Published in final edited form as:
Circ Cardiovasc Qual Outcomes. 2012 November 1; 5(6): e78–e85. doi:10.1161/CIRCOUTCOMES.112.965368.

The Longitudinal Study of Implantable Cardioverter Defibrillators: Methods and Clinical Characteristics of Patients Receiving Implantable Cardioverter Defibrillators for Primary Prevention in Contemporary Practice

Frederick A. Masoudi MD MSPH[1,2], **Alan S. Go MD**[3,4], **David J. Magid MD MPH**[1,2], **Andrea E. Cassidy-Bushrow, PhD, MPH**[5], **Jonathan M Doris, MD**[6,7], **Frances Fiocchi, MPH**[8], **Romel Garcia-Montilla, MD PhD MSc**[9,10], **Karen A. Glenn BS**[2], **Goldberg Robert J, PhD**[11], **Nigel Gupta, M.D.**[6], **Jerry H. Gurwitz, MD**[12], **Stephen C. Hammill, MD**[13], **John J. Hayes, MD**[10], **Nathaniel Jackson, MS**[2], **Kadish Alan, MD**[14], **Michael Lauer, MD,PhD**[15], **Aaron W. Miller, PhD**[9], **Deborah Multerer**[9], **Pamela N. Peterson, MD, MSPH**[1,2,16], **Liza M. Reifler, MPH**[2], **Kristi Reynolds, PhD MPH**[17], **Jane S. Saczynski, PhD**[12], **Claudio Schuger, MD**[18], **Param P. Sharma, MD**[10], **David H. Smith, RPh PhD**[19], **Mary Suits, RN**[10], **Sue Hee Sung, MPH**[3], **Paul D. Varosy, M.D.**[1,2,20], **Humberto J. Vidaillet, MD**[10], and **Robert T. Greenlee, PhD, MPH**[9]

[1]University of Colorado Anschutz Medical Campus, Aurora, CO

[2]Institute for Health Research, Kaiser Permanente Colorado, Denver, Colorado

[3]Division of Research, Kaiser Permanente Northern California, Oakland, California

[4]Departments of Epidemiology, Biostatistics and Medicine, University of California, San Francisco, San Francisco, CA

[5]Department of Public Health Sciences, Henry Ford Hospital, Detroit, Michigan

[6]Kaiser Permanente, Los Angeles Medical Center, Los Angeles, California

[7]UCLA/Geffen School of Medicine, Los Angeles, California

[8]American College of Cardiology Foundation, Washington, DC

[9]Marshfield Clinic Research Foundation, Marshfield, Wisconsin

[10]Marshfield Clinic, Marshfield, Wisconsin

[11]University of Massachusetts Medical School, Worcester, Massachusetts

[12]Meyers Primary Care Institute, Worcester, Massachusetts

[13]Mayo Clinic, Rochester, Minnesota

[14]Touro College, New York, New York

Corresponding Author: Frederick A. Masoudi, MD, MSPH, Associate Professor of Medicine, University of Colorado Denver, Mail Stop B132, 12401 E. 17th Avenue, Room 522, Aurora CO 80045, Phone: 720-848-6580, Fax: 720-848-7315, fred.masoudi@ucdenver.edu.

Conflict of Interest Disclosures: Dr. Masoudi has a contract with the American College of Cardiology Foundation. Dr. Gupta is a site PI for studies funded by Medtronic and St. Jude. Dr. Doris is a site PI for studies funded by Medtronic and St. Jude. Dr. Hayes has served as a consultant for Medtronic and Boston Scientific. Dr. Kadish has received grant support from St. Jude and is a consultant for Impulse Dynamics. Dr. Schuger has received research support from Boston Scientific, St. Jude, and Medtronic.

[15]Kaiser Permanente Santa Clara, Santa Clara, California

[16]Denver Health Medical Center, Denver, CO

[17]Department of Research and Evaluation, Kaiser Permanente Southern California

[18]Henry Ford Hospital Heart & Vascular Institute, Detroit, Michigan

[19]Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon

[20]VA Eastern Colorado Health Care System, Denver, Colorado

Abstract

Background—Implantable cardioverter defibrillators (ICDs) are increasingly used for primary prevention followingrandomized controlled trials (RCTs) demonstrating that they reduce the risk of death in patients with left ventricular systolic dysfunction (LVSD). The extent to which the clinical characteristics and long-term outcomes of unselected, community-based patients with LVSD undergoing primary prevention ICD implantation in a real-world setting compare with those enrolled in the RCTs is not well characterized. The Longitudinal Study of ICDs is being conducted to address these questions.

Methods and Results—The study cohort includes consecutive patients undergoing primary prevention ICD placement between 1/1/2006 and 12/31/2009 in seven health plans. Baseline clinical characteristics were acquired from the NCDRICD Registry. Longitudinal data collection is underway and will include hospitalization, mortality, and resource utilization from the Virtual Data Warehouse. Data regarding ICD therapies will be obtained through chart abstraction and adjudicated by a panel of experts in device therapy. Compared with the populations of primary prevention ICD therapy RCTs, the cohort (n=2,621) is on average significantly older (by 2.5-6.5 years); more often female, more often from racial and ethnic minority groups, and has a significantly higher burden of coexisting conditions. The cohort is similar, however, to a national population undergoing primary prevention ICD placement.

Conclusions—Patients undergoing primary prevention ICD implantation in the Longitudinal Study of ICDs differ from those enrolled in the RCTs that established the efficacy of ICDs. Understanding a broad range of health outcomes, including ICD therapies, in this cohort will provide patients, clinicians, and policy-makers with contemporary data to inform decision-making.

