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How Do Patients Receiving a Secondary Prevention ICD in Clinical Practice Compare with Patients Enrolled in the Antiarrhythmic Versus Implantable Defibrillator (AVID) Trial?

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1. Abstract

1.1. Purpose: It is not known how patients who receive a secondary prevention Implantable Cardioverter Defibrillator (ICD) in clinical practice compare with patients from the Antiarrhythmic Versus Implantable Defibrillator (AVID) trial.

1.2. Methods: We compared the characteristics of patients in the AVID trial with those receiving a secondary prevention ICD in the National Cardiovascular Data Registry (NCDR) ICD Registry. We included all randomized AVID patients and patients in the ICD Registry undergoing first-time secondary prevention ICD implantation (2006-2008). Outcome data for ICD Registry patients were retrieved from the Medicare Claims database. Unadjusted all-cause mortality event rates were summarized with Kaplan-Meier rates.

1.3. Results: A total of 1016 patients and 19,203 patients were included from AVID and the ICD registry, respectively. Compared with patients enrolled in the AVID trial, the ICD Registry patients were older, were more likely to have heart failure and diabetes and less likely to have coronary artery disease and renal disease. Patients in the ICD registry were less often on an antiarrhythmic medication and digoxin. The 3-year mortality rates were 31.4% (95% CI 30.2, 32.5) for the ICD Registry patients, 31.4% (95% CI 25.7, 37.9) for ICD recipients in AVID, and 40.3% (95% CI 34.5, 46.6) for non-ICD patients in AVID.

1.4. Conclusions: Patients receiving a secondary prevention ICD in clinical practice differ significantly from patients in the AVID trial. Unadjusted mortality rates are similar between ICD Registry patients and ICD recipients in AVID and both are lower than rates observed in non-ICD patients in AVID.

2. Introduction

The risk of Sudden Cardiac Death (SCD) is high in suvivors of cardiac arrest due to Ventricular Fibrillation (VF) or Ventricular Tachycardia (VT) as well as in patients with sustained ventricular arrhythmias and structural heart disease [1, 2]. This risk can be significantly reduced with an Implantable Cardioverter Defibrillator (ICD) [1, 2]. The Antiarrhythmic Versus Implantable Defibrillator (AVID) trial that proved the role of ICDs in such patients was published in 1997 [1]. Importantly, this landmark trial proving the efficacy of ICD therapy was the only one of 3 randomized controlled trials that showed significant survival benefit from the ICD in this patient population [1, 3, 4]. Whether the findings of this trial are generalizable to clinical practice needs to be investigated, especially given the cost and potential complications associated with the ICD. Because randomized clinical trials generally enroll patients with fewer comorbidities and are usually conducted in highly controlled and monitored settings, the results of secondary prevention ICD trials may not be generalizable to routine clinical practice. Some studies have demonstrated the lack of generalizability of randomized clinical trials' findings to clinical practice in acute coronary syndromes, heart failure, hypertension, and depression [5-8]. Further, patients enrolled in the AVID trial may markedly differ from those in today's clinical practice since both this patient population and clinical practice have significantly changed since1997 [9]. It is not known how patients who receive an ICD for a secondary prevention indication in clinical practice compare with patients who were enrolled in the AVID trial.

We conducted this study to compare the characteristics of patients enrolled in the AVID trial with those receiving a secondary prevention ICD in the National Cardiovascular Data Registry (NCDR) ICD Registry. We also sought to assess long-term outcomes in the 2 groups.

3. Hypothesis

Patients who receive an ICD for a secondary indication in clinical practice differ significantly from those in the AVID trial.

