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Improve the prevention of sudden cardiac arrest in emerging countries: the Improve SCA clinical study design

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Aims This study aims to demonstrate that primary prevention (PP) patients with one or more additional risk factors are at a similar risk of life-threatening ventricular arrhythmias when compared with secondary prevention (SP) patients, and would receive similar benefit from an implantable cardioverter defibrillator (ICD), or cardiac resynchronization therapy-defibrillator (CRT-D) implant. The study evaluates the benefits of therapy for high-risk patients in countries where defibrillation therapy for PP of SCA is underutilized.

Methods Enrolment will consist of 4800 ICD-eligible patients from Asia, Latin America, Eastern Europe, the Middle East, and Africa. Upon enrolment, patients will be categorized as SP or PP. Primary prevention patients will be assessed for additional risk factors: syncope/pre-syncope, non-sustained ventricular tachycardia, frequent premature ventricular contractions, and low left ventricular ejection fraction. Those PP patients with one or more risk factors will be categorized as '1.5' patients. Implant of an ICD/CRT-D will be left to the patient and/or physician's discretion. The primary endpoint will compare the appropriate ICD therapy rate between SP and 1.5 patients. The secondary endpoint compares mortality between 1.5 implanted and non-implanted patients.

Conclusion The Improve SCA study will investigate a subset of PP patients, believed to be at similar risk of life-threatening ventricular arrhythmias as SP patients. Results may help clinicians identify and refer the highest risk PP patients for ICDs, help local societies expand guidelines to include PP of SCA utilizing ICDs, and provide additional geographical-relevant evidence to allow patients to make an informed decision whether to receive an ICD.

Trial registration NCT02099721.

Keywords Primary prevention • Secondary prevention • Syncope • NSVT • PVCs • LVEF • SCA

Introduction

The use of implantable cardioverter defibrillators (ICDs) in patients who have survived an episode of sudden cardiac arrest (SCA) or sustained ventricular tachycardia (VT) is well established. However, the use of ICDs in patients without a history of SCA, but at high risk of an episode, is less established in some areas of the world. The prevention of sudden cardiac death (SCD) is an important

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What's new?

- Large global study including participation from geographies typically under-represented in previous PP clinical ICD trials including: Asia, Latin America, Eastern Europe, the Middle East, and Africa.
- No prospective data have been collected to determine whether one or more of these risk factors (syncope/pre-syncope, NSVT, frequent PVCs, low LVEF) in a primary prevention ICD population is associated with an increased likelihood of receiving an appropriate ICD therapy.

goal, and the ICD plays a vital role by terminating sudden or unexpected arrhythmias leading to SCA.

Global burden

The burden of SCD varies by geography, though global data are somewhat limited. In the developed countries, such as the USA and the Netherlands, incidence rate estimates, range from 53 to 117 of 100 000 persons per year,[1,2] while in emerging countries, such as China, incidence rates are estimated to be 41.8 of 100 000 persons per year.[3] In Southern India, it is estimated that approximately 700 000 individuals die of SCD each year and SCD to contributes to 10.3% of overall mortality.[4] However, the true incidence rates are often difficult to ascertain, due in part to difficulties in obtaining death certificates as well as the accuracy on the certificate itself (SCD is often unwitnessed).

Despite the prevalence of SCD in emerging countries, ICDs are underutilized as a SCD prevention therapy. In 2011, the ICD implant rate per million persons in China and India were 1.0 and 2.1, respectively.[5] Lack of physician awareness of ICD therapy indications and low patient acceptance are possible reasons for ICD underutilization. For instance, the PLASMA study found that only 13% of patients with a Class I indication were prescribed an ICD/CRT-D in Latin American. Despite this Class I indication for an ICD, the primary reason provided by general cardiologists for not prescribing an ICD was perceived lack of an ICD indication (75% of cases).[6] Likewise, in China, a study found that in 497 patients meeting Class I secondary prevention (SP) indications for an ICD, only 112 (22.5%) accepted an ICD implant. The remaining 385 refused due to economic or other reasons. Factors limiting ICD utilization in China include high cost, the sophisticated technique of implantation, and follow-up procedure, as well as physicians' attitudes toward sudden death.[7] Additional global prospective data are needed to further demonstrate the benefit of ICD implants in emerging countries.

