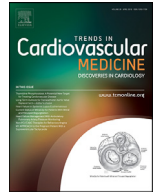




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Rationale and feasibility of the atrioventricular single-lead ICD systems with a floating atrial dipole (DX) in clinical practice

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ABSTRACT

Cardiac implantable electronic devices establish proper therapy for the prevention of sudden cardiac death, significantly reducing the morbidity and mortality of patients with arrhythmias and heart failure. It is well-known that the number of electrodes increases the risk of complications. To preserve the benefit of atrial sensing without the need to implant an additional lead, a single-lead ICD system with a floating atrial dipole (DX ICD lead) has been developed. Besides all of the potential benefits, the necessity of a reliable and stable atrial sensing via the floating dipole could be the main concern against the use of this lead type. In the current generation of DX devices, the specially filtered atrial signal seems to be high enough and stable over time, which is crucial in the early detection of atrial arrhythmias, discrimination between different forms of tachycardias in order to prevent inappropriate ICD therapy, and achieving an optimal atrioventricular and interventricular synchrony in patients with a two-lead CRT-DX system.

The present review summarizes the benefits and potential drawbacks of the DX ICD systems based on the available literature, furthermore, proposes an evidence-based algorithm of ICD type selection.

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Introduction

Cardiac implantable electronic devices (CIEDs) significantly improve the morbidity and mortality of patients suffering from arrhythmias and heart failure. Although these systems have become more and more safe and effective due to significant technical advances of the last decades, a substantial risk for serious complications relates to the transvenously implanted leads. It is also well known that the number of leads increases not only the time of surgery and fluoroscopy but also the risk of complications, particularly of thrombosis, infection, or the need for repeated surgery [1–5]. Different technologies, utilizing extravascular leads, such as the subcutaneous ICD, have been developed to provide the possibility to convert life-threatening ventricular arrhythmias while avoiding complications related to the intravascular lead [6]. These systems are, however, currently limited to patients without the need for

pacings therapy for bradycardia support, cardiac resynchronization, and antitachycardia pacing [7]. It seems reasonable to implant only those leads that are ultimately required.

A single-lead ICD system with a floating atrial dipole (DX technology) was developed to preserve the benefit of sensing atrial activity without the need to implant an additional atrial lead [8]. In the present paper, we summarize the potential benefits and drawbacks of DX technology based on the available evidence in the literature.

Description of the DX technology in implantable defibrillators

DX technology and the term “DX” specify the Diagnostic eXtension capability of the DX ICD lead (DF-1 and DF-4 variants), which is a ventricular ICD lead with an added floating atrial dipole in order to provide atrial sensing in single-chamber ICDs. The technology was implemented in Biotronik ICDs (Biotronik, SE & Co., Berlin, Germany) in the early 2000s under the name of A+ system, and it was relaunched as DX technology in Europe in 2011 and in the US in 2013 [9]. The history of it with a detailed

