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# Benefit of Implantable Cardioverter-Defibrillator Generator Replacement in a Primary Prevention Population-Based Cohort

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## ABSTRACT

**OBJECTIVES** This study investigated the benefit of an implantable cardioverter-defibrillator (ICD) generator replacement in patients who did not have an ongoing theoretical indication for ICD therapy at time of replacement.

**BACKGROUND** Primary prevention ICD therapy is known to reduce mortality in patients with cardiomyopathy and reduced left ventricular systolic function. The data describing outcomes after generator replacement are limited.

**METHODS** This was a retrospective cohort study following patients implanted with primary prevention ICD therapy from 2002 until 2015 who subsequently received a generator replacement. Patients with an ongoing theoretical indication for ICD therapy were defined as either left ventricular ejection fraction ≤35% or having had prior appropriate ICD therapy. Outcomes were mortality, appropriate ICD therapy and shock, inappropriate shock, and device and lead complications.

**RESULTS** A total of 614 patients were identified; 173 (28.2%) underwent a generator replacement and were followed for a mean of 2.9 years after replacement; 144 (83.2%) had an ongoing theoretical indication. Patients with no ongoing theoretical indication (n = 29, 16.7%) had lower mortality (hazard ratio [HR]: 0.39, 95% confidence interval [CI]: 0.15-1.00, p = 0.0495), appropriate shock rate (HR: 0.29, 95% CI: 0.09 to 0.96, p = 0.04), and appropriate ICD therapy rate (HR: 0.30, 95% CI: 0.12 to 0.77, p = 0.012) when compared with patients with ongoing theoretical indication. In the entire cohort, there were low rates of inappropriate shock (4.0%), device complication (5.1%), and lead complication (2.3%).

**CONCLUSIONS** In patients with primary prevention ICD therapy who underwent generator replacement, improved left ventricular ejection fraction and lack of prior appropriate ICD therapy at time of replacement were associated with a lower risk of mortality and incident ventricular arrhythmia. (J Am Coll Cardiol EP 2017;■:■-■) © 2017 by the American College of Cardiology Foundation.

Implantable cardioverter-defibrillators (ICDs) for primary prevention have been shown to improve mortality in patients with ischemic and non-ischemic cardiomyopathy and reduced left ventricular systolic function in randomized clinical trials (1-3). Accordingly, guidelines recommend implantation of primary prevention ICDs for these patients (4,5).

In the current era, it is common for patients to survive beyond their initial prophylactic ICD generator. It is unclear whether further benefit is derived from long-term device therapy, particularly if there has been a change in the patient's cardiovascular condition (6,7). Some patients who originally met criteria for a primary prevention ICD may no longer meet the original implant criteria at the time of generator replacement. This may be of particular relevance in patients who have shown improved left ventricular function, such as patients who have

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**ABBREVIATIONS AND ACRONYMS**

**ATP** = antitachycardia pacing

**CAD** = coronary artery disease

**CRT-D** = cardiac resynchronization therapy with defibrillator

**ICDs** = implantable cardioverter defibrillators

**NSVT** = nonsustained ventricular tachycardia

significant positive left ventricular remodeling with cardiac resynchronization therapy (CRT), or have improvement in left ventricular ejection fraction (LVEF) due to natural disease progression and optimal medical therapy. We sought to determine the outcomes after defibrillator generator replacement in patients with ICDs initially placed for primary prevention based on whether they met an ongoing theoretical indication for device therapy at time of replacement.

## METHODS

**STUDY POPULATION.** Data were analyzed from all patients who underwent ICD or cardiac resynchronization therapy with defibrillator (CRT-D) generator replacement for any reason in the province of Nova Scotia, Canada, between 2002 and 2015. Nova Scotia is a province of approximately 940,000 inhabitants; the new ICD implant rate/million in the Atlantic part of Canada is 186/million (this estimate is from 2010). The protocol was approved by the institutional research ethics board. The patient cohort was derived from a comprehensive provincial ICD registry, details of which have been published previously (8). Follow-up data were available for the entire population of patients with ICDs who resided in the province of Nova Scotia. Patients who underwent primary prevention ICD implantation for ischemic cardiomyopathy (LVEF ≤35% and documented coronary artery disease [CAD]) or nonischemic cardiomyopathy (LVEF ≤35% and New York Heart Association functional class [NYHA] II or greater heart failure) were included in the study. Patients who underwent primary prevention ICD implantation for arrhythmogenic ventricular cardiomyopathy, ion channelopathies, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, or who did not have structural heart disease were excluded from this analysis, as were nonresidents of Nova Scotia. In addition, patients who underwent heart transplantation or who had a left ventricular assist device insertion were excluded.

For the primary population of interest, patients undergoing first generator replacement, generator and lead change, and upgrade from ICD to CRT-D were included. If the procedure was a downgrade to a non-ICD device, the reason for the downgrade was noted, and the patient was excluded from further analysis. If patients were evaluated for generator replacement and the decision was made to not continue ICD therapy, the clinical reason was recorded.

Patient characteristics were recorded at the time of initial device implantation. Ischemic heart disease was defined as presence of coronary disease on coronary angiogram, with at least 70% stenosis in 1 or more epicardial vessels; previous myocardial infarction was documented as a rise in cardiac enzymes or wall motion abnormality on echocardiogram, or previous revascularization.

**COHORTS.** Ejection fractions measured by 2-dimensional echocardiography or nuclear wall motion study within a year of first generator replacement were obtained. If an assessment was not performed within a year of generator replacement, all available LVEF assessments were independently reviewed by 2 investigators, and measurements most approximate to time of generator replacement were used to classify the patient into ≤35% or >35%. If no measurements were available after initial device implantation, the patient was removed from further analysis.

Patients were divided into 2 cohorts based on ongoing theoretical indication at time of first generator replacement. The cohort with ongoing theoretical indication was further classified into those who had appropriate therapy for ventricular arrhythmia (antitachycardia pacing [ATP] or shock) before generator replacement, thus meeting a secondary indication; and those with LVEF ≤35%, either by measured or determined LVEF, thus meeting a primary prevention indication. The remainder of the patients was considered to have no ongoing theoretical indication.

