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Influence of Multimorbidity on Burden and Appropriateness of Implantable Cardioverter Defibrillator Therapies

Alexandra M. Hajduk, PhD, MPH[1], **Jerry H. Gurwitz, MD**[2], **Grace Tabada, MPH**[3], **Frederick A. Masoudi, MD, MSPH**[4,5], **David J. Magid, MD, MPH**[4,5], **Robert T Greenlee, PhD, MPH**[6], **Sue Hee Sung, MPH**[3], **Andrea E Cassidy-Bushrow, PhD**[7], **Taylor I Liu, MD, PhD**[8], **Kristi Reynolds, PhD, MPH**[9], **David H Smith, PhD**[10], **Frances Fiocchi, MPH**[11], **Robert Goldberg, PhD**[2], **Thomas M. Gill, MD**[1], **Nigel Gupta, MD**[12], **Pamela N Peterson, MD, MSPH**[4,5,13], **Claudio Schuger, MD**[14], **Humberto Vidaillet, MD**[15], **Stephen C Hammill, MD**[16], **Heather Allore, PhD**[1,17], **Alan S. Go, MD**[3,18,19] **CVRN Longitudinal Study of Implantable Cardioverter Defibrillators**

[1]Yale University School of Medicine, New Haven, CT

[2]Meyers Primary Care Institute, a joint endeavor of University of Massachusetts Medical School, Fallon Health, and Reliant Medical Group, Worcester, MA

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

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

[5]Institute for Health Research, Kaiser Permanente Colorado, Denver, CO

[6]Marshfield Clinic Research Foundation, Marshfield, WI

[7]Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI

[8]Department of Cardiac Electrophysiology, Kaiser Permanente Northern California, Santa Clara, CA

[9]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA

[10]Center for Health Research, Kaiser Permanente Northwest, Portland, OR

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

[12]Department of Cardiac Electrophysiology, Kaiser Permanente, Los Angeles Medical Center, Los Angeles, CA

[13]Denver Health Medical Center, Denver, CO

[14]Henry Ford Hospital Heart and Vascular Institute, Detroit, MI

Corresponding author: Alan S. Go, MD, Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94612-2304, Tel: 510-891-3422, Fax: 510-891-3508, Alan.S.Go@kp.org.

AUTHOR CONTRIBUTIONS

All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Conception, design, and acquisition of data (Go, Masoudi, Greenlee, Magid, Sung, Cassidy-Bushrow, Fiocchi, Goldberg, Gurwitz, Gupta, Peterson, Schuger, Vidaillet, Hammill). Data analysis and interpretation (Go, Hajduk, Gurwitz, Tabada, Sung). Preparation and review of manuscript: all authors.

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[15]Marshfield Clinic, Marshfield, WI

[16]Mayo Clinic, Rochester, MN

[17]Program on Aging, Yale School of Medicine, New Haven, CT

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

[19]Departments of Medicine, Health Research and Policy, Stanford University School of Medicine, Stanford, CA

Abstract

Objectives: To determine whether burden of multiple chronic conditions (MCCs) influences the risk of receiving inappropriate vs. appropriate device therapies.

Design: Retrospective cohort study.

Setting: Seven U.S. healthcare delivery systems.

Participants: Adults with left ventricular systolic dysfunction receiving an ICD for primary prevention.

Measurements: Data on twenty-four comorbid conditions were captured from electronic health records and categorized into quartiles of comorbidity burden (0-3, 4-5, 6-7 and ≥8). Incidence of ICD therapies (shock and anti-tachycardia pacing therapies), including appropriateness, were collected for three years after implantation. Outcomes included time to first ICD therapy, total ICD therapy burden, and risk of inappropriate versus appropriate ICD therapy.

Results: Among 2,235 patients (mean age 69±11 years, 75% men), the median number of comorbidities was 6 (interquartile range 4, 8), with 98% having at least two comorbidities. During a mean 2.2 years of follow-up, 18.3% of patients experienced at least one appropriate therapy and 9.9% experienced at least one inappropriate therapy. Higher comorbidity burden was associated with an increased risk of first inappropriate therapy (adjusted hazard ratio [HR] for 4-5 comorbidities 1.94 [95%CI:1.14-3.31]; HR 2.25 [95%CI:1.25-4.05] for 6-7 comorbidities; and HR 2.91 [95%CI:1.54-5.50] for ≥8 comorbidities. Participants with ≥8 comorbidities had a higher total burden of ICD therapy (adjusted relative risk [RR] 2.12 [95%CI:1.43-3.16]), higher burden of inappropriate therapy (RR 3.39 [95%CI:1.67-6.86]), and higher risk of receiving inappropriate versus appropriate therapy (RR 1.74 [95%CI:1.07-2.82]). Comorbidity burden was not significantly associated with receipt of appropriate ICD therapies. Patterns were similar when separately examining shock or anti-tachycardia pacing therapies.