Keywords

arrhythmia; electrophysiology; epidemiology

Implantable cardioverter defibrillators (ICDs) have revolutionized the care of patients at risk for sudden cardiac death (SCD). These devices, which detect and treat malignant ventricular arrhythmias, have been used increasingly both because of the evolution of ICD technology and randomized clinical trials (RCTs) demonstrating their mortality benefit in selected populations.[1-4] Because ICD therapy carries risks and is costly, the use and outcomes associated with this therapy outside of selected trial populations and specialized treatment centers have been an increasing focus of interest by patients, clinicians, and policy-makers.

Individuals with left ventricular systolic dysfunction (LVSD) are at substantially higher risk for SCD than the general population, making them one of the largest target populations for consideration of primary prevention ICD therapy. In the last decade, several RCTs have been published, resulting in expanded indications for the use of ICDs to many patients with LVSD. [1-4] With the publication of SCD-HeFT, which demonstrated improved survival with ICD therapy in patients with both ischemic and non-ischemic cardiomyopathy,[4] the Centers for Medicare and Medicaid Services (CMS) expanded its financial coverage for primary

prevention ICDs for its beneficiaries.[5] Guideline recommendations for considering ICD therapy following the publication of SCD-HeFT also expanded to include most patients with LVSD.[6, 7] Currently, the combined number of intervention subjects from the key primary prevention RCTs[3, 4] is exceeded substantially by the number of new primary prevention ICD implants in the US each month.[8]

ICDs are also associated with important risks. ICD implantation can result in procedural complications, which may occur more frequently in practice than in existing clinical trials.[9] ICDs are efficacious because of their ability to detect and appropriately treat life threatening ventricular arrhythmias with anti-tachycardia pacing (ATP) and/or high-energy shocks. However, not all patients with defibrillators receive device therapies upon long-term follow-up,[10] and conversely, ICDs can deliver therapies for inappropriate reasons, particularly supraventricular tachyarrhythmias, including atrial fibrillation, or ICD malfunction.[11, 12] ICD therapies, particularly inappropriate shocks, may be associated with adversepatient health outcomes and higher costs of care.[13, 14]

The expanding use of ICDs underscores the importance of understanding the characteristics of patients receiving ICDs outside of the context of RCTs. Patients studied in RCTs often differ substantially from those receiving therapy in clinical practice.[15] These differences likely modify the effectiveness and safety of ICDs in real-world patient populations with respect to a broad range of outcomes, including mortality, hospitalization, complications, and therapies delivered by the ICD.

The Longitudinal Study of ICDs (LSICD) is designed to investigate a broad range of outcomes including device therapies in a contemporary cohort of patients with LVSD receiving ICDs for the primary prevention of SCD in clinical practice. Our objective is to describe the methods of this multi-center observational study and compare the enrolled cohort with the participants in published RCTs and with a national observational cohort. The purpose of the study is to inform clinical and policy decisions on the use of ICD therapy for primary prevention of SCD in patients with LVSD.

Methods

Setting

The study is being conducted by seven health plans of the HMO Research Network (HMORN), a partnership of 16 research programs within health care systems with large defined health plan populations.[16] The study sites are also members of the National Heart, Lung and Blood Institute-sponsored Cardiovascular Research Network (CVRN) collaborative within the HMORN. The CVRN has established a robust research framework to address a broad spectrum of important issues in large, community-based populations, including evaluation of the adoption and clinical impact of new diagnostic and therapeutic technologies.[17] Institutional review boards at participating sites approved the study. Waiver of informed consent was obtained due to the nature of the study. Drs. Masoudi and Greenlee had access to all data and affirm its accuracy.

Study Population

We assembled a retrospective cohort of subjects (n=2621) with LVSD receiving a first-time ICD implant between January 1, 2006 and December 31, 2009 for primary prevention of SCD at one of 14 hospitals owned by or affiliated with the 7 participating health care systems(Appendix A). All eligible subjects will have follow-up information available on clinical outcomes, device therapies, and health care utilization. Device therapy data will be collected for a maximum of three years following ICD implantation. Because of the planned study end date, some subjects with devices placed in 2009 will be followed for only 2 years.

Member retention in the CVRN is generally high.[17] In a preliminary analysis based on health plan membership data, only 8% of subjects that were health plan members at the time of their ICD implant have dis-enrolled through 2010. Eligibility criteria are broad to maximize generalizability of study findings. Study subjects meet all of the following: 1) ICD indication of primary prevention; 2) no prior ICD; 3) LVSD, defined as a left ventricular ejection fraction of <50%; and 4) membership in one of the participating health plans at the time of study entry or other evidence that the subject was to receive ICD follow-up care through participating health systems. Consecutive eligible subjects from the participating sites are included in the study.

Study Funding and Governance

The LSICD represents an expansion of a 4-site CVRN study funded by NHLBI that was designed to include at least 1 year of subject follow-up for mortality and hospitalization events. The study was expanded with additional support from the Agency for Healthcare Research and Quality (AHRQ) and from the American College of Cardiology Foundation (ACCF), allowing for the inclusion of three additional sites, the collection of ICD therapy data, and extended subject follow-up. The expanded LSICD has a stakeholder committee that includes representatives from the 3 funders as well as representatives from CMS, the Sudden Arrhythmic Death Syndromes Foundation, the Heart Rhythm Society, and a representative from an ICD manufacturer (St. Jude).

