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The cost-effectiveness of primary prophylactic implantable defibrillator therapy in patients with ischaemic or non-ischaemic heart disease: a European analysis

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Aims It remains unclear whether primary prophylactic implantable cardioverter-defibrillator (ICD) therapy is cost-effective compared with a 'no ICD strategy' in the European health care setting. We performed a cost-effectiveness analysis for a cohort of patients with a left ventricular ejection fraction <40% and ischaemic or non-ischaemic heart disease.

Methods and results A Markov decision analytic model was used to evaluate long-term survival, quality-adjusted life years (QALYs), and lifetime costs for a cohort of patients with a reduced left ventricular function without previous arrhythmias, managed with a prophylactic ICD. Input data on effectiveness were derived from a meta-analysis of primary prophylactic ICD-only therapy randomized trials, from a prospective cohort study of ICD patients, from a health care utilization survey, and from the literature. Input data on costs were derived from a micro-cost analysis. Data on quality-of-life were derived from the literature. Deterministic and probabilistic sensitivity analysis was performed to assess the uncertainty. Probabilistic sensitivity analysis demonstrated a mean lifetime cost of €50 685 ± €4604 and 6.26 ± 0.64 QALYs for patients in the 'no ICD strategy'. Patients in the 'ICD strategy' accumulated €86 759 ± €3343 and an effectiveness of 7.08 ± 0.71 QALYs yielding an incremental cost-effectiveness ratio of €43 993/QALY gained compared with the 'no ICD strategy'. The probability that ICD therapy is cost-effective was 65% at a willingness-to-pay threshold of €80 000/QALY.

Conclusion Our results suggest that primary prophylactic ICD therapy in patients with a left ventricular ejection fraction <40% and ischaemic or non-ischaemic heart disease is cost-effective in the European setting.

Keywords Implantable cardioverter-defibrillator • Cost-effectiveness • Primary prevention • Coronary artery disease • Dilated cardiomyopathy

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Introduction

The implantable cardioverter-defibrillator (ICD) has become a proven and well-accepted therapy for both the primary and the secondary prevention of sudden cardiac death (SCD) in patients with ischaemic or non-ischaemic heart disease.[1–5] The European guidelines state that primary prophylactic ICDs are indicated in patients with severe left-ventricular dysfunction with a reasonable life expectancy, who have symptoms in New York Heart Association (NYHA) class I, II, or III.[6] This was confirmed by the European Task Force on Heart Failure.[7]

Implantable defibrillator therapy is expensive, with high upfront costs.[1] Complications of ICD therapy are not to be neglected, and frequent.[8] The cost-effectiveness of primary prophylactic ICD

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therapy was thoroughly evaluated in the American population, both in within-trial evaluations and in lifetime extrapolations.[9–11] The costs and benefits of this therapy in the European health care system, however, remain less clear. A recent industry-driven analysis using Belgian input data showed an economically attractive result.[12] Remarkably, a similar analysis using contemporary source data from the same country resulted in a different conclusion.[13]

From a health care point of view, an intervention is considered cost-effective when its additional benefit is deemed worth its additional costs; cost-effectiveness analysis assesses the 'value-for-money' of an intervention. Cost-effectiveness analyses are sometimes performed alongside a clinical trial. This design has the advantage that data on the effectiveness of the intervention and data on used resources are readily available and have high internal validity. Disadvantages consist mainly of a low generalizability to the 'real world' population (i.e. low external validity), a lack of long-term follow-up data, and unreliable estimates of rare events. An alternative design for cost-effectiveness analyses is the use of a decision model combining the best-available evidence from various sources. For example, a decision model can combine effectiveness data derived from a meta-analysis, data on costs from separate cost-analyses, data on the frequency of rare adverse events from observational studies, and data on long-term follow-up from registries.

The purpose of this study was to determine the cost-effectiveness of primary prophylactic ICD therapy in patients with ischaemic and non-ischaemic heart disease with a left ventricular ejection fraction (LVEF) $\leq$ 40% without previous arrhythmias, as it is currently being performed according to the European guidelines, using a decision modelling approach combining the best-available evidence from various sources.

Methods

Decision model

We developed a Markov decision analytic model to evaluate the cost-effectiveness of primary prophylactic ICD therapy compared with a 'no ICD strategy' in The Netherlands (implying that patients only received an ICD as secondary preventive therapy). The structure of the model is presented in *Figure 1*.

A decision model is a mathematical method to weigh risks, benefits, patient preferences, and costs of clinical strategies. A decision tree models the immediate consequences of clinical strategies, and a Markov model represents the subsequent follow-up. In a Markov model, patients are simulated as they transition between various health states over the course of their remaining lifetime. The analysis of a Markov model provides estimates of the cumulative duration spent in each health state, which is adjusted for the quality-of-life (QOL) in that state, and which is used to estimate the cumulative follow-up costs.

