Combined leadless pacemaker and subcutaneous implantable defibrillator therapy: feasibility, safety, and performance

F.V.Y. Tjong1*, T.F. Brouwer1, L. Smeding1, K.M. Kooiman1, J.R. de Groot1, D. Ligon2, R. Sanghara3, M.J. Schalij4, A.A.M. Wilde1, and R.E. Knops1

1AMC Heart Center, Department of Clinical and Experimental Cardiology, Academic Medical Center, University of Amsterdam, Meibergdreef 9, Amsterdam 1105 AZ, The Netherlands; 2St Jude Medical, Sunnyvale, CA, USA; 3Boston Scientific Corporation, St Paul, MN, USA; and 4Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands

Received 5 November 2015; accepted after revision 28 December 2015; online publish-ahead-of-print 3 March 2016

Aims
The subcutaneous implantable cardioverter-defibrillator (S-ICD) and leadless pacemaker (LP) are evolving technologies that do not require intracardiac leads. However, interactions between these two devices are unexplored. We investigated the feasibility, safety, and performance of combined LP and S-ICD therapy, considering (i) simultaneous device-programmer communication, (ii) S-ICD rhythm discrimination during LP communication and pacing, and (iii) post-shock LP performance.

Methods and results
The study consists of two parts. Animal experiments: Two sheep were implanted with both an S-ICD and LP (Nanostim, SJM), and the objectives above were tested. Human experience: Follow-up of one S-ICD/LP patient with bilateral subclavian occlusion who received an LP and two LP (all Nanostim, SJM) patients (without S-ICD) who received electrical cardioversion (ECV) are presented. Animal experiments: Simultaneous device-programmer communication was successful, but LP-programmer communication telemetry was temporarily lost (2 ± 2 s) during ventricular fibrillation (VF) induction and 4/54 shocks. Leadless pacemaker communication and pacing did not interfere with S-ICD rhythm discrimination. Additionally, all VF episodes (n = 12/12), including during simultaneous LP pacing, were detected and treated by the S-ICD. Post-shock LP performance was unaltered, and no post-shock device resets or dislodgements were observed (24 S-ICD and 30 external shocks). Human experience: The S-ICD/LP patient showed adequate S-ICD sensing during intrinsic rhythm, nominal, and high-output LP pacing. Two LP patients (without S-ICD) received ECV during follow-up. No impact on performance or LP dislodgements were observed.

Conclusion
Combined LP and S-ICD therapy appears feasible in all animal experiments (n = 2) and in one human subject. No interference in sensing and pacing during intrinsic and paced rhythm was noted in both animal and human subjects. However, induced arrhythmia testing was not performed in the patient. Defibrillation therapy did not seem to affect LP function. More data on safety and performance are needed.

Keywords
Pacemaker • Leadless pacing • Subcutaneous ICD • Animal experiments • Human

Introduction
The subcutaneous implantable cardioverter-defibrillator (S-ICD) is a safe and effective alternative to transvenous ICDs, designed to overcome lead-related complications. However, patients with bradycardia or tachycardia pacing indications are excluded from S-ICD therapy as the device lacks these capabilities. Some S-ICD patients develop a pacing indication after implantation and require either conversion to transvenous or epicardial ICD therapy or addition of a transvenous pacemaker. A novel technology that eliminates the need for transvenous leads in bradycardia pacing is the leadless pacemaker (LP). Combining the LP and S-ICD could particularly benefit patients without venous access or with recurrent lead and pocket complications such as pocket infection, endocarditis, or lead failure.