Conclusions: In primary prevention ICD recipients, MCC burden was independently associated with an increased risk of inappropriate but not appropriate device therapies. Comorbidity burden should be considered when engaging patients in shared decision-making about ICD implantation.

Keywords

Comorbidity; multimorbidity; chronic disease; implantable cardioverter defibrillator; patient-centered outcomes

INTRODUCTION

Use of implantable cardioverter defibrillators (ICDs) for the primary prevention of sudden cardiac death (SCD) has grown dramatically in recent decades, based on results from pivotal randomized clinical trials showing 23-60% relative reductions in SCD among selected patients with left ventricular systolic dysfunction[1-4]. National clinical practice guidelines have recommended ICD implantation for primary prevention of SCD in patients with left ventricular ejection fraction (LVEF) ≤35% and New York Heart Association class II or III heart failure who have an estimated life expectancy with good functional status of greater than one year[5]. Under these guidelines, more than half a million Medicare beneficiaries are now eligible for primary prevention ICD implantation[6].

While ICDs are effective in reducing risk of SCD in selected patients with left ventricular systolic dysfunction, they are also associated with potential drawbacks. For example, receipt of shocks (appropriate or inappropriate) can be painful[7] and are associated with increased mortality,[7, 8] higher healthcare utilization[9], psychological distress[10], and reduced quality of life[11]. Evidence also suggests that ICD shocks or anti-tachycardia pacing may be pro-arrhythmic[12] and are associated with myocardial damage [13]—mechanisms that may explain, in part, the increased death rates observed among recipients who receive multiple shocks[8, 14]. Inappropriate shocks—those that result from non-lethal tachyarrhythmias or improper device sensing—account for up to one third of all ICD shocks[12], offer no clinical benefit to patients, and are associated with adverse outcomes[7, 15].

Clinical characteristics that predispose a patient to inappropriate versus appropriate therapy remain poorly understood, and an area of growing interest concerns how comorbidity burden may affect the risk of appropriate and inappropriate ICD therapies. Comorbid conditions such as hypertension[16], ischemic heart disease[17, 18], diabetes mellitus [17, 18], atrial fibrillation[17, 18], chronic lung disease[17, 18], anemia[17, 18], and chronic kidney disease[17, 18] are extremely common among ICD recipients, and the presence of multiple chronic conditions (MCCs) is common[19-21]. Certain conditions such as chronic lung disease[22] and diabetes[23] have been associated with higher risks of appropriate shocks, whereas others (e.g., atrial fibrillation[15, 16, 24], hypertrophic cardiomyopathy[24]) have been associated with a greater incidence of inappropriate shocks. The impact of MCC burden on risks of appropriate and inappropriate ICD therapies has not been systematically evaluated but may be important when counseling patients about the net clinical benefit or harm of primary prevention ICD implantation.

Using data from the multicenter Cardiovascular Research Network Longitudinal Study of Implantable Cardioverter Defibrillators (CVRN LS-ICD), we characterized the prevalence of MCCs in a contemporary, community-based cohort receiving ICD therapies for primary prevention and examined the independent association of MCC burden on the frequency and appropriateness of ICD therapies.

METHODS

Study design and data sources

Data were derived from the CVRN LS-ICD, a retrospective cohort study of primary prevention ICD implant patients recruited from seven health care delivery system members of the CVRN[25], affiliated with the Health Care Systems Research Network[26]. Details of this study have been previously described[27]. Data for the LS-ICD were aggregated from three entities: the National Cardiovascular Data Registry ICD Registry (), the CVRN Virtual Data Warehouse, and an ICD device therapy data repository developed specifically for the LS-ICD[27]. The registry provided data on ICD implantation eligibility and other clinical criteria, device and provider details, and adverse events during the index implant hospitalization. The Virtual Data Warehouse provided longitudinal data on health plan enrollment, insurance coverage details, demographics, comorbidities, health care utilization, pharmacy, and laboratory values. The ICD therapy data repository provided information on device therapies as described in more detail below.

We identified 2,787 patients with left ventricular systolic dysfunction who received a first-time ICD between January 1, 2006 and December 31, 2009 for primary prevention of SCD. Participants were recruited from one of 14 hospitals affiliated with the seven participating health care systems. All eligible patients received a primary prevention ICD, had no prior ICD implantation, had documented left ventricular systolic dysfunction, and were members of a participating health system. We excluded participants who had <1 year of continuous health plan membership before ICD implantation (n=545), those aged <21 years old (n=3), and those who died during the ICD implant procedure (n=7), leaving a total of 2,235 participants for analysis. Participants were followed through December 2011 (mean follow-up: 2.2 years, maximum: 3 years) to ascertain ICD therapy outcomes.

Institutional review boards at all participating sites approved the study, and waivers of informed consent were obtained because of the nature of the study.

