Europace (2009) **11**, 716–726
doi:10.1093/europace/eup068

Lifetime cost-effectiveness of prophylactic implantation of a cardioverter defibrillator in patients with reduced left ventricular systolic function: results of Markov modelling in a European population

Martin R. Cowie[1]*, Deborah Marshall[2], Michael Drummond[3], Nicole Ferko[4], Michael Maschio[4], Matthias Ekman[5], Luc de Roy[6], Hein Heidbuchel[7], Yves Verboven[8], Frieder Braunschweig[9], Cecilia Linde[9], and Giuseppe Boriani[10]

[1]Clinical Cardiology, National Heart and Lung Institute, Imperial College, Dovehouse Street, London SW3 6LY, UK; [2]Faculty of Medicine, Department of Community Health Sciences, University of Calgary and Principal Consultant to i3 Innovus, Calgary, Alberta, Canada; [3]Centre for Health Economics, University of York, York, UK; [4]Health Economics and Outcomes Research, i3 Innovus, Burlington, Ontario, Canada; [5]Health Economics and Outcomes Research, i3 Innovus, Stockholm, Sweden; [6]Cliniques Universitaires UCL de Mont-Godinne, Arrhythmology Unit, Yvoir, Belgium; [7]Clinical EP Laboratory, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium; [8]Priesterse Heidestraat 75, B-3560 Lummen, Belgium; [9]Department of Cardiology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden; and [10]Institute of Cardiology, University of Bologna, S. Orsola-Malpighi University Hospital, Bologna, Italy

Received 24 November 2008; accepted after revision 2 March 2009; online publish-ahead-of-print 9 April 2009

Aims Current European guidelines recommend prophylactic implantation of cardioverter defibrillators (ICDs) in patients with a reduced left ventricular ejection fraction (LVEF) who are not in NYHA class IV and have reasonable life expectancy. Cost and benefit implications of this recommendation have not been reported from a European perspective.

Methods and results Markov modelling estimated lifetime costs and effects [life years (LY) and quality-adjusted LY (QALY) gained] of prophylactic ICD implantation vs. conventional treatment, among patients with a reduced LVEF. Efficacy was estimated from a meta-analysis of mortality rates in the six primary prevention trials with inclusion criteria matching ACC/AHA/ESC Class I or IIa recommendations. Direct medical costs were estimated using Belgian national references. Costs and effects were discounted at 3 and 1.5% per annum, respectively. Probabilistic sensitivity and scenario analyses estimated the uncertainty around the incremental cost-effectiveness ratio. An ICD implantation increased the lifetime direct costs by €46 413. Estimated mean LY/QALY gained were 1.88/1.57, respectively. Probabilistic analysis estimated mean lifetime cost per QALY gained as €31 717 (95% CI: €19 760–€61 316). Cost-effectiveness was influenced most by ICD efficacy, time to replacement, utility, and patient age at implantation.

Conclusion In a European healthcare setting, prophylactic ICD implantation may be cost-effective if current guidelines for patients with a reduced LVEF are followed.

Keywords Cost-effectiveness analysis • Decision analytic model • Europe • Prophylactic implantable cardioverter defibrillator • Sudden death • Left ventricular ejection fraction

* Corresponding author. Tel: +44 207 351 8856, Fax: +44 207 351 8148, Email: m.cowie@imperial.ac.uk

Introduction

An implantable cardioverter defibrillator (ICD) can terminate episodes of ventricular tachycardia or fibrillation, thus reducing the risk of sudden death in patients with a range of cardiac disease. European and North American guidelines strongly recommend the prophylactic implantation of ICDs in patients with a reduced left ventricular ejection fraction (LVEF), provided the patient is not in New York Heart Association functional class IV and has a life expectancy longer than 1 year.[1,2]

Such recommendations have major cost implications for healthcare systems in Europe. Previously, published reports have been based mainly on North American costs and are not directly transferable to the current situation in Europe, or have not included more recent trials and/or used data from individual trials/subgroups rather than meta-analysis of relevant studies, or did not report the incremental cost-effectiveness ratio (ICER).[3–8]

In this analysis, we examine the lifetime benefits, costs, and cost-effectiveness of prophylactic implantation of an ICD in patients with a reduced LVEF as recommended in current guidelines, adopting the perspective of the Belgian healthcare system.

Methods

We based our analysis on a model of the cost-effectiveness of ICD therapy (in addition to conventional pharmacological therapy) to prevent sudden cardiac death (SCD) compared with conventional pharmacological therapy, developed by Sanders *et al.*[6] Our model incorporates four main modifications to the Sanders model: (i) the meta-analysis of mortality rates from the six primary prevention trials for patients fulfilling indications for ICD therapy according to current clinical guidelines[1,2] (*Table 1*); (ii) the modelling of specific categories of deaths derived from the clinical trials: SCD, heart failure death (HFD), other cardiac death (OCD), and non-cardiac death (NCD). In those trials, where 'non-SCDs' were not further classified into 'HFDs' or 'OCDs', we used a pooled estimate based on the other studies to allocate such deaths to one or other of those categories; (iii) incorporating Belgian life tables to adjust the non-cardiac mortality rate as the cohort aged; and (iv) using probabilistic sensitivity analysis (PSA), allowing uncertain parameters to vary randomly within predefined distributions and to assess the overall level of uncertainty about our results. Importantly, the model uses country-specific data inputs for the Belgian population to represent the European context of this analysis.[9]

Incremental cost-effectiveness ratios were estimated based on direct medical costs, life years (LY), and quality-adjusted LY (QALY) gained per patient. All analyses were from the healthcare system perspective over the lifetime of patients. Life years gained and QALY gained were discounted at 1.5% per annum and costs at 3% per annum (as recommended by the Belgian Health Care Knowledge Centre).[10] We performed both deterministic and probabilistic sensitivity analyses on input variables to test the robustness of the model.

Decision analytic model

The decision analytic Markov model, developed in Microsoft Office Excel 2003™, estimated the costs, effects, and incremental cost-effectiveness of prophylactic ICD implantation for primary prevention of SCD compared with conventional therapy (*Figure 1*). The model tracks a hypothetical cohort of patients over time using a 1-month cycle length. Treatment effectiveness is captured in the model by tracking progress to the following health states: well, SCD, HFD, OCD, and NCD. In each model cycle, the patient can remain in the same state or transition to another state, except for ICD complications where the patient can only remain for one model cycle. Patients receiving an ICD can experience operative death, implant-related complications, ICD-related complications, and discontinuation of ICD therapy. Pooled estimates for the probability of ICD and implant-related events are modelled. Base-case model inputs are given in *Table 2*.

