Outcome and Complications After Implantable Cardioverter Defibrillator Therapy in Hypertrophic Cardiomyopathy

Systematic Review and Meta-Analysis

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Background—Previous observational studies demonstrated that patients with hypertrophic cardiomyopathy at risk for sudden cardiac death (SCD) may benefit from implantable cardioverter defibrillator (ICD) therapy. A complete overview of outcome and complications after ICD therapy is currently not available. This study pools data from published studies on outcome and complications after ICD therapy in patients with hypertrophic cardiomyopathy.

Methods and Results—A PubMed database search returned 27 studies on 16 cohorts reporting outcome and complications after ICD therapy in patients with hypertrophic cardiomyopathy. In case of >1 publications on a particular cohort, the publication with the largest number of patients was included in the meta-analysis. ICD interventions, complications, and mortality rates were extracted, pooled, and analyzed. There were 2190 patients (mean age, 42 years; 38% women), most of whom (83%) received an ICD for primary prevention of SCD. Risk factors for SCD were left ventricular wall thickness ≥30 mm (20%), family history of SCD (43%), nonsustained ventricular tachycardia (46%), syncope (41%), and abnormal blood pressure response (25%). During the 3.7-year follow-up, the annualized cardiac mortality rate was 0.6%, the noncardiac mortality rate was 0.4%, and the appropriate ICD intervention rate was 3.3%. The annualized inappropriate ICD intervention rate was 4.8% and the annualized ICD-related complication rate was 3.4%.

Conclusions—This meta-analysis demonstrates a low cardiac and noncardiac mortality rate after ICD therapy in patients with hypertrophic cardiomyopathy. Appropriate ICD intervention occurred at a rate of 3.3%/year, thereby, most probably, preventing SCD. Inappropriate ICD intervention and complications are not uncommon. **(*Circ Heart Fail*. 2012;5:552-559.)**

Key Words: hypertrophic cardiomyopathy ■ implantable cardioverter defibrillator ■ sudden cardiac death ■ prognosis ■ complications

Patients with hypertrophic cardiomyopathy (HCM) are at increased risk for sudden cardiac death (SCD), mostly caused by ventricular arrhythmias. SCD may occur as the initial presentation of HCM, often in asymptomatic or mildly symptomatic patients.[1] In fact, HCM is the most frequent cause of SCD in young people, including trained athletes.[2,3] Implantable cardioverter defibrillator (ICD) therapy may effectively terminate potentially life-threatening ventricular arrhythmias, thereby preventing SCD and prolonging life. Still, ICD therapy is not without risk, because inappropriate interventions and device-related complications may occur.

Clinical Perspective on p 559

Previous observational studies have reported on the use of ICD therapy for primary and secondary preventions of SCD in HCM.[4–30] A complete overview of outcome and complications after ICD therapy in patients with HCM at risk for SCD is currently not available. The goal of this analysis was to pool the individual studies in an effort to examine the precise rate of cardiac and noncardiac mortality, appropriate and inappropriate interventions, and complications. This knowledge may aid clinical decision making and counseling in patients with HCM at increased risk for SCD considered for ICD therapy.

Methods

Study Design

This systematic review and meta-analysis included all available original studies reporting clinical outcome and complications in patients with HCM who underwent ICD implantation. Studies that did not provide data on outcome or complications and review manuscripts were excluded. Studies focussing on SCD in patients with HCM without ICD were excluded.

Literature Search

The online MEDLINE database was searched for literature in March 2012 using PubMed (National Center for Biotechnology Information, US National Library of Medicine, Bethesda, MD). The search strategy

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was hypertrophic cardiomyopathy and defibrillator. No time restriction for publication dates was used. All titles and abstracts of the articles were evaluated. After exclusion based on the title and abstract, full articles were evaluated, and articles meeting the inclusion criteria were identified. In addition, a manual search of the reference lists of the identified studies was performed, and references were evaluated using the same inclusion and exclusion criteria.