**FOLLOW-UP AND OUTCOMES.** The outcome measures were all-cause mortality, time to first appropriate shock, and time to first appropriate shock or ATP, measured from time of first generator replacement. All therapies (shocks and ATP) from the implantable defibrillator were obtained from device interrogation at interval clinic visits, remote follow-ups, and any emergency department visits or hospitalizations. The follow-up schedule was every 6 months either in clinic or through the use of remote monitoring, as per current guidelines (4,9,10). All ICD therapies were independently adjudicated for appropriateness by 2 cardiac electrophysiologists blinded to the cohort allocation of the patient. Any disagreement between the 2 interpretations was resolved by review with a third electrophysiologist, also blinded.

Secondary outcomes were complications and inappropriate therapy. Rates of inappropriate shocks were measured from first generator replacement, whereas rates of complication were measured separately after first and second generator replacement.

If patients were lost to follow-up, the last known date of follow-up was used and data was censored thereafter. Patients who had a device downgraded to a non-ICD after initial device replacement were censored after the date of procedure.

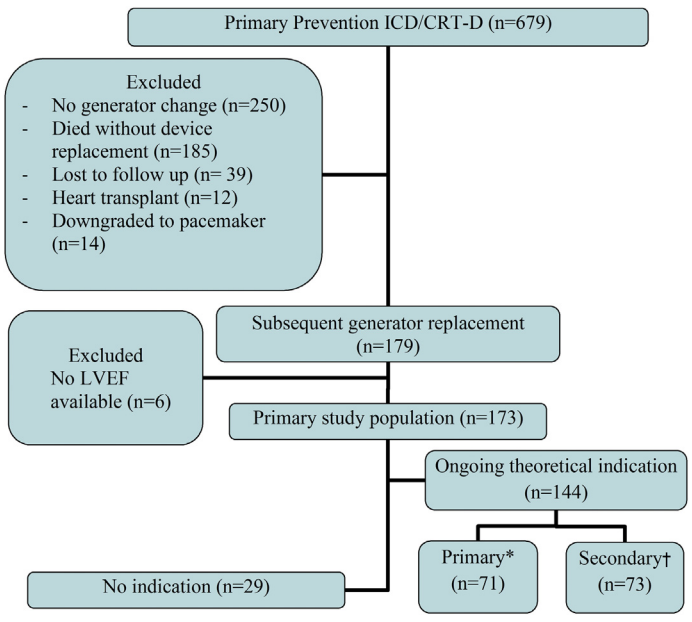
**STATISTICAL ANALYSIS.** Categorical variables were described as frequencies with percentages; continuous variables were described as mean ± SD. Demographic and clinical characteristics were compared between cohorts using either Fisher exact test or chi-square test for categorical data and the Student *t* test for continuous data. Using the Kaplan Meier method, overall survival, therapy-free survival, and shock-free survival was compared between the "no ongoing theoretical indication" cohort and the "ongoing theoretical indication" cohort. The subgroups of the ongoing theoretical indication group (primary and secondary) were analyzed for these same time-to-event outcomes. Cox proportional hazards modelling was performed to determine predictors of outcomes using variables known to influence risk of mortality and ventricular arrhythmia, including age, sex, CAD, diabetes, baseline creatinine, LVEF, and medication use (11,12). Significance tests were 2-sided and a value of $p < 0.05$ considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

## RESULTS

**POPULATION.** There were 614 patients included in the study who had ICDs or CRT-D implanted for primary prevention; of these, 179 (29.2%) underwent a generator replacement (Figure 1). Battery depletion was the primary cause for replacement (n = 114, 63.7%). Other reasons included upgrade to CRT or dual-chamber ICD (n = 34, 19.0%), battery and lead replacement (n = 20, 11.2%), device infection (n = 3, 1.7%), erosion (n = 2, 1.1%), and device advisory (n = 4, 2.2%). There were 37 (20.7%) patients who did not have an LVEF measured within 1 year of generator replacement. After exclusion of 6 (3.4%) patients who did not have LVEF assessment repeated after implantation, 173 patients were included in the study population. Mean time to first generator replacement was 5.2 ± 2.0 years; mean follow-up after replacement was 2.9 ± 2.3 years.

Baseline characteristics are shown in Table 1. The mean age was 67 ± 10.5 years; 79.8% were male. The original indication in 118 (68.2%) patients was an ischemic cardiomyopathy. The mean LVEF at the time of initial device implantation was 24.0 ± 6.0%,

**FIGURE 1 Flow Chart Outlining Population Inclusion and Exclusion**




*Ongoing theoretical primary indication: LVEF ≤35% at time of generator replacement. †Ongoing theoretical secondary indication: appropriate ICD therapy or shock before generator replacement. CRT-D = cardiac resynchronization therapy with defibrillation; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction.

and 68 (39.3%) patients had NYHA functional class III/IV heart failure.

At the time of replacement, there were 144 (83.2%) patients who had an ongoing theoretical indication for therapy: 71 (41.0%) had LVEF ≤35%, 73 (42.2%) had received appropriate therapy; the remaining 29 (16.8%) had not received appropriate therapy and had an LVEF >35%. The mean LVEF at time of replacement was 29 ± 11%; the distribution of LVEF was as follows: 75.7% had an LVEF ≤36%, 19.1% between 36% and 50%, and 5.1% had LVEF ≥50%. A total of 107 (61.8%) patients had a CRT-D after device replacement.

There were several differences in baseline characteristics between the cohorts (Table 1) as well as at time of device replacement (Table 2). Those with no theoretical indication had higher LVEF at initial device implantation (25.7 ± 6.3% vs. 23.6 ± 5.9%, $p < 0.0001$) and at time of device replacement (44.1 ± 6.5% vs. 26.7 ± 9.7%, $p < 0.0001$), longer QRS duration (158 ± 31 ms vs. 141 ± 36 ms, $p = 0.01$), higher prevalence of dilated cardiomyopathy (55.2% vs. 27.1%, $p = 0.004$), higher prevalence of CRT device before replacement (75.9% vs. 37.5%) and after replacement (79.3% vs. 58.3%). Additionally, there were more women in the no ongoing theoretical indication cohort (37.9% vs. 16.7%, $p = 0.02$).

