Rationale and design of the randomized prospective ATLAS study: Avoid Transvenous Leads in Appropriate Subjects

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Background The defibrillator lead is the weakest part of the transvenous (TV) implantable cardioverter defibrillation (ICD) system and a frequent cause of morbidity. Lead dislodgement, cardiac perforation, insertion-related trauma including pneumothorax and vascular injury, are common early complications of TV-ICD implantation. Venous occlusion, tricuspid valve dysfunction, lead fracture and lead insulation failure are additional, later complications. The introduction of a totally subcutaneous ICD (S-ICD) may reduce these lead-related issues, patient morbidity, hospitalizations and costs. However, such benefits compared to the TV-ICD have not been demonstrated in a randomized trial.

Design ATLAS (Avoid Transvenous Leads in Appropriate Subjects) is a multi-centered, randomized, open-label, parallel group trial. Patients younger than 60 years are eligible. If older than 60 years, patients are eligible if they have an inherited heart rhythm disease, or risk factors for ICD-related complication, such as hemodialysis, a history of ICD or pacemaker infection, heart valve replacement, or severe pulmonary disease. This study will determine if using an S-ICD compared to a TV-ICD reduces a primary composite outcome of perioperative complications including pulmonary or pericardial perforation, lead dislodgement or dysfunction, tricuspid regurgitation and ipsilateral venous thrombosis. Five hundred patients will be enrolled from 14 Canadian hospitals, and data collected to both early- (at 6 months) and mid-term complications (at 24 months) as well as mortality and ICD shock efficacy.

Summary The ATLAS randomized trial is comparing early- and mid-term vascular and lead-related complications among S-ICD versus TV-ICD recipients who are younger or at higher risk of ICD-related complications. (Am Heart J 2019;207:1-9.)

Background

Implantable cardioverter defibrillator (ICD) therapy is central to the treatment of individuals at risk for sudden cardiac death (SCD).[1-5] However, transvenous ICD (TV-ICD) system complications are common and include issues related to vascular access, leads, pulse generator and infection.[6] The TV-ICD lead remains the weakest part of the ICD system with lead dislodgement, cardiac perforation, pneumothorax and vascular injury occurring commonly after TV-ICD implantation.[7] Lead-related complications are among the most important causes of ICD-related morbidity.[6] Early and late complications related to TV-ICD leads or from the vascular access required for their implantation are summarized in Table I. These complications reduce patient's quality of life, occasionally result in death, with an increased risk of death at 180 days after implant (hazard ratio (HR) 24.9, 95% CI [2.11–294.26], $P < .001$).[8] Devices-related complications increase also the rate and costs of hospitalizations, and reduce the overall cost-effectiveness of ICD therapy.

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Table I. Summary complications associated with transvenous leads.