Data Extraction

Selected studies were reviewed and relevant patient characteristics, known risk factors for SCD, and follow-up duration were registered. Extracted outcome parameters were as follows: cardiac mortality, noncardiac mortality, heart transplant, appropriate ICD intervention, inappropriate ICD intervention, and complications, including lead malfunction, infection, lead displacement, psychological complication, and total complications. The outcome parameter total complications included all reported ICD-related complications, except inappropriate ICD intervention; this parameter was registered separately. No time restriction for complications was used; both early and late complications were included in the analysis. Studies with overlapping data were identified, and in cases of apparent serial reporting of a particular patient cohort, only the publication with the largest number of patients was included in the meta-analysis. However, all serial publications on a particular cohort were registered and tabulated.

Statistical Analysis

Statistical analysis was performed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA) and SPSS version 15.0 (SPSS Inc, Chicago, IL). Continuous variables were reported as mean. Categorical variables were summarized as percentages. The total number of risk factors for SCD was divided by the total number of patients to assess the average number of risk factors per patient. Heterogeneity among the studies was assessed using the Q test and I^2 index. Random-effects model was used to calculate the summary estimates of the outcome data. From the pooled data, summary estimates of patient characteristics and risk factors for SCD were calculated. Meta-analysis of the outcome data was performed, and weighted event rates and weighted annualized event rates were calculated. Forest plots were constructed using the method of Neyeloff et al.[31]

Results

Search Results

The literature search yielded 469 articles (Figure 1). After review, exclusion, and cross-referencing, a total of 27 observational studies were included in the systematic review (Table 1). Overall, 16 different patient cohorts were identified in these 27 studies.[4–30] Because of apparent serial reporting of patient cohorts and to avoid duplicate entering of data, only 1 study per patient cohort was included in the meta-analysis. Hence, the summary estimate of clinical data and outcome is based on 16 studies.[4,7,9,12–14,16,18–20,24–28,30] Thirteen (81%) studies reported on a population of patients with HCM with an ICD for primary or secondary prevention of SCD, 1 (8%) study focused on patients with HCM with an ICD for primary prevention of SCD, and 2 (13%) studies reported on patients with hypertrophic obstructive cardiomyopathy who underwent alcohol septal ablation and had received an ICD.

Patient Characteristics

There were 2190 patients (mean age, 42 years; 38% women), most of whom (83%) received an ICD for primary prevention of SCD. Risk factors for SCD were left ventricular wall thickness ≥30 mm (20%), family history of SCD (43%), nonsustained ventricular tachycardia (46%), syncope (41%), and abnormal blood pressure response (25%). Patients had on average 1.8 risk factors for SCD. Hypertrophic obstructive cardiomyopathy was present in 27% of the patients.

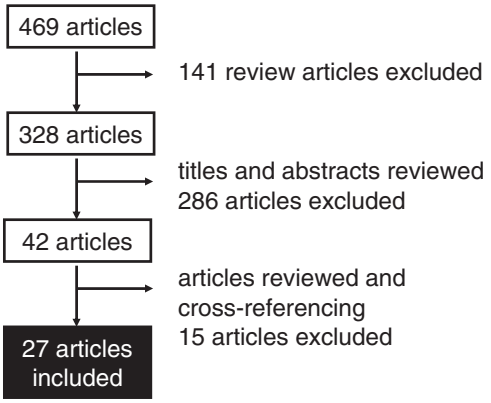

Figure 1. Flow chart of the literature search and study selection. The initial search yielded 469 eligible studies, and 141 review articles were excluded. The remaining 328 studies were evaluated, and on the basis of title and abstract, 286 articles were considered unrelated and were excluded. The remaining 42 articles were evaluated, and after cross-referencing, a total of 27 articles were included in the systematic review and meta-analysis. A total of 15 articles were excluded because of the following reasons: not all patients had hypertrophic cardiomyopathy (n=2), not all patients had an implantable cardioverter defibrillator (n=4), no follow-up data (n=1), study on socioeconomic aspects (n= 2), editorial or case report (n=6).