Assessment of Multiple Chronic Conditions

We selected 24 comorbidities for analysis based on their high prevalence or association with poor outcomes among patients with ICDs. We included 14 of the 15 comorbidities recommended by the U.S. Department of Health and Human Services' Strategic Framework on Multiple Chronic Conditions[28] that are collected by the Centers of Medicare and Medicaid Services, including hypertension, dyslipidemia, coronary heart disease, arthritis, diabetes, chronic kidney disease, depression, chronic obstructive pulmonary disease, dementia, atrial fibrillation/flutter, cancer, osteoporosis, asthma, and stroke. To these 14 conditions, we added pre-existing ventricular tachycardia, sinus node dysfunction, aortic valvular disease, previous valvular surgery, anemia, abnormal thyroid function, peripheral artery disease, chronic liver disease, mobility impairment, and history of gastrointestinal hemorrhage. All comorbid conditions were identified using previously described methods[25, 27, 29] using data on inpatient, emergency, and ambulatory diagnoses and procedures, prescribed medications, and laboratory test results from the Virtual Data Warehouse and NCDR ICD Registry (definitions available on request). The lookback period

to capture comorbidities was up to three years pre-ICD implantation for all participants; comorbidities diagnosed after ICD implantation were not evaluated. Each participant's comorbidities were summed, and participants were categorized into count-based quartiles of one measure of morbidity burden for analysis: 0 to 3, 4 or 5, 6 or 7, and 8 or more comorbidities.

Assessment of ICD therapy

Participants were followed for up to three years after ICD placement for occurrence of ICD therapy (shock or anti-tachycardia pacing [ATP]). Participants were censored at the time of death, health plan disenrollment, receipt of 10 confirmed device therapies, or end of follow-up (December 31, 2011). ICD therapies were identified and confirmed via a standardized protocol that included medical record abstraction at the study site, central clinical review, and expert external adjudication of source documents as previously described[27]. Briefly, data on arrhythmic episodes resulting in ICD therapy were abstracted from device reports (including intracardiac electrograms) and clinical notes (including local provider interpretation). A central review panel, consisting of three electrophysiologists and a hospitalist with expertise in ICD device interpretation[30], confirmed the occurrence of treated episodes[1], determined the initial type of therapy (shock or ATP)[2], determined whether the episode required multiple therapies, and adjudicated the appropriateness of therapy using standardized criteria[3]. As previously described,[31] therapies were classified as appropriate (in response to a potentially malignant ventricular tachyarrhythmia), or inappropriate (due to other causes, including supraventricular arrhythmias, or problems with device sensing or function). Abstraction of ICD therapy was truncated after ten episodes for each participant, and a maximum of three episodes were collected per 24-hour period to limit the potential burden of data generated by "arrhythmic storms."[31] Selected records were double-adjudicated by an external panel of electrophysiologists. All judgments were based on definitions developed through extensive discussion of central and external panel members using literature-based guidance. Disagreement among reviewers was resolved via reviewer conference or arbitration with external experts.

We examined three separate outcomes related to receipt of ICD therapy:[30] time to first therapy (any, appropriate, and inappropriate),[1] total burden of therapy (counts of total therapy, appropriate, and inappropriate over the course of follow-up), and risk (i.e., balance) of inappropriate versus appropriate therapy[2] among the subset of participants who received at least one appropriate or inappropriate ICD therapy (n=562). .

Covariates

Covariates were gathered from the NCDR ICD Registry and each site's VDW, captured during the three-year period before ICD implantation. Demographic characteristics (age, gender, race/ethnicity), smoking status, body mass index and medication use (angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers, aspirin, beta blockers, warfarin, digoxin, statins and antiplatelet agents) were gathered from the VDW. Clinical characteristics (family history of SCD, heart failure, New York Heart Association class, blood pressure, estimated glomerular filtration rate, hemoglobin, serum potassium level, left

ventricular ejection fraction and ICD type) at the time of ICD implantation were gathered from the NCDR ICD Registry.

Analytic Approach

All analyses were performed using SAS software, version 9.3 (Cary, NC). We performed descriptive statistics to examine baseline characteristics across quartiles of comorbidity counts (i.e., 0 to 3, 4 or 5, 6 or 7, and ≥8 comorbidities), using ANOVA for continuous variables and chi-square tests for categorical variables.

We used Cox proportional hazards regression to examine the association of comorbidity counts with time to first ICD therapy (any, appropriate, or inappropriate). We confirmed absence of the violation of the proportional hazards assumption via visual inspection of log-negative log survival curves. We examined the association of comorbidity counts with burden (i.e., total counts) of any, appropriate, and inappropriate ICD therapy using Poisson regression. Finally, we examined the association of comorbidity counts with the risk of receiving inappropriate vs. appropriate ICD therapy using relative risk regression. The referent group for all models were participants in the lowest quartile of comorbidity burden, i.e., the group with 0 to 3 comorbidities. For each outcome, we performed a series of nested models that introduced covariates in the following order: an unadjusted model with comorbidity counts, followed by sequential addition of demographic characteristics and study site; and then baseline medical history, NYHA classification, left ventricular ejection fraction, smoking status, vital signs and laboratory results, baseline medication use and ICD type. Due to prior evidence suggesting atrial fibrillation is a strong risk factor for inappropriate shocks, we performed sensitivity analyses after removing atrial fibrillation as an eligible comorbidity in the comorbidity counts (Supplemental Figure A). We performed additional sensitivity analyses separately evaluating shock therapy and ATP therapies to address potential differences in the association of MCC burden with different types of device therapies (Supplemental Figures B **and** C, respectively).

