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Narrative Review

The subcutaneous implantable cardioverter-defibrillator: Current trends in clinical practice between guidelines and technology progress

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ABSTRACT

The subcutaneous implantable cardioverter defibrillator (S-ICD) is a valuable alternative to the conventional trans-venous ICD (TV-ICD) for the prevention of sudden cardiac death (SCD). Prospective registries showed that the S-ICD is safe and effective in treating ventricular tachyarrhythmias in high-risk patients without pacing indications. While in earlier studies patients implanted with S-ICDs were young and mostly affected by channelopathies, contemporary S-ICD cohorts include patients with severely impaired left ventricular function and significant comorbidities. This review focuses on S-ICD evidence-based use and highlights current gaps between guidelines recommendations and real-world clinical practice.

1. Introduction

The implantable cardioverter-defibrillator (ICD) is the only effective therapy to prevent sudden cardiac death (SCD) in patients with structural heart disease or channelopaties on optimal medical therapy [1,2]. Although the trans-venous ICD (TV-ICD) is safe and effective in treating ventricular tachyarrhythmias (VTA), it is associated with potential short- and long-term lead-related complications. These include complications related to the implant procedure itself (pneumothorax, cardiac tamponade, hemothorax) and those related to the indwelling intracardiac leads (systemic infections or endocarditis, lead failure, venous thrombosis) [3,4]. Indeed, recent meta-analysises revealed an overall complication rate of 9.1% over the first 16 months after implantation [5,6]. Long-term complications increase as a function of follow-up length. Indeed, lead failure was reported to increase progressively with time after implantation reaching an annual rate of 20% in 10-years-old leads [6]. Moreover, lead failure occurs more often in young patients, who expose the leads to greater mechanical stress due to their active lifestyle and longer life expectancy. Of note, recent studies showed that even patients with advanced heart failure (HF) have a 5-year survival rate that is close to 60% [7], raising the question whether "long life expectancy" is a distinct trait of channelopathy/cardiomyopathy patients or a clinical fact that pertains to many other ICD patients. Hence, to overcome many of the complications associated with TV-ICDs, an entirely subcutaneous ICD (S-ICD) has been developed and approved in the clinical practice [8].

2. Methods

Relevant articles in English Language published until August 2018 were identified. Studies were searched from Pubmed using as keywords: implantable cardioverter defibrillator or subcutaneous cardioverter defibrillator. The authors critically reviewed the most relevant studies.

3. S-ICD system and implantation

3.1. S-ICD system

The S-ICD consists of a subcutaneous pulse generator and a subcutaneous lead. The lead is composed of a proximal, a distal sensing electrode and a shock coil [9]. S-ICD does not provide anti-bradycardia or anti-tachycardia pacing (ATP), but can deliver up to 30 s of post-shock trans-thoracic pacing [10]. The device has remote monitoring capability, magnetic resonance compatibility and atrial fibrillation detection [11]. The S-ICD has two programmable tachycardia detection zones: a conditional ventricular tachycardia (VT) and a ventricular fibrillation (VF) zone. In the conditional zone, VTs are discriminated from supraventricular tachycardias (SVTs) by complex morphology-based algorithms, while in the VF zone heart rate is the only criterion to

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define whether shock will be delivered or not.

Pre-implant surface electrocardiogram (ECG) screening is performed to select patients with suitable subcutaneous signals and a screening tool is used to confirm eligibility. Three electrodes are positioned in the same chest position of the S-ICD distal and proximal lead sensing electrodes and pulse generator. ECG recordings are collected in supine and standing postures. With classical manual screening, QRS-T complexes are superimposed on a plastic ruler provided with template boxes. Both the maximal R or S waves of the QRS complex and the T wave have to be comprised within the profile of the template.

More recently, the use of an automatic screening tool (AST) that is based on the same sensing algorithm of the S-ICD has been introduced in clinical practice. AST in envisioned to facilitate screening and reduce subjectivity associated with the manual process. When compared to manual screening, AST is associated with a higher passing rate due to greater tolerance to high-amplitude T-waves [12].

3.2. S-ICD implantation

The conventional S-ICD implantation is performed through three incisions: one on the left-lateral chest for the pulse generator pocket and two parasternal for lead tunnelization. The pulse generator is positioned in a subcutaneous pocket created on the left lateral chest at the fifth intercostal space between the mid and the anterior axillary lines. S-ICD implantation is guided by anatomical landmarks, with the possibility to confirm position by fluoroscopy (Fig. 1).