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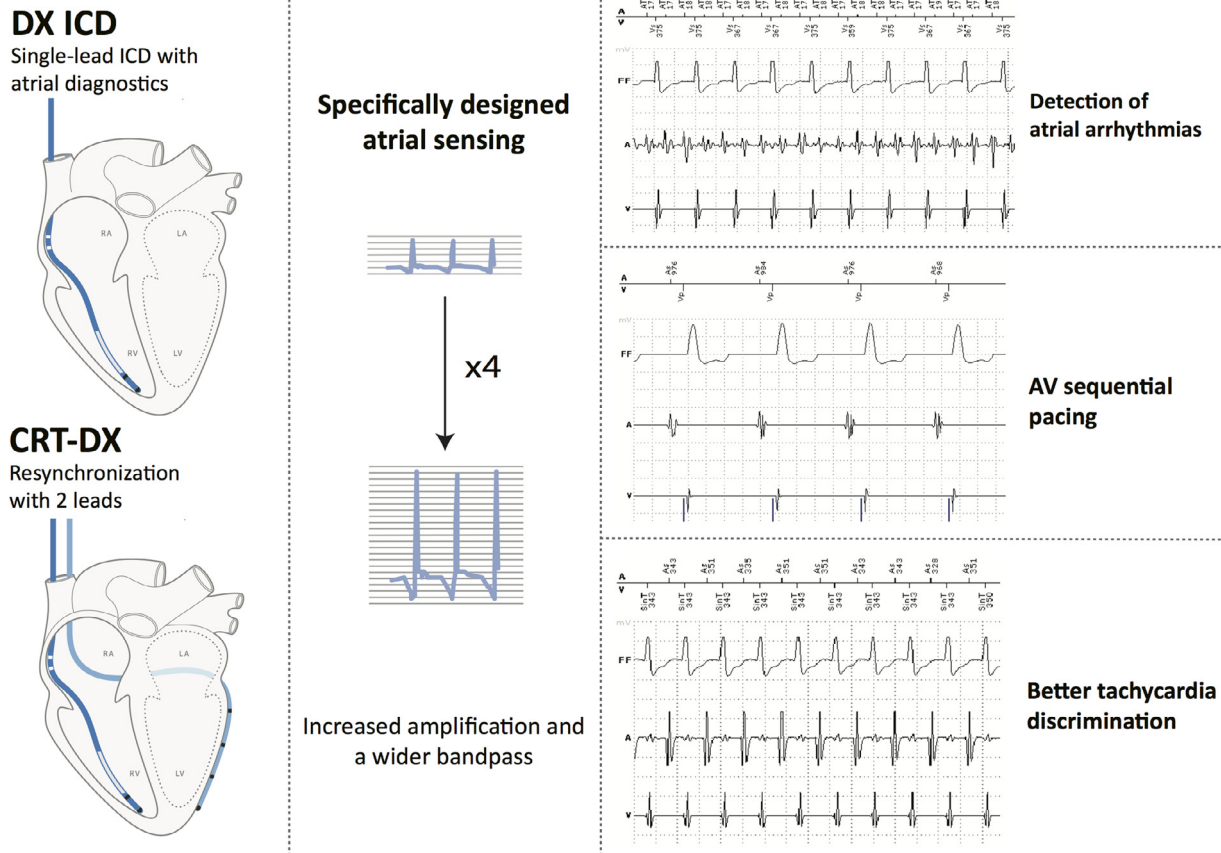


Fig. 1. (Graphical abstract) Overview of the different DX ICD systems and their potential benefits in different clinical situations.

technical description has been published before [8], but some improvements have been made since that time and a 2-lead CRT ICD system has also been introduced. Herein, we predominantly focus on the last generation of these systems and, therefore the terminology “DX” will be used in general. The DX ICD system refers to a “DX” single-lead ICD with atrial diagnostics but without atrial pacing capability, which consists of a DX ICD generator and a DX ICD lead (Fig. 1). The CRT-DX system is a 2-lead CRT-D system, which maintains the AV-synchronous resynchronization therapy via two leads. It consists of a CRT-DX device, a DX ICD lead, and coronary sinus lead (Figs. 1 and 2).

The currently available DX ICD and CRT-DX systems have a stable and reliable atrial sensing, which is based on the optimized atrial dipole spacing, a specifically designed input stage for the atrial sensing, a pre-amplifier, which progressively increases the atrial gain up to fourfold, and a wider bandpass for the frequency range of the atrial channel, respectively. Improvements of the DX technology provide flexibility of lead positioning in the atrium with a reduced risk of far-field oversensing from the ventricle. In addition, the loss of atrial signal results in automatic switching from SMART detection to single-chamber discrimination.

Potential benefits and risks of the DX ICD lead

Clinical benefits related to bradycardia pacing

In daily clinical practice, only 40% of dual-chamber ICD recipients fulfill an indication for dual-chamber pacing [9], however more complications are observed in dual-chamber ICD recipients [1,4,10,11]. Notably, dislodgement of the atrial lead occurs more often compared to the right ventricular leads with an incidence

