Invasive therapy for inherited cardiac arrhythmias: towards a better benefit-risk equilibrium

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Citation for published version (APA):

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Rationale and design of the PRAETORIAN Trial: a Prospective Randomized comparison of subcutaneous and transvenous Implantable cardioverter-defibrillator therapy


*Both authors contributed equally

American Heart Journal 2012 May; 163(5): 753-760
ABSTRACT

Background: Implantable cardioverter-defibrillators (ICDs) are widely used to prevent fatal outcomes associated with life-threatening arrhythmic episodes in a variety of cardiac diseases. These ICDs rely on transvenous leads for cardiac sensing and defibrillation. A new entirely subcutaneous ICD overcomes problems associated with transvenous leads. However, the role of the subcutaneous ICD as an adjunctive or primary therapy in patients at risk for sudden cardiac death is unclear.

Study design: The PRAETORIAN trial is an investigator-initiated, randomized, controlled, multicenter, prospective 2-arm trial that outlines the advantages and disadvantages of the subcutaneous ICD. Patients with a class I or IIa indication for ICD therapy without an indication for bradypacing or tachypacing are included. A total of 700 patients are randomized to either the subcutaneous or transvenous ICD (1:1). The study is powered to claim noninferiority of the subcutaneous ICD with respect to the composite primary endpoint of inappropriate shocks and ICD-related complications. After noninferiority is established, statistical analysis is done for potential superiority. Secondary endpoint comparisons of shock efficacy and patient mortality are also made.

Conclusion: The PRAETORIAN trial is a randomized trial that aims to gain scientific evidence for the use of the subcutaneous ICD compared with the transvenous ICD in a population of patients with conventional ICD with respect to major ICD-related adverse events. This trial is registered at ClinicalTrials.gov with trial ID NCT01296022.
INTRODUCTION

The use of implantable cardioverter-defibrillators (ICDs) is an established therapy for the prevention of death from ventricular arrhythmias. Since the early 1990s, ICDs are widely used.1 These ICDs rely on transvenous leads for sensing of cardiac signals and defibrillation. Recently, a new subcutaneous ICD (S-ICD) was introduced.2 The S-ICD is unique in that its implantation is entirely subcutaneous, eliminating the need for lead placement in or on the heart and simplifying the implant procedure by using anatomical landmarks instead of fluoroscopy imaging.

Initial short-term studies, with the S-ICD system, between 2001 and 2005 were designed to identify the best electrode configuration from 4 possible alternatives.2 The best configuration was subsequently tested to determine the S-ICD defibrillation threshold in comparison with a transvenous ICD (TV-ICD) system. Permanent S-ICD implantation was studied from 2008, with a pilot trial followed by a final study enrolling 55 patients. It was demonstrated that the S-ICD is a safe and feasible device.3 Early clinical experience from The Netherlands reported that the device successfully terminated all episodes of sustained ventricular tachycardia (VT) and ventricular fibrillation (VF).3

The S-ICD system was developed because of its perceived benefits over TV-ICD systems. It is likely that the eliminated need for transvenous lead placement substantially reduces the implant-related complications associated with transvenous lead insertion, most importantly pneumothorax or hematothorax and cardiac perforation. There may also be less risk of infective endocarditis because of the extravascular position. Furthermore, mechanically induced proarrhythmia from the lead and lead-associated tricuspid regurgitation have also been postulated as possible adverse consequences of transvenous lead use. 4, 5

