidism, 9 (9%) drug stopped Metoprolol: 10 (10%) drug stopped ICD: 5 (5.1%) died perioperatively: 3 epicardial device infection, 2 explantation, 6 haematoma, 1 pericardial effusion, 3 pleural effusion, 1 pneumothorax, 3 dislodgement/migration of leads, 5 device dysfunction Overall complications 23%, explantation rate 2.1%

[a] Calculated by the authors using Arcus software.

and analyse were standard and rigorous. The results showed a strongly significant benefit of ICDs, with an RRR of 27% for total mortality, although this increased to just over 30% when transvenous devices only were included. This reduction was mainly due to a 50% reduction in arrhythmic deaths. Competing non-arrhythmic causes of death may, over time, reduce the benefit of ICD. The NNT was calculated to be 29 over 6 years. The meta-analysis shows that patients with an LVEF of less than 35% derived more benefit from ICD than those with better preserved left ventricular function. The analysis found that the benefit of ICDs was independent of β-blockade use. Further combination of results was not possible owing to the heterogeneity of patient characteristics.

Systematic review[37]

CRD score = 5/6.

The systematic review included RCTs evaluating ICDs versus usual care in patients at risk of SCD or ventricular arrhythmia, who had evidence of heart failure or coronary artery disease, and also studies in survivors of cardiac arrest or unstable cardiac rhythms. These inclusion criteria are broader than the scope of this review and included patients with conditions such as hypertrophic cardiomyopathy. Standard systematic review methodologies were followed and reported clearly. Searches of electronic databases including MEDLINE, EMBASE, Cochrane Controlled Clinical Trial Registry, Web of Science, NLM Gateway and Cardiosource were conducted from 1980 to September 2002. Eight trials were included in the final analysis, five primary prevention and three secondary prevention trials. A meta-analysis was performed on all eight trials to derive an overall relative risk for SCD and total mortality. Tests for heterogeneity of included trials were conducted and found no appreciable heterogeneity. Effect estimates were similar in trials of primary and secondary prevention (RR 0.72, 95% CI 0.63 to 0.84 versus RR 0.76, 95% CI 0.65 to 0.89). Random-effects models yielded similar summary relative risk for overall mortality, all-cause mortality in primary prevention and all-cause mortality in secondary prevention (RR 0.72, 95% CI 0.58 to 0.90; RR 0.69, 95% CI 0.46 to 1.03; RR 0.77, 95% CI 0.65 to 0.91). Substantial heterogeneity in total mortality was found between primary prevention trials enrolling high-risk patients and those enrolling moderate-risk patients ($p \leq 0001$), with those at high risk demonstrating a substantial survival benefit of ICD therapy and those at moderate risk failing to show any survival benefit. Combined results of all eight trials showed that ICDs significantly reduced SCD compared with usual care (most commonly amiodarone) (RR 0.43, 95% CI 0.35 to 0.53) and overall mortality (RR 0.74, 95% CI 0.67 to 0.82). ICDs were equally effective in preventing sudden cardiac death in secondary prevention trials (RR 0.5, 95% CI 0.38 to 0.66) and in primary prevention trials (RR 0.37, 95% CI 0.27 to 0.50), regardless of the baseline risk of the patients. The size of benefit in total mortality varied within primary prevention trials depending on baseline risk for SCD of the patient. Funnel plot analysis showed no publication bias. The ARR for total mortality for all eight trials was 8% (95% CI 2 to 13) and NNT 13 (95% CI 8 to 50). This needs caution in interpretation as the ARR depends on baseline risk and length of follow-up, which vary between trials. The review concluded that ICDs prevent SCD regardless of baseline risk, but impact on total mortality is sensitive to baseline risk for arrhythmic death. The evidence reported showed support for the use of ICDs in secondary prevention or for primary prevention in high-risk groups (e.g. patients with coronary artery disease and severe left ventricular dysfunction). The evidence did not show a significant impact on total mortality rates in patients at lower risk for SCD (e.g. patients with left ventricular dysfunction but no coronary artery disease or inducible ventricular arrhythmias).

Caution must be taken in the interpretation of these combined results because of the heterogeneity of the studies and the combination of the trials not using individual patient data.

Health-related quality of life of patients receiving ICDs

Given the problems in interpreting the HRQoL data previously identified, the search was restricted to HRQoL data from RCTs. Since the last HTA report, there have been two studies based on randomised evidence published on the changes in quality of life in patients with ICDs (*Tables 10* and *11*). One further study remains in the public domain only as conference proceedings (MADIT).[38]

Health-related quality of life studies

The published studies found conflicting results, with one showing a clear benefit from ICDs and one reporting no difference between treatment

TABLE 10 *Quality of life studies derived from randomised evidence: trial characteristics*

Study	Patients	No. of patients and dropout rate	Tools used	Outcomes assessed	Follow-up times
AVID, 2002[36]	VF, VT with symptoms	905 randomised, 800 alive at 12 month (88.4%) ICD: 416; AAD: 384	SF-36, QL Index, PCC	SF-36: PCS and MCS; device shocks; adverse reactions	SF-36: baseline, 3, 6, 12 months QL Index: baseline 12 months
CIDS, 2002[35]	Sustained VA	650 randomised, 317 recruited ICD: 157; amiodarone:160 287 alive at 12 months (90.5%), 178 reported	MHI, NHP, postal questionnaires for follow-up	MHI domains: mental health, psychological distress/well-being NHP: energy level, physical mobility, social isolation, emotional reactions, pain, sleep disturbance, lifestyle impairment	Baseline, 2, 6 and 12 months

SF-36 is divided into physical component score (PCS) and mental component score (MCS). On the MHI higher scores indicate better functioning; on the NHP higher scores indicate poorer functioning.
MHI, Mental Health Inventory; NHP, Nottingham Health Profile; PCC, Patient Concerns Checklist; QL Index, Quality of Life Index; SF-36, Short Form 36.

TABLE 11 *Quality of life studies derived from randomised evidence: main results*

Study	Before therapy	Between-group comparison of scores over time; after therapy	Overall comment	Adverse symptoms
AVID, 2002[36]	ICD: PCS: 37.4 ± 10.9 MCS: 45.9 ± 11.8 PCC: 15.9 ± 8.6 QoL: 22.1 ± 4.9 AAD: PCS: 36.5 ± 11.2 MCS: 47.5 ± 11.5 PCC: 16.2 ± 8.9 QL: 21.9 ± 5.0	PCS: $p = 0.001$ MCS: $p = 0.7$ PCC: $p = 0.1$ PCC: decreased over time in both groups ($p = 0.001$) QL: no change over time	No difference in HRQoL of ICD and AAD groups. Adverse symptoms associated with reduced HRQoL. >1 shock vs no shocks associated with decrease in MCS PCS and increases in PCC. ≥3 vs <3 shocks decreased HRQoL	49% 3 months, 36% 6 months, 54% 12 months No difference between groups ($p = 0.8$) 34% cardiovascular, 28% decreased heart failure Severe: 17% 3 months, 7% 6 months, 14% 12 months 35% ICD complication, 18% cardiovascular, 16% decreased heart failure Adverse symptoms as with **ICD**: decreased PCS and MCS **AAD**: decreased PCS **Shocks** 144/373 ≥1 at 1 year (39%), 94% appropriate 49% 1 or 2 shocks, 51% ≥3 shocks 3 months 85 ≥1 shock, 3–6 months 52 ≥1 shock, 6–12 months 55 ≥1 shock

continued

TABLE 11 *Quality of life studies derived from randomised evidence: main results (cont'd)*

Study	Before therapy	Between-group comparison of scores over time; after therapy		Overall comment	Adverse symptoms
CIDS, 2002[35]	**MHI**	**MHI**		HRQoL better in ICD than amiodarone	**Shocks:**
	ICD	**ICD**			≥ 5 worse MHI total index+ psychological distress scores
		6 months	**12 months**		
	Total index 173.2 ± 25.5	183.1 ± 30.2	184.3 ± 27.9		
	Psychological distress 51.3 ± 14.1	45.1 ± 17.6	43.4 ± 15.9	HRQoL benefits lost if numerous shocks	+psychological well-being
	Psychological well-being 58.5 ± 12.7	62.2 ± 13.4	61.7 ± 13.2		NHP emotion
	Amiodarone	**Amiodarone**			HRQoL no change with time
	Total index 180.4 ± 27.8	180.2 ± 31.1	178.3 ± 28.7		
	Psychological distress 47.8 ± 16.5	47.6 ± 18.3	48.8 ± 16.8		
	Psychological well-being 62.2 ± 12.3	61.8 ± 14.1	61.1 ± 13.3		**ICD no shocks:**
	NHP	**NHP**			improvement in MHI psychological distress, total index, NHP sleep disturbance
	ICD	**ICD**			
		6 months	**12 months**		
	Energy 27.5 ± 32.2	18.6 ± 30.1	17.7 ± 26.1		
	Mobility 10.9 ± 12.0	10.5 ± 13.7	9.1 ± 13.6		
	Isolation 8.5 ± 15.4	8.5 ± 15.4	9.8 ± 18.6		
	Emotions 17.3 ± 18.1	11.1 ± 18.2	8.3 ± 16.6		
	Pain 4.4 ± 7.9	7.5 ± 17.1	4.5 ± 9.9		
	Sleep disturbance 31.4 ± 27.4	25.0 ± 29.7	23.9 ± 29.4		
	Lifestyle impairment 2.0 ± 1.9	1.6 ± 1.8	1.6 ± 1.3		
	Amiodarone				
	Energy 24.4 ± 32.4	27.8 ± 32.1	36.8 ± 37.3		
	Mobility 13.2 ± 20.5	15.1 ± 19.2	17.7 ± 19.2		
	Isolation 9.9 ± 17.7	12.2 ± 22.4	11.1 ± 22.6		
	Emotions 14.3 ± 20.1	15.3 ± 22.4	14.5 ± 1 9.6		
	Pain 7.5 ± 15.1	6.3 ± 13.6	8.2 ± 15.4		
	Sleep disturbance 29.6 ± 31.5	30.8 ± 31.0	30.2 ± 32.4		
	Lifestyle impairment 1.6 ± 1.7	1.9 ± 1.9	1.8 ± 1.9		
All quality of life variables improved to a greater extent with time in the ICD group than in the amiodarone group ($p = 0.05$). At 3–6 months and from 6 to 12 months 7/10 variables improved for the ICD group MHI and NHP (statistically significant).					

groups. Both studies had methodological flaws and both used different instruments to measure quality of life. In appraising the quality of life studies several parameters need to be assessed.[39]

- Were validated instruments used to assess outcomes?
- Did the instruments measure both generic and disease-specific outcomes, to allow cross-study comparisons?
- Is follow-up of patients reported, and are the characteristics of patients lost to follow-up reported?
- Was the quality of life data collection given the same priority as data collected for other outcome measures in the RCT?
- Were appropriate methods of analysis used?

AVID[36]

The tools used in this study were valid measures, assessing generic (SF-36) and disease-specific outcomes (QL Index), and the first year of the study was used to establish the reliability of the instruments.

Of the total 1016 patients in AVID, 89% agreed to participate in the quality of life study and 88% of these (800) survived to 12 months. There were differences in the characteristics of those eligible patients participating in the quality of life study, in that they were more likely to be male, be living with a spouse/partner, have graduated from high school, be younger and white than those not participating. Those who survived to 12 months were more likely to have a higher mean LVEF (0.32 versus 0.27), less likely to have a history of heart failure and more likely to have received an ICD. There were no significant differences in the 800 patients randomised to ICD and AAD groups, apart from that the ICD group was more likely to be discharged from hospital on β-blockers (43% versus 16.4%, $p = <0.001$). These differences

leading to less sick people surviving longer may have some influence over the overall direction of the quality of life changes reported. Patients randomised to ICD had lower mean MCS than the AAD group ($p < 0.006$) and this did not vary over the 12 months of follow-up. There were no significant differences in PCC between the ICD and AAD groups at baseline or during follow-up, but PCC declined over time in both groups ($p < 0.001$). The QL Index did not differ between groups and did not differ over the follow-up. Adverse symptoms were associated with significant reductions in PCS and MCS in patients with ICDs and reduced PCS in patients in AAD. The occurrence of shocks versus no shocks was associated with a significant reduction in the quality of life. The development of more frequent shocks was associated with a reduction in the QL Index. The authors suggested that any reductions in shocks will have an effect on the quality of life of patients. Overall, the conclusions of the authors are that there were no differences in quality of life between the ICD and amiodarone groups, and that quality of life related to numbers of shocks received by patients with ICDs.

CIDS[35]

Valid instruments were used to measure generic outcomes. The NHP provides information on six dimensions of health status and the MHI provides information on mental health and psychological well being/distress. No disease-specific tools were used.

There was considerable attrition of the initial 317 patients recruited from the possible 650 to the quality of life study. An extra 250 recruited to CIDS following a change in primary outcome to total mortality were not considered by the study. Of the 317 patients studied, 38 died before the final 12-month follow-up, 22 did not have a baseline assessment and 127 did not have one of the follow-up assessments. The authors attempted to replace the missing baseline data with the mean for the variable across both treatment groups. Data collected at 2 months are not reported. The patients finally included in the analysis ($n = 178$) were those with two follow-ups at 6 and 12 months and baseline data, some of which were derived from mean values. Baseline MHI scores were worse in the ICD than in the amiodarone group. Over the 12-month follow-up, all quality of life measures except for two improved to a significantly greater extent in the ICD group than in the amiodarone group. Improvement in energy level and physical mobility was evident from the 6-month follow-up and only at 12 months did improvements in lifestyle impairment reach significance. The quality of life in the amiodarone group showed no improvement and actually fell in energy level and physical activity from baseline to the 12-month assessment. At 12 months the MHI scores were better in the ICD group compared with a population of factory workers with hypercholesterolaemia, and those in the amiodarone group were worse. Those ICD patients receiving more than five shocks had worse quality of life scores than those receiving fewer or no shocks, and showed no difference to that in the amiodarone group. The authors conclude that quality of life is better with ICD therapy than with amiodarone. The beneficial quality of life effects from ICD are not evident in patients who receive numerous shocks from their device.

MADIT[38]

Unpublished data from the MADIT I and II trials showed no difference in the quality of life between ICD and controls, and found quality of life scores correlating with number of shocks received. This appears to be similar to the conclusions drawn by the AVID study.

Discussion

Since the last review of the effectiveness of ICDs in the management of arrhythmias three RCTs have been published, two primary prevention and one secondary prevention. They show a relative risk reduction in total mortality of patients who are at high risk of SCD due to ventricular arrhythmias not due to reversible causes, compared with patients taking AAD therapies. The ARR ranged from 5.5 to 8% and the RRR from 23.4 to 31%. The results were statistically non-significant in CASH, but significant in MADIT II. One RCT indicates that ICDs do not convey a survival advantage in patients with recent dilated cardiomyopathy and severe left ventricular dysfunction.[34]

There have been two published randomised studies in secondary prevention assessing the quality of life outcomes of patients with ICDs. These showed conflicting results, with one showing an improved quality of life in patients with ICDs and the other showing no difference between the groups of patients having ICD or AAD therapy. Both studies confirmed results from previous non-randomised studies suggesting that in patients with ICDs, their quality of life inversely correlates with the number of shocks delivered by the device.

Quality of studies

Effectiveness trials

The RCTs were generally well conducted, but some methodological issues should be highlighted. RCTs of ICDs pose special problems: comparing drugs and devices raises issues of blinding and compliance; the differential use of β-blockers in ICD groups seen in the trials for which data are available may have contributed to the apparent effectiveness of the ICD,[40] although there is evidence that they do not convey a survival advantage;[19] and the evolution of devices over time makes the applicability of results from trials of older, transthoracic devices (which carry greater risks than transvenous devices) problematic. The use of transthoracic devices (which have a greater morbidity and mortality than transvenous devices) in CASH may have led to an underestimate of the effectiveness of more modern devices. CASH, like CIDS, was underpowered to detect statistically significant differences in outcomes. This was addressed to some extent by a meta-analysis of three secondary prevention trials, CIDS, CASH and AVID,[30] which showed an RRR in total mortality of 27% and in arrhythmic deaths of 52%. Variation in results of the secondary prevention trials may have been caused by differing clinical characteristics of included patients. For example, patients in CASH had higher LVEF and were healthier than those in the other trials, and evidence derived from AVID substudies indicates that these patients may be expected to derive less benefit from ICD therapy than those in AVID. CASH took a long time to recruit, exposing it to rapidly evolving ICD technology that complicated selection and interpretation of the results. There are concerns about the generalisability to the UK, as the trials were conducted mainly in North America and continental Europe. Differences from and similarities to the UK setting need to be explored to determine whether results from existing trials may be directly applicable to the UK. A further meta-analysis combining RCTs of effectiveness of ICDs was conducted in the overview of randomised trials of AADs and ICD for the prevention of sudden cardiac death.[41] (This was not included in this systematic review as it was an overview and not a systematic review using standard methods.) This combined seven RCTs in which patients were randomised to ICD or alternative therapy using the standard fixed effects methods to determine the summary relative risk for arrhythmic death and total mortality.[41] When all trials showing a reduction in mortality in the ICD group were combined the RR was 0.76 (95% CI 0.67 to 0.85), a combined RRR of 24%, with the absolute difference being 5.6% (95% CI 3.0 to 8.0), and the NNT to prevent one death was 18 (95% CI 13 to 31). There was significant heterogeneity between results ($p = 0.006$) and so caution is needed in interpreting these data.

Quality of life studies

The HRQoL studies add to the information gained from the CABG Patch Trial,[16] which showed that patients with ICDs had lower levels of psychological well-being and reduced physical and emotional role functioning than controls at 6 months. Both studies have limitations. The two quality of life studies included in this update included patients with broadly similar characteristics, but arrive at different conclusions about the effect of ICDs on quality of life. They both use valid tools to measure outcomes, and the generic instruments SF-36 and NHP are broadly similar, assessing similar variables. The baseline assessments were performed at differing times in the two studies; in AVID they were done before randomisation, so the patients were not aware of the therapy they would receive, whereas in CIDS some of the baseline assessments were conducted after randomisation, so this knowledge may have had some effect on the consistently lower MHI and NHP scores in the ICD group and the apparent greater improvement in HRQoL over the 6-month follow-up. At 6 months psychological distress was similar in both groups, raising the possibility that the baseline values may not have reflected the actual quality of life and that the changes represented regression to the mean.

The proportion of the trial patients in each study differ in that the AVID HRQoL captured 79% of the total cohort of eligible patients and CIDS captured 45%, which may have led to the smaller study results demonstrating a type I error, that is, the results could be due to chance.

In CIDS, loss to follow-up may have led to a selection bias operating in those patients remaining in the cohort, affecting the results of the study. Those with missing data were more likely to be in poorer health, leading to the possibility that the results may lead to an overestimation of effect. However, the missing data were equally distributed between the treatment groups, potentially reducing this bias. The analysis that replaced missing baseline data may not be appropriate as individual scores may differ considerably from the mean of the group, especially given the small number of patients, again leading to an influence on the estimation of effect.

Generalisability of the results may also be compromised by these missing data. In the AVID study, participation in this study was voluntary, with potential systematic bias being introduced in those who chose to participate. However, the authors made efforts to characterise those groups not included, and made any significant differences explicit. In both studies the follow-up of 1 year did not allow the estimation of quality of life after this time, and it may be that differences between ICD and AAD would emerge if they were followed up for a longer period.

Risk stratification

The secondary prevention trials in this update and previous review have shown that there is a survival advantage in having ICDs in groups of patients with clinically evident ventricular arrhythmias (ARR ranges from 3.7 to 11.3%). Primary prevention trials (MADIT I and MUSTT) also showed an advantage in patients who had electrophysiological evidence of ventricular arrhythmia (ARR from +1.7% to –22.8%). Life-years gained have been found to be modest in some trials; for example, average unadjusted length of additional life was 2.7 months at 3 years in the AVID trial, but the trials have limited follow-up and so the full benefit of ICD therapy may not have been seen. A population-based cohort study from the USA provided information on the use and outcomes of ICDs in pragmatic settings outside trial populations and 'ivory towers'. This showed a big increase in implantations in the USA during 1987–1995, but marked geographical variation in implantation rates. Patient mortality was found to be improving, although this does not appear to be as favourable as suggested by the trial data, with 76.2% alive at 3 years.[42,43]

Risk stratification has been problematic, with no obvious universal candidate test to identify patients who would most benefit from an ICD. The meta-analysis of three of the secondary prevention trials indicated that patients with an LVEF of less than 35% had a marked benefit from ICD and patients with an LVEF of at least 35% had virtually no benefit from ICDs. This difference was statistically significant, suggesting that LVEF may be an important determinant of ICD effect.[30] Evidence supporting this has come from MADIT II.[33] This suggests that the use of LVEF and ECG QRS duration may act as identifiers for patients most likely to benefit from ICDs.

This evidence may considerably widen the indications for ICD therapy, although it is not certain that all patients with CHD and severely affected left ventricular function should have an ICD. More careful screening of potential candidates for prophylactic implantation might decrease complications and costs, yet still maintain the survival advantages shown in the trials.[44]

Gaps in knowledge

Future research could help to inform evidence-based decisions about the use of ICDs. What is needed is, first, information about the benefits and costs of ICDs over the longer term. As most costs occur early in treatment, cost-effectiveness may become more favourable as patients survive longer, the battery life of ICDs extends beyond 6–7 years, patient acceptability increases, the cost of the device is reduced and improvements to efficacy occur. Cost-effectiveness may also improve if simpler (and therefore cheaper) devices are used for relatively uncomplicated cases, and devices are used that minimise unnecessary shocks, leading to an improved quality of life and thus more favourable cost utilities. Second, we need to know more about current patterns of service use, equity of provision between different social groups, and the diffusion and effectiveness of different devices. Third, more evidence is required about the identification of those subgroups of patients who may benefit from an ICD. Evidence supports the view that those patients at high risk of arrhythmic death would most benefit from ICDs. The systematic review of the efficacy of ICDs in people at risk for SCD[37] attempted to collate all of the available published randomised evidence on stratification of patients by this baseline risk to identify these patients, such as those with an LVEF below 35%[19] and a QRS duration above 0.12.[33] Results from CAT show no differences between ICD and amiodarone, supporting the effects on total mortality being sensitive to baseline risk for SCD. Ongoing trials such as the Sudden Cardiac Death in Heart Failure Trial (SCD HeFT; patients with heart failure and LVEF <36%, randomly assigned to placebo, amiodarone or a defibrillator), Amiodarone Versus Implantable Cardioverter-Defibrillator Trial (AMIOVIRT) and Defibrillators in Acute Myocardial Infarction Trial (DINAMIT) will add to the evidence on risk stratification for primary prevention and allow more precise estimates on the impact of ICDs in specific patient groups. Beta-blocker Strategy plus Implantable Cardioverter Defibrillator Trial (BEST-ICD), Defibrillators in Non-Ischaemic Cardiomyopathy Treatment Evaluation (DEFINITE) and Midlands Trial of Empiric Amiodarone versus Electrophysiology Guided Interventions and Implantable Cardioverter

Defibrillators (MAVERIC), will similarly contribute to the evidence. (These trials have been published at the time of going to press and are summarised and discussed in an addendum.) As MAVERIC is a UK-based RCT, awaiting publication and in the public domain as an abstract (with full results made available as a personal communication; Griffith, Birmingham, 2003), it merits further elaboration. The aim of MAVERIC was prospectively to identify patients who would benefit most from ICD therapy by EP, and deliver a mortality benefit over empirical amiodarone comparable to that seen by using empirical ICDs. Patients who had had sustained VT, VF or survived cardiac arrest were randomised to receive either amiodarone or EP-guided therapy of drugs, ICD and myocardial revascularisation. Of the 106 in the amiodarone arm 84 patients (84%) received amiodarone. Of the 108 in the EPS group 31 (29%) received an ICD, 46 (43%) received AADs only and 18 (17%) received myocardial revascularisation but no ICD. The results showed that there was no significant difference in survival or arrhythmia recurrence between the treatment arms at 6 years. However, ICD recipients had a better survival experience than non-ICD recipients (hazard ratio 0.54, $p = 0.0391$). The authors concluded that it was not possible prospectively to ascertain those who would most benefit from ICD therapy by EP or other methods among patients presenting with a sustained ventricular arrhythmia. They also state that routine EP study had no role in the management of patients presenting with SCD, VT and VF, who should receive empirical ICD therapy according to AVID criteria (i.e. the nature and haemodynamic stability of the presenting arrhythmia and LVEF, with those having a more unstable index event or low LVEF having greater benefit from ICD therapy). The trial therefore supports the use of ICD in a selected population, but suggests that EP as a risk stratifier is limited.

Finally, we need to know more about the changes in patients' quality of life that ICDs bring. Results from the HTA work presented in this report will contribute to the evidence base and provide information for service planners and policy makers.

Summary

There is increasing evidence for the effectiveness of ICD therapy compared with usual treatment in the management of ventricular arrhythmias, especially in patients with recurrent unstable arrhythmias and in prevention of additional life-threatening arrhythmias following survival of cardiac arrest, and in preventing SCD in those at high risk. The indications for ICDs may be extended to include those with MI and heart failure, with additional potential impact on the provision of service in the UK in terms of cost and service capacity. Risk stratification tools and algorithms applicable to clinical settings are still needed to identify those subgroups most likely to benefit from ICDs.

In the light of conflicting conclusions from existing studies, further high-quality evidence on the HRQoL of patients with ICDs is required to show whether ICDs are superior to AADs, but current evidence suggests that any overall differences in HRQoL must be relatively small. It seems clear that the quality of life for patients with ICDs is deleteriously affected by recurrent shocks.

Chapter 3

Published economic analyses

Introduction

Since the introduction of the technology there has been interest and concern about its cost-effectiveness and several previous reviews have reported on the early economic evaluations undertaken. The previous HTA review[2] identified eight cost-effectiveness studies and one review paper. Of these, only three were based on RCT evidence (and one of these was only in the form of a conference abstract). The indicative modelling for the UK undertaken by Parkes and colleagues[2] estimated a cost per life-year gained (LYG) of between £40,500 and £87,000 and a cost per quality-adjusted life-year (QALY) gained between £21,300 and £45,800 calculated over a 3-year time-frame.

The four main studies published in the period 1990–1995 all suffer from major weakness in their assumptions about the relative effectiveness of ICDs compared with drug therapy. They pre-date all RCT evidence, and therefore had to rely on expert opinion,[45] comparison of unrelated case series,[46] published literature[47] and assumptions based on time to first shock.[48] Given the recognised and inevitable weakness of the basis for their estimates of clinical effectiveness, the authors of this review did not set out to review these studies further. The search therefore was designed to look at studies that had been based on a specific RCT, or had been able to use RCT evidence in modelling, or had actively chosen to use other sources as a comparison or in preference. In reviewing the papers the main focus was on establishing what was known about the cost-effectiveness of ICDs and the issues that might need to be addressed in any new model incorporating UK (non-trial) data.

Research questions

The detailed questions for the review of cost-effectiveness studies were:

1. What are the conclusions from robust studies of cost-effectiveness about cost per life-year gained or cost per QALY?
2. What appear to be the key parameters driving cost-effectiveness, and how firm are the estimates of these parameters?
3. How much does this cost-effectiveness vary by preidentifiable subgroups of patients?
4. How generalisable are these results likely to be to the UK, where they are not specifically estimated for the UK?

Search strategy

Searches were conducted on MEDLINE, CRC databases [Database of Abstracts of Reviews of Effectiveness (DARE). NHS Economic Evaluations Database (NHS EED), HTA] and Office of Health Economics Health Economic Evaluation Database (OHE HEED). No language restriction was imposed. The inclusion criteria for formal review required that the paper present cost-effectiveness estimates based on original data or economic analyses.

Review papers were checked to see whether they referenced any relevant studies not identified in the primary searches. Given the desire to restrict review to papers informed directly or indirectly by the RCT evidence, the search included papers with publication dates of 1996–2002. (A subsequent updating check in July 2003 was undertaken but revealed no further relevant cost-effectiveness studies.)

The characteristics of the MEDLINE search are summarised in Appendix 4. This search was adapted to the requirements of the other databases searched, with a tendency in these smaller but potentially relevant databases to use terms that were more, rather than less, inclusive.

Search results

The MEDLINE search identified 133 possible papers that were reviewed on the basis of titles and abstracts and, where judged necessary because of inadequate abstracts, full papers were obtained.

Nine papers relating to eight separate studies met the inclusion criteria for full review, all of which

TABLE 12 *Wever and colleagues (1996)*[49]

Wever *et al*. (1996) Cost-effectiveness of the implantable defibrillator as first-choice therapy versus electrophysiologically guided, tiered strategy in post infarct sudden death survivors: a randomised study				
Intervention	Early implantation of ICD			
Comparator	Tiered EP-guided strategy of AAD therapy followed, where necessary and appropriate, by catheter ablation, map-guided surgery and possible late use of ICD			
Source of evidence	RCT (n = 60) for survival and costs, undertaken in two centres in The Netherlands recruiting patients between 1989 and 1993			
Inclusion criteria	Postinfarct survivors of cardiac arrest caused by VT or VF			
Measure of effect	Mean survival time (all-cause mortality)			
Measure of costs	Median health system costs based on billing rates. Uses three alternative cost bases for units of resource (1990, 1992 and 1993) expressed in US dollars			
Period	Median follow-up of 729 days (range 3–1675 days); crude adjustment for censoring; no discounting			
Main results		*Early ICD (n = 29)*	*EP-guided therapy (n = 31)*	*Difference*
	Median cost per patient (1993 price basis) ($)	49,300	50,200	–900
	Mean survival (days)	871	676	195
	Cost per LYG	Early ICD dominates		

were published in English. The searches of the other databases identified a small number of other possible studies, but none met the inclusion criteria of presenting original data and/or formal analysis. Similarly, the check on references from other reviews did not yield any additional studies.

Key information for each of these eight studies has been extracted and is summarised in *Tables 12–20*. A brief interpretive commentary on each is provided below. The first five studies all relate to the use of ICDS in secondary prevention, two further studies relate to primary prevention and the final study covers both.

Studies of cost-effectiveness in secondary prevention

Wever and colleagues, (1996)[49] (*Table 12*)

This was the first study to be published based on patient-specific data from a randomised trial. The comparator in this trial in high-risk patients was a very active intervention in which five of 31 patients received VT surgery and 16 received a late ICD. However, the total sample size of 60 is too small to provide a firm basis for any conclusions, and the study is presented with no indication of the confidence intervals around parameters or of the uncertainty around conclusions. The analytical methodology is not consistent with current accepted standards; for example, use of median costs. It is the only study reviewed here to conclude that ICD therapy is dominant (both more effective and less costly) for the whole patient group considered. This may be an accurate reflection of the true cost-effectiveness of ICD compared with an active comparator regimen in high-risk patients, but given the various reservations the study conclusions need to be treated with considerable caution.

Owens and colleagues, (1997)[50] (*Table 13*)

This study used a complex Markov model. It populated that model with data from a variety of sources, but despite referring to Wever and colleagues[49] it does not appear to use any data from that trial and the other randomised trials were not reported. It gives a useful indication of the possible effect of adjusting from the utility of life of the patient group as a whole (assumed to be around 0.75), but for its base case assumed that there was no difference in utility for patients while 'well' on amiodarone compared with 'well' on ICD. Reflecting the uncertainty, in the absence of strong trial data, the model used two alternative assumptions for the effectiveness of ICDs compared with amiodarone: assumptions of a 20% or 40% RRR in all-cause mortality.

O'Brien and colleagues, (2001)[51] and Sheldon and colleagues, (2001)[52] (*Tables 14* and *15*)

These papers report the results of an economic substudy conducted as part of CIDS. Resource-use data were collected for the first 430 patients of the

TABLE 13 *Owens and colleagues (1997)*[50]

Owens *et al*. (1997) Cost-effectiveness of the implantable cardioverter defibrillators relative to amiodarone for prevention of sudden cardiac death				
Intervention	Third generation ICD only			
Comparators	(a) Amiodarone only; (b) amiodarone crossing to ICD if subsequently at higher risk			
Source of evidence	Complex Markov model, with 1-month cycle, using data from a wide variety of sources including CASH and MADIT RCTs. States included VT, VF, neurological impairment, amiodarone toxicity etc. Key assumption of a constant 20% reduction in RR of all-cause mortality for ICD vs amiodarone only. Used unpublished data on utilities and assumed them equal (0.75) in both arms			
Inclusion criteria	Base case evaluated a 57-year-old patient who had survived previous cardiac arrest (high risk)			
Measure of effect	Life-years and QALYs (all causes of mortality); utility adjustments for baseline, amiodarone, ICD, neurological impairment and temporary events			
Measure of costs	Direct cost of medical care associated with treatment for arrhythmia and sequelae. Expressed as 1995 US dollars			
Period	Lifetime, discounted at 3%			
Base-case results		*ICD only*	*Amiodarone to ICD*	*Amiodarone only*
	Mean cost per patient ($)	88,400	38,600	51,000
	Mean survival (years)	5.64	4.99	4.95
	Mean QALYs	4.18	3.71	3.68
	Cost per LYG ($)	(ICD only compared with amiodarone only) 54,000		
	Cost per QALY gained ($)	(ICD only compared with amiodarone only) 74,400		
Sensitivity analyses	Different underlying relative mortality risk reduction from ICD; intermediate-risk patients			

TABLE 14 *O'Brien and colleagues (2001)*[51]

O'Brien *et al*. (2001).[50] Cost-effectiveness of the implantable cardioverter-defibrillator. Results from the Canadian Implantable Defibrillator Study (CIDS)				
Intervention	ICD implantation (principally transvenous)			
Comparator	Medical management with amiodarone			
Source of evidence	CIDS RCT (n = 659) data for both effects and costs, but resource-use data were derived only from the first 430 (65%) patients enrolled. RCT undertaken in Canada enrolling between 1990 and 1997			
Inclusion criteria	Patients with resuscitated VF or VT, or with unmonitored syncope			
Measure of effect	Mean survival time (all-cause mortality): annual risk of death with ICD –8.3% vs 10.2% with amiodarone (p = 0.14); no adjustment for HRQoL			
Measure of costs	Healthcare payer perspective, based on patient-specific data on hospital LOS (ward and intensive care); ICD implants and generator replacements; cardiac surgical procedures; major and outpatient diagnostic procedures; outpatient physician visits. Unit costs relevant to Ontario and reported in 1999 Canadian dollars			
Period	(a) Fixed period of 6.3 years from randomisation to last observed death in either group, with censoring allowed for in measure of both effect and costs. (b) Additional modelling to 12 years with three different survival assumptions			
Main results		*ICD (n = 212)*	*Amiodarone (n = 218)*	*Difference (95% CI)*
	Mean cost per patient ($)	87,715	38,600	49,115 (25,502 to 69,508)
	Mean survival (years)	4.58	4.35	0.23 (–0.09 to 0.55)
	Cost per LYG ($)			213,543 (88,187 to dominated)
Subgroup analyses	LVEF < 35%: cost per LYG ($) 108,484 LVEF ≥ 35%: cost per LYG ($) Amiodarone dominant			
Extrapolation	To 12 years assuming:			Cost per LYG ($)
	survival curves diverge			99,420
	survival curves parallel			118,668
	survival curves converge			149,710
Sensitivity analyses	Cost of ICD, length of initial inpatient stay, discount rate			

TABLE 15 *Sheldon and colleagues (2001)*[52]

Sheldon *et al*. (2001) Effect of clinical risk stratification on cost-effectiveness of the implantable cardioverter-defibrillator. The Canadian Implantable Defibrillator Study		
Study details	As in *Table 14*	
Further subgroup analyses	Based on risk factors of age ≥ 70 years, LVEF ≤ 35% and NYHA functional class III	
		Cost per LYG ($) (95% CI)
	0 risk factors	Dominated by amiodarone ($488,138 to dominated)
	1 risk factor	$238,388 ($75,825 to dominated)
	2 risk factors	$96,718 ($41,456 to dominated)
	3 risk factors	$23,344 ($6,345 to dominated)
Extrapolation	To 12 years with three alternative assumptions concerning long-term benefit	
Sensitivity analysis	One-way sensitivity analysis to main parameters	

659 enrolled into CIDS. Effectiveness data used in the analysis were for all patients. The analysis based on trial data was for a fixed period of 6.3 years and in addition there were extrapolations to 12 years. The analytical methods were sound. The analysis illustrates well the wide confidence intervals around the estimates of gain in life expectancy and additional costs and hence in the cost-effectiveness ratio. The main analysis, and the additional paper extending the analysis on risk stratification, showed the large differences in mean cost-effectiveness (but with very wide confidence intervals) between groups varying in terms of their clinical risk. For patients with LVEF of 35% and above amiodarone was dominant, but for patients with three risk factors (aged ≥ 70 years, LVEF ≤ 35% and NYHA class III) the cost-effectiveness was very attractive. These differentials reflect considerable variation in net survival between the groups, but very little difference in net costs. The overall cost-effectiveness ratio for the CIDS study reflects that the majority of patients had only one or none of these risk factors.

Larsen and colleagues, (2001)[53] (*Table 16*)

This paper reports the results of the cost effectiveness analysis undertaken as part of the US AVID trial. Data on principal resource use items were collected for 1008 out of the 1016 patients randomised in this trial, and supplemented by more detailed cost data collection on a (non-random) subset of 237 patients. Base-case analysis was for a fixed period of 3 years from randomisation with extrapolation using combined survival data from AVID, CIDS and CASH to 6 years, 20 years and lifetime. The analytical methods were sound. Like the CIDS cost-effectiveness analysis it showed substantial differences in the cost-effectiveness ratio by individual risk factors, particularly baseline LVEF. However, again the study was not powered for subgroup analysis.

Weiss and colleagues, (2002)[54] (*Table 17*)

This is the only study of the eight that derived entirely from a single non-trial observational database. It used Medicare data and matched ICD recipients to 'comparable' non-recipients using propensity scoring. The survival and cost data were for 8 years of follow-up, although only inpatient costs were recorded. This analysis of large-scale observational data appears to have used sound methods (although these can never totally remove concerns about possible differences between the non-randomised groups). These data showed that the survival advantage to defibrillator recipients narrowed substantially between 3 and 8 years, while the cost difference increased over time. However, the analysis provides no confidence intervals around these estimates at 8 years.

Cost-effectiveness studies of primary prevention

Mushlin and colleagues, (1998)[55] (*Table 18*)

This paper reports the cost-effectiveness analysis undertaken as part of the MADIT study. Comprehensive resource-use data were collected principally using billing data for all US patients (181/196), although data were missing for small proportions of patients for specific aspects of resource use. The analytical methods were sound. The resulting cost-effectiveness ratio of $27,000 per LYG was better than that from the later major secondary prevention trials (CIDS and AVID). They suggest that the results would extrapolate to a mean cost per LYG of $16,900 at 8 years.

TABLE 16 *Larsen and colleagues (2002)*[53]

Larsen *et al*. (2002) Cost-effectiveness of the implantable cardioverter-defibrillator versus antiarrhythmic drugs in survivors of serious ventricular tachyarrhythmias. Results of the Antiarrhythmics Versus Implantable Defibrillators (AVID) Economic Analysis Substudy				
Intervention	State-of-the-art ICD implantation; 93% using non-thoracotomy lead system			
Comparator	AAD treatment with amiodarone or sotalol			
Source of evidence	AVID RCT data (n = 1013) for survival and (n = 1008) for main elements of cost. More detailed cost information from 237 patients. RCT undertaken in the USA, enrolling between 1993 and 1997			
Inclusion criteria	Patients who either had been resuscitated from cardiac arrest or had experienced sustained VT and had an LVEF ≤ 40			
Measure of effect	Mean survival time (all-cause mortality)			
Measure of costs	Healthcare system costs (irrespective of payer) based on 1997 US dollars			
Period	(a) Fixed period of 3.0 years from randomisation, with adjustment for censoring and discounting at 3.0% in measure of both effects and costs. (b) Additional modelling to 6 years (based on combined survival data from AVID, CIDS and CASH) and to 20 years and lifetime			
Main results		*ICD (n = 505)*	*Amiodarone (n = 503)*	*Difference (95% CI)*
	Mean cost per patient ($)	85,522	71,421	14,101
	Mean survival (years)	2.48	2.27	0.21
	Cost per LYG ($)			66,677 (30,761 to 154,768)
Subgroup analyses	VF vs VT; LVEF: £35% vs >35%; age: 60–69 vs ≥ 70 years; CAD vs other cause			
Extrapolation		Cost per LYG ($)		
	6 years	79,291		
	20 years	68,378 (survival curves parallel after 6 years) 80,358 (survival curves converge; Weibull extrapolation)		
	Lifetime	67,131 (survival curves parallel after 6 years) 211,128 (survival curves converge; Weibull extrapolation)		
CAD, coronary artery disease.				

TABLE 17 *Weiss and colleagues (2002)*[54]

Weiss *et al*. (2002) Effectiveness and cost-effectiveness of implantable cardioverter defibrillators in the treatment of ventricular arrhythmias among Medicare beneficiaries				
Intervention	Implantation of ICD			
Comparator	Patients not receiving ICD			
Source of evidence	Analysis of unselected population (n = 125,892) of Medicare beneficiaries analysed using multivariable propensity score to match pairs of patients, one who reserved ICD and the other who did not (n = 7612 pairs)			
Inclusion criteria	Patients aged 65 or over, discharged between 1989 and 1995 after hospitalisation with primary diagnosis of VT or VF			
Measure of effect	Mean survival (all-cause mortality)			
Measure of costs	Medicare costs for all hospital admissions based on DRGs expressed as 1999 US dollars			
Period	8-year follow-up; costs and survival discounted at 3%			
Main results		*ICD (n = 7612)*	*Other (n = 7612)*	*Difference (95% CI)*
	Mean cost per patient ($)	78,700	37,200	41,500
	Mean survival (years)	4.6	4.1	0.5
	Cost per LYG ($)			78,400
DRG, diagnostic resource group.				

TABLE 18 *Mushlin and colleagues (1998)*[55]

Mushlin *et al*. (1998) The cost-effectiveness of automatic implantable cardiac defibrillators: results from MADIT				
Intervention	FDA-approved ICDs; initially transthoracic and subsequently non-thoracotomy implantation, plus conventional AAD treatment			
Comparator	A variety of conventional AAD treatments.			
Source of evidence	MADIT RCT data (n = 196). RCT undertaken principally in the USA (36 of 38 centres), enrolling patients between 1990 and 1996. Cost-effectiveness analysis based on 181 US patients			
Inclusion criteria	Patients with asymptomatic non-sustained VT, a prior MI, LVEF £35% and an inducible ventricular tachycardia at EP not suppressed by procainamide			
Measure of effect	Mean survival (all-cause mortality)			
Measure of costs	Health system costs (irrespective of payer) based on adjusted charges and Medicare rates. Expressed as 1995 US dollars			
Period	4-year period allowing for censoring and discounting at 3%			
Main results		*ICD (n = 89)*	*Amiodarone (n = 92)*	*Difference (95% CI)*
	Mean cost per patient ($)	97,560	75,980	21,580 (1,000 to 43,100)
	Mean survival (years)	3.46	2.66	0.80 (0.41 to 1.22)
	Cost per LYG ($)			27,000 (200 to 68,200)
Extrapolation	To 8 years (assuming Weibull extrapolation)		Cost per LYG ($) 16,900	
Sensitivity analyses	Technology changes; methodological change			

(However, the bootstrapped 95% CI of $200 to 68,200 per year is again very wide.)

Sanders and colleagues, (2001)[56] (*Table 19*)

This paper, from the same research group as Owens and colleagues (1997),[50] used a modified version of that earlier Markov model to assess cost-effectiveness in primary prevention in patients who have had an MI. It used a range of possible efficacies for the reduction of SCDs from ICDs and registry data from the USA. The analysis shows that depending upon the efficacy assumption, the use of ICDs in patients with past MI may be cost-effective if they have severely depressed LVEF, but is unlikely to be cost-effective in patients with higher LVEF values.

Modelling of cost-effectiveness in relation to risk for both primary and secondary prevention

Owens and colleagues, (2002)[57] (*Table 20*)

This paper developed the models used by Owens and colleagues (1997)[50] and Sanders and colleagues, (2001)[56] to explore whether risk stratification can be based on the risk of SCD. It demonstrated that the cost-effectiveness of ICDs relative to amiodarone depends on total cardiac risk as well as the ratio of SCD to non-SCD. For any level of overall cardiac mortality risk, cost-effectiveness is best when the ratio of SCD to non-SCD is high.

Comparison of studies

The main characteristics of the studies are summarised in *Table 21*. A wide range of factors makes direct comparison difficult. To ease comparison, particularly with the data and modelling for the UK presented in subsequent chapters, price conversion factors were estimated for each study to convert the cost data into UK pounds at 2001/02 prices (*Table 22*) and a summary of the main results from the studies converted to this common price basis is shown in *Table 23*.

However, the studies also assess cost-effectiveness over different periods. An important conclusion is that not only do the studies differ in their estimates for any specific period, but they are not consistent in terms of their estimated trends in cost-effectiveness as the time-horizon is increased.

TABLE 19 *Sanders and colleagues (2001)*[56]

Sanders *et al*. (2001) Potential cost-effectiveness of prophylactic use of the implantable cardioverter defibrillator or amiodarone after myocardial Infarction

Intervention	Prophylactic implantation of ICD
Comparators	(a) Amiodarone; (b) no AAD treatment
Source of evidence	Markov model: survival and inpatient costs from patient registry relating to hospitals in Seattle, Washington, USA; other data from a variety of sources. Utilities assumed to be equal (0.88) for both arms
Inclusion criteria	Patients admitted to cardiac care unit with MI but without symptomatic sustained ventricular arrhythmia; data for 1988–1994
Measure of effect	Mean survival (all-cause mortality), mean QALYs
Measure of costs	Direct health system costs (medical care associated with inpatient and outpatient treatment) and costs of patient travel and inconvenience (detail unspecified). Expressed as 1999 US dollars
Period	Lifetime; costs and effects discounted at 3%
Main results	Analysed for three levels of LVEF and assuming three levels of ICD efficacy

LVEF cohort	ICD vs no antiarrhythmic treatment		ICD vs amiodarone	
	Cost per LYG ($)	Cost per QALY ($)	Cost per LYG ($)	Cost per QALY ($)
≤ 0.3				
Low efficacy	78,000	88,600	64,900	73,700
Moderate efficacy	52,700	59,800	63,300	71,800
High efficacy	40,600	46,100	63,300	71,700
0.31–0.4				
Low efficacy	164,000	186,300	113,200	128,100
Moderate efficacy	102,800	116,800	173,400	195,700
High efficacy	75,600	85,900	463,800	517,100
>0.4				
Low efficacy	421,700	479,200	183,000	206,400
Moderate efficacy	227,800	258,800	501,500	557,900
High efficacy	157,200	178,600	Dominated	Dominated

TABLE 20 *Owens and colleagues (2002)*[57]

Owens *et al*. (2002) Effect of risk stratification on cost-effectiveness of the implantable cardioverter defibrillator

Intervention	ICD implantation
Comparator	Empiric amiodarone treatment
Source of evidence	Markov model structure as used in Owens *et al*. (1997):[50] various sources of data inputs including trials, utility data from unpublished study assuming HRQoL better with ICD than with amiodarone (0.83 vs 0.80). NB. Parameter values and assumptions differ from Owens *et al*. (1997)[50]
Inclusion criteria	Patient cohorts characterised in terms of their risk of SCD and non-SCDs (2–30% in each case)
Measure of effect	Mean QALYs
Measure of costs	Direct costs of medical care associated with treatment and any complication. Expressed as 1999 US dollars
Period	Lifetime (up to a maximum of 40 years); costs and effects discounted at 3%
Main results	Cost per QALY ($)

	Annual SCD mortality (%)		
Annual non-SCD mortality (%)	2	8	20
2	102,600	37,900	29,900
8	123,400	53,000	39,200
20	180,600	98,400	670,000

TABLE 21 *Comparison of cost-effectiveness studies in secondary prevention*

Economic study no	Study	SP/PP	Principal source of data	Method of implantation	Comparator	Time horizon (discount rate)	Country	Life expectancy (years)		
								ICD	Drug	Difference
1	Wever *et al.*, 1996[49]	SP	Trial	Transthoracic	EP-guided drug therapy	Median 2 years (0%)	Netherlands	2.41	1.99	0.42
2	Owens *et al.*, 1997[50]	SP	Registry	Transthoracic	Amiodarone	Lifetime (3%)	USA	5.64	4.95	0.69
3	O'Brien *et al.*, 2001[51]	SP	CIDS	Transthoracic and transvenous	Amiodarone	6 years (3%)	Canada	4.58	4.35	0.23
4	Larsen *et al.*, 2002[53]	SP	AVID	Transthoracic and transvenous	Amiodarone	3 years (3%)	USA	2.48	2.27	0.21
5	Weiss *et al.*, 2002[54]	SP	Medicare database	Not stated	Usual drug therapy	8 years (3%)	USA	4.6	4.1	0.5
6	Mushlin *et al.*, 1998[55]	PP	MADIT	Transthoracic and transvenous	Conventional therapy (mainly amiodarone)	4 years (3%)	USA	3.46	2.66	0.8
7	Sanders *et al.*, 2001[56]	PP	Patient registry and various trials	Transvenous	Amiodarone	Lifetime (3%)	USA	8.94	8.74	0.2
8	Owens *et al.*, 2002[57]	SP/PP	Various, including meta-analysis of trials	Transvenous?	Amiodarone	Lifetime (3%)	USA	–	–	–

PP, primary prevention; SP, secondary prevention.

TABLE 22 *Conversion factors[a] for costs as expressed in economic studies to UK pounds (2001/02) as used in Chapters 7 and 8*

Study[b]	Original basis	Conversion factor
1	1993 US$	0.49
2 and 6	1995 US$	0.53
3	1999 Canadian $	0.51
4	1997 US$	0.54
5, 7 and 8	1999 US$	0.58

[a] Factors derived by converting to approximate contemporaneous UK prices using gross domestic product (GDP) purchasing power parity (PPP) exchange rate factors (OECD: http://www.oecd.org/std/ppp), and then inflating to 2001/02 using the Hospital and Community Health Services Pay and Prices Index (as reproduced in Curtis and Netten[58]).
[b] Economic study numbers (see *Table 21*).

TABLE 23 *Summary of main results from cost-effectiveness and cost–utility studies*

Key results		ICER as published (currency unit)	ICER in UK£ (2001/02 prices)
Wever *et al.*, 1996[49]		Early ICD dominates	
Owens *et al.*, 1997[50]			
ICD compared with amiodarone only			
High-risk patients			
Cost per LYG	40% RRR	27,300	14,500
Cost per QALY	40% RRR	37,300	19,800
Cost per LYG	20% RRR	54,000	28,600
Cost per QALY	20% RRR	74,400	39,400
Intermediate-risk patients			
Cost per LYG	40% RRR	26,700	14,200
Cost per QALY	40% RRR	36,300	19,200
Cost per LYG	20% RRR	56,000	29,700
Cost per QALY	20% RRR	76,800	40,700
O'Brien *et al.*, 2001[51]			
Trial data to 6 years			
Base case		213,500	108,900
LVEF < 35%: cost per LYG		108,500	55,300
LVEF ≥ 35% : cost per LYG		Amiodarone dominates	
Extrapolation to 12 years			
Benefit continues: cost per LYG		99,400	50,700
Benefit equivalent: cost per LYG		118,700	60,500
Benefit declines: cost per LYG		149,700	76,300
Sheldon *et al.*, 2001[52]			
Cost per LYG (to 6 years)			
0 risk factors		Amiodarone dominates	
1 risk factor		238,400	121,600
2 risk factors		96,700	49,300
3 risk factors		23,300	11,900
Larsen *et al.*, 2002[53]			
Cost per LYG (to 3 years)			
All		66,700	36,000
LVEF £ 35%		60,900	32,900
LVEF > 35%		536,100	289,500
Extrapolations			
6 years		79,300	42,800
20 years: High		68,400	36,900
Low		80,400	43,400
Lifetime: High		67,100	36,200
Low		211,100	114,000
Weiss *et al.*, 2002[54]			
Cost per LYG			
Over 3 years		133,500	77,400
Over 8 years		78,400	45,500
Mushlin *et al.*, 1998[55]			
Within trial (4 years)			
Cost per LYG		27,000	14,300
Extrapolated (8 years)			
Cost per LYG		16,900	9,000
Sanders *et al.*, 2001[56]			
LVEF ≤ 0.30			
Cost per LYG		63,300	36,700
Cost per QALY		71,800	41,600
LVEF > 0.4			
Cost per LYG		501,500	290,900
Cost per QALY		557,900	323,600

ICER, incremental cost-effectiveness ratio.

In particular, the cost-effectiveness analysis based on CIDS assumes that cost effectiveness improves substantially between 6 and 12 years, while the AVID analysis shows deterioration between 3 and 6 years and then little change between 6 and 20 years. The estimates emphasise the uncertainty involved in extrapolating beyond 20 years: the AVID analysis reflects this by estimating the lifetime ICER as $36,200 or $114,000, depending on which of two plausible assumptions is made about the long-term survival hazard function.

Conclusions from the review

Addressing the specific questions raised at the beginning of this chapter:

1. From the existing studies it is not possible to provide a robust estimate of long-term cost effectiveness of ICDs compared with amiodarone. For all but the highest risk patients ICDs are likely to be more expensive, but to offer a degree of benefit. The cost-effectiveness studies based on CIDS, AVID and MADIT provide the best analysis of short-term cost-effectiveness for their respective trial populations, given the technology used in North America during the early 1990s. The modelling studies (and to a large extent the extrapolations provided in the CIDS and AVID trial-based analyses) provide useful indications of possible longer term scenarios, but these scenarios are not evidence based and cost-effectiveness ratios are very sensitive to their assumptions. The analysis based on Medicare data provides a useful confirmation of (past) cost-effectiveness to 8 years. Together, they suggest mean cost-effectiveness in secondary prevention at 8–12 years for their populations, which are very heterogeneous in terms of risk, of between £40,000 and £80,000 per LYG. For primary prevention the economic evidence, although more limited, suggests that over 8 years the ICER might be as low as £8,000.

