Systematic review: Cost-Effectiveness of the Use of Implantable Cardioverter Defibrillator to prevent Sudden Cardiac Death (primary prevention)

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Samenvatting

Achtergrond: Een hartstilstand komt veel voor bij cardiovasculaire aandoeningen en wordt vaak veroorzaakt door aritmie. Met anti-aritmica of met een implanteerbare cardioverter-defibrillator (ICD) kan een hartstilstand voorkomen worden. Primaire preventie is gericht op het voorkomen van een hartstilstand voordat een levensbedreigende situatie zich voordoet. Het implanteren van een ICD is effectief wanneer de patiënt een verminderde pompfunctie heeft (ejectiefractie (EF) <35%) en een New York Heart Association classificatie van II-III

Doel: Het realiseren van een systematisch overzicht van alle gepubliceerde studies die de kosteneffectiviteit van ICD in de primaire preventie van SCD hebben onderzocht. De hoofdvraag van dit onderzoek is in hoeverre is het rendabel, in termen van incrementele kosten per quality-adjusted life year (QALY) en / of gewonnen levensjaar (ICER), om een hartstilstand te voorkomen met een ICD vergeleken met een optimale medische behandeling bij patiënten met aritmie, voordat een hartstilstand optreed?

Methode: De volgende databases zijn gebruikt om relevante kosteneffectiviteit studies te vinden: PubMed (MEDLINE), Centre for Reviews and Dissemination (CRD) waaronder Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) en Health Technology Assessment (HTA) vallen en EMBASE. De belangrijkste zoektermen waren: implanteerbare cardioverter defibrillator, hartritmestoornissen en hartstilstand. De publicaties zijn gescreend op titel en samenvatting (dubbel gescoord) en de volledige tekst. De geïncludeerde studies zijn beoordeeld op kwaliteit.

Resultaten: De selectieprocedure begon met 2.352 artikelen en eindigde met 16 relevante publicaties over de kosteneffectiviteit van ICD. Alle opgenomen studies vergeleken ICD strategie met de conventionele medische behandeling. De kosteneffectiviteit analyses (KEA) en kosten utiliteit analyses (KUA) waren vrijwel altijd gebaseerd op klinische studies (CABG-Patch, DINAMIT, MADIT (I&II), DEFINITE, CAT, AMIOVIRT, MUSTT, COMPANION en SCD-HeFT). De incrementele kosten per gewonnen levensjaar liggen tussen de $24.500 en $235.000 en tussen €24.751 en €59.989. De incrementele kosten per gewonnen QALY liggen tussen $34.000 en $557.900 en tussen €29.530 en €71.428. De factoren die lagere ICER's veroorzaken waren: EF ≤ 30, NYHA-classificatie II en leeftijd ≥ 65.

Conclusie: Sommige studies concluderen dat de ICD kosteneffectief is in vergelijking met de conventionele medische behandeling. Echter, de resultaten van andere analyses concludeerde het tegenovergestelde. Deze verschillen worden veroorzaakt door verschillen in patiënten, kosten en klinische effectiviteit. Daarom is het nodig om de gegevens over

kosten effectiviteit en klinische effectiviteit van patiënten met verschillende risicoprofielen te verzamelen.

Abstract

Background: Sudden cardiac death (SCD) plays an important role in cardio vascular diseases (CVD) and is often caused by arrhythmia. Patients with arrhythmia can be prevented from SCD with antiarrhythmic agents or with an implantable cardioverter-defibrillator (ICD). Primary prevention is focussed on preventing a cardiac arrest before a life threatening situation happen. Implanting a cardioverter-defibrillator is effective when patients have a reduced ventricular pump function (ejection fraction (EF) <35%) and a New York Heart Association classification of II-III

Objective: provide a systematic overview of all published studies that have estimated the cost-effectiveness of ICD in primary prevention of SCD. The main question of this review is to what extent is it cost effective, in terms of incremental cost per quality adjusted life year (QALY) and / or life year gained (LYG) (ICER), to prevent SCD with ICD compared to optimal medical treatment in patients with arrhythmia, before a cardiac arrest happen?

Methodology: The following databases are used to find relevant cost-effectiveness studies: PubMed (MEDLINE), Centre for Reviews and Dissemination (CRD) with Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) included and EMBASE. The most important search terms were: implantable cardioverter defibrillator, heart arrhythmia, sudden cardiac death and heart arrest. The records are screened on title/abstract (double scoring) and full text. The included studies are assessed on quality.

Results: The selection procedure started with 2,352 articles and ended with 16 relevant publications about cost-effectiveness of ICD. All included studies compared ICD strategy with conventional medical treatment. The cost effectiveness analyses (CEAs) and cost utility analyses (CUAs) are almost always based on clinical trials (CABG-Patch, DINAMIT, MADIT (I&II), DEFINITE, CAT, AMIOVIRT, MUSTT, COMPANION and SCD-HeFT). The incremental costs per LYG diverges from $24,500 to $235,000 and from €24,751 to €59,989. The incremental costs per QALY gained diverges from $34,000 to $557,900 and from €29,530 to €71,428. The factors that caused lower ICERs were: EF≤30, NYHA-classification II and age≥65.

Conclusion: Some studies conclude that ICD is cost effective compared to conventional medical treatment. However, the outcomes of other analysis concluded the opposite. These differences are caused by different patient profiles and different costs and clinical

effectiveness values. Therefor it is needed to gather data about costs and clinical effectiveness of patients with different risk profiles.

Introduction

Cardiovascular diseases (CVD) are the cause of death for 17.3 million people. This is one third of the world wide mortality (1). Sudden cardiac death (SCD) plays an important role in CVD and is often caused by arrhythmia (1). Approximately 3 million people die from SCD per year (2). There are a lot of factors increasing the risk of sudden cardiac arrest (SCA) and SCD (for all types of causes): coronary artery diseases (CAD), myocardial infarction (MI), age, hypertension and diabetes mellitus (3)(4).