**TABLE 1 Baseline Population Characteristics**

| | Total Population (N = 173) | Ongoing Theoretical Indication | | No Ongoing Theoretical Indication (n = 29) | p Value‡ |
|---|---|---|---|---|---|
| | | Primary* (n = 71) | Secondary† (n = 73) | | |
| Age (yrs) | 67.0 ± 10.5 | 66.8 ± 10.6 | 68.0 ± 10.3 | 64.7 ± 11.0 | 0.21 |
| Male (%) | 79.8 | 78.9 | 87.7 | 62.1 | 0.02 |
| Initial device implanted | | | | | |
| CRT | 76 (43.9) | 24 (33.8) | 30 (41.1) | 22 (75.9) | 0.0001 |
| Dual chamber | 17 (9.8) | 9 (12.7) | 4 (5.5) | 4 (13.8) | |
| Single chamber | 80 (46.2) | 38 (53.5) | 39 (53.4) | 3 (10.3) | |
| Indication for ICD | | | | | 0.004 |
| IHD | 118 (68.2) | 54 (76.1) | 51 (69.9) | 13 (44.8) | |
| Non-IHD-DCM | 55 (31.8) | 17 (23.9) | 22 (30.1) | 16 (55.2) | |
| Prior CAD | 119 (68.8) | 53 (74.6) | 53 (72.6) | 13 (44.8) | 0.004 |
| NYHA functional class | | | | | 0.07 |
| I | 31 (17.9) | 14 (19.7) | 15 (20.5) | 2 (6.9) | |
| II | 72 (41.6) | 30 (42.3) | 33 (45.2) | 9 (31.0) | |
| III-IV | 68 (39.8) | 26 (37.1) | 25 (34.2) | 17 (60.7) | |
| Initial LVEF (%) | 24.0 ± 6.0 | 24.3 ± 6.1 | 22.9 ± 5.6 | 25.7 ± 6.3 | <0.0001 |
| Atrial fibrillation | 55 (31.8) | 24 (33.8) | 25 (34.2) | 6 (20.7) | 0.19 |
| QRS duration (ms) | 143.7 ± 35.3 | 139.5 ± 35.9 | 141.7 ± 35.3 | 158.0 ± 31.4 | 0.01 |
| Creatinine (mmol/l) | 102.1 ± 31.1 | 100.9 ± 23.6 | 103.7 ± 30.9 | 100.9 ± 46.1 | 0.08 |
| Diabetes | 55 (31.8) | 29 (40.8) | 19 (26) | 7 (24.1) | 0.39 |
| Dyslipidemia | 110 (63.6) | 50 (70.4) | 50 (68.5) | 10 (34.5) | 0.0006 |
| Hypertension | 78 (45.1) | 32 (45.1) | 35 (47.9) | 11 (37.9) | 0.42 |
| Medications | | | | | |
| Beta blocker | 168 (97.1) | 69 (97.2) | 72 (98.6) | 27 (93.1) | 0.20 |
| ACE-I or ARB | 164 (94.8) | 67 (94.4) | 68 (93.2) | 29 (100.0) | 0.36 |
| Spironolactone | 55 (31.8) | 21 (29.6) | 24 (32.9) | 10 (34.5) | 0.83 |
| Loop diuretic | 113 (65.3) | 47 (66.2) | 44 (60.3) | 22 (75.9) | 0.21 |
| Oral anticoagulant | 75 (43.4) | 36 (50.7) | 27 (37) | 12 (41.4) | 0.84 |
| Digoxin | 69 (39.9) | 26 (36.6) | 28 (38.4) | 15 (51.7) | 0.21 |

Values are mean ± SD or n (%). *Ongoing theoretical primary indication: LVEF ≤35% at time of generator replacement. †Ongoing theoretical secondary indication: appropriate ICD therapy or shock before generator replacement. ‡Compared between "ongoing theoretical indication" and "no indication" cohorts.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CRT = cardiac resynchronization therapy; DCM = dilated cardiomyopathy; ICD = implantable cardioverter-defibrillator; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class.

**TABLE 2 Population Characteristics at Time of Replacement**

| | Total Population (N = 173) | Ongoing Theoretical Indication (n = 144) | No Ongoing Theoretical Indication (n = 29) | p Value |
|---|---|---|---|---|
| Age, yrs | 67.0 ± 10.5 | 67.5 ± 10.4 | 64.8 ± 11.0 | 0.21 |
| Device after replacement | | | | 0.046 |
| CRT | 107 (61.8) | 84 (58.3) | 23 (79.3) | |
| Dual chamber | 15 (8.7) | 12 (8.3) | 3 (10.3) | |
| Single chamber | 51 (29.5) | 48 (33.3) | 3 (10.3) | |
| LVEF within 1 year of device replacement (%) | 29.0 ± 11.0 | 26.7 ± 9.7 | 44.1 ± 6.5 | <0.0001 |
| ≤35 | 103 (75.7) | 103 (75.7) | 0 (0.0) | |
| 36-49 | 26 (19.1) | 11 (8.1) | 15 (83.3) | |
| ≥50 | 7 (5.1) | 4 (3.4) | 3 (16.7) | |

Values are mean ± SD or n (%).

Abbreviations as in Table 1.

**TABLE 3 Outcomes by Cohort**

| | Ongoing Theoretical Indication | | | No Ongoing Theoretical Indication (n = 29) |
|---|---|---|---|---|
| | Primary* + Secondary† (n = 144) | Primary (n = 71) | Secondary (n = 73) | |
| Mortality | 41 (28.5) | 22 (31.0) | 19 (26.0) | 5 (17.2) |
| Appropriate ATP/shock | 48 (33.3) | 15 (21.1) | 33 (45.0) | 5 (17.2) |
| Appropriate shock | 29 (20.1) | 9 (12.7) | 20 (27.4) | 3 (10.3) |

Values are n (%). *Ongoing theoretical primary indication: LVEF ≤35% at time of generator replacement. †Ongoing theoretical secondary indication: appropriate ICD therapy or shock before generator replacement.

ATP = antitachycardia pacing.

**OUTCOMES.** Outcomes for all cohorts are shown in Table 3. Among the 173 patients who underwent a generator replacement, 46 patients (26.6%) died during the follow-up period; 53 (30.6%) had either ATP or appropriate shock after replacement; and 19 (12.1%) had only appropriate ATP therapy. Univariate predictors for mortality after undergoing generator replacement are outlined in Table 4 and for appropriate therapy in Table 5. Significant predictors of mortality included age, creatinine level, diabetes, LVEF at time of replacement, and use of loop diuretics and digoxin. Significant predictors for ICD therapy included male sex, CAD, and prior ICD therapy. The indication for generator replacement had no effect on outcomes.