Difficulties in achieving venous access6, which can prolong the procedure and occasionally results in failed ICD implantation, can be avoided. There is no need for radiation exposure for patient or staff because fluoroscopy is not necessary during S-ICD implantation. In addition, implanted transvenous leads are subject to mechanical stress associated with heart motion, body motion, and patient anatomy. Lead failure (eg, lead dislodgement or lead fracture) remains a major limitation in the use of TV-ICD systems over the long term.7–9 Lead failure either generates inappropriate shocks or impedes appropriate therapy. The S-ICD with its entirely subcutaneous and more robust lead probably elongates lead longevity because the lead is less subject to mechanical stress. The S-ICD also promises to offer advantages for extraction procedures, which are associated with substantial morbidity and mortality, when required. These advantages might become particularly evident in cases where lead extraction is indicated because of lead fractures or infections. Finally, benchmark testing of the new morphology-based sensing algorithm in the S-ICD has shown a very high specificity
in detecting ventricular arrhythmias.\textsuperscript{10} Misdetection of supraventricular arrhythmias or noise can lead to inappropriate shock therapy,\textsuperscript{11} and these inappropriate shocks decrease quality of life (QoL) substantially.\textsuperscript{12}

The different design of the S-ICD system has potential disadvantages. These include lack of bradycardia pacing and antitachycardia pacing (ATP) possibilities due to the absence of an endocardial lead. The absence of bradycardia pacing in the S-ICD might lead to more bradycardia-related events such as syncope or even death. Furthermore, if a shock is successfully avoided by ATP in a patient with a TV-ICD, this patient is likely to receive an appropriate shock for the same VT when an S-ICD would have been implanted. These appropriate shocks are referred to as unnecessary shocks of the S-ICD. Unnecessary shocks may decrease QoL\textsuperscript{12} and possibly shorten ICD pulse-generator longevity. Another important drawback may be the size of the can of the S-ICD, especially in children and adults with little subcutaneous tissue. The generator is approximately twice the weight and volume of currently used TV-ICDs. The current 70-mL size is, in part, due to a higher capacity battery, which can achieve the delivery of a high output 80-J shock. This higher output is mandatory because of the higher defibrillation threshold in S-ICD systems due to the extrathoracic position.\textsuperscript{2} The larger generator might increase the risk of skin erosion, patient’s discomfort, and infection as compared with the conventional ICDs. In addition, the heavier weight could cause device dislodgement and could potentially lead to a change of the shock configuration with unpredictable consequences on algorithm detection properties and defibrillation threshold. Neither size nor weight proved to be a significant problem in earlier 70-mL or larger and heavier TV-ICDs, but the position of the S-ICD is different and long-term follow-up is important to assuage this concern. Other questions have arisen regarding the high-energy delivery that could be more uncomfortable and harmful compared with the <40 J delivered by a transvenous system. However, there appears to be little correlation between shock strength and degree of discomfort. Low-energy shocks for conversion of atrial fibrillation produce discomfort described as intolerable by fully conscious patients even at shock strengths as low as 1.0 to 2.5 J.\textsuperscript{13, 14} Moreover, animal experiments show that shocks that reach the heart are actually less harmful with the S-ICD.\textsuperscript{15}

Until now, it is unclear whether the positive aspects of the S-ICD outweigh its disadvantages. To define the role of the S-ICD as an adjunctive or primary therapy in patients at risk for sudden cardiac death, a prospective randomized comparison with the TV-ICD in comparable primary and secondary prevention patients is warranted. The PRAETORIAN trial is an investigator-initiated, randomized, controlled, multicenter, prospective 2-arm trial that compares the relative safety and effectiveness of subcutaneous and TV-ICDs. The primary objective is to study noninferiority of the S-ICD compared with the TV-ICD with respect to inappropriate shocks and major ICD-related complications in patients with a class I or IIa indication for ICD therapy without an indication for pacing.
STUDY DESIGN

Trial oversight
This is an investigator-initiated, multicenter, randomized, controlled, prospective two-arm trial, with blinded evaluation of the endpoints. At least 7 qualified cardiology departments with facilities for ICD implantation in The Netherlands will participate in this trial. All participating centers have ample experience with both S-ICD and TV-ICD implantations. The study was approved by the Medical Ethics Committee at the Academic Medical Center–University of Amsterdam, The Netherlands. Data management and statistical analyses are performed by the data coordinating center (Academic Medical Center, Amsterdam, The Netherlands). Top Medical provided additional support in the form of an unrestricted research grant. No additional extramural funding was used to support this work. All ICD manufacturers that provided products and support during implantation have no role in the oversight or design of the study, or in the analyses or interpretation of the data. The trial is monitored for safety by an independent data and safety monitoring board. Safety is determined by the assessment of major adverse cardiac events and the occurrence of complications. The study is conducted in accordance with the Declaration of Helsinki. The PRAETORIAN trial is registered at ClinicalTrials.gov with trial ID NCT01296022.