Recently, an implantation technique, so called “two incisions technique”, that avoids the superior parasternal incision has been described and is currently widely adopted. Furthermore, a surgical approach has been developed to position the S-ICD can between the anterior surface of the serratus and the posterior surface of the latissimus dorsi muscles (intermuscular implantation). Combined, these two techniques offer the advantages of an implantation that is potentially less prone to infections, damages, skin erosion, and allow better cosmetic results [13,14].

S-ICD implant can be performed under general anesthesia or moderate sedation, although registry data show a widespread use of general anesthesia [15]. Interestingly, a peripheral nerve block technique has been introduced for intraoperative anesthesia and perioperative analgesia consisting in an ultrasound-guided injection of local anesthetic between the serratus and latissimus dorsi muscles (serratus plane block) [16].

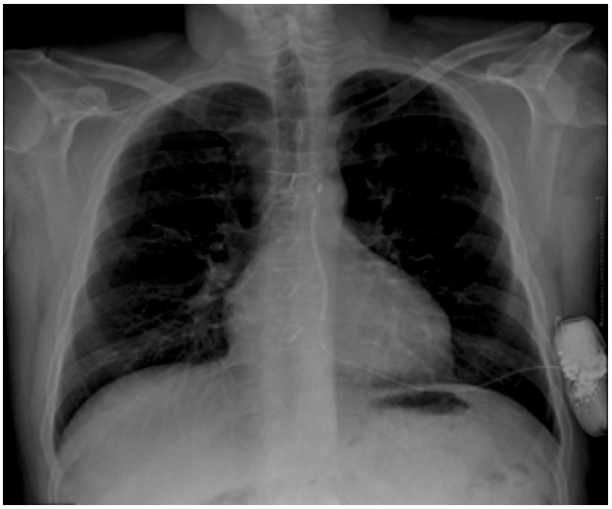

Fig. 1. A 40 year old male patient with post-myocardial infarction left ventricular dysfunction received a subcutaneous implantable cardioverter defibrillator (S-ICD) for primary prevention of sudden cardiac death. The figure shows a chest radiogram with the correct position of the implanted S-ICD.

3.3. Safety and efficacy

Several studies have demonstrated that S-ICD is safe and effective in treating VTAs. The most common complication associated with S-ICD implantation is device infection, with a reported rate of 2.4% over two years [17,18], comparable to that of TV-ICDs. No cases of systemic dissemination of S-ICDs infections have been reported in the registries [17,18]. On the contrary, trans-venous device infections are associate with a 22% to 54% risk of bacteremia and endocarditis, often requiring lead extraction with procedure-related mortality exceeding 2% [19].

The inappropriate shock rate has been reported as 5% to 25% in early S-ICD registries, and is mainly ascribed to T-wave oversensing (TWOS). With enhanced discrimination algorithms, including those specifically designed to overcome TWOS (Smart-Pass), the rate of inappropriate shocks is constantly decreasing (Fig. 2).

The IDE/EFFORTLESS pooled analysis reported a 3-years incidence of inappropriate shocks of 11.7%, due to TWOS (39%) or SVT (24%) [18]. Similar rates were reported in the midterm outcomes of the EFFORTLESS registry [17].

After S-ICD implantation, defibrillation threshold testing (DFT) is typically performed to assess appropriate device implantation. VF conversion failure rate has been reported as 0.2% to 0.4% [18,20,21]. Out of hospital conversion failure rate for spontaneous arrhythmia is 2.6% [15]. Similar conversion failure rate has been reported for TV-ICDs (2.6% in the SIMPLE trial [22], 1.6% in the NORDIC [23], and 1.6% in the SCD-HeFT [24].

4. Clinical studies overview

Since the first report by Bardy et al. [25], 2 large prospective registries, the IDE study [26] and the EFFORTLESS [15] have been conducted to evaluate the performance of the S-ICD in large populations. Combining the IDE and EFFORTLESS registries [18], the mean age of the cohort was 50 ± 17 years and the mean LVEF was 39.4 ± 17.6%. The majority of patients (70%) had a primary prevention indication for ICD, 37.8% had ischemic cardiomyopathy, 10% had channelopaties, 11% had hypertrophic cardiomyopathy, 1% had congenital heart disease and 2.2% had a concomitant pacemaker. EFFORTLESS was the single registry that included patients with end-stage renal disease (ESRD). Only 4% of the IDE/EFFORTLESS pooled cohort had a creatinine clearance of < 45 ml/min and the percentage of patients undergoing chronic dialysis was not reported [18] (Table 1).