Although both devices separately have been tested extensively preclinically and clinically, and are available for commercial use, data...
What’s new?
- Combined leadless pacing and subcutaneous implantable cardioverter-defibrillator therapy is feasible and safe in animals and in first human experience.
- Data from this study support using this combined therapy in clinic, aiming to benefit patients in whom transvenous access is not feasible or desired.
- This combined therapy is the next step in multi-component leadless cardiac rhythm management, with the objective to eliminate transvenous lead-related complications.

on the feasibility and safety of a combined S-ICD and LP are limited to a single case report. Mondesert et al. reported the first human combined implant of an S-ICD and a leadless cardiac pacemaker, and demonstrated adequate sensing of the paced rhythm by the S-ICD and normal function of the LP after an S-ICD shock. Kuschyk et al. reported on three combined S-ICD and transvenous pacemaker implants, and demonstrated excellent function of both devices and no inappropriate shocks.

Interaction between an LP and S-ICD with respect to S-ICD rhythm discrimination during arrhythmia and post-shock LP performance is currently unknown.

Objective
The objective is to report on the feasibility, safety, and performance of combined LP and S-ICD therapy. We assessed this with regard to (i) simultaneous programmer-device communication; (ii) S-ICD rhythm discrimination, during LP communication and pacing; and (iii) post-shock LP performance.

Methods
The study consists of two parts: (i) animal experiments and (ii) human experience (Figure 1). This study is performed at the Heart Center of a tertiary care hospital in Amsterdam, The Netherlands, with ample experience with S-ICDs (since 2009, >200 S-ICD implants) and both commercially available LPs (since 2012, >45 LP implants).

Part I: Animal experiments
We performed a combined implantation of an LP and S-ICD in an ovine animal model. All animal work was approved by the Animal Experimental Committee of the Academic Medical Center, Amsterdam, and carried out in compliance with the Dutch government guidelines.

Preparation of the animals
Two Swifter sheep with a mean weight of 65 kg (range 60–70 kg) underwent general anaesthesia using propofol, fentanyl, and midazolam. The animals were placed in supine position. No anti-arrhythmic drugs were administered.

Implant of the subcutaneous implantable cardioverter-defibrillator
An S-ICD (model 1010, Cameron Health, USA) was implanted under fluoroscopic guidance with the pulse generator on the left lateral side of the chest wall and the coil on the contralateral side, to ensure an adequate shock vector between coil and pulse generator (Figure 2). The S-ICD uses one out of three electrocardiographic recording (‘vectors’) for QRS morphology analysis. An automatic set-up, using radiofrequency (RF) communication, was performed with the Q-Tech™ programmer (Boston Scientific, USA) to determine the optimal sensing vector (Figure 2F).

Implant of the leadless pacemaker
An LP (Nanostim™, St Jude Medical, USA) was implanted in the right ventricular apex using a percutaneous femoral approach, which was described in detail previously. Device-programmer communication was established using conductive communication (Merlin™ programmer and Nanostim Link™, St Jude Medical, USA) after which the baseline performance measures were obtained.

Simultaneous programmer-device communication
Simultaneous programming of the LP and S-ICD and their programmers was performed. Communication between the devices and programmers was assessed as well as the occurrence of any interference.

Subcutaneous implantable cardioverter-defibrillator rhythm discrimination
During leadless pacemaker-programmer communication
S-ICD sensing was evaluated during intrinsic rhythm in all three vectors: primary, secondary, and alternate (Figure 2F) during active LP-programmer communication.

During leadless pacemaker pacing
Bradypacing with the LP was initiated by pacing 10 beats above the intrinsic heart rate in nominal settings (VVI, 2.5 V @ 0.4 ms) and with maximum output (6 V @ 1.5 ms). In addition, the LP was programmed to VOO mode (80 ppm, max output), and subsequently ventricular fibrillation (VF) was induced with a 50 Hz burst to assess accurate detection by the S-ICD. Subcutaneous ICD rhythm discrimination was evaluated in the programmed vector.

Post-shock leadless pacemaker performance
A shock testing protocol consisting of both S-ICD (65 and 80 J) and external defibrillator shocks (200 and 360 J) was conducted in both animals (Supplementary material online, Table S1). The LP performance was evaluated, and the occurrence of LP dysfunction or dislodgement was assessed.