   Estimates of cost per QALY are likely generally to be higher (by perhaps one-third), reflecting the baseline utility value of these patients, irrespective of therapy. The picture would be different if there was clear evidence of a 'routine' difference in HRQoL between ICD and amiodarone patients, but there is no good evidence for this difference.
2. The key parameters appear to be the difference in relative risk of SCD between ICD and amiodarone therapy and the relative risk of SCD and non-SCD in the population, rather than whether it is in the context of primary or secondary prevention. The studies show effectiveness to be dependent on risk factors, whereas costs do not seem to vary consistently with risk. The other important parameter is the period considered, but because of the lack of observed data on long-term effects and costs the long-term picture is unclear.
3. Cost-effectiveness clearly varies substantially by preidentifiable risk factors, particularly LVEF, and probably by age and NYHA classification. (Effects differ and costs do not.) The key issue is the underlying risk of SCD relative to the risk of non-SCD. Differences in results between studies may depend in part on the risk profiles of the populations included. The a priori 'perverse' finding of good cost-effectiveness in primary prevention (in the MADIT-based analysis) reflects the relatively high mortality benefit observed in MADIT, in which the patients were at high risk of SCD.
4. None of the reviewed studies was based on UK data, nor did any attempt to estimate the position in the UK. The AVID and CIDS trials, however, give sufficient information on the pattern of resource use related to clinical practice (e.g. on length of stay for ICD implantation) potentially to adjust the costs to reflect UK practice.

Chapter 4

Assessment of current service for the provision of implantable cardioverter defibrillators in the UK

Introduction

The rate of implantation in the UK is lower than in many other European countries and substantially lower than in North America. Before their dissolution in 2002, most health authorities were commissioning approximately ten new ICD implantations per million population. NICE issued guidance on the use of ICDs in the management of arrhythmias in 2000 for use by commissioning and providing authorities, which is in the public domain for use by the public and patients. There is a national directive to implement this guidance. NICE estimated that following the issuing of its guidance, the level of ICD implantation should rise to 50 devices implanted per million at an estimated cost of £45 million. The derivation of these estimates is not transparent and it is unclear whether they include any additional staffing or service configuration costs, although mention is made of the need for the NHS to consider these.

Establishing a baseline of the current service provides an essential step in monitoring the diffusion of the guidance. To provide such a baseline and to determine the current service activity and configuration, an analysis of the ICD service in the UK was conducted using national routine information sources and a postal questionnaire survey. It assessed the number of ICDs being implanted, the demographics of those people receiving ICDs and the geographical location of implanting centres in the UK. It also conducted equity analyses to assess whether those people with potentially most need for ICD therapy are receiving this treatment.

Aim and objectives

The overall aim was to assess the current use of ICDs in the UK. Specific objectives were:

- to determine the implantation rates in the UK over the past 10 years
- to determine the characteristics of patients receiving ICDs in the UK
- to determine the survival of patients receiving ICDs in the UK
- to determine how the current use of ICDs is related to need by deriving age–gender-standardised rates of ICD implantation and assessing use against proxy measures for need.

A multisource approach was used, which included six distinct methods.

Methods for assessing ICD service in the UK

Derivation of implantation rates and patient characteristics using a national data set

There is a national UK database of pacing and ICD implantations held on behalf of the Medical Devices Agency by the British Pacing and Electrophysiology Group (BPEG), which has been collecting information for over 12 years. Data are collected from each implanting centre using standard forms for each ICD recipient in the NHS and in private providers. These data are collated and analysed by the database management team, and include demographic details, indications for use (such as syncope and palpitations, and whether for primary or secondary prevention), first implantation or reimplantation and outcomes including complications and mortality. Collaboration between this study and the BPEG database was established, and a specification of data required to perform the national evaluation of current provision of ICDs was agreed with the BPEG database management team. Centre-specific implantation information was not made available as this was felt to be confidential. The routine data are approximately 20% incomplete for ICD implantation (Cunningham D, BPEG database manager: personal communication, 2001) and recent work conducted by BPEG has produced a data set from 1998–2000 which was made more complete and 'cleaned'. This data set was used to estimate measures of equity of use. Information presented using this clean data set will be clearly marked. The routine database from BPEG contains information on the country of implantation, by the

(former) district health authority (DHA), and thus regional health authority (RHA), of implantation and by postcodes of recipients of ICDs.

One person (JP) checked through the clean data set 1998–2000. The data set contained a unique identification number, year of implantation, country of implantation, age and gender of the recipient, postcode, DHA code, date of implantation, whether the ICD was a dual-chamber device, underlying aetiology, presenting symptoms, whether the indication was primary or secondary, new/replacement ICD and date of death.

Age–gender indirectly standardised regional rates for England

Because the ICD implantations are predominantly done in men over the age of 55 years, analyses of regional rates need to take this into account. This has been done by indirect age–gender standardisation and deriving indirectly standardised rates of ICD implantation for regions and strategic health authorities (SHAs) in England. Regional rates were standardised to the population of England in 2000. The ICD rate for England was generated using the number of ICDs undertaken in England in 1998–2000 and 2000 estimates of the population of England from the Public Health Common Dataset (2000), and an average annual figure was derived. This rate was stratified by age group and gender. The expected rate for each region was generated by multiplying the English rate by the regional population for each specific age group and gender. The observed number of ICDs for region by age group and gender was also derived. The overall observed over expected ratio was then generated for each RHA and 95% confidence intervals were calculated.

Regional implanting incidence rates were compared with the numbers of implanting centres within each region in England.

Equity of use by ethnic groups

The prevalence of CHD in the Asian ethnic minority is higher than in the general population. By determining the proportion of ICD implantation in those patients with South Asian ethnic origins and comparing the use of ICDs with potential needs in this population, an estimate of the equity of access to this therapy by this population was derived. Nam Pechan Software was used to identify patients with South Asian origins. Ethnic-specific rates for ICD implantation were therefore generated. (Bradford Health Authority, Version 1, 1980).

Equity of use adjusted for need in England

Two proxies for need, CHD and deprivation, were used.

Ischaemic heart disease

As the underlying aetiology in the majority of patients sustaining SCD and being eligible for ICD therapy is ischaemic heart disease (IHD), a reasonable proxy indicator for need may be the standardised mortality rate (SMR) for IHD, which includes ICD-9 codes 410–414. This was derived from the Public Health Common Dataset 1997–1999 (all ages, pooled data for 1997–1999). This was compared with indirectly age–gender standardised RHA ICD use for men and women over 1998–2000. Use–need ratios were derived by comparing the SMR with the age–gender-standardised ICD use, where 1 represented a situation where use exactly matched the English standard of implantation, values above 1 represented use exceeding the standard for England and values below 1 represented use not reaching the standard for England.

Deprivation

Another proxy indicator for need that may be used is deprivation, as the most deprived part of the population has the highest prevalence of CHD and therefore may be most eligible for ICD therapy. Each postcode in the data set was linked to an enumeration district and ward using 1991 census data available from MIMAS (Manchester Information and Associated Services). The census data hold all enumeration districts in England and Wales in 1991, each of which has a Townsend deprivation score. The population was divided into equally sized quintiles based on the Townsend score; those wards with the lowest Townsend scores fell into the first quintile and those with the highest Townsend score (and most deprivation) fell into the fifth quintile. The expected values of ICDs were generated by dividing the number of ICDs in the whole data set (for those ICDs where a deprivation score could be allocated) by the 1991 census population for all wards. This was then multiplied by the population in each age group for men and for women. Observed values were numbers of ICDs by deprivation quintile.

Derivation of centre-specific information using a postal survey

A list of current centres that are implanting ICDs in the UK was obtained from the BPEG national database management team. In consultation with a cardiologist (AG), public health/epidemiologists (JP, DCh) and the national database manager, a

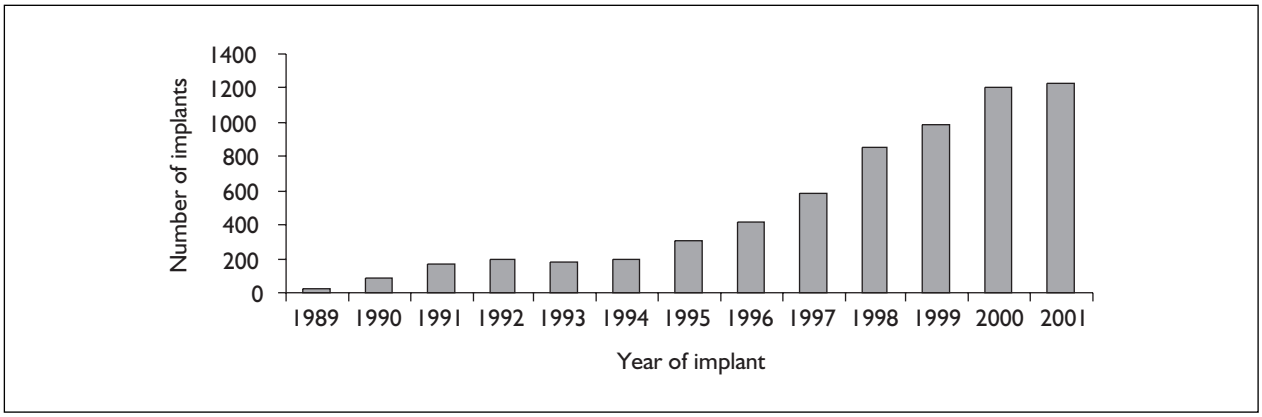

FIGURE 2 *Total number of ICD implants in the UK over time. Implants shown include new and replacement devices*

TABLE 24 *Summary of characteristics of the total numbers of ICD implantation by country*

	England		Wales		Scotland		Northern Ireland		Total
	New	Replacement	New	Replacement	New	Replacement	New	Replacement	
1998	573	128	6	3	58	13	21	6	658 (150)
1999	664	133	16	3	46	24	27	13	753 (173)
2000	767	131	21	2	67	22	55	3	910 (158)
Total	2004	392	43	8	171	59	103	22	2321 (481)
% Dual chamber	22		37		15		29		22
% Male	82		79		79		83		82 (median)

short questionnaire was prepared that aimed to ascertain the activity of the centre, the staff capacity of the centre, some information on clinical practice, perceived barriers and drivers to managing patients eligible for ICD therapy, and comments on future directions of practice in ICD therapy. (The questionnaire is reproduced as Appendix 5.) Questionnaires were sent out to a named consultant in each implanting centre. Non-responders were contacted via e-mail, fax and telephone, with repeat questionnaires sent out to maximise the response rate.

Comparative

UK ICD rates were compared with available ICD data for Europe and the USA.

Results

Current use and trends in ICD implantation in the UK

Location of implanting centres

There are 41 major implanting centres in the UK (1999), a number that has doubled since 1992. The survey indicates that more implanting centres are being planned throughout the UK, and that centres are at different stages of development and activity.

ICD implantation activity

The number of implants in the UK has been increasing over the past decade, but this rise has been much steeper over the past 4 years (49%) (*Figure 2*).

Most of the ICDs in the UK are implanted in males (82%), in centres in England (83%), and are dual chamber only in the minority of cases (22%) (*Table 24*).

The rate of implantation per million population in the UK has increased from 3.8 in 1995 to 20 in 2002 (*Table 25*). As the number of patients whose survival exceeds their device battery life increase, replacement costs become increasingly important and need to be considered in service planning.

Demography

The age of patients being implanted has increased since 1989, with the median age of first implantation over 1998–2000 being 62 years, and higher for men (62 years) than for women (57 years) (*Figure 3*)

Most ICDs are being implanted into men aged 45–75 years old, with women consistently having less than a quarter of the ICDs being implanted,

TABLE 25 *Implantation rate in the UK per million population*

Year	Total rate of implantation per million
1995	3.8
1996	4.8
1997	6.8
1998	11.0
1999	12.6
2000	15.2
2001	19.3
2002	20.9

BPEG data.

TABLE 26 *Underlying aetiology of patients receiving ICD therapy*

Aetiology	*n* (%)
MI and CHD	623 (57)
CHD	111 (10)
Cardiomyopathy	243 (22)
Other	236 (21.7)
Missing	1234
Total	2321

even though the prevalence of underlying aetiologies for SCD, such as CHD, increases after the menopause (*Figure 4*)

Over half of the patients (53%) in the 1998–2000 data set had no record of an underlying aetiology (*Table 26*).

Presenting symptoms were also recorded in the data set, with a similar percentage of missing data (48.5%). Of those records with data on presenting symptoms, most patients (36.9%) presented with a cardiac arrest, followed closely by syncope (34.8%) and dizzy spells. Of those recipients of new ICD implantations who had an indication for implantation recorded, 83% had secondary prevention indications and 17% had primary prevention indications.

Rates in particular populations

Crude numbers of implantations and rates by English region and SHA were derived. The analyses were conducted using the more complete 1998–2000 BPEG data set.

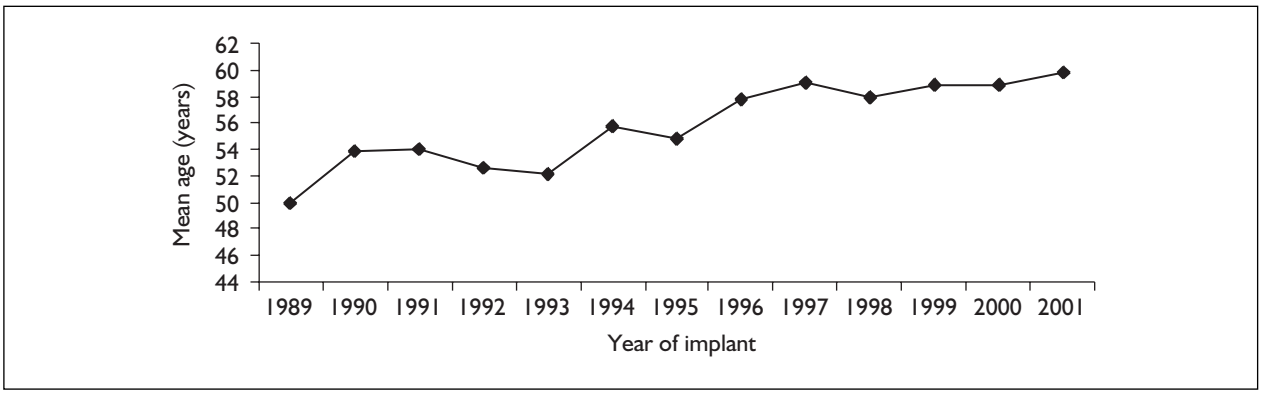

FIGURE 3 *Mean age at first ICD implant*

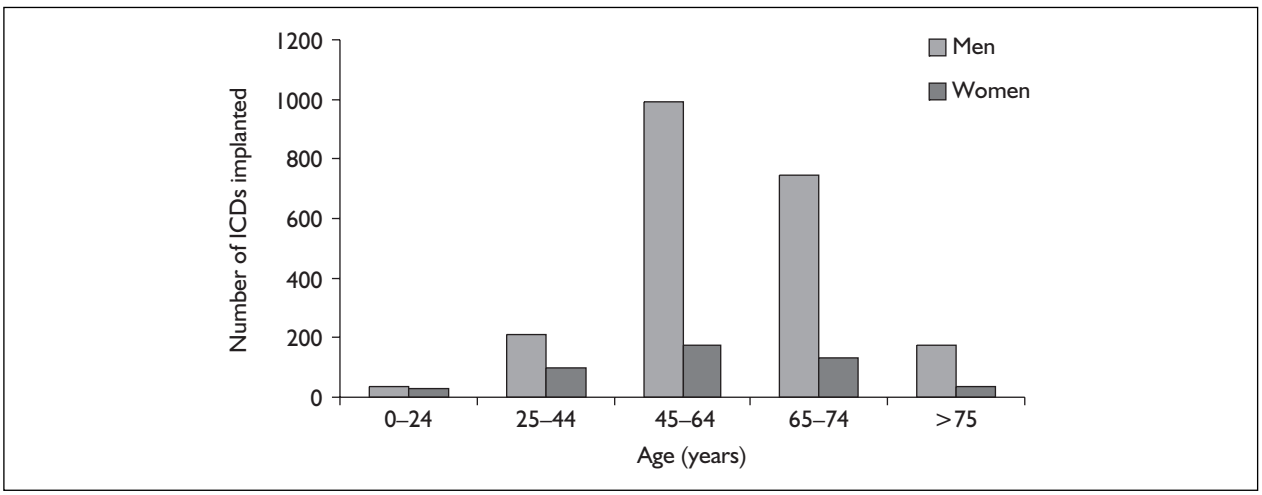

FIGURE 4 *New ICD implantation by age group and gender*

TABLE 27 *Analysis of new ICD implantations by UK country and English region (1998–2000)*

Region of implementation	No. of new ICDs per annum (mean)	Crude use per million per annum[a]	Age–gender-standardised rate (95% CI)[b]
England	668	13.7	1.11 (1.06 to 1.16)
Wales	17	5.8	0.39 (0.28 to 0.51)
Scotland	77	15.1	0.92 (0.80 to 1.07)
Northern Ireland	41	24.3	1.86 (0.53 to 2.26)
England health region			
Eastern	64	11.7	0.95 (0.82 to 1.09)
London	90	12.2	1.04 (0.92 to 1.18)
North West	68	10.2	0.86 (0.75 to 0.99)
Northern and Yorkshire	96	15.2	1.11 (0.98 to 1.26)
South East	132	15.1	1.02 (0.91 to 1.14)
South West	80	9.1	1.25 (1.10 to 1.42)
Trent	74	14.4	1.16 (1.02 to 1.33)
West Midlands	40	7.4	0.61 (0.51 to 0.73)

[a] Using data for which age and gender were available to allow for comparison with age-standardised rate.
[b] ICD rates by country were standardised against the UK population and English regional rates were standardised against the population of England.

Analysis by regional populations in England

Analyses were conducted on new insertions of ICDs, as those patients receiving replacement devices may have characteristics that differ from those receiving their first device and thus may introduce a bias.

Table 27 shows the average number of new ICDs undertaken per year within the 3-year period, the crude rate per million population and the age–gender-standardised ratio for the four UK countries and each English health region. The table shows there was intercountry variation, with Northern Ireland implanting most per million population of the countries of the UK (test for heterogeneity, $p = 0.005$), using the UK as a standard. However, data on country of implantation were derived from the location of the implanting centre and did not take account of cross-country flow, which may have contributed to the lower implantation rate in Wales. There was also significant variation between English health regions in the use of new ICDs (test for heterogeneity, $p = 0.005$). Two regions, the West Midlands and North West, had particularly low use of ICDs given their age–gender structures. There was no consistent geographical pattern at regional level. It is important to remember that the national ICD rate does not meet current need. This analysis simply records relative differences in use between regions using England as a standard. It should also be noted that age and gender information was not available for all cases and data from these cases were therefore not included in *Table 27*.

Figure 5 shows the age–gender-standardised regional rates for England. Two regions are implanting significantly below the average rate for England and three above. There is no consistent north-south divide.

Figure 6 shows that there may be a suggestion of a trend towards generally increasing implantation in the north and decreasing in the south. Caution should be exercised owing to the likelihood of noise in these figures. Trends in this time-frame will be sensitive to issues and changes in funding and staffing, and may not reflect need or demand.

Analysis by strategic health authority

Table 28 shows variation of implantation rates for SHA residents, with no obvious geographical pattern being apparent. There is a wide range of use of ICD, from 40 to 150 over the 3 years 1998–2000. Care should be taken in the interpretation of these results as total crude numbers do not take into account the age–gender distribution of SHA populations, making direct comparisons difficult. To take account of this, age–gender standardisations have been derived. However, crude use does give an indication of the volume of implantation work presently being conducted by SHAs in England.

Figure 7 shows the age–gender-standardised rates of ICD implantations by SHA in England. There was significant variation between SHAs in the use of new ICDs (test for heterogeneity, $p < 0.005$). The figure shows that compared with a standard for England (1.0), there are four SHAs implanting less

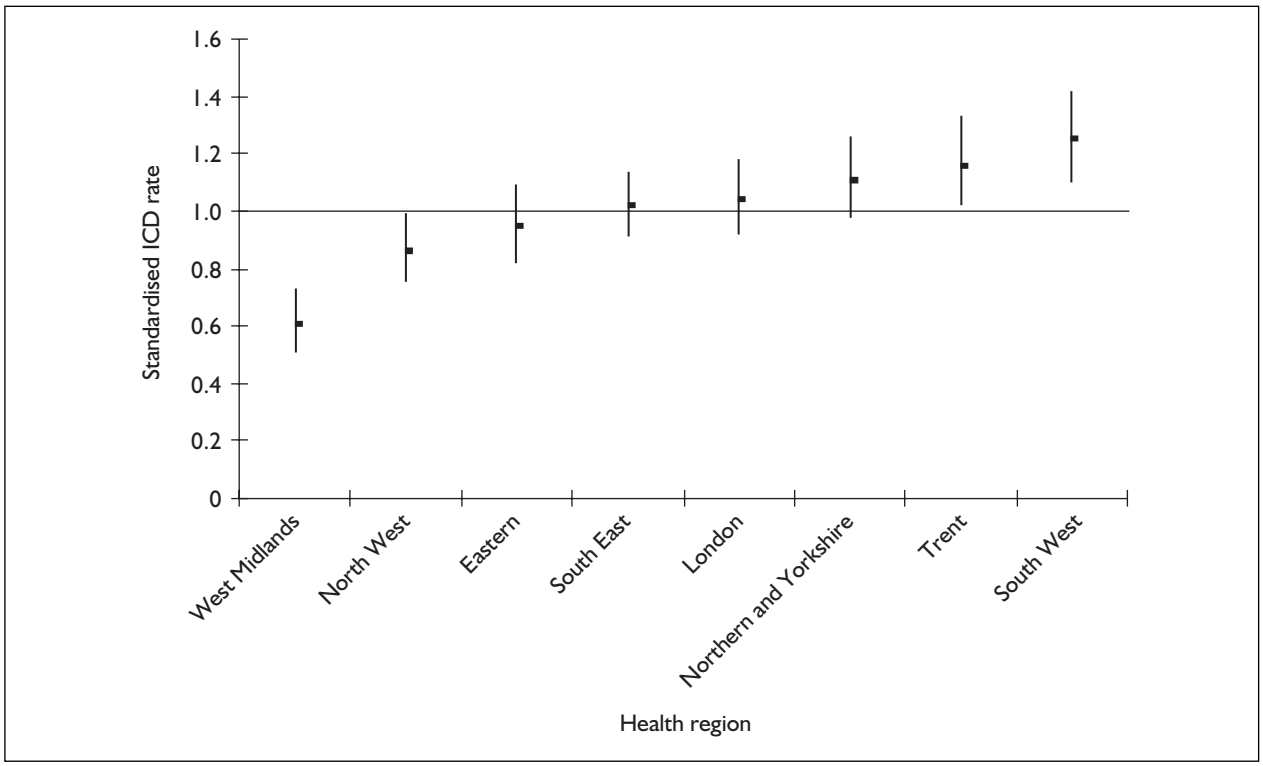

FIGURE 5 *Age–gender standardised ICD rates by English region*

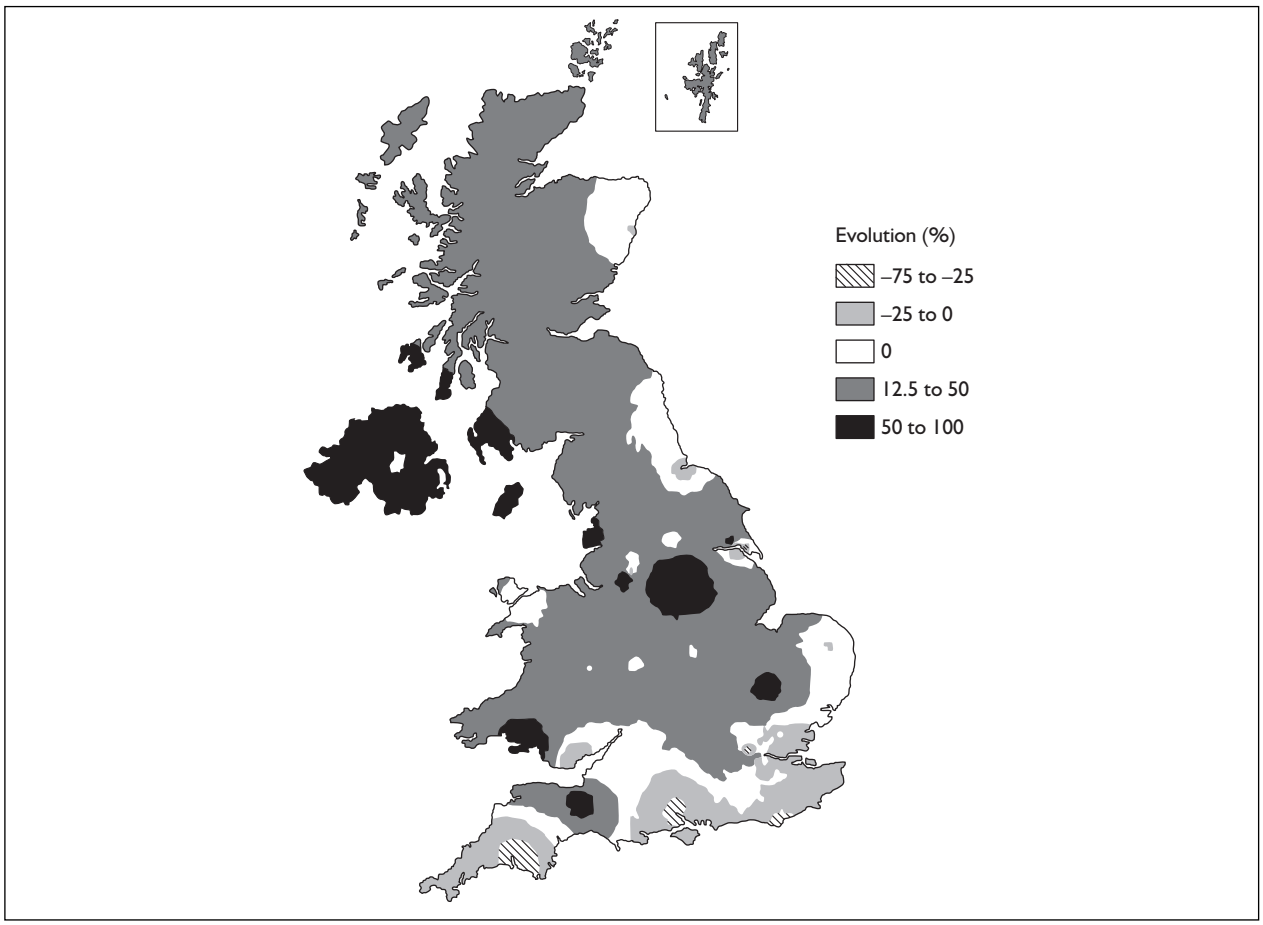

FIGURE 6 *Trend in implantation of ICDs in regions of the UK 1999–2000 (from BPEG)*

TABLE 28 *Current activity (crude numbers of ICD implantations) by English SHA (1998–2000)*

SHA	Replacement ICD	New ICD	Total	ICDs per million population per annum
Norfolk, Suffolk and Cambridgeshire	14	67	81	10.1
Bedfordshire and Hertfordshire	18	47	65	9.7
Essex	12	72	84	14.7
North West London	20	73	93	13.1
North Central London	10	38	48	10.4
North East London	17	52	69	11.8
South East London	6	54	60	12
South West London	13	43	56	10.8
Northumberland, Tyne & Wear	11	55	66	13
County Durham and Tees Valley	7	63	70	18.1
North and East Yorkshire and North Lincolnshire	31	89	120	18.1
West Yorkshire	13	93	106	14.6
Cumbria and Lancashire	10	61	71	10.6
Greater Manchester	14	47	61	5.7
Cheshire and Merseyside	12	104	116	14.5
Thames Valley	20	69	89	10.8
Hampshire and Isle of Wight	25	62	87	11.6
Kent and Medway	14	117	131	24.4
Surrey and Sussex	24	126	150	16.1
Avon, Gloucestershire and Wiltshire	17	82	99	12.5
South West Peninsula	13	73	86	15.3
Somerset and Dorset	6	86	92	24
South Yorkshire	1	40	41	10.2
Trent	19	110	129	14
Leicestershire, Northamptonshire and Rutland	11	84	95	17.9
Shropshire and Staffordshire	9	35	44	11.4
Birmingham and the Black Country	5	49	54	7
Coventry, Warwickshire and Worcestershire	4	36	40	7.9
Total	376	1927	2303	

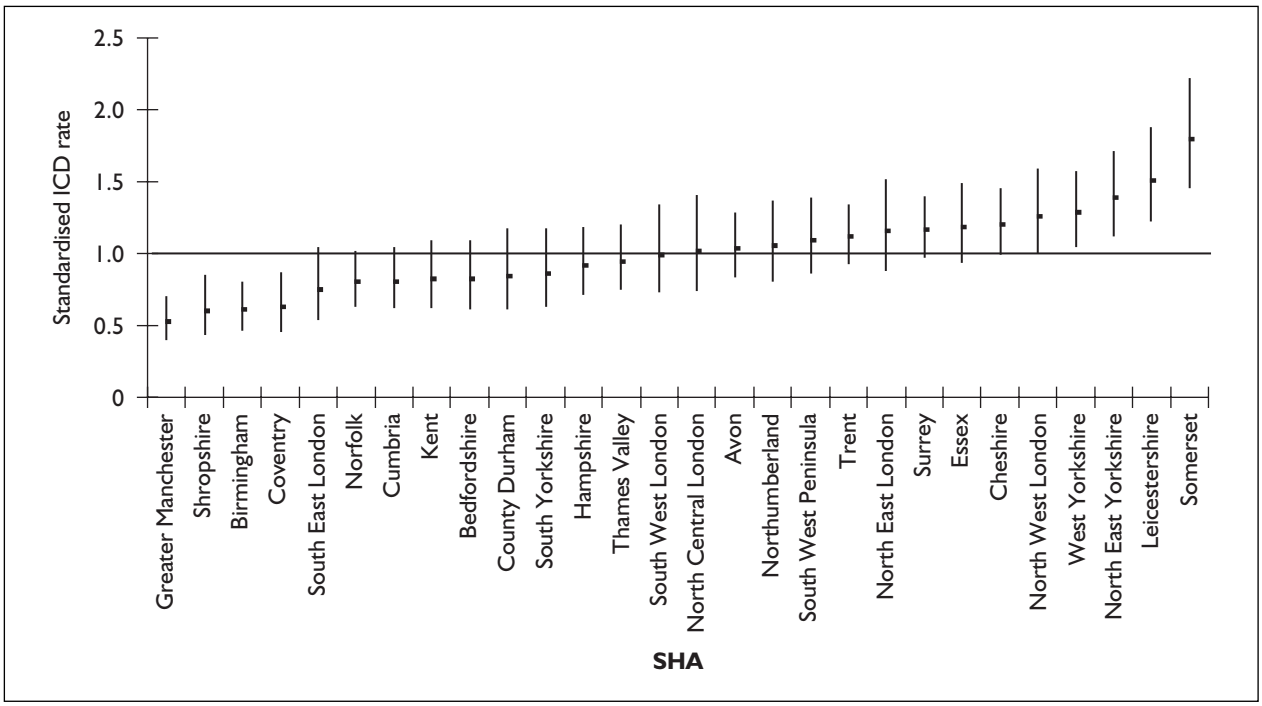

FIGURE 7 *Age–gender-standardised rates for ICD implantation by SHA. For full names of SHAs, see* Table 28.

TABLE 29 *Regional implanting rates by numbers of implanting centres*

Region	Age–gender-standardised use (95% CI)	No. of centres
Northern and Yorkshire	118 (105 to 134)	5
Trent	124 (109 to 141)	4
West Midlands	65 (54 to 78)	1
North West	91 (80 to 105)	5
Eastern	101 (87 to 116)	1
London	111 (97 to 126)	9
South East	108 (97 to 121)	4
South West	131 (115 to 149)	6

TABLE 30 *SHA implanting rates by numbers of implanting centres*

SHA	Age–gender-standardised use (95% CI)	No. of centres
Norfolk, Suffolk and Cambridgeshire	0.80 (0.63 to 1.02)	1
Bedfordshire and Hertfordshire	0.82 (0.62 to 1.10)	0
Essex	1.18 (0.94 to 1.49)	0
North West London	1.59 (1.0 to 1.26)	3
North Central London	1.02 (0.74 to 1.40)	1
North East London	1.16 (0.88 to 1.56)	2
South East London	0.75 (0.54 to 1.05)	2
South West London	0.99 (0.73 to 1.35)	1
Northumberland, Tyne & Wear	1.05 (0.81 to 1.37)	1
County Durham and Tees Valley	0.85 (0.61 to 1.17)	1
North and East Yorkshire and North Lincolnshire	1.39 (1.12 to 1.71)	1
West Yorkshire	1.29 (1.05 to 1.58)	2
Cumbria and Lancashire	0.81 (0.62 to 1.04)	2
Greater Manchester	0.53 (0.40 to 0.70)	2
Cheshire and Merseyside	1.20 (0.99 to 1.46)	1
Thames Valley	0.95 (0.75 to 1.20)	1
Hampshire and Isle of Wight	0.92 (0.71 to 1.18)	1
Kent and Medway	0.82 (0.62 to 1.09)	0
Surrey and Sussex	1.16 (0.97 to 1.40)	2
Avon, Gloucestershire and Wiltshire	1.04 (0.84 to 1.29)	1
South West Peninsula	1.10 (0.87 to 1.39)	4
Somerset and Dorset	1.80 (1.45 to 2.23)	1
South Yorkshire	0.86 (0.63 to 1.17)	1
Trent	1.12 (0.93 to 1.35)	2
Leicestershire, Northampton shire and Rutland	1.51 (1.22 to 1.88)	1
Shropshire and Staffordshire	0.61 (0.43 to 0.85)	0
Birmingham and the Black Country	0.61 (0.46 to 0.81)	1
Coventry, Warwickshire and Worcestershire	0.63 (0.45 to 0.87)	1

and five SHAs more than this standard. Confidence intervals around the age–gender ratios of use were wide because of the small number of ICDs undertaken in each SHA. There appear to be no geographical patterns, although those implanting less tend to be in the midlands and north west and those implanting more in the north. It is important to reiterate that the average for England is considerably below that set by NICE, and further below European and North American countries.

Equity

Several aspects of equity were addressed using the 1998–2000 data set.

Equity of access

The access of patients to implanting centres was crudely assessed for England by looking at the number of centres in each region and each SHA (*Table 29*). The age–gender-standardised rates for each region and SHA were used to compare activity by location with the number of centres in that locality to establish whether any correlation could be found (*Table 30*).

The SHA is ascribed by the postcode of the patient receiving the device. Thus, the population of Dorset and Somerset who have no centre in the SHA still have a relatively high age–gender-

TABLE 31 *Use–need ratios for ICD implantation by English region and gender*

RHA	Age–gender-standardised use (1998–2000)	Use–need ratios, both genders	Use–need, men	Use–need, women
England	100	1.00		
Northern and Yorkshire	118 (105 to 134)	1.11 (0.99 to 1.26)	1.11 (0.97 to 1.27)	1.11 (0.83 to 1.49)
Trent	124 (109 to 141)	1.16 (1.02 to 1.33)	1.18 (1.02 to 1.36)	1.10 (0.8 to 1.52)
West Midlands	65 (54 to 78)	0.62 (0.51 to 0.73)	0.61 (0.50 to 0.74)	0.63 (0.41 to 0.96)
North West	91 (80 to 105)	0.86 (0.75 to 0.99)	0.80 (0.69 to 0.94)	1.13 (0.85 to 1.50)
Eastern	101 (87 to 116)	0.95 (0.82 to 1.09)	0.97 (0.83 to 1.13)	0.84 (0.59 to 1.21)
London	111 (97 to 126)	1.04 (0.92 to 1.18)	1.05 (0.92 to 1.21)	0.99 (0.73 to 1.35)
South East	108 (97 to 121)	1.02 (0.91 to 1.14)	1.04 (0.92 to 1.17)	0.93 (0.71 to 1.22)
South West	131 (115 to 149)	1.25 (1.10 to 1.42)	1.24 (1.08 to 1.43)	1.28 (0.95 to 1.73)

95% CIs are given in parentheses.

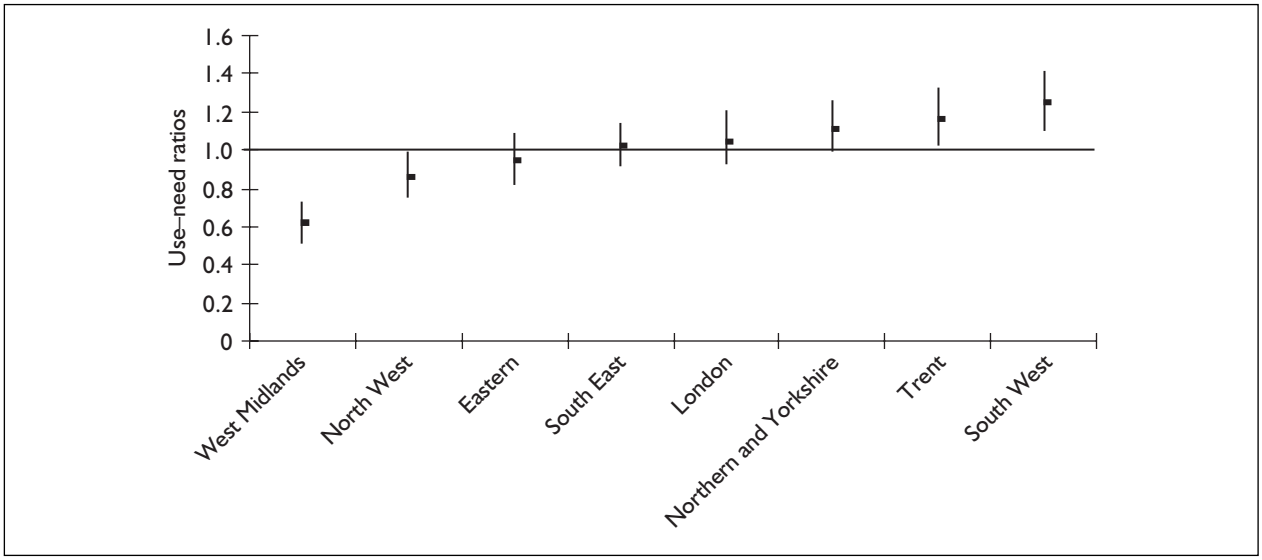

FIGURE 8 *Overall use–need ratio based on IHD SMR and age–gender-standardised rates*

standardised rate of 1.80, as they are implanted in centres outside their own SHA area, entailing more travel than if there were a centre within the SHA. There are nine NHS centres in London, almost one-quarter of the total number of centres, which may be accessible to those in the environs but not those living further away. Between North Essex and Cambridgeshire there are no centres; therefore, when patients are referred they will have a greater distance to travel. There are three SHAs that have no centre (although development of centres has made rapid progress in the past 2 years).

Equity of need

Using SMR IHD as proxy indicator for need for ICD therapy

Using the SMR for IHD and age–gender-standardised ICD use, use–need ratios were derived for English regions (*Table 31* and *Figures 8–10*).

Overall, there are three regions that seem to be implanting at around the standard level of use–need ratio for England. There is no clear north–south divide in the outliers for those regions implanting less than or more than the standard use–need ratio for England, and the location of these outliers is consistent in both genders. Some regions are implanting more than the English standard for women and less for men (North West).

Figure 11 shows that there may be an inverse relationship between ICD use and need, with the people with potentially most need (highest SMR for IHD) receiving the lowest rate of ICD implantation.

Using deprivation as proxy indicator of need

The analysis was based on 1666 ICD implantations for which sufficient data were available to perform

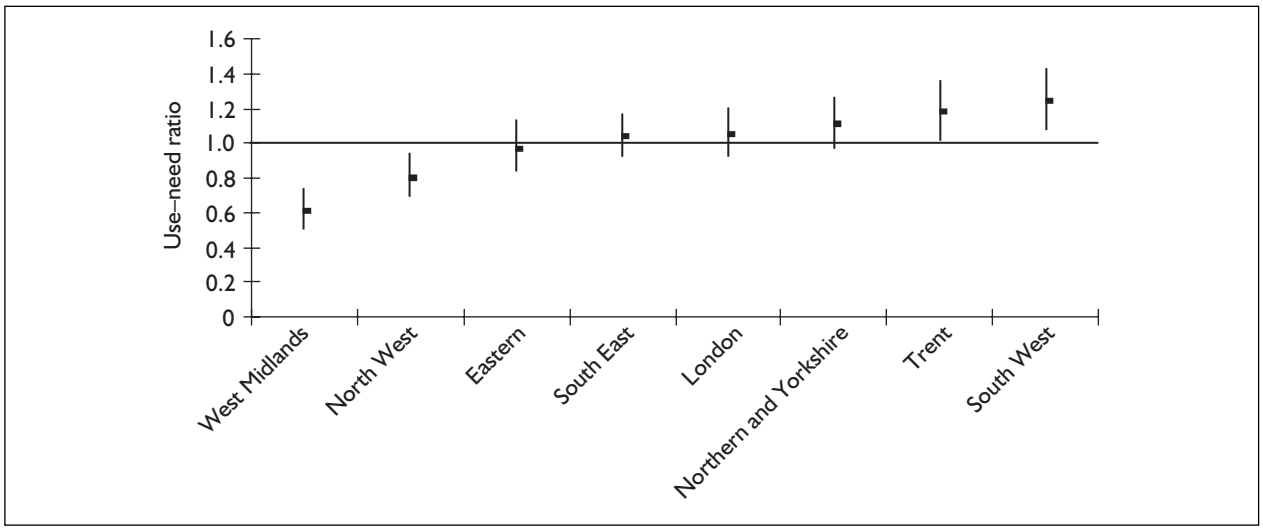

FIGURE 9 *Use–need ratio for ICD implantation in men, by English region*

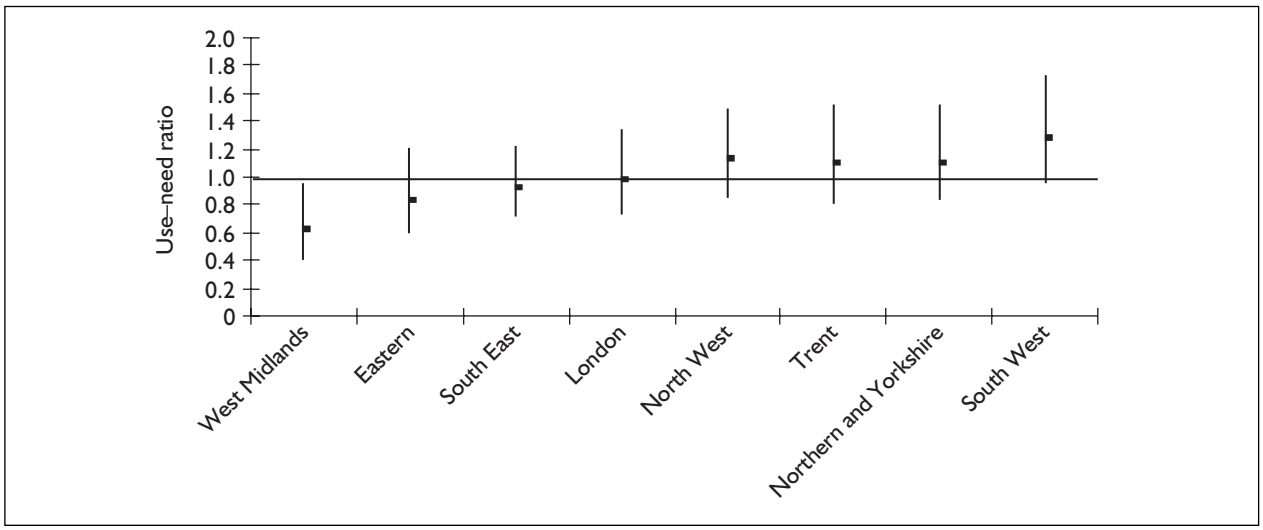

FIGURE 10 *Use–need ratio for ICD implantation in women, by English region*

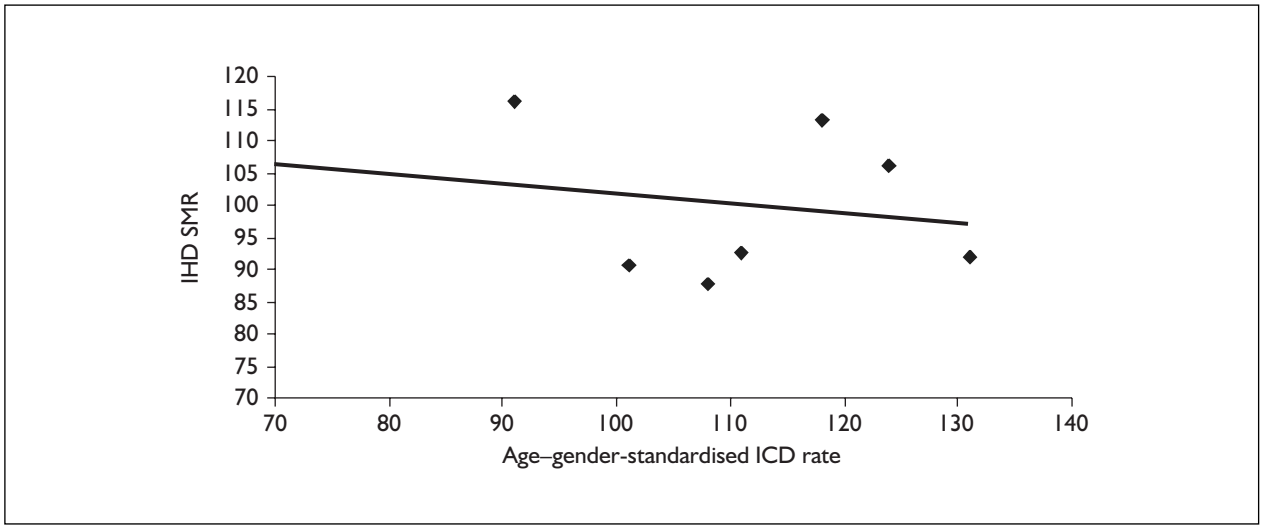

FIGURE 11 *Relationship between standardised ICD use and IHD SMR, by English region*

this analysis. Details of the quintiles used are given in Appendix 6.

Table 32 and *Figure 12* show that more ICDs than expected are undertaken in the least deprived quintiles and fewer ICDs than expected in the most deprived quintiles. However, confidence intervals included 1 for three of the quintiles. A test for trend using a Poisson regression model (with the null hypothesis being that there was no relationship between ICD use and deprivation) and ICD use showed a statistically significant trend with $p = 0.005$. ICD use is decreased with increased deprivation (at a small area level). If need were-being met, and deprivation were an appropriate measure of need, the inverse of this result would be expected, that is, increasing ICD use with increasing deprivation.

TABLE 32 *Age–gender-standardised ICD implantation rate by quintiles of deprivation*

Quintile	Deprivation (95% CI)
1 (least deprived)	1.09 (0.99 to1.21)
2	1.17 (1.06 to 1.29)
3	1.03 (0.93 to 1.15)
4	0.86 (0.77 to 0.96)
5 (most deprived)	0.85 (0.76 to 0.95)

Equity of use by ethnicity

Using computer software to identify South Asian surnames provided an estimate of the implantation rate in this ethnic group. Analysis showed that 2.8% of the total number of ICD patients in the national database was of this ethnicity, whereas the distribution in the general population is 3.3%.[31] The software produces an imperfect estimate, but studies suggest that it is likely to overstate, rather than understate, the proportions that are South Asian.[59] The incidence of premature cardiovascular death in this ethnic group is 46% higher for men and 51% higher in women than the UK average, and using this as a proxy indicator of need for ICDs, it indicates that there may be possible inequity of provision to this population of UK residents. Care should be taken in interpretation, in that the Asian population tend to be younger than the overall population and thus the disparity in use may be partly explained by this factor. Further analyses should be undertaken to take into account the age profile of this population using data from the 2001 Census.

Summary of findings on age–gender-standardised rates and assessment of need

Using BPEG data from 1998 to 2000, it is clear that the UK rates within this period were well below those recommended by NICE (50 per million population), even in the most active of

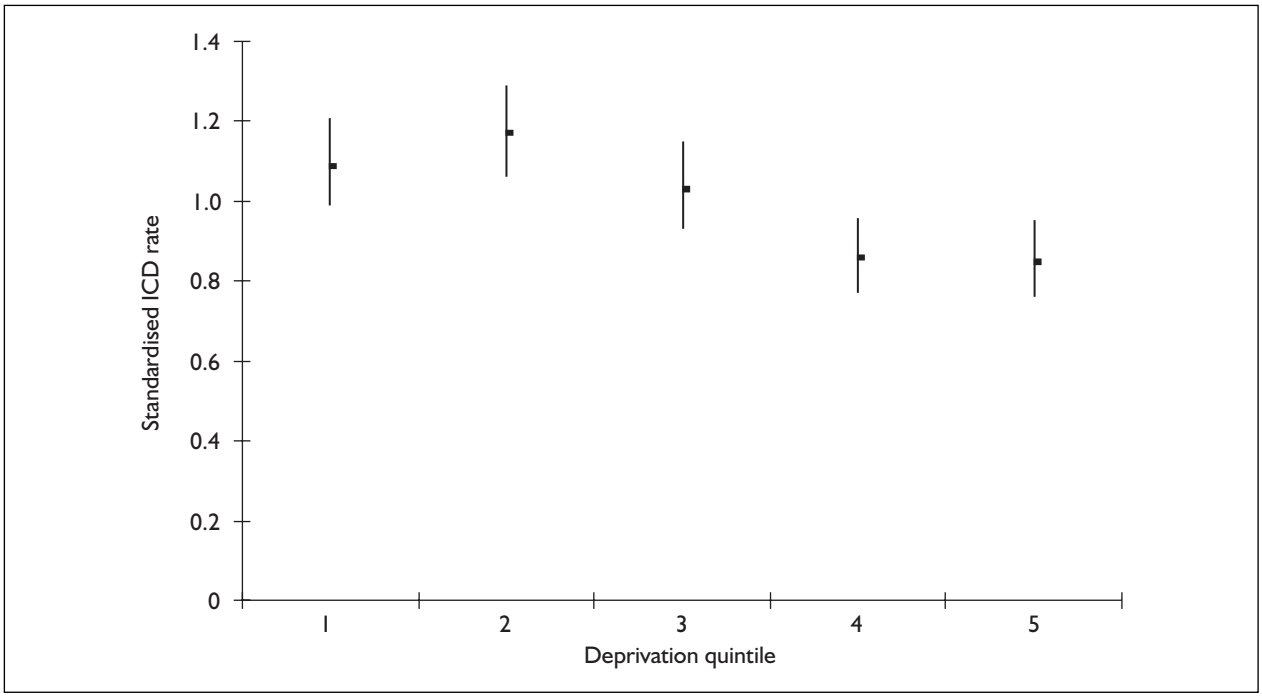

FIGURE 12 *Age–gender-standardised ICD rate by deprivation quintile*

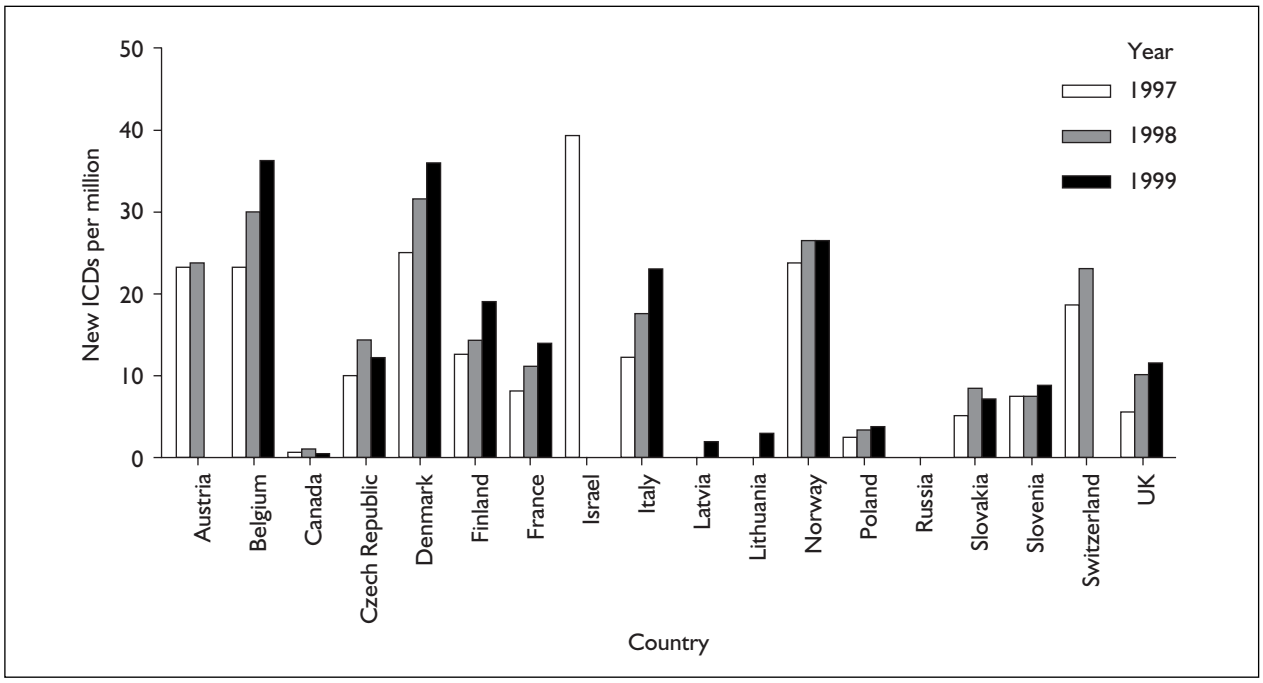

FIGURE 13 *Comparative use of ICD therapy in different countries*

TABLE 33 *International comparison of ICD use*

	No. implanted (2000)	Rate per million (2000)
UK	961	15.2
Denmark	239	47
USA	50,100	184
Spain (1999)	NA	19
Germany (1999)	NA	67
Italy (1999)	NA	25
France (1999)	NA	13
Canada (1999)	NA	35

NA, not applicable.

English health regions. There may also have been inequity of ICD utilisation within England, as suggested by analyses using proxy measures of need. Results from the deprivation analysis strongly suggested that an inverse care law was operating with populations in most need of this therapy receiving the least treatment.

Furthermore, there may be inequity of access, as some SHAs do not have an implanting centre and London has almost one-quarter of the existing centres. There may be variation in ease of access for those patients referred for an ICD, with those living farthest away from the centre experiencing possible reduced access.

The main limitations of these analyses were missing data. However, the distribution of these data was fairly evenly spread among the deprivation quintiles. There were differences in the amount of missing data from various regions, but these were not the regions with the lowest rates of use.

Comparative ICD data

Comparative use of ICD therapy in several countries is shown in *Figure 13* and *Table 33*. Despite the increase in ICD implantation in the UK, rates have remained low compared with many European countries and the USA; 50,100 ICDs were implanted in the USA in 2000 (83% of the total worldwide implantation). Estimates by some experts have stated that even this relatively high rate of use in the USA does not meet the need for this therapy.

Appendix 7 shows that the UK has similar rates of death from CHD to other industrialised countries.