Study Aims

The LSICD has 4 Primary Aims:

Aim 1. To identify the extent to which cohort members meet contemporary RCT-based guideline recommended eligibility criteria, and determine the degree to which this varies across demographic groups.

Aim 2. To assess longitudinal outcomes (ICD-related complications; all-cause mortality; all cause and heart failure hospitalization; and cost) among the cohort of primary prevention ICD patients with LVSD and compare these outcomes with published RCTs.

Aim 3. To identify the patient, device, and provider characteristics associated with these outcomes.

Aim 4. To assess the rates of device therapies (overall, appropriate, and inappropriate) during the first three years after implantation for patients in the following CMS ‘Group B’ subpopulations.[8] These subgroups were identified by a technical expert panel commissioned by CMS as those of particular clinical interest and include:

- **a.** LVEF 31-35% compared with LVEF <=30%.
- **b.** Non-ischemic cardiomyopathy less than 9 months before implantation compared to those non-ischemic cardiomyopathy for a longer period.
- **c.** New York Heart Association (NYHA) Class IV heart failure symptoms receiving a CRT-D compared with CRT-D recipients who have NYHA Class III symptoms.

Data Sources

Three primary data sources are being used for this study.

National Cardiovascular Data Registry (NCDR)

The NCDR ICD Registry provides baseline characteristics for study subjects (Appendix B). The registry was formed in 2005 in response to the coverage with evidence requirement from the CMS, with data collection beginning in 2006. Data of interest from the NCDRICD Registry for this study include ICD eligibility and other clinical criteria, device and provider detail, and adverse events during the index implant hospitalization.

The Virtual Data Warehouse (VDW)

Member sites have mapped and transformed elements from their unique clinical and administrative systems into a distributed data resource with standard variable definitions, referred to as the Virtual Data Warehouse (VDW).[17,18] This common file structure allows a single programmer to write code for distribution to all participating locations for study data extraction with minimal site-specific code adjustment. The present study includes VDW data beginning in 2003 in order to capture up to three years of medical history and comorbidity information prior to ICD device implantation and through 2011 for follow-up after ICD placement. Six primary VDW content areas were selected for the LSICD, including enrollment, demographics, utilization, pharmacy, laboratory test results, and mortality (Appendix C).

Evaluation of the agreement between the values of variables collected in both the NCDR ICD Registry and participating health plan VDW tables indicate that discrepancies are uncommon and agreement is high. For example, the gender value was in agreement 99.4% of the time when present in both locations (Kappa 0.985). Similarly, the mean age at implant was virtually identical (Pearson Correlation Coefficient 0.982). In cases where year of birth or gender were discrepant, data investigations were undertaken at the study sites to update study files with correct information. Agreement was slightly lower but still excellent between VDW and NCDR sources for 6-category race values (Weighted Kappa 0.873) and Hispanic ethnicity (Kappa 0.782). In cases of discrepancies, the study has deferred to the NCDR data values. The Pearson correlation coefficients for common laboratory tests, including creatinine, sodium, BUN, and BNP, between the NCDR and VDW ranged from 0.77-0.97.

ICD Therapy Data

The study will also include data on adjudicated arrhythmia episodes resulting in device therapies (i.e., shocks and ATP) delivered during the first 3 years after device placement for each subject (Appendix D). The process to develop this repository includes manual medical record abstraction at the study sites with central clinical review and adjudication of source documentation. For each treated arrhythmic episode, a copy of the archived device report with intracardiac electrograms, and any relevant clinical notes, including the local provider interpretation, are requested. Additionally, copies of the surgical implant notes and documentation from the last device interrogation for the follow-up period are requested for all subjects (Appendix E).

Following central collation of abstraction records and supporting documentation, a study manager and the study's ICD nurse conduct a completeness/quality review for each subject, and document the local provider interpretations of any potential treated episodes. Records and supporting documentation are then provided to the Central Review panel, which consists of 3 board-certified electrophysiologists and 1 hospitalist physician with expertise in interpreting ICD device reports and clinical records. The Central Review panel confirms or refutes the occurrence of treated episodes, determines the initial type of therapy (ATP or shock), determines whether the episode required multiple therapies, and adjudicates the appropriateness of therapy using standardized criteria. Reviewers also note the extent of

source documentation available for each episode. All reviews are based on standard procedures and definitions included in the Review Glossary developed through extensive discussion of central and external panel members using literature-based guidance (Appendix F). Each record is reviewed independently by 2 of the 4 panelists, with an attempt to resolve any discrepancies via reviewer conference or arbitration as needed.

A separate group of 3 expert electrophysiologists provides external adjudication of treated arrhythmic episodes. Selection of treated episodes for external adjudication includes any with discrepancies that could not be resolved by the Central Review panel, and for quality assurance, random samples of records with resolved discrepancies and of records without any discrepancies. Central Review panel members also can nominate any treated episode for external adjudication.

While the planned length of follow-up is 3 years, abstraction of device therapy data is to be truncated before 3 years of follow-up after reaching the subject's 10^{th} treated arrhythmic episode, provided those 10 episodes include at least one appropriate and one inappropriate therapy. Otherwise, abstraction of device therapy will be continued for the full follow-up period. A maximum of 3 episodes are to be collected and counted from any 24-hour period, in order to limit the potential burden of data generated by “VT storm,” which is not the primary focus of this research.

