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Health economic evaluation of implantable cardioverter defibrillators in hypertrophic cardiomyopathy in adults

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ABSTRACT

Background: Hypertrophic cardiomyopathy is a heterogeneous disease in which an implantable cardioverter defibrillator (ICD) effectively prevents sudden cardiac death in at-risk individuals. Nevertheless, the cost-effectiveness of ICDs in this specific patient group has not been evaluated.
Methods: A Markov cohort model was constructed to simulate the course of identified adult persons with hypertrophic cardiomyopathy with and without an ICD over the course of 12 years based on Swedish disease-specific unit costs. The age distribution was based on empirical data from the nationwide cohort of HCM patients with ICDs (mean age at the time of implant was 51.8 years). The outcomes were costs per saved life and cost per gained quality adjusted life year (QALY).
Results: Of 1000 simulated patients, 402 lives were saved after 12 years with an ICD at a cost of 646,000 Swedish krona (SEK), which corresponds to 57,118 Euro per saved life from the health care sector viewpoint. The cost per gained QALY (the incremental cost effectiveness ratio (ICER)) was 171,000 SEK (15,119 Euro). From a societal viewpoint, including effects on productivity losses, the use of an ICD was absolutely dominant (both cheaper and better, and thus an ICER is of no interest). Both the one-way sensitivity analyses and the probabilistic sensitivity analyses supported the findings in the base option.
Conclusion: For identified patients with hypertrophic cardiomyopathy deemed at high risk of sudden cardiac death, the use of an ICD is extremely cost effective, both in terms of the cost for saved lives and gained QALY.

1. Introduction

Sudden cardiac death (SCD) due to arrhythmias in hypertrophic cardiomyopathy (HCM) is preventable by implantable defibrillators (ICDs). The ICD system provides antitachycardia pacing, cardioversion, bradycardia pacing, and can be combined with cardiac resynchronization therapy when indicated. Several observational studies have proven the efficacy of ICD therapy, although there are no randomized controlled trials specifically in HCM [1]. There are two groups eligible for an ICD: *secondary* prevention after survived ventricular fibrillation or sustained ventricular tachycardia with low blood pressure and *primary* prevention based on judgement of risk factors. These risk factors were endorsed by a transatlantic collaboration in 2003 and revised in 2011 [2–4]. The European Society of Cardiology endorsed the HCM Risk-SCD calculator in 2014, which is based on weighting several factors including age-adjustment [5,6]. In addition to stratification of risk factors, the clinician needs to consider comorbidity and life expectancy (at least 1 year) but also economic factors according to guidelines [6]. Nevertheless, until now there has been a lack of health economic evaluations of ICD treatment in the adult HCM population, which is the purpose of this study using the perspective of the Swedish context.

The aim of this study is to analyze the cost-effectiveness of the use of an ICD among persons with HCM in terms of lives saved and gained quality-adjusted life years (QALY).

2. Methods

2.1. Model overview

A decision analytic model (Markov model) [7], using the software Treeage™ and Microsoft Excel™, was constructed to analyze the cost-

Abbreviations: HCM, Hypertrophic cardiomyopathy; ICD, Implantable cardioverter defibrillator; ICER, Incremental cost-effectiveness ratio; NYHA, New York Heart Association; NHB, Net-monetary health benefit; NMB, Net-monetary benefit; QALY, Quality adjusted life year; SCD, Sudden cardiac death; WTP, Willingness-to-pay.

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effectiveness of ICD treatment with two pathways for patients with HCM: with and without an ICD (Fig. 1). The economic analysis was considered from a health care perspective (base option) and from a societal perspective (sensitivity analysis). The time horizon was 12 years in the base option with a starting age of 50, based on battery longevity of the ICD device, i.e. halfway between expected first and second exchanges**.** The ICD replacement time was estimated based on manufacturers' information and clinical data.

Modeling outcomes were analyzed in two ways: the primary outcome in terms of cost- effectiveness is the costs per saved life, meaning that HCM has a known mortality that can be avoided by the use of an ICD. The secondary outcome is a cost utility analysis, expressed as the cost per gained quality adjusted life year (QALY) in terms of the incremental cost-effectiveness ratio (ICER). The model starts with a simulated cohort of 1000 patients with HCM.