Mortality

The 1998–2000 data set contains mortality data (77 deaths in total) followed to 5 years postimplantation. Such numbers are too small to perform formal survival analysis. UK mortality data from the BPEG database are presented. Deaths are routinely flagged with the Office for National Statistics (ONS) and reported to the BPEG database quarterly. Survival analysis has been performed on over 700 UK ICD patients. Kaplan–Meier survival curves are shown in *Figure 14*. Only those patients of known mortality and positively identified survivors are included. *Figure 14* shows that the 1-year survival is 94%, the 2-year survival is 89.5% and the 5-year survival 76%. Analysis compared 5-year age bands and there is no difference in 5-year survival rates in these age groups ($p = 0.26$), although a trend is seen towards younger groups surviving longer.

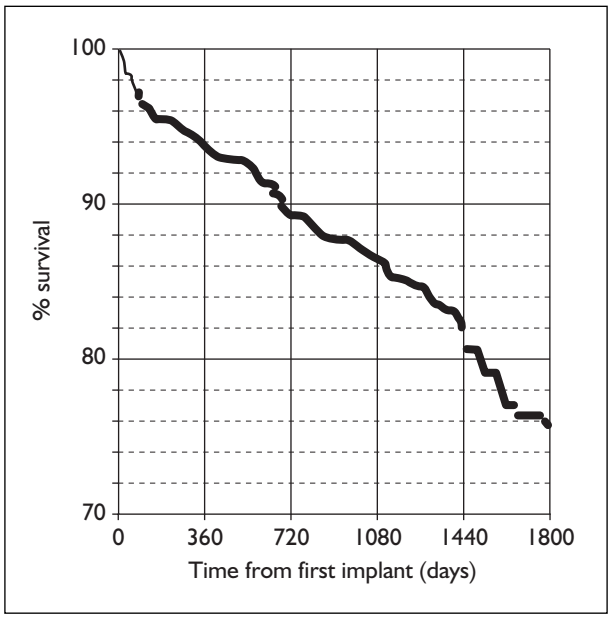

FIGURE 14 *Survival from first ICD implant*

Device longevity

The length of time between replacement devices is of great importance in the economic analysis of ICDs. Kaplan–Meier analysis (*Figure 15*) shows that for the first 3 years there is a 3% explant rate per annum, which rises sharply to 15% per annum. There has been a significant trend towards greater 5-year generator survival since 1991.

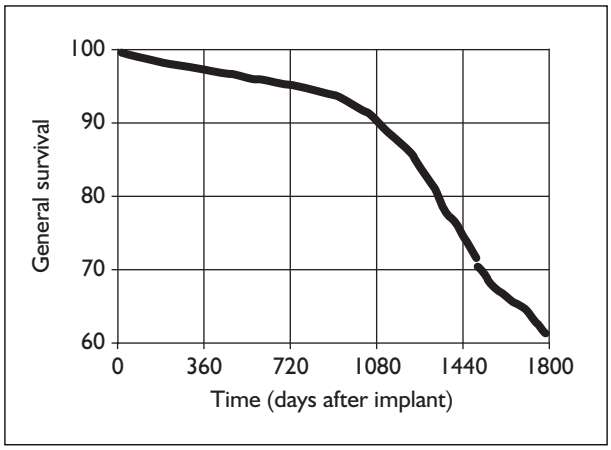

FIGURE 15 *ICD generator longevity*

Survey results

In 2002, 41 UK centres were undertaking ICD implantation, although four or five centres had just begun a service (*Figure 16*). There was a 78% (32/41) response rate to the questionnaire survey. The non-responding centres were evenly spread throughout England (all centres in Scotland, Northern Ireland and Wales responded).

Most of the centres (81%) are serving populations above that of a typical DGH (>500,000), with the majority (63%) serving populations of over 1 million (*Table 34*). This reflects the tertiary nature of many of the centres for this service. The median value for the population served is above 1 million.

The centres are generally implanting more ICDs over the 3-year period (*Figure 17*). Many centres are implanting fewer than 35 ICDs per year, leading to potential training and quality assurance issues.

Overall, the median staffing level for consultant grade is 2 whole-time equivalents (WTE), with 1 WTE NHS specialist registrar (SPR) and 2 WTE technical staff. Over one-quarter of units responding (27%) had no NHS SPR working a significant amount of their time with patients eligible to receive ICDs. Four centres had an SPR [research and development (R&D)] working the equivalent of 4 WTE sessions, but most (87%) had no SPR (R&D) working in the ICD service. This may have training implications for the future ICD service. Seventy-three per cent had no NHS-funded specialist nurse and almost all (97%) had no R&D-funded specialist nurse. Ten per cent had no technical staff, while 16% had more than 5 WTE technical staff working in the ICD service.

There was no statistical association between the number of staff or the professional craft of the staff and the activity of the unit. However, in units implanting higher numbers of ICDs, there were

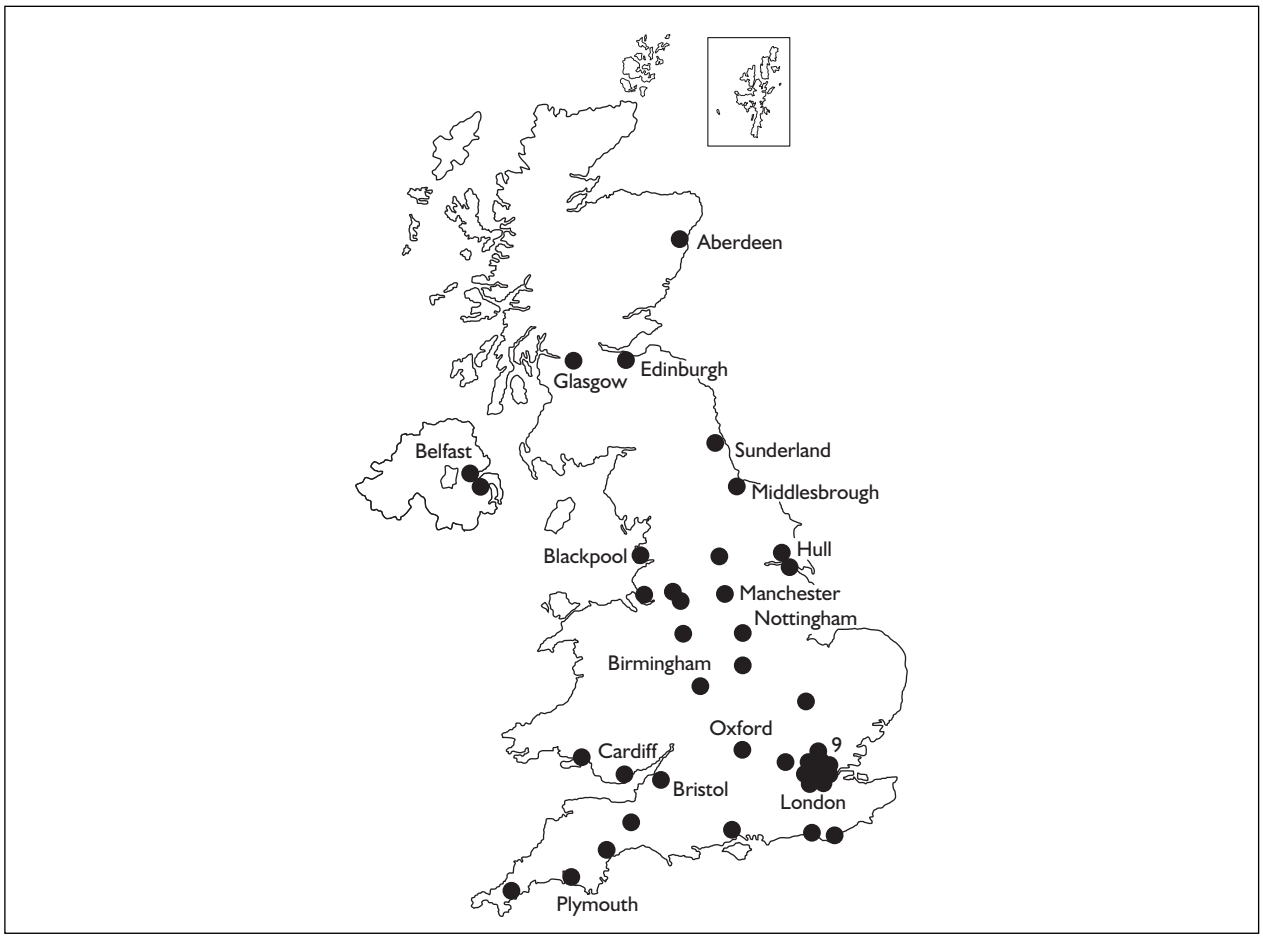

FIGURE 16 *ICD centres in the UK*

TABLE 34 *Size of population serviced by implanting centre*

	%
100,000–300,000	3.1
300,001–500,000	15.6
500,001–1 million	18.8
>1 million	25.0
>2 million	15.6
>3 million	21.9
Total	100.0

higher numbers of consultants available, but this did not reach statistical significance (this may have been due to the small numbers involved).

There is therefore considerable variation in staffing levels and skill mix between implanting centres, leading to potential inequalities of healthcare for this group of patients.

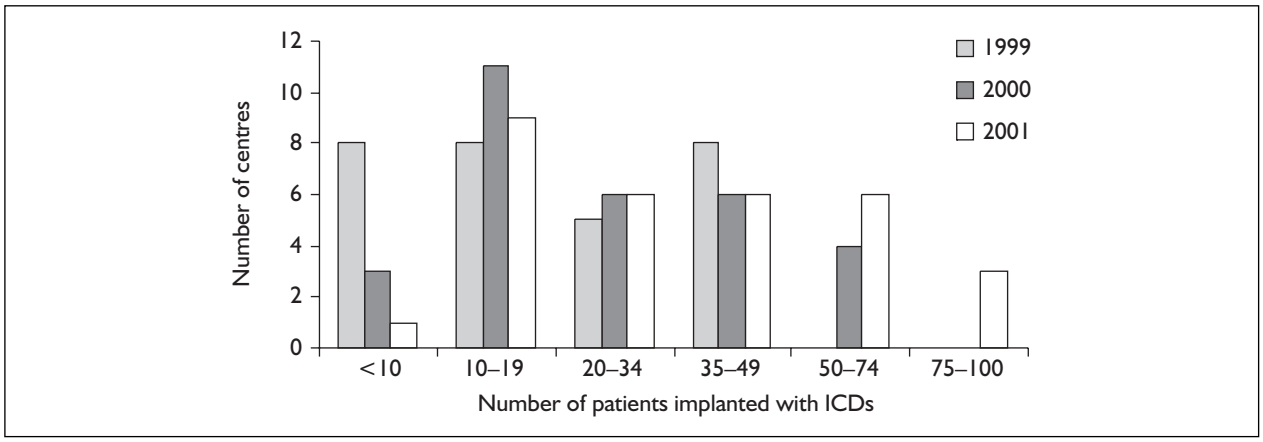

FIGURE 17 *ICD implantation by centre, 1999–2001*

TABLE 35 *Number of EP studies undertaken monthly*

	Frequency	%
1–4	21	76
5–9	5	19
>10	1	4

Electrophysiology studies

Ninety-seven per cent of respondents had facilities to undertake EP studies.

The median number of EPs performed each month was 1–4 (*Table 35*).

The use of EP studies before the insertion of an ICD shows considerable variation in practice, with one-quarter of respondents performing it in less than 10% of cases, while one-tenth of respondents used EP studies in more than half their ICD implantations. EP studies were performed in a median of 10–24% of ICD insertions.

Respondents were asked to mark their responses to whether each factor suggested on the questionnaire was a barrier to care for patients eligible for an ICD as strongly agree, agree, unsure, disagree or strongly disagree. There was a category of 'other' for those barriers that did not appear on the grid.

The three most commonly identified barriers to care for patients who are eligible for ICD therapy were patient identification, staff capacity and funding for treatment (*Table 36*). Comments on barriers included the difficulties in obtaining referrals of eligible patients from secondary or DGH level of care, and the problems of evidence being in the public domain influencing professional equipoise on eligibility criteria, preceding national guidance and therefore funding (e.g. the MADIT II study, providing evidence for ICD therapy in patients with heart failure, has not yet been approved by NICE).

Just under half of the respondents reported that they had a waiting list for ICD implantation (43%). Seventy-one per cent of respondents said that they submitted all of their implanting data to the national database, with 86% submitting 90% or more.

Comments on how respondents envisaged practice changing over the next few years fell into four broad categories, as shown in *Table 37*.

All of the respondents recorded that they expect to have a large increase in numbers of implantations over the next few years. Nearly all of the respondents mentioned setting up of services in DGH settings in a hub and spoke arrangement, or accreditation of centres with specific quality criteria with support from larger centres provided on a need basis.

Key findings and implications for future practice

There is variation in practice leading to potential healthcare inequalities for this group of patients. The key barrier to ICD services was considered to be patient identification, with perceived under-referral of eligible patients from clinicians in non-ICD centres. This may change as more ICD centres develop in DGHs, with wider dissemination of best practice guidelines, and effective education about indications for ICD therapy leading to appropriate patients being identified and referred. However, the staff and funding shortages reported as barriers may hinder such an expansion of service. The possible indications for ICDs, especially those associated with primary prevention, were highlighted as

TABLE 36 *Barriers to care for eligible patients*

	Strongly agree/agree (%)	Unsure (%)	Strongly disagree/disagree (%)
Patient identification	93		7
Clinic waiting times	25	4	72
EP waiting times	22	14	64
Implantation waiting times	25	11	64
Staff capacity	57	7	36
Skill mix	36	7	57
Funding for treatment	46		54
Patient refusal	11		89
Non-attendance		4	96

TABLE 37 *Comments on changing practice*

	Comments
Increase in numbers	Numbers will increase as the centres become more widely known Dramatic increase in numbers Steady increase in numbers mainly limited by staffing and hardware resources Great increase in numbers; double in next year
Expansion of eligibility criteria	Continued expansion of primary prevention indications More primary prevention being done (MADIT II will further increase this) Primary prevention indications will expand service
Configuration and practice	Devolvement to larger DGHs. Increasing number of biventricular units Devolution to implantation at DGH level in hub and spoke arrangement Less EP used Shorter implant times, less GP devolvement to DGHs, home-based monitoring, better distributed support (wider knowledge base) Need to expand facilities for implanting ICDs. Expansion of hub and spoke model of practice to DGH Expansion of service hopefully supported by devolution of service into surrounding DGH Devolution of DGH with stated quality criteria and minimum activity levels, staff and resources and out of hours cover. Not in a hub and spoke, but accreditation and remote support from larger centre No specific recommendations have been made about replacements which are increasing, and these are being included in the allocation of all ICDs at 50 per million population by health authorities NICE is out of date
Staffing	Need designated and funded staff Need for a dedicated fully funded staffed ICD clinic with a staff grade or similar attached and at least 3 days of WTE time for two cardiac technicians Our ICD clinics will have to go to technician only due to increasing workload

DGH, district general hospital.

contributing to the need for expansion of services, with anxieties being expressed about the potential explosion of numbers and the ability of the current providers to give a high-quality service.

Discussion

The evaluation of the national service for patients eligible for ICD therapy indicates that the rates of implantation of ICDs in 2000 did not even approach halfway to the target of the 50 per million population suggested by the NICE guidance, even in the most active of regions. It also highlighted that compared with most other Western European and North American countries the implantation rates in the UK are considerably lower per head of population. This suggests that there is unmet need, assuming appropriate use in other countries.

The service is pressurised at the current levels of activity, with barriers to the management of patients being the identification of those patients who would be eligible for ICDs, staff capacity and funding. The requirement of the services in terms of staffing (electrophysiologically trained cardiologists and specialist technicians), specialist implanting facilities and follow-up clinics to fulfil national guidance even to this modest (compared with USA and Europe) implantation rate are considerable. The shortfall in reaching the NICE target and professional concerns about the ability of the current infrastructure to provide a comprehensive service for patients eligible for ICDs is further compromised when the indications suggested by MADIT II results, which were due to be reviewed by NICE in autumn 2003, are taken into account. The number of potentially eligible patients is increased hugely by extension to patients with a previous history of MI and heart failure (LVEF <35%). The ability of the NHS to manage such an extension needs careful and urgent consideration and planning. These concerns have been reinforced and illustrated by a recent audit of clinical records to determine the eligibility of patients for ICDs against NICE guidance, conducted in a tertiary hospital in the north of England.[60] This study reported underprovision of ICD therapy in the UK, and

that the number of patients eligible for ICDs exceeded that predicted. The annual incidence of patients fulfilling national criteria was about 150 per million, with an additional 'prevalence' pool of about 41 per million. The authors calculate that applying the MADIT II criteria to determine eligibility for ICD would increase the number to 504 per million (new cases) and 311 per million (prevalent cases) per year. This is in excess of the predictions by a factor of between 10 and 25.

At a recent meeting of BPEG to devise best practice guidelines for the use of ICDs for the profession, concerns were raised about the ability of the present services to cope with increased implantation. A national audit was presented of future career intentions of current cardiology SPRs. Only 24 expressed an interest in arrhythmia management, which implies a future shortfall in consultants to lead the service, and an urgent need to address recruitment. In addition, there is already an acute shortage of trained technicians, and an increase in ICD therapy will present further challenges in recruitment and retention of technical staff. Provision of electrophysiologists is low in the UK, with the rate of electrophysiologists to the population in the USA being 1:263,690, in Canada 1:750,000 and in the UK 1:2,800,000. This may lead to staffing problems as ICD use increases, and adds to the debate on the optimum service configuration for the management of those patients eligible for ICD therapy in the UK.

The problem of identification of potentially eligible patients was highlighted as a barrier to patient management. This encompasses equity issues that have been suggested by the results of the evaluation. Inequities in the UK seem to be suggested by the variation in the trends in prevalence of CHD between countries. Although the death rate from CHD has been falling in the UK, it has not fallen as rapidly as in other countries. For example, the death rate for men aged 35–74 years fell by 37% between 1986 and 1996 in the UK, but it fell by 45% in Denmark and Norway (Appendix 7). Reasons for these differences are unclear, but if CHD mortality is a proxy for the need for ICD therapy, then UK practice is lagging behind European practice, with a greater need being met by lower ICD implantation. Inequities in particular groups within the UK population may also exist, in that women are implanted in only 18% of cases. This situation mirrors that found in other cardiovascular interventions such as CABG, which has been found to be lower in women than measures of need might dictate. Other populations that may not be accessing the ICD services are those from South Asian ethnic background, with a known higher than the general population prevalence of CHD and a low ICD implantation rate. In addition, the evaluation points to inequities of need using proxy indicators, with the deprivation indicator strongly suggestive of an inverse care law, with the populations in most need of this therapy receiving the least. For English regions this study has shown specific use–need ratios, deriving the ratio from the SMR for heart disease as a proxy measure for need, which may act as baseline information for particular services to conduct more in-depth local needs assessments and to plan the service for their populations. Some SHAs do not have any implanting centres at present and London has almost one-quarter of the centres. This will lead to variation in ease of access for those patients referred for an ICD and may suggest the possibility that those living farthest away from a centre have reduced access to ICD services, resulting in yet more inequity.

The way in which services are to be arranged to deliver this treatment to an increasing number of patients is being actively looked at by BPEG. Various service configuration strategies are being discussed to provide a high-quality service for patients eligible for ICD therapy, such as a hub and spoke arrangement with a central implanting unit and satellites for patient management and follow-up using standardised best practice guidelines, or accreditation for implantation in district hospitals using quality criteria. Further suggestions include a managed clinical network based on SHA populations. Results from the survey suggest that most of the present centres envisage this devolution of the ICD service, and it is timely to plan this change in configuration with nationally agreed quality criteria and evaluation of configuration models to optimise delivery of a high quality of service.

Strengths of the assessment

The information from the national database is the most comprehensive data set available and full collaboration with the database allowed as full an assessment of national service as is possible within the limitations of the information held by that database.

Novel analyses were performed on this information deriving age–gender-standardised rates for the countries of the UK, English regions and SHAs, and conducting analyses on equity of

use and need, deriving use–need ratios for English regions, deprivation indices for patients receiving ICDs and use by ethnic groups.

A national survey of all implanting centres had a high response rate and gathered information on factors that may influence ICD use, such as workforce, perceived barriers to management, work activity, clinical practice and qualitative information on visions for the future service. This information adds to that available for national and local planning of services.

Limitations of the assessment

The assessment of the national ICD service was largely based on data derived from the national database. This relies on the return of completed standard forms from each implanting centre, and although most centres claim that they return the form in virtually all the patients receiving an ICD, not all the forms are complete, leading to missing information, which leads to any evaluation of a service being less robust than it might be. The data set 1998–2000 was more complete in that efforts had been made to chase missing data. Nevertheless, there were still missing and duplicate data within this data set. The missing data were assessed and found to be distributed in a fairly even way between deprivation quintiles, but there were some differences in the amount of missing data from various regions.

Some access to information was restricted in that information held by the national database on the numbers of devices implanted by each centre was considered to be confidential, and so an estimate was derived by survey information. The database is not easily accessed and remains largely unresponsive to professionals and interested patients. This not only limits the use of these data in informing local services, but also reduces motivation for implanting centres to provide complete and reliable data. As the ICD service rapidly expands, and the need for responsive, sophisticated and regular analyses of data grows, additional resources are urgently required to provide information technology support and dedicated staff to the management team, whose capacity reflects the needs of the service from a decade ago.

Summary

The use of ICD in the UK has increased especially over the past 5 years, but is lower than the target set by NICE and lower than rates in other developed countries. Demographics show that older people are having ICDs and that the majority are male. An increasing number of ICDs is being implanted for primary prevention indications. There are more implanting centres being established and a general change in configuration of services to secondary rather than tertiary centres. Key barriers identified are patient identification, staff capacity and funding. Data show a possible inverse care law operating. The future needs of the ICD service in the UK require urgent planning for the expansion of the service, especially in the light of the potential widening of eligibility criteria to a greater number of patients.

Chapter 5

UK study methods, population characteristics and survival

Background

The background to this report includes information on the epidemiology of ventricular arrhythmias (see Chapter 1) and Chapter 4 has described the shortfall between NHS targets and actual current service provision. Some information on national activity is available from the BPEG registry, but this lacks detailed information on patient characteristics and function, and estimates arising from this source may be biased owing to missing data. Therefore, a small number of active centres was approached to review activity, contrast UK patients with those described in published RCTs and investigate the factors that influenced survival in the UK sample.

Objective

The objective was to describe the characteristics of a sample of UK patients that will be used to inform cost-effectiveness analysis, and to investigate those factors that have influenced survival after ICD implantation.

Methods

Initially, three centres, Newcastle, Papworth and Southampton, agreed to provide data for the trial. Owing to overwhelming clinical workload Newcastle could not undertake data collection and Liverpool was recruited to replace Newcastle. Because of workload and staffing issues, plus the need to retrieve a greater than expected proportion of data from patients' records rather than existing databases, Southampton could not provide patient information by the final data collection deadline of 31 December 2002. Therefore, Liverpool and Papworth have provided data for this report, comprising a total of 291 and 244 implants, respectively.

Details of UK data retrieval are described in *Figure 19* and *Table 38* for clinical information. Implant date, date of birth, gender, survival status and date of death were available for 532 out of 535 patients implanted at the two centres. All other clinical data had to be retrieved from patient records. Because of time constraints, notes were retrieved for all patients receiving an ICD implant between the start of the programme in that hospital and December 1999 inclusive, but for implants from January 2000 to the time of study (May 2002 for Papworth, August 2002 for Liverpool) a random sample of notes would be drawn. This sampling resulted in clinical data collection from 213 out of 244 patients (87%) from Papworth and 213 out of 291 patients (73%) from Liverpool. Slightly more of the recent patients were sampled at Papworth since some data collection constituted a pilot phase during which data clerks were trained and data collection forms were developed.

For patients who were alive at the time of study, clinical data retrieval was almost complete, with only two sets of patient notes not found (2/426, 0.5%). For patients who had died before the time of study Papworth was unable to locate two sets of notes (2/27, 7%) and Liverpool was unable to locate 42 sets of notes (42/54, 78%). Clearly, one cannot assume that missing data have arisen at random, and patients with missing notes are unlikely to be similar to those for whom data are available. Methods for dealing with missing data will be described as they are used in the report.

Results

UK patient sample: clinical data collection

During the study period 535 patients received ICD implants at Papworth or Liverpool. From BPEG returns, this represents approximately 10% of the UK activity. The rise in activity over time can be see in *Figure 20* and this growth mirrors that reported in the rest of the country (*Figure 2*). Eighty-one per cent of patients were men and ages ranged from 17 to 98 years, with almost 80% of patients aged between 50 and 80 years (*Figure 21*). These are similar to characteristics reported in the UK as a whole (see *Figure 4*). In particular, in the

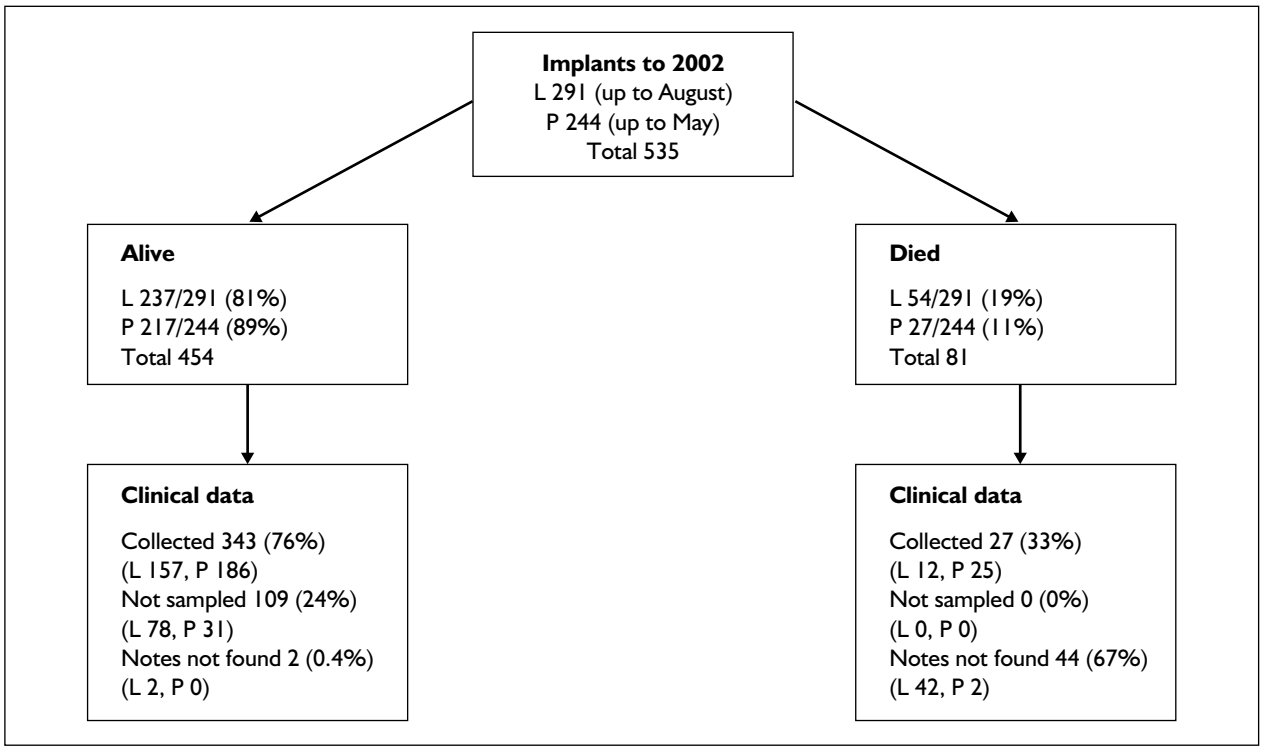

FIGURE 19 *Clinical data collection. L, Liverpool, P, Papworth.*

TABLE 38 *Clinical data collection by year of ICD implant*

Centre	Status	ICD year												
		1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	Total
Papworth	Alive data collected	2	1	3	6	1	6	12	13	29	34	47	32	186
Liverpool	Alive data collected	1	0	2	4	4	4	10	19	32	26	35	20	157
Papworth	Alive not sampled	0	0	0	0	0	0	0	0	0	8	23	0	31
Liverpool	Alive not sampled	0	0	0	0	0	0	0	0	0	18	26	34	78
Papworth	Alive notes not found	0	0	0	0	0	0	0	0	0	0	0	0	0
Liverpool	Alive notes not found	0	0	0	0	0	0	0	0	0	1	1	0	2
	Subtotal (Alive)	3	1	5	10	5	10	22	32	61	87	132	86	454
Papworth	Dead data collected	1	1	0	3	2	2	2	3	2	5	4	0	25
Liverpool	Dead data collected	0	0	1	0	0	0	0	2	0	1	7	1	12
Papworth	Dead not sampled	0	0	0	0	0	0	0	0	0	0	0	0	0
Liverpool	Dead not sampled	0	0	0	0	0	0	0	0	0	0	0	0	0
Papworth	Dead notes not found	0	1	0	0	0	0	0	0	0	1	0	0	2
Liverpool	Dead notes not found	2	2	0	1	3	3	6	8	6	7	3	1	42
	Subtotal (Dead)	3	4	1	4	5	5	8	13	8	14	14	2	81
	Grand total	6	5	6	14	10	15	30	45	69	101	146	88	535

2002 includes implants up to May for Papworth and August for Liverpool.

'cleaned' data supplied by BPEG, covering a 3-year implant period, there were 2353 cases, 81% of which were men, and the mean age was 59 years (SD 13.6). Patients' characteristics for the UK sample are given in *Tables 39* (all UK sample ICD implants) and *40* (UK sample with clinical data retrieval), alongside those of the three published trials of ICD used as secondary prevention (AVID,[17] CIDS,[19] and CASH[18]).

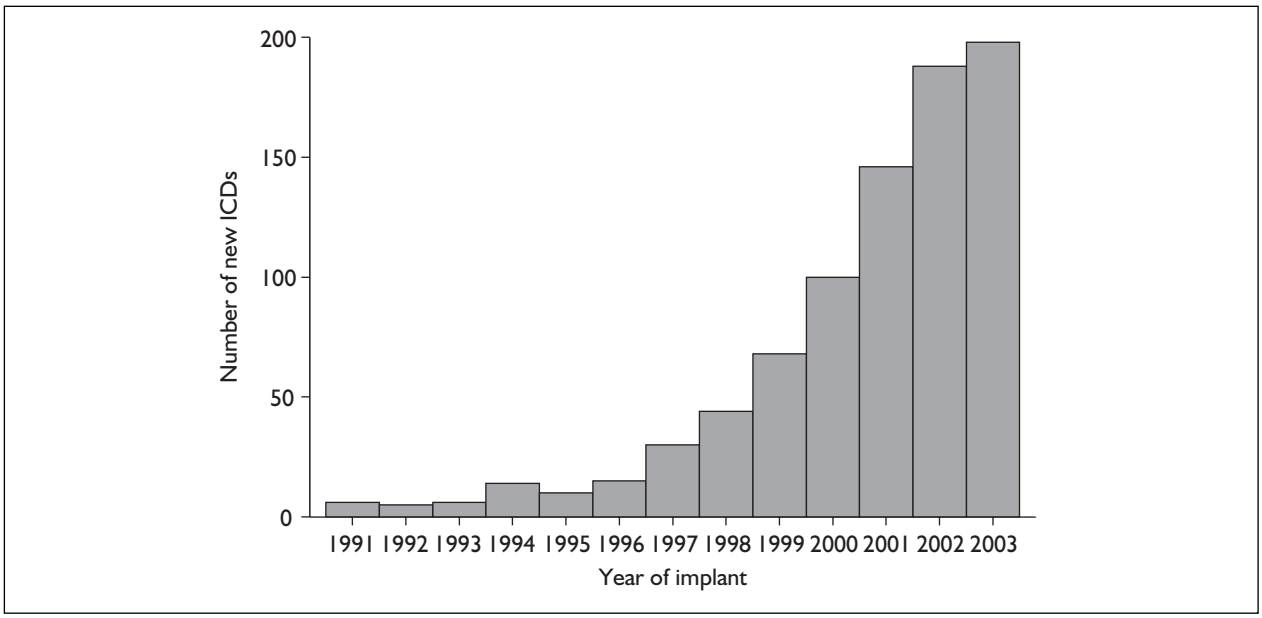

FIGURE 20 *Growth in activity at Liverpool and Papworth (2003 is projected)*

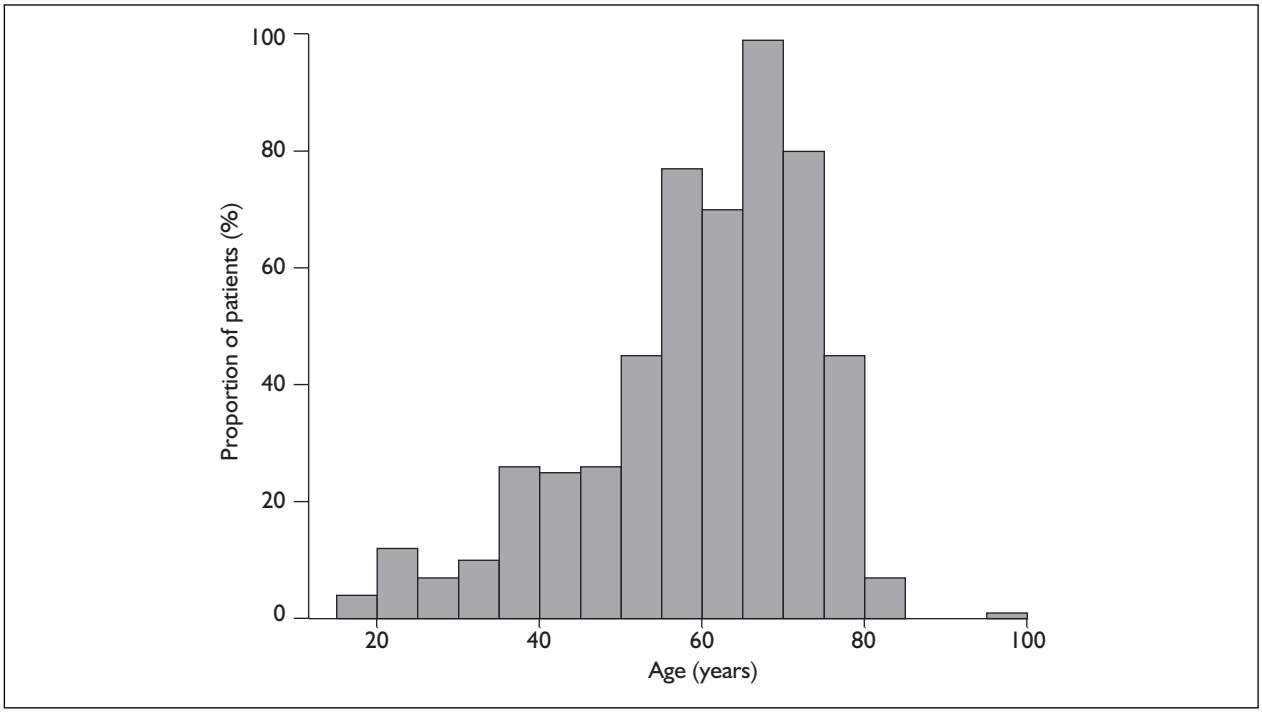

FIGURE 21 *Age at ICD implantation*

TABLE 39 *Characteristics of all Papworth and Liverpool ICD patients compared with patients in RCTs of ICD used as secondary prevention*

	UK (*n* = 535)	AVID (*n* = 1016)	CASH (*n* = 191)	CIDS (*n* = 659)
Dates of implants	1991–2002	1993–1997	1986–1997	1990–1997
Number of ICD implants	535	507	99	328
ICD years of follow-up	1171	801	483	995
Deaths on ICD (% per year)	81 (7%)	80 (10%)	37 (8%)	83 (8%)
Age (years) mean (SD)	60 (14)	65 (11)	58 (11)	63 (10)
Male gender (%)	81%	79%	80%	85%

TABLE 40 *Characteristics of Papworth and Liverpool ICD patients with clinical data available compared with patients in RCTs of ICD used as secondary prevention*

		UK (*n* = 380)	AVID (*n* = 1016)	CASH (*n* = 191)	CIDS (*n* = 659)
Dates of implants		1991–2002	1993–1997	1976–1997	1990–1997
Number of ICD implants		380	507	99	328
ICD years of follow-up		940	801	483	995
Deaths in ICD patients (% per patient-year)		39 (4%)	80 (10%)	37 (8%)	83 (8%)
Age (years), mean (SD)		59 (14)	65 (11)	58 (11)	63 (10)
Male gender (%)		81%	79%	80%	85%
Prior MI		72%	67%	51%	77%
Any CHD		84%	82%	75%	83%
Non-ischaemic cardiomyopathy		3%	15%	11%	10%
LVEF <35%, mean (SD)		63%	32% (13%)	45% (18%)	34% (14%)
NYHA ≥ 3		26%	9%	19%	11%
Presenting arrhythmia	VF	26%	45%	100%	48%
	VT + syncope	27%	21%	0%	13%
	VT, other	37%	34%	0%	25%
	Syncope	10%	0%	0%	14%
ICD patients on amiodarone		44–64%	26%	0%	16%
Amiodarone patients given ICD		NA	12%	5%	16%

Survival data are available for a sample of 535 UK implants, comprising 1171 years of follow-up. From *Table 39* the UK sample has similar annual survival rates, and a comparable age and gender distribution to patients recruited to the three main secondary prevention trials. This is encouraging since patients who take part in RCTs are well known to have superior survival to unselected patient groups from clinical practice, where there may be wider criteria for implantation.

Table 40 compares patients from the UK sample for whom clinical data were available, for which surviving patients are over-represented. This bias is clearly demonstrated by the 4% death rate per year for the UK complete data sample compared with 7% per year for the complete Liverpool/Papworth cohort (see *Table 39*). It should be noted that this table is provided for information only: the analysis is conducted in such a way that bias introduced by missing clinical data is minimised.

Compared with patients in the three main secondary prevention trials, those in the UK complete data sample were slightly younger, had higher NYHA class, were less likely to have non-ischaemic cardiomyopathy and were more likely to present with ventricular tachycardia. These differences are most likely due to the bias inherent in the practice of medicine in the UK compared with the USA and with other countries in Europe. For 10% of UK patients the main presenting symptom was recorded as syncope. However, of those patients for whom the pathway was documented (n = 378) only 12 (3.6%) had not had previous VT or VF and might be termed primary prevention cases.

UK patient sample: survival analysis

Implant date, survival status and date of death were available for all 535 patients implanted at Papworth between 1991 and May 2002 and Liverpool between 1991 and August 2002. Kaplan–Meier survival estimates are plotted for the two centres in *Figure 22*. In *Figure 22* the central survival curve is the Kaplan–Meier survival estimate for Liverpool and Papworth patients combined and the other two curves represent the 95% confidence interval. The 30-day mortality rate was 3/535 (0.6%) and actuarial survival at 1, 3 and 5 years was respectively 92% (90 to 95%), 86% (82 to 90%) and 71% (64 to 79%). This can be compared with pooled data from the ICD arms of the three secondary prevention trials, with corresponding approximate survival rates of 90%, 77% and 66%.[30]

The effect of centre, year of ICD implant, age and gender on postimplant survival can be assessed using 532 of 535 ICD patients implanted at Papworth and Liverpool during the study period. *Figure 23* shows Kaplan–Meier survival curves for these four covariates. Using log-rank tests for exploratory analysis only implant age had a significant effect, with older patients having poorer survival. There was no difference in survival between men and women, suggesting that selection of candidates likely to survive ICD implant is appropriate in this respect. *Table 41*

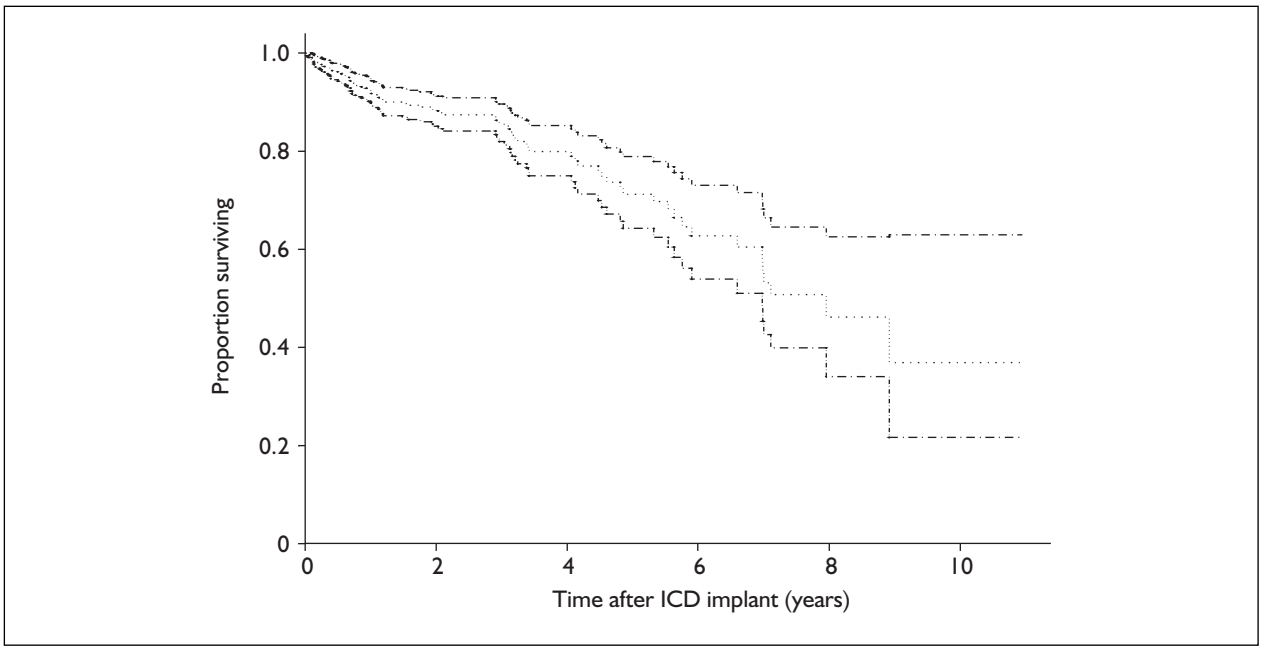

FIGURE 22 *Survival for Papworth and Liverpool ICD patients*

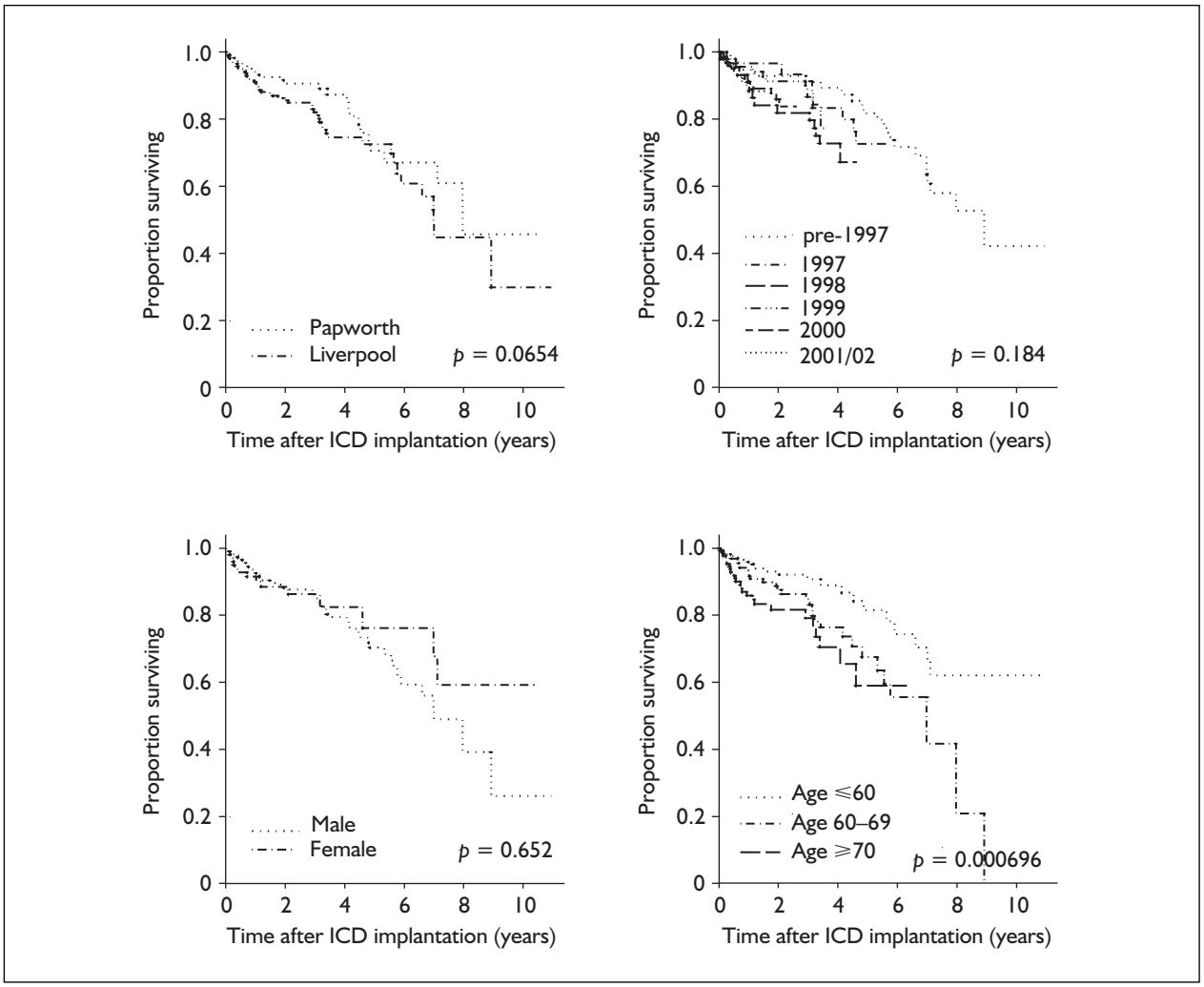

FIGURE 23 *Effect of patient characteristics on survival after ICD implantation: UK sample*

TABLE 41 *Results from univariate and multivariate Cox proportional hazards survival analysis using total UK sample (n = 535)*

	Univariate models		Multivariate model	
Factor	**Hazard ratio (95% CI)**	***p*[a]**	**Hazard ratio (95% CI)**	***p*[b]**
Centre				
Papworth	1.00		1.00	
Liverpool	1.24 (0.98 to 1.55)	0.06	1.15 (0.91 to 1.45)	0.21
Implant year				
Pre-1997	1.00		1.00	
1997	1.52 (0.61 to 3.78)		1.26 (0.49 to 3.21)	
1998	2.80 (1.17 to 6.69)		2.06 (0.83 to 5.08)	
1999	1.69 (0.64 to 4.47)		1.49 (0.56 to 4.02)	
2000	2.67 (1.05 to 6.83)		2.40 (0.92 to 6.26)	
2001/02	2.79 (1.08 to 7.20)	0.16	2.23 (0.85 to 5.89)	0.69
Age at implant (years)				
<60	1.00		1.00	
60–69	2.07 (1.21 to 3.55)		2.03 (1.17 to 3.49)	
≥70	2.97 (1.65 to 5.37)	0.0007	2.61 (1.41 to 4.83)	0.002
Gender				
Male	1.00		1.00	
Female	0.88 (0.50 to 1.55)	0.64	0.99 (0.56 to 1.75)	0.99

[a] *p* from likelihood ratio test, comparing univariate model with null model (cf. forward selection).
[b] *p* from likelihood ratio test, comparing full model with model leaving each factor out (cf. backward selection).

presents results of univariate and multivariate Cox proportional hazards regression. This confirms that the risk of death increases with implant age and that it is independent of centre, year of implant or gender.

From the literature, the clinical variables of interest were LVEF, NYHA score, presenting arrhythmia ventricular tachycardia (versus ventricular fibrillation) and whether or not the implant took place in the same admission as the presenting arrhythmia (pathway). As already discussed, there was a non-negligible amount of missing covariate information and it cannot be assumed to be missing at random. Therefore, two main approaches were taken. First, only patients implanted at Papworth were analysed to assess clinical risk factors for mortality. Although this analysis will result in broadly unbiased estimates of the effects of clinical factors, it has some problems. It will have low power to assess the covariate effects and fails to use all of the available information. In addition, it represents only a single UK centre and is less generalisable than inclusion of two major centres.

Results of survival analyses using Papworth patients

Kaplan–Meier survival estimates are plotted for the main clinical risk factors studied in *Figures 24* and *25* using Papworth patients only. Results of a univariate Cox proportional hazards regression for these variables are given in *Table 42*. Multivariate models were not developed owing to the number of patients for whom risk factors were not measured and the lack of power.

In common with the analysis of the total UK, patients aged 70 years or over at implant had poorer postimplant survival and there was no difference between the genders. Patients aged 60–69 years at implant did not have poorer survival than those aged less than 60, but there were only 12 deaths in the younger group and seven in those aged 60–69 at Papworth. Patients with LVEF below 35% and patients with NYHA class of III or greater had significantly poorer survival. Almost all patients were secondary prevention patients and within this population there was no difference in survival between those presenting with VF and VT or between those discharged following the presenting arrhythmia and those implanted before discharge, although power to identify such differences in the Papworth cohort alone is limited.

A second analysis was carried out using data from all UK patients, using multiple imputation of missing clinical covariates.

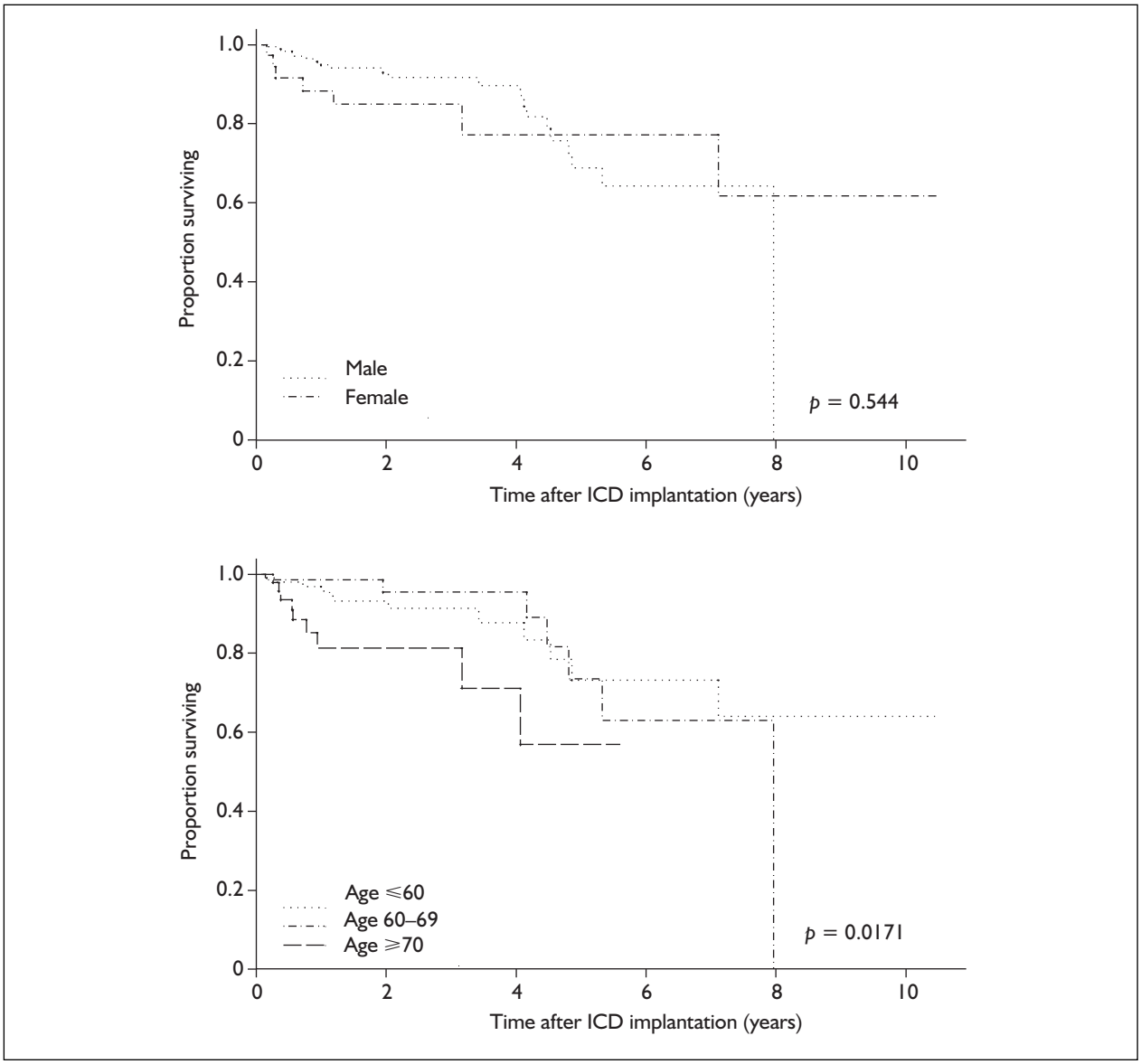

FIGURE 24 *Effect of patient age at implantation and gender on survival after ICD implantation: Papworth sample*

Details of multiple imputation

Figure 26 shows Kaplan–Meier estimates for UK patients with complete covariate data. These are similar to those for Papworth patients alone, but may be biased owing to missing data. For this study, the missing data mechanism was related to the ability to retrieve patient records, particularly those from patients who had died. Stochastic regression imputation was used to estimate values for the missing covariate data. The regression of a missing covariate on age, gender and survival status was estimated from complete cases and the resulting prediction equation was used to impute an estimated value for the missing covariate. Since simple imputation of the predicted value underestimates the covariance of estimates, the missing covariate was simulated from the regression prediction plus a random error. It has been shown that imputing a single value will seriously underestimate the variances of parameters, as it fails adequately to take into account the uncertainty associated with estimating the missing covariates.[61] Therefore, this problem was addressed by repeating the imputation five times,[62,63] so producing five complete data sets from which to estimate covariates for survival. A series of five survival analyses was carried out using Cox proportional hazards regression. Final parameter estimates were calculated as the mean of the estimates from the five survival analyses. Variances of the final parameter estimates were calculated as the mean of the variances from the five analyses plus 1.2 times the variance of the five parameter estimates. The latter term in this sum estimates the contribution to

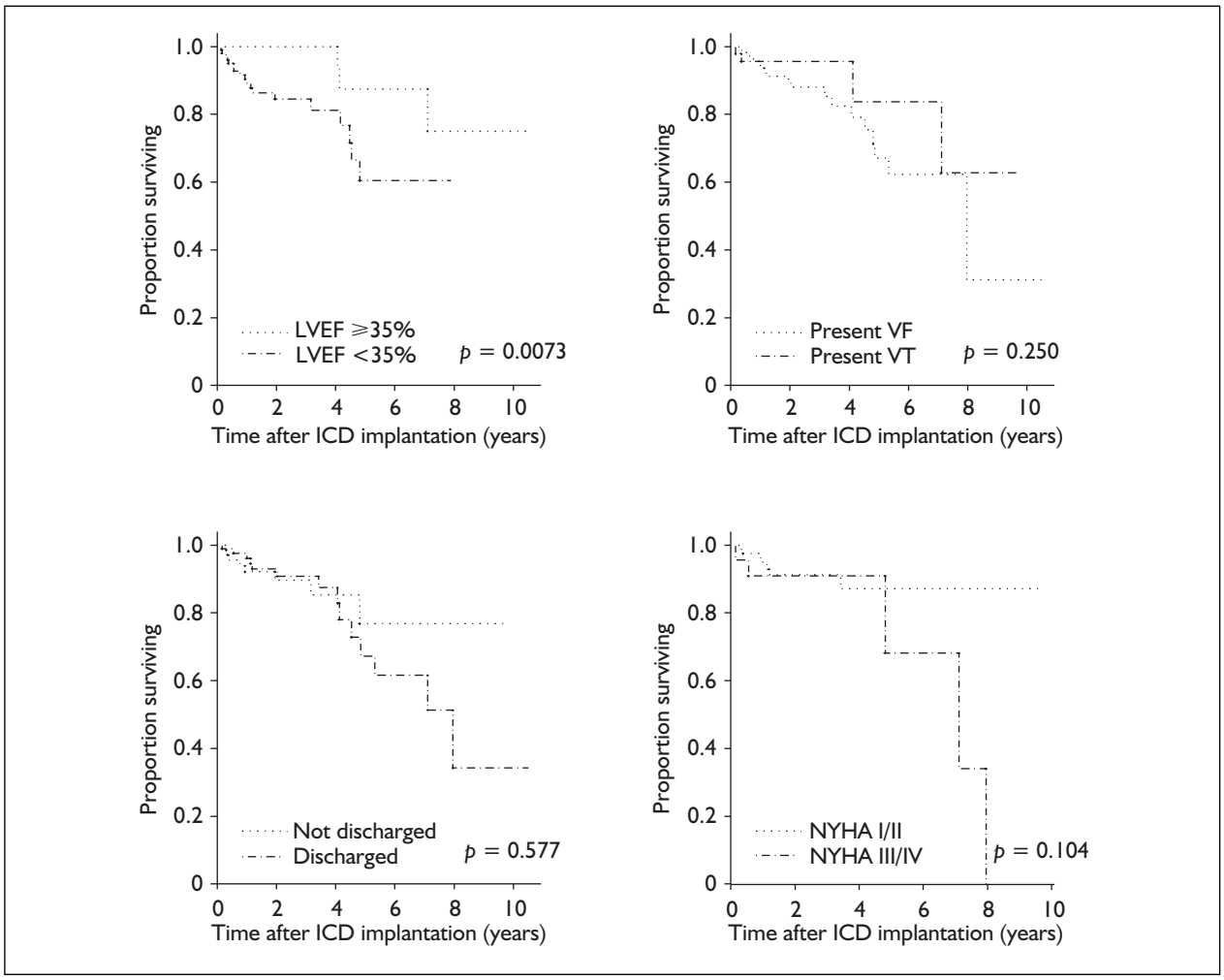

FIGURE 25 *Effect of clinical characteristics on survival after ICD implantation: Papworth sample*

TABLE 42 *Results from univariate Cox proportional hazards survival analysis using total Papworth patients only* (n = *211)*

Factor	Hazard ratio (95% CI)	*p*[a]
Age at implant (years)		
<60	1.00	
60–69	0.50 (0.16 to 1.51)	
≥70	2.64 (1.08 to 6.46)	0.019
Gender		
Male	1.00	
Female	0.87 (0.31 to 2.4)	0.78
LVEF		
≥35%	1.00	
<35%	4.74 (1.37 to 16.5)	0.004
Presenting arrhythmia		
VF	1.00	
VT	0.51 (0.17 to 1.53)	0.24
Pathway		
Not discharged	1.00	
Discharged after arrhythmia	1.37 (0.57 to 3.29)	0.50
NYHA		
<3	1.00	
≥3	2.52 (0.80 to 8.02)	0.13

[a] *p* from likelihood ratio test, comparing univariate model with null model (cf. forward selection).

