Systematic Review

Implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: an updated systematic review and meta-analysis of outcomes and complications

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Background: Since the introduction of the implantable cardioverter-defibrillator (ICD) in patients with hypertrophic cardiomyopathy (HCM), the incidence of sudden cardiac death (SCD) has been significantly reduced. Given its widespread use, it is important to identify the outcomes associated with ICD use in patients with HCM. The present paper is a systematic review and meta-analysis of the rates of appropriate and inappropriate interventions, mortality, and device complications in HCM patients with an ICD.

Methods: We conducted a systematic review and meta-analysis on 27 studies reporting outcomes and complications after ICD implantation in patients with HCM. ICD interventions, device complications, and mortality were extracted for analysis.

Results: A total of 3,797 patients with HCM and ICD implantation were included (mean age, 44.5 years; 63% male), of which 83% of patients had an ICD for primary prevention of SCD. The cardiac mortality was 0.9% (95% CI: 0.7–1.3) per year and non-cardiac mortality was 0.8% (95% CI: 0.6–1.2) per year. Annualized appropriate intervention rate was 4.8% and annualized inappropriate intervention was 4.9%. The annual incidence of lead malfunction, lead displacement and infection was 1.4%, 1.3%, and 1.1%, respectively.

Conclusions: ICD use in patients with HCM produces low rates of cardiac and non-cardiac mortality, and an appropriate intervention rate of 4.8% per year. However, moderate rates of inappropriate intervention and device complications warrant careful patient selection in order to optimize the risk to benefit ratio in this select group of patients.

Keywords: Implantable cardioverter-defibrillator (ICD); hypertrophic cardiomyopathy (HCM); meta-analysis

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Introduction

Hypertrophic cardiomyopathy (HCM) is a cardiac disorder with an incidence of 1 in 200 and is associated with heart failure, embolism and sudden cardiac death (SCD) (1). The incidence of sudden death in HCM is low, around 0.7–1% per annum, and often young patients are affected (2). The use of implantable cardioverter-defibrillator (ICD) protects against SCD secondary to ventricular tachycardia (VT), ventricular fibrillation (VF), or bradycardia, with excellent results (3-8). A major concern with ICD therapy is the delivery of inappropriate shocks, namely in response to supraventricular tachycardia and atrial fibrillation. Furthermore, device complications including infection, lead malfunction, and lead displacements pose additional hazards, particularly in a predominantly young patient cohort who require ICD therapy for life (4,5,7,9,10).

Prior observational studies have reported on the use of ICD therapy, including a meta-analysis which demonstrated

rates of appropriate ICD interventions of 3.3% per year and inappropriate ICD interventions of 4.8% per year (6). However, a number of studies have been published since. Therefore, the goal of the present paper was to perform an updated systematic review and meta-analysis of pooled individual studies to determine the current rate of appropriate and inappropriate shocks, cardiac and non-cardiac mortality, and device complications.

Methods

Literature search strategy

The present systematic review and meta-analysis was performed in accordance to PRISMA and recommended guidelines (11,12). Electronic searches were performed using Ovid Medline, PubMed, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club, and Database of Abstracts of Review of Effectiveness (DARE) from their dates of inception to March 2017. To achieve the maximum sensitivity of the search strategy, we combined the terms: "hypertrophic" and "defibrillator" as either key words or MeSH terms. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies, and assessed using the inclusion and exclusion criteria.

Selection criteria

Eligible studies for the present systematic review and meta-analysis included those in which patient cohorts underwent defibrillator therapy for HCM. Studies that did not include appropriate or inappropriate shocks, mortality, or complications as endpoints were excluded. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for quantitative assessment at each time interval. All publications were limited to those involving human subjects and in the English language. Abstracts, case reports, conference presentations, editorials, reviews and expert opinions were excluded.