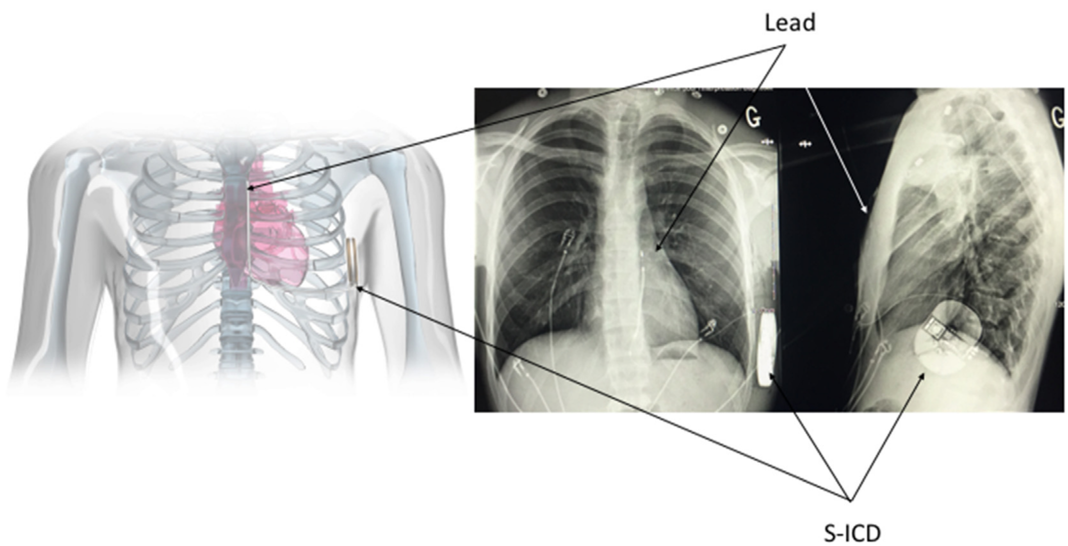
Early Complications (45 days to 6 months)	Rate, %, 95%CI	Source	Studies
Access related	2.1% (1.3–3.3)	Ezzat VA, Open Heart 2015	Meta-analysis (RCTs vs registries)
Pneumothorax / Hemothorax	0.4%	Lee DS, JACC 2010	Retrospective administrative data
	0.7%	Olde Nordkamp LRA, HR 2016	Meta-analysis
	1.1% (0.6–1.8)	Ezzat VA, Open Heart 2015	Meta-analysis (RCTs vs registries)
	1.6%	Kirkfeldt RE, Eur Heart J 2014	Retrospective registry (Danish cohort)
Hematoma	1.0%	Lee DS, JACC 2010	Retrospective registry
	1.2% (0.9–1.7)	Ezzat VA, Open Heart 2015	Meta-analysis (RCTs vs registries)
	1.3%	Olde Nordkamp LRA, HR 2016	Meta-analysis
	2.3%	Simple, Healey J, Lancet 2015	RCT
	2.5%	Kirkfeldt RE, Eur Heart J 2014	Retrospective registry (Danish cohort)
Thrombosis	0.2%	Lee DS, JACC 2010	Retrospective registry
	1.6%	Olde Nordkamp LRA, HR 2016	Meta-analysis
	47/150 (31%)	Korkeila P, Europace 2010	Prospective registry
Lead-related	2.6%	Kirkfeldt RE, Eur Heart J 2014	Retrospective registry (Danish cohort)
	3.4%	Duray GZ, Europace 2009	Retrospective registry
	5.8% (3.3–9.8)	Ezzat VA, Open Heart 2015	Meta-analysis (RCTs vs registries)
	7.0%	Lee DS, JACC 2010	Retrospective registry
Perforation including tamponade	0.4%	Lee DS, JACC 2010	Retrospective registry
	0.6%	Kirkfeldt RE, Eur Heart J 2014	Retrospective registry (Danish cohort)
	1.1%	Olde Nordkamp LRA, HR 2016	Meta-analysis
Displacement	3.1% (1.7–5.8)	Ezzat VA, Open Heart 2015	Meta-analysis (RCTs vs registries)
	3.5%	Olde Nordkamp LRA, HR 2016	Meta-analysis
Tricuspid regurgitation*	17.1%	Arabi P, Cardiol J 2015	Prospective registry
Lead dysfunction	3.0%	Duray GZ, Europace 2009	Retrospective registry
	10%	Olde Nordkamp LRA, HR 2016	Meta-analysis
Generator related	1.5%	Duray GZ, Europace 2009	Retrospective registry
	1.6%	Olde Nordkamp LRA, HR 2016	Meta-analysis
	2.7% (1.3–5.7)	Ezzat VA, Open Heart 2015	RCTs vs registries
Infection	1.3%	Simple, Healey J, Lancet 2015	RCT
	1.5% (0.8–2.6)	Ezzat VA, Open Heart 2015	Meta-analysis (RCTs vs registries)
	2.0%	Kirkfeldt RE, Eur Heart J 2014	Retrospective registry (Danish cohort)
	2.3%	Lee DS, JACC 2010	Retrospective registry
	3%	Olde Nordkamp LRA, HR 2016	Meta-analysis
Others			
Death	0.6%	Simple, Healey J, Lancet 2015	RCT
Myocardial infarction	0.1%	Simple, Healey J, Lancet 2015	RCT
	0.2%	Lee DS, JACC 2010	Retrospective registry
Stroke	0.2%	Simple, Healey J, Lancet 2015	RCT
Pulmonary edema / cardiogenic shock	0.8%	Lee DS, JACC 2010	Retrospective registry
Electrical storm	0.9%	Lee DS, JACC 2010	Retrospective registry
Total	4.4%/y (3.6–5.2)	Olde Nordkamp LRA, HR 2016	Meta-analysis
	9.1% (6.4–12.6)	Ezzat VA, Open Heart 2015	Meta-analysis (RCTs vs registries)
	9.5% (8.7–10.2)	Kirkfeldt RE, Eur Heart J 2014	Retrospective registry (Danish cohort)