In the cohort with no ongoing theoretical indication, 5 (17.2%) patients died after replacement. Mortality at 1, 2, and 5 years was 3.5%, 11.2%, and 18.0%, respectively, and the average rate was 4.0% per person-year. In the cohort with ongoing theoretical indication, 41 (28.5%) patients died; 1-, 2-, and 5-year mortality was 10.9%, 17.4%, 44.1%, respectively, with an average rate of 10.4% per person-year. Patients with no ongoing theoretical indication had significantly reduced mortality (Figure 2) (4.0% vs. 10.4% per person-year, hazard ratio [HR]: 0.39, 95% confidence interval [CI]: 0.15 to 1.00, p = 0.0495) when compared with those with ongoing theoretical indication. When mortality was compared between the no ongoing theoretical indication group and those with a primary prevention indication, there was also a significant difference (Figure 3) (4.0% vs. 11% per person-year, HR: 0.37, 95% CI: 0.14 to 0.98, p = 0.045). No difference in mortality between the primary and secondary prevention groups was observed (Figure 3) (11% vs. 9.8% per person-year, HR: 1.14, 95% CI: 0.61 to 2.11, p = 0.68).

Among 29 patients with no ongoing theoretical indication, 3 (10.3%) received an appropriate shock after replacement, with an average rate of 2.6% per

**TABLE 4 Predictors of Mortality by Univariate Analysis**

| | Hazard Ratio | 95% Confidence Interval | p Value |
|---|---|---|---|
| Age (per yr) | 1.03 | 1.00–1.07 | 0.04 |
| Female | 0.66 | 0.28–1.57 | 0.35 |
| Creatinine (per 10 mmol/l) | 1.09 | 1.02–1.16 | 0.007 |
| CAD | 1.63 | 0.83–3.21 | 0.16 |
| Diabetes | 2.64 | 1.48–4.73 | 0.001 |
| LVEF at time of generator replacement (per 10% decrease) | 1.75 | 1.28–2.44 | 0.0004 |
| ATP or shock before generator replacement | 1.15 | 0.63–2.07 | 0.65 |
| Upgrade to CRT | 0.83 | 0.37–1.85 | 0.64 |
| Use of loop diuretics | 2.57 | 1.24–5.34 | 0.01 |
| Use of digoxin | 2.72 | 1.50–4.92 | 0.0009 |

Abbreviations as in Tables 1 and 3.

person-year, and 0%, 0%, 5.6%, respectively, at 1, 2, and 5 years. There were 5 (17.2%) patients who received either appropriate ATP or shock; average rate was 4.9% per person-year, and 3.7%, 3.7% and 15.8%, respectively, at 1, 2, and 5 years. One patient had LVEF of 47% at time of replacement, and had a known history of frequent nonsustained ventricular tachycardia (NSVT). Two patients had LVEF of 36% and 38% at time of replacement. The two remaining patients did not have LVEF measured within a year of generator replacement. One of these patients had an LVEF of 49% 2 years after replacement, and also had frequent NSVT. The second patient had LVEF of 44% 3 years before generator replacement, and 36% 4 years after replacement. Three of 5 patients had a CRT-D device. Among the 144 patients with an ongoing theoretical indication, 29 (20.1%) received an appropriate shock, an average rate of 9.6% per person-year, and 13.6%, 18.8%, and 32.5%, respectively, at 1, 2, and 5 years.

**TABLE 5 Predictors of Appropriate Therapy by Univariate Analysis**

| | Hazard Ratio | 95% Confidence Interval | p Value |
|---|---|---|---|
| Age (per yr) | 1.02 | 0.99–1.05 | 0.11 |
| Female | 0.36 | 0.14–0.90 | 0.03 |
| Creatinine (per 10 mmol/l) | 1.09 | 1.02–1.16 | 0.43 |
| CAD | 2.67 | 1.34–5.34 | 0.005 |
| Diabetes | 1.41 | 0.79–2.51 | 0.24 |
| LVEF at time of generator replacement (per 10% decrease) | 1.27 | 0.94–1.69 | 0.11 |
| ATP or shock before generator replacement | 3.01 | 1.71–5.29 | 0.0001 |
| Upgrade to CRT | 1.00 | 0.50–1.99 | 0.99 |
| Use of loop diuretics | 0.80 | 0.47–1.39 | 0.44 |
| Use of digoxin | 0.76 | 0.42–1.37 | 0.37 |

Abbreviations as in Tables 1 and 2.

There were 48 (33.3%) patients who received either an appropriate shock or ATP, with a mean rate of 18.6% per person-year, and 21.3%, 35.2%, and 50.1%, respectively, at 1, 2, and 5 years.

Compared to patients with ongoing theoretical indication, patients with no ongoing theoretical indication had a significantly lower risk of appropriate shock after replacement (Figure 4A) (2.6% vs. 9.6% per person-year, HR: 0.29, 95% CI: 0.09 to 0.96, p = 0.04), and a significantly lower risk of any appropriate therapy (Figure 4B) (4.9% vs. 18.6% per person-year, HR: 0.30, 95% CI: 0.12 to 0.77, p = 0.012). When comparing against the primary prevention indication group, the appropriate shock rate in the no indication group was lower but nonsignificant (2.6% vs. 5.7% per person-year, HR: 0.47, 95% CI: 0.12 to 1.75, p = 0.26). The difference in appropriate therapy rate was also nonsignificant (Figure 5) (4.9% vs. 10.8% per person-year, HR: 0.50, 95% CI: 0.18 to 1.39, p = 0.18).