Efficacy of implantable cardioverter defibrillator therapy

Published meta-analyses included patients not eligible for ICD therapy according to current guidelines, and only yielded results for all-cause mortality and cardiac mortality. We conducted a meta-analysis, therefore, to derive pooled estimates for the efficacy of prophylactic ICD mortality compared with conventional medical therapy in patients with left ventricular systolic dysfunction. The meta-analysis included the six randomized controlled trials of primary prevention with ICD therapy compared with conventional medical therapy (AMIOVIRT, CAT, DEFINITE, MADIT I, MADIT II, and SCD-HeFT) for all model endpoints (SCD, HFD, OCD, and NCD).[11–16] Non-SCDs were classified as HFD or OCD in those clinical trials that did not make this distinction.

A pooled estimate of the relative risk for each type of mortality outcome was calculated using the Mantel–Haenszel method with a fixed effects model (all *P*-values for the test of heterogeneity >0.39) using the RevMan Version 4.2.8 software.[17] The annual risk of death was 8.3 and 11.8% for the ICD and conventional therapy groups, respectively, with SCD being the main cause of cardiac death in the conventional therapy group. The relative efficacy of ICD was assumed to be constant over time. An increase in mortality with age was incorporated using life tables for the Belgium general population, which was used to adjust for the increase in the age- and sex-specific death rate from non-cardiac causes as the cohort of patients aged.[9]

For most of the trials, patients in the ICD and the conventional treatment arm were prescribed similar medication. An advisory board of cardiologists from across Europe, including Belgian cardiologists, confirmed that most patients who are on ICD and control therapy were likely to be following drug regimens that may include one or more of the following classes of medication: ACE inhibitors, β-blockers, and amiodarone.

Patient population

The model represents patients with chronic heart failure in NYHA class II or III, or prior myocardial infarction with or without heart failure. All patients had a reduced LVEF ($\leq$35%). Patients with NYHA class IV symptoms were not included. The mean age of individuals recruited to the trials ranged between 58 and 64 years, and the majority ($>$70%) were male. The proportion of patients in NYHA class II or III ranged from 59% in MADIT II to 100% in SCD-HeFT.

Complications of implantable cardioverter defibrillator therapy

For the base-case, the effectiveness of single-chamber ICD therapy (VVI–ICD) was modelled, consistent with Belgian reimbursement policy.[18] Complications associated with implantation, device technology, and the delivery of therapy were included in the model. Estimates of the proportion of patients experiencing such complications (infection, lead dislodgement, shock-related adverse events, and lead failures) were provided by the advisory board whose estimates were

Table 1 Characteristics of patients enrolled in the six studies used in the meta-analysis in this manuscript

Characteristics	AMIOVIRT[14]	CAT[15]	DEFINITE[13]	MADIT I[16]	MADIT II[12]	SCD-HeFT[11]
Patients						
Number of patients	103	104	458	196	1232	1676
Age [mean (SD)] (years)	59 (11.5)	52 (11)	58	63	64	60
Sex (Male%)	70	80	71	92	84	77
NYHA class (%)	NYHA I: 15 NYHA II: 63 NYHA III: 20	NYHA II: 65.3 NYHA III: 34.6	NYHA I: 21.6 NYHA II: 57.4 NYHA III: 21	NYHA I: 35 NYHA II or III: 65	NYHA I: 37 NYHA II: 35 NYHA III: 24 NYHA IV: 5	NYHA II: 70 NYHA III: 30
Duration of CHF	3.2 years	3 months (median)	2.83 years (mean)			24.5 months
Percentage with NICM (%)	100	100	100			47
Previous MI		No		Yes	Yes	
CAD[a]	7%	No	No		Yes	
LVEF [mean (%) (SD)]	23 LVEF $\leq$ 35%	24 (7) LVEF $\leq$ 30%	21.4 LVEF $\leq$ 36%	LVEF $\leq$ 35%	23 LVEF $\leq$ 30%	25 (median) LVEF $\leq$ 35%
NSVT	Yes	Yes	Yes	Yes		
VF		No				
History of atrial fibrillation (%)			24.5		9	15
Previous HF			Yes			
Other criteria	*Exclusion* Age$<$18, NYHA IV, cardiac transplantation, syncope, pregnancy, contraindication to amiodarone or defibrillator therapy, and concomitant therapy with a class I antiarrhythmic drug	*Exclusion* NYHA I and IV	*Exclusion* Permanent pacemakers, NYHA IV, cardiac transplantation imminent, familial cardiomyopathy associated with sudden death, acute myocarditis, and congenital heart disease	*Exclusion* Cardiac arrest or VT causing syncope that was not associated with an MI, MI within the past 3 weeks, and CABG within the past 2 months *Inclusion* Age: 25–80	*Inclusion* Age $>$ 21	
Medications at baseline (%)						
β-Blocker	51.5	3.8	84.9	17	70	69
ACE inhibitors/ARB	85	96.2	96.7	58	70	96
Study design	Multi-centre randomized trial	Multi-centre RCT	Multi-centre RCT	Multi-centre RCT	Multi-centre RCT	Multi-centre RCT
Site	10 US centres	15 Germany centres	USA	30 US centres and 2 European sites	71 US centres and 5 European sites	USA
Comparators[b]	ICD vs. amiodarone	ICD vs.	pharmacologic	ICD vs. pharmacologic	ICD vs. pharmacologic	ICD vs.

pharmacologic	ICD vs. pharmacologic Enrolment period 1997–2001	1996–2001	1991–1997	1998–2002	1997–2001	

NYHA, New York Heart Association; VF, ventricular fibrillation; LVEF, left ventricular ejection fraction; HF, heart failure; NSVT, non-sustained ventricular tachycardia; ACE, angiotensin-converting enzyme; RCT, randomized controlled trial; CHF, chronic heart failure; ICD, implantable cardioverter defibrillator; pharmacologic, optimal pharmacological therapy; ARB, angiotensin receptor blocker; MI, myocardial infarction; NICM, non-ischaemic cardiomyopathy.
[a]CAD: coronary stenosis > 70%.
[b]All patients were strongly encouraged to receive optimal medical therapy with ACE inhibitors, β-blockers, and potassium-sparing diuretics.

informed by the published literature on ICD-related complications (*Table 2*).[11,13,19,20]

Implantable cardioverter defibrillator device replacement was incorporated in the model using a 6-monthly device survival probability distribution, based on data for the GEM II VR (single-chamber ICD), reported in the 2006 Medtronic CRDM Product Performance Report.[21] It was conservatively assumed that all patients would require an ICD replacement after a maximum of 6.5 years. Exact replacement time depends upon the type of defibrillator, battery technology, stimulation and shock energy requirements, the frequency of capacitor reformation, device diagnostics used, lifestyle issues, and other factors. The effect of longer ICD longevity with new generation devices was tested in sensitivity analysis.