Data extraction and critical appraisal

All data were extracted from article texts, tables and figures. Two investigators independently reviewed each retrieved article (Nelson Wang, Ashleigh Xie). Discrepancies between the two reviewers were resolved by discussion and consensus. Extracted outcome parameters were as follows: cardiac mortality, non-cardiac mortality, heart transplant, appropriate ICD intervention, inappropriate ICD intervention, and complications, including lead malfunction, infection, lead displacement, psychological complication, and total complications.

Statistical analysis

A meta-analysis of incidence rates was conducted for the available main perioperative and postoperative variables. Annualized incidence rates for appropriate, inappropriate shocks, as well as complications, were determined using the metarate function for total events per person years. Heterogeneity was evaluated using Cochran Q and I^2 test. All analyses were performed using the meta-package for R version 3.3. P values <0.05 were considered statistically significant.

Results

A total of 1,375 articles were identified using the search strategy and 27 were included (5,7-10) that met our pre-specified search strategy, giving a total of 3,797 patients with HCM and ICD (13-34) (*Figure 1*). The mean follow-up of the studies ranged from 1.5 to 6.3 years. Amongst the 3,797 HCM patients with ICD (mean age, 44.5 years; 63% male), 804 (21%) patients had obstructive HCM. The majority of the patients were given an ICD for primary prevention (83%) compared to secondary prevention (17%). Three of the studies used a subcutaneous ICD (18,22,34). Left ventricular (LV) thickness ≥30 mm, family history of SCD, non-sustained VT, syncope and abnormal blood pressure response to exercise were present in 10%, 26%, 25%, 7% and 22% of the patients respectively (*Table S1*).

The number of studies and total number of patients reporting each outcome of interest in HCM patients with an ICD are shown in *Table 1*. All-cause mortality occurred at a rate of 1.3% (95% CI: 0.9–1.9) per year, of which cardiac mortality occurred at 0.9% (95% CI: 0.7–1.3) per year and non-cardiac mortality at 0.8% (95% CI: 0.6–1.2) per year. *Figure 2* shows the annual rates of appropriate ICD interventions amongst the included studies. The pooled meta-analysis of appropriate intervention rates was 4.8% (95% CI: 3.9–5.9) per year, with significant heterogeneity