5. Current clinical practice and guidelines

Early S-ICD patients were younger, healthier and with fewer comorbidities as compared to typical TV-ICD patients. Moreover, many early S-ICD patients had “niche” indications (e.g. previous ICD infection, congenital heart disease, inadequate vascular access) [15,26]. In contrast, current real-life registries [20,21] include patients with more traditional indications. According to the current European guidelines (ESC 2015) [27], summarized in Table 2, ICD candidates have a class IIa indication for an S-ICD as an alternative to a TV-ICD, unless pacing for bradycardia, tachycardia, or resynchronization is required. Furthermore, ICD candidates with inadequate vascular access, previous removal of an infected TV-ICD system, may benefit from the S-ICD as a valuable alternative to the TV-ICD (class IIb indication). Similarly, the S-ICD may be considered in young patients requiring long-term ICD therapy (class IIb indication) since their long life-expectancy and active lifestyle make them more prone to complications related to the TV-leads.

Recent analyses of S-ICD use in real-life clinical practice [20,21,28] show that S-ICD recipients are more often young and without structural heart disease compared to TV-ICD patients. However, a significant proportion of S-ICD candidates had “common” ICD indications (e.g., severe left ventricular dysfunction, advanced heart failure) and

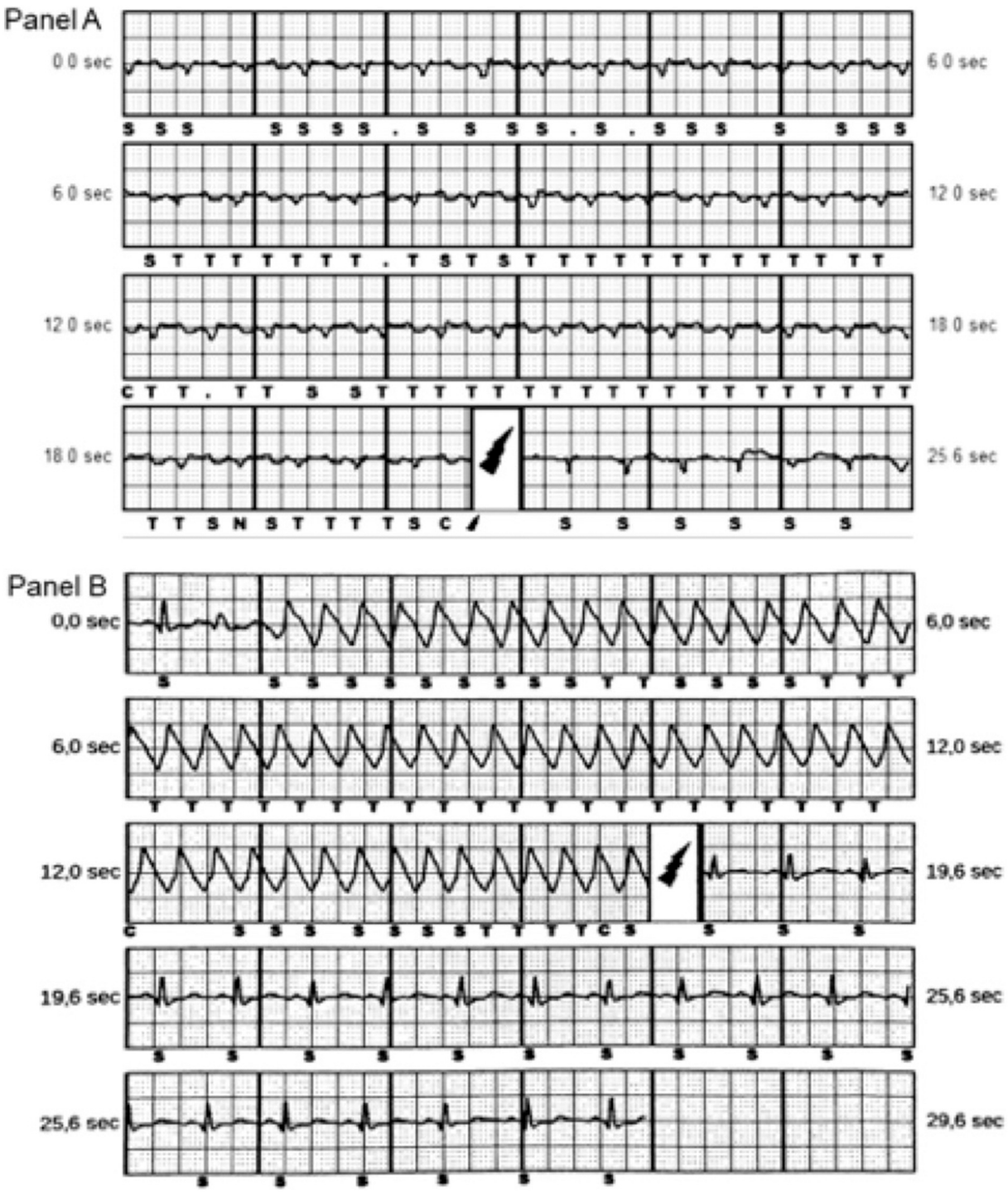

Fig. 2. Panel A: A 16-year-old male patient with massive hypertrophic cardiomyopathy received a subcutaneous implantable cardioverter defibrillator (S-ICD) for primary prevention of sudden cardiac death. The secondary sensing vector was selected. Ten months after implantation, the patient experienced an inappropriate shock due to T-wave oversensing during supraventricular tachycardia. The figure shows the episode inappropriately detected and treated by the S-ICD with an 80 J-shock. An exercise test was performed and heart rate-dependent change in QRS morphology was observed. Changes were less pronounced when sensed with the alternative vector, that was selected by the system and approved by the physician. Panel B: A 33-year-old male patient with end-stage hypertrophic cardiomyopathy received a primary prevention S-ICD. The primary sensing vector was selected. One year after implantation, the patient experienced an episode of fast ventricular tachycardia that was appropriately detected (T markers) and effectively treated by the S-ICD with an 80 J-shock (lightning marker). Time-to-therapy was 15 s.

