Chapter 8
Replacement of Implantable Cardioverter-Defibrillators When Ventricular Function Has Recovered

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Case Presentation

A 68-year-old man with a single-chamber implantable cardioverter-defibrillator (ICD) presented because his ICD was nearing the end of battery life. The ICD was implanted 6 years ago for primary prevention of sudden cardiac death (SCD). He has not had any appropriate ICD shocks. His left ventricular ejection fraction (EF), which was 30% at the time of ICD implantation, has improved to 45% since then. Is the ICD generator replacement justified?

ICD Generator Replacement Statistics

Approximately 30,000 ICD generator replacement procedures are performed in the United States annually for end of battery life, constituting 28% of all ICD procedures [1–3]. The most common reason for ICD generator replacement is the device

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reaching elective replacement indicator (ERI), an alert displayed by the ICD indicating that the battery may reach end of life in the next 3–6 months. It is recommended to replace the ICD generator within 3 months of reaching ERI. Other, less common reasons for replacing ICD generator are infection, upgrade to cardiac resynchronization therapy (CRT), lead or generator malfunction, and advisory recalls for increased risk of failure of ICD components [2–4].

Approximately, 65–70% of primary prevention ICD recipients remain free of appropriate ICD therapy during the lifetime of their initial ICD generator [2, 5, 6]. While it is common practice to routinely replace ICDs that reach ERI, a number of factors may limit the potential benefit of ICD after generator replacement. Patients presenting for ICD generator replacement tend to be older and have more comorbidities than those having initial ICD implant, increasing their competing risk of death from non-cardiovascular causes [1, 5, 7]. In a propensity-matched analysis of the National Cardiovascular Data Registry, survival after ICD replacement was worse compared to initial implant, regardless of device type [2].

Furthermore, ICD generator replacement procedure may be associated with significant complications such as infection, hematoma, or lead damage, which may result in increased morbidity and mortality [2, 8–10]. Indeed, patients presenting for an ICD generator replacement due to ERI have a periprocedural major complication rate of 4–6% [1, 5, 8, 9, 11]. Those who have a concomitant lead replacement have a 6-month complication rate of up to 15% [9]. The highest risk is associated with the need to replace a left ventricular lead with complication rates ranging from 9% to 50% [9].

The risk of mortality after ICD generator replacement is close to 10% at 1 year and up to 50% at 5 years [5, 7, 12–14]. Factors associated with higher mortality include increased age, atrial fibrillation, heart failure, worsened ejection fraction, chronic lung disease, diabetes, renal dysfunction, and history of stroke [1, 15]. Excessive long-term mortality in these cases is a testament to the higher-risk status of these patients rather than the risks of the ICD generator replacement procedure.

Implantable cardioverter-defibrillator generator replacement procedures also have a significant economic burden to the US healthcare system [16, 17]. The approximate cost of a single-chamber ICD replacement was around $18,000 in 2005 but increased to nearly $23,000 by 2013 [7, 18]. Thus, roughly $700 million is spent for ICD generator replacement in the USA each year.

While there is a close audit of indications at initial ICD implantation, routine reassessment of ICD indications is not mandated when these patients present for ICD generator replacement [6]. Identifying the patients who are least likely to benefit from continued ICD therapy may significantly reduce medical expenses by avoiding unnecessary ICD generator replacement.

Frequency of EF Improvement in Patients with ICD

Left ventricular EF is the cornerstone of the criteria used in the decision process to recommend or decline ICD implantation for primary prevention of SCD [19].

Professional society practice guideline statements recommend ICD implantation in patients with EF ≤35% and mild to moderate heart failure symptoms while taking optimal medical therapy [20–22]. The EF cut-off is based on randomized controlled trials, in which patients assigned to ICD and medical therapy were more likely to survive compared to those assigned to medical therapy alone. However, patients presenting for ICD generator replacement have a left ventricular EF that is, on average, 4–5% higher than it had been at the time of the initial ICD implantation [1, 5]. As such, 25–40% of the patients who receive an ICD for primary prevention of SCD experience an improvement in their EF to the extent that they are no longer eligible for ICD therapy when they present for generator replacement. The proportion of patients with EF improvement has been consistent in cohorts that include ICD alone and those that also include CRT [14, 23].