2.2. Model inputs

Unit costs for the direct costs concerning the implantation of the ICD system were obtained from Region Gävleborg, Sweden (Table 1). It is assumed that there will be a need for replacement due to battery depletion every 8th year and lead replacement every 15th year. The costs for complications including inappropriate shocks were based on the national Swedish cohort [8].

Costs paid directly by the patient, such as the fee for outpatient visits, the cost for transportation, and the cost for pharmaceuticals used at home, were not included in the analysis, because these are almost negligible in the Swedish health care system. Costs are expressed as SEK (Swedish krona) and the year of cost was April 2019, when 1 Euro corresponded to 11.31 SEK and 1 US$ to 10.16 SEK. Consumer price Index was used to adjust prices to April 2019 [9]. The discount rate in the base option is 3%. The willingness-to-pay (WTP) for a gained QALY was in the base option assumed to be 600,000 SEK (53,050 Euro) [10,11].

When the societal viewpoint is applied, the effects on production losses need to be considered. For persons of working age, the indirect costs for loss of productivity (because of premature death) were based on the principle of opportunity costs, assuming that average wage reflects loss of productivity. From the governmental organization Statistics Sweden, the average monthly wage in 2018 was obtained for both genders for the age range of 55–66 years, employed in all sectors of the Swedish working market [12]. This includes allowances, regular bonuses, and compensations. Calculated this way, the average monthly wage was 32,271 SEK (2853 Euro) [12]. The average monthly wage was multiplied by 12 to get an annual wage, to which was added 31.42% to include employers' contributions to social insurance [13]. It was assumed that people left the workforce at the end of age 65 years.

2.3. Outcomes

The model predicts the number of survivors of the 1000 persons with HCM in both arms after the simulation and the lives gained is the difference.

QALYs were derived from the Swedish tariff of EQ5D-3L for people at age 50–75 years [14,15]. It is assumed that people with HCM have lower utilities than in the general population (multiplied by 0.8) [15].

2.4. Mortality risks of HCM

The underlying mortality with an ICD (due to other reasons in the general population as well as due to HCM complications not preventable with an ICD) was included in the model as well as the assumed effect of an ICD on survival compared to not have an ICD. The mortality of HCM patients with an ICD was based on empirical data from a national cohort with long-term follow-up [16]. There was no periprocedural mortality. It is then assumed that each delivery of appropriate ICD therapy results in a saved life. This protective effect was in the base case assumed to be 5.3% reduction of mortality per year, which is based on the national cohort of HCM patients with a mixture of different ICD systems; primary-prevention patients constituted the vast majority and had a 4.5% yearly incidence of appropriate ICD therapy while secondary-prevention patients had 7.0% rate [17]. In the model, linear intrapolation was used to adjust for age between the 50 and 75 years of age.

2.5. Sensitivity analysis

Due to the uncertainties and the variability of the underlying inputs and assumptions, the following factors were varied in a one-way sensitivity analysis:

- Viewpoint: societal viewpoint (base option a health care sector viewpont).
- Model period: 6 and 24 years (base option 12 years).
- Discount rates: 1% and 5% (base option 3%).
- Costs of the ICD system (device and leads): 75,000 (6631 Euro) and 150,000 SEK (13,262 Euro) (base case: 37,462 SEK).
- Protective effects with an ICD on mortality due to sudden cardiac death per year: 1.0% worst case, 4.5% primary prevention, 7.0% secondary prevention.

In a probabilistic sensitivity analysis, the distributions for the protective effect of interventions, the price of the ICD, and QALYs were tested with 1000 iterations.

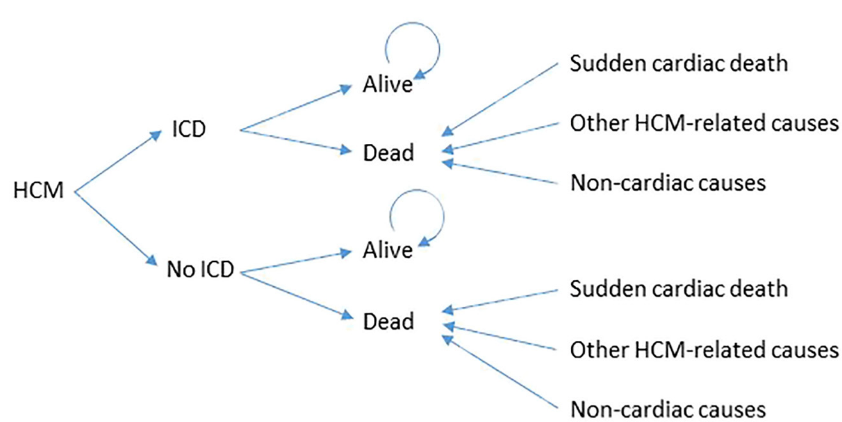

Fig. 1. The structure of the model.