JACC, Journal of American College of Cardiology; HR, Heart Rhythm; Eur Heart J, European Heart Journal.
* Increasing by 2 grades; RCT: randomized controlled trials; CI: confident interval.

Long-term complications are driven primarily by lead-related malfunctions, including lead fracture, insulation failure and lead advisories, which can result in inappropriate ICD therapy, failure to deliver appropriate therapy, device-related infections following device revision, and death.[6,9-15] Young patients are at particularly high risk of ICD-related complications (22% overall; 4.4% per year), primarily due to lead malfunction (10%), lead dislodgement (3.5%) and infection (3%).[16] Device-related infection from pocket infection to endocarditis, venous thrombosis,[17,18] and tricuspid regurgitation due to the TV-ICD lead[19-26] are other potential long-term TV-ICD-related complications (Table I). They can require repeat surgeries, or even to TV-ICD lead extraction procedures, which have a 1 to 2% risk of major morbidity and mortality.[27,28] At the other end of the patient spectrum, dialysis patients also have a high risk of TV-ICD complications, not only due to their generally worse prognosis, but specifically due to the presence of fistulae or shunts, or to the presence of chronic intravascular catheters.[29-31]

The availability of a totally sub-cutaneous ICD (S-ICD) may be able to prevent many vascular-access and lead-related complications. The S-ICD (Boston Scientific,

Figure 1



S-ICD configuration.

Marlborough, Massachusetts) consists of an extra-thoracic pulse generator on the left lateral thoracic wall connected to a single, lumen-free, robust lead with a shocking coil placed in the subcutaneous left parasternal space (Figure 1).[32,33] The lead has a very simple design, and has shown high durability (99.2%, 95%CI [97.8%–100.0%] 5-year complication free survival).[34] Given its location outside of the chest cavity, lacking contact against bones and cardiac structures, long-term reliability is also anticipated to be high. However due to its extra-thoracic configuration, the S-ICD is unable to provide cardiac resynchronization therapy, bradycardia or anti-tachycardia pacing, which could limit its use in several important patient populations. So far, European and FDA post approval registries, and clinical reports have shown an overall shock efficacy and safety comparable to the TV-ICD.[34-48]

At present, the S-ICD has established itself as the treatment of choice for certain patient groups, including those without venous access,[49,50] patients with a mechanical tricuspid valve, or with some repaired congenital heart disease, such as the Fontan circulation.[51,52] However, randomized data comparing early and late outcomes between the S-ICD and TV-ICD are lacking in order to expand the indication of the S-ICD to patients with no pacing or anticipated ATP indications.[53] The aim of this randomized study is to compare head-to-head the S-ICD to the TV-ICD for early- and mid-term complications. The rationale for the S-ICD is to reduce both early and mid-term complications related to the TV-ICD lead, while delivering equivalent efficacy for the termination of ventricular arrhythmias and for patient survival.

Study design

Study objectives

The ATLAS trial seeks to determine if the S-ICD is a safer option for a large population of predominantly younger patients, who have a greater lifetime risk of TV-ICD lead-related complications. This is a multi-centered, randomized, open-label, parallel group trial whose primary objective is to determine if compared to a TV-ICD, a S-ICD reduces a composite outcome of perioperative complications, measured at 6 months following ICD implant.

