Received: 21 June 2024 | Revised: 26 August 2024 | Accepted: 11 September 2024

DOI: 10.1111/jce.16443

ORIGINAL ARTICLE

WILEY

Expert opinion on design and endpoints for studies on catheter ablation of atrial fibrillation

Thorsten Lewalter MD, PhD[1,2] | Carina Blomström-Lundqvist MD, PhD[3,4] | Dhanunjaya Lakkireddy MD[5] | Douglas Packer MD[6] | Ralf Meyer PhD[7] | Malte Kuniss MD[8] | Karl-H. Ladwig MD, PhD[9,10] | Clemens Jilek MD[11,12] | Hans-C. Diener MD, PhD[13] | Giuseppe Boriani MD, PhD[14] | Mintu P. Turakhia MD[15] | Steffen Schneider PhD[16] | Emma Svennberg MD, PhD[17] | Bert Albers PhD[18] | Jason G. Andrade MD[19] | Mirko de Melis PhD[20] | Johannes Brachmann MD, PhD[21]

Correspondence
Thorsten Lewalter, MD, PhD, FESC, Head, Department of Cardiology and Intensive Care, Peter Osypka Heart Center Munich, Hospital Munich South, Am Isarkanal 36, 81379 Munich, Germany.
Email: Thorsten.lewalter@ikms.de

Disclosures: Thorsten Lewalter reports in relation to the topic: moderate speaker honoraria and research support from Boston Scientific, Abbott, Medtronic; Carina Blomström-Lundqvist reports personal fees from Bayer, Medtronic, CathPrint, Organon, Sanofi Aventis, Boston Sci, Johnson & Johnson, Abbott, and Philips outside the submitted work; Malte Kuniss has received grants from Medtronic; Karl-H. Ladwig reports honoraria for lectures from Amgen, AstraZeneca, Bayer Vital, Pfizer; honoraria for advisory board activities from Idorsia, Switzerland, participation in clinical trials (SPIRRCAD, MREDEA, TRACE AF, ARENA) and research funding from German Ministry of Education and Research (GESA Grant application), by the German Centre of Diabetes Research and by the German Heart Foundation; Clemens Jilek reports research grants from Boston Scientific and consulting fees from Biotronik, m3i, and Pfizer; In the last 3 years, Hans-C. Diener received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from: Abbott, BMS, Boehringer Ingelheim, Daiichi-Sankyo, Novo-Nordisk, Pfizer, Portola and WebMD Global. Boehringer Ingelheim provided financial support for research

Abstract

Introduction: Catheter ablation of atrial fibrillation (AF) is frequently studied in randomized trials, observational and registry studies. The aim of this expert opinion is to provide guidance for clinicians and industry regarding the development of future clinical studies on catheter ablation of AF, implement lessons learned from previous studies, and promote a higher degree of consistency across studies.

Background: Studies on catheter ablation of AF may benefit from well-described definitions of endpoints and consistent methodology and documentation of outcomes related to efficacy, safety and cost-effectiveness. The availably of new, innovative technologies warrants further consideration about their application and impact on study design and the choice of endpoints. Moreover, recent insights gained from AF ablation studies suggest a reconsideration of some methodological aspects.

Methods: A panel of clinical experts on catheter ablation of AF and designing and conducting clinical studies developed an expert opinion on the design and endpoints for studies on catheter ablation of AF. Discussions within the expert panel with the aim to reach consensus on predefined topics were based on outcomes reported in the literature and experiences from recent clinical trials.

Results: A comprehensive set of recommendations is presented. Key elements include the documentation of clinical AF, medication during the study, repeated ablations and their effect on endpoint assessments, postablation blanking and the choice of rhythm-related and other endpoints.

For affiliations refer to page 2199.

Abbreviations: AF, Atrial fibrillation; CROM, Clinician-reported outcome measure; ECG, Electrocardiogram; (HR)QoL, (Health-related) Quality of life; ICM, Insertable cardiac monitor; PROM, Patient-reported outcome measure; PVI, Pulmonary vein isolation.

projects; Hans-Christoph Diener received research grants from the German Research Council (DFG) and German Ministry of Education and Research (BMBF); Giuseppe Boriani reported small speaker fees from Bayer, Boehringer Ingelheim, Boston, Daiichi Sankyo, Janssen, and Sanofi outside of the submitted work; Mintu P. Turakhia is an employee and shareholder of iRhythm Technologies. Outside of the submitted work, reports research grants from Bristol Myers Squibb, American Heart Association, Bayer, Gilead Sciences, and the Food and Drug Administration, consulting fees from Medtronic, Pfizer, Johnson & Johnson, Alivecor, and equity from iRhythm, Connect America, Forward, and Evidently; Emma Svennberg is supported by the Stockholm County Council (Clinical researcher appointment), the Swedish Research Council (DNR 2022-01466), the Swedish Heart and Lung foundation, CIMED, and has received lecture fees from Abbott, Bayer, Bristol-Myers Squibb-Pfizer, Boehringer- Ingelheim, Johnson & Johnson, Merck Sharp & Dohme; Bert Albers received a honorarium from CardioVascular Academy gGmbH, Munich, Germany for preparation of this manuscript; Jason G. Andrade reports consulting fees and honoraria from Bayer Healthcare; BMS/Pfizer Alliance; Servier; Medtronic and research grants from Canadian Arrhythmia Network, a Network of Clinical Excellence; Heart and Stroke Foundation of Canada; Michael Smith Foundation for Health Research; Baylis Medical; Medtronic, Inc; Bayer HealthCare; BMS/Pfizer Alliance; Servier; Mirko de Melis is part of the Horizon Europe ITN INSIDE-HEART (G.N. 101119941) and Horizon Europe RIA SMASH-HCM (G.N. 101137115) and is an employee of Medtronic Bakken Research Center; Johannes Brachmann reports advisory board memberships for Johnson & Johnson and iRhythm.

Funding information
Cardiovascular Academy gGmbH, Munich, Germany

Conclusion: This expert opinion provides guidance and promotes consistency regarding design of AF catheter ablation studies and identified aspects requiring further research to optimize study design and methodology.

CONDENSED ABSTRACT: Recent insights from studies on catheter ablation of atrial fibrillation (AF) and the availability of new innovative technologies warrant reconsideration of methodological aspects related to study design and the choice and assessment of endpoints. This expert opinion, developed by clinical experts on catheter ablation of AF provides a comprehensive set of recommendations related to these methodological aspects. The aim of this expert opinion is to provide guidance for clinicians and industry regarding the development of clinical studies, implement lessons learned from previous studies, and promote a higher degree of consistency across studies.

KEYWORDS
atrial fibrillation, catheter ablation, clinical studies, endpoints, postablation blanking, study design

1 | INTRODUCTION

Catheter ablation of atrial fibrillation (AF) has rapidly evolved, and clinical studies have provided extensive evidence regarding the efficacy and safety of the treatment, as well as information about Quality-of-life (QoL), long-term outcomes, Patient-Reported Outcome Measures (PROMs) and health economic aspects across a large variety of regional reimbursement systems. While new energy sources, ablation and mapping technologies enter the clinical arena, comparative research has an increasing importance. Innovative mobile technologies and technology-derived endpoints appear to provide more complete information, and an increased and more diverse participation of patients in clinical trials is needed. Updated and more consistent methodologies in study design, definitions of endpoints, data collection points, and innovative ways in patient follow up potentially improve quality, efficiency and comparability in performing clinical trials and the generation of meta-analyses.

Adequate study design processes reduce the need of study redesign, resubmissions of protocol amendments to Ethic Committees or changes of data fields in trial documentation. In addition, new insights and outcomes reported in the literature warrant a revision of certain aspects related to studies on catheter ablation of AF. This expert opinion is aimed at incorporating these new insights into a comprehensive guidance for the design and choice of endpoints of AF ablation studies. Moreover, it incorporates lessons learned from previous studies and promotes consistency in methodology and definition and assessment of endpoints for AF ablation studies.

2 | METHODS

This manuscript reflects the opinion of a group of subject matter experts with regard to catheter ablation of AF. Experts were selected based on their clinical experience, participation in clinical trials and scientific

publications with regard to AF ablation. Topics were identified during online meetings involving all experts. Four working groups were created to discuss separate sub-areas, including (1) study design, (2) acute and long-term safety and complications, (3) acute efficacy and (4) long-term efficacy. In each working group, topics related to the subarea were discussed and when possible, initial opinions were discussed and proposed. Opinions were based on the experts' interpretation of the most recent data reported in the literature and, where meaningful, their experience from clinical practice. Consensus was reached during a face-to-face meeting and subsequent review and revision of this manuscript. The final manuscript was approved by all experts.

3 | STUDY DESIGN

General topics of trial design as well as specific aspects of AF ablation studies are well-addressed in the literature and textbooks. The 2017 expert consensus statement on catheter and surgical ablation of AF,[1] endorsed by several cardiac societies, provides guidance regarding aspects related to the design of AF ablation trials. The US Food and Drug Administration has issued several guidances related to the design of clinical trials[2] and further overall guidance can be obtained from the guideline for good clinical practice issued by the European Medicines Agency[3] and the ISO 14155 standard.[4] Moreover, the designs of several AF ablation studies, published in the literature, provide relevant examples of study design and underlying considerations.[5–9]

3.1 | Study type

Randomized controlled trials remain the cornerstone of clinical evidence. Particularly, the assessment of new technologies or treatment approaches in comparison to the state of the art is preferably conducted using a randomized treatment allocation. Nevertheless, randomization is not always possible or ethical and the most optimal study approach may depend on the topic being addressed. Nonrandomized comparative studies may be the next best alternative, although the potential for selection bias should be acknowledged. In that respect, consecutive enrollment is strongly recommended to mitigate the risk of bias. Other alternatives include prospective cohort studies, observational studies and retrospective analyses. Options to compare outcomes include the use of an historical control, propensity score matched analysis, or the use of objective performance levels. Obviously, the overall design of a study is an important aspect determining the strength of the provided evidence, and may range from pivotal evidence obtained from a randomized controlled trial to secondary, supporting evidence or data for hypothesis formulation.

