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European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus statement on catheter and surgical ablation of atrial fibrillation

Stylianos Tzeis, (EHRA Chair),[1] Edward P. Gerstenfeld, (HRS Co-Chair),[2] Jonathan Kalman, (APHRS Co-Chair),[3] Eduardo Saad, (LAHRS Co-Chair),[4] Alireza Sepehri Shamloo,[5] Jason G. Andrade,[6] Chirag R. Barbhaiya,[7] Tina Baykaner,[8] Serge Boveda,[9] Hugh Calkins,[10] Ngai-Yin Chan,[11] Minglong Chen,[12] Shih-Ann Chen,[13] Nikolaos Dagres,[14] Ralph J. Damiano,[15] Tom De Potter,[16] Isabel Deisenhofer,[17] Nicolas Derval,[18] Luigi Di Biase,[19] Mattias Duytschaever,[20] Katia Dyrda,[21] Gerhard Hindricks,[14] Meleze Hocini,[18] Young-Hoon Kim,[22] Mark la Meir,[23] Jose Luis Merino,[24] Gregory F. Michaud,[25] Andrea Natale,[26] Isabelle Nault,[27] Santiago Nava,[28] Takashi Nitta,[29] Mark O'Neill,[30] Hui-Nam Pak,[31] Jonathan P. Piccini,[32] Helmut Pürerfellner,[33] Tobias Reichlin,[34] Luis Carlos Saenz,[35] Prashanthan Sanders,[36] Richard Schilling,[37] Boris Schmidt,[38] Gregory E. Supple,[39] Kevin L. Thomas,[32] Claudio Tondo,[40] Atul Verma,[41] Elaine Y. Wan[42]

DOCUMENT REVIEWERS: Daniel Steven (Reviewer Coordinator), Michael-Joseph Agbayani, T. Jared Bunch, Aman Chugh, Juan Carlos Díaz, James V. Freeman, Carina Abigail Hardy, Hein Heidbuchel, Sofian Johar, Dominik Linz, Bart Maesen, Peter A. Noseworthy, Seil Oh, Andreu Porta-Sanchez, Tatjana Potpara, Gerardo Rodríguez Diez, Frederic Sacher, Piotr Suwalski, Serge Alexander Trines.

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From the [1]Department of Cardiology, Mitera Hospital, Athens, Greece, [2]Section of Cardiac Electrophysiology, University of California, San Francisco, USA, [3]Department of Cardiology, Royal Melbourne Hospital and Department of Medicine, University of Melbourne and Baker Research Institute, Melbourne, Australia, [4]Electrophysiology and Pacing, Hospital Samaritano Botafogo, Rio de Janeiro, Brazil and Cardiac Arrhythmia Service, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA, [5]Department of Electrophysiology, Heart Center at University of Leipzig, Leipzig, Germany, [6]Department of Medicine, Vancouver General Hospital, Vancouver, British Columbia, Canada, [7]NYU Grossman School of Medicine, New York, New York, USA, [8]Division of Cardiology and Cardiovascular Institute, Stanford University, Stanford, California, USA, [9]Heart Rhythm Management Department, Clinique Pasteur, Toulouse, France and Universiteit Brussel (VUB), Brussels, Belgium, [10]Division of Cardiology, Department of Medicine, Johns Hopkins University, Baltimore, USA, [11]Department of Medicine & Geriatrics, Princess Margaret Hospital, Hong Kong Special Administrative Region, China, [12]The First Affiliated Hospital of Nanjing Medical University, Nanjing, China, [13]Heart Rhythm Center, Taipei Veterans General Hospital, Taipei, Taiwan, [14]Department of Cardiac Electrophysiology, Charité University Berlin, Berlin, Germany, [15]Division of Cardiothoracic Surgery, Department of Surgery, Washington University School of Medicine, Barnes-Jewish Hospital, St Louis, USA, [16]Cardiovascular Center, OLV Hospital Aalst, Belgium, [17]Department of Electrophysiology, German Heart Center Munich, Technical University of Munich (TUM) School of Medicine and Health, Munich, Germany, [18]IHU LIRYC, Electrophysiology and

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Heart Modeling Institute, Fondation Bordeaux Université and Bordeaux University Hospital (CHU), Cardiac Electrophysiology and Stimulation Department, Pessac-Bordeaux, France, [19]Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA, [20]Department of Cardiology, AZ Sint-Jan Hospital, Bruges, Belgium, [21]Department of Cardiology, Montreal Heart Institute, Université de Montréal, Montreal, Canada, [22]Division of Cardiology, Korea University College of Medicine and Korea University Medical Center, Seoul, Republic of Korea, [23]Cardiac Surgery Department, Universitair Ziekenhuis Brussel - Vrije Universiteit Brussel, Brussels, Belgium, [24]La Paz University Hospital, Idipaz, Universidad Autonoma, and Hospital Viamed Santa Elena, Madrid, Spain, [25]Massachusetts General Hospital and Harvard Medical School, USA, [26]Texas Cardiac Arrhythmia Institute at St. David's Medical Center, Austin, Texas and Case Western Reserve University, Cleveland, Ohio and Interventional Electrophysiology, Scripps Clinic, San Diego, California, USA, [27]Institut Universitaire de Cardiologie et de Pneumologie de Quebec (IUCPQ), Quebec, Canada, [28]Departamento de Electrocardiología, Instituto Nacional de Cardiología «Ignacio Chávez», Ciudad de México, México, [29]Department of Cardiovascular Surgery, Nippon Medical School, Tokyo, Japan, [30]Cardiovascular Directorate, St. Thomas' Hospital and King's College, London, UK, [31]Division of Cardiology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea, [32]Duke University Medical Center, Durham, North Carolina, USA, [33]Ordensklinikum Linz Elisabethinen, Linz, Austria, [34]Department of Cardiology, Inselspital Bern, Bern University Hospital, University of Bern, Bern, Switzerland, [35]International Arrhythmia Center, Cardioinfantil Foundation, Bogota, Colombia, [36]Centre for Heart Rhythm Disorders, University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia, [37]Barts Heart Centre and Welbeck Heart Health, London, UK, [38]Cardioangiologisches Centrum Bethanien, Medizinische Klinik III, Agaplesion Markuskrankenhaus, Frankfurt, Germany, [39]Cardiac Electrophysiology Section, University of Pennsylvania Perelman School of Medicine, USA, [40]Department of Clinical Electrophysiology and Cardiac Pacing, Centro Cardiologico Monzino, IRCCS, Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy, [41]McGill University Health Centre, McGill University, Montreal, Canada, and [42]Department of Medicine, Division of Cardiology, Columbia University Vagelos College of Physicians and Surgeons, New York, New York, USA.

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Section 1: Introduction

1.1 Preamble

In the last three decades, ablation of atrial fibrillation (AF) has become an evidence-based safe and efficacious treatment for managing the most common cardiac arrhythmia. In 2007 the first joint expert consensus document was issued, guiding healthcare professionals involved in catheter or surgical AF ablation [1]. Mounting research evidence and technological advances have resulted in a rapidly changing landscape in the field of catheter and surgical AF ablation, thus stressing the need for regularly updated versions of this partnership which were issued in 2012 and 2017 [2,3]. Seven years after the last consensus, an updated document was considered necessary to define a contemporary framework for selection and management of patients considered for or undergoing catheter or surgical AF ablation. This consensus is a joint effort from collaborating cardiac electrophysiology societies, namely the European Heart Rhythm Association (EHRA), the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin American Heart Rhythm Society (LAHRS).

1.2 Organization of the writing committee

The EHRA, as the leading society, nominated the chair of the document and each of the partner societies nominated a vice-chair. The writing group was defined based on a list of representatives put forward by each organization. The members were qualified in order of preference provided that they did not meet any of the following: part-time employment or salary from a related company, significant stock ownership, holding of a patent which generates significant revenues, receipt of significant royalties for intellectual property related to the topic of the scientific paper. The entire group comprised 44 members and was appointed to section writing teams based on preference and expertise, aiming to cover specific content. All members provided disclosure statements to assess potential conflicts of interest. Details are available in supplementary material online.

1.3 Methods

A detailed survey including 140 questions, was sent to all members, aiming to capture common practice and preferences in the care of patients undergoing AF ablation. After a comprehensive literature search, evaluation of existing evidence, and consideration of the survey results, practical advice was proposed by the writing group in five sections (indications, preprocedural management, ablation strategies, procedural and postprocedural management). The writing group had face-to-face meetings and web-based conference calls discussing proposed guidance and pertinent supporting evidence while consensus modifications were made based on raised comments, thus compiling a final list of clinical advice for the voting process. During voting, each member had the option to agree, disagree, or abstain. Every proposed advice was included only if the voting results (excluding abstention) were at least 80% in support. In total, the suggested clinical advice has been approved by an average of 94% of the writing committee members.

It should be emphasized that the current document is not intended as a guideline and aims to document the current expert consensus in the dedicated narrow field of catheter and surgical AF ablation. Healthcare professionals should refer to the latest guidelines for overall structured management of AF patients [4,5]. In this consensus document, a color-coded classification of proposed clinical advice was used. Classification of different categories of advice and the respective definitions are presented in Table 1. Furthermore, the evidence supporting each advice has been classified in different categories based on the type, quality and quantity of respective sources (Table 2).

1.4 Document review and approval

The draft document was subjected to a peer review process by a review committee whose chair, vice-chairs, and members were assigned by each of the partner societies. All peer

Table 1 Color-coded classification of different categories of advice and respective definition

Definition	Category of Advice
Evidence or general agreement that a given measure is clinically useful and appropriate	Advice TO DO
Evidence or general agreement that a given measure may be clinically useful and appropriate	May be appropriate TO DO
No strong advice can be given, lack of data, inconsistency of data	Area of uncertainty
Evidence or general agreement that a given measure is not appropriate or harmful	Advice NOT TO DO

Table 2 Classification of different types of evidence and respective criteria

Type of evidence - abbreviation	Criteria
META	• Evidence from >1 high-quality RCT • Meta-analyses of high-quality RCTs
RAND	• Evidence from 1 high quality RCT • Evidence from > 1 moderate quality RCT • Meta-analyses of moderate quality RCTs
OBS	• Observational studies or registries • Meta-analyses of such studies
OPN	• Randomized, nonrandomized, observational or registry studies with limitations of design or execution, case series • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects • Consensus of expert opinion based on clinical experience

reviewers were requested to complete a declaration of interest and were not allowed to own stocks or stock options or any type of financial interest in a company marketing electrophysiologic products. Each partnering organization has officially reviewed and endorsed the final document.

1.5 Scope of the document

The objective of this consensus document is to provide practical guidance and set standards in the selection and management (preprocedural, procedural and postprocedural) of patients considered for or undergoing AF ablation. Specific sections are devoted to AF pathophysiology, anatomical considerations, evaluation and management of complications, training, and institutional requirements for AF ablation. The terms and abbreviations used in the consensus statement are summarized in Table 3.

Section 2: Classification – Atrial Fibrillation Pathophysiology

2.1 Definitions

AF is the most common supraventricular arrhythmia characterized by rapid, disorganized atrial electrical activation leading to ineffective atrial contraction. The diagnosis of clinical AF requires rhythm documentation with an electrocardiogram (ECG) tracing. Electrocardiographic characteristics of AF include:

- Absence of distinct P waves on the surface ECG;
- Irregular atrial activations with an atrial cycle length that is usually less than 200 msec;
- "Absolutely" irregular R-R intervals (when atrioventricular conduction is not impaired).

By convention, an AF episode is defined as an arrhythmia that has the electrocardiographic characteristics of AF and persists for at least 30 seconds in an ECG recording (or the duration of a 12-lead ECG) [5]. While the 30-second duration has been employed in previous published consensus statements it is important to recognise that this duration of AF has not been associated with clinically meaningful outcomes or pathophysiological processes. While it has been proposed that 30 seconds of atrial tachyarrhythmia may be a harbinger of more advanced or clinically relevant disease, recent evidence suggests that may not be the case [6]. Moreover, the 30-second sustained AF episode duration was defined in the era of non-invasive intermittent rhythm monitoring and its relevance is unknown when applied to continuous rhythm monitoring [cardiac implantable electronic devices (CIED), implantable cardiac monitors (ICM) or wearable devices (e.g. ECG-tracking smartwatches)] [7].

2.2 Classifications

Although there are several classification systems for AF, for this consensus document, we have continued to endorse the duration-based AF classification system employed by the ACC/AHA/HRS, CCS, CSANZ, and ESC, with slight modifications (Table 4)[5,8–11]. This classification system broadly categorised AF into four clinical patterns, based on the clinical assessment of AF episode duration and persistence: 1) *Paroxysmal AF*, defined as a continuous AF episode lasting longer than 30 seconds but terminating spontaneously or with intervention within 7 days of onset; 2) *Persistent AF*, defined as a continuous AF episode lasting longer than 7 days but less than one year; 3) *Long-standing persistent AF*, defined as continuous AF ≥1 year in duration, in patients where rhythm-control management is being pursued; and 4) *Permanent AF*, defined as AF for which a therapeutic decision has been made not to pursue sinus rhythm restoration.

It is important to recognize that permanent AF represents a therapeutic attitude on the part of a patient and the treating physician rather than on any inherent pathophysiological attribute of the AF. If a rhythm control strategy is recommended after re-evaluation, the AF should be redesignated as paroxysmal, persistent, or long-standing persistent AF. *Early paroxysmal AF* is defined as a continuous AF episode lasting longer than 30 seconds but terminating within 24 hours of onset either spontaneously or with intervention. The 24-hour duration was chosen based on the knowledge that important changes in AF-related electrical and structural remodelling occur over time frames as short as 24 hours [12,13], leading to reductions in cardioversion [14,15] and catheter ablation efficacy [16]. Similarly, AF episodes >24 hours have been associated with increased risk of ischemic stroke or systemic embolism, as well as increased cardiovascular hospitalization, all-cause hospitalization and all-cause mortality [17–19]. *Early persistent AF* is defined as continuous AF of more than 7 days' duration but less than 3 months' duration. Within the context of AF ablation and clinical trials of AF ablation, early persistent AF defines a population of patients in whom better outcomes of AF ablation are anticipated as compared with persistent AF of more than 3 months' duration.

A duration-based AF classification is a relatively straightforward schema that can be employed to standardise reporting, characterize the severity of disease, define patient populations in clinical trials of catheter and surgical ablation of AF, and form the basis of therapeutic recommendations regarding invasive arrhythmia management. However, it is important to recognise that clinical assessment of AF episode duration often underestimates the temporal persistence of AF

Table 3 Abbreviations

Term (abbreviation)	Definition
AAD	Antiarrhythmic drug
ACC	American College of Cardiology
AEF	Atrioesophageal fistula
AF	Atrial fibrillation
AFl	Atrial flutter
AHA	American Heart Association
AI	Ablation index
ANS	Autonomic nervous system
APD	Action potential duration
APHRS	Asia Pacific Heart Rhythm Society
ASD	Atrial septum defect
AT	Atrial tachycardia
ATP	Adenosine triphosphate
AVNRT	Atrioventricular nodal reentry tachycardia
AVRT	Atrioventricular reentry tachycardia
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft
CCS	Canadian Cardiovascular Society
CCT	Cardiac computed tomography
CF	Contact force
CFAE	Complex fractionated atrial electrogram
CMR	Cardiac magnetic resonance
CNS	Cardiac nervous system
CPAP	Continuous positive airway pressure
CS	Coronary sinus
CSANZ	Cardiac Society of Australia and New Zealand
CTI	Cavotricuspid isthmus
DAT	Diagnosis to ablation time
DOAC	Direct oral anticoagulant
EAM	Electroanatomical mapping
ECG	Electrocardiogram
ECGI	Electrocardiographic imaging
EHRA	European Heart Rhythm Association
ERP	Effective refractory period
ESC	European Society of Cardiology
FTI	Force time integral
GCV	Great cardiac vein
GP	Ganglionated plexi
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HFJV	High frequency jet ventilation
HFLTV	High frequency low tidal volume
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HRS	Heart Rhythm Society
ICD	Implantable cardiac defibrillator
ICE	Intracardiac echocardiography
ICM	Implantable cardiac monitor
LA	Left atrium
LAA	Left atrial appendage
LAHRS	Latin American Heart Rhythm Society
LAPW	Left atrial posterior wall
LGE	Late gadolinium enhancement
LoE	Level of Evidence
LIPV	Left inferior pulmonary vein
LMWH	Low molecular weight heparin
LSI	Lesion size index
LSPV	Left superior pulmonary vein
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
OSA	Obstructive sleep apnea
PFA	Pulsed field ablation
PFO	Patent foramen ovale
PN	Phrenic nerve
PPI	Proton pump inhibitor
PV	Pulmonary vein
PVI	Pulmonary vein isolation
PWI	Posterior wall isolation
QoL	Quality of life
RA	Right atrium
RCT	Randomized clinical trial
RF	Radiofrequency
RSPV	Right superior pulmonary vein
SVC	Superior vena cava
SVT	Supraventricular tachycardia
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TTI	Time to isolation
UFH	Unfractionated heparin
VKA	Vitamin K antagonist
VoM	Vein of Marshall

when compared to long-term ECG monitoring, often leading to misclassification between paroxysmal and persistent AF [20,21]. In addition, AF is a chronic progressive disease, evolving often from short paroxysms of AF to more frequent exacerbations of longer-lasting persistent AF. If both paroxysmal and persistent episodes are present, the classification should be defined based on the predominant AF pattern during the preceding 6 months.

2.3 Natural history of AF and AF progression

AF is a chronic progressive disease characterised by exacerbations and remissions. Early in its course, AF is predominantly an isolated electrical disorder, triggered by rapid discharges originating mainly from the PVs, either secondary to enhanced automaticity or triggered activity from afterdepolarizations. These triggered impulses initiate and maintain AF through sustained rapid firing with secondary disorganization into fibrillatory waves. Although re-entry is not usually sustained in a normal atrium, the presence of a vulnerable substrate can perpetuate AF through electrical heterogeneity [e.g., regional differences in conduction velocity, action potential duration (APD), and refractory period], with functional conduction abnormalities promoting re-entrant activity and stabilizing re-entrant circuits. Moreover, the cumulative effect of these intermittent AF episodes is electrical, contractile, and structural remodeling, with fibrosis promoting re-entry through structural conduction abnormalities, and chamber dilatation promoting re-entry. This atrial structural remodeling and worsening of atrial cardiomyopathy promote sustained arrhythmia and underpin the progression from paroxysmal to persistent forms of AF [22].

While a wealth of experimental data exists regarding structural and functional atrial changes that contribute to the development, maintenance, and progression of AF, considerably

Table 4 Proposed classification of atrial fibrillation

Duration-based classification

Paroxysmal - Continuous AF episode lasting longer than 30 seconds but terminating spontaneously or with intervention within 7 days of onset.
- **Early Paroxysmal** - continuous AF episode lasting longer than 30 seconds but terminating spontaneously or with intervention within 24 hours of onset.

Persistent - Continuous AF episode lasting longer than 7 days but less than one year.
- **Early Persistent** - Continuous AF episode lasting longer than 7 days but less than 3 months.

Long-Standing Persistent - Continuous AF episode lasting longer than one year, in whom rhythm-control management is being pursued.

Permanent - AF for which a therapeutic decision has been made not to pursue sinus rhythm restoration.

AF = atrial fibrillation.

less data exist regarding the natural history of AF. The reported rate of AF progression to non-paroxysmal AF types varies substantially due to differences in patient characteristics and comorbidities, study design (retrospective vs. prospective), follow-up duration (progression appears to be non-linear), and arrhythmia monitoring technology (e.g. most used intermittent rhythm assessments which underestimate progression) [7,22,23]. Within these limitations, a proportion of patients presenting with their first AF episode will remain free of further recurrence, particularly if they are young and free of co-morbidities at the time of index presentation [22,24–26]. A metaanalysis of 47 studies reported that the incidence of progression from paroxysmal to non-paroxysmal AF was 7.1 per 100 patient-years of follow-up, with higher incidence in studies with shorter follow-up duration [23]. In a relatively young and healthy population at low risk of AF progression, 7.4% of patients with symptomatic paroxysmal AF receiving first-line antiarrhythmic drug (AAD) therapy experienced an episode of persistent AF over a 3-year follow-up as documented by continuous rhythm monitoring with implantable cardiac device [27]. A recent loop recorder study of 417 paroxysmal AF patients with 2.2 years of follow-up demonstrated progression to persistent or permanent AF in 8.4% (approximately 3.8% annually)[28]. For longer-duration studies the rate of progression has been reported to be 22-36% at 10 years [24,29,30]. Importantly, while AF progression has been associated with worse outcomes, it is unclear whether progression is responsible for or merely a marker of a worse underlying substrate [31,32].

Predictors associated with progression from paroxysmal to persistent AF include increasing age, the presence of structural cardiac pathology (LA dilatation), and an increasing burden of modifiable risk factors and concomitant risk conditions such as hypertension, diabetes mellitus, obesity, heart failure (HF), coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, prior transient ischemic attack (TIA) or stroke, and obstructive sleep apnea (OSA) [25,30,33–36]. Several biomarkers have also been associated with AF progression [28,37].

2.4 Pathophysiology of AF

2.4.1 Genetics of AF

AF is a complex disease where both environmental and genetic factors contribute to disease pathogenesis. Studies have shown familial aggregation and heritability of AF [38,39]. After accounting for established clinical risk factors, individuals with a first-degree relative with AF have a 40% increased risk for AF development [40].

The first rare pathogenic variant linked to familial AF was found in the Kv1.7 voltage-gated potassium channel [41]. Since then, further variants have been identified in genes encoding potassium channels [42–48], sodium channel [49–51], and other non–channel proteins [52,53] in patients and families with AF. In addition, genome-wide association studies comparing AF patients to the general population have associated a common variant at the 4q25 locus, a noncoding region of the genome near the gene PITX2, with a 60% increased risk of developing AF [54]. Further genome-wide association studies have associated single nucleotide polymorphisms at more than 140 loci with AF [55–58]. Single nucleotide polymorphisms identified by genome-wide association studies account for approximately 22% of the risk of developing AF [59].

Polygenic risk scores derived from these single nucleotide polymorphisms have been associated with stroke, outcomes after AF ablation or cardioversion, and response to certain rate and rhythm control medications [60]. Larger, prospective, multiethnic studies will be necessary before clinical application of these scores can be considered.

It may be reasonable to refer patients with onset of AF earlier than 45 years old without any identifiable risk factors to an inherited arrhythmia clinic for consideration of genetic testing and family screening [60]. The 2022 EHRA/HRS/APHRS/LAHRS Expert Consensus Statement on the state of genetic testing for cardiac diseases supports analysis of specific genetic variants (SCN5A, KCNQ1, MYL4 and truncating TTN) in index patients in whom the diagnosis of familial AF is established, based on examination of the patient's clinical history, family history, and ECG characteristics [61]. Currently, there is no role for routine clinical genetic testing in older patients presenting with AF in the absence of familial disease [61].

2.4.2 Molecular basis of AF

AF triggers resulting from ectopic activity within the atria are linked to spontaneous diastolic Ca^{2+}-release from the sarcoplasmic reticulum via leaky ryanodine-receptor channels. Early afterdepolarizations due to loss-of-function mutations in outward potassium channels, or gain-of-function mutations in inward calcium channels leading to a reduced repolarization reserve, have also been linked to spontaneous ectopic activity [62,63]. The canine PVs have been shown to have smaller inward-rectifier K^+-current (IK_1) and L-type Ca^{2+}-current (ICa,L), as well as larger delayed-rectifier K^+-currents, compared with the left atrial cells [63].

Conduction abnormalities have a role in AF pathophysiology, presumably by increasing susceptibility to re-entry and maintenance of AF. The most important determinants of conduction are: (a) structural integrity of atrial tissue, often disrupted by fibrosis; (b) effective cell-to-cell coupling, principally determined by connexin hemichannels in intercalated disks; and (c) integrity of the rapid phase-0 Na^+-current (INa), which provides the electrical energy for conduction [63,64].

2.4.3 Mechanisms of AF initiation and maintenance

2.4.3.1 Role of triggers and automaticity. AF is initiated by triggers and then sustained by distinct mechanisms for longer durations. Ectopic activity, particularly occurring in the PVs, has been shown to have a central role in initiation of AF [65]. Variances in the ion channels and the structure of PV tissue predispose to ectopic activity by (a) reducing APD leading to re-entry, and (b) increasing DADs due to aberrant Ca^{2+}-release leading to spontaneous ectopy [63,66]. Clinically, PVs are noted to have smaller electrogram voltages, slower conduction, shorter effective refractory period (ERP), and a greater vulnerability to AF induction during programmed electrical stimulation [67]. Embryologically, the posterior wall of the LA has the same origin as the PVs, and therefore is considered to have a similar arrhythmogenic role [68]. Other sites of triggered activity include the superior vena cava (SVC), the ligament of Marshall, and the left atrial appendage (LAA), although atrial sites beyond PVs are less clearly linked to AF initiation [69].

2.4.3.2 Role of focal and rotational activity and spiral waves. The concept of small rapidly rotating circuits postulates that fibrillatory conduction is maintained by AF-perpetuating drivers, or localized regions that activate faster compared to the surrounding atrial tissue [70,71]. Rotational and focal drivers of AF have been identified near regions of fibrosis by optical mapping of ex-vivo animal hearts, ex-vivo human atria, and in-vivo human atria [72–74].

Unfortunately, the tools required to demonstrate rotational and focal drivers of AF are limited by the complexity of assessing intracardiac electrograms during fibrillatory conduction, particularly in reference to the accurate identification of local activation timings [75–77].

2.4.3.3 Role of multiwavelet re-entry. The multiple wavelet concept was initially proposed by Garrey [78], refined by Moe with computer modeling studies [79], and later supported by Allessie with mapping of AF in canine atria [80] and human atria [81]. The multiple wavelet theory proposes that multiple AF perpetuating wavelets self-replenish by collision, facilitated by structural obstacles and conduction dissociation between the endocardial and epicardial surfaces of the atrial wall. This theory implies that extensive ablation is required to limit the surface area of conduction and resolve constant replenishment of fibrillatory wavelets. Recent mechanistic evidence from computational models also suggests that smaller areas for fibrillatory waves to propagate are associated with improved long-term postablation outcomes in persistent AF [82].

2.4.3.4 Role of endocardial-epicardial asynchrony. Recent data have found that despite the relatively thin-walled atria, the complex LA anatomy has a structure that, combined with the progression of intramural fibrosis, can contribute to AF maintenance by providing a larger three-dimensional substrate that increases the probability of intramural reentry and AF maintenance. Preclinical and clinical surgical high density mapping studies have found that activation of the endocardium and epicardium are often asynchronous and dissociated during AF, likely exacerbated by slow conduction and intramural conduction delay and block [74,83,84]. These findings have been confirmed in RA recordings in humans with AF undergoing cardiac surgical procedures [85–88] and in LA simultaneous endo-epicardial recordings of patients undergoing catheter ablation of AF [89,90]. Such findings further increase the complex nature of AF and may explain why mapping from the endocardium or epicardium alone have failed to identify the true underlying mechanism of AF.

In summary, the presently available data suggest that both ectopic activity and re-entry play important roles in AF initiation and maintenance of fibrillatory conduction. Moreover, localized driver sites may have a role in AF maintenance independent of the initiating mechanism. The specific mechanisms and determinants remain to be elucidated, along with their implications for therapy.

2.4.4 Structural and electrical remodeling in AF

2.4.4.1 Structural remodeling. The atria of patients with AF often show evidence of structural remodeling. The easiest type of structural change to recognise is LA enlargement, which is seen in many AF patients and correlates with disease progression and outcomes [91,92]. Atrial enlargement provides more atrial tissue to harbor disordered wavelets or drivers, and also correlates with the presence of fibrosis [93]. Atrial fibrosis can be a result of the electrical remodeling of AF, AF-related risk factors, or a fibrotic atrial cardiomyopathy [64,93–96]. The mechanisms of fibrosis and its consequences comprise many phenomena at molecular, organelle, cellular, and tissue level [97]. At the molecular level, dynamic changes occur in the genome, the transcriptome, and the signaling pathways underlying the generation of profibrotic molecules [98]. Cellular changes involve interactions among the various cardiac cells, including myocytes, fibroblasts or myofibroblasts, and inflammatory cells such as macrophages and neutrophils [98,99]. Tissue changes relate to the dynamics of scar, angiogenesis, electrical conduction, and contractility [100]. Fibrosis may also increase the number of fibroblasts, promoting AF by altering the electrophysiological behavior of cardiomyocytes coupled to fibroblasts through cardiomyocyte–fibroblast interactions [99,101](Figure 1).

Atrial fibrosis results in heterogeneous electrical conduction and repolarization, and may facilitate multiple wavelet re-entry or anchor driver regions [102]. Clinically, identification of atrial fibrosis has been challenging, with promising techniques including detection of increased signal intensity on gadolinium-enhanced magnetic resonance imaging (MRI) [103], or identification of low amplitude electrical signals at invasive electrophysiology study [104,105], although a mismatch between these techniques has been suggested [106](section 5.2.1.4).

Another potentially important factor in AF-related atrial remodeling is fatty infiltration, which is known to increase in several pathophysiological conditions and is regarded as arrhythmogenic [107,108]. Epicardial fatty infiltration occurs with

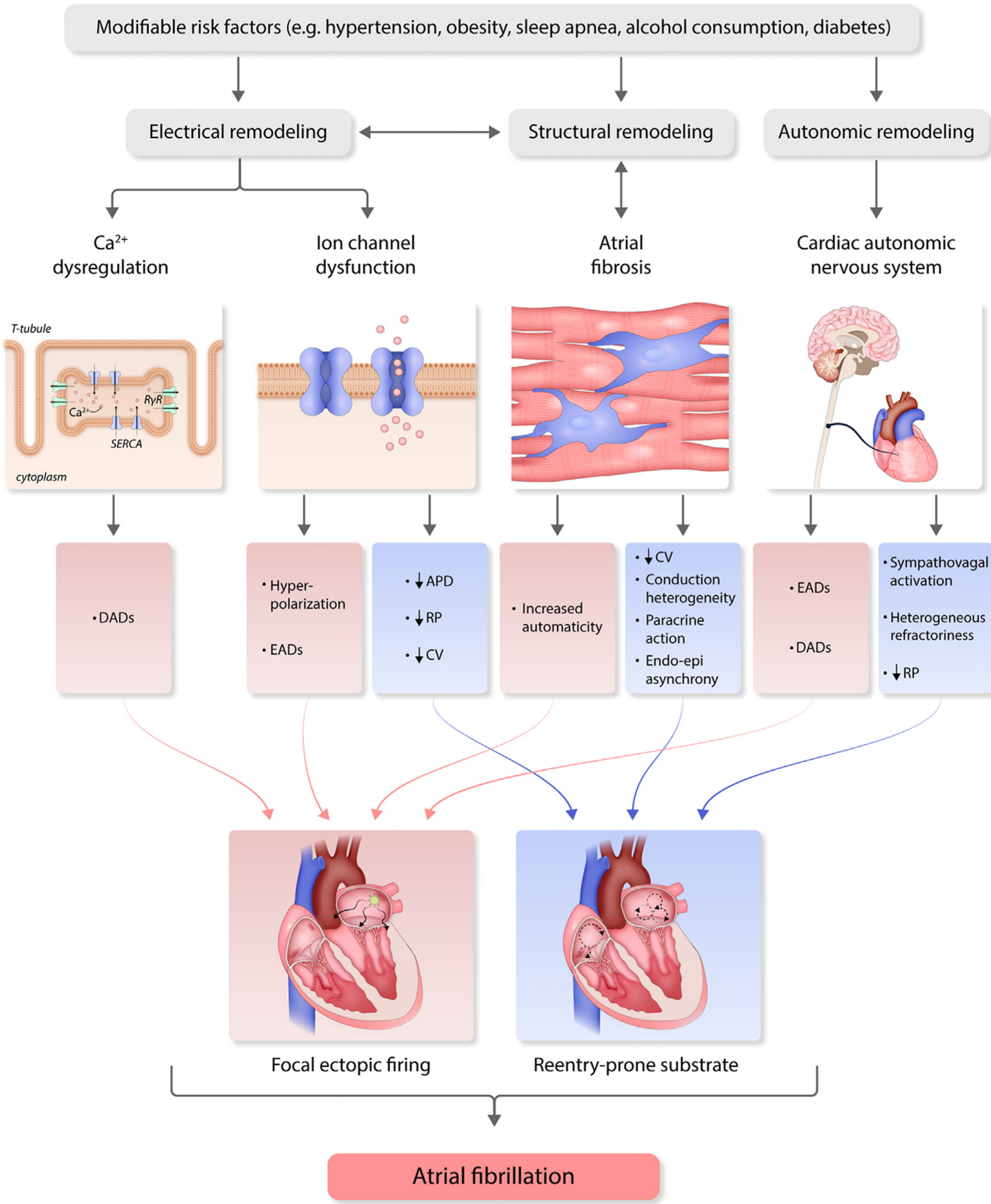


Figure 1
Pathophysiological mechanisms of atrial fibrillation. APD = action potential duration; CV = conduction velocity; DADs = delayed afterdepolarizations; EADs = early afterdepolarizations; RP = refractory period; RyR = ryanodine receptor; SERCA = sarcoplasmic/endoplasmic reticulum Ca2+-ATPase.

obesity and has been associated with AF via structural and electrical remodeling of the atria, via direct infiltration of adipose tissue into the atrial tissue, and via indirect mechanisms through paracrine modulators resulting in inflammation and oxidative stress [109,110](section 5.2.1.4).

Myocardial infiltration by amyloid deposits may also disturb atrial conduction in cardiac amyloidosis [111]. Patients with long-standing AF and rheumatic heart disease have a very high prevalence of atrial amyloidosis [112]. Isolated atrial amyloidosis is more prevalent than amyloid light chain (AL) amyloidosis or wild type (senile) ATTR cardiovascular amyloidosis, with a prevalence of >90% in the ninth decade [113]. Pathophysiologic association between amyloidosis and AF is still under investigation but is considered to relate to structural abnormalities similar to atrial fibrosis.

2.4.4.2 Electrical remodeling. Electrical remodeling in AF patients involves shortened atrial refractory periods from downregulation of Ca^{2+} currents, shortened repolarization and hyperpolarization of atrial cells from increased outward K^+ currents, and conduction slowing from altered expression and localization of connexins between myocytes [114] (Figure 1). Oxidative stress, atrial dilatation, microRNAs, inflammation, and myofibroblast activation also have a role in electrical remodeling [64].

Electrical remodeling, manifested as shortening of atrial refractoriness, develops within the first few days of

AF [100,115]. Several ion channel modifications underlying such electrical changes have been described in animal models and humans [114,116–118]. Dominant frequency of AF is shown to increase gradually after AF onset, stabilizing within two weeks. These dominant frequency changes are associated with downregulation of ICaL and INa, and upregulation of IK1, along with corresponding mRNA or protein changes. Interstitial fibrosis develops at 6–12 months, highlighting increasing tendency of AF to persist over time [119,120]. Sustained AF shortens APD and ERP, decreasing the wavelength and facilitating the acceleration and stabilization of sustained re-entry. The primary determinants of APD shortening are the decrease in ICaL and increase in IK1 [119]. Rapid atrial rates can activate fibroblasts and increase collagen-gene activity, promoting fibrosis and structural remodeling [121].

2.4.5 Autonomic nervous system and its role in AF pathophysiology

The electrophysiology of the heart is highly influenced by the autonomic nervous system (ANS) (section 3.7). Initiation and termination of AF episodes have been linked to changes and abnormalities in cardiac autonomic tone [122–124]. At the whole heart and cellular levels, both extrinsic and intrinsic autonomic modulation has been shown to produce early or delayed after-depolarizations that trigger ectopic firing, and contribute to AF maintenance [125–130].

Autonomic interventions have been shown to modulate AF occurrence. A small randomized trial of vagal stimulation via the tragus reduced AF burden over 6 months [131]. This effect may be mediated by upregulation of small conductance calcium-activated potassium channels in the stellate ganglion [132]. Spinal cord stimulation has also demonstrated a protective effect on AF inducibility in a tachypacing model [133].

Due to the interrelationship between the sympathetic and parasympathetic ANS components, it is not possible to perform selective modulation of the parasympathetic or the sympathetic nervous system alone with direct ablation at ganglionated plexi (GP) sites. However, ablation targeting GP sites has been shown to modulate cardiac autonomic tone and AF inducibility [134–137]. Due to their anatomic location in proximity to the PVs, these GP sites may actually be ablated during a standard pulmonary vein isolation (PVI) procedure.

Section 3: Anatomical Considerations – Implications for Catheter Ablation

3.1 The pulmonary veins – typical anatomy and variants

Atrial fibrillation is regarded as a primarily left atrial arrhythmia, mainly because AF episodes are initiated most commonly by atrial extrasystoles emanating from the PVs. Since the ground-breaking publication of Michel Haissaguerre and colleagues in 1998, multiple studies have shown that unique anatomic features of the PV myocardial sleeves or extensions enable focal automaticity [65,66,138]. In addition to the enhanced focal activity of the PV themselves, anisotropic, heterogeneous conduction in the PV antra creates an environment prone to microreentrant activity, acting like a "repeater" augmenting single ectopics into a burst of fibrillatory activity or PV tachycardia [139,140]. (Section 2.4.3).

The entrance of the PVs to the left atrium (LA) is located on the superior-posterior part, with the inferior PVs entering the LA inferiorly but also posteriorly to the superior PVs. The typical PV branching pattern comprises four separate PV ostia, with a pair of superior and inferior PVs on the left and right posterior aspect. Most common PV variants include a common trunk (either short or long) of the left sided PVs and an additional (middle) PV on the right side [141,142]. Rarely, other atypical variations in PV anatomy may be encountered including an accessory PV draining at the LA roof, a common superior or inferior conjoined vein, three or even all four PVs entering LA together with a common trunk [141–143](Figure 2).

Myocardial sleeves extend into the PVs approximately 2-3cm from the PV-LA junction, often taking a spiraling course [144]. Additionally, the thickness of the LA wall in the region of the PV antra varies from 2mm (posterior wall) up to 8mm at the ridge separating the left superior pulmonary vein (LSPV) from the LAA [68,141,145]. This variance in target lesion depth is one of the challenges in safely achieving transmural and durable PV isolation [146].

3.2 Pulmonary vein epicardial connections

Besides the knowledge of typical PV anatomy and related variants, it is also critical to understand the concept of epicardial connections between PVs and other adjacent atrial structures as it can strongly influence short and long-term achievement of PVI. Although difficult to evaluate, their overall prevalence appears to be as high as 13.5% [147]. The presence of underlying structural heart disease or a patent foramen ovale (PFO) is associated with a higher prevalence of epicardial connections, whereas a left common trunk is associated with absence of epicardial connections [147,148]. Several studies have reported the anatomical distribution and functional impact of these epicardial connections [147–151].

More than half of epicardial connections are located in the left PVs and are mediated by the ligament of Marshall [147]. As described hereafter, the ligament of Marshall is an epicardial structure containing the vein of Marshall (VoM), the Marshall myocardial bundle, and autonomic nerves. Postmortem studies have revealed that, unlike other atrial tracts, the ligament of Marshall is distinctly segregated and insulated from the underlying LA myocardium and connects directly to the coronary sinus (CS) musculature and the LA free wall at the level of the left inferior pulmonary vein (LIPV) [152,153].

Epicardial connections are also located in the right PVs connecting them with the right atrium (RA) or less frequently with distinct areas of the LA. In the former, epicardial connections are supported by muscular strands that connect the muscular sleeves of the right PVs to the RA [153–155]. Epicardial connections between the right PV and the posterior wall of the LA have also been described suggesting variants of the septopulmonary bundle that link the right carina with the posterior wall [147,148,150,156].

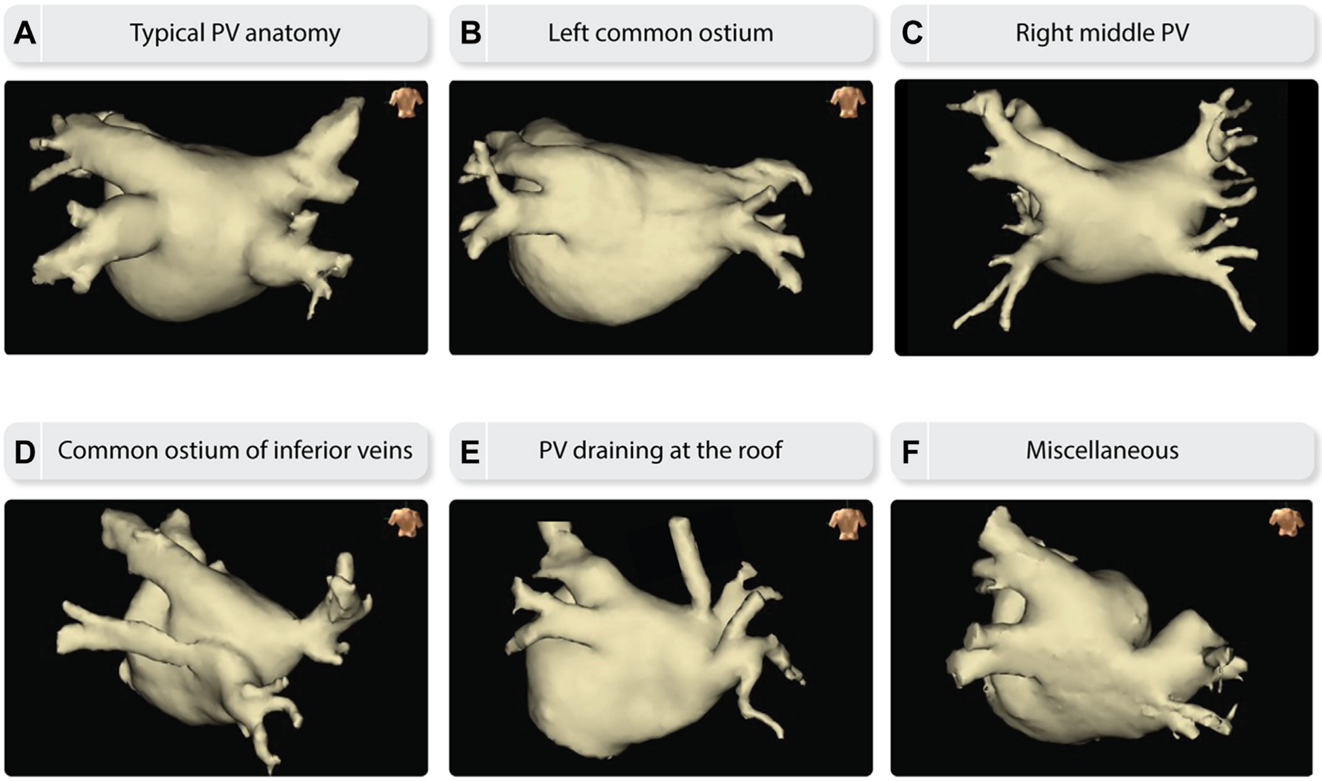


Figure 2
Typical pulmonary vein anatomy and common variants. PV = pulmonary vein.

3.3 Fossa ovalis – interatrial septum (implications for transeptal puncture)

During cardiac development, a complex advancement, growth, and migration of atrial tissue forming the septum primum and then the septum secundum allows the formation of the interatrial septum which eventually separates left from RA [145,157]. During this process, the fossa ovalis is formed, which is where the septum primum overlies the septum secundum. The fossa ovalis represents the thinnest part of the septum and thus is the ideal location for transseptal puncture [145,157,158]. It has an average vertical diameter of 18.5±6.9 mm and an average horizontal diameter of 10.0±2.4 mm [159]. The septal area located superiorly (cranially) to the fossa ovalis is formed by an infolded groove of the atrial wall between the SVC and the right PVs and contains extracardiac adipose tissue [159]. Inadvertent puncture of this area must be avoided since it may result in interatrial septum dissection, atrial wall hematoma or tamponade [160](Figure 3).

In approximately 25-28% of patients, the two membranes that comprise the fossa ovalis do not fuse, so that a PFO is present. This defect varies considerably in size, from a more slit like formation to defects of 19 mm size, with a mean reported PFO diameter of 5mm [161–163]. Although the fossa ovalis is considered to be the optimal site for transseptal puncture, crossing the septum via a PFO during AF catheter ablation has several limitations, since the PFO is located very cranially and anteriorly at the septum, thus impeding access to the caudal parts of the LA (including the inferior PVs) and the right superior pulmonary vein (RSPV), where a steep turn is needed to enter. Hence, some operators prefer to perform transeptal puncture inferior and posterior to a present PFO. Several observational studies have shown that use of a PFO to gain access in the LA during AF catheter ablation does not adversely affect ablation efficacy as compared to needle-assisted LA access [164,165]. However, the presence of a large and/or compliant PFO has been reported as independent predictor of PVI failure and increased arrhythmia recurrence rate following AF catheter ablation [166].

In contrast, "true" atrial septum defects (ASD) are usually located at the site of a transseptal puncture and offer a very convenient access to the LA and the PV region. However, an ASD with a relevant left-to-right shunt results in right atrial volume load with subsequent increased arrhythmogenic remodeling. The latter should be taken into account when individualising AF ablation approach, since in the presence of an ASD, the RA is likely implicated in AF initiation and maintenance and thus should be evaluated as potential ablation target [158,167].

The rare variant of an atrial septum aneurysm (approximately 1-2% of patients) can complicate transseptal puncture. Most commonly, the aneurysm comprises a "floppy septum", which means that true crossing of the septum requires pushing the transeptal needle almost to or even beyond the most left-lateral boundaries of the LA, risking a perforation

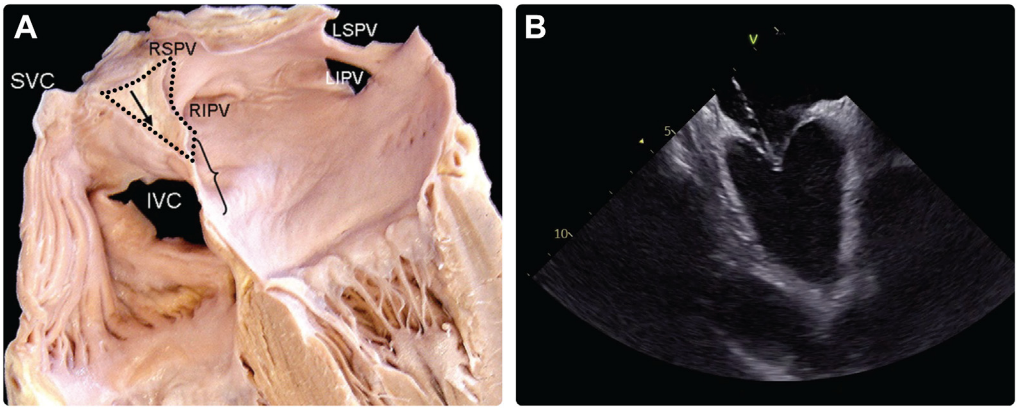


Figure 3
A. Anatomy of interatrial septum and optimal site of transseptal puncture (demarcated with a brace). Black arrow in the dotted area shows the infolded groove of the atrial wall between the SVC and the right PVs filled with extracardiac fat tissue. B. Intracardiac echo view of typical tenting before transeptal crossing. Modified from [159]
IVC = inferior vena cava; LIVP = left inferior pulmonary vein; LSVP = left superior pulmonary vein; RIVP = right inferior pulmonary vein; RSVP = right superior pulmonary vein; SVC = superior vena cava.

of the LA. Available technologies that facilitate crossing of the septum in challenging anatomies are presented in section 7.5 [157,158,161,167,168]. Anatomic variations of interatrial septum and clinical settings that may be encountered during transeptal puncture are presented in Figure 4.

Some patients with AF may have had prior surgical or percutaneous ASD closure. Surgical closure of an ASD with a stitch typically does not impede subsequent transseptal puncture. Use of a pericardial patch to close the ASD may impede crossing of the septum, but there is often room to cross above or below the patch. Direct puncture through the patch with an RF needle is also feasible. Percutaneous closure devices can pose more of a challenge. Typically, there is room inferior-posterior to most ASD closure devices for transeptal access through the native septum using the usual transseptal tools [169]. Occasionally (Figure 4F) an ASD device may cover the entire septum. Crossing through an ASD closure device has been described but should be reserved for highly experienced centers [170].