Model structure

In the 'ICD strategy' of the model, all patients received an ICD (*Figure 1*, 'ICD implantation'). Patients could die perioperatively within the first 30 days. If patients survived, they were at risk of dying, or of developing non-fatal events. Non-fatal events included hospital admissions, ventricular arrhythmias, and adverse events such as inappropriate ICD shocks. Patients could experience a complication, defined as an adverse event requiring an intervention leading to de-implantation of the device and re-implantation of a new ICD (*Figure 1*, 'De-implantation'), or leading to 'ICD revision'. Patients subsequently moved to the 'post-implantation' state. During follow-up in the 'post-implantation' state, patients are at risk of dying, developing non-fatal events, and experiencing complications. We used tunnel states to model elective generator replacements. Device longevity was calculated according to the mean survival of devices used in the time frame under observation, derived from the literature and from a cohort of ICD patients from the Erasmus MC.[14] After the projected lifetime of the initial ICD, patients went to the 'ICD replacement' state of the model and received a new generator. The 'ICD replacement' state is identical in structure to the 'ICD implantation' state, but was modelled with different probabilities, costs, and (dis)utilities.

In the 'No ICD strategy' of the model, all patients were at risk of dying, could experience successfully resuscitated cardiac arrest leading to ICD implantation in a fraction of these patients, and could encounter non-fatal adverse events. All-cause mortality was modelled by multiplying the inverse of the hazard rate ratio (HRR) for all-cause mortality, derived from a meta-analysis of randomized clinical trials comparing primary preventive ICD-only therapy with conservative therapy, by the all-cause mortality rate of ICD patients.[5]

Patients included in the decision analysis

According to the current guidelines of the Dutch Cardiac Society, which are based on the 2006 international guidelines, patients with left-ventricular dysfunction due to coronary artery disease (CAD) or non-ischaemic dilated cardiomyopathy (DCM) were considered eligible for ICD implantation.[6] Patients qualified if they had a left-ventricular ejection fraction $<$40%. Patients were considered to suffer from CAD if a myocardial infarction occurred, if coronary artery bypass surgery or a percutaneous coronary intervention was performed, or if significant coronary artery stenosis was documented with conventional coronary angiography.

Data sources and assumptions

We used both data from the Erasmus MC ICD registry and data from the literature to estimate the variable values (*Table 1*). All variables were estimated with corresponding distributions. A meta-analysis of randomized controlled trials (RCTs) performed in Europe and the USA on the effectiveness of primary prophylactic ICD-only therapy in reducing all-cause mortality was used to derive estimates on effectiveness.[5] This meta-analysis included the first and second 'Multicenter Automatic Defibrillator Implantation Trial' (MADIT-I and MADIT-II), the 'Sudden Cardiac Death in Heart Failure Trial' (SCD-HeFT), the Cardiomyopathy Trial (CAT), the Amiodarone vs. Implantable Cardioverter-Defibrillator Randomized Trial (AMIOVIRT), and the Defibrillator in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE). We assumed that the effectiveness of ICD therapy in reducing all-cause mortality in the RCTs was representative of the Western European setting. Mortality rates for ICD patients were based on the follow-up data of the Erasmus MC ICD registry and on recent literature.[15–17] The Erasmus MC ICD registry comprises a prospectively collected cohort of ICD patients who received an ICD according to the international guidelines, and are also treated pharmacologically according to the guidelines. Based on these data, a survival function was constructed using regression techniques, which was in line with available recent literature on survival of heart failure patients and post-myocardial infarction survival (*Figure 2*).[18,19]

The meta-analysis of RCTs was used to derive estimates on the incidence of mortality of patients in the 'No ICD strategy'. All-cause mortality of patients in the 'No ICD strategy' was calculated by multiplying the inverse of the HRR for all-cause mortality with an ICD vs. no