3.2 | Patient selection

3.2.1 | AF profile

Throughout the study, consistent methodology should be applied to document the cardiac rhythm by an electrocardiogram (ECG) allowing for AF classification according to the definitions provide by current guidelines.[10–13] Specifically, ECG documentation of AF at baseline is a key criterion for study inclusion. Study inclusion should be justified by an ECG recording of the qualifying cardiac rhythm, obtained by validated equipment able to provide at least an ECG rhythm strip in line with the definitions of clinical AF provided by guidelines (i.e., a rhythm characteristic of AF, lasting ≥30 s).[12] In this regard, FDA has cleared several smartwatches for detection and recording of AF. Several studies have reported appropriate AF detection of these devices, albeit with variable reliability.[14–16]

Requirements for documentation of AF depend on the AF subtype. While persistent AF is defined as an arrhythmia ongoing for at least 7 days, it should be recognized that in current clinical practice, patients may undergo cardioversion within 7 days of arrhythmia onset or first detection. Recommendations with regard to documentation of AF throughout the study are provided in Table 1.

3.2.2 | Patient profile

Patient characteristics, social determinants, medical history, comorbidities and concomitant treatments should be comprehensively documented to justify patient selection. Study design should account for differences in treatment responses related to patient characteristics (e.g., age, Body Mass Index, sex, race and ethnicity) and social determinants (e.g., education, income status).[17,18] Therefore, patient recruitment should support diversity, and patients should not, a priori, be excluded on the basis of social determinants. Nevertheless, specific patient groups may be excluded as justified by an analysis of study-related risks and expected benefits.[19] Site selection and geographical distribution of participating sites may influence diversity within the overall study population, due to regional or national patterns of social determinants. Selected patients should reflect the target population and indication for treatment under study.

While patient recruitment may not be balanced for all aspects that potentially influence treatment responses, comprehensive documentation of these aspects is recommended. This will allow analysis of homogeneity of treatment effects among subpopulations. Aspects to be documented for evaluation of homogeneity of treatment effects are part of data collection at enrollment, listed in Table 2.

3.2.3 | Screening, enrollment and baseline data

Typically, patients are screened for eligibility and enrolled after providing informed consent. To allow evaluation of the degree of patient selection, it is important to document the number of patients screened, the number of screening failures, and the number of eligible patients who did not sign an informed consent and therefore were not enrolled.

From patients actually enrolled, comprehensive baseline and demographic data should be collected to allow characterization of the study population. A comprehensive overview of data to be collected at

TABLE 1 Recommendations on documentation of defined AF profiles/types.

1. Requirements depend on AF-subtype:
   - *Paroxysmal AF*: Documentation of an AF episode and sinus rhythm achieved by spontaneous cardioversion in a single or in separate recordings.
   - *Persistent AF*:
     - Classical persistent AF:
       - Continuous ECG monitoring showing uninterrupted AF for at least 7 days (most optimal).
       - Two ECG recordings with ongoing AF separated by at least 7 days.
     - Cardioversion dependent AF:
       - In case of cardioversion within 7 days after arrhythmia onset and without documentation of spontaneous conversion to sinus rhythm: ECG recording of AF prior to cardioversion.
2. Technology: Any available ECG technology capable of providing the required documentation. This includes clinical (12-lead or single-lead) surface ECG, ambulatory Holter monitoring, triggered event recording, external loop recording, insertable cardiac monitor, etc. Recordings or other arrhythmia detection means provided by cardiac implantable electronic devices equipped with an atrial lead (pacemaker, implantable cardioverter-defibrillator) may also be used, but ECG recordings should be inspected to verify and confirm the rhythm classification. Novel technology including smartwatches and other wearable devices may be considered, provided they are equipped with an ECG recording feature, while acknowledging potential issues regarding patient's adherence and detection reliability.

Abbreviation: ECG, electrocardiogram

enrollment is provided in Table 2. Data collection during follow-up, beyond endpoint-related data, is usually a subset of the data listed in Table 2, and should be assessed and documented using identical methods throughout the study.

3.3 | Medication during the study

3.3.1 | Antiarrhythmic drug (AAD) therapy

Evidence from randomized trials suggests that short-term AAD use after RF catheter ablation significantly reduces the risk of early recurrences, but has no effect on the risk of late recurrences.[20–23] Variable approaches regarding AAD use after AF catheter ablation are followed, in daily clinical routine as well as in AF ablation studies. Among five randomized controlled trials included in a meta-analysis comparing catheter ablation versus AAD therapy, three studies allowed the use of class I/III AADs for up to 3 months after ablation, while two studies excluded AADs post-ablation.[24] Several aspects regarding the use of AADs and beta-blockers for antiarrhythmic treatment within a study context should be considered. First, the peri-ablation use of AADs may conceal non-PV triggers and thereby affect procedural outcomes.[25] Second, the use of AADs post-ablation may interfere with rhythm-related endpoints of the trial (e.g., freedom from recurrences off-AAD). Dosing of AAD therapy that is continued postablation should adhere to evidence-based guidelines, avoiding either over- or under-dosing.[10–12] Last, patient conditions may prohibit discontinuation of AAD therapy, e.g. in severe HF with reduced ejection fraction. Application of the recommendations provided in Table 3 should account for these aspects.

3.3.2 | Anticoagulation therapy

Randomized controlled AF ablation studies reported in the literature typically allow the use of anticoagulants after ablation for several months or during the entire study period.[24] Clinical practice may show substantial heterogeneity and insufficient adherence to guidelines[26] regarding post-ablation anticoagulation therapy. To promote consistency in anticoagulation therapy across studies, maximal adherence to guidelines is recommended. For patients on therapeutic anticoagulation therapy, evidence-based guidelines[10–12] recommend to perform the ablation procedure without interruption of anticoagulation therapy. Heparin bridging may increase the bleeding risk and is not supported by the guidelines.[10,12] Heparin is routinely used during the ablation procedure. The study protocol should provide a detailed description of the anticoagulation regimen before, during and after the procedure. Recommendations with regard to anticoagulation therapy within a study context are provided in Table 4.

3.4 | Site selection, investigator qualifications

Clinical centers and individual physicians considered for participation in an AF ablation trial should have documented qualification and sufficient experience in the treatment(s) under study, as well as in conducting clinical studies according to international guidelines and regulations. Requirements with regard to clinical competence related to diagnosis, catheter ablation and follow-up care are provided by several guidance documents.[1,27,28] If physicians have limited experience with a specific device or if a novel technology is studied, a "run-in study phase" should be considered to reduce the learning curve effects in the primary study outcome. The run-in phase duration should mirror the length of the learning curve, when known. Moreover, an investigator training on the study protocol and the clinical procedures involved should be considered.

An important aspect to be considered for selection of investigators is clinical equipoise. A therapeutic bias in favor of a treatment under study, either in a randomized or nonrandomized trial, may hinder an objective evaluation of the treatment, although specific measures can be in place to mitigate bias (e.g., blinded endpoint evaluation).

3.5 | Study oversight

Establishing study committees according to study design needs should be considered. Based on their roles and responsibilities these committees need to be either independent (i.e., composed of

TABLE 2 Information to be documented at enrollment.

- *AF profile:*
  - First year of AF diagnosis
  - AF subtype at first diagnosis
  - AF evaluation:
    - AF subtype
    - Method of AF diagnosis at baseline
  - In case of continuous AF at enrollment: Duration of continuous AF
- *Patient profile:*
  - Demographic data:
    - Age
    - Sex
    - Ethnicity
    - Height and weight/BMI
    - Smoking status
    - Alcohol intake
  - Social determinants:
    - Dietary habits (vegetarian, vegan)
    - Educational level (academic/nonacademic)
    - Income status
    - Marital status, living alone/not alone
  - Comorbidities:
    - Concomitant cardiac arrhythmias:
      - Atrial Flutter - typical/atypical
      - Ventricular extrasystoles
      - VT sustained/nonsustained
      - Micro/macro-reentrant tachycardia
      - Focal tachycardia
      - AVRT
      - AVNRT
      - Supraventricular extrasystoles
      - Other (specify)
    - Concomitant cardiac diseases (e.g., valvular disease, cardiomyopathy, HF with preserved ejection fraction, HF with reduced ejection fraction)
    - Prior stroke, TIA, major bleeding
    - Other concomitant diseases (e.g., OSAS, CKD, COPD, PAD, diabetes, rheumatoid disease, thyroid disease, chronic liver disease)
    - COVID-19 related hospitalizations
  - Risk assessments:
    - Risk factors for AF recurrence
    - CHA_2DS_2-VASc, HAS-BLED
- *Symptoms:*
  - Symptom score
  - EHRA arrhythmia symptoms classification
  - Current NYHA functional class
  - QoL assessment (generic and disease specific)
  - Exercise capacity
  - Cognitive function
- *AF treatment history:*
  - Cardioversions
  - Antiarrhythmic drugs
  - Oral anticoagulation
  - Ablation (with details as far as available):
    - PVI
      - Number of previous ablations
      - Energy:
        - Radiofrequency (point-by-point)
        - Cryoablation
        - Pulsed field ablation
        - Endoscopic laser balloon
        - Other (specify)
      - Bidirectional block achieved?
      - Other non-PVI ablations
        - CTI ablation
        - Other linear lesions
        - Posterior wall isolation
        - Nonpulmonary vein triggers
        - LAA isolation
        - CFAE ablation
        - Ablation of fibrosis identified by voltage mapping/MRI
        - Ablation of rotational activity
        - Ablation of left atrial ganglionated plexi
        - Renal denervation
        - Surgical ablation
    - Vein of Marshall ethanol infusion
    - Hybrid/thorascopic surgical ablation
  - In case of prior AF ablation: information on AF recurrences after ablation:
    - Timing
    - Duration/AF burden
    - Symptomatic/asymptomatic
- *Non-AF-related treatment history:*
  - Cardiovascular/non-AF related:
    - Cardiac Implantable Electronic Devices (e.g. pacemaker, ICD, CRT, ICM)
    - Other cardiac devices (e.g., valves, clips, occlusion devices)
    - Cardiac surgery (e.g., CABG, valve replacement or repair, LAA ligation, closure of septal defects)
    - PCI
  - Other:
    - Surgery and other significant noncardiovascular treatments
- *Medication:*
  - Antiarrhythmic drugs
  - Oral anticoagulation/antithrombotic therapy
  - Other non-AF related medication
- *Preprocedural investigations:*
  - Systolic and diastolic blood pressure
  - 12-lead ECG at enrollment
    - Heart rate
    - Heart rhythm
  - Lab values
    - Hb
    - Creatinine
    - Thyroid function
  - Echocardiography (to be specified if performed in AF or sinus rhythm)
    - LVEF
    - LA size: diameter and volume (indexed value)
    - Valve function
  - Other imaging if performed

Abbreviations: AF, Atrial fibrillation; CABG, coronary artery bypass grafting, CFAE, complex fractionated atrial electrogram; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease, CTI, cavotricuspid isthmus; HF, heart failure; LA, left atrium; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; OSAS, obstructive sleep apnea syndrome; PCI, percutaneous coronary intervention; PVI, pulmonary vein isolation.

individuals not directly involved in the conduct of the study) or will include some or more investigators. Randomized studies typically have independent committees to monitor patient safety (Data Safety Monitoring Board, DSMB) and to adjudicate clinical events relevant for the study endpoints (Clinical Events Committee, CEC). An

TABLE 3 Recommendations on AAD therapy.