Part II: Human experience
We retrospectively reviewed the medical records from all patients who were implanted with an LP between December 2012 and September 2015. Patients were selected for this analysis if they had undergone a combined implant of an LP and an S-ICD; or if they had received an electrical cardioversion (ECV) using an external defibrillator after the LP implant. The need for informed consent was waived by the internal review board of the AMC, Amsterdam, The Netherlands due to the observational nature of the study.

Statistical analysis
Descriptive statistics are presented using mean ± SD for continuous variables and categorical as frequencies and percentages. No inferential statistics were used. All analyses were conducted with SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA).
Results

Part I: Animal experiments

Combined implantation of leadless pacemaker and subcutaneous implantable cardioverter-defibrillator

In both animals, the combined implantation of an S-ICD and LP was successful (Figure 3, Left Panel). Leadless pacemaker baseline performance measures are shown in Table 1 and implant steps in Supplementary material online, Figure S1.

Simultaneous device-programmer communication

Simultaneous communication between programmers and devices was achieved in both animals without interference during sinus rhythm and arrhythmia, but LP telemetry was lost during all episodes of VF induction, mean ± standard deviation (SD) duration: 9 ± 12 sec and in 4 (7%) of 54 shocks for a mean ± SD duration of 2 ± 2 seconds before the return of LP telemetry (Supplementary material online, Figure S2).

Subcutaneous implantable cardioverter-defibrillator rhythm discrimination

During leadless pacemaker-programmer communication

Leadless pacemaker programming and interrogation using conductive communication did not result in electromagnetic (EM) noise and consequent oversensing from the S-ICD. Moreover, conductive communication signals were not observed in any of the electrocardiographic recordings.

During leadless pacemaker pacing

The Secondary vector was optimal in the first animal and the Primary in the second. There was adequate QRS complex sensing in both animals without any T-wave oversensing (TWOS) by the S-ICD, similarly during pacing with nominal and maximum output. No oversensing of the LP pacing artefacts was observed. All episodes of VF (n = 12/12, 100%) were detected correctly by the S-ICD. The mean times to detect VF were 8.4 ± 3.2 and 7.5 ± 4.3 s in animals 1 and animal 2, respectively. The S-ICD was not able to
Figure 2 Subcutaneous ICD implantation steps in a sheep. (A) Creating the subcutaneous pocket, (B) measuring the lead placement, (C) closing the subcutaneous pocket, (D) tunnelling lead from low lateral chest wall incision to high lateral chest wall incision and fixation shock lead, (E) successful ovine S-ICD implant with shock lead placed subcutaneously in right lateral chest wall, and (F) S-ICD sensing vectors projected over ovine chest. Primary vector from electrode proximal of shock coil to the S-ICD can (B-Can); Secondary vector from distal tip of electrode to the S-ICD can (A-Can) and Alternate vector from distal tip of the electrode to electrode proximal of shock coil (A and B).

Figure 3 Fluoroscopy image of combined LP and S-ICD implant. (Left panel) Fluoroscopy image of combined LP and S-ICD implant in a sheep. (Right panel) Fluoroscopy image of combined LP and S-ICD implant in 72-year-old patient. (A) S-ICD shock lead, (B) S-ICD pulse generator, and (C) LP projected over right ventricular apex.
terminate any episodes ofVF (n = 0/12, 0%), and all episodes of VF were terminated with external defibrillator shocks with energies between 200 and 360 J. Subcutaneous ICD rhythm discrimination during maximum-output VOO pacing did not result in underdetection of VF or inadvertent withholding of appropriate shock therapy (Figure 4).

Post-shock leadless pacemaker performance
Both animals received a total of 27 shock each. In Animal 1, a total of 14 shocks (2 @ 65 J; 12 @ 80 J) were delivered by the S-ICD and 13 shocks by an external defibrillator (3 @ 200 J; 10 @ 360 J); in Animal 2, a total of 10 shocks (2 @ 65 J; 8 @ 80 J) were delivered by the S-ICD and 17 shocks by an external defibrillator (17 @ 360 J) as shown in Supplementary material online, Table S1. The post-shock LP performance was largely unaltered in both animals. The R wave amplitudes for sheep 1 and sheep 2 pre and post shock were 12 to 12 and 11 to 8.5 mV and impedances were 900 to 880 and 710 to 670 Ohms respectively. Pacing threshold at 0.4 ms remained stable at 0.5 V. (Table 1). No post-shock device dislodgements and no device resets were observed.