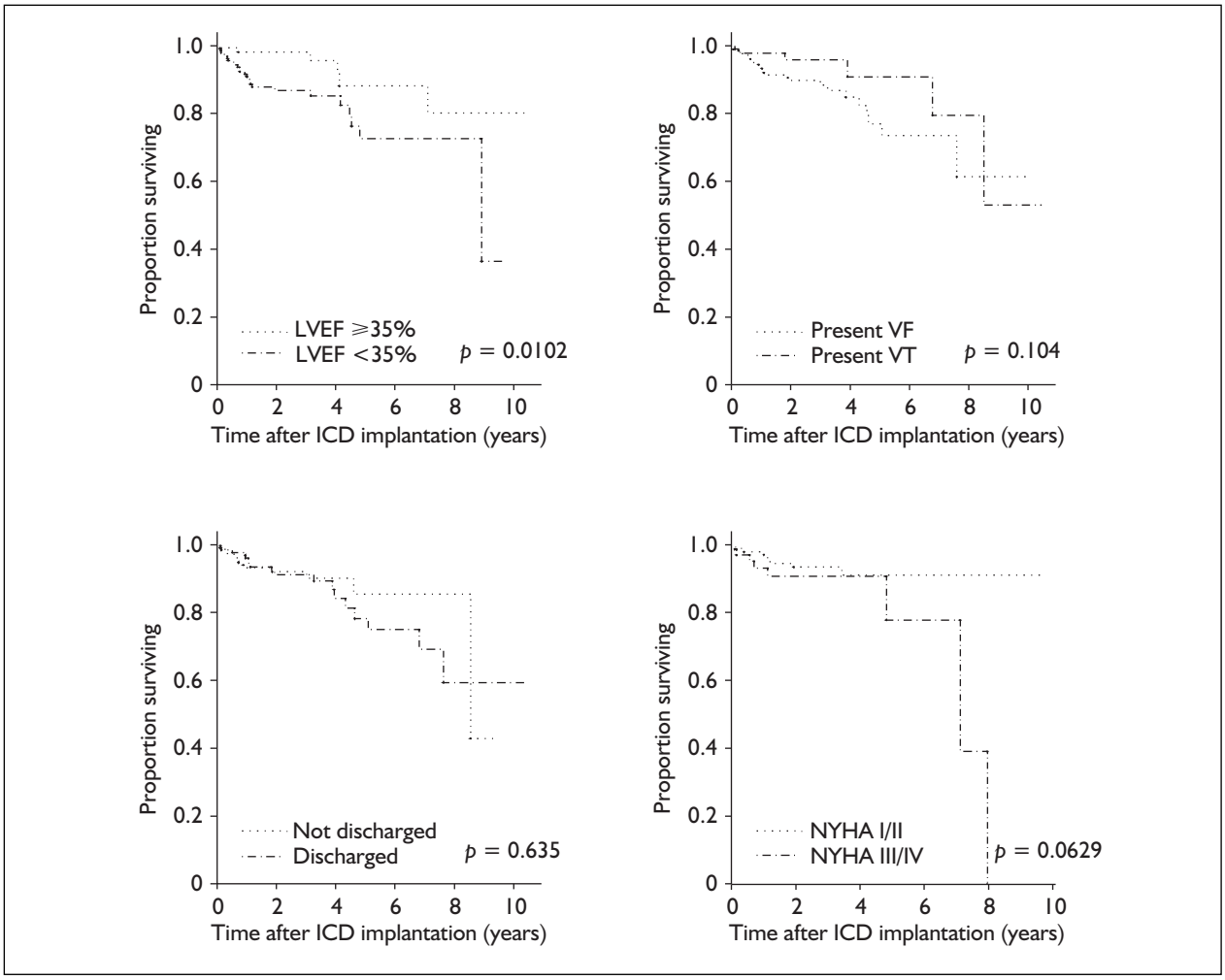

FIGURE 26 *Effect of clinical characteristics on survival after ICD implantation: UK sample with non-missing data*

the variance from imputation uncertainty with a 1.2 continuity correction resulting from the use of five imputations to approximate the full uncertainty of each missing covariate. Inference was based on *z*-scores calculated as the mean parameter estimate divided by its standard error.

Results of survival analysis using multiple imputation

The following regression equations were used to sample missing covariates.

Logit (p(LVEF < 35%)) = 0.0045
+1.2373 (if aged 60–69)
+1.2358 (if aged ≥ 70)
–1.2890 (if female)
+1.2000 (if died)

Logit (p(NYHA ≥ III)) = –1.7251
+1.1603 (if aged 60–69)
+0.7502 (if aged ≥ 70)
+ 0.0822 (if female)
+ 0.8785 (if died)

Logit (p(VT presenting arrhythmia)) = –1.0428
+0.2519 (if aged 60–69)
–0.3069 (if aged ≥ 70)
+0.2606 (if female)
–0.4759 (if died)

Logit (p(discharged)) = 0.1237
–0.0058 (if aged 60–69)
–0.3240 (if aged ≥ 70)
–0.6235 (if female)
+0.3991 (if died)

Table 43 shows the results of survival analysis using multiple imputation. This analysis resulted in greater precision for hazard ratios than the analysis based on Papworth cases alone and should be less biased. Again, the factors affecting survival after ICD implantation were patient age, LVEF of less than 35% and NYHA class of III or more. These factors remained in a multivariate analysis.

TABLE 43 *Results from univariate and multivariate Cox proportional hazards survival analysis using total UK sample with multiple imputation for missing covariates (n = 535)*

	Univariate models		Multivariate model	
Factor	**Hazard ratio (95% CI)**	***p*[a]**	**Hazard ratio (95% CI)**	***p*[a]**
Age at implant (years)				
<60	1.00		1.00	
60–69	2.07 (1.21 to 3.55)		1.60 (0.85 to 3.01)	
≥70	2.97 (1.65 to 5.37)	0.0007	2.09 (1.07 to 4.07)	0.002
Gender				
Male	1.00		1.00	
Female	0.88 (0.50 to 1.55)	0.64	0.83 (0.46 to 1.49)	0.65
LVEF				
≥35%	1.00		1.00	
<35%	3.16 (1.51 to 6.59)	0.0001	2.61 (1.29 to 5.25)	0.003
Presenting arrhythmia				
VF	1.00		1.00	
VT	0.53 (0.26 to 1.10)	0.09	0.55 (0.26 to 1.16)	0.13
Pathway				
Not discharged	1.00		1.00	
Discharged after arrhythmia	1.21 (0.71 to 2.06)	0.47	1.36 (0.83 to 2.22)	0.21
NYHA				
<III	1.00		1.00	
≥III	2.25 (1.25 to 4.04)	0.003	1.77 (1.00 to 3.14)	0.05

[a] *p* from *z*-statistic.

Discussion

Two UK centres with considerable experience of ICD implantation provided patient data so that patient characteristics and survival could be examined in detail and compared with other UK centres and published trials and to inform cost-effectiveness analyses. The UK sample comprised 535 cases, of which 380 supplied clinical data. The demographic characteristics of the UK sample were similar to those of the UK ICD population as a whole and to those patient groups taking part in RCTs of ICD implantation as secondary prevention. There were some differences between the UK sample and RCT patients, but survival rates were similar. Patient age at implantation and functional status measured by LVEF and NYHA significantly affected survival after implant and these factors reflect population characteristics. It cannot be inferred that ICDs are less effective in these patients. Indeed, these patient groups may gain most when compared with continued treatment with AADs.

The benefit of extracting data from a UK sample is that patient experience can be studied in more detail than, for example, a registry can. However, this analysis was limited by the extent of the missing clinical data. It was necessary to use multiple imputation methods. In the analysis it was assumed that missing data were dependent on age at implant, gender and survival status at data retrieval. Thus, missing data for a patient were imputed to reflect the distribution of measurements in patients with similar characteristics. In this way it was intended to maximise the power of the analysis by including all 535 patients and to minimise any bias that may have arisen owing to the non-random, missing data mechanism. All analyses conducted had consistent results and this lends support to these assertions. Ideally, randomised data comparing ICDs with optimal medical management in a UK setting would be available to inform cost-effectiveness modelling. In the absence of a UK-based RCT a larger cohort of patients representing national practice should be used and the authors would call on all centres in future to contribute a complete set of requested core data to the BPEG registry for each and every patient undergoing ICD implantation. The UK sample provides a reasonably representative sample of UK ICD patients from which to estimate mortality after implantation, overall and in important subgroups.

In this sample almost all patients had previously documented VT or VF and so are classed as secondary prevention, although there is evidence from BPEG that implantation in a primary prevention setting is increasing (Chapter 4).

Summary

Two UK centres provided basic data on 535 ICD cases and detailed clinical data on 380 ICD cases. Over 96% underwent ICD implantation for secondary prevention and were similar to ICD patients in the UK as a whole and to those patient groups taking part in RCTs of ICD implantation as secondary prevention. Patient age at implantation and functional status measured by LVEF and NYHA significantly affected survival after implantation and these factors reflect population characteristics. It cannot be inferred that ICDs are less effective in these patients. Indeed, these patient groups may gain most when compared with continued treatment with AADs.

Owing to missing clinical data, stochastic imputation was used to maximise power of the analysis by including all 535 patients and to minimise any bias that may have arisen owing to the non-random, missing data mechanism. All analyses conducted had consistent results and this lends support to these assertions. In the absence of UK-based RCTs ideally a larger cohort of patients representing national practice should be used.

Chapter 6

Patient review: health-related quality of life survey

Background

HRQoL estimates from RCTs of ICD therapy are reviewed in Chapter 2. Against a background of a lack of published HRQoL information from studies of UK patients, and better to inform this review of cost-effectiveness, a cross-sectional survey was undertaken of ICD patients at Liverpool and Papworth.

Objectives

The objectives of the survey were to describe HRQoL for ICD patients at different time-points following implantation, in order to inform economic analyses, and to investigate patient factors that might influence HRQoL.

Methods

Patients

In common with the clinical data retrieval protocol, the survey population comprised all ICD patients implanted at the two centres in the years up to December 1999 and a random sample from those implanted in 2000 and 2001. Following review of the survey protocol by the LRECs concerned, patient and GP contact details were provided by the two hospitals. Before writing to patients, their GPs were contacted to check patients' addresses and to ensure as far as possible that only patients who were alive were approached. The package sent to patients included a letter from their consultant cardiologist (DCo or AG), an information sheet approved by the local research ethics committees and the questionnaires. Of the Liverpool patients, 18 could not be contacted, either because they had left the area or because details could not be obtained from their GP. Thus, a total of 313 patients was approached; details of the numbers by centre and by year, and the response rates, are described in *Figure 27* and *Table 44*.

Survey questionnaire

The survey questionnaire consisted of an ICD-specific measure and three generic measures: the Short Form 36 (SF-36), the Hospital Anxiety and Depression (HAD) questionnaire and the EuroQoL 5 Dimensions (EQ-5D). All of these measures were suitable for self-completion.

At the time of preparing the research protocol, there was a lack of published data from HRQoL studies in the large RCTs. From the published small prospective studies, and from information on the measures being used in the trials, the choice of generic measures was confirmed.

Generic measures

Although the Nottingham Health Profile (NHP) had been used in some studies and was the main generic health status questionnaire in the CIDS trial, it was decided to use the SF-36, the choice of the AVID and DINAMIT groups, because it has been shown to be more sensitive to small differences between groups and over time, and has the added advantage of having well-established UK population norms. The SF-36 aims to describe eight dimensions of HRQoL on a scale of 0 (minimum function) to 100 (maximum function). The dimensions are physical functioning, role limitations due to physical problems, pain, energy/vitality, social functioning, mental health, role limitations due to emotional problems, and general health. These scales can be combined into two composite scales named the physical component score (PCS) and the mental component score (MCS) (see, for example, Ware and colleagues[64]). The commonly used standardisation method was adopted, so that the PCS and MCS are centred around 50 with a standard deviation of 10.

From several studies published in the late 1990s reviewed by Sears and colleagues,[24] evidence was growing that a significant number of ICD recipients was experiencing diagnosable levels of anxiety. A study of 63 patients in Germany[26] reported a clear association between the number of shocks and the frequency of mood disturbances as assessed by the HAD scale. The HAD quantifies two components of mood, anxiety and depression, and has 14 questions requiring a response on four levels. Each component has a measurement scale of 0 (no problems) to 21 (maximum problems). The HAD has been used as a screening tool for intervention therapies, with a component score of

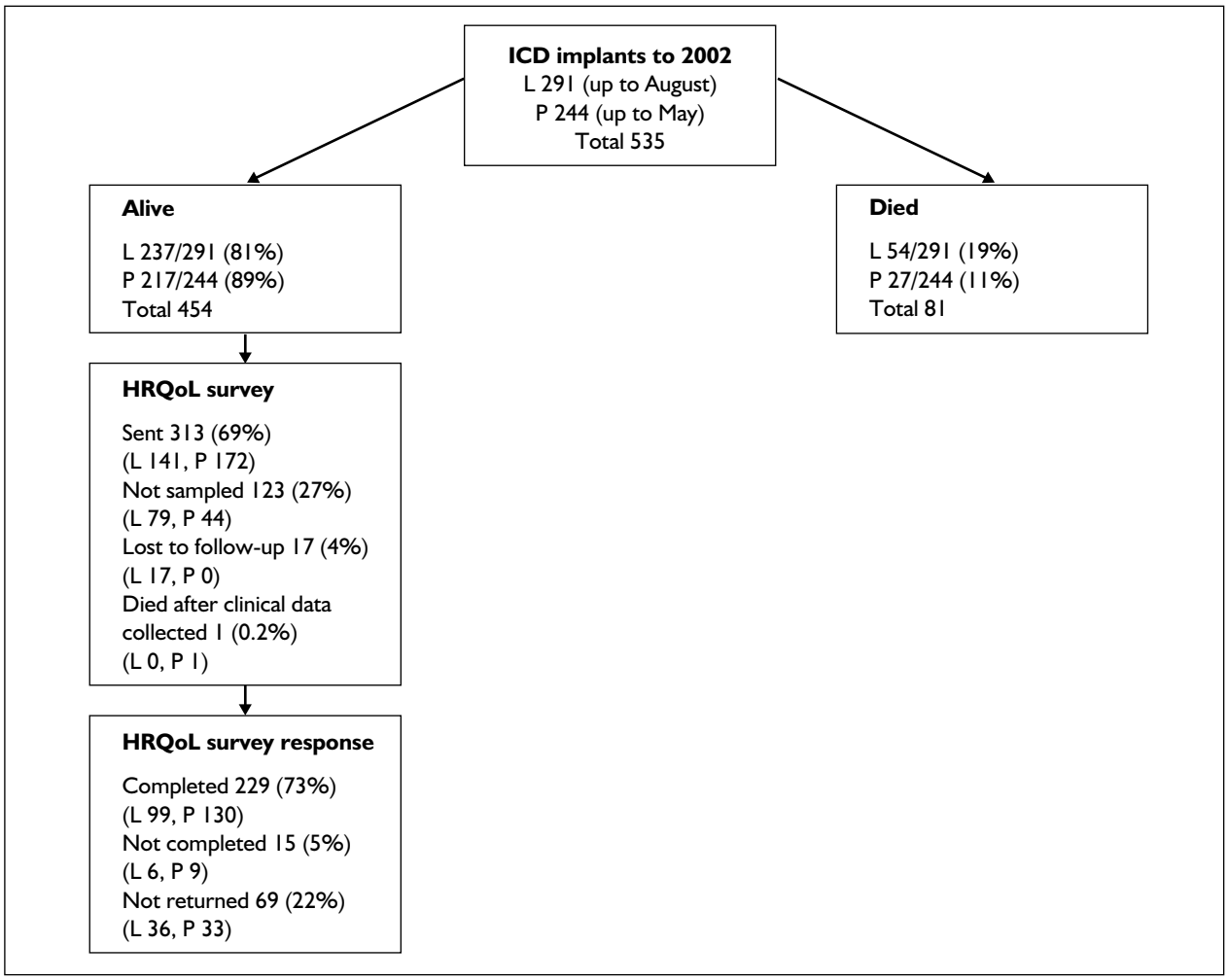

FIGURE 27 *HRQoL data collection. L, Liverpool; P, Papworth.*

TABLE 44 *HRQoL data collection by year of ICD implant*

Centre	Status of data	ICD patients by year of ICD implant												
		1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	Total
HRQoL requested														
Papworth	Data completed	1	1	1	5	1	6	8	9	24	24	40	10	130
Liverpool	Data completed	1	0	0	2	4	4	5	12	22	17	20	12	99
Papworth	Returned not complete	0	0	0	0	0	0	0	1	1	0	3	4	9
Liverpool	Returned not complete	0	0	0	1	0	0	0	1	3	0	0	1	6
Papworth	Not returned	0	0	0	0	0	0	0	1	3	10	11	8	33
Liverpool	Not returned	0	0	2	1	0	0	3	4	6	4	10	6	36
	Subtotal	2	1	3	9	5	10	16	28	59	55	84	41	313
HRQoL not requested														
Papworth	Not sampled/lost	1	0	2	1	0	0	4	2	1	8	16	10	45
Liverpool	Not sampled/lost	0	0	0	0	0	0	2	2	1	24	32	35	96
Papworth	Deaths	1	2	0	3	2	2	2	3	2	6	4	0	27
Liverpool	Deaths	2	2	1	1	3	3	6	10	6	8	10	2	54
	Subtotal	4	4	3	5	5	5	14	17	10	46	62	47	222
	Total	6	5	6	14	10	15	30	45	69	101	146	88	535

2002 includes implants up to May for Papworth and August for Liverpool.

8–10 representing borderline significance and a score of 11 or over considered clinically significant.

The EQ-5D[65] has been used in many studies of cost-effectiveness. It defines health in terms of five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has three levels: no problem, a moderate problem or an extreme problem. Health states defined in terms of the level chosen for each dimension can be valued using utility weights reflecting values from a representative sample of the UK population.[66] These utilities are scaled so that full health = 1 and dead = 0, and allow for severe health states for which quality of life is valued as worse than death.

Disease-specific instrument

There was no validated ICD-specific instrument available at the time of the survey, but from the questionnaires used in CIDS and DINAMIT, the published work from Germany,[26] and in discussion with these investigators, a disease/ICD-specific instrument was compiled and tested with a group of patients. It consisted of sections on employment, driving and general activities, effect of the patient's condition on relationships with partner/family and living with an ICD.

Survey questionnaire pilot study

The pilot study of the full questionnaire, comprising all four instruments, was conducted with ICD patients at Glenfield Hospital, Leicester. As well as completing the questionnaire, patients were asked how long it had taken to complete and for their comments on whether it covered the issues important to living with an ICD, and whether any questions were irrelevant, difficult to understand or difficult to respond to. Of the 28 patients who agreed to take part, 25 recorded the time of completion, which averaged 29 minutes. Comments were provided by 15 patients and of those specific to the questionnaire, they were positive about both the length and the content. The final version of the disease-specific section of the survey questionnaire is provided in Appendix 8 and the patients' comments on the questionnaire are given in Appendix 9.

Clinical variables

The clinical variables of interest were low LVEF (<35%), NYHA score (≥3), presenting arrhythmia (VT or VF) and whether or not the implant took place in the same admission as the presenting arrhythmia (pathway). In common with the survival analysis there was a non-negligible amount of missing covariate information. The missing data mechanism is less clear in the case of HRQoL elicitation since the data are confined to currently living patients. Therefore two approaches were adopted: first, only patients with complete clinical covariate data were analysed, and second, multiple imputation of missing clinical covariates was used.

Results

Response rate

By 31 December 2002, 229 patients (73%) had returned completed questionnaires, 15 (5%) had returned questionnaires that were not filled in and 69 (22%) did not respond. There was no difference between the genders in response rate, with 73% of females and 73% of males returning completed questionnaires. Those patients who completed questionnaires were not significantly younger than those who did not (median age 62 and 63 years, respectively, Wilcoxon signed-ranks test, $p = 0.149$). Age and gender were available for all 229 patients who completed and returned quality of life questionnaires. Thus, the effect on postimplant HRQoL, centre, year of ICD implantation, and age and gender can be assessed using all 229 respondents. Patients who failed to return their questionnaire or returned blank questionnaires were assumed to be missing at random and were not studied further.

Generic questionnaires

The histograms in *Figure 28* give the responses to the components of the three generic instruments and show that patients tend to cluster around the healthy end of each scale, the 'ceiling effect'. This is particularly evident in the EQ-5D utility scale.

Figure 29 summarises the main scales from the generic questionnaires according to the time since ICD implantation and summary statistics are given in *Table 45*. Based on responses to this cross-sectional survey there is no evidence that self-reported HRQoL changes substantially over time. In addition, there were no differences between the two centres and, therefore, all responses were combined for further analysis.

Table 46 shows the results of univariate and multivariate linear regression analyses, using only those patients with actual covariate measurements, for the SF-36 physical and mental scales, anxiety and depression from the HAD and the EQ-5D. There was very little evidence of a relationship between self-reported HRQoL and patients'

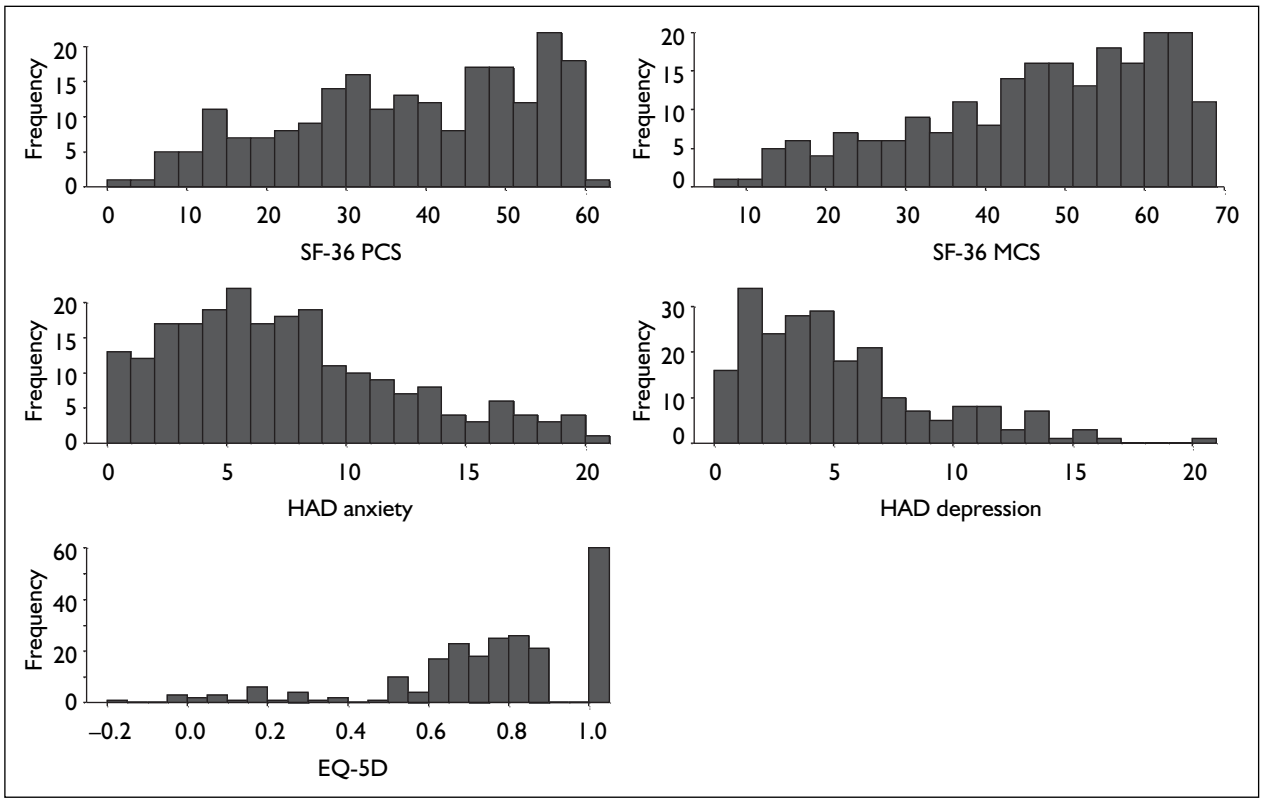

FIGURE 28 *Histograms of responses for the three main generic HRQoL measures*

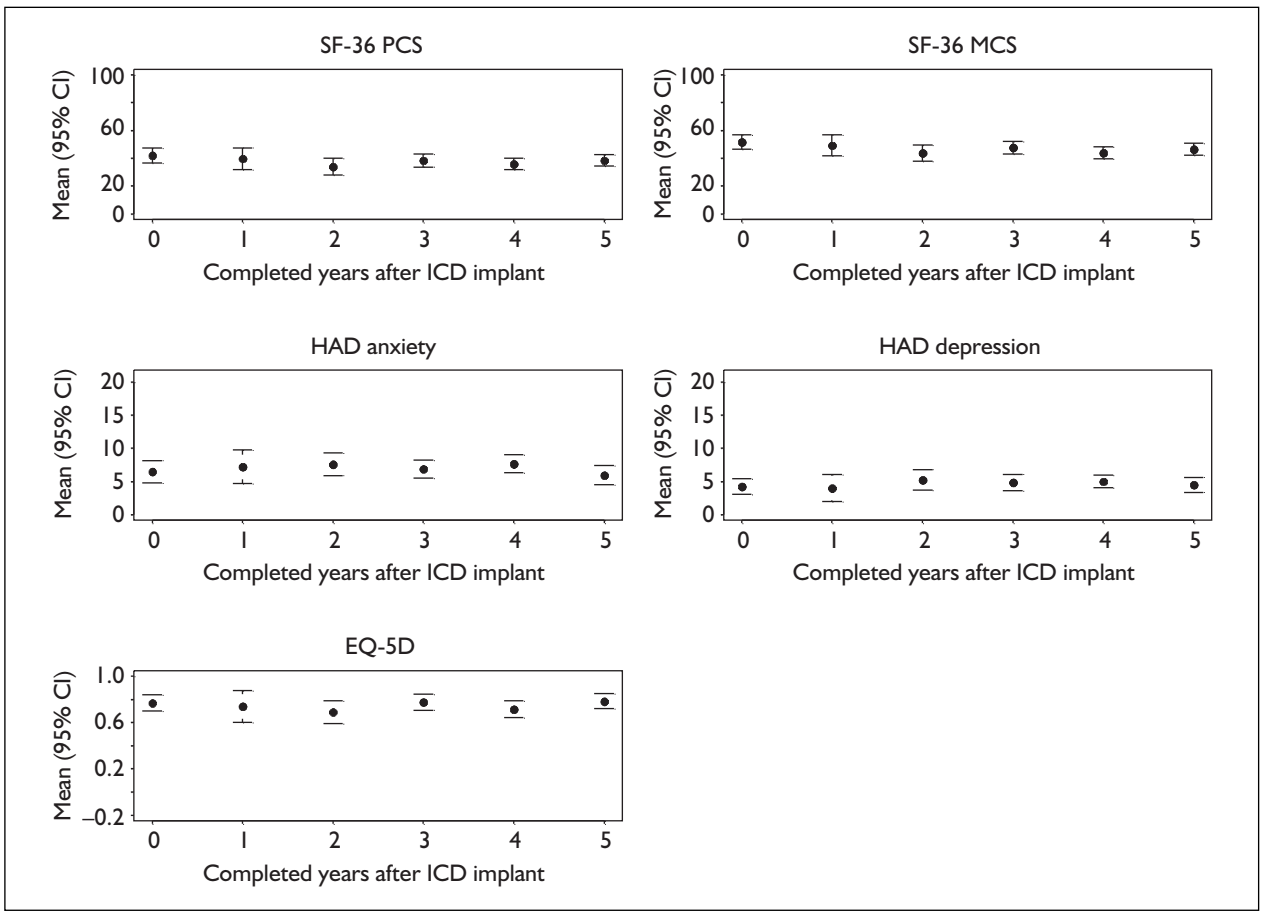

FIGURE 29 *Mean and 95% confidence intervals for the main generic HRQoL measurements against time after ICD implantation*

TABLE 45 *Generic HRQoL measures by time since ICD implantation*

	Time since ICD implantation (years)					
Measurement	**1 (*n* = 42)**	**2 (*n* = 54)**	**3 (*n* = 43)**	**4 (*n* = 37)**	**5 (*n* = 19)**	**≥6 (*n* = 34)**
SF-36 PCS (*n* = 215)[a]	38.6 (13.1)	35.9 (15.2)	38.5 (14.7)	34.1 (17.3)	39.7 (16.7)	42.0 (14.6)
SF-36 MCS (*n* = 215)[a]	46.6 (13.7)	44.0 (15.5)	47.7 (15.0)	43.8 (17.1)	49.4 (15.9)	51.8 (14.3)
HAD anxiety (*n* = 224)[a]	6.0 (4.7)	7.7 (4.9)	6.9 (4.4)	7.6 (5.0)	7.2 (5.4)	6.5 (4.9)
HAD depression (*n* = 224)[a]	4.5 (3.7)	5.0 (3.4)	4.8 (4.0)	5.3 (4.7)	4.0 (4.3)	4.3 (3.4)
EQ-5D (*n* = 229)[a]	0.78 (0.21)	0.71 (0.27)	0.78 (0.23)	0.69 (0.30)	0.74 (0.30)	0.77 (0.20)

Data are shown as mean (SD).
[a] Scores could not be calculated for patients with incomplete responses.

TABLE 46 *Results from univariate and multivariate linear regression analysis using available covariate data* (n = *229)*

	Univariate models		Multivariate model	
Response	**Coefficient (SE)**	***p*[a]**	**Coefficient (SE)**	***p*[a]**
SF-36 PCS				
Female gender	–2.25 (2.64)	0.40	0.23 (4.23)	0.96
Age at implant 60–69 years	0.75 (2.32)	0.75	0.97 (3.49)	0.78
Age at implant ≥ 70 years	–1.79 (2.82)	0.53	–2.04 (5.03)	0.69
LVEF < 35%	–3.86 (2.36)	0.10	–2.88 (3.63)	0.43
Presenting arrhythmia VT	4.01 (2.43)	0.10	2.56 (3.44)	0.46
Discharged pathway	0.52 (2.20)	0.82	–0.23 (3.32)	0.95
NYHA ≥ 3	–6.07 (3.17)	0.06	–5.36 (4.21	0.21
SF-36 MCS				
Female gender	–3.21 (2.65)	0.23	–0.44 (4.14)	0.92
Age at implant 60–69 years	2.75 (2.34)	0.24	2.17 (3.42)	0.53
Age at implant ≥ 70 years	0.37 (2.84)	0.90	1.25 (4.93)	0.80
LVEF < 35%	–1.68 (2.38)	0.48	–3.11 (3.56)	0.38
Presenting arrhythmia VT	3.64 (2.41)	0.13	1.89 (3.38)	0.58
Discharged pathway	–0.85 (2.18)	0.70	–2.11 (3.25)	0.52
NYHA ≥ 3	–5.21 (3.21)	0.11	–4.31 (4.13)	0.30
HAD anxiety				
Female gender	1.46 (0.82)	0.08	0.49 (1.16)	0.68
Age at implant 60–69 years	–1.17 (0.70)	0.10	–1.10 (0.94)	0.24
Age at implant ≥ 70 years	–3.16 (0.85)	0.0002	–2.46 (1.27)	0.06
LVEF < 35%	–0.69 (0.36)	0.36	0.52 (0.97)	0.59
Presenting arrhythmia VT	–0.04 (0.71)	0.96	–0.56 (0.92)	0.55
Discharged pathway	0.44 (0.64)	0.49	1.28 (0.89)	0.15
NYHA ≥ 3	0.85 (0.94)	0.37	1.18 (1.11)	0.29
HAD depression				
Female gender	0.48 (0.66)	0.47	–0.91 (1.02)	0.37
Age at implant 60–69 years	–0.44 (0.58)	0.45	–0.97 (0.83)	0.25
Age at implant ≥ 70 years	–0.70 (0.70)	0.32	–0.27 (1.12)	0.81
LVEF < 35%	–0.26 (0.60)	0.67	–0.44 (0.85)	0.60
Presenting arrhythmia VT	–0.11 (0.57)	0.85	–0.20 (0.81)	0.81
Discharged pathway	0.07 (0.53)	0.89	0.19 (0.78)	0.81
NYHA ≥ 3	0.32 (0.79)	0.69	0.70 (0.97)	0.47
EQ-5D				
Female gender	–0.051 (0.042)	0.22	–0.028 (0.066)	0.67
Age at implant 60–69 years	0.028 (0.037)	0.46	0.043 (0.055)	0.43
Age at implant ≥ 70 years	0.040 (0.044)	0.37	0.019 (0.072)	0.79
LVEF < 35%	–0.053 (0.037)	0.18	–0.068 (0.055)	0.22
Presenting arrhythmia VT	0.013 (0.037)	0.73	0.008 (0.053)	0.88
Discharged pathway	–0.011 (0.034)	0.74	–0.029 (0.051)	0.58
NYHA ≥ 3	–0.094 (0.051)	0.07	–0.091 (0.063)	0.15

Data are shown as mean (SE).
[a] *p* from Wald test.

TABLE 47 *Results from univariate and multivariate linear regression analysis using multiple imputation for missing covariate data (n = 229)*

	Univariate models		Multivariate model	
Response	**Coefficient (SE)**	***p*[a]**	**Coefficient (SE)**	***p*[a]**
SF-36 PCS				
Female gender	–2.25 (2.64)	0.40	–3.30 (2.82)	0.25
Age at implant 60–69 years	0.75 (2.32)	0.75	1.88 (2.46)	0.45
Age at implant ≥ 70 years	–1.79 (2.82)	0.53	–0.56 (2.95)	0.85
LVEF < 35%	–3.28 (2.22)	0.13	–3.30 (2.40)	0.17
Presenting arrhythmia VT	3.12 (2.47)	0.21	3.00 (2.51)	0.25
Discharged pathway	1.35 (2.17)	0.52	0.12 (2.30)	0.98
NYHA ≥ 3	–4.68 (2.43)	0.08	–4.54 (2.60)	0.08
SF-36 MCS				
Female gender	–3.21 (2.65)	0.23	–3.76 (2.83)	0.17
Age at implant 60–69 years	2.75 (2.34)	0.24	3.48 (2.48)	0.16
Age at implant ≥ 70 years	0.37 (2.84)	0.90	0.82 (3.00)	0.79
LVEF < 35%	–1.29 (2.33)	0.58	–1.85 (2.54)	0.46
Presenting arrhythmia VT	2.68 (2.52)	0.29	2.59 (2.58)	0.31
Discharged pathway	0.29 (2.18)	0.89	–0.94 (2.27)	0.67
NYHA ≥ 3	–3.66 (2.49)	0.09	–4.33 (2.70)	0.11
HAD anxiety				
Female gender	1.46 (0.82)	0.08	1.13 (0.85)	0.18
Age at implant 60–69 years	–1.17 (0.70)	0.10	–1.20 (0.74)	0.11
Age at implant ≥ 70 years	–3.16 (0.85)	0.0002	–3.06 (0.90)	0.001
LVEF < 35%	–0.59 (0.68)	0.39	0.14 (0.72)	0.22
Presenting arrhythmia VT	0.16 (0.80)	0.84	–0.03 (0.78)	0.99
Discharged pathway	0.11 (0.74)	0.89	0.25 (0.73)	0.71
NYHA ≥ 3	0.41 (0.78)	0.60	0.63 (0.80)	0.43
HAD depression				
Female gender	0.48 (0.66)	0.47	0.39 (0.70)	0.59
Age at implant 60–69 years	–0.44 (0.58)	0.45	–0.49 (0.62)	0.44
Age at implant ≥ 70 years	–0.70 (0.70)	0.32	–0.69 (0.74)	0.33
LVEF < 35%	–0.06 (0.55)	0.59	0.11 (0.59)	0.86
Presenting arrhythmia VT	–0.06 (0.62)	0.93	–0.07 (0.64)	0.93
Discharged pathway	–0.15 (0.57)	0.80	–0.07 (0.60)	0.91
NYHA ≥ 3	0.32 (0.61)	0.59	0.40 (0.65)	0.54
EQ-5D				
Female gender	–0.051 (0.042)	0.22	–0.061 (0.045)	0.15
Age at implant 60–69 years	0.028 (0.037)	0.46	0.047 (0.040)	0.24
Age at implant ≥ 70 years	0.040 (0.044)	0.37	0.054 (0.046)	0.24
LVEF < 35%	–0.039 (0.036)	0.28	–0.054 (0.039)	0.17
Presenting arrhythmia VT	0.005 (0.043)	0.92	0.007 (0.043)	0.87
Discharged pathway	0.005 (0.037)	0.89	–0.009 (0.040)	0.83
NYHA ≥ 3	–0.067 (0.039)	0.09	–0.069 (0.041)	0.09

Data are shown as mean (SE).
[a] *p* from Wald test.

characteristics. Patients aged 70 or over at implantation were less anxious but even this was attenuated in the multivariate analysis.

Table 47 shows similar results for univariate and multivariate linear regression analyses for the five measurements from the generic questionnaires, using multiple imputation for missing covariates (see Chapter 5). This improves precision only very slightly since the amount of missing covariate data was small for patients alive at the time of the survey. The relationship between patient age and anxiety is clearer, but no other significant effects emerge.

ICD-specific questionnaire

Of the 229 patients in the survey, 194 provided information about current employment status: 54 were in employment, seven were homemakers and one was a student. Of those not working, 110 were

TABLE 48 *Activity limitations*

Most important reason for activity limitation in the last month								
Not limited	**Symptoms**	**Fear of irregular rhythm**	**Concern too active**	**Family concerned**	**Medical advice**	**Transport**	**Other**	**Total**
77 (35.0)	96 (43.6)	19 (8.6)	6 (2.7)	6 (2.7)	3 (1.4)	6 (2.7)	7 (3.2)	220 (100)

Limitations due to heart rhythm problem	**True**	**False**	**Total**
I will not travel very far from home	48 (21.2)	178 (78.8)	226 (100)
I will not travel to places where I think that the hospital facilities are poor	100 (44.4)	125 (55.6)	225 (100)
I will not go to isolated areas, for example into the woods or countryside, on my own	95 (41.9)	132 (58.1)	227 (100)
I will not go to isolated areas, for example into the woods or countryside, even if someone is with me	18 (8.1)	204 (91.9)	222 (100)
I will not go to public places on my own	27 (12.1)	196 (87.9)	223 (100)
I will not go to public places even if someone else goes with me	6 (2.7)	218 (97.3)	224 (100)
I will not stay alone, for example at home, when no one else is with me	12 (5.3)	213 (94.7)	225 (100)
There are particular strenuous activities which I avoid	192 (84.2)	36 (15.8)	228 (100)

Data are shown as *n* (%) of patients.

retired, 21 were not working due to ill-health and one patient was looking for work. Of those patients who had retired, 56 (51%) had retired by choice, 40 (36%) on their doctor's advice and the remainder at the request of their employer. Only 36 patients were living alone; most patients lived with a spouse (151) or with a spouse and/or relatives (30).

With regard to limitations in general activities over the previous month (*Table 48*), 77 patients (33.6%) said that they had not experienced limitations but for the 143 who had, the most important reasons were symptoms and a fear of irregular heart rhythm. Patients were also asked about any limitations in terms of situations that they might avoid, specifically because of their heart condition. The main situations were travel far from home (21%), travel to places with poor hospital facilities (44%), going to isolated places alone (42%) and strenuous activities (84%). None of these measures of activity was related to time since ICD implantation.

In asking patients about the effect of their heart condition on driving, 226 patients responded. Of the 157 patients who said that they were driving, 88 were driving the same amount as before their ICD implantation and 61 (38.9%) were driving less, but of these, only 17 said that it was because of their heart condition. Five patients said that they were driving more since their ICD implantation and three patients did not classify the amount. Of the 69 patients not driving, 25 had never learnt to drive, 15 had had their licence withdrawn by the DVLA owing to a health problem (21.7%) and 28 had stopped driving, of whom 11 (39%) said that this was because of their heart problem.

In considering the effect of the patient's condition on relationships over the previous month, 227 patients provided information: 146 (64%) said that their partner or family had been anxious about them, 136 (60%) said that they had been overprotective of them and 107 (47%) said that they had felt a burden to their partner or family, because of their condition. Again, there was no evidence that these effects were related to time since ICD implantation.

The Living with ICD questionnaire has 19 questions which were scaled from 0 (not at all) to 3 (very much) following the method used by Herrmann and colleagues;[26] the results are presented in *Table 49*. From these, there was evidence of a high level of satisfaction with ICD therapy and over 90% of patients would recommend the therapy to other patients. Around two-thirds of patients thought that the ICD had saved their lives, that it was not a difficult decision to have the implant and that they needed their ICD; 80% of patients felt more independent because of their ICD. There were also positive feelings surrounding the need for repeated check-ups, with only 12% of patients thinking that they were unnecessary and 25% saying that they were, mostly a little, inconvenient. Against this generally

TABLE 49 *Living with an ICD*

	Not at all	A little	Quite a bit	Very much	Total
Does your ICD give you a sense of security?	10 (4.4)	31 (13.6)	59 (25.9)	128 (56.1)	228 (100)
Have you ever had the feeling that the ICD saved your life?	70 (30.7)	19 (8.3)	34 (14.9)	105 (46.1)	228 (100)
Have you felt more independent because you have your ICD?	44 (19.3)	40 (17.5)	64 (28.1)	80 (35.1)	228 (100)
Can you imagine going on holiday with your ICD implanted?	18 (7.9)	27 (11.8)	36 (15.8)	147 (64.5)	228 (100)
Altogether, are you satisfied with your ICD?	2 (9.0)	8 (3.5)	20 (8.8)	198 (86.8)	228 (100)
Would you recommend ICD implantation to other patients in a similar situation?	4 (1.8)	7 (3.1)	11 (4.9)	204 (90.3)	226 (100)
Was the decision to have an ICD implanted difficult for you?	166 (73.5)	32 (14.2)	14 (6.2)	14 (6.2)	226 (100)
How stressful was implantation and ICD tests for you?	96 (42.1)	82 (36.0)	30 (13.2)	20 (8.8)	228 (100)
Has attendance for ICD check-ups been inconvenient?	173 (75.5)	47 (20.5)	9 (3.9)		229 (100)
Do you feel that the repeated check-ups have become unnecessary?	201 (88.2)	18 (7.9)	7 (3.1)	2 (0.9)	228 (100)
Have you been afraid that the ICD might malfunction or that the battery might run out?	104 (45.6)	91 (39.9)	18 (7.9)	15 (6.6)	228 (100)
Have you become more anxious and restless as a result of your ICD treatment?	127 (56.2)	72 (31.9)	18 (8.0)	9 (4.0)	226 (100)
Have you had to take more sedatives since you had your ICD?	186 (81.9)	27 (11.9)	11 (4.8)	3 (1.3)	227 (100)
Are you afraid of certain activities that might bring on a shock?	62 (27.2)	77 (33.8)	43 (18.9)	46 (20.2)	228 (100)
To a certain extent, has the ICD become the centre of your life?	93 (40.8)	74 (32.5)	31 (13.6)	30 (13.2)	228 (100)
Do you feel dependent on your ICD?	57 (25.0)	63 (27.6)	44 (19.3)	64 (28.1)	288 (100)
Do you ever think that you don't need your ICD?	170 (74.6)	42 (18.4)	11 (4.8)	5 (2.2)	228 (100)
Are you bothered or concerned about any aspect of the visible changes at the implantation area?	173 (76.5)	42 (18.6)	8 (3.5)	3 (1.3)	226 (100)
Does the ICD cause you physical discomfort around the implantation area?	103 (45.2)	101 (44.3)	19 (8.3)	5 (2.2)	228 (100)

Data are shown as *n* (%) of patients.

positive picture of living with an ICD, over half of patients said that the implantation and tests were stressful, that they had some physical discomfort around the implantation area and that they were afraid that the ICD might malfunction or that the battery might run out.

Levels of anxiety and depression, as measured by the HAD, were related to various aspects of living with and coping with an ICD. In *Figure 30* the mean scores for each of the 19 questions are plotted by HAD scores. Higher levels of both anxiety and depression were related to eight out of 19 aspects of coping or living with an ICD, including higher dependency on the ICD, increased fears of malfunction, higher intake of sedatives, fear of activity and higher levels of physical discomfort. In addition, patients who were depressed were more likely to find check-ups inconvenient and were less likely to recommend ICD therapy to others. Additional aspects of a high level of anxiety were feelings of dependency, in general, and a low sense of security.

As can be seen from the figures in *Table 50*, almost half of the patients surveyed had not experienced a defibrillator shock and 44% had experienced fewer than five shocks since their ICD implant. Of those patients who had experienced shocks, the vast majority had found the experience unpleasant and over two-thirds of patients felt anxious about receiving shocks. The number of shocks experienced by patients was related to time since implantation. Of the 42 patients who had received their implant in the previous year, 15 (36%) had experienced a shock and only one of these (6.7%) had received five or more shocks. This compares to 22 (65%) of the 34 patients who had had their implant for over 5 years, of whom 12 (54.6%) had experienced five or more shocks.

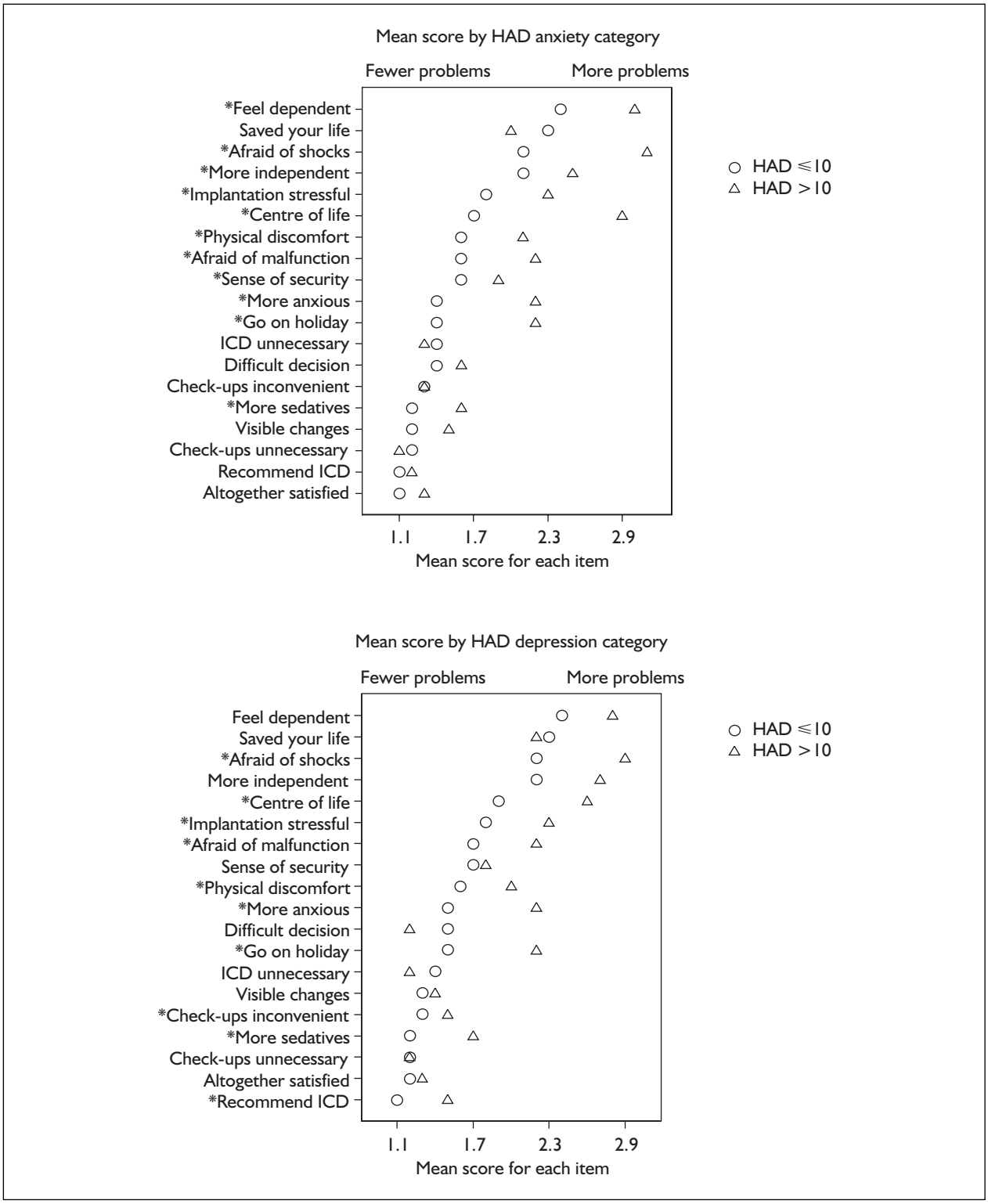

FIGURE 30 *Living with an ICD mean scores by HAD depression and anxiety scales (*p<*0.05)*

The patient group was divided into those who had experienced shocks (group 1) and those who had not (group 0) to explore any effect of shocks on HRQoL. This analysis (*Table 51*) found that those patients who had experienced shocks had significantly poorer levels of quality of life as measured by the SF-36 PCS ($p = 0.02$) and the EQ-5D ($p < 0.01$), and higher levels of anxiety ($p = 0.01$) but not depression.

The mean differences and 95% confidence intervals in the scores between those who

TABLE 50 *Defibrillator shocks*

	Defibrillator shocks					
	None	**1**	**2–4**	**5–10**	**> 10**	**Total**
How many shocks have you received from your ICD?	108 (47.8)	28 (12.4)	41 (18.1)	31 (13.7)	18 (8.0)	226 (100)
	None	**Last week**	**Last month**	**Last 6 months**	**>6 months**	**Total**
How long ago was the last shock?	102 (45.7)	3 (1.3)	11 (4.9)	24 (10.8)	83 (37.2)	223 (100)
	None	**Never**	**Sometimes**	**Always**		**Total**
Have you lost consciousness when you received a shock?	103 (46.2)	93 (41.7)	20 (9.0)	7 (3.1)		223 (100)
	None	**Not at all**	**A little**	**Quite a bit**	**Very much**	**Total**
How unpleasant are the shocks?	102 (45.7)	6 (2.7)	33 (14.8)	38 (17.0)	44 (19.7)	223 (100)
Have you ever felt relieved after a shock?	103 (46.4)	34 (15.3)	27 (12.2)	33 (14.9)	25 (11.3)	222 (100)
Have you felt anxious about receiving shocks?		58 (25.8)	88 (39.1)	41(18.2)	38 (16.9)	225 (100)
Data are shown as *n* (%) of patients.						