Table 1
Unit costs of the model (SEK).

	Time horizon	ICD		no ICD	Source/reference
Cardiologist before ICD implantation	Year 0	4493	NA	0	Local costs at Region Gävleborg
Hospitalization at surgery and sick leave	Every 8th year	17,344	NA	0	Local costs at Region Gävleborg
ICD device and surgery costs	Every 8th year	39,241	NA	0	Local costs at Region Gävleborg
ICD surgery	Every 8th year	14,101	NA	0	Local costs at Region Gävleborg
Battery change	Every 8th year	39,241	NA	0	Local costs at Region Gävleborg
Lead(s)	Every 15th year	13,722	NA	0	Local costs at Region Gävleborg
Remote monitoring equipment	Every 10th year	3142		0	Local costs at Region Gävleborg
Annual costs					
Cardiologist visits	2.5 per year	11,232	1/year	4493	Local costs at Region Gävleborg
Laboratory costs	Per year	2095			Local costs at Region Gävleborg
Pharmaceuticals	Per year	1009	Per year	1009	Pharmaceutical costs in Sweden [39]
Home monitoring (follow-ups)	4 per year	855		0	Local costs at Region Gävleborg
Annualized costs		15,190		5252	
Costs of complications					
Device infections	Per year	555	NA	0	Local costs at Region Gävleborg
Inappropriate shocks	Per year	1014	NA	0	Local costs at Region Gävleborg [33]
Additional surgery due to complications	Per year	1220	NA	0	Local costs at Region Gävleborg [33]
Complications: care after extra surgery	Per year	4331	NA	0	Local costs at Region Gävleborg [33]
All above complications	Per year	7121	NA	0	

2.6. Ethics

This model is based on published data for inputs and no new patient enrolment has been undertaken. Thus an ethical committee judgement was not considered as needed.

3. Results

Of the population considered to be at high risk, more than half of those without an ICD had died at 12 years compared to fewer than 200 who had an ICD (Fig. 2). The cumulated number of saved lives peak after about 15 years, then the numbers decrease somewhat (Fig. 3). The number of saved lives is 402 (Table 2). The numbers needed to treat to save one life during 12 years is 2.5. The relative risk ratio is 0.7 and the absolute risk ratio 0.41. The cost per saved life from the health care viewpoint is about 646,000 SEK (57,117 Euro) (Table 3). In the cost utility analysis, the incremental cost for a gained QALY from the health care system viewpoint was 171,351 SEK (15,150 Euro) which is lower than the assumed WTP level, i.e. 600,000 SEK (53,050 Euro). From the societal viewpoint, an ICD was both cheaper and better in terms of gained QALYs and thus absolutely dominant vs the non-ICD option (and thus an ICER is of no interest). The one-way sensitivity analysis (Table 4) indicates that all options except the “worst case option” were cost-effective vs a WTP of 600,000 SEK per gained QALY from the health care system viewpoint. From the societal perspective, the ICD was dominant (both cheaper and better) than the non-ICD option. The number of saved lives and its corresponding costs varied considerably depending on the assumed protective effect with the ICD (1.0–7.5%). In the review by Schinkel et al. the annual rate 3.3% was reported; it still turned out to be beneficial from both health care and society point of view (Table 4). ICDs are more cost-effective over 12 than 24 years (see also Fig. 3) due to mortality effects. In the probabilistic sensitivity analysis, the health care viewpoint (ICD better but more expensive; 99.8% of iterations were lower than the WTP of 600,000 SEK) and from the societal viewpoint (all iterations better and cheaper) 100% were cost effective. The acceptability curve for the health care sector viewpoint (Fig. 4) indicated that with a WTP of 300,000 SEK (26,525 Euro) per gained QALY, >95% of the iterations were cost effective. When the WTP was about 170,000 SEK (15,030 Euro), the probability of cost-effectiveness was about 50%.

