




# Cardiac Electronic Devices: Future Directions and Challenges

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**Abstract:** Cardiovascular implantable electronic devices (CIEDs) are essential management options for patients with brady- and tachyarrhythmias or heart failure with concomitant optimal pharmacotherapy. Despite increasing technological advances, there are still gaps in the management of CIED patients, eg, the growing number of lead- and pocket-related long-term complications, including cardiac device-related infective endocarditis, requires the greatest care. Likewise, patients with CIEDs should be monitored remotely as a part of a comprehensive, holistic management approach. In addition, novel technologies used in smartwatches may be a convenient tool for long-term atrial fibrillation (AF) screening, especially in high-risk populations. Early detection of AF may reduce the risk of stroke and other AF-related complications. The objective of this review article was to provide an overview of novel technologies in cardiac rhythm-management devices and future challenges related to CIEDs.

**Keywords:** cardiovascular implantable electronic devices, CIEDs, pacemaker, implantable cardioverter-defibrillator, cardiac resynchronization therapy, remote monitoring, wearable technology

## Introduction

Modern cardiology develops and progresses through innovations in technology and a deeper understanding of the pathophysiology of heart diseases. Indeed, marked advances have been made since 1958, when the first pacemaker was implanted.<sup>1</sup> Over the decades, cardiovascular implantable electronic devices (CIEDs) have become the cornerstone of management for patients with brady- or tachyarrhythmias and heart failure (HF) with reduced ejection fraction (EF).<sup>2–5</sup> This is associated with the emergence of complex stimulation systems — pacemakers (PMs), implantable cardioverter-defibrillators (ICDs), cardiac resynchronization therapy (CRT) — and the growing number of patients with different indications treated with CIEDs. Indeed, rhythm-management devices may improve the life expectancy and quality of life of these patients.<sup>1</sup>

Impressive progress in the field of cardiac pacing has led to technical improvements in existing devices and leads, and new ones are constantly emerging. Despite this development, the systems may have a downside associated with early and late (>3 months after implantation) complications of using such CIEDs. Many are related to the weakest links, ie, the transvenous lead and subcutaneous pocket.<sup>6,7</sup> Wireless technology and optimization of pacing systems have emerged to minimize potential CIED side effects. The effective interrogation and monitoring of patients

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with CIEDs to detect arrhythmias or system malfunction assumes even great importance.<sup>8</sup> The objective of this review article was to provide an overview of novel technologies in cardiac rhythm-management devices and future directions and challenges related to CIEDs.

## Search Strategy

We performed a comprehensive literature search using electronic databases (PubMed, ClinicalTrials.gov) to identify relevant studies and systematic reviews reporting on cardiac rhythm-management devices. The following search terms were included (individually and in combination): cardiac implantable electronic devices, pacemaker, implantable cardioverter-defibrillator, cardiac resynchronization therapy, leadless cardiac pacemaker, wearable cardioverter-defibrillator, subcutaneous cardioverter-defibrillator, substernal lead, remote monitoring, atrial high-rate episodes, smartwatch, and wearable technology. Selected articles, clinical trials, and guideline documents were reviewed for inclusion.

## Who is Appropriate for CIEDs?

A challenge is whether a patient appropriately qualifies for CIED implantation, despite the current guidelines.<sup>2–5</sup> SCD-HeFT<sup>9</sup> was a randomized controlled trial (RCT) conducted among 2,521 patients with HF, left ventricular EF (LVEF)  $\leq 35\%$ , and New York Heart Association class II or III. It was found that ICD therapy was related to a 23% reduction of mortality compared with patients treated with amiodarone or placebo.<sup>9</sup> However, the recent results from the DANISH trial<sup>10</sup> did not show a survival benefits among patients with nonischemic HF with ICD implanted as primary prevention of sudden cardiac death (SCD). The exception was the subgroup of patients aged  $<68$  years, in which the risk of all-cause death was significantly lower in the ICD group than the control group (HR 0.64, 95% CI 0.45–0.90). Importantly, 31% of deaths were not related to cardiovascular events, which may also indicate less benefit from ICDs in older and frail patients.<sup>10</sup> Lee et al<sup>11</sup> reported that the presence of ICDs significantly reduced the rate of all-cause death (HR 0.640, 95% CI 0.448–0.915) in patients with ischemic cardiomyopathy, but not among individuals with nonischemic cardiomyopathy (HR 0.984, 95% CI 0.641–1.509) during follow-up of  $3.5 \pm 1.8$  years.<sup>11</sup>

Beyond recommendations about ICD therapy in patients with ischemic cardiomyopathy and poor LVEF, diagnostic algorithms for the identification of patients with relatively preserved LV contractility at increased risk of

major arrhythmic events have been proposed. The PRESERVE EF study<sup>12</sup> was performed among 575 patients of mean age 57 years and LVEF 50.8%. Participants were assessed in two steps: if there were abnormalities on ECG (eg, premature ventricular complexes, unsustained ventricular tachycardia, late potentials, prolonged QTc), patients were referred to programmed ventricular stimulation (PVS). For those with induced ventricular tachyarrhythmia (VT), ICDs were implanted. The primary end point was the occurrence of a major arrhythmic event: sustained ventricular tachycardia/fibrillation, appropriate ICD therapy, or SCD. The study found that 35.5% had abnormal ECG findings, and 27% of those were inducible with PVS. ICDs were implanted in 37 patients (90.2% of inducible subgroup). During the 32-month follow-up, there were no SCDs among ICD patients, whereas nine appropriate ICD shocks were observed. A previous study<sup>13</sup> showed that patients with hypertrophic cardiomyopathy and noninducible arrhythmia with PVS had longer event-free survival. Inducibility with PVS was an independent predictor of SCD or appropriate ICD therapy among patients with hypertrophic cardiomyopathy.<sup>13</sup>