Patients with arrhythmia can be prevented from SCD with antiarrhythmic agents (5). Amiodarone is the most commonly prescribed drug to control the heart rate of patients with arrhythmia (6). Besides antiarrhythmic drug, patients can also be treated with an implantable cardioverter-defibrillator (ICD) or with a combination of these two treatments. When anti-arrhythmic drugs are prescribed in combination with ICD it can reduce the number of shocks that are needed from the ICD to stabilize the heart rate. Stabilizing the heart rate is needed to prevent SCA and SCD (7)(8). There are three main types of ICDs: ventricular chamber, dual chamber (atria and right ventricle) and biventricular defibrillator (atria, right ventricle and left ventricle) (9).

Patients are indicated for ICD when antiarrhythmic drug is not able to control the heart rate (10). Two types of treatment with ICD can be distinguished, primary and secondary prevention of SCA and SCD. Primary prevention is focussed on preventing a cardiac arrest before a life threatening situation happen. Secondary prevention is aimed on stabilizing the hearth rate of a patient after surviving a cardiac arrest (11)(12). Implanting a cardioverter-defibrillator is effective when patients have a reduced ventricular pump function (ejection fraction (EF) <35%) and a New York Heart Association classification of II-III (related to exertion) (7,11,13).

A recent review of randomized clinical trials (RCTs) demonstrated that patients with an EF <35% and a NYHA classification of II-III, despite an optimal and clinical effective medication strategy, do have extra clinical benefit of ICD (reduced mortality rate) (14). However, another study prove that amiodarone is not able to reduce the mortality in patients with arrhythmia (15). The use of ICD is also recommended for patients with a low EF (20-34%) in addition to antiarrhythmic agents (16). Nevertheless, not all the publications about the clinical effectiveness of ICD provide a positive result about the use of ICD. Sometimes, an equal mortality rate reduction was found after comparing ICD with antiarrhythmic drugs (17).

The cost-effectiveness of ICD is also an important aspect since the costs of implanting a cardioverter-defibrillator (without follow-up) is €30,418.08 in The Netherlands (18). A recent review about the cost effectiveness of ICD stated that compared to antiarrhythmic drugs, the use of ICD is cost-effective (19). However, ICD is not cost-effective for all types of patients. ICD seems to be more cost effective for patients high risk of ventricular arrhythmia and SCD, however there is not enough evidence to confirm this statement. Risk stratification is needed to show clear results about cost effectiveness (20,21). There is also not enough evidence about the cost effectiveness for the treatment with ICD in combination with antiarrhythmic agents compared to antiarrhythmic agents alone.

This recent review (19) focussed on primary and secondary prevention of SCD, while this systematic review only focus on primary prevention. There is no doubt about the cost and clinical effectiveness of secondary prevention ((22). This systematic review will provide a overview of all published studies that have estimated the cost-effectiveness of ICD in primary prevention of SCD. The main question of this review is to what extent is it cost effective, in terms of incremental cost per quality adjusted life year (QALY) and / or life year gained (LYG), to prevent SCD with ICD compared to optimal medical treatment in patients with arrhythmia, before a cardiac arrest happen?

Method

A systematic literature search was performed to identify all publications (until 25 March 2014) of economic evaluations assessing the cost-effectiveness of ICD compared with the optimal medical treatment in patients with an EF lower than 35% or a NYHA-classification of II-III. Patients with a genetic disorder were excluded. A set of in- and exclusion criteria, presented in Table 1, were used to select the relevant studies evaluating the cost-effectiveness of ICD. Cost efficiency analyses (CEA) and cost utility analyses (CUA) focussing on primary prevention of SCD were both included. All types of ICDs were included in the systematic review since all ICDs have the same biological mechanism (ECRI Institute 2012). The effectiveness of the studies had to be expressed in quality adjusted life years (QALY) or in life years gained (LYGs), a disease specific outcome. So, only CEAs and CUA's are included. Furthermore, publications needed to be published in the English or Dutch.

Table 1: In- and exclusion criteria

	Inclusion criteria	Exclusion Criteria
Patient	EF lower than 35% or a NYHA-classification of II-III	Patients with genetic disorders of the heart
Intervention	All types of ICD: ventricular chamber, dual chamber and biventricular defibrillator	
Comparator	Optimal Medical Treatment	
Outcome	Life Years Gained (LYG) or Quality Adjusted Life Years compared to costs (QALY)	
Study desing	Cost Efficiency Analyses (CEA) and Cost Utility Analyses (CUA)	
Language	English and Dutch	

EF=Ejection Fraction; ICD=Implantable Cardioverter-Defibrillator; NYHA=New York Heart Association

These criteria were translated into search strategies for different databases. The following databases are used to find relevant cost-effectiveness studies: PubMed (MEDLINE), Centre for Reviews and Dissemination (CRD) with Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) included and EMBASE. The validated CRD search strategy for selecting economic evaluations was used to find cost-effectiveness and cost-utility studies (23) which is appropriate to MEDLINE OVID. Yet, as this strategy is also made available by Neyt and Chalon (24) for MEDLINE PubMed, the strategy is used in this study. This search strategy to find economic evaluations was combined with ICD, SCD and arrhythmias specific search terms: heart arrhythmia, implantable cardioverter defibrillator (EMTREE), arrhythmias, cardiac defibrillators, implantable (MeSH), arrhyth*, fibrillation*, tachycardia, flutter*, defib*, defibrillator, defibrillation, cardioversion, cardioverter, implant*, internal, sudden cardiac

death, heart arrest and cardiac arrest. The full search strategy and the number of records are presented in Appendix.

The selection of the records was performed by a pair of reviewers (MS & CB). First, duplications were removed. Second, the remaining records were screened on title and abstract. Third, full text reading was performed of the records that were potentially relevant after title abstract selection. Full text evaluation was performed by one reviewer (MS) and discrepancies were discussed and resolved by consensus (CB and LB). The reviewers compared their argumentation for in- or exclusion of the publication. The recommendation of the strongest arguments was followed.

After including the relevant studies, based on the in- and exclusion criteria, data was retrieved from the included studies. First of all, data about the general study characteristics (e.g. year, country and population) is extracted. Second, we did the same for specific study characteristic of economic evaluations (e.g. time horizon, perspective and price). After that, we repeated this process for key input parameters, outcomes (LYGs and QALYS) and sensitivity analyses.

The included studies are also evaluated on the overall quality of the study. The checklist of Drummond en Jefferson is used to assess the quality of the studies (25). This checklist is developed to evaluate health related economic evaluations. All aspects of an economic evaluation is included in this checklist (Table 2).