4. Discussion

ICD implantation in HCM is cost effective under most assumptions in a Swedish health care setting. It is cost-effective from both a health care perspective and from a societal perspective. The costs are far below generally accepted thresholds for WTP values. Thus, there should be no

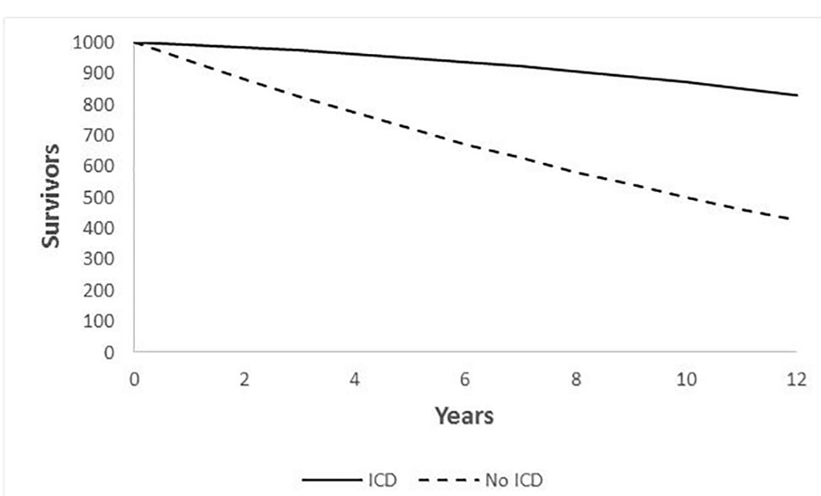

Fig. 2. Base case: a 12-year simulation of the effect of an implantable cardioverter defibrillator (ICD) on survival of a hypothetical cohort of 1000 patients with hypertrophic cardiomyopathy.

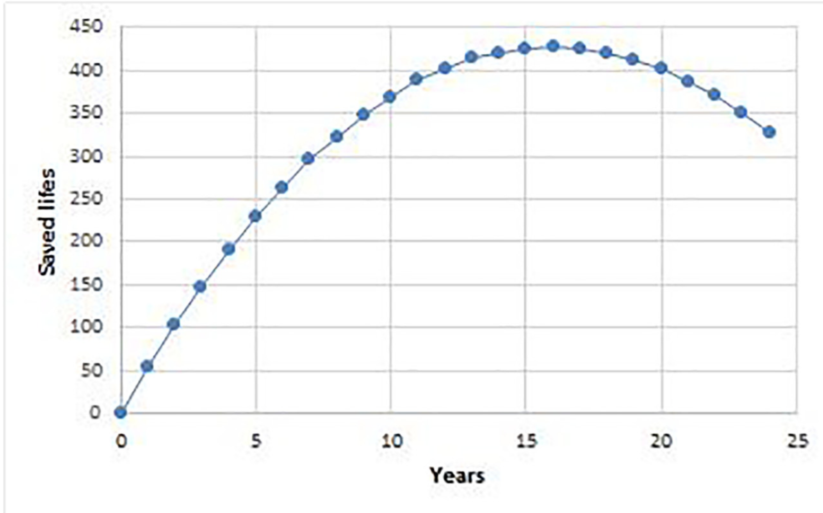

Fig. 3. Saved lives during different durations of modeling scenarios.

economic constraints to deny ICDs to HCM patients who are eligible for an ICD based on the current risk stratification for either primary or secondary prevention.

The ICD represents one of the most important advances in cardiovascular medicine but has had considerable direct costs, at least in the early era. The presumed economic burden of device therapy may have limited its use [18]. Current heart failure guidelines recommend ICD therapy in patients with reduced ejection fraction despite optimal medical therapy based on several studies [19]. In a meta-analysis including AMIOVIRT, CAT, DEFINITE, MADIT, MADIT II, and SCD-HeFT, the ICD was shown to be cost effective [20]. In that study, life-time cost effectiveness in Markov modeling of heart failure patients with reduced ejection fractions, using efficacy data from primary prevention trials and direct medical costs from Belgian national references, found that ICER was 31,717 Euro; far higher than in our study. Another study on primary prevention ICD treatment using similar efficacy data and Dutch data on most unit costs, an ICER of 43,993 Euro was calculated; the device cost was even higher and device longevity assumptions more pessimistic [21]. The authors concluded that this was 65% of the WTP threshold of 80,000 Euro, even though this is not a formally accepted threshold. The World Health Organization (WHO) considers an intervention with ICER below three times the gross domestic product per capita as cost effective [11]. The WTP of 80,000 Euro is exceeded by the vast majority of Western European countries. Over time, the cost of devices has decreased, especially in Sweden due to central procurement. The management of device patients has become more streamlined including shorter hospitalizations, more outpatient surgery, and remote monitoring as a time-saving, cost-effective approach to follow-up [22].