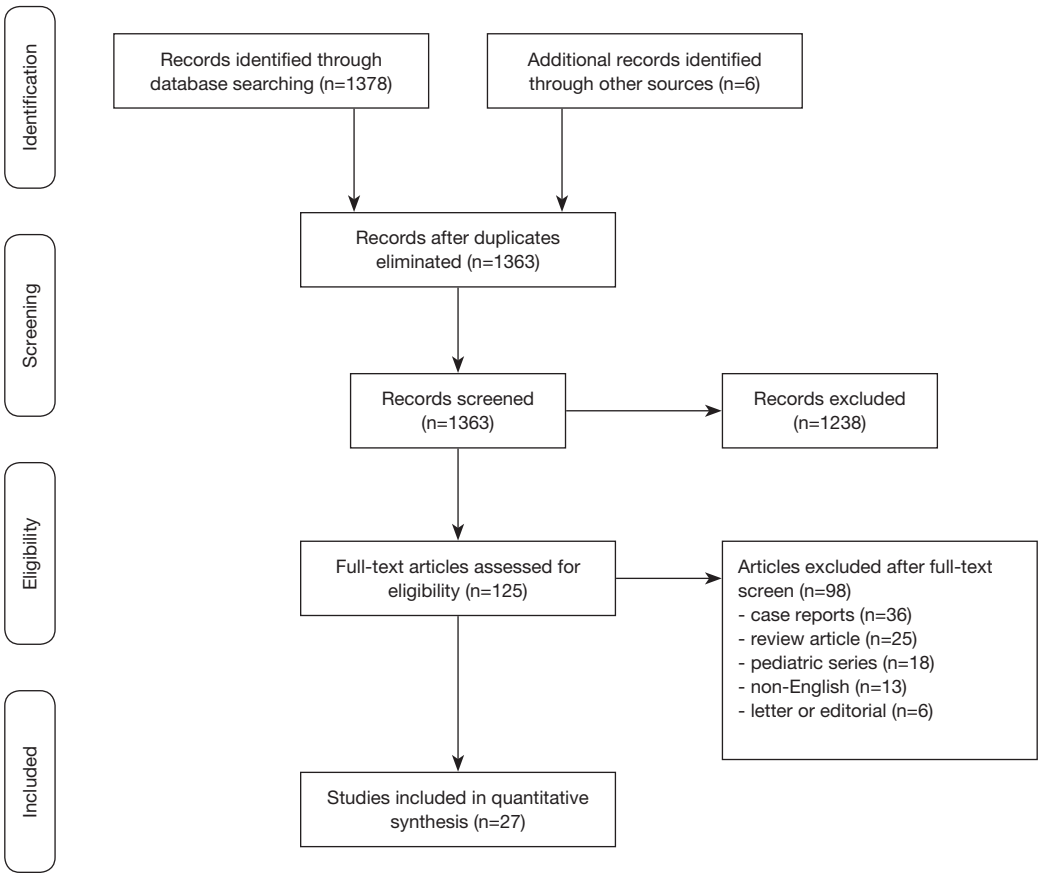

Figure 1 Study selection. Flow chart showing the results in each step of the systematic search to identify studies reporting outcomes for implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy.

between studies (I^2 =84%). Similarly, inappropriate shocks occurred at a rate of 4.9% (95% CI: 3.9–6.0) per year (I^2 =75%) (*Figure 3*). Among six studies (7,8,10,25,29,33), heart transplant was required in 1.6% of patients per year. The annual incidence of lead malfunction and lead displacement was 1.4% (95% CI: 0.8–2.5) and 1.3% (95% CI: 0.8–2.0) respectively. Infection developed in 1.1% (95% CI: 0.7–1.6) of patients per year (*Table 1*).

Discussion

The present meta-analysis shows that rates of appropriate intervention are low, with an annual incidence of 4.8% per annum. Both cardiac and non-cardiac mortality rates are also low in HCM patients with ICD (0.9% per year and 0.8% per year, respectively), highlighting the safety and efficacy of ICDs in HCM.

The spectrum of clinical outcome in HCM is very broad, although most patients have a low annual risk of death, with a mortality rate of 1.3% and risk of sudden death of 0.7% per annum (35). SCD is the most dreaded complication of HCM and occurs in 6% of non-referred HCM patients irrespective of age (35). Risk stratification in HCM is vital in order to assess the need for ICD. Major clinical risk factors for SCD in HCM include prior cardiac arrest, sustained VT, recurrent episodes of unexplained syncope, a first-degree relative with SCD, LV hypertrophy (>30 mm wall thickness), an abnormal systolic blood pressure response during exercise, and non-sustained VT on ambulatory ECG monitoring (36). Although the introduction of ICD has successfully reduced rates of SCD in HCM (37), concerns about high rates of inappropriate shocks exist, and in our study, the annual incidence of inappropriate intervention was 4.9%.

The historic mortality rate of greater than 5% per year for HCM has diminished with the advances in modern