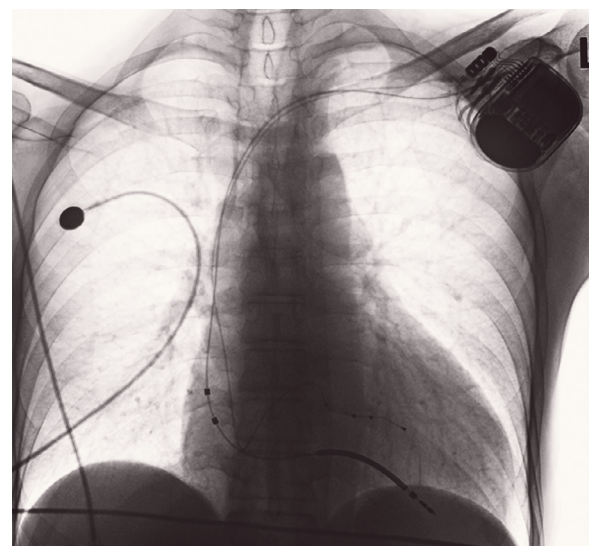


Fig. 2. Chest X-ray of a patient suffering from dilatative cardiomyopathy after an upgrade from DX ICD to CRT-DX with a quadripolar coronary sinus lead.

of up to 1.9% [12]. A need for atrial pacing in the case of symptomatic sick sinus syndrome seems to be a clear indication for implanting an atrial lead and, therefore, in these cases, DX ICD leads are not an option. In selected patients after myocardial infarction and/or who are suffering from heart failure and clinically relevant sinus bradycardia limiting beta-blocker therapy uptitration, the implantation of an atrial lead may be considered. Unnecessary atrial

stimulation is, however, potentially dangerous in that atrial fibrillation is promoted, as observed in several studies [13,14]. Therefore, an additional atrial lead should be avoided in single chamber ICD recipients without sinus node disease. Clinicians tend to choose a dual-chamber system over VVI ICD for patients who still do not fulfill an absolute indication for bradypacing but already have a mild AV or ventricular conduction problem (i.e. first-degree heart block, right or left bundle branch block, wider QRS duration), and may develop higher degree conduction abnormalities later [10]. In the case of concomitant ICD indication and mild AV or ventricular conduction problems, but without an absolute indication for atrial pacing, a DX ICD lead may be an optimal choice. In the case of a left bundle branch block or an expected high rate of ventricular pacing in the future, primary cardiac resynchronization therapy should be strongly considered to prevent a CRT upgrade later on [15].

Cardiac resynchronization via 2 leads (CRT-DX systems)

A special clinical question is whether CRT can be delivered safely with 2 leads (CRT-DX system), since the reduction in the number of the leads is more relevant in these complex multilead systems. Stable atrial sensing is crucial in CRT in order to achieve optimal atrioventricular (AV) and interventricular (VV) timing.

The role of atrial stimulation in CRT recipients without sinus node disease or symptomatic chronotropic incompetence is controversial. In a propensity matched study of CRT-D recipients followed by the LATITUDE remote monitoring system, rate-responsive dual-chamber (DDDR) programming was associated with significant improvement in survival but only for a selected high-risk population identified by heart rate score, a novel parameter of chronotropic incompetence [16]. On the contrary, the composite endpoint of all-cause mortality, heart failure events, NYHA functional class, and patient global self-assessment in a multicenter, 3-arm, randomized study of CRT recipients were not improved by atrial support pacing (DDD-70 or DDDR-40) compared to atrial tracking (DDD-40)[17]. Notably, the 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy recommends using VDD/DDD mode with a base rate of 35–40 bpm to ensure permanent or nearly permanent atrial sensing and to avoid the confounding influences of atrial support [18].

Regarding clinical experience with CRT-DX systems, there is still limited evidence. Biffi and colleagues compared the clinical and technical outcome of 25 CRT-D recipients with conventional 3-lead systems and 12 patients implanted with a CRT-DX [19]. Absolute indication for atrial stimulation was observed in 1.2% of CRT recipients during the 2-year screening period and these patients were accordingly excluded from the study. Besides the classical evaluation of CRT response, chronotropic incompetence was also carefully investigated at baseline and during follow-up. No difference between the 2 groups was observed in terms of NYHA class improvement, LV reverse remodeling, peak cardiopulmonary performance, and the presence of chronotropic incompetence at 12 months. Moreover, no patients developed a need for atrial stimulation at 3-year follow-up and atrial undersensing did not occur. In another publication, 120 subjects with CRT-DX from the Sentus QP-Extended CRT Evaluation with Quadripolar Left Ventricular Leads post approval study (Clinicaltrials.gov Identifier: NCT02290028) were selected and matched with 120 patients with conventional three-lead CRT-D systems. This retrospective subanalysis demonstrated that the CRT-DX system can provide fewer complications driven primarily by lack of RA lead dislodgements, while similar CRT responses were achieved [20].