Patients who experience an improvement in EF are younger, more likely to be women, more likely to be taking heart failure medications, and, most notably, more likely to have nonischemic cardiomyopathy [14, 23]. They also have less comorbidity, smaller left ventricular volume, and lower body mass index [24, 25]. Cardiomyopathy due to reversible causes such as tachycardia, myocarditis, pregnancy, hyperthyroidism, stress, pacing, or alcohol is more likely to improve after the offending etiology is treated or eliminated. Thus, 50% of the individuals with nonischemic cardiomyopathy assigned to ICD in the DEFINITE (Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation) trial experienced a significant (>5% absolute) improvement in EF [13]. In comparison, 20–25% of the patients with ischemic cardiomyopathy experience improvement in EF [26, 27]. Medical therapies and revascularization have been associated with improvement in EF in ischemic cardiomyopathy [28–33]. In addition to the factors associated with a higher likelihood of EF improvement, patients with a baseline EF in the range of 30–35% at the time of ICD implantation are more likely to be ineligible for ICD at the time of battery depletion [7, 26]. These data show that EF improvement is common after ICD implantation and 25–40% of the patients who qualified for ICD on the basis of a low EF will no longer be eligible for ICD implantation by the time they present for generator replacement.
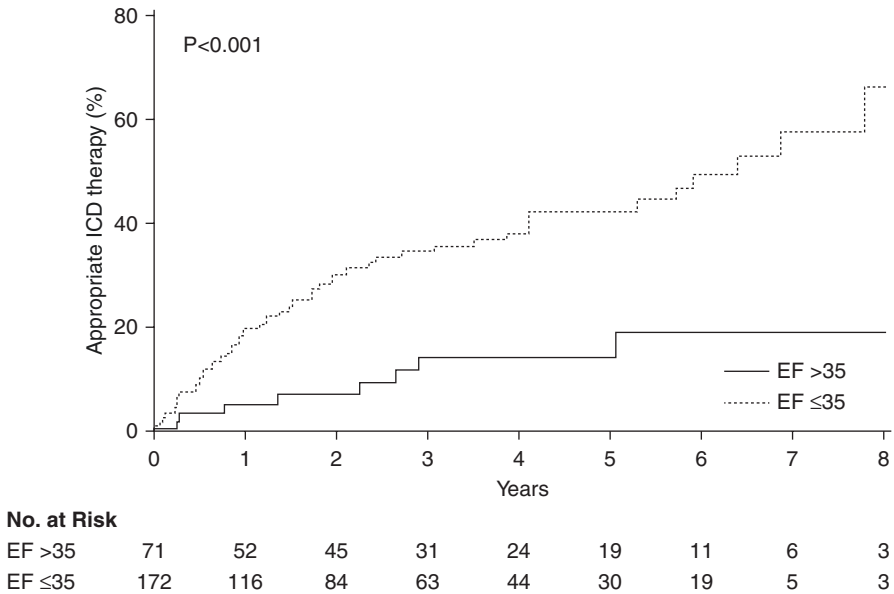
Appropriate ICD Therapy After EF Improvement

With improvement in EF, the incidence of appropriate ICD therapy is reduced but not completely eliminated (Table 8.1) [5, 7, 12–14, 26, 34–41]. In recent cohort studies, improvement in EF was associated with a 70% reduction in the risk of appropriate ICD therapy, which ranged from 2.8% to 5% per year (Fig. 8.1) [5, 7, 14]. Conversely, two earlier studies had found a similar incidence of appropriate ICD shock among patients with improved or unchanged EF [13, 26]. The reason for the dissimilar results in these studies may have been aggressive ICD programming parameters, which have evolved over the years to reduce shocks delivered for arrhythmias that are likely to terminate spontaneously [42].

Table 8.1 Description of the studies assessing the outcomes of patients with and without improvement in left ventricular ejection fraction after defibrillator implantation

Author year	N	Device type	Primary or secondary prevention	Cardiomyopathy	EF improvement criteria	Improved EF	Appropriate ICD therapy improved vs. unchanged EF	Mortality improved vs. unchanged EF
Schaer (2010) [39]	221	ICD or CRT	Primary or secondary	Nonischemic	EF >35%	ICD 44.9% CRT22.5%	28.3% vs. 43.9%	No data
Barsheshet (2011) [40]	749	CRT	Primary	Ischemic or nonischemic	>25% reduction in LVESV from baseline	70.6%	12% vs. 28%	15% vs. 35%
Naksuk (2013) [26]	91	ICD	Primary	Ischemic or nonischemic	EF >35% and >10% improvement from baseline	27%	28% vs. 26%	No data
Manfredi (2013) [12]	357	CRT	Primary or secondary	Ischemic or nonischemic	EF >45%	16.2%	6.9% vs. 20%	No data
Schliamser (2013) [13]	187	ICD	Primary	Nonischemic	>5% improvement in EF from baseline	51.3%	17.3% vs. 13.2%	3.1% vs. 15%
Sebag (2014) [34]	107	CRT	Primary or secondary	Ischemic or nonischemic	EF ≥40%	45%	5% vs. 28%	No data
Kini (2014) [7]	231	ICD or CRT	Primary	Ischemic or nonischemic	EF >40%	26%	8% vs. 38%	No data
Zhang (2015) [14]	538	ICD or CRT	Primary	Ischemic or nonischemic	>5% improvement in EF from baseline or EF >35%	40% (EF improved >5% from baseline) 25% (EF >35%)	3.0% vs. 7.8% (by >5% criterion) or 3.1% vs. 6.8% (by >35% criterion)	7.9% vs. 24% (by >5% criterion)
Kawata (2016) [35]	168	ICD	Primary	Ischemic or nonischemic	EF >35%	47%	11.6 vs. 56.8	No data
Madhavan (2016) [5]	253	ICD	Primary	Ischemic or nonischemic	EF >35%	28%	5%/year vs. 12%/year	5% vs. 7%
House (2016) [36]	125	ICD or CRT	Primary	Ischemic or nonischemic	EF >35%	44%	9% vs. 14%	No data
Madeira (2017) [37]	121	ICD or CRT	Primary or secondary	Ischemic or nonischemic	EF >35%	36%	2.6% vs. 32.9%	10.3% vs. 26.8%
Weng (2017) [38]	173	CRT or ICD	Primary	Ischemic or nonischemic	EF >35%	19%	17.2% vs. 33.3%	17.2% vs. 28.5%
Adabag (2017) [41]	624	ICD	Primary	Ischemic or nonischemic	EF >35%	29.8%	No data	6% vs. 20%

CRT cardiac resynchronization therapy, EF ejection fraction, ICD implantable cardioverter-defibrillator

Fig. 8.1 Cumulative incidence of appropriate ICD therapy after generator replacement among patients with or without EF improvement. (Adopted with permission from Madhavan et al. [5])

Absence of appropriate ICD therapy before generator replacement is not a sufficient reassurance for not having future ICD therapies. Approximately, 20% of patients who had an improvement in EF and no prior appropriate ICD therapies experience their first appropriate ICD therapy after generator replacement [26]. In a cohort study of such patients, the incidence of ICD therapy was 5% per year [5].