Depending on AF-subtype and ablation strategy: - *Paroxysmal AF or Persistent AF treated by PVI alone:* Short-acting AAD therapy should be stopped immediately after ablation. Long-acting AAD therapy should be stopped 2 months before ablation. - *(Long-standing) Persistent AF treated by substrate modification:* Pre- and post-ablation long-acting AAD treatment may be considered.
Beta-blockers: - Recommended to stop immediately after ablation if prescribed for antiarrhythmic treatment only. To be continued if prescribed for other, non-antiarrhythmic indications. If discontinued, blood pressure monitoring is recommended, as uncontrolled hypertension may promote AF recurrences.
Data collection: - Throughout the study, the type, dose and duration of AAD therapy and reason(s) for changes in therapy should be documented.

Abbreviations: AAD, antiarrhythmic drug; AF, Atrial fibrillation; PVI, pulmonary vein isolation

TABLE 4 Recommendations on anticoagulation therapy.

Anticoagulation therapy: - Follow evidence-based guidelines with regard to the use of anticoagulation therapy throughout the study (i.e., pre-ablation, during the procedure, and post-ablation). Data collection: - Throughout the study, the type, dose and duration of anticoagulation therapy and reason(s) for therapy changes should be documented.

overview of committees assuming specific roles in study oversight consistent with Good Clinical Practice rules is provided in Supporting Information S1: Table S1.

3.6 | Procedural data

Procedural parameters to be recorded in an AF ablation study may depend on the study topic and the applied ablation strategy. Nevertheless, it is recommended to record a comprehensive set of procedural data, some of which may not necessarily be directly related to the study endpoints, to document how individual procedures were performed. Availability of this information may facilitate interpretation of outcomes and can help to identify outcome patterns or unforeseen relationships. A comprehensive overview of recommended procedural parameters and their definitions and/or assessments is provided in Table 5. Other data to be collected are discussed specifically related to study endpoints.

3.7 | Recurrences, repeat ablation procedures and treatment failure

After the index procedure, a repeated ablation may be required to maintain sinus rhythm. Such procedures are often referred to as "redo procedures" in a general sense. However, a distinction must be made between repeat ablation procedures to treat recurrences of, or related to, the index AF, versus those targeting other arrhythmias (Table 6). The study protocol should provide criteria to distinguish these different types of repeat ablation procedures. The term "redo procedure" should be used only for true recurrences of the index AF. Such a recurrence is considered a treatment failure. Repeat ablation procedures to treat arrhythmias unrelated to the index AF are not considered redo procedures and do not indicate a treatment failure. As a third category, repeat ablation may be performed to treat iatrogenic left atrial flutter secondary to extensive lesions created during the index procedure. Such procedures are not considered redo procedures, but do indicate a treatment failure because the arrhythmia is strongly related to the treatment. It is recognized that after ablation, arrhythmias may present as a combination of several types of arrhythmias. Nevertheless, any arrhythmia meeting the respective criteria in Table 6 indicates a failure of the index procedure, regardless of whether it presents as an isolated arrhythmia or in combination with other types of arrhythmias.

If the primary outcome of the study is related to the first AF recurrence, a patient undergoing repeat ablation for a true AF recurrence has reached the study endpoint. Nevertheless, other endpoints not related to AF recurrence should be assessed at the scheduled follow-up intervals from the index procedure, and the number of AF ablation procedures per patient should be reported.

3.8 | Health economic studies

Healthcare systems have limited budgets for both funding healthcare technologies for patient care and investments in clinical trials. The methods used in health economics should facilitate resource allocation decisions by evaluating the health gains for the resources spent. Payers and Health Technology Assessment (HTA) agencies are important stakeholders in data from clinical trials; without reimbursement, patients will have very limited access to new treatments.

The initial cost of catheter ablation is higher than antiarrhythmic medication, so cost-effectiveness analysis can provide a more complete assessment of costs and clinical benefits over a longer time horizon. Analyses related to health economics of AF ablation should be considered in the statistical analysis plan, particularly if formal hypothesis testing is to be performed.[29] When the decision is made to conduct an economic evaluation alongside a clinical trial, it is important that a health economic investigator contributes to the design of the study to ensure that the trial will provide the data necessary for a high-quality economic evaluation. Key considerations are noted below. An overview of procedural information that may be recorded for health economic assessments is provided in Supporting Information S1: Table S2. Health-related quality of life

TABLE 5 Recommended procedural parameters to be recorded in a study environment.

Category	Parameter	Definition/assessment
Cardiac rhythm	Cardiac rhythm at start of ablation procedure	Electrocardiographic assessment of rhythm (12-lead preferred)
	Cardiac rhythm after PVI	
	Cardiac rhythm at procedure completion or leaving procedure room	
Procedural timing	Room entry to exit time (room occupancy)	Time from patient entry to exit to/from the procedure room/EP suite (minutes).
	Procedure time	Total time from first vascular puncture to removal of last catheter sheath (minutes).
	Left atrial dwell time	Total time from first transseptal puncture to removal of last sheath from left atrium (minutes or seconds).
	Electroanatomic mapping time	Time from start of EAM map creation to completion of EAM map, not including post-processing time (minutes or seconds).
	Post ablation observation time	Time from the last ablation lesion until last reassessment of acute procedural endpoint, e.g., venous isolation or bidirectional conduction block (minutes or seconds).
Patient management/monitoring	Light sedation/deep sedation/general anesthesia	
	Capnography	
Catheterization and transseptal access	Number of venous access sites	
	Presence of patent foramen ovale	
	Number of independent LA accesses	
	Needle used for LA access	RF, mechanical
	Imaging/other information used to guide transseptal access	Fluoroscopy, TEE, ICE, LA pressure curve
	Visualization of pulmonary veins	Contrast injection, preprocedural CT
Radiation exposure	Fluoroscopy time	Total fluoroscopy exposure duration (minutes or seconds). May be stratified based on procedural endpoints.
	Fluoroscopy dosage	Total fluoroscopy exposure (dose area product: DAP; μGray.m^{2,} DAP indexed to BMI: μGray.m^2/kg/m^2). May be stratified based on procedural endpoints.
	Nonfluoroscopic procedure	Procedural methods to facilitate (near)-zero-fluoroscopic ablation.
Contrast medium	Total volume of contrast	
Anticoagulation	Pre-procedure anticoagulation	Agent, INR within 24 h before the procedure (if applicable)
	Interrupted anticoagulation doses	None, 1 dose, 2 doses
	Use of peri-procedural bridging	
	Intraprocedural anticoagulation	ACT target
Electroanatomical mapping	System employed	Brand/manufacturer
	Mapping catheter employed	Brand/manufacturer
	Total number of mapping points obtained	
Imaging (preprocedural or intra-procedural, except specifically used for transseptal access)	Fluoroscopy	Describe purpose (e.g., assessment of PV/LA anatomy, intraprocedural guidance, etc.)
	Transesophageal echocardiography (TEE)	

TABLE 5 (Continued)

Category	Parameter	Definition/assessment
	Intracardiac echocardiography (ICE)	
	CT scan	
	Late gadolinium enhancement MRI	
	Other	
Ablation catheter(s)	Brand, model	
	Technology	Radiofrequency, irrigated/nonirrigated, contact force sensing
		Cryo-balloon, cryo-catheter
		Pulsed field ablation
		Hot balloon
		Laser balloon
		Other
Ablation parameters	Radiofrequency ablation PVI	Point-by-point/dragging
		Total number of ablation lesions
		Ablation energy duration (seconds)
		Total energy delivered (J)
		Maximum and minimum power output used, by LA region
		Mode of energy delivery and associated parameters (temperature controlled, power controlled, high power short duration, maximum power settings, max. temperature, if applicable)
		Contact force, target range, average CF per RF ablation
		Ablation energy target, if applicable (FTI, LSI, AI)
		Ablation lesions and cumulative energy per PV, and for each non-PV ablation performed.
		First pass isolation rate
	Cryoablation PVI	Total number of ablation lesions
		Cryoablation lesion duration (seconds)
		Use of real-time PV signal monitoring
		Time to isolation (TTI) in each PV, if applicable
		Cryoballoon temperature of each application, at 30 s, 60 s, and nadir temperature
		Rewarming time: time from cessation of cryoballoon application to balloon deflation (seconds).
		Bonus applications: additional cryo-applications after achievement of PV isolation (yes/no)
		Touch-up ablation required (yes/no)
	Pulsed field ablation PVI	Total number of ablation lesions
		Energy type: Bipolar, unipolar, both
		Number of pulses per application
		Number of applications per PV
		Neuromuscular blockade used (yes/no)

(Continues)

TABLE 5 (Continued)

Category	Parameter	Definition/assessment
		Observed microbubbles, per application and assessment method
	Other ablation technologies for PVI (e.g. Hot balloon, laser balloon, RF balloon)	Ablation parameters captured depend on the technology employed, and are consistent with the parameters outlined above.
	Prematurely terminated lesions	Number, reason(s)
	Confirmation of PV isolation	Demonstration of bidirectional block (preferred) or entry block (minimal requirements). Circular mapping catheter, EAM, waiting time Postablation, etc.
	Non-PVI ablation	Targets (LA roof, LA anterior, LA posterior, LA septal, LAA, CS, CTI, etc.).
		Technology used and associated ablation parameters.
Intraprocedural monitoring of complications	Phrenic nerve	Monitoring technique (e.g., phrenic nerve pacing, fluoroscopic visualization, CMAP, DMS, other)
		Number of prematurely terminated lesions
		Occurrence of intraprocedural/acute phrenic nerve injury
		Persistent or resolved when leaving procedure room
	Esophagus	Mechanical deviation employed
		Device used for temperature measurement
		Temperature limit to terminate the ablation lesion, in degrees celsius
		Procedural alteration, e.g. limiting energy application
		Postprocedure, pharmacological prophylaxis
Procedure termination	Reason for termination	As planned, with achievement of pre-defined ablation endpoints
		As planned, but without achievement of (all) pre-defined ablation endpoints
		Unplanned, due to complication
Electrical cardioversion(s) performed during or after the AF ablation procedure	Reason, number and results	
Post procedure	Anticoagulation	Timing of restart (if discontinued)
	AAD	Usage timing of discontinuation

Abbreviations: AAD, antiarrhythmic drug; AF, Atrial fibrillation; CS, coronary sinus; CTI, cavotricuspid isthmus; EAM, electroanatomical map; EP, electrophysiology; LA, left atrium; LAA, left atrial appendage; PVI, pulmonary vein isolation; RF, radiofrequency.

should be assessed using validated QoL instruments, including disease-specific and generic questionnaires,[29,30] accepted in a health technology assessment context. Detailed coverage of health economics aspects is beyond the scope of this expert opinion. These aspects are addressed comprehensively in the literature.