Table 1 Summary of clinical outcomes of studies in the present systematic review

Factors	Year	Cardiac mortality	Non-cardiac mortality	All-cause mortality	Heart transplant	Appropriate ICD intervention	Inappropriate ICD intervention	Lead malfunction	Infection	Lead displacement
First author										
Primo	1998	0	0	0	NA	15.4%	23.1%	0	0	7.7%
Almquist	2005	2.7%	0	2.7%	NA	6.7%	NA	2.7%	NA	2.7%
Lawrenz	2005	0	20.0%	20.0%	NA	26.7%	20.0%	NA	NA	NA
Maron	2007	4.0%	3.8%	NA	NA	20.4%	26.9%	NA	3.8%	NA
Woo	2007	1.6%	0	1.6%	1.6%	31.1%	32.8%	NA	NA	NA
Cuoco	2008	NA	NA	NA	NA	7.3%	NA	NA	NA	NA
Hauser	2008	1.2%	1.5%	2.8%	NA	11.4%	12.3%	4.6%	0.3%	1.5%
Lin	2009	3.9%	3.9%	11.0%	NA	16.0%	23.2%	3.3%	4.4%	NA
Syska	2010	3.8%	0	3.8%	1.0%	26.0%	33.7%	12.5%	4.8%	3.8%
O'Mahony	2012	2.7%	1.2%	2.7%	3.3%	8.4%	16.5%	4.8%	4.8%	4.2%
Alsheikh-Ali	2013	NA	NA	NA	NA	21.5%	NA	NA	NA	NA
Gray	2013	NA	NA	NA	NA	12.8%	11.0%	NA	NA	NA
Prinz	2013	NA	NA	NA	NA	57.5%	9.2%	NA	NA	NA
Shiozaki	2013	NA	NA	NA	NA	50.0%	NA	NA	NA	NA
Vriesendorp	2013	8.2%	2.2%	10.4%	6.0%	28.4%	15.7%	20.1%	5.2%	11.9%
Debonnaire	2014	NA	NA	NA	NA	22.8%	20.7%	NA	NA	NA
Frommeyer	2016	NA	NA	NA	NA	5.6%	22.2%	NA	NA	NA
Konstantinou	2016	NA	NA	NA	NA	27.0%	18.9%	NA	NA	NA
Lambiase	2016	0	0	0	NA	3.0%	10.1%	0	2.0%	3.0%
Magnusson	2016	NA	NA	NA	NA	25.9%	NA	NA	NA	NA
Rigopoulos	2016	0	3.1%	3.1%	NA	12.5%	3.1%	3.1%	3.1%	NA
Ruiz-Salas	2016	NA	0	0	0	16.7%	12.5%	NA	2.1%	4.2%
Thavikulwat	2016	0.7%	3.0%	7.4%	NA	14.8%	20.0%	3.0%	NA	3.7%
Viswanathan	2016	0	NA	NA	NA	15.0%	25.0%	NA	NA	NA
Weinstock	2016	NA	NA	NA	NA	0	6.3%	NA	NA	NA
Francia	2017	1.5%	0	1.5%	NA	21.2%	NA	NA	NA	NA
Wang	2017	6.9%	3.8%	NA	3.8%	15.0%	NA	NA	NA	NA
No. of studies reporting outcome	–	16	16	14	6	27	20	10	10	9
Total no. of patients	–	2,299	2,287	1,621	841	3,737	2,460	1,431	1,775	1,266
Annual event rate (95% CI)	–	0.9 (0.7–1.3)	0.8 (0.6–1.2)	1.3 (0.9–1.9)	1.1 (0.7–1.7)	4.8 (3.9–5.9)	4.9 (3.9–6.0)	1.4 (0.8–2.5)	1.3 (0.8–2.0)	1.1 (0.7–1.6)

No., number; ICD, implantable cardioverter defibrillator; NA, data not available; CI, confidence interval.