Hypothesis
The primary objective of this trial is to demonstrate that the S-ICD is noninferior to the TV-ICD in patients with a class I or IIa indication for ICD therapy without an indication for pacing. After noninferiority is established, statistical analysis will be performed for potential superiority. The primary endpoint is the composite of inappropriate shocks and ICD-related complications. These ICD-related complications enclose ICD-related infection, ICD-related bleeding, thrombotic event, pneumothorax, hematotherax, perforation, tamponade, lead reposition, lead- or device-related complication, and crossover to the other arm. Secondary endpoints include the number of appropriate shocks, inappropriate shocks, complications, crossovers to the other arm, all-cause mortality, major adverse cardiac events, QoL, cardiac (pre-)syncope events, time to successful therapy, first-shock conversion efficacy, implant procedure time, hospitalization rate, and fluoroscopy time. Endpoint definitions are described in Appendix I. A critical event committee centrally reviews all events that are potential endpoints. Additional subgroup analysis will be done for age (<50, 50-75, >75 years), women, body mass index, ischemic cardiomyopathy, diabetes, PR interval >200 milliseconds, a QRS width of ≥120 milliseconds, and left ventricular ejection fraction <35%.

Patient selection
Patients 18 years and older with a class I or IIa indication for ICD therapy are screened for entry into this trial. Patients who are not suitable for TV-ICD implantation, according to the
discretion of the physician, are not screened for enrollment. These broad entry criteria are used to ensure a meaningful representation of current clinical practice. The major exclusion criterion is an indication for pacing therapy. This includes bradycardia pacing, cardiac resynchronization therapy, and ATP for therapy refractory monomorphic VT. Therapy refractory monomorphic VTs are recurrent monomorphic VTs that cannot be managed with medication or ablation therapy. All exclusion criteria are listed in Table 1. If all inclusion criteria and none of the exclusion criteria are met, patients are eligible for the trial and asked to provide written informed consent.

Randomization and treatment
The study flowchart is shown in Figure 1. Using concealed allocation, patients are randomly assigned in a one-to-one fashion to either: (1) S-ICD or (2) TV-ICD. Randomization is stratified by an implanting center using a Web-based program. Implantations of both the S-ICD and TV-ICD are performed under routine protocols. All S-ICDs are manufactured by Cameron Health, San Clemente, CA. All TV-ICDs are single-chamber devices, unless a dual-chamber device is specifically deemed necessary for arrhythmia discrimination. It is at the physician's discretion which manufacturers TV-ICD is used.

Device programming
Nearly all device settings in the S-ICD are automated, except for the use of postshock pacing and the rate cutoff for the conditional (which includes a feature for morphology arrhythmia discrimination) and unconditional shock zone. In this trial, all these program settings are switched “on,” and the discriminator rate cutoff is between 180 and 250 beats/min.

Table 1: Exclusion criteria

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>- Patients with documented therapy refractory monomorphic ventricular tachycardia*</td>
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<tr>
<td>- Patients with ventricular tachycardia less than 170 bpm</td>
</tr>
<tr>
<td>- Patients having an indication for pacing therapy, according to the ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities17</td>
</tr>
<tr>
<td>- Patients failing appropriate QRS/T-wave sensing with the S-ICD ECG patient screening tool provided by Cameron Health</td>
</tr>
<tr>
<td>- Patients with incessant ventricular tachycardia</td>
</tr>
<tr>
<td>- Patients with a serious known concomitant disease with a life expectancy of less than one year</td>
</tr>
<tr>
<td>- Patients with circumstances that prevent follow-up (e.g. no permanent home or address)</td>
</tr>
<tr>
<td>- Patients who are unable to give informed consent</td>
</tr>
</tbody>
</table>