While the effectiveness of ICD therapy in patients with nonischemic dilated cardiomyopathy and reduced LVEF ( $\leq 35\%$ ) is debated, the selection of patients with dilated cardiomyopathy and well-maintained LV contractility (LVEF  $>35\%$ ) at risk of malignant cardiac arrhythmic events who may gain a survival benefit from ICD therapy represents another challenging area. Gatzoulis et al<sup>14</sup> used a two-step algorithm in another study — ReCONSIDER; (NCT04246450) — which is an ongoing prospective observational trial among patients with nonischemic cardiomyopathy aiming to recognize those with a truly high risk of SCD.<sup>14</sup> CMR GUIDE (NCT01918215)<sup>15</sup> is an ongoing RCT to assess myocardial fibrosis and related risk of SCD among patients with LVEF 36%–50% and evidence of fibrosis on optimal HF therapy. Patients are randomized to receive ICD (as primary SCD prevention) or an implantable loop recorder (ILR). The composite primary end point is time to SCD or hemodynamically significant VT.<sup>15</sup>

Another debated issue is the optimal selection criteria for CRT responders, especially among patients with HF, without typical left bundle-branch block.<sup>16</sup> New strategies, such as leadless pacing, optimization of LV-lead position, multipolar LV pacing, alternative right ventricular (RV) pacing, eg, His-bundle pacing or cardiac

contractility modulation, may positively impact on further CIED therapy.<sup>17</sup> MORE-CRT MPP-PHASE II (NCT02006069)<sup>18</sup> is an RCT to assess the impact of multipoint pacing in nonresponders to 6 months of standard biventricular pacing. Preferential LV-only pacing is also considered an alternative to standard biventricular pacing.<sup>19</sup> A prospective randomized study of CRT with preferential adaptive LV-only pacing (AdaptResponse, NCT02205359)<sup>20</sup> is assessing if the new pacing algorithm reduces the incidence of the combined end point of all-cause mortality and HF decompensation compared with conventional CRT among patients eligible for CRT. The AdaptivCRT algorithm optimizes the pacing method and atrioventricular/interventricular delays, based on the current patient's activity and intrinsic conduction.<sup>20</sup>

His-bundle pacing is the most physiological form of ventricular pacing, and appears to be a safe and effective method during long-term follow-up.<sup>21</sup> This approach is considered superior to standard RV pacing and may also improve clinical outcomes in patients with CRT indications.<sup>22</sup> The His-SYNC (NCT02700425)<sup>23</sup> pilot trial was the first RCT comparing His-bundle pacing for CRT (His-CRT) vs biventricular pacing (BiV-CRT) among 41 patients with standard indications for CRT. At 6-month follow-up, His-CRT resulted in QRS narrowing with a nonsignificant trend toward a higher rate of echocardiographic response (91% vs 54%,  $p=0.078$ ) compared with BiV-CRT; however, there were no significant differences in mortality or cardiovascular hospitalization between the groups.<sup>23</sup> As such, large multicenter RCTs are necessary to evaluate the clinical efficacy of His-bundle pacing and also comparing His-CRT and BiV-CRT. It is also open whether patients who qualify for CRT have a survival benefit from ICD. RESET-CRT (NCT03494933) is an ongoing RCT to compare clinical outcomes among patients with a CRT PM vs CRT defibrillator.

A recent European Heart Rhythm Association (EHRA) consensus document on management of arrhythmias and cardiac electronic devices in critically ill and postsurgery patients highlighted the risks and challenges among CIED patients with a terminal illness.<sup>24</sup> In an EHRA survey,<sup>25</sup> 73% of patients declared that CIED implantation improved their quality of life, whereas 36% had concerns about the device, mostly related to ICD shocks, daily activities, or impairment of the device. Indeed, the final decision about CIED implantation should take into account the patient's

age, frailty, cardiac condition, and other comorbidities, concomitant with personal values and preferences.

Therefore, it is often necessary to create novel algorithms for the selection of CRT responders, individualized risk scores for SCD, or procedure-related complications, which may result in a highly individualized approach and targeted CIED implantation. The future may bring patient-specific digital models to calculate the risk–benefit profile and create a simulation — virtual implantation. This might check whether the procedure is feasible and which device is favorable for each patient, but also guide a lead during the real procedure. In addition, CIEDs may be considered a cotreatment of other morbidities, such as hypertension. NCT03757377 is an ongoing RCT evaluating a new PM algorithm that may be useful for patients with indications for antibradycardia pacing and persistent hypertension despite pharmacotherapy.

## The Weakest Links

Transvenous leads represent a major source of CIED complications — not only dislocation or mechanical damage but also tricuspid regurgitation, venous occlusion, superior vena cava syndrome, cardiac perforation, cardiac device–related infective endocarditis (CDRIE) — and subcutaneous pockets: hematoma, decubitus, inflammation.<sup>6,7,26</sup> Palmisano et al<sup>27</sup> reported a higher risk of all-cause death among patients with CIEDs and early complications — pneumothorax (HR 8.731, 95% CI 1.42–53.63) and pocket hematoma (HR 2.515, 95% CI 1.07–5.94) — whereas CDRIE was most markedly related to increased risk of cardiovascular death (HR 4.025, 95% CI 1.5–10.78) during median follow-up of 56.9 months. An EHRA international consensus on how to prevent, diagnose, and treat CIED-infections<sup>28</sup> states that prevention and careful consideration before implantation are the best treatment for CDRIE. Indeed, leadless cardiac PMs (LCPs) and extravascular cardioverter-defibrillators have been designed to minimize complications. Also, an absorbable, antibiotic-eluting envelope has been created to use with CIEDs as a prophylactic strategy to prevent CDRIE.<sup>29</sup> These new technologies have already found a place in everyday clinical practice.