Part II: Human experience

Patients
In total, 3 out of 45 patients who were implanted with an LP were selected for this analysis. These three patients were all implanted with a Nanostim™ LP. One patient, a 72-year-old male with severe hypertrophic cardiomyopathy (HCM) with preserved left ventricular function, indicated for secondary prevention and chronic atrial fibrillation (AF) with slow ventricular response, received an S-ICD after previous infection of a transvenous ICD system and bilateral venous obstruction. In the months following the S-ICD implant, the patient was hospitalized several times with acute heart failure due to slow ventricular rate, and he was concomitantly implanted with an LP in September 2015. The second patient, an 86-year-old male with paroxysmal AF and brady-tachy syndrome with symptomatic conversion pauses, was implanted with an LP in January 2013. At 5 and 6 months post-implant, the patient was treated with two ECVs due to AF with a fast ventricular response (180 bpm). The third patient was an 86-year-old male with syncope and second-degree AV block with a normal echocardiogram, who was implanted with an LP in January 2013. Two days post-implant, the patient was re-admitted due to recurrent syncope based on documented monomorphic ventricular tachycardia (260 bpm) requiring ECV. The LP was subsequently retrieved and a transvenous ICD implanted.

Combined human S-ICD and leadless pacemaker implant
In the patient with severe HCM and an S-ICD requiring pacing, an LP was implanted in the right ventricular apex using a percutaneous femoral approach, as described previously (Figure 3, Right Panel). The capture threshold was 0.25 V @ 0.4 ms, R-wave 10.5 mV, and impedance 430 Ω at discharge. As shown in Figure 5, S-ICD sensing evaluation was performed during intrinsic (Panel A), nominal (2.5 V @ 0.4 ms) (Panel B), and maximum-output LP pacing (6 V @ 1.5 ms) (Panel C). In both Primary and Alternate vectors, adequate sensing and no oversensing or double counting by the S-ICD were observed; the Primary vector was selected in the patient. In the Secondary vector, oversensing and undersensing were observed during intrinsic rhythm and nominal LP pacing, but not during maximum output LP pacing. Further, LP conductive communication during interrogation did not result in EM noise detection by the S-ICD.

Table 1 Leadless pacemaker performance

<table>
<thead>
<tr>
<th>Animal</th>
<th>R-wave baseline (mV)</th>
<th>Capture threshold baseline (V)</th>
<th>Capture threshold end (V)</th>
<th>Impedance baseline (Ω)</th>
<th>Impedance end (Ω)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;12</td>
<td>0.5</td>
<td>0.5</td>
<td>900</td>
<td>880</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>8.5</td>
<td>0.5</td>
<td>710</td>
<td>670</td>
</tr>
</tbody>
</table>

Figure 4 Subcutaneous ICD registers normal tachy markers during high-output VOO pacing. (A) Leadless pacemaker-programmer strip showing VF with VOO pacing artefacts by the LP (80 ppm, maximum output 6.0 V at 1.5 ms). (B) Screen shot of S-ICD-programmer showing simultaneous recording of the induced VF and appropriate VF sensing by the S-ICD visualized by the tachy markers (T) below the rhythm strip. The S-ICD correctly identified the ventricular arrhythmia and began charging before delivering a shock. The pacing artefacts were not interpreted as noise.
During the initial S-ICD implant, 6 months earlier, the patient had a successful defibrillation test (DFT). After careful medical risk/benefit assessment in the patient, it was decided to not repeat a DFT post-LP implant. Two weeks post-implant, S-ICD sensing was evaluated during exercise induced tachycardia and high rate- and output-pacing. No oversensing during high intrinsic or paced rates was observed in the Primary and Alternate vectors. Again, both oversensing and undersensing were observed in the Secondary vector. The LP was programmed to VVI mode with a lower rate of 50 ppm and inactive rate response sensor. At 1 month of follow-up, no adverse events occurred and LP function maintained stable.