comorbidities as compared with patients in the EFFORTLESS/IDE cohort [18,20,21]. In the S-ICD post-approval registry [21], which described the characteristics and acute outcomes of patients implanted with S-ICD in a real-world setting and outside investigational studies, mean age was 52 ± 15 years, consistent with the trend to use the S-ICD in younger patients. The mean LVEF was 32 ± 14.6%, and 74% had congestive heart failure. Remarkably, 13.4% of patients were on dialysis for ESRD. Clinical characteristics of patients that were enrolled in the recently published US-S-ICD Trends study [20] are similar, patients with previous myocardial infarction (40%) and low ejection fraction (average 32%) being largely represented. (Table 1).

In the European Heart Rhythm Association Prospective Survey [29],

Table 1
Clinical features of S-ICD recipients in early vs. contemporary real-life registries.

	IDE [26]	EFFORTLESS [15]	S-ICD Post approval study [21]	US S-ICD trends [20]
N	321	450	1637	3717
Males	74%	72%	69%	69%
Age (years)	52 ± 16	49 ± 18	52 ± 15	53 ± 15
CAD (previous MI)	41%	37%	33%	40%
LVEF (mean)	36 ± 16	42 ± 19	32 ± 14	32 ± 14
Primary prevention	79%	63%	77%	70%
HCM	NA	11%	NA	5%
Channelopathies	NA	13%	4%	8%
Diabetes	NA	12%	34%	38%
AF	15%	17%	16%	20%
CKD	NA (excluded patients with GRF < 30 ml/min	9%	26% (dialysis 13%)	41% (dialysis 20%)
Concomitant PM	1%	3%	3%	2%
CHD	NA	7%	NA	1%

AF: atrial fibrillation; CAD: Coronary artery disease; CHD: Congenital heart disease; CKD: Chronic kidney disease; GFR: glomerular filtration rate; HCM: hypertrophic cardiomyopathy; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PM: pacemaker.

patients with S-ICD were younger, had a higher LVEF, and were less likely to have structural heart disease compared to those implanted with a TV-ICD. In 429 patients, the ICD type was distributed as follow: S-ICD (18.9%), VVI (29.5%), CRT-D (31.6%) and DDD (19.1%). Main reasons for S-ICD choice in this European survey were young patient's age, previous lead-related complications, high risk of infection or previous device infection, desire to preserve the vascular system, and inadequate venous access [29].