3.4 Architecture of left atrial musculature

The orientation of the major atrial muscular bundles has been recognized from anatomical dissections, with mostly circular bundles around the ostia of the PVs, atrioventricular valves, and LAA [171]. The body of the LA is comprised of the venous component located posteriorly, the septum and the vestibular portion which forms the "left atrial outlet" [155]. The vestibule partly forms the mitral isthmus located between the orifice of the LIPV and the annular attachment of the mitral valve [155,172]. Several anatomical isthmuses can be identified between these native obstacles, which have the potential for supporting reentry reentry [173–175]. The body of the LA has relatively smooth wall with a complex architecture of overlapping myofibers of different orientation. The most prominent interatrial muscular connection is the Bachmann's bundle comprised of atrial myocardial strands aligned in a parallel fashion. It extends from the right of the SVC orifice, crosses the interatrial groove and courses along the anterior wall of the LA until the LAA where it divides in two branches that encircle it [171]. The superior part continues along the left lateral ridge and the inferior part towards the atrial vestibule and then merge into the musculature of the lateral and inferoposterior atrial wall [176](Figure 5).

In 1920, Papez first described the septo-pulmonary bundle and the septo-atrial bundle [177]. This terminology directly reflects their different course through the LA components previously described. The two bundles arise from the septum, but the septo-atrial bundle preferentially covers the LA body (as well as the LAA and the vestibule), while the septo-pulmonary bundle mainly encircles the PVs. Both bundles course along the dome and the posterior wall, where the septo-pulmonary bundle epicardially overlaps the septo-atrial bundle to form a bilayer architecture. Until recently, these bundles were not considered to be separated by a layer of insulating tissue [154,171,177,178]. Recently, the septo-pulmonary bundle has been described to be separated from the LA body by fat interposition. This intervening fat layer may act as an insulation preventing transmission of ablation energy to the epicardially situated septopulmonary bundle and thus impairing the achievement of durable PV isolation, complete roof line or posterior wall isolation (PWI) [179].

3.5 Coronary sinus - vein of Marshall

The coronary venous system, with the CS located at its most proximal part, drains approximately 85% of the venous flow into the RA. The great cardiac vein (GCV) ascends into the left atrioventricular groove, where it passes close to the circumflex artery and under the cover of the LAA. The CS has an individualized musculature separated from the LA myocardium by fat, with sparse connections to the posterior wall via discrete muscular tracts [180]. The juncture between the GCV and the CS is marked by the entrance of the VoM [181].

The CS-VoM musculature has an arborized layout. A primary bundle running epicardially along the vein displays secondary bundles insulated into fibro-fatty tissue. Following an epi-endocardial course, these secondary bundles join at the

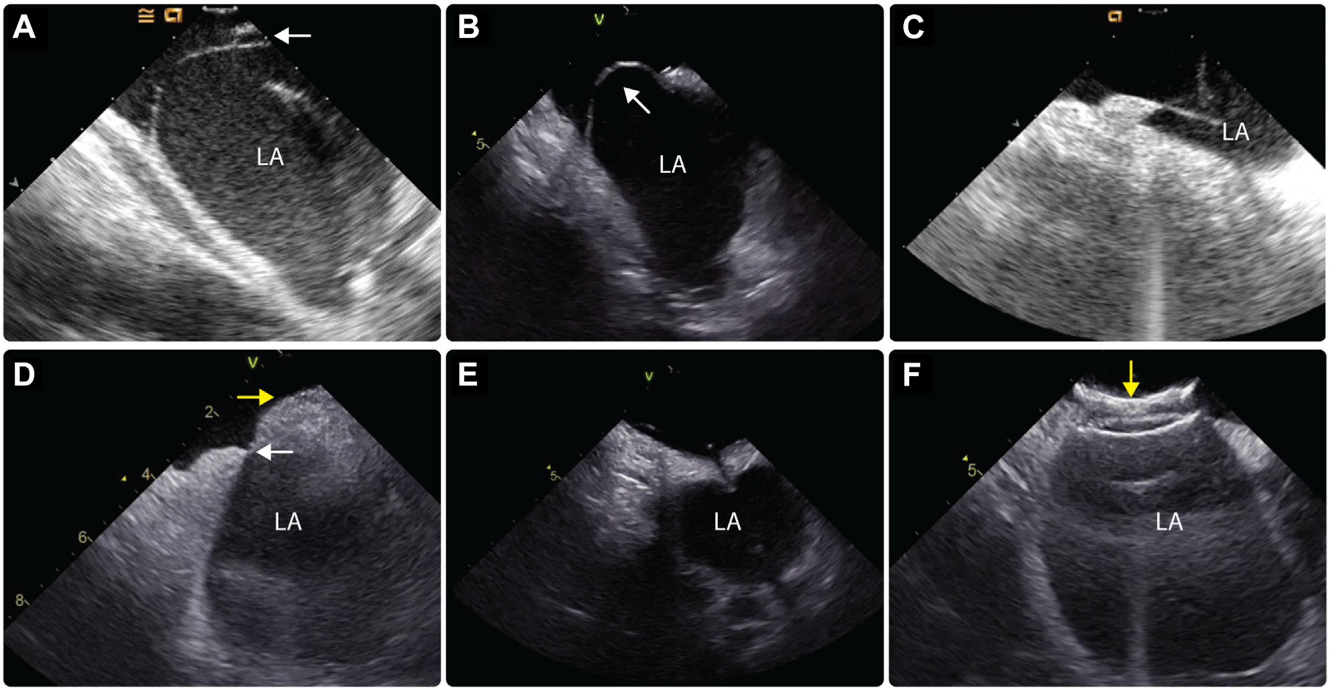


Figure 4
Anatomic variations of the interatrial septum that may be encountered during transeptal puncture. A. patent foramen ovale (white arrow); B. septal aneurysm with large excursion towards the right atrium (white arrow); C. tenting of floppy septum from transeptal needle close to the left atrial wall; D. very small fossa ovalis (white arrow) in a patient with lipomatous septal hypertrophy (yellow arrow); E. standard transeptal needle crossing a pericardial patch; F. atrial septal closure device (yellow arrow) covering almost all of the interatrial septum. LA = left atrium.

bottom with the LA free wall myocardium [180,182–184]. A muscular continuum is observed from the CS to the left PVs, using the VOM as a hub: its primary bundle is connected to the CS musculature near the Vieussens valve, while its secondary bundles are connected to the left PV sleeves at the ridge.

The VoM is an embryological remnant of the left upper caval system resulting from the involution of the left anterior cardinal vein [185]. This vestigial structure is separated into two portions: (a) the extracardiac portion, named the ligament of Marshall, is contained in a fold of pericardium, occluded in almost all cases and associated with branches of extrinsic cardiac nerves, and (b) the intracardiac part that extends from the left lateral ridge (between LAA and left PVs) to the CS, maintaining patency at different distance from its connection with the CS, forming the VoM (also known as oblique vein of the LA). The VoM has an epicardial myocardial sleeve (the Marshall bundle), and neighbors with closely associated autonomic nerve fibers and fat [182,183,186]. The Marshall bundle is an insulated muscular structure that connects to the left atrial myocardium at the level of the left PVs with limited connections to the underlying myocardium along its epicardial course. Several studies have demonstrated that the muscular fibers of the VoM and adjacent structures have a multifaceted proarrhythmic potential, since they may be the source of focal activities, part of reentry circuits and autonomic modulators [187–191]. Being co-localized with arrhythmogenic structures, the VoM may represent an ablation target beyond PVI during AF catheter ablation (section 8.2.7).

The VoM has close anatomical relationship with the mitral isthmus, located between the mitral annulus and the LIPV ostium [155,192] with practical implications during ablation attempts at the mitral isthmus either for left atrial substrate modification or treatment of perimitral flutter[172,193]. Achievement of mitral isthmus block may prove challenging not only due to mitral isthmus wall thickness but also due to its complex anatomy including: (a) the thick left lateral atrial wall, rarely exceeding 4mm [152,194], (b) the VoM [195,196] and (c) the GCV with its musculature extending over 2 to 40 mm, either at the anchored or free wall of the vessel. [197].

3.6 Superior vena cava

Apart from the PVs, the SVC also exhibits myocardial sleeves that extend as much as 4-5cm cranially into the vein [145,198]. Increased length of SVC myocardial sleeves and increased SVC diameter are reported as independent predictors of SVC firing in AF patients undergoing catheter ablation[199]. However, the SVC myocardium has different myocardial origin than the myocardial sleeves of the PVs and hence, the arrhythmogenic potential of the SVC is not prominent. This seems to be especially true for the influent or antral region of the SVC, which is not known to have such anisotropic or heterogenous conduction properties as the PV antral region [200]. Several studies have reported that the SVC acts as an extra-PV trigger in 2-6% of patients [198,201]. In such settings, SVC isolation is usually attempted. SVC isolation can be

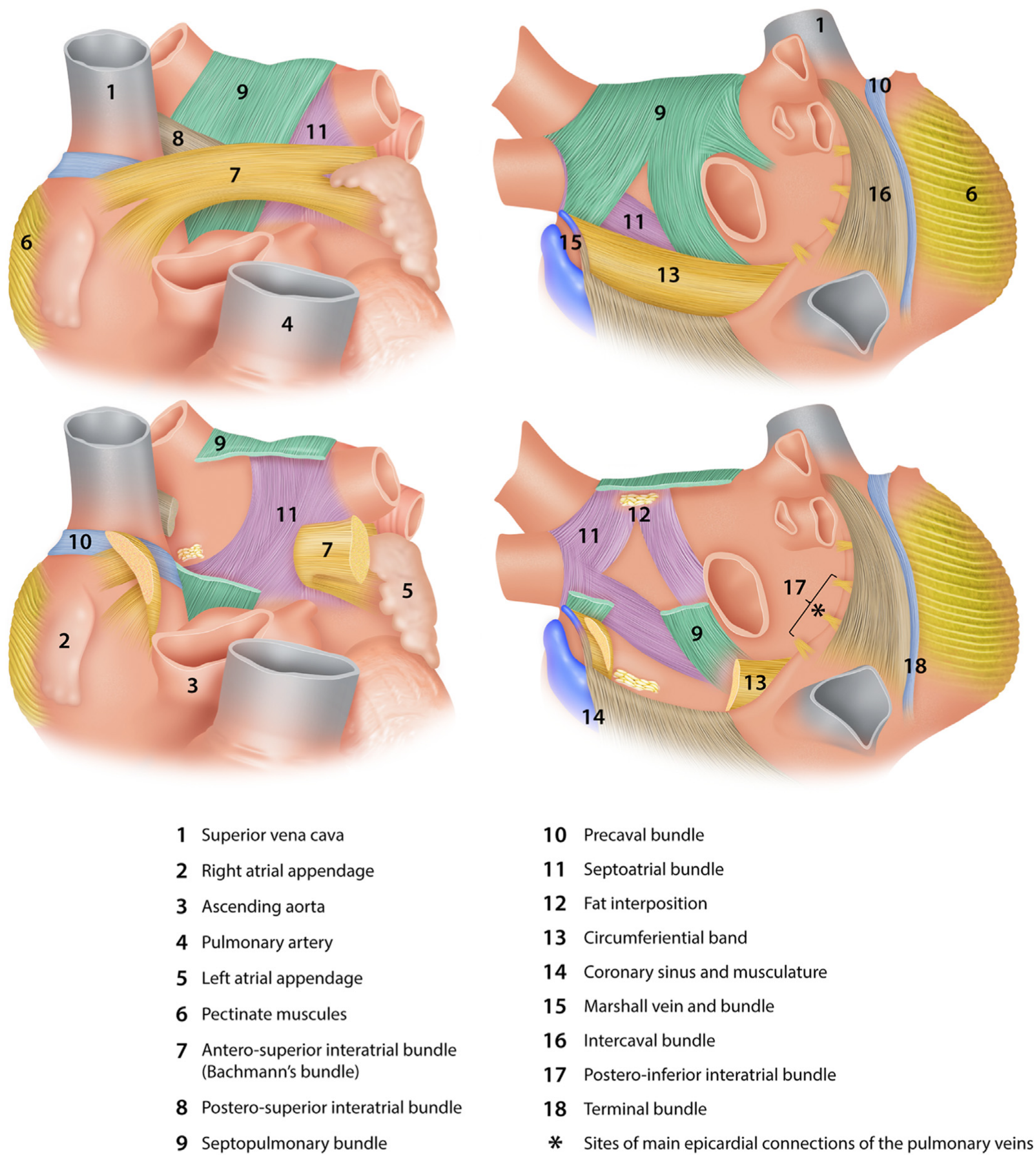


Figure 5
Architecture of atrial musculature. Upper left: main atrial muscular bundles from anterior view. Lower left: transection of the Bachmann's bundle, postero-superior interatrial bundle and the septopulmonary bundle enables visualization of the septoatrial bundle. Upper right: main atrial muscular bundles from posterior view with slight rightward tilting – the stars denote epicardial connections of the right PVs with the right atrium and left atrium posterior wall. Lower right: transection of the septopulmonary bundle coursing epicardially enables visualization of the septoatrial bundle and neighboring fat interposition.

complicated by sinus node dysfunction due to close vicinity of the sinus node to the lateral influx of the SVC into the RA. Delivery of radiofrequency (RF) energy should be avoided in the sinus node region at the base of the RAA joining the SVC and ablation should be interrupted if sinus acceleration or deceleration is observed. Furthermore, collateral damage may occur to the neighboring right phrenic nerve (PN), which should be clearly delineated with high-output pacing prior to ablation [202] (Figure 6)(Section 3.9).

3.7 Autonomic ganglionated plexi

The cardiac nervous system (CNS) plays a crucial role in arrhythmogenesis and more specifically in the initiation and maintenance of AF. The CNS is divided into the extrinsic and the intrinsic CNS [145,202–204]. The extrinsic CNS consists of sympathetic and parasympathetic components and includes neurons in the brain and spinal cord and nerves directed to the heart [205]. The extrinsic parasympathetic fibers are carried almost entirely within the vagus nerve [206]. The extrinsic sympathetic fibers are largely derived from the autonomic ganglia along the cervical and thoracic spinal cord [204,206]. The intrinsic ANS includes autonomic nerve fibers once they enter the pericardial sac, forming a complex network composed of GPs, concentrated within epicardial fat pads [207,208]. These GPs function as integration centers between extrinsic and intrinsic cardiac ANS, and contain predominantly parasympathetic neurons, as well as sympathetic neurons [203,204,209].

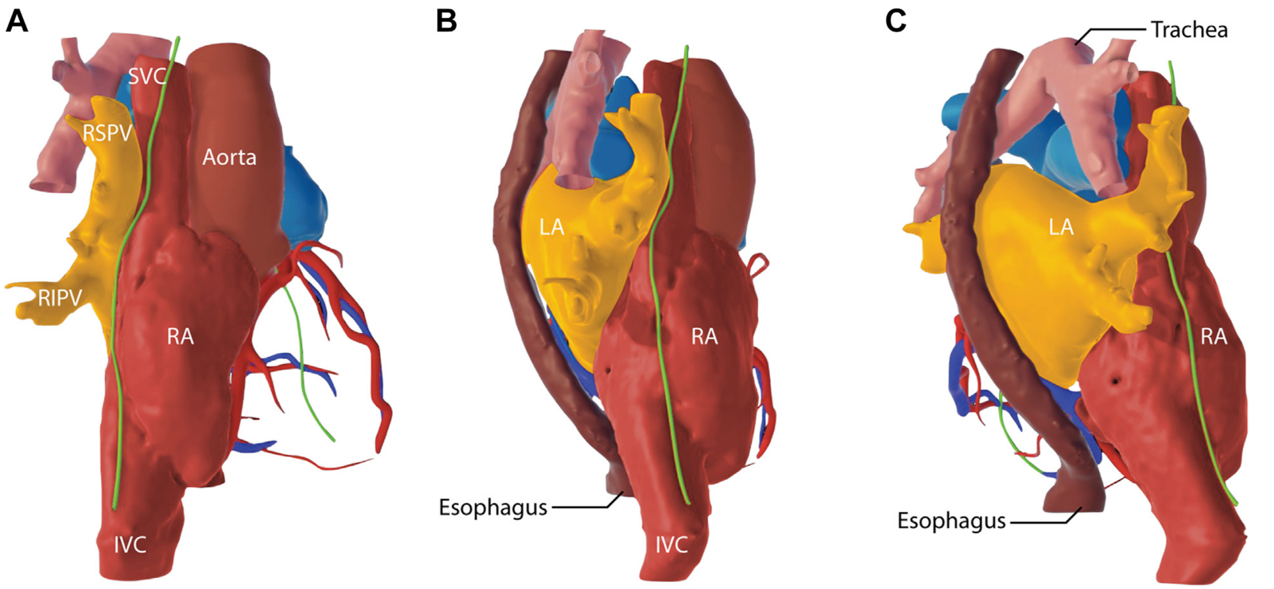


Figure 6
Course of the right phrenic nerve in relation to neighboring structures in different projections (left panel: right anterior oblique; middle pannel: right lateral; right panel: right posterior oblique) - reconstruction from CT scan. IVC = inferior vena cava; LA = left atrium; RA = right atrium; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; SVC = superior vena cava.

GPs are most commonly located at the anterior-superior LA (close to the SVC-RA junction and the anterior aspect of the RSPV), at the inferior-posterior RA/LA junction (adjacent to the interatrial groove), the lateral-posterior (close to LIPV) and lateral-superior LA (between LAA and LSPV), and in proximity to the VoM [202–204,209].

Localization of GPs is feasible with nuclear imaging studies and intraprocedurally with high-frequency stimulation to elicit a vagal response [208,210–213]. However, due to their common localization close to the PVs, it is estimated that the GPs are "collaterally ablated" in 20-50% of AF patients undergoing wide antral circumferential PVI. In line with this, a substantial proportion of patients display signs of autonomic modulation e.g. changes in mean heart rate or heart rate variability, following PVI, a finding which has not been observed in PFA-treated patients [214,215]. Some studies have shown that such an increase in resting heart rate after PVI is associated with a more favorable prognosis [216–218].

3.8 Pericardial reflections

Although less frequent than in ventricular arrhythmia management, pericardial access is sometimes required for the treatment of atrial arrhythmias. Alternative to the conventional endocardial ablation, hybrid strategies have been proposed to improve the transmurality of lesions created during AF ablation with favorable impact on arrhythmia outcome [219–221](section 12). In selected patients, epicardial approach might be an option as second or third ablation strategy to achieve transmural block in areas with protected epicardial connections [222–224]. Therefore, it is important to familiarize with the anatomy of the pericardium, and its anatomic characteristics that impair accessibility in specific areas of the LA during epicardial mapping and ablation. The normal pericardium is a double-layered sac consisting of an outer fibrous envelope and an inner serous sac (divided into a visceral layer and a parietal layer) that is invaginated by the heart. The visceral layer is reflected from the heart back onto the parietal layer along the great vessels including the aorta, pulmonary artery, proximal PVs and vena cavae. These reflections define recesses and sinuses that constrain catheter manipulation. Therefore epicardial mapping of the anterior wall or the mitral annulus is unimpeded whereas the network of pericardial sinuses at the posterior wall limits the catheter from crossing the dome, roof and carina on both sides [224,225].

There are three sinuses in the pericardial space. The *superior sinus* is situated along the right side of the ascending aorta.The *transverse sinus* is located behind the great vessels and has the LA dome as an anterior boundary. Its exploration allows access to the antero-superior aspect of the LA. The *oblique sinus* extends behind the LA between the four PVs. Its exploration allows access to most of the inferior part of the dome and the posterior wall. However, superiorly, the oblique sinus is separated from the transverse sinus by the pericardial reflection connecting left and right PVs. Thus, the middle part of the dome remains inaccessible for epicardial mapping.

3.9 Phrenic nerves

Ablation-induced damage of the PNs, (mainly the right one) is a possible complication of AF catheter ablation (section 11). The anatomical relationship of the right PN to the right PVs is complex, due to the course of the PN in between the RA and LA: cranio-caudally, coming from the lateral aspect of the SVC, it runs in between both atria along the antero-septal portion of the RSPV and turns then via the posterior RA to the lateral RA, where it crosses very often the crista terminalis [145,202](Figure 6). Thus, damage occurs most frequently while isolating the RSPV, especially while using balloon devices [226,227]. There are several potential reasons why a (transient or permanent) palsy of the right PN may occur significantly more often with balloon-shaped than point-by-point RF ablation. First, balloon devices are – by their shape and technical design – placed inside the PVs and ablation energy is delivered (in part) also inside the PVs [226]. Thus, the PN, which runs along the PV, is more often comprised within the most distal extensions of the ablation lesion. Furthermore, the balloon is inflated in the PV with the purpose to obtain maximum contact and occlusion of the PV by the balloon. Therefore, the PV tissue is circumferentially stretched and the PV diameter enlarged, placing the PN closer to the ablation lesion. Proposed measures to prevent the occurrence of PN palsy/paralysis are reported in section 11 [226,228]. Larger diameter of the right PVs and a flat angle between the right PV and the LA body are reported to predict PN damage during PVI, whereas an enlarged LA is potentially protective [228].

There is also an anatomic relationship between the left PN and the LAA, but damage to the nerve is rare when using endocardial ablation techniques. This is because the PN remains along the whole course on the pericardial surface, and does not enter the pericardial space or the epicardium, so that the distance between the endocardial surface close to the PVs and the left PN is usually more than 7-10mm. Localisation and mapping of the left PN with high-output pacing is feasible and avoids its inadvertent injury during LAA isolation using RF or cryoballoon ablation [229]. During surgical/epicardial ablation, protective measures similar to those taken during endocardial PVI for the right PN are recommended.

3.10 Esophagus

Thermal injury to the esophagus by ablation energy is one of the most dangerous and frequently fatal complications of AF ablation [230](section 11). The anatomic course of the esophagus is variable but is more commonly closer to the left PVs [145,202,230–233] (Figure 6). However, it should be kept in mind that the esophagus is a mobile structure and its relative position may change intraprocedurally especially when the patient remains under conscious sedation, allowing esophageal peristalsis to occur [234]. In 67% of patients undergoing AF catheter ablation, the esophagus shifts sideways by ≥2 cm, while in 4% there is a lateral movement exceeding 4 cm [235]. Furthermore, the location, size and shape of the esophagus may be affected by the presence of common esophageal abnormalities such as hiatal hernia.

Apart from the distance between the esophagus and the LA posterior wall, another anatomical factor that influences the probability of thermal esophageal injury is the presence of pericardial fat pads around each PV that are located between the LA and the esophagus and may protect against esophageal lesions during ablation [230,232,233]. Most of the inferior PVs are not covered by fat pads [232].

Furthermore, the movement of the esophagus may be restricted by surrounding mediastinal structures, like the descending aorta, or the spine. In these cases, if the LA wall is "tented" by the ablation catheter posteriorly towards the esophagus, the latter remains entrapped, so that the full impact of the applied energy is absorbed by the esophageal wall. If the ablation damages also the arterioles supplying the esophagus, impairing blood flow to the affected esophageal tissue, the resultant ulcerations may not heal, and may progress to perforation and fistulaization to the pericardium and/or to the LA [232,233](section 11).

Section 4: Indications for Catheter Ablation of Atrial Fibrillation

Indications for catheter ablation of atrial fibrillation	Category of advice	Type of evidence
Patients with AF-related symptoms		
Catheter ablation of AF is beneficial in symptomatic patients with recurrent paroxysmal or persistent AF resistant or intolerant to previous treatment with at least one class I or III antiarrhythmic drug.	Advice TO DO	META [236–242]
Catheter ablation of AF is beneficial as first-line treatment in symptomatic patients with recurrent paroxysmal AF.	Advice TO DO	META [243–249]
Catheter ablation of AF may be reasonable as first-line treatment in symptomatic patients with persistent AF.	Area of uncertainty	OPN
Patients with AF and heart failure		
Catheter ablation is beneficial in patients with AF and left ventricular systolic dysfunction, suspected to be related to arrhythmia-mediated cardiomyopathy, to improve left ventricular function.	Advice TO DO	META [250–254]
It is reasonable to perform catheter ablation in selected patients with AF and heart failure with reduced ejection fraction to reduce cardiovascular hospitalizations and prolong survival, regardless of previous antiarrhythmic drug failure or intolerance.	May be appropriate to DO	META [254–260]

Continued

Indications for catheter ablation of atrial fibrillation	Category of advice	Type of evidence
Patients without AF-related symptoms		
Catheter ablation of AF may be reasonable in selected asymptomatic patients with recurrent paroxysmal or persistent AF following thorough discussion of potential risks and associated benefits.	Area of uncertainty	OPN
Patients with AF and coexistent rhythm disorders		
Catheter ablation of supraventricular tachycardia alone is reasonable in patients with supraventricular tachycardia and AF when the former is considered the main trigger of the latter.	May be appropriate to DO	OBS [261–264]
Catheter ablation of AF is reasonable in patients with AF and symptomatic bradycardia or prolonged sinus pauses upon AF termination to avoid pacemaker implantation.	May be appropriate to DO	OBS [265,266]
Cavotricuspid isthmus ablation with documentation of bidirectional block is reasonable in patients undergoing AF ablation in case of prior history or intraprocedural induction of cavotricuspid isthmus-dependent flutter.	May be appropriate to DO	OBS [267–269]
Patients with atrial fibrillation and other risk factors or diseases		
It is reasonable to use similar indications for AF ablation in older (>75 years of age) patients with AF as in younger patients after taking into account comorbidities and patient preferences.	May be appropriate to DO	OBS [270–272]
Catheter ablation of AF is reasonable in patients with hypertrophic cardiomyopathy after careful consideration of anticipated clinical benefit, associated risk of procedural complications and potential need for more than one procedure.	May be appropriate to DO	OBS [273–279]

This section presents the consensus of the writing group on the indications for catheter ablation of AF. Suggested advice has been formulated based on the presence of AF-related symptoms and the duration-dependent type of AF (section 2) but also in specific patient groups. Advice pertaining to the management of patients with persistent AF are also applicable to those with long-standing persistent AF. The writing group decided not to issue a separate set of advice for long-standing persistent AF due to lack of specific evidence and a high degree of similarity with the management of persistent AF patients.

The final decision regarding patient eligibility for catheter ablation should be refined on an individualized basis, considering factors that influence rhythm outcome including among others age, duration of AF episodes, comorbidities, atrial dilatation, and presence of fibrosis. Furthermore, the selection of catheter ablation versus AADs for rhythm control may also depend on the underlying clinical setting which may limit the use of several AADs and/or may reinforce the need for sinus rhythm maintenance due to associated prognostic benefit. Therefore, the selection of optimal management strategy should be guided by a balanced analysis of the potential clinical benefits of reducing AF burden, the likelihood of achieving it and the associated risk of complications. Finally, patient preferences should be taken into consideration in a shared decision-making process.

4.1 Catheter ablation in patients with AF-related symptoms

Patients with AF may experience different types of symptoms including palpitations, dyspnea, dizziness, fatigue, presyncope and syncope. The presence and intensity of AF symptoms may vary significantly even in the same patient. Several symptom scales (EHRA score, CCS-SAF scale) have been developed to assess AF-related symptoms in a more standardized approach [280,281]. The documentation of correlation between symptoms and underlying rhythm in patients with intermittent AF is challenging, since patient symptomatology is not specific and may be attributed to coexistent cardiovascular conditions or AF risk factors [282]. Symptom-rhythm correlation is low in patients with persistent AF especially in the presence of comorbidities such as HF and diabetes [283,284]. These considerations need to be taken into account when assessing patients' symptomatic status before tailoring management approach.

Several multicenter randomized clinical trials (RCTs) have demonstrated the superiority of catheter ablation over AADs in patients with paroxysmal or persistent AF resistant or intolerant to AADs, in reducing AF recurrences, and improving symptoms and quality of life (QoL) [236–242].

Implementation of an early rhythm control strategy in patients with AF and concomitant cardiovascular conditions is associated with improved cardiovascular outcomes [285]. Antiarrhythmic agents have a modest efficacy in preventing AF recurrences with significant adverse event rates [286,287]. Observational data have shown that invasive intervention early in the natural course of AF results in favorable outcome, with shorter "diagnosis-to-ablation" time related to lower likelihood of arrhythmia recurrence, repeat ablation and cardiovascular hospitalization [288–290]. However, a recent RCT enrolling 100 symptomatic paroxysmal or persistent AF patients demonstrated that a strategy of AAD therapy with 12-month delay in catheter ablation had no impact on arrhythmia-free survival or AF burden over 12-month postablation follow-up as compared to an early ablation strategy (within 1 month) [291]. This study provides reassurance that an initial approach of medical therapy and risk factor management may be reasonable without compromising ablation outcomes. This approach takes into consideration the highly variable natural history of paroxysmal AF (section 2.3).

Several prospective multicenter RCTs have evaluated cryoballoon ablation as first-line treatment in symptomatic paroxysmal AF and demonstrated that it significantly reduces atrial tachyarrhythmia recurrences and improves patients' QoL with similar risk of adverse events as compared to AAD treatment [243–245,292] (Table 5). The superiority of cryoballoon ablation over antiarrhythmic therapy in reducing arrhythmia burden was also verified in the 3-year follow-up of patients enrolled in the EARLY-AF trial with a strict monitoring protocol with implantable loop recorder and scheduled follow-up visits [27]. A crucial question is whether the favorable impact of catheter ablation as first-line treatment in paroxysmal AF patients is specific for cryoenergy ablation or represents a "class effect" irrespective of the employed ablation technology. Prior trials of first-line RF catheter ablation demonstrated modest efficacy in arrhythmia outcome but were limited by high cross-over rates, inconsistent procedural endpoints and lack of procedural standardization [246–248](Table 5). A pooled analysis concluded that RF catheter ablation resulted in significantly higher freedom from AF recurrence compared with AAD therapy in AAD-naïve paroxysmal AF patients [249]. Furthermore, randomized comparison of cryoballoon ablation with RF ablation has demonstrated similar safety and efficacy in arrhythmia outcome in drug-refractory paroxysmal AF patients [293,294].

Recent data have indicated that in addition to traditional physical symptoms, AF may be associated with significant adverse impact on mental health. An observational study found that over one third of patients referred for AF management demonstrated severe psychological distress [295]. A recent randomized trial indicated significant improvements in psychological distress maintained at 12 months associated with catheter ablation but not with active medical therapy [296].

In the real world, RF ablation has greater heterogeneity in procedural results and is less reproducible than cryoablation in paroxysmal AF patients [297]. Furthermore, the center's annual AF ablation caseload is an independent predictor of procedural success only in RF-treated paroxysmal AF patients [297]. Despite variant needs in gaining experience and maintaining skills, an annual operator volume of at least 25 AF ablation procedures and an annual hospital volume of 50 AF ablation cases have been associated with improved procedural outcome [298, 299]. Therefore, procedural volumes should be taken into account when selecting the type of ablation technology to perform first-line catheter ablation.

The value of catheter ablation as first-line rhythm control therapy in persistent AF patients has not been specifically evaluated. Although the relative efficacy of catheter ablation in reducing AF burden and first AF recurrence is similar in paroxysmal and persistent AF types, extrapolation of the beneficial impact of first-line catheter ablation from the paroxysmal to the persistent patient group needs further verification [240,300]. Nevertheless, the discrimination between paroxysmal and persistent AF may be challenging and some patients may present with both paroxysmal and persistent AF episodes. In addition, some patients may present with an early stage of persistent AF which is associated with fewer arrhythmia relapses following ablation compared to longer-lasting persistent AF. Suggested advice for catheter ablation in patients with paroxysmal or persistent AF in relation to the presence of AF-related symptoms is presented in Figure 7.

4.2 Catheter ablation in patients with AF and heart failure

Atrial fibrillation and HF frequently coexist and potentiate each other in a vicious circle (AF begets HF and HF begets AF). Several studies have evaluated potential benefits of AF catheter ablation in patients with HF (Table 6). The favorable impact of catheter ablation in patients with AF and impaired left ventricular systolic function extends beyond rhythm outcome and may frequently result in left ventricular ejection fraction (LVEF) improvement. In the CAMERA-MRI trial, 68 patients with persistent AF and non-ischemic cardiomyopathy were randomized to catheter ablation or medical rate control [250]. All patients had cardiac magnetic resonance (CMR) before enrollment to assess LVEF and late gadolinium enhancement (LGE), indicative of underlying ventricular fibrosis. Patients randomized to catheter ablation had significantly greater LVEF improvement compared to the rate control group, while LVEF normalization was achieved in 58% of patients postablation. These results were maintained during long-term follow-up [251]. The study findings suggest that left ventricular dysfunction was at least partly attributed to arrhythmia-mediated cardiomyopathy and could be reverted with SR maintenance achieved by catheter ablation. On the other hand, patients with more advanced HF are more likely to have established myocardial dysfunction due to structural alterations, pathophysiologically unrelated to AF, which is thus not reversible by catheter ablation (Table 6).

Catheter ablation in HFrEF patients may also have a beneficial impact on patient prognosis. A pooled analysis of randomized data concluded that rhythm control strategy reduces hospitalizations and confers a survival benefit in HFrEF patients when implemented with catheter ablation but not with antiarrhythmic medications [305]. The CASTLE-AF study enrolled patients with paroxysmal or persistent AF and HF (NYHA Class II or above), LVEF <35% and an implantable cardiac defibrillator (ICD) who were unresponsive, intolerant or unwilling to take AADs[306]. Patients were randomized to catheter ablation or medical treatment with rate or rhythm control. Fewer patients in the catheter ablation group had primary endpoint events (death from any cause or hospitalization for worsening HF) at a follow-up of 3.2 years (28.5% vs. 44.6%; hazard ratio, 0.62; $p = 0.007$). Mortality was also significantly

Table 5 Randomized controlled clinical trials comparing catheter ablation versus antiarrythmic drugs as first-line treatment in patients with symptomatic AF

	RAAFT-1 [248]	MANTRA-PAF [246]	RAAFT-2 [247]	STOP AF [243]	EARLY AF [244]	CRYO-FIRST [245]
Year of publication	2005	2012	2014	2021	2021	2021
Sample size (ablation vs AADs)	32 vs 35	146 vs 148	66 vs 61	104 vs 99	154 vs 149	107 vs 111
Mean age (SD), years (ablation vs AADs)	53 (8) vs 54 (8)	56 (9) vs 54 (10)	56 (9) vs 54 (12)	60 (11) vs 62 (11)	58 (12) vs 60 (11)	51 (13) vs 54 (13)
Mean LA diameter (SD), mm (ablation vs AAD)	41 (8) vs 42 (7)	40 (6) vs 40 (5)	40 (5) vs 43 (5)	39 (6) vs 38 (5)	40 (5) vs 38 (7)	37 (6) vs 38 (5)
Mean LVEF (SD), % (ablation vs AAD)	53 (5) vs 54 (6)	LVEF >60% in 80% vs 82%	61 (5) vs 61 (7)	61 (6) vs 61 (6)	60 (7) vs 60 (8)	63 (5.4) vs 64 (5.4)
Paroxysmal AF (%) (ablation vs AADs)	97 vs 95	100 vs 100	99 vs 97	100 vs 100	96 vs 94	100 vs 100
Ablation type	Radiofrequency	Radiofrequency	Radiofrequency	Cryoballoon	Cryoballoon	Cryoballoon
Ablation strategy	PVI	PV encirclement plus roof line, additional ablation lesions allowed	PVI, additional ablation lesions allowed	PVI	PVI	PVI
Acute PVI rate (%)	100		87	98	100	100
Rhythm monitoring protocol	• 1 mo event monitor at 1 and 3 mo and thereafter in case of symptom recurrence AND • 24-h Holter recording before discharge, and at 3, 6, and 12 mo	• 7-d Holter monitor at 3, 6, 12, 18, and 24 mo	• Biweekly TTM	• 12-lead ECG at 1,3,6,12 mo AND • Patient-activated TTM weekly and in case of symptoms AND • 24-h ambulatory ECG monitoring at 6 and 12 mo	• Implantable loop recorder	• 12-lead ECG and 7-d Holter monitor at 1, 3, 6, 9, 12 mo follow-up
Primary endpoint - definition	First recurrence of AF >15 s	AF burden and cumulative burden	First recurrence of AF/AFL/AT >30 s	Initial failure of the procedure; subsequent AF surgery or LA ablation; AF/AFL/AT ≥30 s during ambulatory monitoring or ≥10 s on a 12-lead ECG; cardioversion or Class I or III AAD outside the 90-day blanking period (ablation group only)	First recurrence of AF/AFL/AT ≥30 s or AAD initiation	Free from any AF/AFL/AT >30 s
Follow-up (years)	1	2	2	1	1	1
Recurrence of any atrial tachyarrhythmia (%) (ablation vs AADs)	13 vs 63*	15 vs 29**	54.5 vs 72.1	20.2 vs 35.4	42.9 vs 67.8	17.8 vs 32.4
Treatment effect			0.56 (0.35-0.90)	0.57 (0.36–0.91)	0.48 (0.35–0.66)	0.48 (0.26–0.86)
Serious AEs – no of patients (%) (ablation vs AADs)		13.7 vs 10.8 (N.S)	9.1 vs.4.9	14 vs 14 (N.S)	3.2 vs 4.0 (N.S)	24.3 vs 33.3 (N.S)

(*continued*)

Table 5 Continued

	RAAFT-1 [248]	MANTRA-PAF [246]	RAAFT-2 [247]	STOP AF [243]	EARLY AF [244]	CRYO-FIRST [245]
Findings / Comments (§)	RF ablation superior to AAD.	No significant difference between RF ablation and AADs in the cumulative AF burden over a period of 2 years. § No PVI documentation	RF ablation superior to AAD.	Cryoballoon ablation was superior to AAD.	Cryoballoon ablation was superior to AAD. § Continuous cardiac rhythm monitoring.	Cryoballoon ablation was superior to AAD.

AAD = antiarrhythmic drug; AE = adverse event; AF = atrial fibrillation; AFL = atrial flutter; AT = atrial tachycardia; LA = left atrium; LVEF = left ventricular ejection fraction; NS = non-significant; PVI = pulmonary vein isolation; RF = radiofrequency; SD = standard deviation; TTM = transtelephonic monitoring.
*Symptomatic AF recurrence; p< 0.001
**Recurrence of any AF; p=0.004

reduced in the catheter ablation group (13.4% vs 25.0%; hazard ratio, 0.53; p = 0.01). Therefore, these results were strongly supportive that catheter ablation may favorably affect prognosis in this population, despite study limitations related to sample size, strict selection criteria, generalizability of findings, lack of blinded randomization and treatment allocation. In the AATAC prospective RCT, catheter ablation was also shown to significantly reduce all-cause mortality in ICD/CRT-D recipients with persistent AF and HFrEF (LVEF<40%) as compared to amiodarone treatment [255]. In the recent CASTLE HTx trial, catheter ablation plus optimal medical therapy in patients with symptomatic AF and end-stage HFrEF referred for heart transplantation evaluation, significantly reduced the composite of death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation than medical therapy alone after a median follow-up of 18 months (8% vs 30%; hazard ratio, 0.24; p<0.001)[260].

Proper patient selection is crucial for maximizing benefit from AF catheter ablation in HFrEF patients. Several indicators may help guide this decision (Table 7). Higher NYHA class (III/IV), ischemic HF etiology, paroxysmal AF type, prolonged QRS duration (>120 msec), severe LA dilatation (LAVI>50 mL/m^2), atrial and ventricular fibrosis are predictors of lack of LVEF recovery following catheter ablation in patients with impaired left ventricular systolic function [253,256,307–310].

It is also important to determine the relative chronologic sequence of AF and HF presentation, since patients who develop HF first have a worse prognosis, are less likely to present AF-mediated tachymyopathy and have a poorer outcome after AF ablation [252,311,312]. The Antwerp score based on four simple parameters (wide QRS, known HF etiology, severe atrial dilatation and paroxysmal AF) has been shown to predict left ventricular systolic function recovery after AF ablation in HF patients [307]. Recently, this score was externally validated in a large multicenter study yielding good discrimination and calibration [308]. Nevertheless, even in the presence of less favorable characteristics, some patients with AF and HF may experience improvement in LV systolic function and clinical outcome following SR restoration.

Registry and observational data suggest that catheter ablation significantly reduces arrhythmia recurrences and the risk of cardiovascular events compared to drug therapy in HF patients across all LVEF subgroups, even in heart failure patients with preserved ejection fraction (HFpEF) [309,313–319]. In a pre-specified subanalysis of the CABANA trial in patients with baseline HF symptoms (NYHA Class ≥ II, 79% with LVEF≥50%), catheter ablation conferred significant improvement in arrhythmia recurrence, QoL and survival as compared to pharmacological therapy [257]. In the subgroup of HFpEF patients (LVEF≥50%), ablation reduced mortality by 60% compared to drug therapy [257]. A small, randomized trial demonstrated that AF catheter ablation significantly improved invasive hemodynamic parameters, exercise capacity, and QOL outcomes as compared to medical therapy in patients with HFpEF and concomitant AF [320]. Adequately powered prospective RCTs are needed to provide more robust clinical data.

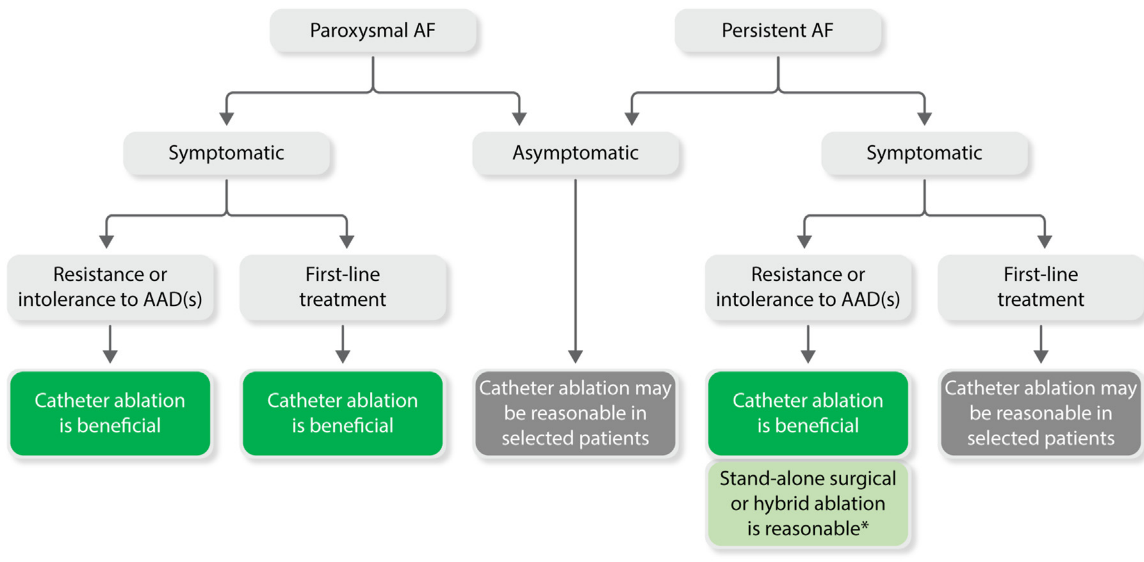


Figure 7
Suggested advice for catheter ablation in patients with paroxysmal or persistent AF in relation to the presence of AF-related symptoms. AAD = antiarrhythmic drug; AF = atrial fibrillation.

4.3 Catheter ablation in patients without AF-related symptoms

The main objective of AF catheter ablation is symptom amelioration and reduction in arrhythmia recurrences. Pertinent benefit, beyond symptomatic control, might justify eligibility of truly asymptomatic AF patients for catheter ablation.

A key issue in the management of patients without symptoms while remaining in AF, is the exclusion of a pseudo-asymptomatic status. Up to 77% of these patients may experience subjective symptomatic amelioration [323], improvement in functional class and decrease in brain natriuretic peptide levels with SR restoration following electrical cardioversion [324]. Therefore, in asymptomatic patients, especially at younger age, a cardioversion is worth attempting to assess potential symptomatic improvement that would enhance patient eligibility for catheter ablation due to reclassification in the symptomatic category.

Atrial fibrillation has significant hemodynamic consequences that may lead to HF and worsen patient prognosis, such as loss of atrial contribution to cardiac output, rapid and irregular heart rate and loss of heart rate adaptation to metabolic demands. Heart rate irregularity results in inefficient cardiac cycles due to inadequate ventricular filling, contributes to hemodynamic impairment and worsens left ventricular systolic and diastolic function[325]. An irregularly paced ventricular rhythm following AV node ablation decreases cardiac output and increases pulmonary wedge pressure as compared with a regular rhythm at the same average cycle length [326]. Therefore, SR maintenance might confer benefit due to prevention of abovementioned AF-mediated hemodynamic sequalae even in the absence of coexisting symptoms.

Apart from symptomatic improvement, catheter ablation is also effective in delaying AF progression from paroxysmal to persistent type (section 2). AF progression to longer-lasting types has an impact on patient outcome since non-paroxysmal AF is associated with significantly increased risk of thromboembolism, HF, hospital admissions and mortality compared to paroxysmal AF [32,327,328]. In the ATTEST trial, catheter ablation significantly delayed AF progression compared to AADs in patients with drug refractory paroxysmal AF [329]. Furthermore, in the 3-year follow-up of the EARLY-AF trial, first-line treatment of paroxysmal AF patients with cryoballoon ablation was associated with significantly lower incidence of persistent AF (HR, 0.25; 95% CI, 0.09 to 0.70) as compared to AAD therapy using continuous cardiac monitoring [27]. Therefore, beyond symptom control, catheter ablation may have a favorable impact by limiting disease progression especially when implemented in early stages of AF natural course.

The largest trial assessing potential prognostic benefits of catheter ablation is the CABANA trial that enrolled 2204 symptomatic patients with AF aged 65 years and older or younger than 65 years with 1 or more risk factors for stroke [330]. Patients were randomized to catheter ablation or AAD/rate control therapy. In the intention-to-treat analysis, catheter ablation did not significantly reduce the primary composite end point of death, disabling stroke, serious bleeding, or cardiac arrest compared with medical therapy over a median follow-up of 48.5 months. However, the study was limited by high crossover rates, while the per-protocol analysis demonstrated significant differences in favor of catheter ablation ($p=0.046$). In addition, the composite secondary endpoint of death from any cause or cardiovascular hospitalization occurred significantly less frequently in the catheter ablation group than in the medical therapy group. Despite these considerations and caveats, the study findings do not support the use of catheter ablation to improve prognosis in

Table 6 Randomized controlled clinical trials comparing catheter ablation versus medical therapy in patients with atrial fibrillation and heart failure with reduced ejection fraction

	PABA-CHF [301]	MacDonald et al. [302]	ARC-HF [303]	CAMTAF [252]	AATAC [255]	CAMERA-MRI [250]	AMICA [304]	CASTLE-AF [256]	CABANA subanalysis [257]	RAFT-AF [253]	CASTLE HTx [260]
Year of publication	2008	2011	2013	2014	2016	2017	2019	2018	2021	2022	2023
Sample size	81	41	52	50	203	66	140	363	778	411	194
Mean age (years)	60.5±8	63±7	63±9	57±11	61±11	61±10	65±8	64±5	68±8	67±8	64±11
AF type	Parox:52% Pers or LS-pers:48%	Pers: 100%	Pers: 100%	Pers: 100%	Pers: 100%	Pers: 100%	Pers: 76.4% LS-pers: 23.6%	Parox: 32.5% Pers:38.3% LS-pers: 29.2%	Parox: 31.6% Pers:55.3% LS-pers:13.1%	Parox: 7.3% Pers: 69.3% LS-pers: 23.4%	Parox: 30% - Pers:56%, LS-pers: 14%
NYHA	NYHA II-III: 100%	NYHA II: 10% NYHA III: 90%	NYHA II: 52% NYHA III: 48%	NYHA II: 46% NYHA III: 54%	NYHA II-III: 100%	Average NYHA: 2.5±0.6	NYHA II: 39% NYHA III: 61%	NYHA I: 11% NYHA II: 60% NYHA III:28% NYHA IV:1%	NYHA II: 76.1% NYHA III:23.7% NYHA IV:0.3%	NYHA II:67% NYHA III:33%	NYHA II:31%, NYHA III:55%, NYHA IV: 14%
Baseline LVEF	28±8%	39±11%	24±8%	33±10%	29±7%	33±9%	26±9%	32±9%	55±8% LVEF≤35%: 8%	41±15% LVEF≤45%: 58%	27±6%
Ischemic etiology	71%	49%	33%	26%	64%	0%	50%	46%	21.9%	31.4%	39%
LA diameter (mm)	48±6		48±7	51±10	47±5	48±7	51±6	49±7	-	46±6	49±7
Follow-up (years)	0.5	0.5	1	0.5	2	0.5	1	3.1±1.6	5	3.2±1.8	1.5±0.5
Control arm - therapy	AV node ablation plus BiV pacing	Rate control	Rate control	Rate control	Rate control Amiodarone	Rate control	Best medical therapy (rate or rhythm control)	Medical therapy (rate or rhythm control)	Medical therapy (rate or rhythm control)	Rate control	Guideline directed medical therapy
Primary outcome	Composite of LVEF, 6-minute walk test distance, and MLWHF score	LVEF	Change in peak O2 consumption	LVEF	Freedom from AF/ AFL/AT >30 sec off AADs	Change in LVEF at 6 months	Absolute increase in LVEF	Composite of all-cause mortality and HF hospitalization	Composite of all-cause mortality, disabling stroke, serious bleeding and cardiac arrest	Composite of all-cause mortality, and HF events	Composite of death from any cause, LVAD implantation or urgent heart transplantation
Mean change in LVEF (ablation vs control)	8±8% vs 1±4%, p<0.001	4.5±11.1% vs 2.8±6.7%, p=0.6	10.9±11.5% vs. 5.4±8.5% p=0.055	8.1% vs -3.6%, p<0.001	8.1±4 vs 6.2±5, p=0.02	18.3% vs 4.4%, p<0.0001	8.8% vs. 7.3% p=0.36	8.0% vs 0.2% p=0.005		10.1±1.2% vs 3.8±1.2% p=0.017 (24 mo)	7.8±7.6 vs 1.4±7.2 (12 mo)
Rhythm outcome (ablation vs control)	12% vs 100% in AF	50% vs 100% in AF	88% vs 8% in SR	19% vs 100% in AF (at 6 months)	70% vs 34% free from AF	25% vs 100% in AF (at 6 months)	73.5% vs 50% in SR (at 1 year)	63.1% vs 21.7% in SR (at 5 years)	44% vs 28% w/o AF recurrence (at 5 years)	85.6% vs 12.9% in SR (at 2 years)	31.4±33.3 vs 8.6±26.3 AF burden reduction at 12 mo
Main findings	Improved composite endpoint	No LVEF improvement	Significant increase in peak O2 consumption	LVEF improvement	Reduction in AF recurrence, unplanned hospitalizations and mortality	LVEF improvement	No LVEF improvement	Reduction in all-cause death or HF hospitalization	Reduction in the primary composite, in all-cause mortality and improvement in QoL	Similar primary outcome (p=0.066) Increase in LVEF	Reduction in the primary composite endpoint

AAD = antiarrhythmic drug; AF = atrial fibrillation; AFl = atrial flutter; AT = atrial tachycardia; AV = atrioventricular; BiV = biventricular; HF = heart failure; LA = left atrium; LS-pers = long-standing persistent; LVEF = left ventricular ejection fraction; MLWHF = Minnesota Living with Heart Failure; NYHA = New York Heart Association; Parox = paroxysmal; Pers = persistent; QoL = quality of life; SR = sinus rhythm.