ICD Interventions and Outcome

During the 3.7-year follow-up, 311 of 2190 (14%) patients had an appropriate ICD intervention (Table 2). The annualized appropriate ICD intervention rate was 3.3% (Figure 2). Data on inappropriate ICD intervention was available in 13 studies. Inappropriate ICD intervention occurred in 388 of 1966 (20%) patients. The annualized inappropriate ICD intervention rate was 4.8% (Figure 3). Mortality data was reported in 13 studies: there were 53 (3%) cardiac deaths and 49 (2%) noncardiac deaths. The annualized cardiac mortality rate was 0.6%, and the annualized noncardiac mortality rate was 0.4%. Five studies reported follow-up data on heart transplantation; this occurred in 28 of 1214 patients (2%), and the annualized heart transplantation rate was 0.5%.

Complications

Information on ICD-related complications was available in 9 of 16 studies, including a total of 1691 patients (Table 2). Of them, 260 (15%) had any form of ICD-related complications. The most frequently observed complication was lead malfunction in 118 (7%). Other complications were infection in 59 (3%) and lead displacement in 28 (3%). Only 1 study provided information on psychological complications; these occurred in 5 of 132 (4%) patients.

Discussion

This meta-analysis demonstrates a low cardiac and noncardiac mortality rate after ICD therapy in patients with HCM.

Table 1. Summary of the Studies Reporting ICD Therapy in Patients With Hypertrophic Cardiomyopathy

Cohort	Region	Author	Year	Population	n	Mean Age, y	Women, %	Primary Prevention, %	Secondary Prevention, %	LVWT ≥30 mm, %	Family History of SCD,%	NSVT, %	Syncope, %	Abnormal BP Response, %	HOCM, %
Aalst, Barcelona	Belgium, Spain	Primo et al[4]	1998	HCM and ICD	13	48	38	77	23	0	NA	NA	46	NA	38
London	United Kingdom	Elliott et al[5]	1999	HCM with VT/VF	6	19	NA	100	0	NA	17	33	50	67	NA
		Kaski et al[6]	2007	ICD in children with HCM	22	14	41	77	23	50	55	5	32	68	36
		O'Mahony et al[7]	2012	HCM and ICD	334	40	38	92	8	15	51	48	39	33	23
ICD in HCM Registry	United States, Italy	Maron et al[8]	2000	HCM and ICD	128	40	31	66	34	8	30	25	32	NA	18
	United States, Europe, Australia	Maron et al[9]	2007	HCM and ICD	506	42	36	76	24	24	51	46	47	NA	5
	United States, Australia	Maron et al[10]	2009	HCM and appropriate ICD intervention	63	43	29	65	35	NA	NA	NA	NA	NA	14
	United States, Australia	Sherrid et al[11]	2009	HCM and ICD	330	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NIH	United States	Begley et al[12]	2003	HCM and ICD	132	34	39	36	64	23	41	63	39	26	38
Sydney	Australia	Jayatilleke et al[13]	2004	HCM and ICD	22	NA	NA	82	18	50	36	27	41	23	NA
Minneapolis	United States	Almquist et al[14]	2005	HCM and ICD	75	37	35	95	5	29	NA	NA	NA	NA	20
		Maron et al[15]	2009	HCM and VT/VF	39	34	44	46	54	23	41	47	NA	NA	16
Bielefeld	Germany	Lawrenz et al[16]	2005	HOCM, ICD, and ASA	15	53	47	40	60	NA	33	33	33	17	100
Warsaw	Poland	Przybylski et al[17]	2005	HCM and ICD	46	32	59	39	61	17	50	54	63	70	17
		Syska et al[18]	2010	HCM and ICD	104	35.6	55	75	25	NA	NA	65	NA	NA	NA
Alicante, Murcia, A Coruna	Spain	Marin et al[19]	2006	HCM and ICD	45	42.8	38	60	40	29	31	64	47	56	44
Sao Paulo	Brazil	Medeiros et al[20]	2006	HCM and ICD	26	42.7	54	62	38	19	58	46	77	NA	NA
Rochester	United States	Cha et al[21]	2007	HCM and ICD for primary prevention	68	43	40	100	0	NA	56	62	29	5	NA
		McLeod et al[22]	2007	HCM and ICD	125	41.0	38	94	6	6	49	38	36	26	56
		Kiernan et al[23]	2008	HCM, ICD, and no ASA or myectomy	69	43.5	29	97	3	1	54	46	30	30	20
		Lin et al[24]	2009	HCM and ICD	181	44	38	86	14	16	56	41	40	1	20
Toronto	Canada	Woo et al[25]	2007	HCM and ICD	61	46	34	82	18	15	46	5	25	NA	NA
Charleston	United States	Cuoco et al[26]	2008	HCM, ASA, and ICD for primary prevention	123	48	34	100	0	11	38	NA	63	34	100