RESULTS

Sample characteristics

Among 2235 eligible patients who received a primary prevention ICD, mean follow-up time was 2.2 (SD= 0.9) years. Mean age was 69 ±11 years, 25% were women, 77% were white/European, and 14% were Hispanic (Table 1). The distribution of ICD type was 33% single chamber, 36% dual chamber and 32% biventricular. Among 24 possible comorbid conditions, the median number of comorbidities per patient was 6 (IQR: 4, 8), and 98% of the cohort had at least two comorbidities. Participants with higher comorbidity burden were more likely to be older, white/European, current or former smokers, have government-based insurance, receive dual-chamber or biventricular ICDs, have a recent admission for heart failure or more symptomatic heart failure, higher systolic blood pressure, lower estimated glomerular filtration rate, higher blood urea nitrogen, lower hemoglobin, longer QRS duration, have abnormal IV conduction, be less likely to receive ACE inhibitor therapy, and more likely to receive an antiplatelet agent, anticoagulant, digoxin or statin (Table 1).

Frequency of ICD therapies

ICD therapy, including shock and ATP, occurred in 605 (27.1%) participants, with a total of 2027 therapies (647 shocks, 1349 ATP) delivered. At least one appropriate shock/ATP occurred in 410 participants (18.3%) and at least one inappropriate shock/ATP occurred in 221 participants (9.9%). Incidence of at least one shock/ATP (any, appropriate, or inappropriate) did not differ significantly according to comorbidity burden in bivariate analyses, but total burden of shock/ATP was significantly higher among participants with ≥8 comorbidities than among participants with lower comorbidity burden (P<0.01) (Figure 1).

Comorbidity burden and time to first ICD therapy

Compared to participants with the lowest comorbidity burden (0 to 3 comorbidities), participants with higher comorbidity burden were at higher risk of receiving a first ICD therapy (any or inappropriate), but not appropriate therapy (Figure 2). For time to first ICD therapy of any kind, only participants with ≥8 comorbidities had a significantly higher adjusted rate of therapy (adjusted hazard ratio [HR] 1.77, 95% CI:1.25-2.51 in the fully adjusted model). The rate of receiving a first inappropriate therapy was greater among participants with 4 or 5 (HR 1.94, 95%CI:1.14-3.31), 6 or 7 (HR 2.25, 95%CI:1.25-4.05), and ≥8 (HR 2.91, 95% CI1.54-5.50) comorbidities (Figure 2). In contrast, comorbidity burden was not independently associated with time to first appropriate therapy in any models.

Comorbidity burden and total burden of ICD therapy

Compared to participants with 0 to 3 comorbidities, those with 6 or 7 comorbidities had a 48% significantly higher adjusted relative risk of any ICD therapy (RR 1.48, 95%CI: 1.03-2.14) and those with ≥8 comorbidities had a more than twofold higher adjusted relative risk of any ICD therapy in fully-adjusted models (RR 2.12, 95%CI:1.43-3.16; Figure 3). Higher comorbidity burden was also associated with a greater burden of inappropriate therapy, with a more than threefold higher adjusted relative risk for ≥8 comorbidities compared with 0 to 3 comorbidities (RR 3.39, 95%CI:1.67-6.86, Figure 3). In contrast, comorbidity burden was not associated with greater burden of appropriate ICD therapy (Figure 3).

Comorbidity burden and risk of inappropriate vs. appropriate device therapy

Finally, for the outcome of the relative balance of receiving inappropriate vs. appropriate therapy, compared to patients who had 0 to 3 comorbidities, only patients with ≥8 comorbidities had a statistically significant higher risk of receiving inappropriate vs. appropriate therapy (RR 1.74, 95% CI:1.07-2.82) in the fully adjusted model (Figure 4).

Sensitivity analyses

Findings from all sensitivity analyses that removed atrial fibrillation from the comorbidity count were in some cases attenuated but not differ materially from our main findings (see Supplementary Figure A). Patterns were also similar when individually examining shock vs. ATP therapies, although there was lower precision in the estimates (Supplemental Figures B **and** C).