Patients with normalized EF constitute a special subgroup of EF improvement. These patients either have a reversible cardiomyopathy or can be classified as super responders to CRT. Super responders to CRT have a similar mortality risk to the general population [12, 40, 43]. Although the risk of appropriate ICD shocks decreases markedly in patients with normalized EF, a small risk remains. In a prospective cohort study by Zhang et al., only 1 of the 35 patients with normalized EF had an appropriate ICD shock during follow-up (1.7 shock/100 person-years) [14]. On the other hand, none of the 18 patients with EF >55% after CRT in a series by Manfredi et al. had appropriate ICD therapy [12].

Patients with CRT are more likely to experience improvement and normalization of LVEF compared to patients with ICD [14]. However, the association between changes in left ventricular EF and ICD therapy appears to be similar in ICD and CRT, suggesting that the improvement in EF itself, but not the means that caused the improvement, is responsible from the favorable results [14].

Collectively, these data show that 20–30% of patients with EF improvement are at risk of receiving appropriate ICD shock/therapy, but the risk appears to be lower

as the EF approaches normal range. The persisting risk of arrhythmias, observed in some patients despite improvement in EF, may be partly explained by the presence of a fixed substrate for ventricular arrhythmias (e.g., fibrosis, myocardial scar, heterogeneous repolarization) that does not resolve even when EF improves [14, 44–49]. However, the other factors associated with a persisting risk of SCD in patients with improved EF are presently unknown.

Do ICDs Reduce Mortality After Improvement of EF?

Left ventricular EF is a major determinant of arrhythmic and non-arrhythmic mortality [50]. Thus, it should come as no surprise that improvement in EF among patients with ICD is associated with improved survival in comparison with unchanged EF in the great majority of the cohort studies to date (Table 8.1). However, because of a lack of a control group without ICD, these cohort studies cannot determine whether ICD improves the likelihood of survival in patients with an improvement in EF. In the absence of prospective randomized controlled trials, we assessed the efficacy of ICD in prolonging survival among patients with improved EF in a secondary analysis of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) [41]. The SCD-HeFT was a randomized controlled trial of ICD, amiodarone, or placebo among 2511 patients with heart failure symptoms and EF $\leq 35\%$ due to ischemic or nonischemic cardiomyopathy [51]. After a median 45.5 months of follow-up, the patients assigned to ICD had a lower likelihood of mortality than those assigned to placebo or amiodarone (22%, 29%, and 28%, respectively), resulting in a 23% reduction in the relative risk and a 7.2% reduction in the absolute risk of mortality in comparison with the placebo group. While not mandated by the study protocol, nearly 75% of the patients in SCD-HeFT had a repeated assessment of EF 1 year after enrollment. Of these, 30% assigned to ICD or placebo showed a significant improvement in EF where the mean EF increased from 27% to 45%. During a median follow-up of 30 months after the repeated EF measurement, all-cause mortality rate was lower in the ICD vs. placebo groups both in patients whose EF improved to levels >35% (2.6% vs. 4.5% per 100-person-year follow-up, respectively) and in those whose EF remained $\leq 35\%$ (7.7% vs. 10.7% per 100-person-year follow-up, respectively) (Fig. 8.2). Compared with placebo, the adjusted hazard ratio for the effect of ICD on mortality was 0.64 (95% CI, 0.48–0.85) in patients with repeated EF $\leq 35\%$ and 0.62 (95% CI, 0.29–1.30) in those with a repeated EF >35% (Table 8.2). There was no interaction between treatment assignment and repeated EF for predicting mortality, suggesting that the efficacy of ICD was similar in patients with improved or unchanged EF. Cumulatively, these results suggest that mortality is lower among patients with improved EF, but ICD remains effective in reducing all-cause mortality among these patients.
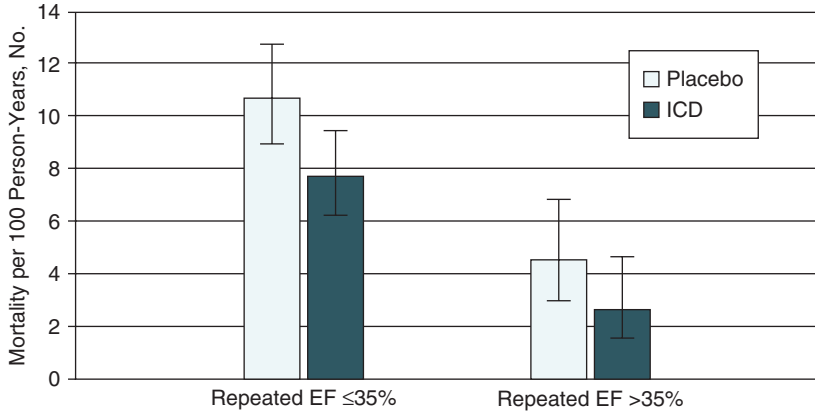
Fig. 8.2 Incidence rate of all-cause mortality of patients assigned to ICD vs. placebo. Adjusted hazard ratios of all-cause mortality in the ICD vs the placebo groups were 0.64 (95% CI, 0.48–0.85) in patients with a repeated ejection fraction (EF) ≤35% and 0.62 (95% CI, 0.29–1.30) in those with an EF >35%. (Adopted with permission from Adabag et al. [41])

