CHAPTER X

Implantation-related complications of implantable cardioverter defibrillators and cardiac resynchronization therapy devices: a systematic review of randomized clinical trials

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ABSTRACT

Worldwide, the number of implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) implantations is increasing drastically and with it, the number of implanting centers. Despite abundant data on the beneficial effect of these devices little is known regarding safety and complication rates. This study systematically reviewed 11 ICD and 7 CRT trials to provide data on the frequency of in-hospital mortality and complications related to the implantation. Average in-hospital mortality was 2.7% in trials utilizing both thoracotomy and non-thoracotomy ICDs, 0.2% in trials utilizing non-thoracotomy ICDs and 0.3% in CRT trials. Pneumothorax rate was similar between the non-thoracotomy ICD and CRT trials (0.9%) Coronary sinus complications occurred in 2.0% of CRT patients. Lead dislodgement rates were higher in CRT trials (5.7%) than in non-thoracotomy ICD trials (1.8%).

INTRODUCTION

Inclusion of implantable cardioverter-defibrillator (ICD) treatment and cardiac resynchronization therapy (CRT) in the guidelines has led to a worldwide drastic increase in implantation rates.[1] Most likely this rate will continue to rise in the future, given the growing number of eligible patients, expanding indications, and existing backlog of device implantations.[1-3] Nevertheless, despite improved training, advancing techniques, and better experience, device implantation is not without complications.

Given the expected growing number of device implantations, data on the safety of the implant procedure are necessary to create reasonable expectations of procedural risk and guidance for (starting) implanting centers. The objective of this review is to assess the frequency of implantation-related complications reported in large, randomized clinical trials—which are under strict control of safety boards—and provide guidance for implanting centers and safety enhancement.

METHODS

Literature review

A comprehensive search of English-language published reports was conducted in PubMed on the following search terms: implantable cardioverter defibrillator, cardiac resynchronization therapy, and biventricular pacing. The search was conducted on October 15, 2010, and was limited to clinical trials. Two independent reviewers (J.B.v.R. and M.K.d.B.) screened and selected the studies. A preliminary screening of titles and abstracts was conducted, and those with potential relevance were retrieved. Disagreements were resolved by consensus or by a third reviewer (L.v.E.).

Selection criteria

Eligible studies were noncrossover randomized clinical trials examining patients undergoing elective ICD or CRT versus controls and reporting on complications or adverse events related to the implant procedure. Data on adverse events from subgroup analyses of these trials were also included. Of 1,026 results for the search term implantable cardioverter defibrillator, 388 results for cardiac resynchronization therapy, and 201 results for biventricular pacing, 18 trials and 3 subgroup analyses were selected for this review.[4-24] (Fig. 1).

The included trials were separated into 3 groups based on the devices used: both thoracotomy and nonthoracotomy ICDs, only nonthoracotomy ICDs, and nonthoracotomy CRTs. The AVID (Antiarrhythmics Versus Implantable Defibrillators) trial—using mainly nonthoracotomy ICDs (93%)—was included in the nonthoracotomy ICD group because Kron et al.[12,22] provided accurate data in a subgroup analysis that included only nonthoracotomy ICDs.