(*Continued*)

Table 1. (Continued)

Cohort	Region	Author	Year	Population	n	Mean Age, y	Women, %	Primary Prevention, %	Secondary Prevention, %	LVWT ≥30 mm, %	Family History of SCD,%	NSVT, %	Syncope, %	Abnormal BP Response, %	HOCM, %
10 centers	United Kingdom, Poland, France	Saumarez et al[27]	2008	HCM and ICD for primary prevention	179	NA	44	100	0	16	13	35	19	22	NA
7 centers	United States	Hauser et al[28]	2008	HCM and ICD	324	47	33	91	9	NA	NA	NA	NA	NA	30
Minneapolis, Rochester	United States	Bos et al[29]	2010	HCM and ICD for primary prevention	177	45.3	37	100	0	14	51	36	43	11	24
Bad Oeynhausen	Germany	Prinz et al[30]	2010	HCM and ICD	50	44	34	96	4	26	28	44	36	30	50
Summary estimate (16 cohorts)					2190	42.3	38	83	17	20	43	46	41	25	27

ICD indicates implantable cardioverter defibrillator; LVWT, left ventricular wall thickness; SCD, sudden cardiac death; NSVT, nonsustained ventricular tachycardia; BP, blood pressure; HOCM, hypertrophic obstructive cardiomyopathy; HCM, hypertrophic cardiomyopathy, NA, not available; NIH, National Institutes of Health; VT, ventricular tachycardia; VF, ventricular fibrillation; ASA, alcohol septal ablation.

In patients with HCM with on average 1.8 risk factors for SCD, appropriate ICD intervention occurred at a rate of 3.3%/year, thereby, most probably, preventing SCD. These findings emphasize the importance of ICD therapy in patients with HCM at risk for SCD.

Current American College of Cardiology Foundation/American Heart Association guidelines[32] recommend comprehensive SCD risk stratification at initial evaluation and on a periodic basis (every 12 to 24 months) for patients with HCM. A personal history for ventricular fibrillation, sustained ventricular tachycardia, or SCD is recommended, and established risk factors for SCD should be evaluated. ICD placement is recommended (class I recommendation) for patients with HCM and prior documented cardiac arrest, ventricular fibrillation, or hemodynamically significant ventricular tachycardia. A comparable decision strategy for ICD implantation for secondary prevention of SCD was applied in the studies included in the present analysis. In the pooled analysis, 17% of the patients with HCM received an ICD for secondary prevention of SCD.

For primary prevention of SCD in patients with HCM, the guidelines state that it is reasonable to recommend (class IIa recommendation) an ICD for patients with HCM with SCD presumably related to HCM in ≥1 first-degree relatives, or a maximum left ventricular wall thickness ≥30 mm, or ≥1 recent unexplained syncopal episodes.[32] An ICD can be useful in select patients with nonsustained ventricular tachycardia in the presence of other SCD risk factors or modifiers or with an abnormal blood pressure response to exercise in the presence of other SCD risk factors or modifiers. It is reasonable to recommend an ICD for high-risk children with HCM, based on unexplained syncope, massive left ventricular hypertrophy, or family history of SCD, after taking into account the relatively high complication rate of long-term ICD implantation.

