


GUIDELINES

JCS/JHRS 2021 guideline focused update on non-pharmacotherapy of cardiac arrhythmias

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Abbreviations: A-ATP, atrial anti-tachycardia pacing; ACC, American College of Cardiology; ACP, advance care planning; ACT, activated clotting time; AF, atrial fibrillation; AHA, American Heart Association; AHRE, atrial high-rate episodes; AVNRT, atrioventricular nodal reentrant tachycardia; BARC, Bleeding Academic Research Consortium; CBA, cryoballoon ablation; CIED, cardiac implantable electronic device; COR, class of recommendation; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; CT, computed tomography; DAP, dose-area product; DAPT, dual antiplatelet therapy; DNAR, Do Not Attempt Resuscitation; DOAC, direct oral anticoagulant; EBM, evidence-based medicine; ESC, European Society of Cardiology; FDA, Food and Drug Administration; GOR, grade of recommendation; HF, heart failure; HFREF, heart failure with reduced ejection fraction; HPSD, high-power short-duration; HRS, Heart Rhythm Society; ICD, implantable cardioverter-defibrillator; JCS, Japanese Circulation Society; JHRS, Japanese Heart Rhythm Society; LOE, level of evidence; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MVP, minimal ventricular pacing; NASPE, North American Society of Pacing and Electrophysiology; NYHA, New York Heart Association; QOL, quality of life; RCT, randomized controlled trial; RFCA, radio-frequency catheter ablation; SCAF, subclinical atrial fibrillation; vHPSD, very high-power short-duration.

Abbreviations of Research Names: AATAC, Ablation vs Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD/CRTD; ABRIDGE-J, Ablation Perioperative Dabigatran in Use Envisioning in Japan; ARISTESiA, Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-Detected Sub-Clinical Atrial Fibrillation; ASSERT, Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial; ASAP, ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology; ATTEST, Atrial Therapy Efficacy and Safety Trial; AXAFA AFNET 5, Anticoagulation Using the Direct Factor Xa Inhibitor Apixaban during Atrial Fibrillation Catheter Ablation: Comparison to VKA Therapy; CABANA, Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients with Atrial Fibrillation; CASTLE-AF, Catheter Ablation for Atrial Fibrillation with Heart Failure; CIRCA-DOSE Study, Cryoballoon vs. Contact-Force Atrial Fibrillation Ablation; EARLY-AF, Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation; EAST-AFNET 4, Early Rhythm-Control Therapy in Patients with Atrial Fibrillation; ELIMINATE-AF, Uninterrupted Edoxaban vs. Vitamin K Antagonists for Ablation of Atrial Fibrillation; EWOLUTION, Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology; FIRE and ICE, Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation; IDE, Investigational Device Exemption; MADIT-II, Multicenter Automatic Defibrillator Implantation Trial II; MARVEL, Micra Atrial Tracking Using a Ventricular Accelerometer; MASS, Micra Accelerometer Sensor Sub-Study; MINERVA, Minimize Right Ventricular Pacing to Prevent Atrial Fibrillation and Heart Failure; MOST, Mode Selection Trial; NOAH-AFNET 6, Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High-Rate Episodes; PANORAMA, Phase IV Long Term Observational Study of Patients Implanted with Medtronic CRDM Implantable Cardiac Devices; PRAGUE-17, Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation; PREVAIL, Prospective Randomized Evaluation of the Watchman Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation versus Long-term Warfarin Therapy; PROTECT-AF, Percutaneous Closure of the Left Atrial Appendage versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation; RATE, Registry of Atrial Tachycardia and Atrial Fibrillation Episodes; RE-CIRCUIT, Randomized Evaluation of Dabigatran Etxelate Compared to Warfarin in Pulmonary Vein Ablation: Assessment of an Uninterrupted Periprocedural Anticoagulation Strategy; SALUTE, A Study to Evaluate the Safety and Effectiveness of the Left Atrial Appendage Closure Therapy Using WATCHMAN for Patients with NVAf at Increased Risk of Thromboembolism in Japanese Medical Environment; SAVE PACE, Search AV Extension and Managed Ventricular Pacing for Promoting Atrio-Ventricular Conduction; SOS AF, Stroke Prevention Strategies Based on Atrial Fibrillation Information from Implanted Devices; STOP AF First, Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation; STOP PERSISTENT AF, Stop Persistent AF; TACTIC-AF, Tailored anticoagulation for non-continuous atrial fibrillation; TRENDS, A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics; VENTURE-AF, Study Exploring Two Treatment Strategies in Patients with Atrial Fibrillation who Undergo Catheter Ablation Therapy; WASP, Watchman Occlusion in Long-standing Persistent Atrial Fibrillation.

This document is an English version of JCS/JHRS 2021 Guideline Focused Update on Non-Pharmacotherapy of Cardiac Arrhythmias reported at the Japanese Circulation Society/the Japanese Heart Rhythm Society Joint Working Group published in 2021 (https://www.j-circ.or.jp/cms/wp-content/uploads/2021/03/JCS2021_Kurita_Nogami.pdf).

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Refer to Appendix 1 for the details of members.

Joint Working Groups: the Japanese Circulation Society, Japanese Heart Rhythm Society, Japanese Association for Thoracic Surgery, Japanese Society of Pediatric Cardiology and

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I | INTRODUCTION

In 2019, the Guidelines for non-pharmacotherapy of cardiac arrhythmias (JCS/JHRS 2019) were published, covering areas such as treatment using cardiac electrical implantable devices (CIEDs), catheter ablation, surgical treatments, and therapies using left atrial appendage occlusion devices.¹ According to the recent dramatic development of non-pharmacotherapy in the field of cardiac arrhythmias, major revisions had been made to the JCS/JHRS 2019 guidelines, owing to critical evaluation by many clinicians. Following the publication of the guidelines, however, more, important clinical evidence had been established in both Japan and abroad, and new concepts of treatment have been created. As updating and disseminating new information directly affects daily clinical practice, we decided to publish “The focused updated guidelines on non-pharmacotherapy of cardiac arrhythmias (JCS/JHRS 2021)” focusing on fields with significant progression, instead of waiting for the next revision of the entire guidelines.

Our standards for selecting the issues in the focused update guidelines were as follows: (1) therapy with a previously undetermined recommendation level that has become specified because of new evidence from both Japan and abroad, (2) newly established therapeutic concepts, and (3) important issues in which omission

in the previous guidelines was inevitable because of word limits. Accordingly, the main features of these focused updated guidelines are as follows.

1.1 | Leadless pacemakers

Although a large international clinical trial to test the utility of leadless pacemakers had been published when the previous guidelines were announced, we did not address the recommendation because it had been suggested that the incidence of complications owing to the small body size of Japanese patients might be higher than in Western patients. However, a subanalysis of a large clinical trial based on Japanese data,² and our subsequent clinical experience, allowed us to describe the recommendation level.

1.2 | Conduction system pacing

The novel anti-heart failure pacing therapy (ie, conduction system pacing [His bundle pacing]) has appeared as a novel but different concept to cardiac resynchronization therapy (CRT). When the previous guidelines were announced, there were no guidelines or expert consensus that clarified the recommended therapeutic level; however, the new ACC/AHA/HRS guidelines in 2019 stated a recommended level,³ and the initial concept of His bundle pacing was extended to conduction system pacing including both His bundle and left bundle pacing. Therefore, based on the present consideration, we describe recommended levels of conduction system pacing.

1.3 | Management of implantable cardioverter defibrillators (ICDs) in end-of-life care

The recently established concept of advance care planning (ACP) has facilitated the process of discussing and making decisions with healthcare patients for their preferred goals of care if they lose their communication ability in the future. When facing the end of life, ICD therapy (especially shock therapy) is not always desired by patients or their families; therefore, the decision to deactivate the ICD therapy can be acceptable. With the overlap in the timing of publishing JCS/JHRS 2021 Statement on Palliative Care in Cardiovascular Diseases,⁴ we decided to describe the class recommendations based on the evidence level and decision-making process in this focused update. In association with ACP, we also mention the indications for ICDs in elderly patients.

1.4 | Transvenous lead extraction

The description of several important aspects of transcutaneous lead extraction (ie, bacteremia without lead infection, superficial infection around the subcutaneous pocket, antibiotic therapy, and CIED re-implantations after lead extraction) were excluded in the previous guidelines but are addressed in the focused update.

1.5 | Antitachycardia pacing (ATP) therapy for atrial tachyarrhythmias

Although large, international clinical trials demonstrating the efficacy of ATP (capabilities to terminate atrial fibrillation [AF] and prevent the aggravation of AF into a persistent type) had been published in other countries when the previous guidelines were announced, we did not address this therapy because of the absence of clinical evidence from Japan and because of word limits. Taking the novel Japanese evidence of ATP for AF with CIEDs⁵ into account, however, we decided to include ATP in the focused update.

1.6 | Management of AF detected by CIEDs

The JCS/JHRS 2020 guidelines on pharmacotherapy of cardiac arrhythmias addressed the clinical significance of asymptomatic (silent) AF and advanced methods of documenting AF.⁶ In response to the guidelines, we prescribe appropriate management of AF detected by CIED monitoring (focusing on anticoagulant therapy especially) in the focused update.

1.7 | Challenges in reducing radiation exposure

The development of 3D mapping systems has largely contributed to identifying the precise position of catheters in the cardiac chambers without fluoroscopic guidance, thereby reducing the exposure to radiation during catheter ablation procedures. Problems due to radiation injury had been mentioned in previous guidelines; however, to promote awareness and knowledge of reducing the radiation exposure of clinicians, we focused on the use of advanced 3D mapping systems to reduce exposure dose. Besides intraoperative radiation exposure, we described unignorable radiation exposure by preprocedural computed tomography (CT) imaging.

1.8 | Novel evidence and advanced technologies for catheter ablation of AF

According to the CABANA study,⁷ a new large randomized clinical trial that tested the prognostic efficacy of catheter ablation in patients with AF, we reconsidered the class recommendations for catheter ablation of asymptomatic AF. Further, we were able to establish the class recommendations for catheter ablation in AF patients with heart failure

based on even higher levels of evidence (ie, a large randomized clinical trial and meta-analysis including several important clinical studies⁸). Furthermore, the efficacy of early rhythm-control therapy for AF, either with antiarrhythmic drugs or catheter ablation (pulmonary vein isolation using the cryoballoon technique), has been reported by several large randomized clinical trials.⁹⁻¹¹ Taking these results into account, we describe the significance of early rhythm-control to prevent deterioration of AF. As for the new technologies of catheter ablation, high-power radiofrequency delivery with a short duration and the expanded use of the cryoballoon technique for persistent AF are addressed.

1.9 | Perioperative anticoagulation therapy for AF ablation

The management of anticoagulation therapy during the peri-catheter ablation period has been rewritten because various important clinical evidence has been documented in both Japan and abroad,¹²⁻¹⁸ and because a supplemental description was needed according to the contents of the Guidelines on non-pharmacotherapy of cardiac arrhythmias (JCS/JHRS 2019).⁶

1.10 | Left atrial appendage closure device

Because percutaneous transcatheter therapies for left atrial appendage occlusion were not reimbursed in Japan when the previous guideline was announced, detailed description of this technology was postponed. However, sufficient clinical experience has since accumulated in both Japan and abroad, to understand the appropriate indications, safety, postoperative management, and long-term efficacy of this therapy.¹⁹ Therefore, we describe the class recommendations for this novel technology in the present focused update.

This set of guidelines recommends indications for non-pharmacotherapy of arrhythmia based on the latest findings and evidence. We first surveyed materials based on evidence from the USA and Europe, then further critically examined the levels of evidence, collected information available in Japan, and examined all material based on the experiences and opinions of members and collaborators in the Joint Working Group. This revision adds new knowledge acquired from advances in diagnostic techniques and treatment methods, or recently reported important evidence, while considering consistency with each of the previously reported guidelines published by the JCS/JHRS Joint Working Group.