6. Specific clinical settings

6.1. Heart failure

Although the S-ICD might be more beneficial in young patients with inherited electrical syndromes and normal LV function, the majority of ICD candidates have heart failure with reduced LVEF. Indeed, primary prevention patients with reduced LVEF represent > 70% of new ICD implants in the US [6]. While these patients are underrepresented in published prospective registries [18,30,31] S-ICD has been shown to be safe and effective in this subgroup of patients [17]. As far as the need for biventricular pacing in HF patients is concerned, the rate of CRT-D upgrade was as low as 4% at 3.4 years in an unselected ICD patients population [32] and 0.4% after 3.1 years in a selected population of S-ICD recipients [17]. The clinical impact of ATP unavailability in HF S-ICD patients has never been systematically explored. While there is concern that patients with ischemic LV dysfunction may be prone to develop monomorphic VTs, the MADIT-RIT study [33] clearly demonstrated that the need for ATP in contemporary ICD patients is largely overstimated. The ongoing Understanding Outcomes with the S-ICD in Primary Prevention Patients with Low Ejection Fraction Study (UNTOUCHED) study [34] will clarify whether with S-ICD the rate of shocks in HF patients is comparable to that observed in TV-ICD patients with optimal programming.

6.2. End-stage renal disease (ESRD)

Patients with ESRD were excluded from the IDE trial and poorly represented in the EFFORTLESS. Conversely, in the US trend analysis [20] and in the post-approval study [21], 13% and 20% of S-ICD implants were performed in patients undergoing chronic dialysis, respectively.

ESRD is a known risk factor for infections, and this risk is even higher in dialysis patients. Of note, dialysis patients implanted with a TV-ICD have high rate of complications, including device-related bacteremia and central venous stenosis [35]. By avoiding endocardial leads, S-ICD is envisioned to prevent bloodstream dissemination of local device infections and vascular complications in this subgroup of patients [36]. In two separate series, S-ICD was safe and effective in dialysis patients, also reducing the risk of endovascular infection [30,37]. In this view, S-ICD may offer a safe alternative to TV-ICD in patients with ESRD. The ongoing multicenter DESIRE (Determination of the Efficacy of Subcutaneous Icd in REnal patients) trial will provide further insights regarding S-ICD safety and efficacy in this high-risk population.

6.3. Hypertrophic cardiomyopathy (HCM)

By preserving the endovascular district, S-ICD intuitively represents a valuable alternative to TV-ICD for HCM patients, who are typically young and with an active lifestyle [38]. Due to the peculiar features of the disease, the use of S-ICDs in HCM patients initially raised significant concerns. Indeed, the increased left ventricular mass and unpredictable electrical substrate might affect defibrillation threshold in HCM. Moreover, high voltage R waves and deep negative T waves may entail TWOS and trigger inappropriate shocks. Finally, the inability to provide anti-tachycardia pacing (ATP) has been perceived as a limitation in HCM patients, who may present monomorphic VTs.

Nowadays, a growing body of evidence suggest that S-ICD is safe and effective in HCM patients. DFT has been shown to be ≤65 J in 98% of patients, consistent with data obtained in non-HCM patients [31,39]. Of note, efficacy in converting induced VF was independent from LV mass [39], which is in agreement with previous studies in TV-ICDs [40]. As far as inappropriate shocks are concerned, in the IDE/EFFORTLESS pooled analysis, the HCM cohort (99 patients) showed the same

Table 2
S-ICD indications according to the European guidelines (ESC 2015) [27].

	Class of indication	Level of evidence
S-ICD should be considered as an alternative to TV-ICD in patients with ICD indication when pacing therapy for bradycardia, cardiac resynchronization or antitachycardia pacing is not needed.	IIa	C
S-ICD may be considered as a useful alternative to TV-ICD when venous access is difficult, after the removal of a TV-ICD for infections or in young patients with a long-term need for ICD therapy.	IIb	C

S-ICD: subcutaneous implantable cardioverter defibrillator; TV-ICD: transvenous implantable cardioverter defibrillator.

Table 3
A proposed approach for S-ICD candidates' selection.