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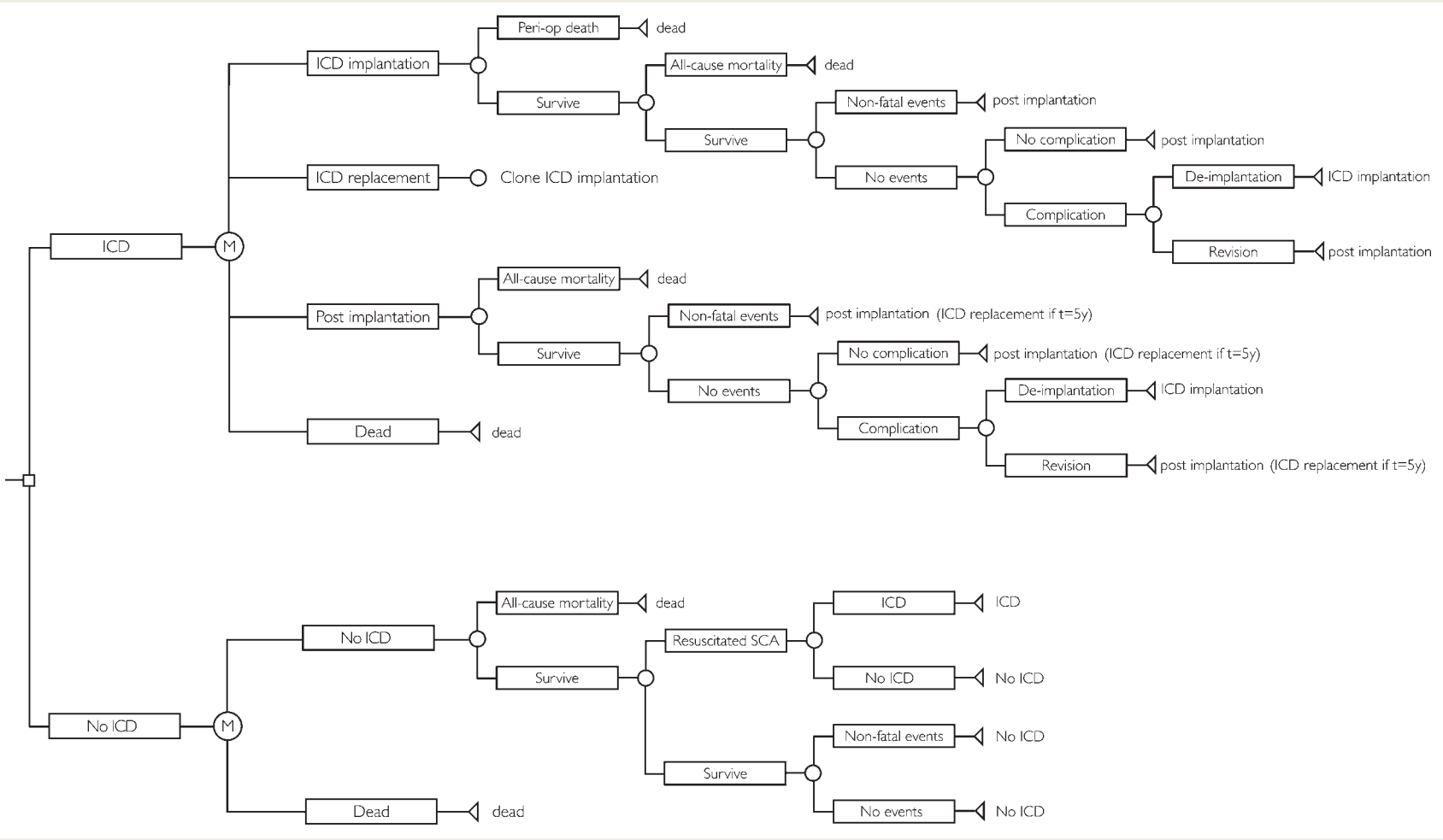

Figure 1 Model structure. The decision tree shows decision nodes as squares (open square), chance nodes as circles (open circle) and Markov nodes (M).

Table 1 Model parameters

Model input	ICD strategy	No ICD strategy	Reference
All-cause mortality	*Figure 2*	*Figure 2*	[15]
HRR all-cause mortality	0.72	1/0.72	[5]
Operative mortality	0.006	N/A	[15,40]
Operative mortality replacement	0	N/A	[15,40]
Non-fatal events	0.60/5 years	0.53/year	[15,21]
Complication related to implantation	0.047	N/A	[15,40]
Complication related to replacement	0.032	N/A	[15,40]
Fraction of complications leading to de-implant/re-implant in implantation cycle	0.06	N/A	[15,40]
Fraction of complications leading to ICD revision in implantation cycle	0.94	N/A	[14,15,40]
Complication in the post-implantation cycle	0.125/5 years	N/A	[15]
Fraction of complications leading to de-implant/re-implant post implantation	0.21	N/A	[14,15,40]
Fraction of complications leading to ICD revision post implantation	0.79	N/A	[14,15,40]
Frequency of generator replacement	Every 60 months	N/A	[14,15]
Resuscitated cardiac arrest	N/A	0.011/2.08 years	[18]
Fraction of resuscitated cardiac arrest patients receiving ICD	N/A	0.55	Assumption
Costs of ICD implantation (€)	30 623	N/A	[14], microcost analysis
Costs of patient follow-up (€/yr)	1224	720	[14], microcost analysis
Costs of non-fatal event (€)	1532	9708	[14,15], microcost analysis
Costs of complication leading to de-implant/re-implant	27308	N/A	[14], microcost analysis
Costs of complication leading to ICD revision	1747	N/A	[14], microcost analysis
Costs of generator replacement	25 776	N/A	[14], microcost analysis
Costs of admission after resuscitated cardiac arrest	N/A	12 676	[15]
Quality-of-life (QALY)	0.88	0.88	[9]
Disutility of ICD implantation	3 days 0.5 QALY	N/A	[22], assumption
Disutility of non-fatal event	10 days 0.5 QALY	10 days 0.5 QALY	[22], assumption
Disutility of ICD revision	20 days 0.5 QALY	N/A	[22], assumption
Disutility of de-implant/re-implant following primary implantation	3 days 0.5 QALY	N/A	[22], assumption
Disutility of late de-implant/re-implant following primary implantation	21 days 0.5 QALY	N/A	[22], assumption
Discount rate costs	4% per annum	4% per annum	[24]
Discount rate utilities	1.5% per annum	1.5% per annum	[24]