DISCUSSION

Within a large, diverse, community-based cohort of primary prevention ICD recipients, we examined the association of comorbidity burden with receipt and appropriateness of ICD therapy. We found that higher comorbidity burden was consistently associated with shorter time to first ICD therapy and higher burden (i.e., counts) of device therapy over three years of follow-up. Furthermore, those with higher comorbidity burden were at greater risk for inappropriate, but not appropriate, therapies. The excess risk of inappropriate ICD therapy was greatest among participants with ≥8 comorbidities, with more attenuated risks observed among participants with 4 or 5 and 6 or 7 comorbidities compared to those with 0 to 3 comorbidities. Patterns were similar when separately examining shocks vs. ATP therapies.

To our knowledge, this is the first published study to report on the association between MCCs and device therapies among primarily older adults receiving a primary prevention ICD. Previous studies have found that selected individual medical conditions increase the probability of receipt of appropriate (e.g., diabetes[23]) and inappropriate (e.g., atrial fibrillation[15]) ICD device therapy. Taken together with existing studies, our results provide strong support for the importance of MCC burden influencing device-related outcomes in persons with a primary prevention ICD.

The reasons for the excess rate of inappropriate device therapies associated with greater comorbidity burden are unclear. Although patients with greater number of comorbidities had significantly higher percentages of atrial fibrillation and non-sustained ventricular tachycardia that can directly lead to increased inappropriate ICD therapy, this did not account for the observed increased risk of inappropriate device therapies. Greater comorbidity burden is also associated with higher levels of circulating inflammatory factors[32] which, in turn, are associated with greater arrhythmogenicity[33]. It is also possible that both higher comorbidity burden and/or selected conditions may lead to other types of metabolic or physiologic changes that affect the sensitivity or accuracy of ICD sensing. Alternatively, device programming differences associated with comorbidity burden or targeted comorbid conditions during the study time period may have influenced the rate and appropriateness of device therapies, but systematic information on device settings was unavailable.

Our study had several notable strengths, including analysis of a large, multi-center cohort that included a wide range of information on comorbid conditions from complementary site-specific electronic medical records and national ICD registry data sources. Our cohort was demographically diverse and included patients from various practice settings and geographic locations throughout the U.S. Importantly, our study ascertained longitudinal information on ICD therapies that were subsequently adjudicated and classified as appropriate or inappropriate by clinical experts using standardized criteria. Our study also had certain limitations. Despite extensive review of available electronic and paper medical records and discussion, 15% of device therapies were unable to be given an appropriateness classification. Additional information on the specific causes of inappropriate device therapy were also unavailable. As noted, detailed information on ICD device settings were unavailable, but our results reflect the heterogeneity of clinical ICD care across the seven

participating health systems during the time period of study. However, given our study time period, our study results may not be fully generalizable to current practice given the evoluation in ICD programming algorithms which reduce inappropriate and appropriate shocks. We also were unable to determine the potential impact of appropriate or inappropriate device therapies on subsequent mortality or other clinical outcomes. As a retrospective study, we also cannot rule out residual confounding of the observed association of MCCs with ICD therapies.

Our results have several important implications for patients and providers. While ICDs reduce the risk of death in high-risk patients, some studies have observed reduced mortality benefit and higher hospitalization rates among ICD recipients with MCCs[21], whereas others have not.[34] ICD shocks are painful[7] and may produce adverse psychological effects[10], particularly among patients with multimorbidity[35]. Additionally, both appropriate and inappropriate shocks may damage myocardium and put patients at increased risk for death[8, 14]. In patients with primary prevention ICDs and multimorbidity, consideration of the type of ICD and settings as well as possible adjustment of adjuvant antiarrhythmic strategies[36, 37] may help to reduce the frequency of inappropriate device therapies and associated negative impacts on patients. The willingness of older patients to accept a medical therapy for primary cardiovascular prevention has been reported to be relatively insensitive to its benefits, but highly sensitive to its adverse effects—emphasizing the need to fully incorporate information on both benefits and harms into decision-making[38]. Given the excess risk of inappropriate ICD therapy associated with greater comorbidity burden, our findings support informing patients with multimorbidity about the spectrum of potential risks and benefits as part of shared decision-making for primary prevention ICD implantation.

CONCLUSIONS

Among adults receiving ICD implantation for primary prevention of sudden cardiac death, greater comorbidity burden was independently associated with time to first ICD therapy and total burden of ICD therapy. These outcomes appear to be driven by excess risk of inappropriate therapies, with no significant difference in risk of appropriate therapies. Additional research is needed to delineate the mechanisms affecting this excess risk and the potential influence of specific comorbid conditions and associated therapies to inform the development of strategies to mitigate the risk of inappropriate device therapy and optimize the net benefit of ICD therapy in the growing population of multimorbid patients receiving primary prevention ICDs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ATP	anti-tachycardia pacing
ICD	implantable cardioverter defibrillator
LS-ICD	Longitudinal Study of Implantable Cardioverter Defibrillators
MCC	multiple chronic conditions
NCDR	National Cardiovascular Data Registry
SCD	sudden cardiac death
VDW	virtual data warehouse

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Impact statement: We certify that this work is novel as it is the first to evaluate the impact of multiple chronic conditions on therapy outcomes among older adults with implantable cardioverter defibrillators for primary prevention of sudden death.

