On September 28, 2012, the US Food and Drug Administration approved the totally subcutaneous implantable cardioverter defibrillator (S-ICD) for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, incessant ventricular tachycardia (VT), or spontaneous, frequently recurring VT that is reliably terminated with antitachycardia pacing (ATP). These devices hold the promise of life-saving defibrillation without some of the known problems of transvenous defibrillator systems (TV-ICD), including limited vascular access, transvenous lead durability, hazardous lead extractions, and risks of bloodstream infections. There are trade-offs with the S-ICD devices including reports of increased infections and the inability to deliver ATP. The subcutaneous position of the electrodes requires higher energy delivery with longer charge times. In addition, sophisticated signal processing is required for accurate arrhythmia detection and diagnosis. As we consider the appropriate patient population for S-ICD therapy, it is important to review the trade-offs of this system compared with traditional TV-ICD systems.

Response by Poole and Gold on p 1251

Detection of Ventricular Arrhythmias
Unlike transvenous ICDs that sense the local ventricular myocardial depolarization with an endocardial bipolar electrode, the S-ICD records a signal from 2 of its 3 subcutaneous electrodes. These are the distal sensing electrode located at the lead tip, a proximal sensing electrode located 14 cm proximal to the distal electrode, and the pulse generator itself. By their nature, the S-ICD signals are more susceptible to external and myopotential noise, as well as T-wave oversensing. Thus, sophisticated algorithms have been developed to filter noise from the true cardiac signals. Nevertheless, oversensing is responsible for the majority of inappropriate shocks in these systems as reported in a recent multicenter case–control study.

The competing concern is that of undersensing true arrhythmias that can lead to delays in therapies. The best data available on S-ICD time to therapy come from the pivotal Investigational Device Exemption (IDE) trial presented to the Food and Drug Administration. These data come from 321 attempted S-ICD implants and subsequent defibrillation testing of induced ventricular fibrillation (VF). The S-ICD manufacturer, Cameron Health, defined time to therapy in an analysis of induced arrhythmia episodes as the interval starting 2 seconds after the last induction artifact (a delay to allow recovery from amplifier saturation) and ending at the onset of the shock. Time to therapy encompasses the total time to detect a ventricular arrhythmia, charge the capacitors, confirm the sustained nature of the ventricular arrhythmia, and deliver the shock. Time to therapy is longer in S-ICD devices than in TV-ICD devices, in part, because of longer charge times. In the briefing packet for the Food and Drug Administration Circulatory System Devices Panel Meeting on April 26, 2012, Cameron Health noted that although charge time cannot be ascertained separately by the user, capacitor charge...
time to 65 J during induction testing is typically 7 seconds, and typical charge times to 80 J are <10 seconds and remain <15 seconds at elective replacement indicator under typical conditions.\(^3\) These charge times are longer than those required to charge TV-ICDs, but that is not the whole story.