Table 7 Characteristics associated with LVEF recovery in response to AF catheter ablation in patients with impaired left ventricular systolic function.

Characteristics	Evidence
Lower NYHA class	Lower NYHA class (I-II) at presentation is a predictor of significant LVEF recovery following AF ablation when compared with higher NYHA class (III-IV) in patients with HFrEF [256].
Non-ischemic etiology	Nonischemic HF etiology is a significant predictor of LVEF improvement after AF ablation in patients with HFrEF [256].
Persistent AF	Persistent AF is an independent predictor of LVEF improvement and left ventricular reverse remodelling after AF ablation in patients with impaired LVEF [307,308,321,322].
Narrow QRS	Narrow QRS ($\leq$120 msec) is an independent predictor of LVEF recovery after AF ablation in patients with impaired LVEF [307,308].
Absence of CMR-detected atrial fibrosis	Extent of atrial fibrosis is inversely correlated to LVEF response following AF catheter ablation in patients with HFrEF [310].
Absence of CMR-detected ventricular fibrosis	Absence of ventricular fibrosis is an independent predictor of LVEF normalization after AF catheter ablation in patients with non-ischemic cardiomyopathy and persistent AF [250].
Postcardioversion EF and NYHA improvement	Improvement in functional status and/or LVEF after cardioversion is indicative of underlying tachyarrhythmia-mediated cardiomyopathy and a favorable response to catheter ablation in HFrEF patients.
Absence of severe atrial dilatation	Absence of severe atrial dilatation (LAVI$\leq$50 mL/m^2) is an independent predictor of LVEF recovery after AF ablation in patients with impaired LVEF [307,308].
AF preceding HF or simultaneous AF and HF diagnosis	Patients with simultaneous AF and HF diagnosis, or AF history preceding HF diagnosis are more likely to present normalization of LVEF and resolution of HF symptoms following catheter ablation [252,312].

AF = atrial fibrillation; CMR = cardiovascular magnetic resonance; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LA = left atrial; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

the general population of asymptomatic patients with AF. However, in the CABANA trial, the clinical outcome of ablation versus AAD therapy demonstrated an age-based variation with the largest relative and absolute prognostic benefit seen in patients younger than 65 years, suggesting that selected patient subgroups may have clinical outcome benefit from catheter ablation [331]. Furthermore, a prespecified analysis of the EAST-AFNET 4 trial, showed that an early systematic rhythm control strategy (mainly with AADs) confers a similar degree of outcome benefit in symptomatic and asymptomatic AF patients [332].

4.4 Patients with AF and coexistent rhythm disorders

4.4.1 AF and supraventricular tachycardia

Paroxysms of AF are commonly triggered by ectopic beats from the PVs [65]. However, other types of supraventricular tachycardia (SVT), such as atrioventricular nodal reentry tachycardia (AVNRT), focal atrial tachycardia (AT) or atrioventricular reentry tachycardia (AVRT) may trigger AF, especially in younger patients [333]. The incidence of AF in patients with paroxysmal SVT is higher than in age-matched normal populations, while 12% of patients with known SVT also experience AF episode within 12 months of follow-up [334]. Furthermore, a small subgroup of patients who are referred for AF catheter ablation, ranging from 7.6% to 10.1%, also have inducible SVT [261,262]. Sciarra et al. reported that the role of SVT as AF trigger could be verified in 42.3% of patients with AF and inducible SVT, as evidenced by spontaneous conversion of SVT to AF [261]. In these patients, elimination of the SVT only, without AF catheter ablation, may be sufficient for a favorable rhythm outcome with freedom from AF recurrences ranging from 70% to 92.3% during follow-up [261,263,264]. Observational trials have demonstrated an age-related increase in the risk of AF recurrence in patients with coexistent SVT and AF following ablation of the SVT only, with age over 50 years indicative of high AF recurrence rate [264,335]. Therefore, in patients with coexistent SVT and AF, preferably in the younger age group, and only when the former is considered the main trigger of the latter, it is reasonable to simplify the ablation strategy to elimination of the SVT only. AF ablation would then be deferred depending upon AF recurrence following SVT ablation.

4.4.2 AF and sinus node dysfunction

Symptomatic prolonged sinus pauses are common upon AF termination and may be aggravated by atrioventricular node blocking agents and AADs. This often leads to the indication for pacemaker implantation. AF catheter ablation is effective in preventing both AF recurrences and sinus pauses upon AF termination, likely due to autonomic modulation [265]. Chen et al. reported that 95.3% of patients with paroxysmal, AF-related, symptomatic prolonged sinus pauses who underwent

AF catheter ablation no longer needed a pacemaker and had significantly higher freedom from AF recurrences and tachycardia-related hospitalizations compared to those treated with permanent pacemaker implantation and AADs [266]. Although sinus node dysfunction in the presence of paroxysmal AF is mainly attributed to electrical remodeling [336], underlying sinus node structural remodeling may also be present in a few cases [337,338]. A minority of patients with coexistent AF and sinus node dysfunction will still require permanent pacemaker implantation following catheter ablation due to underlying structural alteration of the sinus node [339]. However, the vagal denervation that occurs with catheter ablation results in a higher resting heart rate, which may also help a patient compensate for co-existent sinus node dysfunction, even if AF recurs. AF recurrence rate was significantly higher in patients requiring pacemaker implantations after AF ablation than those that did not [339,340].

4.4.3 AF and atrial flutter

Cavotricuspid isthmus (CTI) dependent atrial flutter (AFl) is frequent in patients with AF, either spontaneously or during type IC AADs or amiodarone therapy [267]. The two arrhythmias have mechanistic and pathophysiological linkage with short bursts of AF frequently preceding and triggering AFl development [341]. Scharf et al. reported that spontaneous or pacing induced AFl occurrence during AF ablation procedure is predictive of symptomatic AFl during post PVI follow-up, with 24% of patients who did not undergo CTI ablation during the PVI procedure experiencing symptomatic AFl recurrence during a mean follow-up of 609±252 days [267]. These findings are supportive of CTI ablation in case of AFl occurrence during AF ablation procedure. Contradictory findings have also been reported. Wazni et al. in a trial conducted at the beginning of the AF ablation era advocated that PVI only, without CTI ablation, suppressed both AF and typical AFl recurrences [268]. However, in this patient series, CTI block reduced early AFl recurrences, since 55% of patients not receiving CTI ablation experienced episodes of typical AFl within the first 8 weeks following catheter ablation and 20% needed electrical cardioversion [268]. Based on the concept that PV ectopics are main triggers of typical AFl, the CRAFT trial tested the hypothesis whether cryoballoon PVI was superior to CTI ablation as first-line therapy in patients with typical AFl without prior AF documentation. The primary efficacy outcome measure (time to first recurrence of sustained symptomatic atrial arrhythmia) was similar between the compared groups, although patients subjected to PVI had a 5-fold higher likelihood of flutter recurrence within one year (10% vs 2%, $p=0.07$)[342].

In recent catheter ablation trials, recurrence rates are not negligible and therefore patients with both AF and typical AFl may still be prone to AFl recurrence following PVI since even short bursts of AF may trigger AFl. In addition, CTI ablation reduces the likelihood of AFl recurrence if AAD is administered following AF catheter ablation.

Non-CTI dependent AFl is also encountered following AF ablation especially after extensive ablation lesion sets in the context of persistent AF ablation [339,343]. However, these types of macroreentrant ATs may resolve spontaneously in some patients, and therefore catheter ablation should be deferred for several months and beyond the blanking period unless non-CTI dependent AFl episodes are recurrent, highly symptomatic and resistant to AADs and cardioversion (section 9).

4.5 AF with other risk factors or diseases

4.5.1 Older patients with AF

Some centers may withhold ablation therapy in older patients [344]. This reluctance stems from a perceived less favorable risk to benefit ratio of catheter ablation in elderly patients. Two recent metanalyses of observational studies demonstrated similar AF ablation success rates with a significantly higher risk of complications in patients >75 years as compared to younger ones [270,271]. However, contradictory results have also been reported. Data from a Danish nationwide cohort study reported a similar incidence of periprocedural complications and AF relapse in patients ≥75 years subjected to catheter ablation as compared to patients aged 65-74 years [272].

At present it is unclear whether a specific technology of AF catheter ablation should be preferred in elderly patients due to associated enhanced safety profile. In a propensity matched comparison of older patients ≥75 years, cryoballoon ablation was associated with similar efficacy and safety, but with shorter procedural time as compared to RF ablation [345]. Furthermore, a subanalysis of the CABANA trial found no prognostic benefit of CA in patients ≥75 years of age, with similar rates of complications and AF recurrences postablation [331].

4.5.2 AF and hypertrophic cardiomyopathy

Atrial fibrillation is highly prevalent in patients with hypertrophic cardiomyopathy (HCM) [346,347].These patients often have limited options for antiarrhythmic therapy, due to hypertrophy and underlying structural heart disease. However, AF is often poorly tolerated and impairs clinical outcome in HCM patients, thus stressing the need to pursue sinus rhythm maintenance in many patients [348].

Several studies have evaluated the efficacy of catheter ablation in HCM patients with AF. Three meta-analyses have reported significantly lower freedom from AF/AT recurrences in patients with as compared to those without HCM after single and multiple catheter ablations [273,274,279]. Recent studies have shown that catheter ablation has comparable efficacy in HCM patients as compared to the general patient population when treating paroxysmal AF [275,276]. However, results are poorer in patients with persistent AF [273,275,276]. Therefore, early invasive intervention, before progression of AF and/or underlying atrial substrate, is of primary importance in HCM patients to increase success rates.

Non-PV triggers are commonly involved in AF pathophysiology in HCM patients and are documented in many patients with arrhythmia recurrence following catheter ablation, thus supporting the concept of extensive ablation lesion sets to increase success rate [277]. However, adjunctive ablation beyond

PVI was not associated with additional benefit in a large multicenter cohort of HCM patients undergoing AF catheter ablation [276]. The use of RF versus cryoballoon ablation has no impact on procedural outcome among HCM patients [276]. Furthermore, the risk of major procedural complications appears to be increased in HCM patients as compared to the general AF population [276]. Despite a temporal decline in the incidence of procedural complications in HCM patients, real-world data verify the still high periprocedural morbidity and mortality [278].

4.5.3 Patients with AF and obesity - physical inactivity - obstructive sleep apnea

Obesity and physical inactivity are associated with increased risk of AF [349], and reduced efficacy of AF ablation [350,351](section 5.1.2). Obesity also increases the risk of complications of catheter ablation and increases radiation to both the patient and personnel [352](section 11). Comprehensive management of these modifiable risk factors improves the outcome of catheter ablation [353,354],[355,356] (section 5.1). However, weight reduction and improvement in cardiorespiratory fitness requisites lengthy efforts with slow yielding results that may be difficult to sustain in long-term. Furthermore, prolonged delays from AF diagnosis to catheter ablation adversely affect success rates [288–290]. Therefore, catheter ablation of AF should not be deferred in obese or physical inactive patients who have initiated lifestyle interventions and are showing progress toward their pertinent lifestyle goals. Individualized risk-benefit assessment is needed in patients with morbid obesity [body mass index (BMI) > 40kg/m^2] due to a higher complication rater rate and lower long-term freedom from AF [350–352]. Evaluation at a comprehensive weight loss clinic may be useful to determine eligibility for medications or surgical approaches to facilitate weight loss. (section 5.1.2).

Obstructive sleep apnea is associated with AF [355] and up to 45% of patients referred for AF ablation have OSA [356]. Patients with OSA have a significantly increased risk of AF recurrence following CA compared with those without OSA [357–360]. Treatment with continuous positive airway pressure (CPAP) appears to significantly reduce the risk of AF recurrence or progression in patients with AF and OSA [361,362]. CPAP therapy also results in reversal of atrial remodelling in AF patients [362]. For these reasons some centers are reluctant to perform AF ablation before OSA evaluation and potential initiation of CPAP treatment. The rate of AF recurrence following PVI is similar between CPAP-treated OSA patients and non-OSA patients [357]. In addition, PVI considerably reduces the burden of paroxysmal AF in OSA patients, but the use of CPAP following ablation has not been shown to further reduce the risk of AF recurrence in a recent randomized study which was though lacking sufficient statistical power (section 5.1.3.) [363]. Finally, there are no controlled studies comparing AF ablation followed by OSA treatment vs OSA treatment followed by AF ablation if needed. At present time there is no evidence supporting the concept that CPAP may completely prevent AF recurrences and the need for CA at follow-up.

Section 5: Atrial Fibrillation Risk Factors and Preprocedural Management

Atrial fibrillation risk factors and preprocedural management	Category of advice	Type of evidence
Modifiable risk factors		
Comprehensive management of AF risk factors should be undertaken to improve the outcomes of catheter ablation of atrial fibrillation.	Advice TO DO	OBS [353,354,364–366]
Preablation anticoagulation strategy		
Patients with stroke risk factor(s) (CHA_2DS_2-VASc score ≥1 in males and ≥2 in females) or with increased risk of thrombus* should receive oral anticoagulation therapeutically for at least 3 weeks before AF catheter ablation. **persistent AF, hypertrophic cardiomyopathy, rheumatic heart disease or cardiac amyloidosis*	Advice TO DO	OBS [367–380]
Catheter ablation of AF without interruption of anticoagulation is beneficial in patients who have been therapeutically anticoagulated with either vitamin K antagonists or DOACs.	Advice TO DO	META [381–395]
For patients anticoagulated with a DOAC prior to AF catheter ablation, it is reasonable to hold one dose prior to AF catheter ablation with early reinitiation post ablation.	May be appropriate TO DO	META [396–400]
Imaging for exclusion of atrial thrombus		
Transesophageal echocardiography or cardiac computed tomography within 48h prior to catheter ablation or intraprocedural intracardiac echocardiography are reasonable imaging options for exclusion of atrial thrombus.	May be appropriate TO DO	OBS [401–410]

(continued)

Continued

Atrial fibrillation risk factors and preprocedural management	Category of advice	Type of evidence
Imaging for exclusion of atrial thrombus is reasonable in patients with stroke risk factor(s) (CHA_2DS_2-VASc score ≥1 in males and ≥2 in females) or with increased risk of thrombus* presenting for AF catheter ablation who have not received anticoagulation therapeutically for 3 weeks or longer. **persistent AF, hypertrophic cardiomyopathy, rheumatic heart disease or cardiac amyloidosis*	May be appropriate TO DO	OBS 367–380
Imaging for exclusion of atrial thrombus may be reasonable in patients with increased risk of thrombus** even if therapeutically anticoagulated for 3 weeks or longer. ***CHA_2DS_2VASc score ≥3, persistent AF, hypertrophic cardiomyopathy, rheumatic heart disease or cardiac amyloidosis*	Area of uncertainty	OBS 367–380

5.1 AF risk factors

Several risk factors for AF development and recurrence following catheter ablation have been identified, many of which are modifiable. These include traditional modifiable risk factors such as hypertension [411–414], and diabetes [364,415–419], but also emerging factors such as obesity [109,420–422], metabolic syndrome [423–425], physical inactivity [426–430], OSA [358,359,431,432], alcohol consumption [365,433,434], and smoking [366,435]. There is compelling evidence to suggest that management of these risk factors has the potential to reduce AF burden and improve the outcomes of ablation strategies to maintain SR. In practice, although there have been variable results when targeting risk factors in isolation, comprehensive management in specific risk factor management clinics has been shown to be effective in conferring tangible clinical improvements [353,354]. In addition, there are cardiovascular co-morbidities that warrant specific treatments and may have a role in improving the outcomes of catheter ablation.The recently described HEAD2TOES schema with targets for secondary prevention of AF is presented in Figure 8 [436]. Below we discuss the evidence pertaining to each of these modifiable factors (Supplementary Table 1).

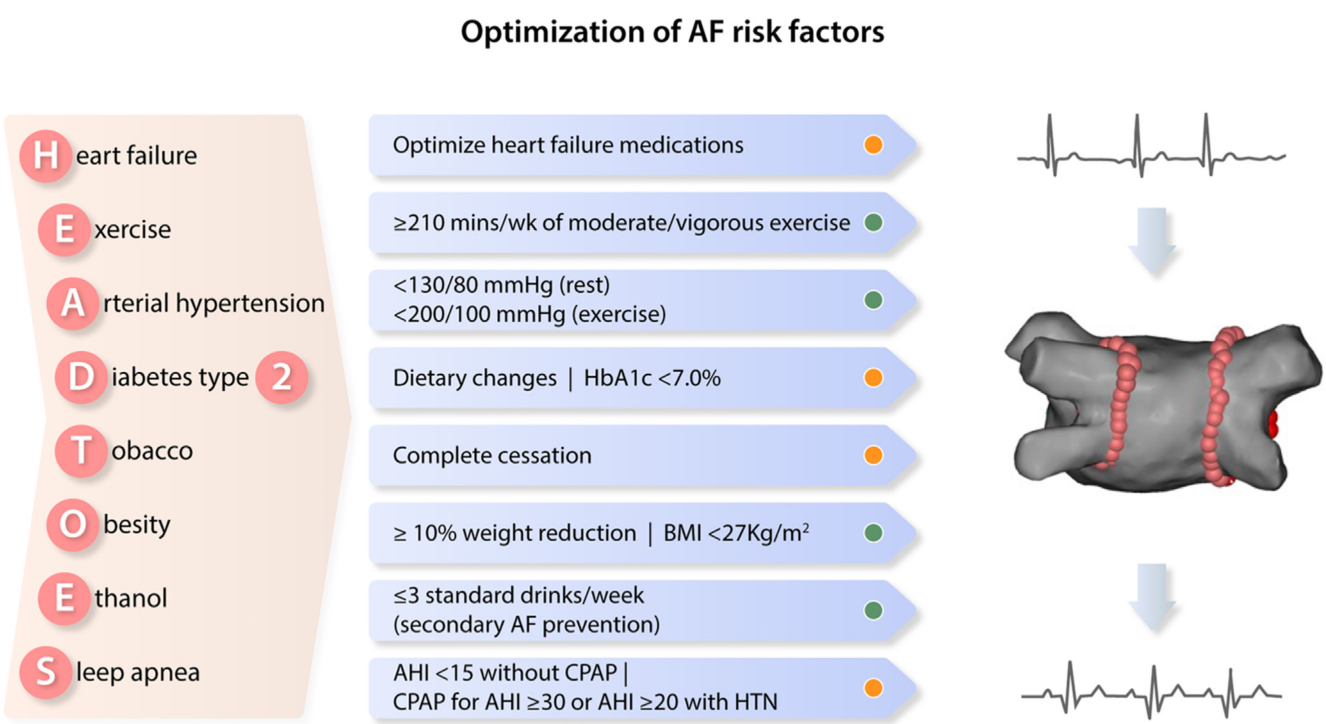


Figure 8
Risk factors and respective targets for AF prevention in patients considered for or undergoing AF ablation – the HEAD2TOES schema (green light: established evidence – orange light: evolving evidence). AF = atrial fibrillation; AHI = apnea-hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; HbA1c = glycated hemoglobin; HTN = hypertension; wk = week.

5.1.1 Hypertension

Hypertension is one of the most significant risk factors for AF development. [451–453]. It increases left ventricular wall thickness and diastolic dysfunction which mediate adverse atrial remodelling associated with increased left atrial pressure, wall thickness, fibrotic changes, and dilatation. In addition, the increased activation of the renin-angiotensin-aldosterone system in hypertensive patients mediates atrial fibrosis and electrophysiological remodeling thus promoting AF [454].

Discrepant results have been reported regarding the impact of uncontrolled hypertension on AF ablation outcome. In an observational study including 531 patients who underwent AF catheter ablation, uncontrolled hypertension was significantly associated with postablation arrhythmia recurrence after confounder adjustment [414]. In contrast, a registry analysis showed that patients with a diagnosis of hypertension, without information regarding the efficiency of antihypertensive management, had similar rhythm outcome after catheter ablation to those without hypertension [440]. In the SMAC-AF randomized trial, short-term aggressive blood pressure (BP) treatment (target systolic BP ≤120mmHg) for a median duration of 3.5 months before scheduled AF catheter ablation in patients with hypertension did not reduce arrhythmia recurrence following ablation as compared to standard BP treatment (target systolic BP < 140mmHg)[438]. Although treating modest hypertension in isolation has not proven to be of benefit, when undertaken in the setting of a comprehensive risk factor management program in overweight and obese individuals it has been associated with higher rate of SR maintenance after catheter ablation [353].

Renal artery denervation, a procedure developed for the treatment of resistant hypertension, has also a potential antiarrhythmic role. In a small, randomized study of 27 patients with drug-resistant hypertension scheduled for AF catheter ablation, combined renal artery denervation and PVI resulted in significant BP reduction and a higher freedom from AF recurrence at 12 months compared to PVI only [437]. In the larger, multicenter ERADICATE-AF RCT, 302 patients with hypertension resistant to at least one antihypertensive medication undergoing paroxysmal AF ablation, were randomized to catheter ablation alone or ablation plus renal denervation [439]. Addition of renal denervation to catheter ablation significantly increased freedom from AF recurrence at 12 months as compared to ablation alone. The underlying mechanisms explaining the favorable impact of renal artery denervation on AF burden have not been clarified. It has been postulated that this effect may be due to BP control itself, or to direct antiarrhythmic actions of renal artery denervation including reduction in central sympathetic output and attenuation of atrial structural and electrophysiological remodeling remodeling [455].

5.1.2 Obesity

Obesity is a pandemic and contributes significantly to the increasing prevalence of AF worldwide. The correlation between obesity and AF is well-recognized [456]. A metaanalysis of 51 studies reported that for every 5-unit increase in BMI, there was a 29% greater excess risk of incident AF and a 13% increased likelihood of AF recurrence following ablation [457]. Related mechanisms include structural and electrophysiological atrial remodelling [109,458,459]. In addition, cardiac imaging studies have shown that obesity is associated with increased epicardial and pericardial fat deposition adjacent to the LA [460]. Increased pericardial and epicardial fat is associated with AF, likely through direct fatty infiltration of the LA and/or paracrine effects attributable to released cytokines and chemokines [461].

Based on the findings of the ESC-EHRA AF Ablation Long-Term Registry, patients with BMI over 30 kg/m^2 had 1.2-fold increased likelihood of AF recurrence following catheter ablation as compared to overweight patients [420]. A single-center retrospective study enrolling 2715 consecutive patients undergoing AF catheter ablation concluded that BMI over 35 kg/m^2 was an independent predictor of worse postablation rhythm outcome [422]. In an observational study which categorised patients who underwent ablation by BMI, AF recurrence was higher in all high-BMI groups as compared to normal weight controls [350].

The role of weight-loss in patients undergoing AF ablation has also been examined in several studies. The ARREST-AF study evaluated the value of a comprehensive risk factor management approach in patients undergoing AF ablation and showed that aggressive risk factor management achieved significantly greater weight-loss and increased freedom from AF [353]. In contrast, a small non-randomized study in patients with morbid obesity and long-standing persistent AF undergoing AF ablation, reported that weight loss did not improve either AF symptom severity or freedom from AF recurrence at 1 year follow-up [444]. The prospective SORT-AF trial randomized patients with symptomatic AF and BMI 30-40 kg/m^2 undergoing AF ablation to a supervised structured weight management program or to usual care on the day of the procedure and evaluated potential impact on rhythm outcome assessed by invasive monitoring [446]. The primary endpoint of AF burden did not differ between compared groups probably due to a high rate of non-compliance in the intervention group, a modest weight loss achieved and a rather short postablation follow-up.

Bariatric surgery may also have a positive impact on postablation AF recurrence rate in patients with morbid obesity. In a retrospective cohort study of 239 patients with morbid obesity, bariatric surgery prior to AF ablation was associated with reduced risk of AF recurrence and reduced rate of repeat AF ablation. Prospective RCTs are needed to confirm the positive impact of surgical weight loss procedures [445].

5.1.3 Obstructive sleep apnea

Obstructive sleep apnea is a chronic condition characterized by recurrent pharyngeal collapse leading to repetitive interruption of ventilation during sleep. It is increasingly recognized as a critical risk factor in a variety of cardiovascular conditions and has recently been shown to double the risk of incident AF [462]. Both the acute effects of apnoeic episodes and the chronic effects of long-term OSA contribute to the increased risk of AF. The transient hypoxaemia associated with pharyngeal collapse is postulated to mediate changes in atrial ERP acutely and subsequently to enhance susceptibility to AF induction and maintenance [463]. In the long-term, OSA mediates significant haemodynamic changes resulting in increased LA pressures and LA enlargement [464]. OSA is also known to induce a systemic inflammatory and pro-thrombotic state which increase the likelihood of fibrotic changes and electrophysiological remodelling within the atria [465].

Mounting evidence suggests that OSA is also associated with worse outcomes following catheter ablation [358,359,431,432]. Metaanalyses report that patients with OSA have a significantly increased risk (ranging from 25% to 70%) for AF recurrence following AF catheter ablation [359,431]. Observational studies and meta-analyses concluded that the use of CPAP as a treatment strategy for OSA is associated with improved patient outcome following ablation [447,466]. A recent study in patients with OSA and AF demonstrated that CPAP therapy reverses electrical remodelling as documented by high density right atrial mapping [362]. Randomized evidence on the impact of CPAP treatment on arrhythmia outcome after ablation is sparse. In a recent study, 83 patients with paroxysmal AF and OSA undergoing PVI were randomized to either CPAP or standard of care without any difference in postablation AF recurrence as documented by implantable loop recorders. Of note this was a small study and probably without adequate statistical power to detect subtle treatment differences [363].

Importantly, treatment of OSA in the context of a comprehensive risk factor management strategy has been associated with improved ablation outcomes [353,354]. In the ARREST-AF study, patients were offered therapy if the apnea–hypopnea index (AHI) was ≥30/h or if it was >20/h with resistant hypertension or problematic daytime sleepiness [353]. However, proponents of treating sleep apnea are increasingly utilizing therapy with an AHI ≥15/h in patients with AF [362]. This latter trigger for treatment is being prospectively evaluated in the SNORE-AF study (ACTRN12621001213831).

5.1.4 Alcohol consumption

Long-term alcohol intake is associated with incident AF in a dose-dependent manner [467]. High quantities of alcohol consumption (more than three standard drinks per day) increase the risk of AF development by almost 35%, with a more significant effect in males. However, there is limited association with incident AF in those who limit alcohol consumption to less than 1 standard drink per day. Proposed mechanisms underlying this association include pleiotropic effects of alcohol on atrial electrical properties: conduction slowing and shortening of the atrial ERP [468], alterations in autonomic nervous control of the heart [469] and an increase in circulating plasma free fatty acids, which have been shown to be arrhythmogenic [470]. Structural LA remodelling may also be implicated in the association of alcohol consumption with AF development, since chronic alcohol consumption has been identified as a predictor of LA enlargement [471]. Furthermore, chronic alcohol consumption is closely associated with other independent AF risk factors including hypertension, obesity and OSA.

Several studies support a relationship between alcohol consumption and AF recurrence following ablation. In a study of patients with paroxysmal AF undergoing ablation, those consuming alcohol had higher AF recurrence rates after first catheter ablation compared to those who did not, though this difference was attenuated after repeat ablations [433]. In an observational study of symptomatic patients with paroxysmal AF, alcohol consumption was an independent predictor of low-voltage zones assessed by LA voltage mapping and AF recurrence following catheter ablation [434]. Contradictory results regarding potential association of alcohol consumption with substrate remodelling (atrial low voltage and conduction slowing) have been reported [468,472]. The association of alcohol consumption with adverse postablation rhythm outcome has also been validated in studies using objective markers of alcohol use, such as ethyl glucuronide levels in hair, thus overcoming potential bias in patient self-reporting [473].

Several studies have evaluated the impact of alcohol abstinence on clinical outcome after AF ablation either alone or in the context of a comprehensive risk factor management. Alcohol reduction of ≥1% from baseline to 1-year follow-up is independently associated with a lower risk of postablation arrhythmia recurrence [365]. Therefore, it is reasonable to reduce alcohol consumption to fewer than 30 g/week (3 standard drinks) in individuals undergoing catheter ablation of AF as part of a comprehensive management of risk factors [353,354].

5.1.5 Physical inactivity

Physical activity and exercise are linked with cardiovascular health. Increasing evidence supports that sedentary lifestyle increases the risk of incident AF [474]. Regular light-to-moderate exercise has been shown to reduce the risk of AF development [475]. However, the relationship between physical exercise and incident AF does not appear to be linear. Several cohort studies have shown that exercise intensity has a U-shaped relationship with AF, with highly active subjects exhibiting increased risk of incident AF compared to moderately active individuals [475–477]. Regular moderate-intensity exercise would, therefore, appear to be the key in reducing risk of AF.

Physical activity is also important in secondary AF prevention. In the CARDIO-FIT study, cardio-respiratory fitness (a surrogate for physical activity) measured by metabolic equivalents was associated with reduced AF burden and symptom severity in obese individuals with symptomatic AF. Each unit increase in metabolic equivalent was associated with 13% decline in the risk of AF recurrence [478]. In a recent prospective RCT (ACTIVE-AF), implementation of a supervised exercise-based intervention with progressively increased aerobic exercise up to 210 minutes per week significantly reduced arrhythmia recurrence by 50% and improved symptom severity as compared to usual care [479].

Several studies have evaluated the impact of physical activity and cardiorespiratory fitness on clinical outcome following catheter ablation (Supplementary Table 1). Higher cardiorespiratory fitness measured with the use of exercise stress test is associated with reduced arrhythmia recurrence and mortality following ablation [426]. In the subgroup of highly trained athletes, several rather small observational studies have shown that catheter ablation is similarly effective as in the general population [427,429,480,481]. The largest observational study in 144 athletes undergoing ablation found a similar arrhythmia recurrence rate following PVI as compared to a matched cohort of non-athletes [427]. In a randomized study including persistent AF patients treated with AF ablation, participation of patients in an exercise-based cardiac rehabilitation program improved exercise capacity after a 6-month follow-up without associated reduction in AF recurrence as compared to usual care [430]. The latter finding may be due to insufficient sample size and limited patient follow-up. Based on the existing evidence, individuals undergoing catheter ablation of AF should follow a training program of at least moderate aerobic exercise for a minimum of 210 minutes per week to improve rhythm outcome [478].

5.1.6 Diabetes mellitus

A number of studies have confirmed diabetes mellitus as an independent risk factor for AF [482]. Through increased production of reactive oxygen species and advanced glycation end-products, diabetes has been shown to result in fibrotic changes as well as ion channel and gap junction remodelling within the atria [483]. These changes increase conduction heterogeneity, reduce conduction velocity and prolong APD, promoting an electrophysiological milieu that favors AF development.

The association between diabetes mellitus and AF recurrence following ablation has been demonstrated in several studies. Metabolic syndrome, which encompasses disorders of BP, fasting sugar state, body weight and lipids, has been associated with poor AF catheter ablation outcomes [423–425]. In a prospective study including 1496 patients with non-paroxysmal AF undergoing catheter ablation, metabolic syndrome was associated with higher AF recurrence rates [425]. In the German Ablation Registry, diabetic patients experienced a similar rate of AF recurrence as compared to those without diabetes at 12 months of follow-up [416]. In contrast, another observational study of 2504 patients undergoing AF ablation concluded, after propensity matched analysis, that diabetes was an independent predictor of postablation AF recurrence.[417] Smaller observational studies have also demonstrated the detrimental impact of diabetes mellitus on catheter ablation outcome [418].

In addition, preablation glycaemic control has been shown to affect arrhythmia recurrences after ablation [364]. Patients with glycated haemoglobin (HbA1c) >9% were more than twice as likely to experience AF recurrence following AF ablation compared to those with an HbA1c <7. In multivariate analysis, improved glycemic control prior to ablation, defined as > 10% reduction in HbA1c during the last 12 months prior to ablation, was an independent predictor of arrhythmia-free survival after ablation [364]. Therefore, in the context of a multidisciplinary risk factor management approach, optimized glycemic control should be set as a treatment objective in diabetic patients undergoing AF ablation to improve rhythm outcome.

5.1.7 Smoking

Several long-term prospective observational cohort studies have identified smoking as an independent predictor of incident AF [484–486]. Most of these studies showed that the risk was higher in those who continued smoking compared with those who were able to quit. Proposed implicated mechanisms include increased sympathetic tone, oxidative stress, inflammation and atrial fibrosis. In the presence of AF, smoking increases the risk of thromboembolism and mortality, even after adjusting for well-recognized risk factors used in stroke risk stratification schemes.[487]. In a matched case-control study including AF patients with a low stroke risk (CHA_2DS_2-VASc score 0 in men or 1 in women), smoking was the only independent predictor associated with ischemic stroke. These findings provide strong evidence that smoking cessation should be an important part of AF risk factor management [488].

There is limited data exploring the relationship between smoking and AF ablation. In a small study of 59 patients who underwent PVI, smoking was associated with a three-fold relative risk of AF recurrence. [435]. In another retrospective study of persistent AF patients undergoing ablation, smokers had a significantly higher incidence of non-PV triggers compared to non-smokers without associated difference in long-term ablation outcomes [366]. Implementation of smoking cessation in the context of a structured risk factor management program significantly improves long-term outcome in symptomatic AF patients undergoing AF ablation [443].

5.1.8 Cardiovascular comorbidities

Cardiovascular disease contributes to the development of AF. There is considerable evidence supporting the association of AF with HF and valvular heart disease. In patients with severe rheumatic mitral stenosis, reduction of chronic stretch after mitral commissurotomy results in reversal of atrial structural remodelling and associated conduction abnormalities [489]. In HFrEF patients, HF-directed therapy reduces AF recurrence, cardiovascular hospitalization and mortality [490–492]. Although not specifically studied in the context of AF catheter ablation, optimizing therapy directed at these underlying conditions, when indicated, may improve AF ablation outcomes. Therefore, guideline-recommended HF treatment should be undertaken in patients undergoing catheter ablation of AF.

5.2 Preprocedural management

5.2.1 Preprocedural predictors of AF recurrences

AF recurrence following catheter ablation is not uncommon and remains a notable problem [493]. Several preprocedural factors are associated with increased risk of AF recurrences, including modifiable comorbidities (Section 5.1), AF type and duration, LA size, and abnormal atrial substrate as detected by electrocardiography and cardiac imaging [5]. Consideration of these predictors of postablation rhythm outcome is important to drive patient selection for AF ablation.

5.2.1.1 AF type and duration. The association of AF type with postablation recurrence rates has been widely investigated. Despite variation associated with the type and intensity of postablation rhythm monitoring, postablation arrhythmia recurrence rate is lower in patients with paroxysmal as compared to those with persistent AF [243–245,366,494–498]. Apart from AF type, the time interval from AF diagnosis to ablation (DAT) is a predictor of postablation AF recurrence [288,290,499–502]. Each year increase in DAT increases the risk of AF recurrence by 20% after adjustment for baseline comorbidities and medications [499]. A metaanalysis of 6 observational studies with a total of 4950 patients demonstrated that DAT less than 1 year was associated with a lower AF recurrence rate (relative risk: 0.73) compared with DAT >1 year [288].

5.2.1.2 Left atrial size. Several studies showed that LA size is an independent preprocedural predictor of AF recurrence following AF ablation [411,503–506]. A linear relationship has been reported between the increase in LA anteroposterior diameter and the mean predicted proportion of patients with AF recurrence after AF ablation [411]. Although linear LA measurements are widely used in everyday practice and clinical trials, they may underestimate LA dilatation, since LA enlargement is asymmetric, mainly occurring in the medial-lateral and superior-inferior axes and to a lesser extent in the anteroposterior axis, due to constrainment of the LA within the thoracic cavity. LA volume is a more accurate indicator of LA size and it has been shown to independently predict AF recurrence following catheter ablation in a metaanalysis of 13 studies [504]. LA dilatation is suggestive of underlying atrial remodeling and correlates with AF progression and presence of fibrosis (section 2)[91–93].

5.2.1.3 Electrocardiographic predictors. Electrocardiography is a widely available and inexpensive tool for evaluation of atrial substrate [507,508]. Several P wave indices have been associated with AF recurrences following catheter ablation [509–513]. In a recent meta-analysis of 14 studies with 1674 patients, maximal P wave duration and P wave dispersion were shown to predict postablation AF recurrences [514]. Prolonged P wave duration on amplified 12-lead surface ECG also correlates with the extent of LA low voltage substrate and a cutoff value ≥150 ms was shown to identify persistent AF patients at increased risk for arrhythmia recurrence following PVI [515,516]. In addition, several signal-averaged P wave parameters, including total filtered P-wave duration, have been proposed to reflect the extent of underlying atrial remodeling and predict postablation AF recurrences [507,508,517]. However, signal-averaged ECG measurements are rarely used in everyday practice.

5.2.1.4 Preprocedural imaging of atrial structure. Preprocedural documentation of atrial structural changes is useful to identify patients with advanced atrial remodeling and AF progression, who are less likely to have a favorable response to catheter ablation. Preprocedural imaging may provide relevant prognostic information with implications for guiding selection of patients considered more suitable candidates for ablation. Atrial fibrosis is the primary structural change associated with atrial cardiomyopathy, AF progression and persistence and can be detected and quantified by LGE-MRI [99,103,518–521]. In the DECAAF study, the extent of preablation fibrosis as assessed by LGE-MRI, was an independent predictor of arrhythmia recurrence following AF catheter ablation [103]. Implementation of this imaging modality requires experience in atrial LGE imaging and specific image sequences. Lack of reproducibility in atrial fibrosis assessment based on LGE measurement has limited its widespread adoption. Furthermore, discrepancies have been reported in the extent and distribution of fibrotic areas documented by LGE-MRI as compared to low-voltage areas identified during LA catheter-based mapping [106,522].

Cardiac computed tomography (CCT) may be used to quantify left atrial epicardial adipose tissue which is related to AF recurrence after catheter ablation. Several observational studies and a metanalysis have shown that epicardial adipose tissue volume or thickness have a negative impact on AF ablation outcomes [523–527]. Discrepant results have also been reported [528,529]. In a retrospective observational study, enhanced attenuation of posterior LA adipose tissue, as an imaging marker of local inflammation, was associated with increased risk of AF recurrence in patients undergoing catheter ablation [529].

Preprocedural imaging may also be useful for anatomic modeling to guide the ablation procedure. Though most patients have typical PV anatomy (Section 3.1), unusual PV variants (PV draining at the roof, common trunk) occur and may influence choice of ablation approach and modality (single shot vs. point by point ablation). While postablation imaging is no longer routinely performed to check for PV stenosis in the absence of symptoms, preprocedural imaging in patients who have undergone prior RF ablation may be reasonable to identify unrecognized significant stenosis and/or avoid ablation in areas of mild-moderate PV narrowing.

5.2.2 Preprocedural pharmacological treatment

5.2.2.1 Preprocedural anticoagulation. Based on currently used stroke risk assessment that guides decision making on eligibility for antithrombotic treatment, patients with AF and stroke risk factor(s) (CHA_2DS_2-VASc score ≥1 in males and ≥2 in females) who are scheduled for AF catheter ablation should receive oral anticoagulation therapeutically for at least 3 weeks prior to ablation [9,530]. This panel of experts shares the opinion that a minimum of 3-week therapeutic anticoagulation before AF catheter ablation is also beneficial in patients with the lowest CHA_2DS_2-VASc score (0 in males and 1 in females) if they are considered to have increased risk of thrombus due to persistent AF type or specific underlying heart disease (HCM, rheumatic heart disease, cardiac amyloidosis) (section 5.2.3.1.).

In the pre-DOAC era, several trials validated the superiority of performing catheter ablation without warfarin interruption [381–383]. COMPARE AF was a large, randomized trial which demonstrated that undergoing AF ablation on uninterrupted vitamin K antagonist (VKA) compared with VKA interruption and bridging with low molecular weight heparin (LMWH) resulted in a significantly lower incidence of thromboembolic events and was associated with a lower minor bleeding risk [384]. Importantly, there was no increased incidence of major bleeding in the uninterrupted group. In the VENTURE-AF, RE-CIRCUIT, AXAFA-AFNET5 and ELIMINATE-AF trials, patients undergoing AF ablation on uninterrupted rivaroxaban, dabigatran, apixaban and edoxaban respectively were compared to patients undergoing AF ablation on uninterrupted warfarin [385–388]. The primary endpoint used in these studies varied slightly, as did the outcomes. In VENTURE-AF, the primary endpoint of major bleeding did not differ between the rivaroxaban and warfarin groups [385]; in RE-CIRCUIT, the primary endpoint of major bleeding occurred significantly less frequently with dabigatran compared with warfarin [386]; in the AXAFA-AFNET5 and ELIMINATE-AF the primary composite outcome of all-cause death, stroke or major bleeding did not differ between the DOAC (apixaban or edoxaban respectively) and warfarin groups [387,388]. Meta-analyses have documented a significant relative risk reduction in major bleeding (50-55%) with uninterrupted DOAC as compared to uninterrupted warfarin strategy at the time of AF ablation [389,390]. Taken together these studies provide strong evidence in favour of the use of uninterrupted anticoagulation with either DOACs or VKA during AF ablation procedures.

Several randomized trials have shown comparable efficacy and safety of a minimally interrupted DOAC anticoagulation strategy, skipping a single dose at the day of the procedure, as compared to uninterrupted strategy [396–400]. A recent meta-analysis including 2168 patients reported similar rate of adverse clinical events (major bleeding, thromboembolic events) with minimally interrupted (holding morning DOAC dose on the day of the procedure without any LMWH bridging) as compared to an uninterrupted DOAC strategy [531]. However, there was no sign of lower bleeding rates with preprocedural DOAC interruption [531]. The randomized trials supporting the minimally (single-dose) interrupted DOAC strategy had several limitations: most were single-center, mainly performed in Asian populations and the sample size was insufficient to document non-inferiority. It is though acknowledged that conduction of an adequately powered randomized trial comparing the two preprocedural anticoagulation strategies based on standard sample size calculations is rather unrealistic due to a prohibitive sample size related to the very low event rate.

A survey of the writing group showed that 47% of the members routinely implement an uninterrupted anticoagulation strategy when performing AF catheter ablation, while 53% use a minimally interrupted anticoagulation approach (single skipped DOAC dose).

5.2.2.2 Preprocedural antiarrhythmic drug treatment. Many patients undergoing AF ablation are already on prior AAD treatment when scheduled for AF ablation. Optimal handling of AAD before ablation has not been clarified. Observational data support that failure of amiodarone to restore and maintain sinus rhythm prior to AF ablation is not associated with poor procedural outcome [532]. A retrospective observational study in 180 consecutive patients undergoing their first ablation procedure demonstrated a similar rate of symptomatic AF recurrences in patients undergoing ablation while taking AAD as compared to those who were not on an AAD at the time of ablation, at 6 months and at the end of follow-up (mean 24 months)[533].

Prior trials of persistent AF ablation employing extensive substrate ablation evaluated the impact of AAD continuation on intraprocedural sinus rhythm restoration and procedural outcome. In a retrospective study of persistent AF patients undergoing a stepwise AF ablation, preprocedural amiodarone prolonged AF cycle length during catheter ablation and reduced substrate ablation needed to achieve sinus rhythm without favorable impact on long-term outcome [534]. A multicenter prospective randomized study of long-standing persistent AF patients on amiodarone therapy undergoing PVI plus substrate ablation also demonstrated that amiodarone continuation during ablation significantly reduced the procedure, RF and fluoroscopy times [535]. However, amiodarone continuation was associated with significantly increased late recurrence rates which was attributed to AAD-mediated masking of non-PV triggers [535]. In the absence of definitive evidence suggesting an impact of AAD continuation at the time of AF ablation on procedural outcome, pertinent recommendations cannot be issued.

5.2.3 Imaging for exclusion of thrombus

5.2.3.1 Candidates for thrombus screening prior to ablation. The presence of atrial thrombus is a contraindication for catheter ablation due to associated risk of procedural thromboembolic complications. In this context, patients undergoing catheter ablation should be screened to rule out the presence of thrombus. A survey of the writing group showed that 59% of the members routinely employ imaging for thrombus exclusion in all patients undergoing AF ablation irrespective of presenting rhythm, AF type and prior anticoagulation. However, the adoption of uninterrupted periprocedural anticoagulation strategy has reduced substantially the rate of periprocedural stroke thus calling into question the need for routine screening of all patients undergoing AF ablation [401,536,537]. Furthermore, several baseline factors increase the risk of thrombus detection and/or procedural thromboembolic event, supporting the adoption of a selective, individualized strategy of thrombus surveillance in patients undergoing AF ablation.

The writing group suggests that imaging for thrombus exclusion is reasonable in patients who are considered eligible for anticoagulation before AF catheter ablation (CHA_2DS_2-VASc score $\geq$1 in males and $\geq$2 in females, persistent AF, HCM, cardiac amyloidosis or rheumatic heart disease – see below) but have not received anticoagulation therapeutically for 3 weeks or longer.

In the context of maximizing procedural safety, screening for thrombus may be reasonable even if patients have received therapeutic anticoagulation for 3 weeks or longer prior to catheter ablation in the presence of any of the following factors.

A. High CHA_2DS_2VASc score. In an early trial assessing the value of systematic screening with transesophageal echocardiography (TEE) before AF catheter ablation, the prevalence of thrombus or sludge was shown to increase with increasing $CHADS_2$ score [538]. In a recent trial of consecutive DOAC-treated AF patients, higher CHA_2DS_2VASc score significantly predicted the presence of TEE-detected LA thrombus before catheter ablation or scheduled electrical cardioversion [367]. A recent metaanalysis of 35 studies assessing the prevalence of LA thrombus in adequately anticoagulated patients with AF/AFl undergoing TEE before cardioversion or AF catheter ablation demonstrated a significantly higher prevalence of LA thrombus in patients with CHA_2DS_2VASc scores $\geq$ 3 as compared with those with scores $\leq$ 2 (6.3% vs 1.1%, p<0.001)[368]. Therefore, preprocedural imaging for thrombus exclusion may be a reasonable approach in patients with CHA_2DS_2VASc score $\geq$ 3 scheduled for AF catheter ablation even if adequately treated with therapeutic oral anticoagulation for at least 3 weeks.