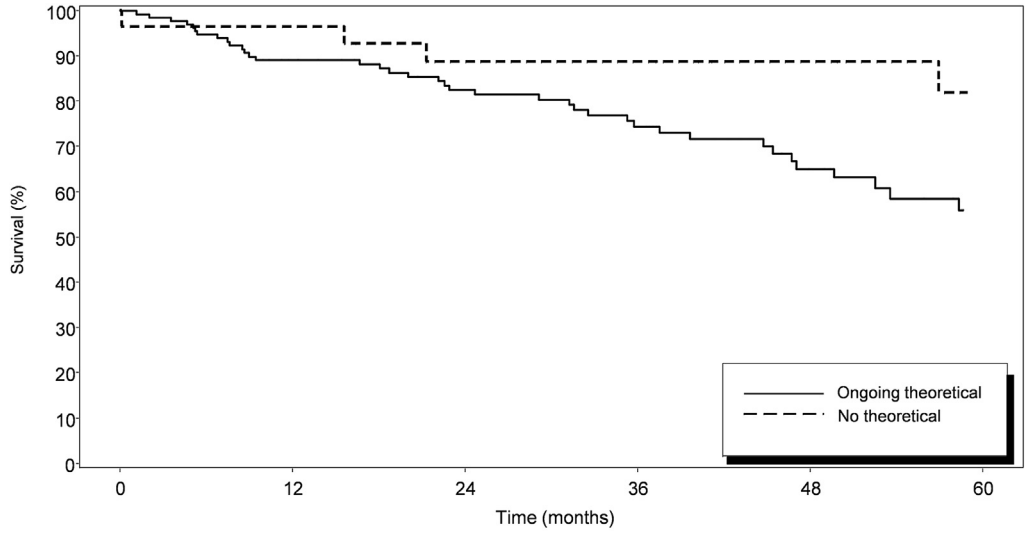
**EFFECT OF CRT.** A total of 107 patients had CRT-D devices after generator replacement. Eighty-four patients (78.5%) had theoretical ongoing indication, and 23 (21.5%) did not. There were 30.8% (n = 33) who had an improvement of LVEF to >35% at time of replacement and 63.6% (n = 68) who continued to have LVEF ≤35%. In the non-CRT group (n = 66), 16.7% (n = 11) had improvement of LVEF >35%, whereas 74.2% (n = 49) continued to have LVEF ≤35%.

Those with an improvement in LVEF to >35% had a significantly lower rate of mortality (HR: 0.36, 95% CI: 0.15 to 0.88, p = 0.026), and appropriate shock (HR: 0.28, 95% CI: 0.08 to 0.97, p = 0.045), than those who did not. The rate of appropriate therapy was lower but nonsignificant (HR: 0.45, 95% CI: 0.20 to 1.01, p = 0.054).

**INAPPROPRIATE SHOCKS AND COMPLICATIONS.** Overall, there were 7 (4.0%) patients who experienced inappropriate shocks after replacement. Four (2.8%) were in the theoretical indication group; all had primary indication. The remaining 3 (10.3%) were in the no ongoing theoretical indication group.

Among 215 device replacements, including first and second device replacements and those without follow-up LVEFs, the total complication rate was 5.1% (n = 11). Among 179 first device replacements, 8 (4.4%) patients experienced complications. Four developed pocket infection, 3 of whom received another device replacement as a result. One developed pulmonary edema, 1 developed subclavian thrombosis, and 2 had generator malposition. Among 36 second device replacements, there were 3 (8.3%) patients with complications, all infections. One of these patients received a subsequent device replacement as a result.

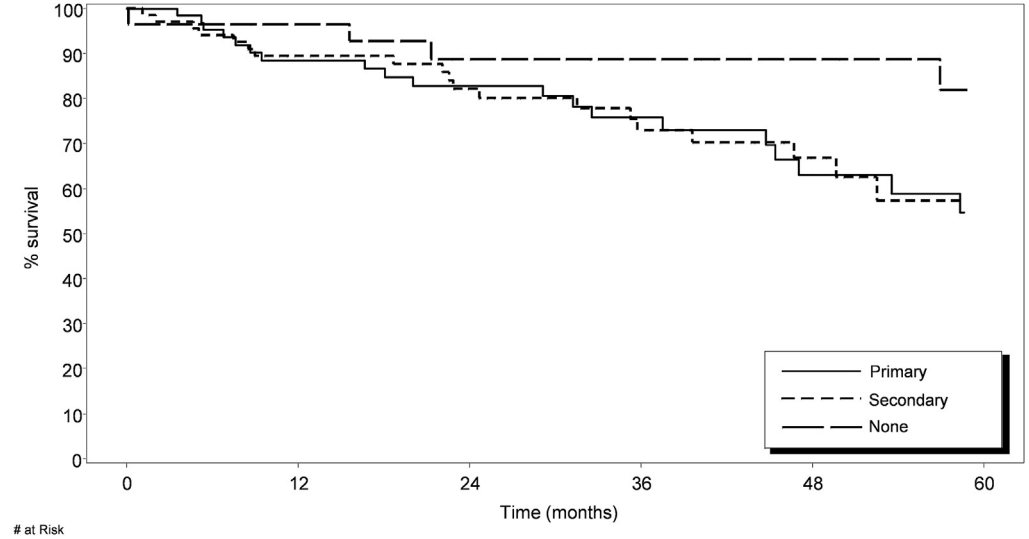
**FIGURE 2 Mortality After Generator Replacement by Ongoing Theoretical Indication at Time of Replacement**




| # at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Ongoing theoretical | 143 | 104 | 84 | 60 | 36 | 20 |
| No theoretical | 29 | 26 | 21 | 19 | 14 | 11 |

Theoretical indication defined as either ongoing primary indication, LVEF ≤35%, or ongoing secondary indication, prior ICD therapy, at time of generator replacement. Abbreviations as in Figure 1.