Healthcare resource use

The advisory board of cardiologists also provided consensus advice on the model structure, the assumptions behind the pooling of the clinical trial efficacy data, and provided estimates of the frequency of resource use associated with ICD-implant and ICD-related adverse events.

Costs

The base-case analysis applies an initial device cost for a single-chamber ICD of €16 650 + €1772 for the leads and €16 650 for an ICD replacement device, based on the official reimbursement price in Belgium.

The procedural costs of an initial ICD implant, subsequent revision or replacement, and ICD-related complications (infection, dislodgement, and inappropriate shocks) were derived from the 'Technical Cell' of the federal public service of Public Health and of the Health Insurance [Institut National d'Assurance Maladie-Invalidité (INAMI)/Rijksinstituut voor Ziekte en Invaliditeitsverzekering (RIZIV)][22] and include physician fees, medication, hospital stay, and laboratory utilization.

Typical costs unrelated to ICD therapy include follow-up medical costs (inpatient and outpatient). For the base-case, we used cost data from a Belgian-specific heart failure cost study.[23]

Quality-of-life

A utility score of 0.85 was assigned to the ICD and conventional therapy groups, on the scale where 0.0 equals death and 1.0 corresponds to perfect health, based on the data collected using the time trade-off technique in the SCD-HeFT study.[24] It was assumed that quality-of-life did not change as a result of the implantation of an ICD.[24,25] However, patients who experience an ICD-related complication (e.g. lead infection, inappropriate shocks, and dislodgement) received a quality-of-life decrement equivalent to 3.5 days per month, making their utility 0.75 [$0.85 \times (26.5/30) = 0.75$], based on the method adopted by Sanders *et al.*[6]

Sensitivity analyses

One-way deterministic sensitivity analyses were performed to assess whether the results were affected by changes in the assumptions. The parameters examined in sensitivity analyses were clinical (e.g. conventional therapy mortality, ICD efficacy, replacement rates, and age at the time of ICD implantation), cost (ICD device costs and long-term costs of chronic heart failure), utility parameters (ICD-related and conventional therapy-related utilities), and discount rates.

An additional analysis was conducted to investigate the potential impact on the cost-effectiveness of ICD therapy of variations in the absolute risk of SCD and variation in the competing risks of death. For this analysis, we varied the annual all-cause mortality rate and the ratio of HFD to SCD, a similar method to a previous analysis.[26]

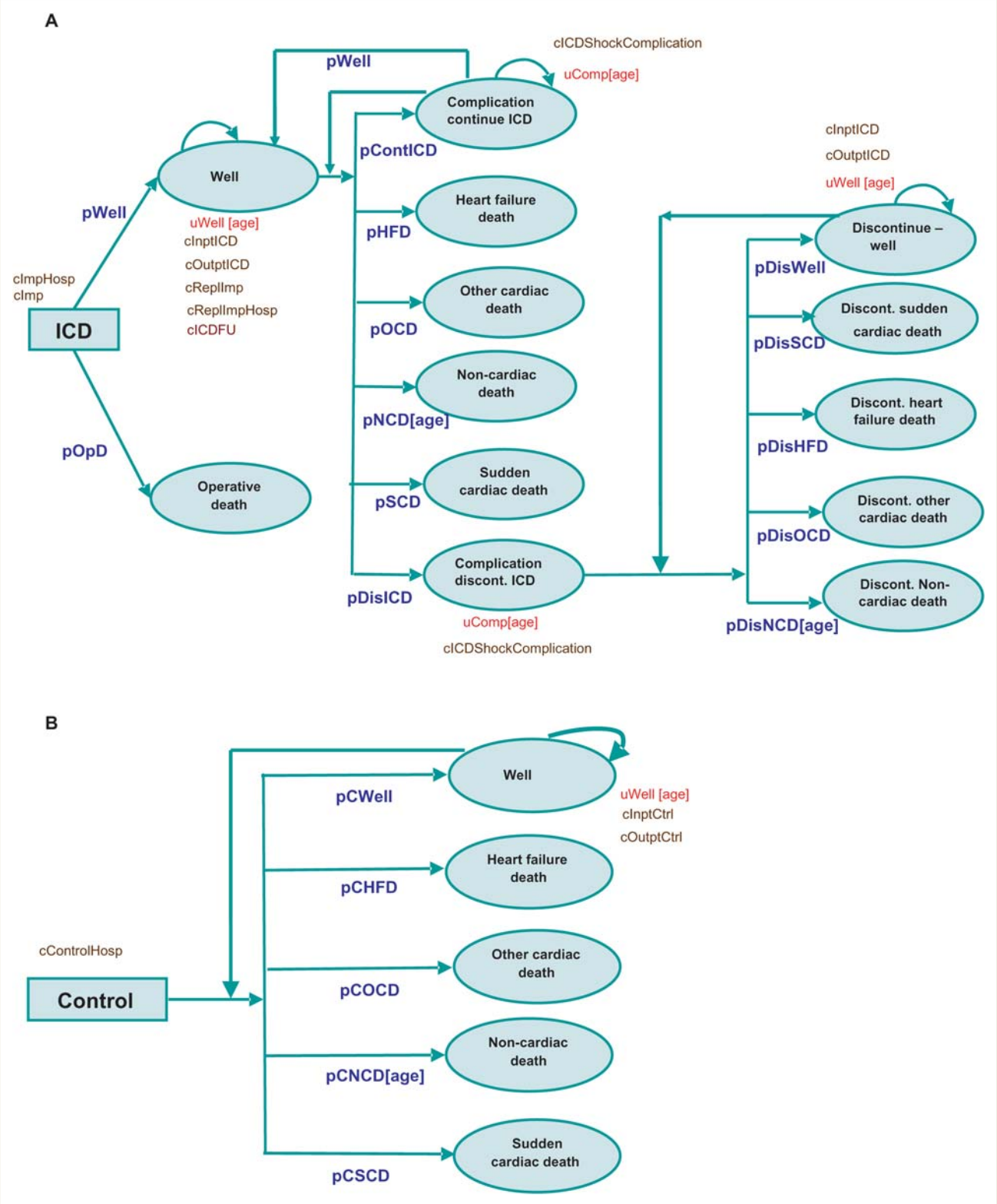

Figure 1 Schematic diagram of the model: (*A*) implantable cardioverter defibrillator arm and (*B*) control arm.