Table 8.2 Incidence rates of all-cause mortality and SCD in the ICD and control groups in each EF category

	No.		100 Follow-up	Incidence Rate Mortality per 100
EF Group	Patients	Deaths	Person-years	Person-year Follow-up (95% CI)
All-Cause Mortality				
EF ≤35%				
ICD	438	89	11.5	7.7 (6.3-9.5)
Placebo	464	125	11.7	10.7 (8.9-12.7)
EF > 35%				
ICD	186	12	4.6	2.6 (1.5-4.6)
Placebo	185	22	4.9	4.5 (3.0-6.8)
SCD				
EF ≤ 35%				
ICD	438	14	11.5	1.2 (0.7-2.0)
Placebo	464	46	11.7	3.9 (2.9-5.2)
EF > 35%				
ICD	186	3	4.6	0.6 (0.2-2.0)
Placebo	185	4	4.9	0.8 (0.3-2.2)

Abbreviations: EF, ejection fraction; ICD, implantable cardioverter defibrillator; SCD, sudden cardiac death.

Proposed Algorithm

Patients who present for ICD generator replacement should be reevaluated for the appropriateness of continued ICD therapy (Fig. 8.3). The evaluation should first exclude any potential contraindications, such as advanced malignancy, that may have developed since the initial implant. A repeat echocardiogram to assess left ventricular function is prudent, if one has not been performed since the initial ICD implantation. A frank discussion to learn the patient's values and wishes about continued ICD therapy is of utmost importance to help guide the decision and to clarify potential misconceptions.
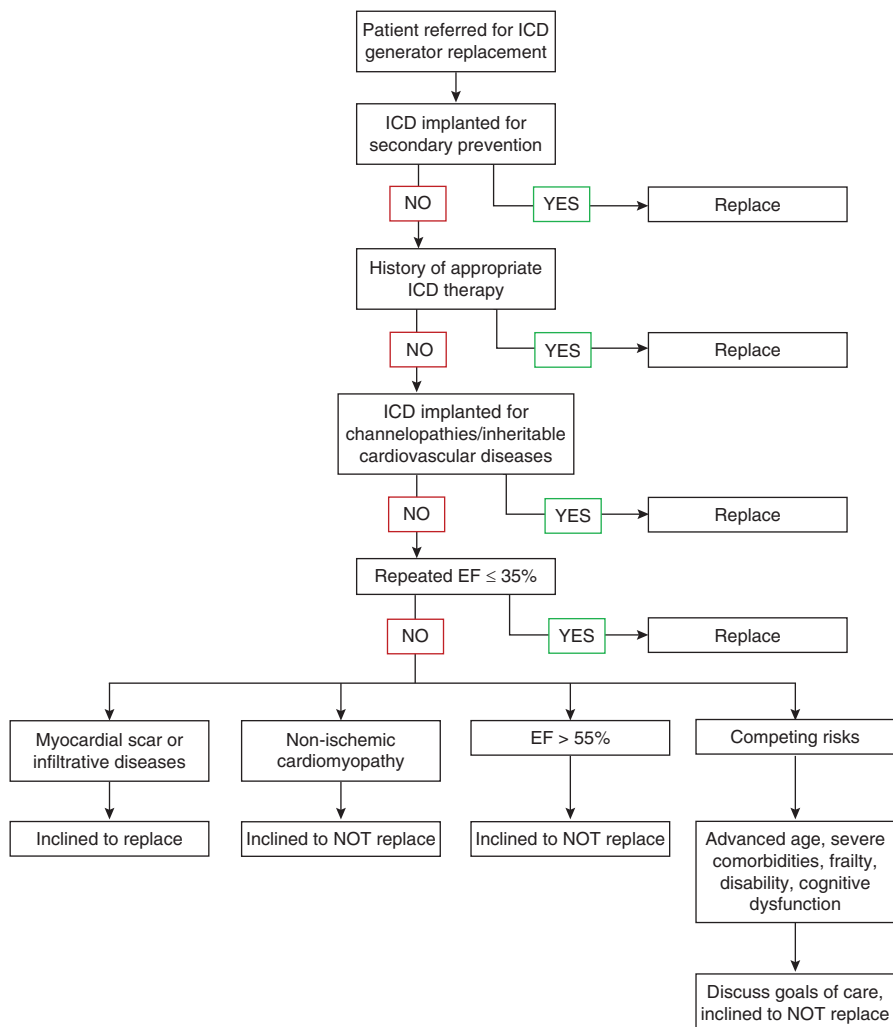

Fig. 8.3 Recommended algorithm for patients who present for ICD generator replacement

We recommend replacement of the generator if the original indication for ICD was secondary prevention of SCD. The risk of appropriate ICD therapy is higher (10%/year versus 5%/year) if the ICD was implanted for secondary prevention of SCD [52].