Table 2

Checklist Drummond et al.
Q1. Was a well- defined question posed in an answerable form?
Q2. Was a comprehensive description of the competing alternatives given?
Q3. Was the effectiveness of the programme or services established?
Q4. Were all the important and relevant costs and consequences for each alternative identified?
Q5. Were costs and consequences measured accurately in appropriate physical units?
Q6. Were the cost and consequences valued credibly?
Q7. Were costs and consequences adjusted for differential timing?
Q8. Was an incremental analysis of costs and consequences of alternatives performed?
Q9. Was allowance made for uncertainty in the estimates of costs and consequences?
Q10. Did the presentation and discussion of study results include all issues of concern to users?

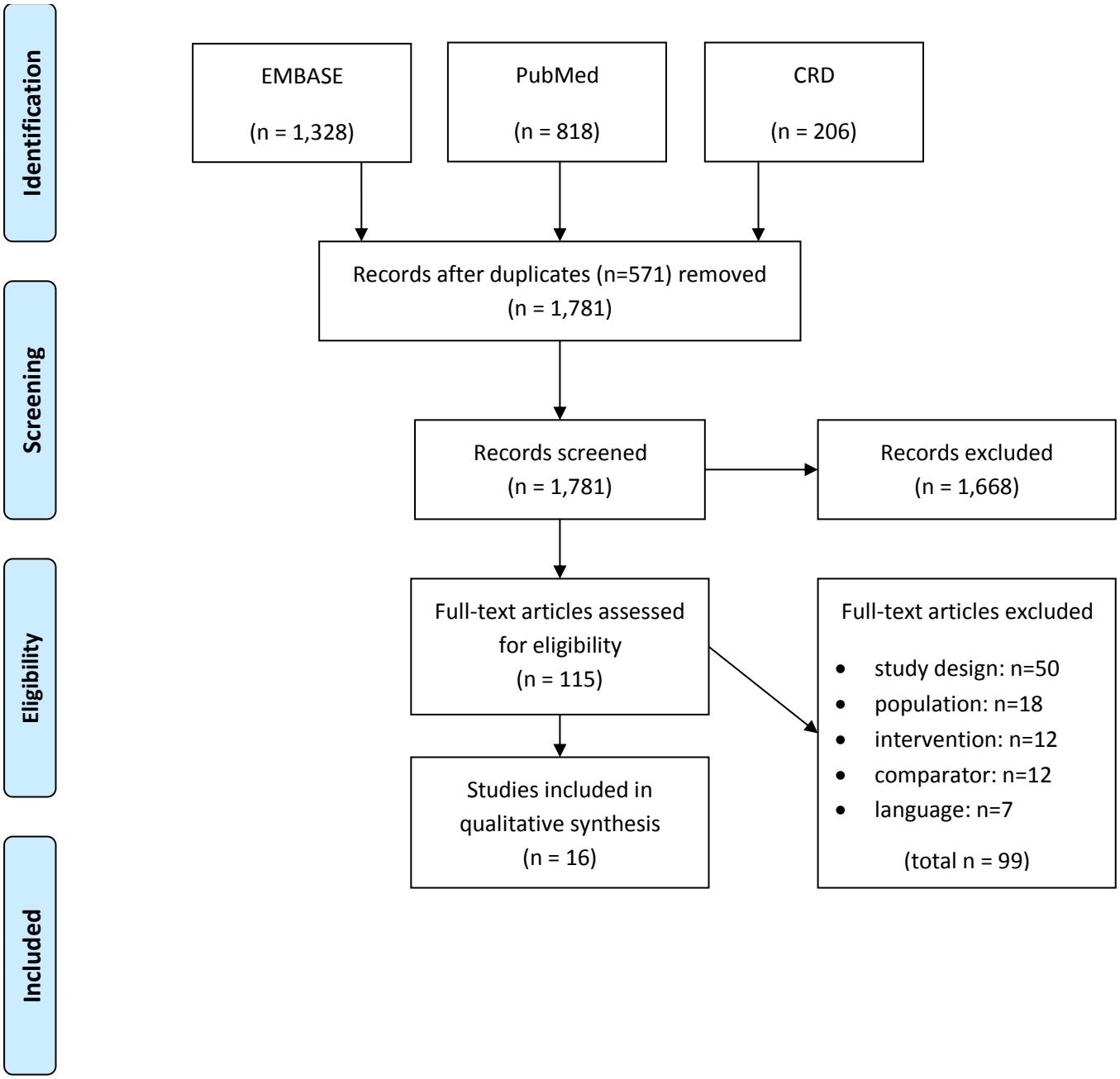
Q=Question

Results

The result section is divided in several parts. First, the results of the search strategy are showed. Second, the general and specific study characteristics are presented and compared. It is important to know what type of economic evaluations are included. Each study did select specific patient profiles, interventions and methods (general characteristics). The specific characteristics are strongly related to economic evaluations (e.g. perspective, time horizon and discount rate). Third, the key parameters are presented, which underlie the results of the models. The presented outcomes are the incremental costs per QALY / LYG gained. Fourth, the quality of the sensitivity analysis and of the evaluation in general are assessed for each included study.

The selection procedure started with 2,352 articles and ended with 16 relevant publications about cost-effectiveness of ICD (26-41). After removing 571 duplicates, 1,668 records were excluded based on title and abstract. Full text evaluation was performed on 115 publications, leading to 16 publications that met inclusion criteria (Figure 1).

PRISMA Flow Diagram



All included studies compared ICD strategy with conventional medical treatment. The cost effectiveness analyses (CEAs) and cost utility analyses (CUAs) are almost always based on clinical trials (CABG-Patch, DINAMIT, MADIT (I&II), DEFINITE, CAT, AMIOVIRT, MUSTT, COMPANION and SCD-HeFT), except for 2 studies (27,37). The studies are performed in different parts of the world (USA, Europe and Brazil). Most of the studies did report incremental costs related to LYGs or QALYs or both. Three studies reported only incremental costs related to LYGs (26,32,41) and two publications did only report incremental costs compared to QALYs (27,40) (Table 3).