The annual all-cause mortality rates considered in these analyses were: 2.5, 5.0, 10.0, 15.0, 20.0, 25.0, and 30.0%. For each of these seven mortality rates, five different ratios of HFD to SCD were considered: 1:10, 1:3, 2:3, 1:1, and 3:2.

Probabilistic sensitivity analysis with 1000 simulations was undertaken to assess the joint uncertainty of costs and effects. In the PSA, the uncertainty of the cost-effectiveness estimate was explored by defining probability distributions for the key model variables rather

Table 2 Base-case model inputs

Model input	ICD therapy	Conventional therapy	Data sources
One-month death probability			
Sudden cardiac death	0.0015	0.0042	Meta-analysis: AMIOVIRT,[14] MADIT I,[16] MADIT II,[12] SCD-HeFT,[11] CAT,[15] and DEFINITE[13]
Heart failure death	0.0029	0.0029	
Other cardiac death	0.0004	0.0002	
Non-cardiac death	0.0024	0.0031	
All-cause	0.0072	0.0105	
Initial implant operative death probability	0.003	Not applicable	Advisory board
Pooled mean follow-up (months)	28		AMIOVIRT,[14] MADIT I,[16] MADIT II,[12] SCD-HeFT[11] CAT,[15] and DEFINITE[13]
Pooled mean age (years)	61.1		
Gender (%)	79.5 (male) 20.5 (female)		
One-month probability of ICD complications (inappropriate shocks)	0.0047	Not applicable	Advisory board (5.5% per year)
One-month probability of discontinuing ICD after inappropriate shocks	0.00065	Not applicable	Advisory board (0.76% per year)
Monthly probability of a lead replacement due to failure following initial implant	0.0025	Not applicable	Advisory board (3% per year)
Monthly probability of a lead replacement due to failure following replacement implant	0.0051	Not applicable	Advisory board (6% per year)
Probability of a lead infection at initial implant	0.01	Not applicable	Advisory board
Probability of a lead dislodgement at initial implant	0.01	Not applicable	Advisory board
Probability of a lead dislodgement at replacement ICD implant	0.01	Not applicable	Advisory board
Probability of a lead infection at replacement ICD implant	0.02	Not applicable	Advisory board
ICD device cost (€)			Medtronic
Initial device + leads	18 422	Not applicable	
Replacement device	16 650		
ICD type	VVI–ICD	Not applicable	RIZIV/INAMI[22]
ICD replacement rate	See distribution in text: 100% replaced over 6.5 years	Not applicable	Medtronic performance report[21,33–35,37]
ICD procedure cost (€) (2006)			
Initial	4650	Not applicable	RIZIV/INAMI[22]
Replacement	1436		
Lead replacement cost per event (lead failure) (€) (2006)	6422	Not applicable	RIZIV/INAMI[22]/advisory board
ICD complications cost (€) (2006)			
Lead infection	28 410	Not applicable	RIZIV/INAMI[22]/advisory board
Lead dislodgement	2551		
Inappropriate shocks	120		
Monthly long-term inpatient and outpatient cost (€) (2006)	244		Annemans *et al.*[23] and Muls *et al.*[36]
ICD additional monthly follow-up cost (€) (2006)	20	Not applicable	Nomenclature and advisory board
Duration of ICD benefit	Lifetime	Not applicable	Assumption
Utility of heart failure patient annual	0.85		Mark *et al.*[24]
Utility of ICD complications state (annual)	0.75	Not applicable	Sanders *et al.*[6]
Discount rate (%)			
Outcomes	1.5		Belgian Health Care Knowledge Centre (2006)[10]
Costs	3.0		

ICD, implantable cardioverter defibrillator; RIZIV/INAMI: Rijksinstituut voor Ziekte en Invaliditeitsverzekering/Institut National d'Assurance Maladie-Invalidité.

than using deterministic values. These variables include the transition probabilities between different states in the model as well as the health utilities associated with different states (*Figure 1*).

Results

Efficacy of implantable cardioverter defibrillator therapy

The meta-analysis demonstrated a significant reduction in sudden cardiac mortality (and all-cause mortality) associated with the addition of ICD therapy to conventional pharmacological therapy with an RR of 0.37 (95% CI: 0.28–0.48) for SCD and RR of 0.72 (95% CI: 0.64–0.82) for all-cause mortality. Tests for heterogeneity were non-significant.

Deterministic base-case analysis

Prophylactic implantation of an ICD improved life expectancy relative to conventional therapy alone by 2.22 years (discounted, 1.88 years) on average for each patient (*Table 3*). The ICD cohort experienced lower all-cause mortality throughout the model time horizon (see Supplemental material online, *Figure S1*). There were ~50% fewer SCD in those implanted with an ICD device compared with those on conventional therapy, with the benefit of ICD continuing throughout the time horizon (see Supplemental material online, *Figure S1*). Similarly, ICD improved QALY relative to conventional therapy, with a discounted value of 1.57 years (undiscounted, 1.86 years).

On average, 0.51 inappropriate shocks per individual were experienced over the lifetime of the cohort. There was an average of 0.38 lead failures requiring lead replacements per individual over the lifetime of the cohort, based on advisory board estimates of 3 and 6% lead failure rate per year after initial implant and replacement implant, respectively. An average of 0.04 lead dislodgement and infections per individual were predicted over the lifetime of the cohort. The average number of ICD replacements over an individual's lifetime was estimated to be 1.03.

Prophylactic implantation of an ICD led to higher costs compared with conventional therapy (an additional €46 413). The majority of the ICD cost is the device and implant procedure cost (~70% per person on average); the costs of ICD-related complications are relatively small.