B. Persistent AF. Multiple anticoagulation trials have validated that persistent AF patients, even if adequately anticoagulated, are more likely to experience thromboembolic events as compared to those with paroxysmal AF after adjustment for baseline variables [328,369–371]. In an older retrospective study of 1058 AF patients undergoing systematic screening with TEE to rule out atrial thrombus before AF ablation, patients with persistent AF had a 3% incidence of LAA thrombus as compared to 0.5% in patients with paroxysmal AF presenting in normal sinus rhythm [538]. In a multicenter retrospective study of 414 consecutive AF patients undergoing TEE before scheduled electrical cardioversion or ablation, LAA thrombus was documented in 15 patients and 93.3% of those had persistent AF [367]. In a recent prospective registry, 900 patients with at least 3 weeks of prior uninterrupted therapeutic anticoagulation underwent AF ablation without any type of imaging screening. In total, 4 (0.32%) thromboembolic complications were documented, and all occurred in patients with persistent AF [537]. In a recent metaanalysis of 14653 adequately anticoagulated patients with AF/AFl undergoing TEE before cardioversion or AF catheter ablation, non-paroxysmal AF was associated with a 4-fold higher LA thrombus prevalence as compared to paroxysmal AF [368]. Based on the abovementioned evidence, persistent AF patients have an increased risk of LA thrombus despite their anticoagulation status.

C. Hypertrophic cardiomyopathy – rheumatic heart disease – cardiac amyloidosis. AF patients with HCM have significantly higher incidence of ischemic stroke compared to those without HCM [372]. HCM patients with AF categorized as low risk based on their CHA_2DS_2VASc score (0 in men or 1 in women) have a significantly greater stroke risk than AF patients without HCM and a CHA_2DS_2VASc score of 2 [372]. In a large cohort of patients with AF undergoing TEE, HCM patients had a significantly higher risk of LA thrombus than matched control subjects (8.8% vs 4.1%; p<0.001) despite high rates of anticoagulation at the time of TEE and continuously for 1 month prior [380].

Several small observational studies have shown that patients with rheumatic mitral stenosis have a substantially increased incidence of LA thrombus as documented by TEE even when in sinus rhythm, varying from 2.4 to 25% [373–375].

Patients with cardiac amyloidosis have an increased incidence of intracardiac thrombus, even in the absence of AF/AFl, due to the amyloid infiltration which results in atrial enlargement, mechanical dysfunction and blood stasis [376,377]. In a series of 116 autopsies, intracardiac thrombus was identified in 33% of amyloidosis cases, with AL amyloidosis and AF being independently associated with thromboembolism [376]. In a single-center, retrospective analysis of patients referred for elective direct cardioversion for atrial arrhythmias, patients with cardiac amyloidosis had 10 times higher rate of TEE-documented LA/LAA thrombus as compared to a matched cohort (28.5% versus 2.5%) even if anticoagulated for $\geq$ 3 weeks before TEE [378]. In a more recent observational study, LA thrombus was present in 14% of patients with cardiac amyloidosis referred for electrical cardioversion, despite prior anticoagulation, mainly with DOACs [379].

Based on the abovementioned evidence, patients with HCM, rheumatic heart disease or cardiac amyloidosis are considered as high-risk for stroke and therefore routine preprocedural screening for thrombus exclusion may be reasonable irrespective of their CHA_2DS_2VASc score or previous anticoagulation.

5.3.2.2 Imaging modalities for thrombus exclusion. Several imaging modalities may be used for exclusion of atrial thrombus in patients undergoing AF ablation. The selection of a particular imaging tool is based on patient's characteristics, physician preference and expertise, institutional availabilities and cost. Available options are discussed below.

A. Transesophageal echocardiography. Transesophageal echocardiography has long been used in the preablation setting since it enables reliable exclusion of atrial thrombus and assessment of LA size, functional parameters and valvular disorders. In an early large prospective intraoperative study, TEE had a sensitivity and specificity of 100% and 99% respectively for identifying atrial thrombi as compared to direct visual inspection of LA content [539]. However, TEE is a semi-invasive procedure requiring sedation and esophageal intubation, occasionally limited by subjective estimates and is not devoid of complications (0.18-2.8%) which may be associated with major morbidity (0.2%) and rarely, mortality (<0.01-0.02%) [540,541]. TEE prior to the ablation procedure may lengthen the procedure and general anesthesia time, while it can prove helpful in guiding transeptal puncture.

B. Cardiac computed tomography. Delayed phase CCT is a useful and reliable imaging modality for exclusion of atrial thrombus. Incorporation of late acquisition protocols reduces false positive rates by providing a time delay to allow enhanced LAA contrast opacification and differentiate whether a low attenuation region is due to thrombus or circulatory stasis and low blood flow. A meta-analysis of 22 studies demonstrated that CCT had a sensitivity and specificity of 0.99 and 0.94 respectively versus TEE [409]. Delayed imaging CCT protocols significantly improved specificity as compared to early imaging protocols [408,409]. A recent prospective cohort analysis evaluating optimal time delay for late phase CCT protocols demonstrated that even a 3-min delay may be associated with false positive results, while a 6-min delayed acquisition protocol is optimal due to associated 100% specificity [410]. Related disadvantages include (a) the risk of contrast-induced nephropathy which is low in patients with normal renal function and reversible in most cases and (b) the related radiation exposure, which is though relatively low (< 3 millisieverts) with contemporary technology CT scans [408,542,543].

Another prerequisite for recommending CCT for exclusion of atrial thrombus prior to AF ablation is its performance within 48 hours prior to ablation to prevent the likelihood of de novo thrombus formation in the waiting period between screening and ablation.

C. Cardiac magnetic resonance imaging. Cardiac MRI enables imaging of atrial anatomical features and structural changes that are important for procedural planning. (section 5.2.1.4) It also has a favorable diagnostic performance for assessment of atrial thrombus.[544–546]. A recent meta-analysis of 4 CMR studies, reported a sensitivity and specificity of 0.80 and 0.98, respectively, as compared to TEE [409]. However, the existing trials supporting the role of CMR for thrombus exclusion are limited, single-center, rather small in number, heterogeneous in type of MRI sequence used and with uncertain reproducibility. Large-scale studies with standardized and consistent CMR protocols are needed to support the value of MRI as reasonable imaging option for exclusion of atrial thrombus in the preablation setting.

D. Intracardiac echocardiography. Intracardiac echocardiography (ICE) is increasingly used as an alternative to TEE for exclusion of LAA thrombus at the time of AF ablation [402]. In an early study comparing ICE with TEE in patients undergoing AFl ablation, ICE showed very high correlation with TEE for detection of LA stunning [403]. Since then, several prospective studies comparing ICE with TEE for detection of LAA and/or LA thrombus have indicated that ICE is as effective as TEE [404,405]. The ICE-CHIP study compared ICE with TEE and observed a non-significant trend to increased thrombus detection with TEE [406]. However, ICE imaging was performed from the RA, and it is now well-established that optimal LAA views are obtained when the ICE catheter is positioned in the right ventricle or the pulmonary artery [407] ICE may also have a role for LA thrombus screening after a recent equivocal or even negative TEE in patients undergoing AF ablation [407]. In a prospective multicenter registry of 6186 patients undergoing AF ablation on uninterrupted DOAC anticoagulation, ICE was used to screen for LA/LAA thrombi. In this population with mean $CHAD_2S_2$-VASc score of 2.9, no thrombi were observed and only one TIA occurred [401]. In practices familiar with ICE, it is reasonable to use ICE, with imaging from the RV inflow tract or pulmonary artery, instead of TEE to screen for LA/LAA thrombi prior to ablation. Since ICE may be used at some centers to guide transeptal puncture and monitor for complications, use of ICE to screen for thrombi may save procedural time and cost (compared to additional TEE or CCT performance).

A survey of the writing group showed that 59% of the writing group members mainly use TEE for exclusion of LA thrombus, 18% use ICE and 23% use cardiac CT.

Section 6: Mapping and Ablation Tools for Atrial Fibrillation Catheter Ablation

6.1 Mapping tools

6.1.1 Invasive mapping tools

6.1.1.1 Electroanatomical contact mapping. Mapping and ablation require precise navigation within the chamber of interest. Electroanatomical mapping (EAM) systems allow for three-dimensional (3D) visualization of the anatomy of any heart chamber, delineation of AT/AFL circuits, catheter positioning and catheter manipulation without use of fluoroscopy. Accurate anatomical reconstruction of the 3D shell of the chamber of interest is of the utmost importance. However, inaccuracies are caused by continuous motion of the heart, patient breathing and body movement. All available EAM systems have a set of algorithms to account for movement (including respiratory gating). Mapping can be performed either with point-by-point acquisition using the ablation catheter, or more frequently, using dedicated multielectrode catheters.

In general, there are two types of EAM systems. Impedance-based systems utilize a transthoracic electrical field for catheter localisation which is created by surface patch electrodes that emit high-frequency electrical signal in three orthogonal axes. Drawbacks include that the field is non-linear, impedance is affected by changes in tissue properties, and the coordinate system (patches) can move. Magnetic field-based systems, on the other hand, are not affected by tissue differences and are inherently linear and stable over time. Magnetic sensors are needed to visualize catheters, so map creation is only possible with sensor-enabled catheters. The coordinate system is often linked to the fluoroscopy unit under the patient and can be distorted by metal (bed, flat detector, ICDs, etc.).

Several EAM systems are currently on the market. The CARTO 3 (Biosense Webster, Irvine, CA, USA) is a hybrid system which uses magnetic technology for localization of dedicated mapping and ablation catheters and current-based technology for visualization of electrodes and shaft of other EP catheters. Integration of ICE into the CARTO mapping system (CARTOSOUND, Biosense Webster, Irvine, CA, USA) enables the construction of the 3D shell of the chamber of interest from a series of ICE-acquired chamber contours with associated reduction in fluoroscopy time even to zero to zero [547,548].

The Ensite NavX (Precision) EAM system (Abbott, Chicago, Il, USA) uses both voltage and impedance data for localization of proprietary and non-proprietary mapping and ablation catheters. In addition, the system integrates magnetic information for dynamic optimization of 3D models (field scaling) when sensor-enabled catheters are used. The latest generation of the Ensite NavX (Ensite X) EAM system uses magnetic-based data from sensor-enabled catheters to create 3D maps, also maintaining the option to rely on impedance data for map creation and catheter visualization.

The Rhythmia system (Boston Scientific, Marlborough, MA, USA) uses a combination of magnetic and impedance-based location technology and allows for automated high-density mapping using a dedicated steerable 64-electrode mini basket catheter (Figure 9).

Multimodality approaches allow for image integration of pre-acquired CCTs and MRIs with real-time 3D EAM maps or ICE imaging. Accuracy is critically dependent on fusion quality (including the use of fiducial points in both images). In addition, 3D rotational angiography images can be merged with live 2D fluoroscopy and thus obviate the need for pre-interventional imaging. The quality of EAM acquired with multi-electrode catheters has generally reduced the need for fusion with pre-acquired images due to the higher resolution of the former and errors associated with the latter.

The quality of electrogram acquisition is crucial for accurate annotation of signals, particularly in low voltage areas and diseased atrial tissue. Furthermore, mapping catheters now have multiple bipoles with smaller electrodes for signal recording, allowing faster acquisition of high-quality signals (Figure 9). Synthesizing all this information from multiple electrograms requires mathematical algorithms which automate electrogram annotation and timing.

Newer modules are helping operators to delineate complex tachycardias. A new module in the latest CARTO 3 platform provides an algorithm which computes conduction velocity based on collected electrograms and applies a global best-fit solution when displaying wave propagation (Coherent Mapping)[549]. Activation direction mapping in the latest generation EnSite X system uses "omnipolar" EGMs correcting for voltage differences caused by directionality of the electrical wavefront in relation to the mapping electrodes. Using these corrected electrograms, the system can compute a beat-by-beat vector direction of the wavefront and present the information in a propagation map [550]. The incremental

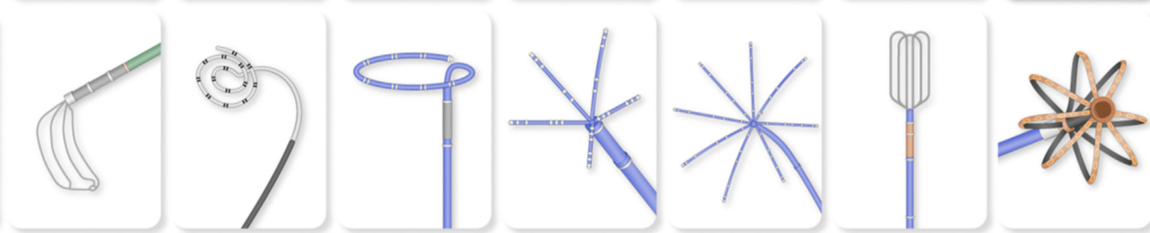
Catheter	Advisor HD Grid	Reflexion HD	Lasso	Pentaray	Octaray	Optrell	Intellamap Orion
Company	Abbott	Abbott	Biosense Webster	Biosense Webster	Biosense Webster	Biosense Webster	Boston Scientific
Catheter figure							
Number of electrodes	16	20	10-20	22	48	48	64
Electrode spacing	3 mm	2-7-2 mm	4.5 mm (15 mm) 6.0 mm (20 mm) 8.0 mm (25 mm) 2-6-2 mm (variable15-25 mm)	4-4-4 mm 2-6-2 mm	3-3-3-3-3 mm 2-2-2-2-2 mm 2-5-2-5-2 mm	2.4 mm	2.5 mm
Size of electrodes	1 mm	1 mm (except tip which is 2 mm)	1 mm	0.76 mm	0.46 mm	0.46 mm 0.9 mm²	0.4 mm²

Figure 9
Multielectrode mapping catheters

value of both coherence and omnipolar mapping in the management of complex atrial tachyarrhythmias needs to be proven in prospective studies.

EAM systems have attempted to incorporate algorithms for mapping persistent AF. CARTOFINDER is an algorithm used to map focal and rotational sources during AF, with clinical trials pending [551–553]. Both CARTO and Ensite include optional algorithms for automated detection of CFAE during AF and tagging of respective areas on the 3D anatomical map. Other algorithms are in development (section 6.4.).

The evolution of ablation indicators (section 8.1.2.2) incorporating power, ablation duration and contact force (CF) in one formula to assess lesion quality has further leveraged EAM systems. RF-based ablation incorporating CF-sensing ablation catheters combined with quality lesion indicators allows for automated tagging of ablation points to interactively review the position and quality of RF lesions.

Using EAM systems has proven to reduce fluoroscopic duration and dose [554–556]. However, studies assessing the clinical benefit of safety and efficacy in various arrhythmias have initially shown mixed results [557–561]. The implementation of the CLOSE protocol in RF-based AF catheter ablation has proven both effective and safe [562–567] and consequently standardized the PVI procedure using the CARTO mapping system. (section 8.1.2.2)

The cost of the ablation procedure is inevitably increased when using EAM systems with high complexity (multipolar catheters, mapping system upgrades). This cost needs to be weighed against the benefits described above. However, the future role of 3D EAM systems in PVI procedures using single-shot or large footprint ablation catheters is at present unclear.

6.1.1.2 Non-contact mapping. Most EAM systems require contact between the mapping catheter and cardiac tissue to accurately record cardiac potentials. It is difficult, however, to achieve stable, complete contact of multipolar or even single point catheters on the cardiac surface, and therefore, interpolation algorithms are required to smooth out the electrical data collected. This limits both the spatial and temporal accuracy of such recordings and can obscure finer, detailed patterns of activation. It is also difficult to obtain a global, instantaneous, panoramic view of a chamber's activation sequence when recordings of the various chamber segments are collected sequentially in a stepwise fashion.

Non-contact mapping utilizes a large, multipolar catheter positioned within the chamber of interest to record global far- and near-field unipolar electrograms. These electrograms are then typically fed into a mathematical algorithm which can interpolate and extrapolate global activation based on the "ground-truth" of the recorded unipoles [568]. The resulting activation patterns can then be projected onto a map surface.

One system (AQMap, Acutus Medical) utilizes a multisplined, 48 electrode catheter, equipped with ultrasound transducers for reconstruction of the anatomic surface, which records unipolar electrograms and then uses an inverse algorithm to calculate the "charge density" on each point of the map surface [568]. Charge density is calculated from the local unipolar voltage but filters out putative far-field effects to provide a higher-resolution local electrical activation. Early results have suggested that complex atrial activations during AF can be identified, but the additive effect of targeting these activations in the persistent AF ablation strategy is not well-established [569]. Furthermore, the system loses accuracy when the cardiac surface of interest is 40 mm or more from the catheter [570].

Electrographic flow mapping (Ablamap, Ablacon) utilizes a large basket catheter to record unipolar electrograms which are then interpolated and processed into a beat-by-beat electrical intensity map [571]. As the electrical intensity changes beat-by-beat in AF, the Horn-Schunk iterative algorithm calculates the flow pattern seen during AF over time. Regions with divergent flow patterns can be labelled as "sources" which can then be targeted for ablation. The recently announced FLOW-AF trial randomized persistent or long-standing persistent AF patients with recurrent, symptomatic AF despite at least one prior AF ablation procedure to PVI plus electrocardiographic flow-guided source ablation or to PVI only. Adjunctive ablation of electrocardiographic flow sources resulted in significant improvement in 1-year freedom from AF [572].

6.1.1.3 Spatiotemporal dispersion mapping. Mapping and ablation of regions exhibiting complex fractionated atrial electrograms (CFAE) was pioneered many years ago by the work of Nadamanee [573]. However, the STAR AF II trial did not show an incremental benefit in rhythm outcome when CFAE ablation was performed in addition to PVI during AF ablation [574]. Several studies have shown promising results regarding the efficacy and safety of AF ablation guided by spatiotemporal electrogram dispersion [575–577]. Seitz and colleagues described an ablation approach where regions displaying spatiotemporal "dispersion" were targeted [575]. Dispersion areas were visually identified and defined as clusters of electrograms, either fractionated or nonfractionated, that displayed interelectrode time and space dispersion at a minimum of 3 adjacent bipoles such that activation spans the AF cycle length. These electrograms could be continuously fractionated, burst fractionated, or of very rapid cycle length. Areas displaying spatiotemporal electrogram dispersion can be identified either manually or automatically with the use of machine and deep learning algorithms (VOLTA VX1) that perform real-time analysis of electrograms recorded by multipolar catheters and then annotate areas of interest on the 3D anatomical shell which represent potential ablation targets [578]. The TAILORED AF trial (NCT04702451) is comparing an ablation strategy targeting areas of spatio-temporal dispersion identified with the use of this artificial intelligence software algorithm in combination with PVI to PVI alone in patients with persistent AF and will provide further data on the efficacy of this approach. Stability and reproducibility of identified target sites displaying spatiotemporal dispersion needs to be documented.

6.1.2 Non-invasive mapping tools

6.1.2.1 Electrocardiographic imaging. In recent years, a drive towards better understanding of AF mechanisms has resulted in the emergence of new forms of AF mapping technology which employ the principle of phase mapping, a mathematical approach for the assessment of spatial and temporal periodicity in tissue electrical activity and identification of periodic rotations or 'rotors' [579]. Optical mapping work in animal models provides compelling evidence for the existence of rotors and their role in AF perpetuation and these insights served as the basis for clinical translation to AF mapping [580].

Electrocardiographic imaging or ECGI mapping is a non-invasive phase-mapping approach which utilizes a 252-body surface electrode array and patient specific heart-torso geometries to display virtual cardiac potentials on the epicardial surface. Activation mapping in AF allows identification of re-entrant and focal activities generated from unipolar electrograms combined with phase-mapping analysis. Potential advantages over conventional invasive mapping systems include non-invasive, simultaneous, global characterization of bi-atrial electrical activity, albeit at a lower mapping resolution [581]. Three-dimensional imaging acquisition is central to the technique for generation of individualised anatomical models of the atria and torso volume conductor. CT imaging is most commonly utilised due to its speed, widespread availability and high-resolution imaging with the obvious disadvantage of exposure to ionizing radiation [582]. MRI provides better soft tissue delineation albeit at a lower resolution, while eliminating radiation risk [520]. However, higher costs and longer scan times limit its applicability. The recently developed imageless ECGI overcomes the need for CT or MRI imaging by estimating the cardiac geometry and location inside the patient's thorax based on electrical, statistical and thoracic geometrical information [583].

The ECGI technique was first applied in a study of continuous bi-atrial activation mapping validated against invasively generated electroanatomic maps [584]. In this study multiple concurrent wavelets were identified as the most common pattern of activation and ablation near ECGI-identified critical sites resulted in restoration of sinus rhythm. Using commercially available mapping systems, unstable re-entry circuits with varying spatio-temporal activity were described as the predominant sustaining mechanism in persistent AF patients [585,586]. In patients with ablation-induced AF termination, arrhythmia-free survival was 85% at one year [585]. In the AFACART study, an ablation strategy consisting of targeted ablation of AF drivers and PVI, followed by LA linear ablation if AF persisted, resulted in 77% freedom from AF at one year in a cohort of persistent AF patients with continuous AF duration less than 1 year [587]. Driver-only ablation resulted in AF termination in 64% of patients [587]. The TARGET-AF1 trial reported a 65% freedom from recurrent AF/AT at one year in persistent AF patients undergoing PVI plus ECGI-guided ablation with a high rate of AF termination during driver ablation [588].

More recently, ECGI findings indicative of AF complexity, including number, distribution and density pattern of AF re-entrant sites have been associated with AF termination during ablation [589,590]. The ongoing STRATIFY trial will further evaluate the role of ECGI-based assessment of AF complexity for prediction of ablation efficacy (NCT04578275).

Inherent limitations of ECGI relate to electrode density and mapping resolution. Transformation of electrograms using phase-mapping is a complex process and an obvious disadvantage is the limited ability for raw signal analysis by the operator prior to transformation. In addition, ECGI mapping is costly and time consuming. Finally, the lack of a gold standard for validating the existence of rotors/drivers and conflicting results using ECGI versus other phase mapping approaches have fueled skepticism about validity and reproducibility [579,585,586].

Nevertheless, ECGI remains the only modality capable of simultaneous bi-atrial electrical characterization in AF. Further assessment in randomized trials as well as technological improvements to streamline workflows are needed before it can be incorporated as a valid tool in the routine invasive management of AF patients.

6.1.2.2 Magnetic resonance imaging fibrosis guidance. - Magnetic resonance imaging has been used to identify areas of atrial fibrosis in patients scheduled for AF catheter ablation [105,591,592]. However, adequate spatial resolution remains problematic in the thin-walled LA and reproducibility of the different imaging techniques across centers remains low (section 5.2.1.4). Several RCTs have failed to document that ablation of MRI-detected fibrotic areas provides incremental benefit in postablation rhythm outcome (section 8.2.6.).

6.2 Ablation tools

6.2.1 Radiofrequency ablation

Radiofrequency catheter ablation is a widely employed thermal-based technique with documented beneficial effect on rhythm outcome as compared to medical therapy in paroxysmal and persistent AF patients [236–238]. Initial studies reported on PVI using non-irrigated catheters with RF delivery in temperature-controlled mode. Since the introduction of irrigated catheters, RF is most often delivered in power-controlled mode with conventional power settings between 20 to 40 watts. The positive impact of CF measurement on procedural and RF time and recurrence rates [593–596] has resulted in the adoption and widespread use of irrigated CF-sensing catheters and additionally facilitated the development of algorithms aimed at real-time assessment of lesion quality including the Force Time Integral (FTI) [597], Lesion Size Index (LSI)[598] and Ablation Index (AI) [566,599] (section 8.1.2.2). Within the last years, the employment of point-by-point workflows using CF-sensing catheters and focusing on optimized and contiguous lesions has resulted in improved outcomes for paroxysmal AF, with high first pass isolation rates and one-year success rates [562,563,566,567].

More recently, focus has centered on enhanced lesion formation for durable PVI, with increased power delivery proposed to improve lesion quality and reduce procedure times. Experimental studies have demonstrated shallower and wider lesions with higher power, shorter duration lesions [600,601] and several clinical studies have underscored the enhanced procedural efficiency and preserved safety profile associated with 40-50W ablation in power-controlled mode [602–607]. In a recent small RCT comparing high power (50W) versus standard power (30W anterior / 25W posterior wall) RF ablation in patients undergoing PVI, the former resulted in significantly shorter time to achieve PVI, higher freedom from arrhythmias at 12 months and a trend toward increased asymptomatic cerebral emboli [608]. Furthermore, power-controlled ablation at 70W over 5-7 seconds is associated with significantly greater procedural efficiency, fewer AF recurrences and a similar safety profile to conventional power protocol (30-40 W for 20-40 s) [609,610]. The absence of use of AI or LSI to standardize the lesion set in these latter studies may limit the reproducibility of the results. Care should be exercised using higher power at the posterior wall due to potential inadvertent overshoot and "heat stacking" when applying consecutive lesions in close proximity, although it is also possible that a high-power short duration protocol may be safer over the esophagus due to less depth of penetration (section 11.3.1.) [607,611]. Based on recent RCT findings, high-power short-duration ablation may be associated with increased risk of asymptomatic cerebral emboli (section 11.2.3).

The reduced accuracy of tissue-temperature feedback during high power irrigated ablation has led to the development of novel catheters equipped with multiple thermocouples capable of accurate, real-time tissue temperature monitoring, allowing RF delivery in temperature-controlled mode using low irrigation flow rates (QDOT Micro, Biosense Webster; DiamondTemp, Medtronic). The randomized DIAMOND-AF study demonstrated similar safety and efficacy of the DiamondTemp Ablation system compared to standard CF-guided ablation with higher overall power delivery and reduced procedure times using temperature-controlled ablation [612]. The CF-sensing QDOT catheter is capable of energy delivery of up to 50W in 'QMODE' with a recent study supporting the safety and efficacy of this modality with a first pass isolation rate of 92% and no esophageal injury on post procedural endoscopy [613]. Furthermore, this catheter is capable of very high power delivery at 90W over 4 seconds (QMODE+). Several pre-clinical studies report a predominant resistive form of tissue heating with 90W/4second ablation with a high rate of contiguity and transmurality [600,614–616]. In contrast, in a recent canine study, lesion size was smallest with RF applications at 90W/4seconds, followed by 50W/10seconds and greatest with 30W/30seconds [617]. The QDOT-FAST study, demonstrated the feasibility and safety of 90W/4second ablation in paroxysmal AF patients undergoing PVI [618]. The safety profile of this ablation workflow was further supported in a study showing lack of esophageal injury [619]. More recently, a small non-randomized study reported significantly reduced procedural times with 90W/4second versus conventional 25-40W ablation with a similar safety profile [620]. In contrast, a further comparative study suggested an overall similar procedure time (with time being lost due to a lower rate of first-pass isolation with 90W/4second ablation protocol) [614]. In the multicenter randomized POWER PLUS trial, first-time PVI with very high power short duration (90W/4second) RF ablation resulted in a significant but modest reduction in procedure time with similar safety and 6-month arrhythmia recurrence rate as compared to 35/50W AI-guided conventional ablation [621]. Furthermore, despite the potential of high-power short-duration ablation to alleviate the issue of catheter instability, when it does occur it may have a greater impact on lesion formation particularly in areas of increased tissue thickness such as the carina.

In summary, contiguous, point-by-point RF ablation for PVI has evolved into a clinically safe and efficacious procedure. With high or very high power ablation (in temperature or power-controlled mode), procedural times of close to or less than one hour are achievable with similar safety and efficacy profiles [604,614]. In the absence of definite randomized data on long-term outcomes, the decision to opt for novel higher power strategies may come down to operator preference or patient profile (shorter procedure times are preferable in awake patients, whereas low fluid delivery may be advantageous in patients with HF). Large-scale randomized trials are needed to determine the long-term efficacy of such novel strategies.

A multielectrode RF balloon catheter (HELIOSTAR, Biosense Webster) has also been used for PVI [622]. This single-shot ablation device is compatible with a 3D EAM system (CARTO) and is equipped with 10 irrigated, flexible electrodes that independently deliver RF energy, thus allowing customization of energy delivery in a focal, segmental, or circumferential approach. Furthermore, the use of an integrated, intraluminal, circular diagnostic catheter enables real-time recording of PV electrograms. Observational studies have demonstrated that PVI with this multielectrode RF balloon catheter may have favorable safety and effectiveness in paroxysmal AF patients [623–626].

Another recent development in the field of RF ablation is a larger footprint, single tip ablation device. Instead of a 3-4 mm terminal tip which is irrigated, this catheter employs a lattice spherical structure which is 9 mm in diameter and the surface of the sphere contains 9 mini-electrodes (0.7 mm) which also contain thermocouples [627]. The system delivers temperature-controlled, contact sensing-facilitated RF with saline irrigation sprayed from the center of the catheter which does not impact temperature sensing at the surface of the catheter in contact with the tissue. The system delivers high current RF to achieve a uniform current cloud on the lattice spherical surface [627]. In an initial pilot study, the system demonstrated a very high incidence of durable PVI and linear lesion block [627]. The system has also incorporated PFA offering versatility in type of delivered energy [628].

6.2.2 Cryoablation and ultra-low temperature cryoablation

6.2.2.1 Conventional cryoballoon technologies. Cryotherapy, or the use of freezing temperatures to elicit a specific tissue response, has a long history of safe and effective use in medicine. After open cardiac surgery applications had developed in the 1960s and 1970s, the first clinical experience using a focal tip cryoablation catheter - targeting the AV node - was described in 2001 [629]. Finally, the development of a balloon-based cryothermy in the beginning of the 21st century has led to a striking uptake in cryoablation for AF ablation. A single shot balloon design delivers significant benefits over a focal design. Firstly, it allows procedural simplification (no need for mapping systems, potential time gains) and second, it blocks antegrade flow from the targeted PV, thereby eliminating balloon heating by the blood pool and greatly enhancing cryoablation efficacy. However, a caveat related to the absence of mapping system in the cryoballoon procedural workflow is the increased fluoroscopy exposure [630].

All currently available cryoballoon catheters have an open inner lumen to allow insertion of a guidewire or a diagnostic catheter, and use N_2O as a coolant, exploiting the Joule-Thomson gas expansion effect to achieve temperatures down to a theoretical minimum of -89°C. The first-generation cryoballoon (Artic Front, Medtronic, Inc) showed superiority over AADs in a randomised setting [631]. However, over 80% of patients with AF recurrence after first generation cryoballoon ablation showed PV reconnection at the time of repeat ablation and over 50% had reconnection of more than one PV [632]. The second-generation cryoballoon (Arctic Front Advance, Medtronic, Inc.) was introduced in 2012 and incorporates a modified refrigerant injection system characterized by 8 injection jets in a more distal balloon position. Thus, a more homogeneous cooling of the complete distal balloon hemisphere, including the distal tip, is achieved.

More recently, the POLARx (Boston Scientific) cryoballoon catheter received approval and clinical experience has accumulated. A recent multicenter registry has validated the procedural safety and efficacy of this cryoballoon for the treatment of patients with paroxysmal AF [633]. Despite similarities in ablation technique and catheter design, important differences exist as compared to other cryoballoons [634,635]. In the COMPARE-CRYO trial, 201 symptomatic paroxysmal AF patients undergoing their first PVI procedure were randomised to cryoballoon ablation using either the POLARx or the Arctic Front catheter and were monitored with an ICM. The freedom from arrhythmia recurrence at 12 months was similar in both groups, but the use of the POLARx balloon resulted in significantly higher rate of phrenic nerve palsies that did not recover within 24 hours [636].

The FIRE AND ICE trial compared energy modalities for AF ablation and randomised 762 patients with drug-refractory PAF to treatment with either the second-generation cryoballoon or conventional RF using a prospective multicenter design. The study showed cryoballoon ablation to be non-inferior to RF ablation with respect to its primary endpoints of efficacy and safety and reported a possible reduction in rehospitalization or reablation in secondary analyses [294,637]. Phrenic nerve injury was the most commonly reported complication at discharge in the cryoballoon ablation group (2.7%). Permanent PN palsy was reported in 0.3% of patients. More recently, the CIRCA-DOSE trial evaluated contemporary approaches to PVI using latest generation technology in both the cryoballoon ablation as well as the RF ablation arms using an ICM for postablation rhythm monitoring [630]. In this trial, no difference in 1-year efficacy (freedom from atrial tachyarrhythmia) was confirmed between the compared groups, whereas continuous monitoring showed median AF burden reduction of >99% with both ablation technologies.

6.2.2.2 Ultra-low temperature cryoablation. An innovative approach using highly compressed liquid nitrogen allows a change from the liquid to the gaseous phase without the associated volume expansion and thus without the associated problems of vapour lock when using liquid nitrogen in closed circuit catheters [638]. The implications are that an ablation energy source with a far wider therapeutic margin can be used – liquid nitrogen boils at minus 189°C – and that cryocatheter design is no longer constrained by the need for occlusion.

Currently, a single platform using this technology is commercially available in the EU (iCLAS, Adagio Inc) and is undergoing clinical evaluation in the US (IDE # G180263). The iCLAS system allows the use of variable shape catheters that enable rapid reconfiguration of the catheter to the desired target tissue. The recently published first in man CRYOCURE-2 observational study reported promising acute procedural results and 12-month freedom from atrial arrhythmias in a mixed paroxysmal and persistent AF population [639]. Potential synergies between ultralow temperature cryoballoon and pulsed field ablation (PFA) may exist, such as guaranteed tissue contact and elimination of microbubbles. Evidence for this strategy is currently limited and a trial assessing its usefulness is underway (NCT05408754).

6.2.3 Pulsed field ablation

6.2.3.1 Biophysics & mechanisms. In contrast to RF or cryothermy, irreversible cardiac electroporation is considered a non-thermal energy source, meaning the cell death induction is not dependent on thermal processes. Instead of exposing cells to a thermal insult, electrical fields are applied to the cells leading to a disruption in cell membrane integrity and function [640]. This short-term disruption then leads eventually to cellular death and replacement fibrosis. Ablation using irreversible electroporation is more commonly referred to as pulsed field ablation (PFA).

The exact mechanism of PFA-induced cell death is not known [640]. Application of electrical fields of sufficient strength will lead to accumulating charge on cell membranes which can result in development of nanopores in the membrane surface and increased membrane permeability. This permeability disrupts the intra- and extracellular concentration gradients required for cellular homeostasis. If the electrical field application is sufficiently long, alterations in cellular pH, generation of reactive oxygen species, release of mitochondrial cytosome c, and other processes all result in a progression to cellular apoptosis combined with some immediate cellular necrosis [641–643]. These processes occur over days to weeks and lead eventually to replacement fibrosis over 4-8 weeks. Unlike thermal ablation, PFA does not permanently disrupt the local tissue extracellular matrix structure or vascular supply [644], which is a critical element in why PFA may not result in as much collateral damage to non-cardiac tissues [640].

Electrical field ablation was pioneered in the eighties when Scheinman and colleagues delivered a full defibrillator shock through a catheter in the heart [645]. The investigators achieved heart block, but the accompanying heat and barotrauma sidelined direct current ablation and paved the way for RF ablation. The key technological advance for today's PFA is that a "large charge" can be broken up into a series of multiple applications of very brief duration. Since the cardiac cell is like a capacitor which can store charge, the intensity of the electrical field will depend on the total duration of the exposure (number of repeated applications) in addition to the actual voltage delivered [640].

Key parameters for PFA include voltage, pulse width, waveform (biphasic vs. monophasic) and polarity (bipolar vs. monopolar). Increasing voltage will increase treatment effect but can also generate unwanted heating, gaseous microbubbles, and barotrauma [642,646]. Most systems approved or in development today are utilizing voltages of 500-2000 V peak-to-peak for each application. Monopolar PFA delivers energy from a single catheter to a return ground patch. Bipolar PFA delivers energy between adjacent electrodes and is more suited to larger, efficient, multipolar ablation catheters. Pulse width is also critical for treatment effect and minimization of gaseous emboli, muscle contraction and unwanted heat generation. Most systems are utilizing pulse widths in the microsecond range. Delivery of pulses (typically 10-20) usually occur in a series called a "packet" or "train" and then multiple trains (1-7) may be delivered over several seconds.

Although PFA is supposed to be non-thermal, the recipes used for ablation today encroach on the thermal threshold. For biphasic, bipolar pulses, there can be 5-40°C rises in tissue surface temperature [640,647,648]. However, these rises are for such brief duration (a few milliseconds) that significant thermal damage does not occur. Contact between the tissue and catheter is still required for optimal PFA delivery [649]. Whether CF is required for optimal PFA delivery is still an open question.

6.2.3.2 Efficiency and safety – key advantages. Since PFA can be delivered over several milliseconds and several packets can be delivered within seconds, procedural efficiency is one of the key advantages of this energy source. Furthermore, PFA can be easily delivered in large-footprint (so-called "single shot") devices which can achieve large lesions around the PVs and on the posterior wall with ease. Even in the early evaluation studies, where operators were very early in their learning curve, LA dwell times were only 60-90 minutes or less [650,651]. Now that some systems are available commercially, early registries report average procedure times close to or even less than one hour for AF ablation [652,653].

The safety profile of PFA also makes it very promising for cardiac ablation. With thermal ablation, there has always been a low, but detectable, risk of collateral damage to the lung, esophagus, and PN. Esophageal damage can lead to fatal complications such as an atrial-esophageal fistula (section 11.3.1). Early preclinical data has suggested that the field threshold for damaging cardiac cells is much lower than that required for smooth muscle (esophagus) [654], vascular (veins and arteries) [644], and nerve cells [655]. Adipose tissue is an excellent insulator for electricity and even thin fat layers separating esophageal tissue from the LA may have a significant protective effect [640]. Preclinical data have confirmed that clinical PFA systems approved or under development do not cause long-term esophageal damage [647,656,657]. Esophageal temperature rises are not seen during ablation over the esophagus in humans [651]. While acute PN capture can occur during PFA applications, PN palsy is very rare [652]. Even when PN palsy occurs, it typically recovers within a few hours [658]. PFA also does not appear to cause PV stenosis [652,659]. Skeletal muscle contraction was a problem with early versions of PFA, but with the implementation of more optimized waveforms (biphasic especially), this risk is reduced, and most studies have shown that PFA can be safely performed without the use of paralytics [650,651,660].

Microbubble formation has been observed with most PFA systems. It is unclear if this is due to unwanted heat generation, an electrolytic effect on water, or displacement of nitrogen gas [642]. The size of the bubbles appears to be small (<40 μm)[661] and if gaseous, they should spontaneously resorb prior to causing significant cerebral ischemia. Early studies have suggested a low rate of silent cerebral emboli on cerebral MRI post-PFA ablation (3%), but further studies are required to confirm the potential risk of these bubbles [650,662]. High Joule monophasic pulse deliveries, for example, can cause very large volumes of these bubbles and have been associated with ST segment elevation and MRI lesions indicating embolic ischemia [663].

Coronary arterial spasm has been reported with PFA deliveries in proximity to coronary vessels [664,665](section 11.2.2). The spasm persisted even after delivery was terminated and required injection of intracoronary nitroglycerin to terminate the process. Cough has also been frequently reported even in anesthetized patients, which may be due to field stimulation of the J receptors within the PVs or due to bronchial stimulation [640]. In large cohorts of unselected patients, the safety profile of PFA was consistent with preferential tissue ablation [652,653].

6.2.3.3 Efficacy of PFA. PFA can be delivered from a variety of different catheter shapes and styles. It can be delivered from larger, multipolar catheters creating a "large footprint" ablation. It can also be delivered from balloon-style devices. Finally, it can also be delivered from standard point-by-point RF-style catheters (3.5 mm tip) and even larger tip catheters (like the 9 mm lattice sphere)[666,667]. PFA deliveries can cause myocardial cell stunning and disappearance of electrical signals. Therefore, acute disappearance of electrograms cannot necessarily predict long-term success. Repetitive applications of PFA around the veins may push the field penetration (and therefore lesion depth) to achieve better results [651].

Early studies using a pentaspline multielectrode PFA catheter have shown that optimized biphasic, bipolar PFA deliveries can achieve very high rates of durable PVI at a 3-month remapping procedure [650]. Few one-year follow-up studies have been published to date. A pooled analysis of 3 nonrandomised prospective studies reported a 78.5% freedom from any atrial arrhythmia at 1 year in paroxysmal AF patients [660]. Multicenter registries (MANIFEST-PV and EU-PORIA) using this pentaspline multielectrode PFA catheter reported one-year arrhythmia-free survival of 78.1% and 74% respectively, in real-world mixed paroxysmal and persistent AF populations undergoing PVI, without a standardised rhythm monitoring protocol [653,668].

Recent evidence supports the efficacy and safety of other PFA systems. In the large-scale, prospective, multicenter PULSED AF trial, PFA resulted in 100% acute PVI rate with a low rate of primary safety adverse events (0.7% without PV, esophageal or PN complications) and 12-month clinical success rates consistent with those reported in thermal catheter ablation studies with similarly rigorous rhythm monitoring (66.2% in paroxysmal AF and 55.1% in persistent AF)[669]. A biphasic PFA system with a variable-loop circular catheter integrated with a 3D maping system showed a 71% one-year atrial arrhythmia freedom without device-related serious adverse events in a paroxysmal AF patient population [670]. A focal 9-mm lattice-tip catheter able to deliver both RF and PF energy recently demonstrated 78% freedom from atrial arrhythmias at 12 months with primary safety endpoint rate of 0.6% in a mixed paroxysmal and persistent AF patient population. Invasive remapping demonstrated PVI durability in 97% of PVs and 91% of all deployed linear lesions using the optimized waveform [671].

In the recent ADVENT trial, 607 patients with drug-refractory paroxysmal AF were randomised either to PFA with the pentaspline catheter or to thermal ablation (either CF-sensing RF or cryoballoon ablation). After a 12-month follow-up, PFA was shown to be non-inferior to thermal ablation in respect to efficacy (composite of acute procedural and chronic success) and safety (device- and procedure-related serious adverse events) [672]. Results of the SINGLE SHOT CHAMPION (NCT05534581) and BEAT AF (NCT05159492) RCTs will shed further light on the long-term efficacy and safety of PFA for AF ablation as compared to RF and cryoballoon ablation.

6.2.4 Laser ablation

A laser balloon ablation system transmits light energy through a balloon filled with deuterium oxide ("heavy water") to perform PVI. The lumen of the 16F catheter contains a fiber optic endoscope that allows PVI under direct visualization. The balloon is quite compliant, allowing a variable inflation diameter (25–32mm), depending on PV size. Once inflated, the operator can visualize the edge of the balloon and the PV antra. The laser can then be delivered in a 30-degree arc around the antrum of the vein. Energy can be titrated from 5.5 to 12 W for 20-30 seconds depending on the thickness of the tissue and the proximity to the esophagus [673]. A newer development is the ability for the catheter to rotate the laser arc 360 degrees around the PV in a continuous sweep to avoid gaps and reduce procedure times compared with the segmental lesions delivered with the old system [673].

Several studies sought to compare the safety and efficacy of laser balloon ablation with radiofrequency or cryoballoon ablation. In an early multicenter, prospective RCT, laser ablation resulted in similar one-year freedom from AF when compared to wide-area circumferential RF ablation in persistent AF patients [674]. Evidence from both comparative and randomised trials and from a metaanalysis demonstrated similar efficacy and safety of laser balloon compared to cryoballoon ablation [675–677]. How laser will fit in a post-PFA world remains to be seen.

6.3 Robotic and magnetic catheter navigation

The concept of remote catheter navigation was developed many years ago and was quite promising for some time. The benefit was that operators could reduce radiation exposure for themselves (and possibly the patient) and reduce the risk of occupational injury associated with wearing medical protective gear. The systems fell into two main categories: (1) magnetically assisted catheter control, such as the Niobe (Stereotaxis Inc., USA) and the Magnetecs system; and (2) robotic assisted catheter control, such as the Sensei robotic catheter system (Hansen Medical, USA) the Amigo remote catheter system (Catheter Precision, USA). As AF ablation procedures have become shorter (single-shot technologies) and radiation exposure very low (electroanatomic mapping, "zero" fluoroscopy techniques), the use of these remote navigation systems has become more niche and is not being widely adopted. Evidence from non-randomised trials and metaanalyses demonstrate that AF ablation guided by remote magnetic navigation is associated with similar efficacy as manual navigation but showed reduced periprocedural complications, reduced fluoroscopy time and prolonged procedure time [678–680]. The high cost of installation and disposables is a key barrier to wider adoption. In a post-PFA world when procedural times will be further reduced, the advantage of such systems for AF ablation will be further limited.

6.4 Future developments

6.4.1 Mapping tools

Future mapping catheters are being developed which will allow for accommodation of larger numbers and smaller electrodes to increase the resolution of maps. Three-dimensional printing of electrodes is also allowing large numbers of electrodes to be placed on flexible surfaces. Already the Orion basket mapping catheter (Boston Scientific, Boston, MA) exemplifies this technology. Future grid and basket designs will be developed.

The development of the "near" unipole reference is a new advance which will be expanded in multiple catheters. This was first seen on the Sphere 9 catheter where the indifferent electrode is placed on the shaft of the catheter, close to the mapping elements, rather than at Wilson's Central Terminal. This produces a unipolar signal with less far-field artifact.

Future basket designs will also feature algorithms which can measure far-field signals and subtract them from unipolar recordings. This will allow for cleaner, localized unipolar recordings which may enhance accuracy in defining propagation of wavefronts and identifying local arrhythmia sources.

Artificial intelligence will be further incorporated into mapping system algorithms to help identify critical zones for arrhythmia initiation or perpetuation, particularly for complex arrhythmias like AF (section 6.1.1.3). The main limitation to this approach is the "black box" nature of artificial intelligence algorithms which may limit operator acceptance.

6.4.2 Ablation tools

Combined thermal/pulsed field modalities may overcome several limitations of the currently available PFA systems. Combined pulsed field cryoablation using ultralow cryothermy can create deeper lesions by delivering subtherapeutic cryoablation to create ice which acts as an electrical insulator. Large voltages of PFA can then be delivered without causing heating, bubbles, or muscle contraction because of the ice on the catheter[681]. Combined RF-PF may allow for preconditioning of the tissue with low dose RF, dropping local impedance and increasing intracellular fluid, which could allow for increased PFA efficacy.

Even subtherapeutic doses of PFA can cause electrical stunning of cardiomyocytes such that signals disappear very quickly. Disappearance of signals, however, does not guarantee a fully developed lesion. Repeated deliveries may be used to achieve durability, but this is still empiric. Other electrogram characteristics or new lesion assessment technologies (such as optical assessment of tissue birefringence) may be required to acutely assess whether a fully transmural lesion has been developed with PFA.

Real-time guidance of ablation procedures with magnetic resonance systems has been proposed for some time and early feasibility studies have been performed [682]. However, the approach has been limited by the size of the MRI system, the current inability of an operator to function comfortably in the environment, and the limited spatial resolution of the various catheters within real-time, non-processed MRI imaging. As the resolution of systems improve, and the size of MRI machines decreases, this may eventually become a possible way to perform ablation without any risk of fluoroscopic exposure. Current mapping systems, however, are already enabling near-zero fluoro procedures and could slow down development of MRI-guided ablation systems.

Carbon-beam or other high-energy, heavy ion beams may be used to non-invasively beam radiation into specific cardiac structures to achieve ablation. Preliminary preclinical data show that beams can be targeted to the atrioventricular node, the PV-atrial junction, and the left ventricle [683]. While the non-invasive nature of the ablation is enticing, the complexity and cost of installing such systems (such as MRI guidance) is sure to be a limiting factor.

Section 7: Procedural Management and Techniques

Procedural management and techniques	Category of advice	Type of evidence
Ultrasound guidance is beneficial for vascular access during AF catheter ablation to reduce the risk of vascular complications.	Advice TO DO	OBS 684–690
Heparin should be administered during AF catheter ablation and adjusted to achieve and maintain an ACT of at least 300 seconds.	Advice TO DO	OBS 691–695
Administration of initial heparin bolus before transeptal puncture is reasonable, especially when performed under echocardiographic guidance.	May be appropriate TO DO	OBS 696–698
Use of an esophageal temperature probe may be reasonable during thermal AF ablation procedures to monitor esophageal temperature and help guide energy delivery.	Area of uncertainty	RAND 699–704

7.1 Anesthesia and ventilation during AF Ablation

An AF ablation procedure can be performed under general anesthesia, deep sedation or conscious sedation based on patient and procedural characteristics, physician experience, anesthesia availability and institutional protocols. A multidisciplinary approach, involving electrophysiologists and anesthesiologists, is necessary to develop a safe and effectively structured anesthesia protocol.

7.1.1 General anesthesia versus sedation

General anesthesia is the most commonly used anesthetic method in patients undergoing AF ablation. Under deep sedation, the anesthesia depth approaches that of general anesthesia and in most centers either an anaesthesiologist, a second physician or a specially trained nurse is required to be present [705]. For conscious sedation, patients are able to respond purposefully to verbal commands.

An analysis of the National Anesthesia Clinical Outcomes Registry that included 51070 cases of AF ablations from 2013 to 2018 showed that 94% of cases were performed under general anesthesia in the US [706]. In addition, the worldwide EHRA survey in 2021 showed that the most commonly used anesthetic technique was general anesthesia (40.5%), followed by conscious sedation (32.0%) and deep sedation (27.5%). However, this varied by continent, and in Europe, conscious sedation was still the most commonly used technique (38%). Between 2010 and 2019, the proportion of procedures performed under general anesthesia and deep sedation increased by 4.4% and 4.8% respectively, whereas the use of conscious sedation decreased by 9.2% [705].