Table 3: PICO

Authors	Country	Type	Methods	Population	Comparator
Mushlin et al. (1998)	USA	CEA	Based on model (MADIT)	NSVT, prior MI, EF <35% and inducible VT	Conventional medical therapy
Sanders et al. (2001)	USA	CEA CUA	Based on Markov Model (databases)	Past MI, NSVT	No treatment Amiodarone
Chen L & Hay J. (2004)	USA	CUA	Based on Decision Model (literature, databases and clinical experts)	NYHA functional class II or III	Standard drug therapy
Sanders et al. (2004)	USA	CEA CUA	Based on Markov Model (MADIT II)	MI and EF ≤ 30%.	Conventional drug treatment
Sanders et al. (2005)	USA	CEA CUA	Based on Markov Model (multiple trials)	CABG-Patch, DINAMIT, MADIT (I&II), DEFINITE, MUSTT, COMPANION and SCD-HeFT patient population	Control therapy
Al-Khatib et al. (2005)	USA	CEA	Based on Decision Model (MADIT II)	MI and EF ≤ 30%.	Conventional drug therapy
Feldman et al. (2005)	USA	CEA CUA	Bases on model (COMPANION)	EF ≤ 35%, QRS duration of ≥ 120 ms., a PR interval of > 150 ms.	Optimal pharmacological therapy
Zwanziger et al. (2006)	USA	CEA	Based on model (MADIT II)	MI and EF ≤ 30%.	Conventional medical therapy
Mark et al. (2006)	USA	CEA CUA	Based on model (SCD-HeFT)	NYHA II-III and EF ≤ 35%	Amiodarone
Neyt et al. (2008)	Belgium	CEA CUA	Based on Markov Model (SCD-HeFT)	NYHA II-III and EF ≤ 35%	Conventional drug therapy
Cowie et al. (2009)	Belgium	CEA CUA	Based on Markov Model (trials)	AMIOVRIT, CAT, DEFINITE, MADIT I-II and SCD-HeFT Profile	Conventional medical therapy
Ribeiro et al. (2010)	Brazil	CEA CUA	Based on Markov Model (trials)	CHF, EF <35%, NYHA II-III, 60 years old	Conventional drug therapy
Ribeiro et al. (2010)	Brazil	CEA CUA	Based on Markov Model (trails)	CHF, EF <35%, NYHA II-III, 60 years old	Conventional drug therapy
Sanders et al. (2010)	USA	CEA CUA	Based on Markov Model (trials)	MADIT I-II, MUSTT, DEFINITE and SCD-HeFT Profile	Conventional drug therapy
Gandjour et al. (2011)	Germany	CEA CUA	Based on Markov Model (MADIT II)	MI and EF ≤ 30%.	Conventional drug therapy

Smith et al. (2013)	The Netherlands	CUA	Based on Markov Model (trials)	Patients with EF <40 and heart disease, without previous arrhythmias (MADIT I-II, SCD-HeFT, CAT, AMIOVIRT and DEFINITE)	No ICD strategy

AMIOVIRT=Amiodarone versus Implantable Defibrillator; CABG-Patch=Coronary Artery Bypass Graft (CABG) Patch Trial; CAT= Cardiomyopathy Trial; CEA=Cost Efficiency Analyses; CHF=Chronic Heart Failure; COMPANION= Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure Trial; CUA=Cost Utility Analyses; DEFINITE=The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation Trial; DINAMIT= The Defibrillator in Acute Myocardial Infarction Trial; EF=Ejection Fraction; ICD=Implantable Cardioverter-Defibrillator; MADIT=Multicenter Automatic Defibrillator Implantation Trial; MI=Myocardial Infarction; MUSTT= The multicenter unsustained tachycardia trial; NSVT=Non-Sustained Ventricular Tachycardia; NYHA=New York Heart Association; PICO=Population Intervention Comparison Outcome; PR/QRS=graphical points on a electrocardiogram; SCD-HeFT=Sudden Cardiac Death in Heart Failure Trial; VT= Ventricular Tachycardia

Most studies stated the perspective that they have adopted in the economic analyses. However, the meaning of the perspective 'societal', varied between the authors. Most of these studies only include direct medical costs, while some also include indirect medical cost and non-medical cost (36,37). The time horizon of the analyses differs from 3.5 (41) years to lifetime (26-28,30,31,33,36-40). The discount rate is 3% for the USA and Brazilian studies, whereas Belgium and Dutch studies used to the split discount rate for costs and effects (3% and 1,5%) except for Gandjour et al. (30) (Table 4).

Table 4: Study characteristics

Authors	Perspective (author)	Time Horizon	Discount Rate	Price, year
Mushlin et al. (1998)	NS	4 years	3%	Dollars, 1995
Sanders et al. (2001)	Societal	Lifetime	3%	Dollars, 1999
Chen L & Hay J. (2004)	Societal	Lifetime	3%	Dollars, 2002
Sanders et al. (2004)	Societal	Lifetime	3%	Dollars, 2002
Sanders et al. (2005)	Societal	Lifetime	3%	Dollars, 2005
Al-Khatib et al. (2005)	Societal	Lifetime	3%	Dollars, 2002
Feldman et al. (2005)	Health Care Payer	7 years	3%	Dollars, 2004
Zwanziger et al. (2006)	Societal	3.5 years	3%	Dollars, 2001
Mark et al. (2006)	Societal, no nonmedical costs	Lifetime	3%	Dollars, 2003
Neyt et al. (2008)	Health insurance	Lifetime	3% cost, 1.5% effect	Euro, 2005
Cowie et al. (2009)	Health care perspective	Lifetime	3% cost, 1.5% effect	Euro, 2006
Ribeiro et al. (2010)	Provider and payer	20 years	3%	Brazilian real, 2007
Ribeiro et al. (2010)	Provider	20-years	3%	Dollars, 2007
Sanders et al. (2010)	Societal	Lifetime	3%	Dollars, 2009
Gandjour et al. (2011)	Health care payer	Lifetime	3%	Euro, 2009
Smith et al. (2013)	Societal	Lifetime	4% cost, 1.5% effect	Euro, 2010

NS=Not Stated

The hazard ratio in the included studies, which showed the difference between the hazard rates of ICD implantation and standard medical treatment (clinical effectiveness), varies between 0.64 (32) and 0.86 (39). A HR below 1 means that the ICD strategy reduces the mortality rate compared to standard medical treatment. Not all the studies included the same key input parameters, or they did not show them, so it is difficult to compare. The implantation costs of the ICD with the device itself fluctuates from $22,447 (34) to $44,565 (32) and from €17,152 (30) to €30,623 (40). However, Mushlin et al. (32) is the oldest study included. That could be an explanation for the high costs. During the past years the cost of ICD is reduced trough technological improvements (19). Replacement costs varies from $12,749 (27) to $22,578 (39) and from €14,201 (30) to €32,664 (33). Neyt et al. (33) is aware of the high costs and blame it on the low number of cases on which the value is based (Table 5).