Data Management

All study data will be compiled for analysis at the study-coordinating center (Kaiser Permanente Colorado Institute for Health Research). Following necessary amendments to hospital registry agreements with the ACCF (i.e., Data Release Consent Forms), NCDR-ICD data from 14 cooperating hospitals in the seven study sites were transmitted to the corresponding study site investigators to match to health plan membership and assign unique study IDs. Data Use Agreements (DUAs) were also obtained between study sites and Kaiser Permanente Colorado; subsequently NCDR-ICD data for all matched subjects were transmitted from the ACCF to the study-coordinating center. For VDW data, analytic programs were composed at the study-coordinating center and distributed to study site programmers.

Therapy data collection and adjudication are being coordinated by Marshfield Clinic Research Foundation, which has DUAs with all other study sites for this purpose. Training has been provided to site abstractors through in-person meetings, web seminars, regular abstractor team conference calls, and ongoing one-on-one communication with the therapy collection coordinator. A central program has been distributed to sites to periodically generate batches of subjects for abstraction based on date of implant and vital status. A Microsoft Access (Redmond, WA) database has been developed to track initial receipt of therapy abstraction records, and to monitor progress through intake review, central clinical review and resolution, and the external adjudication processes (Appendix G). The data captured on abstraction and review forms are entered into the database with quality assurance monitoring. Once complete, final therapy data will be forwarded from Marshfield Clinic Research Foundation to the study coordinating center at Kaiser Permanente Colorado to be combined with NCDR-ICD and VDW data for each subject.

Study Timeline

A cohort of 2621 subjects has currently been assembled. A pilot study of abstraction and review procedures was conducted in the summer and fall of 2010, with final procedure modifications completed in early 2011. For the pilot, each site submitted therapy data on at least 6 subjects, half with one or more treated arrhythmic episodes. A brief summary of

therapy collection pilot results for the 43 subjects and their 493 interrogations, and 162 treated episodes can be found in Appendix H. Therapy collection will continue into the summer of 2012, with final review and adjudication of records in the fall of 2012. Clinical outcomes will be analyzed beginning in 2012. Final data merger and analyses involving therapy data will occur in early 2013. A list of study team members at all sites is included in Appendix J.

Statistical Analysis

The demographic and clinical characteristics of the population of the Longitudinal Study of ICDs were compared with two primary categories of patients from the published literature. First, we compared our sample with the published data characterizing the populations who underwent ICD placement from MADIT-II and SCD-HeFT, the RCTs that largely form the basis of current guideline recommendations for primary prevention ICD therapy (Table 1).[3, 4] Second, a national population of patients undergoing primary prevention ICD placement in 2006 and 2007 from the NCDRICD Registry was also examined.[19] This allowed for a comparison with a larger community-based population of patients receiving ICD therapy for similar indications. Continuous variables (reported as means with standard deviations) were compared across groups using Student's t-tests; categorical variables were compared using chi-square tests. All analyses were performed using SAS statistical software, version 9.1.3 (Cary, NC). A two-sided P value less than 0.05 was considered statistically significant.

Results

The Study Cohort

During the enrollment period (1/2006-12/2009) in the seven health plans, 3,254 patients underwent primary prevention ICD placement. Of these, 520 were excluded because they were undergoing device revision or replacement. Of the remainder undergoing first-time ICD placement for primary prevention, 98 had normal LVEF and 15 had no documented LVEF assessment; these patients were also excluded. Thus, the study cohort was comprised of 2,621 patients with LVSD undergoing first-time ICD implantation for the primary prevention of SCD.

CVRN Longitudinal Study of ICDs Cohort Compared with Primary Prevention RCTs

The characteristics of the study cohort and those of the MADIT-II (n=742) and SCD-HeFT (n=849) trials are shown in Table 2. The mean age of the cohort was 66.7 ± 11.7 years, which was higher than that of the populations from the RCTs, ranging from almost 7 years higher than the mean age of the SCD-HeFT population to nearly 3 years higher than the average age of the population of MADIT-II. One quarter of the population was female, significantly higher than that of MADIT-II, but similar to that of SCD-HeFT. Almost one third of the population was non-White, compared with 23% in SCD-HeFT; information on race was not reported in MADIT-II.

With respect to clinical characteristics, left ventricular systolic function was clinically similar (25%± 6.9) in the cohort compared with the patient populations enrolled in the RCTs (MADIT II 23%±5; SCD HeFT 23.5%±7). The majority of the cohort had symptoms of NYHA class II or III (86.3%), a proportion that was significantly higher than the populations of the MADIT II trial but lower than the SCD-HeFT population. In general, the proportion of patients in the cohort with comorbid conditions, including diabetes mellitus, hypertension, and atrial fibrillation/flutter was significantly higher than in the RCTs. Comparisons of medication use were limited by the availability of reported data in the RCTs; however, patients in the cohort were significantly more likely to receive beta

blockers and statins than the populations of the RCTs and significantly less likely to receive digoxin than the populations in the RCTs.

Longitudinal Study of ICDs Cohort Compared with a National Primary Prevention Cohort

In general, the cohort was similar to the national cohort of patients undergoing primary prevention ICD placement in 2006-2007 from NCDR (Table 3). However, the cohort was on average 1 year younger and a larger proportion of cohort members were non-white. The prevalence of comorbidities were similar, and rates of medication therapy at discharge after device placement were also similar, with the exception of statins, which were more frequently prescribed in the study cohort than in the national cohort.