Clinical study

An ICD may be implanted in a patient for either secondary or primary prevention (PP) of SCA. Secondary prevention refers to the use of ICDs for the prevention of SCD in patients who have survived a prior SCA or sustained VT, whereas PP refers to the use of ICDs in individuals who are at risk for, but have not yet had a documented episode of sustained VT, VF, or resuscitated cardiac arrest.

Implantable cardioverter defibrillation therapy for SP of SCD is a generally accepted treatment strategy, as the patient has previously experienced a life-threatening ventricular arrhythmia. In fact, in emerging countries such as India, South Korea, and Taiwan, most ICDs implanted are for a SP indication.[5] In contrast, use of ICDs for PP of SCD may be limited in emerging countries, in part, due to a perceived lower risk of the patient experiencing a life-threatening ventricular arrhythmia. The intent of the Improve SCA study is to evaluate risk factors that may identify a subset of PP patients who have a similar risk of an appropriate ICD therapy as SP patients.

The four risk factors which may be associated with a higher risk of SCA, include syncope or pre-syncope (due to suspected VT), very low left ventricular ejection fraction (LVEF $<$ 25%), non-sustained ventricular tachycardia (NSVT; three or more consecutive beats at $>$100 beats per min lasting 30 s), and frequent premature ventricular contractions (PVCs; average of 10 or more PVCs per h) (*Table 1*). PP patients meeting one or more of these risk factors may have a risk of ventricular arrhythmias more similar to SP patients, thus forming a subgroup called the 1.5 prevention indication group.

Syncope/pre-syncope

Implantable cardioverter defibrillation therapy is indicated for SP of SCA (Class IA) in patients with syncope of undetermined origin with clinically relevant, haemodynamically significant sustained VT or VF induced at an electrophysiology study. In addition, an ICD is Class IIa indicated for PP of SCA in patients with unexplained syncope, significant LV dysfunction, and non-ischaemic dilated cardiomyopathy. However, as demonstrated previously, a history of syncope may be an important risk factor in patients with cardiovascular disease at risk for SCA,[8–11] especially in those with heart failure.

Low left ventricular ejection fraction

Decreased LVEF has been associated with an increased mortality risk and an LVEF of $\leq$35% is currently considered a primary risk factor for SCA.[12] Data compiled from four randomized trials, pooled to create a cohort of 2828 patients, showed that each 10% reduction in LVEF $<$ 40% independently conferred a 39% increase in risk for arrhythmic cardiac mortality over a 2-year period.[13] In this analysis, the lowest number of patients needed to prevent one death with an ICD was when an LVEF was between 16 and 25%. In the Improve SCA study, an LVEF less than 25% is considered to be very low LVEF and is criteria for a 1.5 prevention patient.

Non-sustained ventricular tachycardia

A meta-analysis of 11 studies (n = 4387) found NSVT to be a statistically significant predictor for arrhythmic events in patients with LV dysfunction.[14] Furthermore, the SCD-HeFT trial concluded that NSVT was independently associated with a $>$4 times increased risk of appropriate ICD therapies.[15] In this study, NSVT is defined as three or more consecutive ventricular beats at a rate of more than 100 beats per min which spontaneously terminates within 30 s.

Frequent premature ventricular contractions

A link between PVCs and VTs is well documented,[16–19] suggesting that PVCs are a marker of high risk for ventricular arrhythmias and

Table 1 1.5 Prevention definition

Condition	Details

Syncope or pre-syncope	Within the past 12 months:
	• Pre-syncope/dizziness/lightheadedness due to suspected VT
	• Syncope due to suspected VT
	• Unexplained syncope or pre-syncope, after ruling out these causes:
	  • Syncope due to carotid sinus hypersensitivity
	  • Vasovagal syncope
	  • Syncope due to bradycardia
	  • Syncope due to SVT