A selection of methodological and practical issues to consider for ablation studies is provided below.

Patient-relevant outcomes are preferred for economic analyses, primarily mortality and quality of life and hard clinical endpoints such as stroke. Intermediate or surrogate measures such as AF recurrence or left ventricular ejection fraction are used only to the degree that a causal relationship has been established with patient-relevant outcomes.

Quality Adjusted Life Years (QALYs) combine mortality and quality of life into one measure, which is most often used for cost-effectiveness analysis. However, QALYs are not universally accepted on methodological grounds and may not be applicable in some countries, so it is advisable to consult local health economists.

A health-related quality of life instrument with utility weights—for example EQ-5D—is needed to estimate QALYs, and patients must complete it at multiple time points.

Hospitalization is grouped amongst other costs and not generally considered as a health outcome when calculating an incremental cost effectiveness ratio. A composite endpoint including hospitalization will need to be disaggregated for economic analysis.

TABLE 6 Recommendations regarding recurrences and repeat ablation procedures: nomenclature and endpoint assessment.

1. Arrhythmias treated by repeated ablation after the index procedure:
   - *Repeated ablation procedure for unrelated arrhythmias:* An arrhythmia that is definitely unrelated to the original AF treated during the index procedure: ablation is NOT considered a redo procedure within the context of an AF ablation study, but an isolated treatment of an unrelated arrhythmia. This arrhythmia is not considered a recurrence and does not indicate a failure of the index treatment.
   - *Repeated ablation procedure for related arrhythmias:* A left atrial tachycardia not present prior to but appearing after the AF ablation index procedure, consistent with iatrogenic left atrial flutters secondary to extensive lesions or an organized AF related tachycardia. This arrhythmia is not considered a recurrence but does indicate a failure of the index treatment.
   - *Redo procedure for related arrhythmias not due to the above mechanisms:* An arrhythmia that may possibly be related to the original AF or with an unclear relationship with the original AF: ablation is considered a redo procedure. The arrhythmia is considered a recurrence and indicates a failure of the index treatment.
2. Data to be recorded for a repeated ablation procedure:
   - Reason for repeat ablation (consistent with the categories in point 1)
   - AF burden since index ablation (if possible)
   - AF progression
   - AAD use before repeated ablation, including agent(s) and duration
   - Variation, frequency and duration of arrhythmia-related symptoms pre- and post-index ablation during sinus rhythm and AF
   - Evidence of PV stenosis
   - Ablation strategy on chronically isolated pulmonary veins

Abbreviations: AAD, antiarrhythmic drug; AF, Atrial fibrillation; PV, pulmonary vein

Healthcare resource use can normally be recorded on trial case report forms with little extra burden, but sometimes additional information will be required from medical records, patient questionnaires, and secondary data sources such as insurance claims data. Timely access to secondary data can be problematic and should be verified upfront.

Some economic analyses of AF ablation studies had to incorporate high numbers of cross-overs after the primary endpoint of arrhythmia recurrence occurred. Too high rates of cross-over between treatment groups will confound an economic analysis, and likely cannot be adjusted for with statistical analyses. Every effort should be made to minimize cross-overs. This includes both early cross-over before primary endpoint occurrence, or afterwards if the primary endpoint is not a patient-relevant outcome.

3.9 | Statistics, analysis and reporting

All statistical analyses should be pre-defined in a statistical analysis plan.[31,32] Any analyses outside of this plan should be explicitly reported as exploratory or ad-hoc. Sample size calculations should be based on realistic assumptions supported by literature-reported event rates. Expectations about patient recruitment should be achievable and sample size estimations should account for realistic patient attrition rates. In studies assessing composite endpoints, a separate statistical analysis for each individual component should be presented. Time-to-event analyses should consider the impact of competing risks,[33] especially in relatively old patient populations, typically enrolled for AF studies. Blinded assessment of primary endpoints, preferably by an independent core laboratory, is recommended.

Reports from studies with multiple study arms should present point estimates of event rates per study arm in addition to estimates for differences in treatment effects between the study arms. Such outcomes should be reported at all time-points specified in the protocol. Randomized controlled trials should report event rates per study arm as well as for the pooled population.

Inclusion of dedicated analyses to evaluate homogeneity of treatment effects among groups representing various social determinants (race, gender, etc.) should be considered. Underrepresented groups should be identified and consequences with regard to conclusions drawn from the study results should be discussed.

Additional analysis to better understand the true treatment effects and interference by other aspects may be considered. In case of frequent cross over in a randomized study, treatment effects may be compared between patients randomized to a treatment and those who crossed over to that treatment. If applicable, ablation outcomes in patients undergoing concomitant procedures during the ablation procedure may be compared with those in patients undergoing ablation only.

4 | ACUTE EFFICACY OUTCOMES

4.1 | Acute success: Overview and definitions

Studies on ablation efficacy usually apply a variety of definitions for success of the acute treatment, including device or technical success, ablation success and procedural success. Clear definitions and consistent use will help to compare outcomes of studies, e.g., to compare outcomes of the same device or strategy in different populations or to compare various strategies in similar cohorts.

Device success is related to the intended performance metrics of an (investigational) medical device (e.g., successful vascular access and navigation to the target site(s), successful registration and mapping, successful delivery of ablation energy, etc.). A device/technical failure is defined as the inability for the medical device to attain its intended performance metrics or an adverse event directly related to the use of the device. This includes events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the device, and events resulting from use errors or intentional misuse of the device. Ablation success is defined as the achievement of the primary procedural electrophysiological (EP) endpoint of the ablation procedure, with

TABLE 7 Definitions for success.

Device success	Correct, failure-free functioning of the device.
Ablation success	The achievement of the primary procedural electrophysiological endpoint of the ablation procedure, assessed during the index ablation procedure. This endpoint is a pre-defined demonstration of successful ablation, using a methodology depending on the ablation strategy.

ablation failure being defined as the inability to achieve this primary procedural EP endpoint for any reason.

Procedural success is typically defined as successful ablation with no major procedure-related complications. While procedural success is a combination of efficacy and safety, safety is typically also reported separately. It is questionable whether procedural success should account for intra-procedural complications only, or also for major procedure-related complications that become apparent after completion of the procedure. Following the provided definition, device or ablation success may be achieved while experiencing a procedural failure. Also, procedural success can be achieved despite a device failure. Therefore, the use of procedural success is of limited explanatory value with regard to ablation efficacy, if not confusing. Consequently, it is recommended not to use this parameter. Recommended definitions to be used in an AF ablation study are provided in Table 7.

4.2 | EP endpoints for AF ablation

As noted, the achievement of ablation success depends on the EP endpoint of an AF ablation procedure. Various EP endpoints and assessment methods may be defined, depending on the specific ablation strategy. An overview of EP endpoints and their assessment is provided in Table 8.

The primary EP endpoint for all AF catheter ablation procedures is complete electrical isolation of the pulmonary veins (pulmonary vein isolation, PVI). This endpoint applies to any type of AF (i.e., paroxysmal, persistent or long-standing persistent), and to index procedures as well as redo ablation procedures. Other endpoints may be added depending on ablation strategies employed in addition to PVI or to ablation of specific AF subtypes. While these endpoints may be assessed for additional evaluation purposes, not all have been shown to predict long-term success. Recent findings suggest that a waiting period for assessment of PV reconnection might be redundant with the advent of improved ablation technologies.[34] Others have questioned the value of intraprocedural assessment of PV reconnection to predict long-term success.[35] Therefore, demonstration of the primary endpoint of PVI may be sufficient to achieve acute ablation success and procedural success.

5 | LONG-TERM EFFICACY OUTCOMES

5.1 | Follow-up

The optimal duration of follow-up after catheter ablation depends on many aspects, such as the endpoints to be assessed, the expected rate of endpoint-indicating events, the expected treatment effect, the characteristics of enrolled patients and the planned number of patients to be enrolled. By default, assessing the outcomes of AF ablation requires relatively long follow-up periods. Especially the evaluation of hard clinical endpoints such as mortality or stroke should be based on long follow-up durations, for example, 3 years or more. For the assessment of rhythm-related endpoints or a comparative analysis of new ablation technologies, shorter follow-up duration (e.g., 1 year) may be sufficient. The study protocol should provide justification of the follow-up duration, based on the number of endpoint-related events expected to occur during follow-up.

5.2 | Ablation efficacy endpoints: Overview

Obviously, the preferred primary endpoint in an AF ablation study strongly depends on the main objective of the trial (Table 9). Further details on these endpoints are discussed in the following sections. A mechanistic trial includes a primary endpoint related to arrhythmia characteristics, such as a recurrence metric or arrhythmic burden. At least as a secondary objective, such an outcome may be evaluated in a subgroup of patients not receiving antiarrhythmic medication during the follow-up period. For a clinical efficacy study, the primary endpoint reflects the indication or clinical condition that is targeted by the treatment under study, such as AF-related symptoms, morbidity or mortality. Other aspects relevant for the choice of the primary endpoint include the specific characteristics of the study population in terms of the AF subtype and etiology, co-morbidities, risk factors, and symptom status.[36] Also, additional criteria may be considered when designing a trial for regulatory purposes.