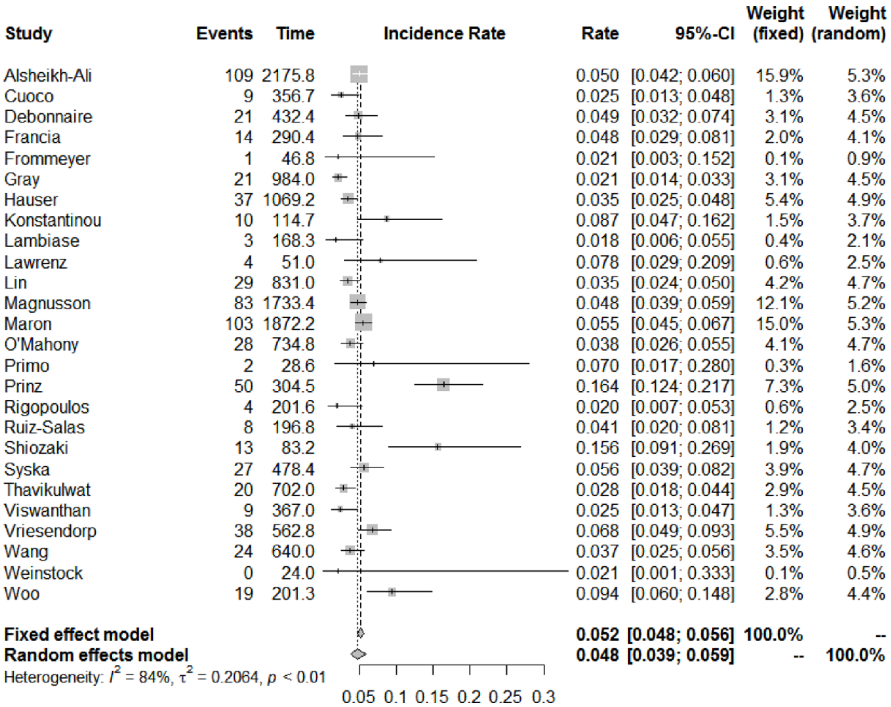

Figure 2 Annual incidence of appropriate ICD interventions. Forest plot for the annual rate of appropriate shocks with implantable cardioverter defibrillator in hypertrophic cardiomyopathy. Rate is expressed as events per year. ICD, implantable cardioverter-defibrillator; CI, confidence interval.

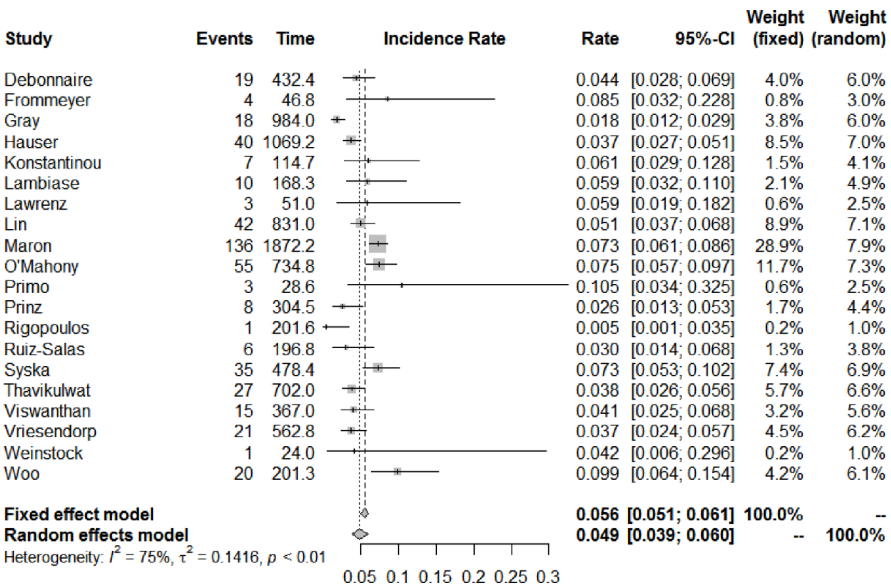

Figure 3 Annual incidence of inappropriate ICD interventions. Forest plot for the annual rate of inappropriate shocks with implantable cardioverter defibrillator in hypertrophic cardiomyopathy. Rate is expressed as events per year. ICD, implantable cardioverter-defibrillator; CI, confidence interval.

medical management (35,37). Primary prevention through ICDs, advanced heart failure strategies, anticoagulation for stroke prophylaxis, and septal myectomy have reduced current mortality rates to about 0.5% per year, similar to that of the general population (35,37). Today, elderly patients with HCM represent around 30% of the HCM population (38,39). These patients have a more benign phenotype, with very low rates of HCM-related deaths (39,40).

The pooled analysis demonstrates that inappropriate ICD intervention is common, consistent with a prior meta-analysis, which showed a similar event rate (4.8%/year). In our study, there was significant heterogeneity in rates of inappropriate shock, likely reflecting the differences in the underlying populations, in particular rates of atrial fibrillation and supraventricular tachycardias. Patients with HCM may be more vulnerable to ICD-related complications and inappropriate ICD therapy because of their young age at implantation and increased prevalence of atrial fibrillation (9).