In the deterministic base-case analysis, therefore, ICD therapy costs more and is more effective than conventional therapy alone. For patients with a mean starting age of 61 years, the estimated cost-effectiveness of ICD therapy compared with conventional therapy is €24 751 per LY gained and €29 530 per QALY gained (*Table 3*).

Table 3 Life years, quality-adjusted life years, costs, and incremental cost effectiveness ratios for implantable cardioverter defibrillator compared with conventional therapy

Intervention	LY	QALY	Cost (€)	ICER (€/LY)	ICER (€/QALY)
Discounted					
ICD	8.58	7.27	64 600	24 751	29 530
Conventional therapy	6.71	5.70	18 187		
Difference	1.88	1.57	46 413		
Undiscounted					
ICD	9.52	8.06	75 262	24 271	29 009
Conventional therapy	7.30	6.20	21 366		
Difference	2.22	1.86	53 896		

ICD, implantable cardioverter defibrillator; ICER, incremental cost-effectiveness ratio; LY, life years; QALY, quality-adjusted life years.

Validation of the model

We used inputs for costs, efficacy, and utility reported in the Sanders model to validate our model.[6] We also compared the model-predicted mortality among patients receiving conventional therapy with that reported in the clinical trials using the same follow-up time period to ensure our extrapolations and assumptions of constant monthly mortality were validated.

Compared with the empiric trial period, our Markov model predicted mortality rates associated with conventional therapy within 5% relative to the mortality rates reported in the individual trials over the same time period. For the ICD strategy, our model matched the trial results within 5% of the reported mortality rates except for the DEFINITE trial, in which our estimated mortality rate was 11.2% at 29 months, whereas the actual rate was 12% (a 7% relative difference).

When the input values in our model were changed to mirror the values reported by Sanders *et al.*[6] for six separate clinical trials, our Markov model predicted ICERs of ICD therapy compared with conventional therapy that were no more than 7% different from those reported by Sanders *et al.*[6]

Deterministic sensitivity analysis

Overall, the results were most sensitive to assumptions about the efficacy of ICD therapy using a one-way deterministic sensitivity analysis (*Figure 2*). The base-case analysis considered an ICD efficacy estimate based on pooled estimates of ICD and control mortality rates, respectively. The sensitivity analysis examined the effect of differences in the ICD efficacy using the data from the MADIT I ('high' efficacy; HR = 0.46)[16] and SCD-HeFT trials ('low' efficacy; HR = 0.77).[11] The other parameters that most influenced the ICERs were replacement period, utility, age at the time of ICD implantation, and discount rates. The results were least sensitive to varying the ICD device cost, conventional therapy mortality, and long-term costs. Nonetheless, for all values tested in the deterministic sensitivity analysis, the ICERs are in a range that is commonly considered economically attractive (ranging from €13 727 to €37 363).

The results of the sensitivity analyses to investigate the impact of variation on the absolute risk of SCD and competing risks of death showed that ICD therapy is more cost-effective (lower ICER) as the ratio of HFD to SCD decreases, i.e. as SCD is the main cause of death. There is a U-shaped relationship between the

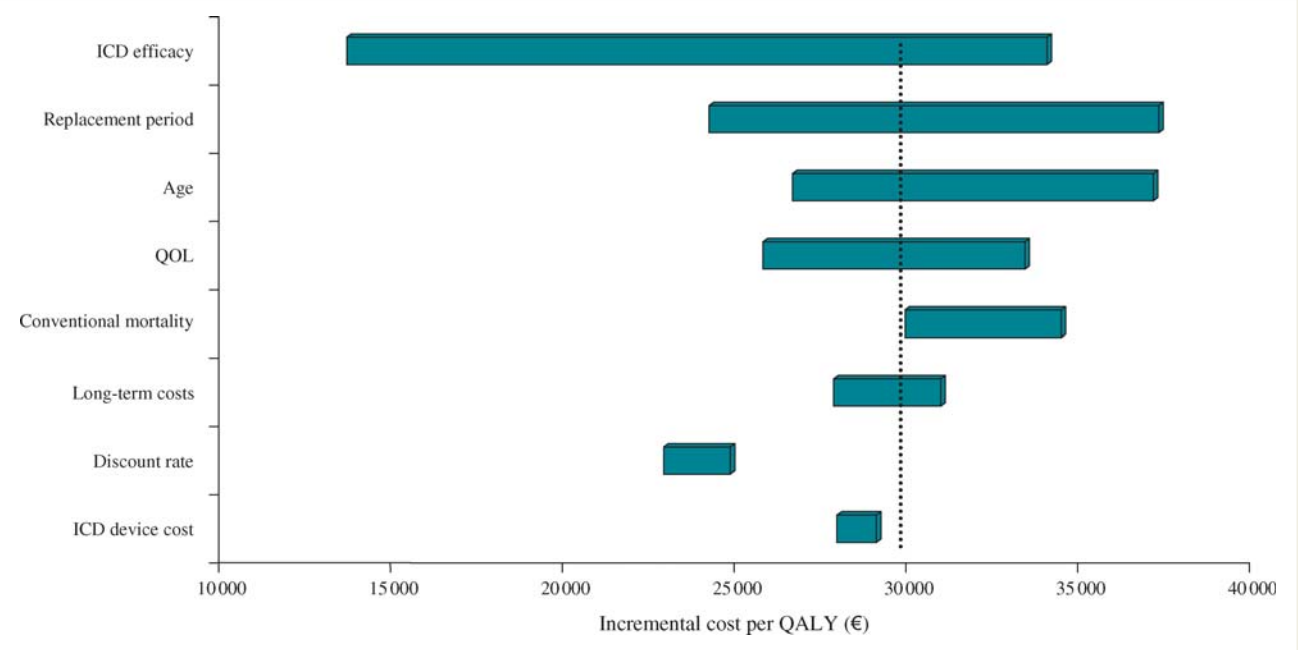

Figure 2 Tornado diagram showing the results of deterministic one-way sensitivity analyses, comparing implantable cardioverter defibrillator and conventional therapy relative to base incremental cost-effectiveness ratio of €29 530 per quality-adjusted life year. The dotted line is a reference line, indicating the value of the incremental cost per quality-adjusted life year in the base-case. QALY, quality-adjusted life years; QOL, quality-of-life. For input variables, please see *Table S1* (included in Supplemental material section).