ACC, American College of Cardiology; AHA, American Heart Association; ECG, electrocardiogram; HRS, Heart Rhythm Society. * Therapy refractory monomorphic VTs are recurrent monomorphic VTs that cannot be managed with medication of ablation therapy
The programming of the TV-ICD in this trial is based on the PREPARE trial and is as follows: >167 beats/min monitor zone, >182 beats/min fast VT zone with 1 episode of ATP followed by shocks, and >250 beats/min VF zone with shocks only (Table 2). However, device programming in the PREPARE trial was based on manufacturer-specific settings of only Medtronic devices (Minneapolis, MN). Therefore, device programming for TV-ICDs produced by other manufacturers is selected as strict as possible to the settings in the PREPARE trial. Appendix II provides recalculation of the PREPARE programming for all ICD manufacturers. The implanting physician can deviate from this recommended device programming, according to his/her discretion to fit specific patient concerns with the rationale entered into the study file.

**Follow-up**

All patients included in this trial are treated according to the current American College of Cardiology/American Heart Association/European Society of Cardiology Committee guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Data collection includes VT/VF and SVT episodes, other recorded episodes, device programming, and adverse events. Additional information about QoL is obtained and measured by using the standard validated 36-Item Short Form Health Survey questionnaire and the Duke Activity Status Index.
All patients visit the outpatient clinic at least once within 2 months after implantation. Thereafter, patients are evaluated by the outpatient clinic at intervals of 6 months. The median estimated study follow-up is 30 months. Patients are encouraged to contact their physician for any concerns or for any device therapy or complications.

**Statistical considerations**

The study is powered for the composite primary end point of inappropriate shocks and ICD-related complications at a median follow-up of 30 months. The sample size of 700 patients for this trial has been determined, so there would be a sufficient number of patients to provide a high degree of confidence (power >80%) for evaluating our primary endpoint of the S-ICD compared with the TV-ICD. The primary analysis is designed to test whether the S-ICD is noninferior to the TV-ICD. After noninferiority is established, statistical analysis will be done for potential superiority. The trial will be analyzed under the principle of modified intention to treat. Patients who have not received either an S-ICD or a TV-ICD are not analyzed.

With 350 patients in each study group, the study has 86% power to claim noninferiority of the S-ICD with respect to the composite primary endpoint of inappropriate shocks and ICD-related complications with a 1-sided \( \alpha \) of 5%, an assumed 17.2% incidence at 30 months of the primary endpoint (based on the data of the PREPARE\(^\text{18}\) and SCD-HeFT\(^\text{19}\) trial), and a relative noninferiority boundary of 1.45 (absolute boundary 25.0%).

The amount of inappropriate shocks in patients with a TV-ICD is based on the amount of inappropriate shocks in the PREPARE trial\(^\text{18}\), which was designed to demonstrate that strategically chosen ICD VT or VF detection and therapy parameters can reduce the combined incidence of device-delivered shocks, arrhythmic syncope, and untreated sustained

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**Table 2: PRAETORIAN ICD device settings**

<table>
<thead>
<tr>
<th></th>
<th>Transvenous ICD</th>
<th>Subcutaneous ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arrhythmia detection zones</strong></td>
<td>Monitor zone</td>
<td>Fast VT zone</td>
</tr>
<tr>
<td></td>
<td>&gt;167 bpm</td>
<td>&gt; 182 bpm</td>
</tr>
<tr>
<td><strong>Time to initiate therapy</strong></td>
<td>11 seconds</td>
<td>10 seconds</td>
</tr>
<tr>
<td>(charge for shock or ATP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Charge time ICD (expected)</strong></td>
<td>7-8 seconds</td>
<td></td>
</tr>
<tr>
<td><strong>Time to shock therapy (expected)</strong></td>
<td>14-18 seconds</td>
<td></td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>No therapy</td>
<td>(1) 1 burst of ATP(^*)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2) Shocks at maximum output</td>
</tr>
<tr>
<td><strong>Pacing programming</strong></td>
<td>VVI 40 bpm</td>
<td>Postshock pacing: “On”</td>
</tr>
</tbody>
</table>