We also recommend generator replacement if there was an appropriate ICD therapy (shock or antitachycardia pacing) during the lifetime of the initial device. In addition to the host factors such as the rate and frequency of the ventricular tachycardia/ventricular fibrillation, the likelihood of appropriate ICD shocks also depends on the programmed tachycardia therapy parameters with a rise in the likelihood with more aggressive programming schemes. Indeed, it has been well documented that some ICD shocks for ventricular tachycardia/ventricular fibrillation are delivered prematurely for arrhythmias that would have terminated anyway. While we support utilization of newer ICD programming schemes to prevent inappropriate and appropriate—but unnecessary—shocks, we also recommend replacing the ICD generator in patients with prior appropriate ICD shock because of the increased risk of future shocks in these patients.

We also recommend generator replacement in patients with channelopathies/inheritable arrhythmogenic syndromes due to the continuation of risk. Similarly, patients whose EF remains ≤35% continue to be at SCD risk and should undergo generator replacement.

On the other hand, some patients who are no longer eligible for ICD due to improvement in EF deserve a fair discussion of whether the SCD risk warrants continuation of ICD therapy. Patients with nonischemic cardiomyopathy have a lower risk of SCD and may not benefit from ongoing ICD therapy if EF has improved [53, 54]. Patients with normalized EF (>55%) may also not benefit from continued ICD therapy [12, 14, 40, 43]. On the other hand, patients with a prior myocardial scar may continue to benefit from ICD even if their EF is better [49].

Older patients who have developed competing risks of death due to new comorbidities (e.g., renal failure) or those with frailty, disability, or cognitive dysfunction should have an opportunity to reevaluate continued ICD therapy with an extensive discussion of goals of care [55, 56]. In cases with difficulty in assessing risk additional markers such as inducibility of ventricular tachycardia, or magnetic resonance imaging to identify and quantify fibrosis may be useful [5, 57].

Management of Unreplaced ICDs

There is very limited data on whether or not to explant the ICD that has reached ERI and does not need replacement. Some device manufacturers recommend explanting the ICD to avoid any potential harm from erratic device behavior. The rationale for this recommendation comes from the concern that as the battery continues to deplete, the performance of the transistors (electrical switches) within the ICD may become unpredictable due to the lack of current supplied to these components, which control a number of functions including sensing, pacing, and shock delivery. However, other manufacturers note that at battery depletion, the ICD will revert to

storage mode in which no functionality is present. Thus, although no data are available, it is very unlikely for an ICD at the end of life to be able to generate enough power to deliver a shock. Indeed, in our limited experience, patients prefer leaving the device in order to avoid the burden and stress of the explant procedure. In two anecdotal cases, we have left the device without any negative clinical consequences.

However, patients with CRT defibrillator constitute a special situation. Even if the decision is made *not* to replace a CRT defibrillator, the device, in most instances, should be replaced with a CRT pacemaker to continue synchronization of the left ventricle, particularly if the patient is a "responder" to CRT. Similarly, among patients with a pacing indication who do not wish continued ICD therapy, the ICD should be replaced with a pacemaker [58, 59].

References

1. Kramer DB, Kennedy KF, Spertus JA, Normand SL, Noseworthy PA, Buxton AE, Josephson ME, Zimetbaum PJ, Mitchell SL, Reynolds MR. Mortality risk following replacement implantable cardioverter-defibrillator implantation at end of battery life: results from the NCDR. Heart Rhythm. 2014;11(2):216–21. PMID: 24513917.
2. Kramer DB, Kennedy KF, Noseworthy PA, Buxton AE, Josephson ME, Normand SL, Spertus JA, Zimetbaum PJ, Reynolds MR, Mitchell SL. Characteristics and outcomes of patients receiving new and replacement implantable cardioverter-defibrillators: results from the NCDR. Circ Cardiovasc Qual Outcomes. 2013;6(4):488–97. PMID: 23759471.
3. Merchant FM, Quest T, Leon AR, El-Chami MF. Implantable cardioverter-defibrillators at end of battery life: opportunities for risk (re)-stratification in ICD recipients. J Am Coll Cardiol. 2016;67(4):435–44. PMID: 26821633.
4. Gakenheimer L, Romero J, Baman TS, Montgomery D, Smith CA, Oral H, Eagle KA, Crawford T. Cardiac implantable electronic device reutilization: battery life of explanted devices at a tertiary care center. Pacing Clin Electrophysiol. 2014;37(5):569–75. PMID: 24359248.
5. Madhavan M, Waks JW, Friedman PA, Kramer DB, Buxton AE, Noseworthy PA, Mehta RA, Hodge DO, Higgins AY, Webster TL, Witt CM, Cha YM, Gersh BJ. Outcomes after implantable cardioverter-defibrillator generator replacement for primary prevention of sudden cardiac death. Circ Arrhythm Electrophysiol. 2016;9(3):e003283. PMID: 26921377.
6. Kramer DB, Buxton AE, Zimetbaum PJ. Time for a change—a new approach to ICD replacement. N Engl J Med. 2012;366(4):291–3. PMID: 22276818.
7. Kini V, Soufi MK, Deo R, Epstein AE, Bala R, Riley M, Groeneveld PW, Shalaby A, Dixit S. Appropriateness of primary prevention implantable cardioverter-defibrillators at the time of generator replacement: are indications still met? J Am Coll Cardiol. 2014;63(22):2388–94. PMID: 24727249.
8. Krahn AD, Lee DS, Birnie D, Healey JS, Crystal E, Dorian P, Simpson CS, Khaykin Y, Cameron D, Janmohamed A, Yee R, Austin PC, Chen Z, Hardy J, Tu JV, Ontario ICD Database Investigators. Predictors of short-term complications after implantable cardioverter-defibrillator replacement: results from the Ontario ICD database. Circ Arrhythm Electrophysiol. 2011;4(2):136–42. PMID: 21325209.
9. Poole JE, Gleva MJ, Mela T, Chung MK, Uslan DZ, Borge R, Gottipaty V, Shinn T, Dan D, Feldman LA, Seide H, Winston SA, Gallagher JJ, Langberg JJ, Mitchell K, Holcomb R, REPLACE Registry Investigators. Complication rates associated with pacemaker or implantable cardioverter-defibrillator generator replacements and upgrade procedures: results from the REPLACE registry. Circulation. 2010;122(16):1553–61. PMID: 20921437.