Methods

This study will recruit patients referred for ICD implantation for primary or secondary indications according to current guidelines,[49,50] without any indication for pacing or cardiac resynchronization therapy. Inclusion and exclusion criteria are summarized in Table II. Patients will be eligible if they are younger than 60 years old; or if older with an inherited heart rhythm disease or who are at increased risk of complications such as patients with chronic obstructive pulmonary disease, patients with a prior ICD or pacemaker related infection and patients with a prior heart valve replacement.

ATLAS will exclude patients who have a strong indication for either a TV-ICD or S-ICD (Table II), or patients likely to develop an indication for cardiac pacing, such as patients with a PR interval of more than 240 milliseconds. This is based on the Madit II study, where patients with a PR interval of more than 200 milliseconds had a higher need for pacing during follow-up.[54]

Table II. Inclusion / exclusion criteria.

INCLUSON CRITERIA	EXCLUSION CRITERIA
• Patient is ≥ 18 - 60 years old AND has a standard indication for ICD; **OR** • Patient is > 60 years old AND has any one of the following present: ✓Inherited arrhythmia syndrome (i.e. Long QT, Brugada, ARVC, hypertrophic or dilated cardiomyopathy, early repolarization syndrome, idiopathic VF, etc.) ✓Prior pacemaker or ICD removal for infection ✓Need for hemodialysis ✓Prior heart valve surgery (repair or replacement) ✓Chronic obstructive pulmonary disease (with $FEV_1 < 1.5$ L)	• Mechanical tricuspid valve • Fontan repair • Presence of an intra-cardiac shunt • Known lack of upper extremity venous access • Need for cardiac pacing for bradycardia indication • PR interval of > 240 msec • Patients with permanent pacemaker • Clinical indication for biventricular pacing • Patients unwilling to provide informed consent or comply with follow-up • Pregnant at time of enrollment and implant • Patients who currently have a ventricular assist device (i.e. LVAD)

ICD, Implantable cardioverter defibrillator.
FEVl, Force expiratory volume.
LVAD, Left ventricular assistant device.
VF, Ventricular fibrillation.

Ethical considerations

The safety and health of the patients is of primary concern. In all respects, this study shall be conducted pursuant to the "Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects". Ethical approval to participate in this study is required from each participating institution.

Intervention

Eligible and consenting patients will be randomized 1:1 to receive either a market-approved single-chamber TV-ICD, from any manufacturer (control arm), or to a Boston Scientific Emblem™ S-ICD, or subsequent generation Boston Scientific S-ICD (experimental arm). Patients in both arms will be followed both in clinic and using remote monitoring.

After enrollment, but prior to randomization, all patients will undergo screening for both QRS morphology and surface T-wave sensing, using both the right and left parasternal coil positions, and with testing in at least two postures (e.g. supine, seated, standing, etc.). Repeat screening with exercise testing will be performed for all patients with hypertrophic cardiomyopathy, and for any other patient who has only one acceptable resting vector. Patients who do not pass screening (in at least one acceptable vector) will be classified as screen failure, will not be randomized, but will continue to have follow-up in a registry (Table III). They will typically be implanted with a standard TV-ICD. All patients will have a transthoracic echocardiogram (TTE) done within 12 months prior to ICD.

Randomization will be performed using an interactive web-based randomization system (IWRS). and will be stratified by clinical site and by patient history of an inherited arrhythmia disorder.

TV-ICD systems will be implanted using standard techniques. Venous access technique (ultrasound use, venography, axillary vs. sub-clavian vs. cephalic vein) will be recorded. Patients assigned to have an S-ICD will have this procedure done using general anesthesia or conscious sedation, depending on local practice, and the implant will be conducted using either a 2 or 3-incision technique.[55,56] S-ICD implantation will be performed by experienced investigators who have independently completed a minimum of 5 S-ICD implants prior to the trial. Defibrillation safety margin testing (DFT) will be recommended in all S-ICD implant but will be left to the discretion of the implanting physician. For TV-ICD, it will be left to the discretion of the implanting physician based on current guidelines.[50] All patients will have standardized programming of ICD therapies to allow comparison between treatment arms. Programming parameters are summarized in Table II. Post-operatively, a postero-anterior and lateral chest X-Ray will be obtained for all S-ICD patients.