TABLE 51 *Generic HRQoL measures by defibrillator shocks*

Generic measure	**Group 0 No shocks**		**Group 1 ≥ 1 shock**		***p***
	n	**Mean (SD)**	***n***	**Mean (SD)**	
SF-36 PCS	103	40.6 (14.0)	109	35.7 (15.8)	0.02
SF-36 MCS	103	49.0 (14.6)	109	45.1 (15.5)	0.06
HAD anxiety	108	6.1 (4.7)	114	7.7 (4.8)	0.01
HAD depression	108	4.2 (3.6)	114	5.2 (4.1)	0.06
EQ-5D	108	0.8 (0.2)	118	0.7 (0.3)	<0.01

TABLE 52 *Generic HRQoL measures by defibrillator shocks, unadjusted and adjusted for implant age, gender and LVEF*

Generic measure	**Unadjusted**		**Adjusted**	
	Mean difference between group 1 and group 0 (95% CI)	***p***	**Mean difference between group 1 and group 0 (95% CI)**	***p***
SF-36 PCS	–4.9 (–8.9 to –0.9)	0.02	–5.7 (–10.2 to –1.2)	0.01
SF-36 MCS	–3.9 (–7.9 to 0.02)	0.06	–4.1 (–8.7 to 0.4)	0.08
HAD anxiety	1.6 (0.4 to 2.9)	0.01	1.8 (0.3 to 3.1)	0.01
HAD depression	1.0 (–0.1 to 2.0)	0.06	1.2 (0.05 to 2.4)	0.04
EQ-5D	–0.09 (–0.16 to –0.03)	<0.01	–0.11 (–0.18 to –0.04)	<0.01

experienced shocks and those who did not are shown in *Table 52*. A negative value for the SF-36 scales and the EQ-5D social tariff indicates lower HRQoL for patients who had shocks, and a positive value for the HAD scales indicates greater problems for patients having shocks. These results demonstrate that shocks are significantly associated with HRQoL even when adjusted for age, gender and low LVEF. In addition, shocks are associated with greater anxiety and depression.

TABLE 53 *SF-36 scores for ICD survey and UK general population*

SF-36 subscale	ICD survey population				UK general population norms (n = 525)
	n	Mean (SD)	Min	Max	Mean (SD)
Physical functioning	228	59.9 (28.7)	0.0	100	76.2 (22.3)
Role physical	217	49.5 (42.3)	0.0	100	75.9 (37.5)
Role mental	217	68.7 (41.7)	0.0	100	84.8 (30.6)
Social functioning	224	70.9 (30.4)	0.0	100	86.2 (22.7)
Mental health	224	73.3 (20.5)	0.0	100	76.4 (18.4)
Vitality	224	51.5 (23.2)	0.0	95	61.8 (21.2)
Pain	225	76.5 (26.4)	11.1	100	76.9 (24.0)
General health	224	54.9 (23.7)	5.0	100	68.1 (21.9)

Discussion

This survey of a large group of UK patients who received their ICD implant between 1991 and 2002 has provided important information about HRQoL. The mean scores and range for the eight SF-36 dimensions, where the maximum score of 100 represents maximum function, are given in *Table 53* alongside those of the UK general population norms for the 60–64 age group. The survey group dimension means ranged from as low as 50 for physical functioning, 52 for vitality and 60 for role physical, to 71 for social functioning, 73 for mental health and 77 for pain.

The composite PCS and MCS are most often reported and the general population means were 50 for each scale. In comparing the survey results to another UK patient group, the means of 37.8 for PCS and 46.7 for MCS were almost identical to those at 1 year after implantation, in a longitudinal study of 62 ICD patients in Liverpool (not published). This same study found a significant improvement from preimplant scores in the MCS at 1 year and in the social functioning dimension at 6 months and 1 year.

The levels of anxiety and depression in the present survey patients (>10 scores) were 22% for anxiety and 11% for depression. The HAD means of 7.0 for anxiety and 4.7 for depression were again very close to those from the Liverpool longitudinal study group at 1 year after treatment.

In this cross-sectional survey there was no evidence of differences in HRQoL between those patients in the first year of their implant and those in subsequent years in all measures. This is perhaps not surprising for the generic scales which are best suited to comparisons before and after treatment and between groups receiving active and inactive treatments, where sizeable differences might be expected. Even with the limitations of this type of survey, it is more surprising that greater disease-specific differences over time were not found. However, the results provide useful descriptive information about living with an ICD and may help to identify or confirm elements of concern, attitude and behaviour in patients, which could be alleviated or at least moderated with assistance and support from health professionals, with a resulting positive effect on HRQoL.

The one factor that was clearly related to time since implantation was the proportion of patients receiving shocks, rising from 36% in the first year to 65% of patients after 5 years, and the number of shocks experienced, rising from 7% to 55% experiencing five or more shocks in the same periods. The findings of a relationship between shocks experienced by patients and their physical HRQoL, plus anxiety, were independent of implant age, gender or low LVEF, and support those found in the Hermann study[26] and in AVID,[17] CIDS,[19] and MADIT.[13]

In a recent meta-analytical review of the psychosocial impact of the ICD,[67] the authors reached four main conclusions: there were no significant differences in psychosocial outcome between ICD patients and AAD-treated patients, or between preimplant and postimplant ICD patients, or between shocked and non-shocked ICD patients and, finally, the evidence showed that ICD patients reported significantly worse psychological and physical functioning compared with other cardiac patients. Burke and colleagues[67] argue that these findings suggest that the unchanging or deteriorating levels of psychosocial functioning in ICD patients may occur as a result of variables associated with the underlying condition, rather than as a direct response to

implantation of the device. The authors further comment, however, that the design limitations of the 20 studies in their analysis make it difficult to determine cause and effect, and that more randomised controlled trials are needed. Their analysis did not include the AVID or CIDS RCT data reported in 2002 (a full discussion of the limitations of these trials and their conflicting results with regard to HRQoL can be found in Chapter 2), but both studies confirmed results from non-randomised studies suggesting that patients who had experienced shocks had significantly poorer HRQoL in some dimensions.

Herrmann and colleagues[26] argue that the effect of shock frequency on physical and social aspects of QoL may be secondary to its effects on anxiety and depression in that a fear of recurrent shocks can lead to an anxious avoidance of physical and social activities and produce a feeling of ICD dependence. This leads them to suggest two treatment options: the first is what many studies have concluded, that efforts to reduce ICD shock frequency will have a beneficial effect; the second is that simple self-report questionnaires such as the HAD might be used in clinical practice to identify patients who may be helped with psychotherapeutic support. This is also a theme of the review conducted by Sears and colleagues in 1999,[24] in which they discuss possible interventions and quote an RCT comparing active individual cognitive-behavioural therapy in newly implanted patients, with no intervention.[68] With findings of less depression, anxiety and general psychological distress in the treatment group at 9 months, the authors argue that these results support the view that systematic interventions should be considered and further work done on their cost-effectiveness. A further proposition which supports the need to explore appropriate interventions is that not all high anxiety scores are related to shocks; some patients interpret bodily symptoms as signs of danger and believe that they have a heightened risk of sudden death, and it is this fear that heightens their anxiety.[69] Interventions designed to prevent or reduce anxiety, resulting in a positive effect on patients' attitudes to a wide range of activities, may be the best way forward in enhancing the benefits of ICD therapy, by tackling the fears associated with both the underlying disease and the technology.

Strengths of the study

This study has provided reliable data on HRQoL for a large group of ICD recipients, including some long-term data in patients who have been living with an ICD for over 5 years. Using both generic and disease-specific instruments, the study has been able to demonstrate the relationships over time and the factors associated with poor HRQoL. The EQ-5D has provided the first utility measurements for a large sample of ICD recipients in the UK and can be used in UK-specific cost-effectiveness estimates. Since HRQoL is a crucial element of these studies, it was important to have UK-based estimates to improve cost-effectiveness. Attention can be directed towards addressing the limitations and difficulties experienced by ICD patients that have been identified in this study.

Limitations of the study

No RCTs of ICDs against alternative therapies have been conducted in the UK, so it was not possible to identify a good control group for this study. In addition, owing to time constraints a longer clinical study was not possible. Therefore, although the current cross-sectional study gives some information about patients' experience and HRQoL at different points in time, evidence of changes over time cannot be inferred uncritically.

The disease-specific instrument in this study used questions derived from previous studies and was piloted to ensure good face validity. However, it has not been validated in large populations of ICD patients and would benefit from further psychometric testing. This is outside the scope of the current study.

Summary

This first large cross-sectional survey of HRQoL in UK ICD patients found no evidence of consistent change over time since implantation. Six out of the eight dimensions of the SF-36 were significantly below the levels of the general population. Clinically important levels of anxiety were found in 22% of patients and younger patients were significantly more anxious. These results were comparable with findings from a UK longitudinal study of 62 patients at 1 year from implantation, with regard to the SF-36 dimensions and the HAD.

There was evidence of a high level of satisfaction with ICD therapy. Over 90% of patients would recommend the therapy to other patients and around two-thirds of patients thought that the ICD had saved their lives. There were also positive feelings surrounding the need for repeated check-ups, with only 12% of patients thinking that they were unnecessary and 25% saying that they were, mostly a little, inconvenient.

Regarding daily activities, a large proportion of patients (84%) said that they avoided strenuous activities, and levels of both anxiety and depression were related to various aspects of living with and coping with an ICD. These included higher dependency on the ICD, increased fears of malfunction and fear of activity. Patients who found their check-ups inconvenient and were less likely to recommend ICD therapy to others were more likely to be depressed.

Over 50% of the study population had experienced shocks from the ICD, with 20% experiencing five or more and two-thirds of patients saying that these shocks were either quite a bit or very unpleasant. Patients who had suffered shocks had significantly poorer levels of HRQoL, as measured by the physical component scale of the SF-36 and the EQ-5D, as well as higher levels of anxiety and depression, and this was independent of implant age, gender and LVEF. The number of shocks that patients received was related to the time since implantation.

To maximise the potential benefits of ICD therapy, there is a need to reduce the number of inappropriate shocks and to investigate further the clinical effectiveness and cost-effectiveness of providing support for patients aimed at reducing anxiety.

Chapter 7

Analyses of patient-specific data on resource use and costs

Introduction

The background to the collection of clinical and resource-use data is set out in Chapter 5. The analysis in this chapter is derived from details in patient notes. In general, data relate to 211 Papworth patients and 167 Liverpool patients, although full data were not available in all cases.

Indication for ICD

The indications for ICD are characterised in terms of presenting pathways. The distribution of patients according to indication (pathway to admission) is shown in *Table 54*, and in greater detail by period in *Table 55*.

Of these patients, 68 at Papworth and 33 at Liverpool had previously received a CABG. Six had received heart transplants at Papworth, whereas none of the Liverpool patients had received heart transplants. In total, 120 of the Papworth patients and 122 of the Liverpool patients were being treated with amiodarone before ICD implantation.

Consultations associated with implantation of an ICD

At least one, and possibly two, routine consultations are normally associated with the implantation, although these are not explicitly included in the data gathered for the study. Allowance is made for one such consultation in the estimation of an individual patient's cost.

Time spent in hospital before an operation

The time spent in hospital before an operation has fallen at Papworth in recent years, to an estimated 3.9 days for 2001/02 (*Table 56*). The values for Liverpool differ markedly in the periods observed from those for Papworth. These values may be affected by the scheduling of the use of a theatre for performing implantation. For example, at Papworth, a patient admitted on a Monday will typically wait until a Friday morning for an implant. At Liverpool the practice has been to supplement regular sessions (sometimes two in a week) with sessions at other times, when the need for an ICD is identified.

As would be expected the pathways differ most in terms of the period in hospital immediately before implantation (*Table 57*), with pathways 1 and 3 associated with longer stays before implantation.

Implantation

Implantation of an ICD required about 1.16 hours of theatre time on average (Papworth data) during 2002/03, but this varied from around 30 minutes to more than 2 hours (*Table 58*). Times during other years appear to have been similar. The implantation normally occurred in an operating theatre, but was performed in a catheter laboratory for four of the Papworth patients and three of the Liverpool patients. Costs in a catheter laboratory are likely to be less than in an operating theatre. Times spent in the theatre at Liverpool (based on data for a small cohort of recent patients) appear to be slightly longer. It appears that the duration of the operation is not significantly affected by whether or not more than one lead is used.

Only two or three makes of ICD (principally from manufacturers Medtronic and Guidant) are normally used in Papworth and Liverpool. Two basic configurations of ICD are available, the single-chamber and dual-chamber type. Base prices for these two types complete with leads differ by as much as £2000 before VAT and discounts. More expensive subtypes of ICD configured to give higher defibrillation shocks than the standard models, and dual-chamber devices 'with atrial therapies' or 'with resynchronisation' are available, but are currently used in less than 3% of patients. However, this use is increasing. The precise model of ICD used varies considerably (for example, it appears that at

TABLE 54 *Distribution of Papworth patients (n = 211) and Liverpool patients (n = 167) by indication/pathway on admission*

	Resuscitated out of hospital following cardiac arrest (VF) and transferred as inpatient	Previously discharged following out-of-hospital cardiac arrest (VF) and referred to clinic	In hospital after VT and transferred as inpatient	Previously discharged after VT, referred to clinic	Patient having had no VT or VF, referred to clinic primary prevention group	Pathway not coded
Papworth (pathway known = 183/211)	20	33	59	65	6	28
Liverpool (pathway known = 148/167)	23	12	54	53	6	19
Papworth (% where pathway known)	10.9	18.0	32.2	35.5	3.3	NA
Liverpool (% where pathway known)	15.5	8.1	36.4	35.8	4.1	NA
Overall of those known (*n* = 331/378)	43	45	113	118	12	NA
Overall (% of those known)	13.0	13.6	34.1	35.6	3.6	NA

TABLE 55 *Distribution of patients by indication/pathway for admission, at the two sites, in different periods*

	Timing of insertion of ICD					
	Papworth			Liverpool		
Indication/pathway for admission	Pre 1999	1999 and 2000	2001 and 2002	Pre 1999	1999 and 2000	2001 and 2002
Resuscitated out of hospital following cardiac arrest (VF) and transferred as inpatient	3	9	8	7	11	5
Previously discharged following out-of-hospital cardiac arrest (VF) and referred to clinic	11	10	12	6	4	2
In hospital after VT and transferred as inpatient	15	5	29	9	23	26
Previously discharged after VT, referred to clinic	17	12	25	6	17	20
Patient having had no VT or VF, referred to clinic primary prevention group	0	4	2	2	0	4
Pathway not coded	10	12	6	7	5	6

TABLE 56 *Resource use: time in hospital immediately before and after the procedure, by date of implantation of ICD*

	Papworth				Liverpool			
	Admission to implant (days)	***n* for admission to implant and implant to discharge**	**Days in ICU/ITU**	**Implant to discharge from ICD (days)**	**Admission to implant (days)**	***n* for admission to implant and implant to discharge**	**Days in ICU/ITU**	**Implant to discharge from ICD (days)**
Mean, overall (both sites)	5.9	329	0.3	3.2	–	–	–	–
Mean, all dates	6.4	178	0.02	4.0	5.4	151	0.72	2.2
Minimum, all dates	0.0		0.0	0.0	0.0		0.0	1.0
Maximum, all dates	53.0		2.0	149.0	43.0		15.0	28.0
SD, all dates	8.5		0.2	11.1	6.4		2.2	3.5
Mean, 1991 to end of 1998	9.3	51	0.02	8.4	4.8	41	1.2	3.3
Mean, 1999 and 2000	6.8	57	0.05	2.9	5.3	52	0.4	1.8
Mean, 2001 and 2002	3.9	70	0.01	1.8	5.9	58	0.7	1.7
Minimum 2001/02	0.0		0.0	0.0	0.0		0.0	1.0
Maximum 2002/02	53		1.0	12.0	27.0		15.0	17.0
SD, 2001/02	7.9		0.1	1.9	5.9		2.5	2.5

ICU, intensive care unit; ITU, intensive therapy unit.

TABLE 57 *Resource use, time in hospital peri-implantation according to indication/pathway on admission*

	Papworth			Liverpool		
	Admission to implant (days)	**Days in ICU/ITU**	**Implantation to discharge from ICD (days)**	**Admission to implant (days)**	**Days in ICU/ITU**	**Implantation to discharge from ICD (days)**
Mean pathway 1	8.9	0.0	2.9	7.2	0.4	1.3
Min. pathway 1	0.0	0.0	1.0	0.0	0.0	1.0
Max. pathway 1	26.0	0.0	9.0	43.0	7.0	4.0
Mean pathway 2	4.7	0.03	7.8	1.0	0.0	1.3
Min. pathway 2	0.0	0.0	1.0	1.0	0.0	1.0
Max. pathway 2	26.0	1.0	149	1.0	0.0	2.0
Mean. pathway 3	7.7	0.05	3.4	7.0	1.0	2.4
Min. pathway 3	0.0	0.0	1.0	0.0	0.0	1.0
Max. pathway 3	29.0	2.0	13	19.0	15.0	24.0
Mean. pathway 4	3.8	0.0	3.5	1.7	0.1	1.8
Min. pathway 4	0.0	0.0	1.0	0.0	0.0	1.0
Max. pathway 4	51.0	0.0	29	8.0	2.0	9.0
Mean. pathway 5	0.8	0.0	1.8	5.5	2.2	4.2
Min. pathway 5	0.0	0.0	1.0	1.0	0.0	1.0
Max. pathway 5	2.0	0.0	2.0	28.0	13.0	10.0
Mean. pathway unknown (not coded)	10.3	0.0	3.5	10.8	2.0	4.2
Min. pathway unknown	1.0	0.0	0.0	0.0	0.0	0.0
Max. pathway unknown	53.0	0.0	12.0	27.0	8.0	28.0

Key to pathways: 1, resuscitated out of hospital following cardiac arrest (VF) and transferred as inpatient; 2, previously discharged following out-of-hospital cardiac arrest (VF) and referred to clinic; 3, in hospital after VT and transferred as inpatient; 4, previously discharged after VT, referred to clinic; 5, patient having had no VT or VF, referred to clinic (primary prevention group); pathway not coded.

TABLE 58 *Time in theatre for implantation, 2002 and 2003 values at Papworth and Liverpool*

Site	Mean time (minutes)	Max. time (minutes)	Min. time (minutes)
Papworth (n = 77)	70.4	150	30
Liverpool (n = 10)	79	180	35

TABLE 59 *Cost of ICDs (with leads), 2002/03 values (Papworth)*

Mean (for 77 patients) (£)	Min. (£)	Max. (£)	Mean + VAT (£)	Min. + VAT (£)	Max. + VAT (£)
16,402	13,489	18,506	19,272.40	15,850	21,745

TABLE 60 *Estimated proportion of ICDs (first implant) that were dual chamber devices*

Site and timing of implant	Estimated proportion of dual-chamber devices in those implanted	%
Papworth		
Pre-1999	4/57	7.0
1999/00	26/71	36.6
2001/02	30/73	41.1
Liverpool		
Pre-1999	1/47	2.1
1999/00	8/56	14.3
2001/02	35/63	55.6

least 11 models were used in a group of 77 patients treated at Papworth in 2002/03) (*Table 59*).

At many sites a representative of the ICD manufacturer may be present at the operating theatre with spare equipment. Depending on the patient's reaction to test shocks, an alternative device and/or set of leads may be fitted, having been taken from the representative's stock. The cost of boxes and/or leads can be affected by whether or not stocks are held on a consignment basis. Estimations made here assume that a consignment situation does not exist. (If it did, a notional premium of 10% would need to be added.)

Estimates of average costs of the use of ICDs will be affected by the different proportions of the two main types that are implanted. The National Service Framework for ICDs, written in 2002, suggests that a typical mix of devices would be 60% single-chamber type and 40% dual-chamber type. A preliminary screening of the patient data indicates that the proportion of devices that were dual-chamber devices (but excluding atrial therapy types) was in the order of 48% of those implanted in 2001/02 (*Table 60*).

As stated above, implantation very rarely occurred anywhere other than in an operating theatre, so costs have been assessed using theatre costs only. Radiology is used to help to position the leads, but the costs of this are covered in the estimation of cost for the theatre. The average time in theatre at Papworth for implantation for 2000/01 was within 0.5% of the value for 2002/03.

Immediately postimplantation

Patients have remained in hospital after the implantation for a mean of 1.8 days in recent years; before 1998, this used to be about 11 days on average. For some patients, some of this time may be spent in an ICU or ITU. Further tests are conducted in this period to assess the functioning of the device.

Papworth's practice relating to discharge has changed in recent years. They used to operate on a Friday and discharge patients on a Sunday morning, now they still operate on Friday, but aim to discharge patients on a Saturday, so one might expect the average length of stay after implantation to be less after this change (*Table 56*).

Costs of implantation admission

Unit costs and estimates of resource use per patient for the admission including implantation are summarised in *Tables 61–64*. These costings give an average total cost for implantation (over the study period) of £23,275 for Papworth and £22,083 for Liverpool. Analysed by pathway, there is some variation between groups and the relativities are not entirely consistent between Papworth and Liverpool, partly because of the relatively small numbers by group. *Table 64* suggests that costs (all at 2001/02 prices) have declined slightly at Papworth over the period, but the decline is less clear at Liverpool.

Papworth

The above estimate assumes a mix of 60/40 single- versus dual-chamber devices, and an average price per device with leads (after a discount for usage of between 10 and 20 devices per annum) of £17,924. Substituting an estimated price (after applying a discount for usage of between 10 and 20 devices per annum) for single-chamber device with leads (£17,341 including VAT), and assuming that all implantations were of single-chamber devices, gives a slightly reduced total of £22,692. Substituting an estimated price (after a discount for usage of between 10 and 20 devices per annum) for a dual-chamber device with leads (£18,801 including VAT) and assuming that all implantations were of dual-chamber devices gives a total of £24,152.

Liverpool

Equivalent alternative costings for Liverpool give a total of £21,500 if all single-chamber devices were used and £22,960 assuming that all devices were dual chamber.

It is possible to examine the costs around the time of implantation for individual patients and an analysis of such costs is given in *Table 64* (using the unit costs for the two centres). Where necessary, costs have been adjusted to 2001/02 value using the Personal Social Services Research Unit Hospital and Community Health Services (PSSRU HCHS) index.

Postdischarge costs

For a well-state patient, the fixed costs of implantation are followed by the daily costs of

TABLE 61 *Basis for the synthesis of the fixed costs of an implantation using Papworth costs and Papworth resource use, adjusted for inflation*

Procedure or item, and year to which costing data apply	Unit costs 2001/02 (£)	Quantity per patient, from usage over whole study period	Cost per patient, 2001/02 (£)
Diagnosis			
Consultation with ICD specialist preadmission	108.00	1.00	108.00
ECG at implantation (2001)	55.00	0.12	6.58
Holter at implantation (2000)	88.56	0.03	2.54
ETT at implantation (2000)	86.48	0.01	0.83
Echocardiography (2001)	55.00	0.42	23.35
Angiography (2002) peri-implantation assessment only	556.03	0.75	414.40
Nuclear scan	184.00	0.04	7.81
MRI (2003) peri-implantation	483.51	0.05	25.09
EP study pre-ICD (2002/03)	1,590.73	0.37	585.27
X-ray at implant, posterior/anterior and lateral	33.00	0.11	3.74
Treatment			
Day in ward preimplantation (2000)	302.15	3.92	1,187.10
ICD (inc. VAT) (2002/03), including leads	17,924.00	1.00	17,924.00
Variables for implant (2002/03)	483.5	1.00	2,127.42
Ablation (2002/03)	3,762.64	0.02	71.33
Theatre time, per hour (2002/03)	1,608.65	1.17	1,886.78
ICU bed (2000)	672.07	0.01	8.27
Day in ward postimplantation (2000)	302.15	1.79	540.10
Correction to days in ward postimplantation for time in ICU, daily rate	–302.15	0.01	–3.72
Total for implantation (mean)			**23,275.00**

ETT, exercise tolerance test; MRI, magnetic resonance imaging.

TABLE 62 *Basis for the synthesis of the fixed costs of an implantation using Liverpool costs (where available) and Liverpool resource use, adjusted for inflation*

Procedure or item, and year to which costing data apply	Unit costs 2001/02 (£)	Quantity per patient, from usage over whole study period	Cost per patient, 2001/02 (£)
Diagnosis			
Consultation with ICD specialist preadmission	114.11	1.00	114.11
ECG at implantation (2002)	18.37	0.00	0.00
Holter at implantation (2002)	56.09	0.00	0.00
ETT at implantation (2002)	56.09	0.00	0.00
Echocardiography (2002)	17.41	0.18	3.12
Angiography (2002)	633.39	0.68	428.08
Nuclear scan (Papworth cost used)	184.00	0.01	1.27
MRI (Papworth cost used)	483.51	0.00	0.00
EP study pre-ICD (2002/03), major diagnostic	1,979.47	0.42	832.74
X-ray at implant, posterior/anterior and lateral	44.48	0.00	0.00
Treatment			
Day in ward preimplantation (2002)	141.19	5.90	832.93
ICD (inc. VAT) (2002/03), including leads	17,924.00	1.00	17,924.00
Variables for implant (2002/03) £2200 Papworth consumption and cost	483.51	1.00	483.51
Ablation (2002/03) (Papworth costs)	3,762.64	0.06	233.54
Theatre time, per hour (2002/03), Papworth consumption	229.18	1.17	268.91
ICU bed (2000)	1,145.91	**0.71**	818.52
Day in ward postimplantation (2000)	141.18	1.72	243.41
Correction for days in ICU, subtracted at rate for days in other ward	−141.18	0.71	−100.85
Total for implantation			**22,083.00**

TABLE 63 *Means of costs per patient perimplantation according to indication/pathway for admission, using a device cost of £17,924 and unit costs of the respective centres*

	Mean cost (£)	Min. cost (£)	Max. cost (£)	*n*
Papworth				
Pathway 1	25,318	21,644	30,929	19
Pathway 2	23,705	20,704	32,278	26
Pathway 3	24,956	21,062	32,218	53
Pathway 4	24,897	20,704	44,575	59
Pathway 5	22,049	21,260	23,456	6
Pathway unknown (not coded)	25,850	21,309	43,211	19
Liverpool				
Pathway 1	21,854	18,932	32,036	19
Pathway 2	19,500	19,073	21,070	10
Pathway 3	21,980	19,073	36,279	43
Pathway 4	20,172	18,932	24,020	45
Pathway 5	24,956	18,932	37,217	4
Pathway unknown	23,531	19,779	32,699	18

Key to pathways: 1, resuscitated out of hospital following cardiac arrest (VF) and transferred as inpatient; 2, previously discharged following out-of-hospital cardiac arrest (VF) and referred to clinic; 3, in hospital after VT and transferred as inpatient; 4, previously discharged after VT, referred to clinic; 5, patient having had no VT or VF, referred to clinic primary prevention group; pathway not coded.

TABLE 64 *Individual cost data for peri-implantation costs using a device cost of £17,924*

	Mean (£)	Min. (£)	Max. (£)	SD (£)	*n*
Overall	22,555	18,931	37,217	2,895	320
Papworth					
To 1999	24,191	20,920	34,673	2,407	51
1999/2000	23,277	20,812	28,547	1,753	59
2001/02	22,415	20,704	32,921	1,926	72
Liverpool					
To 1999	22,454	19,073	37,217	4,093	42
1999/2000	21,044	18,932	32,036	2,302	49
2001/02	21,788	18,931	36,279	3,895	47

TABLE 65 *Distribution during the peri-implantation period of events from a list of major diagnostic tests*

	Angiography, no. of tests	Echocardiography, no. of tests	Nuclear scan, no. of tests	MRI, no. of scans	EP study no.	Ablations, no.
Papworth, in 203 patients	154	88	9	11	75	2
Liverpool, in 161 patients	102	28	1	0	64	11
Overall, in 364 patients	256	116	10	11	139	13

TABLE 66 *Distribution during the peri-implantation period of events from a list of minor diagnostic tests*

	ECG	Holter	ETT	X-ray lateral and/or anterior/posterior	Other tests
Papworth, in 209 patients	25	6	2	24	1
Liverpool, in 166 patients	0	0	0	0	0
Overall, in 375 patients	25	6	2	24	1

medication and such regular check-ups as are routinely required, including outpatient diagnostic tests, both major and minor (*Tables 65–68*). For the purpose of the cost-effectiveness model (Chapter 8) these costs were estimated as an average cost per day postimplantation.

Of around 360 occasions when these minor diagnostic tests occurred at follow-up, there were apparently only four occasions when two or more tests were done on the same day (and another six occasions when they were done within a few days of each other); therefore, it seems appropriate to estimate costs for such tests as if they were independent of each other (*Table 69*).

Medication

Most patients are given medication following the implantation, an average of at least two drugs (*Tables 70* and *71*), although some patients received no medication. The normal procedure at Papworth is to leave patients on the medication (and dose) that they were receiving before implantation. One consequence of this is that some patients continue to receive amiodarone (and compounds with similar therapeutic action).

The data for Papworth patients are based on 143 discharge or follow-up records for patients before 1999, 167 records for patients in 1999 and 2000 and 42 records for 2001/02. This cohort comprises 54 patients who had their first ICD before 1999, 68 who had implants in 1999/00 and 11 who received implants in 2001/02.

The data for Liverpool patients are based on 93 discharge or follow-up records for patients before 1999, 137 records for patients in 1999 and 2000, and 153 records for 2001/02. This cohort comprises 47 patients who had their first ICD before 1999, 58 who had implants in 1999/00 and 62 who received implants in 2001/02.

TABLE 67 *Use of tests after discharge, according to date of admission/implantation*

Site and period	ECG	Holter	ETT	X-rays	Angiography	Echocardiography	Nuclear scan	EP study no.	Ablation	Patient days
Papworth										
To 1999	36	6	2	69	9	36	0	2	0	112,596
1999/2000	30	1	4	37	1	15	0	2	1	61,205
2001/02	38	2	2	58	9	7	0	0	4	29,877
Liverpool										
To 1999	1	6	4	49	6	8	0	0	0	95,176
1999/2000	1	4	1	43	2	12	0	2	0	299,310
2001/02	0	3	0	27	7	7	0	1	0	22,048

TABLE 68 *Approximate numbers of diagnostic tests per patient-day postdischarge*

Site and period	ECG	Holter	ETT	X-rays	Angiography	Echocardiography	Nuclear scan	EP study no.	Ablation
Papworth									
To 1999	0.00031973	5.3288E-05	1.7763E-05	0.00061281	7.99318E-05	0.000319727	0	1.77626E-05	0
1999/2000	0.00049016	1.6339E-05	6.5354E-05	0.00060453	1.63385E-05	0.000245078	0	3.26771E-05	1.63385E-05
2001/02	0.00127188	6.6941E-05	6.6941E-05	0.00194129	0.000301235	0.000234294	0	0	0.000133882
Liverpool									
To 1999	1.0507E-05	6.3041E-05	4.2027E-05	0.00051484	6.30411E-05	8.40548E-05	0	0	0
1999/2000	3.341E-06	1.3364E-05	3.341E-06	0.00014366	6.68204E-06	4.00922E-05	0	6.68204E-06	0
2001/02	0	0.00013607	0	0.0012246	0.000317489	0.000317489	0	4.53556E-05	0
Proposed estimate to prime a model	0.00075	0.00006	0.00006	0.00075	0.00005	0.00024	0	0.00003	0.00001

TABLE 69 *Costs of diagnostic tests per day (well state, after discharge) calculated for individuals, according to date of implantation (2001 prices)*

	Mean (£)	Min. (£)	Max. (£)	SD (£)	*n*
Overall	0.4890	0	28.9434	2.4360	372
Papworth					
All possible	0.7385	0	28.9434	3.1775	211
To 1999	0.6718	0	28.600	3.8188	56
1999/00	0.2026	0	3.3626	0.5799	71
2001/02	1.2358	0	28.9433	3.8857	84
Liverpool					
All possible	0.1620	0	5.8021	0.5649	160
To 1999	0.0690	0	0.4932	0.1115	46
1999/00	0.1069	0	1.4742	0.2748	56
2000/01	0.2867	0	5.8021	0.8794	58

Scrutiny of self-reported medication in patient survey forms completed in 2002 indicates that over 70% of patients were taking ACE inhibitors, about one-sixth of them taking enalapril. It was considered appropriate to substitute the estimated usage of any kind of ACE inhibitor for the values entered for enalapril, and the average cost of such medication was based on the cost of enalapril.

At discharge the average Papworth patient is recorded as receiving an average of 2.07 classes of medicines (range 0–5), while the average Liverpool patient received 2.33 (same range). The pattern of prescribing in terms of medicines/classes seems to differ slightly between first and subsequent records of medication, and the average number of medicines as well as the average costs of medication increased over time.

For costing purposes, clinical advice on 'normal' dosage has been used. The daily cost of medication in 2001/02 is estimated at £0.9864 per patient at Papworth and £0.8727 per patient at Liverpool using British National Formulary (BNF) 43 prices (plus VAT).

Follow-up consultations

The normal procedure at Papworth is for well patients to return after implantation at 1 month (changing to 6 weeks), 3, 6 and 12-months and 12-monthly thereafter, but a clear pattern matching these intervals cannot be recognised in the relevant data set.

Data on nearly 3000 follow-up consultations, for the 378 patients, were analysed. The majority of such consultations were with an ICD consultant (*Tables 72–74*), and since few are with either GPs or nurses it is proposed to cost these as specialist consultations. This pattern may not be repeated in other hospitals, where events may be arranged so that patients are seen by cardiac technicians alone. The typical follow-up consultation at Papworth and Liverpool is almost invariably carried out with a cardiac technician present.

If the total of patient days (from implant date) for the patients in this data set is divided by the number of consultations, this gives an average interval of 140 days between consultations. This is of the order that may be expected if patients came for follow-up consultations on the usual Papworth schedule.

The estimated cost per day of providing these consultations at the Papworth cost for a consultation is approximately £0.77 overall, £0.66 for Papworth and £1.15 for Liverpool patients.

If the cost of consultations is estimated based on the standard Papworth schedule, the cost would be £0.59 per day (just a little less than that actually observed).

Additional hospitalisations

Patients are admitted after adverse events and various procedures may be performed. The codes used to categorise the reasons for admission to be used in the cost-effectiveness model are:

- code 1 Arrhythmia
- code 2 Other cardiac
- code 3 Other non-cardiac
- code 4 ICD maintenance
- code 5 ICD replacement
- code 6 Amiodarone problems.

TABLE 70 *Probability of receiving medication at discharge and follow-up points: Papworth and Liverpool patients, according to date of follow-up*

	Mean numbers of prescriptions, by type of medicine, per patient as assessed at follow-up occasion					
	Papworth			Liverpool		
Medicine	**Pre-1999**	**Implants 1999/2000**	**2001/2002**	**Pre-1999**	**Implants 1999/2000**	**2001/02**
Carvedilol	0.0067	0.0241	0.1712	0.0217	0.0146	0.0915
β-Blocker	0.1342	0.2108	0.2342	0.1613	0.2701	0.1895
Bisoprolol	0	0.0241	0.1486	0.0108	0.0438	0.0850
Amiodarone	0.4940	0.4458	0.4955	0.6452	0.5912	0.5987
Sotalol	0.1812	0.1024	0.0676	0.0215	0.0803	0.0654
Flecainide	0	0.0663	0.0135	0.0215	0.0073	0
Propafenone	0	0	0	0	0	0
ACE inhibitors	0.7400	0.7400	0.7400	0.5000	0.5000	0.51
Statins	0.2215	0.5663	0.5180	0.1935	0.4599	0.5686
Aspirin	0.4295	0.4639	0.5676	0.5269	0.6277	0.6537
Warfarin	0.3034	0.2327	0.2067	0.2796	0.1606	0.2549
Average no. of drugs per patient	2.4269	2.8763	3.1629	2.3820	2.7555	3.0072

TABLE 71 *Average cost of drugs per day per patient at time of follow-up (not according to when devices were first implanted), at March 2002 prices*

	Mean daily cost of prescriptions per patient per follow-up, at March 2002 prices (£)					
	Papworth			Liverpool		
Medicine	**Pre-1999**	**Implants 1999/2000**	**2001/02**	**Pre-1999**	**Implants 1999/2000**	**2001/02**
Carvedilol	0.0051	0.0183	0.1299	0.0165	0.0111	0.0694
β-Blocker (Atenolol)	0.0056	0.0088	0.0097	0.0067	0.0112	0.0079
Bisoprolol	0	0.0194	0.1199	0.0087	0.0353	0.0685
Amiodarone	0.1108	0.1206	0.1341	0.1746	0.1600	0.162
Sotalol	0.0124	0.0070	0.0047	0.0015	0.0055	0.0045
Flecainide	0	0.0405	0.0083	0.0131	0.0045	0
Propafenone	0	0	0	0	0	0
ACE inhibitors		0.0124	0.0047	0.1290	0.1290	0.1290
Statins	0.1509	0.3859	0.3530	0.1319	0.3135	0.3875
Aspirin	0.0047	0.0051	0.0063	0.0058	0.0079	0.0073
Warfarin	0.0436	0.0334	0.0293	0.0400	0.0230	0.0365
Average cost per patient	0.5243	0.8300	0.9864	0.5280	0.7000	0.8727

TABLE 72 *Distribution of follow-up consultations according to who was seen*

Seen by whom at follow-up	Papworth	Liverpool	Total
ICD consultant	1122	1387	2509
Other consultant	48	232	280
GP consultation	2	2	4
Nurse consultation	1	3	4
Extra ICD follow-up	26	85	111
A&E	0	4	4
Unknown	20	38	58

A&E, accident and emergency.

TABLE 73 *Number of follow-up consultations per patient*

	No. of patients	Min. follow-ups	Max. follow-ups	Mean follow-ups per patient	SD
Papworth	209	0	48	6.0431	7.2186
Liverpool	166	0	47	10.6627	9.2853

TABLE 74 *Estimates for the intervals between follow-up consultations for Papworth patients alone*

	Mean	Max	Min	SD
From implantation (n = 626)	145	469	0	130
After first follow-up (n = 469)	154.8	469	0	108.4

Papworth data include 153 admissions covering 137 patients and Liverpool data include 166 admissions covering 150 patients. The reason for admission is coded for 147 of the Papworth admissions and 149 of the Liverpool admissions (*Table 75*). The length of stay and costs of additional hospitalisations are given in *Tables 76* and 77.

TABLE 75 *Distribution of coded events related to additional hospitalisations*

Hospital	Admissions	Primary cause for admission categorised	Primary cause of admission related to ICD	Primary cause of admission not related to ICD	Days in ICU/ITU	Died in hospital	Code 1 Arrhythmia	Code 2 Other cardiac	Code 3 Other non-cardiac	Code 4 ICD maintenance	Code 5 ICD replacement	Code 6 Amiodarone problems
Papworth	287	135	117	18	2 (1/45 patients)	4	57	16	7	37	30	0
Liverpool	246	149	97	52	99 (43/49 patients)	1	48	32	13	24	32	0
Totals	543	284	214	70	101	5	105	48	20	71	62	0

TABLE 76 *Lengths of stay used in the build-up of costs for additional hospitalisations*

Site and code	Total LOS, in category	Total ICU days, will be subtracted from LOS	Events for which LOS could be calculated	Average LOS days
Papworth				
Code 1	235	2	50	4.7000
Code 2	99	0	16	6.1875
Code 3	10	0	6	1.6667
Code 4	184	0	35	5.2571
Code 5	123	0	28	4.3929
Code 6	0	0	0	0
Unknown cause	6	0	6	3.1667
Liverpool				
Code 1	235	57	47	5.0000
Code 2	108	13	32	3.3750
Code 3	94	6	13	7.2308
Code 4	85	0	23	3.6957
Code 5	86	15	31	2.7742
Code 6	0	0	0	0
Unknown cause	17	8	18	4.4444

TABLE 77 *Average costs of additional hospitalisations according to reason for admission*

	Events	Patients in this cohort	Total cost of events (£)	Mean cost per event (£)	Mean cost per day (£)
Papworth (from 135 patients)					
Code 1 Arrhythmia	57	38	167,204	2,933	624
Code 2 Other cardiac	16	14	45,635	2,852	461
Code 3 Other non-cardiac	7	5	3,022	432	259
Code 4 ICD maintenance	37	10	154,536	4,177	795
Code 5 ICD replacement	30	17	605,868	20,196	4,597
Code 6 Amiodarone problems	0	0	0	–	–
Unknown	6	6	50,738	8,456	2,670
Liverpool (from 150 patients)					
Code 1 Arrhythmia	48	31	102,650	2,139	428
Code 2 Other cardiac	32	17	62,382	1,949	578
Code 3 Other non-cardiac	13	11	31,402	2,416	334
Code 4 ICD maintenance	24	16	44,203	1,842	498
Code 5 ICD replacement	32	26	56,7589	17,737	6,393
Code 6 Amiodarone problems	0	0	0	–	–
Unknown	17	11	175,395	10,317	2,321

Chapter 8

Description of cost-effectiveness model and input parameters

Background

Recent published cost-effectiveness analyses of ICDs based on trials and subsequent economic modelling were reviewed in Chapter 3. These are consistent in showing a small but significant survival advantage from ICD. However, the magnitude of that advantage depends on the trial or model and the period considered. For example, the economic analysis of AVID[53] estimated a survival advantage of 0.21 years over a 3-year time-horizon, the analysis of CIDS[51] showed a survival advantage of 0.23 years over a 6-year time-horizon, and the model based on observational data on Medicare patients[54] suggested a survival advantage of 0.5 years over an 8-year period. Similarly, while all but one trial showed management with ICD to be more expensive than drug therapy, the magnitude of the extra cost varied. Resultant incremental cost per life-year gained ranged from an estimate that ICD therapy was dominant (i.e. it offered a survival advantage at a lower cost,[49] to a cost per LYG of £108,900 thousand.[51] The range of ICERs becomes much greater still once subgroups are considered. For low-risk subgroups the CIDS analysis suggested that amiodarone therapy dominated.[52]

Interpreting these published studies in the context of what they suggest for the UK is difficult. None of these studies used UK or specifically UK-relevant data. The earlier HTA review[2] produced an indicative estimate of short-term (3-year) cost per LYG for the UK of between £40,500 and £87,000. This and other studies have shown that the results are sensitive to any assumption of an ongoing HRQoL advantage for ICDs. Therefore, a new modelling exercise was undertaken based on trial data, but adjusting for known UK parameter values from the UK study sample described in Chapters 5 and 6.

Objective

The objective was to estimate the cost-effectiveness of ICD implantation compared with amiodarone treatment in the UK, in terms of NHS costs per QALY, estimated over a 20-year horizon.

Methods

Data collection

A UK sample comprising all 535 patients implanted with ICDs in Liverpool and Papworth NHS trusts in the period 1991–2002 was identified. (Full details of this UK sample are given in Chapter 5.) Survival status was available for all 535 patients. Clinical and costing information was available for 380 patients. To maximise the amount of usable information and minimise bias associated with data availability, a mixture of multiple imputation methods was used (see below). Since over 96% of these patients had previously documented cardiac arrest (VF) or VT the cost-effectiveness analysis will focus on secondary prevention.

The investigators of the Canadian ICD trial (CIDS) have provided the present reviewers with patient-specific resource-use information for the 430 patients (212 ICD, 218 amiodarone) who took part in the cost-effectiveness substudy of the CIDS trial. In this subgroup there were 146 deaths (69 ICD, 77 amiodarone) and the mean follow-up time was 3.68 years, with a maximum follow-up of 7.04 years.

Thus, the experience of UK ICD patients from the present sample will be used to estimate UK-specific survival and admission rates, with data from the CIDS study being used to estimate the relative survival and admission rates between ICD and amiodarone patients.

Cost accumulation model

Costs of treating a patient were divided into initial fixed costs and those that accrued over time according to patient experience. For ICD patients, initial costs included the cost of the ICD implant operation, the device itself and hospital stay surrounding the time of implantation. If ICDs were not available, the best available treatment would be AADs and the initial cost would include

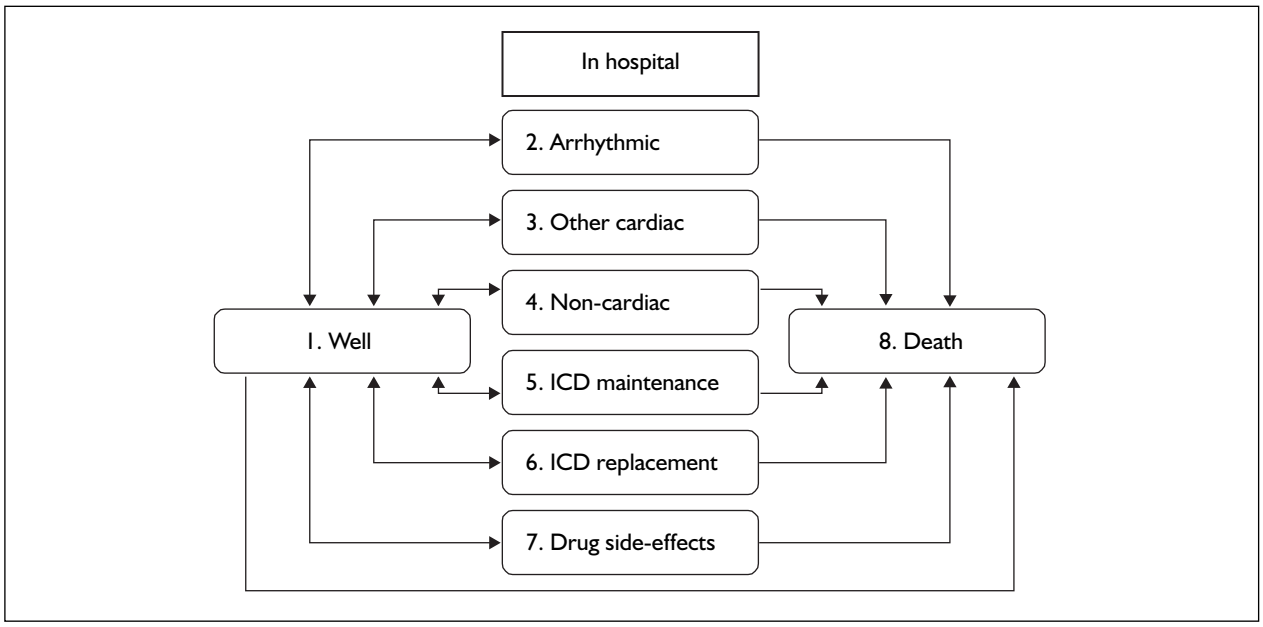

FIGURE 31 *Markov model for hospitalisation*

only that proportion of hospital resource use that can be attributed to the initial management of the presenting arrhythmia, rather than the ICD implantation. However, the long-term cost of a treatment choice depends on how the patient's condition develops in the future. It was assumed that most future costs are incurred during periods of hospital stay, and therefore the model for cost accumulation was based on hospital admissions.

Markov model

Patient follow-up is restricted to 5 years in the current published trials and 10 years in the UK sample. To assess the potential cost implications of ICD implants over 20 years for implanted patients, a discrete-time Markov model was constructed[70] to extrapolate patient experience of clinical events beyond that currently observed (*Figure 31*). At any day in their follow-up a patient is in one of eight states: out of hospital (denoted as well), in hospital for one of six reasons, or dead. The patient moves randomly between states on a daily basis. A patient who is well on one day may remain well, or be admitted to hospital for one of six reasons, or die on the next day. A patient who is in hospital on any given day may remain in hospital, be discharged to the well state, or die on the next day. The rates at which these events occur are controlled by transition probabilities $\{p_{rs}: r = 1, \ldots, 8, s = 1, \ldots, 8\}$, where p_{rs} is the probability of occupying state s on the following day given that the patient is in state r on the current day. For simplicity, transfers between all hospital states are not permitted by the model, and the very small number of such hospital transfers in the data is ignored. Thus, the transition probabilities can be written as a matrix:

$$\begin{bmatrix} p_{11} & p_{12} & p_{13} & p_{14} & p_{15} & p_{16} & p_{17} & p_{18} \\ p_{21} & p_{22} & 0 & 0 & 0 & 0 & 0 & p_{28} \\ p_{31} & 0 & p_{33} & 0 & 0 & 0 & 0 & p_{38} \\ p_{41} & 0 & 0 & p_{44} & 0 & 0 & 0 & p_{48} \\ p_{51} & 0 & 0 & 0 & p_{55} & 0 & 0 & p_{58} \\ p_{61} & 0 & 0 & 0 & 0 & p_{66} & 0 & p_{68} \\ p_{71} & 0 & 0 & 0 & 0 & 0 & p_{77} & p_{78} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

Fitting the model to data

To fit this model, the histories of hospital admission and discharge dates from the Canadian CIDS trial and UK sampled observational data were used. These are expressed as a set of counts of transitions between each pair of states r and s, split by individual. The model is implemented in practice as a set of seven multinomial models for the outgoing transitions from each state. A summary of the total numbers of transitions between pairs of states for the CIDS data is given in *Table 78*.

There are 578,865 transitions in all, covering a total of 1586 years of patient follow-up. There were 146 deaths, with a crude death rate of approximately 1 per 11 years. A summary of the total numbers of transitions between pairs of states for the UK sample is given in *Table 79* for one of the imputed data sets.

In the UK sample there were 426,149 transitions, covering a total of 1166 patient-years at risk, based on 532 patients. There were 80 deaths in

TABLE 78 *Counts of daily transitions between pairs of states for CIDS patients*

From state	To state							
	Well	**Arrhythmic**	**Other cardiac**	**Non-cardiac**	**ICD maintenance**	**ICD replacement**	**Amiodarone problems**	**Death**
Well	567,328	209	508	340	144	36	10	145
Arrhythmic	208	1,269	0	0	0	0	0	0
Other cardiac	508	0	3,740	0	0	0	0	1
Other non-cardiac	339	0	0	2,817	0	0	0	0
ICD maintenance	144	0	0	0	776	0	0	0
ICD replacement	36	0	0	0	0	107	0	0
Amiodarone problems	9	1	0	0	0	0	191	0

TABLE 79 *Counts of daily transitions between pairs of states for UK patients (imputation 1)*

From state	To state							
	Well	**Arrhythmic**	**Other cardiac**	**Non-cardiac**	**ICD maintenance**	**ICD replacement**	**Amiodarone problems**	**Death**
Well	424,726	130	52	25	80	74	0	79
Arrhythmic	129	440	0	0	0	0	0	0
Other cardiac	53	0	131	0	0	0	0	0
Other non-cardiac	25	0	0	94	0	0	0	0
ICD maintenance	79	0	0	0	268	0	0	1
ICD replacement	74	0	0	0	0	175	0	0
Amiodarone problems	0	0	0	0	0	0	0	0

this group, with a crude death rate of approximately 1 per 14.5 patient-years.

Explanatory variables

The transition probabilities will depend on various patient-specific covariates, so that the model can be used to forecast costs and survival for given patient populations. Let x_i be a vector of covariates for patient i, and let β_{rs} be the corresponding vector of effects for the transition from state r to state s. A set of multinomial logistic regressions is used to model the transition probabilities. From each state r, the log of each outgoing transition to state s, relative to the transition to the baseline state 1, is a linear function of the covariates.

$$\log(p_{rs}/p_{r1}) = \mu_{rs} + \beta_{rs}^T x \qquad (r = 1, \ldots, 7; s = 2, \ldots, 8)$$

In fitting the model to the combined Canadian and UK data, the following covariates are included:

- age at the time of transition (below 60, 60–69 or 70 years and above)
- gender (0 = male, 1 = female)
- LVEF (0 = >35, 1 = ≤35)
- treatment (0 = ICD, 1 = amiodarone)
- country of data (0 = Canada, 1 = UK).

Thus, the experience of UK ICD patients from the sample will inform the baseline hazard rates (μ_{rs}), with data from the CIDS study being used to estimate the relative admission rates between ICD and amiodarone patients ($\beta_{rs}^T x$, where x is a marker for treatment with amiodarone).

Age is handled differently to the other covariates, as it is fitted as a time-dependent effect. Therefore, the transition count data are separated into three groups according to the age at the time of transition: below 60, 60–69 or 70 years and above. There were 48, 84 and 93 deaths in the respective age groups, with corresponding crude death rates of 1 per 21, 35 and 9 years in each age group.

The following assumptions about the Markov model have been made:

- The Markov assumption means that the probability of making a transition depends only on the current state a patient is in and the current covariates and not on the history of the patient.

- A non-homogeneous Markov process which changes according to the age of the patients has been adopted.
- Since there are so few deaths while in hospital, the death rate is assumed to be the same from all living states (1–7).
- No hospital admissions for amiodarone toxicity were observed in the UK data, so related transitions are assumed to be the same as those observed in the Canadian data; that is, p_{17} and p_{77} are independent of country of implant. The daily cost of an admission for amiodarone toxicity is adjusted to account for this unrealistic assumption.
- Once a patient has been admitted to hospital for a particular reason it is assumed that length of stay is common to all groups within each country (UK/Canada); that is $\{p_{jj}; j = 2, \ldots, 7: p_{j1}; j = 2, \ldots, 7\}$ are independent of age, gender, LVEF and treatment group, but depend on whether the implant took place in the UK or Canada.

Missing data

The two main sources of missing data, missing covariate data and missing hospitalisation data, have been handled differently.

The covariates of age, gender, country of implant and treatment groups were complete in all but three out of 965 cases. The three cases have been dropped. LVEF was missing for 232 UK cases. For these cases the probability of having an LVEF of less than 35% was estimated using logistic regression with age, gender and survival status as predictors (see Chapter 5). The estimated coefficients were:

$$\begin{aligned}\text{Logit}(p(\text{LVEF} < 35\%)) = {} & 0.0045 \\ & +1.2373 \text{ (if aged 60–69)} \\ & +1.2358 \text{ (if aged } \geq 70) \\ & -1.2890 \text{ (if female)} \\ & +1.2000 \text{ (if died)}\end{aligned}$$

Since the model was implemented using Markov chain Monte Carlo methods, missing values for LVEF could be imputed using Bayesian simulation, a method akin to multiple imputation.[62] This method samples values of the missing covariates from the prior distribution, derived from the above regression. It will include full uncertainty about the missing covariates in the estimates of covariate effects, but will use all available data with minimum bias.