Discussion

The Longitudinal Study of ICDs is designed to assess a broad range of patient outcomes, including ICD therapies, in a contemporary community population of patients receiving an ICD for the primary prevention of SCD. This cohort differs substantially from participants enrolled in the RCTs that form the basis of current guideline recommendations for primary prevention ICD implantation in that the cohort was older, had a higher proportion of women and non-white patients, and had a significantly higher burden of comorbid illnesses. The cohort is similar to a national cohort of patients undergoing primary prevention ICD placement, suggesting that the patient population of this study is typical of patient populations seen in a broad range of community practices in the US. Thus, this study will be able to provide valuable insights into the frequency and determinants of outcomes of patients receiving primary prevention ICD therapy.

Although studies of patients receiving ICDs in community practice exist, they have a variety of relevant limitations. Reports of national populations of patients using Medicare billing data have the advantage of substantial sample size. However, they are restricted to older patients with Medicare coverage and lack the ability to identify important clinical characteristics of the patient population.[20] National registry data, on the other hand, include a broader range of patients with respect to age, clinical characteristics, and insurance coverage. However, the NCDRICD Registry itself only captures data from the episode of care when the ICD was implanted, and thus must be linked to external sources of longitudinal data to assess outcomes after hospital discharge. Other observational studies of ICD therapy have attempted to examine longitudinal mortality in ICD recipients but have been restricted to modest-sized samples with limited representativeness.[21] The Advancements in ICD Therapy (ACT) registry included mortality data for 4,556 patients undergoing first-time ICD placement in 264 centers. However, enrollment in this registry was performed in 2004-2006 (i.e. around the time of the publication of SCD-HeFT, which had important implications for subsequent guidelines); did not focus on primary prevention ICDs; and only included patients who received defibrillators from a single manufacturer.[22] The Longitudinal Study of ICDs is comprised of a large, contemporary population of consecutive patients receiving ICD therapy in seven large health systems regardless of device manufacturer; includes detailed clinical data; and will follow patients longitudinally for a broad range of outcomes, including mortality, hospitalizations, ICD-related complications and ICD therapies.

Although previous studies have elucidated the differences between patients enrolled in clinical trials and those treated in general practice for several cardiovascular conditions, few have directly explored these differences in patients receiving ICD therapy. It is well known, for instance, that only a minority of elderly patients hospitalized for heart failure would meet the enrollment criteria for landmark RCTs of heart failure pharmacotherapy.[15] Furthermore, in general, elderly patients remain excluded from many cardiovascular trials.[23] These

observations emphasize the importance of studying representative cohorts of patients receiving therapies in real-world clinical settings to further inform our understanding of outcomes after the implementation of guideline-based recommendations for care.

Because ICDs reduce mortality by preventing SCD, their impact on health outcomes may be attenuated in the face of competing risks such as those conferred by coexisting illnesses.[24] In this community-based cohort of patients undergoing ICD placement, the burden of coexisting illnesses—both cardiovascular and non-cardiovascular—was significantly higher than in the patient populations enrolled in the RCTs that form the basis of current guideline recommendations. While the comorbidity burden in community populations has been characterized in populations with heart failure,[25] and has to some extent been described using administrative data for populations receiving ICDs,[20] it has not been well-studied using clinical data in representative cohorts of patients undergoing ICD implantation in typical clinical practice settings.

To the extent that evidence-based medical therapies for heart failure may also modify a patient's risk for SCD, differences in the use of various therapies in this study cohort compared with the patients enrolled in published RCTs may also have implications for studying short and long-term outcomes in community practice. Heart failure pharmacotherapy has evolved substantially over the last decade; recent guidelines recommend ACE inhibitors (or ARBs) and beta-blockers for all patients with LVSD and without contraindications regardless of symptoms.[6, 7] Optimal medical therapy for LVSD has evolved since the conduct of the RCTs of ICDs for primary prevention, however, particularly with respect to beta-blockers and aldosterone antagonists. Observational studies suggest important gaps in evidence-based therapy in patients undergoing ICD placement.[26] The rates of evidence-based medical treatment for LVSD are significantly higher in this cohort than in the landmark RCTs when comparing therapy at the time of ICD implantation. These differences may influence the risks for adverse outcomes in contemporary cohorts of patients receiving ICDs compared with those reported in the published RCTs.

Certain issues should be considered in the interpretation of the results of this study. First, this cohort includes only patients with health insurance, which may reduce generalizability of results for patients with limited access to care. However, member sites in the study include a variety of health finance models, and provide care through commercial as well as government insurance, including Medicaid, Medicare managed care, and supplemental policies for subjects with fee for service Medicare. Accordingly, the cohort has notable diversity across age, gender, racial/ethnic, and socioeconomic groups.[17] Furthermore, it is reassuring that the study cohort was similar to the larger national population of patients included in the NCDRICD Registry. Second, since the study includes only patients receiving ICD therapy, it will not be possible to make comparisons with patients who were otherwise eligible but did not receive an ICD. However, we will identify rates and outcomes in ICD recipients and evaluate them within the context of those reported in the RCTs, which are currently the principal source of evidence that informs contemporary treatment guidelines. Finally, we are not at this point able to identify with precision patients with coexisting conditions that would motivate ICD implantation but that were typically excluded from the RCTs (e.g. long QT syndrome). However, including such patients, who are likely to be younger and with fewer comorbidities than patients without these conditions, would typically attenuate the differences between our study population and those of the RCTs. Ultimately, these conditions will be identified during the therapy adjudication phase of the study and will be analyzed as a subset of the entire population in the outcomes analyses.