ICER and annual mortality for the conventional therapy group. High ICERs (less cost-effective) occur when the annual mortality rate in the conventional therapy group is low. The ICER rapidly decreases (becomes more cost-effective) as the annual rate of mortality increases, until the lowest point is reached at ~12.5% annual mortality. The ICER then very gradually increases (less cost-effective) as the mortality rate rises further (*Figure 3*).

Probabilistic sensitivity analysis

In the PSA, the cost-effectiveness of ICD compared with conventional therapy was €31 717 per QALY gained (95% CI: €19 760–€61 316 per QALY). The cost-effectiveness acceptability curve (*Figure 4*) shows the probability (on the *y*-axis) that the ICD therapy is cost-effective compared with conventional therapy for a range (on the *x*-axis) of maximum monetary values that a decision-maker might be willing to pay (WTP) per QALY.[27,28] The probability that ICD is cost-effective is estimated at 85% for a WTP of €40 000 per QALY, at 93% for a WTP of €50 000 per QALY, and at 97% for a WTP of €60 000 per QALY.

Discussion

We have found that under most assumptions in a European healthcare setting, the prophylactic implantation of an ICD has a cost-effectiveness ratio below €50 000 per QALY in patients with an increased risk of SCD because of a reduced LVEF (≤35%), applying Belgian healthcare resource utilization rates and costs.

Based on the relevant randomized clinical trials, we modelled the lifetime benefit of an ICD implantation and estimated that this adds 2.22 undiscounted years of life. This is substantial and compares favourably with other interventions in such patients. Also, the incremental cost-effectiveness of ICD implantation in appropriate patients is similar to that of many interventions currently considered good value for money for patients with cardiac disease.[29–31]

A lifetime horizon is relevant to policymakers and is preferred to within-trial analyses, which are likely to lead to poor estimates of a lifetime value as incremental costs are largely the result of the initial intervention, but benefits are likely to accrue well beyond the duration of the clinical trial.

Our results show less heterogeneity than the analysis from Sanders *et al.*,[6] due to the exclusion of studies that included patients undergoing coronary artery bypass surgery or in the acute phase of myocardial infarction. We found no evidence of meaningful variation in the efficacy of ICD therapy in the trials included in this study, but acknowledge that cost-effectiveness is likely to be different in other patient populations. Cost-effectiveness was most sensitive to ICD efficacy, replacement period, utility, age at the time of ICD implantation, and discount rates.

Our estimates are in line with the most recent results of Sanders *et al.*,[6] although the estimates of cost-effectiveness from North America vary widely.[3,6,7]

The implementation of the current guidelines for prophylactic implantation of ICDs[1] is far from complete across Europe, and implantation rates vary widely across Europe.[32] Moreover, Europeans are much less likely to be given this therapy than patients living in North America. Although full implementation of this therapy has potentially high cost and organizational

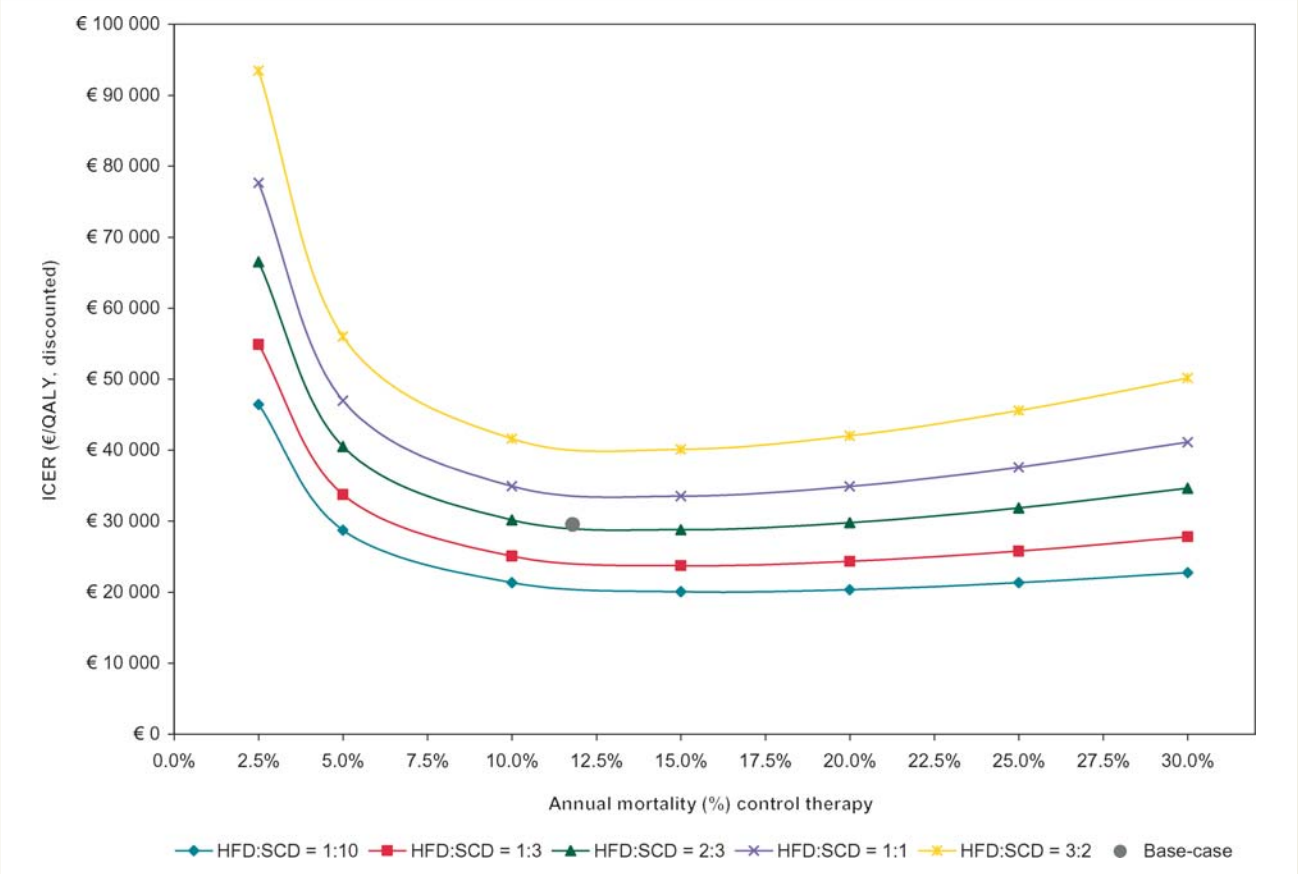

Figure 3 Cost-effectiveness (€/quality-adjusted life year, discounted) of implantable cardioverter defibrillator therapy for various combinations of annual mortality rate for the control therapy cohort and ratios of heart failure death to sudden cardiac death. HFD, heart failure death; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SCD, sudden cardiac death.