Low LVEF	LVEF < 25% measured within 6 months of enrolment or implant If history of MI, LVEF must be collected at least: • 40 Days post-MI if there was no revascularization • 90 Days post-MI if there was revascularization (e.g. percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)
NSVT	A history of NSVT since HF diagnosis in Medical Records OR A history of NSVT documented from an IPG (implantable pulse generator) on an EGM strip in the medical records, where the physician rules out SVT or ventricular artefact OR NSVT measured on an ambulatory monitor (e.g. Holter, patch) WHERE Non-sustained VT is defined as 3 or more consecutive beats at >100 beats per minute lasting less than 30 s
Frequent PVCs	History of frequent PVCs within 12 months OR Frequent PVCs on an ambulatory monitor (e.g. Holter) test lasting at least 20 h OR A history of frequent PVCs documented from an IPG on an EGM strip in the medical records, where the physician rules out SVT or ventricular artefact. WHERE 'Frequent PVCs' is defined as an average of 10 or more PVCs per hour while monitored If history of MI, PVCs must be collected at least: • 40 days post-MI if there was no revascularization • 90 days post-MI if there was revascularization (e.g. percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)

mortality in patients with structural heart diseases. In patients with a recent myocardial infarction (MI), burden of PVCs greater than an average of 10 per h on a 24-h Holter was associated with a 2.24 increased risk of SCA. The report by Bigger demonstrated that the survival rate was lowest in patients with LVEF < 30% and PVCs >10 beats per h.[20]

Thus, the aim of the study is to demonstrate that PP patients with one or more of these additional risk factors (syncope/pre-syncope, NSVT, frequent pre-ventricular contractions, and low LVEF) are at a similar risk of life-threatening ventricular arrhythmias when compared with SP patients and would receive similar benefit from an ICD or CRT-D implant.

To preliminarily test this hypothesis, the OMNI study (ClinicalTrials.gov ID: NCT00277524), an ICD registry with 2242 primary and SP patients in the USA, was analysed. Out of 1894 PP patients, 990 (52%) qualified for 1.5 prevention based on either an LVEF < 25% or history of NSVT (baseline PVC and syncope data were unavailable). There was a statistically significant 24% difference between time to first true VT/VF between primary and secondary patients (*Figure 1*, left panel), but the difference between 1.5 prevention and SP was much smaller (9%) and not statistically significantly different (*Figure 1*, right panel).

Methods

The Improve SCA study is a prospective, non-randomized, non-blinded, multi-site global study. The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki. Patient Informed Consent will be obtained prior to their participation and Ethics Committee approval will be obtained for participating sites.

Study population

The study will enrol patients who meet a guideline recommendation for a single, dual, or triple chamber ICD. Patients currently implanted with pacemaker receiving a device upgrade to an ICD are eligible.

The study plans to initially enrol 4800 patients; however, a sample size re-estimation will be performed approximately 1.5 years after study start using baseline assumptions from study enrolments to that point. Enrolment of 4800 patients is expected to take 2 years.

Key inclusion criteria

- Class I indication for implantation of an ICD according to the ACC/AHA/HRS or ESC Guidelines.[21,22]