In addition to alleviating pain and anxiety, an important goal for anesthesia during AF ablation is to minimize patient movement as this improves catheter stability. Therefore, general anesthesia and deep sedation have frequently been preferred. A prior prospective study randomized 257 patients undergoing ablation for paroxysmal AF to either conscious sedation or general anesthesia and demonstrated significantly improved 17-month ablation efficacy with general anesthesia. General anesthesia was also associated with shorter fluoroscopy and procedure times [707]. Other retrospective studies and a meta-analysis have also observed better outcomes when general anesthesia is used compared to conscious sedation and this finding was associated with improved CF and greater first pass isolation [707–710]. General anesthesia has also been found to be as safe as conscious sedation in terms of total complications and serious adverse events [710]. With the increasing use of cryoablation for PVI, a number of studies have demonstrated the feasibility of conscious sedation for this technique with similar efficacy and complication rates to general anesthesia, but with significantly reduced total procedure duration due to reduced anesthetic time [711–713]. With the emergence of PFA, there may be a swing back towards the use of general anesthesia to reduce PFA-related pain and prevent discomfort due to contraction of the diaphragm [650–652,714–716]. However, recent studies have documented the safety and efficacy of deep sedation protocols during AF ablation with PFA [715,716]. A survey of the writing group showed that 52.8% of the writing group members use general anesthesia during AF ablation procedures, 27.8% use deep sedation and 19.4% use conscious sedation.

7.1.2 Ventilation

Catheter-tissue CF and catheter stability are critically influenced by respiration. An early study demonstrated greater CF when ablation was performed during periods of apnea with implications for ablation time to achieve PVI and acute reconnection rates [717]. Ventilation modulation has been employed in several studies to improve catheter stability and contact. Beyond using periods of apnea, techniques have included high frequency jet ventilation (HFJV) and high frequency low tidal volume (HFLTV) ventilation. HFJV has been shown to improve catheter stability [718,719]. A recent prospective registry indicated that use of HFJV in patients undergoing PVI for paroxysmal AF using CF catheters was associated with decreased arrhythmia recurrence without appreciable increase in adverse procedural events [718]. HFJV is most suitable for patients with normal pulmonary physiology and chest wall compliance. Hypotension requiring administration of vasopressors is significantly more frequent during HFJV cases as compared to those using standard ventilation [718]. Complications which have been described with the use of HFJV have included airway dehydration, inadequate oxygenation and ventilation, respiratory acidosis, barotrauma, gastric distension and aspiration [720,721]. Both due to these potential complications and lack of widespread availability of dedicated ventilators, adoption of HFJV during PVI has been relatively limited.

A simpler alternative strategy which has recently been described is the use of conventional ventilators to deliver HFLTV ventilation. Several studies demonstrated that HFLTV ventilation was associated with improved catheter CF and stability, higher first pass PVI rate and shorter total procedural and RF times without an increase in complications [722–724]. This technique has been more widely adopted due to its ease of use. A recent large prospective multicenter registry enrolling paroxysmal AF patients undergoing catheter ablation demonstrated that HFLTV ventilation improved freedom from atrial arrhythmia recurrence, AF-related symptoms, and AF-related hospitalizations in comparison to standard ventilation [725].

A survey of the writing group showed that 5.6% of the writing group members routinely use HFJV and 29% routinely use HFLTV ventilation during RF ablation procedures.

7.2 Vascular access

Femoral venous access for AF ablation may be obtained using anatomical markers or under ultrasound guidance. Significant vascular complications which may occur include inadvertent arterial puncture, arteriovenous fistula, pseudoaneurysm formation, access site hematoma, and retroperitoneal bleed [726,727](section 11.3.6). When traditional anatomical marking is used for vascular access, an inferior approach is associated with increased risk of femoral pseudoaneurysm and arteriovenous fistula, while a superior approach may be associated with an increased risk of retroperitoneal bleeding. Evidence from observational studies and meta-analyses has indicated that use of ultrasound-guided vascular access significantly reduced the risks of vascular complications, postprocedural pain and prolonged bruising [685,688–690]. A multi-center RCT comparing ultrasound-guided venipuncture versus an anatomically guided approach was terminated early due to substantially lower than expected complication rates [686]. Nevertheless, analysis of data collected, demonstrated that first-pass success in gaining femoral vein access was higher in the ultrasound-guided group, while puncture time, extra puncture attempts, inadvertent arterial puncture and unsuccessful cannulation were all significantly lower in the ultrasound-guided group [686]. In an era where AF ablations are increasingly performed on uninterrupted anticoagulation, the risks associated with vascular complications need to be minimised. Therefore, preventive measures including ultrasound-guided venipuncture, should be implemented routinely.

A survey of the writing group showed that 75.7% of the writing group members routinely use ultrasound guidance for vascular access during AF catheter ablation.

7.3 Continuous arterial blood pressure monitoring

Continuous arterial BP monitoring via an intra-arterial line is utilized in many laboratories to monitor patients undergoing AF ablation (39.5% of the writing group members routinely use invasive arterial BP monitoring during AF catheter ablation). Limited data comparing outcomes with invasive versus non-invasive BP monitoring exists. A retrospective multi-center study of 362 patients having AF ablation under general anesthesia found no difference in complication rates between the invasive and the non-invasive BP monitoring group [728]. In theory, an arterial line may provide critical early indication to the presence of a major complication such as pericardial tamponade. Whether this justifies the routine use of invasive hemodynamic monitoring or would indeed improve outcomes is not established. In patients with impaired ventricular function, hemodynamic instability and significant comorbidities, the use of invasive BP monitoring may be reasonable on an individualized basis.

7.4 Anticoagulation during AF ablation

Meticulous sheath handling and optimal intraprocedural anticoagulation with unfractionated heparin (UFH) is critical to prevent thromboembolic complications and the development of silent cerebral infarction [691,692,694,695,729]. A single non-randomized study evaluated the impact of flushing the transeptal sheath prior to vascular entry using 2U/cc heparin concentration as compared with a flush containing 1000U/cc heparin on the incidence of thrombus formation on the transeptal sheath [730]. ICE was used to screen for thrombus. Patients having received a low dose heparin flush prior to intravenous access had a significantly higher incidence of thrombus formation compared with the high dose heparin group (9% versus 1%) within 5-15 minutes of entering the LA. Notably however, the procedures were not performed on uninterrupted OAC, heparin was not administered until after the second transeptal crossing, the initial UFH bolus was at least 5000 units and the target ACT was only 250-300. It remains unclear whether a strategy of heparinised saline infusion of sheaths is important in the context of a contemporary anticoagulation strategy. Nevertheless, 84% of the writing group members reported using heparinized sheath irrigation.

Most of the evidence regarding UFH administration during AF ablation was derived from patients taking VKA. Studies that investigated the use of UFH in patients on uninterrupted DOAC have shown that higher amounts of intraprocedural UFH were needed to achieve target ACT and not all DOACs interact with UFH in the same way [731–736]. Post-hoc analysis of RE-CIRCUIT showed that patients on dabigatran required similar amounts of UFH to achieve therapeutic ACTs compared to VKA, while other studies indicated that more UFH were needed in patients taking factor Xa antagonists [733–736]. From literature review, a great amount of variability exists across different practices on intraprocedural UFH dosing protocols. Specific dosing regimens should be tailored to the patient population, medication use, the last dose of OAC as these factors impact the amount of UFH needed to achieve therapeutic anticoagulation [736–738].

A metanalysis of 19 studies involving 7150 patients concluded that patients with ACT > 300 sec during AF catheter ablation had significantly reduced risk of thromboembolic complications without increased risk of bleeding as compared to those with ACT < 300 sec, irrespective of the type of oral anticoagulation used periprocedurally [693]. A survey of the writing group showed that 61% of the members employ a target ACT > 300 sec during AF ablation, while 34% a value > 350 sec.

Evidence supports initial heparin bolus administration before transeptal puncture. Observational studies in patients undergoing AF ablation have demonstrated that UFH administration before transeptal puncture is associated with a reduced incidence of ICE-detected thrombus as compared to those receiving UFH after transeptal puncture [696,697]. A prospective observational study in 280 patients undergoing AF ablation under VKA treatment, reported that compliance to a periprocedural anticoagulation protocol including UFH administration before transeptal puncture, maintenance of therapeutic preprocedural INR and consistent procedural ACT levels > 300 sec resulted in significantly reduced incidence of silent cerebral ischemia after ablation [698]. In addition, the increasing use of ICE significantly decreases the risk of transeptal puncture associated bleeding. A survey of the writing group showed that 74% of the members administer initial UFH bolus before transeptal puncture.

In the event when anticoagulation needs to be reversed due to intraprocedural complications such as cardiac perforation and cardiac tamponade, UFH can be reversed with protamine administration. This was validated by a RCT showing that protamine expedites vascular hemostasis after AF ablation [739]. If bleeding stops, reversal of OAC is not suggested to protect against periprocedural thromboembolic risk. If bleeding persists despite protamine administration, fresh frozen plasma can be administered in warfarin-treated patients, idarucizumab to reverse dabigatran and andexanet for reversal of factor Xa inhibitors [740,741]. If specific reversal agents are not available, prothrombin complex concentrates (Factors II, VII, IX, and X) can be administered to achieve immediate hemostasis and should be preferred over recombinant activated factor VIIa due to the latter's prominent procoagulant effect [742].

7.5 Transseptal puncture

Transseptal puncture can now be performed with several different technologies. In addition to the conventional needle, transseptal access can also be gained using a RF needle or a needle free technique. Several RCTs have compared the RF needle with a standard approach. These studies found that transeptal puncture with an RF needle was associated with significantly shorter time required for transseptal LA access, shorter fluoroscopy requirement, lower rate of transseptal failure, and fewer visible plastic shavings after needle advancement. Complication rates did not differ [743,744]. However, one of these studies had a transseptal failure rate of 28% and an incidence of visible plastic shavings of 33% which are not consistent with the actual very low incidence of these two events in clinical practice [743]. Furthermore, the time savings of 20 seconds to several minutes seem insignificant in a clinical or lab usage context. Neither study addressed the additional cost associated with use of the RF needle. Indeed, uptake of the RF needle has varied widely and in many countries is not in routine use. An observational study also found that use of the RF transseptal needle was associated with a lower incidence of MRI-confirmed silent cerebral lesions [745].

The needle-free transeptal approach can be achieved with the use of specific wires. A transeptal wire (Safesept, Pressure products, San Pedro CA) is safe and effective in gaining left atrial access without a need for transeptal needle or exchange for a standard guidewire [746]. In a large, retrospective single-center analysis it was shown to significantly reduce the risk of transeptal puncture-related cardiac tamponade [747]. A newer technology is an RF wire that can be used to cross the septum and provide support for the transeptal sheath (Versacross, Boston Scientific). The RF wire forms a pigtail end that can be advanced into the SVC to guide initial sheath placement. When pulled into the sheath the wire straightens out, and upon "tenting" of the septum, RF is applied to the tip of the wire and the wire is advanced into the LA, reforming the pigtail end that can be advanced into a PV and allow the sheath to be atraumatically advanced. This system can be useful in cases of redo ablation or prior ASD closures to prevent the "jumping" across the septum that may occur with standard needles.

With circumferential RF ablation both the single (two sheaths via one transeptal puncture site) and double transeptal (each sheath via a separate transeptal puncture site) approaches have been used (50% of the writing group members use single and 50% double transeptal access). A prospective study comparing single vs double transseptal in patients undergoing AF ablation revealed no difference in procedure time, fluoroscopy time, complication rates or AF recurrence between the two approaches [748].

The use of steerable sheaths during AF ablation facilitates catheter navigation, manipulation and is associated with increased catheter stability [749]. In an earlier prospective RCT, the use of steerable sheath significantly reduced arrhythmia recurrences 6 months after AF ablation and was the only independent predictor of rhythm outcome [750]. The introduction of steerable sheaths that can be visualized on 3D electroanatomical maps facilitates fluoroless understanding of their positioning. Integration of visualizable steerable sheaths in AF ablation workflows has been shown to reduce fluoroscopy exposure as compared to the use of conventional steerable sheaths [751–754].

7.6 The use of intracardiac echocardiography

The use of ICE during AF ablation offers multiple benefits in different stages of the procedure. As already presented in detail (section 5.3.2.2), ICE is useful to screen for LA/LAA thrombus at the time of catheter ablation. ICE use has also a favorable impact on procedural duration and safety. Observational studies and 2 meta-analyses indicated that ICE use in AF ablation was associated with significant reductions in fluoroscopy time, procedure time, and complication rates compared to AF ablation without ICE [755–758]. In a propensity score matched analysis, ICE was associated with a significantly lower incidence of complications and repeat ablation [757]. A retrospective analysis of a national representative database including 299,152 patients undergoing AF ablation over a 14-year period reported that the use of ICE was significantly increased over the years and led to significant reduction in complication rate, in-hospital mortality and length of hospital stay [759]. A more recent propensity score matched analysis from a nationwide database validated the favorable impact of ICE use on in-hospital mortality, readmission rate and length of stay without increase in healthcare-associated cost [760].

ICE may also be used as an adjunct to AF ablation tools to guide safe and efficient energy delivery. Direct visualization of the LA posterior wall and the adjacent esophagus may guide titration of power and duration at these high-risk areas to reduce the risk of collateral damage during energy delivery [761]. ICE use allows real-time visualization of PV anatomy preventing inadvertent intra-PV RF energy delivery that increases the risk of PV stenosis. ICE is also useful in validating proper PV occlusion during cryoballoon ablation either with color-flow Doppler assessment of PV leakage or with evaluation of microbubble backflow to the LA after saline injection in the internal lumen of the cryoballoon [762–764]. The latter approach is feasible, safe and useful in patients with contraindication to iodinated contrast medium [765]. ICE has been used to measure LA wall thickness in different segments of the PV periphery and accordingly adjust target AI during RF energy delivery [766]. Employment of a tailored AI protocol based on ICE-measured LA wall thickness significantly increased acute procedural success and freedom from AF recurrence rate following PVI in paroxysmal AF patients compared to a FTI protocol [766].

Factors limiting the adoption of ICE use in routine AF ablation workflow include associated increase in procedural cost and the need for a second operator or multitasking by a single operator. A survey of the writing group showed that 47.4% of the members routinely use ICE during AF ablation. Therefore, in practices familiar with ICE, it is reasonable to use ICE to exclude thrombi and enhance procedural safety and efficiency during AF ablation.

7.7 Fluoroless ablation

Radiation exposure during catheter ablation of AF can cause potential delayed complications both in patients and operators that include acute and subacute skin injury, cataract and malignancy [767]. In addition, wearing of lead over time can lead to orthopedic injuries (back pain, disc herniations) in operators and laboratory staff. Traditionally, many steps during an AF catheter ablation require fluoroscopy, including catheter positioning, transeptal puncture, PV angiography and ablation. Studies have shown that the lifetime risk of excess fatal malignancies normalized to 60 minutes of fluoroscopy was 0.07% for female and 0.1% for male patients and that obese patients receive more than twice the effective radiation dose of normal-weight ones during AF ablation procedures [768,769].

Fluoroscopy times were frequently in excess of 60 minutes in the initial years of AF ablation. However, a single-center analysis of over 2300 AF ablations indicated that fluoroscopy times and doses have dramatically decreased over a 12-year period [770]. Indeed, today, fluoroscopy times and doses generally average fewer than 10 minutes and 1000 mGycm^2 for radiofrequency AF ablation procedures predominantly associated with positioning of diagnostic catheters and transeptal puncture [771]. The use of advanced 3D mapping systems has largely obviated the need for fluoroscopy after LA access has been achieved. When considering low dose pulsed fluoroscopy of 2–5-minute duration with collimation [772,773], the effective radiation dose is as low as 1 mSv; equivalent to approximately 4 months background radiation. Whether zero fluoroscopy meaningfully reduces the risk associated with 3-5 minutes of fluoroscopy remains unproven. Electrophysiologists should be familiar with measures that reduce radiation exposure of patients and cath lab personnel which include, but are not limited to, fluoroscopy system customization, workflow adaptations (frame rate, collimation, cine, projection angle, sensitive areas) and shielding measures [774,775].

Nevertheless, in recent years there has been an initiative to perform zero-fluoroscopy AF ablation. A number of studies have demonstrated that fluoroless transeptal puncture and AF ablation can be performed with TEE and/or ICE guidance with similar procedural duration, acute success rate, procedural complication rate, and one-year AF recurrence rate to a minimal fluoroscopy approach [776–784]. In up to 37% of patients in some series, complete fluoroless ablation could not be achieved and minimal rescue fluoroscopy was needed to confirm catheter location and to assess for potential complications [777,779,780].

The increasing use of cryoablation has again resulted in significantly longer fluoroscopy times, when compared with RF ablation, with reported times of approximately 20 minutes [294]. Fluoroless cryoballoon ablation has not been widely adopted both because of the need to identify balloon positioning at the PV ostium and to prove occlusion of the vein with contrast injection. A single observational study of 50 patients found that fluoroless cryoablation is achievable with similar outcomes to a fluoro-guided procedure but this approach is not in wide clinical usage [785]. A survey of the writing group showed that 18.4% of the members routinely perform fluoroless RF ablation.

7.8 Esophageal temperature management

Animal models and clinical series have documented that esophageal perforation develops in the presence of underlying esophageal tissue injury [786,787]. Therefore, because of the rarity of atrioesophageal fistula (AEF) occurrence, endoscopically detected esophageal lesions are considered as a surrogate indicator for potential development of AEF.

Studies evaluating the relationship between measured esophageal heating during RF AF ablation and detection of esophageal ulceration on postprocedural endoscopy have yielded divergent results. In a cohort of patients undergoing their first RF ablation under continuous esophageal temperature monitoring using an infrared thermography system, peak esophageal temperature was predictive of thermal esophageal lesions detected by postablation endoscopy [701]. A retrospective study of 43 patients who underwent high power (50W) short duration (6-7 seconds) ablation found no difference in peak esophageal temperatures measured on the multielectrode S-Cath probe (Circa Scientific, LLC, Englewood, CO), between those patients who developed compared with those who did not develop esophageal abnormalities (including small ulcers, non-bleeding erosions, erythema and esophagitis). However, it was not determined whether the peak temperatures occurred in anatomic relationship to the esophagus. [702]. A meta-analysis of studies reporting prevalence and prevention of endoscopically detected esophageal lesions following AF ablation found a lesion prevalence of 11% and no difference with or without the use of oesophageal temperature monitoring [703].

Since then, a prospective randomized study of 86 patients has found no difference in new endoscopically detected esophageal lesions when comparing ablation with versus without luminal esophageal temperature monitoring (S-Cath, Circa Scientific, LLC, Englewood, CO), with an overall prevalence of 9% [699]. However, ablation was not terminated until the esophageal temperature reached 42°C. Achievement of an esophageal temperature of 42°C was predictive of esophageal lesions raising the possibility that an approach limiting temperature rise to more conservative levels may potentially be effective in preventing esophageal lesion formation. In another prospective RCT, esophageal temperature monitoring using an intraluminal probe (SensiTherm™, FIAB, Firenze, Italy) had no significant impact on the incidence of endoscopically diagnosed esophageal lesions. The total prevalence of esophageal lesions was 10% and peak temperature measured by the thermoprobe did not correlate with the incidence of esophageal lesions [700]. In a consecutive series of 120 patients undergoing high power (50W), short duration RF ablation, the endoscopic detection of ulceration was compared between an initial group with use of a Circa oesophageal temperature probe (maximum allowable temperature of 39°C) and a second group without esophageal temperature monitoring [704]. The overall incidence of new endoscopically detected lesions was only 2.5% with no difference between the groups. The authors used a series of measures to avoid overheating the esophagus such as not performing contiguous lesions over the esophagus and allowing time between lesions for cooling, suggesting that this approach may be most important. Based on the existing evidence, the use of esophageal temperature monitoring during AF ablation has not resulted in reduced risk of endoscopically detected esophageal lesions. Esophageal temperature probes with varied numbers of temperature sensors and varied temporal responsiveness are available for clinical use,[788,789] but the esophagus is broad relative to the spatial resolution of even multisensor temperature probes, and severe esophageal temperature rise may remain undetected when the sensor is >2 cm away from the ablation catheter [790].

Mechanical esophageal deviation has been reported, but its use has been limited to a small number of patients at a limited number of centers [791]. Significant esophageal deviation related trauma has been reported when trying to achieve the extent of mechanical esophageal deviation required to avoid esophageal heating and it remains unclear whether the benefits of esophageal deviation exceed the risks [791].

Esophageal cooling has also been evaluated for reducing the severity of esophageal heating. A systematic review of 4 RCTs found that esophageal cooling reduced the risk of severe esophageal injury during AF catheter ablation [792]. A single-center study randomized 188 patients undergoing RF ablation to either active esophageal cooling at 4°C using the ensoETM device (Attune Medical, USA) or standard practice with a single-sensor temperature probe. Esophageal endoscopy was performed in 120 patients one week following ablation and demonstrated significantly higher occurrence of thermal injury in the control group as compared to those receiving esophageal protection [793]. The use of esophageal cooling has also been shown to improve postprocedural freedom from AF recurrences [794]. The challenge with these studies is that the AEF is such a rare complication that it is unlikely any RCT will show a true difference in that endpoint. In a retrospective analysis of RF ablation cases from 30 US hospitals, the rate of AEF was significantly lower in the group of 14224 patients who received active esophageal cooling as compared to the control cohort of 10962 patients who underwent RF ablation without esophageal cooling but under esophageal temperature monitoring in >90% of cases (0% vs 0.146%) [795].

Additional strategies that may be considered for limiting severe esophageal heating include altering ablation lesion set to avoid ablation of atrial tissue directly overlying the esophagus [796], avoiding higher CF during LA posterior wall ablation [797], and avoiding consecutive ablation lesions at sites with risk of esophageal injury [790]. Use of PFA may also mitigate this risk.

A survey of the writing group showed that 50% of the members routinely use an esophageal temperature probe during catheter ablation procedures to monitor esophageal temperature during energy delivery. Furthermore, as a strategy to avoid severe esophageal heating during RF catheter ablation, 84.2% of the members avoid high CF during energy delivery at the posterior wall, 76.3% reduce ablation power and/or duration at the posterior wall, 63.2% avoid consecutive lesions at sites with risk of esophageal injury, 10.5% use mechanical esophageal deviation and 2.6% esophageal cooling.

Section 8: Ablation Strategies

Ablation strategies	Category of advice	Type of evidence
Pulmonary vein isolation		
Electrical isolation of the pulmonary veins is required during all AF ablation procedures.	Advice TO DO	META 236,238,241,243–245,247,248,253,294,304,574,630,798
Achievement of electrical isolation requires, at a minimum, assessment and demonstration of entrance block into the pulmonary veins.	Advice TO DO	META 236,238,241,243–245,247,248,253,294,304,574,630,798–802
A waiting period (e.g. 20 minutes) following initial PV isolation may be reasonable to monitor for PV reconnection.	Area of uncertainty	RAND 803–810
Administration of adenosine 20 minutes following initial PV isolation, with reablation if PV reconnection occurs, may be reasonable to improve PVI durability.	Area of uncertainty	RAND 804,806–808,811–817
Pace-capture-guided approach following PVI using radiofrequency energy may be reasonable to improve PVI durability.	Area of uncertainty	RAND 818–820
Adjunctive ablation targets beyond PVI		
If linear ablation lesions are deployed, mapping and pacing maneuvers are required to document conduction block.	Advice TO DO	OBS 821–828
If a reproducible focal trigger that initiates AF is identified outside the PV ostia at the time of an AF ablation procedure, ablation of the focal trigger is beneficial.	Advice TO DO	OBS 829–833
Vein of Marshal ethanol infusion is reasonable to facilitate achieving block in the lateral mitral isthmus in patients with mitral annular flutter.	May be appropriate TO DO	OBS 196,834–836

Continued

Ablation strategies	Category of advice	Type of evidence
Ablation of areas of abnormal myocardial tissue identified with voltage mapping during sinus rhythm may be reasonable during persistent AF ablation.	Area of uncertainty	META [837–839]
Vein of Marshal ethanol infusion may be reasonable during persistent AF ablation.	Area of uncertainty	RAND [840–844]
Mapping and ablation of non-PV triggers may be reasonable during persistent AF ablation.	Area of uncertainty	OBS [829–833,845]
Isolation of the left atrial posterior wall may be reasonable during repeat ablation of persistent AF.	Area of uncertainty	META [846–857]
Ablation of MRI-detected atrial delayed enhancement areas is not beneficial during persistent AF ablation.*	Advice NOT TO DO	META [858,859]

*It is reasonable to enroll patients in prospective randomized clinical trials to assess the utility of newer technologies.

8.1 Pulmonary vein isolation

8.1.1 Endpoint of pulmonary vein isolation

Pulmonary vein isolation is the cornerstone of AF ablation and is required during all AF ablation procedures. The endpoint of PVI is achievement of electrical disconnection between the PVs and the LA. This disconnection can be verified by documenting the absence of wavefront propagation from the LA to the PV (entrance block) and/or from the PV to the LA (exit block). PV entrance block is confirmed with disappearance or dissociation of PV potentials recorded usually with a multipolar catheter. PV exit block is verified in the presence of non-conducted spontaneous PV activity (isolated PV ectopics, PV tachycardia or PV AF) or during non-conducted PV pacing. During pacing from the vein to assess PV to LA conduction, it is important to verify local PV capture (usually recorded on a multipolar catheter) and to avoid inadvertent far-field capture of the LAA (when pacing anteriorly in the left PVs) or SVC (when pacing anteriorly in the RSPV) that could erroneously suggest the presence of persistent electrical connection [860,861]. Pacing the posterior and proximal aspect of the PVs is a simple method to avoid far-field capture of these structures. Differential pacing maneuvers, catheter placement in adjacent structures and gradual decrease of pacing output to demonstrate loss of far-field capture have also been proposed to differentiate far-field from near-field capture [861]. Following PVI, it may not be possible to demonstrate PV sleeve capture in up to 20% of patients. This finding correlated with PV entrance block and with adenosine proof isolation [862].

Initial studies of segmental PVI using non-irrigated catheters reported persistent PV to LA conduction in almost 40% of cases in the presence of entrance block, stressing the need to include exit block documentation in the PVI procedural endpoint [863]. However, recent studies of circumferential PVI using contemporary RF ablation technology have indicated that unidirectional exit conduction in the presence of documented entrance block is extremely infrequent [800]. Duytschaever et al. reported a 0.6% prevalence of residual PV–LA conduction after proven entry block [801].

Few studies have also assessed the impact of bidirectional versus unidirectional (entrance only) block on acute PV reconnection rate and long-term arrhythmia outcome after PVI. Chen et al. showed that bidirectional block of the PV–LA junction is associated with reduced intraprocedural reconnection incidence compared to unidirectional block [802]. However, in a retrospective cohort analysis, inability to demonstrate exit block was not associated with increased risk of PV reconnection in redo procedures [800].

The reported very low rates of persistent PV-LA conduction in the presence of entrance block using contemporary ablation technology indicate that this finding alone is an adequate procedural endpoint during PVI. However, exit block documentation may prove useful when verification of entrance block is ambiguous.

8.1.2 Pulmonary vein isolation using radiofrequency energy

8.1.2.1 Electrogram parameters and impedance change. Changes in electrogram morphology have been proposed as indicators of lesion transmurality during RF energy delivery to achieve PVI [597,864–867]. Elimination of the negative component of the atrial unipolar electrogram during PVI procedure following the contiguous "point-by-point" approach was demonstrated to be a marker of transmural lesion creation in both animal and human studies [868,869]. However, electrogram morphology-guided ablation has yielded variable long-term outcomes when compared to ablation guided by contemporary lesion quality indicators (section 8.1.2.2) [870,871]. In a recent study using AI and CLOSE protocol-guided PVI, change in the unipolar electrogram was not found to correlate with RF markers of an adequate lesion. Changes in unipolar electrogram morphology indicative of transmurality are completed within 5 to 7 seconds of energy application, well before completion of AI-guided delivery of high-quality lesion [872,873].

Electrode impedance has long been proposed as an indicator of electrode-tissue contact and lesion size [874]. Insufficient impedance fall (<10 Ω) has been associated with LA to PV conduction recovery [875]. However, the quantitative relationship between real-time contact and impedance drop is complex and varies according to parameters including absolute force and catheter orientation [876–880]. Local impedance monitoring using an ablation catheter with microelectrodes incorporated into the catheter tip (IntellaNav Mifi OI™, Boston Scientific, USA) may improve the utility of impedance monitoring for lesion prediction [881–883]. Further work is needed to refine the precise roles of catheter and generator-derived biophysical parameters to reliably predict lesion formation and the impact on clinical outcome.

8.1.2.2 Lesion quality indicators. The advent of irrigated RF catheters with incorporated CF sensing mechanisms has seen the parallel development of real-time lesion prediction algorithms integrating biophysical data (power, temperature, duration of RF delivery and CF) to provide an estimate of critical lesion characteristics including area, depth and continuity [884]. Early experience of CF and its impact on electrical reconnection after PVI was reported in multiple prospective studies including TOCCATA, EFFICAS I and EFFICAS II, revealing a higher likelihood for reconnection with lower CF and FTI values achieved [885–888]. In the EFFICAS II study, lesion contiguity was associated with more durable PVI [888]. Although important first steps, these FTI-based studies did not incorporate RF power or regional variation in LA wall thickness. In addition to these parameters, catheter stability, contact angle and respiration are important determinants of RF lesion formation [885,889–892].

The AI is a marker of lesion quality that incorporates CF, time and power in a weighted formula. It has provided accurate estimation of lesion depth in animal studies [893] and a strong correlation with impedance drop during LA ablation [894]. Although attractive to standardise workflow, none of the available lesion prediction tools has yet incorporated real-time measurement of atrial wall thickness to guide RF delivery and provide relatively crude estimates of transmurality [895,896].

The CLOSE protocol refers to PV encirclement using CF-sensing catheter targeting an interlesion distance ≤6mm and AI ≥400 at posterior/inferior walls and ≥550 at roof/anterior wall [897]. The proof-of-concept AI targets have been associated with high first-pass isolation rates, and both low rates of acute PV reconnection and atrial tachyarrhthmia recurrence in prospective studies. In a pilot study, the incidence of first pass and adenosine-proof isolation were both 98%, and single-procedure success was 91.3% at one year [566]. Strict application of criteria for contiguity and AI in CLOSE-guided PVI was shown to improve procedural and one-year outcome over conventional CF-guided PVI [898–900]. In the CLOSE to CURE study, PVI using the CLOSE protocol resulted in significant reduction in the atrial tachyarrhthmia burden (documented by implanted cardiac monitor) which was maintained during longer follow-up [563].

A recent randomized study indicated that the optimal interlesion distance in AI-guided ablation may be less than the 5-6 mm incorporated in the CLOSE protocol with an interlesion distance of 3-4mm providing higher first-pass isolation with lower AI targets and shorter procedure duration [901]. Optimal interlesion distance may also vary according to the anatomic region being ablated [902]. High-power short-duration (HPSD) circumferential PVI (50W at all sites) using a standard CLOSE protocol approach has been shown to reduce both total procedural duration and RF time, without increasing the complication rate compared to lower power settings [704,903–907].

The LSI is another proprietary multi-parametric index incorporating time, power, CF and impedance during ablation which also predicts the extent of myocardial tissue lesions. Further studies on the value of quality lesion indications for PVI and ablation beyond the PVs are warranted.

A survey of the writing group showed that 82% of the TF members routinely use lesion quality indicators to guide energy delivery during PVI with RF ablation.

8.1.2.3 Waiting phase. In the non-CF-monitoring ablation era, early detection (within 30 to 60 minutes with or without adenosine challenge) of PV reconnection and adjuvant ablation of PV reconnection sites was reported to reduce AF recurrence rate after PVI [803,811,908–911]. Others demonstrated that immediate ablation of early detected reconnection may not improve the long-term outcomes despite the association of acute PV reconnection with late AF recurrence [807]. More recently, the use of the aforementioned lesion quality prediction tools has called into question the necessity of a waiting phase after initial PVI. It is now known that suboptimal tissue-catheter CF during RF delivery can be associated with spontaneous early reconnection or dormant conduction after PVI [912]. In the CIRCA-DOSE study, using contemporary AF ablation technologies, spontaneous reconnection was elicited in 5.4% of PVs in 16.0% of patients and was significantly more prevalent among patients treated with CF-RF ablation as compared to cryoballoon ablation (22.3% vs 12.8%, $p=0.03$) [808]. While CF catheters were used in this study, AI, interlesion distance and other key features of the CLOSE protocol were not. Interestingly, acute intraprocedural PV reconnection, even when eliminated by adjuvant ablation, was associated with significantly higher arrhythmia recurrence rate only in the cryoablation group and not in the RF group. The implications of these differences remain uncertain and the overall recurrence rates between the two approaches did not differ [808].

Several studies have specifically evaluated whether the incorporation of a waiting period in the procedural workflow improves arrhythmia outcome among patients undergoing radiofrequency PVI using contemporary technology. A multicenter randomized study assessing potential impact of a 30-minute waiting period and/or adenosine triphosphate (ATP) testing after PVI on long-term 3-year outcome demonstrated no improvement in freedom from AF recurrence when using any of these strategies [809]. Another prospective multicenter study randomized consecutive paroxysmal AF patients to AI-guided PVI with versus without a 20-minute waiting period and also found similar rates of arrhythmia recurrence at 1-year follow-up [810].

In the context of these data and taking into consideration that a waiting period considerably prolongs procedure duration without documented improvement in arrhythmia-free outcomes, its incorporation in contemporary procedural workflows is no longer considered necessary. However, the value of a waiting phase after PVI with newly introduced ablation protocols or energy sources, including PFA, merits further assessment.

A survey of the writing group showed that 57% of the TF members employ a waiting period of at least 20 min following initial PVI when performing RF ablation with CF-sensing catheters.

8.1.2.4 Adenosine testing. Intravenous adenosine (or ATP) can be used to unmak dormant conduction across circumferential PV ablation lines [808,812,913,914]. Adenosine dose and the time elapsed since initial PVI are determinants of adenosine-induced PV reconnection [915,916]. Adenosine is given as a rapid bolus followed by saline bolus at a dose required to achieve at least one blocked P wave or a sinus pause > 3 seconds [808,813,917] with 12-18 mg of adenosine being sufficient to achieve atrioventricular block in most patients [813].

Although some data suggest that use of adenosine to identify dormant conduction and guide further ablation may improve outcomes [812], contradictory results have also been reported [815,816]. The routine use of adenosine has not been consistently associated with improved outcomes when compared with a no adenosine strategy [815]. A recent study indicated that patients without spontaneous or adenosine-provoked PV reconnection had better outcomes than those with acute reconnection despite undergoing further ablation. Although the authors suggested that efforts should be directed toward ensuring an ideal ablation lesion at the first attempt to achieve durable PVI, this finding may also point to anatomic variations that render durable isolation more difficult to achieve [808].

In the CIRCA-DOSE study using CF catheters and FTI but not AI or the CLOSE protocol, adenosine-mediated reconnection was observed in 5.7% of PVs in 17.2% of patients and was significantly more common after CF-RF ablation as compared to cryoballoon ablation (31.3% vs 10.2%, p<0.001) [808]. Adenosine-mediated reconnection was associated with higher AF recurrence rates in the cryoballoon-treated patients but not with use of RF when additional ablation was performed to achieve PVI. Studies using the CLOSE protocol have indicated significantly higher rates of adenosine proof isolation compared with a standard approach to PVI (97% vs 82%) and this translated into improved outcomes [567]. Furthermore, a multicenter randomized study evaluating potential benefit derived from employment of ATP testing and/or prolonged waiting periods after PVI, reported no significant differences in freedom from AF recurrence over standard care [809].

Taking into consideration (a) the high rate of adenosine proof PVI with contemporary RF ablation technology including the CLOSE protocol, (b) the lack of documented benefit on long-term outcomes derived from adenosine testing post PVI when contemporary RF technology is used, (c) the questionable value of adjunctive ablation at adenosine-unmasked reconnection sites for long term outcomes and (d) the increment in procedural time and cost when employing adenosine testing, routine use of adenosine testing post PVI is not a requirement.

A survey of the writing group showed that 21.6% of the TF members routinely employ adenosine testing after initial PVI when performing RF ablation with CF sensing catheters.

8.1.2.5 First-pass isolation. First-pass isolation is defined as achievement of PVI upon completion of the encirclement of ipsilateral PVs. First-pass isolation is an indicator of high-quality lesion set with favorable impact on procedural outcome. In a real-world setting, first-pass isolation is highly predictive of 12-month clinical success after CF-guided ablation in paroxysmal AF patients [918], while the absence of first-pass isolation is associated with inferior PVI durability and AF ablation outcomes [919]. CLOSE protocol-guided PVI is associated with higher incidence of first-pass isolation of the PVs and higher single-procedure arrhythmia-free survival at 1 year as compared to conventional CF-guided PVI [566,567,920]. First-pass isolation is associated with reduced likelihood of acute PV reconnection, and therefore whenever achieved, the waiting phase post-PVI may be obviated.

8.1.2.6 Loss of pace capture along PVI. The pace capture approach is an adjunctive technique to evaluate the integrity of a circumferential ablation lesion set [817–819,921–923]. In this method, bipolar pacing at a high output (10 mA, 2 ms pulse width) is attempted along the ablation line [818,819,921]. The sites of local LA capture during sinus rhythm are identified and ablated further until local capture is lost. The pertinent procedural endpoint is PVI with absence of pace capture along the entire circumferential PVI line [818,923].

A RCT including paroxysmal AF patients revealed that the rate of freedom from AF was higher with a pace-guided approach than the conventional method at 12 months as well as after a 5-year follow-up [818]. However, other studies have not reproduced these findings [819].

A survey of the writing group showed that 31.6% of the TF members routinely perform pace capture testing along the ablation line after initial PVI when performing RF ablation.

8.1.2.7 Inducibility of AF after pulmonary vein isolation. Electrophysiological and pharmacological stimulation approaches are sometimes performed to test for inducibility of AF following PVI. Generally, stimulation protocols consist of rapid atrial pacing and/or high-dose isoproterenol infusion, which can vary widely between centers. Inducible AF has been defined as anything from 30 sec to 10 minutes of AF with no clear consensus on this. In the event of inducible AF, several studies have tested the value of additional ablation targeting atrial tissue displaying CFAE and low voltage areas [223]. However, AF meeting the above definitions can be induced in up to 49.5% of patients with no history of clinical AF [924]. Inducibility is dependent on the induction protocol, the number of induction attempts and the definition of inducibility. Contradictory results have been reported **regarding** the prognostic value of noninducibility or change in inducibility status after AF catheter ablation on long-term freedom from recurrent arrhythmias [925–928].

A survey of the writing group showed that 15.8% of the TF members routinely employ AF inducibility after initial PVI when performing RF ablation.

8.1.3 Pulmonary vein isolation with cryoballoon ablation

The cryoballoon is a double layer balloon that is introduced into the LA via a steerable sheath (section 6.2.2.1). Navigation to the individual PV is achieved by a circular mapping catheter advanced through the central catheter lumen and can be used to map PV potentials and thereby document PVI. Exceptionally, a stiff guidewire may be used if balloon positioning is difficult. To completely occlude the PV, the balloon is positioned in alignment with the PV axis and specific maneuvers with the steerable sheath are performed (hockey stick, pull down). The degree of occlusion may be verified by injection of contrast agent through the central lumen. Commonly, a 4 step grading score is used to describe the degree of occlusion [929] although other imaging modalities such as TEE or ICE may be used to reduce fluoroscopy exposure to near zero (section 7.6). [930]. Invasive pressure monitoring through the central lumen has been described as a reliable tool to assess PV occlusion [931]. Very recently, wide band dielectric imaging, a non-fluoroscopic imaging modality, was reported to accurately assess PV occlusion and guide cryoballoon-based PVI [932].

Various dosing strategies have been proposed. In animal experiments, single applications with 120 second, 180 second and 240 second freezing times led to transmural lesions and a high rate of durable PVI [933,934]. In the randomized FIRE and ICE trial, a bonus application was added to the 240 second index application [294]. In a more recent randomized study, no differences in PVI durability nor in clinical outcome were observed after 2x120 second versus 2x240 second cryolesions per PV [293,935]. Other studies showed that an empiric bonus application does not improve outcome, if PVI occurs within 75 seconds after starting the cryoapplication (time to isolation – TTI)[936,937]. Findings from a metaanalysis endorse the use of a single freeze application approach, the latter resulting in shorter procedure times and a lower adverse event rate without compromising efficacy [938].

The optimal freeze duration is subject to controversy. Since side effects at adjacent structures, such as the PN and the esophagus, usually occur beyond 180 seconds, shorter application times may be desirable to maximize safety [939]. However, data from remapping studies indicate a higher rate of durable PVI after single 240 second freeze applications compared to 180 seconds without associated increase in complication rates [940]. Alternatively, individualized dosing strategies are used, where the cryoapplication duration consists of the TTI plus a fixed time interval. In two randomized comparisons of a single 180 second fixed cryoapplication protocol compared to a TTI plus 60-90 seconds guided approach, no differences in freedom from atrial tachyarrhythmias were seen [941,942].

Most commonly, the TTI is used as a marker of adequate lesion formation. In addition, the slope of the temperature curve, the minimal temperature and the thaw time have been reported to be associated with durable PVI [943–945]. On the other hand, achievement of balloon temperatures < -60°C (using the Artic Front device) may prompt termination of energy delivery to avoid collateral damage. In clinical practice, the procedure is usually concluded after the last energy application and documentation of PVI. However, a waiting time of 20 minutes or provocation maneuvers such as adenosine testing to assess LA to PV reconduction have been evaluated (sections 8.1.2.3 and 8.1.2.4).

In patients with variant PV anatomy, e.g. common trunks, PVI using the 28mm cryoballoon may be more challenging. In patients with short common trunks, sequential treatment of the individual branches is usually performed. In patients with long common trunks, a segmental approach with different balloon orientations (superior, inferior) may be applied. In various studies, a similar clinical outcome was reported following cryoballoon ablation in patients with standard PV anatomy as compared to those with common PV ostium [946–948]. However, contradictory results have also been reported [949].

A survey of the writing group showed that 55% of the writing group members employ cryoablation dosing algorithms to modify cryolesion duration based on real-time monitoring of elimination of PV potentials and 55% stop prematurely the deployment of cryolesion after the first 60 sec if elimination of PV potentials has not been achieved. In the absence of real-time recording of PV potentials during cryoballoon ablation, 43.8% of the TF members deliver a cryolesion of 180 sec, 9.4% of 210 sec and 47% of 240 sec duration.

8.2 Adjunctive ablation targets beyond pulmonary vein isolation

8.2.1 Cavotricuspid isthmus

Catheter ablation is the recommended treatment for the management of patients with CTI- dependent AFl due to the high success rates associated with low risk of procedural complications [269]. In the CF catheter ablation era, lesion quality indices can be employed to standardize lesion deployment and procedural workflow during CTI ablation [950–952].

A survey of the writing group shows that 92.1% of the writing group members perform CTI ablation in patients with prior history or intraprocedural induction of CTI-dependent AFl during AF catheter ablation. A suggested approach regarding CTI ablation in patients undergoing AF ablation and pertinent supporting evidence are presented in section 4.4.3.

8.2.2 Linear lesions

The origins of linear ablation for AF lie in the Cox maze procedure and its subsequent iterations (section 12). The most common sites for linear ablation are the LA roof joining the superior aspects of the PV encircling lesion sets, the region of tissue between the anteroinferior aspect of the left PV encirclement and the lateral mitral annulus (the "mitral isthmus") and an anterior line between the anterior mitral valve annulus and either the right PV encirclement (most common) or to the roof line or to the left PV encirclement.

The incremental benefit of linear ablation beyond PVI to prevent AF recurrence has not been demonstrated in prospective RCTs, although it is indicated for the interventional management of macroreentrant AT which may be encountered either during an AF catheter ablation procedure or during follow up [821,822]. Incomplete linear ablation, i.e. delivering lesions in a linear pattern without achieving block, has the potential to be proarrhythmic and create the substrate for left ATs and therefore should be avoided [825,828].

The STAR-AF II study reported no improvement in ablation efficacy with linear ablation (lateral mitral line and roof line) in addition to PVI over PVI alone in patients with persistent AF [574]. It should be noted that in the subgroup of patients allocated to the PVI plus lines group, bidirectional block across both roof and mitral lines was achieved in 74% of patients. In a STAR AF II subanalysis, freedom from arrhythmia recurrence was similar among patients with as compared to those without complete linear block [824]. These data indicate that empirical linear ablation does not confer incremental benefit over PVI alone among persistent AF patients, irrespective of the quality of the deployed linear lesion and the achievement of bidirectional block [824]. Evidence from meta-analyses also support this conclusion [953,954]. Further prospective, multicentre studies of linear ablation with durable bidirectional conduction block may be warranted to establish its role in selected patients with AF [955].

A survey of the writing group showed that 0% of TF members routinely perform empiric linear ablation (other than to isolate the posterior wall) during ablation of paroxysmal AF and 13.2% of TF members when performing ablation of persistent AF.

8.2.3 Complex fractionated atrial electrograms ablation

Complex fractionated atrial electrograms represent low-voltage (0.06-0.25 mV peak-to-peak bipolar amplitude), fractionated, high frequency electrograms recorded during AF and were proposed to represent sites of potential drivers for AF thus serving as a potential target for catheter ablation. This approach was widely adopted for both paroxysmal and persistent AF [956]. However, the pathophysiologic mechanisms underpinning the creation and stability of CFAE and their contribution to AF maintenance were never clarified [957]. Furthermore, there was no universally accepted definition allowing for standardization.

The multi-center prospective STAR AF II study randomized 589 patients with persistent AF to PVI plus linear ablation (259 patients), PVI plus ablation of CFAE (identified by automated software in the mapping system, 263 patients) or PVI alone (67 patients) and demonstrated no benefit of either of these approaches over PVI alone [574]. The CHASE AF study randomized 205 patients to PVI alone or PVI plus CFAE ablation. The latter group also underwent linear ablation if atrial macroreentry occurred. There was no significant improvement in arrhythmia-free survival with addition of CFAE ablation [958]. A meta-analysis comprising 1415 patients from 13 studies concluded that despite acceptable procedural safety, CFAE ablation did not improve arrhythmia-free survival in paroxysmal, persistent or in long-lasting persistent AF [959]. In a recent, large meta-regression and trial sequential analysis, CFAE ablation was shown to be ineffective as an adjunctive strategy in persistent AF ablation and further study of this ablation approach was considered futile [953]. The enthusiasm for CFAE ablation to treat AF has therefore waned and should be avoided in most cases to avoid proarrhythmic lesions.

8.2.4 Stepwise approach to AF ablation

The stepwise approach, which incorporated both linear ablation and defragmentation to target termination of persistent AF either directly or via intermediate AT has gradually fallen out of favor. The procedure demonstrated early promise in patients with persistent and long-standing persistent AF particularly when achievement of sinus rhythm was used as an endpoint [242,960]. However, subsequent studies have not reproduced these initial results reporting poor 5-year clinical outcomes (20.1% single procedure and 55.9% multiple procedure arrhythmia-free survival at 5-years) [961]. Recurrence rates of atrial tachyarrhythmias are high, reflecting the proarrhythmic effect of either incomplete linear ablation and/or iatrogenic islands of atrial scar caused by CFAE ablation which may serve as anchors or isthmus borders for macro- and localised reentry [961]. In a recent metaanalysis, a stepwise strategy for persistent AF ablation had no significant impact on freedom from atrial arrhythmia recurrences [953].

8.2.5 Left atrial posterior wall isolation

The left atrial posterior wall (LAPW) shares a common embryological origin with the PVs and shares some of the PV arrhythmogenic properties [962,963]. Extensive parasympathetic neural plexi located at the LAPW and extending to the PV antrum may also contribute to the initiation and maintenance of AF [207,208,964].Therefore, electrical isolation of the LAPW as an adjunct to PVI seems to be a reasonable approach to increase the success rate of catheter ablation in AF patients.

Several catheter ablation techniques have been proposed for achievement of PWI including: (a) posterior wall box isolation (circumferential PVI with deployment of roof and inferior lines connecting the superior and inferior margins of PV rings respectively), (b) single ring isolation (en bloc encirclement of PVs and posterior wall)[965,966], (c) posterior wall debulking (extensive focal ablation of the posterior wall without linear lesion deployment) [846]. Cryoballoon ablation has also been used for PWI, although adjuvant RF ablation may be needed in up to 45.5% of patients [967–970]. Posterior wall ablation is also feasible with a pentaspline PFA catheter [666,971,972]. In the PersAFOne study, PFA ablation under ICE guidance resulted in low voltage posterior wall homogeneity with first pass in all 24 patients without primary safety events. Interestingly, invasive remapping 2-3 months post ablation demonstrated no evidence of conduction through the posterior wall in 100% of patients and partial voltage recovery of the PW ablated area in 3 out of 21 patients [666].