The recommendation of classes and evidence levels used in this set of guidelines conform to those of the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS) guidelines.²⁰ The recommended class of indications for each diagnosis and treatment method is classified as I, IIa, IIb, or III, and the level of evidence is classified as level A, B, or C (Tables 1, 2). The guidelines also state the grade of recommendation and level of evidence based on the "Medical Information Network Distribution

TABLE 1 Class of recommendation

Class I	Evidence and/or general agreement that a given procedure or treatment is useful and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given procedure or treatment
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the given procedure or treatment is not useful/effective, and in some cases may be harmful

TABLE 2 Level of evidence

Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized clinical trial or large-scale non-randomized studies
Level C	Consensus of opinion of the experts and/or small-size clinical studies, retrospective studies, and registries

TABLE 3 MINDS grades of recommendation

Grade A	Strongly recommended and supported by strong evidence
Grade B	Recommended with moderately strong supporting evidence
Grade C1	Recommended despite no strong supporting evidence
Grade C2	Not recommended because of the absence of strong supporting evidence
Grade D	Not recommended as evidence indicates that the treatment is ineffective or even harmful

The grade of recommendation is determined based on a comprehensive assessment of the level and quantity of evidence, variation of conclusion, extent of effectiveness, applicability to the clinical setting, and evidence on harms and costs. (From MINDS Treatment Guidelines Selection Committee, 2007.²¹)

TABLE 4 MINDS levels of evidence (in literature on treatment)

I	Systematic review/meta-analysis of randomized controlled trials
II	One or more randomized controlled trials
III	Non-randomized controlled trials
IVa	Analytical epidemiological studies (cohort studies)
IVb	Analytical epidemiological studies (case-control studies and cross-sectional studies)
V	Descriptive studies (case reports and case series)
VI	Not based on patient data, or based on opinions from a specialist committee or individual specialists

(From MINDS Treatment Guidelines Selection Committee, 2007.²¹)

Service (MINDS) Handbook for Clinical Practice Guideline Development 2007²¹, published by the MINDS Evidence-based Medicine dissemination promotion project as a guideline preparation method (Tables 3, 4). However, the MINDS Grade of Recommendation and Level of Evidence should be used only as a reference, as this system regards the evidence level in a fundamentally different manner. The MINDS level of evidence (levels of evidence in literature on treatment) is a classification based on research design, and the highest level was adopted when multiple papers were considered.

This set of guidelines is designed to be used as a reference by doctors diagnosing and treating diseases in clinical practice, but the final decision should be made by the attending physicians after ascertaining the patient's condition. Even when selecting a diagnosis or treatment that does not follow the guidelines, the decision of the attending physicians should be prioritized in consideration of the individual patient's situation. In actual clinical settings, it is more important for the attending physicians to make the judgment after considering the clinical background and social situation of each patient fully while complying with the guidelines.

II | CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICES (CIEDS)

2.1 | Pacemakers

2.1.1 | Leadless pacemaker

Although the leadless pacemaker is an emerging pacing technology, the clinically available mode of a leadless pacemaker in Japan, as of January 2021, is VVI; therefore, an appropriate indication should be considered. Symptomatic bradycardic atrial fibrillation (AF) is a Class I indication. Patients with atrioventricular (AV) block without AF or sinus node dysfunction might benefit from the leadless VVI pacemaker only when the risk of implantation of the atrial lead is higher than its benefit, the patient has severe frailty, is bed-ridden, or has less than 1-year survival (Table 5).

An investigational device exemption (IDE) study included 36 patients from Japan.² Albeit a smaller body status, the safety and efficacy endpoints in Japanese patients were comparable to those in patients from the rest of the world. Cardiac perforation occurred in approximately 1%, and 15% of them required surgical repair.² Given that the risk factors for cardiac perforation include female sex, old age (≥ 85 years), chronic respiratory disease, body mass index $< 20 \text{ kg/m}^2$, congestive heart failure, and steroid use, a typical candidate for a leadless pacemaker may be high-risk.^{22,23} Hence, a careful risk evaluation is important.

The leadless pacemaker is MRI conditional (1.5 and 3 T).²⁴ There are no established data on radiation therapy, but a case study reported that up to 30 Gy radiation therapy in a patient with mediastinal malignancy with a leadless pacemaker inside the radiation field yielded no remarkable damage to the pacemaker.²⁵ Nevertheless, it is recommended that electrical parameters should be checked prior to and after radiation therapy or MRI.^{24,25}

TABLE 5 Recommendations and Evidence Levels for VVI Leadless Pacemaker

	COR	LOE	GOR (MINDS)	LOE (MINDS)
For patients with symptomatic bradycardia AF, in whom venous access should be preserved, or with venous occlusion or stenosis, VVI leadless pacemaker is recommended	I	B	B	III
For non-AF bradycardiac patients with condition that precludes the use of a transvenous pacemaker, including compromised venous access and the need to preserve venous access, VVI leadless pacemaker should be considered	IIa	B	C1	III
For patients who underwent CIED extraction due to infection and completed the antibiotic treatment, VVI leadless pacemaker may be considered	IIb	C	C1	IVa

Abbreviations: AF, atrial fibrillation; CIED, cardiac implantable electronic device; COR, class of recommendation; GOR, grade of recommendation; LOE, level of evidence.

Leadless pacemaker in hemodialysis patients

In hemodialysis patients, the leadless pacemaker is often chosen due to the venous occlusion caused by previous hemodialysis catheters, to improve the patency of an arteriovenous fistula, or to minimize the infection rate. In 3 studies of the Micra transcatheter pacing system (IDE, Micra Transcatheter Pacing System Continued Access Study, and Post-Approval Registry), 201 out of 2,819 patients (7%) were under hemodialysis.²⁶ A majority of the patients (72%) had conditions that precluded transvenous pacing, including the need to preserve venous access (79%), prior infection (20%), and venous occlusion (17%). A successful implant was achieved in 98%, and safety and electrical parameters were similar to non-hemodialysis patients. Although an infection rate of 8% has been reported with conventional pacemakers,²⁷ no infection was reported in these patients.

Extraction

Worldwide experience with successful retrieval of the leadless pacemaker has been reported.²⁸ Data from the manufacturer recorded 40 successful retrievals, and operators for 29 successful retrievals provided information. Of the 29 retrievals, 11 were during the index procedure; 18 retrievals were performed after a median of 46 days (1–95 days). Reasons included threshold increment after tether removal (n = 5), loss of capture (n = 3), dislodgement (n = 3) for immediate retrieval, and elevated threshold at follow-up (n = 11), endovascular infection (n = 1), need for transvenous device (n = 2), and CRT upgrade (n = 1) for delayed retrieval. Average time of the retrieval and fluoroscopy was 63.11 min and 16.7 min, respectively, and no adverse events were observed.

Infection

Leadless pacemaker implantation following CIED infection. Of the 1820 patients in the Micra post approval registry, 105 had re-implantation of leadless pacemaker within 30 days after CIED extraction.²⁹ The extracted CIEDs were pacemakers (70.5%), CRT-P (9.5%), and ICD/

CRT-D (12.4%), and 93% were complete explants. Pacing-dependent patients underwent a same-day implant more frequently, and non-dependent patients underwent the implant after a median of 7 days; 91% had IV antibiotics pre-implantation, and 42% had them post-implantation as well. During an average of 8.5 months, 2 patients died of sepsis, and 4 patients required a system upgrade, but no leadless pacemaker was explanted due to re-infection. This finding might suggest that a leadless pacemaker is reasonably safe with no recurrent device infection, which may be due to the absence of a subcutaneous pocket, a smaller surface area as compared with the transvenous lead, a greater tendency of encapsulation, and a high-flow environment in the heart cavity.

Bacteremia/endocarditis following implantation of a leadless pacemaker. A total of 16 out of 720 patients (2.2%) in the IDE study developed 21 serious cases of bacteremia or endocarditis during follow-up.³⁰ Infection occurred at a mean of 4.8 months after implantation; 13 events were caused by Gram-positive organisms and 3 by Gram-negative bacteria. Two of the three cases of endocarditis resulted in death; one patient with prosthetic aortic valve endocarditis died immediately postoperatively, the other with aortic valve endocarditis 108 days post leadless pacemaker implantation refused surgical intervention. All but 2 patients responded well to antibiotics, and no persistent bacteremia was observed after antibiotic cessation.

Future pacing mode (VDD)

Micra™, the clinically available leadless pacemaker in Japan as of January 2021, provides accelerometer-based rate-adaptive pacing. Accelerometer signals identify 4 distinct segments of cardiac activity: isovolumic contraction and mitral/tricuspid valve closure (A1), aortic/pulmonic valve closure (A2), passive ventricular filling (A3), and atrial contraction (A4). Using the downloadable algorithm with accelerometer-based atrial sensing, the MARVEL study showed that AV synchrony improved in patients with complete AV block from

37.5% to 80% compared with VVI mode.³¹ An improved automated algorithm was evaluated in patients with sinus rhythm with complete AV block in the MARVEL 2 study.³² Median AV synchrony significantly improved in VDD mode compared with VVI mode (27% vs. 94%). AV synchrony ranged from 89.2% during the resting period to 69.8% while standing. The decline in AV synchrony could be due to orthostatic tachycardia or a decrease in the A4 signal because of reduced venous return.

2.1.2 | Conduction system pacing

Long-lasting right ventricular (RV) pacing produces an iatrogenic desynchronized contraction of the left ventricle (LV), and possibly induces reduced contraction and mechanical remodeling of the LV.^{33,34} To resolve this issue of RV pacing, several animal and clinical studies have demonstrated that artificial pacing of the His bundle instead of the RV can provide long-term physiological ventricular conduction.³⁵⁻³⁷ However, when this concept was initially proposed, permanent and stable His bundle pacing was technically difficult at that time, and therefore, this method was not widely used (Table 6).

Recently, however, a newly designed pacing lead and delivery system aimed at pacing the His bundle has emerged and provided >80% success rate,³⁸⁻⁴³ and the method has been taken up very rapidly since. More recently, this concept has been further developed to enable transeptal left bundle pacing,⁴⁴ and His bundle and left bundle pacing have become collectively known as "conduction system pacing".

His bundle pacing for patients with bradycardia

Several clinical studies have demonstrated the efficacy of His bundle pacing for patients with bradycardia (mainly atrio-ventricular

block) who have an indication for permanent pacing with a normal or moderately reduced LV ejection fraction (LVEF) (Table 7).³⁸⁻⁴³ Two randomized clinical trials compared the efficacy of RV pacing to that of His bundle pacing using a crossover design (switching from one pacing method to the other within a fixed period),^{38,41} and demonstrated that His bundle pacing improved LVEF. However, the results from the 2 studies were not consistent regarding the improvement in NYHA functional class and 6-min walk distance. Two clinical observational trials, in which the patients were separately assigned to His bundle pacing at a certain hospital and RV pacing at a second hospital, showed an improvement in LVEF³⁹ and reduction in heart failure hospitalizations.⁴² Furthermore, a meta-analysis accumulating data from many trials revealed LVEF improvement in patients with a preoperative LVEF <50%.⁴³ To date, however, the efficacy of His bundle pacing has not been confirmed by large randomized clinical trials; previous clinical studies were small-scale, and did not show an improvement in the mortality rate as a single primary endpoint.

At present, we recommend that it is reasonable to perform His bundle pacing instead of RV pacing in patients with atrioventricular block who have an indication for permanent pacing with 36%>LVEF>50% and who are expected to require ventricular pacing over time. However, for patients with normal cardiac function, the adverse effects of RV pacing on LV performance can be expected to be insignificant; therefore, an indication for His bundle pacing should be carefully considered. Additionally, upgrading to His bundle pacing in patients with preexisting standard RV pacing and moderately reduced LVEF (36%–50%) may impose an additional risk of lead extraction or lead implantation, and the clinical evidence of this challenge is not adequate. Implantation of His bundle pacing lead in patients with sick sinus syndrome but without a conduction system disturbance may cause iatrogenic injury to the conduction system;

	COR	LOE	GOR (MINDS)	LOE (MINDS)
Indication for His bundle pacing for patients with bradycardia				
In patients with atrioventricular block who have an indication for permanent pacing with an LVEF between 36% and 50% and are expected to require ventricular pacing over time, it is reasonable to perform His bundle pacing	IIa	A	B	II
In patients with atrioventricular block who have an indication for permanent pacing with a normal LVEF, His bundle pacing may be considered	IIb	C	C1	III
Indication for His bundle pacing as an alternative method for CRT				
In patients with heart failure who have an indication for CRT but not cardioverter-defibrillator, His bundle pacing may be considered when trans-cardiac vein pacing is ineffective or impossible for any reason	IIb	C	C1	VI

TABLE 6 Recommendations and evidence levels for His bundle pacing

Abbreviations: COR, class of recommendation; CRT, cardiac resynchronization therapy; GOR, grade of recommendation; LOE, level of evidence; LVEF, left ventricular ejection fraction.