Key exclusion criteria

- ≤18 years of age

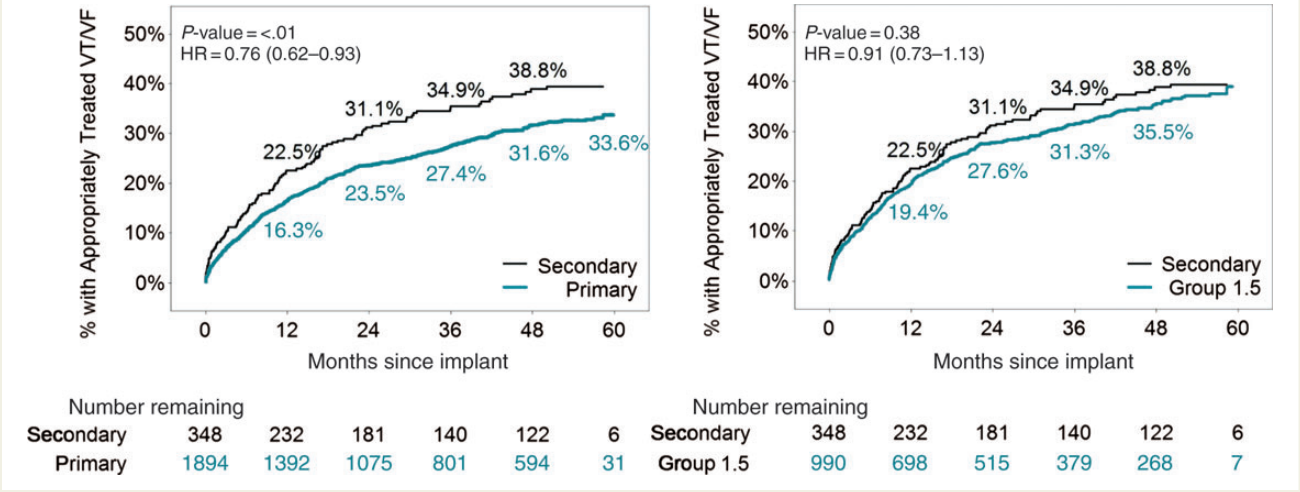

Figure 1 Time to first appropriate VT/VF therapy in the OMNI clinical study. The panel on the left compares time with first treated VT/VF episode between PP and SP patients, and the panel on the right shows the results of the Improve SCA primary objective, comparing 1.5 prevention with SP. The *P*-values are from log-rank tests where a low *P*-value indicates a difference in the two curves.

- Any contraindication for ICD/CRT-D

Patient categorization

Patients will be assessed at baseline to determine whether they are in the SP or PP group. At the baseline visit, all who have been identified as PP will be assessed to see if they meet 1.5 prevention criteria (*Table 1*). If one or more criteria are met, this patient will be classified as a 1.5 patient.

Each patient will have all four criteria assessed at baseline using either recent tests or post-enrolment evaluations. Assessment for history of syncope or pre-syncope may be via medical records or patient recollection and must have occurred within 12 months of enrolment. LVEF assessment may be from multigated acquisition scan (MUGA), echocardiography, or magnetic resonance imaging (MRI) and must be within 6 months of enrolment. If the patient has a history of MI, the LVEF assessment must have been performed at least 90 days or 40 days post-MI depending on whether the patient was revascularized or not, respectively. Similarly, PVC burden must have been measured during a 24-h ambulatory test (at least 20 h) within 12 months of enrolment, with the same post-MI waiting period. Finally, NSVT can be found from medical records, or if there is no evidence of NSVT, then a 24-h ambulatory test will be done to look for NSVT. This can be the same test as is used for PVCs.

Choice of implant

Implant of an ICD will be based on the patient and physician's discretion. Reasons for declining an implant will be collected. Implanted patients will receive a Medtronic market-released ICD/CRT-D and will be programmed according to current evidence-based shock minimization settings (*Table 2*) to ensure consistency between groups in detecting and treating VT/VF episodes.

All implanted patients will be followed, along with PP patients who elect to not be implanted. Secondary prevention patients who reject implant will be exited from the study upon implant refusal. *Figure 2* shows the allocation of patient groups by indication and implant status.

Follow-up and data collection

Patients will be followed up every 6 months until the last patient reaches the 24-month follow-up. At each 6-month visit (which can be performed in-person or by phone), patients will be asked whether they are taking Amiodarone, whether there has been a change in their device status (e.g. explant or new implant), and patients who are implanted with an ICD will have their device data downloaded using a CareLink™ remote monitoring transmission or in-person device interrogation.

Study objectives

Primary objective

(1) Demonstrate that appropriate VT/VF therapy rates (shock and ATP) for patients meeting 1.5 prevention criteria implanted with a Medtronic device (ICD/CRT-D) are equivalent (within 30%) to rates in patients meeting SP criteria.

Secondary objective

(1) Compare the mortality rates for patients meeting 1.5 prevention criteria between those implanted with a device (ICD/CRT-D) and those not implanted.

Ancillary objectives

(1) Evaluate the cost effectiveness of ICDs/CRT-Ds in patients meeting 1.5 prevention criteria.
(2) Collect patient rationale for not receiving a device.
(3) Evaluate appropriately treated VT/VF rates within patients who have Chagas disease.