To provide optimal CRT, the reliable detection of atrial fibrillation (AF) and an adequate mode switch is crucial, independent from the type of atrial sensing electrodes. In CRT recipients with

permanent AF, atrial lead is usually not implanted, however, a spontaneous reversion into sinus rhythm may occur in up to 10% [21]. These patients may have a benefit from a CRT-DX system as they can have an AV synchronous pacing without risking an additional atrial lead implantation. CRT upgrading is burdened by complications and infection primarily owing to the lead number [15] and, therefore, upgrading a DX ICD device - with an already proven stable atrial sensing - seems to carry lower risk (Fig. 2). In the THINGS registry, one out of the 140 ICD DX patients developed an indication for upgrading the device to a cardiac resynchronization therapy defibrillator (CRT-D): the upgrading was successfully completed using the same DX technology with a two-lead CRT-D system [22].

Despite these encouraging observational data related to the utilization of the CRT-DX system, randomized controlled trials including upgrade from DX ICD to CRT-DX are highly warranted in this field.

Tachycardia discrimination to prevent inappropriate ICD therapy

Differentiation of supraventricular and ventricular tachycardias are one of the most exciting but sometimes also the most challenging areas of cardiac electrophysiology. The availability of atrial electrograms in addition to ventricular IEGM and far-field electrograms improves the correct interpretation of stored arrhythmia events [9]. Dual-chamber ICDs could provide better automatic discrimination between SVT and VT based on atrioventricular dissociation, although clinical studies investigating this issue have controversial results, especially the ones used morphology discriminators in single-chamber devices [23–25].

Nonetheless, according to the HRS/EHRA/APHS/SOLAECE expert consensus, improved SVT-VT discrimination should not be considered as an indication for a dual- vs. single-chamber ICD [26]. Moreover, the programming of morphology discriminators (i.e. Far-Field Morphology, MorphMatch, RhythmID, and Wavelet) are recommended in single-chamber ICDs and the programming of dual-chamber algorithms (plus morphology, if available) in devices with an atrial lead.

The DX ICD system with atrial-sensing electrodes offers the same discrimination capability as dual-chamber ICDs (i.e. SMART algorithm) besides the single-chamber discrimination algorithms. In some early studies of the DX ICD system, inappropriate therapies were observed in up to 7.8–8.6% of the cases, depending on the follow-up duration [27,28]. In a novel publication, however, this was only 0.83% during the mean follow-up of 1.3 years [20], and in another cohort of 150 DX ICD recipients with a median follow-up of 12 months, there were no inappropriate ICD therapies observed at all [29]. The observed improvement in the rate of inappropriate ICD therapies is most likely due to the more conservative programming of major arrhythmia discriminators, high VT detection cut-off rate, and prolonged detection time. In a comparative, prospective, single-center study of 212 consecutive patients who underwent conventional (VVI) or DX single-lead ICD implantation, the incidence of inappropriate ICD therapies in the DX-group was significantly lower compared to the VVI-group (1/77 [1%] vs. 12/135 [9%], $p = 0.028$) [30].

Although dual chamber algorithms would be logically preferable, it is not clear which discriminator should be empirically programmed as the first choice in these devices, since no head-to-head comparison between morphology and dual-chamber discrimination modes of Biotronik devices (i.e. MorphMatch vs. SMART) is available. For note, dual-chamber discrimination may be preferred for atrial arrhythmias with slow and regular ventricular rhythms, as suggested in the THINGS registry [22]. Moreover, in the case of inappropriate discrimination, changing the discrimination type

between morphology and dual-chamber algorithms should be considered.