TABLE 7 Summary of studies of His bundle pacing

Study design	No. of patients	FU (months)	Indication of pacing	LVEF (pre-HBP)	LVEF (post-HBP)	LVEF (post-RVP)	Success rate of HBP	Results
Occhetta et al, 2006, <i>JACC</i> ³⁸								
Randomized, crossover, RVP vs. HBP	18	12	AVJ ablation for AF	51.3%	53.4%	50.0%	95.8%	HBP improved NYHA class, 6-min walk distance, QOL, and hemodynamic status
Sharma et al, 2015, <i>Heart Rhythm</i> ³⁹								
Observational, RVP vs. HBP	192; RVP 98 HBP 94	24	AVB 62% SSS 38%	56.0%	UD	UD	80.0%	HBP improved the incidence of an admission due to heart failure, but not the mortality rate
Vijayaraman et al, 2015, <i>JACC Clinical Electrophysiology</i> ⁴⁰								
Observational, single arm	100	19	AVB	54.0%	UD	None	84.0%	Significant increase in the pacing threshold, pacing failure was observed in 5%
Kronborg et al, 2014, <i>Europace</i> ⁴¹								
Randomized, crossover, RVP vs. HBP	38	12	AVB	50.0%	55.0%	50.0%	UD	HBP improved LVEF, but not NYHA class, 6 min walk distance, and QOL
Abdelrahman et al, 2018, <i>JACC</i> ⁴²								
Observational, RVP vs. HBP	765; RVP 433 HBP 332	24	AVB 65% SSS 35%	54.5%	UD	UD	91.6%	HBP improved the composite endpoint (total mortality, heart failure admission, and upgrade to BiVP). The incidence of heart failure admissions was significantly reduced as the sole endpoint
Zanon et al, 2018, <i>Europace</i> ⁴³								
Meta-analysis for HBP	1,438	16.9	AVB 62.1% SSS 34.2%	42.8% (31% in a group with a previous LVEF <50%)	49.5% (42% in a group with previous LVEF <50%)	None	84.8%	HBP significantly improved LVEF in patients with a previous LVEF <50%

Abbreviations: AF, atrial fibrillation; AVB, atrioventricular block; AVJ, atrioventricular junction; BiVP, biventricular pacing; FU, follow-up period; HBP, His bundle pacing; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; QOL, quality of life; RVP, right ventricular pacing; SSS, sick sinus syndrome; UD, undetermined.

therefore, the indication for His bundle pacing should be very carefully considered.

Role of His bundle pacing in patients with a conduction disturbance and heart failure (CRT-Compatible Patients)

Role of His bundle pacing in patients who do not respond to CRT or in whom LV pacing via a cardiac vein is impossible. The efficacy of His bundle pacing in patients who had been proven to be non-responders to CRT was evaluated in 2 small-scale studies⁴⁵⁻⁴⁸ (Barba-Pichardo et al [n = 16]⁴⁵ and Sharma et al [n = 8],⁴⁸ which demonstrated a significant improvement in LVEF after His bundle pacing (LVEF increased from 29% to 36% and from 30% to 38%, respectively). Sharma et al evaluated His bundle pacing in 25 patients in whom CRT was impossible due to trans-venous LV pacing failure, and found an improvement in NYHA class and reduction in heart failure admissions (Table 8).⁴⁸

Role of antecedent His bundle pacing in candidates for CRT. Three different clinical studies attempted to perform His bundle pacing antecedently in candidates for CRT (Table 8).⁴⁵⁻⁴⁸ One randomized study compared the efficacy of HBP to that of CRT using a crossover study design in 29 patients, and showed a significant improvement in LVEF and NYHA functional class for whichever method that was used.⁴⁶ Furthermore, 2 other single-arm observational studies demonstrated a significant improvement in LVEF and NYHA functional class.^{47,48}

Indication for His bundle pacing in candidates for CRT. As there are no data showing the long-term superior efficacy of His bundle pacing over CRT, and because a pacing impulse delivered at the His bundle may fail to capture the left bundle in patients with left bundle branch block, antecedent His bundle pacing without a CRT attempt is difficult to recommend. Therefore, His bundle pacing in candidates for CRT can be considered as an alternative option when (1) heart failure is deteriorating even after CRT, when there is (2) no optimal cardiac vein for LV pacing, (3) an unacceptable increase in the LV pacing threshold, (4) unavoidable phrenic nerve stimulation, (5) repeated dislodgement of the trans-venous LV lead, (6) technical limitations, or when (7) CRT is impossible due to complications or the clinical situation.

Role of left bundle pacing

To resolve several problems of His bundle pacing, such as an increase in the pacing threshold and inability of left bundle capture in patients with complete left bundle branch block, a novel technique has emerged, aimed at pacing the left bundle directly by implanting a pacing lead at a distal site on the ventricular septum toward the LV.⁴⁹⁻⁶¹ Although this method has been shown to be superior to His bundle pacing in reducing the pacing threshold,⁵⁹ several concerns have been reported^{49,61}: perforation of the ventricular septum, injury to the conduction system, dislodgement of the lead, injury to the coronary artery (septal branch) and thromboembolism.^{51,59-61} Furthermore, because the follow-up intervals of the studies^{49,50,56} were ≤ 3 months, the long-term efficacy of left bundle pacing has

not been clarified. Some investigators have assumed that left bundle branch pacing can be an alternative method to CRT; however, the significance of this method is still unknown owing to the lack of evidence from a randomized clinical trial including a large number of heart failure patients.⁵⁸

2.2 | Implantable cardioverter-defibrillators

2.2.1 | Deactivating ICD in end-of-life care

Whether to deactivate an implantable cardioverter defibrillator (ICD) that was implanted and has been maintained before the patient had reached the end of life remains controversial. Shock therapy not only causes pain to the patient but also distresses the family members who provide care for the patient, thereby contradicting the purpose of palliative care in terminally ill patients. A retrospective observational study of 49 ICD patients who were considered to be near the end of life notwithstanding any cardiovascular disease reported that 42.9% experienced ICD activation within the year before death. Moreover, ICDs were not deactivated in 24.5% of patients, even after an end-of-life diagnosis was made, and only one-third of ICDs were deactivated.⁶² A subanalysis of data from the MADIT-II study, which reported the ICD therapy status in 98 terminally ill patients, revealed that of 47 patients without ICD deactivation who did not establish Do Not Attempt Resuscitation (DNAR) orders, 6 (13%) experienced ICD shock therapy within 1 week before death, and 9 (19%) experienced ICD shock therapy within 24 hours of death.⁶³ A Swedish observational study reported that 32 of 65 ICD patients with DNAR orders had deactivated ICDs, and 10 of 33 patients without deactivation experienced ICD shock therapy within 24 hours of death.⁶⁴ Among 51 ICD patients who were diagnosed with end stage heart failure at the Tokyo Women's Medical University Hospital between 2010 and 2018, 12 of 39 patients with DNAR orders had deactivated ICDs. In addition, 21 patients (41%) experienced shock therapy within 3 months before death, 14 patients (27%) experienced shock therapy within 1 month before death, and 12 patients (24%) experienced electrical storms (including antitachycardia pacing) within 1 month before death.⁶⁵ Thus, the worsening condition of terminally ill patients might contribute to the development of ventricular arrhythmias requiring ICD therapy. To avoid painful shock from the viewpoint of palliative care, cardiologists and healthcare professionals should discuss deactivation of ICDs in patients with end stage disease with the patients/family members (Table 9).

Regarding the deactivation of ICDs, discussion is required before confirming the will of patients and families during the planning of end-of-life care based on advance care planning (ACP). This process needs to consider the ethics, cognitive ability of patient, etc, and judgment should be made not only by cardiologists and nurses but also based on consultation with palliative care and medical teams (including psychiatrists and psychologists); sufficient informed consent, depending on

TABLE 8 Summary of studies comparing the efficacy of His bundle pacing to that of CRT

Study design	No. of patients	FU (months)	QRS morphology	Pre-QRS width (ms)	Post-HBP QRS width (ms)	Post-Bi-V QRS width (ms)	Pre-LVEF	Post-HBP LVEF	Post-BiVP LVEF	HBP success rate	Results
Barba-Pichardo et al, 2013, <i>Europace</i> ⁴⁵											
Observational, single arm (unsuccessful CRT patients enrolled)	16	31.3	CLBBB (100%)	166	97	None	29%	36%	None	75%	Comparison between pre- and post-HBP. LVEF, NYHA class, and reduction in LAD, LVESD, and LVEDD significantly improved
Lustgarten et al, 2015, <i>Heart Rhythm</i> ⁴⁶											
Randomized, crossover, BiVP vs. HBP	29	12	CLBBB (97%)	169	Non-selective 160, Selective 131 HBP+LVP 145	165	26%	32%	31%	72%	Comparison of the two groups. LVEF, NYHA class and distance of 6-min walk in both groups significantly and equally improved
Ajjola et al, 2017, <i>Heart Rhythm</i> ⁴⁷											
Observational, single arm	21	12	CLBBB (81%)	180	129	None	25%	41%	None	76%	Comparison between pre- and post-HBP. LVEF, NYHA class, and reduction in LVEDD significantly improved
Sharma et al, 2018, <i>Heart Rhythm</i> ⁴⁸											
Observational, single arm	Total 106	14	BBB (42%) non-BBB (16%) RVP (32%)	BBB 163 non-BBB 103 RVP 177	BBB 116 non-BBB 108 RVP 125	None	30%	44%	None	90%	Comparison between pre- and post-HBP. LVEF and NYHA class significantly improved, but the reduction in LVEDD did not. As for cases with a previous LVEF ≤35% (n = 72), LVEF improved from 25% to 40%
Group 1: LVP failure (n = 25), CRT non-responder (n = 8)	33		BBB (64%) non-BBB (6%) RVP (30%)	BBB 161 non-BBB 90 RVP 175	BBB 115 non-BBB 105 RVP 115	None	26%	30%	None	91%	7 of the 8 CRT non-responder cases responded to HBP, and LVEF improved from 30% to 38%
Group 2: AVB, BBB, RVP	73		BBB (37%) non-BBB (21%) RVP (42%)	BBB 164 non-BBB 105 RVP 179	BBB 116 non-BBB 108 RVP 125	None	32%	44%	None	89%	

Abbreviations: AVB, atrio-ventricular block; BBB, bundle branch block; BiVP, bi-ventricular pacing; CLBBB, complete left bundle branch block; CRT; cardiac resynchronization therapy; FU, follow-up period; HBP, His bundle pacing; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVP, left bundle pacing; NYHA, New York Heart Association; RVP, right ventricular pacing.

the individual situation, should be provided (Figure 1).⁴ The preparation of ACP directives at the end of life plays an important role with respect to the patient's will. Of course, the content of such directives can be subsequently changed.

The HRS Expert Consensus Statement states that communication on ICD deactivation is essential; communication is an ongoing process that starts when informed consent is obtained prior to ICD implantation and continues as the patient's condition and treatment goals change with disease progression.⁶⁶ However, a previous report found that only 4% of patients discussed ICD deactivation with their

physician in the clinical setting.⁶⁷ According to the survey results of ICD patients with malignancies whose prognoses were relatively easy to predict, 35.3% of patients with stage IV cancer underwent ICD deactivation.⁶⁸

Thus, there are several possible reasons for disconnecting between the recommendations and actual clinical situations. Medical staff do not actively discuss end-of-life topics and tend to postpone certain issues, such as the deactivation of ICDs, until just before death.⁶⁹ A survey in the USA reported that some clinicians thought that a DNAR order did not mean that ICD should be deactivated, and

	COR	LOE	GOR (MINDS)	LOE (MINDS)
In ICD patients who are the end of life, the deactivation decision should be made with support from a multidisciplinary team after obtaining sufficient information about the ICD for the patient and family	IIa	C	C1	VI

TABLE 9 Recommendations and evidence levels for deactivation of ICDs

Abbreviations: COR, class of recommendation; GOR, Grade of Recommendation; ICD, implantable cardioverter-defibrillator; LOE, level of evidence.