5.3 | Endpoint assessment: Blanking period

The evaluation of rhythm-related endpoints is based on arrhythmia recurrences after catheter ablation. Historically, a 2–3 months blanking period is used, and recurrences within the blanking period are not accounted for in the endpoint assessment. Application of postablation blanking is based on the consideration that early recurrences are due to acute processes resulting from ablation, rather than being associated with long-term treatment failure. Therefore, study protocols strictly adhering to blanking do not permit additional therapies such as repeat ablations during the blanking period.

However, mounting evidence suggesting that early recurrences may be less benign and predictive of late recurrences warrants

TABLE 8 Definitions of electrophysiological endpoints for ablation of AF.

Ablation strategy/target	Endpoints and associated definitions	
Primary procedural endpoint: Pulmonary vein isolation		
Circumferential PVI	Electrical isolation of all PVs, defined as bidirectional conduction block in each PV. Optimally, bidirectional block should be demonstrated, while the minimum requirement is demonstration of entry block.	*Demonstration of entrance block:* should be assessed using a multielectrode mapping catheter positioned at the PV antrum, and with the assistance of pacing maneuvers to distinguish far-field atrial potentials from PV potentials (e.g. during distal coronary sinus or left atrial appendage pacing when assessing the left PVs). *Demonstration of exit block:* Should be demonstrated through the observation of dissociated spontaneous discharges within the PV or through the use of pacing maneuvers within the pulmonary vein. Local PV capture without conduction to the LA must be demonstrated when PV pacing is performed. *Adenosine challenge:* Provocative testing with adenosine may be considered following a 20 min observation period. If adenosine testing is performed the endpoint is the elimination of dormant conduction in each PV, as assessed by injections of 12 mg or more of adenosine to obtain at least one blocked P wave or a pause ≥3 s. Note: not recommended as there is no clear evidence for this assessment with modern ablation tools currently used.
Endpoints for adjunctive ablation strategies beyond PVI		
Ablation of non-PV triggers	Ablation of triggers until inability to provoke a non-PV trigger that reproducibly initiates AF with high-dose isoproterenol infusion (starting at 3 μg/min and incrementing every 2–3 min to 6, 12, and 20 μg/min) or progressive rapid atrial burst pacing.	
Linear left atrial ablation	Endpoints include demonstration of bidirectional conduction block, using differential pacing maneuvers in sinus rhythm (with or without electroanatomic activation mapping), arrhythmia termination and loss of signal amplitude, demonstration of double potentials, and nonexcitability during high-output pacing (at least 8.0 V/1.0 ms) along the complete ablation line.	
Ablation of low-voltage areas	Elimination of local electrograms with confirmation of nonexcitability during high-output pacing (at least 8.0 V/1.0 ms) from the ablation catheter's distal bipole within the low voltage area targeted for ablation.	
CFAE ablation	Complete elimination of the areas identified with CFAEs. Endpoints of CFAE ablation include AF termination to sinus rhythm, conversion of AF to an organized atrial tachycardia or flutter, and/or noninducibility. Lesion endpoints include elimination of local electrograms with confirmation of nonexcitability during high-output pacing (at least 8.0 V/1.0 ms).	
Substrate isolation (posterior wall, LAA, SVC)	Demonstration of bidirectional conduction block (both entrance and exit block) using differential pacing maneuvers in sinus rhythm.	
Ganglionated plexi ablation	This strategy is currently not well established with no clear definitions for endpoints. Typical endpoints include local ablation until the elimination of the positive response to high frequency stimulation.	
Rotational activity or dominant frequency ablation	This strategy is currently not well established with no clear definitions for endpoints. Typical endpoints include complete elimination of the areas identified with focal rotational activity or on dominant frequency mapping. Lesion endpoints include elimination of local electrograms with confirmation of nonexcitability during high-output pacing (at least 8.0 V/1.0 ms).	
Vein of Marshall ethanol infusion	Voltage map to quantify ethanol-induced scar.	
Additional procedural responses to ablation of persistent AF		
Procedural termination of persistent AF	AF termination to sinus rhythm or conversion of AF to an organized atrial tachycardia or flutter may be considered a secondary endpoint of persistent AF ablation, however there is no clear evidence that AF termination predicts improved long-term outcomes. While AF termination may be associated with a favorable prognosis, it is not clear that AF termination is responsible for the improved outcome or is merely a marker of patients with less severe substrate (e.g., a subgroup with a limited and ablation sensitive set of driver mechanism).	
AF noninducibility	Noninducibility of AF with high-dose isoproterenol infusion or progressive rapid atrial burst pacing may be considered a secondary endpoint of persistent AF ablation, however there is no clear evidence that noninducibility predicts improved long-term outcomes. While noninducibility may better predict procedural outcome compared to AF	

(Continues)

TABLE 8 (Continued)

Ablation strategy/target	Endpoints and associated definitions
	termination, the value of AF noninducibility as a procedural endpoint is likely to be dependent on the induction protocol and on the cut-off duration used to define sustained AF.

Abbreviations: AF, atrial fibrillation; CFAE, complex fractionated atrial electrogram; LA, left atrium; LAA, left atrial appendage; PV, pulmonary vein; PVI, pulmonary vein isolation; SVC, superior vena cava.

reconsideration of the postablation blanking concept. An overview of meta-analyses and systematic reviews pertaining to postablation blanking and early recurrences is provided in the supplemental information. Overall, these analyses[37–41] indicate that blanking may be shortened substantially and that early recurrences, particularly those at more than 4 weeks after the index procedure, predict late recurrences and therapy failure. Specific recommendations regarding postablation blanking are provided in Table 10.

5.4 | Rhythm-related endpoints for ablation efficacy

5.4.1 | Choice of rhythm-related endpoint

Long-term endpoints related to cardiac rhythm include binary endpoints (present or absent) and quantitative endpoints. An overview of rhythm-related endpoints is presented in Table 11.

A major objective of AF ablation for patients as well as physicians is to improve health-related or disease-specific quality of life (QoL). Consequently, AF ablation efficacy may be evaluated using a rhythm-related endpoint that correlates with these QoL improvements. Several studies have indicated that patients may experience improved QoL after AF ablation despite occasional recurrences of AF.[42–45] Therefore, endpoints related to the number, frequency or timing of individual AF recurrences, particularly recurrences of short duration, may not be optimal to assess ablation efficacy. In contrast, a decrease in AF burden following AF ablation has been reported to correlate with QoL improvements.[6,43–47] Moreover, AF burden after ablation is associated with hard clinical endpoints (e.g., the composite of all-cause death and hospitalization for worsening heart failure in the CASTLE-AF study[48]) and with increased healthcare utilization in the CIRCA-DOSE study.[43] AF burden incorporates symptomatic and asymptomatic AF episodes and thereby provides a clinically more relevant assessment of ablation efficacy, compared to methods based on symptomatic episodes only.[36] Therefore, a meaningful efficacy-related objective of AF ablation appears to be the reduction of AF burden over a longer period, rather than the complete elimination of AF recurrences. Consequently, AF burden is strongly recommended as the primary rhythm-related endpoint for AF ablation efficacy studies.

Within this context, AF burden represents the percentage of the entire monitoring duration during which the patient is in AF. As for any rhythm-related endpoint, detection of AF is based on a (somewhat arbitrary) cut-off value for the duration of an individual arrhythmia episode. Most studies using intermittent monitoring (ambulatory Holter monitoring, triggered event recording, etc.) apply a 30 s threshold for recurrent arrhythmia episodes, while most algorithms incorporated in an ICM require a 2 min episode for automated detection of AF. While this cut-off value may strongly influence the assessment of endpoints related to a single recurrence (e.g., time to first recurrence), it has limited effects on AF burden.[49]

5.4.2 | Assessment of rhythm-related endpoints

For any rhythm-related endpoint, the reliable and consistent detection of individual arrhythmia recurrences is crucial. Several technologies for recurrence detection are available, including intermittent ECG recording, ambulatory Holter monitoring, event recording, wearable ECG recording technologies, mobile device-based recordings and insertable cardiac monitoring (ICM). Several studies have shown underreporting of AF episodes using intermittent monitoring, resulting in an overestimation of ablation efficacy. Using computational simulation, Aguilar et al.[50] estimated the yield of arrhythmia detections from various monitoring techniques. These simulations were based on ICM-detected arrhythmias in 346 patients monitored for 12 months after catheter ablation of paroxysmal AF. While ICM monitoring indicated an overall arrhythmia-free survival of 52.6%, other intermittent monitoring modalities consistently provided overestimated survival rates, ranging from 66.2% to 92.5%. Using ICM monitoring as the gold standard, the sensitivity of other monitoring approaches for detection of atrial tachycardia recurrences ranged from 15.8% to 71.3% with negative predictive values between 56.9% and 79.5%. Similarly, a meta-analysis of AF ablation trials[51] showed lower recurrence rates when using intermittent monitoring compared to continuous monitoring, specifically in paroxysmal AF populations. When using intermittent monitoring, the monitoring duration was not significantly associated with the yield of arrhythmia detection.

5.4.3 | Recommendations for rhythm-related endpoints

Considering all available technologies, continuous cardiac rhythm monitoring using an ICM is considered the gold standard for AF ablation studies and recommended as the preferred assessment method for rhythm-related endpoints in mechanistic trials (Table 12).

TABLE 9 Recommended primary and secondary endpoints for evaluation of long-term AF ablation efficacy.

Treatment/ indication	Primary endpoint[a]	Secondary endpoint(s)
Mechanistic AF ablation trials		
– Reduction of AF burden – AF regression – Prevention of AF progression	ICM-detected AF burden (% of time in AF)	Rhythm-related endpoints: - Time to first recurrence - Freedom from recurrences - Freedom from any atrial arrhythmia - Freedom from any atrial arrhythmia off-AAD - Number of AF episodes - AF density
Clinical efficacy trial		
Symptom reduction HRQoL improvement	PROM	- ICM-detected AF burden - Intermittent 7-days ambulatory Holter monitoring - ICM-detected activity of daily living
Survival improvement	Mortality	- PROM - ICM-detected AF burden
Stroke reduction	Ischemic stroke TIA Peripheral embolism	- Mortality - Hospitalization - PROM - ICM-detected AF burden
Reduction of composite hard AF-related outcomes	Composite endpoint: Mortality, stroke, worsening HF, ACS	- ICM-detected AF burden - PROM - Hospitalization
Heart failure-related endpoints	HF-related hospitalization	- ICM-detected AF burden - PROM - LVEF - Walking distance
Reduction of health care use	Composite endpoint: CV hospitalization, emergency department visits, outpatient visits	- ICM-detected AF burden - PROM - AF-related hospitalization
Effect on cognitive function	Cognitive function tests	- ICM-detected AF burden - PROM
Effect on depression	Depression tests	- ICM-detected AF burden - PROM

[a]Further details on these endpoints are presented in the following sections.