Table 5: key input parameters

	Effectiveness		Costs					
Authors	**Hazard ratio / % mortality reduction**	**Sources effectiveness**	**Costs ICD implantation**	**Costs replacement**	**Costs Follow-up**	**Costs comparator**	**Costs Follow-up**	**Sources Costs**
Mushlin et al. (1998)	0.46/ 54%	(42)	$44,565 (incl. ICD: $19,790) 30-day interval	-	$1,384/ month	$18,880 30-day interval	$1,915/ month	MADIT
Sanders et al. (2001)	60%	MITI Registry	$44.200 (incl. ICD: $25,000)	$12,800	$13.300 (3 years)	$19.200	$13.300 (3 years)	MITI Registry
Chen L & Hay J. (2004)	12% (of CHF)	(43,44)	$37,363 (incl. ICD)	$12,749	-	-	-	DRGs
Sanders et al. (2004)	0.69/ 31%	MADIT II	ICD alone: $25,000	$21,742	-	$23,314	-	DRGs, MITI Registry
Sanders et al. (2005)	-		$27,975	$18,390	-	-	-	DRG's
Al-Khatib et al. (2005)	0.69/ 31%	MADIT II	$42,416 (incl. ICD: $19,185)	$17,493	-	-	-	DRG's
Feldman et al. (2005)	0.64	COMPANION	$29,500	$20,461	-	-	-	DRG's
Zwanziger et al. (2006)	0.667	MADIT II	$32,578 (incl. ICD: $22,284)	-	$1,489/month	-	$1,357/month	Medicare, (32)
Mark et al. (2006)	0.77	SCD-HeFT	-	-	-	-	-	SCD-HeFT, hospital's Medicare Report, Medicare Fee Schedule, 2003 Red Book
Neyt et al. (2008)	0.77	SCD-HeFT	€27,116	€32,664	€8,351 (1st year)	-	€7,413/year + €4.89/month	Belgian ICD registry
Cowie et al. (2009)	0.77	SCD-HeFT	€23,072 (incl. ICD: €18,422)	€18,086 (incl. ICD: €16,650)	€264/month	-	-	RIZIV/INAMI, advisory board
Ribeiro et al. (2010)	26% decrease RR	(45)	R$30,460 (public) R$41,428 (private)	R$29,408 (public) R$39,997 (private)	R$3,182/year (public) R$7,174/year (private)	-	-	Hospital Admission Authorization, SUS, mean values of 17 hospitals.
Ribeiro et al. (2010)	0.75 RR	(45)	$22,447	$21,671	$2,335/year	-	-	Public Healthcare System Brazil (1PPP US$ = 1.357 R$)

Sanders et al. (2010)	0.38-0.86	Trials	$31,990	$22,578	$580/month	-	-	MITI Registry, 2009 Medicare Inpatient Prospective Hospital Payment system, DRGs
Gandjour et al. (2011)	0.71	MADIT II	€17,152	€14,201	€9,799/year	-	-	Hospital Remuneration System (DRGs)
Smith et al. (2013)	0.72	(46)	€30,623	€25,776	€1,224/year		€720/year	Erasmus MC ICD Registry, Microcost analysis, (47)

COMPANION= Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure Trial; DRG=Diagnosis-Related Group; ICD=Implantable Cardioverter-Defibrillator; MADIT=Multicenter Automatic Defibrillator Implantation Trial; MITI= Myocardial Infarction Triage and Intervention; PPP= Purchasing Power Parity; RR= Relative Risk; RIZIV/INAMI= Rijksinstituut voor Ziekte- en Invaliditeitsverzekering /l'institut national d'assurance maladie invalidité; SCD-HeFT=Sudden Cardiac Death in Heart Failure Trial

The studies have presented the effectiveness in LYGs and QALYs. These outcomes are compared with the incremental costs through incremental cost effectiveness ratios (ICERs). These ICERs show the incremental costs per LY or QALY gained. Although these outcomes can be compared, the input parameters and populations included are not the same. The incremental costs per LYG diverges from $24,500 (38) to $235,000 (41) and from €24,751 (28) to €59,989 (33). The incremental costs per QALY gained diverges from $34,000 (38) to $557,900 (37) and from €29,530 (28) to €71,428 (33). The authors conclusion about the cost effectiveness of ICD compared to conventional medical treatment is ambiguous. Seven authors considered the ICD-strategy cost effective, compared to an optimal medical strategy (26,28,29,31,37,38,40). Three authors concluded the same, though only for patients with an high risk profile (32,34,35). Four authors disagreed with this statement and claimed that treatment with ICD is not cost effective related to standard medical treatment (27,30,33,41). Two other authors were not able to underpin a statement (36,39). A couple of studies did subgroup analysis (31,37,41). The factors that caused lower ICERs were: EF≤30, NYHA-classification II and age≥65. However, the included study with a population of older patient (age≥65) does not support the ruling on the last factor (39) (Table 6).