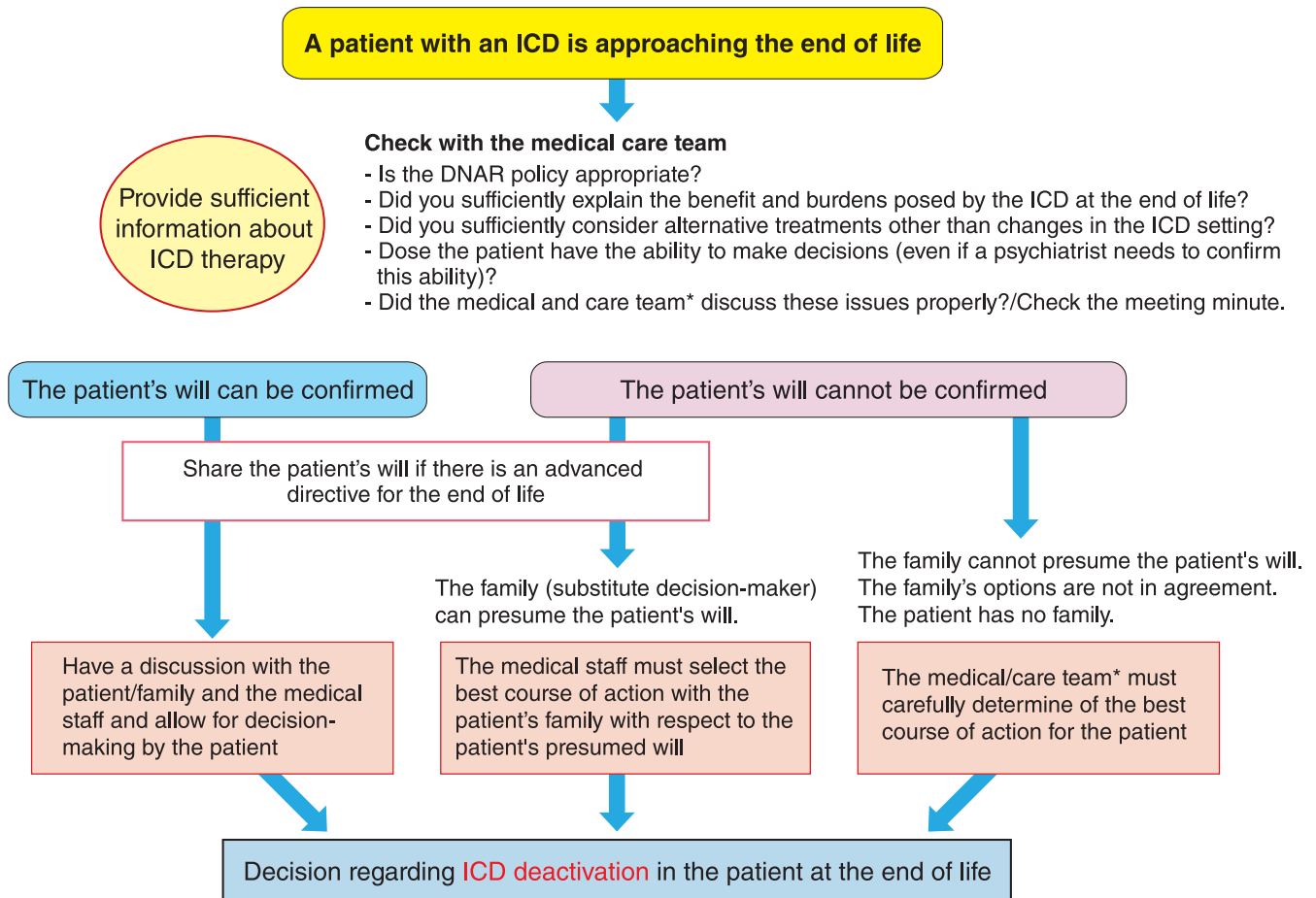


FIGURE 1 Discussion process to determine whether to deactivate an implantable cardioverter-defibrillator (ICD). Regarding ICD deactivation at the end of life, shared decision-making should be performed after obtaining sufficient information based on ethical background and advance care plan. Additional factors such as unnecessary physical and psychological distress caused by ICD shock therapy at the end of life, and the disadvantages of not being treated for a life-threatening arrhythmia because of a deactivated ICD should be discussed with a multidisciplinary team* including cardiologists (heart failure specialists and arrhythmia specialists), heart-failure nurses, arrhythmia specialists, psychiatrist, clinical psychologist, and palliative care staff members. It should also be conveyed to the patient and family that their decision can be subsequently changed. If the patient's will cannot be confirmed, the medical staff together with the family members should select the best choice for the patient after obtaining sufficient information about the ICD with respect to the patient's presumed will. If the patient's presumed will cannot be confirmed, a multidisciplinary medical/care team should carefully determine the best course of action. DNAR, Do Not Attempt Resuscitation. (From JCS/JHFS 2021 Statement on Palliative Care in Cardiovascular Diseases. 2021.⁴)

one-quarter of clinicians thought that ICD deactivation was ethically considered suicide assistance.⁶⁷

Besides deactivation, not replacing the device is another option for treatment withdrawal. In addition, ICD can be deactivated while maintaining bradycardia pacing or biventricular pacing to

prevent the worsening of heart failure symptoms and impairment of quality of life. These decisions should be determined following the steps described above.

In ICD patients who are at the end of life notwithstanding any cardiovascular disease, the deactivation decision should be made

closely with clinical psychologists, psychiatrists, and palliative care teams based on full evaluations of the psychological and physical stresses caused by ICD shock therapy while maintaining good communication with the patient's family.

2.3 | Transvenous lead extraction

2.3.1 | Indication for lead extraction due to definite device infection

Early removal of the total device system (the device and all leads) is a Class I indication for a definite CIED infection, such as device pocket infection or lead infection with vegetation, regardless of whether there are any systemic infection symptoms or bacteremia.

2.3.2 | Indication for lead extraction for bacteremia without a definite device infection

Early removal of the total device system is not always a Class I indication for bacteremia without a definite device-related infection. First-line management should be investigation of the infection focus, removal of all easily extracted lines, such as a central venous catheter and temporary pacing wire, and administration of antibiotics based on susceptibility testing results for identified bacteria. If the infection focus is unclear and the clinical course is poor, an indication for lead extraction should be considered based on the pathogenic bacteria, the patient's status, and the risk related to lead extraction.⁷⁰ The following recommendations for lead extraction are based on specific pathogenic bacteria.

Staphylococcus Aureus, *Coagulase-Negative Staphylococci*, *Propionibacterium spp.*, and *Candida spp*

Early removal of the total device system is recommended for patients with an implanted CIED device and an occult blood stream infection caused by *Staphylococcus aureus*, coagulase-negative staphylococci (CNS), *Propionibacterium spp.*, or *Candida spp.* *Staphylococcus aureus* is an especially virulent bacterium that can cause tissue-destructive effects and severe clinical symptoms.⁷¹ CNS, such as *S epidermidis*, are weakly pathogenic bacteria; however, the incidence of device pocket infections due to CNS is high.⁷² *Propionibacterium spp.* are Gram-positive anaerobic rod bacteria that produce a biofilm similar to *S aureus* and CNS, resulting in antibiotic refractoriness in cases where the device remains in the patient.⁷³ *Candida spp.* may cause a refractory blood stream infection, especially in compromised hosts, due to biofilm production.⁷⁴

Alpha-/Beta-Hemolytic Streptococcus spp. and *Enterococcus spp*

Early lead extraction is recommended for bacteremia caused by alpha-/beta-hemolytic *Streptococcus spp.* and *Enterococcus spp.* Lead extraction should also be attempted if the bacteremia is recurrent or

refractory to antibiotic therapy. The risk of a concomitant infection with the device is considered low.⁷⁵

Gram-negative bacteria and Streptococcus Pneumoniae

Lead extraction is recommended if the bacteremia from Gram-negative bacteria or *S pneumoniae* is recurrent or refractory to antibiotic therapy. The risk of a concomitant infection with the device is considered low, and antibiotic therapy only may be curative.⁷⁵

2.3.3 | Strategy for superficial device pocket infections

A superficial pocket infection does not reach the device, is caused by surface skin closure sutures, and occurs within 30 days of device implantation. Oral antibiotics effective against *Staphylococcus aureus* should be administered and local lesion care to the superficial infection site is mandatory for at least 7-10 days until pocket redness and systemic symptoms, such as fever and inflammatory reactions, disappear. Superficial lesions should be treated in the same way as device infections if the lesions are refractory or associated with apparent infectious symptoms.

2.3.4 | Management after lead extraction for device infection and implantation of a new device

Antibiotic therapy based on the results of sensitivity testing is mandatory after the removal of an entire CIED system (including the leads). A bacterial examination of a swab or tissue culture from the surgical pocket,⁷⁶ the tip or entirety of the extracted lead,⁷⁰ and the removed device⁷⁷ should be performed on more than 2 sets of blood cultures before administering antibiotics.

The antibiotic administration period is at least 2 weeks without a blood stream infection for pocket infections, at least 2 weeks without lead or valvular vegetations for blood stream infections (4 weeks is recommended for *Staphylococcus aureus* infections), at least 2-4 weeks for lead vegetations, and at least 4-6 weeks for valvular vegetations.⁷⁰

Implantation of a new device after CIED system removal should be carefully evaluated, and discontinuation of the device may be considered if there is no (or a lesser) indication for implantation. When implantation of a new device is indicated, the site opposite the original site is recommended. A device without the need for transvenous leads, such as a subcutaneous ICD or leadless pacemaker, may be useful. A new device should be implanted after confirmation of negative blood cultures for 72 hours after the lead extraction; however, the timing can be delayed based on the patient's systemic symptoms and the bacterial source, such as an infective abscess. The use of a wearable cardioverter defibrillator can be considered until implantation for high-risk patients with life-threatening arrhythmias.

2.4 | Role of cardiac implantable electrical devices in the termination and prevention of atrial arrhythmias

Among patients with a CIED, it is important to prevent the occurrence and persistence of atrial arrhythmias (ATAs) including atrial fibrillation (AF). Previous studies have shown that patients with paroxysmal AF have significantly lower incidences of stroke and all-cause mortality compared with patients with persistent AF.⁷⁸⁻⁸⁰ Botto et al reported that combining data on AF duration with that on scores of thromboembolic risk (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke, or transient ischemic attack [CHADS₂]) could clearly discriminate the risk of thromboembolic events in patients with a dual-chamber rate-responsive pacemaker.⁸¹ In a large series of patients with an ICD or a cardiac resynchronization therapy device with defibrillator (CRT-D), Vergara et al indicated that atrial high-rate episodes occurred during the 48 hours preceding lethal ventricular tachyarrhythmias (VAs), which were detected by the shock device system in $\approx 20\%$ of the patients with VAs.⁸² Moreover, Nakajima et al reported that some patients developed heart failure (HF) after transient AF attacks, even in CRT responders, mainly due to the loss of percent of bi-ventricular pacing.⁸³ Because the appearance and persistence of ATAs are associated with several risks of stroke, VAs, and HF, therapeutic intervention should be executed in such patients with a CIED and ATAs.

Research into the utility of CIED functions for rhythm control to prevent and terminate ATAs has been conducted for some time.⁸⁴ There are several device-based approaches for the prevention of ATAs, including multisite atrial pacing and pacing algorithms to increase the frequency of atrial pacing. However, their effectiveness in preventing and terminating ATAs are not sufficient for clinical use.^{85,86} The SAVE PACe trial showed that pacemaker implantation and the use of new device-based algorithms of dual-chamber minimal ventricular pacing (MVP) could significantly suppress progression to persistent AF in patients with sick sinus syndrome, intact atrioventricular conduction, and a normal QRS interval (7.9% [MVP group] vs. 12.7% [control group], hazard ratio [HR]: 0.60, 95% confidence interval [CI]: 0.41-0.88; $P = .009$).⁸⁷ However, a recent meta-analysis on the efficacy of MVP revealed that a low burden of percent of ventricular pacing did not significantly suppress AF progression.⁸⁸

Atrial antitachycardia pacing (A-ATP) has been investigated for its efficacy in terminating ATAs since the early first decade of the 2000s. A-ATP is likely to be effective for atrial flutter and atrial tachycardias, however, it may sometimes progress to AF after using A-ATP. The ATTEST trial was a randomized clinical study that evaluated the efficacy of preventive pacing and the first generation of A-ATP in patients with a pacemaker.⁸⁹ The 324 patients who had ACC/AHA/NASPE Class I or II indication for a standard dual-chamber pacemaker⁹⁰ and a history of ATAs were randomized into first generation of A-ATP therapies ON or OFF using the ATA prevention algorithm. In each group, the burden and frequency of ATAs were assessed during the 3-month study period and the median ATA burden was 4.2 h/month in the ON group vs. 1.1 h/month in the OFF group ($P = .20$). In addition, the median ATA frequency was 1.3 episodes/month (ON) vs. 1.2 episodes/

month (OFF) ($P = .65$). The preventive pacing and first generation of A-ATP did not significantly reduce either the ATA burden or frequency.⁸⁹

Subsequently, the second generation of A-ATP (ReactiveATP™), which can be delivered at the onset of arrhythmia as well as during its dynamic changes towards slower or more organized rhythms, was developed. The MINERVA trial was a randomized clinical study to evaluate the efficacy of combination therapy of atrial preventive pacing, second-generation A-ATP, and MVP in patients with a pacemaker.⁹¹ A total of 1,166 patients who had ACC/AHA/NASPE Class I or II indication for a standard dual-chamber pacemaker⁹⁰ and a history of ATAs were randomly assigned to (1) not using any algorithm (control DDDR group), (2) using atrial preventive pacing, second-generation A-ATP, and MVP (DDDRP + MVP group), and (3) using only MVP (MVP group). During a median follow-up of 34 months, the 2-year incidence of a composite clinical endpoint including all-cause death, cardiovascular hospitalization, or permanent AF was significantly lower in the DDDRP + MVP group as compared with the control DDDR group (HR: 0.74, 95% CI: 0.55-0.99, $P = .04$), while no significant difference was observed between the DDDRP + MVP and MVP groups (HR: 0.93, 95% CI: 0.68-1.26, $P = .63$ vs. the MVP group). As for secondary endpoint of progression to permanent AF, the DDDRP + MVP group showed a significantly lower risk than the control DDDR group (HR: 0.39, 95% CI: 0.21-0.75, $P = .004$) and the MVP group (HR: 0.49, 95% CI: 0.25-0.95, $P = .034$). Padeletti et al analyzed the MINERVA trial data and highlighted that the generalized estimation of equation-adjusted efficacy of the second generation of A-ATP was 44.4% (95% CI: 41.3%-47.6%) in the DDDRP + MVP group.⁹² In addition, the risk of progression to permanent AF was significantly reduced in patients with high efficacy ($>44.4\%$) of the second generation of A-ATP (HR: 0.32, 95% CI: 0.13-0.78, $P = .012$).