Early detection of atrial arrhythmias

Atrial fibrillation (AF) is associated with substantial mortality and morbidity, including stroke, heart failure, cognitive decline, depression, impaired quality of life, and hospitalizations [31]. Atrial fibrillation increases the risk of stroke fivefold, but even a short, subclinical device detected atrial high rate episode (AHRE) is associated with an increased stroke risk of 0.8–1% per year compared with CIED patients without AHRE [32]. Early detection of silent atrial fibrillation may help reducing stroke risk, prevention of heart failure exacerbation, and avoiding atrial remodeling.

In the prospective, multicenter SENSE trial, 150 patients without a prior history of AF were implanted with a DX ICD system and the incidence of AHRE detection at 12 months were compared to age, sex, and left ventricular ejection fraction matched single- and dual-chamber ICD cohorts. The rate of AHRE detection was significantly higher in the DX cohort compared to the single-chamber cohort (13% vs. 5.3%, $p = 0.026$), but not significantly different compared to the dual-chamber cohort (13% vs. 13%, $p = 1.00$) [29]. In the most recently published prospective, observational, multicenter THINGS registry clinical outcomes of patients implanted with DX ICD with atrial sensing capability (ICD DX group, $n = 140$) were compared to those implanted with conventional single-chamber ICD (ICD VR group, $n = 236$) [22]. The likelihood of atrial tachyarrhythmia detection was almost fourfold greater in the DX ICD group (11.4% vs. 3.6% within 2 years, adjusted HR 3.85, 95% CI 1.58–9.41, $p = 0.003$). Arrhythmias diagnosed in that way often led to clinical interventions, mainly by the initiation of oral anticoagulation therapy.

These data strongly support the utilization of a DX ICD over conventional single-chamber ICDs, especially for patients with a higher risk for AF. In a proposal for ICD selection published some years ago [33], a device with an algorithm for AT/AF detection was recommended for single chamber ICD candidates with a CHADS score ≥ 2 , representing patients with an elevated risk of atrial arrhythmias. Clinical conditions associated with elevated stroke risk beyond the ones incorporated into the CHADS score are described in detail by the most recent ESC guidelines for the diagnosis and management of AF [31]. Accordingly, the majority of typical ICD recipients would benefit from the AF monitoring capability of the DX technology; however there is no scientific evidence on hard clinical outcomes available. Combination of remote monitoring and the detection of atrial arrhythmias helps to start an early, appropriate anticoagulation therapy for patients suffering from asymptomatic AF events. The ongoing randomized DX-AF study is aimed to demonstrate that the DX ICD system combined with remote monitoring will facilitate the adequate recognition of sub-clinical AF and ultimately stroke prevention with similar safety profile compared to VVI-ICD (NCT03110627).

Known and potential risks of the DX system

The previously discussed potential benefits rely on a stable atrial signal via the floating dipole. A randomized study in 2011 reported that arrhythmia discrimination was similar in 249 patients with an early generation of the DX ICD system (A+ system) compared to dual-chamber ICD, however the percentage of patients with atrial over- or undersensing was significantly higher in the A+ arm [34]. In another early study of 43 patients with the Lexos A+ model, atrial undersensing was never documented [35].

The system has undergone a series of modifications to optimize atrial sensing. In the current generation of the devices, average atrial signal amplitudes range from 1.8 to 8.7 mV and have

