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EDITORIAL COMMENT

Secondary Prevention

A Blast From the Past*

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The indication for a secondary prevention implantable cardioverter-defibrillator (ICD) has been incontrovertible for patients without a clear and completely reversible cause for ventricular arrhythmia occurrence. A broad group of patients who have survived cardiac arrest due to ventricular fibrillation (VF) or hemodynamically significant sustained ventricular tachycardia (VT) are candidates for an ICD, receiving the highest level of recommendation in practice guidelines (1,2). The evidence supporting the use of ICD therapy rests upon randomized clinical trials that were conducted many years ago, in the 1980s and 1990s. Of the 3 most often cited trials (3-5), only the AVID (Antiarrhythmics Versus Implantable Defibrillators) trial found a statistically significant benefit to ICD therapy compared with patients treated with antiarrhythmic drugs (predominantly amiodarone), with a 2-year absolute and relative mortality reduction of 6.9% and 27%, respectively (2-year mortality: 18.4% for ICD and 25.3% for control patients) (3). The smaller CIDS (Canadian Implantable Defibrillator Study) randomized 331 patients to receive an ICD and 328 patients to amiodarone. Two-year mortality was 14.8% and 21.0%, respectively (4). The relative risk reduction for ICD therapy was 19.7% ($p = 0.142$).

The current study by Katz et al. (6) in this issue of *JACC: Clinical Electrophysiology* uses the NCDR (National Cardiovascular Data Registry) ICD Registry to describe patterns of ICD implantation for secondary prevention indications in contemporary practice, representing a very heterogeneous population. This study included 46,685 patients enrolled into the NCDR ICD Registry between 2006 and 2009. The indication for the ICD in 78% of the patients was sudden cardiac death (SCD) or VT, and in 22% of patients, the ICD was implanted for syncope.

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Despite the differences in time periods, improved usage of guideline-directed medical therapy, and better ICD technology with enhanced programmable options in more recent years, what is strikingly apparent is that outcomes for those enrolled in the NCDR and those studied in the randomized clinical trials are not dramatically different. Mortality rates in the NCDR at 1 and 2 years were 10% and 16%, respectively, compared with 8% to 11% and 15% to 18%, respectively, among ICD patients enrolled in the secondary prevention randomized trials (3-5). Contemporary ICD patients appear to be slightly older, with a higher left ventricular (LV) ejection fraction (EF) despite more severe heart failure when compared with patients in AVID and CIDS, the 2 largest secondary prevention randomized trials (3,4). Key clinical characteristics comparing patients in the NCDR to those in AVID, CIDS, and CASH (Cardiac Arrest Study Hamburg) are shown in **Table 1**. Most notable is that the proportion of patients with ischemic heart disease in the randomized clinical trials was 73% to 83% compared with only 64% in the NCDR. Mortality rates among patients with nonischemic heart disease are generally less than those with ischemic causes of heart disease. These observations, along with the higher LVEF of 36% among the NCDR patients compared

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TABLE 1 Patient Characteristics, Treatment, and Outcome in ICD Randomized Clinical Trials for Secondary Prevention (for ICD Groups, Unless Otherwise Specified)

	NCDR	AVID	CIDS	CASH
Study dates	2006–2009	1993–1997	1990–1997	1987–1998
Subjects, n	46,685	1,016	659	191
ICD group	46,685	507	328	99
Medical therapy group	–	509	331	189
Enrollment criteria	Cardiac arrest, VF, VT, syncope	Cardiac arrest, VF, VT	Cardiac arrest, VF, VT, syncope	Cardiac arrest, VF
Primary endpoint	Mortality	Mortality	Mortality	Mortality
Age, yrs	66 ± 14	65 ± 11	63 ± 9	58 ± 11
Male	73	78	85	79
Underlying heart disease				
CAD	64	81	83	73
Nonischemic CM	23	15	10	12
LVEF	36 ± 15	32 ± 13	34 ± 14	46 ± 19
NYHA functional class ≥3	32	7	11	18
Presenting arrhythmia				
VF	51	45	45	100
VT with syncope	–	21	16	0
VT, other	27*	34	24	0
Syncope	22	0	15	0
Beta-blocker on discharge	84	42	33	0
ACE inhibitor on discharge	60	69	–	45
ARB on discharge	12	–	–	–
ICD, thoracotomy device	0	5	11	56
Mean follow-up, months	–	18 ± 12	36	57 ± 34
1-yr mortality				
Antiarrhythmic drug group	–	17.7	11.2	15.2
ICD group	10.4	10.7	9.5	8.1
2-yr mortality				
Antiarrhythmic drug group	–	25.3	21.0	27.2
ICD group	16.4	18.4	14.8	17.2

Values are mean ± SD or %, unless otherwise indicated. *With or without syncope, not specified.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CM = cardiomyopathy; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.

with 32% in the AVID and 34% in the CIDS ICD patients, respectively, should have resulted in an observed lower mortality in the NCDR patients. Focusing on the larger AVID trial for comparison, we see that this was true by 2 years (16.4% in NCDR vs. 18.4% in the AVID ICD patients), but was not the case at 1 year (10.4% in NCDR vs. 10.7% in the AVID ICD patients). Another important difference among the patients enrolled in the trials compared with the NCDR is that the background medical therapy was underprescribed relative to contemporary "optimal" and "guideline-directed" medical therapy. Specifically, medications that have been previously shown to reduce mortality in patients with reduced LV function, such as beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, were underutilized in ICD trials.

The current paper also adds to our knowledge about outcomes of patients presenting with syncope thought to be arrhythmic in the setting of underlying structural heart disease. Despite a Class IIa recommendation for such patients, only 1 trial (CIDS) included patients such as these, and even then only a small number—49 total patients who received an ICD (2,4). On the other hand, 22% or 10,270 patients with syncope were included in the NCDR. The 1-year mortality rate among the syncope patients was 9.2%, compared with 10.9% in the NCDR patients with sudden cardiac arrest or VT ($p < 0.001$). Although the syncope patients had a significantly lower hazard of death at 1 year compared with those in the sudden cardiac arrest/VT group, after multivariable models adjusted for differences in baseline characteristics, it is interesting to note that this difference was no longer present at 2 years. This finding points out the high risk associated with syncope, even when VT is undocumented. Although ICD events during follow-up are not available in the NCDR, other studies have shown high appropriate ICD therapy rates in syncope patients with both ischemic and nonischemic heart disease (7–9).

Despite the availability of randomized clinical trials evaluating the efficacy of ICD therapy in patients who present with sustained ventricular arrhythmias and published guidelines formalizing recommendations for ICD implantation, there are still many "gaps" in the guidelines. For example, we continue to struggle with the management of patients who experience sustained ventricular tachycardia early (<48 h) after myocardial infarction (MI) or revascularization. In the current NCDR study, the authors chose to look at a time frame around ICD therapy that is important in primary prevention ICD-indicated patients: 40 days. The results of the DINAMIT (Defibrillator in Acute Myocardial Infarction Trial), and IRIS (Use of Implantable Defibrillator in High-Risk Patients Early After Acute Myocardial Infarction) trials showed no benefit of prophylactic ICDs in reducing all-cause mortality in patients with low EF who were within 40 or 30 days, respectively, of acute MI (10,11). Although these findings are not applicable to secondary prevention ICD considerations, the observation that 13% of the NCDR patients experienced an MI within 40 days before ICD implantation in the current NCDR study is interesting.

According to the 2008 practice guidelines, "ICD therapy is indicated in patients who are survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes (Level of Evidence: A)" (2). Admittedly, it may