To compare real-world TV-ICD performance with the S-ICD, we gathered data on time to therapy using Cameron’s definition for 287 devices tested at implant at Massachusetts General Hospital between May 2008 and May 2012. Because we do not have access to detection and charge times separately in the S-ICD devices, we must compare the composite time to therapy. The data reflect implant defibrillation testing during which the vast majority of induced arrhythmias are VF. Devices manufactured by St Jude Medical (n=117), Boston Scientific (n=61), and Medtronic (n=116) were included in this analysis. The Figure shows the distribution of times to therapy from the Massachusetts General Hospital cohort (white) compared with the time to therapy reported by Cameron Medical for the S-ICD (black). Time to therapy at implant represents a best case scenario because the device battery is at beginning of life. The TV-ICDs had time to therapy of 7.1±1.8 seconds (mean±SD), whereas the S-ICD had time to therapy of 14.6±2.9 seconds. The TV-ICD distribution is tight, with a 5% to 95% range for time to therapy of 2.25 to 7.55 seconds. Inspection of the S-ICD data, however, shows an asymmetrical tail for the S-ICD extending to >24 seconds for time to therapy. Cameron reported that 88% of the implant tests had times to delivery of <18 seconds and that 95% of episodes had time to therapy of <21 seconds compared with 7.55 seconds for the TV-ICD. Given the estimated 7-second S-ICD charge time, this means that arrhythmia detection took >10 seconds in >10% of S-ICD patients. With the well-established doctrine that early defibrillation is a major determinant of resuscitation success,\(^4\) these data raise an unanswered question in the field of ICD programming, how long is too long? The concern is that for VF, undersensing by the S-ICD results in unprecedented delays in therapy delivery. The data reflect implant defibrillation testing during which the vast majority of induced arrhythmias are VF. Devices manufactured by St Jude Medical (n=117), Boston Scientific (n=61), and Medtronic (n=116) were included in this analysis. The Figure shows the distribution of times to therapy from the Massachusetts General Hospital cohort (white) compared with the time to therapy reported by Cameron Medical for the S-ICD (black). Time to therapy at implant represents a best case scenario because the device battery is at beginning of life. The TV-ICDs had time to therapy of 7.1±1.8 seconds (mean±SD), whereas the S-ICD had time to therapy of 14.6±2.9 seconds. The TV-ICD distribution is tight, with a 5% to 95% range for time to therapy of 2.25 to 7.55 seconds. Inspection of the S-ICD data, however, shows an asymmetrical tail for the S-ICD extending to >24 seconds for time to therapy. Cameron reported that 88% of the implant tests had times to delivery of <18 seconds and that 95% of episodes had time to therapy of <21 seconds compared with 7.55 seconds for the TV-ICD. Given the estimated 7-second S-ICD charge time, this means that arrhythmia detection took >10 seconds in >10% of S-ICD patients. With the well-established doctrine that early defibrillation is a major determinant of resuscitation success,\(^4\) these data raise an unanswered question in the field of ICD programming, how long is too long? The concern is that for VF, undersensing by the S-ICD results in unprecedented delays in therapy delivery.

Recent data in ICD literature have supported device programming that allows longer times to therapy to minimize unnecessary shocks. One of the most convincing of these studies was the PainFREE Rx II (Prospective Randomized Multicenter Trial of Empirical Antitachycardia Pacing Versus Shocks for Spontaneous Rapid Ventricular Tachycardia in Patients with Implantable Cardioverter-Defibrillators) trial that studied TV-ICD programming strategies of standardized ATP versus shock alone as the initial therapy of spontaneous fast VT.\(^5\) The investigators found that the ATP-driven protocol reduced shocks by 15% and that the delay in time to therapy did not result in increased episodes of syncope. We highlight 2 salient points: first, the zone was fast VT, not VF; second, the time to therapy in the shock group was 10.7±0.7 seconds, whereas in the ATP group it was 12.7±0.8 seconds, both still relatively short. The related EMPIRIC (A comparison of empiric to physician tailored programming of implantable cardioverter-defibrillators) trial compared VF detection criteria of 18 of 24 beats with physician-tailored programming and found that the longer EMPIRIC 18/24 detection criteria resulted in fewer shocks without increased syncope.\(^6\) Although the investigators did not report the time to therapy, subjects in the Massachusetts General Hospital cohort who used the 18/24 detection criteria had a time to therapy of 8.2±1.0 seconds (n=96), still much shorter than the S-ICD time to therapy.

Extending this trend even further, investigators have explored in nonrandomized observational trials the use of 30/40 criteria for detection of VF,\(^7,8\) Use of this criterion for diagnosis of VF resulted in significant reduction in ICD shocks without increased syncope. Again, the time to therapy was not reported, but authors of the RELEVANT (Role of long detection window programming in patients with Left Ventricular dysfunction, non-ischemic etiology in primary prevention treated with a biventricular ICD) study did report a 6-second increase in the detection time compared with controls, which were programmed at 12 of 16 beats.\(^7\) This would translate to roughly a 4-second increase compared with what was observed in our Massachusetts General Hospital cohort (where 88% were programmed 18/24) or a mean of ≈12 seconds. Thus, even the longer VF detection times studied to date have never approached those seen in the upper reaches of the S-ICD times.