Statistical methods

For the primary objective, all episodes classified by the ICD as VT/VF will be adjudicated by a committee based on EGM data as being either true VT/VF or false episodes. Time to the first true, treated (by ATP or shock) VT/VF episode will be the endpoint of interest and it will be compared between implanted SP patients and implanted 1.5 prevention patients. The hazard ratio of 1.5 prevention to SP will be computed along with a 95% lower confidence bound. If the lower confidence bound is greater than 0.70 (the non-inferiority margin), then non-

Table 2 Programming requirements at implant

Parameter	Required programming
VFDI	300 ms
VFNID	30/40
VT enable	ON
VTDI	360 ms
VTNID	24
SVT limit	260 ms
High rate timeout	
All zones	OFF
VF zone only	DR/CRT-D: OFF; VR: ON− 0.75 min timeout
AF/AFl rejection	ON
Sinus tach	ON
Wavelet[a]	ON, 70%
EGM 2	Can-RV Coil or RV Coil−SVC Coil
Wavelet template	Perform manual template collection at all visits
T wave discrimination	ON
RV lead noise	ON+ 0.75 min timeout
RV lead integrity	ON
Stability	OFF
Onset	OFF
Monitor zone	ON (Monitor)
VT monitor interval	450 ms
VT monitor NID	32
Confirmation+	ON
VF therapy #1	ATP during charging and Max output shock
ATP delivery R-R	240 ms
Therapy type	Burst
Smart mode	ON
Chargesaver	ON, Successful ATP:1
VT Rx 1	ATP Burst 8@88% (3 seq)
Monitored EGMs	EGM 1 and EGM 2
EGM 1	Atip-Aring or RV Sense Vector
Pre-arrhythmia EGM	ON continuous for first 12 months of follow-up

[a]Wavelet is only available VR devices and Protect/Evera DR/CRT and Viva CRT devices. PR Logic is not available in VR devices.

inferiority will be demonstrated. Additional analyses of the primary endpoint, such as looking at individual factors of the 1.5 criteria or other variables, may be performed.

A program simulating the study was used to determine a sample size of 4800 patients has 80% power to declare non-inferiority. Many of the assumptions that fed into the program, including the percentage of patients in various subgroups, were difficult to make as little data are available. Initial estimates based on input from the study Steering Committee assume 40% of subjects enrolled will be PP subjects, and of these 50% will be 1.5 prevention patients. Because of this, the study has implemented a sample size re-estimation, which will occur 1 year later after the 400th patient has been enrolled or once 2000 patients have been enrolled. At that time, most assumptions will be re-estimated based only on enrolment (not follow-up) data to date. Because no comparisons will be done at the point of re-estimation, alpha is not affected and the final analysis can compare the *P*-value with a 0.05 alpha level.

The secondary objective will compare mortality rates between implanted and non-implanted 1.5 prevention patients. Because this is a non-randomized study, it is important to control for variables that may not be matched between the two groups. This endpoint will be analysed using Cox proportional hazards methods with the following pre-defined covariates: age, sex, QRS duration, ischaemic/non-ischaemic, left bundle branch block (LBBB), NYHA class, diabetes, and the four 1.5 prevention criteria: syncope, LVEF (treated as a continuous variable), NSVT, and frequent PVCs. It is noteworthy that CRT is not among the covariates. There are two reasons for this: it may not be possible to determine whether the non-implanted group would have received ICD or CRT-D; and covariates already included would likely be very predictive of CRT or no CRT. The difference in mortality will be considered significant if the *P*-value of the ICD/no ICD variable is significant after adjusting for all the covariates (full model). Since it is well known that all covariates listed affect mortality, there will be no elimination of covariates from the model based on their *P*-value. While differences in mortality will be evaluated, the study is not powered to detect a meaningful difference (>6%).

While less likely, it is possible that covariates will affect the primary endpoint, so the same list of covariates, plus CRT/no CRT (since all patients included in the primary objective are implanted) will be used in a secondary covariate analysis of the primary endpoint.

Study organization

The Improve SCA study organization includes a Steering Committee with members representing different geographies and responsible for advising the study on study design and execution, and an independent Episode Review Committee responsible for adjudicating episodes of VT/VF.