In the present analysis, the majority of studies did not provide clear information on the clinical decision strategy for ICD implantation for primary prevention of SCD. Complete information on all 5 established risk factors for SCD in patients with HCM was available in only 7 of 16 (44%) cohorts. Primary prevention of SCD in patients with HCM depends on the presence of SCD risk factors and modifiers; therefore, complete information on all established risk factors is highly relevant. All reported cohorts were collected before publication of the current practice guideline on HCM, and it is not certain that the results from the pooled analysis also apply to patients with HCM who currently receive an ICD. Nevertheless, the present analysis demonstrates that patients with HCM with an ICD had on average 1.8 risk factors for SCD. Consequently, the population in the pooled analysis was at high risk for SCD and is probably comparable to the population that should be considered for ICD implantation according to the current guideline.[32]

The pooled analysis demonstrates that inappropriate ICD intervention and complications are not uncommon (4.8%/year and 3.4%/year, respectively). Previous studies suggested that patients with HCM are more vulnerable to ICD-related complications and inappropriate ICD therapy because of young age at implant and increased prevalence

Table 2. Summary of Clinical Outcome

Cohort	Author	Year	Follow-Up, y	Appropriate Intervention, %	Inappropriate Intervention, %	Complications, %					Mortality, %		Heart transplant, %
						Lead Malfunction	Infection	Lead Displacement	Psychological	Any	Cardiac	Noncardiac	
Aalst, Barcelona	Primo et al[4]	1998	2.2	15	23	0	0	8	NA	8	0	0	NA
London	Elliott et al[5]	1999	6.1	50	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Kaski et al[6]	2007	1.7	18	18	5	5	NA	8	18	0	0	0
	O'Mahony et al[7]	2012	3.6	8	16	5	6	4	NA	18	3	1	3
ICD in HCM Registry	Maron et al[8]	2000	3.1	23	25	9	2	NA	1	14	NA	NA	NA
	Maron et al[9]	2007	3.7	20	27	7	4	NA	NA	12	4	4	2
	Maron et al[10]	2009	NA	100	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Sherrid et al[11]	2009	3.7	17	NA	NA	NA	NA	NA	NA	NA	NA	NA
NIH	Begley et al[12]	2003	4.8	20	23	5	3	NA	4	28	3	2	2
Sydney	Jayatilleke et al[13]	2004	2.9	32	9	NA	5	NA	NA	5	NA	NA	NA
Minneapolis	Almquist et al[14]	2005	3.6	7	NA	3	NA	3	NA	8	3	0	NA
	Maron et al[15]	2009	9.4	41	28	NA	NA	NA	NA	NA	13	5	NA
Bielefeld	Lawrenz et al[16]	2005	3.4	27	20	NA	NA	NA	NA	NA	0	20	NA
Warsaw	Przybylski et al[17]	2005	2.4	28	30	7	4	2	NA	13	0	2	4
	Syska et al[18]	2010	4.6	26	35	13	5	2	NA	24	2	2	NA
Alicante	Marin et al[19]	2006	2.7	22	29	NA	2	NA	NA	NA	0	4	NA
Sao Paulo	Medeiros et al[20]	2006	1.6	15	NA	NA	NA	NA	NA	NA	4	0	NA
Rochester	Cha et al[21]	2007	3.4	13	15	NA	NA	NA	NA	NA	NA	NA	NA
	McLeod et al[22]	2007	4.4	10	NA	NA	NA	NA	NA	NA	2	2	NA
	Kiernan et al[23]	2008	4.4	17	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Lin et al[24]	2009	4.9	16	23	13	4	NA	NA	26	3	8	2
Toronto	Woo et al[25]	2007	3.3	13	33	13	NA	NA	NA	NA	2	0	2
Charleston	Cuoco et al[26]	2008	2.9	7	NA	NA	NA	NA	NA	NA	NA	NA	NA
10 centers	Saumarez et al[27]	2008	4.3	3	3	NA	NA	NA	NA	NA	1	0	NA
7 centers	Hauser et al[28]	2008	3.3	11	12	5	0.3	3	NA	7	1	2	NA
Minneapolis, Rochester	Bos et al[29]	2010	4.6	14	27	NA	NA	NA	NA	NA	3	5	NA
Bad Oeynhausen	Prinz et al[30]	2010	2.0	10	6	NA	NA	NA	NA	NA	NA	NA	NA
Event rate (95% CI)				13.7 (9.9–17.5)	19.0 (12.6–25.4)	6.2 (4.1–8.3)	3.1 (1.2–5.0)	2.7 (1.6–3.9)	3.8 (0.5–7.1)	14.9 (9.9–19.9)	2.2 (1.5–2.8)	1.4 (0.8–1.9)	2.2 (1.3–3.0)
Annualized event rate (95% CI)				3.3 (2.2–4.4)	4.8 (2.9–6.7)	1.5 (0.9–2.1)	0.6 (0.1–1.0)	1.0 (0.5–1.4)	0.8 (–0.8 to 2.3)	3.4 (2.5–4.3)	0.6 (0.2–0.9)	0.4 (0.09–0.7)	0.5 (0.1–1.0)