In MADIT-RIT (the multicenter automatic defibrillator implantation trial-reduce inappropriate therapy), the VF zone was programmed from the standard 1-second delay to 2.5 seconds.\(^8\) This will add 1.5 seconds to the time to therapy. Similar programming in our Boston Scientific cohort would result in an increase from 6.2±1.1 seconds to 7.7 seconds, still far shorter than times seen in the S-ICD IDE trial. As the authors point out in the discussion of the MADIT-RIT trial, the benefits of delayed programming are probably related to the benign nature of arrhythmias in the range of 170 to 200 bpm that mostly originate in the atria and would terminate spontaneously, as well as the tendency of true ventricular arrhythmias in this range to terminate spontaneously. However, these data do not imply that this approach would hold in the true malignant ventricular arrhythmias in the VF zone, and we should not use this trial to underestimate the importance of rapid therapy for high-rate malignant arrhythmias.

There are several important points to be made. First is that although trends in device programming do support longer
detection times to allow termination of nonsustained rhythms without an apparent penalty of increased syncope, times to therapy as long as those seen in the S-ICD population have not been well studied. The range of times to therapy in the S-ICD data was 9.6 to 29.7 seconds. In 2 cases, investigators had to intervene at >30 seconds to deliver a manual shock because the S-ICD had still not delivered therapy for VF. In one case, the sensing vector was subsequently changed with successful follow-up testing, whereas in the other no changes were made, but 5 more tests were successful with an average time to therapy of 19.3 seconds. Review of the device log file in this second case showed that cyclic variation in the VF signal amplitude resulted in undersensing and consequent failure to deliver the therapy. Although the factors that determine whether a patient loses consciousness are complex, it is hard to imagine that >20 seconds of VF is compatible with sustained consciousness. In addition, note that the times reported here for the S-ICD are for a 65-J shock. In the real world, the device delivers 80 J shocks that will require an additional 3 to 8 seconds of charge time.

Will prolonged S-ICD detection times occur in the real world? In a case report from earlier this year, Jarman et al\textsuperscript{10} reported their early experience with the S-ICD in 16 patients. Of the 3 appropriate shocks delivered for VF, 2 had delays in detection with times to therapy of 24 and 27 seconds. Both these patients had syncope. In addition, in the largest multicenter report of S-ICD performance to date,\textsuperscript{2} a spontaneous VF is described that was appropriately detected and shocked but only after 24 seconds.

These observations raise many questions about the tradeoffs involved in the S-ICD device with regard to reliable detection of ventricular arrhythmias, specifically VF. For TV-ICDs, there is a correlation between the recorded ventricular electrogram amplitude or R wave in normal sinus rhythm and the amplitude in VF.\textsuperscript{11,12} What about the S-ICD? Keep in mind that S-ICD subjects had already undergone prescreening in an attempt to ensure they had adequate surface electrograms before implant. Are there characteristics that might predict which patients are at risk for undersensing their VF with consequent delays in therapy? Are such undersensing events patient specific or episode specific? Are there programming changes that could be used to tailor the sensing algorithm to individual patients? There were too few clinical events in the IDE trial to establish any confidence around the question of syncope. Will the increased delay to treatment translate into more syncope in S-ICD–treated patients than in TV-ICD patients? At what point do delays in therapy begin to affect the success of the shock? Finally, we must keep in mind that underdetection of VF by any ICD will not necessarily be disclosed by device interrogation but may show up simply as sudden death. This is especially true for the S-ICD that has limited electrogram storage capacity.