## Leadless Cardiac Pacemakers

An LCP is a small (volume 0.8 cm<sup>3</sup>) single-chamber PM that is implanted directly into the RV by a special catheter and introducer sheath via transfemoral access.<sup>30</sup> Therefore, it does not require the subcutaneous pocket or transvenous lead.<sup>31</sup> The first LCP was Nanostim (St Jude Medical), implanted worldwide between 2013 and 2016. The device

was recalled in 2016, due to battery failures, but the concept of LCPs has been widely accepted.<sup>32</sup>

At present, the only type of LCP available on the market is the Micra transcatheter pacing system. The pacing mode is similar to transvenous PMs, so an LCP may be used as an alternative device.<sup>30,33</sup> However, the system is limited to the RV component, meaning that an LCP may be indicated only for patients requiring single-chamber pacing, eg, permanent atrial fibrillation (AF) with bradycardia or for those with low expected stimulation percentage.<sup>30</sup> As such, patients with missing or difficult venous access, with a history of CDRIE, and indications for ventricular single-chamber pacing are considered good LCP candidates. Importantly, the potential benefits of LCPs must be confronted with the limited data on the long-term follow-up, and also the procedure of device replacement or retrieval is still debated.<sup>34</sup> According to a national expert consensus document of the Austrian Society of Cardiology, LCP retrieval should not be recommended as a routine procedure and should be limited only to specific issues, ie, endocarditis or system upgrades.<sup>34</sup> One worldwide experience of 40 successful device retrievals revealed that it may be feasible and safe if performed with a special sheath and a snare catheter and introduced via femoral access. The most common reasons for extraction included elevated pacing threshold, endovascular infection, and indications for a system upgrade to a transvenous device.<sup>35</sup> If it is necessary to replace the battery, a new LCP may be implanted next to old devices without extraction of previous ones; however, current clinical experience is very limited.<sup>34</sup>

The results of the Micra Transcatheter Pacing Study<sup>36</sup> showed the safety and efficacy (primary safety and efficacy end points were reached in 96% and 98.3%, respectively) of LCPs among 725 patients who had undergone device implantation. Likewise, the Micra Post-Approval Registry<sup>37</sup> reported a high rate of successful LCP implantations (99.1%) with a low risk of major complications (2.7%) among 1,817 patients. During follow-up of 12-months postprocedure, complication rates in LCP patients were significantly lower (HR 0.37, 95% CI 0.27–0.52) than a historical transvenous PM group. The most common complications in the LCP group were pacing issues (0.72%), groin injury (0.61%), cardiac effusion/perfusion (0.44%), and infection (0.17%).<sup>37</sup> In another study, El-Chami et al<sup>38</sup> reported on the safety and feasibility of

LCPs, also in patients after PM extraction and a recent CDRIE.

Piccini et al<sup>39</sup> compared clinical outcomes among 720 patients successfully implanted with LCPs, based on ventricular pacing indications: individuals with AF (68.3%) and those without AF (31.7%). Reasons for selecting LCPs in the non-AF group included an expectation of infrequent pacing (66.2%) and advanced age (27.2%). During 24 months of follow-up, there were no significant differences between the groups in occurrence of the composite primary outcome (cardiac failure, PM syndrome, or LCP-related syncope).<sup>39</sup> In another study, the safety and mortality of LCP implantation was assessed and stratified by whether patients were precluded from transvenous PMs.<sup>40</sup> It was found that 19.4% of patients were ineligible for traditional PMs because of venous access issues or prior CDRIE. Both acute and total mortality at 36 months (2.75% vs 1.32% [ $p=0.022$ ] and 38.1% vs 20.6% [ $p<0.001$ ], respectively) were significantly higher in the precluded patients than the non-precluded; however, the mortality rate among precluded patients was similar to historical transvenous PM group.<sup>40</sup>

Despite concerns regarding LCPs in frail elderly patients, because of implant-sheath size and risk of perforation, Micra implantation also appears to be safe and feasible among those individuals.<sup>41,42</sup> However, RCTs directly comparing the efficacy and safety of LCPs vs transvenous PMs are needed. In the EHRA prospective survey,<sup>43</sup> the overall use of LCPs in daily clinical practice remains low, constituting only 9% of all procedures and 36% of single-chamber PM implants. LCP recipients were more often male (74% vs 54%) and had a history of valvular heart disease (45% vs 35%), AF (65% vs 23%), and other comorbidities (66% vs 52%) than those with transvenous single-chamber PMs, but no significant association was observed with patients' age.<sup>43</sup> LCP implantation was successful in 98% of recipients, and the only procedure-related complication was groin hematoma.<sup>44</sup> Indeed, leadless devices are still in development, and there are also the prototypes of dual-chamber systems,<sup>45</sup> which may be used in a wider group of patients. As such, LCPs are a potential game changer for modern CIEDs.