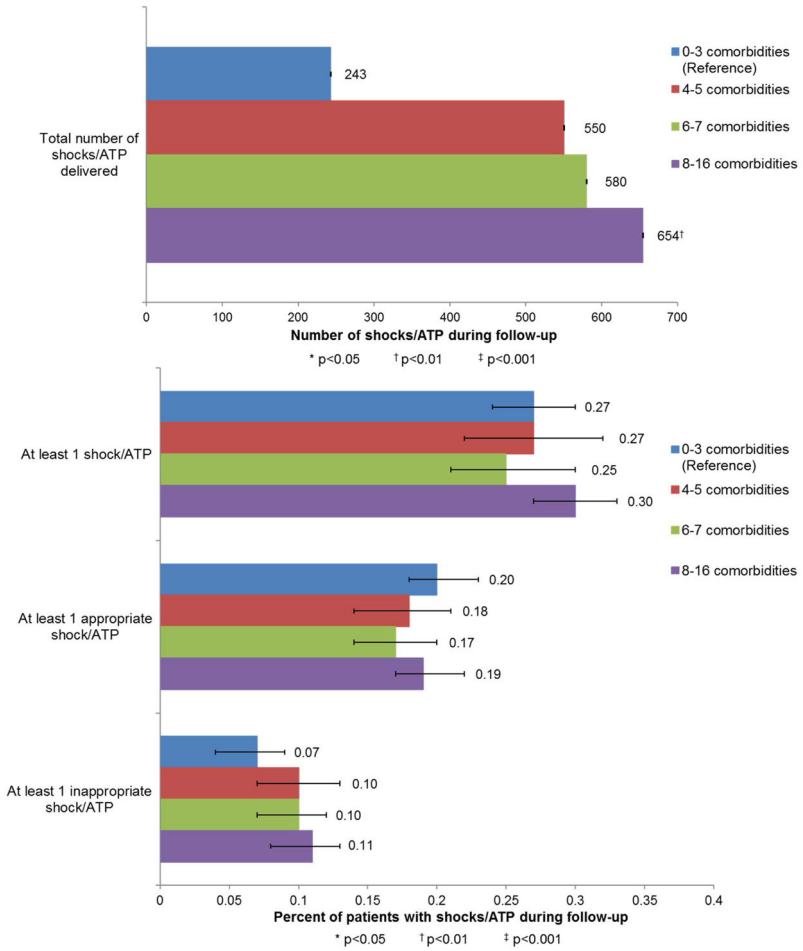

Figure 1.

Frequencies of shock/ATP, stratified by quartiles of comorbidity count in adults with a primary prevention ICD.

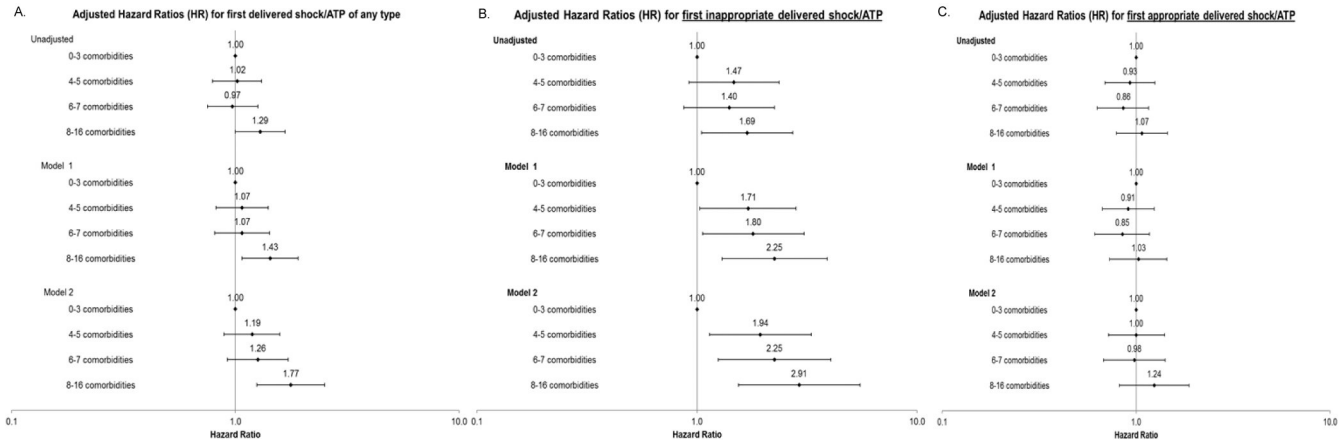

Figure 2. Association of baseline counts of comorbidities and time to first shock/ATP among 2235 participants who received a primary prevention ICD for cox proportional hazard regression models.

Panel A represents results for time to first delivered device therapy of any type; panel B represents time to first inappropriate device therapy, and panel C represents time to first appropriate device therapy.