**Efficacy of Cardioversion/Defibrillation**

In addition to concerns about reliability of arrhythmia detection, there are also uncertainties about the efficacy of S-ICD shocks for defibrillation. Of the 321 subjects in the IDE trial who underwent attempted S-ICD implant, 7 (2.2%) did not receive the device as a result of incomplete or unsuccessful acute VF conversion testing.\textsuperscript{3} In addition, 10 more subjects received S-ICDs but did not complete the VF conversion testing protocol, with 11 of these 17 incomplete test subjects receiving ≥1 failed shock. Why so many incomplete tests? Conversion success was defined as 2 consecutive successful conversions of induced VF out of a possible 4 attempts in the same shock polarity\textsuperscript{3} with attempts in reverse polarity specified as well. Thus, for a patient to fail, they would need to go through ≥3 tests at each polarity, receiving 6 shocks plus ≤6 external rescue shocks before meeting the definition of failure. By this definition, there were no failures in the pivotal trial, but 5.3% (17/321) of subjects in whom an S-ICD was attempted did not complete the testing protocol. In fairness, it seems that 5 of these 17 subjects could not be induced into sustained VF at the time of implant. The recently published multicenter experience showed a 10% (7/67) defibrillation test failure that was not different from their control group\textsuperscript{6} but higher than previously reported studies of transvenous systems.\textsuperscript{13} In another study including 40 patients who underwent S-ICD implants, the DFT (defibrillation threshold testing) failure was 2.5% (1/40).\textsuperscript{14} Combining the IDE and these 2 series, the overall DFT failure rate is ≈4.7% (20/430). Factors that predispose to elevated DFTs in TV-ICD have been previously identified,\textsuperscript{15} but the predictors of S-ICD conversion failure may not be the same (COPD [chronic obstructive pulmonary disease], anatomic factors). So although many practitioners now elect to forego DFT testing based on the large body of clinical data, a similar body of knowledge and degree of confidence are yet to be developed for the S-ICD.

Defibrillation of spontaneous arrhythmias is known to be less effective than what we observe at implant testing. For instance, despite 93% to 95% first-shock success at implant for TV-ICDs, first-shock success rates for spontaneous arrhythmias vary from 83% to 93%.\textsuperscript{15,17} Real-world experience with the S-ICD is limited, but the IDE data reported a 93% first-shock success in 16 subjects with 28 discrete VT/VF episodes, which is in contrast to a more recent report of 57% first-shock success in 4 subjects with 21 VT/VF episodes.\textsuperscript{14} Clearly, larger experience is required to provide confidence around these estimates, but if a significant proportion of patients with S-ICD will require multiple shocks, it will introduce further delays in definitive treatment for their ventricular arrhythmias. Some have argued that defibrillation of spontaneous arrhythmias is the true test of any implantable defibrillator and that the limited data available for the S-ICD in this setting did not justify its approval.\textsuperscript{18}

**Antitachycardia Pacing**

Early studies of the benefits of ATP showed dramatic reductions in the number of shocks delivered with attendant improvement in quality of life.\textsuperscript{5,19} Thus, it became standard in the field to program ATP routinely for initial treatment of
ventricular arrhythmias. Recent technological advances in TV-ICDs allow ATP delivery during charging, enabling an initial round of ATP to be delivered without delaying a shock. More recently, however, several studies have explored the use of longer detection times in ICD programming.\textsuperscript{6,8,9} Even from the earliest ICD trials, we knew that each ICD shock was not equivalent to a life saved, suggesting that a significant proportion of the treated arrhythmias would have stopped on their own.\textsuperscript{20} These suspicions have been confirmed by newer data showing that longer detection times can lead to fewer therapies.\textsuperscript{6–9} Thus, the question now arises on whether ATP is therapeutic or whether it might simply introduce a long enough delay to allow nonsustained episodes to terminate spontaneously. MADIT-RIT showed that a strategy of delayed treatment was associated not only with significantly less inappropriate ATP, but also with less appropriate ATP, suggesting that many ventricular arrhythmias do terminate spontaneously.\textsuperscript{9} The counter argument is that even in the MADIT-RIT high-rate and delayed therapy arms, ATP comprised >50% of appropriate therapies. Additional early data support ATP efficacy of ≤50% even in the setting of longer programmed detection times.\textsuperscript{21} Clinically, ATP has a clear benefit for a subset of patients; however, identifying these patients in advance remains clinically challenging. Patients with documented nonsustained VT are thought to be more likely to benefit from ATP, and a significant majority of patients with ICD indications will have NSVT (non-sustained VT) if investigated thoroughly enough. Thus, the ultimate effect of the inability of S-ICD to deliver ATP is currently difficult to predict. One opinion is that the S-ICD should be limited to patients without a history of monomorphic VT.\textsuperscript{2} Another approach would be to consider using the S-ICD only in patients where the likelihood of MMVT (monomorphic VT) is low such as in patients with long-QT syndrome or Brugada syndrome where the arrhythmia is more likely to be polymorphic VT or VF. However, these are the arrhythmias for which reliable detection is in question.