At the 6-months follow-up visit, patients will have a TTE to assess for lead-related complications, specifically moderate-to-severe or severe tricuspid insufficiency or a new pericardial effusion. A health-related quality of life (QOL) measure will be taken at both baseline and 6-month follow-up visits, with a device specific quality of life (QOL) measure (SF-36) and numeric pain rating scale (NRS). Patients will be followed for 24 months, with the possibility to extend follow-up to 48 months, to measure 1) Mid-term device-related complications; 2) Mortality (total and arrhythmic death); 3) Rate and success of appropriate ICD therapies. The patient flow diagram for the study is shown in Figure 2.

Outcomes

A composite primary outcome will be used, which captures the major early complications occurring within 6 months of ICD implantation, including hemothorax or

Table III. Device Programming.

	TV-ICD	S-ICD
Pacing	VVI 40 bpm	Post-pacing off
Tachycardia detection	- Primary prevention or LV dysfunction: VT zone 200 bpm, VF zone 250 bpm - Secondary prevention: 10–20 beats under clinical VT - Syndromes with polymorphic VT or VF without LV dysfunction: VF zone between 200 and 250 bpm	- Conditional zone for all patients: ○ Primary prevention: between 200 and 220 bpm ○ Secondary prevention: 10–20 beats under clinical VT - VF zone set at 250 bpm
Tachycardia treatment	- All shocks with maximum energy - Polarity reversed for the last shock - ATP for tachycardia less than 250 bpm - Discrimination algorithm on physician discretion	- All shocks with maximum energy - Polarity reversal on Emblem Boston Scientific algorithm

S-ICD Configuration Screening

T wave sensing results at rest in 2 positions	HCM	Exercise testing	Randomization	Registry
3 vectors failed	No	N/A	No	Yes
3 vectors failed	Yes	N/A	No	Yes
3 vectors passed	No	N/A	Yes	No
3 vectors passed	Yes	Yes		
		with at least 1 same vector passed	Yes	No
		without any vector passed	No	Yes
2 vectors passed	No	N/A	Yes	No
2 vectors passed	Yes	Yes		
		with at least 1 same vector passed	Yes	No
		without any vector passed	No	Yes
2 vectors passed	No	N/A	Yes	No
2 vectors passed	Yes	Yes		
		with at least 1 same vector passed	Yes	No
		without any vector passed	No	Yes

VF, Ventricular fibrillation.
VT, Ventricular tachycardia.
bpm: Beat per minute.
HCM, Hypertrophic cardiomyopathy.
N/A, no applicable.