ICD, implantable defibrillator; QALY, quality-adjusted life-year; N/A, not applicable.

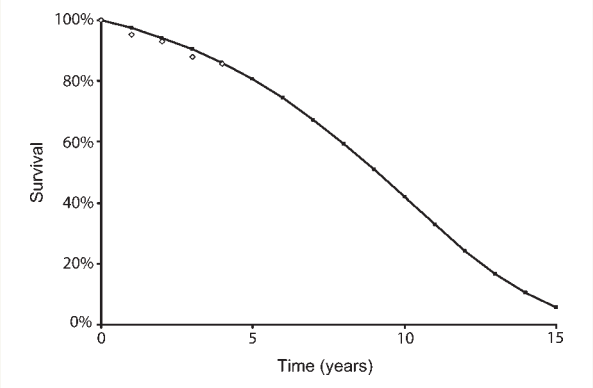

Figure 2 Survival function used in the model. The short-term survival (until 5 years) was based on the Erasmus MC implantable cardioverter-defibrillator registry (open diamonds), the long-term follow-up was based on literature (black dots).

ICD (derived from the meta-analysis) by the absolute all-cause mortality rate among patients with an ICD (derived from the Erasmus MC ICD registry). Costs were estimated for ICD implantation, routine follow-up, and for events occurring during follow-up by a micro-costing analysis according to the bottom-up approach.[20] Estimates on the frequency of events during follow-up were derived from the current literature. Additional information on frequency of events was derived from a survey among general practitioners.[21,22] These data were translated into a cost estimate, reported in Euro's for the year 2010. The price of the ICD was estimated by using the weighted average (for the proportion of used device types) of ICD retail prices of three academic medical centres in The Netherlands for the year 2010. All costs calculated before 2010 were adjusted for inflation by using the standard consumer price index.[23] Quality-of-life estimates were derived from the literature.[9]

Data analysis

The decision was analysed from the societal perspective. Model-based calculations were made using a cycle length of 1 month. We modelled a lifetime horizon. A willingness-to-pay (WTP) threshold of €80 000/

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QALY was used, as recommended by the Dutch Council for Public Health.[24] If the incremental cost-effectiveness ratio (ICER) (i.e. difference in costs divided by the difference in effectiveness of strategy A, compared with strategy B) is lower than the WTP threshold, we conclude that strategy A is a cost-effective alternative compared with strategy B. In deterministic one- and two-way sensitivity analysis, we assessed the effect of varying each parameter across its distribution. The Net Health Benefit (NHB) can be interpreted as the net benefit of investing in a certain strategy compared with the minimal net benefit that society would want in return for this investment. Mathematically, this can be expressed as NHB = E−(C/WTP), where NHB is the Net Health Benefit of a certain strategy, E is the effect of the strategy (QALYs associated with the strategy), C the lifetime costs of the strategy, and WTP the societal willingness-to-pay threshold level. The strategy with the highest NHB can be considered the most favourable strategy.

Probabilistic sensitivity analysis was performed using the outcome distributions of 100 000 Monte Carlo simulations.[25,26] We calculated the probability that the 'ICD strategy' was cost-effective compared with the 'no ICD strategy' for varying willingness-to-pay thresholds, which yielded an acceptability curve. To quantify the value of obtaining more information through future research, we estimated the expected value of perfect information (EVPI) per individual.[27]

Results

Reference-case analysis

The reference-case analysis showed that ICD therapy was associated with a lifetime cost of €86 759 and an effectiveness of 7.08 QALYs. Patients in the control strategy accumulated a lifetime cost of €50 685 and 6.26 QALYs. The ICER was €43 993/QALY gained.