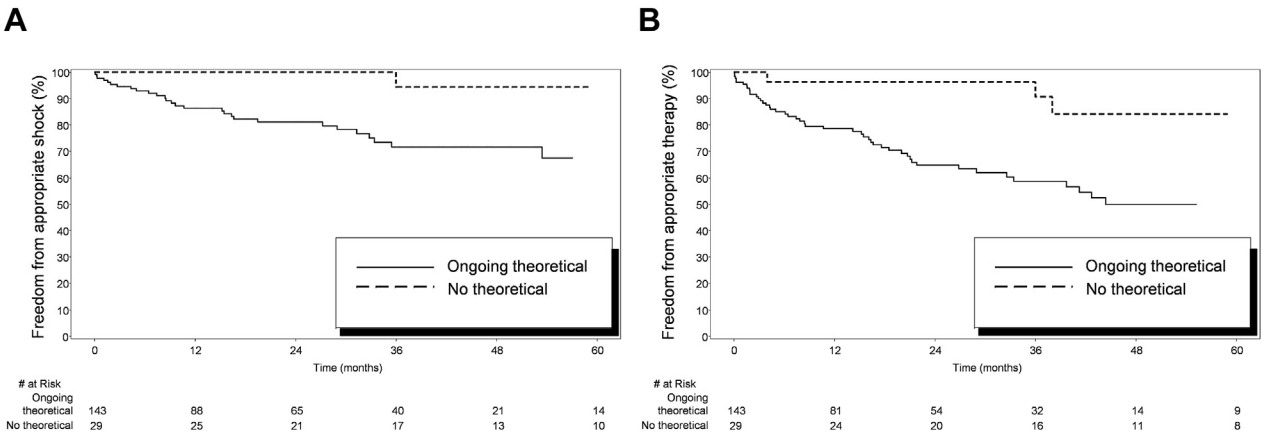
**FIGURE 3 Mortality After Generator Replacement by Ongoing Theoretical Indication at Time of Replacement**




| # at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Primary | 71 | 50 | 41 | 31 | 18 | 12 |
| Secondary | 72 | 54 | 43 | 29 | 18 | 8 |
| None | 29 | 26 | 21 | 19 | 14 | 11 |

Primary indication defined as LVEF ≤35%, secondary indication defined as prior ICD therapy, at time of generator replacement. Abbreviations as in Figure 1.

**FIGURE 4** Appropriate Shock and Appropriate ICD Therapy After Generator Replacement by Ongoing Theoretical Indication at Time of Replacement

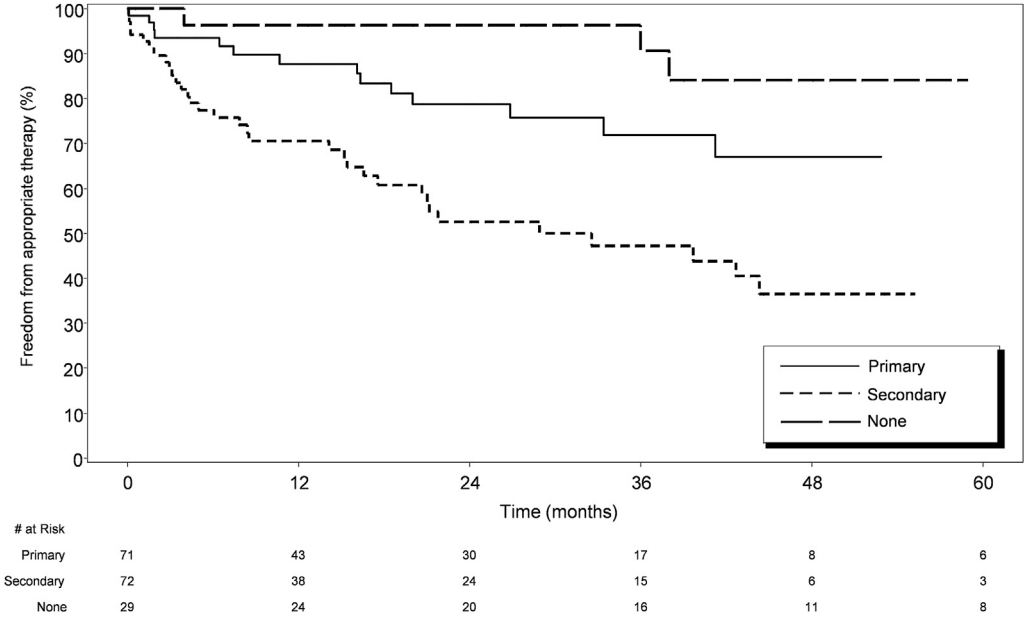



**(A)** Shock therapy. **(B)** ICD therapy. Theoretical indication defined as either ongoing primary indication, LVEF ≤35%, or ongoing secondary indication, prior ICD therapy, at time of generator replacement. Abbreviations as in Figure 1.

Among patients with ongoing theoretical indication, there were a total of 170 device replacements and 10 patients (5.9%) had a complication. Among those with no ongoing theoretical indication, there were 39 device replacements; 1 (2.6%) patient had an infection.

Among all 215 device replacements, there were 5 (2.3%) lead complications. There were 3 high thresholds, 1 loss of capture, and 1 dislodgement. All 5 had ongoing theoretical indication: 4 had secondary indication and 1 had primary indication. Two had an upgrade to CRT at time of generator replacement; 2 patients had

**FIGURE 5** Appropriate ICD Therapy After Generator Replacement by Ongoing Theoretical Indication at Time of Replacement




Primary indication defined as LVEF ≤35%, secondary indication defined as prior ICD therapy at time of generator replacement. Abbreviations as in Figure 1.

**TABLE 6 Summary of Previous Studies Following Patients After ICD Generator Replacement Comparing Outcomes by LVEF or Prior Therapy**