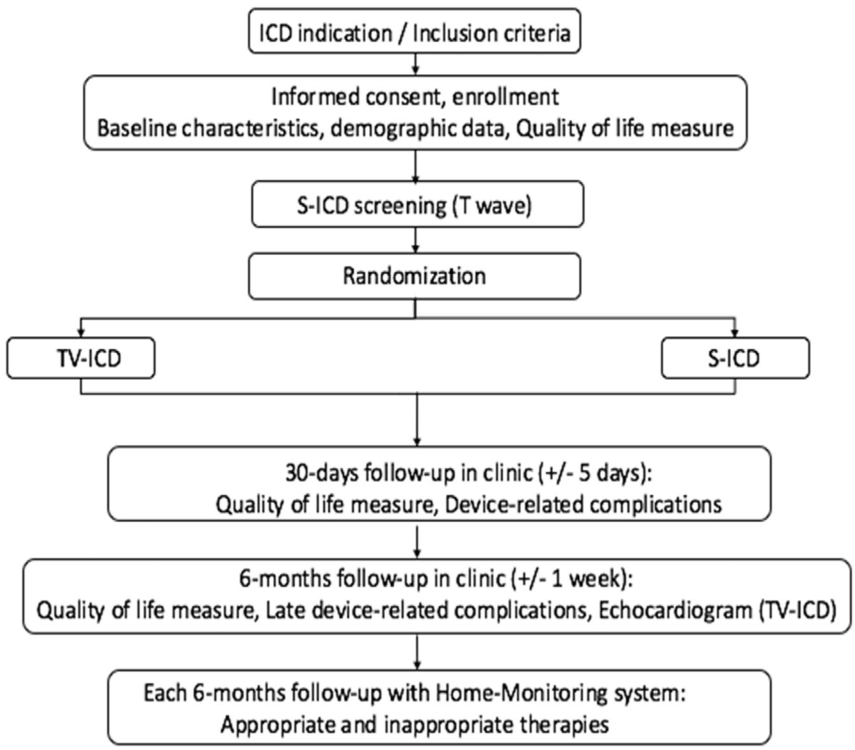
pneumothorax; cardiac perforation, tamponade, pericardial effusion or pericarditis; lead dislodgement or loss of pacing/sensing requiring revision; new moderate–severe or severe tricuspid insufficiency (3+ or 4+); ipsilateral upper extremity deep venous thrombosis (Table IV). A secondary 6-month safety composite, with an estimated incidence of 4.5%, will include, in addition to the above complications, device-related infection requiring surgical revision; significant wound hematoma (requiring evacuation or interruption of oral anticoagulation); myocardial infarction; stroke and death. As many of the components of this composite relate to the TV lead, a relatively large effect size (75% reduction in the primary outcome) is predicted for this study (Table IV).

If the S-ICD indeed has a lower risk of short-term complications, then the next logical question will be "does it deliver equivalent long-term effectiveness for treating ventricular arrhythmias". Thus, an additional mid-term efficacy outcome will be a composite of failed appropriate clinical shocks or arrhythmic death. Death will be categorized as either arrhythmic or non-arrhythmic, according to the methods of Hinkle-Thaler. This composite was the primary outcome of the recent SIMPLE trial.[7] Given its relatively short anticipated follow-up period, the ATLAS trial will likely have only a limited number of these efficacy outcome events. However, if the trial is positive for its primary outcome, a decision will be made to include patients into a long-term follow-up phase to gather more information on the secondary outcome.

Statistical methods

The primary analysis will be a comparison of the proportion of patients at 6 months with at least one of the components of the primary outcome and will be compared between treatment groups using a Chi-squared test. A categorical outcome was chosen as most of these events will occur in a very narrow window of time, and the differences

Figure 2



Atlas study Flow-chart. Total follow-up of 24 months. ICD, Implantable Cardioverter DefibrillatorTV-ICD, Trans-Venous Implantable Cardioverter DefibrillatorS-ICD, Subcutaneous Implantable Cardioverter Defibrillator.

Table IV. Estimated incidence of complications due to transvenous leads.

Complication	Estimated Rate
Early avoidable, lead-related complications	
Pneumothorax/hemothorax	1.5% at 30-days
Cardiac perforation, effusion, tamponade, pericarditis	1.0%
Lead dislodgement, loss of sensing/pacing	3.0%
New, severe tricuspid insufficiency	3%
Ipsilateral upper extremity DVT	0.3%
Need to revise dialysis access	0.2%
Total	9%
Other early complications	
Death	0.6%
Myocardial Infarction	0.1%
Stroke	0.2%
Significant wound hematoma	2.3%
Device-related infection	1.3%
Total	4.5%

in precise timing between events are less important, and subject to ascertainment bias. The secondary perioperative safety outcome and the late safety outcome will be presented and compared in the same fashion.

The primary endpoint will be evaluated using a superiority design. A sample size of 500 patients, followed to 6 months, will provide 85% power to detect a 75% reduction in the primary outcome, assuming a rate of 8% in the TV-ICD arm and a 2% drop-out rate. Total long-term device-related complications will be displayed for both treatment arms using the Kaplan–Meier method, and compared using a log-rank test. The occurrence of failed ICD shock or arrhythmic death, and all-cause mortality will also be presented and compared in this fashion.