4. Methods

We used data from the NCDR ICD Registry and the AVID trial. ICD Registry: The American College of Cardiology operates the National Cardiovascular Data Registry (NCDR), a comprehensive, outcomes-based cardiovascular quality improvement program encompassing both in-patient and ambulatory clinical registry programs. The NCDR programs use clinical data for the development and assessment of performance and quality metrics, quality improvement programs, and peer-reviewed outcomes research. The methods and quality metrics implemented in the NCDR have been published previously [10, 11]. Data are captured electronically and submitted into a secure, centralized database. NCDR programs include robust data quality processes, including an independent audit program. Details of NCDR data elements and definitions and participating sites are available on NCDR's website. A waiver of written informed consent and authorization for this study was granted by Advarra. In 2005, after CMS expanded the coverage indications for primary prevention ICDs to incorporate the findings from SCD-HeFT and MADIT II, the National Cardiovascular Data Registry (NCDR) ICD Registry became the mandated national registry, compiling data on Medicare patients implanted with primary prevention ICDs. Patient-level data are submitted by participating hospitals on a quarterly basis. The quality of data entered into the registry is ensured by quality checks, outlier analyses, and audits [10]. For the current analysis, the NCDR ICD Registry was used to identify a "clinical practice" cohort of patients with a secondary prevention ICD.

The Antiarrhythmics Versus Implantable Defibrillator (AVID) trial, conducted 1993-97, randomized 1016 patients who had survived life-threatening ventricular arrhythmias to an ICD or antiarrhythmic medication (mostly amiodarone; a few sotalol). Survival was better in the ICD arm, with a 7% absolute difference in event rates at 1 year and similar or larger differences at later time points, and hazard ratio = 0.62. Because the trial was stopped early, average follow-up was only 18 months. For the current analysis, the AVID trial was used to identify a "randomized clinical trial" cohort of patients with a secondary prevention ICD.

4.1. Patient Population

We analyzed patient-level data in the AVID trial. The original study included patients who were resuscitated from near-fatal VF; sustained VT with syncope; or sustained VT with an ejection fraction of 40% or less and symptoms suggesting severe hemodynamic compromise due to the arrhythmia (near-syncope, congestive heart failure, and angina). If patients underwent revascularization, the ejection fraction had to be ≤ 40% for them to be eligible for the study [12].

In the NCDR ICD Registry, we identified patients who received a secondary prevention ICD between January 1, 2006, and December 31, 2008 (n=74,912) who had a history of primary VT/VF, monomorphic or polymorphic sustained VT and syncope, or monomorphic or polymorphic sustained VT and ejection fraction ≤ 40%. Patients were excluded if they did not have prior Vsyncope due to VT (n=33,657), had a heart transplant (n=104), a prior ICD (n=17,824), NYHA Class IV at the time of implant (n=1362), or if they received a biventricular ICD (n=2762) during the index procedure. All Registry patients meeting the inclusion criteria are included in summaries of patient characteristics.

4.2. Statistical Analysis

Categorical variables are shown as percentages (n) and were compared with Pearson chi-square tests. Continuous variables are shown as medians (25th–75th percentiles) and were compared with Wilcoxon rank sum tests. Outcome data for ICD Registry patients were retrieved from the Medicare Claims database which only includes patients who are 65 years or older. Patients were excluded if the index admission could not be linked to Medicare data (n=13,047). Outcome analyses in the AVID cohort were confined to patients who were 65 years or older at the time of randomization. Unadjusted all-cause mortality event rates are summarized with Kaplan-Meier rates.

5. Results

All randomized patients (N=1016) were included from the AVID trial and 19,203 patients were included from the ICD registry.

Patient characteristics are shown in (Table 1). Compared with patients enrolled in the AVID trial, the ICD Registry patients were significantly older (25% vs. 18% were older than 75 years), had a higher ejection fraction (35% vs 30%), and were more likely to have heart failure (69% vs 57%) and diabetes (32% vs. 24%). Patients in the

ICD Registry were less likely to have coronary artery disease (65% vs 81%) and renal disease (6% vs 9%). In terms of medications at discharge, patients in the ICD registry were less often on an anti-arrhythmic medication (33% vs 52%) and digoxin (13% vs 44%). Patients in the ICD Registy more often received a beta-blocker (83% vs 29%) and a statin (62% vs 13%).

A total of 572 (n=56%) AVID patients who were 65 years or older at the time of the index admission were included in outcome summaries. From the ICD Registry, a total of 6,156 patients could be linked to the Medicare Claims database and were included in outcome summaries. Rates of all-cause mortality in the 2 groups are displayed in (Table 2). The 3year mortality rates were 31.4% (95% CI 30.2, 32.5) for the ICD Registry patients, 31.4% (95% CI 25.7, 37.9) for ICD recipients in AVID, and 40.3% (95% CI 34.5, 46.6) for non-ICD patients in AVID. Due to significant differences in baseline characteristics, event rates were not formally compared as no statistical test can reliably adjust for such differences especially in the presence of small sample sizes.