MARVEL (NCT03157297)<sup>46</sup> was a recent study of a new LCP algorithm to synchronize ventricle pacing with atrial sensing (synchronous atrioventricular [AV] pacing). Consequently, MARVEL 2 (NCT03752151)<sup>47</sup> revealed that the new algorithm provided successful AV-synchrony pacing (mean 89.2%) among 75 LCP recipients

with sinus rhythm and AV block. Notably, the atrial sensing algorithms were safe, and there were neither pauses nor episodes of PM-mediated tachycardia.<sup>47</sup> The technology is currently used in a new Micra AV device (approved by the US Food and Drug Administration in January 2020), broadening potential indications to LCP implantation.<sup>48</sup> Further innovations, such as compatibility with extravascular ICDs, leadless CRT, renewable batteries, or less invasive implantation procedures, are highly anticipated.

## Wireless Cardiac Resynchronization Therapy

The SELECT-LV study<sup>49</sup> investigated the clinical efficacy and safety of wireless stimulation endocardially for CRT (WiSE-CRT) pacing via an LV endocardial electrode and a pulse generator (implanted subcutaneously). The trial was conducted among 35 patients with HF and indications for biventricular pacing who were nonresponders to traditional CRT or implantation of a coronary sinus lead was not possible. The feasibility and efficacy of WiSE-CRT were reported. Rates of successful implantation and effective CRT pacing were high (97.1%), with a substantial improvement (84.8%) in the clinical composite score at 6 months; however, the rate of early serious complications was 31.5% at 1-month postprocedure follow-up (8.6% within 24 hours and 22.9% between 24 hours and 1 month).<sup>49</sup> According to recent data from a Multicenter International Registry of the WiSE-CRT pacing system,<sup>50</sup> implantation of the device was feasible in 94.4% of patients and 70% of those reported improvement in of HF symptoms. Complication rates differed among the centers: 4.4%, 18.8%, and 6.7% within <24 hours, 1–30 days, and 1–6 months, respectively.<sup>50</sup> Likewise, the SOLVE-CRT trial<sup>51</sup> is an ongoing RCT assessing the safety and effectiveness of the WiSE-CRT in nonresponders to traditional CRT.

## Extravascular Cardioverter–Defibrillators

### Wearable Cardioverter–Defibrillators

European Society of Cardiology (ESC) guidelines for the management of patients with ventricular arrhythmias and prevention of SCD<sup>5</sup> state that a wearable cardioverter-defibrillator (WCD) attached to a vest may be considered a bridge in patients with transient impaired LVEF, post-myocardial infarction (<40 days), postpartum cardiomyopathy, myocarditis (until recovery), or for those awaiting heart transplantation. VEST<sup>52</sup> was an RCT of 2,302 subjects with

acute myocardial infarction and LVEF  $\leq 35\%$  designed to compare a WCD group vs a no-device group, with both groups receiving optimal pharmacotherapy. The study found that the WCD did not have a significant impact on the composite primary end point (SCD and death from sustained VT) during 90 days postinfarct.<sup>52</sup> Adherence to wearing the defibrillator was an important issue that conditioned the results of the VEST study, as highlighted by the on-treatment and per-protocol analyses that found a benefit of the wearable defibrillator in the group of patients selected for high compliance to apply the device.<sup>53</sup> Data from the WEARIT-II Registry<sup>54</sup> showed a high rate of VT — 3% among patients with ischemic and congenital heart disease and 1% among nonischemic patients — during 3 months of WCD use. In total, there were 120 VT episodes recorded in 41 patients, and 54% of those received appropriate WCD therapy. In sum, 840 patients (42%) were implanted with an ICD, and LVEF improvement was the most common reason for ICD removal.<sup>54</sup> The EHRA survey<sup>55</sup> reported that WCDs were used as a temporary solution, mostly for patients after CDRIE and awaiting ICD reimplantation or with transient LVEF impairment, after recent myocarditis/myocardial infarction, or before heart transplantation. Notably, the most common contraindications for WCD use were life expectancy <12 months and noncompliance.<sup>55</sup>

## Subcutaneous Cardioverter–Defibrillator

Subcutaneous cardioverter-defibrillators (sICDs) are implantable devices comprising a subcutaneous pulse generator and subcutaneous lead to deliver a shock as VT therapy. According to the current ESC guidelines, sICDs may be an alternative for patients who require an ICD but do not have an indication for ventricular pacing, CRT, or antitachycardia pacing.<sup>5</sup> The American Heart Association guidelines<sup>4</sup> recommend sICDs for patients without proper venous access or at high risk of CDRIE. Boersma et al<sup>56</sup> reported low periprocedural complication rates, with 99.6% successfully implanted devices and high defibrillation efficacy (99.2% during defibrillation testing) among 1,116 patients who had undergone sICD implantation as primary prevention of SCD. In another study, Boersma et al<sup>57</sup> indicated a low risk of infection in sICD recipients, even in individuals with a history of CDRIE and explanted transvenous ICDs.

Results from an EHRA prospective survey on sICD use showed that sICDs were favorable among younger patients and those with lead-related complications or elevated risk/history of CDRIE, taking into consideration patient

preferences and active lifestyle. Of note, need for ventricular antitachycardia pacing, CRT, or permanent pacing were benefiting, the transvenous ICD.<sup>58</sup> Implantation time and periprocedural complication rates were similar in both subgroups.<sup>59</sup> Since 2010, when sICD became available for patients, this technology has been evolving.<sup>60</sup> Various ongoing clinical trials have been designed to assess new extravascular systems, eg, EV ICD (NCT04060680) and ASE (NCT03802110), for testing new shock configurations.