**Post-shock leadless pacemaker performance**

One patient received an ECV at 3 days post-LP implant, the second patient, after 5 and 6 months of follow-up. In both patients, the performed ECVs ($n = 3$) did not result in alteration of the electrical LP function.
measurements, mode reversion, device resets, or LP dislodgements (Supplementary material online, Table S2).

Discussion

This study on combined implantation of an LP and S-ICD provides several key findings regarding feasibility, safety, and performance. First, simultaneous communication of both the LP and the S-ICD with their programmers did not result in interference in sensing, programming, or interrogation. Second, LP-programmer communication did not result in EM noise oversensing by the S-ICD. Third, detection of VF by the S-ICD was successful during nominal and high output leadless pacing in the animal model. However, no induced arrhythmia testing was performed in humans. Lastly, LP performance and position after multiple 80 J S-ICD and 360 J external shocks were not affected.

Simultaneous device-programmer communication

Conductive communication from the LP to the programmer can be disrupted by other electrical devices (e.g., external defibrillator) that are in close proximity of the LP surface electrodes and result in temporary loss of sensing markers on the LP programmer signal strip. Loss of communication occurred during all episodes of VF induction (50 Hz burst) and during 7% of the administered shocks (Supplementary material online, Figure S2), but not during simultaneous S-ICD-programmer communication through RF. This demonstrates that both devices can be simultaneously programmed and interrogated to ensure optimal pacing and sensing configurations.

S-ICD rhythm discrimination during leadless pacemaker-programmer communication

A previous report by Sharma et al. showed EM noise after each QRS complex during LP conductive communication on a 12-lead electrocardiogram strip. Electromagnetic noise caused by conductive communication was not observed in either animal or human combined implants, and rhythm discrimination by the S-ICD during conductive communication did not result in detection of EM noise. Therefore, LP-programmer communication does not place the patient at risk for inappropriate shocks by the S-ICD and does not require the S-ICD to be switched off during conductive communication.14,15

S-ICD rhythm discrimination during leadless pacemaker pacing

It is of utmost importance that sensitivity for VF detection of the S-ICD is not reduced by the concomitantly implanted LP in any pacing mode due to the potential lethal consequence of underdetection of VF. The key finding of this study is that none of the tested pacing modes in the animal model resulted in underdetection of VF. However, this was not tested in humans. After careful medical risk/benefit assessment in the combined LP/S-ICD patient, it was decided to not repeat a DFT post-LP implant. The risks associated with inducing ventricular arrhythmia in this patient with severe hypertrophic cardiomyopathy and acute heart failure outweighed the risk of possible VF undersensing during LP pacing. This risk of not testing was deemed acceptable based on the initial successful DFT at S-ICD implant ~6 months earlier, the data from our animal studies which showed no VF underdetection, and evidence from a previous study by Kuschcyk et al.15 showing no adverse device interaction with combined S-ICD and transvenous bipolar pacemakers. In future, LP/S-ICD patients without high DFT risks defibrillation testing should be considered to ensure proper VF sensing during LP pacing.

An interesting observation in the animal model was that the LP interpreted VF as noise and subsequently converted to VOO pacing, mode reversion, a designed LP safety feature. The VOO pacing at 80 ppm at maximum output did not change VF detection by the S-ICD (Figure 4). A recent report by Akin et al.15 demonstrated a non-reversible polarity switch of a transvenous DDD pacemaker from bipolar to unipolar pacing after an S-ICD shock (65 J), resulting in underdetection of VF. This illustrates the contraindication of unipolar pacing in concomitant ICD therapy. The risk of polarity switch in the LP is irrelevant as the LP cannot switch to unipolar pacing. Nevertheless, more evidence is required on S-ICD rhythm discrimination during bipolar LP pacing in patients and requires careful assessment.