Table 1: Patient characteristics at the time of index hospitalization (all patients were included in this table).

	AVID	ICD Registry	P
N	1016	19,203	
Treatment (randomized for AVID)			
ICD	50% (507)	100% (19,203)	
Anti-arrhythmic therapy	50% (509)	—	
Index arrhythmia			<.0001
VF	45% (455)	61% (11,669)	
Sustained VT	55% (561)	39% (7,534)	
Demographics			
Age[1]			<.0001
< 55 years	15% (153)	24% (4,626)	
55-64 years	29% (291)	24% (4,554)	
65-74 years	38% (388)	27% (5142)	
≥ 75 years	18% (184)	25% (4,881)	
Male	79% (807)	72% (13,873)	<.0001
Non-white race	14% (138)	15% (2,824)	0.31
Measurements			
LVEF (%)	30 (20-39)	35 (25-45)	<.0001
Arrhythmia history/ECG			
Prior AF or flutter	23% (237)	31% (6,023)	<.0001
Prior VF (including index)	46% (468)	61% (11,669)	<.0001
Prior VT (including index)	57% (579)	83% (15,931)	<.0001
Prior syncope	13% (133)	47% (9,094)	<.0001
Medical history			
HF	57% (583)	69% (13,270)	<.0001
NYHA Class (for patients with CHF)			0.0004
I	36% (209)	36% (6,823)	
II	48% (280)	42% (7,990)	
III	16% (94)	23% (4,320)	
CAD	81% (828)	65% (12,440)	<.0001
Prior MI	67% (681)	56% (10,664)	<.0001
Prior PCI	10% (97)	32% (6,236)	<.0001
Prior CABG	30% (305)	26% (5,070)	0.011
Cerebrovascular disease	14% (145)	14% (2,663)	0.72
Hypertension	56% (567)	72% (13,756)	<.0001
Diabetes	24% (247)	32% (6,066)	<.0001
Renal disease	9% (89)	6% (1,151)	0.0004
COPD	16% (164)	21% (4,127)	<.0001
Medications at discharge (for pts discharged alive)			
N	995	19,074	
Antiarrhythmic	52% (533)	33% (6,283)	<.0001
ACE-inhibitor or ARB[3]	68% (692)	68% (12,899)	0.75
Beta blocker	29% (291)	83% (15,899)	<.0001
Digoxin	44% (445)	13% (2,426)	<.0001
Statin	13% (130)	62% (11,788)	<.0001

[1] Exact age is not given in the AVID database; instead, age in 5 year categories is given, ranging from <35, 35-39,80-84, 85+.

[2] Baseline = randomization for AVID and implantation for the ICD Registry.

[3] There were no ARBs in AVID.

Categorical variables are shown as percent (n) and compared with Pearson chi-square tests. Continuous variables are shown as median (25th–75th percentiles) and compared with Wilcoxon rank sum tests.

Table 2: All-cause mortality for AVID and ICD Registry patients (only patients ≥ 65 years of age were included in this table).

	ICD Registry	All AVID	AVID ICD	AVID Antiarrhythmic
N	6,156	572	278	294
Follow-up duration among non-event pts (years)				
Median	5.2	2.9	2.8	3
25^{th}, 75^{th} percentiles	5.2, 5.2	2.0, 3.7	2.0, 3.6	2.2, 3.7
Min, max	5.2, 5.2	0.3, 5.2	1.0, 5.2	0.3, 5.2
Total deaths	2942	207	86	121
Event rates (Kaplan-Meier)				
1 year: Event rate (95% CI)	15.0% (14.2, 16.0)	17.0% (14.1, 20.3)	13.7% (10.1, 18.3)	20.1% (16.0, 25.2)
Number at risk	5,230	472	238	234
2 years: Event rate (95% CI)	23.5% (22.5, 24.6)	26.2% (22.7, 30.1)	21.8% (17.3, 27.2)	30.4% (25.4, 36.1)
Number at risk	4,711	337	170	167
3 years: Event rate (95% CI)	31.4% (30.2, 32.5)	36.0% (31.8, 40.5)	31.4% (25.7, 37.9)	40.3% (34.5, 46.6)
Number at risk	4,227	187	89	98