The landmark trials SCD-HeFT and MADIT II reported ICERs of 34,900 US$ and 70,200 US$ in a U.S. context when a life-time horizon was applied [23]. The median age in SCD-HeFT at implant was 60.1 years and mean age in MADIT II was 64.4 years [24,25]. In Sweden, the mean age at ICD implant for any indication is approximately 63 years [26]. Notably, Sweden has low implant rates compared to many other European countries even though is unknown if this can be generalized into indications specifically addressing HCM as the underlying etiology [27]. HCM patients with ICDs tend to be younger, have less comorbidity and a longer life expectancy than typical ICD recipients. In the Swedish national cohort of HCM patients with ICDs, the mean age at the time of implant was 51.8 years [16].

Chan et al. enrolled patients from routine clinical care, i.e. beyond randomized clinical trials of highly selected groups, and found advantageous health economies even in patients above 75 years of age, but ICER rose slightly in those with multiple comorbid conditions [28]. Although decisions about the use of an ICD need to be individualized for a particular patient, these findings suggest that specific subgroups should not be excluded from consideration for ICD implant. Health economy evaluations of early trials showed a wide range of cost-effectiveness ratios. In the CIDS, >90% of the incremental benefit fell to 25% of the patients who had at least two of the following risk factors: New York Heart Association (NYHA) functional class III, age over 70 years, and EF below 35% [29]. Because of the 3.6 greater survival in MADIT, the cost-effectiveness ratio was less than half that found in AVID [30,31]. It was this survival difference rather than the cost difference that led to substantial differences in cost-effectiveness. The same interpretation holds true for the differences reported in the SCD-HeFT trial, in which NYHA II was beneficial in terms of costs compared to NYHA III [24]. Historically, most of the ICD costs are borne upfront whereas the survival benefits are accrued gradually over the years [23,32]. Further improvements in health care management and lower unit costs are reflected in our analysis of HCM patients.

The ICD's efficacy in treatment of life-threatening arrhythmias even in HCM populations has been clearly demonstrated [1,6]. The annualized incidence of appropriate ICD therapy is a surrogate for efficacy. In

Table 2
Base option: cost effectiveness of ICD: costs per saved life (SEK).

	Health care viewpoint	Societal viewpoint
Saved lives	402	402
Numbers needed to treat, 12 years	2.5	2.5
Relative risk ratio	0.70	0.70
Absolute risk ratio	0.41	0.41
Cost per saved life	646,317	<0

Table 3
Basic option: cost utility analysis.

	Costs	Incremental Cost	QALYs	Incremental QALYs	ICER	NMB[a]	NHB[a]
Health care system viewpoint							
ICD	298,924	259,819	6.19	1.52	171,351	652,181	1.087
No ICD	39,105		4.68				
Societal viewpoint							
ICD	638,947	−924,460	6.19	1.52	Dominant	1,836,460	3.060
No ICD	1,563,407		4.68				

NMB, net-monetary benefit; NHB, net-monetary health benefit: WTP, willingness-to-pay.
[a] WTP 600,000 SEK/QALY.

Table 4
One-way sensitivity analysis.