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation; HF, heart failure; HRQoL, health-related quality of life; ICM, insertable cardiac monitor; PROM, patient reported outcome measurement.

5.4.4 | Additional aspects

Irrespective of the type of rhythm-related endpoint and the applied detection technology, the following aspects should be considered with regard to the assessment of the endpoint.

- When using a rhythm-related endpoint directly related to individual arrhythmia episodes, the study protocol needs to define the minimal duration of an episode to be accounted for in the endpoint assessment. When using an ICM, a cut-off of 6 min appears to be appropriate, as shorter episodes hardly contribute to the total AF burden.[49]
- For the assessment of rhythm-related endpoints, recurrences and their effect on endpoint assessment should be clearly defined, aligned with the recommendations on recurrences and repeat ablation procedures.
- If the study includes a comparison of AF ablation outcomes versus preprocedural AF characteristics, a duration of preprocedural cardiac rhythm monitoring should be defined depending on the AF subtype (paroxysmal vs. persistent).

5.5 | Patient-reported outcome measures

A wide variety of patient-reported outcome measures (PROMs) is available to evaluate the effect of AF ablation experienced by the patient. An overview of these measures is provided in Supporting Information S1: Table S3. It is recommended to include at least one generic health-related QoL (HRQoL) outcome, for instance using the SF-36, SF-12, EQ-5D or PROMIS assessment. The use of such a generic assessment allows a HRQoL comparison with other diseases. HRQoL has been shown to correlate with AF burden, but less with AF recurrences.[6,46,47] In addition, a variety of AF-specific PROMs are available.[52] The AFEQT and AFSS assessments seem to perform best, although the need for further research on reliability and validity of AF-specific QoL assessments is emphasized in the literature.[53,54] PROMs may be complemented with daily activity levels measured by implantable or wearable devices, which have been reported to show a strong association with the occurrence of AF.[55,56]

Several aspects need to be accounted for when reporting and interpreting PROMs. The patient's perception as assessed by the PROM instrument may be influenced by the open-label nature of AF

TABLE 10 Recommendations on postablation blanking.

1. The duration of a postablation blanking period should be limited as much as possible, for instance to a 1 month or maximally a 45 days period.
2. Arrhythmia recurrences within the blanking period are not considered a treatment failure.
3. Treatment of arrhythmias occurring during the blanking period should be defined in the study protocol with differentiation between arrhythmias unrelated to the original AF, arrhythmias with unclear or possible relationship and true recurrences of the original AF.
4. Postablation blanking should not be applied in the assessment of primary study endpoints that are not directly related to individual arrhythmia recurrences (e.g., cumulative AF burden, quality of life, hard clinical endpoints).
5. Blanking may be applied (with duration as short as possible) in the assessment of time to AF recurrence or after ablations of persistent AF by complex, more extensive procedures beyond PVI, where a postablation inflammatory process may be expected.
6. Studies applying postablation blanking should report on recurrences within the blanking period and provide separate analyses investigating their effect on the endpoint assessment.
7. Irrespective of the duration of the postablation blanking period, safety-related events occurring during the blanking period should be accounted for in the assessment of safety.

Abbreviation: AF, atrial fibrillation.

TABLE 11 Rhythm-related endpoints for assessment of long-term ablation efficacy.

Binary endpoint	Freedom from any AF/AT[a]
	Freedom from any AF/AT[a] off antiarrhythmic drugs
Quantitative endpoints	Time to first/second/third AF/AT recurrence[a]
	Number of recurrent AF/AT episodes
	AF/AT burden (percentage of time)
	AF progression/regression
	AF density

Abbreviation: AF, atrial fibrillation.

[a]Traditionally, the cut-off for an AF episode has been 30 s.

ablation studies, the rhythm status during the assessment and the patient's awareness of the actual rhythm, for example, as indicated by a smartwatch. The recall period covered by the assessment varies across PROM instruments and should be explicitly reported. Of note, not all PROM assessments are validated for use with a smartphone.

5.6 | Clinician-reported outcome measures

Clinician-reported outcome measures (CROMs) include the Canadian Cardiovascular Society Severity of Atrial Fibrillation (CCS-SAF) Scale, the European Heart Rhythm Association (EHRA) score and the Specific Activity Scale (SAS). Overall, CROMs have not shown to be related to hard clinical outcomes.

TABLE 12 Recommendations on rhythm-related endpoints.

1. AF burden measured by continuous cardiac rhythm monitoring is strongly recommended as the preferred rhythm-related endpoint for the evaluation of clinical efficacy of catheter ablation.
2. Currently, the technology and assessment methods implemented in an insertable cardiac monitor (ICM) provide the most reliable measurement of AF burden.
3. Acknowledging device costs and reimbursement issues, the most optimal rhythm assessment method may be selected, according to the type of the study (RCT or cohort study) and the novelty of the tested technology (new technology tested vs. confirmation vs. 'real world validation').
4. Novel technologies such as AF burden measurement by smartwatches and other wearable devices may be considered as alternatives to an ICM, provided an ECG recording feature is included. However, issues with regard to patient's adherence and artifacts due to movements should be acknowledged.

Abbreviations: AF, atrial fibrillation; ECG, electrocardiogram.

5.7 | AF characteristics

AF characteristics may be assessed as a primary or secondary endpoint in a clinical efficacy trial (Table 13).

The preferred assessment to evaluate AF progression or regression is ICM-detected AF burden. However, it is difficult to state which increase in AF burden would represent a clinically relevant progression of AF. Such an increase may be related to the decision when to re-ablate after the index procedure, or to the degree of AF burden that would indicate an increased risk of mortality.

5.8 | Hard clinical endpoints

Hard clinical endpoints are frequently used in AF ablation studies.[36] An overview of these endpoints and their individual components is provided in Table 14.

5.9 | Cognitive function/mental disorders

AF ablation studies may assess cognitive function and mental status, using generally available and accepted tests, for example, Trail making tests, Mini-mental test, depression tests. A correlation has been shown between cognitive function and the detection of new silent lesions after AF ablation. Therefore, the presence of new silent cerebral lesions detected by postablation MRI may be included as an endpoint.

5.10 | Treatment burden, health economics

Several endpoints relevant for treatment burden and/or health economics can be assessed in an AF ablation trial. An overview of these endpoints is provided in Table 15.

TABLE 13 AF characteristics.

Characteristic	Description
AF progression/regression	Change in AF temporal profile
	AF burden
AF cardiomyopathy	LA volume index
	LA function, echo strain
	LA fibrosis, MRI
AF biomarkers	NT-proBNP
	Troponin
4S scheme score	Sum of scores

Abbreviations: AF, atrial fibrillation; LA, left atrium; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

TABLE 14 Hard clinical endpoints.

Endpoint	Components
Mortality	Cardiovascular mortality All-cause mortality Definitions according to VARC-3 recommendations[57]
Stroke	Ischemic stroke All strokes Transient ischemic attacks (TIA) Definitions according to VARC-3 recommendations[57]
Bleeding/hemorrhages	Intracranial bleeding Major bleeding Fatal bleeding
Heart failure	HF-related in-patient hospitalization HF-related out-patient hospitalization Progression/worsening of HF Change in LVEF Changes in diuretic medication NYHA functional class Minnesota Living with Heart Failure Questionnaire Kansas City Cardiomyopathy Questionnaire 6 min walking distance
Exercise capacity	6 min walking distance
Cognitive function	
Depression	
Hospitalization	

Abbreviations: HF, heart failure; LVEF, left ventricular ejection fraction

5.11 | Composite endpoints

Composite endpoints may combine various outcomes such as mortality, stroke, worsening heart failure, acute coronary syndrome, etc. However, it should be acknowledged that individual components of a composite endpoint may have different importance, clinical relevance and consequences for the patient. It is recommended to avoid a combination of rhythm-related endpoints (e.g., arrhythmia recurrences) and hard clinical endpoints (e.g., mortality, worsening heart failure) into a single composed endpoint. Also, it is recommended that, besides reporting the composite endpoint, all individual components of a composite endpoint should be reported separately.

TABLE 15 Endpoints related to treatment burden and health economics.

Health care use	Composite of all hospitalizations
	AF-related hospitalization
	HF-related hospitalizations
	Emergency department visits
	Outpatient visits
	Psychological counseling
Treatments used	Cardioversion
	Repeat ablations
	Antiarrhythmic drugs
Health economics	Cost-effectiveness: - Natural units - Life years gained - Recurrences prevented
	Cost-utility (Quality Adjusted Life Years: QUALY)
	Cost-benefit (monetary unit)

Abbreviations: AF, atrial fibrillation; HF, heart failure.

6 | SAFETY

6.1 | Definitions and adverse event characterization

Safety of AF ablation is characterized by the occurrence or absence of adverse events, related to the devices and/or the ablation procedure. Within a study context, characterization of an adverse event should include timing of the event, relatedness to the procedure and/or the device, treatment and outcome, and the severity of the event (see Table 16). Investigators are encouraged to report in more detail on unanticipated adverse events. In this regard, an event may be unexpected by its nature and/or incidence rate (i.e., a known event that occurs at a rate higher than expected for the specific treatment or population).

Any adverse event with a (likely or causal) relationship with the procedure is considered a procedure-related complication, irrespective of the timing of the event. An adverse event related to a device, used during the procedure is by definition also a procedure-related adverse event, but should be reported as a separate category. In addition to device-related adverse events, it is recommended to report all device failures or malfunctions, irrespective of their

TABLE 16 Characterization of adverse events within a study context.