Table 6 Outcomes

Authors	Total Cost	Effectiveness		Incremental Cost-Effectiveness Ratios of ICD vs Comparators		Author's conclusion
		LY	QALY	Cost/LY	Cost/QALY	
Mushlin et al. (1998)	ICD: $97,560 CMT: $75,980	ICD: 3.46 MT: 2.66	N/A	$27,000	N/A	Cost-effective (only high risk patients)
Sanders et al. (2001)	ICD: $123,700 Ami: $86,200	ICD: 7.08 Ami: 6.49	ICD: 6.23 Ami: 5.71	EF≤0.30: $63,300 EF 0.31-0.4: 173.400 EF>0.40: $501,500	EF≤0.30: $71,800 EF 0.31-0.4:195,700 EF>0.40: $557,900	Cost-effective
Chen L & Hay J. (2004)	ICD: $122,947 MT: $25,223	ICD:8.3 MT: 5.0	ICD: 2.9 MT: 1.9	–	$97,863	Not cost-effective
Sanders et al. (2004)	ICD: $166,800 MT: $85,900	ICD: 9.60 MT: 7.01	ICD: 9.96 MT: 5.10	$36,700	$50,900	NS (further research needed)
Sanders et al. (2005)	ICD: $106,100-$184,900 MT: $37,800-$84,400	ICD: 5.88-11.75 MT: 4.01-9.44	ICD: 4.31-8.53 MT: 4.01-6.87	$24,500-$50,700	$34,000-$70,200	Cost-effective
Al-Khatib et al. (2005)	ICD: $131,490 CMT: $40,661	ICD: 10.88 CMT: 8.26	-	$50,500	–	Cost-effective
Feldman et al. (2005)	ICD: $82,236 CMT: $46,021	ICD: 4.15 CMT: 3.37	ICD: 3.15 CMT: 2,30	$46,700	$43,000	Cost-effective
Zwanziger et al. (2006)	ICD: $84,100 MT: $44,900	ICD: 2.89 MT: 2.72	–	$235,000	–	Not cost-effective (short term)
Mark et al. (2006)	ICD: $61,938 Ami: $49,338	ICD: 10.87 Ami: 8.41	–	$38,389	$41,520	Cost-effective
Neyt et al. (2008)	ICD: €27,116	ICD: 1.22 (increment)	ICD: 1.03 (increment)	€59,989	€71,428	Not cost-effective
Cowie et al. (2009)	ICD: €64,600 MT: €18,187	ICD: 8.58 MT: 6.71	ICD: 7.27 MT: 5.70	€24,751	€29,530	Cost-effective
Ribeiro et al. (2010)	ICD: R$96,131-R$84,824 MT:R$33,408-R$101,330	ICD: 6.99 MT: 5.95	ICD: 6.15 MT: 5.23	R$60,121 (public) R$80,029 (private)	R$68,318 (public) R$90,942 (private)	Cost-effective (only high risk patients)
Ribeiro et al. (2010)	ICD: $70,841 MT: $24,619	ICD: 6.99 MT: 5.95	ICD: 6.15 MT: 5.23	$44,304	$50,345	Cost-effective (only high risk patients)
Sanders et al. (2010)	Cost difference. of ICD vs MT $65,352 to $111,460	65y: ICD: 6.43-10.46 MT: 3.92 -7.86 75y: ICD: 5.66-8.76 MT: 3.61-6.58	65y: ICD: 4.67-7.56 MT: 2.86-5.70 75y: ICD:4.04-6.25 MT: 2.58-4.70	65y: $26,661- $99,666 75y: $28,200-$107,208	65y: $37,031-$138,458 75y: $39,564-$150,421	NS (further research needed)
Gandjour et al. (2011)	ICD: €101,860 MT: €56,280	ICD: 8.5 MT: 6.7	ICD: 5.3 MT: 4.3	€33,105	€44,736	Not cost-effective
Smith et al. (2013)	ICD: €86,759 No ICD: €50,685	-	ICD: 7.8 No ICD: 6.26	-	€43,993	Cost-effective

CMT=Conventional Medical Treatment; EF=Ejection Fraction; ICD=Implantable Cardioverter-Defibrillator; LYG=Life Year Gained; MT=Medical Treatment; NS=Not Stated; QALY=Quality Adjusted Life Year

All the included studies performed a type of sensitivity analysis to test the impact of the key input parameters on the ICERs. There are differences between the types of sensitivity analyses that are performed and the amount of key input parameters included in the analyses. Almost all CEAs en CUAs included the key parameters used for the costs (e.g. implantation costs, replacement costs and follow-up costs), clinical effectiveness (HR) and utility (quality of life) except for Mushlin et al (32), Zwanziger et al. (41) and Sanders et al. (39) (Table 7). Replacement of the ICD is an important factor related to high costs. The costs of the replacement is in all studies included in the sensitivity analyses. However the period between the initial implantation and the replacement can also cause a whole different ICER. 11 of the 16 studies included this factor into the sensitivity analysis (26,28-32,36,38-41). Sanders et al. (37), Chen & Hay (27), Neyt et al (33) and both studies of Ribeiro et al. (34,35) did not investigate the influence of ICD replacement on the ratios.

Table 7

Authors	Type	Patient characteristics	Time horizon	Discount rate	Type of ICD technology	Replacement ICD*	Cost**	Clinical effectiveness***	Utilities^	Subgroups	Crossovers^^
Mushlin et al. (1998)	NS	-	+	-	+	+	+	-	-	+	+
Sanders et al. (2001)	Probabilistic	+	-	+	-	-	+	+	+	-	-
Chen L & Hay J. (2004)	Multivariate	-	-	+	-	-	+	+	+	-	-
Sanders et al. (2004)	One-way	+	-	+	-	+	+	+	+	-	-
Sanders et al. (2005)	NS	-	+	-	-	+	+	+	+	-	
Al-Khatib et al. (2005)	One-way	-	+	-	-	+	+	+	+	-	-
Feldman et al. (2005)	Probabilistic Univariate	-		+	-	+	+	+	+	-	-
Zwanziger et al. (2006)	NS	-	-	-	-	+	+	-	-	+	-
Mark et al. (2006)	NS	-	+	+	-	+	+	+	-	+	-
Neyt et al. (2008)	Probabilistic Univariate Scenario	-	-	+	-	-	+	+	+	-	-
Cowie et al. (2009)	Probabilistic Univariate Multivariate Scenario	-	-	+	-	+	+	+	+	-	-
Ribeiro et al. (2010)	Multivariate	-	-	+	+	-	+	+	+	-	-

Ribeiro et al. (2010)	Probabilistic Univariate Multivariate	-	-	+	+	-	+	+	+	-	-
Sanders et al. (2010)	NS	-	-	+	-	+	+	-	+	-	-
Gandjour et al. (2011)	Probabilistic Univariate Multivariate	-	-	-	-	+	+	+	+	-	-
Smith et al. (2013)	Probabilistic Univariate Multivariate	-	-	-	-	+	+	+	+	-	-

* Period between implantation and replacement
** Costs of ICD implantation and optimal medical treatment
*** Hazard ratio, mortality rate
^ Quality of life
^^ Crossovers between optimal medical treatment group and ICD implanatation

The quality of the included studies is assessed by answering the 10 questions of the Drummond checklist (25). All of the included CEAs and CUAs did score 7 out of 10 or higher. The weakest points of the studies are the descriptions of the intervention and the comparators, the presentation of the costs and input parameters and the critical view on their own method. The study of Sanders et al (38), Feldman et al (29), Mark et al. (31) and Ribeiro et al. (34) scored 10 out of 10. Smith et al. (40) was the study with the 'lowest' quality (7 positive answers out of 10) (Table 8).