Prior trials investigating PWI plus PVI in comparison with PVI alone in patients with AF have yielded conflicting results (Table 8). Although smaller non-randomized, retrospective trials showed promising results, more recent large prospective RCTs have demonstrated negative results. Yu et al randomized 113 patients to PVI alone or PVI plus posterior LA isolation and an anterior line and demonstrated no improvement in outcome [973]. The POBI-AF trial randomized 217 patients with persistent AF to PVI alone or PVI plus posterior wall box isolation, the latter defined as voltage abatement <0.1mV, bidirectional block of the roof line and documentation of both entrance and exit block. Sixty-nine percent of the posterior LA isolation group also underwent an anterior line. Using intermittent Holter monitoring, the reported freedom from any documented AF without AADs was similar in the PVI alone and the PVI plus PWI groups [847]. In the recent CAPLA study, 338 patients with symptomatic persistent AF undergoing first-time RF ablation were randomized to either PVI (wide antral circumferential) plus PWI (roof and floor line deployment plus ablation of earliest electrograms within the box if needed) or PVI alone. CF sensing catheters were used with specific lesion quality targets and the follow-up monitoring was intense (twice daily ECG transmissions). There was no difference in the primary study endpoint with 53.3% freedom from AF at 12 months in the PVI group as compared to 54.1% in the PVI+PWI group [848].

One explanation for the lack of incremental benefit from catheter ablation of the LAPW could be the inability to achieve durable electrical isolation. Pertinent challenges stem from (a) the significant variation in thickness of the septopulmonary bundle that is the dominant structure in the LAPW, (b) difficulties in achieving transmural lesion at the LAPW roof due to insulation of the epicardial muscular bundle by fat interposition [179], (c) a tendency to lower the power and duration of energy delivery during LAPW ablation to prevent thermal injury to the neighboring esophagus [974,975]. In fact, LAPW reconnection rates have been reported to be as high as 40-100%, with predominantly posterior location, while an association has been shown between LAPW reconnection and elevated esophageal temperature during the index procedure [975–977]. Alternate explanations for lack of demonstrated benefit from PWI include: (a) PVI alone using a wide antral isolation strategy already encompasses much of the LAPW, potentially leaving little additional benefit from roof and inferior lines; (b) the contribution of the posterior LA to persistent AF mechanism is not universal and a "one-size fits all" approach may be ineffective, or (c) survival of epicardial LAPW tissue. This allows the possibility that posterior LA isolation may have a role in a specific group of persistent AF patients. In a recent sub-group analysis of the CAPLA study, it was found that patients with short cycle length posterior LA activity did derive a benefit from PWI, indicating that this may be a determinant of which patients will have improved outcomes with this additional step [978].

Hybrid ablation has also been used to target LAPW as part of an ablation strategy in patients with persistent and long-standing persistent AF (section 12.3.3.2.)

A survey of the writing group showed that 15.8% of the TF members perform PWI during first-time and 26.3% when performing redo ablation of paroxysmal AF. Furthermore, 31.6% of the TF members perform PWI during first-time and 65.8% when performing redo ablation of persistent AF.

8.2.6 Substrate ablation

A range of conditions has been demonstrated to promote the development of abnormal atrial substrate [981]. These include classically recognised factors associated with AF such as hypertension, HF [982], diabetes and advanced age [983]. Recently, other conditions have been shown to drive atrial substrate development such as obesity [109,984], sleep disordered breathing [362], excess alcohol intake [468,985] and prolonged high intensity training in certain athletic sports [986]. The pathophysiologic mechanisms underlying areas of abnormal electrical substrate includes include regional fibrosis, loss of cellular coupling due to loss of connexin, inflammation and adipocyte infiltration into tissues [108,526]. These changes promote AF initiation and maintenance (Section 2.4 – Figure 1).

Electroanatomical mapping and cardiac MRI have both been utilized to define the atrial substrate, albeit using quite different surrogates of atrial fibrosis – bipolar voltage and late gadolinium signal intensity respectively. Ablation guided by electroanatomical voltage mapping is a patient-tailored approach targeting low voltage areas, either by encirclement leading to isolation or direct ablation of the entire low voltage area [839,987]. Endpoints of this approach include local voltage reduction, elimination of fractionated electrograms and regional isolation. Preliminary observational studies suggested the potential for favorable outcome[846,988–990]. Several randomized trials have evaluated whether adjuvant ablation of low voltage areas may provide incremental benefit on rhythm outcome among paroxysmal or persistent AF patients. In the VOLCANO trial including 398 patients with paroxysmal AF and the STABLER-SR II trial including 300 patients with persistent AF, low voltage area ablation in addition to PVI did not improve arrhythmia-free survival [837,991]. However, the recent STABLE-SR-III trial randomized 438 older patients with paroxysmal AF to PVI plus low-voltage area ablation or PVI alone and showed a significant incremental benefit derived by low-voltage area ablation in this patient population [992]. In all trials, left atrial voltage mapping was performed during sinus rhythm with a low-voltage cutoff < 0.5mV.

A recent prospective RCT presented evidence supporting the concept of substrate ablation in persistent AF patients [838]. The ERASE AF study enrolled 324 patients who were randomized to PVI only (163 patients) or PVI plus substrate modification (161 patients). Substrate modification was only performed in the subset of patients (34%) found to have low voltage regions (voltage threshold 0.5mV) during sinus rhythm mapping. The primary study end point (first recurrence

Table 8 Clinical trials comparing left atrial posterior wall isolation plus pulmonary vein isolation (PVI) versus PVI alone in atrial fibrillation patients undergoing catheter ablation

Study	Study design	Number of patients	Ablation strategy	Outcome
Wong et al. 2023 [979]	Randomized controlled trial	67 persistent AF patients (PVI+PWI: 39, PVI: 28)	PVI vs PVI+PWI PWI: Box with additional ablation lesions within the box as needed.	No difference in atrial arrhythmia recurrence rate between PVI+PWI and PVI only groups at a median follow-up of 12.4±3.0 months (25.6% vs 28.6%; p=0.79)
Kistler et al. 2023 [848]	Randomized controlled trial	338 symptomatic persistent AF patients (first ablation) (PVI+PWI: 170, PVI: 168)	PVI (wide antral circumferential) plus PWI (roof and floor line deployment plus ablation of earliest electrograms within the box if needed) or PVI alone	No difference in the primary study endpoint at 12 months, with 52.4% freedom from recurrent atrial arrhythmia after a single ablation procedure without AADs in the PVI+PWI group as compared to 53.6% in the PVI group (p=0.98).
Jiang X et al. 2022 [849]	Pooled analysis of 26 studies (9 RCTs)	3,287 paroxysmal and persistent AF patients receiving PVI+PWI	PWI: Both box and non-box ablation lesions	In persistent AF, adjunctive PWI was associated with substantially lower recurrence of all atrial arrhythmias (risk ratio: 0.74; 95% CI: 0.62-0.90, p<0.001) and AF (risk ratio: 0.67; 95% CI: 0.50-0.91, p=0.01), particularly when only randomized data were examined. PVI+ PWI using a non-box lesion was associated with significantly less recurrence of AF (OR: 0.30; 95% CI: 0.22-0.41).
Jankelson et al. 2022 [980]	Consecutive series	321 paroxysmal AF patients (PVI: 214; PVI+PWI: 107)	PVI vs PVI+PWI PWI consisted of a roof line connecting the left and right superior PVs along with a low posterior line connecting the inferior PVs.	Recurrence at 1 year: PVI group: 14% vs PVI+PWI group: 15% (p=0.96)
Ahn J et al. 2022 [970]	Randomized controlled trial	100 persistent AF patients undergoing first ablation (PVI only: 50 vs PVI+ PWI: 50) with cryoballoon	PWI: additional cryoballoon ablation lesions at 9-13 different locations on the LA posterior wall.	Atrial tachyarrhythmia recurrence during a mean follow-up of 457.9 ± 61.8 days: PVI only: 46% PVI+PWI: 24%, p =0.035
Sirico G et al. 2021 [850]	Consecutive series	73 persistent and long-standing persistent AF patients receiving PWI +PVI	PWI: roofline joining the two superior PVs and inferior line linking the 2 inferior PVs.	PWI + PVI was able to reduce the mean atrial arrythmic burden by more than 50% compared with preablation, reporting very low levels (≤ 5%) over 2 years

(*continued*)

Table 8 Continued

Study	Study design	Number of patients	Ablation strategy	Outcome
Tokioka S et al. 2021 [851]	Consecutive series	181 persistent AF patients (PVI only: 91 vs PVI+ PWI: 90)	PWI: PentaRay was placed at the posterior wall to record electrical potentials. Endpoint was defined as the absence of electrical activity and inability to capture from within the posterior wall during pacing by PentaRay with 5-mA output from the posterior LA	At a median follow-up of 19 months: AF recurrence: PVI only: 47.3% PVI + PWI: 31.1% (p=0.35) Persistent AF recurrence: PVI only: 20.9% PVI + PWI: 5.6% (p=0.002)
Pothineni et al. 2021 [852]	Consecutive series	196 paroxysmal (61%) and persistent (39%) AF patients undergoing repeat ablation (PVRI: 93; PWI±PVRI: 103)	PVRI vs PWI±PVRI PWI consisted of linear lesions across the LA roof and floor connecting the previous circumferential lesion sets that were used for left and right PVI, with additional lesions at sites of earliest activation within the "box" if needed.	Freedom from atrial arrhythmias off AADs at 1 year: PVRI: 69.9% vs PWI±PVRI: 43.7% (p=0.5)
Salih et al. 2020 [853]	Meta-analysis of 6 studies	1.334 persistent AF patients (PVI: 663; PVI+PWI: 671)	PVI vs PVI+PWI	At 21.6 ± 13 months: AF recurrence rate: PVI only: 29.1% PVI+PWI: 19.8%, risk ratio: 0.64; 95% CI: 0.42-0.97, p<0.04 Atrial arrhythmia recurrence rate: PVI only: 41.1% PVI+PWI: 30.8%, risk ratio: 0.75; 95% CI: 0.60-0.94, p<0.01
Sutter J S et al. 2020 [854]	Retrospective study	558 persistent AF patients undergoing initial and repeat ablation (PVI: 255, PVI+PWI: 78, PVI+ lines: 225)	PVI vs PVI+PWI vs PVI+ lines PWI: Linear ablation along the LA roof to connect left and right superior PVs and linear ablation along the LA floor to connect inferior PVs. Lines: one or more of the following: mitral isthmus, LA roof or cavotricuspid isthmus line	Sinus rhythm at 6 months: PVI: 73.9% vs PVI+ lines: 72.2% vs PVI+ PWI: 57.7%
Yamaji H et al. 2020 [855]	Randomized controlled trial	Persistent AF patients without LA low voltage area EP-test subgroup: 57 (+PWI: 24; -PWI: 33)	+PWI: PVI+PWI+SVCI+CTIA -PWI: PVI+SVCI+CTIA PWI: roof line joining the two superior PVs and inferior line connecting the two inferior PVs.	AF/AT recurrence at median 62.7 weeks: +PWI: 25% vs –PWI: 15% (p=0.311)

Lee J M et al. 2019 [847]	Randomized controlled trial	207 persistent AF patients (PVI: 105; PVI+PWI: 102)	PVI vs PVI+ PWI PWI: roof line joining the two superior PVs and inferior line connecting the two inferior PVs with touch-up ablation at the PW if needed to achieve exit block (additional anterior line at the physician's discretion).	Freedom from atrial arrhythmia without AAD at 1 year: PVI: 50.5% vs PVI+PWI: 55.9% (p=0.522)
McLellan et al. 2017 [856]	Consecutive series	161 persistent AF patients undergoing circumferential PVI followed by PWI (No adenosine challenge: 107, adenosine challenge: 54) *Adenosine challenge to assess dormant conduction in the PVs and PW	PWI: roof and inferior wall lines with the endpoint of bidirectional block	Adenosine-induced reconnection of the PW was demonstrated in 17%. Freedom from recurrent atrial arrhythmia at 19±8 months: adenosine challenge: 65% vs no adenosine challenge: 40% (p<0.01)
Bai R et al. 2016 [846]	Prospective non-randomized trial	52 persistent AF patients (PVI only: 20; PVI+PWI: 32) All patients, underwent a second procedure 3 months after the first procedure.	PWI: PVI was extended to the CS and to the left side of the interatrial septum, along with extensive ablations on the LAPW. At 3 months, EP study was performed in all patients to confirm durability of the PWI and PVI.	Freedom from atrial arrhythmia without AADs at 1-, 2- and 3-year follow-up: PVI: 20%, 15% and 10% respectively PVI+PWI: 65%, 50% and 40% respectively, p<0.001
Kim J S et al. 2015 [857]	Randomized controlled trial	120 persistent AF patients (PVI+lines: 60 vs PVI+lines+PWI: 60)	Roof, anterior perimitral and CTI lines with conduction block were performed in all patients. PWI: additional posterior inferior line connecting inferior PVs.	Recurrence at 1 year: PVI+lines: 36.7% vs PVI+lines+PWI: 16.7%, p=0.02

AAD = antiarrhythmic drug; AF = atrial fibrillation; CI = confidence interval; CS = coronary sinus; CTIA = cavotricuspid isthmus ablation; EP = electrophysiological; LA = left atrium; LAPW = left atrial posterior wall; OR = odds ratio; PV = pulmonary vein; PVI = pulmonary vein isolation; PVRI = pulmonary vein reisolation; PWI = posterior wall isolation; RCTs = randomized controlled trials; SVCI = superior vena cava isolation.

of an atrial arrhythmia > 30 seconds after a single procedure) was reached in 50% of PVI only patients and 35% of PVI plus substrate modification group at 12 months (HR=0.62, 95% CI=0.43-0.88, p=0.006) [838].

Despite recent encouraging results, methodologic challenges inherent to the strategy of low voltage-guided substrate modification remain. Voltage measurements are not only dependent on rhythm status (AF vs sinus rhythm), size and configuration of the recording electrodes and catheter-tissue contact but can also vary up to 3-fold according to atrial rate and wavefront directionality [993]. Furthermore, voltage parameters indicative of abnormal substrate lack objective definition and low voltage cutoffs vary considerably among different investigators. A one size fits all voltage cutoff does not consider regional variations in atrial wall thickness, nor again the nature of the recording electrodes. Ultimately, identification of substrate may require a more sophisticated analysis incorporating not only voltage but also electrogram morphology and possibly measures of regional atrial conduction.

Cardiac MRI-LGE has been used to identify and localize cardiac fibrotic areas in a variety of cardiac diseases, including AF [92,105,520]. Attempts to "calibrate" electroanatomic voltage mapping using MRI-LGE have reported LA voltages between 0.2-0.45mV as demarcating LA scar [994]. Correlations of variable strength between LA voltage mapping and atrial histology have been reported [105,520,995]. The DECAAF study reported that the severity of MRI-defined atrial fibrosis was a predictor of AF recurrence following AF catheter ablation, thereby supporting a role for MRI-LGE in the preprocedural evaluation of atrial substrate (section 5.2.1.4). This requires considerable experience of atrial LGE imaging, specific imaging sequences and access to a reproducible image processing workflow which to date has limited the widespread uptake of this technique.

In the ALICIA trial, 155 symptomatic, drug-refractory AF patients (54% paroxysmal AF) undergoing first or repeat ablation were randomized to either PVI or PVI plus MRI-guided ablation of fibrotic areas by either homogenization or isolation [858]. Fibrotic areas outside the PV antra were identified in only half of the patients, and their ablation did not reduce arrhythmia recurrence rate at 1 year of follow-up [858]. In the recent much larger DECAAF-II trial, 843 persistent AF patients were randomized to either MRI-guided fibrosis ablation plus PVI or PVI alone. The primary composite of atrial arrhythmia recurrence or repeat ablation did not differ between the two groups after a median follow-up period of 273 days, (43.0% vs 46.1%; p=0.63). Furthermore, there was a significantly higher occurrence of the primary safety composite outcome in the fibrosis-guided ablation plus PVI group (2.2% vs 0%, p=0.001), largely driven by higher ischemic stroke events [859]. Therefore, one should avoid additional ablation based on MRI-detected fibrosis pending development of better MRI resolution and future studies.

A survey of the writing group showed that 0% of the TF members perform ablation of MRI- or voltage mapping-detected abnormal atrial myocardial areas during first-time and 18.4% during redo ablation of paroxysmal AF. Furthermore, 13.2% of the TF members perform ablation of MRI- or voltage mapping-detected abnormal atrial myocardial areas during first-time and 31.6% during redo ablation of persistent AF.

8.2.7 Vein of Marshall ablation

The VoM is an embryological remnant of the left upper caval system that possesses arrhythmogenic potential and has been proposed as a target during AF catheter ablation [996](Section 3.5). Ethanol infusion into the VoM has been proposed as an adjunctive ablation strategy in persistent AF, acting not only by eliminating this arrhythmogenic structure but also providing collateral benefits including autonomic modulation and partial ablation of LA areas that are routinely targeted during circumferential isolation of left PVs and lateral mitral isthmus line deployment [835]. In a large cohort of consecutive patients treated with ethanol infusion in the VoM, the reported feasibility was almost 90% during the first attempt, with previous CS ablation reported as the only predictor of failure, while the reported complication rate was 2.0% [997].

The VENUS trial was a prospective RCT that evaluated potential incremental benefit derived by VoM ethanol infusion in addition to an extensive ablation procedure containing many components of the stepwise approach. In this study, the majority of patients received mitral isthmus ablation, LAPW isolation and CFAE ablation. The study demonstrated that adjunctive VoM ethanol infusion significantly improved the off-AAD arrhythmia-free survival (49.2% vs 38%, p=0.04) [840]. Although these data are encouraging, the standard ablation procedure in this study was extensive, non-standardised, with significant differences between the compared groups and included, at the operator's discretion, empiric linear ablation, CFAE ablation and LAPW isolation most frequently in combination. In a VENUS substudy, the favorable impact of VoM ethanol infusion was potentiated when performed in high-volume centers and when perimitral block was achieved [843]. The benefit of VoM ethanol infusion when added to PVI has yet to be shown to improve outcomes over PVI alone.

In a recently published randomized trial, VoM ethanol infusion as the first step in mitral isthmus linear ablation was shown to significantly reduce the number of RF applications needed to achieve mitral isthmus block [836]. Pambrun et al. recently reported results of the "Marshall-PLAN" procedure for persistent AF. This procedure adds VoM ethanol infusion to a lesion set including PVI, linear lesions (posterior mitral line, roof line and CTI line), LA ridge, "saddle" (between the LSPV and the LAA), and extensive CS ablation [193]. Implementation of this ablation strategy in an observational cohort of 75 consecutive patients with persistent AF (duration 9±11 months) resulted in a 72% freedom from arrhythmia recurrence at 12 months off-AAD after a single procedure [844]. A randomized trial comparing the Marshall-PLAN ablation approach to PVI only in persistent AF patients is ongoing (NCT 04681872).

A survey of the writing group shows that 5.3% of the TF members employ VoM ethanol infusion when performing first-time persistent AF ablation and 26.3% during redo ablation of persistent AF.

8.2.8 Ablation of non-pulmonary vein triggers

PVI is a highly effective procedure in patients with paroxysmal AF, in whom spontaneous PV firing is frequently the only trigger for AF paroxysms [998]. However, recurrence of arrhythmia has been reported in up to 20% of paroxysmal AF patients in the presence of isolated PVs [999,1000]. These observations have driven approaches toward identification and targeting of non-PV triggers. Non-PV triggers have been described originating from specific anatomic regions including the LAPW, SVC, CS, VoM, crista terminalis, interatrial septum, LAA [1001]. In addition, persistent left SVC has also been reported as a site of AF triggers [1002].

Electrical LAA isolation has been proposed as a strategy to eliminate potential LAA triggers with varying reported success. In the prospective, randomized BELIEF trial, 173 patients with long-standing persistent AF were randomized to either empirical endocardial LAA electrical isolation plus extensive ablation (PVI plus ablation of PW, part of the LA septum, non-PV triggers and SVC) versus extensive ablation alone at the index procedure. At 12-month follow-up, patients with LAA isolation had a higher freedom from atrial arrhythmias [1003]. A large propensity score-matched study and a metaanalysis of nine studies in non-paroxysmal AF patients undergoing catheter ablation concluded that LAA isolation significantly increased freedom from all atrial arrhythmia recurrence without increased risk of acute procedural complications [1004,1005]. In a meta-analysis of 7 studies assessing impact of LAA isolation on AF recurrence utilizing various approaches, including ablation, surgery and ligation by Lariat, LAA isolation was shown to be associated with a significantly lower rate of AF/AT recurrence [1006]. The authors concluded that further randomized studies were nevertheless required to confirm safety and efficacy of this approach. However, the multicenter prospective randomized aMAZE trial in 610 patients with symptomatic persistent and long-standing persistent AF, did not show a benefit in arrhythmia-free survival with addition of LAA ligation with the Lariat epicardial suture device on top of PVI (404 patients) versus PVI alone (206 patients) [1007].

Several studies have reported a high incidence of LAA thrombus formation and increased risk of thromboembolism after endocardial LAA isolation using RF energy despite adequate OAC therapy [1008–1010]. Intracardiac thrombus formation is identified in one fifth of patients undergoing wide area LAA isolation and the respective rate of stroke/TIA is 6-9.8% [1008,1009]. Interventional LAA occlusion may be protective against thromboembolism in this clinical setting [1008]. In a non-randomized study of 166 patients with durable LAA isolation, interventional LAA occlusion was associated with significant reduction in thromboembolic complications as compared to OAC therapy [1011]. Randomized trials are needed to document the efficacy of this preventive approach. Considering the modest evidence supporting the value of LAA isolation as a standalone adjunct to PVI in persistent AF patients and the associated increased risk of thrombus formation and thromboembolism, this ablation strategy may be only justified during redo ablation procedures in persistent AF patients and after informing the patient for the need of permanent thromboprophylaxis or mechanical closure of the LAA.

Routine identification and ablation of non-PV triggers is limited by the absence of standardized induction protocols, differences in trigger definition and paucity of prospective randomized studies indicating a benefit of this approach either in denovo or repeat procedures. Induction protocols have used varying amounts of isoprenaline up to 20mcg/minute or higher and burst pacing to induce AF followed by cardioversion to initiate trigger activity. Variable trigger definitions have been proposed, including triggers resulting in AF paroxysms or repetitive focal activity even isolated atrial ectopics. In a randomized study of persistent AF patients, empiric ablation of common non-PV trigger sites in addition to PVI did not improve outcome compared to PVI combined with ablation of only documented non-PV triggers [845]. Prevalence of triggered ectopics has varied widely according to population and technique used [1012–1014]. More data are needed to establish a consensus on the characterization and ablation of non-PV triggers.

A survey of the writing group showed that 31.6% of the writing group members employ mapping and ablation of non-PV triggers during first-time and 68.4% during redo ablation of paroxysmal AF, while 34.2% during initial ablation of persistent AF and 73% during redo ablation of persistent AF. Furthermore, 83.8% of writing group members employ mapping and ablation of non-PV triggers in redo AF ablation procedures when all PVs remain isolated. In addition, 0% of the TF members perform LAA isolation during first-time persistent AF ablation and 5.3% when performing redo persistent AF ablation.

8.2.9 Ganglionated plexi ablation

The cardiac ANS plays an important role in the initiation and maintenance of AF [123,126,208,210,211,1015–1022]. The GP, containing the cardiac parasympathetic and sympathetic ganglia, are located on the epicardial aspect of the PV antra and are frequently ablated during PVI (section 3.7). Their functional localization is possible with high-frequency stimulation, (cycle length 50 ms, 12–15 V, 10ms pulse width), manifesting as sinus bradycardia or AV nodal conduction delay or block [1016,1022]. However, the sensitivity of endocardial high-frequency stimulation to identify GP sites is not optimal [210].

Ganglionated plexi ablation plus PVI has been variably reported to improve the outcome following AF ablation in some randomized clinical trials [1023,1024]. However, in the prospective randomized AFACT study, adjunctive epicardial GP ablation during thoracoscopic AF surgery did not improve freedom from AF recurrence but was associated with an increased risk of major complications [1025]. Due to the inconsistent RCT outcomes and the technical challenges associated with high-frequency stimulation, the level of evidence in support of this approach is modest.

A survey of the writing group showed that 2.7% of the TF members perform GP ablation during first-time ablation of paroxysmal or persistent AF ablation and 0% during redo ablation of paroxysmal or persistent AF.

Section 9. Postprocedural Management

Postprocedural management	Category of advice	Type of evidence
Systemic anticoagulation is beneficial for at least 2 months following catheter ablation of AF.	Advice TO DO	OPN
Postprocedural initiation of DOACs rather than VKAs is beneficial in patients not previously on anticoagulation undergoing AF ablation.	Advice TO DO	META [1026–1030]
Adherence to AF anticoagulation guidelines is beneficial for patients who have undergone an AF ablation procedure, regardless of the apparent success or failure of the procedure.	Advice TO DO	OPN
Administration of antiarrhythmic drugs following AF catheter ablation is reasonable in selected patients to prevent early postablation AF recurrence.	May be appropriate TO DO	META [1031–1038]
In patients who have not been anticoagulated prior to AF catheter ablation or with interrupted anticoagulation prior to ablation, administration of a DOAC 3 to 5 hours after achievement of hemostasis is reasonable.	May be appropriate TO DO	OPN
A same day discharge protocol is reasonable in selected patients undergoing AF ablation.	May be appropriate TO DO	OBS [1039–1047]
Administration of proton pump inhibitors for 2-4 weeks following catheter ablation may be reasonable to reduce the risk of esophageal lesions.	Area of uncertainty	OBS [1048–1050]
Discontinuation of anticoagulation may be reasonable 12 months following catheter ablation after shared decision making in patients with CHA_2DS_2VASc score 1 in males and 2 in females in the absence of clinical symptoms or documented AF recurrence when patients and their physician are committed to long-term rhythm monitoring.*	Area of uncertainty	OPN
Patients in whom discontinuation of anticoagulation is being considered based on patient values and preferences should undergo continuous or frequent ECG monitoring to screen for AF recurrence.	Area of uncertainty	OPN

*Daily pulse or ECG monitoring, ECG-based wearables or invasive rhythm monitoring.

9.1 Sheath removal – hemostasis achievement

After completion of the ablation procedure, ensuring adequate hemostasis is of primary importance to reduce the risk of vascular complications. Sheaths can be removed after waning of heparin's anticoagulant effect or while the patient is on full anticoagulation. In the former case, sheaths should be removed when the ACT is less than 200-250 sec or after reversal of heparin effect with protamine infusion. Two RCTs and a recent metaanalysis of five studies have consistently shown that the use of protamine after catheter ablation significantly expedites vascular hemostasis and patient ambulation by about 3 hours without associated increase in vascular or thromboembolic complications [1051–1053]. This favorable effect should be weighed against a 1.2% risk of adverse reaction to protamine often presented with profound hypotension [1054]. A survey of the writing group showed that 57.9% of the writing group routinely use protamine to reverse heparin anticoagulation effect after completion of AF ablation.

A figure-of-eight suture technique (with the use of either a knot or a three-way stopcock to secure suture in place) has been proposed for achieving hemostasis after catheter ablation obviating the need for manual compression of the puncture site [1055–1057]. This technique significantly reduces the time required for hemostasis and patient's postprocedure time in the electrophysiological lab, without associated increase in bleeding complications as compared to manual compression [1056,1057]. Closure of venous access sites with specialized devices also shortens time to postablation hemostasis and patient ambulation and reduces the need for pain medications, without significant difference in the incidence of minor or major access site complications [1058].

9.2 Duration of hospitalization - same day discharge

Catheter ablation for AF has typically been performed as an in-patient procedure with at least one overnight stay. Given the increasing demand for AF ablation, same day discharge protocols have increasingly been adopted to minimize health care resource utilization [1039–1041]. Avoiding overnight hospital stay increases patient satisfaction and may also have benefits for the patients such as reduced risk of infection. Metaanalyses of observational studies have shown that same day discharge was successful in >80% of the planned cases and the reported safety outcomes were favorable. No differences in 30-day complications or 30-day readmissions were identified between the patients with same-day discharge compared to those with overnight hospital stay [1042,1043,1046]. Moderate quality evidence from a recent randomized trial supports the safety of same day discharge after cryoballoon AF ablation [1044]. Feasibility and safety of same day discharge has been reported even when implemented as default management strategy in consecutive patient cohorts [1045]. Overall, same day discharge after AF ablation appears to be a safe strategy in selected patients provided that appropriate institutional protocols and patient pathways are established to identify suitable patients and ensure adequate follow-up [1047]. Eligibility criteria for same day discharge include, but are not limited to, uncomplicated catheter ablation, at least 3 to 6 hours of postprocedural monitoring, achievement of complete hemostasis, well-tolerated ambulation, normal vitals signs at discharge, absence of symptoms or concerning comorbidities [1039]. A standardised same day discharge protocol based on specific eligibility criteria has been described and its safety has been validated in a large multicenter prospective registry [1046].

A survey of the writing group showed that 23.7% of the members implement a default strategy of same day discharge, while 57.9% employ a same day discharge management protocol in selected patients following AF catheter ablation.

9.3 Postprocedural pharmacological management

9.3.1 Anticoagulants

9.3.1.1 Early postprocedural (2 months). Anticoagulation is recommended for at least 2 months following catheter ablation for all patients regardless of CHA_2DS_2-VASc score in prior guidelines and consensus documents [5,1059]. This is due to endothelial damage, an inflammatory state and potential stunning of atrial myocardium following ablation and/or cardioversion. In patients not previously on anticoagulation, initiation of DOACs rather than VKA is preferred postablation because of the immediate effect that does not require bridging with UFH or LMWH [1026–1030]. In patients who had not been anticoagulated or who did not take their last DOAC dose prior to the procedure, administration of the DOAC 3-5h after sheath removal is advisable, provided there is no evidence of mechanical complications. In patients who require lifelong anticoagulation with VKA (eg mechanical heart valve or rheumatic heart disease), it is recommended that ablation be performed on uninterrupted VKA [299].

9.3.1.2 Late postprocedural (more than 2 months). The management of anticoagulation beyond the early postprocedural period after AF ablation remains controversial. Prior guidelines have recommended continuing anticoagulation based on the patient's stroke risk profile rather than the presumed success or failure of the ablation [5,1059].

In the absence of high-quality evidence, long-term anticoagulation after AF ablation in patients with CHA_2DS_2-VASc score $\geq$2 for men or $\geq$3 for women is considered beneficial for a number of reasons: (1) recurrences of AF are common both early and late following AF ablation; (2) asymptomatic AF is common, and is even more common following than prior to AF ablation [1060]; (3) there have been no large, randomized prospective trials that have assessed the safety of discontinuing anticoagulation in this patient population; (4) while registry data suggested a lower risk for stroke in patients undergoing AF ablation compared to matched AF controls [1061,1062], the largest prospective randomized trial on AF ablation, the landmark CABANA trial, failed to show a reduction in the risk of subsequent stroke in patients undergoing ablation [1063]. This is in line with a meta-analysis of randomized controlled trials of AF ablation vs. AAD treatment, which also did not find a significant benefit of ablation over AAD treatment with regards to the subsequent risk of stroke [258]; (5) several studies have shown a temporal dissociation between ischemic stroke and episodes of AF [1064–1066], which suggests that AF might be a marker of increased thromboembolic risk rather than a causal factor; (6) stroke risk is a lifelong consideration and increases with age such that patients many years from an apparently successful ablation will be at higher risk than when the decision to stop anticoagulation was made.

Arguments against the long-term management of postablation anticoagulation based solely on stroke risk score include: (1) patients in SR without evidence of AF have generally no indication for anticoagulation; (2) long-term and possibly life-long continuation of anticoagulation has a small, yet significantly increased risk of severe bleeding complications, which in some patients may outweigh the potential benefits on stroke prevention.

In the absence of RCTs comparing cessation vs. continuation of anticoagulation after AF ablation, several meta-analysis have summarized available data from non-randomized studies [1067–1069]. In summary, a decreased thromboembolic risk and a favorable net clinical benefit from continued anticoagulation was generally seen in patients with CHA_2DS_2-VASc $\geq$ 2, while no significant benefit was found from continued anticoagulation in patients with a CHA_2DS_2-VASc $\leq$ 1. This is important when interpreting individual studies that did not show an increased stroke risk with discontinuation of anticoagulation after AF ablation. Many AF ablation cohorts are skewed towards enrolment of low-risk patients with CHA_2DS_2-VASc $\leq$ 1. Accordingly, the overall background stroke risk in those cohorts is low and the number of potential high-risk patients with CHA_2DS_2-VASc $\geq$2 often too small to show a disadvantage of discontinuation of anticoagulation.

The ongoing OCEAN trial (Optimal Anti-Coagulation for Enhanced-Risk Patients Post–Catheter Ablation for Atrial Fibrillation, NCT02168829) is enrolling subjects at risk for stroke as indicated by a CHA_2DS_2-VASc $\geq$1 and who have not had clinically apparent atrial arrhythmias for at least 12 months after their most recent AF ablation [1070]. Eligible patients are randomized to anticoagulation with rivaroxaban 15mg daily vs. aspirin 75-160mg daily and followed for the primary composite endpoint of clinically overt stroke, systemic embolism, and covert stroke based on brain MRI during 3 years of follow-up. The results of OCEAN will provide important data to inform future management of anticoagulation after successful AF ablation. Additional clinical trials however will be needed to define the long-term stroke risk and the need for continued anticoagulation after AF ablation overall as well as for selected patient subgroups, especially in those with presumptive successful AF elimination after ablation.

9.3.1.3 Candidates to discontinue anticoagulation. Discontinuation of anticoagulation may be considered in several patient categories following AF catheter ablation.

A Low-risk patients (CHA_2DS_2-VASc 0 in men and 1 in females). In low-risk patients, anticoagulation should be discontinued 2 months after ablation regardless of the ablation outcome. Based on current guidelines, risk-benefit assessment does not justify antithrombotic protection in these patients, irrespective of their rhythm status [530].

B Intermediate-risk patients (CHA_2DS_2-VASc 1 in men and 2 in females). In this patient category, discontinuation of anticoagulation may be considered 12 months following catheter ablation in the absence of clinical symptoms or electrocardiographically documented AF recurrence. The writing group suggests deferral of OAC discontinuation until the completion of 12 months following catheter ablation in this patient category, to increase the likelihood of selecting patients with truly successful AF elimination. A proposed prerequisite to maximise safety after discontinuation of anticoagulation is that both patients and their physicians are committed to long-term rhythm monitoring (daily pulse or ECG monitoring, digital heart rhythm devices or invasive monitoring) to screen for AF recurrence and guide accordingly reinitiation of anticoagulant treatment.

C Higher risk patients (CHA_2DS_2-VASc $\geq$2 in men and $\geq$3 in women). In higher risk patients, anticoagulation should not be discontinued for several reasons mentioned above. However, if discontinuation of anticoagulation is being considered based on strong patient values and preferences and despite prior clarification of pertinent exposure to increased thromboembolic risk, patients should be placed under regular rhythm monitoring to screen for AF recurrence. As stated above, this may include daily pulse or ECG monitoring, digital wearable heart rhythm devices or invasive monitoring and selection of monitoring option should be individualised after detailed discussion with the patient. In case of documented AF recurrence, therapeutic anticoagulation should be reinitiated. In addition, LAA occlusion may be discussed as an alternative approach. The ongoing OPTION trial (NCT03795298) is a prospective, randomized study to determine if LAA closure is a reasonable alternative to OAC in patients after AF ablation.

9.3.1.4 Targeted anticoagulation (on demand) post ablation. When assessing the need for continued anticoagulation after AF ablation beyond the blanking period, the key question is whether the ablation was successful in eliminating AF. Unfortunately, the answer to this question is difficult to ascertain in most patients. The exception are patients with implantable cardiac devices including pacemakers, ICDs and ICM. In addition to the binary detection of episodes of AF recurrence, implantable devices can also quantify the burden and duration of AF episodes, both of which correlate with stroke risk [1071,1072]. Most of the implantable cardiac devices have remote monitoring capabilities and could potentially be used to guide intermittent "on-demand" anticoagulation during periods of AF. This strategy could be attractive in patients with paroxysmal AF, especially in younger, active ones that may have a risk for bleeding complications related to everyday activities.

The first large, randomized trial, IMPACT, showed no benefit of such an intermittent on-demand anticoagulation strategy over standard continued anticoagulation in 2718 ICD-patients with regards to thromboembolism and bleeding [1073]. Amongst other factors, the use of VKA in the majority of patients, rather than DOACs, might have negatively affected the results of this study given the delay in achieving therapeutic anticoagulation. More recently, two small pilot studies have tested the strategy of an intermittent on-demand anticoagulation with DOACs in device recipients. Using single-arm designs in 48 patients and 59 patients, such an approach was feasible and decreased anticoagulation utilization by 75% and 94% respectively [1074,1075]. The studies were not designed to assess the clinical outcomes of stroke or bleeding.

The concept of using continuous ECG monitoring by means of ICM or intensified non-invasive ECG monitoring using wearable devices is of potential interest as an adjunctive tool to guide anticoagulation after AF ablation. This strategy needs to be tested in prospective studies using appropriate cutoffs for AF burden and AF duration before it could be recommended for routine clinical practice. Furthermore, the strategy of "on-demand" anticoagulation is limited by the reported temporal dissociation between AF and stroke, which casts doubt on the value of guiding initiation and discontinuation of anticoagulation based on rhythm criteria [1064,1065]. A prospective randomized study testing the strategy of intermittent versus continuous DOAC administration based on symptoms and smartwatch-detected AF is currently underway (REACT-AF).

9.3.2 Antiarrhythmic drug treatment

Several prospective RCTs assessed the value of routine AAD administration in the immediate postablation period [1031–1036]. EAST-AF was the largest study and randomized 2038 AF patients (68% paroxysmal) to 3 months of AAD treatment post ablation or standard medical therapy without AAD. While more patients remained free from atrial arrhythmias during the 3 month-blanking period in the AAD group (59.0% vs. 52.1%, p=0.01), no difference was observed 1 year after ablation (69.5% vs. 67.8%, p=0.38) [1031]. Aggregation of all studies in meta-analyses confirmed the effectiveness of short-term AAD therapy in preventing early but not late relapses after discontinuation [1037,1038]. Given the psychological and financial burden of arrhythmia-related hospitalizations and cardioversions during the blanking period, short-term continuation of AAD for several months after the ablation should be considered in selected patients to prevent early AF recurrence, particularly those with persistent AF prior to ablation or who have tolerated antiarrhythmic medications prior to ablation. In others who experience AAD-related side effects, discontinuation after ablation is reasonable.

A survey of the writing group showed that 57.8% of the writing group members administer AADs during the blanking period as a strategy to prevent early AF recurrences after paroxysmal AF ablation and 86.8% after persistent AF ablation.

9.3.3 Proton pump inhibitors

Damage of the esophagus is one of the most feared complications of AF ablation. Esophageal lesions on routine endoscopy were found in 10-15% and ulcerations in about 5% of patients after AF ablation [703]. Atrioesophageal fistulae occur in 0.016-0.1% of AF ablation procedures [1076–1085]. It is hypothesized that AEF results from a double hit injury starting with a transmural ablation lesion extending through the atrial wall to the esophagus followed by subsequent ulcer erosion from gastro-esophageal reflux (section 11.3.1) [1086]. Based on this presumed mechanism, administration of proton pump inhibitors (PPI) to prevent ulceration has been widely adopted after LA ablation procedures [1048]. Evidence to support or disprove this practice is limited. A preclinical study found that progression of esophageal ulcer and development of AEF after ablation was associated with reflux esophagitis [1049]. A substudy of the MADE-PVI trial suggested a reduction in esophageal lesions as assessed by endoscopy in patients with preprocedural use of PPI [1050]. However, in a large-scale, retrospective, propensity score-matched analysis, the use of PPI before or on the day of ablation was not associated with reduced mortality or severe esophageal injury within 30 days postablation [1087]. Adequately powered clinical trials to establish the efficacy of pharmacological prophylaxis to reduce AEF are lacking and unlikely to be feasible given the low incidence of AEF.

Preclinical experience suggests a very low risk (if any) for esophageal injury [656] with PFA and no AEF has been reported with early clinical use so far [652,653]. Accordingly, the value of PPI postablation treatment in PFA cases is less compelling.

A survey of the writing group showed that 79% of the TF members employ short-term administration of PPI as a strategy to prevent esophageal lesions following catheter ablation when using non-PFA energy sources, while 54% when using PFA.

9.3.4 Anti-inflammatory agents

Early AF recurrence in the first few weeks following AF ablation has been linked to inflammation induced by the ablation procedure. Routine anti-inflammatory treatment may reduce the incidence of early relapses of AF after ablation and potentially also long-term recurrence.

Colchicine has been studied for this purpose in two prospective randomized trials. A 3-month course of treatment with colchicine 0.5mg twice daily compared to placebo resulted in a reduction of AF recurrence up to 90 days (16% vs. 34%, p=0.01) [1088]. Interestingly, the 3 month-treatment with colchicine also improved long term outcomes with reduced recurrence rates at one year (31% vs. 50%, p=0.01) [1089]. The benefit in terms of AF recurrence also translated into benefits in QoL and psychological score. However, these data have not been reproduced and are limited by small sample size.

Corticosteroids have also been used as a short-term treatment after AF ablation to reduce recurrences [1090–1094]. Study designs were inconsistent with regards to the duration of steroid treatments (single-dose vs. several days). Most of the studies showed a decrease in early recurrence rates until 3 months, but no difference with regards to late recurrence. It is also possible that steroids may limit ablative lesion healing. In view of the potential side effects of steroids, when applied over weeks or even months, as well as the limited and inconclusive data available, steroids after ablation should only be used cautiously and for short durations.

9.4 Rhythm monitoring following catheter ablation

Arrhythmia monitoring post ablation is useful to detect asymptomatic postprocedural arrhythmia recurrences and determine the etiology of symptomatic palpitations. Palpitations may result from recurrent AF or other atrial tachyarrhythmia, but may also result from atrial or ventricular premature beats and therefore are not an accurate predictor of AF recurrence [1095]. In the CIRCA-DOSE trial, only 45% of the symptom-triggered activations were adjudicated as AFl or AF during the postablation continuous monitoring of paroxysmal AF patients using an ICM [7].

Multiple studies have demonstrated that asymptomatic AF commonly occurs in patients following catheter ablation. Two studies reported that the proportion of asymptomatic AF events was 11%–35% prior to and 53%–65% after ablation [1096,1097]. In another study assessing the correlation between symptoms and underlying rhythm following AF catheter ablation, 53.8% of recorded AF episodes were asymptomatic, with an increase in asymptomatic episodes from the acute to the chronic period after ablation [1098]. In the DISCERN-AF study, continuous monitoring of symptomatic AF patients before and after catheter ablation with an ICM demonstrated that the ratio of asymptomatic to symptomatic AF episodes significantly increased from 1.1 before to 3.7 after ablation with 12% of patients having asymptomatic recurrences only [1060]. In the CIRCA-DOSE study, the 1-year arrhythmia-free survival based on the presence of documented recurrence of either symptomatic or asymptomatic atrial tachyarrhythmia lasting >30 seconds on continuous cardiac monitoring was 52.6%, while the respective survival free from symptomatic only arrhythmia recurrences was 85.3% [7]. Consequently, symptoms are not well correlated with postablation AF burden, stressing the need for postprocedural follow-up strategies consisting of continuous or intermittent ambulatory rhythm monitoring in addition to symptom-driven rhythm assessments.

9.4.1 Continuous postablation rhythm monitoring

Continuous rhythm monitoring includes ICM, pacemakers, or ICDs, and allows for continuous, remote, long-term monitoring in asymptomatic and symptomatic individuals. Pacemakers and ICDs with an atrial lead may record intracardiac atrial electrograms and detect atrial high-rate episodes as an indicator of AF occurrence. The positive predictive value of recorded atrial high-rate episodes varies upon the programmed rate and duration thresholds, with false-positive rates of 17.3% for episodes lasting >6 min and 3.3% with threshold duration > 6 hours [1099]. Long-term subcutaneous ICM can facilitate continuous AF monitoring based on R-R interval analysis over a time period of up to 4.5 years [1100,1101]. These continuous ECG monitoring devices have been used in several studies to evaluate the results of surgical or catheter AF ablation [7,244,1102,1103]. Although ICM hold promise for the determination of AF burden in the long term, AF detection algorithms are primarily based on R-R interval regularity, and pertinent limitations include reduced specificity due to undersensing of beats, oversensing of myopotentials, and irregular atrial and ventricular premature beats, as well as limited memory resulting in electrograms not being retrievable to verify the correct rhythm diagnosis [1104,1105]. Continuous rhythm-monitoring devices are more expensive, require implantation, and may not be available in all healthcare settings. A continuous rhythm monitoring strategy, although invasive, overcomes many of the limitations of intermittent monitoring in assessing arrhythmia recurrence and offers the opportunity to determine the most accurate estimate of AF ablation outcomes [1104–1106]. In those patients in whom the decision is made to continue long-term anticoagulation regardless of ablation outcome, the cost and effort of continuous rhythm monitoring is likely not warranted.

9.4.2 Intermittent postablation rhythm monitoring

Intermittent rhythm monitoring includes standard 12-lead ECGs, ambulatory patch or electrode ECG monitors, transtelephonic monitoring systems and patient and automatically activated external recorders [1107,1108]. The wide availability of direct-to-consumer mobile health devices for heart rate and rhythm assessment equipped with either ECG- or photoplythesmography-based technology has increased the availability of rhythm monitoring options in the postablation setting [1109,1110]. In a study conducted after AF ablation, a smartphone-based single-lead system was compared to transtelephonic monitor ECGs with 100% sensitivity and 97% specificity in detecting AF or AFl [1108]. A pilot randomized study demonstrated that the use of a self-monitoring strategy with an ECG-based hand-held device for rhythm assessment in patients after AF ablation resulted in a similar rate of AF detection and less requirement for additional ECG monitoring as compared to the standard-of-care follow-up practice [1111]. Furthermore, long-term intermittent monitoring with an ECG-based hand-held device was shown to be significantly more effective in detecting AF recurrences after AF ablation as compared to short, continuous (Holter) heart rhythm monitoring [1112]. The potential of integrating similar monitoring paradigms in the postablation care of AF patients is being evaluated in a multicenter international project [1113].

Intermittent monitoring is limited by reduced sensitivity in detecting sporadic arrhythmias, resulting in underdetection of recurrences, which inflates estimates of arrhythmia-free survival. Such misclassification errors likely affect the accuracy and precision of comparative risk estimates. In a secondary analysis of the CIRCA-DOSE trial enrolling paroxysmal AF patients undergoing catheter ablation, the sensitivity for detecting postablation arrhythmia recurrences was shown to increase with the intensity of intermittent rhythm monitoring [7]. Commonly employed intermittent monitoring protocols (three short duration 24- and 48-hour ambulatory Holter ECG monitors) failed to detect a considerable proportion of recurrences (sensitivity 15.8% and 24.5% respectively) and demonstrated poor agreement with the true AF burden [7]. Based on computational simulation, an intermittent postablation monitoring with a minimum cumulative duration of 28 days on an annual basis, using serial longer-term (7-day and 14-day) ambulatory ECG devices provides a reasonable arrhythmia detection (sensitivity nearly 60%) and quantification of AF burden (nearly 80% agreement) as compared to the gold standard of continuous monitoring with ICM [7]. In a recent systematic review, intermittent monitoring was associated with detection of significantly less atrial arrhythmia recurrences than continuous monitoring in paroxysmal AF, but not in persistent AF or paroxysmal-persistent combined arms [1114].

9.4.3 Practical considerations on postablation rhythm monitoring

The suggested pattern and intensity of postablation rhythm monitoring should be tailored based on whether patient management is part of routine clinical care or part of a clinical research trial. Monitoring strategies implemented during routine clinical care may be less strict and standardized than in clinical trials, since documentation of asymptomatic arrhythmia recurrences in everyday practice does not affect decision making in postablation management except in patients where discontinuation of anticoagulation is considered or in the presence of impaired ventricular function (section 9.3.1.3). In this context, as part of routine clinical care, rhythm status should be assessed during regular follow-up within 2-3 months after ablation with a minimum standard of a 12-lead ECG. In the absence of symptoms, all patients should be evaluated on an annual basis thereafter with a 12-lead ECG in every follow-up visit (section 9.5). In case of arrhythmia symptoms, some type of intermittent rhythm monitoring is suggested. Intensity and type of monitoring should be individualized based on symptom severity, frequency, availability of monitoring tools, associated cost and patient preferences.