proven to be stable through long-term follow-ups in different body postures or lead positions, with very few reported cases of atrial undersensing [27,28,36,37]. In a recent study of 93 patients with Linx S DX ICD leads followed by remote-monitoring system, the investigators confirmed that the lead demonstrated excellent functioning regarding the chronic stability of the cardiac signals [36]. In spite of signal stability, a high-rate of misclassification of arrhythmia were observed that was primarily caused by far-field oversensing of the ventricular signal in the atrial channel. Apart from 7.5% inappropriate ICD therapy, in three patients, VT episodes were classified as supraventricular and accordingly remained untreated. The reason for misclassifications was a single beat atrial undersensing due to ventricular blanking and the device switched from the dual-chamber to the single-chamber algorithm (i.e. onset/stability). Although in this way the risk of inappropriate therapy is theoretically reduced, whenever the switch in the discrimination algorithm occurs during an episode of ventricular arrhythmia, the arrhythmia onset criterion is lost and the malignant arrhythmia remains undiagnosed, as pointed out by Safak et al. [36]. A similar case of atrial undersensing by the DX ICD lead resulting in detection failure of a slow ventricular tachycardia was reported with a newer generation of DX ICD (Biotronik Irtavia 7 VR-T DX) [38]. In the setting of loss of atrial sensing, morphology discrimination may be a more effective SVT/VT discrimination strategy, but the combination of morphology discrimination with the SMART algorithm is not a programmable option at the present time.

The most recent data from the THINGS registry show 98.6% sensitivity of appropriate atrial signal detection (median P wave at baseline 5.5 mV, at the 2-year follow-up 5.5 mV). Intermittent inadequate atrial sensing was observed in two patients (1.4%) with a mean atrial signal amplitude of 0.4 mV [22]. Similarly, in the SENSE trial, the mean sensed atrial amplitude with the DX ICD lead was 8.0 ± 5.0 mV at implant and 7.3 ± 4.8 mV at the 12-month follow-up [29]. Moreover, the accuracy of AHRE detection in the DX cohort was comparable to that of the dual-chamber cohort (13% of AHRE detections in the DX cohort and 9% in the dual-chamber cohort were false positives). Individual cases of electromagnetic interference caused by signal amplification have also been reported [39,40].

Regarding operative parameters, neither procedure/fluoroscopy durations nor perioperative complication rates seem to be higher than the ones observed during conventional VVI ICD implantations [29,30]. Defibrillators with DX technology already have the option to be remotely monitored, which provide the possibility of early detection and analysis of the potential risks detailed above.

There are also some open questions as potential cons for the utilization of the DX system, such as long-term performance of the lead or lead extraction. There is actually no research available related to cost-effectiveness and, therefore, any statement on this issue is also not possible.

Proposal for ICD selection

Based on scientific evidence of the DX ICD and CRT-DX systems, as summarized in this review, the current European and American guidelines regarding cardiac pacing, resynchronization therapy, and the recommended screening of atrial fibrillation [26,31,41–43], we suggest considering the following clinical questions in the case of a planned ICD implantation.

§ Is there a need for the implantation of a left ventricular lead?

- Symptomatic heart failure, LVEF $\leq 35\%$ and LBBB QRS > 130 ms
- Symptomatic heart failure, LVEF $\leq 35\%$ and non-LBBB QRS > 150 ms
- Narrow QRS but LVEF 36–50% and anticipated requirement for significant ventricular pacing [44]

