Primary prevention ICD generator at end of life: to replace or not to replace?

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Implantable cardioverter-defibrillators (ICDs) are the cornerstone of therapy for primary prevention of sudden cardiac death in patients with severely depressed left ventricular ejection fraction (EF) ≤35%, irrespective of the aetiology.[1–3] Current device guidelines and appropriate use criteria lay profound emphasis on the baseline left ventricular EF and New York Heart Association functional class in selecting appropriate candidates for primary prevention ICD implantation.[4 5] However, these society guidelines do not provide guidance regarding a decision about replacing ICD generators, especially in patients who have not had any appropriate ICD therapies during the lifespan of the device and/or in whom the left ventricular EF improves to >35% at the time of reimplantation. Prior studies have shown that among primary prevention ICD recipients, about 75% do not experience any appropriate ICD therapies during the lifetime of their first ICD generator[6 7] and about 25%–40% have improvements in their left ventricular EF >35% after ICD implantation.[7–12] Furthermore, patients requiring generator replacements are older and have significantly greater comorbidities compared with the initial recipients.[6 13 14] A significant proportion of ICD-related procedures in the USA, approximately 40%, involve ICD generator replacement based on the National Cardiovascular Data Registry data.[6] Device replacements are associated with substantial healthcare costs and greater risk of major complications compared with initial implant.[15 16] This raises a critical question as to whether the risk of sudden cardiac death warrants ICD generator replacement in patients who have not had any prior appropriate ICD therapies. Does improvement in left ventricular EF >35% lower the risk of sudden cardiac death negating the potential benefits of ICD?

In this issue of the *Journal*, Looi *et al*[17] report their single-centre outcomes in patients with heart failure after primary prevention ICD generator replacement.

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Of 385 patients with primary prevention ICD/CRT-D (cardiac resynchronization therapy-defibrillator) devices implanted between 2007 and 2015, 61 (16%) underwent pulse generator replacement. Twenty-one (34.4%) patients had a device upgrade. The mean time between the initial implant and generator replacement was 5.8 years. The mean longevity of the device did not differ between the device types (single chamber vs dual chamber vs CRT-D vs S-ICD (subcutaneous-ICD) device; p=0.24). Patients who presented for generator replacement had a significantly higher left ventricular EF (31.2±11. vs 24.8±5.2, p<0.01), higher prevalence of diabetes mellitus (p=0.04) and lower mean estimated glomerular filtration rate (p=0.02). Of 61 patients, 18 (30%) had received prior appropriate ICD therapies. When stratified based solely on left ventricular EF at the time of reimplant, 41 patients (67%) met the criterion for device replacement. Twenty patients (33%) had their left ventricular EF improved >35%. These patients were more likely to be women, with history of non-ischemic cardiomyopathy, had CRT-D devices, and had higher use of ACE inhibitors/angiotensin II receptor blockers and beta-blockers.

During a mean follow-up period of 1.8±1.5 years, 13 patients (21%) received appropriate ICD therapies (anti-tachycardia pacing/shock). Among the 20 patients who underwent ICD device replacement despite no longer meeting accepted indications for primary prevention ICD therapy, 10% (2/20) received appropriate ICD therapies compared with 26.8% (11/41) who continued to meet primary prevention ICD indications. The cumulative risks of appropriate ICD interventions after 1, 3 and 5 years after generator replacement in those who no longer met indications were 0%, 25% and 62.5% and in those who continued to meet primary prevention ICD indications were 3%, 28.4% and 85.9%, respectively (log-rank p=0.23). Although the authors state that 20 patients did not meet an indication for generator replacement based on improvement in EF, 5 of these patients received appropriate ICD therapy and would likely be considered to have an ongoing indication for secondary prevention ICD.

There were a total of 6 (9.8%) procedure-related complications: 1 haematoma, 1 infection requiring intravenous antibiotics and 4 lead revisions. Half of these complications occurred in patients undergoing device upgrade at the time of generator replacement. A total of 5 patients (8.2%) died during follow-up after generator replacement from end-stage heart failure.