High efficacy of A-ATP in patients with congenital heart disease accompanying ATAs has been reported.^{93,94} Kramer et al revealed that implantation of an atrial antitachycardia pacing device was associated with reduced direct current cardioversion burden, and the overall success rate of A-ATP was 69% in a cohort of 91 patients with congenital heart disease and ATAs.⁹⁵ Although there are few studies assessing the efficacy of A-ATP in patients with an ICD or a CRT device, Crossley et al analyzed the data obtained from a large device database of a remote monitoring system (Medtronic CareLink™) and reported the effectiveness of the second generation of A-ATP.⁹⁶ Among 1,062 patients with an ICD, the use of the second generation of A-ATP was associated with reduced risk of ≥ 7 days of ATAs as compared with no use, even after controlling for other covariates (HR: 0.58, 95% CI: 0.43-0.77). As for the patients with CRT-D, the use of the second generation of A-ATP significantly reduced the risk of risk of ≥ 7 days of ATAs compared with no use (HR: 0.73; 95% CI: 0.57-0.93). In addition, Ueda et al showed the efficacy of the second generation of A-ATP in CRT patients: 23 of 44 patients (52%) received a total of 2,862 ATP deliveries during a mean follow-up of 832 days, and the median success rate of A-ATP was 23.6% (interquartile range: 12.5%-50.0%) in the A-ATP group.⁵

Along the way, there have been several studies reporting the efficacy of the second generation of A-ATP; however, the effectiveness differs according to each individual and the results may vary in

each study. Subanalysis of the MINERVA trial indicated that a cycle length of ATAs ≤ 210 ms or relatively irregular AA intervals of the ATAs was associated with low efficacy of the second generation of A-ATP.⁹² Moreover, the efficacy of the second generation of A-ATP is much lower in patients with a CRT device than in those with a pacemaker.⁵ Further prospective studies including a larger number of patients are needed to evaluate how to use the second generation of A-ATP and when to terminate its function.

2.5 | Device-detected atrial fibrillation (AF)

CIEDs can record intracardiac electrograms, thereby allowing continuous monitoring of cardiac atrial/ventricular arrhythmias. As remote monitoring has become a popular and guideline-recommended standard ambulatory medical care tool for most CIED patients,¹ the opportunity to detect subclinical cardiac arrhythmias (especially subclinical atrial fibrillation [AF]) has been increasing (Table 10).

2.5.1 | Prevalence of CIED-detected AF

A number of studies have recorded the incidence of CIED-detected AF. In the ASSERT trial of 2,580 patients receiving a pacemaker or ICD, subclinical AF was documented in 261 patients (10.1%) within 3 months after implantation. In another pooled analysis of 3 prospective studies (TRENDS, PANORAM, and SOS AF), which included 6,580 patients with implanted CIEDs without a history of AF, around one-third had a daily AF burden of ≥ 5 /min and $>20\%$ of them had a daily AF burden ≥ 23 /h during a mean follow-up of 2.4 years.⁹⁷ In another study using a home monitoring database, a total of 3 004 763 transmissions from 11,624 CIED patients were analyzed; subclinical AF was detected in $\approx 60\%$ of the patients with a pacemaker and in $\approx 10\%$ of those with an ICD,⁹⁸ thereby indicating that subclinical AF is commonly detected regardless of CIED type. Furthermore, other studies report that the remote monitoring system can detect 95% of asymptomatic AF,⁹⁹ and that the time to the first diagnosis of AF is earlier than with the traditional monitoring system.¹⁰⁰ These data demonstrate that subclinical AF is detected earlier and more frequently in CIED patients, especially with combined use of a remote monitoring system.

TABLE 10 Recommendations and evidence levels for the management of device-detected AHREs

	COR	LOE	GOR (MINDS)	LOE (MINDS)
In patients with device-detected AHREs, further evaluation to document clinically relevant AF is recommended	I	B	A	IVa
In patients with device-detected AHREs, anticoagulation therapy is reasonable in patients with CHADS ₂ score ≥ 1 by taking the efficacy and safety into consideration on an individual basis	IIa	B	C1	IVa

Abbreviations: AF, atrial fibrillation; AHRE, atrial high-rate episode; COR, class of recommendation; GOR, Grade of Recommendation; LOE, level of evidence.

2.5.2 | Clinical significance of CIED-detected AF

It has been reported in previous studies that newly detected AF in CIED patients is associated with heart failure admission, appropriate ICD discharge, and death,¹⁰¹ and also closely related to the development of stroke/systemic embolic events (Table 11).¹⁰²⁻¹⁰⁶ Accordingly, early detection and management of CIED-detected AF, especially the indication of anticoagulation therapy to prevent stroke/systemic embolic events, are the most important for physicians.

2.5.3 | Diagnostic accuracy of CIED-detected AF

Although CIED-detected AFs are recorded as atrial high-rate episodes (AHREs), AHREs and AF are not strictly the same. Thus, careful interpretation is needed if the AHREs are silent. As the cause of false positives, the oversensing of far-field R-wave, lead noise, and other atrial arrhythmias can be considered. As the cause of false negatives, undersensing during the blanking period can be considered; however, diagnostic accuracy has been improved in the recent CIEDs, because the sensing of the atrial electrogram during the blanking period is currently enabled.^{107,108}

In an analysis of a duration-based study of CIED-detected AHREs, true atrial tachycardia/AF was 82.7% and false positives were 17.3% for AHREs lasting < 6 minutes; however, false positives dropped to 6.8%, 3.3%, and 1.8% when the threshold duration was increased to 30 minutes, 6 hours, and 24 hours, respectively.¹⁰⁹

2.5.4 | Anticoagulation therapy for CIED-detected AF

A number of studies report that CIED-detected AF is closely associated with an increased risk of stroke, but the cutoff value of AF duration is still unclear (Table 11).¹⁰²⁻¹⁰⁶ Based on the initial ASSERT study,¹⁰⁴ anticoagulation was recommended for patients with > 5 -6 minutes of device-detected AF in the ESC guideline 2016¹¹⁰; this recommendation was deleted after a subanalysis that showed that stroke/systemic emboli occurred only in patients with > 24 hours of device-detected

TABLE 11 Studies of device-detected atrial fibrillation

Author, Year	Study	Contents	Results
Hearley et al, 2012 ¹⁰⁴	ASSERT	n = 2,580 (pacemaker 2,451/ICD 129) Follow-up the patients for 3 months to detect AHREs (mean 2.5 years) AHREs definition: Atrial rate >190 bpm for >6 min	AHREs associated with ischemic stroke or systemic embolism
Shanmugan et al, 2012 ¹⁰⁵	Home monitor CRT	n = 560 heart failure patients with CRT Follow-up patients after introducing home monitoring AHREs definition: Atrial rate >180 bpm for at least 1% or total of 14 min/day	AHREs of 3.8 h over 24 h associated with thromboembolic events
Boriani et al, 2014 ¹⁰²	SOS AF project	n = 10,016 (pacemaker/ICD/CRT) Pooled analysis from 5 prospective studies AHREs definition: Atrial rate >175 bpm, lasting ≥20 s	Among the thresholds of AF burden, 1 h was associated with the highest hazard ratio for ischemic stroke
Glutzer et al, 2009 ¹⁰³	TRENDS trial	n = 3,045 (pacemaker/ICD/CRT) Annualized thromboembolic event rates according to AHREs burden subsets: zero, low (<5.5 h), and high (≥5.5 h) AHREs definition: Atrial rate >175 bpm, lasting ≥20 s	AHREs burden ≥5.5 h associated with thromboembolic events
Van Gelder et al, 2017 ¹⁰⁶	ASSERT subanalysis	n = 2,455 (patients in whom the longest episode was ≤6 min were excluded from the analysis, n = 125) AHREs definition: Atrial rate >190 bpm for >6 min	AHREs >24 h associated with an increased risk of ischemic stroke or systemic embolism

Abbreviations: AF, atrial fibrillation; AHRE, atrial high-rate episode; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.

AF (Figure 2).¹⁰⁶ Presently, there is no recommendation regarding the duration of CIED-detected AF in the AHA/ACC/HRS guideline focus update 2019¹¹¹ or the ESC guideline 2020.¹¹² However, the positive result from a recent prospective study (TACTIC-AF),¹¹³ which allowed intermittent anticoagulation guided by CIED-detected AF duration (restart anticoagulation in patients with AF lasting ≥6 minutes or with a total AF burden <6 h/day), and the summarized data from previous studies,^{111,114} clearly show there is definitely a positive relationship between the duration of CIED-detected AF and embolic events. As the majority of evidence for the indication of anticoagulation for stroke/systemic emboli is surface ECG-detected AF, further evaluation is needed for CIED-detected AF. Prospective studies on the feasibility of anticoagulation in patients with CIED-detected AHREs are currently underway (NOAH-AFNET 6¹¹⁵ and ARISTESiA¹¹⁶ trials); the findings from these trials will be helpful for us. At present, the indication of anticoagulation for device-detected AF should be considered individually based on the following: duration and burden of CIED-detected AF, patient's risk factors for stroke/systemic emboli, etc (Table 10).

III | CATHETER ABLATION

3.1 | Reducing radiation exposure

The 3-dimensional electroanatomical mapping systems and force-sensing catheters have contributed to reducing radiation exposure during catheter ablation. Catheter positioning, anatomic information, and contact with the myocardium can be monitored without fluoroscopy. In a prospective, multicenter, randomized controlled

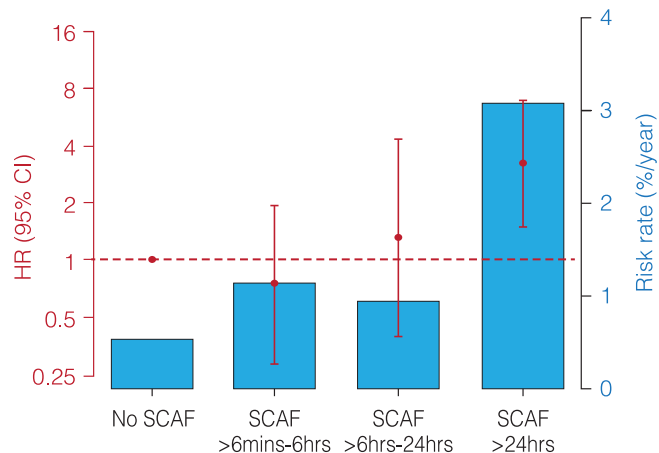


FIGURE 2 Hazard ratio and risk rate of ischemic stroke and systemic embolism. Hazard ratio and risk rate are presented in red and blue respectively. CI, confidence interval; HR, hazard ratio; SCAF, subclinical atrial fibrillation. (From Van Gelder et al. 2017¹⁰⁶ by permission of Oxford University Press on behalf of the European Society of Cardiology.)

trial that included 262 patients who underwent electrophysiologic studies for SVT, patients were randomized to receive a minimally fluoroscopic approach (MFA) using the EnSite™ NavX™ navigation system or the conventional approach. Significant reductions in patients' radiation dose, total fluoroscopy time, and operator radiation dose were documented in the MFA group, without compromising efficacy or safety. Additionally, a 96% decline in the risks of cancer incidence and mortality was estimated.¹¹⁷

The use of fluoroscopic imaging integrated with a 3D electroanatomical mapping system, instead of the conventional electroanatomical mapping system, during AF ablation was shown to further reduce radiation exposure, without complicating the workflow or compromising acute/mid-term efficacy and safety.¹¹⁸ Fluoroscopy time was reduced by 84%, and radiation dose was reduced by 73%. Most of the fluoroscopic guidance was used for femoral vein/artery puncture, placement of catheters and transseptal puncture, reconstruction of the left atrium and pulmonary vein angiography, and mapping; basically, near-zero fluoroscopy was used for the ablation process itself. The radiation exposure trend in a single center over the 7 years between 2010 and 2016 has been reported.¹¹⁹ Procedures included catheter ablation and device implantation. Fluoroscopic time, dose–area product, and effective dose decreased for ablation, but not for CRT device implantation. Recognizing the importance of radiation reduction in addition to technological advancements is crucial. Several studies have reported on zero or near-zero fluoroscopy ablation.^{120–122} A meta-analysis of 10 studies involving 2,261 patients who underwent zero or near-zero fluoroscopy ablation showed significant reductions in fluoroscopy time, ablation time, and radiation dose in comparison with the conventional approach, and showed similar procedure duration, success rate, complication rate, and recurrence rate.¹²³