Deterministic sensitivity analysis

The model was sensitive to variations in the effectiveness of the primary prophylactic ICD therapy, the price of the ICD, the longevity of the ICD, the QOL of patients in the 'ICD strategy' and in the 'no ICD strategy', and the follow-up costs of patients in the 'ICD strategy'. One-way sensitivity analysis demonstrated that the ICER remains under the WTP ratio of €80 000/QALY gained under the reference-case assumptions, if:

- The HRR for ICD therapy in reducing all-cause mortality, compared with the 'no ICD strategy' is ≤0.85 (*Figure 3*);
- The price of the ICD is ≤160% of the reference-case price (*Figure 4*);
- The longevity of the ICD is ≥3 years;
- The QOL of ICD patients is ≥0.83 QALYs;
- The QOL of patients in the 'no ICD strategy' is ≤0.90 QALYs;
- The follow-up costs of patients in the 'ICD strategy' remain lower than 4.5 times the cost assumed in the reference case.

The effect of variation of both the price of the ICD and the effectiveness of primary prophylactic ICD therapy is illustrated in *Figure 5*. This graph shows that the 'ICD strategy' becomes more attractive when the effectiveness of primary prophylactic ICD therapy is high, and when its price is low.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis, using a Monte Carlo simulation of 100 000 samples, estimated that the 'ICD strategy' was associated with a lifetime cost of €86 759 ± €3343 and an effectiveness of 7.08 ± 0.71 QALYs. Patients in the 'no ICD strategy' accumulated €50 685 ± €4604 and 6.26 ± 0.64 QALYs, yielding an ICER of €43 993/QALY gained. Using a willingness-to-pay threshold of €80 000/QALY, the 'ICD strategy' was cost-effective compared with the 'no ICD strategy' in 65% of simulations (*Figure 6*). The EVPI was estimated at €18 175 per patient.

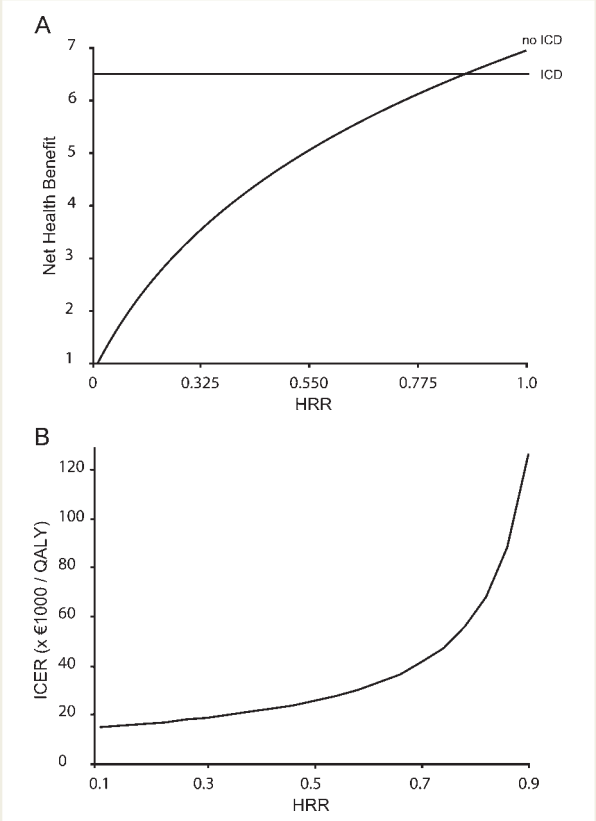

Figure 3 Deterministic sensitivity analysis. (*A*) One-way sensitivity analysis on the effectiveness of implantable cardioverter-defibrillator (ICD) therapy: net health benefit (NHB) as a function of the HRR of primary prophylactic ICD therapy compared with the 'no ICD' strategy. The NHB can be interpreted as the net benefit of investing in a certain strategy compared with the minimal net benefit that society would want to return for this investment. Mathematically, this can be expressed as NHB = E−(C/WTP), where NHB is the Net Health Benefit of a certain strategy, E is the effect of the strategy (QALYs associated with the strategy), C the lifetime costs of the strategy, and WTP the societal willingness-to-pay threshold level. The strategy with the highest NHB can be considered the most favourable strategy. (*B*) One-way sensitivity analysis on the effectiveness of ICD therapy: ICER as a function of the HRR of primary ICD therapy compared with the 'no ICD' strategy.