## Substernal Leads

ASD2<sup>61</sup> was the first human study to evaluate a novel approach to ICD therapy — substernal leads. Pacing threshold, sensing, and defibrillation efficacy were assessed among 79 patients who had undergone lead implantation. The lead was placed into the substernal space via subxiphoid access, and a defibrillation-patch electrode or active can emulator (subcutaneous) was set in the left mid-axillary line. It was found that R-wave amplitudes were compliant with ICD sensing (median R-wave 2.4 mV), successful ventricular pacing rates were 97.4%, and defibrillation efficacy was >80% with a single shock of 30 J. The lower shock energy (compared with the sICD's 80 J) may be beneficial for battery longevity.<sup>61</sup> Indeed, substernal lead therapy may be feasible, and results are promising. Nevertheless, neither long-term follow-up data nor risk of infection and lead extraction are available. Indeed, substernal lead therapy may be feasible, and results are promising. Nevertheless, neither long-term follow-up data nor risk of infection and lead extraction are available (Table 1).

## Remote Monitoring of Patients with Cardiac Electronic Implantable Devices

Patients with CIEDs usually have routine in-person appointments to verify whether the device is functioning adequately

and for assessment of clinical findings every 6–12 months.<sup>62</sup> In addition, unscheduled clinic visits may be necessary in cases of system malfunction or worsening of health status.<sup>62</sup> However, the conventional monitoring of CIEDs, resulting in limited contact with patients, is insufficient and outdated. Digital health-care models and remote control of devices are the future of modern medicine and cardiology. They involve patients taking an active role in their own clinical care, and such a personalized approach, including shared decision-making, is crucial (Table 2).<sup>63</sup>

Teletransmission systems transfer data recorded from the patient's device to a database, where the data are available to the health-care team. New systems transmit the data via the patient's smartphone or tablet. As such, telemonitoring allows assessment of the relevant technical parameters of the device, ie, battery status, electrode function, and system compatibility, on an ongoing basis. It also provides key clinical information, such as stimulation percentage, stored arrhythmic episodes, or current intracardiac electrograms.<sup>8,62</sup> The daily telemetric care of a large population of such CIED patients may be considered triage of high-risk patients, with ongoing selection of individuals who require urgent medical intervention.<sup>64</sup>

According to expert consensus, remote monitoring should be available for all patients with CIEDs as part of the standard follow-up strategy, but in particular for patients with HF and cardiac arrhythmias.<sup>8,62</sup> There is urgent need for integrated medical care for patients with HF. Telemetric data may help to recognize current clinical status and device alarm. Of note, telemetric care is crucial to diagnose and monitor episodes of arrhythmia, especially life-threatening episodes of VT and ICD-delivered shocks (appropriate or inappropriate). As a result, the health-care team may efficiently modify pharmacotherapy or plan any further treatment strategy (Table 3). Importantly, the effectiveness of the therapy may be assessed on an ongoing basis.<sup>64</sup> A survey from the Health Economics

**Table 1** Comparison of Implantable Cardioverter Defibrillators

	Transvenous ICD	Subcutaneous ICD	Substernal Lead
Intracardiac lead	+	–	–
Ventricular pacing	+	–	+
Antitachycardia pacing	+	–	+
Defibrillation efficacy	+	+	+
Shock energy	40 J	80 J	40 J
Implantation procedure	Feasible	Feasible	Feasible
Periprocedural complication rates	4%	4%	Unknown
Risk of infection	8.9/1,000 device-years	Low	Unknown

**Note:** Data from references 56, 57, 59, 61, and 113.

**Abbreviation:** ICD, implantable cardioverter defibrillator.

**Table 2** Expected Advantages of Remote Monitoring of Cardiac Electronic Implantable Devices

<ul style="list-style-type: none"> <li>• Selection of patients who require urgent medical intervention</li> <li>• Key information about the function of the device</li> <li>• Reduction of in-person visits</li> <li>• Patient has an active role in therapeutic process</li> <li>• Economic issues: decreased use of health-care resources and cost savings</li> <li>• Essential part of the integrated medical care of patients with heart failure and arrhythmias</li> <li>• Safe, easy, and feasible method</li> </ul>
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**Table 3** Remote Monitoring of Patients with Cardiac Resynchronization Therapy

Most Common "Unscheduled" Alerts	Most Common Medical Interventions	Medical Interventions
CRT pacing <95% (63%)	Any medical intervention (63.9%)	None — 36.1%
VT/VF episodes (24.9%)	Device reprogramming (46.8%)	One — 38.4%
AF de novo (15.7%)	Qualification for any ablation (12.6%)	≥Two or more — 25.5%

**Notes:** Data from Liberskaet al.<sup>64</sup>

**Abbreviations:** CRT, cardiac resynchronization therapy; VT, ventricular tachycardia; VF, ventricular fibrillation; AF, atrial fibrillation.

**Table 4** Atrial High-rhythm Episodes: Common Causes of Atrial Fibrillation Misdetections,

<ul style="list-style-type: none"> <li>• Atrial undersensing</li> <li>• Ventricular far-field oversensing</li> <li>• Atrial noise: external interference/lead dislocation/lead fracture</li> <li>• Ineffective atrial pacing</li> </ul>
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**Notes:** Data from Jędrzejczyk-Patej et al<sup>67</sup> and Gorenek et al.<sup>68</sup>

Committee of the EHRA<sup>25</sup> showed that early recognition of AF among PM patients, lead failure in ICD patients, and HF worsening in CRT patients were considered essential advantages of remote monitoring.