Timelines

The first Improve SCA patient was enrolled on 26 March 2014. Final study results are expected in 2019.

Discussion

The 1.5 prevention criteria were developed in 2008 in collaboration with physicians in China to assist in the identification of PP patients at highest risk of SCA. While each of these factors have been independently associated with an increased risk of life-threatening ventricular arrhythmias and/or SCA, no prospective data have been collected to determine whether one or more of these factors in a PP ICD population is associated with an increased likelihood of receiving an appropriate ICD therapy. Furthermore, the geographies represented in the Improve SCA study have had little involvement in previous PP trials and, thus, there are limited local data demonstrating the benefit of ICDs in these geographies' PP patients.

While retrospective analyses have identified other risk factors that may be associated with ICD therapy in PP patients, the focus is placed on survival benefit, or identifying patients at risk of dying who already have an ICD implanted, which may be most relevant to regions where PP ICD therapy adoption is widespread. However, in regions with more limited health care resources, such as those in the present trial, the goal is to identify the subgroup of PP patients at highest risk for SCA who may receive the greatest benefit from ICD therapy.

There are two goals in this study. First, identify a subgroup of PP population who are at a highest risk for VT/VF events and may

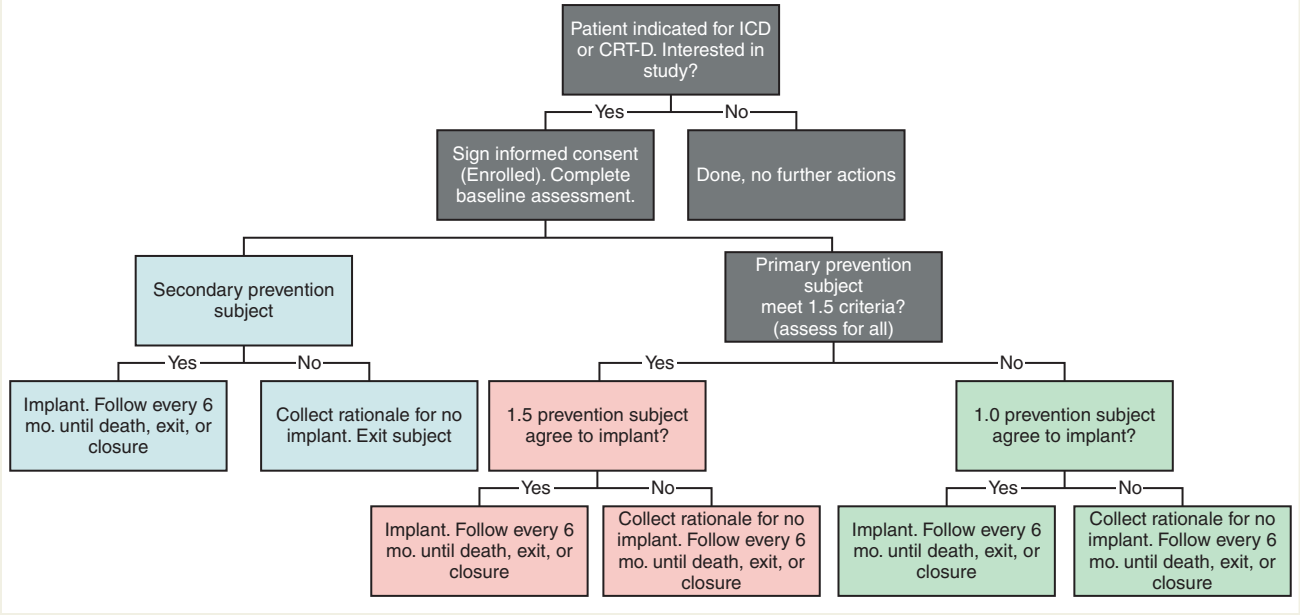

Figure 2 Study flow chart.

receive similar ICD benefit as the SP population. Second, establish clinical evidence that is more relevant to the regions where this study is conducted as the patient characteristics are different from those in Western countries where more ICD clinical trials have been performed.