Pulmonary vein isolation by cryoballoon ablation (CBA) has been as effective and safe as conventional radiofrequency catheter ablation (RFCA) since the launch of the 2nd-generation cryoballoon catheter. In addition, the procedure time of CBA is significantly shorter than that of RFCA.^{124,125} Recently, the safety and efficacy of CBA have been shown for both paroxysmal and persistent atrial fibrillation (AF),^{126,127} and its indication has been expanded (insurance reimbursement from November 2020 in Japan). However, the fluoroscopy time in CBA is longer than that in RFCA,^{124,125} and extended radiation exposure is a concern. The mean fluoroscopy time in the FIRE and ICE study¹²⁴ was 16.6 ± 17.8 minutes in the RFCA group and 21.7 ± 13.9 minutes in the CBA group ($P < .001$). In the CIRCA-DOSE study,¹²⁵ the median fluoroscopy time in the RFCA group was 5.2 minutes, whereas in the CBA group (CRYO-4 and CRYO-2) it was 17.2 minutes and 19.0 minutes, respectively (both $P < .001$). It is possible to shorten the fluoroscopy time in RFCA by improving the accuracy of the 3D navigation system. However, fluoroscopy is necessary for manipulation of the catheter and sheath to isolate the pulmonary vein and for the confirmation of pulmonary vein occlusion in CBA. Therefore, the exposure dose in CBA tends to be higher than in RFCA. To evaluate the degree of pulmonary vein occlusion with a cryoballoon, 2 methods that significantly reduce radiation exposure without compromising efficacy and safety have been proposed. One method confirms leakage using an intracardiac echo Doppler,^{128,129} and the other predicts the degree of occlusion from pressure changes and pressure waveforms by measuring the balloon tip pressure.^{130–132} Although the benefits of bonus-freeze have not been evident since the launch of the 2nd-generation cryoballoon, it has been reported that bonus freezing prolongs both procedure time

and fluoroscopy time, and increases complications.¹³³ The exposure dose is significantly reduced by changing from the conventional 2-time bonus-freeze method to a 1-time method (single freeze). In addition, there is a study that found the 3D mapping system effectively reduces radiation exposure¹³⁴; however, there are also drawbacks such as increased costs.

A significant proportion of the overall exposure to ionizing radiation in patients undergoing AF ablation is contributed by preprocedural CT. It has been reported that the radiation dose of preprocedural CT (9.4 ± 5.8 mSv) is drastically greater than that of the ablation procedure (2 ± 2 mSv), amounting to 82% of the total radiation dose.¹³⁵ In addition to fluoroscopic time, the projection angle, position, collimation, frame rate, pulse rate, magnification, use of cine, and body status also affect the radiation dose. Knowledge of the practical use of fluoroscopy is crucial. It has been shown that fluoroscopic time and radiation dose during AF ablation significantly reduced following a lecture on radiation reduction.¹³⁶ Additionally, using a radiation safety time-out, a novel checklist using the concept of “as low as reasonably achievable (ALARA)”, setting a low frame rate, adjusting the patient table height as close as safely possible to the intensifier, proper collimation, use of shields, dosimeter, and protectors have been shown to reduce radiation exposure.¹³⁷

3.2 | Atrial fibrillation (AF)

3.2.1 | Indications

Prognosis after AF ablation

CABANA trial. The recent catheter ablation vs. anti-arrhythmic drug treatment for atrial fibrillation (CABANA) trial⁷ demonstrated that AF ablation was not superior to drug therapy for the primary composite endpoint (death, disabling stroke, serious bleeding, or cardiac arrest) in the intention-to-treat analysis; however, suppression of the secondary composite endpoint (death from any cause or cardiovascular hospitalization) was observed in the AF ablation group. Furthermore, AF ablation was superior to drug therapy in the primary composite endpoint ($P = .046$) in the per-protocol analysis. The quality of life (QOL) analysis also reported that AF ablation was significantly superior to drug therapy in improving QOL score.¹³⁸ Although CABANA was the first, large-scale randomized controlled trial (RCT) to reveal the influence of AF ablation on the prognosis of AF patients, it failed to yield new evidence of an improvement in the long-term prognosis (Table 12).

EAST-AFNET 4⁹. This international RCT trial was the first to report that early rhythm-control therapy was associated with a lower risk of adverse cardiovascular outcomes than the usual care in patients with early AF. Patients with early AF (diagnosed ≤ 1 year before enrollment) and cardiovascular conditions were randomly assigned to receive either early rhythm-control (antiarrhythmic drug treatment of atrial AF ablation) or usual care (mainly rate-control treatment). The trial was stopped for efficacy at the 3rd interim

analysis after a median follow-up of 5.1 years per patient, because of results that a first-primary-outcome event occurred less often in patients who were assigned to receive early rhythm-control (3.9 per 100 person-years) than usual care (5.0 per 100 person-years) ($P = .005$). Although catheter ablation was performed in a relatively small number of patients (19.4% in the early rhythm-control group, 7.0% in usual care group), this study showed for the first time the effect of early rhythm control treatment in improving the outcome of AF patients.

AF catheter ablation in patients with HF

A meta-analysis of six RCTs comparing the efficacy rates between pharmacotherapy (rate or rhythm control therapy) and catheter ablation in a total of 775 HF patients with reduced cardiac function has been published.¹³⁹⁻¹⁴⁴ AF ablation significantly reduced all-cause mortality (9.0% vs. 17.6%) and HF hospitalizations (16.4% vs. 27.6%) when compared with drug therapy.⁸ Furthermore, ablation improved left ventricular ejection fraction (LVEF: mean difference, 6.95%) and QOL.

This focused update determined that the role of catheter ablation therapy in AF patients with HF is an established option to improve prognosis, and recommend that "AF catheter ablation may be reasonable in selected patients with symptomatic AF and HF with reduced left ventricular ejection fraction (HFrEF) to potentially lower mortality rate and reduce hospitalization for HF" as a Class IIa recommendation.

In the latest ESC guideline 2020,¹¹² AF catheter ablation is included as a Class I recommendation to restore LV function when AF-mediated tachycardia-induced cardiomyopathy (ventricular dysfunction secondary to rapid and/or asynchronous/irregular myocardial contraction, partially or completely reversed after treatment of the causative arrhythmia) is highly suspected. This set of guidelines also determined that catheter ablation therapy in AF patients with tachycardia-induced cardiomyopathy is a more positive option that can be expected to improve prognosis.

3.2.2 | Methods

High-power short-duration (HPSD) method

HPSD ablation (45-70 W for 5-10 s) for the treatment of AF is emerging as an alternative to conventional ablation (20-40 W for 20-40 s).^{145,146} During radiofrequency (RF) ablation, tissue heating

occurs via 2 mechanisms of resistive (direct) and conductive (indirect) heating. Resistive heating is an active process and rapidly begins and ends with the initiation and cessation of RF energy application. Conductive heating is a passive and time-dependent process as heat is transferred away from the ablation lesion core. Compared with conventional ablation, HPSD has been shown to create a wider lesion without obvious increase of lesion depth,^{147,148} which may be a preferred RF application method for atrial thin muscles.¹⁴⁹ Although the efficiency and safety of HPSD method have been shown in a nonrandomized study,^{150,151} there has been no RCT comparing HPSD and conventional methods.

Recently, the efficiency and safety of the very HPSD (vHPSD) method using a novel contact force-sensing catheter has been reported from Western countries. The RF energy is applied with 90 W for 4 s, using a temperature-control mode (surface temperature: 65-70°C), which results in substantially shorter procedural and fluoroscopic times as compared with the standard method, with similar efficiency and safety.¹⁵²

Balloon ablation as a first-choice therapy for AF

Recently, two RCTs evaluated the availability of cryoballoon ablation as a first-choice treatment for paroxysmal AF. In the STOP AF first trial,¹⁰ 203 patients were randomly assigned to receive treatment with antiarrhythmic drugs (class I or III agents) or pulmonary vein isolation (PVI) with a cryoballoon. After a follow-up period of 12 months, treatment success (freedom from initial failure of the procedure or atrial arrhythmia recurrence) was more evident in the ablation group than in the drug group (74.6% vs. 45.0%, $P < .001$). Although 2 primary safety endpoint events (pericardial effusion and myocardial infarction) occurred, serious procedure-related adverse events were rare.

In the EARLY-AF trial,¹¹ 303 patients with symptomatic, paroxysmal, untreated AF were randomly assigned to undergo cryoballoon ablation or to receive antiarrhythmic drug therapy for initial rhythm control. All patients received an implantable cardiac monitoring device to detect atrial tachyarrhythmia. At the 1-year follow-up, recurrence of atrial tachyarrhythmia was less frequent in the ablation group than in the drug-treatment group (42.9% vs. 67.8%, $P < .001$). The occurrence of serious adverse events was similar in both groups (3.2% in ablation group vs. 4.0% in drug-treatment group).

With documentation of the efficacy and safety of cryoballoon ablation as the initial treatment for paroxysmal AF in these 2 RCT trials, the popularization of first-choice PVI treatment for paroxysmal AF is anticipated to accelerate.

	COR	LOE	GOR (MINDS)	LOE (MINDS)
AF catheter ablation may be reasonable in selected patients with symptomatic AF and HFrEF to potentially lower mortality rate and reduce hospitalization for HF	IIa	B	B	II

TABLE 12 Recommendations and evidence levels for catheter ablation for atrial fibrillation in heart failure

Abbreviations: AF, atrial fibrillation; COR, class of recommendation; GOR, grade of recommendation; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LOE, level of evidence.

Balloon ablation for persistent AF

The indication of catheter ablation using balloon devices has been limited to PVI for paroxysmal AF in Japan, because PVI was thought to be efficient in treating only early-stage (paroxysmal) AF but not efficient enough for treating more advanced (persistent) AF. No ablation lesion set has been demonstrated to improve outcomes of patients with persistent AF beyond that of PVI alone in a recent RCT.¹⁵³

The STOP persistent AF trial¹²⁶ is a prospective, multicenter, single-arm, FDA-regulated trial designed to evaluate the safety and efficacy of PVI-only cryoballoon ablation for drug-refractory persistent AF (continuous episode <6 months) in 165 subjects (including 15 Japanese patients). Among them, 54.8% achieved the primary efficacy endpoint (12 months' freedom from ≥ 30 s of atrial tachyarrhythmias), and 86.8% were free from repeat ablation. The primary safety event rate was 0.6%. Significant improvements in QOL and AF-related symptoms were also observed. Based on these results, the indication of cryoballoon ablation was expanded to persistent AF in both USA and Japan in 2020. Nevertheless, it is important to note that the approved procedure is a "PVI-only" approach for drug-refractory persistent AF, and the efficacy and safety of cryoballoon application other than PVI have not been confirmed and is off-label for the time being.

3.2.3 | Perioperative anticoagulant therapy

Thromboembolism is one of the most serious complications of AF ablation, and appropriate pre-, intra-, and post-operative anticoagulant therapy are extremely crucial in minimizing its risk. Based on new knowledge of the anticoagulants used in preoperative management, the description and part of the recommendation table have been revised (Table 13).

Interruption and continuation of preoperative anticoagulants

The preoperative anticoagulant, warfarin, used to be discontinued, and ablation was performed after heparinization; however, cerebral embolisms often occurred after restarting warfarin postoperatively. Therefore, ablation with continuous administration of warfarin was attempted. As compared with the group in which warfarin was discontinued preoperatively and bridged to high-dose or low-dose heparin, Wazni et al reported significantly less hemorrhagic and blood deficiency complications in the continuous warfarin group.¹⁵⁴

Direct oral anticoagulants (DOACs) have been available in Japan since 2011, and 4 types, namely, dabigatran, rivaroxaban, apixaban, and edoxaban, are currently being used. Because the half-life of DOACs is short (≈ 5 -17 hours) and the time to reach the peak level is short, they are frequently used as an alternative anticoagulant to warfarin because of their efficacy and safety.

Therefore, the possibility of continuous administration of DOACs as with warfarin during the perioperative period of ablation has been discussed. With a short half-life and a fast peak level after oral administration, it is thought that a temporary suspension may be advantageous to avoid hemorrhagic complications such as cardiac

tamponade, puncture site bleeding, and the onset of thromboembolism in the high-risk group. However, there has been concern about the onset of ischemic complications due to emboli during a temporary drug suspension. The aforementioned speculation and concern were issues that needed to be verified.