There are no randomised controlled trial data on outcomes in patients with primary prevention ICD who are referred for elective generator replacement due to battery depletion and had no appropriate therapies in the past and/or who had improvement in their left ventricular EF. Although a small, retrospective, single-centre study, the results of the present study adds to the existing knowledge, showing that at the time of reimplant, left ventricular EF as a sole risk marker for assessing future arrhythmic death is far from ideal.[17] Although the risk of ICD therapies was lower in patients with improved EF >35%, the cumulative risks of subsequent appropriate ICD interventions did not differ compared with those who continued to have persistently depressed EF ≤35%.[17] The present study, however, was unable to identify predictors that would identify lower risk individuals at the time of reimplant for future ICD therapies.

Few observational studies have analysed the outcomes of primary prevention ICD recipients who were referred for generator replacement and had improvement in the EF >35%.[7 9 11 12 18] Two large studies are worth mentioning. Madhavan *et al*[7] reported outcomes in 253 primary prevention ICD patients who never received an appropriate ICD therapy and were referred for generator replacement at two tertiary medical centres. EF improved to >35% in 28% of patients at generator replacement. During a median follow-up of 3.3 years after generator replacement, 27% experienced appropriate ICD therapy. Importantly, patients with EF >35% continued to be at a significant risk for appropriate ICD therapy after generator replacement (5% per year), although at a lower rate than patients with a persistently low EF ≤35% (12% per year).[7]

In the Sudden Cardiac Death in Heart Failure Trial substudy, 1273 patients with reduced EF ≤35% assigned to ICD versus placebo were analysed.[18] During a median follow-up of 30 months, EF improved to >35% in about 30% of patients in each group. Compared with placebo, the adjusted HR for the effect of ICD on mortality was 0.64 (95% CI 0.48 to 0.85)

in patients with a repeated EF of ≤35% and 0.62 (95% CI 0.29 to 1.30) in those with a repeated EF >35%. These data suggest that patients who had an improvement in EF >35% during follow-up accrued a similar mortality benefit with ICD as those whose EF remained ≤35%.[18] Similar findings were reported in other smaller studies where improvement in EF >35% was associated with lower risk of ICD therapies; however, the residual arrhythmic risk was significant enough to warrant ongoing ICD therapy.[9 11 12] Furthermore, heart failure is a progressive disorder. The left ventricular EF may subsequently decline after an initial improvement, thus placing a patient at risk for sudden death if generator replacement is not considered.

We would like to echo the concern raised by the authors of the present study. The fact that the risk of sudden arrhythmic death among those with improved EF and no prior ICD therapies is not zero does not necessarily imply that generator replacement should be performed routinely in all of these patients. The decision to perform a generator replacement should be made after considering carefully the relative balance between competing risks of arrhythmic and non-arrhythmic death.[19] Compared with an initial ICD implant, patients receiving replacement devices are older, have more significant comorbidities and have shorter life expectancy, all of which may limit the benefit of ICD therapy following generator replacement.[19] Additionally, generator replacements are associated with significant healthcare expenditure and associated complications, including infection, which may increase the risk of mortality.[15 16]

The present study, along with previously published reports, underscores the limitations of left ventricular EF as a sole marker of future arrhythmic risk. These studies have taught us that patients continue to be at significant risk for ventricular arrhythmias despite improvement in left ventricular EF >35%. The pivotal randomised controlled trials of primary prevention ICD included only high-risk patients with left ventricular EF <35%.[1–3] There has been no randomised controlled trial to date of primary prevention ICD implantation in patients with EF >35%. If proven in a prospective study, it will have significant implications on risk stratification in patients with left ventricular EF >35%. Future prospective studies should also use other markers for better risk stratification, such as detection of myocardial scarring by cardiac MRI in addition to left ventricular EF prior to ICD implantation.[20 21] In conclusion, it is reasonable to offer generator replacement for primary prevention ICD patients with improved EF >35% after carefully considering the risks of arrhythmic and non-arrhythmic death with an individual patient.

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