	S-ICD	TV-ICD
ICD candidates with anti-bradycardia pacing or CRT indication		√
Secondary prevention of monomorphic VT likely responsive to ATP		√
Young patients with cardiomyopathies or channelopathies	√	
LV dysfunction (EF ≤ 35%) with life expectancy > 10 years	√	
Inadequate vascular access (dialysis, CHD)	√	
High infection risk (diabetes, dialysis, previous removal of an infected TV-ICD)	√	

ATP: anti-tachycardia pacing, CHD: congenital heart disease, CRT: cardiac resynchronization therapy, EF: ejection fraction, LV: left ventricular, S-ICD: subcutaneous implantable cardioverter defibrillator; TV-ICD: transvenous implantable cardioverter defibrillator, VT: ventricular tachycardia.

incidence of inappropriate shocks (12.5%) than the non-HCM cohort (10.3%) [31]. Of note, inappropriate shocks were mainly due to TWOS [31]. Careful screening for S-ICD compatibility [39,41,42], and improvements in S-ICD discrimination algorithms [43,44] may significantly reduce the incidence of inappropriate shocks.

Fig. 2 shows examples of inappropriate and appropriate S-ICD shocks in two HCM patients.

Finally, the "true" need of ATP in HCM patients is still a matter of debate. In the MADIT-RIT study [33], delayed VT therapy ICD programming resulted in a 5 fold decrease in any occurrence of appropriate ATP interventions without affecting the rate of appropriate shocks or the risk of syncope [33]. Although it is unknown whether this applies also to HCM patients, it is reasonable that more conservative ICD programming would reduce unnecessary ATP for short-lasting monomorphic VTs and result in predominance of polymorphic VTs and VF as the trigger of ICD interventions in HCM patients.

6.4. Congenital heart disease (CHD)

Patients with CHD represent a minority of ICD candidates. TV-ICD implantation may be troublesome in CHD patients due to challenging venous access to the right ventricle (e.g., extracardiac Fontan, anomalous or occluded veins) and intracardiac shunts with potential thromboembolic risk. Moreover, very young age entails a high long-term risk of device infection or lead failure.

In the IDE/EFFORTLESS pooled analysis, the CHD cohort consisted of 19 patients in which S-ICD proved to be safe [18]. However, none of these patients had any appropriate shocks during follow-up [45]. Few long-term follow-up studies reported S-ICD efficacy in CHD patients [46,47]. A major limitation in the use of S-ICD in CHD patients might be the potential risk to develop pacing indication during follow-up. However, sporadic cases have been reported in which combined implantation of an S-ICD and a pacemaker was feasible and safe [48].

6.5. Concomitant pacing system

Pacemaker patients who develop the need for an ICD usually undergo device upgrade by adding a trans-venous ICD lead with or without extraction of the existing pacing lead. Alternatively, an S-ICD may be implanted that coexist with the previously implanted pacing system, thus avoiding the risks associated with device upgrading. In the IDE/EFFORTLESS pooled analysis, 2.2% of S-ICD patients had a concomitant pacemaker [18]. Among paced patients, a higher proportion of S-ICD screening eligibility was reported among those with right ventricular (RV) septal pacing as compared to RV apical pacing [49]. This might be of concern when S-ICD is combined with a leadless pacemaker, which is commonly implanted in an apical position [49]. However, S-ICD compatibility with leadless pacemakers has been reported [50,51]. Also, biventricular pacing was associated with higher candidacy rate as compared to RV pacing alone [49]. In non-pacing-dependent patients, the screening QRS-T morphology should be obtained both during paced and spontaneous rhythm [41]. It is advisable to disable the post-shock pacing of S-ICD to avoid interference with the pacemaker. Of note, unipolar pacing is not compatible with S-ICD. Although a concomitant pacemaker is associated with higher risk of inappropriate shocks in the mid-term EFFORTLESS analysis [52], other studies did not show a higher incidence of inappropriate S-ICD therapies in pacemaker patients [53].

7. Conclusions

While in the early S-ICD experience the ideal candidates were young, with less advanced heart disease and comorbidities, its use is rapidly expanding and current recipients are increasingly more similar to "standard" ICD candidates. Importantly, the S-ICD seems to be a valuable alternative for specific subgroups of patients in whom the TV-ICD may present mid- and long-term disadvantages, including young patients, dialysis patients, CHD and pacemaker carriers. Ongoing randomized prospective studies [54,55] will provide a head-to-head comparison of S-ICDs and TV-ICDs that will assist in appropriate device selection for most ICD candidates. Finally, we present in Table 3 a proposed approach to select patients who may benefit more from the S-ICD technology based on clinical experience and the current guidelines.

Conflict-of-interest statement

Dr. P. Francia received research and educational grants from Boston Scientific.

Dr. R. Cappato has equity and intellectual property rights with Cameron Health.

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