Timing		
Intra-procedural	Any adverse event, regardless of the cause, occurring or first observed inside the EP room.	
Peri-procedural	Any adverse event, regardless of the cause, occurring or first observed inside the EP room or within 30 days after the procedure.	
Late	Any adverse event, regardless of the cause, occurring or first observed more than 30 days after the procedure.	
Relatedness		
Device-related	Any adverse event, regardless of its timing, which is related to the use of the device, either intended or unintended, or to a failure of the device to achieve its intended performance. By definition, a device-related adverse event is a special type of procedure-related adverse event.	Classifications of relatedness: - Definitely related - Potentially related - Definitely unrelated
Procedure-related	Any adverse event, regardless of its timing, which has a causal relationship with the procedure.	
Unrelated	An adverse event of which a relationship with the device and/or a failure of the device, and with the procedure can be excluded.	
Treatment	Description of the treatment	Treatment description may include an indication of no treatment, or details of actual treatment, e.g. pericardiocentesis, surgery, etc. The description should include a clear indication of the level of invasiveness of the treatment.
Outcome	Description of the outcome of the adverse event, both when treated or untreated.	Classifications of outcome: - Resolved - Unresolved with no further action or investigation planned - Unresolved with further action or investigation planned or ongoing
Severity: Major adverse event	An event resulting in a life threatening illness or injury, a permanent impairment of a body structure or function, prolonged hospitalization, medical or surgical intervention to prevent permanent impairment, fetal distress, death or congenital abnormalities or birth defects, or in a patient's death. In addition, an event with significant, persistent impact on a patient's quality of life should also be classified as a major adverse event.	
Anticipated event	An event that may be expected to occur during an AF ablation procedure, depending on the applied technology and ablation strategy. The event may be expected based on complications reported in the literature and/or when included as a potential complication in the device labeling.	

involvement in, and/or causal relationship with a procedure-related adverse event. Components of procedural safety may be presented separately depending on their timing, including intra-procedural complications (occurring during the ablation procedure), peri-procedural complications (within 30 days after completion of the procedure), and late complications (more than 30 days of the procedure). Treatment of adverse events, or refraining from treatment, should be described for each event, irrespective its timing and relatedness. The outcome of each event is to be classified with respect to resolution or relevant consequences. In this regard, an event is considered to be resolved if treatment can be concluded with no long-standing significant consequences for the patient. Depending on the study reporting procedures, the outcome of an adverse event may need to be reported at various follow-up visits and may change during the course of the study.

Independent of the above aspects, adverse events should be classified as minor or major. The study protocol should provide a precise definition of major adverse events, either by a qualitive description or by a list of specific events. Nevertheless, major adverse events should minimally include events that result in a life threatening illness or injury, a permanent impairment of a body structure or function, prolonged hospitalization, medical or surgical intervention to prevent permanent impairment, fetal distress, death or congenital abnormalities or birth defects, or a patient's death.[58]

6.2 | Overview of complications

Complications should be reported individually, rather than as a group or category (e.g., groin hematoma, fistula, pseudoaneurysm, reported separately, rather than reporting access site complications as a whole). An overview of common procedure-related complications that should at least be recorded is provided in Supporting Information S1: Table S4. The list provided in this table may be used to develop a case report form listing potential procedure-related complications to be checked by the investigator at completion of each individual procedure.

6.3 | Evaluation of procedural safety

If safety is a primary endpoint, adjudication of adverse events by an independent clinical events committee (see Supporting Information S1: Table S1) is strongly recommended, specifically for evaluation of the safety of a novel device or treatment strategy.

When the purpose of a study is to demonstrate safety of AF ablation, event rates observed during the study should be compared with pre-defined quantitative acceptance criteria, that is, maximum allowable complication rates. These acceptance criteria should be based on the state of the art, and be as specific as possible for the AF ablation strategy under study, the intended patient population and other conditions specifically addressed by the study. The development of acceptance criteria for procedural safety should also account for a benefit-risk evaluation for the specific ablation strategy and patient population. A justification for safety-related acceptance criteria based on these considerations should be provided in the study protocol, with reference to sources in the literature or other clinical experience. Depending on the purpose and topic of the study, the primary evaluation of procedural safety may address overall safety (e.g., a total complication rate, accounting for all procedural complications) or focus on specific complications (e.g., for evaluation of a novel ablation technology with specific procedure-related risks).

7 | DISCUSSION

This expert opinion provides comprehensive guidance for the design and choice of endpoints for AF ablation studies, while accounting for outcomes and new insights recently reported in the literature. Besides recommendations that may alter approaches used in the past, the consistent use of definitions, documentation requirements, choice of endpoints and their assessment may facilitate a higher level of consistency in studies included in meta-analyses and improve the reliability of conclusions drawn from big-data approaches.

A key recommendation of this expert opinion is the strong reduction of postablation blanking to 1 month or maximally 45 days. Obviously, this represents a change compared to the traditional 3-month blanking period that is currently used in many AF ablation studies. Nevertheless, as early arrhythmia recurrences are reported to predict late treatment failure,[37–42] a strongly reduced postablation blanking period appears to be justified. Accounting for early post-blanking recurrences in the assessment of rhythm-related endpoints may lead to reduced efficacy rates. To further evaluate this aspect, researchers are encouraged to provide separate analyses exploring how rhythm-related outcomes are affected by incorporating recurrences within the blanking period, or to disclose sufficiently detailed time-to-event data allowing these analyses by others. An additional topic for analysis may be the extent to which early recurrences predict late recurrences indicating therapy failure, depending on the time to the first early recurrence.

Another important recommendation of this expert opinion is to differentiate between repeated ablation procedures for treatment of different types of arrhythmias, and the way they are accounted for in the study endpoint. Incorporation of recurrences in mechanistic study endpoints depends on their relationship with the original AF or with lesions created during the index procedure. Besides promoting consistent and well-defined nomenclature, the recommended categorization of repeated ablation procedures aims at achieving outcomes from mechanistic AF ablation trials that optimally reflect the true efficacy of the ablation procedure.

The use of ICM-measured AF burden is strongly recommended as the preferred rhythm-related endpoint for evaluation of ablation efficacy. This recommendation is based on the clinical relevance of AF burden, representing symptomatic and asymptomatic recurrences,[36] and its association with QoL and hard clinical endpoints.[6,43–48] AF burden is a robust parameter for the evaluation of catheter ablation as it is rather insensitive to the precise definition of the minimum duration of a recurrent arrhythmia.[49] Moreover, while this expert opinion strongly recommends the reduction of postablation blanking, the actual duration of the blanking period is expected to have only limited effect on an evaluation based on AF burden assessed over a relatively long period. As to the documentation of AF recurrences and measurement of AF burden, the superiority of an ICM over other technologies has been clearly demonstrated.[50,51] However, budgetary limitations may hinder the application of this technology. ICMs are relatively expensive, and processing the large amount of data provided by these devices may be time consuming. Researchers should carefully weigh the benefits and disadvantages of ICMs in relation to the objective of their study. Less expensive alternatives, such as smartwatches and other wearable devices, may be considered, but issues related to the reliability of arrhythmia detection and patient adherence should be acknowledged.

AFFILIATIONS

[1]Department of Cardiology and Intensive Unit Care, Hospital Munich South, Peter Osypka Heart Center, Munich, Germany

[2]University of Bonn, Bonn, Germany

[3]Department of Cardiology, School of Medical Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

[4]Department of Medical Science, Uppsala University, Uppsala, Sweden

[5]Kansas City Heart Rhythm Institute and Research Foundation, Overland Park, Kansas, USA

[6]Mayo Clinic-St. Mary's Hospital, Rochester, Minnesota, USA

[7]Director Clinical Research, Medtronic Cardiac Ablation Solutions, Medtronic GmbH, Meerbusch, Germany

[8]Department of Cardiology, Kerckhoff Heart Center, Bad Nauheim, Germany

[9]Department of Psychosomatic Medicine and Psychotherapy, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

[10]German Center for Cardiovascular Research (DZHK), Partnersite Munich Heart Alliance, Munich, Germany

[11]Department of Cardiology, Peter Osypka Heart Center, Hospital Munich South, Munich, Germany

[12]Technical University Munich (TUM), Munich, Germany

[13]Institute for Medical Informatics, Biometry and Epidemiology, Neurology Emeritus, Medical Faculty of the University Duisburg-Essen, Head Unit of Neuroepidemiology, Essen-Werden, Germany

[14]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, Italy University of Modena and Reggio Emilia, Modena University Hospital, Modena, Italy

[15]Department of Medicine (Cardiovascular Medicine) and Center for Digital Health, Stanford University, Stanford, California, USA

[16]Stiftung Institut für Herzinfarktforschung - Foundation IHF, Ludwigshafen, Germany

[17]Department of Medicine Huddinge, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden

[18]Albers Clinical Evidence Consultancy, Winterswijk Woold, The Netherlands

[19]Vancouver General Hospital, Vancouver, Canada

[20]Medtronic Bakken Research Center, Maastricht, The Netherlands

[21]Medical School REGIOMED, REGIOMED-Kliniken Coburg Germany and University of Split School of Medicine, Split, Croatia

ACKNOWLEDGMENTS

Open Access funding enabled and organized by Projekt DEAL.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Dhanunjaya Lakkireddy http://orcid.org/0000-0002-1492-2693
Karl-H. Ladwig http://orcid.org/0000-0002-0221-311X
Hans-C. Diener http://orcid.org/0000-0002-6556-8612
Giuseppe Boriani http://orcid.org/0000-0002-9820-4815
Mintu P. Turakhia http://orcid.org/0000-0001-8025-0904
Bert Albers http://orcid.org/0009-0002-9956-5193
Mirko de Melis http://orcid.org/0000-0002-9223-4183