Study organization

The study will be centrally coordinated by the Population Health Research Institute (PHRI), of Hamilton Health Sciences and McMaster University. ATLAS is an investigator-initiated study, supported by a research grant from Boston Scientific Corporation to PHRI. The authors are solely responsible for the drafting and editing of the manuscript and its final contents. There was no specific funding provided for the creation of this manuscript.

Steering and data monitoring committees

ATLAS Steering Committee will be responsible for the design, execution, analysis, and reporting of the study, and will assign appropriate responsibilities to the other study committees. The Steering Committee will hold the primary responsibility for publication of the study results. This committee will convene regularly (at least every 6 months) by telephone conference or meetings to address policy issues and to monitor study progress, execution and management. The Steering Committee will include Principal Investigators and Clinical Investigators from some of the participating centers as well as a representative of Boston Scientific who will retain non-voting status as members of the Steering Committee. The committee will also include the chairs of the clinical and device adjudication committees, an ICD programming chair, a chair of the S-ICD implant technique committee, a publications committee chair and a patient engagement committee chair. The patient-engagement committee will be charged with measuring health-related quality of life, and factors influencing patient decision making. Generic instruments, such as the SF-36 will be used given the ease of calculating health utilities; however tools will be developed specifically for the ICD population, which can hopefully capture the impact from important differences between TV-ICD and S-ICD devices. The impact of such differences on patient acceptance of ICD therapy will also be studied.

Adjudication committees

Two central committees will review all events for this trial: one will review clinical events and the other one will review all device therapies. An adjudication manual will be developed and govern the committees' activities.

Recruitment rate

Fourteen centers in Canada have been confirmed for recruitment. Five to 6 patients per week are recruited, 187 patients have already been enrolled. With the same rate of inclusion we can hope finishing recruitment within 18 months. Update letters are send every month to centers to keep them informed about the recruitment, the message is reinforced every time we have a steering committee, and personal phone calls to the local principal investigators are done.

Discussion

Although the TV-ICD has been implanted for many years, its long-term complications remain significant.[6,7,16,57,58] To avoid implant-related and long-term complications, and to offer possibilities to implant patients previously contraindicated for TV-ICD, the S-ICD has been developed.[32,33] It is already helpful in particular situations, such as patients without any more venous access, without access to the sub-pulmonary ventricle due to a congenital heart disease (CHD) or a cardiac surgery or remaining intracardiac shunts. Since the first human implantation performed more than 10 years ago,[32] the S-ICD has been shown to be safe and effective to treat ventricular arrhythmias, with cohort studies showing similar first-shock efficacy compared to the TV-ICD.[35-45] However, the first S-ICD generation had a significant rate of complications driven by inappropriate shocks, mainly due to T wave over-sensing (TWOS). Implantation techniques, lead and generator positioning, device's programming have been greatly improved.[46] New algorithms have also been developed.[46-48] These changes have resulted in lower inappropriate shocks.[39,48] Recent studies comparing S-ICD patients with TV-ICD patients in propensity-matched cohorts have shown a similar incidence of appropriate and inappropriate shocks in both group.[43] Moreover, lead complications were lower in S-ICD than in TV-ICD in these studies (0.8% vs 11.5%, P = .03).[43] The S-ICD was associated with a relative risk reduction of device-related complication of 70% (HR = 0.3, 95% CI [0.12–0.76], P = .01).[43]

Guidelines currently recommended S-ICD in patients without venous access, without access to the sub-pulmonary ventricle or with previous TV-ICD complications.[49,50] If randomized studies, including ATLAS and PRAETORIAN (Prospective, RAndomizEd comparison of subcuTaneOus and tRansvenous ImplANtable cardioverter-defibrillator therapy),[53] demonstrate a significant reduction in short and mid-term complications with the S-ICD compared to the TV-ICD, but demonstrated similar clinical effectiveness, this would favor expanding the use of the S-ICD to a more general population of ICD recipients. In patients who don't require pacing, particularly younger patients and those with primary prevention indications, the use of an S-ICD could significantly reduce the morbidity, cost and mortality of early and late complications related to the TV lead system. This could improve the cost-effectiveness of ICD therapy for the overall population of recipients.

Disclosure

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