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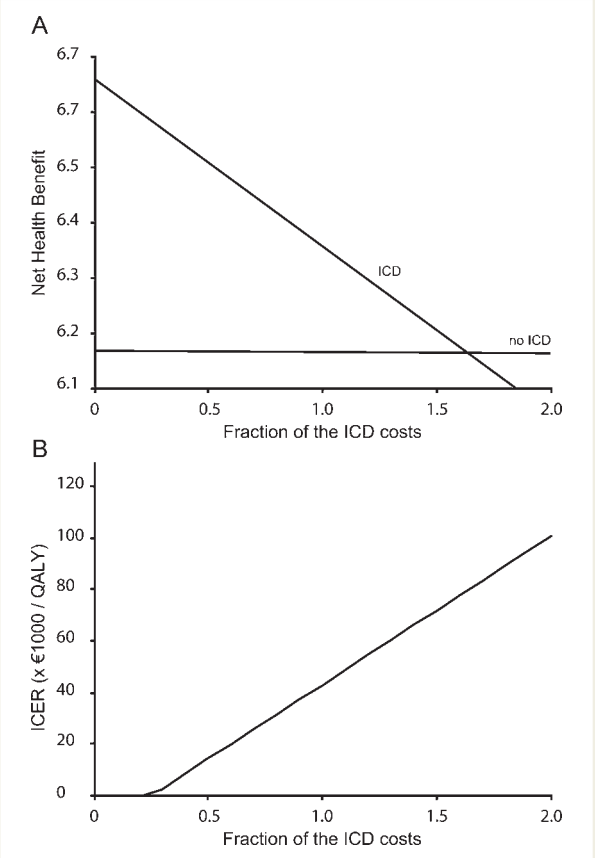

Figure 4 Deterministic sensitivity analysis. (*A*) One-way sensitivity analysis on the cost of the implantable cardioverter-defibrillator (ICD) device: net health benefit (NHB) as a function of the fraction of the price of the device (where 1 represents the reference-case input variable). See legend of *Figure 3* for explanation of NHB. (*B*) One-way sensitivity analysis on the cost of the ICD device: incremental cost-effectiveness ratio as a function of the fraction of the price of the device (where 1 represents the reference-case input variable).

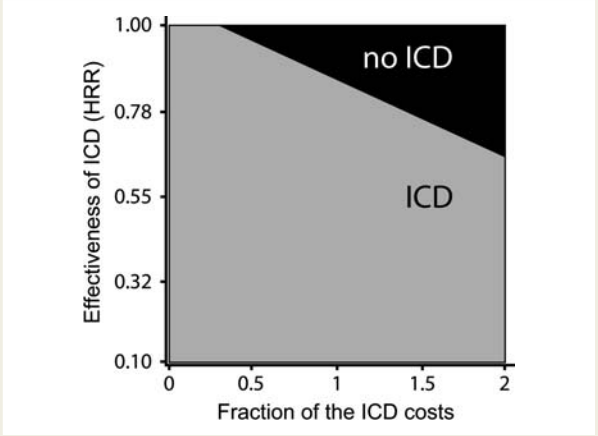

Figure 5 Two-way deterministic sensitivity analysis. Two-way sensitivity analysis of the cost of the implantable cardioverter-defibrillator (ICD) and the effectiveness of primary prophylactic ICD therapy [expressed as the hazard rate ratio (HRR) of ICD therapy compared with optimal medical therapy]. At high values of the fraction of the price of the ICD (i.e. expensive ICDs) and at values of the HRR closer to 1 (i.e. low effectiveness of ICD therapy in reducing all-cause mortality), the 'no ICD strategy' yields the highest effectiveness and lowest costs.

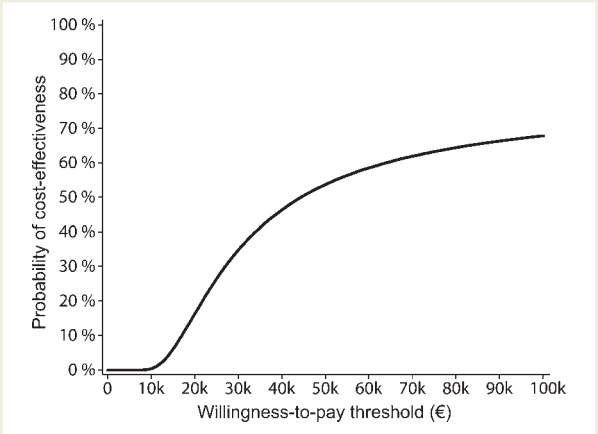

Figure 6 Probabilistic sensitivity analysis: acceptability curve for 'ICD strategy'. The acceptability curve plots the probability that a certain strategy is cost-effective given a particular WTP threshold level. We ran 100 000 Monte Carlo probabilistic simulations that used random draws from distributions that represent uncertainty around parameter estimates. We used a WTP threshold level of €80 000/QALY. In 65% of simulations, the 'ICD strategy' was cost-effective compared with the 'no ICD strategy', which corresponds with a 65% probability of cost-effectiveness.