Post-shock leadless pacemaker performance

The S-ICD showed correct VF sensing in all episodes, but failed to cardiovert VF in the sheep model. In both animals, maximal effort was put into obtaining an optimal shock vector to lower the defibrillation threshold by using fluoroscopy to determine the borders of the heart. However, only external defibrillation shocks with high output (200 and 360 J) were successful, indicating a suboptimal S-ICD shock vector. In relation to the very posterior position of the sheep heart in the supine position, rather than the typical sternal placement of the S-ICD electrode, the electrode was placed along the right axillary line. The large distance from the coil (right axillary) to can (left axillary), as shown in Figure 2, may have led to failure to convert the induced VF in this animal model. Importantly, to ensure testing of post-shock LP performance with shock waves that are powerful enough to cardiovert VF, external defibrillation shocks (200–360 J) were administered in addition to S-ICD shocks (65–80 J).

The LP showed adequate function and position in both animals after delivering multiple S-ICD and external defibrillation shocks. This was also observed in two patients who were electrically cardioverted post-LP implantation using an external defibrillator. Subcutaneous ICD shock testing was not performed in these patients. The risk of LP dislodgement is the highest during the first weeks post-implant as fibrosis formation at the ventricular fixation site is ongoing.20 This was also observed in a recent study where all device dislodgements (n = 6/526, 1.3%) occurred within the first 14 days (range: 1–14 days) post-implant.5 Although device dislodgements have not been observed after LP implant in the present study, awareness of the dislodgement risk as a consequence of S-ICD defibrillation testing is warranted.
Clinical implications
Combined LP and S-ICD therapy is the first step towards completely abandoning transvenous leads. Future approaches may consist of communicating LPs and subcutaneous defibrillators in order to reduce intracardiac hardware, delivering both bradycaardi and anti-tachycardia pacing, as well as potentially multi-chamber pacing. Moreover, rhythm confirmation by the LP enhances the S-ICD rhythm discrimination and may further reduce inappropriate shocks.

Limitations
There are several limitations of this study. First, we studied only one of the currently available LPs, and therefore, we cannot draw any conclusions for the other available RV leadless pacing or LV leadless pacing devices currently available. Second, evaluation of combined S-ICD and LP implants was limited to acute performance and complications. Studies with longer follow-up duration and greater numbers are needed to assess safety and long-term performance of combined implants. Third, in the sheep model, the S-ICD failed to cardiovert VF. Different (smaller) animal models such as porcine or canine could be considered for future experiments to obtain optimal, clinically relevant, S-ICD shock vectors. Fourth, this study was performed in a tertiary cardiology centre with ample experience with both technologies and is not advised for centres inexperienced with either device. Finally, VF detection by the S-ICD during pacing by the LP was only tested in the animal experiments.

Conclusion
Combined implantation of the LP and S-ICD was successful in two animals and one human subject. No interference in sensing and pacing during intrinsic and paced rhythm was noted in our animal model and human subject, however induced arrhythmia testing was not performed in the patient. Defibrillation therapy did not seem to affect LP function. However, more data on combined LP and S-ICD performance during pacing, VF, and shocks are required before broader adoption can be considered. This novel approach may hold benefits for patients in whom a transvenous approach is not feasible or desired.

Supplementary material
Supplementary material is available at Europace online.

Conflict of interest: R.E.K. received research funding from Boston Scientific Corporation and St Jude Medical. J.R.d.G has received research funding and honoraria from St Jude Medical, Medtronic, Atricure and a personal grant from NWO/ZonMW VIDI 016.146.310. A.A.M.W. is part of an advisory board of Sorin. K.M.K. received consulting honoraria from Boston Scientific Corporation. R.S. was at the time of this study a Boston Scientific Corporation employee. D.L. is a St Jude Medical employee. Part of this study has been presented at the Annual Heart Rhythm Society, Boston, MA in May 2015.

References