*Consists of 8 intervals with a pacing length of 88% of the tachycardia length*
symptomatic VT/VF. In 12 months, 3.6% of the patients with standardized ICD settings experienced inappropriate shock therapy. The recalculated amount of inappropriate shocks for 30-month follow-up is approximately 7%, assuming that there is a slightly higher incidence of inappropriate shocks in the first 12 months. Furthermore, the amount of complications is based on the SCD-HeFT trial, which was a randomized trial on amiodarone vs the TV-ICD in patients with New York Heart Association class II or III congestive heart failure and a left ventricular ejection fraction of ≤35%. The SCD-HeFT trial demonstrated 5% acute complications and 9% chronic complications in the TV-ICD during 45.5 months of follow-up. This indicates that during 30 months of follow-up, 10.93% (5 + 9 × [30/45.5]) of the participants will likely have ICD-related complications. Considering the overlap of patients with both inappropriate shocks and complications, the expected rate of ICD-related adverse events in the TV-ICD is 17.2% on a per-patient–based analysis [(7.0 + 10.93) – (0.07 × 10.93)]. In addition, an event-based analysis will be done.

For a superiority analysis, with 350 patients in each arm, the study has 83% power with a 2-sided $\alpha$ of 5% to detect a relative risk of 0.55 in patients with the S-ICD, with an assumed incidence of 17.2% of the primary end point in the TV-ICD. The relative risk is derived from the following assumptions. In the S-ICD with 30 months of follow-up, we assume that 4.2% of the participants will have inappropriate shocks due to superior detection algorithm (40% less than in the TV-ICD). Also, we assume that there are 5% patients with acute complications (equal to that in the TV-ICD) and 5.47% patients with chronic complications (50% less than in the TV-ICD). Considering the overlap of patients with both inappropriate shocks and complications, the expected rate of ICD-related adverse events in the S-ICD is (4.2 + 5.47) – (0.042 × 5.47) = 9.4%. The assumed absolute difference of 7.8% (17.2-9.4) is recalculated into a relative risk of 0.45.

**DISCUSSION**

Implantable cardioverter-defibrillators are widely used to prevent fatal outcomes associated with life-threatening arrhythmic episodes in a variety of cardiac diseases. The new entirely subcutaneous ICD may overcome problems associated with transvenous leads. The PRAETORIAN trial is a large, randomized comparative evaluation of the inappropriate shock and complication rate of the S-ICD and the TV-ICD and should improve our understanding of where this new therapy can best be used as part of our clinical armamentarium.

**Endpoint**

The choice of the composite primary endpoint of inappropriate shocks and ICD-related complications was preferred above all-cause mortality, as practical, reasonably achievable, and pertinent to most cardiologists. Mortality event rates in both groups are presumed to
be low, leading to an extremely large trial size if this would serve as a primary endpoint. Moreover, safety and efficacy of the S-ICD have been demonstrated in earlier trials, and Food and Drug Administration approval is expected in the near future (ClinicalTrials.gov NCT01064076). To study the clinical importance of the S-ICD, it is highly relevant to study the comparative rate of major ICD-related adverse events of the 2 device systems. One may debate the equivalency of inappropriate shocks with complications, especially serious complications such as tamponade or infection, but they are of sufficient concern to most patients and cardiologists to be practically equivalent, particularly given concerns over the negative inotropic consequences of high-voltage shocks. Nevertheless, the 2 categories of adverse events are separately analyzed for readers of the trial results to interpret the effect of each problem independently.