Discussion

The present study addresses the cost-effectiveness of primary prophylactic ICD therapy in patients with ischaemic or non-ischaemic heart disease in a European country. The major finding of this study is that primary prophylactic ICD-only therapy, applied according to the European guidelines, is cost-effective under the reference case assumptions. Probabilistic sensitivity analysis showed that the probability of cost-effectiveness is 65% at a WTP threshold of €80 000/QALY gained, which is a fairly high threshold but nevertheless an accepted threshold in several Western European countries.

Cost-effectiveness of primary prophylactic ICD therapy in the USA

The cost-effectiveness of primary prophylactic ICD therapy was evaluated in the milestone randomized clinical trials on primary prophylactic ICD therapy.[10,11] The ICERs calculated from these studies range from €30 300 to €348 000 per QALY gained, considering the duration of the trial as time horizon. Model-based studies showed a wide spread of ICERs ranging from $34 900/QALY gained for the second Multicenter Automatic Defibrillator

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Implantation Trial (MADIT II), to $70 200/QALY gained for the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) when a lifetime horizon was applied.[9] In spite of the differences between the USA and Europe in costs of procedures and follow-up, the findings from the latter study [taking the dollar-to-euro exchange rate of 2010 (0.755) into account] are in line with our results.

Cost-effectiveness of primary prophylactic ICD therapy in Europe

Published data on the cost-effectiveness of primary prophylactic ICD therapy in Europe is scarce. A recent cost-effectiveness analysis of primary prophylactic ICD therapy in Belgium, with contributors of the device industry, reported an ICER of €31 717/QALY gained, projected over a lifetime horizon.[12] Remarkably, the Belgian Health Care Knowledge Center (KCE) performed an evaluation of the cost-effectiveness of primary prevention ICD therapy in Belgium in the same era, and presented an ICER of €71 428/QALY gained over a lifetime horizon.[13] This difference may be explained by several factors as unrepresentative costs of ICD therapy, the optimistic device longevity, and different long-term survival extrapolations.[28,29]

Current analysis in the context of prior studies

The present study shows an ICER of €43 993/QALY gained, with a probability of cost-effectiveness of 65%. These results suggest that primary prophylactic ICD therapy in patients with ischaemic or non-ischaemic heart disease and a LVEF $< 40\%$ is cost-effective in Europe. In order to reflect the current clinical practice in Europe, we used evidence from all RCTs that did not incorporate function-improving therapy (e.g. cardiac resynchronization therapy or coronary revascularization procedures) in their design.[5] This may have caused an underestimate of the effectiveness of ICD therapy, and prevents the additive effect of the concomitant function-improving therapies being counted towards the effect of the ICD therapy.[30–32] Neyt *et al.*[13] used data from the SCD-HeFT trial as the only source for effectiveness, which does not reflect the current evidence that led to the guidelines on the indication of primary prophylactic ICDs. Furthermore, recent real-world European data on the incidence of mortality, ICD interventions, and hospitalizations were incorporated in our model in order to represent the current clinical situation more accurately.

Results from sensitivity analysis

Deterministic sensitivity analysis showed that the effectiveness of ICD therapy in preventing mortality, the costs and longevity of the ICD, the QOL of patients in the 'ICD strategy' and in the 'no ICD strategy', and the follow-up costs of patients in the 'ICD strategy' are parameters that have significant impact on the cost-effectiveness. ICD therapy was to be preferred over the 'no ICD strategy' as long as the HRR for preventing all-cause mortality remains ≤ 0.85. A recent meta-analysis, used to estimate the effectiveness in the present study, showed a HRR $= 0.73$ (95% CI 0.64–0.82) for ICD therapy in patients with ischaemic and non-ischaemic heart disease.[5] To appreciate this threshold value of HRR ≤ 0.85 in its context, one should keep the results of the second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) in mind. These two landmark randomized controlled trials that led to the current guidelines revealed a hazard ratio of 0.65 (95% CI 0.51–0.93), and a hazard ratio of 0.77 (95% CI 0.62–0.96) for MADIT-II and SCD-HeFT, respectively. More extensive risk stratification could increase the effectiveness even further. In MADIT-II eligible subjects, using sophisticated electrocardiographic parameters improved the cost-effectiveness of primary prophylactic ICD therapy, as was also suggested in more recent studies.[33–35] Furthermore, additional diseases affect long-term prognosis, and may limit the effectiveness of the ICD. It may therefore be justifiable not to use this therapy in patients with extensive comorbidity.[36–38]

It is intuitive that ICD therapy becomes economically more attractive as ICD prices decline, and as ICD longevity increases. This was confirmed in the deterministic sensitivity analysis. The fact that the costs of ICD therapy vary widely between European countries complicates the judgment of cost-effectiveness in Europe as a whole. Different cost-effectiveness studies used different QOL estimates for ICD patients. Sensitivity analysis showed that the 'ICD strategy' is to be preferred over the 'no ICD strategy', if QOL of ICD patients is ≥ 0.83 QALYs, or ≤ 0.90 QALYs for similar patients without ICD. These results show that the difference in QOL estimates between cost-effectiveness studies does not solely drive the different conclusions.