AF ablation with continuous preoperative DOAC administration

The comparison of continuous administration of warfarin and continuous administration of a DOAC during the perioperative period of ablation has been reported in 4 DOAC RCTs. The results for the 4 types of DOACs are compared and shown in Figure 3.¹⁵⁵⁻¹⁵⁸

In the RE-CIRCUIT study¹⁵⁵ using dabigatran, there was no significant difference in ischemic complications between the dabigatran continuation and warfarin continuation groups. In terms of safety, however, the warfarin continuation group experienced cardiac tamponade, inguinal hematomas, etc, and major bleeding events were significantly higher (1.6% vs. 6.9%). Although there was a large racial difference in bleeding complications, no significant difference was observed between the 2 groups among Japanese patients who participated in the study (1.6% in the dabigatran group vs. 2.2% in the warfarin group).

In the VENTURE-AF study¹⁵⁶ of rivaroxaban, a comparison between the rivaroxaban continuation and warfarin continuation groups showed no significant differences in efficacy or safety, and ablation while continuing rivaroxaban was also allowed. This study was characterized by a small number of patients ($n = 124$) and an extremely small number of events (0.0% vs. 2.4%) in both groups as compared with other studies.

In the AXAFA AFNET 5 study¹⁵⁷ using apixaban, a comparison between the apixaban continuation and warfarin continuation groups exhibited no significant differences in efficacy or safety. Furthermore, the detection rate of asymptomatic microinfarcts using brain MRI was similar. The characteristics of this study were that the event occurrence rate was slightly high in both groups (4.0% vs. 4.7%), but the average CHA₂DS₂-VASc score of the target patient group was also considered to be a factor.

In the ELIMINATE-AF study¹⁵⁸ using edoxaban, as with rivaroxaban and apixaban there were no significant differences regarding the efficacy or safety between the edoxaban continuation and warfarin continuation groups. Hemorrhagic complications were slightly higher in the edoxaban continuation group but there was no significant difference (2.4% vs. 1.7%).

AF ablation with interruption of preoperative DOACs

On the other hand, there have been several studies, including RCTs, reporting on AF ablation with perioperative interruption of DOACs.¹²⁻¹⁵ In the ABRIDGE-J study¹² conducted in Japan using dabigatran, the short-term interrupted dabigatran group ($n = 220$) and continuous warfarin group ($n = 222$) showed no significant difference in terms of ischemic complications. In terms of safety, however, as was observed in the RE-CIRCUIT study, the occurrence of cardiac tamponade and femoral hematoma complications was significantly higher in the warfarin continuation group than in the minimally-interrupted dabigatran group (1.4% vs. 5.0%).

	COR	LOE	GOR (MINDS)	LOE (MINDS)
For patients with persistent AF or those with high risk of embolism (CHADS ₂ score ≥ 2), systemic anticoagulation with warfarin or a DOAC is reasonable for ≥ 3 weeks prior to AF ablation	IIa	C	C1	VI
For patients who have been therapeutically anticoagulated with warfarin or dabigatran, performance of the ablation procedure without interruption of warfarin or dabigatran is recommended	I	A	A	I
For patients who have been therapeutically anticoagulated with rivaroxaban, apixaban, or edoxaban, performance of the ablation procedure without interruption of rivaroxaban, apixaban, or edoxaban is reasonable	IIa	B	B	II
For patients who have been therapeutically anticoagulated with a DOAC prior to AF ablation, it is reasonable to interrupt 1 or 2 dose(s) of DOAC prior to AF ablation with its re-initiation post-ablation	IIa	B	B	II
Heparin should be administered immediately following femoral venous puncture or transeptal puncture during AF ablation procedures, and adjusted to achieve and maintain an ACT ≥ 300 s	I	B	B	III
Systemic anticoagulation with warfarin or a DOAC is recommended at least 3 months post AF ablation, regardless of the apparent success or failure of the AF ablation procedure	IIa	C	C1	VI
For patients with a high risk for embolism (CHADS ₂ score ≥ 2), continuation of systemic anticoagulation with warfarin or a DOAC should be considered even after 3 months of AF ablation, considering AF recurrence during the follow-up period	IIa	C	C1	VI

TABLE 13 Recommendations and evidence levels for anticoagulation strategies pre-, intra-, and post-ablation of atrial fibrillation

Abbreviations: ACT, activated clotting time; AF, atrial fibrillation; COR, class of recommendation; DOAC, direct oral anticoagulant; GOR, Grade of Recommendation; LOE, level of evidence.

Furthermore, a study by Nakamura et al,¹³ as an RCT conducted in Japan, compared the occurrence of embolisms and hemorrhagic complications in the continuous and minimally-interrupted groups for the 4 DOACs used in Japan; for all DOACs, there was no significant difference between the 2 groups. Furthermore, MRI revealed no significant difference in the occurrence of asymptomatic micro-cerebral embolisms between the 2 groups.

The decision to continue or suspend the drug is left to the standards of the facility, discretion of the operator, and situation surrounding the case (risk of thromboembolisms and bleeding); however, fine adjustments such as the timing of the final preoperative administration and the time of ablation (morning or afternoon) may be considered.

In an integrated analysis of the RE-CIRCUIT study¹⁵⁵ with the continuous administration of dabigatran and the ABRIDGE-J study¹² with minimally interruption of dabigatran,¹⁵⁹ 1.9% of the major bleeding events occurred within 8 hours of the final oral administration of

dabigatran, 0% between 8 and 24 hours, and 3.5% beyond 24 hours from the start of the ablation procedure. Major bleeding events were significantly lower in the group between 8 and <24 hours.

Reversal agents for various anticoagulants

The continuation of anticoagulants is desirable, considering the suppression of thrombus formation during the perioperative period of ablation, but the presence of an anticoagulant reversal agent is important when bleeding complications such as cardiac tamponade occur during the course of procedure. Reversal agents, such as protamine for heparin and vitamin K for warfarin, are also being developed for DOACs.

For dabigatran, the specific reversal agent, idarucizumab, is currently used in clinical practice during bleeding complications. In a multicenter study in Japan, Okishige et al¹⁶ reported 21 cases of perioperative cardiac tamponade due to the continuous

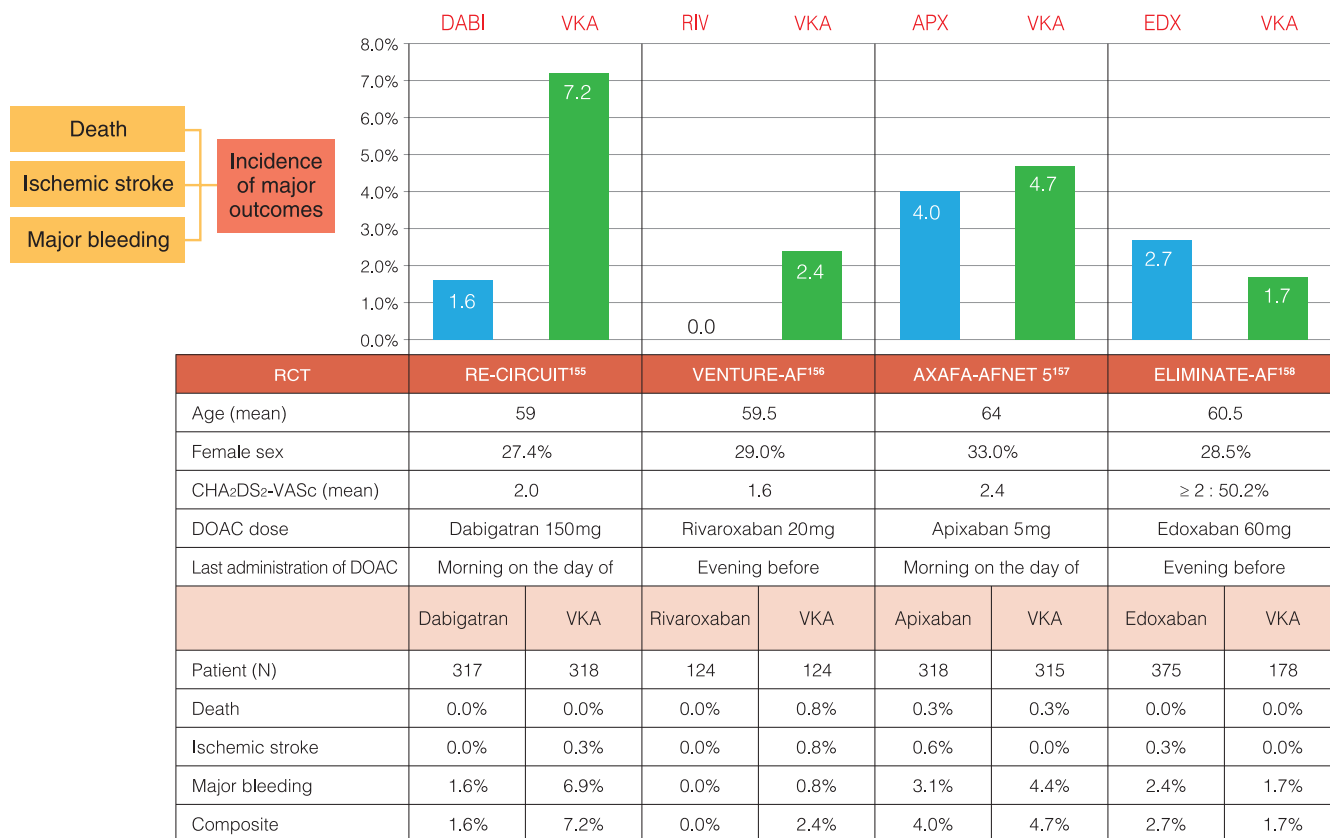


FIGURE 3 Ablation of atrial fibrillation (AF) with continuous preoperative administration of a direct oral anticoagulant (DOAC). APX, apixaban; DABI, dabigatran; EDX, edoxaban; RCT, randomized controlled trial; RIV, rivaroxaban; VKA, vitamin K antagonist

administration of dabigatran on the morning of the ablation procedure. Hemostasis was confirmed an average of 2.1 hours after the administration of idarucizumab in 16 of the 21 patients, and only 1 patient required a surgical repair.

Furthermore, based on the RE-CIRCUIT study¹⁵⁵ and the availability of a reversal agent, studies on switching from other anticoagulants to dabigatran during the perioperative period of ablation have been conducted,^{17,18} and switching has been shown to have an inhibitory effect on cerebral embolisms, including those that are asymptomatic.

Reversal agents (andexanet alfa) for factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) have also been developed and their effectiveness has been reported¹⁶⁰ (not approved in Japan yet). Currently, multicenter, prospective, open-label studies are being conducted in Japan, North America, and Europe.

IV | LEFT ATRIAL APPENDAGE CLOSURE DEVICE

4.1 | Randomized trial of the WATCHMANTM device

In Western countries, several left atrial appendage closure (LAAC) devices have been launched. The efficacy and safety of the WATCHMANTM device against long-term oral warfarin have been

evaluated in 2 randomized controlled trials (RCTs): PROTECT AF¹⁶¹ and PREVAIL.¹⁶² In a combined analysis of these two RCTs,¹⁶³ there were no significant differences in the primary efficacy endpoints (stroke, systemic embolism, and cardiovascular death/death with an unknown cause) and the primary safety endpoints (serious bleeding, and procedure-related complications) between the WATCHMANTM device and long-term oral warfarin groups. Although there was no significant difference in the incidence of cerebral infarction events between groups, the incidences of hemorrhagic stroke (hazard ratio [HR]: 0.2, 95% confidence interval [CI]: 0.07-0.56, $P = .0022$), disabling/fatal stroke (HR: 0.45, 95% CI: 0.21-0.94, $P = .034$), and cardiovascular death/death with an unknown cause (HR: 0.59, 95% CI: 0.37-0.94, $P = .027$) were significantly lower in the WATCHMANTM group. The results indicated that the LAAC device could serve as an alternative to oral anticoagulant (OAC) for non-valvular atrial fibrillation (NVAF) patients at high risk for bleeding events. In the SALUTE study ($n = 42$) verifying the efficacy and safety of the WATCHMANTM device in Japanese NVAF patients at risk for cerebral infarction (CHA₂DS₂-VASc score ≥ 2), the procedure success rate and complication rate were similar to those reported in previous studies.¹⁶⁴ During a 2-year follow-up, there were 3 ischemic events (7.1%) without any sequelae.¹⁹ Successful LAAC, defined as a peri-device leak ≤ 5 mm, was achieved in all patients, but an asymptomatic device thrombus was detected in 2 patients (4.8%).¹⁹ In a combined analysis of 2 RCTs and 2 large registries, the incidence of device thrombus was 3.7%,¹⁶⁵ similar to that of the SALUTE trial.