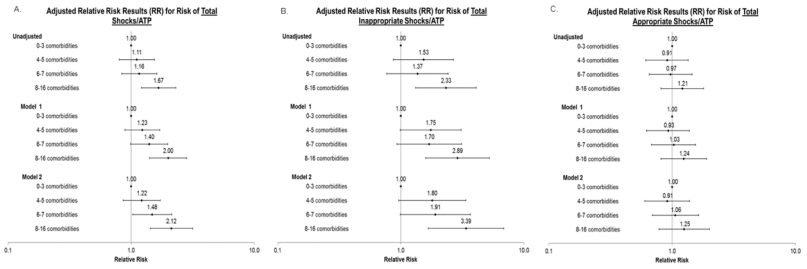

Figure 3. Association of baseline counts of comorbidities and burden of total delivered shocks/ATPs among 2235 participants who received a primary prevention ICD.

Panel A represents results for burden of device therapy of any type; panel B represents burden of inappropriate device therapy, and panel C represents burden of appropriate device therapy.

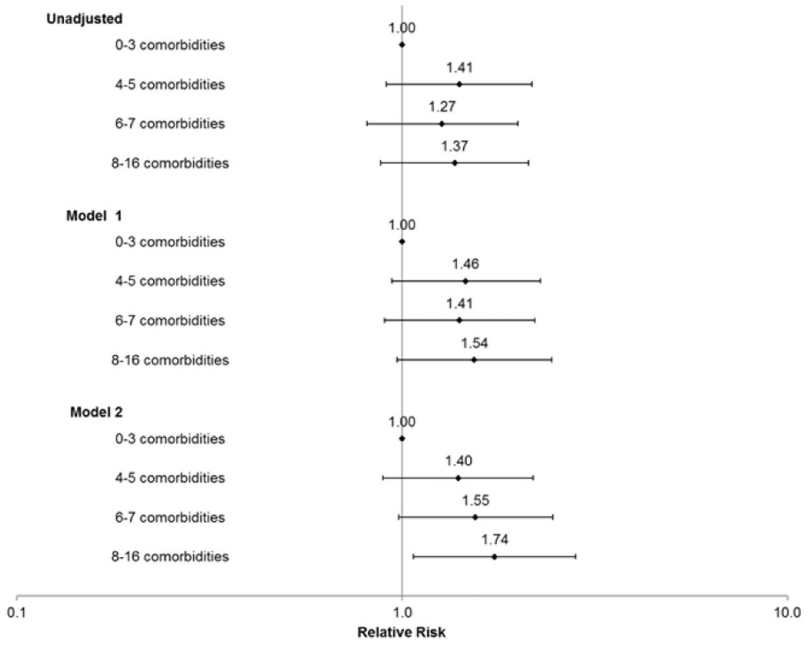

Figure 4.

Association of baseline counts of comorbidities with risk of receiving an inappropriate shock/ATP vs. appropriate shock/ATP among 562 adults who received at least one inappropriate or appropriate shock from primary prevention ICD.

Table 1.

Baseline characteristics of adults receiving implantable cardioverter defibrillator for primary prevention for sudden cardiac death, overall and stratified by quartile of comorbidity burden.