Reports from large multicentre registries with predominantly patients with ischemic heart disease demonstrated an early complication rate varying from 3.3% to 11% during the hospital admission for ICD implantation (41,42). In the present study, the rates of infection, lead displacement and malfunction were not uncommon, with annual rates of 1.1%, 1.3% and 1.4%, respectively. The recent advent of subcutaneous ICD represented a new alternative to traditional transvenous defibrillators. Subcutaneous ICDs pose a major advantage of less serious complications from lead failure and infection, because removal of subcutaneous ICD is a lower risk procedure compared to the removal of transvenous leads. Furthermore, the absence of a lumen in the subcutaneous leads may theoretically reduce the risk of lead failure (34). However, a subcutaneous ICD provides neither bradycardia pacing nor anti-tachycardia pacing capabilities, which limits the suitability of subcutaneous devices for certain patients who require pacing.

Given the potential complications and moderate rates of inappropriate shocks, it is important to carefully select patients who may gain the most benefit from ICD. Unlike other cardiomyopathies such as ischemic (43) or dilated (44) cardiomyopathy, use of an ICD for primary prevention of SCD in HCM is not based on randomized prospective clinical trials. The recently updated guidelines and quantitative risk estimation model (HCM Risk-SCD) have now included age, left atrial diameter and LV outflow tract gradient into the risk stratification of patients, together with traditional risk factors of family history of SCD, maximal LV wall thickness, unexplained syncope, and non-sustained VT. The evidence for the new guidelines was developed from a multicenter, retrospective, longitudinal cohort study of 3,675 patients with HCM (45). The model predicts that one SCD will be prevented every 5 years if 16 patients with a 5-year risk of SCD that is greater than or equal to 4% are given ICD therapy (45). Validation studies have suggested that the new model is superior to traditional models based on bivariate risk factors (29,46). Future studies into the role of cardiac magnetic resonance imaging may further improve the current risk models.

Limitations

The present paper has several limitations to note. The included studies were all observational and subject to significant heterogeneity, with differing population characteristics and risk profiles. There was also insufficient data to perform subgroup analyses. Secondly, the decision strategy for ICD implantation was not included in most studies. The present data does not provide time to event analyses, and crude annual event rates may not give as accurate a representation of the true incidence. There has been significant progress in the evolution of ICD implantation and the available devices and leads that have been developed. These technological advances may have contributed to some of the heterogeneity in the data. Although our results offer insight on the major clinical endpoints of HCM patients with ICD therapy, there was inadequate data for assessment of the psychological impact of these devices and their influence on quality of life.

Conclusions

Rates of appropriate ICD intervention rates are 4.8% per year, which most likely has reduced the incidence of SCD. Cardiac and non-cardiac mortality rates are low with ICD therapy in patients with HCM. However, inappropriate shocks and lead complications are not uncommon, and therefore HCM patients warrant careful risk stratification in order to accurately individualize the risk and benefits of this device.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Characteristics of included studies of ICD therapy in patients with hypertrophic cardiomyopathy