With respect to the ICD therapy data that are currently being collected, subjects in the study will have received a variety of different ICD devices with different features and technology,

without guidance from the study regarding device programming or settings. Thus, the study is evaluating ICD clinical care as optimized for each patient by the providers involved in the case. The “real world” nature of the project also introduces variability based on how the clinical sites and different device manufacturer systems archive relevant interrogation data. Based on pilot abstraction work for this study, we expect that electrograms and other interrogation detail will be missing for a portion of treated arrhythmic episodes, precluding centralized adjudication in those instances and increasing reliance on local provider interpretations as documented in the clinical notes. To explore the potential impact of this limitation, and to support informed sensitivity analysis of our results, the study plans an evaluation of the agreement level between local provider interpretation and centralized adjudication results when both elements are available. Also, the assessment of initial type of therapy (ATP vs. shock) will be limited by the inability to definitively exclude ATP during device charge if such information was not explicitly documented in the archived medical records.

Conclusions

The Longitudinal Study of Implantable Cardioverter Defibrillators is a unique multistakeholder, multi-center initiative involving a diverse, contemporary care cohort of primary prevention ICD patients established to address major knowledge gaps related to the optimal use of ICDs for primary prevention of SCD. This community-based cohort of patients receiving ICDs differs substantially from the populations that were enrolled in the RCTs that form the basis of clinical practice guidelines. Specifically, these patients are older, included more women, have a substantial burden of important co-existing illnesses, and are more likely to receive evidence-based medications for heart failure. These differences highlight the importance of understanding the outcomes of patients who receive this therapy in contemporary, real-world clinical settings. Analysis of study data generated by the LSICD will not only provide direct evidence to address CMS Group B coverage questions related to ICD therapy, but will serve as a novel research platform to answer future questions in order to improve clinical outcomes in this high-risk and growing population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources This project was funded under Contract No. 290-05-0033 from the Agency for Healthcare Research and Quality, US Department of Health and Human Services as part of the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) program; and by the American College of Cardiology Foundation; with support from the National Heart, Lung, and Blood Institute (U19HL091179). While the sponsoring organizations have been involved in discussions of this research as it has progressed and have provided oversight and guidance, the authors of this report are solely responsible for its content. Sponsorship may not be construed as an endorsement of all statements in the report by the Agency for Healthcare Research and Quality, the National Heart, Lung, and Blood Institute, the US Department of Health and Human Services or the American College of Cardiology Foundation.

Dr. Saczynskiis supported in part by funding from the National Institute on Aging (K01AG33643).Dr. Peterson is supported by funding from Agency for Healthcare Research and Quality (K08HS019814). Dr. Vidaillet is supported in part by he Clinical and Translational Science Award program of the NIH (UL1RR025011).

References

1. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients

with coronary disease at high risk for ventricular arrhythmia. New Engl J Med. 1996; 335:1933–1940. [PubMed: 8960472]

2. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. New Engl J Med. 1999; 341:1882–1890. [PubMed: 10601507]
3. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. New Engl J Med. 2002; 346:877–883. [PubMed: 11907286]
4. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, vidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. New Engl J Med. 2005; 352:225–237. [PubMed: 15659722]
5. McClellan MB, Tunis SR. Medicare coverage of ICDs. New Engl J Med. 2005; 352:222–224. [PubMed: 15659721]
6. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Riegel B, Tarkington LG, Yancy CW. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. Circulation. 2008; 117:e350–408. [PubMed: 18483207]
7. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults. Circulation. 2009; 119:1977–2016. [PubMed: 19324967]
8. Hammill SC, Stevenson LW, Kadish AH, Kremers MS, Heidenreich P, Lindsay BD, Mirro MJ, Radford MJ, Wang Y, Lang CM, Harder JC, Brindis RG. Review of the Registry's first year, data collected, and future plans. Heart Rhythm. 2007; 4:1260–1263. [PubMed: 17765637]
9. Al-Khatib SM, Lucas FL, Jollis JG, Malenka DJ, Wennberg DE. The relation between patients' outcomes and the volume of cardioverter-defibrillator implantation procedures performed by physicians treating Medicare beneficiaries. J Am CollCardiol. 2005; 46:1536–1540.
10. Levy WC, Lee KL, Hellkamp AS, Poole JE, Mozaffarian D, Linker DT, Maggioni AP, Anand I, Poole-Wilson PA, Fishbein DP, Johnson G, Anderson J, Mark DB, Bardy GH. Maximizing survival benefit with primary prevention implantable cardioverter-defibrillator therapy in a heart failure population. Circulation. 2009; 120:835–842. [PubMed: 19704100]
11. Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P, Schuger C, Steinberg JS, Higgins SL, Wilber DJ, Klein H, Andrews ML, Hall WJ, Moss AJ. Inappropriate implantable cardioverter-defibrillator shocks in MADIT-II: Frequency, mechanisms, predictors, and survival impact. J Am Coll Cardiol. 2008; 51:1357–1365. [PubMed: 18387436]
12. Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, Reddy RK, Marchlinski FE, Yee R, Guarnieri T, Talajic M, Wilber DJ, Fishbein DP, Packer DL, Mark DB, Lee KL, Bardy GH. Prognostic importance of defibrillator shocks in patients with heart failure. N Engl J Med. 2008; 359:1009–1017. [PubMed: 18768944]
13. Mark DB, Anstrom KJ, Sun JL, Clapp-Channing NE, Tsiatis AA, Davidson-Ray L, Lee KL, Bardy GH. Quality of life with defibrillator therapy or amiodarone in heart failure. N Engl J Med. 2008; 359:999–1008. [PubMed: 18768943]
14. van Rees JB, Borleffs CJ, de Bie MK, Stijnen T, van Erven L, Bax JJ, Schalij MJ. Inappropriate implantable cardioverter-defibrillator shocks: Incidence, predictors, and impact on mortality. J Am CollCardiol. 2011; 57:556–562.
15. Masoudi FA, Havranek EP, Wolfe P, Gross CP, Rathore SS, Steiner JF, Ordin DL, Krumholz HM. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. Am Heart J. 2003; 146:250–257. [PubMed: 12891192]

16. Greenlee RT, Coleman LA, Nelson AF, Selby JV. Partnerships in translation: Advancing research and clinical care. The 14th annual HMO Research Network Conference Clin Med & Research. 2008; 6:109–112.