**Device selection and programming**

In our trial, the preferred TV-ICD is a single-chamber device. There is an ongoing debate about the benefit of a dual-chamber device to enhance SVT discrimination and, thereby, reduce inappropriate shock therapy. However, implantation of a dual-chamber device might also lead to extra implant-related complications (eg, pneumothorax and lead dislodgement) and prolonged procedure time. Therefore, in this study, only single-chamber devices will be used, unless the implanting physician prefers a dual-chamber device for additional arrhythmia discrimination, like in real-world clinical practice.

Programming of the TV-ICD in this trial is based on the PREPARE trial, which demonstrated that standard ICD settings lead to a significant shock reduction of ~50%. Key strategies in the PREPARE trial included detecting only fast tachycardias, detecting only sustained tachycardias, and applying ATP as first therapy for fast VTs. In the PRAETORIAN trial, this is achieved by using the following rate cutoffs: >167 beats/min monitor zone, >182 beats/min fast VT zone with 1 episode of ATP followed by shocks, >250 beats/min VF zone with shocks only. Device programming for the S-ICD is programmed comparably with the TV-ICD settings with rate cutoffs >180 beats/min in the conditional zone and >250 in the unconditional zone. However, the absence of an endocardial lead precludes the possibility to program ATP in the S-ICD arm. Several studies have suggested that ATP terminates 85% to 90% of the slow VTs (ventricular rate <188-200 beats/min), with a 1% to 5% risk of acceleration. In the prospective PainFREE Rx trial, ATP demonstrated to terminate spontaneous fast VT (average ventricular rate 188-250 beats/min) in 77% with similar low acceleration rates. However, in PainFREE, a substantially higher percentage of VT events in the ATP arm was reported, and the syncope and mortality rates trended higher for the ATP arm even after the relatively brief follow-up period of only 11 months. Therefore, empiric ATP may prevent painful shocks, but it is not clear at what cost. Moreover, earlier studies testing for ATP for induced fast VT had lower success rates (41%-68%) and higher acceleration rates (5%-55%), perhaps, in part, because they were treating induced rather than spontaneous VT, but it may be that they
represented reality. Consequently, the acceleration of nonsustained VT by ATP may explain the higher adverse event rates in PainFREE II.

The debate about the usefulness of ATP therapy is also predicated on the belief that monomorphic VT is the dominant mode of death in patients with cardiac disease. However, years of electrocardiogram data of out-of-hospital cardiac arrest studies show that most patients have VF, where ATP has no benefit. Moreover, SCD-HeFT demonstrated that few primary prevention patients had monomorphic VT <220 beats/min, let alone recurrent monomorphic VT <220 beats/min. Most patients had VF, ventricular flutter, or very fast monomorphic VT. Thus, ATP therapy may not apply in most patients. Until now, it remains unclear whether the lack of ATP capability in the S-ICD may be a limitation of this device in most patients. By programming at least 1 sequence of ATP in the TV-ICD arm, the PRAETORIAN trial aims to determine to which degree the lack of ATP function leads to more appropriate shocks in patients with an S-ICD.

**SUMMARY**

Transvenous ICD systems, although widely used, have certain limitations largely attributable to the endovascular position of the leads and problems related to structural integrity over the long term. Transvenous leads are increasingly being recognized as the weak link in sudden cardiac death prevention. At present, the S-ICD is often only seen as a viable alternative to conventional ICD therapy in patients with lead complications, venous occlusions, and anatomical peculiarities. However, the randomized PRAETORIAN trial aims to gain scientific evidence for the use of the S-ICD compared with the TV-ICD in a group of patients with conventional ICD indications with respect to major ICD-related adverse events.


## APPENDIX

### Appendix I: PRAETORIAN endpoint definitions

#### General endpoints

**Major adverse cardiac event (MACE)**
- 1) cardiac death (all deaths are considered cardiac unless an unequivocal non-cardiac cause can be established),
- 2) myocardial infarction (defined according to “The myocardial infarction classification and criteria for diagnosis” by the Academic Research Consortium (ARC) and is adapted from the Global Task Force definitions for myocardial infarction),
- 3) percutaneous coronary intervention (PCI),
- 4) coronary artery bypass grafting (CABG) and/or
- 5) any valve surgery.