4.2 | Considerations in Japanese patients

During the SALUTE trial, all patients received a ≥ 27 mm WATCHMAN™ device; a ≥ 27 mm device was used in $< 40\%$ of the enrolled patients in the PROTECT-AF and PREVAIL trials. In the WASP registry enrolling patients from Asia and the Pan-Pacific region, significantly larger devices were implanted when compared with Western countries¹⁶⁶; therefore, race may affect LAA size. A larger LAA orifice has been reported as a predictor of device thrombus,¹⁶⁵ and worsening of residual peri-device leak was significantly frequent in longstanding persistent AF patients with a WATCHMAN™ device ≥ 27 mm.¹⁶⁷ Hence, further evaluation of the incidence of device thrombus or residual peri-device leak in Japanese patients who receive larger devices is required, with larger sample sizes.

4.3 | LAAC as an alternative option to DOAC

Non-inferiority of the LAAC to direct oral anticoagulants (DOACs) was demonstrated in the left atrial appendage closure vs. novel anticoagulation agents in atrial fibrillation (PRAGUE-17) trial.¹⁶⁸ Patients with NVAF requiring OAC, with a history of bleeding requiring intervention or hospitalization, a cardioembolic event while taking an OAC, and/or CHA₂DS₂-VASc ≥ 3 and HAS-BLED ≥ 2 , were enrolled and randomized to receive LAAC or DOAC. The implanted devices were either Amulet™ (61.3%), Watchman™ (35.9%), or Watchman-FLX™ (2.8%), and most patients received dual anti-platelet therapy (DAPT). During a median follow-up of 19.9 months, the annual rates of the primary outcomes (stroke, transient ischemic attack, systemic embolism, cardiovascular death, major or non-major clinically relevant bleeding, or procedure-/device-related complications) were 10.99% with LAAC and 13.42% with DOAC (HR: 0.84; 95% CI: 0.53-1.31; $P = .44$). Among patients at high risk for stroke and bleeding, LAAC was non-inferior to DOAC in preventing composite cardiovascular events.

4.4 | Peri-procedural complications

Several critical peri-procedural complications, such as cardiac tamponade, thromboembolism, peri-device leak, and device embolism, have been reported. Procedure-related complications were especially observed during the pivotal PROTECT-AF trial, but these adverse events declined with increasing operator experience.¹⁶⁹

Although peri-procedural complications requiring surgical intervention are rare, the rate of cardiac tamponade was 1.2% in the post FDA approval USA experience,¹⁷⁰ and 31% of the cases required surgical intervention. Embolization of a large sized device (≥ 27 mm) into the left atrium or left ventricle can cause hemodynamic instability, thereby prompting urgent surgical device retrieval.¹⁷¹ Therefore, it is important to evaluate the morphology of left atrial appendage before procedure, and perform LAAC with a surgical back-up.

4.5 | Indications

In Japan, LAAC is approved for NVAF patients indicated for long-term OAC with a high risk of bleeding (HAS-BLED ≥ 3 , a history of BARC type 3 bleeding, requiring DAPT ≥ 1 year, multiple episodes of falls requiring interventions, or a history of cerebral amyloid angiopathy).¹⁷² Patients with a history of a cardioembolic event while taking an OAC or poor compliance with OAC therapy are not eligible for LAAC. In contrast to OACs, the effectiveness and safety of LAAC in patients with chronic renal failure regardless of severity have been reported.^{173,174} However, a significant association between acute kidney disease (an absolute or a relative increase in serum creatinine of > 0.3 mg/dL or $\geq 50\%$ of baseline value) and higher mortality was reported, thus requiring preventive strategies, especially in patients with chronic kidney disease.¹⁷⁵ In the ESC and AHA/ACC/HRS guidelines,^{110,176} percutaneous LAAC is classified as a Class IIb indication for stroke prevention in patients at an increased risk of stroke and with contraindications to long-term OAC therapy. Previous studies have shown the superiority of LAAC to long-term warfarin,¹⁶³ and non-inferiority to DOACs¹⁶⁸; thus, LAAC could be considered in NVAF patients and those with an increased risk of stroke and contraindications to long-term OAC (Class IIb, Table 14). The procedural success rate and safety in the SALUTE trial were similar to those in the studies from Western countries, but the sample size was small and appeared to have different characteristics (ie, larger device size). A registry with a larger sample size is required to establish the evidence for LAAC in Japanese patients.

4.6 | Post-procedural anti-thrombotic regimen

An animal study demonstrated that the anti-thrombotic effect of the LAAC device appears at 90 days after endothelialization of the

	COR	LOE	GOR (MINDS)	LOE (MINDS)
Percutaneous left atrial appendage closure may be considered in patients with non-valvular AF who are at an increased risk of stroke and have contraindications to long-term anticoagulation	IIb	B	B	II

TABLE 14 Recommendations and evidence levels for left atrial appendage closure device

Abbreviations: AF, atrial fibrillation; COR, class of recommendation; GOR, Grade of Recommendation; LOE, level of evidence.

device.¹⁷⁷ Nevertheless, a combined analysis of 2 RCTs and 2 registries revealed that 3.7% of patients suffered from device thrombosis, and a majority of the thrombi was found after cessation of warfarin at 45 days.¹⁶⁵ In an observational registry, an antithrombotic regimen using DOAC and antiplatelet therapy demonstrated similar efficacy to that of warfarin.¹⁷⁸ In patients ineligible for OAC due to high bleeding risk, an antithrombotic regimen using DAPT was investigated. In the ASAP trial, an antithrombotic regimen using DAPT was used in patients contraindicated for OAC, and device thrombus was observed in 4.0% of them.¹⁷⁹ In the EWOLUTION registry, DAPT was used in 62% of the patients, and device thrombus was found in 4.0%.¹⁸⁰ There is no RCT comparing antithrombotic regimens using warfarin with antiplatelet therapy vs. DAPT, but combined analysis of 6 large studies using propensity-matched analysis showed that device thrombosis was significantly more frequent in patients receiving DAPT.¹⁸¹ Therefore, antithrombotic therapy using OACs should be considered for patients who are eligible, but in patients with high bleeding risk and those contraindicated for using OACs, an antithrombotic regimen should be considered individually, as well as surveillance for device thrombus.

In patients with device thrombus, there was an approximately 4-fold increase in the incidence of thromboembolism, though resolution of device thrombus could be achieved in a majority of cases under OAC.^{165,182} However, recurrence of device thrombus was reported in 34.8% of patients after discontinuation of OACs.¹⁸³ Therefore, an antithrombotic regimen after device thrombus resolution should be considered individually, taking into account the bleeding risk.

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APPENDIX 1. DETAILS OF MEMBERS

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- Akihiko Nogami, MD, PhD, Department of Cardiology, Faculty of Medicine, University of Tsukuba

APPENDIX 2 DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST (COI): JCS/JHRS 2021 GUIDELINE FOCUSED UPDATE ON NON-PHARMACOTHERAPY OF CARDIAC ARRHYTHMIAS

Author	Potential COI of the participant				Speakers' bureau	Payment for manuscripts	Research grant	Scholarship (educational) grant	Endowed chair	Other rewards	Potential COI of the marital partner, first degree family members, or those who share income and property	Declaration about the head of your affiliated organization/department (if the participant is conducting joint research with the head of the organization/department)
	Employer / leadership position (private company)	Stock or stock options	Intellectual property / royalties	Intellectual property / royalties								
Chair: Takashi Kurita					Medtronic Japan Co., Ltd. BIOTRONIK Japan, Inc Bayer Yakuhin, Ltd. Daiichi Sankyo Company, Limited Bristol-Myers Squibb Nippon Boehringer Ingelheim Co., Ltd.							
Chair: Akihiko Nogami					Abbott Japan LLC Johnson & Johnson KK Bayer Yakuhin, Ltd. Bristol-Myers Squibb Nippon Boehringer Ingelheim Co., Ltd. Daiichi Sankyo Company, Limited Medtronic Japan Co., Ltd.			Medtronic Japan Co., Ltd. DVx Inc				
Member: Masahiko Goya					Japan Lifeline Co., Ltd. Daiichi Sankyo Company, Limited Medtronic Japan Co., Ltd.		Japan Lifeline Co., Ltd.					
Member: Masaomi Kimura					Johnson & Johnson KK Medtronic Japan Co., Ltd. TORAY INDUSTRIES, INC. Abbott Medical Japan LLC Boston Scientific Japan KK Bayer Yakuhin, Ltd. Nippon Boehringer Ingelheim Co., Ltd.			Fukuda Denshi Co., Ltd Medtronic Japan Co., Ltd.				
Member: Kengo Kusano					Medtronic Japan Co., Ltd. Bristol-Myers Squibb Bayer Yakuhin, Ltd.		Medtronic Japan Co., Ltd.					
Member: Shigeto Naito					Daiichi Sankyo Company, Limited Johnson & Johnson KK							
Member: Takashi Noda					Medtronic Japan Co., Ltd. Boston Scientific Japan KK							
Member: Tsuyoshi Shiga					Daiichi Sankyo Company, Limited Ono Pharmaceutical Co., Ltd. Bristol-Myers Squibb		Daiichi Sankyo Company, Limited Ono Pharmaceutical Co., Ltd.					

APPENDIX 2 (Continued)

Potential COI of the participant		Potential COI of the marital partner, first degree family members, or those who share income and property		Declaration about the head of your affiliated organization/department (if the participant is conducting joint research with the head of the organization/department)							
Employer / leadership position (private company)	Stock or stock options	Intellectual property / royalties	Speakers' bureau	Payment for manuscripts	Research grant	Scholarship (educational) grant	Endowed chair	Other rewards	Potential COI of the marital partner, first degree family members, or those who share income and property	Research grant	Scholarship (educational) grant
Member: Morio Shoda							BIOTRONIK Japan, Inc Medtronic Japan Co., Ltd. Boston Scientific Japan KK Abbott Medical Japan LLC				
Member: Kyoko Soejima	Abbott Medical Japan LLC Johnson & Johnson KK Bayer Yakuhin, Ltd. BIOTRONIK Japan, Inc Bristol-Myers Squibb Daiichi Sankyo Company, Limited Nippon Boehringer Ingelheim Co., Ltd. Medtronic Japan Co., Ltd. Johnson & Johnson KK BIOTRONIK Japan, Inc Bristol-Myers Squibb Daiichi Sankyo Company, Limited Nippon Boehringer Ingelheim Co., Ltd.										
Member: Hiroshi Tada						Abbott Medical Japan LLC CENTRAL MEDICAL Co., Ltd. D-sense Novartis Pharma KK Bayer Yakuhin, Ltd. Ono Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited Nippon Boehringer Ingelheim Co., Ltd. Takeda Pharmaceutical Company Limited					

(Continues)

APPENDIX 2 (Continued)

Author	Potential COI of the participant				Payment for manuscripts	Research grant	Scholarship (educational) grant	Endowed chair	Other rewards	Potential COI of the marital partner, first degree family members, or those who share income and property	Declaration about the head of your affiliated organization/department (if the participant is conducting joint research with the head of the organization/department)
	Employer / leadership position (private company)	Stock or stock options	Intellectual property / royalties	Speakers' bureau							
Member: Teiichi Yamane	Abbott Japan LLC KANEKA CORPORATION Bayer Yakuhin, Ltd. Bristol-Myers Squibb Daiichi Sankyo Company, Limited TORAY INDUSTRIES, INC. Nippon Boehringer Ingelheim Co., Ltd.			Bayer Yakuhin, Ltd.	Nippon Boehringer Ingelheim Co., Ltd.						
Member: Hiro Yamasaki	Medtronic Japan Co., Ltd. Japan Lifeline Co., Ltd.										
External Evaluation Committee: Takeshi Kimura	Abbott Vascular Japan Co., Ltd. Sanofi KK Bristol-Myers Squibb Boston Scientific Japan KK Kowa Company, Ltd., Nippon Boehringer Ingelheim Co., Ltd.			Edwards Lifesciences Corporation EP-CRSU Co., Ltd. Pfizer Japan Inc Kowa Company, Daiichi Sankyo Company, Limited	Astellas Pharma Inc MID, Inc Otsuka Pharmaceutical Co., Ltd. Daiichi Sankyo Company, Limited Mitsubishi Tanabe Pharma Corporation Nippon Boehringer Ingelheim Co., Ltd. Takeda Pharmaceutical Company Limited						
External Evaluation Committee: Shun Kohsaka	Bristol-Myers Squibb Pfizer Japan Inc Bayer Yakuhin, Ltd. AstraZeneca KK			Bristol-Myers Squibb Daiichi Sankyo Company, Limited							
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Notation of corporation is omitted.											
No potential COI for the following members.											
External Evaluation Committee: Yoshifusa Aizawa, Tohru Ohe											