The opportunity comes from dual-chamber devices that can also monitor atrial rhythm, allowing the possibility of recognizing arrhythmias and AF. These recorded events are called atrial high-rate episodes (AHREs), more often of short duration, lasting a few seconds to minutes.<sup>65,66</sup> The key issue is to diagnose real episodes of AF or atrial flutter, and thus it is necessary to evaluate stored current intracardiac electrograms and exclude false episodes (Table 4).<sup>65–68</sup>

Among 2,718 individuals with HF and CIEDs, AHREs were found in 34.8%, whereas AF was confirmed in 91% by atrial electrograms.<sup>69</sup> In an observational study of 304 patients with HF and CRT with a defibrillator, AHREs were found in 57.9% of patients within 2.5 years postimplantation.<sup>67</sup> After inspection, 89.2% of AHREs were truly AF and 62% of these were AF de novo.<sup>67</sup>

A significant benefit of telemonitoring may be obtained by patients with previously undetected “silent” AF. An active search for real arrhythmia and related risk factors is a significant part of individualized approaches among patients with CIEDs. Miyazawa et al<sup>70</sup> revealed that age ≥65 years, diabetes mellitus, congestive HF, and left atrial volume index >34 mL/m<sup>2</sup> were independent factors of AF de novo in patients with CIEDs. Indeed, detecting asymptomatic AF with an adequate therapeutic response may prevent potential complications, eg, stroke/thromboembolic events and AF-related morbidity. However, there remains a gap in the data regarding the management of patients with AHREs without a proper AF diagnosis.

How much AHRE is too much? This is the big question that derives from lack of knowledge on what the number of AHREs is and their minimum duration, which actually increases significantly the thromboembolism risk.<sup>68,71–73</sup> One study among patients with dual-chamber CIEDs showed an increased risk of thromboembolism (HR 3.40, 95% CI 1.38–8.37) and all-cause death (HR 3.47, 95% CI 1.51–7.95) among patients with AHRE.<sup>74</sup> Of note, the West Birmingham Atrial Fibrillation Project reported that among CIED patients, a higher risk of thromboembolic events was related to comorbidities (ie, CHA<sub>2</sub>DS<sub>2</sub>VASc score), but not AHRE per se.<sup>75</sup> Indeed, Pastori et al<sup>76</sup> reported that AHREs ≥5 minutes (HR 1.788, 95% CI 1.247–2.562), diabetes mellitus (HR 1.909, 95% CI 1.358–2.683), HF (HR 2.203, 95% CI 1.527–3.178), and coronary artery disease (HR 1.862, 95% CI 1.293–2.681) were significantly related to the risk of major adverse cardiovascular events in patients with CIEDs. Furthermore, Boriani et al<sup>77</sup> found that among patients with AF duration ≥5 minutes and CIEDs, female sex (HR 3.43, 95% CI 1.05–11.18) and history of coronary artery bypass surgery (HR 4.34, 95% CI 1.44–13.13), but not higher burden of AF, were independent predictors of stroke.<sup>77</sup>

New-onset AF is detected earlier in patients with remote monitoring than standard clinical care.<sup>78–80</sup> Also, treatment of arrhythmia is initiated significantly earlier (3 vs 54 days), but does not improve clinical outcomes of HF patients in term of stroke and bleeding prevention, based on introduction or termination of oral anticoagulation (OAC).<sup>69</sup> Perino

et al<sup>81</sup> conducted a study of 2,101 patients with CIEDs on remote monitoring and AF duration >6 minutes (detected by device). Among these patients, OAC users had a significantly lower risk of stroke than a no-anticoagulation group (HR 0.68, 95% CI 0.47–0.97). Of note, a reduction in strokes with anticoagulation was reported in patients with AF duration >24 hours (HR 0.27, 95% CI 0.14–0.51).<sup>81</sup>

There is a beneficial effect of OAC in stroke prevention in CIED patients with documented AF, while evidence of benefit is missing for AHRE (without formal AF diagnosis).<sup>65,68,71,72,82,83</sup> An ongoing RCT, NOAH-AFNET 6 (NCT02618577),<sup>84</sup> is comparing edoxaban vs aspirin or no treatment among patients with AHRE (without AF) and two or more stroke risk factors. The primary outcome is time to first ischemic event or cardiovascular-related death.<sup>84</sup> The ARTESiA (NCT01938248)<sup>85</sup> trial is comparing apixaban vs aspirin in terms of stroke and systemic embolism in this group of patients.

The CASTLE-AF<sup>86</sup> trial was designed to compare the clinical outcomes of AF patients with HF and implanted ICDs. Subjects were randomized to catheter ablation or guideline-adherent medical therapy. The major exclusion criteria were heart-transplant candidacy or planned cardiovascular intervention. Patients who underwent catheter ablation had significantly lower risk of any-cause death (13.4% vs 25.0%, HR 0.53, 95% CI 0.32–0.86), cardiovascular-related death (11.2% vs 22.3%, HR 0.49, 95% CI 0.29–0.84), and hospitalization due to worsening of HF (20.7% vs 35.9%; HR 0.56, 95% CI 0.37–0.83), than the medical therapy group.<sup>86</sup>