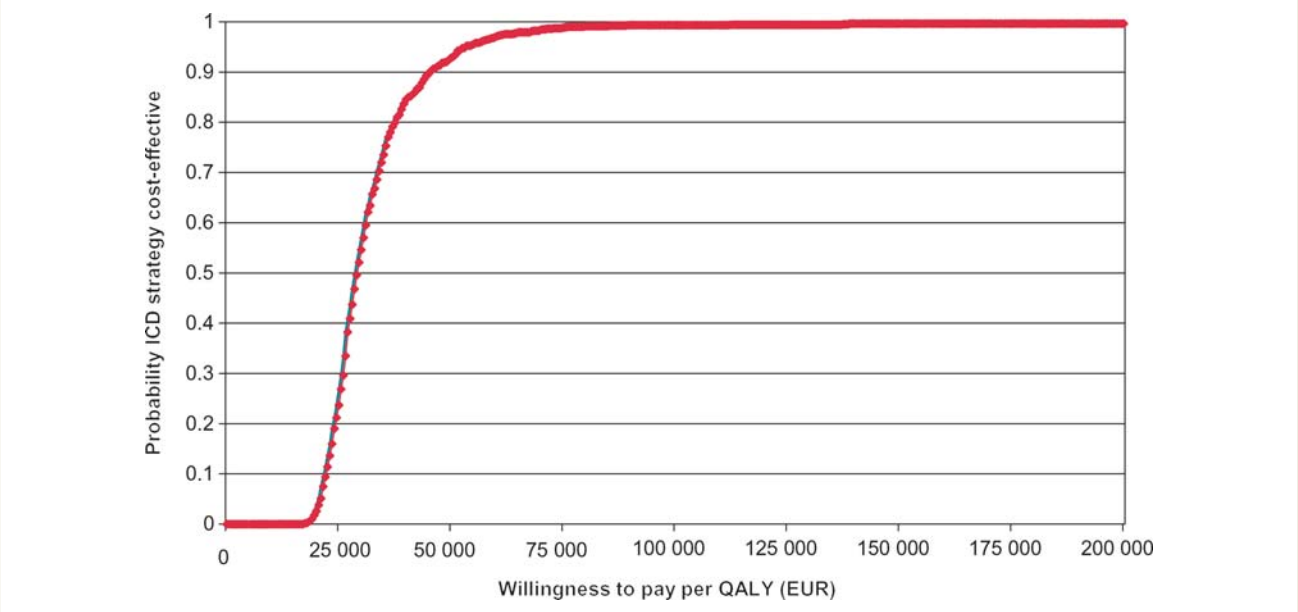

Figure 4 Cost-effectiveness acceptability curve for implantable cardioverter defibrillator therapy in addition to conventional pharmacological therapy compared with conventional pharmacological therapy alone.

implications for European healthcare systems, this analysis indicates that such expenditure represents good value for money.

Our study has several limitations. We projected costs and benefits to a lifetime horizon, but the results were robust to most reasonable changes in the assumptions we employed. The difference between the central estimate of the ICER provided by the deterministic analysis compared with the probabilistic analysis was reassuringly small (€29 530 vs. €31 717 per QALY gained). International guidelines provide rather broad brush recommendations as to which patients should be considered for ICD therapy, with little discussion of detailed patient characteristics or specific device technology. If clinicians extend the use to patients not included in the randomized trials, then the value for money of ICD implantation is unknown. Our analysis is limited to single-chamber ICDs and cannot be extrapolated to more sophisticated devices, including those with the additional capability of cardiac resynchronization.

A newer generation of devices with improved battery capacity as well as newer lead and circuitry technology further improves the expected device longevity, and it is likely that the cost-effectiveness of this therapy will further improve.

Supplementary material

Supplementary material is available at *Europace* online.

Acknowledgements

In November 2006, a European advisory board met and provided guidance and consensus from clinical advisors (cardiologists) on clinical and economic model inputs. The advisory board included cardiologists from Spain, Belgium, Italy, Germany, Sweden, and the UK. The advisors were Dr M.R.C., Dr Juan Delgado, Dr F.B., Dr Uwe Wiegand, Dr Marco Metra and Dr L.R. In addition, a second Belgian advisor was consulted for expert input (Dr H.H.). Editorial assistance was provided by Dr. Gordon Brooker, Phocus Services Ltd, Basel, Switzerland. i3 Innovus Division of Ingenix Pharmaceutical Services (UK) Ltd, Maidenhead, UK and i3 Innovus, Burlington, Ontario, Canada are the institutions where the work was performed.

Conflict of interest: M.R.C. has a consultancy agreement with Medtronic and receives, on behalf of his University, unconditional research grants from Medtronic. D.M. and M.D. are consultants to i3 Innovus, a global health economics research company that receives payment from Medtronic and other device and pharmaceutical manufacturers for research. N.F. and M.M. are employed by i3 Innovus, a division of i3 Canada, Inc. Y.V. was a former employee of Medtronic Bakken Research Center, B.V. M.E.'s work on this project was funded by a grant from Medtronic. L.R. has received consultancy fees from Medtronic. H.H. receives, on behalf of his University, unconditional research grants from Medtronic and Boston Scientific; he is a Member of the Physician Advisory Board of St Jude Medical and is Co-ordinating Clinical Investigator of the Biotronik-sponsored EuroEco trial. F.B. receives research funding from Medtronic, serves as a consultant for Medtronic and Boston Scientific, and has received speaker's honoraria from several device manufacturers. C.L. has received research grants, speaker's honoraria, and consulting fees from Medtronic and speaker's honoraria and consulting fees from St Jude Medical.

Funding

This work was supported by Medtronic International Trading Sárl and Medtronic Bakken Research Center B.V.