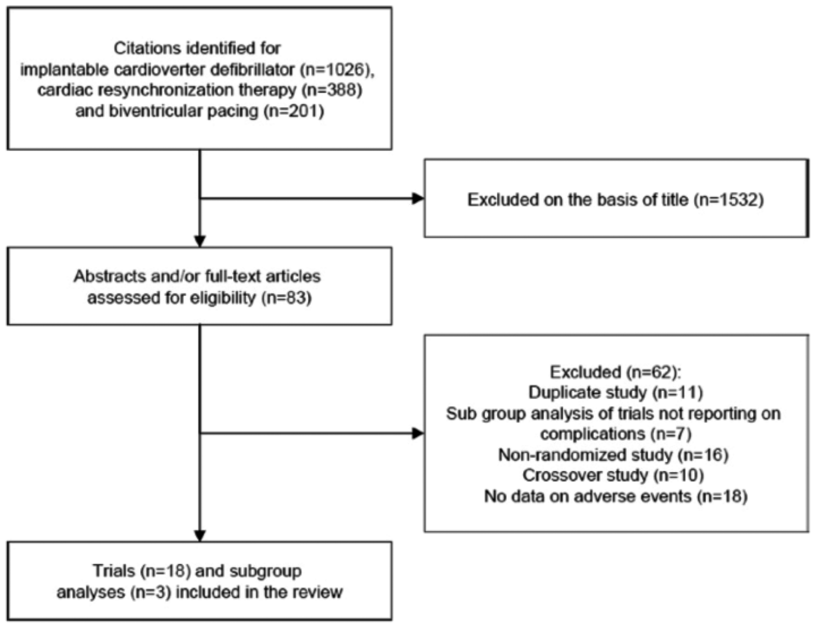

Figure 1. : Systematic review and article selection. Flowchart demonstrating the search strategy and exclusion of articles.

RESULTS

Included studies

Twelve trials assessing ICD efficacy were selected, including the ICD-treated arm of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) study. Year of publication ranged from 1996 to 2009. [4-14,21] Of these, 4 trials used both thoracotomy and nonthoracotomy ICDs, which resulted in successful implantation in 932 of 951 patients (98.0%).4,5,13,14 In the remaining 8 nonthoracotomy ICD trials, implantation was successful in 3,787 of 3,828 patients (98.9%). Significantly lower successful implantation rates were observed in the 7 selected CRT trials: 4,175 of 4,512 (92.5%) attempted implantations were successful.[15-21] In Table 1, an overview of the trials with key baseline clinical characteristics is presented.

Mortality

Average in-hospital mortality of the trials using both thoracotomy and nonthoracotomy ICDs was 2.7% (Table 2). Nonthoracotomy ICD trials reported significantly lower rates: of 3,016 patients, 5 patients died in-hospital (0.2%) and 13 patients within 30 days (0.6%). Importantly, all in-hospital deaths happened during the IRIS (Immediate Risk Stratification Improves Survival) trial, which disproved that ICDs provide survival benefit when implanted within 40 days following myocardial infarction.[11] Hence, this study population consisted of

Table 1: *Baseline characteristics of the included studies*

Author	Trial name	Year	Device + procedure	Thoracotomy ICD, (%)	Patients, n	Attempted first procedures, n	Successful implants*, n, (%)	Mean age, years	Male, n (%)	Mean LVEF	Ischemic heart disease, n (%)	NYHA II or III, n (%)	NYHA IV, n (%)	Duration, mo
Thoracotomy and non-thoracotomy ICD systems														
Moss	MADIT [4]	1996	ICD	47	95	95	94 (99)	62±9	87 (92)	27±7	95 (100)	60 (63)	Excluded	27
BiggerJr	CABG Patch [5]	1997	ICD+-CABG	100	446	446	434 (97)	64±9	386 (87)	27±6	446 (100)	317 (71)	NR	32±16
Connolly	CIDS [13]	2000	ICD	10	328	311	310 (99)	63±9	280 (85)	34±15	272 (83)	NR	NR	36
Kuck	CASH [14]	2000	ICD	56	99	99	94 (95)	58±11	78 (79)	46±19	72 (73)	76 (77)	0 (0)	57±34
Non-thoracotomy ICD systems														
AVID investigators	AVID [12, 22]	1997	ICD	0	539	539	539 (100)	65±11	424 (79)	32±13	438 (81)	NR	NR	27±13
Moss	MADIT II [6]	2002	ICD	0	742	742	721 (97)	64±10	631 (85)	23±5	742 (100)	379 (60)	37 (5)	20
Bansch	CAT [7]	2002	ICD	0	50	50	50 (100)	52±12	43 (86)	24±6	Excluded	50 (100)	Excluded	25
Hohnloser	DINAMIT [8]	2004	ICD	0	332	312	312 (100)	62±11	252 (76)	28±5	332 (100)	III: 100 (30)	Excluded	30±13
Kadish	DEFINITE [9]	2004	ICD	0	229	227	227 (100)	58 [21-78]	160 (70)	22[7-35]	Excluded	171 (75)	Excluded	29±14
Bardy	SCD-HeFT [10]	2005	ICD	0	829	812	811 (99)	60, median	639 (77)	24, median	431 (53)	829 (100)	Excluded	46
Moss	MADIT-CRT [21]	2009	ICD-arm	0	731	731	712 (97)	64±11	553 (76)	24±5	401 (55)	II: 618 (85)	Excluded	29
Steinbeck	IRIS-trial [11]	2009	ICD	0	445	415	415 (100)	63±11	345 (78)	35±9	445 (100)	NR	NR	37
Non-thoracotomy CRT systems														
Abraham	MIRACLE [15, 24]	2002	CRT	0	571	568	526 (92)	64±11	308 (68)	22±6	245 (54)	III: 412 (91)	41 (9)	6
Young	MIRACLE ICD [16, 24]	2003	CRT	0	429	421	379 (88)	67	283 (77)	24±6	257 (70)	III: 328 (89)	41 (11)	6
Bristow	COMPANION [17]	2004	CRT	0	1212	1212	1080 (89)	67	812 (67)	21	655 (54)	III: 1054 (87)	158 (13)	16, median
Cleland	CARE-HF [18, 23]	2005	CRT	0	409	404	390 (97)	67, median	304 (74)	25, median	165 (40)	III: 386 (94)	23 (6)	29
Beshai	RethinQ [19]	2007	CRT	0	250	176	172 (98)	59	111 (65)	25±5	90 (52)	III: 171 (99)	Excluded	6
Linde	REVERSE [20]	2008	CRT	0	684	642	621 (97)	63	479 (79)	27±7	333 (55)	II: 503 (82)	Excluded	12
Moss	MADIT-CRT [21]	2009	CRT-arm	0	1089	1089	1007 (93)	65±11	814 (75)	24±5	598 (55)	II: (937, 86)	Excluded	29