In the clinical trial setting, it is evident that continuous invasive monitoring represents the gold standard of postablation monitoring and intermittent monitoring of prolonged duration with longer-term ambulatory ECG devices stands as best alternative [7]. However, their standardized employment in clinical trials would increase substantially the cost of trial conduction and would prevent consistency in trial reporting and comparisons with historical controls. In addition, the availability of longer-term ambulatory ECG devices is limited in several practices thus impairing widespread implementation of prolonged duration monitoring regimens with longer-term ambulatory ECG devices. Furthermore, prolonged-duration intermittent rhythm monitoring can be burdensome for patients and may result in reduced compliance.

Based on the above considerations, the writing group suggests that, in the clinical trial setting, and in the absence of invasive monitoring, a minimum of 24-hour continuous Holter type monitor should be considered every three months for the first year following catheter ablation, preferably in combination with symptom-based monitoring. Where available, longer duration recordings with 7- or 14-day continuous monitoring are preferable.

9.5 Early recurrences after ablation – post ablation blanking period

9.5.1 Incidence and pathophysiology of early recurrence after AF ablation

Recurrences of atrial tachyarrhythmia (AF or AFl or AT) may occur in the initial weeks to months after catheter ablation, leading to unplanned hospitalizations or emergency department visits [1115]. Some of these early recurrences may resolve with time. Therefore, employment of an initial blanking or blinding period is recommended when reporting efficacy outcomes [1116]. Recurrence of any type of atrial tachyarrhythmia during that period is not counted as treatment failure and invasive treatment like repeat ablation is usually not considered. However, the underlying pathophysiological mechanism responsible for early recurrence of AF, without late AF occurence, is not well understood [1117].

Short-term processes lasting hours to days and long-term processes lasting weeks to months may be operative during the initial period after AF ablation. These processes may be proarrhythmic or antiarrhythmic. Short-term processes include ischemia, myocardial necrosis, oxidative stress and myocardial edema [1118–1120]. Long-term processes include local and systemic inflammation [1119–1123], nerve sprouting after neural damage [1124], proliferative tissue repair and scar maturation [1120,1125–1127]. Better understanding of the underlying mechanisms for early recurrence and delayed response to ablation will potentially lead to identification of therapeutic targets for AF ablation. Furthermore, the duration of blanking period can also be better defined.

The incidence of early recurrences after AF ablation is highly dependent on the type and intensity of implemented monitoring protocol (section 9.4). As a result, there is remarkable variability in the reported incidence of early recurrences after AF ablation which ranges from 16-67% [1128–1130]. In a prespecified analysis of the CIRCA-DOSE study, the rate of early postablation recurrences documented by continuous rhythm monitoring was 61%, with a median interval of 12 days between the index ablation procedure and the first early recurrence [1128]. Several studies have shown similar incidence of early recurrences between RF and cryoballoon ablation [1128,1131].

Multiple predictors for early recurrences after AF ablation have been identified and many are also predictive of late recurrence and long-term treatment failure [1132–1141]. Baseline characteristics predictive of early recurrences after AF ablation include older age, female gender, presence of structural heart disease, longer AF duration prior to ablation, non-paroxysmal AF, higher CHA_2DS_2-VASc scores, larger LA size, impaired renal function, heart failure and presence of LA epicardial adipose tissue [526,1136–1142]. Acute procedural predictors for early recurrences after AF ablation include incomplete PVI and multiple AF foci [1143–1145]. Other predictors include markers of inflammation and increased levels of C-reactive protein and homocysteine[1146,1147].

9.5.2 Duration of blanking period

The blanking period following catheter ablation has been introduced to blind monitoring and efficacy assessment during the initial postablation phase during which detected recurrences do not necessarily indicate treatment failure. It should be noted that the absence of early recurrences during the blanking period is strongly predictive of freedom from late recurrence. Calkins et al. reported that patients free from AF recurrence during the 3-month blanking period have 90% likelihood of remaining free from AF recurrence at a 12-month follow-up or longer (89% negative predictive value for paroxysmal and 91% for persistent AF)[1135]. On the other hand, the predictive value of an early recurrence for a late recurrence is highly variable. Special characteristics of early recurrences after AF ablation have been identified to be more predictive of later recurrence and bear important implications for the optimal blanking period. Increasing number of early recurrences within the blanking period is predictive of late recurrence. In a study involving 300 patients undergoing AF ablation with PVI and elimination of non-PV triggers, patients experiencing multiple early recurrences spanning the initial six-week postablation period had lower long-term ablation success compared to those with **isolated or no** early recurrences [1148]. A single center study of 196 consecutive patients undergoing AF ablation using continuous monitoring during follow-up demonstrated that the higher the burden of AF recurrences during the blanking period, the higher the likelihood of long-term AF recurrence [1149].

Multiple studies have shown that the timing of early recurrences within the blanking period is crucial in the prediction of long-term ablation failure. In a study involving 331 patients undergoing cryoballoon ablation for AF, all patients who experienced early recurrence in the second half of the 3-month blinding period developed late recurrence of AF afterwards [1150]. In a retrospective analysis of 3681 AF patients treated with cryoballoon ablation, early recurrence within one month after ablation was shown to significantly predict the occurrence of long-term arrhythmia recurrences [1151]. In the ADVICE trial, 401 patients with paroxysmal AF undergoing PVI were followed for 12 months with transtelephonic monitoring [1152]. Early recurrence of atrial tachyarrhythmia occurred in 44.6% of patients and the risk of late recurrence varied significantly according to the timing of the early recurrence. One-year freedom from AF recurrence was 77.2% in patients without early recurrence compared with 62.6%, 36.4% and 7.8% in patients with early recurrence in the 1st, 2nd and 3rd months after ablation respectively [1152]. In a prespecified substudy of the CIRCA-DOSE trial, occurrence of early recurrence in the 1st, 2nd and 3rd month of blanking period was associated with 4.9-, 26.8- and 63.4-times higher likelihood of late recurrence of atrial tachyarrhythmia [1128]. Early recurrences occurring later than 52 days following catheter ablation had a 95% specificity for predicting late recurrence [1128]. Several studies have also shown that the risk of late recurrence is inversely related to the timing of early recurrence within the blanking period [1153–1155].

With the current evidence, a consensus among the members of this writing group has been reached to recommend an 8-week blanking period after AF ablation. This cutoff was agreed while placing emphasis to minimize misclassification of patients with early recurrences that are not indicative of treatment failure, and their pertinent exposure to an unnecessary need for redo ablation procedure. The writing group supports the use of the revised 8-week blanking period in future clinical trial design.

9.5.3 Management of early recurrences after catheter ablation

Pharmacological management has been shown to prevent early arrhythmia recurrences following catheter ablation (section 9.3.2). Early postablation recurrences may be a transient finding in some patients. Therefore, aggressive management may be unnecessary due to increased likelihood of spontaneous remission. However, a watchful waiting approach with rate control medication allows persistence of AF facilitating the atrial remodeling process. Delayed implementation of rhythm control interventions contributes to long-term failure of SR maintenance [1156]. Based on this concept, prompt management of early recurrence is favored to pursue SR maintenance.

9.5.3.1 Electrical cardioversion. Several studies have evaluated the impact of electrical cardioversion of early recurrences after AF ablation on long-term arrhythmia-free survival, providing conflicting results. Reported inconsistency may be due to variance in AF type, timing of cardioversion in relation to recurrence onset, intensity of rhythm monitoring during follow-up and definition of AF recurrence.

In a study of 55 patients who underwent AF catheter ablation and required electrical cardioversion for persistent AF or atrial flutter, 84% of patients experienced recurrence during a mean follow-up of 15 months [1157]. No difference in outcome was observed for early (within 90 days of ablation procedure) or late (90 to 180 days following ablation procedure) cardioversion. In a retrospective study of 180 patients (60% persistent AF) who underwent electrical cardioversion due to early AF recurrence (within 7 days) following radiofrequency AF ablation, successful electrical cardioversion occured in two thirds of patients, but had no impact on long-term rhythm outcome compared with unsuccesful cardioversion [1158].

In contrast, other studies reported beneficial effect of timely electrical cardioversion for early recurrence after AF ablation. In a large propensity score matched cohort of patients with early recurrence following catheter ablation, successful electrical cardioversion was associated with significant reduction in the one-year AF recurrence rate [1159]. In a prospective cohort, early cardioversion of postablation recurrences was associated with a favorable long-term rhythm outcome [1160]. In a study of patients undergoing surgical AF ablation, postoperative implementation of an intensive rhythm control strategy, including systematic use of cardioversion, led to a significantly higher proportion of patients maintained in sinus rhythm during follow-up [1161]. Timely cardioversion of early recurrences after catheter ablation also impacts long-term rhythm outcome. In a retrospective analysis of 384 consecutive patients with persistent arrhythmia following catheter ablation, early cardioversion with 30 days of arrhythmia recurrence was an independent predictor of sinus rhythm maintenance [1162].

With the current evidence, it is reasonable to consider cardioversion in patients with early recurrence after catheter ablation, especially within 30 days of arrhythmia onset. If early AF recurs after cardioversion, pharmacological pretreatment and waiting several weeks for inflammation to subside before repeat cardioversion is reasonable.

9.5.3.2 Early reablation. Early reablation is another possible treatment option for early recurrences after catheter ablation. Few studies have evaluated the impact of early reablation on long-term rhythm outcome. In a retrospective study of 302 consecutive AF patients, early reablation within the first month after the index procedure was shown to significantly reduce the incidence of further recurrences with an associated increase in the total number of procedures over the entire follow-up [1163]. In the STOP-AF trial, 245 patients with paroxysmal AF were randomized to either medical therapy or cryoballoon ablation. Early AF recurrence within the first 3 months after ablation occurred in 51.5% of patients and was significantly associated with late recurrence. Early reablation was independently associated with lower risk of late recurrence. However, patient allocation to reablation was non-randomized and nearly half of patients with early recurrence not receiving early reablation did not develop late recurrence [1164].

Despite the efficacy of early reablation in reducing the incidence of late recurrences, the rationale of implementing an invasive procedure with inherent risks and associated costs to treat a potentially transient arrhythmia is debated. Therefore, the writing group suggests that reablation of atrial tachyarrhythmia recurrences within the blanking period is not recommended unless recurrent, highly symptomatic and resistant to AADs and cardioversion.

9.6 Patient follow-up following catheter ablation

After undergoing AF ablation, all patients should be seen in follow-up within 2-3 months. Thereafter, all patients should be assessed on an annual basis by physicians (family physicians, internists, cardiologists or cardiac electrophysiologists) with a minimum standard of a 12-lead ECG in the absence of symptoms. Patients experiencing arrhythmia-related symptoms should undergo additional intermittent rhythm monitoring (section 9.4.3). Comprehensive management of AF patients based on the "Atrial Fibrillation Better Care" (ABC) pathway is recommended (54). 'A' stands for Anticoagulation/Avoid stroke, 'B' stands for Better symptom management and 'C' stands for Cardiovascular and Comorbidity optimization. The implementation of ABC pathway has been shown to reduce health-related costs, improve cardiovascular outcome and reduce cardiovascular and all-cause mortality as compared with usual care [1165–1170]. A similar integrated management of patients following catheter ablation is suggested.

9.7 Atrial tachycardia following AF ablation

9.7.1 Incidence – underlying mechanisms

The incidence of AT following AF ablation varies from less than 5% to 40% and is associated with the strategy and extent of prior ablation [343,821,825,1171–1179]. Atrial tachycardias after AF ablation can be due to a focal (automatic or triggered activity) or reentrant mechanism (macroreentrant or microreentrant). They are frequently associated with reconnection of previously isolated PVs [1171,1180], and may be focal, from the PV itself, or due to reentry between multiple sites of reconnection. In a recent multicenter study using high-resolution mapping, 7% of AT after AF ablation were PV-gap reentrant ATs with distinct circuits and two critical isthmuses at the entrance and exit gaps of previous PV isolation lines [1181].

Macroreentrant AT is the most common form and is seen with higher incidence after extensive LA ablation [821,1182,1183]. Linear ablation combined with PVI may result in reentrant AT because of conduction gaps and non-transmural ablation lesions [172,174]. Complex fractionated atrial electrogram-based ablation is also associated with high AT incidence [956,1184].

The incidence of AT after cryoballoon ablation is 3–11%, and more than half of these ATs are macroreentrant [1185–1190]. Cryoballoon ablation may result in more antral and generous posterior LA debulking during PV isolation compared to RF [1191,1192], narrowing the posterior wall isthmus regions and potentially increasing the likelihood of macroreentrant tachycardias.

Many patients present with recurrent AT after prior surgical ablation, with macroreentry responsible for the majority of AT mechanisms; CTI flutter represents 24-32%, mitral flutter 18-32%, and roof-dependent flutter 12-16% of AT during follow-up catheter ablation procedures [1193,1194].

9.7.2 Management

Management of AT post AF ablation depends on the pattern and timing of occurrence, type of prior ablation, and intensity of symptoms. ATs often occur during the blanking period after ablation without necessarily predicting procedure failure [343]. Atrioventricular nodal agents should be maximized to achieve ventricular rate control. In the case of severe symptoms, earlier intervention may be required. Class III AADs may be preferred if pharmacologic treatment of post ablation AT is needed. Electrical cardioversion is generally the first step for symptomatic persistent AT occurring early after AF ablation. If AT recurs soon after an early cardioversion, it may be worth waiting at least 2 weeks for ablation-related inflammation to subside before performing a repeat cardioversion. Up to a third of ATs have been reported to resolve in the first three months after AF ablation [343,1182]. However, after this time frame it is reasonable to pursue an ablation strategy if pharmacological control is ineffective or not desired.

It is beyond the scope of this document to provide insights into invasive management of AT following AF catheter ablation. In general, a multilevel strategy with assessment of tachycardia ECG characteristics, CS and biatrial activation pattern using multipolar diagnostic catheters and ultra-high density atrial mapping complemented by entrainment maneuvers is suggested to unravel underlying AT mechanism, which is the key to ablation success [1195–1198]. Despite pertinent challenges in ablation of AT after AF ablation (difficulty in achieving transmurality, epicardial-dependent tachycardias, safety concerns in specific areas), recent studies have shown very promising results in acute AT termination and long-term SR maintenance [1199,1200].

Section 10: Ablation Outcome and Efficacy

10.1 Acute procedural success

Pulmonary vein isolation is the cornerstone of AF ablation. Electrical isolation of the PVs is recommended during all AF ablation procedures and isolation should be minimally confirmed by assessment of entry block within the PVs (section 8.1.1).

Due to the high recurrence rate observed in patients with persistent and long-standing persistent AF with PVI alone, efforts were made to identify additive strategies to improve the outcomes of AF ablation. These strategies have included linear RF lesions in the LA and RA, CFAE ablation, GP ablation, ablation of non-PV triggers, isolation of the LAA, ablation of fibrotic areas identified by voltage mapping or MRI, PWI, ablation of rotational activity and VoM alcohol ablation [840,848,853,858,859,1003,1005,1201–1205]. Up to now, none of these strategies have been broadly adopted. Therefore, in persistent AF, ablation beyond PVI is of unclear benefit. However, if linear ablation lesions are deployed during AF ablation procedures, then confirmation of bidirectional block with mapping and pacing maneuvers is a required procedural endpoint (section 8).

10.2 AF recurrence endpoints

Since the first AF ablation consensus statement published in 2007, AF ablation success has been defined in a dichotomous manner by the absence of any atrial arrythmia lasting greater than 30 seconds off AADs. Overwhelming evidence indicates that this 30-second cutoff does not correlate with symptom severity, is not associated with cardiovascular outcomes and results in marked underestimation of treatment efficacy [19]. There is still uncertainty around the duration of AF leading to an increased risk of stroke [19,1206,1207]. A recent secondary analysis of the CIRCA-DOSE trial reported that a 1-hour duration threshold of postablation AF recurrence is associated with subsequent patient clinical outcome, since longer AF episode recurrences resulted in significantly increased healthcare utilization and impaired disease-specific QoL [1208].

Until we have more data on duration thresholds of AF recurrence associated with patient clinical outcome, we continue to recommend reporting the 30-second threshold data to allow comparison with earlier literature. Furthermore, it seems rational to move toward reporting AF burden to define ablation outcomes in a more granular fashion rather than necessarily considering a procedure as successful or unsuccessful based on any single cutoff value (section 10.3). It also remains important to report all categories of recurrence transparently, such as freedom from symptomatic atrial arrhythmias, AF recurrence separately from other atrial arrhythmias, single and multiple procedure success rates, and success on and off antiarrhythmic therapy. Success rate should be reported at 1 year and after single and multiple procedures.

10.3 AF burden endpoints

Given the challenges of achieving 100% AF freedom, AF burden has emerged as an important endpoint of AF ablation. Although it is best measured with continuous monitoring (via ICM, pacemakers or ICDs), it can also be assessed with intermittent external monitoring. However, commonly employed short-duration (24- and 48-hour) ambulatory monitors may overestimate the true AF burden. Computational simulation of different monitoring strategies demonstrated that intermittent monitoring duration is inversely related to observed AF burden. A reasonable assessment of true AF burden is achieved by at least 28 days of annual cumulative intermittent noninvasive monitoring using serial longer-term (7-day and 14-day) ambulatory ECG devices [7].

Recent data have indicated the clinical relevance of reporting AF burden as a procedural endpoint of catheter ablation. By studying AF burden, a striking AF reduction is often observed following ablation despite AF recurrences being recorded [630]. Reduced AF burden following AF ablation is also associated with improvement in QoL [1209]. In CASTLE-AF, a trial of patients with AF and HFrEF randomized to catheter ablation or drug therapy, a 50% lower AF burden at 6 months was associated with a decrease in the primary endpoint of all-cause mortality and HF hospitalization, and a reduction in all-cause mortality. However, AF recurrence as a dichotomous variable (defined as a 30-second or more AF recording) was not predictive of the primary composite outcome or mortality [1210]. In a recent subanalysis of the CIRCA-DOSE study, postablation burden > 0.1% was associated with significantly increased risk of healthcare utilization (emergency room visit, all-cause hospitalization, cardioversion, and repeat ablation) [1208]. It seems unlikely however that a single AF burden cutoff point accurately reflects each of the endpoints of symptom severity, health care utilization and cardiovascular outcomes. It is probable that the relationship between AF burden and these endpoints will vary between patients dependent on other factors (eg $CHAD_2S_2$-VASc score for thromboembolic risk).

Based on the above considerations, reporting AF burden as the outcome of AF ablation trials is strongly advised especially in trials with prolonged cumulative intermittent or continuous postablation rhythm monitoring.

10.4 AF progression endpoints

Progression from paroxysmal to persistent and permanent AF occurs in some patients and achievement of rhythm control gets more difficult as AF progress to the persistent stage and beyond (section 2.3). In the ATTEST study, AF ablation was superior to AADs in delaying progression from paroxysmal to persistent AF [1211]. In the CABANA trial, catheter ablation was shown to have a significant impact on the natural history of AF and protect against AF progression to persistent and long-standing persistent types [1212]. More recently, the EARLY AF trial provided longer term follow-up in 303 patients with paroxysmal AF randomized to first-line rhythm control therapy with either cryoballoon ablation or antiarrhythmic medications [27]. After three years, patients in the cryoablation group were less likely to progress to persistent AF compared to patients treated with AADs (1.9 vs. 7.4%; HR 0.25, 95% CI, 0.09 to 0.70) [27] (section 4.1). Although not widely reported in clinical trials, the reduction in AF progression with ablation is an important metric.

10.5 AF related symptoms

Although reported in trials, the endpoint of AF related symptoms is difficult to clearly assess. Even in patients with highly symptomatic AF, as many as half of all episodes may occur without associated symptoms. The ratio of asymptomatic to symptomatic episodes increases up to four-fold postablation, perhaps due to shorter AF durations, slower ventricular rate, or autonomic modulation after the procedure [1060](section 9.4). Double-blind treatment allocation is not easily feasible in trials evaluating the effect of AF ablation and therefore improvement in symptoms can also partially be related to a placebo effect. Moreover, symptomatic and asymptomatic episodes often co-exist in the same patient. Nevertheless, since AF ablation partly serves as a treatment primarily for symptom amelioration, it is relevant to report AF related symptoms, keeping in perspective that symptoms should not serve as a surrogate to assess AF burden nor other clinical endpoints such as stroke, hospitalization and mortality.

10.6 Quality of life assessment

Quality of life should remain an important endpoint for AF ablation studies, but not necessarily the primary endpoint. QoL is limited by treatment expectancy bias. QoL can be measured both using well-established scales like the SF-36 and EQ5D, but also using more specific scales such as the AFEQT, MAFSI, AFSS or Symptom Severity Score [1059]. AF specific scales are associated with increased sensitivity and are more effective in discriminating between patients with successful and failed ablation [1059]. Studies using both general and specific scales showed improvement in QoL with catheter ablation over AAD [1213–1216]. The CAPTAF trial, using QoL as primary endpoint, concluded that QoL improvement was greater with ablation compared to AAD, despite the fact that freedom from AF and number of cardioversions were similar in both groups; however AF burden was reduced to a greater extent in the ablation group compared to the AAD group [1209]. In a CIRCA-DOSE subanalysis, significant impairment in AF-specific QoL following catheter ablation was demonstrated only in patients with postablation AF episode durations > 24h or AF burdens > 0.1% as compared to patients without AF recurrence [1208].

Section 11: Complications

11.1 General considerations

Catheter ablation for AF is a complex electrophysiology procedure. Due to its invasive nature requiring vascular access, catheter manipulation and energy delivery in the LA, which is thin-walled and neighbors organs potentially susceptible to thermal damage, AF ablation has a relevant complication rate. This is particularly important because in most cases, the aim of the procedure is mainly symptomatic improvement.

Major complications are usually defined as complications that result in permanent injury or death, require intervention for treatment, prolong or require hospitalization. The rate of complications after AF ablation lies, as consistently reported by administrative databases, large registries and randomized trials, in the range of 2.5-8% [298,1063,1083,1084,1217–1220]. In-hospital deaths are very rare. Contemporary in-hospital death rates (in experienced units) are usually in the range of 0.05 to 0.1% [1084,1217–1221]. Although cumulative experience and technical advances would be expected to lead to a significant decrease in the procedural complication rate, reports of time trends of the complication rates provide conflicting results [1063,1084,1217,1218,1220]. A recent pooled analysis of adjudicated safety outcomes exclusively from RCTs demonstrated a significant decrease in the overall rate of complications related to AF catheter ablation in the more recent period (2018-2022) as compared with the preceding 5-year period (3.8% vs 5.3%, respectively) [1219]. Importantly, some complications such as pericardial tamponade, stroke or esophageal perforation may be severe or immediately life-threatening and require urgent or emergent management. For this reason, awareness of the different complications and knowledge of their presentation pattern and management are mandatory.

Several studies have assessed sex-based differences in AF ablation adverse events. In an observational cohort study of 58960 patients undergoing AF ablation from 2016 to 2020, female gender was independently associated with a higher risk of hospitalization > 1 day, major and any adverse events [1222]. This gender disparity in AF complication rates has been shown to persist over time and may be attributed to higher burden of associated comorbidities, delayed referral for catheter ablation, higher rate of non-paroxysmal AF type among females as well as anatomical differences between genders [1223,1224].

The main complications of catheter ablation for AF are listed in Table 9. In this section, the presentation, investigation, treatment as well as methods to prevent these complications will be discussed.

Table 9 Main complications of catheter ablation of atrial fibrillation

Complication type	Complication rate
Periprocedural death	0.05-0.1%
Atrioesophageal fistula	0.02-0.1%
Periprocedural thromboembolic event	0.15-0.5%
Cardiac tamponade	0.4-1.3%
Severe pulmonary vein stenosis	0-0.5%
Permanent phrenic nerve palsy	0.08-0.1%
Vascular complications	1-4%*
Asymptomatic acute cerebral lesions	5-30%

*without ultrasound-guided vascular puncture

11.2 Factors associated with procedural complication rate

11.2.1 Procedural volume

Reports consistently demonstrate a correlation between procedural volume and safety outcomes in catheter ablation of AF. Overall complication rates [1217,1225,1226] and early mortality [1221,1226] after catheter ablation of AF are higher in low-volume than in high-volume centers. Although the annual center caseload cutoff for the definition of low- and high-volume centers may vary between studies, the effect remains consistent. The magnitude of this effect is substantial. Particularly for early mortality, high volume centers are reported to have rates as low as one third of those reported by low volume centers [1217,1221,1225]. Thus, operator experience appears to be the most critical factor to decrease complications. Indeed, no other technological or procedural aspect has been reported to be associated with such a decisive reduction of complications. These data strongly emphasize the need for structured education and training in the field of AF ablation (see section 13).

11.2.2 Type of energy source

Radiofrequency and cryoenergy have been used the last two decades in the majority of AF ablations. Apart from these, PFA is a novel emerging and promising energy source that is expected to gain a significant role in the coming years. Other sources have been applied during the last two decades for AF ablation but have not found a way into broad clinical application.

Despite obvious differences between the main energy sources, the complication rates between RF and cryoablation do not seem to differ significantly, although the type of complications differ [293,294,1227,1228]. Persistent PN palsy following PVI is observed almost exclusively after cryoablation whereas esophageal perforation is, in the vast majority, a consequence of RF ablation [1078]. The respective data for PFA are still limited, but the existing evidence indicate an overall complication rate that is not higher than with the other two energy sources [653,660,672,1229]. Due to the specific effect of electroporation on cardiomyocytes, adverse extracardiac effects such as esophageal damage are expected to be significantly limited, if not absent, after PFA (section 11.3.1).

11.2.3 Role of ablation protocols

Radiofrequency ablation had been initially performed with power settings of 30-35W at the anterior LA wall and reduced power of 20-25 W at the posterior wall to reduce complications such as cardiac perforation and damage to the esophagus. In recent years, ablation protocols with increased power have been introduced. These are based on power settings of 50 W up to 90 W with respective limitation of the maximal duration of energy application at each ablation site. Initial concerns of a potentially increased complication rate due to the higher energy power were not confirmed. Indeed, existing data confirm the safety of this approach, albeit without indication of any considerable reduction in complication rates [609,1230–1232]. In particular, there is no indication for an increased rate of esophageal damage, although related impact, either positive or negative, would be difficult to detect given the rarity of this complication [605]. A recent RCT comparing higher power (40W) short duration versus lower power (25W) longer duration ablation on posterior wall with specific AI targets demonstrated an equivalent risk of esophageal thermal injury (4.5%) as documented by postablation endoscopy [1233].

Recent trials suggest that the type of implemented RF ablation protocol may have an impact on the rate of postablation asymptomatic cerebral emboli. In a prospective randomized trial, high-power short-duration (70W for 9-10 sec) RF ablation for PVI was associated with significantly higher rate of MRI-detected subclinical strokes as compared to conventional ablation-index guided (25-40W) ablation [610]. Another smaller RCT comparing high versus standard power RF ablation for PVI also demonstrated a trend toward more asymptomatic cerebral emboli with high-power short-duration ablation [1234].

11.2.4 Time course of complications and implications for discharge practice

With increasing experience and optimization of workflows, same day discharge of patients has been implemented for many different interventional cardiac procedures. Although traditionally patients stayed in the hospital for at least one night after AF catheter ablation, several centers moved to same-day discharge, since the majority of relevant complications occur in the first few hours after the procedure [1235]. Indeed, several reports from different hospital settings demonstrate the safety of same-day discharge [1041,1043,1236]. Interestingly, these reports pertain to both cryoablation and RF ablation [1043]. Thus, with respect to complications, same-day discharge after an uneventful AF ablation appears safe provided that specific criteria are met (section 9.2).

11.3 Presentation, treatment and prevention of specific complications

11.3.1 Esophageal perforation

Esophageal injury is a rare but lethal complication of AF catheter ablation [1081]. It occurs with a time delay after the procedure with a reported incidence which varies from 0.016% to 0.1% [1078–1085]. The respective incidence in large surveys enrolling more than 100000 AF ablations ranges from 0.016% to 0.026% [1078–1080]. In the largest, multinational POTTER-AF registry enrolling a total of 553729 catheter ablation procedures in 214 centers, the incidence of AEF was 0.025%. Also noteworthy is that the incidence of AEF varied markedly between centres (maximum of 0.4%, minimum 0.0066%; $p < 0.01$), implicating some aspect of modifiable ablation technique in the occurrence. The median time from catheter ablation to symptom onset and to AEF diagnosis was 18 (range: 0-60) and 21 (range: 2-63) days respectively [1078].

Three main types of esophageal injury are observed: atrial-esophageal fistula, atrial-pericardial fistula, and esophageal hematoma. These types of complication are caused by thermal damage to the esophagus that is in close vicinity to the posterior LA wall [1237]. It is observed almost exclusively after RF ablation but rare cases of esophageal perforation after cryoablation have been described [1077]. In the POTTER-AF registry the incidence of AEF was significantly higher in RF as compared to cryoballoon ablation (0.038% vs 0.0015%, $p<0.0001$). PFA is described to have a specific effect on cardiac myocytes and is expected to be associated with a substantially lower risk of esophageal injury. Initial clinical data with MRI imaging seem to corroborate this assumption [1238], but definite conclusions cannot be drawn yet due to the very low incidence of this complication and the limited number of procedures performed so far with PFA.

Notably, esophageal lesions detected during routine endoscopy as potential precursors of perforation are common after ablation and lie in the 10% range [700], but only a small minority will advance to esophageal perforation. The most common symptoms of esophageal perforation are fever, chest pain or odynophagia and neurological events (septic emboli), but patients can present with esophageal bleeding, hematemesis, systemic emboli, septic shock or death septic shock or death [1078] (Figure 10).

Chest CT with intravenous contrast is the preferred modality to document the diagnosis of AEF [1078]. Typical findings include air in the mediastinum or contrast extravasation to the pericardium, mediastinum, or esophagus. However, a normal chest CT scan does not rule out the presence of an AEF and therefore in case of high clinical suspicion, ongoing vigilance and repeat imaging is recommended to ensure prompt diagnosis and timely intervention. An LGE-MRI is also useful for documentation of AEF diagnosis [1239]. If AEF is suspected, a barium swallow is contraindicated as entry of barium into the circulation could be fatal. Furthermore, endoscopy with air insufflation should be avoided in patients with symptoms suggestive of AEF, due to the risk of massive, life-threatening air embolism. This is particularly important in a patient with acute gastrointestinal bleeding during the post-ablation period, when endoscopy is often the first diagnostic test performed on an emergency basis. However, esophageal endoscopy with CO_2 insufflation may be performed with relative safety, usually in patients with high-risk features but negative initial chest CT scan, since CO_2 is rapidly absorbed into the blood with minimal risk of gaseous embolism. Early recognition of an AEF is critical and thus it is important to inform patients of warning related symptoms and to advise them to contact their AF ablation center directly in case of occurrence (Figure 10).

Several approaches have been proposed for reducing the risk of this complication, including visualization of the course of the esophagus by integration of the CCT or CMR images in the 3D mapping systems or by ICE, avoiding ablation or reducing CF and ablation power in the vicinity of the esophagus or at the LA posterior wall, or by employing esophageal temperature monitoring, esophageal cooling or deviation [1237,1240,1241]. However, the impact of these preventive measures has not been clearly documented (section 7.8) [700,792–795]. A widely used strategy is the routine use of PPIs for a limited period following the procedure. Nevertheless, there is no substantial evidence for the benefit of this practice (section 9.3.3). Given the rarity of the complication, conclusive evidence will be difficult to obtain.

Treatment of an AEF is a medical emergency that requires urgent surgical repair [1078,1242,1243]. Case series have reported an 83% to 100% mortality without surgical repair compared with a 34% mortality with surgical repair [1242,1243]. Several case reports have been published describing favorable outcomes with esophageal stent placement for treatment of an esophageal perforation or an esophageal pericardial fistula [1243–1246]. In the POTTER-AF registry, overall mortality in patients with AEF was 65.8% and was significantly lower following surgical (51.9%) or endoscopic treatment (56.5%) as compared with conservative management (89.5%) [1078].

In summary, esophageal perforation is a rare but unpredictable and immediately life-threatening complication. Prompt diagnosis and surgical treatment are typically needed. Awareness of patients and physicians is of paramount importance.

11.3.2 Periprocedural thromboembolic events

Thromboembolic events are one of the most significant complications of AF ablation (Figure 11). These manifest in almost

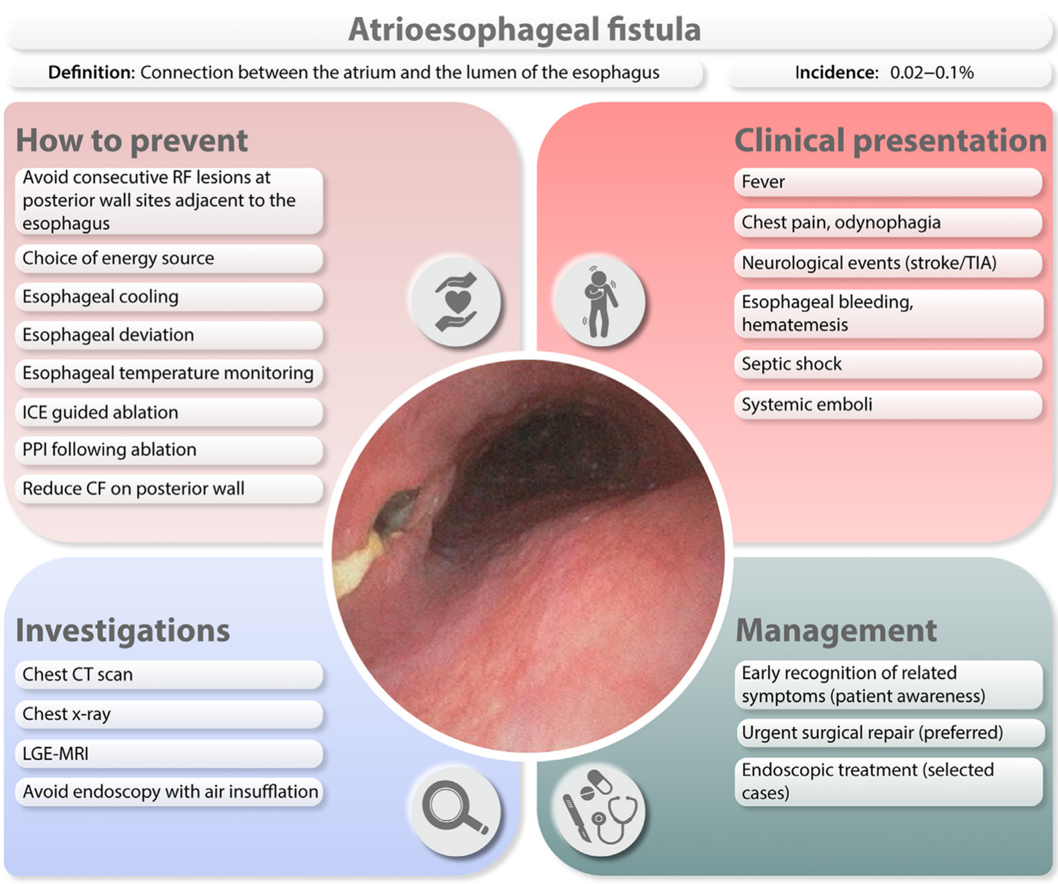


Figure 10
Prevention, clinical presentation investigation and management of atrioesophageal fistula. CF = contact force; CT = computed tomography; ICE = Intracardiac echocardiography; LGE = late gadoliniun enhancement; MRI = magnetic resonance imaging; PPI = proton pump inhibitors; RF = radiofrequency; TIA = transient ischemic attack.

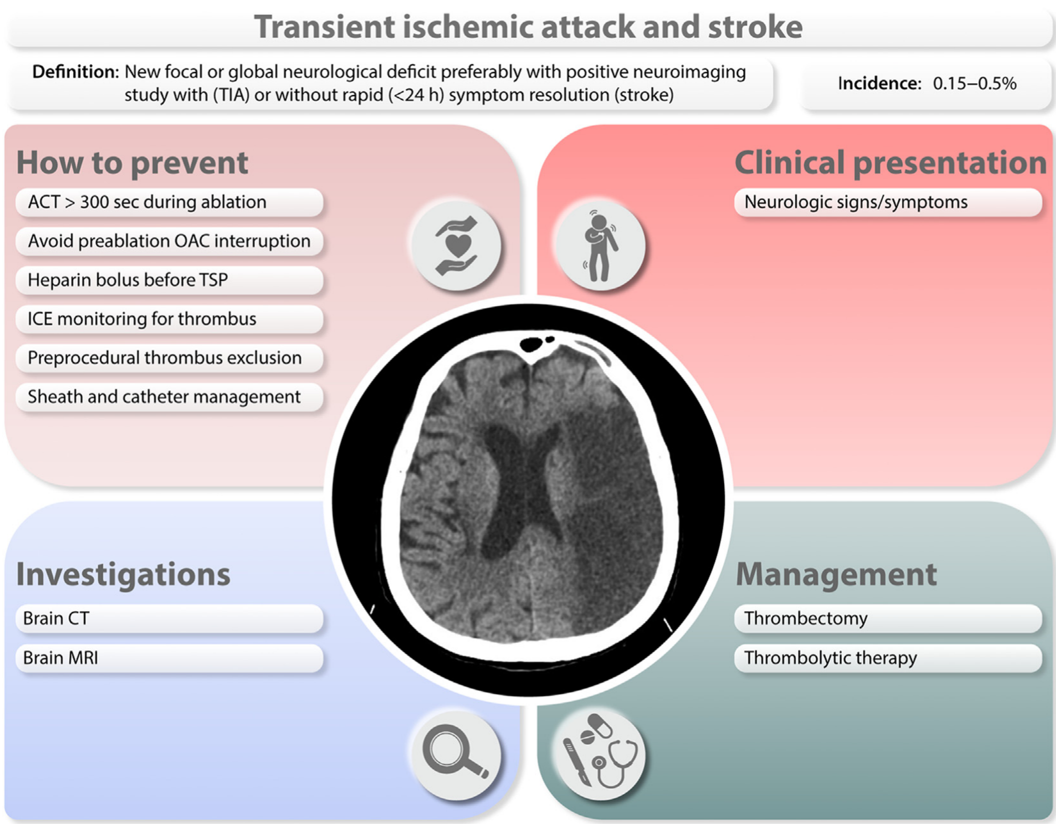


Figure 11
Prevention, clinical presentation, investigation and management of transient ischemic attack/stroke in the postablation setting. ACT = activated clotting time; CT = computed tomography; ICE = Intracardiac echocardiography; MRI = magnetic resonance imaging; OAC = oral anticoagulants; TIA = transient ischemic attack; TSP = transeptal puncture.

all cases as strokes or TIA. In contemporary large series, the incidence of stroke or TIA after catheter ablation lies in the range of 0.15 to 0.5% [1084,1217,1219,1220]. Thromboembolic events typically occur within 24 hours of the ablation procedure, with the high-risk period extending for the first 2 weeks following ablation [1247,1248]. Potential reasons of thromboembolic complications include the development of thrombi on or within sheaths and ablation catheters introduced into the LA, char formation at the tip of the ablation catheter, mobilization of a preexisting LA thrombus, and electrical cardioversion during the procedure. Therefore, a strict anticoagulation protocol during the procedure with heparin administration (even before transeptal puncture), regular ACT measurements and maintenance of an ACT of at least 300 seconds, as well as meticulous attention to sheath management are recommended (section 7.4). Routine imaging screening for the presence of atrial thrombus reduces the rate of thromboembolic complications (section 5.2.3).

Diagnosis of thromboembolic events is usually straightforward. The manifestations depend on the location of the occlusion within the arterial tree. Treatment also varies according to the location of the embolus and, importantly for cerebral embolic events, the time interval between symptom onset and diagnosis. Peripheral arterial embolisation might be amenable to surgical thrombectomy, whereas cerebral embolisation has traditionally been managed conservatively. There is however growing interest in aggressive early management of such events, using either thrombolytic drugs or percutaneous interventional techniques. The involvement of neurologists and interventional radiologists with experience in the interventional treatment of the cerebral arterial tree is of major importance.

11.3.3 Asymptomatic cerebral lesions

As recognized in recent years, catheter ablation for AF results in asymptomatic acute cerebral lesions that can be detected by high-resolution diffusion-weighted brain MRI. Hyperintensity in T2-weighted fluid attenuated inverse recovery sequence (FLAIR positivity) is useful in differentiating acute from chronic cerebral ischemic lesions [1249]. The prevalence can be as high as 30% without difference between patients on VKA and patients on DOACs [387,388,1250]. These lesions are considered silent ischemic cerebral lesions since no grossly detectable symptoms are present. Recent data support that high-power short-duration ablation protocols may increase the risk of asymptomatic cerebral emboli (section 11.2.3)[1234].

Subtle cognitive dysfunction has been reported early (3 months) after AF ablation when compared to patients undergoing SVT ablation or patients being treated medically [1251]. In another study with longer follow-up, early postablation cognitive dysfunction was transient with complete recovery at 12 months of follow-up. Indeed, a higher percentage of ablation treated patients demonstrated cognitive improvement at 12 months compared to medically treated patients [1252]. There are multiple potential mechanisms by which early post AF ablation cognitive dysfunction may occur, but several studies have found no relationship between asymptomatic cerebral lesions on MRI and cognitive decline [1252–1254].

11.3.4 Cardiac tamponade

Cardiac tamponade remains the most frequent, potentially life-threatening complication of AF catheter ablation. In recent large surveys, the reported incidence varies from 0.4% to 1.3% [1084,1217–1220]. Women seem to have a higher risk for tamponade than men [1224,1255]. The substantially higher incidence of cardiac tamponade during AF ablation compared with other cardiac electrophysiology procedures can be attributed to a number of procedural differences, including the need for transeptal puncture, extensive intracardiac catheter manipulation and ablation, and the need for systemic anticoagulation during the procedure. The most common causes of cardiac perforation leading to cardiac tamponade during AF ablation are (1) misdirected transeptal puncture with the puncture performed too posteriorly exiting the RA into the pericardium before entering the LA or with the puncture advanced too much and exiting the LA via the roof, LAA, or the lateral LA wall (**section 3.3**); (2) direct LA mechanical trauma during catheter manipulation and ablation and (3) overheating during RF energy delivery, with or without the development of a steam pop. Excessive power, temperature, and force applied at the tip of the catheter might also contribute.

The need for periprocedural and intraprocedural anticoagulation with heparin infusion to achieve an ACT > 300 seconds may increase the volume of bleeding if perforation occurs. Concerns of increased bleeding risk related to uninterrupted anticoagulation have not been confirmed. Previous studies showed that uninterrupted VKA anticoagulation did not result in higher incidence of tamponade compared with interrupted VKA anticoagulation therapy with bridging heparin [381,382,829,1014,1256,1257]. Several RCTs comparing uninterrupted DOAC therapy with uninterrupted VKA anticoagulation demonstrated the safety of a periprocedural regimen with uninterrupted DOACs [386,388,1258]; this anticoagulation regimen has become current standard in most high-volume centers (section 5.2).

The impact of technical aspects of the ablation procedure to the risk of tamponade is not clear. A randomized study reported substantially lower tamponade rates in procedures performed with cryoballoon ablation compared with RF energy [294] but observational data do not confirm this finding [1227]. Although it was anticipated that the introduction of CF-sensing catheters would reduce the rate of tamponade, this was not confirmed in clinical trials [1259]. The use of ICE is important for early diagnosis but also prevention of cardiac tamponade. In a large nationwide cohort study including more than 100.000 patients who underwent AF ablation, the absence of intraprocedural ICE use was associated with 4.85-fold increased risk for cardiac perforation [1260](section 7.6).

Cardiac tamponade presents either as an abrupt or as a gradual BP decrease (Figure 12). In the latter case, administration of fluid might return BP to normal before further subsequent decline. It is vital that operators and staff be vigilant to the development of cardiac tamponade, as a delay in diagnosis can be fatal. Due to the immediately life-threatening character of this complication, if not managed appropriately, the development of hypotension during an AF ablation procedure should be assumed to indicate tamponade until proven otherwise. An early sign of cardiac tamponade is a reduced or absent movement of the excursion of the cardiac silhouette on fluoroscopy with a simultaneous BP fall. The diagnosis is confirmed by immediate echocardiography. Importantly, the presentation of cardiac tamponade might be delayed and can occur any time from an hour after the procedure to weeks later [1261]. The incidence of delayed tamponade was 0.2% in a worldwide survey report [1261]. Most, but not all, patients presented with warning symptoms, and some presented with hypotension and shock.

Early recognition and rapid appropriate treatment of cardiac tamponade is mandatory to prevent irreversible deterioration in perfusion of the brain and other organs. In a dedicated worldwide survey, cardiac tamponade was reported to be the most frequent cause of periprocedural death, with 25% of all fatalities occurring in association with this complication [1262]. Most cardiac tamponades can be managed successfully by immediate percutaneous drainage. Percutaneous drainage is best achieved by subxiphoid Seldinger puncture of the pericardial sac and placement of an intrapericardial catheter, such as a pigtail catheter. The puncture can be performed either with fluoroscopic guidance based on anatomic landmarks or with echocardiographic guidance [1263]. Usually, BP promptly increases after initial aspiration. Once the pericardial space has been drained, the patient needs to be monitored for ongoing bleeding with the drainage catheter left in place. Continuation of bleeding after aspiration of a substantial amount of blood indicates an extensive perforation that may need surgical repair. Although these are the minority of cases [1264,1265], it is for this reason that AF ablation procedures should only be performed in hospitals equipped or prepared to manage these types of emergencies with access to emergency surgical support. Several case series have reported the feasibility and safety of immediate direct autotransfusion of the blood aspirated from the pericardial space through a femoral vein, without the use of a cell saver system, to reduce the need for allotransfusion following emergency pericardiocentesis in patients undergoing cardiac electrophysiology procedures [1266,1267]. Reversal of anticoagulation with protamine may be helpful to stop bleeding, but it may also lead to thrombus formation in the pigtail catheter if bleeding has not stopped. Therefore, protamine should be administered once the rate of aspiration decreases significantly. The drainage catheter is usually left in place for at least

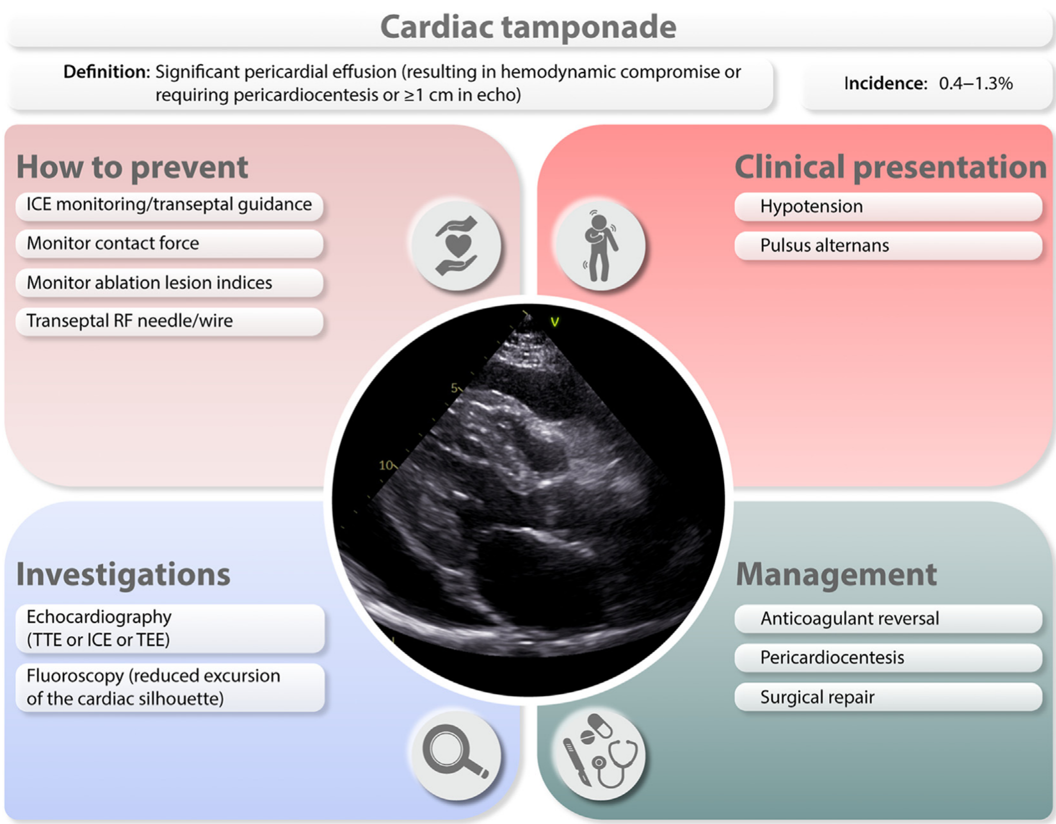


Figure 12
Prevention, clinical presentation, investigation and management of periprocedural cardiac tamponade. BP = blood pressure; ICE = Intracardiac echocardiography; RF = radiofrequency; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

12 hours following placement. However, observational studies have shown that early removal of the pericardial drain within the electrophysiology laboratory, after exclusion of blood reaccumulation, is safe and effective in reducing in-hospital stay and the need for analgesia as compared to delayed drain removal [1266,1268]. In patients anticoagulated with warfarin, fresh frozen plasma may be administered. Specific reversal agents for NOACs are available and provide the opportunity to immediately reverse the anticoagulant effect but do not seem to play any substantial role in clinical practice (section 7.4).