10. Lovelock JD, Cruz C, Hoskins MH, Jones P, El-Chami MF, Lloyd MS, Leon A, DeLurgio DB, Langberg JJ. Generator replacement is associated with an increased rate of ICD lead alerts. Heart Rhythm. 2014;11(10):1785–9. PMID: 24953380.
11. Gould PA, Krahn AD, Canadian Heart Rhythm Society Working Group on Device Advisories. Complications associated with implantable cardioverter-defibrillator replacement in response to device advisories. JAMA. 2006;295(16):1907–11. PMID: 16639049.
12. Manfredi JA, Al-Khatib SM, Shaw LK, Thomas L, Fogel RI, Padanilam B, Rardon D, Vatthyam R, Gemma LW, Golden K, Prystowsky EN. Association between left ventricular ejection fraction post-cardiac resynchronization treatment and subsequent implantable cardioverter defibrillator therapy for sustained ventricular tachyarrhythmias. Circ Arrhythm Electrophysiol. 2013;6(2):257–64. PMID: 23443618.
13. Schliamser JE, Kadish AH, Subacius H, Shalaby A, Schaechter A, Levine J, Goldberger JJ, DEFINITE Investigators. Significance of follow-up left ventricular ejection fraction measurements in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation trail (DEFINITE). Heart Rhythm. 2013;10(6):838–46. PMID: 23422221.
14. Zhang Y, Guallar E, Blasco-Colmenares E, Butcher B, Norgard S, Nauffal V, Marine JE, Eldadah Z, Dickfeld T, Ellenbogen KA, Tomaselli GF, Cheng A. Changes in follow-up left ventricular ejection fraction associated with outcomes in primary prevention implantable cardioverter-defibrillator and cardiac resynchronization therapy device recipients. J Am Coll Cardiol. 2015;66(5):524–31. PMID: 26227190.
15. Voight J, Akkaya M, Somasundaram P, Karim R, Valliani S, Kwon Y, Adabag S. Risk of new-onset atrial fibrillation and stroke after radiofrequency ablation of isolated, typical atrial flutter. Heart Rhythm. 2014;11(11):1884–9. PMID: 24998999.
16. Hospital outpatient prospective payment – final rule with comment period and CY2013 payment rates. Centers for Medicare & Medicaid Services, Jan 18, 2011. http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Hospital-Outpatient-Regulations-and-Notices-Items/CMS-1589-FC.html.
17. Physician fee schedule. Centers for Medicare & Medicaid Services, July 12, 2018. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/index.html.
18. Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. N Engl J Med. 2005;353(14):1471–80. PMID: 16207849.
19. Adabag S, Hodgson L, Garcia S, Anand V, Frascone R, Conterato M, Lick C, Wesley K, Mahoney B, Yannopoulos D. Outcomes of sudden cardiac arrest in a state-wide integrated resuscitation program: results from the Minnesota Resuscitation Consortium. Resuscitation. 2017;110:95–100. PMID: 27865744.
20. Al-Khatib SM, Stevenson WG, Ackerman MJ, Gillis AM, Bryant WJ, Hlatky MA, Callans DJ, Granger CB, Curtis AB, Hammill SC, Deal BJ, Joglar JA, Dickfeld T, Kay GN, Field ME, Matlock DD, Fonarow GC, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart rhythm J 2018;15(10): e73–e189.
21. Vakil K, Kazmirczak F, Sathnur N, Adabag S, Cantillon DJ, Kiehl EL, Koene R, Cogswell R, Anand I, Roukoz H. Implantable cardioverter-defibrillator use in patients with left ventricular assist device: a systematic review and meta-analysis. JACC Heart Fail. 2016;4(10):772–9. PMID: 27395347.
22. Vakil K, Duval S, Cogswell R, Eckman P, Levy WC, Anand I, Dardas T, Adabag S. Impact of implantable cardioverter-defibrillators on waitlist mortality among patients awaiting heart transplantation: an UNOS/OPTN analysis. JACC Clin Electrophysiol. 2017;3(1):33–40. PMID: 29759692.
23. Smer A, Saurav A, Azzouz MS, Salih M, Ayan M, Abuzaid A, Akinapelli A, Kanmanthareddy A, Rosenfeld LE, Merchant FM, Abuissa H. Meta-analysis of risk of ventricular arrhythmias after improvement in left ventricular ejection fraction during follow-up in patients with primary prevention implantable cardioverter defibrillators. Am J Cardiol. 2017;120(2):279–86. PMID: 28532779.