AVID = Antiarrhythmics Versus Defibrillators; CABG Patch = Coronary Artery Bypass Graft Patch Trial; CARE-HF = Cardiac Resynchronization – Heart Failure Trial; CASH = Cardiac Arrest Study Hamburg; CAT = Cardiomyopathy Trial; CIDS = Canadian Implantable Defibrillator Study; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure Trial; CRT = Cardiac Resynchronization Therapy; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT = Defibrillator In Acute Myocardial Infarction Trial; ICD = Implantable Cardioverter Defibrillator; IRIS-trial = Immediate Risk-Stratification Improves Survival trial; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MADIT-CRT = Multicenter Automatic Defibrillator Trial with Cardiac Resynchronization Therapy; MIRACLE = Multicenter Insync Randomized Clinical Evaluation; MIRACLE-ICD = Multicenter Insync ICD Randomized Clinical Evaluation; NR = Not Reported; RethinQ = Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial; *successful implants of all attempted procedures.

Table 2: *In-hospital mortality and death within 30 days post-implantation*

Trial name	Year	Pts. undergoing implantation, n	In-hospital mortality n,(%)	Death within 30 days, n (%)
Thoracotomy and non-thoracotomy ICD systems				
MADIT	1996	95	0 (0.0)	0 (0.0)
CABG Patch	1997	446	12 (2.6)	24 (5.2)
CIDS	2000	311	NR	2 (0.6)
CASH	2000	99	5 (5.1)	NR
Total		951	17 (2.7)	26 (3.1)
Non-thoracotomy ICD systems				
AVID	1997	539	NR	6 (1.1)
MADIT II	2002	742	0 (0.0)	NR
CAT	2002	50	0 (0.0)	0 (0.0)*
DINAMIT	2004	312	0 (0.0)	0 (0.0)*
DEFINITE	2004	227	0 (0.0)	0 (0.0)*
MADIT-CRT (ICD-arm)	2009	731	0 (0.0)	0 (0.0)*
IRIS	2009	415	5 (0.8)*	7 (1.7)
Total		3016	5 (0.2)	13 (0.6)
Non-thoracotomy CRT systems				
MIRACLE	2002	568	2 (0.4)*	2 (0.4)*
MIRACLE ICD	2003	421	0 (0.0)	5 (1.2)
COMPANION	2004	1212	8 (0.6)*	17 (1.4)
CARE-HF	2005	409	0 (0.0)	1 (0.2)*
RethinQ	2007	176	0 (0.0)	0 (0.0)
MADIT-CRT (CRT-arm)	2009	1089	1 (0.1)	0 (0.0)
Total		3875	11 (0.3)	26 (0.7)

*related to implantation; Data not reported in SCD-HeFT, REVERSE. Abbreviations as Table 1.

patients at high risk of death, explaining the high in-hospital mortality.