There were 165 patients for whom hospital admissions data were not available. In theory it is possible to use Bayesian simulation within the model to estimate the distribution of admissions. However, since this would mean introducing an extra 2000 parameters it would slow down convergence considerably. Therefore, multiple stochastic regression imputation was used as an approximation. Five complete hospital admissions data sets were constructed with missing admissions and lengths of stay simulated from a series of Poisson regressions, with age, gender, survival status and length of follow-up as predictors. Details of regression coefficients are available on request. Five transition matrices and resulting covariates were estimated using winBUGS. Final parameter estimates were calculated as the mean of the estimates from the five survival analyses. Variances of the final parameter estimates were calculated as the mean of the variances from the five analyses plus 1.2 times the variance of the five parameter estimates. The latter term in this sum estimates the contribution to the variance from imputation uncertainty, with 1.2 a continuity correction resulting from the use of five imputations to estimate the full uncertainty of each missing covariate.

Bayesian implementation

The model is implemented using Bayesian methods. This allows prior beliefs about the parameters to be quantified. These beliefs are derived from the opinions of cardiac experts and previous ICD trials and studies. With the aid of Markov chain Monte Carlo simulation these prior beliefs can be combined with the information in the data to obtain posterior distributions for the model parameters. The posterior distributions then quantify the uncertainty about the true values of the parameters.

Prior distributions

The results of the AVID and CASH trials were combined crudely to construct a 'prior' for the effects of treatment on survival. The AVID hazard ratio (HR) of 0.62 based on 1016 patients and the CASH HR of 0.83 based on 288 patients may be combined to give a linear treatment effect of

$$1016 \log(0.62) + 288 \log(0.83)/(1016 + 288) = -0.414.$$

Assuming a normally distributed treatment effect, the corresponding respective 95% confidence intervals of 0.47 to 0.81 and 0.52 to 1.33 suggest a combined standard deviation of

$$((1016 \log(0.81) + 288 \log(1.33))/(1016 + 288) + 0.414)/1.96 = 0.159$$

where 1.96 is the 97.5% percentile of the standard normal distribution. Thus, normal prior distributions with mean –0.414 and SD 0.159 were used for the treatment effects on each of the seven relative transition probabilities to death. Non-informative priors were assumed for all other parameters.

To implement the model, WinBUGS was run for 1000 iterations, retaining the last 700 iterations to form the posterior sample. Convergence was rapid and occurred within 200 iterations.

Table 80 shows posterior estimates of relative rates of hospital admission and death for the set of covariates. In common with the exploratory analysis of the UK sample the death rate does not depend on patient gender and is similar for UK and CIDS patients. Older patients are at greater risk of death, as are patients with low LVEF. The

TABLE 80 *Relative probabilities of transition from well to hospital admission or death (baseline is male, age < 60 years, LVEF ≥ 35%, ICD, implanted in Canada)*

Transition from well	Covariate	Relative rate	95% CI
Admission for arrhythmia	Female	1.33	(1.01 to 1.75)
	Age 60–69	1.34	(1.02 to 1.78)
	Age ≥ 70	0.93	(0.68 to 1.26)
	LVEF < 35%	1.89	(1.46 to 2.45)
	Amiodarone	0.71	(0.54 to 0.94)
	Implant in UK	0.71	(0.55 to 0.91)
Admission for other cardiac reasons	Female	0.86	(0.67 to 1.09)
	Age 60–69	1.14	(0.92 to 1.42)
	Age ≥ 70	1.08	(0.87 to 1.36)
	LVEF < 35%	2.23	(1.83 to 2.71)
	Amiodarone	1.15	(0.97 to 1.38)
	Implant in UK	0.14	(0.10 to 0.20)
Admission for non-cardiac reasons	Female	1.32	(1.02 to 1.71)
	Age 60–69	1.08	(0.82 to 1.40)
	Age ≥ 70	1.19	(0.91 to 1.56)
	LVEF < 35%	1.38	(1.10 to 1.72)
	Amiodarone	1.13	(0.91 to 1.40)
	Implant in UK	0.10	(0.06 to 0.17)
Admission for ICD maintenance	Female	1.06	(0.72 to 1.56)
	Age 60–69	0.57	(0.41 to 0.80)
	Age ≥ 70	0.52	(0.37 to 0.73)
	LVEF < 35%	1.36	(0.99 to 1.85)
	Amiodarone	0.09	(0.05 to 0.17)
	Implant in UK	0.34	(0.25 to 0.46)
Admission for ICD replacement	Female	1.15	(0.70 to 1.88)
	Age 60–69	1.15	(0.72 to 1.84)
	Age ≥ 70	0.80	(0.45 to 1.41)
	LVEF < 35%	0.81	(0.52 to 1.25)
	Amiodarone	0.02	(0.01 to 0.21)
	Implant in UK	1.32	(0.85 to 2.04)
Admission for amiodarone toxicity	Female	0.00	(0.00 to 14.16)
	Age 60–69	1.05	(0.21 to 5.21)
	Age ≥ 70	0.96	(0.17 to 5.39)
	LVEF < 35%	1.03	(0.27 to 3.97)
	Amiodarone	6.48	(1.60 to 26.24)
	Implant in UK	1.00	NA
Death	Female	1.14	(0.80 to 1.61)
	Age 60–69	1.42	(0.99 to 2.05)
	Age ≥ 70	2.13	(1.49 to 3.05)
	LVEF < 35%	2.61	(1.85 to 3.69)
	Amiodarone	1.33	(1.06 to 1.67)
	Implant in UK	0.88	(0.65 to 1.20)

NA, covariate not included for this admission type.

TABLE 81 *Effect of country on probability of staying in hospital (baseline is Canada)*

Reason for admission	Chance of remaining in hospital the following day for UK patients relative to CIDS (95% CI)
Arrhythmia	0.56 (0.43 to 0.72)
Other cardiac reasons	0.34 (0.23 to 0.52)
Non-cardiac reasons	0.46 (0.24 to 0.86)
ICD maintenance	0.66 (0.23 to 1.84)
ICD replacement	0.93 (0.49 to 1.37)
Amiodarone toxicity	NA

NA, in base-case analysis the Canadian rate is assumed for UK patients owing to sparse data.

death rate for patients aged 60–69 years was lower than for younger patients. Amiodarone patients are at increased risk of death, with a relative risk of 1.33, very similar to that reported in the meta-analysis of secondary prevention trials.[30]

In general, women have more admissions than men, particularly for arrhythmia and non-cardiac reasons. Similarly, hospital patients with low LVEF have more hospital admissions, particularly for arrhythmia and non-cardiac reasons. The middle age group (60–69 years) is less likely to be admitted for any reason. As expected, there is a low rate of admission for ICD implants and repairs for those patients assigned amiodarone treatment and a low rate of admission for amiodarone toxicity for those patients assigned an ICD.

It should be emphasised that the increase in hospital admissions for arrhythmia, ICD maintenance and replacement seen in the ICD patients relative to amiodarone patients is taken directly from results of the CIDS cost-effectiveness data.

Once admitted to hospital, UK patients were significantly less likely to remain in hospital than CIDS patients, with the exception of readmissions for ICD replacement (*Table 81*). Thus, length of stay in hospital was significantly shorter for UK patients for all admissions except for ICD replacement.

Using the model to estimate cost-effectiveness

Using Monte Carlo simulation of the parameters of the Markov model, the joint distribution of the cost and effectiveness of ICDs can be estimated, relative to AADs alone for UK patients.

In this framework, at time t a patient is in one of eight states. Initially, all patients begin in the well state. Denote the distribution of patients among the states by the vector $\pi_0 = (1, 0, 0, 0, 0, 0, 0, 0)^T$. The probability of moving between states in time interval $t - 1$ to t is governed by the probability matrix P_t above. This P_t depends on t through the time-dependent covariate 'age group'. Thus, the marginal probability at time t has the relationship:

$$\pi_t = \pi_{t-1} P_t$$

If the initial cost of the procedure is c_0 and the cost of spending a day in each state is c_k, $k = 1, \ldots, 8$, then the expected cost of a treatment per patient is given by:

$$E_c = c_0 + \sum \pi_t c^T$$

Where c is the vector $(c_1, \ldots, c_8)^T$. To incorporate discounted costs at a rate of δ_c per day this becomes:

$$E_c = c_0 + \sum [\pi_t c^T / (1 + \delta_c)^{t-1}]$$

Similarly, if the benefit of being in each state can be denoted by the vector b, with discount rate of δ_b per day, the total expected benefit is:

$$E_d = \sum [\pi_t b^T / (1 + \delta_b)^{t-1}]$$

Thus, when survival is the outcome of interest the vector b is $(1, 1, 1, 1, 1, 1, 1, 0)^T$, so that each living state has a value of 1, irrespective of admission to hospital, and being dead has a value of 0. When quality-adjusted survival is the outcome of interest the vector b can contain values less than 1 to reflect information about the value of being in different states post-ICD implant or during amiodarone therapy. In the base-case analysis, using the data from the UK survey and published trials, it is assumed that all patients have a utility of 0.75 and this is constant across time after implant and for treatment with ICD or amiodarone (see Chapter 6).

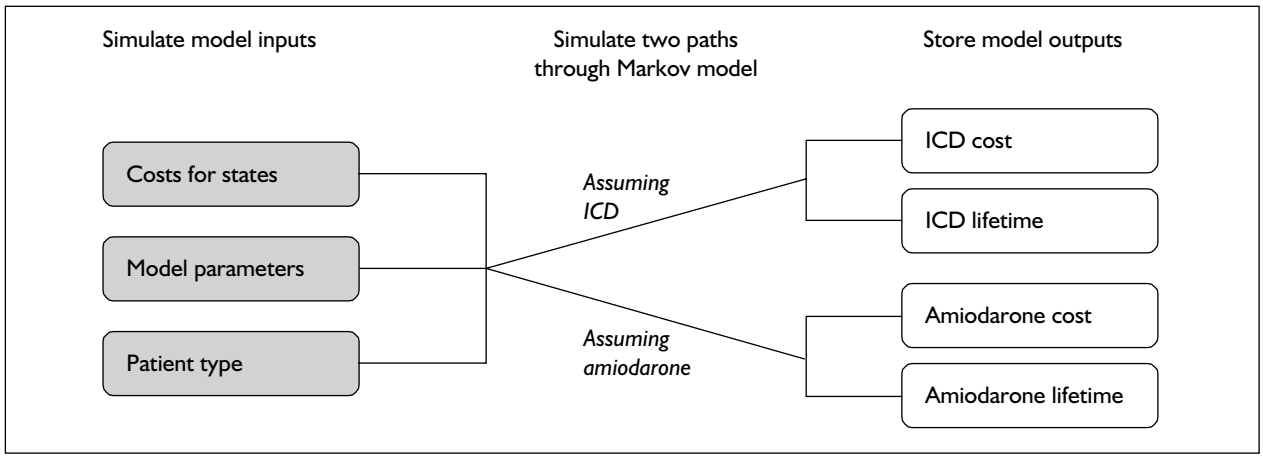

FIGURE 32 *Simulation of cost-effectiveness*

Implementing the cost-effectiveness model

To estimate the distribution of the cost-effectiveness of ICD therapy relative to amiodarone use, Monte Carlo simulation from the distribution of expected cost and expected benefit is used, conditional on treatment group. There are several inputs to this model whose true values are unknown; therefore, the uncertainty is quantified by assuming distributions for the inputs. First, the posterior distribution is used for the Markov model parameters. In the base case distributions are not given to the unit cost per day spent in each state under each treatment, but this may be relaxed in future analyses. Finally, a type of population to simulate is chosen by specifying a distribution for age and the proportions of individuals in each category, for example 80% males and 63% with LVEF below 35%, as in the UK sample.

The estimation proceeds as follows (*Figure 32*). These four steps are repeated a large number of times, say 1000, to produce a simulated distribution of 1000 estimates.

1. Fix patient characteristics for the group of interest.
2. Simulate values for the model parameters and calculate transition matrices.
3. Use these inputs to calculate expected costs and benefits for ICD treatment and amiodarone treatment.
4. Store the simulated total costs and benefits under each treatment.

Initial cost estimates

All patients have an initial cost. For ICD patients this will include the device and leads, implant costs, associated tests and hospital stay. Implant data were available for 318 patients with an average cost of £23,608.30 (see Chapter 7 and *Table 82*).

To estimate an initial cost for amiodarone as the baseline treatment the following strategy was followed. For 135 ICD patients the implantation took place during the admission precipitated by the presenting arrhythmia (pathways 1 and 3). For these patients the initial cost was divided between the preprocedural hospital stay arising from the presenting arrhythmia and the cost arising from the ICD implant itself. The costs associated with preprocedural hospital stay attributable to the presenting arrhythmia were assumed to be equivalent to the initial cost for an amiodarone patient. For these 135 patients the mean cost associated with the presenting arrhythmia was £2875.46. For the remaining 183 patients with detailed implant cost data who were not admitted to hospital owing to their presenting arrhythmia (pathways 2 and 4) the initial costs for amiodarone were assumed to be zero. Taking a weighted average of these two groups the initial cost for a patient treated with amiodarone was estimated to be £1220.52 (£2875.46 × 135/318 + 0 × 183/318).

The effect of patient characteristics on implant costs is summarised in *Table 82*. Implant costs were significantly lower for patients implanted in recent years than for those implanted before 1999. As expected, those patients who had an ICD implanted in the same admission as the presenting arrhythmia (pathways 1 and 3) had significantly higher costs reflecting the longer preimplant stay in hospital. Patient age at implant and LVEF were not associated with implant costs, but the mean cost for men was £1150 less than that for women (linear regression, $p = 0.048$). Similar effects were noted for preimplantation costs associated with the presenting arrhythmia.

TABLE 82 *Effect of patient characteristics on initial implant costs*

Factor	No. of implants	ICD implant cost, mean (SD)	No. of preimplants[a]	Preimplant cost attributed to presenting arrhythmia, mean (SD)[a]
Overall	318	£23,608 (3,958)	135	£2,875 (2,191)
Implant				
Pre-1999	91	£24,961 (4,492)	31	£3,641 (2,129)
1999–2000	109	£23,361 (3,560)	49	£3,190 (2,445)
2001–2002	118	£22,793 (3,616)	55	£2,164 (1,771)
Pathway				
1	38	£24,808 (4,141)	38	£3,146 (2,553)
2	34	£22,576 (3,084)	0	
3	97	£24,644 (3,690)	97	£2,770 (2,036)
4	104	£22,134 (3,338)	0	
5	10	£23,396 (5,606)	0	
Implant age (years)				
<60	140	£23,422 (3,787)	56	£2,936 (2,435)
60–69	106	£23,871 (4,214)	44	£2,977 (1,962)
≥70	72	£23,584 (3,930)	35	£2,651 (2,093)
Female	56	£24,556 (4,980)	29	£3,361 (2,701)
Male	262	£23,406 (3,683)	106	£2,743 (2,024)
LVEF ≥35	99	£23,618 (3,654)	40	£2,844 (2,243)
LVEF <35	163	£23,841 (3,777)	74	£3,132 (2,334)

[a] For 135 patients who were implanted during admission to hospital for the presenting arrhythmia.

Results

Validity of the model

To assess the validity of the model 1000 patients with characteristics similar to the UK sample were simulated and survival was compared with the actuarial survival estimates of the UK sample. The simulated patients had a mean age of 60 years (SD 14), were 80% male and LVEF was under 35% for 63% of them. *Figure 33* shows Kaplan–Meier estimates of the simulated and actual survival rates.

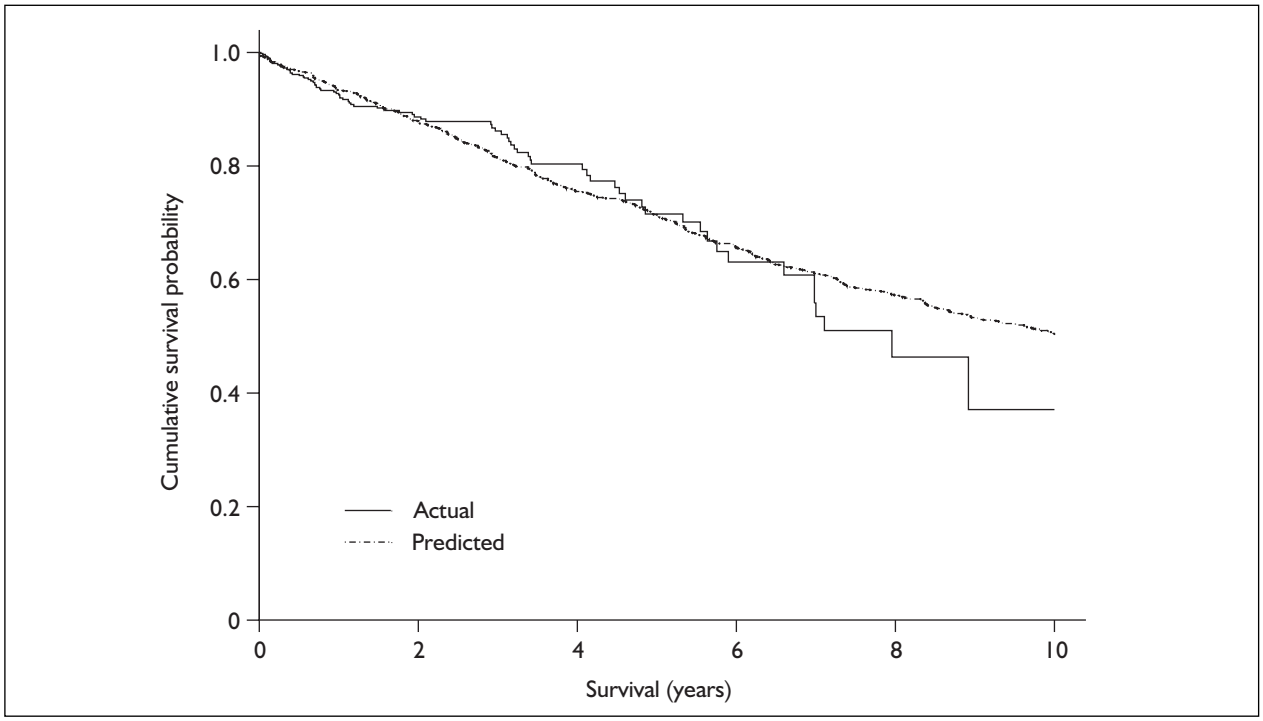

FIGURE 33 *Comparison of UK sample and model predicted survival*

For the first 6–7 years after ICD implantation the agreement was excellent, but after 7 years the simulated survival appeared to be superior to the model estimates. There may be a number of reasons for this. The most important reason is that the Markov assumption may not accurately reflect the longer term survival characteristics of the sample. Estimates of the baseline hazard rate will be dominated by the first 6 years after implantation. Beyond this time there are no CIDS data and only 56 UK patients, with seven deaths recorded after 6 years. Therefore, in the base case it was assumed that the baseline hazard is constant until a patient changes age group. Sensitivity to this assumption is assessed later.

Since cost-effectiveness estimates have been published for the CIDS trial, the reported expected life-years gained can be compared with estimates from the model. O'Brien and colleagues[51] reported undiscounted, mean survival in the CIDS ICD and amiodarone groups over 6.33 years of 4.91 years and 4.65 years, a difference of 0.26 years (3 months). Setting the model to calculate expected lifetimes for a Canadian population with a mean age of 63, with 85% male and 60% with LVEF < 35%, undiscounted mean survival was 4.98 for ICD patients and 4.61 for amiodarone, a difference of 0.37 years (4 months). The corresponding figures assuming 3% discount were 4.58 years for ICDs and 4.35 years for amiodarone in O'Brien's analysis[51] and 4.63 years for ICDs and 4.34 years for amiodarone using the present model. The model slightly overestimates the survival benefit attributed to ICD implantation. This is expected since the survival benefit is influenced by the inclusion of AVID and CASH results via the prior distribution, both of which showed a greater effect of ICDs on survival. There may also be shrinkage towards the UK estimates.

UK cost-effectiveness estimates

The base-case costs, discount rates and utility assumptions are summarised in *Table 83*.

Average implantation costs for the patients with usable clinical information were used. For amiodarone initial costs were derived from the proportion of ICD implant resource use, which was attributed to the presenting arrhythmia rather than the implant itself. Daily costs for each hospital admission were calculated as the event costs divided by the average number of days in hospital. The average of Papworth and Liverpool costs were taken for each event.

TABLE 83 *Base-case initial costs, daily state costs and utilities (discount rate used in base case was 6% for costs and 1.5% for benefits)*

State	ICD	Amiodarone
Total initial costs c_0	£23,608.30	£1,220.52
Daily cost for each state		
1. Out of hospital	£2.30	£2.43
2. Arrhythmic	£526.00	£526.00
3. Other cardiac	£519.50	£519.50
4. Non-cardiac	£296.50	£296.50
5. ICD maintenance	£646.00	£646.00
6. ICD replacement	£5495.50	£5495.50
7. Amiodarone side-effects	£122.00	£122.00
8. Death	£0	£0
Utilities		
All years after start	0.75	0.75

Base-case discount rates were based on NICE guidance at the time of the analysis and set at 6% for costs and 1.5% for benefits.[1] Based on the UK sample data utilities were set at 0.75 for both groups and for all times after the start of the study.

Cost-effectiveness over a 5-year horizon

Initially, cost-effectiveness was estimated over a 5-year horizon for the average UK population, with age distribution taken from the UK sample, 80% male and 63% LVEF of less than 35%. Although this was not the main focus of this study it provided a comparison between UK estimates and published trial-based estimates. Using 1000 simulations from the posterior distributions of the Markov model parameters the mean incremental costs for ICDs, relative to amiodarone therapy, over 5 years were £45,847 (95% CI £28,046 to £81,653). The mean LYG for ICDs over 5 years was 0.20 years (95% CI 0.02 to 0.50) or 2.4 months. Both incremental costs and life-years gained were significantly different from zero, although the mean gain in life-years was small. Using these mean estimates, for a UK population the ICER over a 5-year horizon would be £229,235. The ICER is high compared with published trial-based and model-based estimates, due to both the lower estimated gain in life years and the higher follow-up costs. The mortality rate in the UK sample of ICD patients was lower than that of all three main secondary prevention trials (see *Tables 39* and *80*) and the relative increase in mortality due to amiodarone treatment has been estimated at 1.33, based on these three secondary prevention trials. These combined assumptions result in a smaller estimated difference in absolute survival over the 5-year period than was assumed in other cost studies, and hence a larger ICER.

Cost-effectiveness over a 20-year horizon

For the base case cost-effectiveness was estimated over a 20-year horizon for a population with age, gender and LVEF distribution the same as in the UK sample. Providing that mortality rates remain constant over time after implantation, the estimated costs over a 20-year horizon are plotted in *Figure 34* for ICDs, amiodarone and for the incremental costs. Using 1000 simulations from the posterior distributions of the Markov model parameters, the mean incremental costs for ICDs over 20 years were £70,930 (95% CI £34,955 to £142,414). The distribution of both costs and cost differences is skewed. *Figure 35* shows the estimated distribution of mean life-years over a 20-year horizon for ICDs, amiodarone and for the gain in life-years attributed to ICD implantation. The mean LYG for ICDs over 20 years was 1.24 (95% CI 0.29 to 2.32).

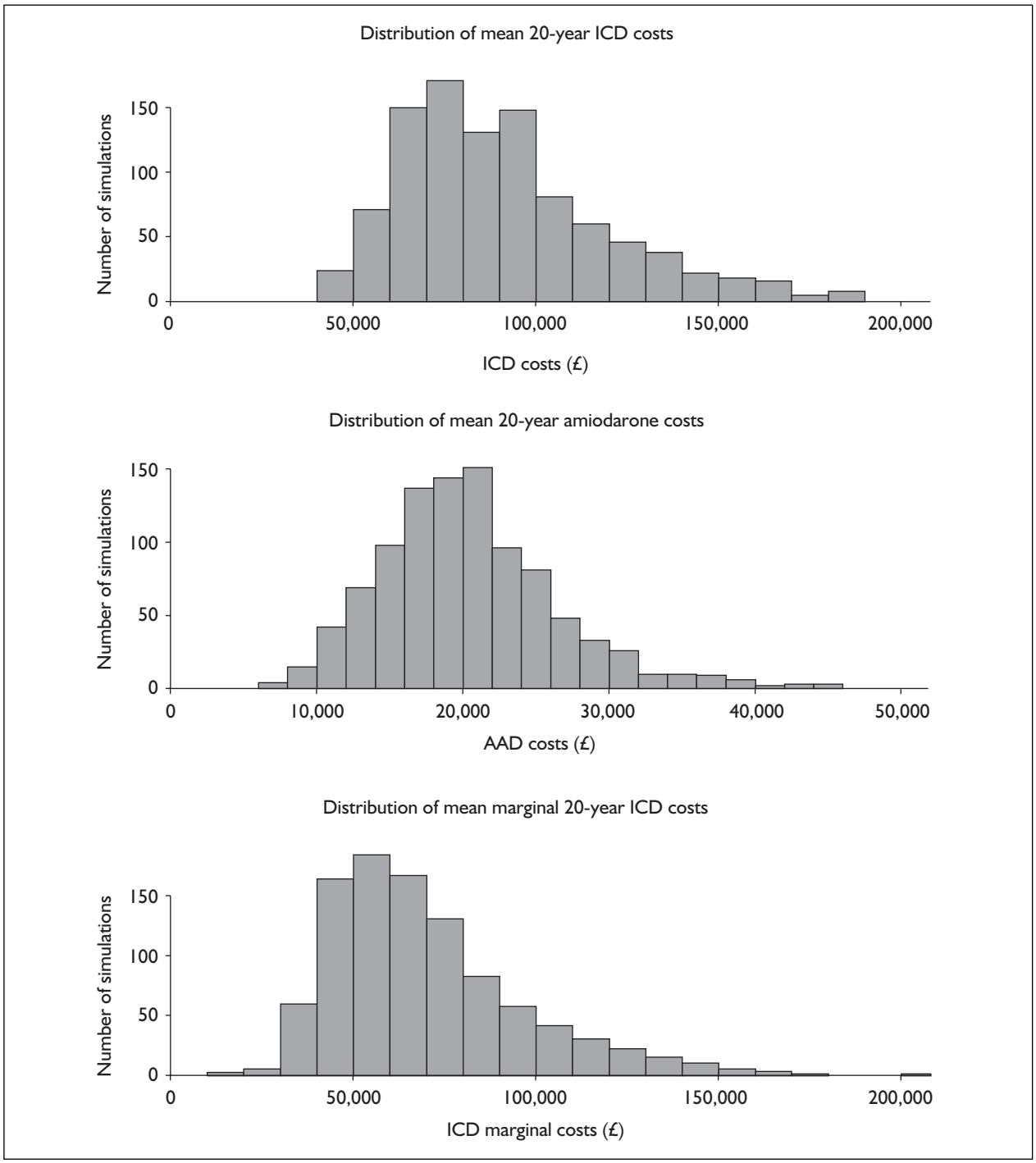

FIGURE 34 *Estimated costs over 20 years*

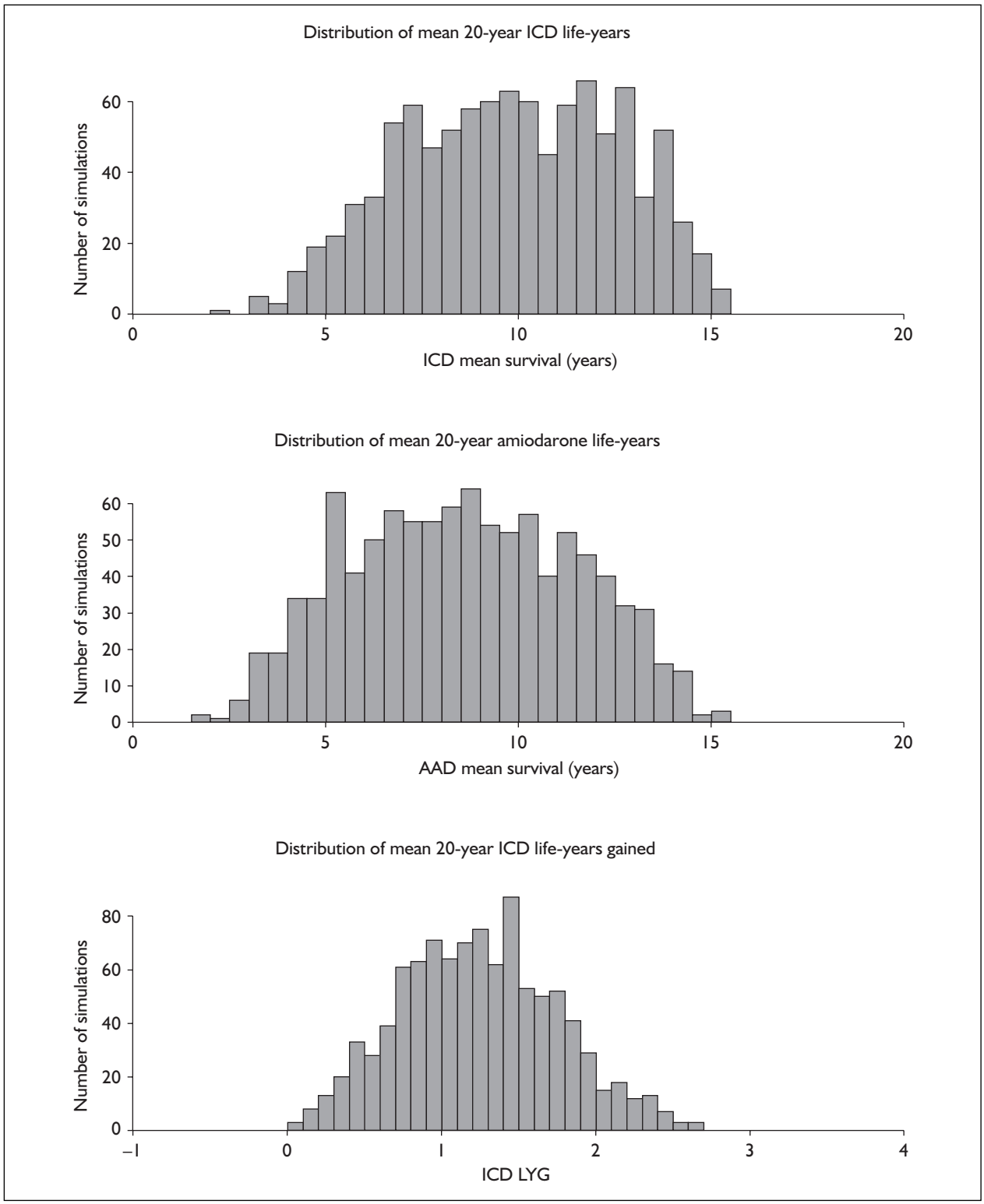

FIGURE 35 *Estimated distribution of mean life-years over 20 years*

Both incremental costs and life-years gained were significantly different from zero, although confidence intervals were wide, partly due to the uncertainty inherent in extrapolating to 20 years and partly due to the uncertainty in parameter estimates.

Simulated incremental costs and life-years gained were plotted in the cost-effectiveness plane in *Figure 36*. Using these mean estimates, for an average UK patient the ICER over a 20-year horizon would be £57,104. Based on this analysis there is a low probability that the cost-effectiveness

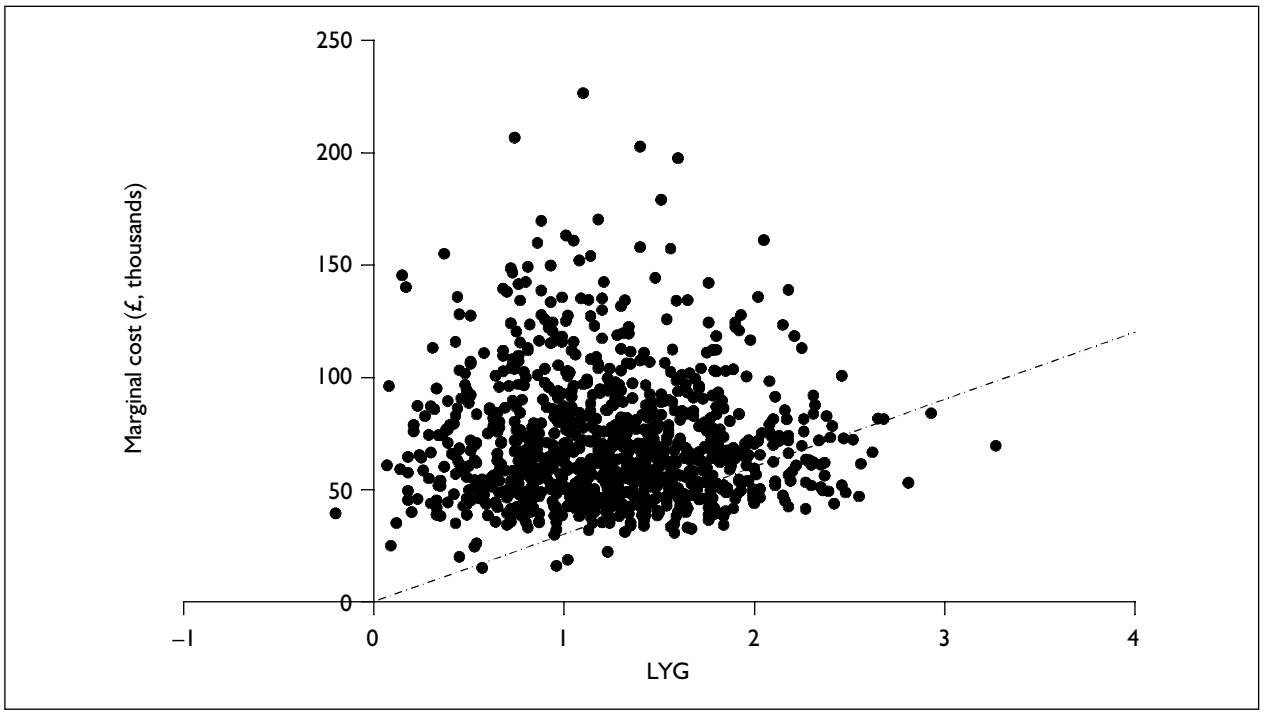

FIGURE 36 *Cost-effectiveness plane for ICD implantation versus amiodarone over a 20-year horizon. Dashed line represents £30,000 per LYG*

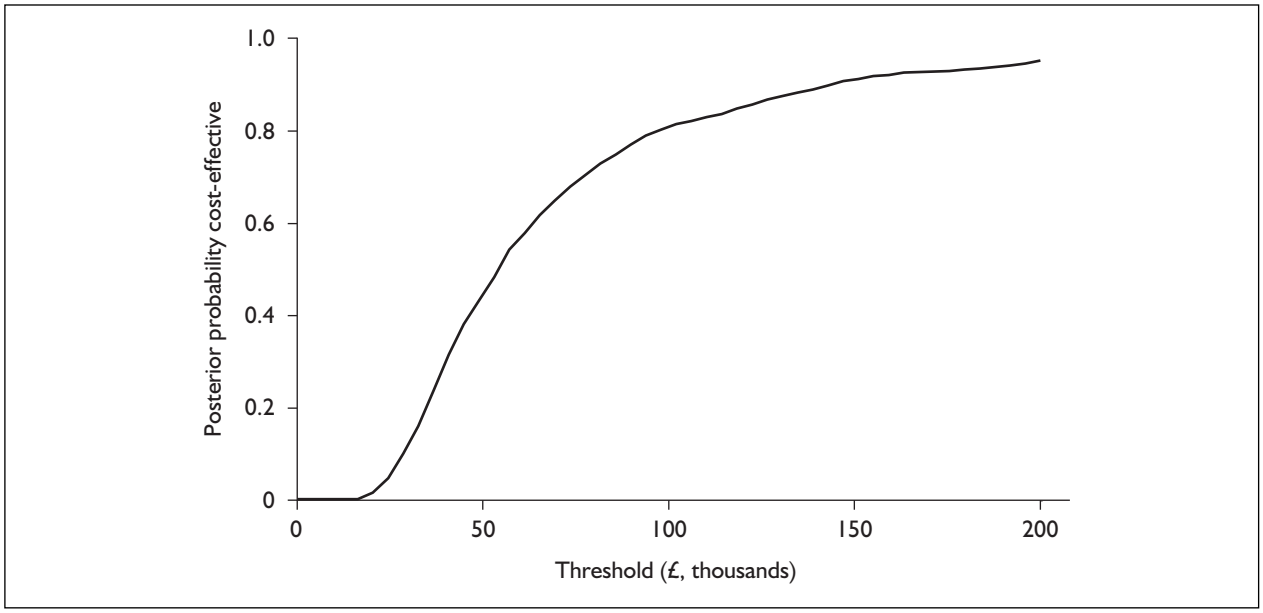

FIGURE 37 *CEAC for ICD implantation relative to Amiodarone over a 20-year horizon*

ratio would fall below the commonly applied threshold of £30,000 per LYG.

Using the simulated distributions of incremental cost and life-years gained the probability that the cost-effectiveness ratio would exceed a given threshold can be estimated. *Figure 37* shows the cost-effectiveness acceptability curve (CEAC) for different values of the acceptable threshold. At values around £100,000 there is a high probability that ICDs will be cost-effective under base-case assumptions.

Figure 38 plots the cumulative costs for ICD and amiodarone therapy over time after implantation or commencing drug therapy. For procedures such

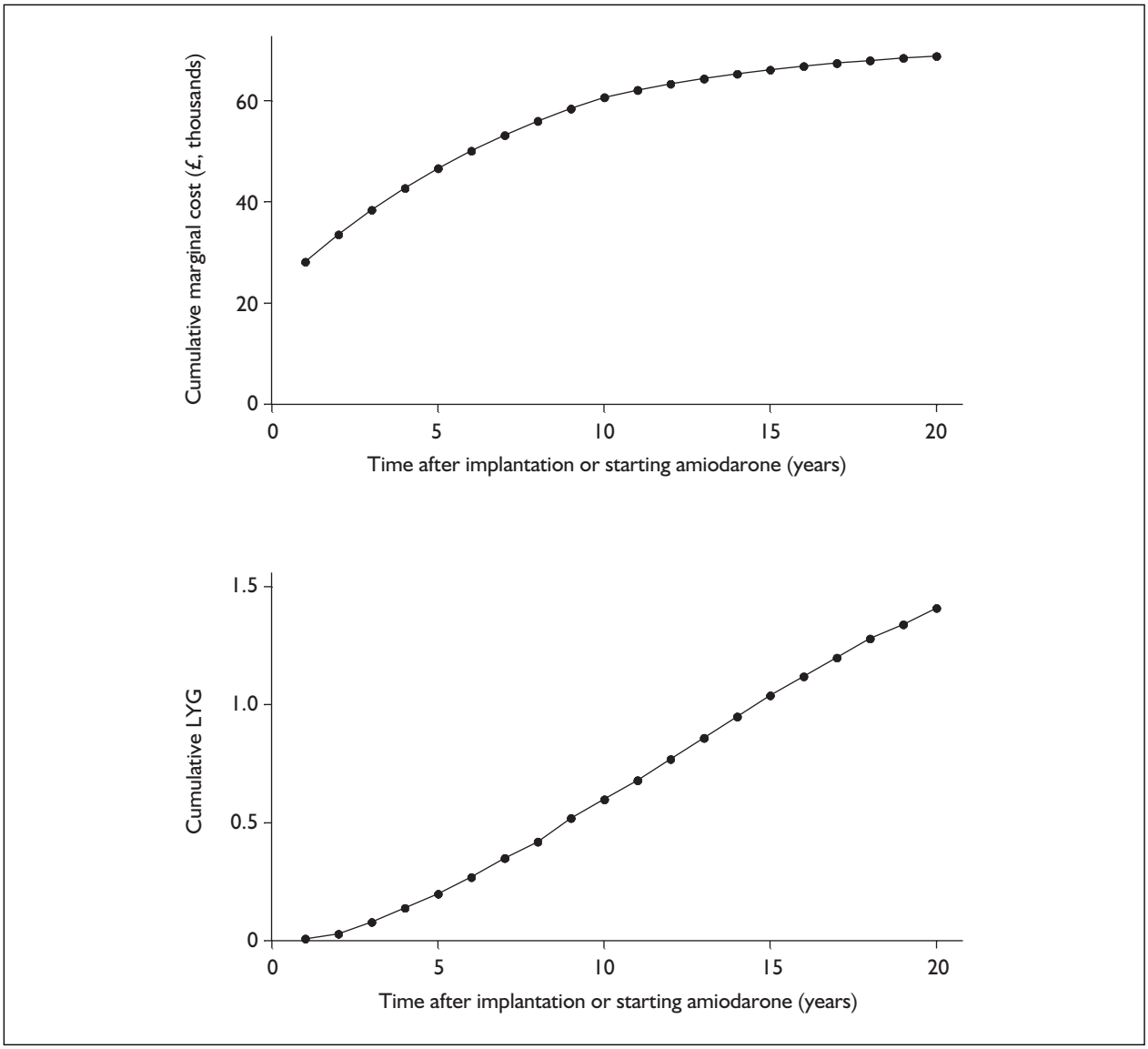

FIGURE 38 *Increasing incremental costs and benefits over time (undiscounted)*

as ICDs the accepted wisdom is that initial high fixed costs will, to some extent, be offset by lower variable costs thereafter. However, the incremental costs for ICD continue to increase over time.

The breakdown of expected follow-up costs by state is given in *Table 84* for an 'average' UK patient. It is clear that hospital admission for ICD maintenance and replacement accounts for the majority of follow-up costs. It is assumed that these will continue at the same rate as observed in the UK data. As ICDs evolve and become more reliable maintenance and replacement should account for fewer follow-up costs. Assumptions regarding the reliability of ICDs and replacement rates are explored in the sensitivity analysis.

In addition, ICD patients were more likely to be admitted following an arrhythmia owing to their greater survival rate.

The base-case analysis assumes a utility of 0.75 for all patients and at all times after implantation, which is equivalent to multiplying LYG by 0.75. This leads to an incremental cost per QALY of £76,139. Further assumptions about utilities will be investigated in sensitivity analyses.

Sensitivity analysis

Effect of patient characteristics

To investigate the effect of patient characteristics the expected incremental costs and benefits, evaluated at the posterior means of the Markov

TABLE 84 *Expected follow-up costs and time spent in each state over a 20-year time-horizon for an 'average' UK patient (age 60 years, 80% male, 63% LVEF <35%)*

		ICD	Amiodarone	Difference
Totals	Expected cost	£87,184	£18,379	£68,805
	Expected years of life	9.87	8.46	1.41
	Expected QALYs	7.41	6.35	1.06
	Expected cost per LYG			£48,734
	Expected cost per QALY gained			£64,979
Cost per state (excluding initial costs)	Well	£6,117	£5,718	£398
	Arrhythmic	£10,168	£6,495	£3,673
	Other cardiac	£2,613	£2,673	–£60
	Other non-cardiac	£1,112	£1,112	£1
	ICD maintenance	£5,095	£418	£4,667
	ICD replacement	£38,444	£587	£37,857
	Amiodarone side-effects	£27	£156	–£129
	Death	£0	£0	£0
Lifetimes per state over 20 years (years)	Well	9.7190	8.3806	1.3384
	Arrhythmic	0.0689	0.0431	0.0259
	Other cardiac	0.0183	0.0183	0.0000
	Other non-cardiac	0.0139	0.0135	0.0004
	ICD maintenance	0.0287	0.0023	0.0264
	ICD replacement	0.0249	0.0004	0.0246
	Amiodarone side-effects	0.0008	0.0046	–0.0038
	Death	10.1255	11.5372	–1.4117

Costs and effects evaluated at posterior means of model parameters for an 'average' patient are different to population posterior expected costs and effects owing to skewed distributions. These quantities are for illustration only.

TABLE 85 *Expected costs (£) and effectiveness estimates over a 20-year horizon using base case assumptions and posterior means of model parameters*

Population			Incremental cost	LYGs	QALYs gained	Cost per life-year	Cost per QALY
LVEF ≥35	*Male*	Age 50	£85,249	0.94	0.71	£90,690	£120,920
		Age 60	£79,112	1.16	0.87	£68,200	£90,933
		Age 70	£62,534	1.33	1.00	£47,018	£62,691
LVEF ≥35	*Female*	Age 50	£93,778	1.04	0.78	£90,397	£120,530
		Age 60	£86,779	1.24	0.93	£70,180	£93,573
		Age 70	£67,435	1.40	1.05	£48,017	£64,023
LVEF <35	*Male*	Age 50	£67,309	1.41	1.06	£47,732	£63,643
		Age 60	£60,565	1.40	1.05	£43,160	£57,547
		Age 70	£46,600	1.35	1.01	£34,532	£46,043
LVEF <35	*Female*	Age 50	£72,186	1.45	1.09	£48,965	£66,486
		Age 60	£64,715	1.39	1.05	£46,420	£61,893
		Age 70	£48,649	1.29	0.97	£37,576	£50,101
UK average patient (age 60, 80% male, 63% LVEF <35%)			£68,805	1.41	1.06	£48,734	£64,979

Costs and effects evaluated at posterior means of model parameters for an 'average' patient are different to population posterior expected costs and effects owing to skewed distributions. These quantities are for illustration only.

model parameters, were calculated for a range of population groups. These are summarised in *Table 85*, where it was assumed that all subgroups are subject to the same ICD treatment effect.

The incremental costs associated with ICD implantation decreased with age, since older patients had lower life expectancy and hence lower follow-up costs. The life-years gained over

TABLE 86 *Sensitivity of expected costs (£) and effectiveness estimates over a 20-year horizon to different assumptions about model parameters*

Sensitivity analysis		Incremental cost	LYGs	QALYs gained	Cost per life-year	Cost per QALY
Base case for a UK average patient (age 60, 80% male, 63% LVEF <35%)		£68,805	1.41	1.06	£48,734	£64,979
Replacement and maintenance						
Admissions reduced by 25%		£53,130	1.40	1.05	£37,838	£50,451
Admissions reduced by 50%		£44,470	1.40	1.05	£31,818	£42,424
Mortality relative to base case						
From 6 years	From 10 years					
1.0	1.5	£67,654	1.35	1.01	£50,111	£66,815
1.0	2.0	£66,735	1.28	0.96	£52,106	£69,475
1.5	1.5	£65,245	1.23	0.92	£53,074	£70,766
1.5	2.0	£64,390	1.14	0.85	£56,687	£75,582
2.0	2.0	£62,746	1.02	0.77	£61,494	£81,991
Lifetime model		£71,382	2.22	1.67	£32,110	£42,813
Discount 3.5% costs and 3.5% survival		£76,069	1.14	0.86	£66,587	£88,782
Utility estimates						
ICD	*AAD*					
0.75	0.65	£68,805	1.41	1.91	£48,734	£36,115
0.83	0.8	£68,805	1.41	1.43	£48,734	£48,260
LVEF < 35%						
Common treatment effect		£61,777	1.41	1.06	£43,794	£58,392
Subgroup-specific treatment effect		£62,980	2.01	1.50	£31,407	£41,876

Costs and effects evaluated at posterior means of model parameters for an 'average' patient are different to population posterior expected costs and effects owing to skewed distributions. These quantities are for illustration only.

20 years increased with age for patients with good function, but decreased with age for patients with poor function, indicating that there was a correlation between age at implantation and LVEF. The overall effect was of increased cost-effectiveness of ICDs with age at implantation. Thus, even though older patients had shorter life expectancy, they were more likely to gain from ICD implantation. Similarly, even though patients with LVEF below 35% had significantly poorer survival after ICD implantation (see Chapter 5), they had both lower costs and greater gain in mean survival than patients with LVEF of 35% and above, and therefore had lower ICERs.

Women were more likely to be admitted to hospital and use more resources than men, but otherwise had similar cost-effectiveness ratios.

From this analysis it appeared that targeting those patients at greatest risk of SCD, through either age or poor LVEF, would increase the overall cost-effectiveness of ICDs.

Other deterministic sensitivity analyses

A number of sensitivity analyses was undertaken to assess the importance of assumptions regarding hospital admission rates, mortality rates, discount rates and quality of life. In addition, the effect of extrapolating the model beyond 20 years was examined. The results are summarised in *Table 86*.

The base case assumed that hospital admissions for ICD maintenance and replacement will be constant across time after implantation. This may not be realistic for two reasons: first, currently used ICDs may be more reliable than those in the UK sample and replacement rates may be lower in the future and, second, replacement rates may decrease over time after implantation. Since admissions to hospital for maintenance and replacement are expensive and account for a large proportion of the follow-up costs, reducing the rate of these events by 50%, from approximately 6% to 3% per year, will have a very large effect on incremental costs and hence the ICER (*Table 86*). An ICER of £31,818 per life-year is closer to the commonly cited threshold for cost-effectiveness of a health intervention.

Base-case estimates depended heavily on extrapolating CIDS and UK data. In particular, a 70-year-old patient was assumed to have the same chance of survival in the first year after ICD

implantation as a patient who was 50 at implant has at 20 years after the initial implantation. Thus, if age-specific mortality rates are different for different periods after implantation estimates will be inaccurate. This is a strong assumption and worthy of detailed sensitivity analysis. *Figure 33* showed that the mortality rates are accurate up to 6 years after implantation. *Table 86* summarises the results, assuming that the survival rate changes after 6 years and after 10 years. Increases in the underlying mortality rate had the effect of decreasing both the incremental cost and the absolute life-years gained due to ICD, with resultant increase in the ICER. Increasing the mortality rate after 10 years with an ICD by 50% of the base-case mortality had the effect of decreasing the incremental costs by £1151, and doubling the estimate of mortality after 10 years decreased the marginal costs by £2070. Corresponding decreases in LYG were 0.06 and 0.13, respectively. The resulting increases in the ICER estimates were £1377 and £3372, respectively. Since the mean survival time for an average ICD patient is 9.87 years, changes to assumptions about the hazard rate after 10 years had a small impact on the ICER. Increasing the mortality rate at 6 years after ICD implantation had a greater impact on the ICER.

The model used a 20-year time-horizon since longer term extrapolation of event rates is very difficult to justify. A lifetime model using base-case assumptions increased the incremental costs only slightly to £71,382 and increased mean LYG to 2.22 for an average patient. The corresponding ICER was £32,110.

The sensitivity of the estimates to discount rates was assessed by repeating the simulations using an annual rate of 3.5% for both costs and benefits as currently proposed by HM Treasury.[71] Under this assumption the mean incremental cost of ICDs for an average UK patient over 20 years was £76,069 and the mean LYG was 1.14. This increases the ICER to £66,587.

In the CIDS substudy of quality of life there was some evidence that ICD patients had superior quality of life, although no utility measure was reported. For the base case equivalent quality of life was assumed for ICD and amiodarone patients, set close to the average for the UK sample of 0.75. A credible alternative is that ICD patients have a slightly higher utility than amiodarone patients, but that the difference will be small, at most 0.1 units. In the sensitivity analysis it was assumed that ICD patients had a utility of 0.75 and amiodarone patients 0.65. This changed the QALYs gained to 1.91 with a corresponding ICER of £36,115 per QALY. In their cost-effectiveness model Owens and colleagues[57] use previously unpublished utility estimates of 0.83 on ICD therapy and 0.80 on drug therapy. Adopting these utility values, the cost per QALY would be £48,260.

In the analyses for *Table 85* it was assumed that all subgroups were subject to the same ICD treatment effect. In the meta-analysis published by Connolly and colleagues[30] there was a significant treatment by subgroup interaction for LVEF and for implantation after 1991. That is, patients with LVEF below 35% and those implanted with an ICD after 1991 had a significantly greater benefit from ICDs than other groups. For patients with low LVEF an HR of 0.66 for ICDs was estimated and it is useful to investigate the effect of altering the ICD effect for this subgroup. Using the overall estimate of the effect of ICD implant the ICER was estimated to be £43,794 per life-year for patients with LVEF below 35%. In comparison, using the subgroup-specific estimate of the effect of ICD implant the ICER is £31,407 per life-year.

Assessment of NICE recommendations 2000

The above cost-effectiveness analysis was based on all patients implanted with ICDs at two large implanting centres in the UK, Liverpool and Papworth, between 1991 and 2002, and on the results of the three major secondary prevention trials comparing ICDs with AADs. Although the analysis directly reflected the mix of patients implanted in the UK, around one-third of these UK patients had an LVEF in excess of 35%. (The threshold recommended in the current NICE guidance is an LVEF ≤ 35%.) Thus, on average, the patients in the original base-case analyses had a lower baseline hazard than would be the case for patients meeting the NICE criteria. Since cost-effectiveness estimates were sensitive to baseline hazard it was considered important and appropriate to investigate cost-effectiveness in patients satisfying ICD implantation criteria in the NICE guidance. The following analyses were undertaken, based on the characteristics, baseline and relative hazards, and costs of the subset of patients in the original model who met NICE criteria with respect to LVEF.

Additional analyses were undertaken to investigate the effect of other externally proposed cost and utility assumptions. These are not based on or derived from the evidence base relating to observed UK practice. The same base case and

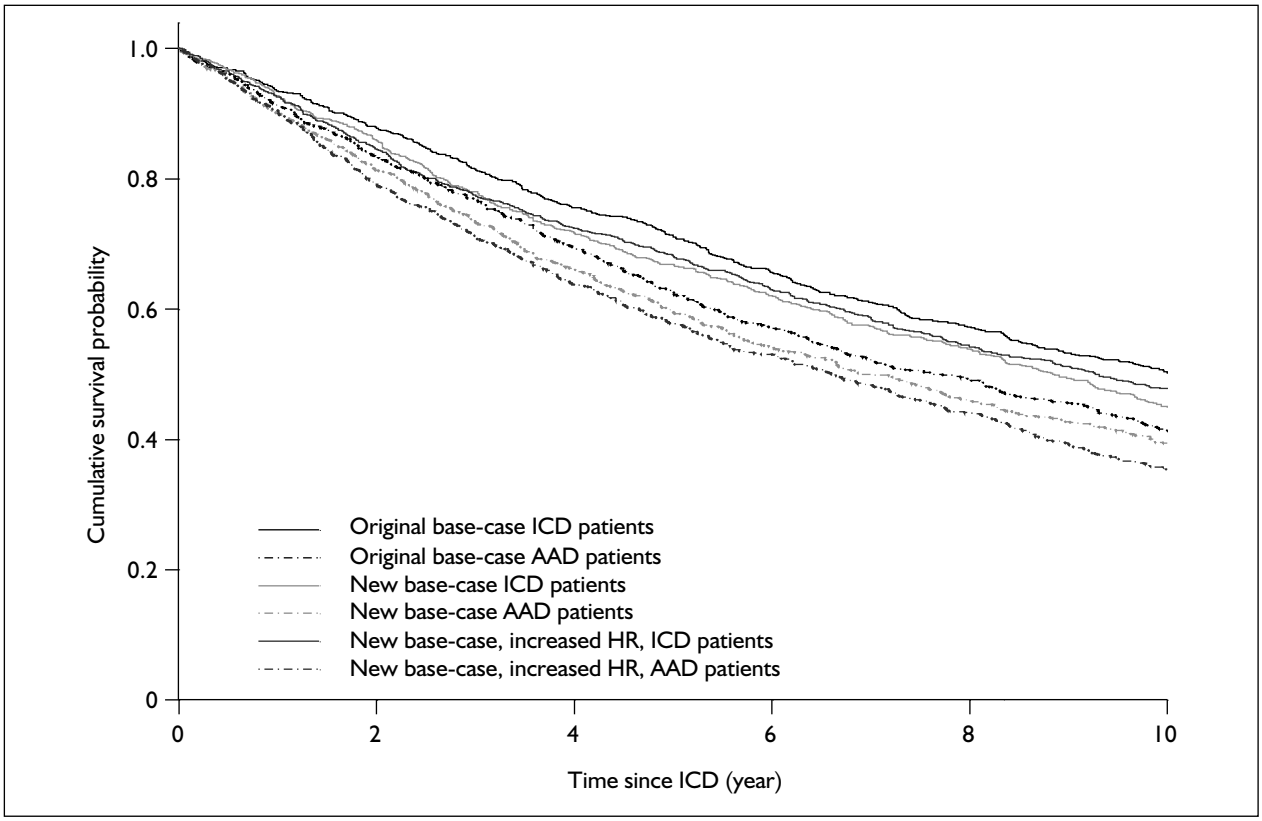

FIGURE 39 *Survival rates for ICD and amiodarone patients for original base case, new base case and new base case with subgroup-specific hazard ratio*

alternative assumptions regarding utilities were used as in the original base-case analysis.