The results of this study may be beneficial in helping clinicians identify and refer the highest risk PP patients for ICDs, help local societies expand guidelines to include PP of SCA utilizing ICDs, convince regulators to provide coverage for ICD implants in these patients, and provide additional local evidence to allow patients to make an informed decision whether to receive an ICD.

Conclusion

Primary prevention of SCA remains an important global issue. The Improve SCA study will study a subset of PP patients, believed to be at highest risk of SCA. This study aims to demonstrate that a subset of PP patients will have a similar benefit from ICD therapy as SP patients.

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Conflict of interest: S.Z., D.A.R., A.R.C., B.S., A.H., C.K.C., D.H., Y.B.L., Y.H.K. receive honoraria from Medtronic. J.C. and S.W. are employed by Medtronic.

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External implantable defibrillator as a bridge to reimplant after implantable cardioverter-defibrillator explant

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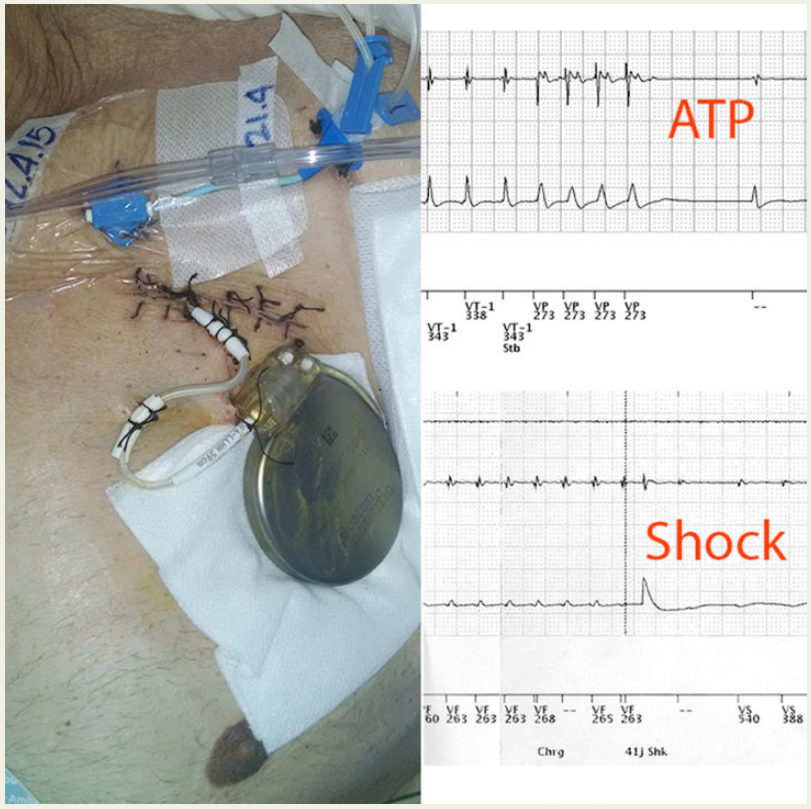
When an infection induces the complete removal of an implantable-cardioverter defibrillator (ICD), the subsequent reimplant may be safely bridged by an external ICD, connected to a transvenous defibrillating lead inserted through the site of extraction. We present the case of a 67-year-old male with systemic infection originating from a previously implanted single-chamber ICD, who underwent complete transvenous extraction. A 'temporary' dual-coil active fixation DF4 lead was placed in the right ventricle apex and connected to an external resterilized VVI-ICD (see *Figure*, left; passive can shock configuration). During a subsequent electrical storm with repeated sustained ventricular tachycardias, the device provided efficacious antitachycardia pacing and shock (*Figure*, right). Our case demonstrates that temporary external ICD is a safe, reliable, and cost-effective option to avoid prolonged hospitalization and immobilization in intensive care units during antimicrobial therapy for patients undergoing ICD explant for infection. Attention must be payed to the choice of the external device (shock configuration with passive can is mandatory) and of the lead (dual coil is needed and we suggest active fixation).



The full-length version of this report can be viewed at: http://www.escardio.org/Guidelines-&-Education/E-learning/Clinical-cases/Electrophysiology/EP-Case-Reports.