Table 8

Cecklist Drummond et al.	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Mushlin et al. (1998)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Sanders et al. (2001)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Chen & Hay (2004)	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Sanders et al. (2004)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Sanders et al. (2005)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Khatib et al. (2005)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Feldman et al. (2005)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zwanziger et al. (2006)	Yes	No	Yes	No	yes	yes	Yes	Yes	Yes	yes
Mark et al. (2006)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Neyt et al. (2008)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Cowie et al. (2009)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Ribeiro (2010) public/private	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ribeiro (2010) public	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Sanders et al. (2010)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Grandjour et al. (2011)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Smith et al. (2013)	Yes	No	No	Yes	no	Yes	Yes	Yes	Yes	Yes

Discussion

In the past years, a couple of systematic reviews are published about the cost-effectiveness of ICD(19-21). The most recent review focused on primary and secondary prevention of SCD (19). However the conclusions about primary prevention do not differ from the conclusion of this systematic review.

It is difficult to make a clear statement about the cost-effectiveness of the ICD. The ICERs of LYs and QALYs are spread in a wide range. There are a couple of reasons to explain this wide range of outcomes. First, the economic evaluations are conducted in different countries with different costs and health systems. So, different unit costs and differences in resources utilized can be an important factor to the wide spread ICERs. The ICD in older studies is more expensive and caused a also an increased ICER (32). So, ICD is difficult to compare than medication, because the ICD is subject to technological and price changes. Second, the threshold for incremental costs per QALY gained for medical interventions is not the same in the countries were the studies took place. In the USA the threshold is estimated at $50,000-$100,000, in the United Kingdom at £20,000-30,000 and in The Netherlands at €20,000(48,49).This threshold is not objectively determined, because that is not possible. Third, the studies methods are not fully comparable. The ICD intervention is comparable in all the included studies. However, the included population, the comparator, valuta and the design of the study are not the same (e.g. time horizon, discount rate, based on a databases or an RCT). It is important to be aware of these differences, therefore we tried to display these differences as clear as possible (in tables).

Another important factor is that the cost-effectiveness is varying within the population. The ICD strategy is in some studies more cost effective in subgroups with high risks of SCD. Therefore, stratification of subgroups is an important method to clarify the differences between patients characteristics. Some studies tried to explain the variances in the included population, but they always stated that further research is needed to draw a clear conclusion.

Strengths and limitations

There are several limitations of this study. First, the quality of the included studies is explored. The overall conclusion about the quality is very positive. All the studies seem to have a good quality. However, the Drummond checklist is more focused on transparency than on quality (25). This checklist is used because this list is developed using the guidelines for submission of CEAs and CUAs. Second, the search strategy did not include two studies which were very important to include in the systematic review, because the search terms

were not corresponding with the title and abstract of the articles. These two publications were included trough ‘snowballing’ (searching in reference list of references). This systematic review also has strengths. The method of this study is strong. The search strategy is validated and applied to multiple databases and the results are assessed trough double scoring.

Recommendations

Given the conclusions of this systematic reviews and the included economic evaluations. It is needed to perform a cost-utility analysis or/and a cost-effectiveness analysis about primary prevention of SCD in patients with prior MI and arrhythmia. This analyse has to focus on different populations with the related different risks. At the moment, we cannot draw a clear conclusion about the whole population, because the differences within the populations are too large. Therefor it is needed to gather data about costs and clinical effectiveness of patients with different risk profiles.

For a new systematic review about the cost efficiency of ICD versus conventional medical treatment, first, it is needed to improve the search strategy to avoid ‘snowballing’. Second, next to the Drummond checklist, it is possible to assess the included studies on more content related items.

Conclusion

The main question of this review is to what extent is it cost effective, in terms of incremental cost per Quality Adjusted Life Year (QALY) gained and / or Life Year Gained (LYG), to prevent a SCD with ICD compared to optimal medical treatment in patients with arrhythmia, before a cardiac arrest happen? The answer to this important question is not very simple. Some studies conclude that ICD is cost effective compared to conventional medical treatment. However, the outcomes of other analysis concluded the opposite. These differences are caused by different patient profiles and different costs and clinical effectiveness values. The factors that caused lower ICERs were: lower device costs, EF≤30, NYHA-classification II and age≥65. But the evidence of these factors are still not convincing and unequivocal. It is needed to split the patient population into homogeneous subgroups to draw a clear conclusion about the cost effectiveness of implantable cardioverter-defibrillators.

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Appendix

EMBASE		
#1	'economics'/de OR 'cost'/exp OR 'health economics'/de OR 'pharmacoeconomics'/de OR economic:ab,ti OR cost:ab,ti OR costs:ab,ti OR costly:ab,ti OR costing:ab,ti OR price:ab,ti OR prices:ab,ti OR pricing:ab,ti OR pharmacoeconomic:ab,ti OR (expenditure*:ab,ti NOT energy:ab,ti) OR 'value for money':ab,ti OR budget*:ab,ti	839,020
#2	((energy OR oxygen) NEAR/3 cost):ab,ti OR (metabolic NEAR/3 cost):ab,ti OR ((energy OR oxygen) NEAR/3 expenditure):ab,ti	24,319
#3	#1 NOT #2	833,330
#4	'implantable cardioverter defibrillator'/exp OR defib*:ab,ti OR defibrillator:ab,ti OR defibrillation:ab,ti OR cardioversion:ab,ti OR cardioverter:ab,ti OR (internal NEAR/3 defibrillator*):ab,ti OR (internal NEAR/3 defibrillation):ab,ti OR (internal NEAR/3 cardioverter):ab,ti OR (implant* NEAR/3 cardioverter):ab,ti OR implant*:ab,ti OR internal:ab,ti OR (cardiac NEAR/3 defibrillation):ab,ti OR (implant:ab,ti AND defib:ab,ti) OR (internal:ab,ti AND defib:ab,ti) OR (cardiac:ab,ti AND defib:ab,ti)	679,833
#5	'heart arrhythmia'/exp OR arrhyth*:ab,ti OR fibrillation*:ab,ti OR tachycardia:ab,ti OR flutter*:ab,ti	377,724
#6	#4 AND #5	39,230
#7	#3 AND #6	1,371
#8	[letter]/lim OR [editorial]/lim	1,310,080
#9	#7 NOT #8	1,328