6. Discussion

This study assessed how patients receiving a secondary prevention ICD in clinical practice compare with patients in the only randomized clinical trial that showed benefit of secondary prevention ICDs. Our analysis shows that patients receiving a secondary prevention ICD in clinical practice are significantly different from patients enrolled in the AVID trial. Despite these differences and our inability to report adjusted outcomes, at least numerically, the rates of death at 1, 2, and 3 years in the ICD registry were comparable to those observed in ICD recipients in the AVID trial and these rates were lower than those seen in non-ICD patients in the AVID trial.

Our results are not surprising as randomized clinical trial populations are typically "healthier" than patients seen in clinical practice. Further, patients and clinical practice have changed appreciably since 1997. As seen in other patient populations, patients have become older and more morbid than in previous years. Among patients with sudden cardiac arrest, the incidence of ischemic heart disease seems be decreasing while other conditions such as hypertensive cardiomyopathy seem to be increasing [13]. Another important change is the improved use of life-prolonging medications such as beta-blockers, angiotensin receptor neprilysin inhibitor, and mineralocorticoid receptor antagonists. A similar analysis comparing patients receiving a primary prevention ICD in the ICD Registry with those of patients enrolled in the pivotal ICD trials showed that patients in the ICD Registry were significantly older and had a greater burden of coexisting illnesses than trial patients [3]. Despite these differences in patient characteristics, ICD Registry patients had similar survival to matched patients in the clinical trials [3].

Importantly, our study demonstrates widespread adoption of guideline-directed medical therapy, namely use of beta-blockers, in this cohort of patients with a low ejection fraction. The use of spironolactone, not assessed in AVID and so not included in the current study, may also be greater in contemporary clinical practice. Our study also shows low use of digoxin and antiarrhythmic drugs, both of which may have a negative impact on survival.

While outcomes of the 2 groups could not be formally compared in the present study due to small sample sizes, numerically, the rates of death in the ICD registry were comparable to those observed in ICD recipients in the AVID trial. Also, a recent analysis of the NCDR ICD Registry showed that almost 4 in 5 older patients receiving a secondary prevention ICD survive at least for 2 years [14]. A trial of secondary prevention ICDs versus no ICDs in a contemporary cohort will likely never be feasible due to the widespread acceptance of the importance of the ICD in such high-risk populations. Thus, the AVID trial will continue to serve as the foundation of professional guideline recommendations to offer an ICD to AVID-like patients, and the results of the current analysis appear to support this practice [9].

Several limitations of this analysis should be considered when interpreting the results. In the timeframe of this study, inclusion of patients in the NCDR was required as a condition for reimbursement to Medicare beneficiaries undergoing primary prevention ICD implantation, but there is no such requirement for secondary prevention ICDs. However, 91% of participating sites also include data regarding secondary prevention ICDs. Thus, the data and related study results reflect the centers/practices participating and may not be generalizable to larger U.S. or non-U.S. practice. Although sites are expected to submit comprehensive data for all patients meeting registry inclusion criteria, some eligible patients may not be included. Although we chose to include patients in the earlier period of the NCDR registry (2006-2008) to have a population more comparable to the one in the AVID trial, our NCDR population is similar to a more contemporary NCDR population [14, 15]. Due to the small sample size for outcomes analysis, it was not possible to present a formal comparison of outcomes between the trial and the registry population.

7. Conclusions

Despite significant differences in patient characteristics and discharge medications between patients enrolled in the AVID trial and those receiving a secondary prevention ICD in clinical practice, unadjusted mortality rates are similar between ICD Registry patients and ICD recipients in AVID and both are lower than rates observed in non-ICD patients in AVID.

8. Disclaimer

This research was supported by the American College of Cardiology's National Cardiovascular Data Registry (NCDR). The views expressed in this manuscript represent those of the author(s), and do not necessarily represent the official views of the NCDR or its associated professional societies identified at CVQuality.ACC.org/NCDR.

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