NA indicates not available; ICD, implantable cardioverter defibrillator; HCM, hypertrophic cardiomyopathy; NIH, National Institutes of Health.

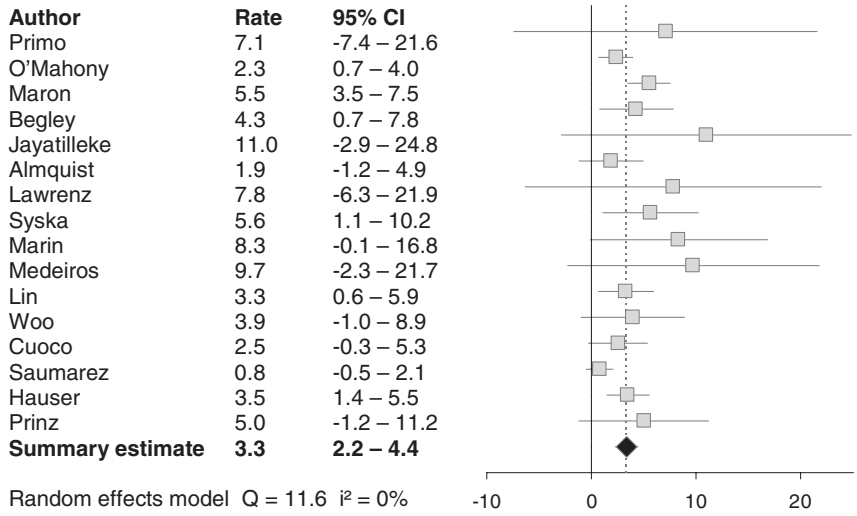

Figure 2. Forest plot of annualized appropriate implantable cardioverter defibrillator intervention rate (%/year).

of atrial fibrillation.[24] Reports from large ICD registries, including predominantly patients with ischemic heart disease, demonstrate an early complication rate varying from 3.3% to 11% during the hospital admission for ICD implantation.[33,34] Long-term follow-up data on ICD-related complications in general practice are not available, hampering comparison of the inappropriate ICD intervention and ICD-related complication rates observed in patients with HCM. Most patients with HCM who underwent ICD implantation were young (mean age, 42 years), and, therefore, the risk of ICD-related complications should be carefully considered and discussed with the patient during the decision-making process before implantation. This is particularly relevant because of the long periods that young patients will live with the implanted device and leads. Only 3 studies[6,8,12] reported the occurrence of ICD-related psychological complications. The psychological and behavioral aspects of ICD therapy in patients with HCM should receive more attention because many patients with HCM considered for ICD therapy are otherwise healthy and often asymptomatic young individuals.

Limitations

This systematic review and meta-analysis has inherent limitations. The data were extracted from observational studies. A potential risk of pooling data from different studies is to mix patients with different clinical characteristics and SCD risk profile. The decision strategy for ICD implantation was not specified in most studies. The currently available studies have reported on outcome and complications after ICD therapy in populations with predominantly adult patients with HCM, except the study by Kaski et al.[6] More information is desired concerning ICD therapy in children and adolescents with HCM. Data on cycle length of the arrhythmia and type of arrhythmia were not available in the majority of studies. Finally, the first report was from 1998, and over the years significant progress in ICD devices and leads has been made, and experience with implantation and follow-up has increased.