Characteristic	Overall (N=2235)	0 to 3 comorbidities (N=317)	4 or 5 comorbidities (N=650)	6 or 7 comorbidities (N=681)	≥8 comorbidities (N=587)	P-value
Age, years, Mean (SD)	68.5 (10.9)	59.7 (13.4)	66.2 (10.5)	70.9 (9.2)	72.9 (7.9)	<0.001
Women, n (%)	567 (25.4)	88 (27.8)	147 (22.6)	174 (25.6)	158 (26.9)	0.23
Race, n (%)						0.25
White/European	1711 (76.6)	226 (71.3)	494 (76.0)	531 (78.0)	460 (78.4)	
Hispanic, n (%)	313 (14.0)	38 (12.0)	88 (13.5)	109 (16.0)	78 (13.3)	0.41
Current or former tobacco use, n (%)	1275 (57.0)	153 (48.3)	352 (54.2)	386 (56.7)	384 (65.4)	<0.001
Insurance type, n (%)						<0.001
Government	1358 (60.8)	106 (33.4)	330 (50.8)	477 (70.0)	445 (75.8)	
Commercial	30 (1.3)	9 (2.8)	12 (1.8)	4 (0.6)	5 (0.9)	
HMO	842 (37.7)	202 (63.7)	305 (46.9)	199 (29.2)	136 (23.2)	
None / self pay	5 (0.2)	0 (0.0)	3 (0.5)	1 (0.1)	1 (0.2)	
Follow-up, mean (SD), yr	2.2 (0.9)	2.3 (0.9)	2.3 (0.8)	2.2 (0.9)	2.0 (1.0)	<0.001
ICD device type, n (%)						<0.001
Single chamber	728 (32.6)	132 (41.6)	257 (39.5)	187 (27.5)	152 (25.9)	
Dual chamber	797 (35.7)	84 (26.5)	220 (33.8)	274 (40.2)	219 (37.3)	
Biventricular	710 (31.8)	101 (31.9)	173 (26.6)	220 (32.3)	216 (36.8)	
Pre-implantation left ventricular ejection fraction, %, mean (SD)	25.2 (6.6)	23.6 (6.5)	24.8 (6.5)	25.5 (6.6)	26.0 (6.7)	<0.001
Comorbidities, per person						
Mean (SD)	6.0 (2.4)	2.3 (0.9)	4.5 (0.5)	6.5 (0.5)	9.1 (1.3)	<0.001
Median (interquartile)	6.0 (4.0-8.0)	3.0 (2.0-3.0)	5.0 (4.0-5.0)	6.0 (6.0-7.0)	9.0 (8.0-10.0)	<0.001
Range	0.0-16.0	0.0-3.0	4.0-5.0	6.0-7.0	8.0-16.0	
Comorbidities, n (%) *3 years prior to or on index date*						
Atrial fibrillation or flutter	729 (32.6)	33 (10.4)	129 (19.8)	232 (34.1)	335 (57.1)	<0.001
Aortic valvular disease	878 (39.3)	54 (17.0)	173 (26.6)	272 (39.9)	379 (64.6)	<0.001
Cerebrovascular disease	321 (14.4)	7 (2.2)	47 (7.2)	98 (14.4)	169 (28.8)	<0.001
Coronary artery disease	1477 (66.1)	97 (30.6)	406 (62.5)	488 (71.7)	486 (82.8)	<0.001
Ventricular tachycardia						<0.001
Non-sustained VT	334 (14.9)	15 (4.7)	67 (10.3)	105 (15.4)	147 (25.0)	
Monomorphic sustained VT	34 (1.5)	1 (0.3)	9 (1.4)	9 (1.3)	15 (2.6)	
Polymorphic sustained VT	15 (0.7)	3 (0.9)	2 (0.3)	4 (0.6)	6 (1.0)	
Previous valvular surgery	131 (5.9)	2 (0.6)	18 (2.8)	36 (5.3)	75 (12.8)	<0.001
Abnormal sinus node function	394 (17.6)	13 (4.1)	61 (9.4)	136 (20.0)	184 (31.3)	<0.001
Peripheral artery disease	61 (2.7)	0 (0.0)	4 (0.6)	17 (2.5)	40 (6.8)	<0.001
Hypertension	1651 (73.9)	124 (39.1)	426 (65.5)	576 (84.6)	525 (89.4)	<0.001
Dyslipidemia	1866 (83.5)	160 (50.5)	532 (81.8)	610 (89.6)	564 (96.1)	<0.001
Anemia	543 (24.3)	11 (3.5)	94 (14.5)	176 (25.8)	262 (44.6)	<0.001

Characteristic	Overall (N=2235)	0 to 3 comorbidities (N=317)	4 or 5 comorbidities (N=650)	6 or 7 comorbidities (N=681)	≥8 comorbidities (N=587)	P-value
Diabetes mellitus	952 (42.6)	35 (11.0)	223 (34.3)	331 (48.6)	363 (61.8)	<0.001
Abnormal thyroid function	260 (11.6)	8 (2.5)	43 (6.6)	89 (13.1)	120 (20.4)	<0.001
Chronic liver disease	73 (3.3)	5 (1.6)	12 (1.8)	25 (3.7)	31 (5.3)	<0.01
Asthma	312 (14.0)	20 (6.3)	65 (10.0)	92 (13.5)	135 (23.0)	<0.001
Chronic obstructive pulmonary disease	568 (25.4)	31 (9.8)	113 (17.4)	182 (26.7)	242 (41.2)	<0.001
Chronic kidney disease	1136 (50.8)	46 (14.5)	231 (35.5)	405 (59.5)	454 (77.3)	<0.001
Chronic cancer	222 (9.9)	9 (2.8)	34 (5.2)	84 (12.3)	95 (16.2)	<0.001
Gastrointestinal hemorrhage	54 (2.4)	0 (0.0)	3 (0.5)	9 (1.3)	42 (7.2)	<0.001
Depression	405 (18.1)	27 (8.5)	85 (13.1)	112 (16.4)	181 (30.8)	<0.001
Dementia	76 (3.4)	1 (0.3)	8 (1.2)	20 (2.9)	47 (8.0)	<0.001
Arthritis	716 (32.0)	32 (10.1)	134 (20.6)	239 (35.1)	311 (53.0)	<0.001
Osteoporosis	153 (6.8)	8 (2.5)	16 (2.5)	53 (7.8)	76 (12.9)	<0.001
Mobility impairment	63 (2.8)	0 (0.0)	7 (1.1)	13 (1.9)	43 (7.3)	<0.001