	Cost per life saved			ICER	
	Saved lives	Viewpoint		Viewpoint	
	(of 1000)	Health care	Societal	Health care	Societal
Base option	402	646,317	Dominant	171,351	Dominant
24-Year model	327	1,196,902	Dominant	117,279	Dominant
6-Year model	263	557,131	Dominant	302,420	Dominant
Primary prevention (4.5% survival gap)	356	725,181	Dominant	195,572	Dominant
Best case (7.0% survival gap)	487	540,164	Dominant	138,399	Dominant
Review Schinkel et al.[1] (3.3% survival gap)	278	919,105	Dominant	254,087	Dominant
Worst case (1.0% survival gap)	96	2,602,005	Dominant	760,665	Dominant
Less complications (25% less)	402	605,822	Dominant	160,615	Dominant
Cost of ICD system 75,000 SEK	402	863,302	Dominant	228,878	Dominant
Cost of ICD system 150,000 SEK	402	1,189,690	Dominant	315, 410	Dominant
Discount rate 1%	402	706,362	Dominant	161,766	Dominant
Discount rate 5%	402	595,423	Dominant	181,637	Dominant

ICER, incremental cost-effectiveness ratio.

the one-way sensitivity analysis using a wide range of estimates, it turns out that a 4.5% incidence based on real-life data yields an ICER of 195,572 SEK (17,291 Euro) but with 1.0% incidence, the amount increases to 760,665 SEK (67,255 Euro). Furthermore, to reflect the incidence rate of 3.3% reported in the meta-analysis by Schinkel et al.[1] the corresponding analyses supported the conclusions from the base option even though it was less beneficial. It probably reflects several international scenarios and provides improved generalizability. This is important because HCM is in many ways a heterogenous disease particularly with regard to prognosis and the incidence of SCD. In fact, most ICD patients have a life expectancy near normal [33–35]. Therefore, it is crucial to use evidence- based risk stratification to select patients for ICD therapy. Even though an ICD may be lifesaving and HCM patients report gratitude for this safety, complications including inappropriate shocks are frequent and non-negligible and may undermine trust among health care providers for primary prevention [36,37]. Lead performance is still the weakest link in an ICD system [38]. On the other hand, despite several treatment options for HCM, there is still no effective therapy for the underlying disease and it is well known that there remains for these patients an unpredictable risk for SCD. Therefore, an ICD should be offered after careful selection based on risk markers and clinical judgement in patients with HCM. Provided there is adherence to general management guidelines, this approach is acceptable from a health economy perspective.

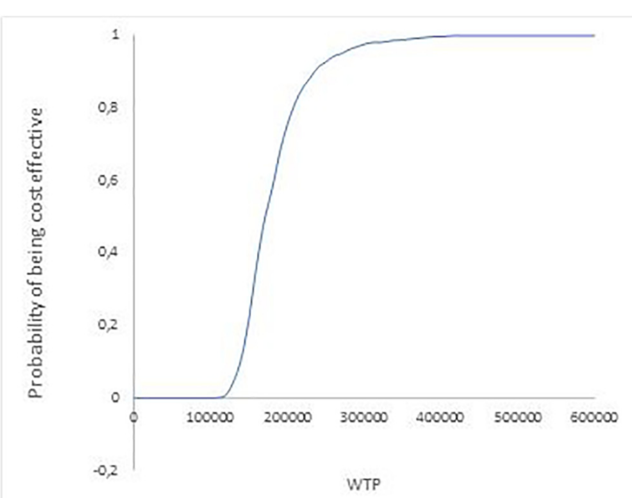

Fig. 4. Acceptability curve at difference levels of willingness-to-pay (WTP) per gained quality adjusted life year (QALY) in SEK for the health sector viewpoint.

4.1. Limitations

This study has several limitations. The annualized risk of SCD prevented by the ICD is assumed to be linear which cannot be known beyond the studied period. In fact, secondary prevention patients have an increased risk for SCD the first year, which declines thereafter. Not every ventricular tachyarrhythmia terminates in SCD in patients without an ICD; some episodes would have terminated spontaneously on their own even if an ICD might have detected them and delivered therapy. An ICD also protects against bradycardia death, but it is unknown if this offsets the overestimation that unnecessary appropriate ICD therapy may imply. This study was based on historical data of patients stratified for SCD. It remains to be seen if this study population is valid for patients eligible for ICDs based on current European guidelines using the modified selection tool. The assumptions in this study are based on the Swedish health care system and society which may limit generalizability.

5. Conclusions

For identified persons with HCM with increased risk of SCD, the use of ICDs is extremely cost effective, both in terms of the cost for saved lives and gained QALY.

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CRediT authorship contribution statement

Peter Magnusson: Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Data curation, Writing - original draft, Visualization, Project administration. **Anders Wimo:** Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Data curation, Writing - original draft, Visualization, Supervision.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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