Future Studies

ICD therapy has proven benefits in patients with HCM at increased risk for SCD. Future studies on ICD therapy for prevention of SCD in patients with HCM are needed to refine risk stratification for SCD and to define the role of other risk markers, including cardiac magnetic resonance imaging. There are indications that patients with HCM with extensive delayed enhancement on contrast-enhanced cardiac magnetic resonance imaging are at increased risk of ventricular arrhythmias. Efforts to further reduce inappropriate ICD

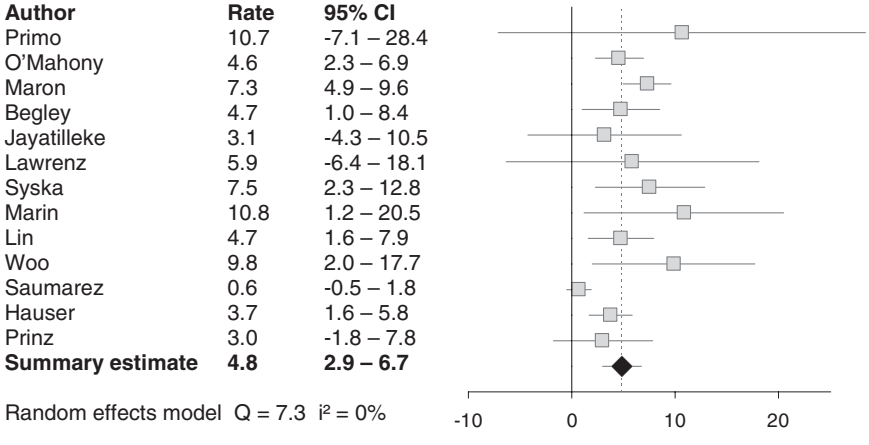

Figure 3. Forest plot of annualized inappropriate implantable cardioverter defibrillator intervention rate (%/year).

intervention and complication rates may have substantial clinical and financial benefits. Authors of future reports on ICD therapy in patients with HCM are encouraged to provide complete information on the clinical characteristics of the study population, established clinical risk factors for SCD, decision strategy for ICD implantation, and device-related complications and outcome (including at least appropriate and inappropriate ICD intervention, and cardiac and noncardiac mortality).

Conclusions

This meta-analysis demonstrates a low cardiac and noncardiac mortality rate after ICD therapy in patients with HCM. Appropriate ICD intervention occurred at a rate of 3.3%/year, thereby, most probably, preventing SCD. Inappropriate ICD intervention and complications are not uncommon (4.8%/year and 3.4%/year, respectively). The benefits and risks of ICD therapy in patients with HCM should be carefully weighted.

Disclosures

None.

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CLINICAL PERSPECTIVE

Patients with hypertrophic cardiomyopathy (HCM) are at increased risk for sudden cardiac death (SCD), most frequently caused by ventricular arrhythmias. Implantable cardioverter defibrillator (ICD) therapy may effectively terminate life-threatening ventricular arrhythmias and thereby prevent SCD. However, ICD therapy is not without risk, because inappropriate ICD interventions and device-related complications may occur. Although previous studies have reported on the use of ICD therapy for prevention of SCD in patients with HCM, a complete overview of outcomes and complications after ICD therapy in patients with HCM is not available. In this meta-analysis, we demonstrate a low cardiac and noncardiac mortality rate after ICD implantation in patients with HCM. Appropriate ICD intervention occurred at a rate of 3.3%/year, thereby, most probably, preventing SCD. Inappropriate ICD intervention and complications occurred at a rate of 4.8%/year and 3.4%/year, respectively, in these patients. The most frequently observed complication was lead malfunction in 7%. Other complications were infection in 3% and lead displacement in 3%. Consideration of these outcome and complication data may help clinicians in decision making and counseling of patients with HCM at increased risk for SCD considered for ICD therapy. Additional research is warranted to further reduce inappropriate ICD intervention and complication rates.