Noseworthy et al<sup>87</sup> assessed the generalizability of the CASTLE-AF trial among patients with AF and HF treated with ablation (n=7,465) or standard medical therapy (n=282,366). They found that only 7.8% of patients would have been eligible for CASTLE-AF. Catheter ablation was related to a lower risk of the primary outcome among all patients (HR 0.81, 95% CI 0.76–0.87) vs standard medical therapy, specifically in the CASTLE-AF-eligible subgroup (HR 0.82, 95% CI 0.70–0.96), but not in patients who met the exclusion criteria.<sup>87</sup> Likewise, the CABANA<sup>88</sup> trial revealed that among AF patients, catheter ablation did not significantly lower the primary composite end point of death, disabling stroke, major bleeding, or cardiac arrest compared with a medical therapy group. In an observational real-world patient study,<sup>89</sup> assessing catheter ablation was related to a reduction in the composite end point vs medical therapy (HR 0.75, 95% CI 0.70–0.81). The risk reduction associated with ablation was higher among CABANA-eligible patients (HR 0.70, 95% CI 0.63–0.77).<sup>89</sup>

The possibility of remote monitoring may facilitate comprehensive care management for patients with CIEDs.<sup>90</sup> However, RCT-based data are heterogeneous in terms of telemonitoring effectiveness, ie, improvement of outcomes for HF patients with CIEDs (Table 5).<sup>91–95</sup> The benefits of monitoring may be dependent on the health-care team's reaction to the transmitted data. Therefore, remote monitoring should not be considered a treatment per se, but may allow for a more appropriate medical response to device alerts.<sup>95,96</sup> Consequently, further developments should be focused on improving the technical issues and efficiency of telemonitoring, eg, artificial intelligence to for triage of high-risk patients or integration of the data with electronic medical records or extra features to monitor potential comorbidities. Another challenge is the accessibility, feasibility, and adherence to therapeutic protocols by both groups — physicians and patients. Further studies are needed to identify novel functions with a positive impact on clinical outcomes.<sup>97</sup>

## Novel Approaches Incorporating Cardiac Rhythm–Monitoring Technology

### Implantable Loop Recorder

The ILR is a type of long-term cardiac rhythm–monitoring device that is inserted underneath the chest skin. It is a safe and effective tool in the diagnosis of unexplained syncope, arrhythmias, or cryptogenic stroke, and is indicated for patients with recurring symptoms but too infrequent to be diagnosed with conventional ECG monitoring techniques.<sup>98,99</sup> In patients with recurrent symptomatic palpitations, the ILR may be a useful diagnostic approach for evaluation.<sup>100</sup> Of note, recent studies of ILRs have shown their feasibility to detect and record asymptomatic AF. One RCT (CRYSTAL-AF)<sup>101</sup> was conducted to compare ECG monitoring with an ILR vs conventional follow-up among 441 patients after cryptogenic stroke. The primary end point was time to first AF detection within 6 months. ILRs were superior to standard monitoring in detecting AF: AF was detected in 8.9% of patients in the ILR group vs 1.4% of patients in the control group (HR 6.4, 95% CI 1.9–21.7) during 6 months of follow-up.<sup>101</sup> The LOOP (NCT02036450) study was designed to determine whether initiation of OAC if AF were detected with ILRs would reduce the risk of stroke among 597 patients aged ≥70 years with stroke risk factors. First insights from the LOOP study revealed



**Table 5** Studies of Remote Monitoring of Cardiac Electronic Implantable Devices

	Type	Design	Follow-Up	Results	Findings
Hindricks et al <sup>91</sup>	RCT	n=716 patients with HF and ICD/CRT Telemonitoring group (n=333) vs control group (n=331)	12 months	Worsened composite clinical score: 18.9% vs 27.2%, OR 0.63 (95% CI 0.43–0.90) Death: 3.0% vs 8.2%	Telemonitoring improves clinical outcomes for HF patients
Sardu et al <sup>92</sup>	RCT	n=191 patients with HF and CRT Telemonitoring group (n=89) vs control group (n=94)	12 months	HF hospitalization: 15.7% vs 28.7% HR 0.6 (95% CI 0.42–0.79)	Telemonitoring may predict HF hospitalization
Morgan et al <sup>94</sup>	RCT	n=1,650 patients with HF and ICD/CRT Telemonitoring group (n= 824) vs control group (n=826)	24–42 months	Primary end point (first death from any cause or unplanned hospitalization for cardiovascular reasons): 42.4 vs 40.8%, HR 1.01 (95% CI 0.87–1.18)	Telemonitoring does not improve outcomes for HF patients
Boriani et al <sup>93</sup>	RCT	n= 865 patients with HF and CRT Telemonitoring group (n= 437) vs control group (n=428)	24 months	Primary end point (composite of death and cardiovascular and device-related hospitalization): 29.7% vs 28.7%, HR 1.02 (95% CI 0.80–1.30) 41% reduction in in-person visits in telemonitoring group	Telemonitoring does not improve outcomes for HF patients Better use of health-care resources and cost savings
Tajstra et al <sup>95</sup>	RCT	n=600 patients with HF and ICD/CRT Telemonitoring group (n=299) vs control group (n=301)	12 months	Primary end point (composite of all-cause death and cardiovascular-related hospitalization): 39.5% vs 48.5% OR 1.24 (95% CI 1.0–1.5)	Telemonitoring improves clinical outcomes for HF patients

**Abbreviations:** RCT, randomized controlled trial; HF, heart failure; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy.

that during 40 months of follow-up, AF was detected in 209 (35%) patients.<sup>102</sup> In addition, AF was silent in 90% of patients at debut, and 87% never noticed AF-related symptoms. The average heart rate during AF was only moderately elevated to 96 beats/minute, whereas average daytime sinus rate was 72 beats/minute.<sup>103</sup>