Follow-up costs of ICD patients in a non-trial setting in Europe are difficult to estimate, as no complete registry of all health care usage of these patients is available. In order to obtain the most realistic estimate of the cost-effectiveness of defibrillator therapy in Europe, we conducted a health care utilization survey among the general practitioners of all ICD patients included in the prospectively collected Erasmus MC ICD registry and among general practitioners of patients from the Academic Medical Center (AMC), Amsterdam.[22] A limitation of this approach is the potential of underestimation of the incidence of health care utilization because of under-reporting. However, it seems unlikely that the actual health care utilization would be more than 450% of the reported utilization. Deterministic sensitivity analysis showed that if this were not the case, the ICER would stay under the WTP threshold. Probabilistic sensitivity analysis was performed using Monte Carlo simulation. In contrast to 'Markov cohort simulation' (i.e. the technique used in the 'reference-case analysis'), which uses the point estimate of each model parameter, probabilistic (Monte Carlo) sensitivity analysis uses random draws from distributions that represent uncertainty around each of the parameter estimates. This analysis showed that in 65% of all simulations, the 'ICD strategy' was cost-effective compared with the 'no ICD strategy', which corresponds to a 65% probability of cost-effectiveness when considering all known uncertainty.[25,26]

The EVPI represents the monetary price that one would be willing to pay in order to gain perfect information. We estimated the EVPI at €18 175 per patient. This is a large amount and implies that the uncertainty in the current analysis justifies pursuing this topic in future research in order to obtain more information.[27]

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Cost-effectiveness in Europe as a whole?

In the present study, we included European source data to the extent possible, in an attempt to obtain a representative estimate of the cost-effectiveness of primary prophylactic ICD therapy in Europe. However, no universally accepted WTP threshold exists among European countries. Therefore, although the outcomes of our analysis are likely to be generalizable, one can question whether the conclusion is generalizable to all European countries. The World Health Organization (WHO) provides a simple rule-of-thumb: all interventions with ICERs below three times the Gross Domestic Product (WHO-WTP) per capita can be considered cost-effective.[39] In 2010, the WHO-WTP threshold exceeded €80 000 for all countries in the European Economic Area, except for France, Italy, Portugal, Spain, and the UK. Nevertheless, the WHO-WTP threshold was above €50 000 in all countries, supporting the generalizability of the conclusion from our reference-case analysis. Nowadays, appropriate allocation of health care resources is becoming more and more complex as a result of increasing life expectancy of patients and increasing health care costs per patient, coupled with diminishing resources due to the global financial crisis. In this perspective, it can be questioned whether the WTP threshold used in the present study is still valid in the current financial situation. We feel that this question reaches beyond the scope of this article.

Limitations

This analysis has several limitations. The frequency of ICD interventions as observed in a large tertiary hospital was extrapolated to a lifetime horizon. Whereas limiting the analysis to the time frame of the observed data underestimates the (cost-)effectiveness of ICD therapy, extrapolating the data may have overestimated it. The estimates of health care costs during follow-up were based on a questionnaire with a limited response rate. Therefore, selection bias cannot be excluded. This could have caused an underestimation of the incidence of health care utilization and thereby overestimation of the cost-effectiveness of ICD therapy. However, since this questionnaire was sent to general practitioners instead of patients, selection due to unreported mortality or inability to respond because of severe illness is unlikely. Finally, we did not distinguish between ischaemic and non-ischaemic heart disease patients. According to the meta-analysis of pooled RCTs, the HRRs for all-cause mortality with an ICD were very similar in these two groups, which would lead to similar cost-effectiveness results, justifying our approach in using a weighed pooled HRR.

Conclusions

Primary prophylactic ICD therapy in patients with a left ventricular ejection fraction <40% and ischaemic or non-ischaemic heart disease, if applied according to the international guidelines, given the current knowledge and best-available evidence, appears a cost-effective therapy in Europe. There is, however, still a large degree of uncertainty and the cost-effectiveness depends on the effectiveness of ICD therapy in preventing mortality, the costs and longevity of the ICD, the QOL of patients with and without ICD, and the follow-up costs of patients. Future research is necessary to clarify these issues and to improve risk stratification in order to target those patients that can benefit most from ICD therapy and therefore increase cost-effectiveness.

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