Who Are the Candidates for S-ICD?
The design of the S-ICD system limits its application to patients without an indication for pacing. Although there are no clear data on the incidence of bradyarrhythmias among ICD candidates, there are studies suggesting a prevalence of ≤4% among community-dwelling elderly patients.\textsuperscript{24} Furthermore, a significant proportion of ICD candidates with heart failure, low ejection fraction, and left bundle branch block have CRT (cardiac resynchronization therapy) pacing indications.\textsuperscript{25,26} Interestingly, a recent single-center study, including 399 consecutive ICD-implanted patients, found 5.1% upgrade to CRTD (cardiac resynchronization therapy defibrillator) during 5-year follow-up. Importantly, according to this study, using more liberal criteria for CRTD, such as New York Heart Association II to IV, ejection fraction ≤30%, and QRS ≥130 ms, would lead to 42% upgrade during 5 years.\textsuperscript{27} Apart from the bradypacing and biventricular pacing are those patients who might benefit from ATP. Given the lack of ATP in the S-ICD, careful consideration needs to be given to its use in patients with previously documented monomorphic VT. Primary prevention patients present a greater challenge because downstream arrhythmias are not always predictable. However, patients with ischemic cardiomyopathy are more likely to have nonsustained monomorphic VT, and therefore, the S-ICD may not be the first choice for primary prevention in patients with ischemic heart disease. Given the uncertainties surrounding the S-ICD, it would seem premature to recommend its widespread adoption in all patients without a pacing indication who are at elevated risk of SCD (sudden cardiac death). However, a case could be made for those individuals in whom a TV-ICD carries elevated risk. We highlight 2 patient groups for which TV-ICD systems pose elevated risks and who, therefore, might be considered for S-ICD therapy:

1. Patients in whom TV-ICDs pose risk from the perspective of venous access or infectious risk. This includes patients who have had previous venous access issues, making the implantation of a transvenous device difficult or unacceptably risky. Also included are patients with end-stage renal disease on hemodialysis who have limited access options and also have an elevated risk of device infection.\textsuperscript{28} For similar reasons, immunocompromised patients who need a device could be considered for an S-ICD.

2. The second group is those patients who are young and are, therefore, at greater lifelong risk of complications from TV-ICDs. Long-term TV-ICD therapy in young patients carries significant risk with need for lead revisions and eventual limited vascular access. These elevated risks may be mitigated by the S-ICD system, which might justify its use. However, it is these young patients who are exposed to the lifelong risk of potentially fatal arrhythmias and, therefore, need the best protection available. There are still uncertainties around whether the S-ICD offers the best protection in these active young patients, given its long time to therapy and the relatively
high tendency for T-wave oversensing with resulting inappropriate shocks. Here, the balance between the established record of TV-ICDs must be weighed against the known weaknesses of these systems.

Conclusions

It is still early in the life cycle of the subcutaneous ICD. Undoubtedly, we will see improvements in the device, including reduction in size and the ease of the implant procedure, which are expected to reduce the rate of infections. Furthermore, refinement of the algorithms for detection and diagnosis of ventricular arrhythmias may improve VF detection. Although there are many reasons to be enthusiastic about this exciting new technology, we cannot allow our enthusiasm to cloud our critical appraisal of the S-ICD. Whatever trade-offs exist should be thoroughly explored and understood before determining its ultimate role in our clinical practice.

Disclosures

None.