Interestingly, in a large registry including patients with heart failure undergoing ICD implantation in 2004 and 2005, Swindle et al.[25] reported a relatively high in-hospital mortality of 1.0%, and comparable findings were reported by Reynolds et al.[26] in Medicare patients (0.9%). Most likely, the strict inclusion criteria of the trials—creating a more healthy population—and the experience of the implanting centers have led to this in-hospital mortality rate difference in favor of the trials.

For CRT patients, the average in-hospital mortality was 0.3% and mortality within 30 days was 0.7%. Given these findings, it seems that in-hospital mortality was not affected by the more complex and time-consuming CRT implant procedures, conducted in generally sicker patients. This was also observed by Reynolds et al.[26] in 30,984 Medicare patients: in-hospital mortality for CRT patients (1.1%) was comparable to that for ICD patients (0.9%; $p = 0.07$).

Complications during implantation

Pneumothorax

For implanting nonthoracotomy ICD or CRT leads, venous access can be achieved via the cephalic, subclavian, or axillary vein. Of these, the blind puncture approach of the subclavian vein is most associated with the risk of a pneumothorax.[27] The selected trials did not specifically report on the implantation technique used; however, for patients receiving nonthoracotomy devices, the incidence of pneumothorax was relatively low: a pneumothorax was observed in 14 of 1,497 ICD implantations (0.9%) and in 30 of 3,300 CRT implantations (0.9%) (Table 3). In perspective, the Medicare registry[26] reported 1.0% for ICD patients and 1.2% for CRT patients (p = NS), whereas Peterson et al.[28] reported in the National Cardiovascular Data Registry ICD Registry on 0.51% for CRT patients.

Table 3: *Pneumothorax related to implantation of non-thoracotomy devices*

Trial name	Year	Patients undergoing implantation, n	Events, n (%)
Non-thoracotomy ICD systems			
AVID	1997	539	6 (1.1)
DEFINITE	2004	227	2 (0.9)
MADIT-CRT (ICD-arm)	2009	731	6 (0.8)
Total		1497	14 (0.9)
Non-thoracotomy CRT systems			
MIRACLE	2002	568	1 (0.2)
MIRACLE ICD	2003	421	3 (0.7)
CARE-HF	2005	404	2 (0.5)
RethinQ	2007	176	2 (1.1)
REVERSE	2008	642	4 (0.6)
MADIT-CRT (CRT-arm)	2009	1089	18 (1.7)
Total		3300	30 (0.9)

Data not reported in CAT, MADIT II, DINAMIT, SCD-HeFT, IRIS, CIDS, COMPANION. Abbreviations as Table 1.

Complications Related to the Left Ventricular Lead

All included CRT trials used CRTs with transvenously implanted leads. The most common complications included coronary vein dissection (1.3%) and coronary vein perforation (1.3%). Of note, the earlier conducted studies reported higher incidences of coronary vein–related complications than the more recently conducted studies (Table 4). Possibly the growing experience of physicians combined with the technical progress of the left ventricular lead has contributed to this decreasing trend in coronary vein complications. Overall, complications related to coronary veins occurred in 2.0%. In other published

data, no large national registries have reported on the complication rates in CRT patients alone, but smaller analyses have reported on higher perioperative left ventricular lead complication rates ranging from 1.9% to 4.6%.[24,29-31]

Implantation-related complications during follow-up

Pocket Hematoma

On average, pocket hematomas occurred in 2.2% of nonthoracotomy ICD recipients and in 2.4% of CRT recipients (Table 5). However, in routine clinical practice, the actual incidence of pocket hematomas is probably higher because most trials only reported hematomas requiring surgical reintervention, which was indicated in a minority of cases.[32] Although the development of pocket hematoma is not directly life threatening and can be adequately treated, early reintervention is associated with a 15-fold increased risk of infection.[33]