New base-case model

The new base case restricts analysis to patients with LVEF below 35% to reflect existing NICE recommendations. For these patients the mean age was 63 years (SD 11.7) and 87% were male. Survival rates for the original and new base cases are compared in *Figure 39*.

A higher proportion (50%) of this subset of ICD implants took place during the admission for the presenting arrhythmia in patients with LVEF below 35% than in patients with an LVEF of 35% or above (44%). This had the effect of increasing mean initial implant costs to £23,841 (SD £3777) for ICD patients and increasing mean initial costs for amiodarone patients to £1566.

In the new base-case analysis all other cost estimates were unchanged and discount rates remained at 6% for costs and 1.5% for effects (*Table 87*). The UK ICD sample data were explored to assess the relationship between low LVEF and utility, overall and across time after ICD implantation. Patients with LVEF below 35% had only slightly lower utility and there was no evidence that this varied over time. Therefore, the original assumption of utility equal to 0.75 for both groups was retained and this was examined further in sensitivity analyses.

New base-case cost-effectiveness estimates

Providing that mortality rates remain constant over time after implantation, over a 20-year horizon and using 1000 simulations from the posterior distributions of the Markov model parameters, the mean incremental costs for ICDs over 20 years were £66,607 (95% CI £32,277 to £136,582). The mean LYG for ICDs over 20 years was 1.23 (95% CI 0.15 to 2.3).

Simulated incremental costs and LYG are plotted in the cost-effectiveness plane in *Figure 40*. Using these mean estimates, for a UK patient with LVEF below 35% the ICER per LYG over a 20-year horizon would be £54,152. The difference in marginal costs and life-years gained between the original base case and the new base case is small, since mortality rates were higher for both ICD and AAD patients, so that the extra benefit was small in absolute terms. The dashed line represents a threshold of £30,000 per LYG. The probability of ICDs being cost-effective using a £30,000 per LYG threshold in UK patients with LVEF below 35% is 15.5%.

TABLE 87 *New base-case initial costs, daily state costs and utilities (discount rate used in base case was 6% for costs and 1.5% for benefits)*

State	ICD	Amiodarone
Total initial costs c_0	£23,841	£1,566
Daily cost for each state		
1. Out of hospital	£2.30	£2.43
2. Arrhythmic	£526.00	£526.00
3. Other cardiac	£519.50	£519.50
4. Non-cardiac	£296.50	£296.50
5. ICD maintenance	£646.00	£646.00
6. ICD replacement	£5495.50	£5495.50
7. Amiodarone side-effects	£122.00	£122.00
8. Death	£0	£0
Cost per event		
2. Arrhythmic	£2,536	£2,536
3. Other cardiac	£2,401	£2,401
4. Non-cardiac	£1,424	£1,424
5. ICD maintenance	£3,009	£3,009
6. ICD replacement	£18,967	£18,967
7. Amiodarone side-effects	£2,253	£2,253
Utilities		
All years after start	0.75	0.75

In the base-case analysis and at all times after implantation a utility of 0.75 is assumed for all patients, which is equivalent to multiplying LYG by 0.75. This leads to an incremental cost per QALY of £72,399 and the posterior probability that the incremental cost per QALY was less than £30,000 was 4.5% (*Figure 40*).

To explore cost drivers further a breakdown was produced of expected follow-up costs by state for an average UK patient with LVEF below 35% (*Table 88*). These figures are derived from calculating the costs for an average patient conditional on the posterior means of the model parameters. These conditional estimates are slightly different to posterior means owing to the skewness in the distributions of costs and, to a lesser extent, effects. However, they do demonstrate the relative contribution of state costs to the total. Of the £58,887 total incremental cost associated with ICDs for the average person, £22,275 (38%) resulted from initial implant costs and a further £32,424 (55%) was attributed to ICD maintenance (£4319, 7%) or replacement (£28,105, 48%). Compared with the original base-case analysis, initial costs associated with implantation account for a greater proportion of the marginal cost (38% versus 33%) and replacement costs account for less of the marginal costs (48% versus 55%). This results from the shorter life expectancy in both ICD and AAD patients in this high-risk group compared with the original base case.

Probabilistic sensitivity analyses

Probabilistic sensitivity analysis undertaken consisted of estimating posterior distributions for the incremental costs and QALYs gained and using them to estimate CEACs. These analyses are averaged over the patient population of interest. The CEAC for the new base case is only slightly superior to that for the original base case (*Figure 41*). Increasing the relative hazard by using the subgroup-specific hazard ratio of 0.66 improves cost-effectiveness rather more. For example, the probability of being cost-effective exceeds 0.5 if the amount that one is willing to pay is £72,360 per QALY gained in the original base case, £67,362 per QALY gained in the new base case and £48,358 per QALY gained using the subgroup-specific hazard ratio (*Table 89*). The corresponding incremental costs per LYG were £54,270 per LYG in the original base case, £50,521 per LYG in the new base case and £36,269 per LYG using the subgroup specific hazard ratio (*Table 89*).

In common with the original base case the initial implant and hospital admissions for ICD maintenance and replacement accounted for the majority of the incremental cost. *Figure 42* shows the effect on the CEAC for alternative assumptions about these costs. First, a mean acquisition cost (including implant) of £16,250 was assumed based on manufacturers' estimates derived from the NHS Purchasing and Supplies Agency (personal

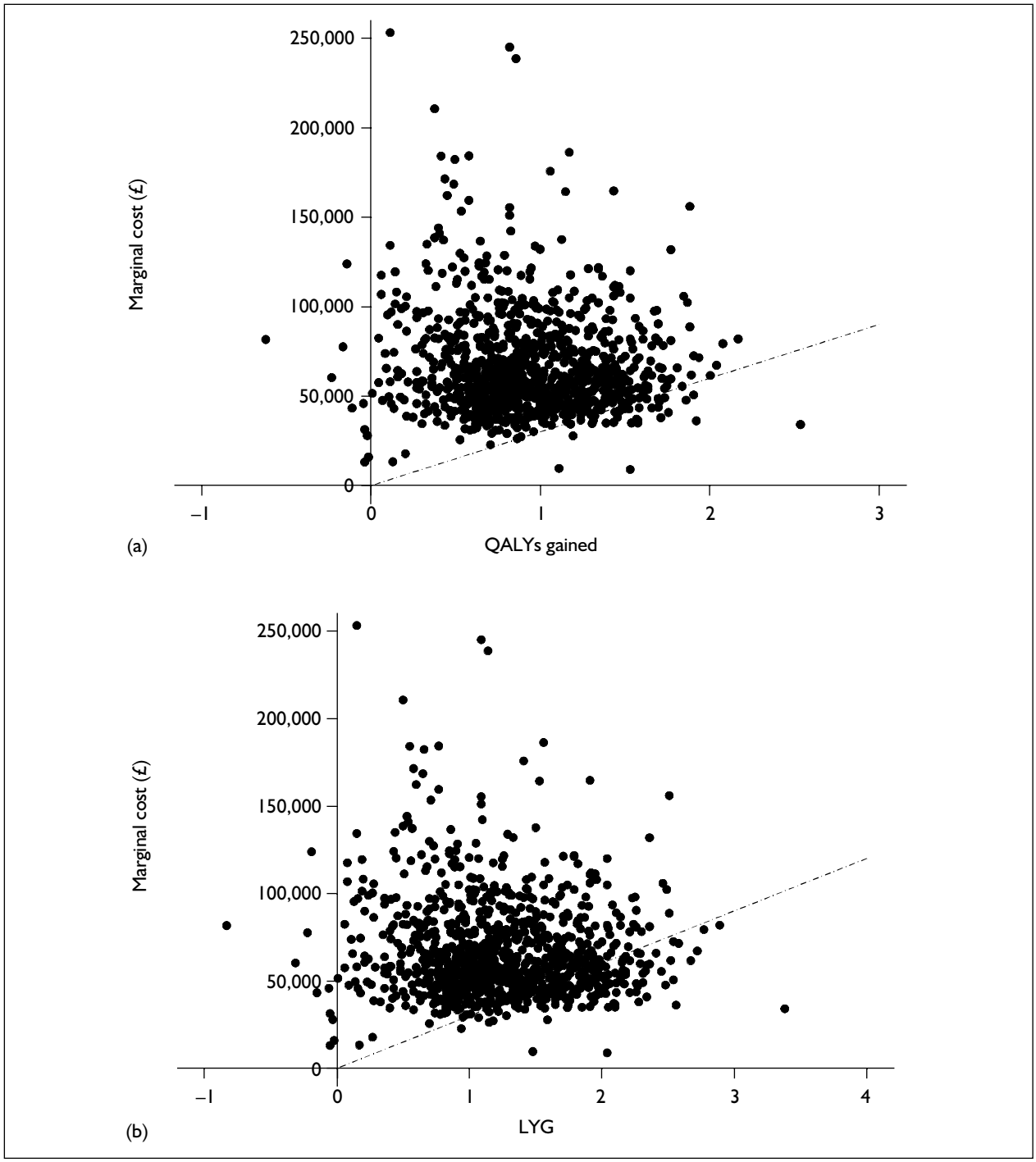

FIGURE 40 *Cost-effectiveness plane for (a) QALYs gained and (b) LYG for ICD implantation versus amiodarone over a 20-year horizon in patients with LVEF <35%. Dashed line represents £30,000 per QALY/LYG.*

communication). If the estimates of the costs associated with the initial implant and with each replacement were reduced to £16,250, incremental costs would be reduced by £11,548, with a corresponding improvement in the CEAC (*Figure 42*). Similarly, if the rate of hospital admissions for ICD maintenance and replacement were reduced by 50%, from approximately 6% to 3% per year, it would have a considerable effect on incremental costs and hence the ICER. If both were to be reduced the CEAC would improve further (*Figure 42*).

The original analysis and the analysis based on NICE guidelines assumed that mortality and hospital admission rates remained constant up to

TABLE 88 *Expected follow-up costs and time spent in each state over a 20-year time-horizon for an 'average' UK patient with LVEF <35% (age 63 years, 87% male)*

		ICD	Amiodarone	Difference
Totals	Expected cost	£76,389	£17,502	£58,887
	Expected years of life	7.90	6.53	1.37
	Expected QALYs	5.93	4.90	1.03
	Expected cost per LYG			£42,966
	Expected cost per QALY gained			£57,288
Cost per state (excluding initial costs)	Well	£5,085	£4,610	£475
	Arrhythmic	£10,229	£6,377	£3,852
	Other cardiac	£2,940	£2,919	£21
	Other non-cardiac	£1,029	£995	£34
	ICD maintenance	£4,693	£374	£4,319
	ICD replacement	£28,530	£425	£28,105
	Amiodarone side-effects	£42	£235	–£193
	Death	£0	£0	£0
Lifetimes per state over 20 years (years)	Well	7.7611	6.4538	1.3074
	Arrhythmic	0.0666	0.0404	0.0262
	Other cardiac	0.0198	0.0191	0.0007
	Other non-cardiac	0.0123	0.0115	0.0008
	ICD maintenance	0.0254	0.0020	0.0234
	ICD replacement	0.0178	0.0003	0.0175
	Amiodarone side-effects	0.0012	0.0066	–0.0054
	Death	12.0958	13.4663	–1.3705

Costs and effects evaluated at posterior means of model parameters for an 'average' patient with low LVEF are different to population posterior expected costs and effects owing to skewed distributions. These quantities are for illustration only.

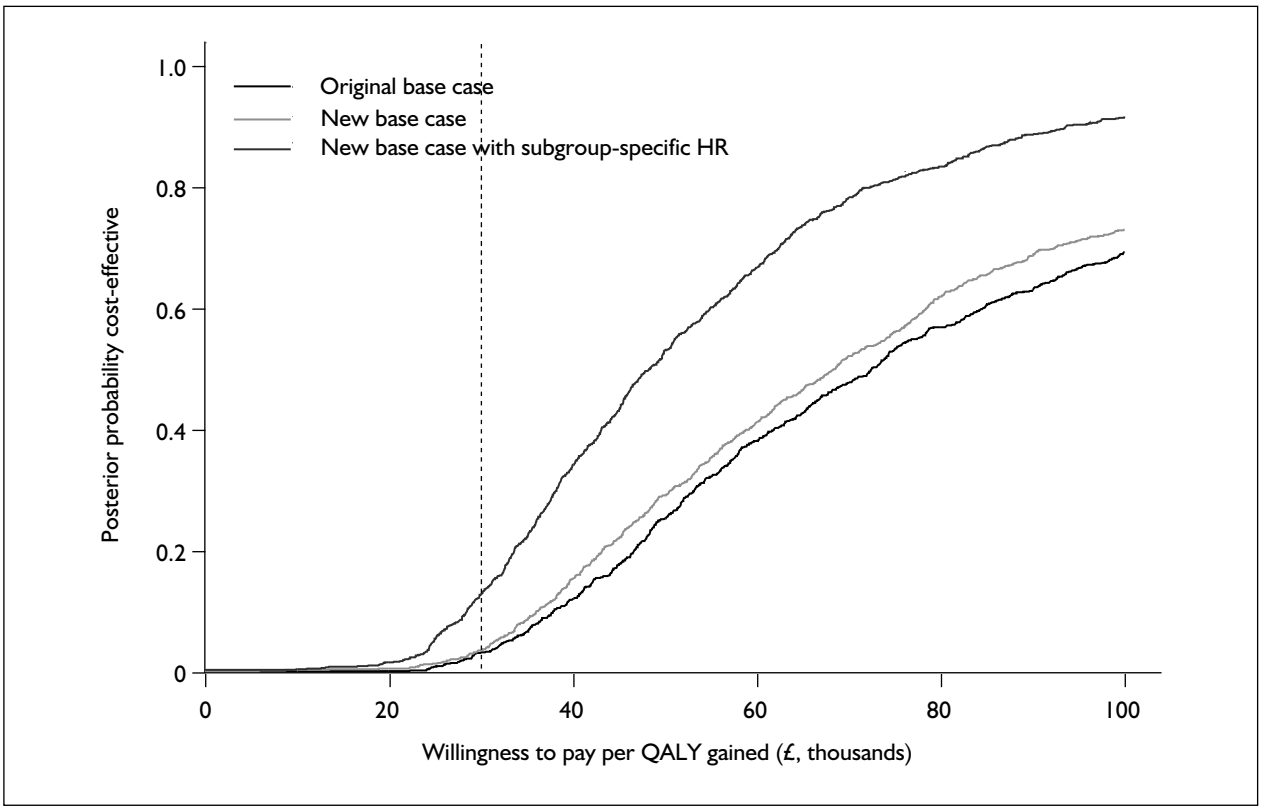

FIGURE 41 *CEAC for ICD implantation relative to amiodarone over a 20-year horizon for original base case, new base case and new base case with a subgroup-specific hazard ratio. Dashed line is £30,000.*

TABLE 89 *Probabilistic sensitivity analysis of expected costs (£) and effectiveness estimates over a 20-year horizon*

Sensitivity analysis	Incremental cost	QALYs gained	ICER per QALY
Utility estimates 0.75 for ICD and 0.75 for AAD			
New base case	£66,607	0.92	£72,399
Subgroup-specific treatment effect	£68,724	1.34	£51,287
ICD implant costs (device and variable costs) set to £16,250	£55,059	0.93	£59,204
Replacement and maintenance			
Admissions reduced by 25%	£51,627	0.90	£57,363
Admissions reduced by 50%	£39,814	0.93	£42,811
Implant £16,250+			
Admissions reduced by 25%	£43,840	0.93	£47,140
Admissions reduced by 50%	£32,740	0.92	£35,587
Lifetime model	£73,463	1.52	£48,372
Utility estimates 0.75 for ICD and 0.65 for AAD			
New base case	£66,607	1.75	£38,061
Subgroup-specific treatment effect	£68,724	2.13	£32,265
ICD implant costs (device and variable costs) set to £16,250	£55,059	1.76	£31,284
Replacement and maintenance			
Admissions reduced by 25%	£51,627	1.74	£29,671
Admissions reduced by 50%	£39,814	1.76	£22,622
Implant £16,250			
Admissions reduced by 25%	£43,840	1.76	£24,909
Admissions reduced by 50%	£32,740	1.74	£18,816
Lifetime model	£73,463	2.49	£29,521
Utility estimates 0.83 for ICD and 0.8 for AAD			
New base case	£66,607	1.27	£52,446
Subgroup-specific treatment effect	£68,724	1.71	£40,189
ICD implant costs (device and variable costs) set to £16,250	£55,059	1.28	£43,015
Replacement and maintenance			
Admissions reduced by 25%	£51,627	1.25	£41,302
Admissions reduced by 50%	£39,814	1.28	£31,105
Implant £16,250			
Admissions reduced by 25%	£43,840	1.28	£34,250
Admissions reduced by 50%	£32,740	1.26	£25,984
Lifetime model	£73,463	1.97	£37,260
	Incremental cost	**LYGs**	**ICER**
Estimating LYG			
New base case	£66,607	1.23	£54,152
Subgroup-specific treatment effect	£68,724	1.78	£38,609
ICD implant costs (device and variable costs) set to £16,250	£55,059	1.24	£44,402
Replacement and maintenance			
Admissions reduced by 25%	£51,627	1.20	£43,023
Admissions reduced by 50%	£39,814	1.24	£32,108
Implant £16,250			
Admissions reduced by 25%	£43,840	1.24	£35,354
Admissions reduced by 50%	£32,740	1.22	£22,836
Lifetime model	£73,463	2.02	£36,279

20 years with no extra costs or benefits accruing after 20 years. This time-horizon was chosen to enable a wide range of sensitivity analyses to be completed in a timely fashion, and based on the fact that assumptions about extrapolation of trial and UK sample data beyond the period of observation cannot be verified. However, assuming that the mortality and hospital admission rates remain constant over the lifetime of ICD patients, the ICER is reduced to £48,372 per QALY (*Table 89*). If, in addition, an acquisition/implant cost of £16,250 and a replacement cost of £16,250 are assumed, the cost is further reduced to £39,277. Finally, if the cost of implant and replacement is assumed to be £16,250, and the replacement rate is reduced by 50%, then the lifetime model would result in an ICER of £22,712, a cost-effective scenario.

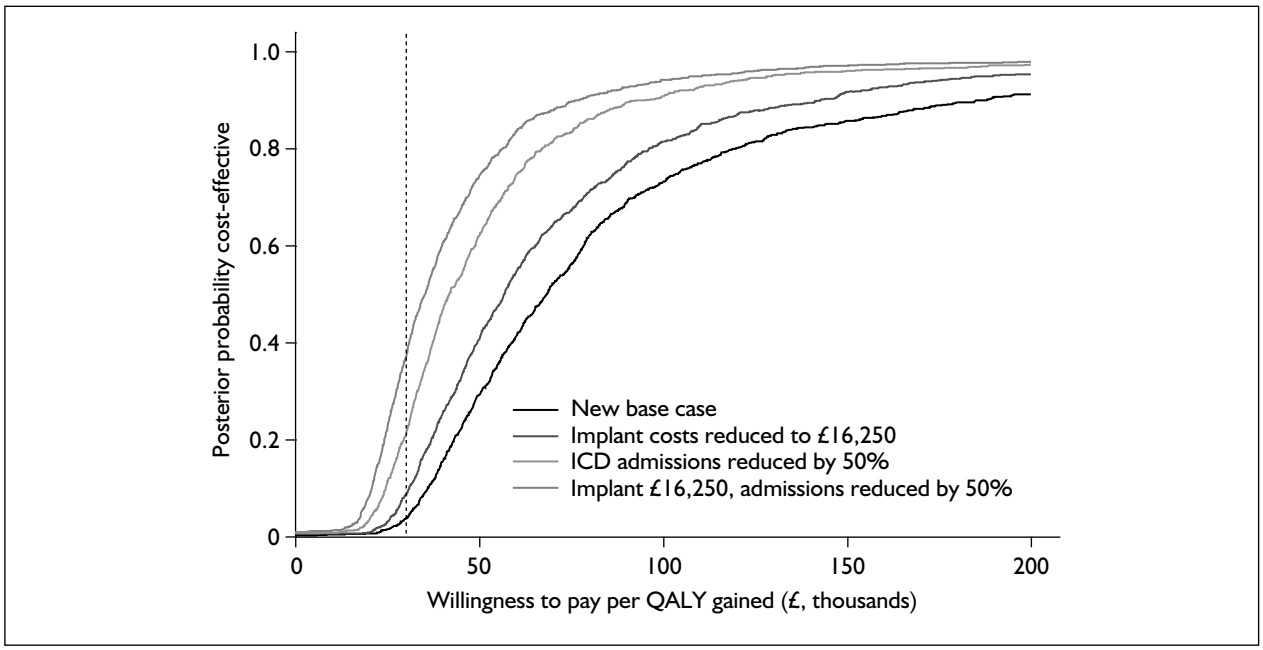

FIGURE 42 *CEAC for new base case compared with implant/replacement costs reduced to £16,250, repair/replacement admissions reduced by 50%, implant/replacement costs £16,250 and repair/replacement admissions reduced by 50%. Dashed line is £30,000.*

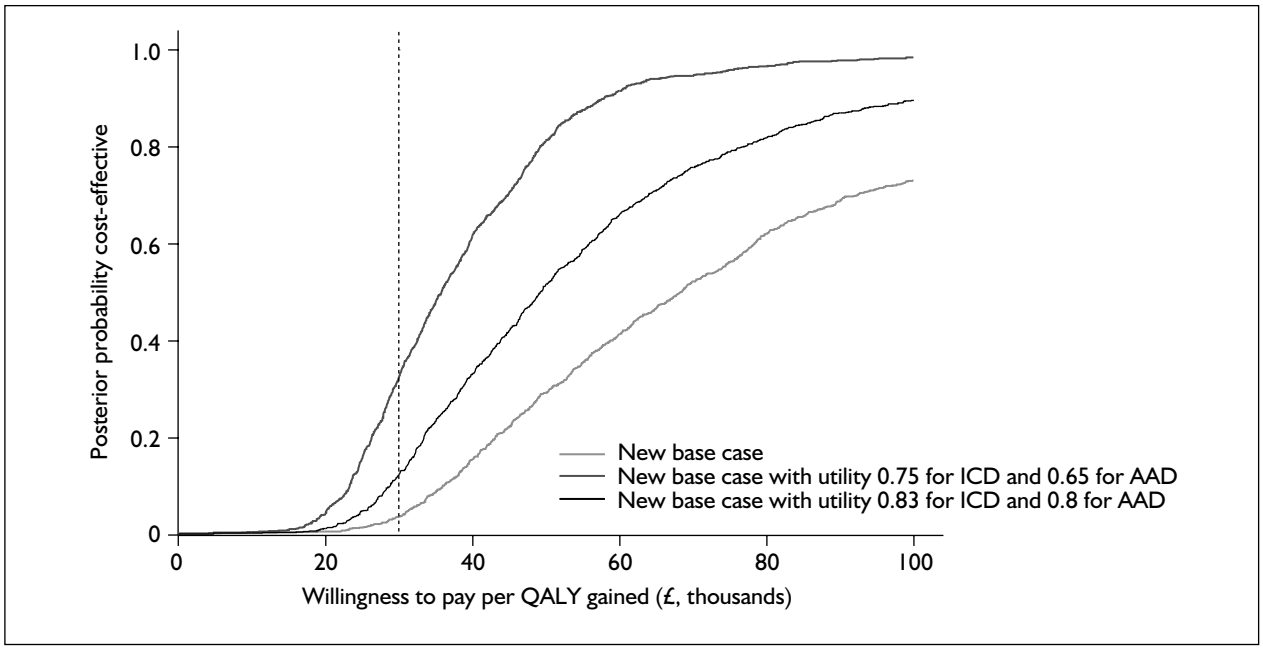

FIGURE 43 *CEAC for new base case and for two alternative assumptions about utilities. Dashed line is £30,000.*

On the basis of the UK ICD sample data, for the new base case an equivalent quality of life was assumed for ICD and amiodarone patients, set close to the average for the UK sample of 0.75. A credible alternative is that ICD patients have a slightly higher utility than amiodarone patients, but that the difference will be small, at most 0.1 units. In the sensitivity analysis it was assumed that ICD patients had a utility of 0.75 and amiodarone patients 0.65.

In their cost-effectiveness model Owens and colleagues,[57] use previously unpublished utility estimates of 0.83 on ICD therapy and 0.80 on drug therapy. *Table 89* and *Figure 43* show the impact of these alternative assumptions on the CEAC.

Deterministic sensitivity analyses

Expected costs and effects were estimated for an 'average' UK patient with LVEF below 35%,

TABLE 90 *Deterministic sensitivity analysis of expected costs (£) and effectiveness estimates over a 20-year horizon for an average UK patient with LVEF <35% compared with new base case*

Sensitivity analysis			Incremental cost	LYGs	QALYs gained	Cost per life-year	Cost per QALY
Base case for an average UK patient with LVEF <35% (age 63, 87% male)			£58,887	1.37	1.03	£42,966	£57,288
ICD implant costs (device and variable costs) set to £16,250			£46,568	1.37	1.03	£33,977	£45,303
Replacement and maintenance							
Admissions reduced by 25%			£49,939	1.36	1.02	£36,613	£48,818
Admissions reduced by 50%			£41,629	1.36	1.02	£30,657	£40,876
Implant costs set to £16,250							
ICD admissions reduced by 25%			£38,923	1.36	1.02	£28,537	£38,049
ICD admissions reduced by 50%			£31,826	1.36	1.02	£23,438	£31,250
Mortality relative to base case							
	From 6 years	*From 10 years*					
	1.0	1.5	£58,556	1.32	0.99	£44,461	£59,281
	1.0	2.0	£58,271	1.27	0.95	£45,825	£61,100
	1.5	1.5	£57,439	1.17	0.88	£49,074	£65,431
	1.5	2.0	£57,227	1.14	0.85	£50,316	£67,088
	2.0	2.0	£56,410	1.04	0.78	£54,450	£72,600
Lifetime model			£59,899	1.71	1.28	£35,078	£46,771
Utility estimates							
	ICD	*AAD*					
	0.75	0.65	£58,887	1.37	1.68	£42,966	£35,025
	0.83	0.8	£58,887	1.37	1.33	£42,966	£44,157

Costs and effects evaluated at posterior means of model parameters for an 'average' patient with low LVEF are different to population posterior expected costs and effects owing to skewed distributions. These quantities are for illustration only.

conditional on the posterior means of the model parameters. These estimates are different from the posterior expected costs and effects owing to the skewed shape of their distributions. Consequently, the estimates from the deterministic analyses do not provide a correct estimate of the ICER (which can only be reliably obtained from the probabilistic analyses). Thus, they are intended simply as a guide to the relative change in costs and effects that might be expected under a range of assumptions about model inputs. *Tables 90* and *91* contain results from a range of deterministic sensitivity analyses using the new base case for an average UK patient with low LVEF, with common relative hazard (*Table 90*) and subgroup-specific relative hazard (*Table 91*). ICDs are cost-effective at £30,000 per LYG in almost all scenarios if one assumes subgroup-specific hazard ratios. However, if this is not a reasonable assumption then ICDs are only cost-effective at this level either if implant and ICD-related follow-up costs are reduced or if there is superior utility associated with ICDs.

Figure 44 shows the cost per LYG and cost per QALY gained for an average UK patient with low LVEF against different values of the cost of implantation and replacement of an ICD. This demonstrates that if one assumes the overall relative benefit for ICDs the cost of a device would have to be in the order of £10,000 for the device and implant to be cost-effective at the £30,000 per QALY threshold. If subgroup-specific hazards were appropriate or if improved quality of life could be demonstrated, a device and implant cost of approximately £16,250 would be sufficient to ensure that ICDs were cost-effective for the average UK patient with low LVEF.

Base-case estimates depended heavily on extrapolating CIDS and UK data. In particular, a 70-year-old patient was assumed to have the same chance of survival in the first year after ICD implantation and at 20 years after the initial implantation. Thus, if age-specific mortality rates are different for different periods after implantation, estimates will be inaccurate. *Tables 90* and *91* summarise the results from assuming that the survival rate changes after 6 years and after 10 years. Increases in the underlying mortality rate had the effect of decreasing both the

TABLE 91 *Deterministic sensitivity analysis of expected costs (£) and effectiveness estimates over a 20-year horizon for an average UK patient with LVEF <35% compared with new base case and assuming subgroup-specific hazard ratio*

Sensitivity analysis			Incremental cost	LYGs	QALYs gained	Cost per life-year	Cost per QALY
Base case for an average UK patient with LVEF <35% (age 63, 87% male) HR = 0.66			£60,015	1.94	1.46	£30,894	£41,192
ICD implant costs (device and variable costs) set to £16,250			£47,692	1.94	1.46	£24,550	£32,734
Replacement and maintenance							
Admissions reduced by 25%			£51,050	1.94	1.45	£26,369	£35,158
Admissions reduced by 50%			£42,726	1.93	1.45	£22,138	£29,518
Implant costs set to £16,250							
ICD admissions reduced by 25%			£40,031	1.94	1.45	£20,677	£27,569
ICD admissions reduced by 50%			£32,920	1.93	1.45	£17,058	£22,744
Mortality relative to base case	*From 6 years*	*From 10 years*					
	1.0	1.5	£59,660	1.87	1.40	£31,885	£42,513
	1.0	2.0	£59,354	1.81	1.36	£32,786	£43,715
	1.5	1.5	£58,465	1.67	1.25	£34,968	£46,624
	1.5	2.0	£58,238	1.63	1.22	£35,781	£47,708
	2.0	2.0	£57,365	1.49	1.12	£38,521	£51,362
Lifetime model			£61,198	2.36	1.77	£25,936	£34,568
Utility estimates	*ICD*	*AAD*					
	0.75	0.65	£60,016	1.94	2.05	£30,894	£29,231
	0.83	0.8	£60,016	1.94	1.79	£30,894	£33,505

Costs and effects evaluated at posterior means of model parameters for an 'average' patient with low LVEF are different to population posterior expected costs and effects owing to skewed distributions. These quantities are for illustration only.

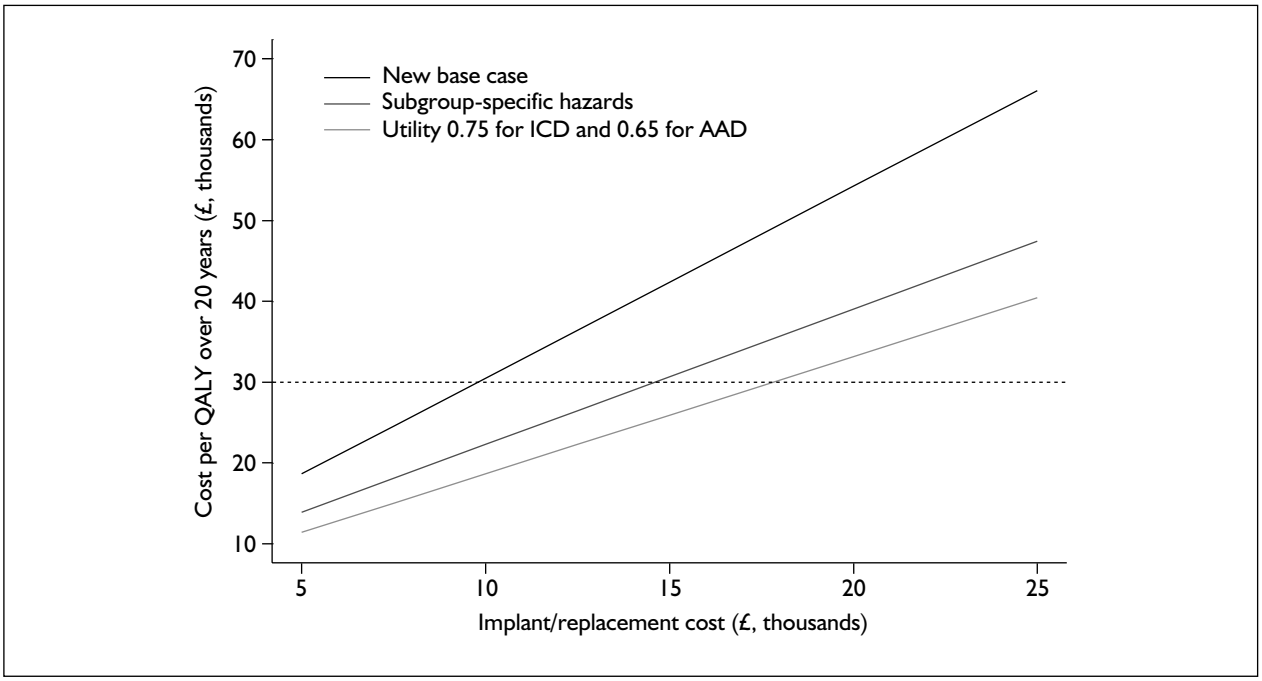

FIGURE 44 *Cost per QALY for a range of implant/replacement costs assuming all patients have LVEF <35%, for new base case, new base case with subgroup-specific hazards, and new base case with superior quality of life for ICD patients*

incremental cost and the absolute QALYs gained due to ICD, with a resultant increase in the ICER. Since the mean survival time for the new base case was lower (and more so when assuming the subgroup specific hazard ratio) than the original base case, changes to the assumptions about the hazard rate had a smaller impact on the ICER compared with the original base-case analysis.

Discussion

Cost components

This economic analysis used a UK sample of 535 ICD patients, combined with relative event rates from three secondary prevention trials (CIDS, AVID, CASH) to demonstrate that mean incremental costs for ICDs over a 20-year horizon were £70,930 (£34,955 to £142,414) per patient. These cost estimates have large variance, partly due to the inherent variability in extrapolating over a 20-year horizon, but also due to the wide variability in patients who are implanted and the lack of robust inputs to some parts of the model. For example, patients under 60 years of age may expect to have a longer lifetime with their ICD and are likely to have their device replaced at least once. In the base case the number of replacements was not limited and this led to high variable follow-up costs. Older patients with shorter expected lifetime are less likely to require a replacement.

Based on the CIDS data patients treated with amiodarone had few hospital admissions for arrhythmia and for ICD repair and replacement. This meant that incremental costs for ICDs continued to increase as follow-up progressed, although the extent of increase was reduced over time. The cost estimates for the practice are heavily dependent on the number of admissions for maintenance and replacement. Both CIDS and UK patients required replacements within a 6-year follow-up period and for the UK the hospital admission rate for replacement was 6% per patient-year. This appears to be in line with national activity reported in the BPEG database of 3% per year for the first 3 years rising to 15% after 3 years (see Chapter 3). In addition, the rate of hospital admission for ICD maintenance, including replacement or repositioning of leads, was 6% per year. Extrapolating over 20 years has substantial resource-use implications given the high cost of ICD units. This is in contrast to the recent industry-sponsored model which assumed that variable follow-up costs for ICDs were less than those for amiodarone patients.[72] West's model[72] assumed that ICDs would not be replaced over a 6-year horizon, presumably owing to reliability determined in laboratory tests. Improving reliability of the devices when used in the field, so that admissions for replacement and maintenance are reduced to 3% per year, would bring cost-effectiveness estimates nearer to acceptable levels.

Effectiveness

The mortality rate for UK ICD patients was slightly lower than that for Canadian patients when adjusted for age, gender and low LVEF (relative hazard 0.88, 95% CI 0.65 to 1.20). In addition, the crude mortality rate over the period of study was 7%, which was lower than both the CASH (8% per annum) and AVID trials (10% per annum). Thus, using relative risks from the secondary prevention trials resulted in a smaller gain in absolute survival for UK patients. Over a 20-year horizon, the mean LYG for a UK ICD patient was 1.24 (95% CI 0.29 to 2.32).

Cost-effectiveness estimates

The average ICER over a 20-year horizon was estimated to be £57,104 per LYG (£70,930/1.24). This figure is broadly in line with estimates from other RCT-based estimates summarised in Chapter 3 of this report. Published, trial-based, economic analyses generally have a short time-horizon and the expected gain in survival is less than 12 months in all time-threshold studies (see *Table 21* and associated references). These publications have suggested that the ICER will decrease with follow-up as the expected gain in survival accrues. Although this may be true, observations regarding reliability of the ICD and hospital admissions suggest that incremental costs will also continue to increase. Thus, the behaviour of the ICER in the long term is not obvious and will depend on the relative speed at which the costs and benefits accrue. When observed short-term mortality and hospital admission rates were extrapolated over the lifetime of the patients the ICER was more favourable, but there is little empirical evidence to support this.

The base-case analysis assumed that hazard rates were constant within the three age groups, younger than 60, 60–69, and 70 years and older. This may not be realistic since a patient diagnosed with arrhythmias and receiving an ICD at 70 years of age may have better survival than a 70-year-old who had an ICD implanted 10 years previously, at 60 years of age. Changing assumptions about the baseline hazard after 6 years with an ICD had the effect of decreasing the life-years gained as well as

decreasing incremental costs. The ICER increased with increasing hazard rates.

The model demonstrated excellent fit to the data over a period of 6 years from implantation when there were sufficient data. However, extrapolation of survival beyond this point requires careful analysis. Simple extrapolation of the base case to 20 years led to an expected ICER of £48,734 per LYG or £64,979 per QALY for an average UK patient. Both figures are considered high. Extending the time-horizon from 20 years to a lifetime model reduced the estimated ICER to £32,110 per LYG, but is based on the assumption that the treatment effect will be maintained in the long term. Detailed examination of the differences between 20 years and the lifetime model showed that estimated LYG altered slightly for patients with low LVEF (e.g. 1.40 to 1.79 years for a 60-year-old man), but to a greater extent for patients with an LVEF of 35% or above (e.g. 1.16 to 3.15 years for a 60-year-old man). The interpretation is that low-risk patients will accrue a small benefit in survival in the first 20 years after ICD implantation, but as their risk of death increases the potential benefit will increase, provided that the treatment effect persists in the long term. It is likely that the model underestimates long-term mortality as the death rate is assumed to be constant in three broad age groups. In particular, in the model all patients aged over 70 have the same death rate as ICD recipients aged over 70, there being insufficient information for finer estimation. As discussed above, if the longer term mortality rate was higher than that observed in the short-term patient follow-up, the ICER would be increased.

Limitations

One limitation of this analysis is that one cannot be confident of the robustness of long-term models that extrapolate beyond the period of observation and there is even less confidence in extrapolation beyond 20 years. Cost-effectiveness estimates are very sensitive to assumptions about long-term survival and treatment effects, and these assumptions cannot be tested with currently available data. The BPEG database was not sufficiently complete to allow useful synthesis of trial and registry data. Alternative sources of information such as mortality rates from the ONS population statistics have been investigated and confirm the sensitivity of estimates to assumptions about long-term mortality rates and treatment effects. The most reliable models produced resulted in discounted LYG over a 20-year horizon of 1.4 years and over a lifetime of 1.77 years.

Cost-effectiveness increased with patient age and was greater for patients with low LVEF. In short, targeting high-risk patients will result in greater gain in absolute survival due to ICD implantation. To some extent, high-risk patients can be defined by age and LVEF, although newer methods for identifying those at risk of fatal arrhythmic events are important. The prediction of risk will never be absolutely accurate, but refinement of strategies using established[73] and novel techniques[74] if used appropriately will enhance cost-effectiveness.

In the UK sample of patients, 96% were classed as secondary prevention cases and the analysis used relative risks and relative admission rates exclusively from secondary prevention RCTs. Therefore, one limitation of these results is that they will not necessarily apply to patients implanted for primary prevention. Cost-effectiveness in these cases is likely to depend heavily on patient selection and will be most favourable for patients for whom high risk of sudden cardiac death can be established.

The other major determinant of cost-effectiveness was quality of life in the ICD and AAD groups. It is clear that estimates of quality of life have a major impact on cost-effectiveness estimates, but information from randomised studies is sparse and limited by methodological problems (see Chapter 2). Although this study was able to provide utilities for a large cross-section of UK ICD recipients, ideally these models should include UK-relevant outcomes from randomised or scientifically rigorous, controlled studies. In addition, the evidence for improved quality of life in ICD recipients is weak, particularly since there is a negative impact on quality of life following discharge of the devices. Inappropriate shocks need to be minimised and further study of quality of life in this subgroup of patients would provide a stronger evidence base for this part of the analysis.

Implications for policy

Restricting the analysis to patients with low LVEF, and hence changing the underlying baseline mortality rates, had little impact on the net gain in survival and hence on incremental cost-effectiveness, if the relative hazard for ICDs against AAD use is assumed to be the same as for other groups. However, if one assumes a treatment–subgroup interaction for patients with low LVEF, the cost difference increases because the AAD group have lower survival and therefore lower costs, but this is balanced by a much larger gain in life-years. Therefore, the cost-effectiveness estimate is much more favourable. In the absence

of a demonstrated interaction effect the overall result is a more appropriate estimate of the relative hazard and subgroup-specific estimates are known to exaggerate the truth (see, for example, Assman and colleagues,[75] and Pocock and colleagues[76]). In reality, the relative hazards for this group may lie somewhere between the overall estimate and the subgroup-specific estimate.

If the initial implant costs, including equipment and hospital costs, could be reduced to £16,250, and/or ICD readmissions could be reduced to around 3% per annum, ICDs may be considered cost-effective at the £30,000–40,000 threshold. However, neither of these alternative cost assumptions is consistent with the observed UK data.

Restricting the analysis to patients with LVEF below 35%, as previously recommended by NICE, even with the most optimistic assumptions about costs, is insufficient to give a mean incremental cost per QALY of less than £30,000. To be confident that ICDs are cost-effective for this group (at a maximum acceptable ICER of £30,000 over 20 years) requires both that the incorporation of a subgroup specific hazard ratio is valid and that either costs can be considerably reduced or a substantial utility advantage is assumed. Alternatively, if treatment effects and replacement rates are unchanged the cost of implant and replacement (including the device) would need to be approximately £10,000 to ensure cost-effectiveness over 20 years.

Summary

ICD implantation when used as secondary prevention is expensive and costs between £30,000 and £90,000 per QALY gained over 20 years, depending on model assumptions and subgroups studied. The base-case analysis for secondary prevention resulted in an ICER of £57,000 per LYG or £76,000 per QALY over a 20-year horizon. Patients with low LVEF or who are older at presentation are at higher risk of SCD and so are most likely to benefit, but more sensitive and specific markers of SCD are required. Patients with LVEF below 35% had an ICER of £54,000 per LYG or £72,000 per QALY over 20 years. Extrapolating over the lifetime of the patients gave a more favourable ICER for patients with low LVEF of £36,279 per LYG or £48,372 per QALY. In sensitivity analysis, assuming the subgroup-specific hazard ratio for this group of patients the ICER becomes £51,000 per QALY. Reduction of the cost of implant/replacement to £16,250 and improvements in the reliability of ICDs (repair/replacement rates of 3% per patient-year) when used in the field would reduce the ICER to £35,500 per QALY in these patients. Increasing HRQoL for ICD patients, possibly by reducing the number of inappropriate shocks, would have a large impact on the ICER, reducing it to £38,000 per QALY over 20 years in patients with low LVEF. To be confident that ICDs are cost-effective for patients with low LVEF (at a maximum acceptable ICER of £30,000 over 20 years) requires both that the incorporation of subgroup-specific hazard ratio is valid and that either costs can be considerably reduced or a substantial utility advantage is assumed. Alternatively, if treatment effects and replacement rates observed in the UK sample and CIDS are accurate, the cost of implant and replacement (including the device) would need to be approximately £10,000 to ensure cost-effectiveness over 20 years.

Chapter 9

Conclusions, implications and recommendations

Introduction

The NICE guidance to the NHS on the use of ICDs in the management of ventricular arrhythmias, published in September 2000, estimated that it would lead the ICD implantation rate to rise from 17 per million population to 50 per million. Since then further trial evidence has been published and has been reviewed here. This report has gone on to provide original data and analysis on the situation in the UK and a new model of cost-effectiveness relevant to the UK. This final chapter attempts to summarise the key additions to the evidence base, their implications for cost-effective clinical policy and the further implications of such policy changes for the NHS. In addition, it discusses what would now appear to be the most important gaps in our knowledge, and indicates the areas of research and monitoring that might best fill those gaps. This study was accurate at the time of preparation of this report. In this rapidly developing field a number of RCTs was published during the review of the report and these are summarised in an addendum.

The epidemiology of sudden cardiac deaths

Estimation of the incidence of SCD and of life-threatening ventricular arrhythmias remains problematic, not least because of a wide variation in definitions. Evidence on the incidence of SCD in Scotland suggests that rates in men rise from 210 per 100,000 (aged 55–64 years) to 2147 per 100,000 (aged 85 years and over), while in women the equivalent rates are considerably lower, 68 per 100,000 rising to 1609 per 100,000.[10] The trend in incidence appears to be of declining rates.

Survival rates for out-of-hospital SCD episodes in Britain are about 2%. The population incidence of patients surviving SCD episodes was estimated as 2.4 per 100,000 in Scotland,[6] but 12 per 100,000 in a (later) study from the USA.[5] About 15% of sudden cardiac episode survivors will experience another SCD episode within 1 year. Untreated, the recurrence is usually fatal. Risk factors for SCD include:

- a previous SCD episode
- previous VT
- a prior MI
- CHD
- familial cardiac conditions
- poor cardiac function
- heart failure.

The evidence on effectiveness of treatments

Treatments are aimed at suppressing or terminating the arrhythmia and the main treatments are AAD therapy, of which amiodarone is the most commonly used drug for long-term management, or ICDs, which actively sense and can terminate life-threatening tachyarrhythmias.

Since the previous HTA review in 2000, the key additions to the evidence base have been:

- the publication of a longer term follow-up report on the CASH trial[32]
- reports of two new RCTs: MADIT II[33] and CAT[34]
- a meta-analysis (using individual patient data) from the three main secondary prevention trials (AVID, CASH and CIDS).[30]

The longer term results from CASH confirmed a continuing but declining benefit from ICDs compared with AAD therapy.

The new evidence from MADIT II concerned primary prevention in patients with previous AMI and with impaired left ventricular function (LVEF <30%). This showed a survival advantage for ICD patients (RRR 30%, ARR 6%). The life-years saved were moderate, but follow-up was only to 20 months, at which point the trial was stopped prematurely because of the statistically significant survival advantage. MADIT II significantly increases the evidence to support the clinical benefit of ICDs as primary prevention and could be seen as a basis for the possible extension of clinical indications for ICDs, raising further the required levels of ICD implantation. Many commentators still consider that the evidence from additional ongoing trials will be necessary before

the recommendations arising from MADIT II should be fully implemented.

The results from CAT, a pilot study to determine the effectiveness of ICDs in the management of patients with dilated cardiomyopathy of recent onset and with impaired left ventricular function, showed no evidence of survival benefit from using ICDs in this group.

The meta-analysis of secondary prevention trials showed a strongly significant benefit of ICDs with an RRR of 27% for total mortality, which increased further to 30% when only the more recently implanted devices with transvenous leads were included. It also confirmed that patients with an LVEF below 35% derived significantly greater benefit than those with better cardiac function, but was not able to identify other significant factors that stratified patients in terms of benefit. This meta-analysis was part of the evidence base considered by NICE.

There is now conflicting evidence from RCTs on the relative HRQoL from ICDs and AAD therapy. The analysis of the AVID trial data concluded there were no differences in HRQoL between the two arms, but that the quality of life of ICD patients fell as the number of shocks received increased. From an abstract it would appear that the HRQoL results from MADIT will accord with these AVID findings. However, the HRQoL data from CIDS indicate that quality of life was better with ICDs than with amiodarone, but this advantage was not evident in patients who received numerous shocks. The strength of the CIDS evidence is weakened by the size of and attrition to the HRQoL subsample and by the fact that the baseline data reflect that, in some cases, patients already knew to which treatment they had been allocated.

Despite these additions to the evidence base confirming benefit in both primary and secondary prevention, the RCT data remain relatively short term compared with the periods over which cost-effectiveness needs to be considered.

Published economic analyses

The review identified a number of recent studies of the cost-effectiveness of ICDs versus amiodarone. Four were based on specific trials, three on models incorporating data from a variety of sources and one based on an analysis of the Medicare database. While they all confirm the existence of a survival benefit, and all but the methodologically weakest study suggest that this is associated with an additional cost, their estimates of incremental cost and survival, and hence the estimates of incremental cost per life-year gained, vary considerably. In secondary prevention the results suggest that ICDs will be more cost-effective in higher risk patients (specifically those with an LVEF <35%), but even for these patients the ICER may be unacceptably high.

The RCT evidence supporting primary prevention appears to lead to an ICER that may, counter to a priori logic, be more attractive than for secondary prevention. Based on MADIT I, the cost-effectiveness analysis by Mushlin and colleagues[55] produces a base-case ICER of £13,200 per LYG. This appears to be because of the high risk of SCD in the patients in MADIT I, all of whom had had a prior AMI, LVEF below 35% and inducible VT in EP studies not suppressed by procainamide.

This indeed appears to be the strongest general conclusion from these analyses, that cost-effectiveness varies very considerably between groups (and hence studies) and in this the ICER falls as the relative and absolute risks of SCD increase.

None of these detailed studies had used UK data or were designed to reflect UK practice and hence the need remains for such a UK-focused study, as identified in the previous review of ICDs for the HTA Programme.[2]

The published cost-effectiveness studies emphasise, however, that results will be sensitive to the subgroups considered, the assumptions about long-term benefit and the assumption of differential quality of life.

Assessment of current service provision in the UK

The review of ICD activity in the UK found that:

- use of ICDs has increased by 49% in the past 4 years, but the rate of 20.0 per million in 2002 was much lower than the target set by NICE
- the number of major implanting centres (41) has doubled since 1992
- 82% of ICDs are implanted in men
- the largest proportion of ICDs is implanted in the 45–64 years age group

- there appears to be considerable variation in age-gender-standardised rates of implantation by SHA and by region
- the data suggest that there may be some inequity in use of ICDs in relation to social deprivation and South Asian ethnicity
- dual-chamber devices are used in 22% of cases
- survival from first ICD implant in the UK is 94% at 1 year and 90% and 76% at 2 and 5 years, respectively
- device longevity is reflected in a 3% explant rate per annum in the first 3 years, which rises sharply to 15% per annum.

Multiple methods had to be used to ascertain current patterns of ICD implantation and outcomes, reflecting the absence of a single, complete and reliable source of data. The national pacemaker and ICD database maintained by BPEG is potentially a very valuable resource. It could provide crucial information with which to inform planners, commissioners and providers of arrhythmia and ICD services both locally and nationally. As with many databases, at present it appears to be underfunded and understaffed and is unable to provide as responsive a service as may be required by healthcare professionals, managers and patients. There is scope to improve and expand this service, making it more accessible to those who supply data and enlarging the data set that is collected to encompass the wider epidemiology of arrhythmias and ICD implantation. Collation and analysis could be performed on a more regular basis, and service configuration and practice could be monitored and information provided for audit, driving up the quality of patient care. Exemplars exist in other cardiac services and in renal medicine.

Review of patient characteristics

A review was conducted of data on cohorts of patients implanted between 1991 and 2002 in two centres, Papworth and Liverpool:

- the total number of patients implanted was 535, of whom 454 were still alive
- actuarial survival was 92%, 86% and 71% at 1, 3 and 5 years, respectively
- multivariate analysis showed that mortality increased with age at implant and for patients with low LVEF (< 35%) and lower NYHA class, but was independent of centre, year of implant or gender
- the characteristics of the patients implanted in this sample appeared to be similar to those for the UK as a whole (as shown in BPEG data).

Compared with patients in the ICD arms of AVID, CASH and CIDS:

- they were similar in terms of gender (81% male) and mortality rates (7% per annum)
- they tended, however, to be slightly younger (mean age 60 years) and had higher NYHA class, fewer had non-ischaemic cardiomyopathy and more presented with VT.

The authors attempted to access detailed data on a sample of 426 of the 535 and were able to access notes on 380 of these. There was a bias in this accessed sample, which included disproportionately few of the notes of patients from Liverpool who had died; appropriate methods were used to handle non-random missing data.

Survey of health-related quality of life

The cross-sectional survey of ICD patients who had received their implant between 1991 and 2002 achieved a 73% response rate of 229 completed questionnaires with no obvious bias in the responses. The main findings were that:

- from the SF-36, the mean scores in six out of eight of the dimensions were significantly lower than for a representative age-matched UK population
- clinically important levels of anxiety were found in 22% of patients
- there were no differences in HRQoL observable over time from implant, or between centres
- the only patient characteristic that appeared to be related to HRQoL was age at implant, with older patients demonstrating less anxiety than younger patients
- patients who had experienced a shock (ICD discharge) had consistently poorer HRQoL than those who had not, and the difference was significant for the SF-36 PCS, EQ-5D and HAD anxiety scores
- by year 5, 65% of patients had experienced at least one shock
- a large proportion of patients (84%) said that they avoided strenuous activities
- levels of anxiety and depression were related to various aspects of living with and coping with an ICD.

However, there was a high level of satisfaction with ICD therapy. Over 90% of patients would recommend the therapy to other patients and two-thirds thought that the ICD had saved their lives. The results from this cross-sectional survey suggest a need to reduce the number of inappropriate shocks and to investigate the possibility of providing additional support to patients to reduce their anxiety.

Analysis of resource use and costs

The analysis of resource use and costs was based on data relating to 211 Papworth patients and 167 Liverpool patients. The mean cost of the device, its implantation and associated inpatient stay was estimated as £23,275 for Papworth and £22,083 for Liverpool. When grouped by presenting pathway the means ranged from £22,049 to £25,850 for Papworth and from £19,500 to £24,956 for Liverpool, but the individual patient range was from £18,932 to £44,575. There was some evidence that these costs were falling slightly over time (assuming a fixed device cost), reflecting reduced lengths of stay. For the purposes of modelling cost-effectiveness the initial cost was estimated as £23,608 for ICD patients and £1220.52 for the initial stay for amiodarone patients.