## Wearable Technology

Wearable technologies provide the possibility of continuous rhythm monitoring and display a real-time heart rate, as well as a review of heart-rate trends.<sup>104</sup> For example, Dörr et al<sup>105</sup> conducted a study using smartwatches among 508 patients of mean age 76.4 years, 46.6% of whom had previously diagnosed AF. High sensitivity, specificity, and accuracy (93.7%, 98.2%, and 96.1%, respectively) in detecting AF was observed. The authors speculated that AF detection may be feasible with high diagnostic precision using commercial

smartwatches. Likewise, attaining proper signal quality during algorithm use was highlighted as the main limitation.<sup>105</sup>

The possibility of cardiac rhythm monitoring via smartwatches was assessed in two large population-based cohort studies in the US and China. The Apple Heart Study<sup>106,107</sup> involved 419,297 participants aged  $\geq 22$  years without a history of AF. The idea of the study was to find out if a mobile application could recognize irregular heart rate and AF from data collected on the Apple Watch. During follow-up, an irregular pulse was detected in 0.52% of participants. Consequently, they were monitored by ECG patch for 7 days for arrhythmia, and AF was diagnosed in 34%. Notably, AF was observed more often among participants aged  $\geq 65$  years (3.2% vs 0.16% in participants aged  $< 40$  years) and men (0.7% vs 0.26% in women). Likewise, 76% of notified participants contacted their health-care provider, 33%

were referred to a specialist, and 36% required further investigations.

The Huawei Heart Study<sup>108</sup> conducted in China on 187,912 participants of mean age 35 years found that 424 (0.23%) individuals were notified of suspected AF, and AF was finally confirmed by clinical evaluation in 87% of those. Researchers highlighted that AF suspicion and identification significantly increased with age. Of note, the majority of patients entered a program of integrated AF management, and approximately 80% of high-risk patients were successfully anticoagulated.<sup>108</sup> Subsequent to the Huawei Heart Study, mAFA II<sup>109</sup> was a cluster RCT to assess the impact of integrated care using a mobile AF application (mAFA) compared with usual care on clinical outcomes among 3,324 AF patients with two or more stroke risk factors.<sup>109</sup> The trial demonstrated that rates of composite outcome (ischemic stroke/systemic thromboembolism, death, and rehospitalization) and rehospitalization were lower among mAFA patients vs the usual-care control group (1.9% vs 6.0%, HR 0.39, 95% CI 0.22–0.67 and 1.2% vs 4.5%, HR 0.32, 95% CI 0.17–0.60, respectively).<sup>109</sup> In an ancillary analysis of mAFAII, proactive assessment of bleeding risks using the HAS-BLED score resulted in mitigation of modifiable bleeding risk factors, fewer bleeding events and an increase in OAC uptake compared to usual care.<sup>110</sup> Another approach was illustrated with the NOMED-AF (NCT03243474) study,<sup>111</sup> which assessed the prevalence of AF and concomitant comorbidities in a population aged  $\geq 65$  years. Long-term ECG monitoring was enabled by special vests equipped with electrodes and recorder. Data were transmitted to the monitoring platform every 24 hours. The study identified high-risk populations, requiring more intense AF screening.<sup>111</sup>

The data available show that wearable technology using photoplethysmographic sensors, which detect blood volume changes, may recognize irregular heart rhythm, including previously unknown AF (Table 6).<sup>106–108</sup> As such, smartwatches may be convenient tools for long-term AF screening in large populations, especially in high-risk patients. Early AF detection may reduce the burden of stroke and other AF-related complications. Future studies may demonstrate the utility of wearable technology in AF integrated care and optimize a holistic approach within individuals with AF. Likewise, the advance of artificial intelligence may support treatment and assist in diagnosis, management, and prediction of occurrence of arrhythmia or other heart diseases.<sup>112</sup>

**Table 6** Wearable Technologies – an Insight from Observational Studies

	Apple Heart Study <sup>106,107</sup>	Huawei Heart Study <sup>108</sup>
Type	Prospective cohort	Prospective cohort
Patients	n=419,297	n=187,912
Design	Individuals without AF monitored for irregular rhythm Possible AF, confirmed on ECG	Individuals monitored for pulse rhythm Possible AF, confirmed by clinical evaluation
Technology	Apple Watch	Wristband (Honor Band 4) or wristwatch (Huawei Watch GT, Honor Watch)
Follow-up	8 months	7 months
Results	2,161 participants (0.52%) received notifications of irregular pulse 34% of those were truly AF PPV: 84 (95% CI 76–92)	424 participants (0.23%) received a “suspected AF” notification 87% of those were truly AF PPV: 91.6 (95% CI 91.5–91.8)

**Notes:** Data from Turakhia et al [2019]<sup>106</sup>, Perez et al [2019]<sup>107</sup>, Guo et al [2020].<sup>108</sup>

**Abbreviations:** ECG, electrocardiography; AF, atrial fibrillation; PPV, positive predictive value.

## Conclusion

The future of cardiac rhythm-management devices looks bright, but incorporation and adoption of new technologies remains a challenge. There is an immense need for an individualized approach with targeted CIED implantation and personalized risk stratifications. Further studies are needed to identify novel strategies and technologies with a positive impact on patient diagnosis and treatment. Novel solutions may see a move away from transvenous leads to leadless systems, with combinations of different individualized pacing and monitoring functions. Relevant developments and innovations of devices, implantation processes, and postprocedure follow-up may improve clinical outcomes among patients.

## Disclosure

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