PUBMED		
#1	("Economics"[Mesh:noexp]) OR ("Costs and Cost Analysis"[Mesh]) OR ("Economics, Dental"[Mesh:noexp]) OR ("Economics, Hospital"[Mesh]) OR ("Economics, Medical"[Mesh:noexp]) OR ("Economics, Nursing"[Mesh]) OR ("Economics, Pharmaceutical"[Mesh]) OR (((((((((economic*[Title/Abstract]) OR cost[Title/Abstract]) OR costs[Title/Abstract]) OR costly[Title/Abstract]) OR costing[Title/Abstract]) OR price[Title/Abstract]) OR prices[Title/Abstract]) OR pricing[Title/Abstract]) OR pharmacoeconomic*[Title]) OR ((expenditure*[Title/Abstract]) NOT energy[Title/Abstract]) OR (value for money[Title/Abstract]) OR (budget*[Title/Abstract])	
#2	((energy expenditure[Title/Abstract]) OR oxygen expenditure[Title/Abstract]) OR (metabolic cost[Title/Abstract]) OR ((energy cost[Title/Abstract]) OR oxygen cost[Title/Abstract])	
#3	#1 NOT #2	582,462
#4	("Defibrillators, Implantable"[Mesh]) OR (implant*[Title/Abstract]) OR (defib*[Title/Abstract]) OR (defibrillator[Title/Abstract]) OR	286,623

	(defibrillation[Title/Abstract]) OR (cardioversion[Title/Abstract]) OR (cardioverter[Title/Abstract]) OR ((internal AND defibrillator*)[Title/Abstract]) OR ((internal AND defibrillation)[Title/Abstract]) OR ((internal AND cardioverter)[Title/Abstract]) OR ((implant* AND cardioverter)[Title/Abstract]) OR ((implant* OR internal)[Title/Abstract]) OR ((cardiac AND defibrillation)[Title/Abstract]) OR ((implant AND defib)[Title/Abstract]) OR ((internal AND defib)[Title/Abstract]) OR ((cardiac AND defib)[Title/Abstract])	
#5	(Arrhythmias, Cardiac"[Mesh]) OR (Arrhyth*[Title/Abstract]) OR (Fibrillation*[Title/Abstract]) OR (Tachycardia[Title/Abstract]) OR (Flutter*[Title/Abstract])	143,867
#6	(#4 AND #5)	17,079
#7	(#3 AND #6)	618
#8	((letter[Publication Type]) OR (editorial[Publication Type]) OR (historical article[Publication Type]))	1,479,537
#9	#7 NOT #8	579
#10	(((sudden cardiac death) or (heart arrest) or (cardiac arrest)))	65,393
#11	#10 and #4	8,485
#12	#11 and #3	469
#13	#12 not #9	276
#14	#13 not #8	239
#15	#9 or # 14	818

CRD		
#1	MeSH DESCRIPTOR Defibrillators, Implantable EXPLODE ALL TREES	186
#2	MeSH DESCRIPTOR Arrhythmias, Cardiac EXPLODE ALL TREES	680
#3	(implantable) OR (cardioverter) OR (defibrillator) IN DARE, NHSEED, HTA	367
#4	(arrhythmia) OR (fibrillation) OR (tachycardia) IN DARE, NHSEED, HTA	997
#5	(cardioversion) OR (defibrillation) IN DARE, NHSEED, HTA	123
#6	(flutter) IN DARE, NHSEED, HTA	65
#7	(#1 OR #3 OR #5) IN DARE, NHSEED, HTA	459
#8	(#2 OR #4 OR #6) IN DARE, NHSEED, HTA	1,091
#9	(#7 AND #8) IN DARE, NHSEED, HTA	206

Included MeSH-terms (PubMed en CRD)

- Arrhythmia, Sinus
    - Sick Sinus Syndrome
    - Sinus Arrest, Cardiac
- Atrial Fibrillation
- Atrial Flutter
- Bradycardia
- Brugada Syndrome
- Cardiac Complexes, Premature
    - Atrial Premature Complexes
    - Ventricular Premature Complexes
- Commotio Cordis
- Heart Block
    - Adams-Stokes Syndrome
    - Atrioventricular Block

    - Bundle-Branch Block
    - Sick Sinus Syndrome
    - Sinoatrial Block
- Long QT Syndrome
    - Andersen Syndrome
    - Jervell-Lange Nielsen Syndrome
    - Romano-Ward Syndrome
- Parasystole
- Pre-Excitation Syndromes
    - Lown-Ganong-Levine Syndrome
    - Pre-Excitation, Mahaim-Type
    - Wolff-Parkinson-White Syndrome
- Tachycardia
    - Tachycardia, Paroxysmal
    - Tachycardia, Reciprocating +
    - Tachycardia, Supraventricular +
    - Tachycardia, Ventricular +
- Ventricular Fibrillation
- Ventricular Flutter

Included Emtree-terms (Embase)

- atrioventricular junction arrhythmia
- bradycardia
- cardiac channelopathy
- cardiopulmonary arrest
- commotio cordis
- experimental arrhythmia
- heart atrium arrhythmia
- heart fibrillation
- heart muscle conduction disturbance
- heart palpitation
- heart preexcitation
- heart proarrhythmia
- heart ventricle arrhythmia
- pacemaker failure
- parasystole

- reentry arrhythmia
- tachycardia