**Hospitalization rate**
The hospitalization rate is the number of days a patient is admitted to the hospital associated with ICD implantation.

#### ICD related endpoints

**Appropriate shock**
Shock therapy for ventricular fibrillation, which is defined as chaotic asynchronous fractionated activity of the heart. Also shock therapy for ventricular tachycardia is considered as an appropriate shock.

**Inappropriate shock**
Shock therapy for anything else but ventricular fibrillation or ventricular tachycardia. This can be due to, for example, supraventricular tachycardia with fast ventricle response (including sinus tachycardia and atrial fibrillation), T-wave oversensing, detection of physiological- or other non-cardiac activity and lead- or device failure.

#### ICD-related complications

**ICD-related infection**
An ICD related infection is an infection involving the subcutaneous pocket containing the device and/or the subcutaneous or transvenous leads. By definition an ICD related infection requires lead- or device extraction. Also any systemic infection without cause that requires lead- or device removal is counted as an ICD related infection.

**ICD-related bleeding**
A bleeding, also called pocket hematoma, is defined as a swelling of the pocket with the need for reoperation, blood transfusion or for prolonged hospitalization.

**Thrombotic event**
A thrombotic event is any event involving a thrombotic clot, which needs to be treated by anticoagulants. This includes a vena subclavia or vena cava thrombosis as well as deep vein thrombosis (DVT) or the consequence of DVT: an acute pulmonary embolism. Both a vena subclavia thrombosis and DVT need to be confirmed by contrast venography or ultrasonography. An acute pulmonary embolism needs to be confirmed by computer tomography (CT) or other imaging techniques.

**Pneumothorax**
A pneumothorax is an accumulation of air or gas in the pleural cavity, resulting in the absence of lung markings over the lung field seen on a chest X-ray. It can be a complication of lead placement. This diagnosis is confirmed by a radiologist. By definition a pneumothorax requires intervention or elongation of hospitalization.

**Hematothorax**
A hematothorax is an accumulation of blood in the pleural cavity. This diagnosis is confirmed by a radiologist or by pleural puncture. By definition a hematothorax requires intervention or elongation of hospitalization.
**Perforation**
Cardiac perforation can occur during lead placement in the heart in patients treated with a TV-ICD. It can result in cardiac tamponade and death. Clinical manifestations such as chest pain, dyspnea and hypotension, in conjunction with a new pericardial effusion, changes of lead signals (increase in lead impedance and decrease of sensing signal) or change of lead position on chest X-ray after TV-ICD implantation is defined as TV-ICD related cardiac perforation.

**Tamponade**
Cardiac tamponade is defined as pericardial effusion causing hemodynamic compromise and requiring drainage.

**Lead reposition**
Need for lead reposition is defined as a dislocated lead in which a new procedure has to occur for lead repositioning.

**Lead- or device related complication**
Lead- or device related complications are defined as all complications that are felt to be related to the ICD lead and/or generator system and require medical or surgical interventions for correction or more frequent ICD surveillance (including lead fracture, lead insulation defects and premature battery depletion).

**Crossovers to the Other Arm**
A crossover to the other arm is defined as a patient who for any reason after randomization is switched to the other ICD arm.

**Therapy in ATP- or Conditional Zone**
The ATP zone is the VT zone between ~180 and 250 bpm in which the TV-ICD gives a pacing therapy that consists of a single sequence of 8 pulses at 88% of the VT cycle length. If this therapy fails to correct the arrhythmia, shock therapy is delivered. The Conditional zone is the VT zone between 180 and 250 bpm in which the S-ICD gives shock therapy.

**Quality of Life**
The quality of life (QoL) is measured by the Duke Activity Status Index (DASI) and SF-36 questionnaires.

**Cardiac (pre-)syncope events**
Cardiac syncope is a loss of consciousness due to cerebral hypoperfusion caused by cardiac arrhythmias or presumed cardiac arrhythmias.