REFERENCES

1. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. 2017;14(10):e275-e444.
2. Food and Drug Administration. *Clinical Trials Guidance Documents. 2023*. Food and Drug Administration. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trials-guidance-documents
3. European Medicines Agency. *Guideline for good clinical practice E6(R2) Step 5. 2016*. European Medicines Agency. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-good-clinical-practice-e6r2-step-5_en.pdf
4. International Organization for Standardization. *ISO 14155:2020 Clinical investigation of medical devices for human subjects - Good clinical practice. 2020*. International Organization for Standardization. https://www.iso.org/standard/71690.html
5. Packer DL, Mark DB, Robb RA, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA*. 2019;321(13):1261-1274.
6. Blomström-Lundqvist C, Gizurarson S, Schwieler J, et al. Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation: the CAPTAF randomized clinical trial. *JAMA*. 2019;321(11):1059-1068.
7. Duytschaever M, De Pooter J, Demolder A, et al. Long-term impact of catheter ablation on arrhythmia burden in low-risk patients with paroxysmal atrial fibrillation: the CLOSE to CURE study. *Heart Rhythm*. 2020;17(4):535-543.
8. Andrade JG, Champagne J, Dubuc M, et al. Cryoballoon or radiofrequency ablation for atrial fibrillation assessed by continuous monitoring. *Circulation*. 2019;140(22):1779-1788.
9. Kheiri B, Simpson TF, Przybylowicz R, et al. Ablation versus antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation: a meta-analysis of randomized trials. *Circ Arrhythm Electrophysiol*. 2021;14(8):e009692.
10. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the heart rhythm society. *Circulation*. 2014;130(23):e199-e267.
11. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American college of Cardiology/American heart association task force on clinical practice guidelines and the heart rhythm society. *J Am Coll Cardiol*. 2019;74(1):104-132.
12. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2020;42(5):373-498.
13. Cheung CC, Nattel S, Macle L, Andrade JG. Management of atrial fibrillation in 2021: an updated comparison of the current CCS/CHRS, ESC, and AHA/ACC/HRS guidelines. *Can J Cardiol*. 2021;37(10):1607-1618.
14. Wasserlauf J, Vogel K, Whisler C, et al. Accuracy of the apple watch for detection of AF: a multicenter experience. *J Cardiovasc Electrophysiol*. 2023;34(5):1103-1107.
15. Lee C, Lee C, Fernando C, Chow CM. Comparison of apple watch vs Kardia Mobile: a tale of two devices. *CJC Open*. 2022;4(11):939-945.
16. Abu-Alrub S, Strik M, Ramirez FD, et al. Smartwatch electrocardiograms for automated and manual diagnosis of atrial fibrillation: a comparative analysis of three models. *Front Cardiovasc Med*. 2022;9:836375.
17. Westerman S, Wenger N. Gender differences in atrial fibrillation: a review of epidemiology, management, and outcomes. *Curr Cardiol Rev*. 2019;15(2):136-144.
18. Tamirisa KP, Al-Khatib SM, Mohanty S, et al. Racial and ethnic differences in the management of atrial fibrillation. *CJC Open*. 2021;3(12 suppl):S137-S148.
19. FDA Enhancing the diversity of clinical trial populations—Eligibility criteria. *Enrollment practices, and trial designs guidance for industry*. FDA; 2020.
20. Chen W, Liu H, Ling Z, et al. Efficacy of short-term antiarrhythmic drugs use after catheter ablation of atrial fibrillation-a systematic review with meta-analyses and trial sequential analyses of randomized controlled trials. *PLoS One*. 2016;11(5):e0156121.
21. Kaitani K, Inoue K, Kobori A, et al. Efficacy of antiarrhythmic drugs short-term use after catheter ablation for atrial fibrillation (EAST-AF) trial. *Eur Heart J*. 2016;37(7):610-618.
22. Roux J, Zado E, Callans DJ, et al. Antiarrhythmics after ablation of atrial fibrillation (5A Study). *Circulation*. 2009;120(12):1036-1040.
23. Leong-Sit P, Roux JF, Zado E, et al. Antiarrhythmics after ablation of atrial fibrillation (5A Study): six-month follow-up study. *Circ Arrhythm Electrophysiol*. 2011;4(1):11-14.

24. Turagam MK, Musikantow D, Whang W, et al. Assessment of catheter ablation or antiarrhythmic drugs for first-line therapy of atrial fibrillation: a meta-analysis of randomized clinical trials. *JAMA Cardiol*. 2021;6(6):697-705.
25. Mohanty S, Di Biase L, Mohanty P, et al. Effect of periprocedural amiodarone on procedure outcome in patients with longstanding persistent atrial fibrillation undergoing extended pulmonary vein antrum isolation: results from a randomized study (SPECULATE). *Heart Rhythm*. 2015;12(3):477-483.
26. Arbelo E, Brugada J, Lundqvist CB, et al. Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry. *Eur Heart J*. 2017;38(17):ehw564.
27. Maury P, Defaye P, Klug D, et al. Position paper concerning the competence, performance and environment required in the practice of complex ablation procedures. *Arch Cardiovasc Dis*. 2019;112(1):67-73.
28. Kuck KH, Böcker D, Chun J, et al. Qualitätskriterien zur durchführung der katheterablation von vorhofflimmern. *Der Kardiologe*. 2017;11(3):161-182.
29. Ramsey SD, Willke RJ, Glick H, et al. Cost-effectiveness analysis alongside clinical trials II-An ISPOR good research practices task force report. *Value Health*. 2015;18(2):161-172.
30. Arbelo E, Aktaa S, Bollmann A, et al. Quality indicators for the care and outcomes of adults with atrial fibrillation. *EP Europace*. 2021;23(4):494-495.
31. Gamble C, Krishan A, Stocken D, et al. Guidelines for the content of statistical analysis plans in clinical trials. *JAMA*. 2017;318(23):2337-2343.
32. EMAICH Topic E 9—Statistical principles for clinical trials. *Step 5—Note for guidance on statistical principles for clinical trials*. EMA.
33. Troendle JF, Leifer ES, Kunz L. Dealing with competing risks in clinical trials: how to choose the primary efficacy analysis? *Stat Med*. 2018;37(19):2787-2796.
34. Sousa PA, Barra S, Adão L, et al. Assessment of the need of a waiting period after pulmonary vein isolation with the ablation index software. *J Cardiovasc Electrophysiol*. 2022;33(8):1725-1733.
35. Jiang R, Chen M, Yang B, et al. Intraprocedural endpoints to predict durable pulmonary vein isolation: a randomized trial of four post-ablation techniques. *Europace*. 2019;22(4):567-575.
36. Camm AJ, Reiffel JA. Defining endpoints in clinical trials on atrial fibrillation. *Eur Heart J Suppl*. 2008;10(suppl H):H55-H78.
37. Vrachatis DA, Papathanasiou KA, Kossyvakis C, et al. Early arrhythmia recurrence after cryoballoon ablation in atrial fibrillation: a systematic review and meta-analysis. *J Cardiovasc Electrophysiol*. 2022;33(3):527-539.
38. Calkins H, Gache L, Frame D, et al. Predictive value of atrial fibrillation during the postradiofrequency ablation blanking period. *Heart Rhythm*. 2021;18(3):366-373.
39. Saglietto A, Ballatore A, Xhakupi H, et al. Evidence-based insights on ideal blanking period duration following atrial fibrillation catheter ablation. *EP Europace*. 2022;24(12):1899-1908.
40. Quan D, Huang H, Kong B, Li Q, Liao J, Wang G. Predictors of late atrial fibrillation recurrence after cryoballoon-based pulmonary vein isolation: a meta-analysis. *Kardiol Pol*. 2017;75(4):376-385.
41. Bordignon S, Barra S, Providencia R, et al. The blanking period after atrial fibrillation ablation: an European Heart Rhythm Association survey on contemporary definition and management. *EP Europace*. 2022;24(10):1684-1690.
42. De Becker B, El Haddad M, De Smet M, et al. Early atrial fibrillation recurrence post catheter ablation: analysis from insertable cardiac monitor in the era of optimized radiofrequency ablation. *Heart Rhythm*. 2024;21(5):521-529.
43. Andrade JG, Deyell MW, Macle L, et al. Healthcare utilization and quality of life for atrial fibrillation burden: the CIRCA-DOSE study. *Eur Heart J*. 2023;44(9):765-776.
44. Essebag V, Azizi Z, Alipour P, et al. Relationship between quality of life and burden of recurrent atrial fibrillation following ablation: CAPCOST multicentre cohort study. *EP Europace*. 2020;22(7):1017-1025.
45. Mantovan R, Macle L, De Martino G, et al. Relationship of quality of life with procedural success of atrial fibrillation (AF) ablation and postablation AF burden: substudy of the STAR AF randomized trial. *Can J Cardiol*. 2013;29(10):1211-1217.
46. Terricabras M, Mantovan R, Jiang C, et al. Association between quality of life and procedural outcome after catheter ablation for atrial fibrillation: a secondary analysis of a randomized clinical trial. *JAMA Netw Open*. 2020;3(12):e2025473.
47. Jansson V, Bergfeldt L, Schwieler J, et al. Atrial fibrillation burden, episode duration and frequency in relation to quality of life in patients with implantable cardiac monitor. *Int J Cardiol Heart Vasc*. 2021;34:100791.
48. Brachmann J, Sohns C, Andresen D, et al. Atrial fibrillation burden and clinical outcomes in heart failure. *JACC Clin Electrophysiol*. 2021;7(5):594-603.
49. Wechselberger S, Kronborg M, Huo Y, et al. Continuous monitoring after atrial fibrillation ablation: the LINQ AF study. *EP Europace*. 2018;20(Fi_3):f312-f320.
50. Aguilar M, Macle L, Deyell MW, et al. Influence of monitoring strategy on assessment of ablation success and postablation atrial fibrillation burden assessment: implications for practice and clinical trial design. *Circulation*. 2022;145(1):21-30.
51. Unni RR, Prager RT, Odabashian R, et al. Rhythm-Monitoring strategy and arrhythmia recurrence in atrial fibrillation ablation trials: a systematic review. *CJC Open*. 2022;4(5):488-496.
52. Blomström-Lundqvist C, Svedung Wettervik V. Reflections on the usefulness of today's atrial fibrillation ablation procedure endpoints and patient-reported outcomes. *EP Europace*. 2022;24(supplement 2):ii29-ii43.
53. Sale A, Yu J. Quality of life instruments in atrial fibrillation: a systematic review of measurement properties. *Health Qual Life Outcomes*. 2022;20(1):143.
54. Kotecha D, Ahmed A, Calvert M, Lencioni M, Terwee CB, Lane DA. Patient-reported outcomes for quality of life assessment in atrial fibrillation: a systematic review of measurement properties. *PLoS One*. 2016;11(11):e0165790.
55. Bonnesen MP, Frodi DM, Haugan KJ, et al. Day-to-day measurement of physical activity and risk of atrial fibrillation. *Eur Heart J*. 2021;42(38):3979-3988.
56. Semaan S, Dewland TA, Tison GH, et al. Physical activity and atrial fibrillation: data from wearable fitness trackers. *Heart Rhythm*. 2020;17(5 Pt B):842-846.
57. Généreux P, Piazza N, Alu MC, et al. Valve academic research consortium 3: updated endpoint definitions for aortic valve clinical research. *Eur Heart J*. 2021;42(19):1825-1857.
58. Clinical Evaluation. The Global Harmonization Task Force, Study Group 5.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lewalter T, Blomström-Lundqvist C, Lakkireddy D, et al. Expert opinion on design and endpoints for studies on catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2024;35:2182-2201. doi:10.1111/jce.16443