First author	Year	Sample size (n)	Study period (y)	Country	Institution	FU (years)	Age	Male (%)	Obstructive (%)	ICD for primary prevention of SCD (%)	LV thickness ≥30 mm (%)	Family history of SCD (%)	Non-sustained VT (%)	Syncope (%)	Abnormal BP response (%)
Primo (26)	1998	13	NA	Belgium; Spain	Onze Lieve Vrouw Hospital; University of Barcelona	2.2	48	62	38	15	NA	NA	NA	NA	NA
Almquist (13)	2005	75	1993–2004	USA	Minneapolis Heart Institute	3.6	36	65	20	95	29	NA	NA	NA	NA
Lawrenz (23)	2005	15	1996–2001	Germany	University of Muenster	3.4	53	53	100	40	NA	20	13	20	7
Maron (5)	2007	506	1986–2003	USA, Europe, Australia	HCM ICD II Registry	3.7	42	64	25	76	NA	NA	NA	NA	NA
Woo (10)	2007	61	1996–2003	Canada	Toronto General Hospital	3.3	46	66	0	82	NA	NA	NA	NA	NA
Cuoco (15)	2008	123	NA	USA	Medical University of South Carolina; Baylor College	2.9	48	66	100	100	11	38	NA	63	34
Hauser (20)	2008	324	1992–2007	USA	7 Centers	3.3	47	67	30	91	NA	NA	NA	NA	NA
Lin (9)	2009	181	1988–2005	USA	Mayo Clinic	4.9	44	62	20	86	14	48	35	34	3
Syska (7)	2010	104	1996–2006	Poland	Warsaw Institute of Cardiology	4.6	36	45	46	75	23	81	35	69	NA
O'Mahony (25)	2012	334	1992–2009	UK	St Georges Hospital & Heart Hospital	2.2	40	62	23	92	14	47	44	36	30
Alsheikh-Ali (14)	2013	506	1986–2003	USA, Europe, Australia	Multicenter	4.3	41	64	NA	76	NA	41	NA	43	NA
Gray (19)	2013	164	1997–2011	Australia	Royal Prince Alfred Hospital	6	42	62	NA	91	24	41	36	29	NA
Prinz (27)	2013	87	2000–2011	Germany	Ruhy University	3.5	50	60	63	98	30	30	74	38	20
Shiozaki (30)	2013	26	NA	Brazil	Sao Paulo	3.2	39	46	NA	81	25	48	67	35	15
Vriesendorp (8)	2013	134	1994–2011	Netherlands, Belgium	Thoraxcenter, Erasmus; University Hospital Leuven	4.2	44	66	NA	69	23	47	57	28	NA
Debonnaire (16)	2014	92	NA	Netherlands	Leiden Medical Center	4.7	50	68	18	76	11	51	37	21	NA
Frommeyer (18)	2016	18	2010–2015	Germany	University of Muenster	2.6	35	83	17	78	NA	NA	NA	NA	NA
Konstantinou (21)	2016	37	1999–2012	USA	Minneapolis Heart Institute	3.1	49	76	27	100	38	38	59	38	35
Lambiase (22)	2016	99	2009–2013	USA, New Zealand, Netherlands, UK	EFFORTLESS & IDE	1.7	42	75	NA	88	8	NA	35	15	NA
Magnusson (24)	2016	321	1995–2012	Sweden	Swedish ICD Registry	5.4	52	51	NA	74	18	19	43	26	5
Rigopoulos (28)	2016	32	2009–2012	Germany	Leopoldina Hospital	6.3	50	53	17	97	17	50	54	63	NA
Ruiz-Salas (29)	2016	48	2002-2014	Spain	Hospital Universitario Virgen de la Victoria	4.1	44	67	100	100	22	53	56	50	6
Thavikulwat (31)	2016	135	2000–2013	USA	Bluhm Cardiovascular Institute	5.2	48	63	NA	93	NA	NA	NA	NA	NA
Viswanathan (32)	2016	60	1999–2012	Canada	University Health Network	5.1	44	73	23	NA	13	18	57	33	6
Weinstock (34)	2016	16	2012–2015	USA	Tufts Medical Center	1.5	40	NA	50	81	14	28	29	29	8
Francia (17)	2017	66	2001–2012	Italy	St Andrea Hospital	4.4	45	62	12	98	35	61	68	26	NA
Wang (33)	2017	160	2000–2013	USA	Tufts Medical Center	4	47	61	46	97	7	27	43	25	19

BP, blood pressure; FU, follow-up; ICD, implantable cardioverter-defibrillator; LV, left ventricle; NA, not available; SCD, sudden cardiac death; VT, ventricular tachycardia; HCM, hypertrophic cardiomyopathy.