| First Author (Ref. #) | Initial Implant Device and Indication | Cohort After Generator Replacement Cohort | Sample Size | Outcome | Annualized Event Rate (%) | Follow-Up After Generator Replacement |
|---|---|---|---|---|---|---|
| Erkapic (17) | ICD only Primary or secondary | Prior therapy | 245 | Mortality | 6.2 | 22 ± 16 months |
| | | No prior therapy | 265 | | 4.5 | |
| Madhavan (7) | ICD only Primary | EF ≤35% and no prior therapy | 181 | Mortality | 7 | 5.8 yrs (IQR 4.2–8.1 yrs) |
| | | EF >35% and no prior therapy | 72 | | 5 | |
| Erkapic (17) | ICD only Primary or secondary | Prior therapy | 245 | Appropriate therapy | 23.8 | 22 ± 16 months |
| | | No prior therapy | 265 | | 10.5 | |
| House (23) | ICD and CRT-D Primary | EF ≤35% and no prior therapy | 70 | Appropriate therapy | 6.7 | 25 ± 18 months |
| | | EF >35% and no prior therapy | 55 | | 4.4 | |
| Kawata (6) | ICD only Primary | EF ≤35% or prior ICD therapy | 109 | Appropriate therapy | 11.4 | 41.2 ± 26.5 months |
| | | EF >35% and no prior ICD therapy | 59 | | 2.3 | |
| Kini (24) | ICD and CRT-D Primary | EF ≤35% or prior ICD therapy | 93 | Appropriate therapy | 10.7 | Unknown |
| | | EF ≥40% and no previous ICD therapy | 59 | | 2.8 | 3.5 ± 2.0 yrs |
| Madhavan (7) | ICD only Primary | EF ≤35 and no prior therapy | 181 | Appropriate therapy | 12 | 3.3 yrs (IQR 1.8–5.3 yrs) |
| | | EF >35% and no prior therapy | 72 | | 5 | |
| Naksuk (25) | ICD only Primary | Nonimproved LVEF | 66 | Appropriate therapy | 20 | 2.1 ± 1.5 yrs |
| | | EF >35% and increase by ≥10% | 25 | | 21.8 | 2.2 ± 1.6 yrs |
| Sebag (26) | CRT-D only Primary | EF <40% or prior ICD therapy | 68 | Appropriate therapy | 12.7 | 26.4 ± 14.4 months |
| | | EF ≥40% and no prior ICD therapy | 39 | | 2.3 | |
| Naksuk (25) | ICD only Primary | Nonimproved LVEF | 66 | Appropriate shock | 13.8 | 2.1 ± 1.5 yrs |
| | | EF >35% and increase by ≥10% | 25 | | 16.4 | 2.2 ± 1.6 yrs |
| Merchant (27) | ICD and CRT-D Primary or secondary | Prior ICD therapy | 7,973 | Any ICD shock | 14.6 | 1.9 ± 1.2 yrs |
| | | No prior ICD therapy | 16,230 | | 5.2 | |
| Sebag (26) | CRT-D only Primary | EF <40% or prior ICD therapy | 68 | Inappropriate therapy | 3.2 | 26.4 ± 14.4 months |
| | | EF ≥40% and no prior ICD therapy | 39 | | 2.3 | |

CRT-D = cardiac resynchronization therapy with defibrillation; EF = ejection fraction; IQR = interquartile range; other abbreviations as in Table 1.

a battery and lead change for lead fracture and malfunction; 1 patient had a battery replacement only.

## DISCUSSION

This was a retrospective cohort study of patients with a primary prevention indication for ICD or CRT-D who subsequently underwent a generator replacement. Over a mean follow-up of approximately 3 years, the annual rate of appropriate therapy was significantly lower in those with no ongoing theoretical indication, defined by improved LVEF and no history of appropriate ICD therapy, as compared to those with an ongoing theoretical indication. Mortality was found to be significantly lower, with a 61% relative risk reduction in those with no ongoing theoretical indication. Overall, inappropriate shocks and generator replacement-related complications were low in all groups. The presence of cardiac resynchronization therapy may have contributed to the improvement in LVEF from initial device implantation to device replacement; a prior systematic review (13) found that this is associated with reduced ICD therapy.

Five of 29 patients with no ongoing theoretical indication received ICD therapy after replacement. Four of these 5 patients had either LVEF between 35% and 40% or frequent NSVT. It is known that patients with NSVT may receive a greater benefit from ICD therapy; MUSTT (Multicenter Unsustained Tachycardia Trial) (14) and MADIT-I (Multicenter Automatic Defibrillator Implantation Trial I) (15) inclusion criteria included the presence of NSVT. It is possible that these 4 patients, although not meeting an ongoing theoretical indication at time of replacement, were at higher risk.

Our therapy and shock rates were comparable to those described by a systematic review (16), which found an annualized rate of 10.5% among 7 studies of patients with primary or secondary indication at initial implantation and subsequent generator replacement. There have been a number of studies that have explored ventricular arrhythmia requiring ICD therapy and mortality after ICD generator replacement in cohorts with improved LVEF or lack of prior ICD therapy (**Table 6**). Two prior studies found no mortality difference, which was also observed in our study. Erkapic et al. (17) compared patients by presence of prior ICD therapy (HR 1.23, 95% CI: 0.67 to 2.26, p = 0.509), whereas Madhaven et al. (7) compared patients, all of whom had not had prior therapy, by LVEF ≤35 at time of replacement (HR 1.10, p = 0.68). However, lower rates of appropriate therapy and shock have been described, similar to our findings.

Our study shows that in a population without ongoing theoretical indication, defined by improved LVEF and absence of prior therapy at time of generator replacement, there is a lower risk of ventricular arrhythmia requiring ICD therapy and shock. Our rate was also lower than previously described in primary prevention patients after initial implantation. Of the 2 original landmark trials following outcomes after initial ICD implantation, SCD-Heft (Sudden Cardiac Death in Heart Failure Trial) had an average annual therapy rate of 7.5%/year (3). Although the original MADIT-II study did not report therapy rates, subsequent analysis showed 24.1% of patients received appropriate therapy over a mean follow-up of 21 months (18). This could be explained by a higher adherence to optimal medical therapy in the contemporary era; our rate of beta-blocker therapy was 97%, compared to 70% in MADIT-II and SCD-Heft (1,3). Long-term follow-up data from MADIT-II patients, 8 years after randomization, showed a continued mortality benefit for patients who received ICD therapy, but repeat LVEF measurements were not available in this cohort, hence the effect of LVEF improvement is unknown (19).

There were significantly fewer women who had an ongoing indication for replacement. This may be explained by women having lower incidence of appropriate ICD therapy before replacement (14.3% vs. 34.8%); this has been shown in previous studies (20–22). We also found that females were at a lower risk of ICD therapy after replacement (HR 0.36, 95% CI: 0.14 to 0.9, p = 0.03).

**STUDY LIMITATIONS.** There are some limitations associated with our study. The retrospective and noncontrolled nature of the study carries inherent limitations. Factors that led to appropriate therapy or improvement in LVEF before generator replacement could contribute to the difference in outcomes after generator replacement. Although we found lower rates of therapy in the cohort with no ongoing theoretical indication, it is difficult to extrapolate this finding to patients who may otherwise not receive a generator replacement; we were unable to assess the number of patients who were evaluated for a replacement but did not receive one, thus we did not follow these patients. The appropriate therapy rate in the no indication group may be an overestimate as it is biased by those patients where both physicians and patients felt the need for ongoing device therapy.