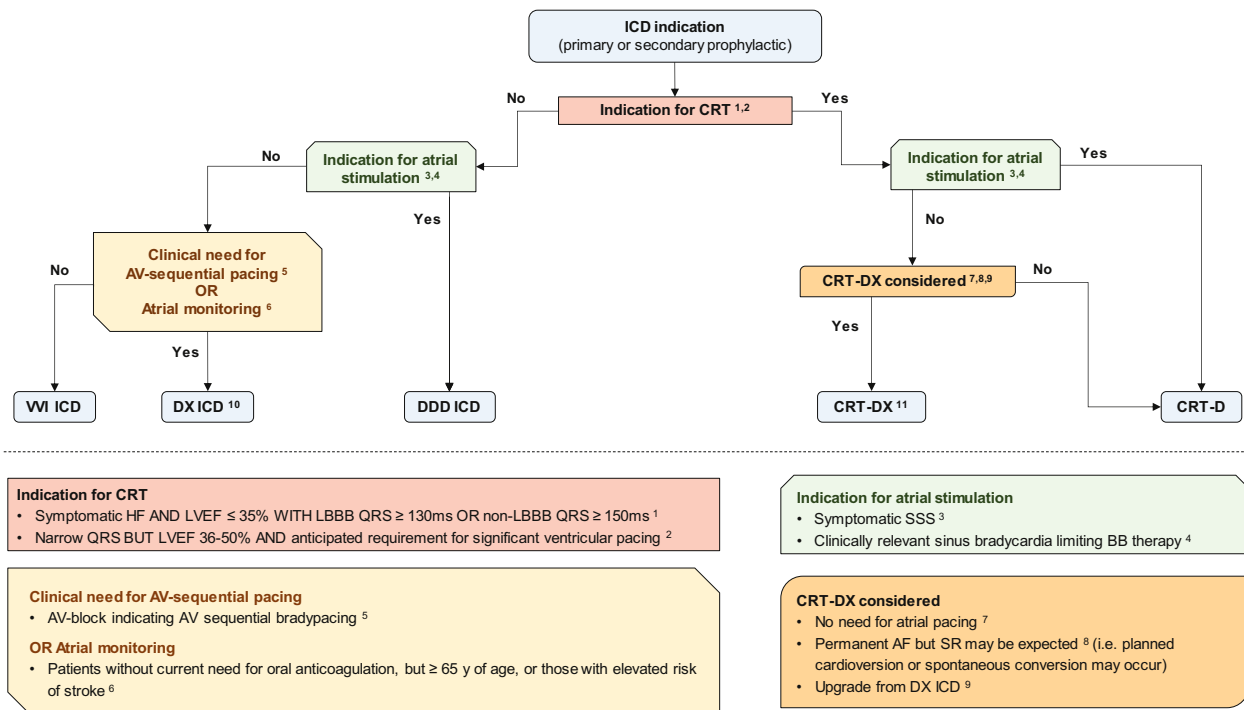


Fig. 3. Proposed flowchart of device selection for ICD recipients, focusing on the DX technology. References used in the flowchart: 1. [41,43]; 2. [42,43,44]; 3. [26,41,42]; 4. [41,43]; 5. [41,42]; 6. [22,29,31-33]; 7. [1-5,9-12,16-18]; 8. [21]; 9. [22]; 10. [1-5,8-14,23-28,30,34-37]; 11. [15,19,20,23-26]. Abbreviations used in the flowchart: AF: atrial fibrillation, AV: atrioventricular, BB: beta-blocker, CRT: cardiac resynchronization therapy, ICD: implantable cardioverter defibrillator, LBBB: left bundle branch block, LVEF: left ventricular ejection fraction, SR: sinus rhythm, SSS: sick sinus syndrome.

§ Is there a current or expected need for atrial stimulation requiring a separate atrial lead?

- Clinically relevant sick sinus syndrome (SSS) or chronotropic incompetence requiring atrial pacing
- Clinically relevant sinus bradycardia limiting beta-blocker therapy initiation or uptitration

§ Could the patient benefit from an additional atrial sensing dipole (DX)?

- Therapeutic consequence of the detection of a silent atrial arrhythmia
- Need for AV sequential right ventricular pacemaker stimulation
- Permanent AF but sinus rhythm may return (i.e. planned cardioversion or spontaneous conversion may occur)

§ Is the atrial sensing of the formerly implanted DX ICD system stable enough in case of the need for an upgrade to CRT-D?

To help the selection of the ICD type to be implanted, we have developed a decision-making flowchart, which is shown in Fig. 3. The decision flowchart defines the potential indications of DX technology. In these cases, besides the DX technology, the full scope of algorithms, functions, physical properties, and economic aspects of the available ICD systems have to be evaluated and the device with the highest potential benefit for the patient has to be implanted.

Conclusion

Due to reliable atrial sensing, the DX ICD system offers an additional atrial intracardiac electrogram, with the early detection of atrial arrhythmias, possibly improved supraventricular tachycardia discrimination and atrioventricular sequential pacing in single-lead devices. Moreover, the CRT-DX system provides the possibility of cardiac resynchronization therapy via 2 leads. DX technology may lead to lower procedural complexity, a lower radiation dose, and

lower implant complications due to the lack of an additional atrial lead. Based on the available scientific evidence, the use of the DX ICD and CRT-DX systems may be a reasonable option in carefully selected patients, but further clinical research is warranted regarding this new technology.

Declaration of Competing Interest

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