References


Response to Moshe Rav Acha, MD, PhD, and David Milan, MD

Jeanne E. Poole, MD; Michael R. Gold, MD, PhD

Rav Acha and Milan provide several reasons why they think that an subcutaneous implantable cardioverter defibrillator (S-ICD) should not be considered for primary prevention of sudden death in patients who do not require pacing. Their major concerns include the prolonged time to therapy with the S-ICD, defibrillation efficacy of the system, and the need for pacing either as antitachycardia therapy or for bradycardia/CRT (cardiac resynchronization therapy) postimplant. Much of the evidence they present in favor of their position comes from single center, retrospective, anecdotal observations. We feel that assessment of this technology is better served from prospective, controlled studies with independent adjudication. We address their concerns sequentially.

There is no disagreement that the time to therapy of the S-ICD is longer than for transvenous ICDs. However, to argue that this is a limitation of the device is simply falling into the trap that has plagued the programming of ICDs for decades. The engineering advances to shorten charge times and detection intervals have clearly resulted in an increase of both inappropriate and unnecessary appropriate therapies. PainFREE Rx II (Prospective Randomized Multicenter Trial of Empirical Antitachycardia Pacing Versus Shocks for Spontaneous Rapid Ventricular Tachycardia in Patients with Implantable Cardioverter-Defibrillators), PREPARE (Primary Prevention Parameters Evaluation), and EMPIRIC (A comparison of empiric to physician tailored programming of implantable cardioverter-defibrillators) showed this clearly. However, MADIT-RIT (the multicenter automatic defibrillator implantation trial-reduce inappropriate therapy) demonstrated that the impact of such aggressive programming was much greater than anticipated previously. Detection delays of 30 s were associated with much fewer therapies with no increased incidence of syncope. Moreover, limiting therapies with detection prolongation and high rate cutoffs were associated with decreased mortality. The theoretic risk of syncope should not lead to programming that increases shocks and mortality. In fact, in the IDE (Investigational Device Exemption) trial of the S-ICD, there was only 1 episode of arrhythmic syncope among 314 patients followed for a mean duration of 661 days.

The second argument centers on concerns of defibrillation efficacy. A rigorous defibrillation testing algorithm was developed and approved by the FDA (US Food and Drug Administration) for assessment of this system. This required 2 consecutive successful first shock defibrillations with a safety margin of 15 J. This was achieved by 100% of patients who completed the protocol. As with all studies, some patients do not complete such a rigorous protocol, but sensitivity analysis, assuming that all protocol violations would be failures, still showed an efficacy well above the predefined threshold based on similar studies of transvenous ICDs. More importantly, in our opinion, is the observations from the extended, preplanned follow-up of the IDE cohort and the European EFFORTLESS (Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness of the S-ICD) registry. All ventricular arrhythmias spontaneously terminated or were terminated by the S-ICD, and there were no cases of sudden death.

Finally, the need for pacing postimplant was raised as a concern. The need for such pacing is low based on data from large randomized studies such as SCD-HeFT (Sudden Cardiac Death Heart Failure Trial) and MADIT II (the multicenter automatic defibrillator implantation trial II). Moreover, if such pacing is needed then pacemakers can be implanted, and they are compatible with an S-ICD if so desired? REPLACE (Implantable Cardiac Pulse Generator Replacement Registry) and other registries have shown quite conclusively that upgrades of previously implanted transvenous devices are associated with much higher complication rates than de novo implants. Accordingly, implanting transvenous ICDs in all patients because some may need upgrades in the future is a strategy that will lead to worse outcomes.

As discussed in our article, we are not arguing that the S-ICD should replace the transvenous ICD in its present form. However, we are doing a disservice to our patients if it is not part of our armamentarium for the prevention of sudden death. We advocate an individualized approach including careful evaluation of the advantages and limitations of the S-ICD followed by discussion with the patient to determine the best device in each situation.
Who Should Receive the Subcutaneous Implanted Defibrillator?: Timing Is Not Right to Replace the Transvenous Implantable Cardioverter Defibrillator

Moshe Rav Acha and David Milan

Circ Arrhythm Electrophysiol. 2013;6:1246-1251
doi: 10.1161/CIRCEP.113.000445

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/6/6/1246