**Time to Successful Therapy**
Time to therapy is the time between the start of VT or VF until the first successful ATP episode or successful shock. This includes the time of sensing and charging.

**First Shock Conversion Efficacy**
First shock conversion efficacy is the percentage of patients with VT or VF who are successfully converted with the first shock given by the TV-ICD or S-ICD.

**Implant Procedure Time**
Implant procedure time is the time between the first incision and placement of the last suture (skin-to-skin time).

**Fluoroscopy Time**
Fluoroscopy time is the total time that fluoroscopy is used during the implantation of either the transvenous ICD or subcutaneous ICD.
### Appendix II: Suggested ICD device settings to establish proper time to charge or initiate ATP (derived from PREPARE settings)\(^1\)

#### Medtronic: \((VF \text{ and } Fast \text{ VT via } VF: X \text{ out of } Y, \text{ monitor: intervals to detect})\)

<table>
<thead>
<tr>
<th>Setting</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF zone</td>
<td>30/40 NID</td>
</tr>
<tr>
<td>Fast VT zone</td>
<td>30/40 NID</td>
</tr>
<tr>
<td>Monitor zone</td>
<td>32 intervals</td>
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</table>

#### St. Jude Medical: \((\text{intervals to detect})\)

<table>
<thead>
<tr>
<th>Setting</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF zone</td>
<td>30 intervals</td>
</tr>
<tr>
<td>Fast VT zone</td>
<td>30 intervals</td>
</tr>
<tr>
<td>Monitor zone</td>
<td>30 intervals</td>
</tr>
</tbody>
</table>

#### Biotronik: \((\text{in VF zone: } X \text{ out of } Y, \text{ in other zones: intervals to detect})\)

<table>
<thead>
<tr>
<th>Setting</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF zone</td>
<td>25/31 NID (maximal (X) out of (Y) setting for Biotronik VF zone)</td>
</tr>
<tr>
<td>Fast VT zone</td>
<td>30 intervals</td>
</tr>
<tr>
<td>Monitor zone</td>
<td>30 intervals</td>
</tr>
</tbody>
</table>

#### Boston Scientific: \((\text{combination of } X \text{ out of } Y (8/10) \text{ and duration in seconds})\)

<table>
<thead>
<tr>
<th>Setting</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF zone</td>
<td>8/10 NID + duration: 5 sec ((8 \times 240 \text{ ms} = 1.9 \text{ sec} + 5 = \text{ approx. 7 sec}))</td>
</tr>
<tr>
<td>Fast VT zone</td>
<td>8/10 NID + duration: 7 sec ((8 \times 333 \text{ ms} = 2.6 \text{ sec} + 7 = \text{ approx. 10 sec}))</td>
</tr>
<tr>
<td>Monitor zone</td>
<td>8/10 NID + duration: 7 sec</td>
</tr>
</tbody>
</table>

#### Sorin: \((\text{combination of } \% \text{ out of } Y (80%/12) \text{ and persistence in number of intervals})\)

<table>
<thead>
<tr>
<th>Setting</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF zone</td>
<td>80%/12 NID + persistence: 20 intervals ((80%/12 = 9.6 \times 240 \text{ ms} = 2.3 \text{ sec} + (20 \text{ intervals} \times 240 \text{ ms} = 4.8 \text{ sec} = \text{ approx 7 sec}))</td>
</tr>
<tr>
<td>Fast VT zone</td>
<td>80%/12 NID + persistence: 20 intervals ((80%/12 = 9.6 \times 333 \text{ ms} = 3.2 \text{ sec} + (20 \text{ intervals} \times 333 \text{ ms} = 6.6 = \text{ approx 10 sec}))</td>
</tr>
<tr>
<td>Monitor zone</td>
<td>80%/12 NID + persistence: 20 intervals</td>
</tr>
</tbody>
</table>

ICD, Implantable cardioverter-defibrillator; ATP, antitachycardia pacing; VF, ventricular fibrillation; VT, ventricular tachycardia; NID, numbers of intervals to detect