## CONCLUSION

This study showed both mortality reduction and lower rate of ventricular arrhythmias among patients who initially receive ICDs for primary prevention and have no ongoing theoretical indication at time of generator replacement. We identified several risk factors that may be helpful in determining which patients would benefit most from ongoing high-voltage therapy; in those with no ongoing theoretical indication, close follow up to ascertain a change in LVEF or clinical status may be helpful in determining future risk to determine whether ongoing device therapy with defibrillation is required.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** As patients with primary prevention ICDs survive past their initial indication for device therapy, the benefit of high-voltage therapy from an ICD is unknown. We identified a population, characterized by LVEF >35% and absence of prior ICD therapy at time of device replacement, who are at low risk of mortality and ventricular arrhythmia.

**TRANSLATIONAL OUTLOOK:** The findings of this paper highlight the need for further research into the benefit of ongoing high-voltage therapy in patients with an initial indication for primary prevention of ventricular arrhythmia. Further development and validation of tools to predict and stratify individual patients' risk will aid patients' and clinicians' decisions regarding generator replacement.

## REFERENCES

**1.** Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–83.

**2.** Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151–8.

**3.** Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–37.

**4.** Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2013;127:e283–352.

**5.** Tang AS, Ross H, Simpson CS, et al. Canadian Cardiovascular Society/Canadian Heart Rhythm Society position paper on implantable cardioverter defibrillator use in Canada. Can J Cardiol 2005;21 suppl A:11A–8A.

**6.** Kawata H, Hirai T, Doukas D, et al. The occurrence of implantable cardioverter defibrillator therapies after generator replacement in patients who no longer meet primary prevention indications. J Cardiovasc Electrophysiol 2016;27:724–9.

**7.** Madhavan M, Waks JW, Friedman PA, et al. Outcomes after implantable cardioverter-defibrillator generator replacement for primary prevention of sudden cardiac death. Circ Arrhythm Electrophysiol 2016;9:e003283.

**8.** Parkash R, Sapp JL, Basta M, et al. Use of primary prevention implantable cardioverter-defibrillators in a population-based cohort is associated with a significant survival benefit. Circ Arrhythm Electrophysiol 2012;5:706–13.

**9.** Gillis AM, Philippon F, Cassidy MR, et al. Guidelines for implantable cardioverter defibrillator follow-up in Canada: a consensus statement of the Canadian Working Group on Cardiac Pacing. Can J Cardiol 2003;19:21–37.

**10.** Yee R, Verma A, Beardsall M, Fraser J, Philippon F, Exner DV. Canadian Cardiovascular Society/Canadian Heart Rhythm Society joint position statement on the use of remote monitoring for cardiovascular implantable electronic device follow-up. Can J Cardiol 2013;29:644–51.

**11.** Saxon LA, Bristow MR, Boehmer J, et al. Predictors of sudden cardiac death and appropriate shock in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Trial. Circulation 2006;114:2766–72.

**12.** Lee DS, Hardy J, Yee R, et al. Clinical risk stratification for primary prevention implantable cardioverter defibrillators. Circ Heart Fail 2015;8:927–37.

**13.** Chatterjee NA, Roka A, Lubitz SA, et al. Reduced appropriate implantable cardioverter-defibrillator therapy after cardiac resynchronization therapy-induced left ventricular function recovery: a meta-analysis and systematic review. Eur Heart J 2015;36:2780–9.

**14.** Buxton AE, Lee KL, DiCarlo L, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 2000;342:1937–45.

**15.** Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933–40.

**16.** Lewis KB, Stacey D, Carroll SL, Boland L, Sikora L, Birnie D. Estimating the risks and benefits of implantable cardioverter defibrillator generator replacement: a systematic review. Pacing Clin Electrophysiol 2016;39:709–22.

**17.** Erkapic D, Sperzel J, Stiller S, et al. Long-term benefit of implantable cardioverter/defibrillator therapy after elective device replacement: results of the INcidence free SUrvival after ICD REplacement (INSURE) trial—a prospective multicentre study. Eur Heart J 2013;34:130–7.

**18.** Moss AJ, Greenberg H, Case RB, et al. Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. Circulation 2004;110:3760–5.

**19.** Goldenberg I, Gillespie J, Moss AJ, et al. Long-term benefit of primary prevention with an implantable cardioverter-defibrillator: an extended 8-year follow-up study of the Multicenter Automatic Defibrillator Implantation Trial II. Circulation 2010;122:1265–71.

**20.** van der Heijden AC, Thijssen J, Borleffs CJ, et al. Gender-specific differences in clinical outcome of primary prevention implantable cardioverter defibrillator recipients. Heart 2013;99:1244–9.

**21.** Seegers J, Conen D, Jung K, et al. Sex difference in appropriate shocks but not mortality during long-term follow-up in patients with implantable cardioverter-defibrillators. Europace 2016;18:1194–202.

**22.** Sjoblom J, Kalm T, Gadler F, et al. Efficacy of primary preventive ICD therapy in an unselected population of patients with reduced left ventricular ejection fraction. Europace 2015;17:255–61.

**23.** House CM, Nguyen D, Thomas AJ, Nelson WB, Zhu DW. Normalization of left ventricular ejection fraction and incidence of appropriate antitachycardia therapy in patients with implantable cardioverter defibrillator for primary prevention of sudden death. J Card Fail 2016;22:125–32.

**24.** Kini V, Soufi MK, Deo R, et al. Appropriateness of primary prevention implantable cardioverter-defibrillators at the time of generator replacement: are indications still met? J Am Coll Cardiol 2014;63:2388–94.

**25.** Naksuk N, Saab A, Li JM, et al. Incidence of appropriate shock in implantable cardioverter-defibrillator patients with improved ejection fraction. J Card Fail 2013;19:426–30.

**26.** Sebag FA, Lellouche N, Chen Z, et al. Positive response to cardiac resynchronization therapy reduces arrhythmic events after elective generator change in patients with primary prevention CRT-D. J Cardiovasc Electrophysiol 2014;25:1368–75.

**27.** Merchant FM, Jones P, Wehrenberg S, Lloyd MS, Saxon LA. Incidence of defibrillator shocks after elective generator exchange following uneventful first battery life. J Am Heart Assoc 2014;3:e001289.

**KEY WORDS** generator replacement, implantable cardioverter-defibrillator, primary prevention, sudden cardiac death, ventricular tachycardia