17. Go AS, Magid DJ, Wells B, Sung SH, Cassidy-Bushrow AE, Greenlee RT, Langer RD, Lieu TA, Margolis KL, Masoudi FA, McNeal CJ, Murata GH, Newton KM, Novotny R, Reynolds K, Roblin DW, Smith DH, Vupputuri S, White RE, Olson J, Rumsfeld JS, Gurwitz JH. The Cardiovascular Research Network (CVRN): a new paradigm for cardiovascular quality and outcomes research. Circ Cardiovasc Qual Outcomes. 2008; 1:138–147. [PubMed: 20031802]

18. Selby JV, Lee J, Swain BE, Tavel HM, Ho PM, Margolis KL, O'Connor PJ, Fine L, Schmittdiel JA, Magid DJ. Trends in time to confirmation and recognition of new-onset hypertension, 2002-2006. Hypertension. 2010; 56:605–611. [PubMed: 20733092]

19. Peterson PN, Daugherty SL, Wang Y, Vidaillet HJ, Heidenreich PA, Curtis JP, Masoudi FA. Gender differences in procedure-related adverse events in patients receiving implantable cardioverter-defibrillator therapy. Circulation. 2009; 119:1078–1084. [PubMed: 19221223]

20. Curtis LH, Al-Khatib SM, Shea AM, Hammill BG, Hernandez AF, Schulman KA. Sex differences in the use of implantable cardioverter-defibrillators for primary and secondary prevention of sudden cardiac death. JAMA. 2007; 298:1517–1524. [PubMed: 17911496]

21. Chan PS, Nallamothu BK, Spertus JA, Masoudi FA, Bartone C, Kereiakes DJ, Chow T. Impact of age and medical comorbidity on the effectiveness of implantable cardioverter-defibrillators for primary prevention. Circ Cardiovasc Qual Outcomes. 2009; 2:16–24. [PubMed: 20031808]

22. Epstein AE, Kay GN, Plumb VJ, McElderry HT, Doppalapudi H, Yamada T, Shafiroff J, Syed ZA, Shkurovich S. Implantable cardioverter-defibrillator prescription in the elderly. Heart Rhythm. 2009; 6:1136–1143. [PubMed: 19539542]

23. Cherubini A, Oristrell J, Pla X, Ruggiero C, Ferretti R, Diestre G, Clarfield AM, Crome P, Hertogh C, Lesauskaite V, Prada GI, Szczerbinska K, Topinkova E, Sinclair-Cohen J, Edbrooke D, Mills GH. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. Arch Intern Med. 2011; 171:550–556. [PubMed: 21444844]

24. Clarke B, Howlett J, Sapp J, Andreou P, Parkash R. The effect of comorbidity on the competing risk of sudden and non-sudden death in an ambulatory heart failure population. Can J Cardiol. 2011; 27:254–261. [PubMed: 21459274]

25. Havranek EP, Masoudi FA, Westfall KA, Wolfe P, Ordin DL, Krumholz HM. Spectrum of heart failure in older patients: Results from the national heart failure project. Am Heart J. 2002; 143:412–417. [PubMed: 11868045]

26. Hauptman PJ, Swindle JP, Masoudi FA, Burroughs TE. Underutilization of beta-blockers in patients undergoing implantable cardioverter-defibrillator and cardiac resynchronization procedures. Circ Cardiovasc Qual Outcomes. 2010; 3:204–211. [PubMed: 20197509]

Table 1

Randomized Trials of ICD Therapy to Prevent Sudden Cardiac Death in Patients with Left Ventricular Systolic Dysfunction

Trial	Year	N (1)	Inclusion Criteria (2)
MADIT-II (3)	2002	742	• Prior myocardial infarction • NYHA I-III symptoms at enrollment • LVEF≤0.30 • Optimal medical therapy
SCD-HeFT (4)	2005	829	• Chronic stable heart failure • NYHA II-III symptoms • LVEF ≤0.35 • LSVD of ischemic or non-ischemic etiology • Optimal medical therapy

Notes: (1) number of patients randomized to ICD therapy; (2) enrolled patients without a history of sudden cardiac death or syncope attributed to ventricular arrhythmias; (3) randomized comparison of ICD therapy with medical therapy; (4) randomized comparison of ICD therapy with medical therapy or medical therapy plus amiodarone.