Table 5: *Implant site hematoma or bleeding*

Trial name	Year	Successful implants, n	All events, n (%)	Duration, mo
Thoracotomy and non-thoracotomy ICD systems				
MADIT*	1996	94	1 (1.1)	27
CABG Patch†	1997	434	22 (4.9)	0.5†
CASH‡	2000	94	6 (6.1)	57±34
Total		622	29 (4.7)	
Non-thoracotomy ICD systems				
AVID‡	1997	539	8 (1.5)	27±13
CAT‡	2002	50	2 (4.0)	25
MADIT-CRT (ICD-arm)‡	2009	712	18 (2.5)	29
Total		1301	28 (2.2)	
Non-thoracotomy CRT systems				
RethinQ‡	2007	172	2 (1.2)	6
REVERSE‡	2008	621	5 (0.8)	12
MADIT-CRT (CRT-arm)‡	2009	1007	36 (3.3)	29
Total		1800	43 (2.4)	

Data not reported in MADIT-II, DINAMIT, DEFINITE, SCD-HeFT, IRIS, CIDS, MIRACLE, COMPANION, MIRACLE ICD, CARE-HF. Abbreviations as Table 1.
*no time frame indicated; †complications occurred within 30 days following implantation
‡complications occurred during follow-up

Lead Dislodgement

The overall incidence of lead dislodgement was 1.8% for nonthoracotomy ICDs. Unfortunately, the rate was not specified for type of lead (atrial or ventricular located lead), and varying time frames during which lead dislodgements occurred were reported (Table

6). Nevertheless, from other published reports, one can imply that the majority of lead dislodgements occur during hospitalization because acute dislodgement rates of 0.56% for single-chamber ICDs and 0.97% for dual-chamber ICDs have been observed.[34]
CRT trials demonstrated higher rates of lead dislodgement, varying from 2.9% to 10.6%. In total, 184 (5.9%) leads dislodged during and after 3,095 successful implantations. Although it has been suggested in published reports that the difference in lead dislodgement between ICD and CRT may simply be a function of having more leads implanted, subgroup analysis of the collective MIRACLE ICD (Multicenter In Sync Randomized Clinical Evaluation Implantable Cardioverter Defibrillator) study demonstrated that postoperatively disproportionally higher lead dislodgement rates were observed for left ventricular leads than for right atrial and right ventricular leads (6.8%, 1%, and 0.6%, respectively).[24,34] This high rate reflects the limited anatomic choices for the placement of the left ventricular lead and challenges to obtain a stable pacing site.

Table 6: *Lead dislodgement during follow-up in non-thoracotomy requiring implanted devices*

Trial name	Year	Successful implants, n	All events, n (%)	Duration, mo
Non-thoracotomy ICD systems				
AVID†	1997	593	8 (1.5)	27±13
CAT*	2002	50	2 (4.0)	0.5*
DEFINITE†	2004	227	6 (2.6)‖	29±14
Total		870	16 (1.8)	
Non-thoracotomy CRT systems				
MIRACLE†	2002	526	31(5.9)	6
MIRACLE ICD‡	2003	379	11(2.9)	6
CARE-HF*	2005	390	11(2.8)	0.5*
RethinQ§	2007	172	13 (7.6)¶	6
REVERSE§	2008	621	66 (10.6)	12
MADIT-CRT (CRT-arm)*	2009	1007	44 (4.4)#	0.5*
Total		3095	176 (5.7)	

Data not reported in MADIT, CABG-Patch, MADIT II, DINAMIT, SCD-HeFT, MADIT-CRT (ICD-treated arm), IRIS, COMPANION. Abbreviations as Table 1. *complications occurred within 30 days following implantation; †complications occurred during follow-up; ‡complications occurred during hospitalization; §no time frame indicated; ‖included also lead fracture; ¶Five cases (2.9%) involved left lead; #included left ventricular lead only.

Study limitations

Because of its design, this systematic review is subject to some important limitations. No corrections were made for heterogeneity among the selected trials, for trial quality, or for publication bias. Reported complication rates are presented without confidence intervals. Trials lacking safety data were excluded. Furthermore, clear definitions of the complications were not always provided. Finally, lead dislodgements develop over time, and different follow-up durations might have influenced the rates.

CONCLUSIONS

This systematic review on the safety and complication rates reported in major randomized ICD/CRT clinical trials provides guidance and expectations for patients and implanting physicians. From the results, it becomes clear that trials that used both thoracotomy and nonthoracotomy ICDs reported significantly higher in-hospital mortality and higher complication rates. Furthermore, implantation of the left ventricular lead was associated with the most complications.

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