References

1. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M *et al.* ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death—executive summary: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Eur Heart J* 2006;**27**:2099–140.
2. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, Freedman RA, Gettes LS *et al.* ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008;**51**:e1–62.
3. Al Khatib SM, Anstrom KJ, Eisenstein EL, Peterson ED, Jollis JG, Mark DB *et al.* Clinical and economic implications of the Multicenter Automatic Defibrillator Implantation Trial-II. *Ann Intern Med* 2005;**142**:593–600.
4. Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C *et al.* A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and the modelling of cost-effectiveness and cost-utility for these groups in a UK context. *Health Technol Assess* 2006;**10**:1–180.
5. Caro JJ, Huybrechts KF, De Backer G, De Bacquer D, Closon MC. Are the WOSCOPS clinical and economic findings generalizable to other populations? A case study for Belgium. The WOSCOPS economic analysis group. West of Scotland Coronary Prevention Study. *Acta Cardiol* 2000;**55**:239–46.
6. Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. *N Engl J Med* 2005;**353**:1471–80.
7. Zwanziger J, Hall WJ, Dick AW, Zhao H, Mushlin AI, Hahn RM *et al.* The cost effectiveness of implantable cardioverter-defibrillators: results from the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. *J Am Coll Cardiol* 2006;**47**:2310–8.
8. Van Brabandt H, Thiry N, Neyt M, van den Oeyer R, Galloo P, Vanoverloop J *et al.* De implanteerbare defibrillator: een health technology assessment (HTA). Report No. 58A (D2007/10.273/21). Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE); 2007.
9. Life Tables for WHO Member States. http://www.who.int/whosis/database/life_tables/life_tables.cfm
10. Cleemput I, Van Wilder P, Vrijens F, Huybrechts M, Ramaekers D. Guidelines for pharmacoeconomic evaluations in Belgium. Health technology assessment (HTA). Report No. 78C (D/2008/10.273/27). Brussels: Health Care Knowledge Centre (KCE); 2008.
11. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–37.
12. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS *et al.* Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;**346**:877–83.
13. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP *et al.* Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;**350**:2151–8.
14. Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL *et al.* Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia—AMIOVIRT. *J Am Coll Cardiol* 2003;**41**:1707–12.
15. Bansch D, Antz M, Boczor S, Volkmer M, Tebbenjohanns J, Seidl K *et al.* Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy: the Cardiomyopathy Trial (CAT). *Circulation* 2002;**105**:1453–8.
16. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H *et al.* Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial investigators. *N Engl J Med* 1996;**335**:1933–40.

17. Review Manager (RevMan) [computer program]. *Version 4.2 for Windows*. Copenhagen: The Nordic Cochrane Centre; 2003.
18. Convention entre le comité de l'assurance soins de santé de l'Institut National Assurance Maladie-Invalidité et l'établissement hospitalier, Brussels, 1 July 2007. (Available on http://inami.fgov.be/care/fr/revalidatie/convention/defibrillator/index.htm, last accessed March 2009).
19. Klein RC, Raitt MH, Wilkoff BL, Beckman KJ, Coromilas J, Wyse DG *et al.* Analysis of implantable cardioverter defibrillator therapy in the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. *J Cardiovasc Electrophysiol* 2003;**14**:940–8.
20. Scuffham P, Chaplin S. Economic evaluation study of implantable cardioverter defibrillators. National Institute for Clinical Excellence, York Health Economic Consortium, September 2003.
21. Medtronic CRDM Product Performance Report GEM II VR (single chamber). www.crdmppr.medtronic.com
22. INAMI. http://tct.fgov.be/etct/
23. Annemans L, Block P, Rompay W, Closon M. Evaluation of the costs of heart failure in Belgium. *Value Health* 1998;**1**:55–6.
24. Mark DB, Nelson CL, Anstrom KJ, Al Khatib SM, Tsiatis AA, Cowper PA *et al.* Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation* 2006;**114**:135–42.
25. Noyes K, Corona E, Zwanziger J, Hall WJ, Zhao H, Wang H *et al.* Health-related quality of life consequences of implantable cardioverter defibrillators: results from MADIT-II. *Med Care* 2007;**45**:377–85.
26. Owens DK, Sanders GD, Heidenreich PA, McDonald KM, Hlatky MA. Effect of risk stratification on cost-effectiveness of the implantable cardioverter defibrillator. *Am Heart J* 2002;**144**:440–8.
27. Fenwick E, Byford S. A guide to cost-effectiveness acceptability curves. *Br J Psychiatry* 2005;**187**:106–8.
28. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;**10**:779–87.
29. Tengs TO, Adams ME, Pliskin JS, Safran DG, Siegel JE, Weinstein MC *et al.* Five-hundred life-saving interventions and their cost-effectiveness. *Risk Anal* 1995;**15**:369–90.
30. Boriani G, Biffi M, Martignani C, Gallina M, Branzi A. Cost-effectiveness of implantable cardioverter-defibrillators. *Eur Heart J* 2001;**22**:990–6.
31. Neumann PJ, Rosen AB, Weinstein MC. Medicare and cost-effectiveness analysis. *N Engl J Med* 2005;**353**:1516–22.
32. Ector H, Vardas P. Current use of pacemakers, implantable cardioverter defibrillators, and resynchronization devices: data from the registry of the European Heart Rhythm Association. *Eur Heart J Suppl* 2007;**9**:144–9.
33. St Jude Medical. Product performance report: cardiac rhythm management. 2007.
34. Ellinor PT, Guy ML, Ruskin JN, McGovern BA. Variability in implantable cardioverter defibrillator pulse generator longevity between manufacturers. *Pacing Clin Electrophysiol* 2003;**26**:71–5.
35. Senaratne J, Irwin ME, Senaratne MP. Pacemaker longevity: are we getting what we are promised? *Pacing Clin Electrophysiol* 2006;**29**:1044–54.
36. Muls E, Van Ganse E, Closon MC. Cost-effectiveness of pravastatin in secondary prevention of coronary heart disease: comparison between Belgium and the United States of a projected risk model. *Atherosclerosis* 1998;**137**:S111–6.
37. Hauser R, Hayes D, Parsonnet V, Furman S, Epstein A, Hayes J *et al.* Feasibility and initial results of an internet-based pacemaker and ICD pulse generator and lead registry. *Pacing Clin Electrophysiol* 2001;**24**:82–7.