Cost-effectiveness modelling

A discrete-time Markov model using eight states (well, in hospital for one of six reasons or dead) was used, and incorporated data on histories of hospital admissions and discharge dates from the Canadian CIDS trial, relative mortality rates from the AVID and CASH trials, the present patient sample and UK costs derived from Liverpool and Papworth. The model was implemented using Bayesian methods in WinBUGS to estimate a joint distribution of cost and effectiveness of ICDs relative to AADs for UK patients. The model simulated the actual survival well up to 7 years. Over a 5-year time-horizon the mean ICER would be £229,235. Over a 20-year time-horizon the model estimated a mean ICER of £70,930 (95% CI £34,955 to £142,414). In terms of QALYs the baseline assumption was of no difference between ICDs and amiodarone, with a mean utility value of 0.75 in each group.

Sensitivity analyses show that cost per life-year or QALY decreases with age, is lower for patients with LVEF below 35%, improves substantially if ICD patients are assumed to enjoy a better HRQoL and continues to look more attractive if the results are extrapolated to patients' lifetimes. However, none of the sensitivity analyses produced a cost per QALY lower than £36,000. The ICER per life-year over a 20-year period probably lies in the range £30,000–90,000. However, even the 20-year results rely on extrapolating benefits far beyond observed data.

Clinical policy implications

The rates of postimplantation hospitalisation in the patients at both Liverpool and Papworth were substantially higher than is implied by the manufacturers' evidence on the technical longevity of the devices and their batteries. The reasons for rehospitalisation are replacement for technical failure, replacement for other reasons (e.g. the area of implant has become infected), non-replacement technical problems requiring reattachment, repositioning or replacement of leads, and faulty discharging of the device.

These various causes lead to a significant ongoing cost of hospitalisation (and sometimes device or lead replacement), which considerably increases the cost-effectiveness ratio. The implications of these findings are that:

- assumptions in earlier studies that improvements in device longevity would improve cost-effectiveness have not been fully realised
- it would appear that the solution lies not simply in improving the technical characteristics of the device but also in reducing the likelihood of these in-use problems.

NHS service and monitoring implications

The reviewers see a strong need for a complete robust and well-validated data set of all implantations with key clinical characteristics of the recipients, key information on the device and survival follow-up. It has been suggested that the British Cardiovascular Intervention Society (BCIS) database provides an example of the sort of quality that can readily be achieved. The authors recommend that the Department of Health, the Medical Devices Agency, the ICD implantation centres and the manufacturers collectively consider how the quality and completeness of the database could be improved.

The survey provided clear evidence about the HRQoL and utility values of ICD patients; they were generally high and broadly consistent with the norms for an appropriately age- and gender-adjusted general population. Again, no clear differences between subgroups were apparent, nor was there evidence of any change over time from implantation. This study could throw no light on the issue of whether quality of life is superior with ICDs or with drug treatment. The trials to date have been inconsistent on this issue; AVID found no difference, but CIDS reported a superior HRQoL for ICD patients.

The modelling confirms that a substantial difference in HRQoL in favour of ICD would have a significant favourable effect on cost-effectiveness. Although it would be clearly desirable to obtain good comparative data, the authors are uncertain whether any small study of patients receiving the two treatments would show any difference that could safely be attributed to the device, as distinct from other characteristics that may have led to the choice of therapy that they received. A very large comparative study is needed, including substantial data to enable adjustments of the observed differences in quality of life to differences in the clinical or social characteristics or history of the patients, and this should probably be multicentre.

Interventions designed to prevent or reduce anxiety in the ICD patient, resulting in a positive effect on patients' attitudes to a wide range of activities, may be the best way forward in enhancing the benefits of ICD therapy by tackling the fears associated with both the underlying disease and the technology. Further work is needed on the cost-effectiveness of such interventions.

Further cost-effectiveness modelling, underpinned by an improved ICD database with reliable long-term follow-up, is required. This needs now to begin fully to address the cost-effectiveness of primary prevention, particularly as the results from other primary prevention trials are added to those from MADIT II.

Research implications and priorities

The absence of a robust measure of the incidence of SCDs is noted. This may be an area where further organisational changes with improved data collection would help. However, to be effective this will require the co-ordination of information from a wide range of sources, including the records of pathology services and coroners' offices.

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Contribution of authors

Martin Buxton (Professor of Health Economics) undertook the review of economic studies, supervised the analysis of the resource-use and cost data, and advised on the modelling of cost-effectiveness. Noreen Caine (Density Director of R&D) supervised the management of all the data collection exercises and led the design and analysis of the health-related quality of life survey. Debbie Chase (Senior Research Fellow) provided the analysis of epidemiology and assisted in the study of service provision. Derek Connelly and Andrew Grace (Consultant Cardiologists) provided access to and interpretation of the Papworth and Liverpool data respectively and both advised on clinical aspects of the study and report. Chris Jackson (Research Associate) constructed the economic model. Julie Parkes (Lecturer in Public Health) undertook the review of effectiveness and health-related quality of life and supervised the work on epidemiology and service provision. Linda Sharples (MRC BioStatistician) undertook the statistical analyses, supervised the construction of the economic model and led the process of integrating the various components into the final draft. Martin Buxton, Noreen Caine, Andrew Grace, Julie Parkes and Linda Sharples took prime responsibility for producing the final report.

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Appendix 1

Search strategies

MEDLINE search strategy

#1 explode "Incidence"/ all subheadings
#2 explode "Prevalence"/ all subheadings
#3 incidence
#4 prevalence
#5 incidence or prevalence
#6 explode "Risk-Factors"/ all subheadings
#7 explode "Time-Factors"/ all subheadings
#8 explode "Cohort-Studies"/ all subheadings
#9 epidemiol*
#10 aetiolog*
#11 etiolog*
#12 epidemiol* or aetiolog* or etiolog*
#13 natural*
#14 disease*
#15 progress*
#16 course*
#17 histor*
#18 (natural* or disease*) near1 (progress* or course* or histor*)
#19 #18 or #12 or #8 or #7 or #6 or #5 or #2 or #1
#20 explode "Tachycardia,-Ventricular"/ all subheadings
#21 explode "Ventricular-Fibrillation"/ all subheadings
#22 "Death,-Sudden,-Cardiac"/ all subheadings
#23 ventricular
#24 tachycardia
#25 fibrillation
#26 ventricular near1 (tachycardia or fibrillation)
#27 sudden
#28 death
#29 sudden near2 death
#30 explode "Sudden-Infant-Death"/ all subheadings
#31 #29 not #30
#32 explode "Arrhythmia"/ all subheadings
#33 arrhythmia*
#34 #32 or #33
#35 ventricular
#36 #34 near ventricular
#37 explode "Syncope"/ all subheadings
#38 syncop*
#39 #19 and (#20 or #21 or #22 or #26 or #31 or #36 or #37 or #38)
#40 explode "Prognosis"/ all subheadings
#41 prognosis
#42 #40 or #41
#43 explode "Survival-Analysis"/ all subheadings
#44 explode "Heart-Arrest"/ all subheadings
#45 #42 or #43 or #44
#46 (#45 or #19) and (#20 or #21 or #22 or #26 or #31 or #36 or #37 or #38)

EMBASE search strategy

#1 incidence
#2 explode 'incidence-' / all subheadings
#3 ((natural*) or (disease*)) near1 ((progress*) or (course*) or (histor*)) (65864 records)
#4 (epidemiol*) or (aetiolog*) or (etiolog*) (1053487 records)
#5 prognosis
#6 explode 'prognosis-' / all subheadings
#7 explode 'cohort-analysis' / all subheadings
#8 cohort near1 stud*
#9 explode 'risk-factor' / all subheadings
#10 explode 'survival-' / all subheadings
#11 (incidence) or (explode 'incidence-' / all subheadings) or (((natural*) or (disease*)) near1 ((progress*) or (course*) or (histor*))) or ((epidemiol*) or (aetiolog*) or (etiolog*)) or (prognosis) or (explode 'prognosis-' / all subheadings) or (explode 'cohort-analysis' / all subheadings) or (cohort near1 stud*) or (explode 'risk-factor' / all subheadings) or (explode 'survival-' / all subheadings)
#12 explode 'heart-ventricle-tachycardia' / all subheadings
#13 explode 'heart-arrhythmia' / all subheadings
#14 ((explode 'heart-arrhythmia' / all subheadings) or arrhythmia*) near ventricular
#15 explode 'syncope-' / all subheadings
#16 syncop*
#17 explode 'heart-ventricle-fibrillation' / all subheadings
#18 explode 'sudden-death' / all subheadings
#19 ((incidence) or (explode 'incidence-' / all subheadings) or (((natural*) or (disease*)) near1 ((progress*) or (course*) or (histor*))) or ((epidemiol*) or (aetiolog*) or (etiolog*)) or (prognosis) or (explode 'prognosis-' / all subheadings) or (explode 'cohort-analysis' / all subheadings) or (cohort near1 stud*) or (explode 'risk-factor' / all subheadings) or (explode 'survival-' / all subheadings)) and ((explode 'heart-ventricle-tachycardia' / all subheadings) or (((explode 'heart-

arrhythmia' / all subheadings) or arrhythmia*) near ventricular) or (explode 'syncope-' / all subheadings) or (syncop*) or (explode 'heart-ventricle-fibrillation' / all subheadings) or (explode 'sudden'death' / all subheadings')) and (LA=ENGLISH)

#20 (nonhuman in der) not ((nonhuman in der) and (human in der))
#21 #19 not #20

Appendix 2

Lefevre search strategy for identifying RCTs

implantable cardiac defibrillator
implant* defib* (ft)
implant* defib* (ft)
ventricul* arrythm*(ft)
cardi* arrest*(ft)
defibrillators implantable(mh)
ventricular fibrillation(mh)
heart arrest(mh)
quality of life (mh)
implant* and defibrill* (mh)
sudden cardiac death (mh)
vent* arrhy* (mh)
clinical trial (pt)
english (lg)

Search strategy for RCTs

RANDOMIZED-CONTROLLED-TRIAL in PT
"RANDOMIZED-CONTROLLED-TRIALS"/ all subheadings
"RANDOM-ALLOCATION" in MIME, MJME
random* or alloc* or assign*
(#4 in TI) or (#4 in AB)
#1 or #2 or #3 or #5
CONTROLLED-CLINICAL-TRIAL in PT
CLINICAL-TRIAL in PT
explode "CLINICAL-TRIALS"/ all subheadings
(CLIN* near TRIAL*)
(#10 in TI) or (#10 in AB)
"CROSS-OVER-STUDIES" in MIME, MJME
cross-over near (stud* or trial* or design*)
crossover near (stud* or trial* or design*)
#7 or #8 or #9 or #11 or #12 or #13 or 14
"DOUBLE-BLIND-METHOD" in MIME, MJME
"SINGLE-BLIND-METHOD" in MIME, MJME
(singl* or doubl* or trebl* or tripl*) near (blind* or mask*)
(#18 in TI) or (#18 in AB)
#16 or #17 or #19
"PLACEBOS"/ all subheadings
placebo* in TI
placebo* in AB
#21 or #22 or #23
explode "RESEARCH-DESIGN"/ all subheadings
TG=COMPARATIVE-STUDY
explode "EVALUATION-STUDIES"/ all subheadings
"FOLLOW-UP-STUDIES" in MIME, MJME
"PROSPECTIVE-STUDIES" in MIME, MJME
control* or prospectiv* or volunteer*
(#30 in TI) or (#30 in AB)
#25 or #26 or #27 or #28 or #29 or #31
#6 or #15 or #20 or #24 or #32
(TG=ANIMAL) not ((TG=HUMAN) and (TG=ANIMAL))
#33 not #34

Appendix 3

Quality assessment criteria

Instrument to measure the likelihood of bias in RCTs

Questions to assess the likelihood of bias

1. Was the study described as randomised (this includes the use of the words such as randomly, random and randomisation)?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

Scoring the items

- Either give a score of 1 point for each 'Yes' or 0 points for each 'No'. There are no in-between marks.
- Give 1 additional point if:
  - for question 1, the method to generate the sequence of randomisation was described and it was appropriate (table of random numbers, computer generated, etc.) and/or
  - if for question 2 the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.)
- Deduct 1 point if:
  - for question 1, the method to generate the sequence of randomisation was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.) and/or
  - for question 2, the study was described as double blind but the method of blinding was inappropriate (e.g. comparison of tablet versus injection with no double dummy).

Guidelines for assessment

Randomisation

A method to generate the sequence of randomisation will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next.

Methods of allocation

Using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

Double blinding

A study must be regarded as double blind if the term 'double blind' is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned. (Note: it should be noted that in the RCTs included in this study no Jadad score exceeds 3 because insertion of an ICD is virtually impossible to double blind.)

Withdrawals and dropouts

Participants who were included in the study but did not complete the observation period or were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

Criteria for assessing good-quality systematic reviews

Systematic reviews were examined to determine how many of the following criteria for methodological quality they met.

1. Does the review answer a well-defined question? A good review should focus on a well-defined question, making the objectives of the review easy to understand. The most important components in a review question include the target population, healthcare intervention and outcomes of interest.
2. Was a substantial effort made to search for all the relevant literature?
3. Are the inclusion/exclusion criteria reported and are they appropriate? Criteria for the inclusion of individual studies in a review have two major dimensions: relevance and validity. A relevant study should be useful to answer review questions in terms of patients, intervention and outcomes. The validity issue is related to the methodological standard of an individual study.
4. Is the validity of included studies adequately assessed?

5. Is sufficient detail of the individual studies presented? Details of the individual studies included in a review include study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, dropout rate, effectiveness results and side-effects. The importance of the study details may differ for different review topics.
6. Have the primary studies been combined or summarised appropriately?

If at least four of the criteria are met the paper will be considered to be of good quality.

Appendix 4

Search for cost-effectiveness studies

MEDLINE

No.	Search history
1	DEFIBRILLATORS, IMPLANTABLE/ or Defibrillators.mp.
2	Economics.mp. or ECONOMICS/
3	Cost-benefit analysis.mp or Cost-Benefit Analysis/
4	Costs.mp or "Costs and Cost Analysis"/
5	2 or 3 or 4
6	1 and 5
7	limit 6 to yr=1996-2002

This produced 133 papers for consideration.

In addition, more inclusive searches were undertaken of the smaller, but more focused, CRD or OHE HEED databases. Although additional papers identified in these searches were considered, no additional papers for inclusion in this review were identified from these other sources.

Appendix 5

National survey of ICD service provision

Your replies will be treated in strict confidence

Name Hospital

1. What is the approximate size of the catchment population for your ICD practice?
   100,000–300,000
   300,001–500,000
   500,001–1 million
   >1 million
   >2 million
   >3 million

2. What was the number of new and replacement ICDs put in by your unit in each of the following years? Please tick appropriate boxes.

	1999		2000		2001	
	New	**Replacement**	**New**	**Replacement**	**New**	**Replacement**
<10						
10–19						
20–34						
35–49						
50–74						
75–100						
>100 (please specify)						

3. Please indicate which grades of staff are significantly involved in the care of patients who are eligible/receive ICDs at your hospital. [Write approximate numbers of whole time equivalent (WTE) staff in the appropriate boxes.]

Staff description	**WTE**
Consultant, Senior Lecturer or Professor	
Associate specialist or Staff grade	
SPR NHS	
SPR R&D	
Specialist nurse NHS funded	
Specialist nurse R&D funded	
Technical staff	
Other please specify	

4a. Do you have facilities to conduct electrophysiological study (EPS)? **Yes/No**

If Yes

4b. How many EPS studies per month in patients eligible for ICD (approximately)?

_____

4c. In how many cases of ICD implantation has EPS been conducted? (Please ring)

0% 0–4% 5–9% 10–24% 25–49% 50–74% >75% 100%

5. Please indicate your response to each of the given statements describing possible barriers to care for patients eligible for ICD by ticking the appropriate boxes.

	Strongly agree	**Agree**	**Unsure**	**Disagree**	**Strongly disagree**
Patient identification/diagnosis					
Clinic waiting time for initial referral					
EPS waiting times					
Implantation waiting times					
Staffing capacity					
Staffing skill mix					
Funding for treatment					
Patient refusal					
Patient non-attendance					
Other, please specify					

Please write any additional comments below

_____

_____

6a. Is there a waiting list for ICD implantation? **Yes/No**

If Yes

6b. What is the current median waiting time for a device?

7. What percentage of your ICD data are routinely entered into the ICD national database? (Please ring)

0–19% 20–39% 40–49% 50–59% 60–69% 70–79% 80–89% 90–99% 100%

8. How do you envisage practice for patients eligible for ICD changing at your unit over the next one/two years? (Please use extra sheet of paper if required)

Thank you very much for taking the time to fill in this questionnaire. Your contribution is very much valued.

(An additional sheet was attached for further comments on current or future service provision for ICD therapy.)

Appendix 6

Deprivation analysis

By using transform/categorise variables commands in SPSS, this continuous variable can be grouped into five quintiles (*Table 92*).

Table 93 shows the minimum and maximum values for each quintile.

These quintiles can be applied to wards associated with ICDs in the BPEG data set. *Table 94* shows the number of ICDs that fall into each of the five census-derived Townsend score quintiles.

Table 95 shows the minimum and maximum Townsend scores for wards associated with ICDs in each of the five quintiles.

TABLE 92 *Five quintiles of Townsend deprivation scores from the 1991 census*

		Frequency	%	Valid %	Cumulative %
Valid	1	1896	19.9	19.9	19.9
	2	1910	20.1	20.1	40.0
	3	1903	20.0	20.0	60.0
	4	1897	19.9	19.9	80.0
	5	1903	20.0	20.0	100.0
Total		9509	100.0	100.0	

TABLE 93 *Townsend score minimum and maximum values for each quintile*

***N*tiles of townsend**	***n***	**Min.**	**Max.**
1	1896	–9.04	–2.95
2	1910	–2.94	–1.60
3	1903	–1.59	0.09
4	1897	0.10	2.82
5	1903	2.83	15.54
Total	9509	–9.04	15.54

TABLE 94 *Number of ICDs in each of the five census-derived quintiles*

		Frequency	%	Valid %	Cumulative %
Valid	1	325	11.2	14.8	14.8
	2	338	11.6	15.4	30.2
	3	447	15.4	20.4	50.6
	4	503	17.3	22.9	73.5
	5	582	20.0	26.5	100.0
	Total	2195	75.6	100.0	
Missing system		708	24.4		
Total		2903	100.0		

TABLE 95 *Minimum and maximum Townsend scores for ICD wards*

***N*tiles of townsend**	***n***	**Min.**	**Max.**	**Median**
1	325	–8.00	–2.99	–3.6600
2	338	–2.98	–1.70	–2.2800
3	447	–1.69	–0.05	–0.8500
4	503	–0.04	2.89	1.2500
5	582	2.90	13.62	5.3500
Total	2195	–8.00	13.62	–0.0900

Appendix 7

International comparisons of coronary heart disease

Age-standardised rates are presented in *Figures 45* and *46*.

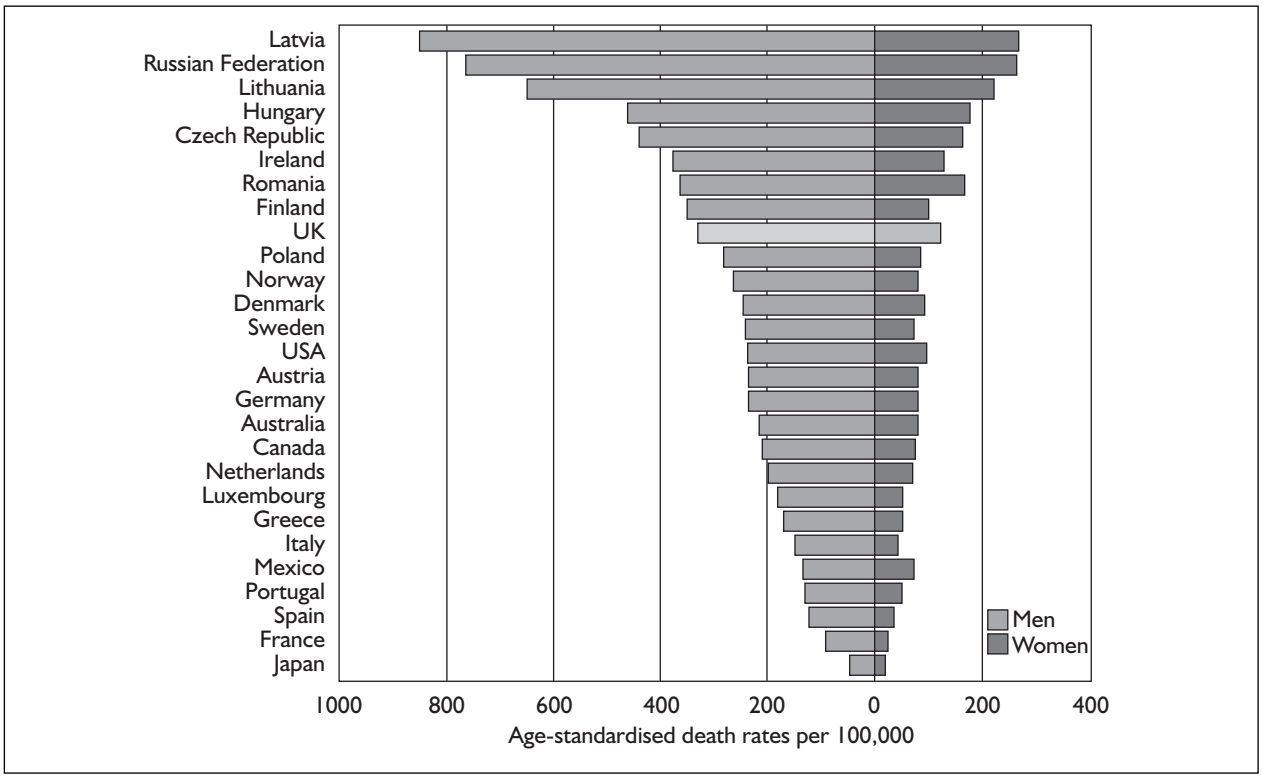

FIGURE 45 *International comparison age-standardised mortality rates for CHD*

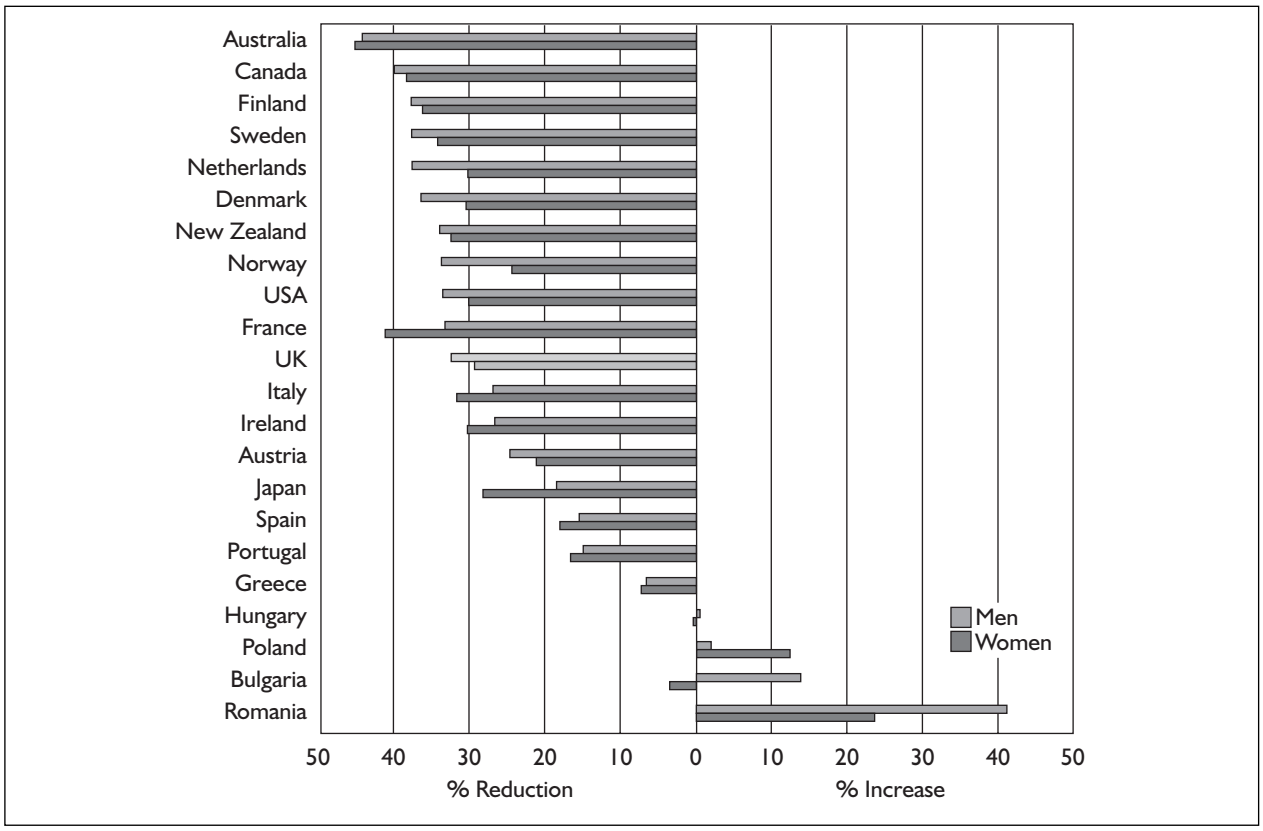

FIGURE 46 *International comparison of rates of decline in CHD*

Appendix 8

ICD questionnaire

You and your ICD

This questionnaire will give us a picture of your experiences with your ICD. We want to find out how the device has affected your activities and how you have reacted to it physically, psychologically and emotionally. The questionnaire is divided into sections which relate to different areas of your life.

Please mark the appropriate box with a cross like this for each question. ☒

EMPLOYMENT

1a. Employment status/size of organisation

The following questions refer to your current main job, or (if you are not working now) to your last main job. Please choose one box only per question.

i) Employee or self-employed

Do (did) you work as an employee or are (were) you self-employed?

Employee ☐

Self-employed with employees ☐

Self-employed/freelance without employees (go to question iv) ☐

ii) Number of employees (Employees)

For employees: indicate below how many people work (worked) for your employer at the place where you work (worked).

For self-employed: indicate below how many people you employ (employed). Go to question iv when you have completed this question.

1 to 24 ☐

25 or more ☐

iii) Supervisor Status

Do (did) you supervise any other employees?

A supervisor or foreman is responsible for overseeing the work of other employees on a day-to-day basis.

Yes ☐

No ☐

iv) Occupation

Please cross one box to show which **best** describes the sort of work you do.
(If you are not working now, please cross a box to show what you did in your last job).

PLEASE CROSS ONE BOX ONLY LIKE THIS: ☒

Modern professional occupations ☐

such as: teacher - nurse - physiotherapist - social worker - welfare officer - artist - musician - police officer (sergeant or above) - software designer

Clerical and intermediate occupations ☐

such as: secretary - personal assistant - clerical worker - office clerk - call centre agent - nursing auxiliary - nursery nurse

Senior managers or administrators ☐
(usually responsible for planning, organising and co-ordinating work and for finance)
such as: finance manager - chief executive

Technical and craft occupations ☐
such as: motor mechanic - fitter - inspector - plumber - printer - tool maker - electrician - gardener - train driver

Semi-routine manual and service occupations ☐
such as: postal worker - machine operative - security guard - caretaker - farm worker - catering assistant - receptionist - sales assistant

Routine manual and service occupations ☐
such as: HGV driver - van driver - cleaner - porter - packer – sewing machinist - messenger - labourer - waiter/waitress - bar staff

Middle or junior managers ☐
such as: office manager - retail manager - bank manager - restaurant manager - warehouse manager - publican

Traditional professional occupations ☐
such as: accountant - solicitor - medical practitioner - scientist - civil/mechanical engineer

1b. Which ONE of the following statements BEST describes your current employment situation?

In full time employment	☐	In part time employment	☐
Presently not working due to ill health	☐	Not employed and looking for work	☐
Retired by own choice	☐	Retired on doctor's advice	☐
Retired at request of employer	☐	Homemaker	☐
Student	☐	Other	☐

If 'Other', please specify:

DRIVING

2. Do you drive? Yes ☐ *(Choose ONE option in 2a below)*
No ☐ *(Choose ONE option in 2b below)*

2a. The same amount as before my ICD implantation ☐
Less than before ICD implantation because of my heart rhythm problem ☐
Less than before ICD implantation but not because of my heart rhythm problem ☐
More than before my ICD implantation ☐

2b. I never learnt to drive ☐
Licence withdrawn by DVLA due to ICD or other health problems ☐
I stopped driving before my ICD implantation ☐
I stopped driving since my ICD implantation because of my heart rhythm problem ☐
I stopped driving since my ICD implantation but not because of my heart rhythm problem ☐

LIVING SITUATION

3. What is your *current* living situation?

I live alone ☐ I live with my spouse ☐ I live with relative(s) ☐

I live with my spouse and relative(s) ☐ Other ☐

If 'Other' please specify:

ACTIVITIES

4. If any of your activities were limited in the *last month*, what was the most important reason, and what other reasons from the list below would also apply?

Activities were not limited in the last month ☐

	Most important reason (tick ONE)	*Reasons which also apply*
Symptoms (fatigue, shortness of breath, etc.)	☐	☐
Fear of bringing on an irregular heart rhythm	☐	☐
Concern or worry about being too active	☐	☐
Concern from partner or family members	☐	☐
Instructions from my doctor or other health care provider	☐	☐
Transportation limitations	☐	☐
Other reasons	☐	☐

Continue to Question 5

5. Consider each statement below in relation to any limitations in how you live your life <u>because of your heart rhythm problem</u>.

<u>For example</u> – In 5h
If you avoid particular strenuous activities <u>because of your heart rhythm problem</u> your answer would be <u>TRUE</u>

However, if you avoid particular strenuous activities for another reason or you do not avoid strenuous activities, your answer would be <u>FALSE</u>

		<u>True</u>	**<u>False</u>**
5a.	I will NOT travel very far from home	☐	☐
5b.	I will NOT travel to places where I think that the hospital facilities are poor	☐	☐
5c.	I will NOT go to isolated areas, for example, into the woods or countryside, on my own	☐	☐
5d.	I will NOT go to isolated areas, e.g. into the woods or countryside, even if someone is with me	☐	☐
5e.	I will NOT go to public places on my own	☐	☐
5f.	I will NOT go to public places even if someone else goes with me	☐	☐
5g.	I will NOT stay alone, for example at home, when no one else is with me	☐	☐

5h. There are particular strenuous activities which I avoid ☐ ☐

5i. From time to time (or more frequently) I do NOT sleep well ☐ ☐

RELATIONSHIPS

6. *In the past month*, how much of the time were your partner or family members anxious about you, as a result of your heart rhythm problem?

Not at all ☐ Sometimes ☐ Very often ☐

Nearly all of the time ☐

7. In the past month, how much of the time were your partner or family members over-protective towards you as a result of your heart rhythm problem?

Not at all ☐ Sometimes ☐ Very often ☐

Nearly all of the time ☐

8. In the past month, how much of the time did you feel a burden to your partner or family members as a result of your heart rhythm problem?

Not at all ☐ Sometimes ☐ Very often ☐

Nearly all of the time ☐

9. Since your ICD implantation, has your relationship with your partner:

Improved ☐ Stayed the same ☐ Got worse ☐

I had no partner when my ICD was implanted ☐

LIFE WITH YOUR ICD

10. Was the decision to have an ICD implanted difficult for you?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

11. How stressful was the implantation procedure and ICD tests for you?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

12. Has it been inconvenient for you to attend your ICD check-ups?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

13. Do you feel that the repeated check-ups have become unnecessary?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

14. How many shocks have you received from your ICD?

Haven't had a shock ☐ 1 shock ☐ 2–4 shocks ☐

5–10 shocks ☐ More than 10 shocks ☐

15. How long ago was the last shock?

Haven't had a shock ☐ In the last week ☐ In the last month ☐

In the last 6 months ☐ More than 6 months ago ☐

16. Have you lost consciousness when you receive a shock?

Never had a shock ☐ Never ☐ Sometimes ☐ Always ☐

17. How unpleasant are the shocks?

Haven't had a shock ☐ Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

18. Have you ever felt relieved after a shock?

Haven't had a shock ☐ Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

19. Have you felt anxious about receiving shocks?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

20. Have you been afraid that the ICD might malfunction or that the battery might run out?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

21. Does your ICD give you a sense of security?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

22. Have you become more anxious and restless as a result of your ICD treatment?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

23. Have you had to take more sedatives since you had your ICD?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

24. Have you ever had the feeling that the ICD saved your life?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

25. Have you felt more independent because you have your ICD?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

26. Are you afraid of certain activities that might bring on a shock?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

27. Can you imagine going on holiday with your ICD implanted?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

28. To a certain extent, has the ICD become the centre of your life?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

29. Do you feel dependent on your ICD?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

30. Do you ever think that you don't need your ICD?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

31. Are you bothered or concerned about any aspect of the visible changes at the implantation area?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

32. Does the ICD cause you physical discomfort around the implantation area?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

33. Altogether, are you satisfied with your ICD?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

34. Would you recommend ICD implantation to other patients in a similar situation?

Not at all ☐ A little ☐ Quite a bit ☐ Very much ☐

35a. Do you suffer from any of the following conditions or illnesses?

	Yes	No
Heart trouble	☐	☐
Arthritis or rheumatism	☐	☐
Cancer	☐	☐
Emphysema/chronic bronchitis/asthma	☐	☐
Rectal problems	☐	☐
Kidney/prostate problems	☐	☐
Diabetes	☐	☐
Missing or paralysed limb, such as hand, foot, arm or leg	☐	☐
Sight problems	☐	☐
Hearing problems	☐	☐
Stroke or brain haemorrhage	☐	☐
Broken or fractured bone (recovery)	☐	☐
Chronic nervous or emotional problems	☐	☐
Gastric disorders (ulcers, hiatus hernia, etc.)	☐	☐
Hypertension (high blood pressure)	☐	☐
Epilepsy	☐	☐
Chronic back pain	☐	☐
Liver disorders	☐	☐
Thyroid disorders	☐	☐
Other	☐	☐

If 'Other', please specify:

35b. Do any of these conditions interfere with your physical activity?

Yes ☐ No ☐

If 'Yes', please specify:

Write the names of the prescribed medications that you are currently taking. Please print clearly.

1.

2.

3.

4.

5.

6.

Date questionnaire completed D D / M M / Y Y Y Y

Thank you for taking the time to fill out this questionnaire.

Now take a few minutes to review your answers, ensuring that you have not left any questions out.

Please return it using the supplied stamped addressed envelope

Thank you

Acknowledgement: Questions from 'You and your ICD' are taken from the following source: Dr Christoph Herrman, University of Göttingen, DINAMIT, CIDS.

Appendix 9

Survey questionnaire pilot study: patients' comments

Time requirement of questionnaire was 'satisfactory'. Some comments regarding other health problems: 'only part of ICD which gives patient real concern is that if it developed a shock, patient could not drive for 6 months which would reduce life style (on other hand it gives patient confidence and patient is still able to write to us).'

'Did not ask about effects on partner.'

Patient also has pacemaker which has increased activity level (ICD in 1998, PM in 2001).

Questionnaire was 'fairly comprehensive' ... 'My understanding of what an ICD is: the support I would expect if the ICD cut in providing life support, from the hospital staff. Stress is one of the reasons I retired and the cause of my heart condition. Stress and anxiety I believe are different. I can get anxious/concerned about an issue without getting stressed now, a condition I think I manage successfully.'

Commented that results affected by recent shock … 'also the fact that I receive a 6 months driving ban every time I receive a shock adds a great deal to my stress.'

'Some questions seem to repeat those posed at an earlier stage.'

'It is a very good questionnaire and the length of time was no problem. If anyone is waiting to have an ICD I would definitely say go for it, as it is a life saver.'

'Quite sufficient, and covers all details.'

Length of questionnaire 'seems about right'; found questionnaires interesting to complete.

Length of questionnaire was 'pretty straightforward'.

"Irrelevant: employment, activities – 4 not applicable, 5 no room, Your ICD – decision taken by surgeon and wife, 27 has no box for 'going on holiday as usual. Generally did not think questionnaire related to my circumstances; 'I am 77 years old and have had an ICD for 2 years. Most of the things I cannot do are because of age, nothing else, e.g. driving at night and long distances. My partial deafness causes more problems than my ICD."

'Felt that age should have been asked about, also marital status.'

Wanted 'questions on your personal or private life that could be affected'.

Patient will go to public places but has to leave if overcrowded: no longer feels comfortable in public places.

'Straightforward and relevant.'

Appendix 10

Comparison of unit costs at the time of implanting the ICD

TABLE 96 *Comparison of unit costs peri-implantation, converted to 2001 pounds*

	Unit costs (£2001)	
	Liverpool	**Papworth**
Diagnosis		
Cost of consultation with ICD specialist pre-admission	114	108
Cost of ECG at implantation	18	55
Cost of Holter at implantation	56	89
Cost of ETT at implantation	56	86
Cost of X-ray at implant PA and lateral	44	33
Cost of echocardiography	17	55
Cost of angiography	633	556
Cost of nuclear scan	**184**	**184**
Cost of MRI peri-implantation	**484**	**484**
Cost of EP study pre-ICD	1,979	1,591
Cost of ablation	**3,763**	**3,763**
Cost of day in ward preimplantation	141	302
Treatment		
Cost of box (plus VAT)	17,924	17,924
Cost of variables for implant operation estimate of £2200	**483**	**483**
Cost per hour of theatre time	229	1,608
Cost of ICU bed	1,146	672
Cost of day in ward postimplantation	141	302

Common costs from Papworth are used (in bold).

Appendix 11

Other costs used for estimating costs of hospitalisation

TABLE 97 *Costs used in estimating the costs of hospitalisation*

	Papworth estimate (£)	Liverpool estimate (2002 £)	Cost (2001 £)	NHS reference (£ 2001)	NHS description and other notes
Replacement of box			2369		
Reposition/adjust lead			2369		
Additional lead			2369		
Replacement lead (1.5× standard op.)			3554		
Remove device and lead			2369		
Battery replacement			2369		
Defibrillator replacement			2369		
Replacement of internal defibrillator wire (2× standard op.)			4738		
Reburial			2369		
Costs from minor tests at follow-up, other					
Upper gastrointestinal endoscopy		450	120	F120p	NHS OP, upper gastrointestinal endoscopy, examination alone in medical gastroenterology
Chest X-ray			146	E05op	NHS OP, intermediate radiology in cardiology category
Abdominal X-ray			146	E05op	NHS OP, intermediate radiology in cardiology category
Ultrasound kidneys		90	100	L10op	NHS OP, urology ultrasound scan
Transplant assessment	2005				
Cardioversion			100		
Cardiopulmonary exercise test	295				
Tilt test	422	56			
Transoesophageal echocardiography	265	60			
Venogram			130		
Abdominal scan			51	RBC2	
Pre-shock VF			100		
Cardiac catheter			1718	E3/14	NHS IP, compromise cardiac catheterisation, with and without complications
CABG			5483	E04	NHS IP, coronary bypass
Direct current cardioversion			100		
MUGA scan 48-hour tape	184				
Angioplasty			2428	E15	NHS IP, percutaneous transluminal coronary angioplasty
Implantation DDDR, assume need capital cost as well			2493	EO7	NHS IP pacemaker implant for AMI, heart failure or shock, is another price for without
24 hr ECG	58				

continued

TABLE 97 *Costs used in estimating the costs of hospitalisation (cont'd)*

	Papworth estimate (£)	Liverpool estimate (2002 £)	Cost (2001 £)	NHS reference (£ 2001)	NHS description and other notes
Sigma DR pulse generator inserted	3595				
Ppm inserted	2343				
Debridement and resuturing	6051				
Excise and drain haematoma	6051				
Nuclear scan	184				
Reprogramme ICD			130		
ICD modification			130		
ICD interrogation			130		
Retest device			130		
Full ICD			130		
Pacing tests			130		

Source: hospital.
DDDR, dual-chamber rate-adaptive pacemaker; DR, dual chamber rate responsive; IP, inpatient; MUGA, multiple gated acquisition; OP, outpatient; Ppm, permanent pacemaker.

Addendum

Developments in ICD technology since the UK study

Background

The data on UK patients collected in this study showed that ICDs were usually implanted in a secondary prevention context in the UK and that most of the published RCTs of ICDs, which reported survival and HRQoL, involved patients who had already had a sudden cardiac episode. Therefore, the body of this report has concentrated on the cost-effectiveness of ICD use in secondary prevention and was an accurate picture of the published evidence up to the end of 2003 and of clinical practice in the UK in the period up to mid-2002. However, this is a rapidly developing field and there have been changes in technology and some important primary research published since the study was conducted. This addendum aims to summarise subsequent developments that occurred during the review process and discuss their main implications for ICD use in the UK.

Brief review of recently published ICD trials

During the period of review of this report five new RCTs were published in full,[77–81] all in a primary prevention setting. In addition, two meta-analyses,[82,83] one cost-effectiveness study including eight primary prevention ICDs[84] and an HTA systematic review[29] have been published. These are reviewed briefly here.

Amiodarone versus Implantable Cardioverter-Defibrillator Trial (AMIOVIRT)[77]

The AMIOVIRT trial was in non-ischaemic dilated cardiomyopathy patients with asymptomatic non-sustained VT, an LVEF of 35% or below and NYHA class I–III. Mean age was 59 years (SD 12) and 71% were men. The investigators randomised 51 patients to receive transvenous ICD and 52 to amiodarone, with an average follow-up of 2 years (range 0.1–4.8 years) before stopping the trial on the basis of a futility rule; that is, there was little chance of detecting a survival benefit if the trial were to continue. During the trial there were six deaths in the ICD group and seven in the amiodarone group, with cumulative survival at 1 and 3 years of 96% and 88% in the ICD group and 90% and 87% in the amiodarone group (log-rank test, $p = 0.8$). Arrhythmia-free survival was greater in the control group at 82% and 73% at 1 and 3 years compared with 78% and 63% for the ICD group. In addition, 4% of ICD patients had episodes of syncope during follow-up and 22% were prescribed amiodarone. Among the 52 patients assigned to amiodarone 6% had syncope, 48% discontinued amiodarone owing to side-effects and 15% ($n = 8$) had an ICD implanted. This trial also included HRQoL assessment. Results from the Quality of Well Being Schedule and the State Trait Anxiety Inventory administered at 12 months' follow-up were similar in the two groups.

Comparison Of Medical Therapy Pacing and Defibrillation Trial (COMPANION)[78]

This trial was, strictly speaking, a resynchronisation trial, although it has some features relevant to ICD. A total of 1520 patients with either ischaemic or non-ischaemic dilated cardiomyopathy was recruited. All had an LVEF of 35% or lower, QRS interval greater than 120 ms and PR interval greater than 150 ms on ECG, were in sinus rhythm, NYHA class III or IV and had a recent (in last 12 months) hospital admission for heart failure. The mean age was 67 years and 67% were men. Patients were randomised in a 1:2:2 ratio to optimal medical management (MM) ($n = 308$), MM plus pacemaker ($n = 617$) or MM plus ICD–pacemaker ($n = 595$). Median follow-up was approximately 16 months, during which there were 77, 131 and 105 deaths, respectively, in the three groups. Mortality rates at 12 months were 19%, 15% and 12%. Compared with optimal MM the pacemaker had a relative risk of death from any cause of 0.76 (95% CI 0.58 to 1.01, $p = 0.06$) and the pacemaker–defibrillator a relative risk of 0.64 (95% CI 0.48 to 0.86, $p = 0.004$). In addition, using the Minnesota Living with Heart Failure questionnaire, the COMPANION trial demonstrated that both the pacemaker and

pacemaker–defibrillator groups had significantly better HRQoL than the MM arm at 3 and 6 months, and that these two arms had similar HRQoL throughout. A large proportion of trial patients reported adverse events during follow-up, 61% in the MM group, 66% in the pacemaker group and 69% in the pacemaker–defibrillator group.

Defibrillator Implantation in Non-Ischaemic Dilated Cardiomyopathy (DEFINITE)[79]

The DEFINITE trial recruited solely non-ischaemic cardiomyopathy patients with LVEF below 36%, premature ventricular complexes or non-sustained VT and symptomatic heart failure with NYHA class less than IV. There were 458 patients randomised to either standard heart failure MM or ICD in addition to MM. Age at recruitment ranged from 20 to 83 years, with a mean of 58 years, and 71% were men. During mean follow-up of 29 months there were 68 deaths, 28 in the ICD group and 40 in the control group. Compared with the MM group the ICD groups had relative risk of overall mortality of 0.65 (95% CI 0.40 to 1.06, $p = 0.08$). Almost all the reduction in relative risk was due to SCDs, which were observed in three ICD patients and 14 MM patients (RR = 0.20, 95% CI 0.06 to 0.71, $p = 0.006$). During the study 23/229 (10%) control patients required ICD owing to syncope or deteriorating heart failure and prolonged QRS interval. During follow-up of the ICD arm the following unwanted effects were reported: one device was explanted and one was deactivated, and there were six lead dislodgements/fractures, three venous thromboses, one infection, 13 ICD replacements owing to deteriorating heart failure and prolonged QRS or sinus node dysfunction.

ICD in Acute Myocardial Infarction Trial (DINAMIT)[80]

This trial randomised patients with an LVEF of 35% or below, NYHA class less than IV and impaired autonomic function to single-chamber ICD ($n = 332$) or MM ($n = 342$) at a range of 6–40 days after AMI. The mean age was 62 years and 76% were men. Although ICDs reduced the rate of arrhythmia-related deaths the overall mortality was not reduced (RR = 1.08, 95% CI 0.76 to 1.55) and ICD implant was not recommended in this situation.

Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)[81]

In the largest trial to date, 2521 patients with either ischaemic or non-ischaemic congestive heart failure, NYHA class II or III and an LVEF of 35% or below were randomised to ICD ($n = 829$), amiodarone ($n = 845$) or placebo ($n = 847$). The median age was 60 years and 77% were men. All patients were maintained on standard heart failure medical management and the ICD patients were implanted with shock only, single-lead devices which were conservatively programmed. The median follow-up was 45.5 months with a range of 24–72.6 months. During follow-up there were 182 deaths in the ICD group, 240 in the amiodarone group and 244 in the placebo group. Compared with placebo amiodarone did not confer a survival advantage RR of 1.06, 95% CI 0.86 to 1.30, $p = 0.53$). However, ICD patients had significantly lower all-cause mortality than the placebo group, (RR = 0.77, 95% CI 0.62 to 0.96, $p = 0.007$). Owing to reported side-effects the placebo was discontinued in 189 patients (22.3%) and amiodarone was discontinued in 269 (31.8%). In the amiodarone arm 4% had increased tremor and 6% had increased hypothyroidism, 188 (22.2%) had an ICD implanted. In the ICD arm there was one unsuccessful implant and 32 devices were removed. The annual shock rate was 7.5%, split between those judged to be appropriate (5.1%) and inappropriate (2.4%).

Meta-analysis of primary and secondary prevention trials in patients with non-ischaemic cardiomyopathy[82]

In this well-conducted meta-analysis eight trials that included patients with non-ischaemic cardiomyopathy were identified, five in primary and three in secondary prevention settings. The five primary prevention trials were CAT,[34] AMIOVIRT,[77] DEFINITE,[79] SCD-HeFT[81] and COMPANION,[78] and included 1854 patients. In this study a fixed effects estimate of relative risk of all-cause mortality for ICDs was 0.69 (95% CI 0.55 to 0.87, $p = 0.002$). Although these trials varied in their patient populations, particularly in the severity of disease, the results were robust to the exclusion of any individual trial. However, there was limited power to detect heterogeneity with such a small number of trials. Owing to improved medical therapy in the era of these recent trials the relatively low annual mortality means that the absolute reduction in mortality was in the order of 2% per year, so that approximately 25 patients would need to be treated to prevent one death per year. The three secondary prevention trials found were AVID,[17] CIDS[19] and CASH,[18] but only the first two provided enough information on the non-ischaemic subgroup to be included in a meta-analysis. The meta-analysis estimate of relative risk was the same as that for primary prevention

studies (RR =0.69, 95% CI 0.39 to 1.24, $p = 0.22$), but the small combined sample size of 256 means that this is not significant at traditional thresholds.

Meta-analysis of ten primary prevention trials[83]

In this study ten trials (MADIT I,[13] CABG Patch,[16] MUSTT,[15] CAT,[34] MADIT II,[33] AMIOVIRT,[77] COMPANION,[78] DEFINITE,[79] DINAMIT[80] and SCD-HeFT[81] were combined in a meta-analysis representing 3530 ICD and 3723 control patients. The combined estimate of RR was 0.75 (95% CI 0.63 to 0.91, $p = 0.003$). Conclusions were not sensitive to the removal of any single trial, but there was significant heterogeneity ($p = 0.0005$). Since CABG Patch patients had concomitant bypass surgery, DINAMIT patients had very recent AMI and the MUSTT patients included were from the non-randomised subgroup, an analysis was also undertaken with these trials excluded. This second analysis gave a similar RR of 0.74 (95% CI 0.67 to 0.83, $p < 0.00001$), and there was no longer significant heterogeneity among the seven trials ($p = 0.39$). This study noted the need for better risk stratification or lowering of the cost of the device in order for ICD use to be cost-effective.

Cost-effectiveness of implantable cardioverter-defibrillators[84]

This recent study, published in the *New England Journal of Medicine* used a Markov model including costs, quality of life and survival to estimate incremental cost-effectiveness of ICD compared with control treatment, based on eight primary prevention RCTs. The trials included were CABG Patch,[16] MUSTT,[15] MADIT I,[13] MADIT II,[33] DEFINITE,[79] DINAMIT,[80] COMPANION[78] and SCD-HeFT,[81] and separate cost-effectiveness estimates were derived for each trial. Trial results were extrapolated beyond the follow-up period of the trials (range 16–41 months) to the lifetime of the patients. In the extrapolation, control group mortality was assumed to continue, but US age-gender mortality rates were incorporated to account for the ageing population. In the model, the benefit of ICD estimated by the relative risk in each trial continued over the lifetime of the patients. As in Sanders,[56] a utility of 0.88 was assumed for both groups, although this was down-weighted to account for age, gender and hospital episodes of the patients. The costs of ICD implant (US$27,975) and replacement (US$18,390) were based on Medicare payments and professional fees. Single-chamber ICD costs and complication rates, and replacement every 5 years, were assumed for all patients. Some deterministic sensitivity analysis was undertaken, but the estimates did not include confidence intervals and model inputs were assumed to be fixed. This study found that the relative risk of death was negatively correlated with control group risk; thus, those at higher risk had most to gain. Health and economic outcomes varied widely among the trial populations, with the control treatment being both cheaper and more effective in two trials (CABG Patch and DINAMIT) to a cost per QALY of US$34,000 and $34,900 in MUSTT (uncontrolled EP arm) and MADIT I, respectively. The latter two trials with the most favourable cost-effectiveness estimates are based on patients with inducible VT during EP study. For the remaining four trials (MADIT II, DEFINITE, COMPANION, SCD-HeFT) the cost per QALY ranged from US$50,300 to $70,200. Apart from variation among trials, cost-effectiveness was most sensitive to assumptions about baseline risk of the patients, cost of the ICD implant, frequency of generator replacement, HRQoL and the time-horizon over which estimates are extrapolated.

UK HTA systematic review of implantable cardioverter defibrillators[29]

Bryant and colleagues[29] present a systematic review of eight RCTs and 11 economic assessments of ICDs used in primary and secondary prevention settings, but no new economic modelling. This review mirrored the present study in concluding that there was evidence of improved survival due to ICDs, but conflicting evidence on the effect of ICDs on HRQoL. HRQoL was related to multiple shocks. Incremental cost per QALY ranged from US$71,700 to $558,000 in the published studies that were reviewed. The report called for further research on risk stratification of patients in whom ICDs are most likely to be clinically and cost-effective.

Implications of recent published evidence

The new studies reviewed in this addendum generally support the effectiveness of ICDs in preventing death, mainly owing to the reduction of SCD, in a primary prevention setting. Relative risks in these trials ranged from 0.64 in DEFINITE[79] to 1.08 in DINAMIT.[80] DINAMIT recruited patients immediately after AMI and the negative results in this trial would argue against this strategy. Indeed, the economic analysis by Sanders[84] reported that ICD implant was both more expensive and less effective than MM in this situation. The other trial with negative results,

AMIOVIRT,[77] was stopped early after recruiting only 103 patients and it is unlikely that such a small trial would have sufficient power to identify modest risk reductions. The other three recently published trials had relative risks of 0.64 (COMPANION[78]), 0.65 (DEFINITE[79]) and 0.77 (SCD-HeFT[81]). Cost-effectiveness was shown to be associated with relative risk and in these trials the lifetime cost per QALY was assessed at US$50,300, $51,300 and $70,200. In Sanders[84] cost-effectiveness was most favourable in older trials requiring EP studies to confirm inducible VT, such as MADIT I[13] and MUSTT[15] (non-randomised substudy). This confirms the importance of identifying those with most to gain from ICD therapy, using either EP studies or other risk stratification criteria, such as a wide QRS complex in association with impaired left ventricular function (COMPANION[78]). This was also noted in the meta-analysis by Nanthakumar and colleagues,[83] and follows from the meta-analysis by Desai and colleagues,[82] which estimated that 25 non-ischaemic cardiomyopathy patients need to be treated to prevent one death.

Despite COMPANION,[78] DEFINITE[79] and SCD-HeFT[81] having similar baseline mortality and risk reduction to the UK secondary prevention patients, cost-effectiveness estimates based on these trials were more favourable than the lifetime estimates for the present base case. Lower utilities, higher implant and replacement costs, and higher replacement rates observed in the UK study group are the likely reasons, as all were shown to have a significant influence on ICER estimates. For this rapidly developing technology, with fewer devices implanted in a theatre and shorter length of stay for patients than during the UK study period, it is likely that the cost per QALY has decreased in recent years. However, information on the effect of ICDs on HRQoL remains patchy and inconsistent and is the main area for further research in these patients.

What is clear from these and previous studies is the effect that multiple shocks have on HRQoL and therefore the effectiveness and cost-effectiveness of the devices. SCD-HeFT reported that almost one-third of shocks were not appropriate. Further research to minimise the frequency of inappropriate shocks would have a significant impact on the lives of ICD recipients.

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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@hta.ac.uk
http://www.hta.ac.uk

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