Abbreviations: LVEF=left ventricular ejection fraction; LVSD=left ventricular systolic dysfunction; NYHA=New York Heart Association; VT=ventricular tachycardia

Table 2

Comparison of the Longitudinal Study of ICDs (LSICD) with MADIT-II and SCD-HeFT Trials

Variable	LSICD	MADIT-II	SCD-HeFT
N	**2621**	**742**	**829**
Age (years) at implant	66.7 (11.6)	64 (10.0) ¶	59.9 (11.9) ¶
Female gender	663 (25.3%)	119 (16.0%)¶	190 (23.0%)
Non-white race	858 (32.7%)	--	189 (23.0%)¶
Heart failure history	2513 (95.9%)	--	829 (100%)¶
NYHA Class		¶	¶
I	299 (11.4%)	260 (35.0%)	0 (0.0%)
II	1235 (47.1%)	260 (35.0%)	580 (70.0%)
III	1026 (39.1%)	185 (25.0%)	249 (30.0%)
IV	55 (2.1%)	37 (5.0%)	0 (0.0%)
II or III	2261 (86.3%)	445 (60.0%)¶	829 (100.0%)¶
LVEF (%, mean, SD)	25.0 (6.9)	23.0 (5.0)¶	23.5 (7.0) ¶
Ischemic heart disease	1670 (63.7%)	742 (100.0%)¶	432 (52.0%)¶
Previous CABG	811 (30.9%)	430 (58.0%)¶	--
Previous PCI	799 (30.5%)	334 (45.0%)¶	--
Chronic lung disease	508 (19.4%)	--	171 (21%)
Diabetes mellitus	1099 (41.9%)	245 (33.0%)¶	253 (31.0%)¶
Hypertension	1916 (73.1%)	393 (53.0%)¶	453 (55.0%)¶
Atrial fibrillation or flutter	823 (31.4%)	67 (9.0%)¶	141 (17.0%)¶
LBBB	710 (27.1%)	141 (19.0%) ¶	--
QRS duration ≤ 0.12 seconds	1132 (43.2%)	371 (50.0%)	--
Non-sustained VT	366 (14.0%)	--	210 (25.0%)¶
BUN>25 mg/dL	900 (34.3%)	215 (29.0%)§	--
Creatinine (mg/dL)	1.5 (2.9)	--	1.2 (0.4)¶
Medications*			
ACE Inhibitor	1739(66.6%)	505 (68.0%)§	684 (83%)¶
ARB	549 (21.0%)	--	114 (14.0%)¶
Aspirin	1756(67.3%)	--	477 (58.0%)¶
Beta Blocker	2385(91.4%)	519 (70.0%)¶	576 (69.0%)¶
Coumadin	834 (32.0%)	--	266 (32.0%)
Digoxin	784 (30.0%)	423 (57.0%)¶	552 (67.0%)¶
Statin	2025(77.6%)	497 (67.0%)¶	312 (38.0%)¶

Notes: ~ = p<0.05;

§ = p<0.01;

¶ = p<0.001;

-- = not reported;

* = medications at discharge after ICD placement. All continuous variables listed as means and standard deviations

Abbreviations: ACE=angiotensin Converting enzyme; ARB=angiotensin receptor blocker; CABG=coronary Artery bypass graft surgery; IQR=interquartile range; LBBB=left Bundle branch block; LVEF=left Ventricular ejection fraction; NYHA=New York Heart Association; PCI=percutaneous coronary intervention; SD=standard deviation

Table 3

Comparison of the Longitudinal Study of ICDs (LSICD) Cohort with a US National Sample of Primary Prevention ICD Recipients in 2006-2007

Variable	LSICD	NCDR National
N	**2621**	**110,455**
Age (yrs) at implant	66.7 (11.6)	67.7 (12.5)¶
Female gender	663 (25.3%)	30014 (27.2%)~
Non-white race	858 (32.7%)	20925 (18.9%)¶
History of heart failure	2513 (95.9%)	93717 (84.9%)¶
NYHA Class		¶
I	299 (11.4%)	8917 (8.1%)
II	1235 (47.1%)	38887 (35.3%)
III	1026 (39.1%)	57617 (52.2%)
IV	55 (2.1%)	5034 (4.6%)
LVEF (%)	24.9 (6.9)	25.1 (8.1)
Ischemic heart disease	1670 (63.7%)	72718 (65.8%)~
Previous CABG	811 (30.9%)	39615 (35.9%)¶
Previous PCI	799 (30.5%)	35475 (32.1%)
Chronic lung disease	508 (19.4%)	24667 (22.3%)¶
Diabetes	1099 (41.9%)	41936 (38.0%)¶
Hypertension	1916 (73.1%)	82431 (74.6%)
Atrial fibrillation or flutter	823 (31.4%)	33759 (30.6%)
LBBB	710 (27.1%)	32289 (29.2%)~
Non-sustained VT	366 (14.0%)	23683 (21.4%)¶
Creatinine (mg/dL)	1.5 (2.9)	1.4 (1.1)
Systolic blood pressure	124.3 (20.3)	129.77 (22.1)¶
Medications		
ACE-inhibitor	1739(66.6%)	69231 (64.7%)¶
ARB	549 (21.0%)	18542 (17.1%)¶
Aspirin	1756(67.3%)	71542 (65.7%)~
Beta Blocker	2385(91.4%)	94777 (87.0%)¶
Coumadin	834 (32.0%)	30563 (27.9%)¶
Digoxin	784 (30.0%)	32229 (29.3%)
Statin	2025(77.6%)	68307 (62.3%)¶

Notes:

~ = p<0.05;

§ = p<0.01;

¶ = p<0.001;

all continuous variables listed as means and standard deviations;

* medications at discharge after ICD placement

Abbreviations: ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; CABG=coronary artery bypass graftsurgery; LBBB=left bundle branch block; LVEF=left ventricular ejection fraction; NYHA=NewYork Heart Association; PCI=percutaneous coronary intervention; VT=ventricular tachycardia.