24. Pires LA, Ghio S, Chung ES, Tavazzi L, Abraham WT, Gerritse B. Relationship between acute improvement in left ventricular function to 6-month outcomes after cardiac resynchronization therapy in patients with chronic heart failure. Congest Heart Fail. 2011;17(2):65–70. PMID: 21449994.

25. Hsu JC, Solomon SD, Bourgoun M, McNitt S, Goldenberg I, Klein H, Moss AJ, Foster E, MADIT-CRT Executive Committee. Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: the MADIT-CRT (multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy) study. J Am Coll Cardiol. 2012;59(25):2366–73. PMID: 22698490.

26. Naksuk N, Saab A, Li JM, Florea V, Akkaya M, Anand IS, Benditt DG, Adabag S. Incidence of appropriate shock in implantable cardioverter-defibrillator patients with improved ejection fraction. J Card Fail. 2013;19(6):426–30. PMID: 23743493.

27. Naksuk N, Adabag S. What to do about primary-prevention implantable cardiac defibrillators in patients with improved ejection fraction. Curr Heart Fail Rep. 2014;11(2):197–200. PMID: 24500435.

28. Cintron G, Johnson G, Francis G, Cobb F, Cohn JN. Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. The V-HeFT VA Cooperative Studies Group. Circulation. 1993;87(6 Suppl):VI17–23. PMID: 8500235.

29. Konstam MA, Rousseau MF, Kronenberg MW, Udelson JE, Melin J, Stewart D, Dolan N, Edens TR, Ahn S, Kinan D, et al. Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. Circulation. 1992;86(2):431–8. PMID: 1638712.

30. Packer M, Colucci WS, Sackner-Bernstein JD, Liang CS, Goldscher DA, Freeman I, Kukin ML, Kinhal V, Udelson JE, Klapholz M, Gottlieb SS, Pearle D, Cody RJ, Gregory JJ, Kantrowitz NE, LeJemtel TH, Young ST, Lukas MA, Shusterman NH. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. Circulation. 1996;94(11):2793–9. PMID: 8941104.

31. Adabag S, Roukoz H, Anand IS, Moss AJ. Cardiac resynchronization therapy in patients with minimal heart failure: a systematic review and meta-analysis. J Am Coll Cardiol. 2011;58(9):935–41. PMID: 21851882.

32. St John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, Loh E, Kocovic DZ, Fisher WG, Ellestad M, Messenger J, Kruger K, Hilpisch KE, Hill MR, Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation. 2003;107(15):1985–90. PMID: 12668512.

33. Vakil K, Florea V, Koene R, Kealhofer JV, Anand I, Adabag S. Effect of coronary artery bypass grafting on left ventricular ejection fraction in men eligible for implantable cardioverter-defibrillator. Am J Cardiol. 2016;117(6):957–60. PMID: 26803382.

34. Sebag FA, Lellouche N, Chen Z, Tritar A, O'Neill MD, Gill J, Wright M, Leclercq C, Rinaldi CA. 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(12):1368–75. PMID: 25066404.

35. Kawata H, Hirai T, Doukas D, Hirai R, Steinbrunner J, Wilson J, Noda T, Hsu J, Krummen D, Feld G, Wilber D, Santucci P, Birgersdotter-Green U. The occurrence of implantable cardioverter defibrillator therapies after generator replacement in patients who no longer meet primary prevention indications. J Cardiovasc Electrophysiol. 2016;27(6):724–9. PMID: 26915696.

36. 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(2):125–32. PMID: 26522819.

37. Madeira M, António N, Milner J, Ventura M, Cristóvão J, Costa M, Nascimento J, Elvas L, Gonçalves L, Mariano Pego G. Who still remains at risk of arrhythmic death at time of implantable cardioverter-defibrillator generator replacement? Pacing Clin Electrophysiol. 2017;40(10):1129–38. PMID: 28842918.

38. Weng W, Sapp J, Doucette S, MacIntyre C, Gray C, Gardner M, Abdelwahab A, Parkash R. Benefit of implantable cardioverter-defibrillator generator replacement in a primary prevention population-based cohort. JACC Clin Electrophysiol. 2017;3(10):1180–9. PMID: 29759503.

39. Schaer B, Theuns DA, Stitcherling C, Szili-Torok T, Osswald S, Jordaens L. Effect of implantable cardioverter-defibrillator on left ventricular ejection fraction in patients with idiopathic dilated cardiomyopathy. Am J Cardiol. 2010;106(11):1640–5. PMID: 21094367.

40. Barsheshet A, Wang PJ, Moss AJ, Solomon SD, Al-Ahmad A, McNitt S, Foster E, Huang DT, Klein HU, Zareba W, Eldar M, Goldenberg I. Reverse remodeling and the risk of ventricular tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). J Am Coll Cardiol. 2011;57(24):2416–23. PMID: 21658562.

41. Adabag S, Patton KK, Buxton AE, Rector TS, Ensrud KE, Vakil K, Levy WC, Poole JE. Association of implantable cardioverter defibrillators with survival in patients with and without improved ejection fraction: secondary analysis of the sudden cardiac death in heart failure trial. JAMA Cardiol. 2017;2(7):767–74. PMID: 28724134.

42. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, Estes NA 3rd, Greenberg H, Hall WJ, Huang DT, Kautzner J, Klein H, McNitt S, Olshansky B, Shoda M, Wilber D, Zareba W, MADIT-RIT Trial Investigators. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med. 2012;367(24):2275–83. PMID: 23131066.

43. Manne M, Rickard J, Varma N, Chung MK, Tchou P. Normalization of left ventricular ejection fraction after cardiac resynchronization therapy also normalizes survival. Pacing Clin Electrophysiol. 2013;36(8):970–7. PMID: 23718783.

44. Adabag AS, Therneau TM, Gersh BJ, Weston SA, Roger VL. Sudden death after myocardial infarction. JAMA. 2008;300(17):2022–9. PMID: 18984889.

45. Adabag AS, Maron BJ, Appelbaum E, Harrigan CJ, Buros JL, Gibson CM, Lesser JR, Hanna CA, Udelson JE, Manning WJ, Maron MS. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. J Am Coll Cardiol. 2008;51(14):1369–74. PMID: 18387438.

46. Adabag S, Rector TS, Anand IS, McMurray JJ, Zile M, Komajda M, McKelvie RS, Massie B, Carson PE. A prediction model for sudden cardiac death in patients with heart failure and preserved ejection fraction. Eur J Heart Fail. 2014;16(11):1175–82. PMID: 25302657.

47. Adabag AS, Maron BJ. Implications of arrhythmias and prevention of sudden death in hypertrophic cardiomyopathy. Ann Noninvasive Electrocardiol. 2007;12(2):171–80. PMID: 17593187.

48. Al Aloul B, Adabag AS, Houghland MA, Tholakanahalli V. Brugada pattern electrocardiogram associated with supratherapeutic phenytoin levels and the risk of sudden death. Pacing Clin Electrophysiol. 2007;30(5):713–5. PMID: 17461883.

49. Gulati A, Jabbour A, Ismail TF, Guha K, Khwaja J, Raza S, Morarji K, Brown TD, Ismail NA, Dweck MR, Di Pietro E, Roughton M, Wage R, Daryani Y, O'Hanlon R, Sheppard MN, Alpendurada F, Lyon AR, Cook SA, Cowie MR, Assomull RG, Pennell DJ, Prasad SK. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. JAMA. 2013;309(9):896–908. PMID: 23462786.

50. Adabag AS, Luepker RV, Roger VL, Gersh BJ. Sudden cardiac death: epidemiology and risk factors. Nat Rev Cardiol. 2010;7(4):216–25. Epub 2010 Feb 9. PMID: 20142817.

51. 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, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH, Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med. 2005;352(3):225–37. PMID: 15659722.

52. van Welsenes GH, van Rees JB, Borleffs CJ, Cannegieter SC, Bax JJ, van Erven L, Schalij MJ. Long-term follow-up of primary and secondary prevention implantable cardioverter defi-brillator patients. Europace. 2011;13(3):389–94. Epub 2011 Jan 5. PMID: 21208947.
53. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjær H, Brandes A, Thøgersen AM, Gustafsson F, Egstrup K, Videbæk R, Hassager C, Svendsen JH, Høfsten DE, Torp-Pedersen C, Pehrson S, DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med. 2016;375(13):1221–30. PMID: 27571011.
54. Anantha Narayanan M, Vakil K, Reddy YN, Baskaran J, Deshmukh A, Benditt DG, Adabag S. Efficacy of implantable cardioverter-defibrillator therapy in patients with nonischemic car-diomyopathy: a systematic review and meta-analysis of randomized controlled trials. JACC Clin Electrophysiol. 2017;3(9):962–70. PMID: 29759721.
55. Adabag S, Vo TN, Langsetmo L, Schousboe JT, Cawthon PM, Stone KL, Shikany JM, Taylor BC, Ensrud KE. Frailty as a risk factor for cardiovascular versus noncardiovascular mortality in older men: results from the MrOS sleep (outcomes of sleep disorders in older men) study. J Am Heart Assoc. 2018; 7(10): e008974.
56. Garcia S, Ko B, Adabag S. Contrast-induced nephropathy and risk of acute kidney injury and mortality after cardiac operations. Ann Thorac Surg. 2012;94(3):772–6. PMID: 22835553.
57. Buxton AE, Lee KL, Hafley GE, Pires LA, Fisher JD, Gold MR, Josephson ME, Lehmann MH, Prystowsky EN, MUSTT Investigators. Limitations of ejection fraction for prediction of sudden death risk in patients with coronary artery disease: lessons from the MUSTT study. J Am Coll Cardiol. 2007;50(12):1150–7. PMID: 17868806.
58. Coumbe AG, Naksuk N, Newell MC, Somasundaram PE, Benditt DG, Adabag S. Long-term follow-up of older patients with Mobitz type I second degree atrioventricular block. Heart. 2013;99(5):334–8. PMID: 23086974.
59. Moulki N, Kealhofer JV, Benditt DG, Gravely A, Vakil K, Garcia S, Adabag S. Association of cardiac implantable electronic devices with survival in bifascicular block prolonged PR inter-val on electrocardiogram. J Interv Card Electrophysiol. 2018;52:335–41. Epub ahead of print PMID: 29907894.