11.3.5 Pulmonary vein stenosis

Pulmonary vein stenosis is a well-recognized complication of AF ablation that results from thermal injury to the PVs. With the transition from ostial to antral ablation and the increased awareness that energy delivery within the PVs should be avoided, the rate of this complication has reduced significantly so that it is currently exceedingly rare. In large contemporary series of AF ablations, the reported incidence of severe PV stenosis is 0-0.5% [1084,1219,1269]. Nevertheless, cases of asymptomatic PV stenosis or moderate PV narrowing may not be taken into account. PV stenosis has been described for both point-by-point RF ablation as well as cryoballoon ablation [799,1270–1273]. There are limited data regarding the impact of RF power on the rate of PV stenosis [605,618,1274]. The highest risk for PV stenosis is associated with RF ablation close to the PV orifices and/or within the PVs, with significantly higher incidence compared with antral ablation [799]. Ablation within the PVs should be avoided but can occur due to shifts in the 3D electroanatomic map, respiratory motion, poor catheter stability, and/or operator inexperience.

Symptoms usually occur weeks to months after the ablation procedure and include dyspnea, hemoptysis, cough, (recurrent) pulmonary infections or pneumonia, and chest pain [1272,1275–1277]. These may lead to misdiagnoses such as pneumonia, pulmonary embolism, or even lung cancer; therefore, patients should be informed about the importance of returning to the ablation center if such signs or symptoms develop. According to the percentage reduction of the luminal diameter, the severity of PV stenosis is generally defined as mild (<50%), moderate (50%–70%), or severe (>70%). Notably, patients with severe stenosis of a single PV may remain asymptomatic [1277].

Diagnosis is made by CT angiographic imaging, MRI, perfusion scans, TEE, or invasive PV angiography. The preferred imaging modality is MRI or CT angiography because they allow precise visualisation of the location and severity of PV narrowing. Additional advantage of MRI is the option of simultaneous assessment of pulmonary perfusion data.

Treatment of PV stenosis is difficult. Interventional treatment is indicated in the presence of symptoms.

Asymptomatic or mildly symptomatic PV stenoses should be managed conservatively with watchful waiting, given that symptomatic amelioration has been observed after PV stenosis or occlusion without treatment due to the formation of collateral vessels [1278]. For symptomatic patients, PV angioplasty should be considered. The dilation procedure is often complex, especially if the target PV is completely occluded as evidenced by lack of visualization using either direct angiography via the LA or anterogradely via pulmonary artery angiography. Electroanatomic 3D mapping with registration of the anatomy of the LA and the PVs, as well as fusion with the reconstructed LA from the imaging scan before the index procedure, enables a precise localization of the occluded PV [1279]. Baseline CT angiography or MRI is more helpful in defining the PV anatomy.

Many PV stenoses are rigid and difficult to dilate. Even after acutely successful angioplasty, PV restenosis occurs in up to 50% of cases [1272,1276,1277,1280]. Percutaneous treatment of PV stenosis with stenting is associated with reduced risk of restenosis as compared to balloon angioplasty, particularly with the use of larger diameter and drug-eluting stents [1272,1276,1277,1280]. Nevertheless, even after stenting, restenosis rates are high [1276,1277,1281]. There is only limited data on the role of surgical treatment of PV stenosis. Connecting the patch to the proximal end of the stenosis is challenging because this end is buried in the lung parenchyma. Given this difficulty and the excessive risk, there is no evidence for recommending surgical treatment in patients with recurrent PV stenosis after AF ablation. Even for patients with recurrent severe and persistent problems due to restenosis despite interventional treatment, recurrent infection and hemoptysis are uncommon, manageable, and the need for lobectomy or pneumonectomy is very rare [1276]. Therefore, repeat percutaneous intervention is the treatment of choice for cases of PV restenosis after angioplasty.

11.3.6 Phrenic nerve palsy

Phrenic nerve palsy is a significant complication of AF ablation and results from direct PN injury. The right PN is most commonly affected because it descends in close proximity to sites of ablation in the SVC and both right-sided PVs. It courses slightly further from the RIPV so that injury during treatment of this vein is less common than that occurring with RSPV ablation. Injury of the left PN may also occur during ablation of the LAA due to its course anterior to the base of the LAA. (section 3.9).

PN palsy is observed with all technologies of thermal AF ablation, but the vast majority of cases occur after cryoablation [244,294,1227,1282]. With cryoballoon ablation, most PN injuries are transient and resolve before the end of the procedure [1283]. Based on recent PFA registries, the occurrence of PN palsy following ablation with the pentaspline, multielectrode PFA catheter is exceedingly rare [653,1229].

In patients with persistent PN palsy, recovery of nerve function may occur within weeks and in the vast majority by 12 months, although 18–24 months might be required in some patients [1270,1284]. In a large multinational registry enrolling 17356 patients undergoing cryoballoon-based PVI, PNI recovered in 97.0% of patients at 12 months, with only 0.1% of the overall population showing permanent PNI [1283]. In recent large surveys, the reported incidence of permanent PN palsy ranges from 0.08% to 0.1% [1084,1219,1283].

Several mechanisms have been proposed to explain the increased incidence of PN injury after balloon-based AF ablation. First, wedging or exerting force to direct the balloon into the RSPV for complete PV occlusion can distort the anatomy and decrease the distance between the RSPV endocardium and the right PN [227]. Second, a small balloon size relative to PV diameter can increase the likelihood of distal ablation in the vein. Studies have shown a higher risk of PN injury associated with the smaller 23-mm balloon compared with the larger 28-mm balloon, the latter resulting in more proximal energy application [239,1270]. The smaller balloon is potentially advanced further within the PV, causing distortion of the anatomy, creating a higher susceptibility to PN thermal injury. Third, the use of additional freeze cycles can increase the risk of dose-dependent nerve palsy [1187]. PN palsy can also occur during antral ablation using RF energy. This likely results from thermal injury to the PN as it courses anterior to the right PVs. Another common scenario of PN palsy is during electrical isolation of the SVC using point-by-point RF ablation (section 3.9).

PN palsy can be asymptomatic but typically causes dyspnea, tachypnea, cough, hiccups, and thoracic pain (Figure 13). The diagnosis is suggested when newly elevated hemidiaphragm with or without atelectasis of the ipsilateral lung base is observed on postprocedure chest x-ray. When suspected, diaphragm excursion should be evaluated using fluoroscopy (sniff test) or ultrasound to confirm the diagnosis.

A number of strategies have been employed to prevent PN palsy. These include limiting ablation to antral regions with various balloon maneuvers; preablation high-output pacing to establish whether the PN can be captured from the proposed ablation site before energy delivery; PN mapping with anatomic tagging of its course using an EAM system to guide safe deployment of ablation lesions; and monitoring of diaphragmatic excursion with abdominal palpation, fluoroscopy, or intracardiac ultrasound while pacing the PN from the SVC or subclavian vein during ablation [1285]. Monitoring the effects of right PN pacing is now considered a standard part of cryoballoon ablation and should also be considered during RF energy delivery at the anterior part of the rights PVs and during SVC isolation (Figure 6). Finally, diaphragmatic electromyography for direct monitoring of diaphragmatic compound motor action potentials during ablation is a technique for early detection of PN palsy that has been reported to reduce incidence of palsy [1286,1287]. Compound motor action potentials are recorded using body surface electrodes, esophageal electrodes, or a diagnostic catheter positioned in the hepatic vein. A decrease in the amplitude of the myopotential by 30% is more sensitive than abdominal palpation for predicting the subsequent reduction in diaphragmatic excursion and PN palsy [1288].

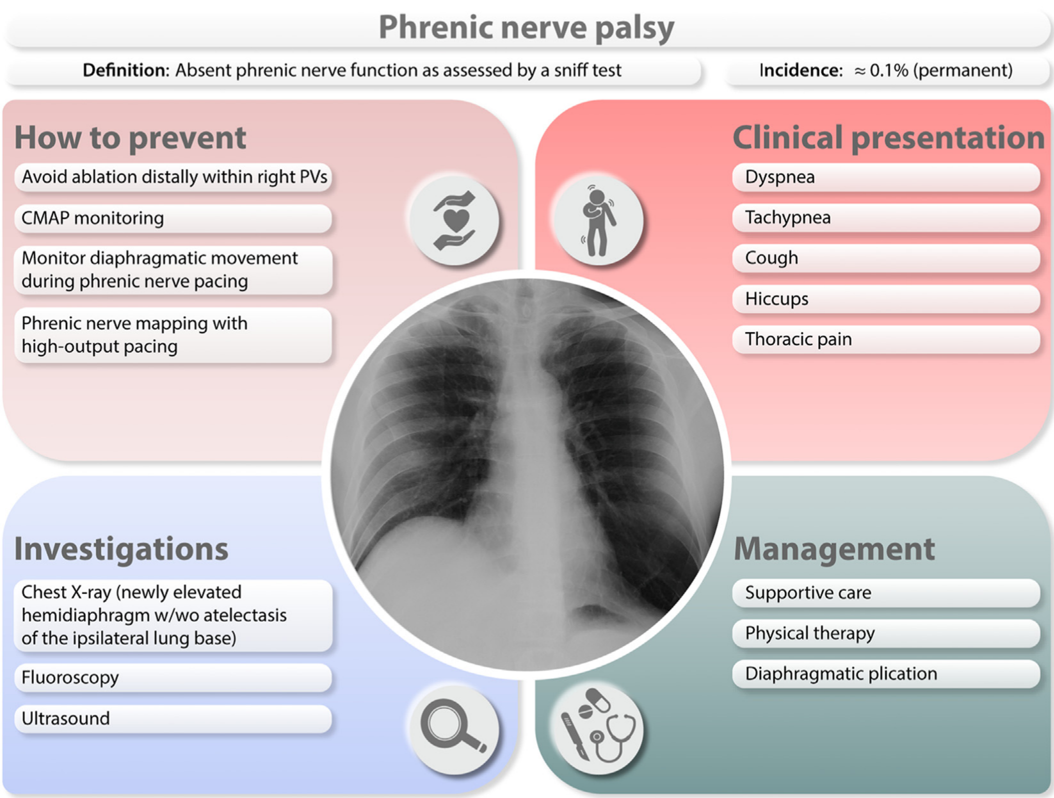


Figure 13
Prevention, clinical presentation, investigation and management of phrenic nerve palsy. CMAP = compound motor action potential; PN = phrenic nerve; PV = pulmonary vein; w/wo = with or without.

Energy delivery should be interrupted immediately at the first sign of PN injury.

There is no active treatment known to facilitate PN healing. In highly symptomatic patients, physical therapy of intercostal muscles and scalenes can improve breathing. In patients with permanent nerve palsy, surgical treatment with diaphragmatic plication can improve dyspnea and functional status.

11.3.6 Vascular complications

Vascular complications are the most common major complications of catheter ablation for AF and include groin hematoma, pseudoaneurysm of the femoral artery, arteriovenous fistula, and retroperitoneal bleeding. Current estimates of incidence range from 1% to 4% [1084,1217–1219]. The incidence of vascular complications that result from AF ablation is lower than those reported for ventricular tachycardia ablation, in which femoral arterial access is used in many cases [1289,1290].

Most groin hematomas can be managed conservatively or with ultrasound-guided compression. However, complications such as femoral pseudoaneurysm, arteriovenous fistula, and retroperitoneal bleeding might require blood transfusion and/or surgical or percutaneous repair, which leads to increased morbidity and prolonged hospital stay [1291]. Rarely, a large dense hematoma can lead to neurological sequelae.

The incidence of these complications may be related to the number and size of the venous sheaths used, insertion of an arterial pressure line, and perhaps to the intensity of anticoagulation management before, during, and after the procedure. Recent randomized studies did not provide any indication for increased risk of vascular complications under uninterrupted DOAC compared with uninterrupted VKA anticoagulation [387].

The approach used for femoral venous access may affect the risk of vascular complications. When an inferior approach to femoral vein access is used, small medial branches of the femoral artery, which can run across and superficial to the femoral vein, might be penetrated before entry to the femoral vein, possibly leading to a femoral pseudoaneurysm and arteriovenous fistula. When a superior approach is used, there is an increased risk of retroperitoneal bleeding.

Several studies have consistently demonstrated the safety and the beneficial effect of ultrasound guided puncture for vascular access. This is an easy-to-learn technique that requires standard equipment and significantly reduces vascular complications in electrophysiology procedures [684–687]. For this reason, ultrasound guidance is recommended for vascular access during AF catheter ablation to reduce the risk of vascular complications (section 7.2).

11.3.7 Other complications of AF ablation

Apart from the aforementioned serious complications, catheter ablation for AF may lead to several other complications, some of which may be significant.

11.3.7.1 Air embolism. Air embolism may occur acutely during an AF ablation procedure. The most common cause is introduction of air via the transseptal sheath, either through the infusion line, or due to suction when catheters are removed. Immediate diagnosis and treatment are based on clinical suspicion and depends on the site of embolization within the vascular tree. A common presentation of air embolism during AF ablation is acute inferior ischemia and/or complete atrioventricular block as result of the preferential downstream migration of air emboli into the right coronary artery. Supportive care usually results in complete resolution of symptoms and signs within minutes. However, pacing and cardiopulmonary resuscitation might be needed if the hypotension and AV block persist, but almost always patients recover completely [1292]. Air embolism to the cerebral vasculature can be associated with altered mental status, seizure, and focal neurological signs. Treatment should be initiated immediately if cerebral air embolism is suspected. The most important initial step is to maximize cerebral perfusion by the administration of fluids and supplemental oxygen, which increases the rate of nitrogen absorption from air bubbles. For large air emboli, it might be beneficial to briefly suspend the patient in a head-down position [1293].

To prevent air embolism, it is imperative that all infusion lines are monitored closely for bubbles. When catheters are removed, they should be withdrawn slowly to minimize suction effects, and the fluid column within the sheath should be aspirated simultaneously. Particular care is advised when inserting and removing balloon catheters through large sheaths [1294].

11.3.7.2 Acute coronary artery stenosis and occlusion. Injury to the coronary arteries during AF ablation is rare. The circumflex artery is in close proximity to the lateral LA and can potentially be injured during ablation at sites adjacent to its course within the CS, the lateral mitral isthmus, or the base of the LAA. Coronary artery injury can manifest as ventricular fibrillation or with features of acute myocardial infarction with ST segment changes occurring during ablation [1295,1296]. Immediate coronary angiography reveals the occlusion site and facilitates revascularization (section 11.2.2). `

The sinus node artery originates from the proximal circumflex artery in one-third of cases and then courses along the anterior LA and then the septal SVC and could therefore be susceptible to injury during ablation. Ablation at the anterior LA and septal RA has been reported to result in injury of the sinus node artery presenting with sinus arrest during or within 1 hour of ablation without evidence of other electrocardiographic changes associated with coronary occlusion [1295,1297]. Permanent pacemaker insertion may be required to treat this complication.

Emphasis should be placed on recent reports of severe coronary spasm during catheter ablation with the pentaspline PFA catheter [653,1298]. This adverse event mostly occurs during PFA application adjacent to a coronary artery (proximity-related). More rarely, a generalized coronary spasm has been described even when ablating remotely to a coronary artery. This adverse event can be mitigated by nitroglycerin administration before PFA applications at high-risk areas. However, it remains unclear if nitroglycerine pretreatment will eliminate any direct coronary artery injury from PFA [1299]. In general, these findings raise caution on the use of the pentaspline catheter for PFA delivery in proximity to a coronary artery, as during CTI or mitral isthmus ablation [664,1298].

11.3.7.3 Mitral valve trauma and curvilinear catheter entrapment. Entrapment of a circular multielectrode mapping catheter by the mitral valve apparatus is an uncommon but established complication of AF ablation [1300–1304]. It results from inadvertent positioning of a multielectrode catheter close to the mitral valve or into the left ventricle, often during attempts to position the catheter into the LIPV or when using such catheters to create electroanatomic maps of the LA. This complication should be suspected when attempts to reposition the catheter into another PV are met with resistance. When suspected, it is important to confirm the diagnosis with echocardiography. One option is to administer high dose adenosine to cause AV block, thereby relieving tension in the mitral apparatus and freeing up the catheter tip [1305]. Although successful freeing of the catheter has also been reported with gentle clockwise catheter manipulation and advancing the sheath into the ventricle, there have also been a number of cases reported in which the mitral valve apparatus and/or papillary muscles are torn during attempts to free the catheter [1301,1304,1306,1307]. There have also been several cases reported in which the distal tip of the circular catheter broke off during attempts at catheter removal and had to be subsequently removed either with a snare or with an open surgical procedure [1302,1303,1306]. In these cases, if gentle attempts to free the catheter fail, elective surgical removal of the catheter should be performed. To prevent this complication, circular and multispline catheters should be manipulated with extreme caution near the mitral valve. Furthermore, extreme vigilance is warranted during catheter manipulation at the vicinity of mechanical mitral valves due to increased risk of entrapment. In case of entrapment of a multispline catheter in a mechanical mitral valve, extensive traction increases the risk of mechanical valve damage or shearing of catheter splines. Different techniques to release entrapped multipolar catheters using the ablation catheter have been proposed [1308–1310].

11.3.7.4 Stiff left atrial syndrome. First described after mitral valve surgery, stiff LA syndrome was later recognized as a rare complication of LA catheter ablation, typically after multiple ablations [1311–1314]. Extensive LA ablation has been associated with worsening of echocardiographicaly measured LA stiffness [1315]. Symptoms include unexplained dyspnea and signs of right HF. Diagnostic findings include new or worsening pulmonary hypertension, LA diastolic abnormalities, LA hypertension, and large V waves on LA pressure or pulmonary capillary wedge pressure tracings [1314]. The complication appears to be associated with extensive LA ablation particularly in patients with small LA size, high LA pressures, preexisting severe LA scarring, and comorbidities as diabetes and OSA [1312].

Most patients show symptomatic improvement after diuretic therapy, which appears to be more effective for this syndrome than for other forms of pulmonary hypertension [1316]. In contrast, another study reported a case of stiff LA syndrome after AF catheter ablation that failed with furosemide and spironolactone, but which responded to sildenafil [1317].

11.3.7.5 Gastric hypomotility. Gastric hypomotility may occur in the setting of AF ablation due to inadvertent injury of the anterior vagal esophageal plexus usually when RF energy is applied to the LA posterior wall [1318–1320]. Endoscopically detected gastric hypomotility has also been reported in 10-18% of patients undergoing cryoballoon AF ablation [1321–1323]. Common symptoms include nausea, vomiting, bloating, and abdominal pain developing within a few hours to a few weeks after the ablation procedure [1324–1326]. Symptomatic but also asymptomatic gastric problems may be frequent after ablation [1325,1326]. The time to recovery is variable, with some patients recovering within 2 weeks, but others requiring a much more protracted time to recovery, occasionally greater than 3 months [1318].

Diagnostic evaluation can include endoscopy or a barium swallow to look for residual food after an overnight fast, abdominal CT scan that shows marked gastric dilation, or real-time MRI to assess gastric motility and pyloric spasm [1327].

Management of this complication depends on the severity of symptoms and whether gastric hypomotility or pylorospasm predominates. Dietary modification with small, low-fat, and low-fiber meals may be adequate to alleviate symptoms. Pharmacological treatment can be used to relieve symptoms (antiemetics) and to promote gastric contractility. In the latter category several agents have been proposed including erythromycin, domperidone and metoclopramide [1328,1329]. Metoclopramide treatment should not extend beyond 12 weeks due to associated risk of movement disorders. Domperidone has a substantially lower risk of central nervous system side effects but it has been associated with QT prolongation [1329]. In patients with predominant pylorospasm, intrapyloric injection of botulinum toxin or different types of surgical pyloric interventions have been proposed as treatment options [1330].

Section 12: Surgical and Hybrid Atrial Fibrillation Ablation

Surgical and hybrid AF ablation	Category of advice	Type of evidence
Concomitant surgical AF ablation is beneficial in patients with paroxysmal or persistent AF undergoing left atrial open cardiac surgery regardless of prior antiarrhythmic drug failure or intolerance.	Advice TO DO	META [1331–1342]
Concomitant surgical AF ablation is beneficial in patients with paroxysmal or persistent AF intolerant or refractory to previous antiarrhythmic drug therapy, undergoing closed (non-left atrial open) cardiac surgery.	Advice TO DO	META [1331–1334,1336–1340,1343–1345]
Biatrial Cox maze procedure or a minimum of PVI plus left atrial posterior wall isolation is beneficial in patients undergoing surgical AF ablation concomitant to left atrial open cardiac surgery.	Advice TO DO	RAND [1332,1334,1335,1343,1346–1351]
Documentation of exit and/or entrance block across pulmonary veins and completeness of deployed lines is beneficial during surgical AF ablation.	Advice TO DO	OPN
Exclusion of the left atrial appendage is beneficial as a part of surgical AF ablation procedures (stand-alone or concomitant).	Advice TO DO	RAND [1352–1358]
Concomitant surgical AF ablation is reasonable in patients with paroxysmal or persistent AF prior to initiation of class I or III antiarrhythmic therapy, undergoing closed (non-left atrial open) cardiac surgery.	May be appropriate TO DO	META [1331–1341,1343–1345,1351,1359–1361]
Stand-alone surgical or hybrid ablation is reasonable in symptomatic patients with persistent AF with prior unsuccessful catheter ablation and also in those who are intolerant or refractory to antiarrhythmic drug therapy and prefer a surgical/hybrid approach, after careful consideration of relative safety and efficacy of treatment options.	May be appropriate TO DO	META [1331–1341]
Stand-alone surgical or hybrid ablation may be reasonable in symptomatic patients with paroxysmal AF with prior unsuccessful catheter ablations who prefer a surgical/hybrid approach, after careful consideration of relative safety and efficacy of treatment options.	Area of uncertainty	RAND [1362–1365]

12.1 Technology and techniques

Radiofrequency ablation and cryoablation are the two dominant technologies used today due to their safety and efficacy profiles and will be the only ones discussed in this section. While there have not been any RCTs to compare the efficacy of one ablation technology to another, these technologies have had proven clinical efficiency over the last two decades.

To date, a prospective, multicenter, non-randomized clinical trial, AtriCure Bipolar Radiofrequency Ablation of Permanent Atrial Fibrillation (ABLATE), has resulted in specific FDA approval for surgical treatment of AF [1366]. This device was used on patients with non-paroxysmal AF undergoing concomitant coronary artery bypass graft (CABG) and/or valve procedures and Cox maze IV ablation and resulted in a 76% freedom from AF recurrence off AADs at 6 months with a major perioperative adverse event rate of 9%.

Surgical ablation procedures for AF can be grouped into three different groups: 1) a full, biatrial Cox maze procedure; 2) PVI or posterior LA isolation alone, or 3) PVI combined with an extended left atrial lesion set. All surgical AF ablation approaches are combined with LAA exclusion. At present, it is recommended that the term "Cox maze procedure" is appropriately used only to refer to a biatrial lesion set including specific transmural lesions that extend between nonconductive tissues (valve annulus or vena cava or another lesion) (Figure 14) [1367]. The best late rhythm outcomes have been shown with the full biatrial Cox maze procedure, while a certain subgroup of patients, such as those with paroxysmal AF, have reasonable results with more limited lesion sets [1368].

12.1.1 Energy sources

12.1.1.1 Radiofrequency energy. Radiofrequency energy can be delivered by either unipolar or bipolar electrodes which can be either dry or irrigated. Irrigation helps to deliver RF energy uniformly and to prevent char formation by keeping temperatures cooler at the tissue interface [1369]. Unipolar RF ablation works by delivering RF energy from the probe directly to the tissue. The unipolar devices do not provide surgeons with transmurality indicators. In contrast, bipolar RF can be either directional or constrained and transmurality can be implied by the manufacturer's dose-response algorithms. The directional bipolar devices have two side-by-side electrodes that are applied to the tissue surface, with the energy passing through the tissue between them. The constrained bipolar devices consist of a clamp with two jaws which are applied on opposite sides of atrial tissue. The energy passes through the tissue between the two jaws. When the conductance falls to a stable minimum, transmurality is inferred.

Unlike bipolar RF devices, unipolar ones have failed to consistently create transmural lesions and have a risk of forming endocardial char or thrombus [1370–1373]. Both unipolar and directional bipolar RF energy sources have had difficulty creating transmural lesions when used from the epicardial surface on the beating heart [1374]. This difficulty is due to the circulating intracavitary blood flow which produces convective cooling. To overcome this problem, devices have employed suction to pull the atrial tissue into apposition, thus partially ameliorating the circulating heat sink. RF ablation with constrained bipolar devices has allowed for faster, and more efficient ablation due to direct contact with the tissue. Since the tissue is ablated between the jaws of a clamp, the energy delivery is focused and isolated from the surrounding circulating intracavitary blood reservoir, allowing for more effective creation of lesions on both the beating and arrested heart.

Factors that affect lesion size and depth are power, impedance, ablation duration, temperature, and CF [1375–1378]. The generators of the irrigated and non-irrigated bipolar RF clamps produce power transmitted to the electrodes and these data are used to predict the transmurality of the lesion. The generators of irrigated clamps do this by measuring the impedance between electrodes, varying the power according to the impedance, and terminating power delivery once the

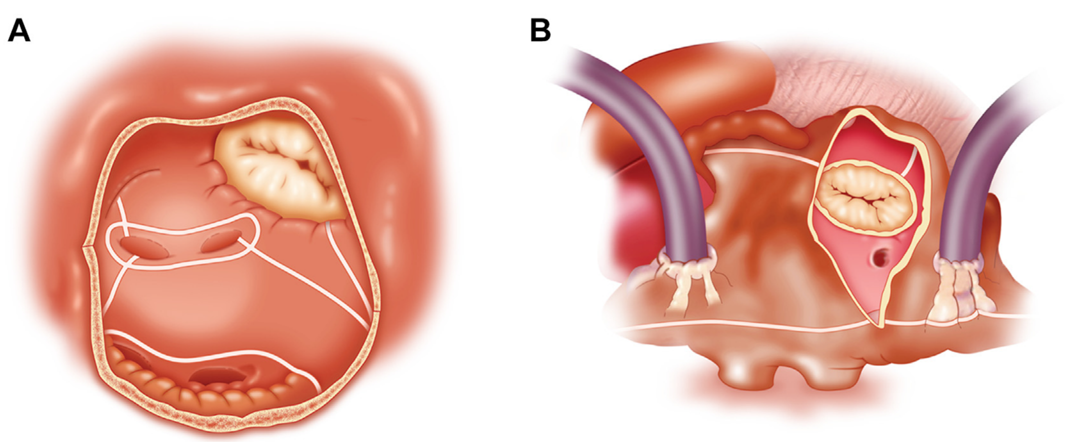


Figure 14
Lesion sets of the Cox maze IV procedure. Left panel: left atrial lesion set including: (a) left atriotomy, (b) ablation around the left-sided PVs, (c) ablation around the right-sided PVs, (d) posterior wall box lesion, (e) line connecting left PV lesion to excluded LAA, (f) line connecting box lesion to mitral annulus (g) cryoablation to the epicardial ostial region of the coronary sinus (not shown) - Right panel: right atrial lesion set including: (a) right atriotomy extending over crista terminalis, (b) line from the atriotomy to the superior and inferior vena cava posterior to the crista terminalis (to avoid injury to the sinoatrial node), (c) line connecting the atriotomy to the tricuspid annulus (2 o' clock relative to the valve) and (d) line connecting the right atriotomy to the right atrial appendage.

feedback program detects a steady state plateau [1369]. On the other hand, the generators of non-irrigated clamps measure conductance and continue ablation until a stable low conductance is reached. Voltage is varied according to the conductance, resulting in a safe delivery of energy to the tissue [1375]. Care should be taken to clean the electrodes after every 2-3 ablations with the non-irrigated clamps because char decreases conductance, which can result in non-transmural lesions. Importantly, in a human heart ex-vivo model a double ablation without unclamping improved lesion transmurality. Epicardial fat and muscle thickness can also decrease conductance and limit ablation depth [1375]. The ablation duration affects the tissue temperature profile. Cardiac muscle exposed to temperature of 55°C or higher for more than a few seconds will show irreversible coagulation necrosis [1379]. Lastly, adequate but not excessive CF is needed to achieve a reliable transmural lesion [798,1380].

12.1.1.2 Cryoenergy. Cryoablation has been used since the 1960's to ablate cardiac tissue. It is the second most common ablation technology used for surgical ablation. In contrast to RF energy, cryothermy creates homogenous scars in a non-directional pattern. Cryoablation is safe because cold temperatures do not denature proteins, and thus preserves fibrous tissue and the extracellular matrix, which makes it an ideal technology for ablation around valvular tissue [1381,1382]. Temperature, probe size, frequency, duration of ablation, and the cryogen cooling agent are all factors that determine the lesion's volume and depth [1383]. The cryoablation probes deliver very low temperatures to cause irreversible cell death, and actively measure the probe-tissue interface temperature through a thermocouple. The potential disadvantages are the relatively longer time to create a lesion (2 to 3 minutes) and the difficulty creating a lesion on the beating heart due to the heat sink effect created from circulating intracavitary blood [1384,1385]. Due to this, cryoablation should not be used to create epicardial lesions off cardiopulmonary bypass. To create a reliable uniform and continuous cryolesion, a critical lethal temperature of less than -30°C must be reached during ablation [1383].

12.1.2 Specific ablation tools

12.1.2.1 Radiofrequency ablation tools.

Unipolar devices. Unipolar RF devices come in varying lengths and can measure the electrode interface temperature with or without a suction stabilization device to enhance tissue contact. They can either be irrigated or non-irrigated. Despite the variety of unipolar devices, as mentioned above, they have had limited success in creating transmural lesions consistently [1371,1372,1386]. None have been FDA-approved for surgical treatment of AF. The only FDA-approved unipolar device is for hybrid therapy of persistent and long-standing persistent AF (EPi-Sense Guided Coagulation System with Visitrax, AtriCure, Inc.) and is described below (section 12.3.2.2).

Bipolar clamp devices. The only ablation device with FDA approval for the treatment of AF during concomitant cardiac procedures, is the bipolar, non-irrigated RF clamp (Isolator Synergy clamp, AtriCure Inc., Mason, OH). In a chronic animal study using this device with a single application, all lesions produced were transmural [1387]. However, in clinical experience, multiple applications are needed to achieve exit block. In a recent human ex-vivo heart explant model, a single application resulted in only 65% of lesions being transmural throughout their entire length. Inability to achieve transmurality was related to the increased thickness of atrial tissue and the presence of epicardial fat. Application of two successive ablations without unclamping resulted in 100% lesion transmurality [1375]. In comparison, irrigated bipolar RF clamps, Cardioblate BP2 and LP (Medtronic Inc., Minneapolis, MN), use a similar algorithm to provide real time measurements of lesion transmurality based on impedance. This device has also been studied in porcine models and showed a high rate of lesion transmurality. Using the same ex-vivo human heart model, it has also been shown that a double application without unclamping results in significantly increased rate of lesion transmurality compared to single application (92% versus 74%)[1388]. Most recently, another bipolar RF ablation device (Isolator Synergy EnCompass Clamp, AtriCure Inc., Mason, OH) has been tested experimentally and has been shown to produce reliable transmurality and isolation of the entire posterior left atrial wall and all four PVs with a single application in an in-vivo beating heart model [1389]. Further clinical trials will be needed to test its clinical performance.

Directional (non-clamp) devices. There are several directional unipolar and bipolar RF devices, with or without suction assistance, that can be applied either on the epicardium or endocardium. The ablation times range from 10 to 40 seconds per the manufacturer's instructions with the highest risk of ablation gaps at the end of the devices, thus continuous lesions should be overlapped to increase transmurality. The two non-suction assisted bipolar RF devices are the Isolator pen (AtriCure, Inc.) and Coolrail device (AtriCure, Inc.). In both acute and chronic animal models, the creation of transmural lesions has been inferior to bipolar RF clamps [1386,1390,1391]. Furthermore, the Coolrail device should be used with caution as it has been associated with a few case reports of AEFs following AF ablation [1392]. Rinsing the pericardium with saline may be used to prevent AEF during ablation with the Coolrail device.

The two suction-assisted RF devices on the market are the Cobra Fusion 150 (AtriCure, Inc.) and EPi-Sense Coagulation System with VisiTrax (AtriCure, Inc.). The Cobra Fusion device has both unipolar and bipolar RF energy delivery capabilities. During ablation delivery, suction should be maintained at -500 mmHg for 1 to 2 minutes depending on the tissue thickness and desired temperature setting per the manufacturer's instructions. In an acute porcine beating heart model, delivery of two separate applications (initial bipolar followed by unipolar energy without disrupting the suction) from an epicardial approach resulted in 68% rate of lesion transmurality [1371]. The EPi-Sense device is a 3 cm long, suction-assisted, irrigated unipolar RF device. The lesion transmurality of this device has been variable in multiple animal studies from 15% to 100% [1386 1393]. However, its clinical performance has been validated in the treatment of patients with persistent and long-standing persistent AF in the setting of a minimally invasive hybrid approach (section 12.3.3.2) [219].

12.1.2.2 Cryoablation tools. There are two available cryogen sources on the market, nitrous oxide and argon, which have been tested and shown to be efficacious in animal and donor human transplant heart models [1381, 1394, 1395]. Nitrous oxide has a higher heat absorption than argon. The argon device (Cardioblate CryoFlex, Medtronic Inc.) reaches a minimum temperature of -160°C. The two nitrous oxide devices (cryoFORM and cryoICE, AtriCure, Inc.), reach minimal probe temperatures of -50°C to -70°C. Both companies have designed long malleable disposable probes to adjust to the complex atrial anatomy. In a chronic ovine model using the cryoICE (AtriCure, Inc.) device, transmurality was achieved in almost all atrial lesions (98%) performed endocardially [1396]. Similarly, in a chronic canine model, use of the CryoFlex clamp and probe (Medtronic Inc.) resulted in 93% tissue section transmurality of all LAA and PV lesions and 84% tissue section transmurality in all Cox maze linear lesions [1397]. There have been no surgical cryoablation devices that have yet received an FDA indication for the treatment of AF, but there are ongoing clinical trials with both the nitrous oxide and argon devices.

12.1.3 Procedural targets and lesion sets

Due to a lack of randomized trials, there is insufficient high-quality data on what should be the most important targets during surgical ablation. This section will review what is known from retrospective case series and the few randomized trials that have been performed.

12.2.3.1 Pulmonary vein isolation. As with catheter ablation, PVI is a foundational part of all surgical AF ablation procedures. Although documentation of exit and/or entrance block across PVs is preferred, it is infrequently performed. Intraoperative mapping has documented complex activation patterns both in the left and right atrium in patients with long-standing persistent AF undergoing surgery for AF and mitral valve disease, **indicating** that a simplified approach with PVI alone may not be adequate during concomitant surgical ablation [1398]. Similar to catheter ablation of persistent AF, surgical PVI alone has had disappointing late results. In a single center cohort of consecutive patients with medically refractory symptomatic AF, a minimally invasive surgical approach employing PVI combined only with ablation of autonomic ganglionic plexi and ligament of Marshall resulted in a single procedural success rate of 37.8% after a 5 year follow-up using ECG and transtelephonic monitoring [1399]. Retrospective observational data suggest that surgical ablation with PVI alone is inferior to the biatrial maze procedure in patients with persistent or long-standing persistent AF [1400]. One randomized trial on non-paroxysmal AF patients undergoing mitral valve surgery reported similar rate of freedom from AF with PVI as compared to the biatrial maze procedure [1368]. However, the study was under-powered to adequately answer the question of which lesion set was more efficacious.

12.1.3.2 Isolation of the left atrial posterior wall. Isolation of the entire LA posterior wall and all four PVs is the most important part of surgical ablation procedures. In a large retrospective study of patients undergoing the Cox maze IV procedure, failure to isolate the entire posterior LA resulted in only 33% freedom from AF off AADs at 5 years compared to a 66% freedom in patients who underwent posterior LA isolation ($p=0.017$) [1349]. An incomplete lesion set is even more impactful in patients undergoing mitral valve surgery. In such patients, the failure to isolate the entire posterior LA during a Cox maze procedure was the only independent predictor of procedural failure and resulted in 6.7 fold increased risk of AF recurrence [1401]. Due to anticipated improvement in rhythm outcome with LA posterior wall isolation, a minimum of PVI plus LA posterior wall isolation should be performed in patients undergoing surgical AF ablation.

12.1.3.3 Right and left atrial linear lesions. Linear lesions interrupting the CTI in the RA and the mitral isthmus in the LA aim to prevent macroreentrant tachycardias. Catheter ablation data suggest that macroreentry is the predominant mechanism of atrial tachycardias in patients with prior history of mitral valve surgery. In many cases macroreentrant circuits are located in the right atrium, but left-sided circuits may also occur particularly if a concomitant Maze procedure was performed [1402]. In a single-center analysis of consecutive persistent AF patients undergoing thoracoscopic ablation, adjunctive CTI ablation significantly increased freedom from atrial tachyarrhythmia recurrence [1403]. The superior-inferior vena cava ablation line anchors the RA isthmus line and thus serves an important role in preventing late RA flutter. Documentation of completeness is beneficial in all deployed linear lesions during surgical AF ablation.

12.1.3.4 Ganglionated plexus ablation. There has been interest in GP ablation in stand-alone surgical AF ablation procedures. An epicardial antral PVI and posterior box lesion including the ligament of Marshall results in collateral ablation of most atrial GP. Therefore, it is difficult to evaluate the additional role of GP ablation on top of epicardial PVI plus PWI using bipolar clamps. The only randomized study examining the efficacy and safety of additional GP ablation in patients undergoing thoracoscopic surgery showed no incremental benefit in AF recurrence rate and a significantly higher rate of major procedural complications in patients randomized to GP ablation [1404]. Therefore, with the exception of a clinical trial setting, GP ablation should not be performed during surgical AF ablation.

12.1.3.5 Ligament of Marshall. There are no data from the surgical literature to support the ligament of Marshall as a target for ablation. However, this structure is usually divided while isolating the left PVs during surgical ablation procedures.

12.1.3.6 Left atrial appendage exclusion. Exclusion of the LAA is a standard part of all surgical AF ablation procedures and is discussed in detail in section 12.4.

12.2 Concomitant surgical ablation of atrial fibrillation

Patients undergoing cardiac surgery frequently have concomitant AF which if untreated, has been shown to increase the risk of postoperative ischemic stroke and to negatively impact long-term survival [1350,1359,1405]. Surgical ablation of AF combined with LAA exclusion or excision restores sinus rhythm and atrial contraction and reduces the risk of thromboembolism. In this section, the efficacy, safety, and optimal lesion set of concomitant AF ablation during cardiac surgical procedures are discussed. It is noteworthy that in patients eligible for cardiac surgery and concomitant AF ablation it is often challenging to differentiate whether patient reported symptoms are related to underlying cardiac disease or coexistent AF.

12.2.1 Efficacy of concomitant AF surgery

Concomitant AF surgery has been shown to increase SR maintenance rate in multiple randomized and non-randomized trials [1331–1333,1351,1359]. A metaanalysis of 23 RCTs demonstrated that AF ablation concomitant to cardiac surgery results in increased freedom from AF at 12 months [1406]. Several trials have demonstrated a reduced incidence of stroke at 5 years postoperatively [1334,1335,1343,1360,1361]. Improvement of long-term survival after concomitant surgical AF ablation has not been proved by a RCT. However, an analysis of the US Society of Thoracic Surgeons AF database with propensity matching showed that concomitant surgical AF ablation was associated with a reduction in 30-day mortality [1331]. In addition, several retrospective and propensity-matched studies as well as large national registries have demonstrated that the performance of surgical AF ablation concomitant with other cardiac procedures (particularly mitral valve surgery and CABG) was associated with improved long-term survival [1336–1341,1344,1345]. In a retrospective propensity score-matched analysis of a nationwide registry, concomitant surgical ablation for AF in patients undergoing isolated CABG was shown to significantly improve long-term survival rates [1345]. Improved QoL at a long-term postoperative follow-up period has also been demonstrated in patients who underwent AF surgery with SR restoration [1407,1408].

12.2.2 Safety of concomitant AF surgery

Several studies, including RCTs, have demonstrated that concomitant AF surgery is safe and does not increase operative mortality [1336,1337,1350,1360,1409]. Although a propensity score matching study showed an increased incidence of acute kidney injury after AF surgery, the associated long-term risks were offset by the significant survival benefit derived from the concomitant Cox maze procedure [1410].

Postoperative atrial tachyarrhythmias and new permanent pacemaker implantation are the typical complications potentially related to AF surgery. Incomplete linear lesions with residual conduction and inappropriate surgical techniques are mainly responsible for postoperative occurrence of predominantly macroreentrant ATs [1411]. Intraoperative verification of conduction block, particularly to ensure PVI, may reduce the incidence of AT due to incomplete ablation [1412].

Increased incidence of new permanent pacemaker implantation after the Cox maze procedure has been demonstrated in many studies [1331,1406,1413,1414]. However, in a recent large European registry of patients undergoing valve surgery, surgical AF ablation was not associated with increased need for permanent pacemaker implantation [1415]. Sinus node dysfunction requiring permanent pacemaker implantation can occur in up to 10% of patients after the Cox maze procedure for non-paroxysmal AF and may be a result of unmasking preexisting sick sinus syndrome [1416]. In addition, mechanical or thermal injury to the sinus or atrioventricular node and interruption of the conduction system arterial supply are the main intraoperative reasons for postoperative bradycardia and in-hospital permanent pacemaker implantation [1416]. Multidisciplinary collaboration between cardiothoracic surgeons and electrophysiologists, proper training on ablation techniques and deployment of complete linear lesions may reduce the incidence of postoperative atrial tachyarrhythmias and permanent pacemaker implantation and enhance patient outcomes [1360, 1417].

12.2.3 Optimal lesion set in patients undergoing left atrial open procedures

The biatrial Cox maze procedure is the preferred procedure for surgical AF ablation during open LA procedures and achieves high rates of AF conversion to SR and freedom from AF recurrence [1350,1409,1418]. However, recognizing that surgical training and experience may vary across centers, the writing group suggests that biatrial Cox maze procedure or a minimum of PVI plus LA posterior wall isolation is required in patients undergoing surgical ablation concomitant to LA open cardiac surgery. The lesion set of the Cox maze IV procedure is shown in Figure 14.

12.2.4 Optimal lesion set in patients undergoing non-left atrial open procedures

Fewer patients undergoing non-LA open procedures, such as aortic valve replacement or CABG, have undergone concomitant AF ablation compared to those with LA open procedures, because of necessity of adding an LA incision to perform ablation in the LA. Epicardial PVI alone has been performed more often than a biatrial maze procedure in AF patients undergoing non-LA open procedures, and this might have led to biased analyses of the data [1419]. A dilated LA has been shown to be associated with worse AF-free and event-free survivals after PVI for patients with paroxysmal AF undergoing non-LA open cardiac surgery [1420]. Several studies have shown that biatrial maze procedure is associated with superior rhythm outcome and a lower risk of adverse events and long-term overall mortality compared to left atrial lesion sets following surgical AF ablation concomitant to nonmitral valve surgery [1414, 1421–1423].

However, many surgeons are reluctant to increase procedural complexity and risks by performing AF ablation through an atriotomy [1424]. Therefore, selection of PVI combined with PWI or other modified procedure should be individualized in patients undergoing surgical ablation concomitant to closed (non-left atrial open) cardiac surgery. Further clinical studies are needed to clarify the optimal lesion set in these patients and to further elucidate associated risks and benefits.

12.3 Stand-alone surgical ablation of atrial fibrillation

12.3.1 Stand-alone Cox maze procedure

The largest series of stand-alone Cox maze IV procedures (236 consecutive patients, 59% prior failed catheter ablation, median duration of preoperative AF 6.2 years) demonstrated very high late efficacy in sinus rhythm maintenance (89% and 77% freedom from recurrent atrial tachyarrhythmias at 5 and 10 years respectively), irrespective of AF type or surgical approach (median sternotomy versus minimally invasive approach), without 30-day mortality [1346]. Benussi et al. reported on 59 patients undergoing stand-alone Cox maze procedure with similar excellent early and late outcomes with 84% of patients remaining in sinus rhythm at 7 years, without 30-day mortality or late strokes [1347]. In 133 patients undergoing minimally invasive, stand-alone Cox maze procedure (78% long-standing persistent AF), Ad et al. reported a 73% freedom from atrial tachyarrhythmias off AADs at 5 years with only one late stroke and no associated mortality [1348]. These case series demonstrate the low mortality and excellent late outcomes achieved by Cox maze procedure as stand-alone treatment in a challenging group of patients with the majority having long-standing persistent AF of long duration. It is important to point out that these procedures were done with cardiopulmonary bypass, which may explain the safety of this procedure. Unfortunately, there have been no prospective multicenter trials of the stand-alone treatment of AF with the Cox maze procedure.

12.3.2 Minimally invasive surgical - hybrid AF ablation

Minimally invasive techniques have been introduced in AF surgery aiming to reduce surgical invasiveness while maintaining efficacy in rhythm outcome. These approaches combine sternotomy-sparing minimal surgical incisions with different access sites, endoscopic visualization, with or without catheter ablation at the same or at a different stage (hybrid ablation). The reduced invasiveness of these techniques as compared to the surgical Cox maze procedure has rendered these approaches more attractive to patients and surgeons. Evidence in different AF patient categories is accumulating to establish efficacy and safety. However, comparison of different study results is limited by nonuniformity in patient populations and lack of standardized surgical technique, ablation technology and deployed lesion sets.

During the last decade, the "hybrid" approach, consisting of a combined surgical-percutaneous catheter ablation strategy has garnered increasing acceptance in clinical practice, with promising rhythm outcomes [221,1425–1432]. A key aspect of this treatment strategy is that it harmonizes epicardial and endocardial ablation components to effectively target key drivers of AF, including the PVs and the LA posterior wall. There are different surgical modalities to achieve the target of PVI and LA posterior wall isolation. In this section, we discuss the two main techniques currently employed in clinical practice.

Hybrid ablation combines expertise from the surgical and electrophysiology teams to achieve an optimal result. Coordination and collaboration among the multidisciplinary team members are paramount to a successful program. The timing of the epicardial and endocardial stage of the hybrid ablation procedure varies based on institutional practice. In the single stage model, epicardial and endocardial procedures can occur back-to-back in the same suite or separate suites, or over sequential days. Completion of both phases in the same session prolongs procedural time which may add additional risk in patients with comorbidities. For dual staged programs, the epicardial component typically occurs in the cardiac operating room and the endocardial component is scheduled approximately 2-4 months later in the electrophysiology laboratory, aiming to complement the epicardial component with touch-up lesions, ensuring isolation of PVs, LA posterior wall and epicardially deployed linear lesions. The impact of different procedural timing on patient outcomes is unknown. The minimally invasive surgical part of the hybrid procedure is most frequently performed using a video-assisted thoracoscopic surgical approach or with the "convergent" approach.

12.3.2.1 Thoracoscopic surgical approach. The thoracoscopic approach is performed under general anesthesia with double-lumen endotracheal tube placement for selective lung ventilation. On the right side, a camera port is placed in the fifth intercostal space midaxillary line, a 5 or 10 mm working port in the sixth or seventh intercostal space anterior axillary line and a 5-mm working port in the third intercostal space anterior axillary line. The pericardium is opened anterior to the PN. Blunt dissection is used to open the transverse and oblique sinuses. Antral isolation of the right PVs as a pair is performed with repetitive applications using a bipolar RF clamp (section 12.1.2). The same port incisions are made on the left side but placed more posteriorly. The pericardium is opened posterior to the PN. In patients with severe chronic obstructive pulmonary disease, thoracoscopic epicardial isolation of the PVs can be performed only on the left, and the right PVs subsequently isolated from the endocardium to avoid bilateral sequential lung deflation. An alternative would also be a convergent procedure using subxiphoid access along with Lariat closure of the LAA. After PVI documentation, a roof line (connecting both superior PVs) and an inferior line (connecting both inferior PVs) is made epicardially using directional ablation devices (section 12.1.2) to create box isolation of the LA posterior wall (Figure 15). As an alternative, one epicardial box lesion including the posterior left atrial wall and the PVs can be created using only the irrigated bipolar biparietal Cardioblate Gemini-S (Medtronic Inc.,

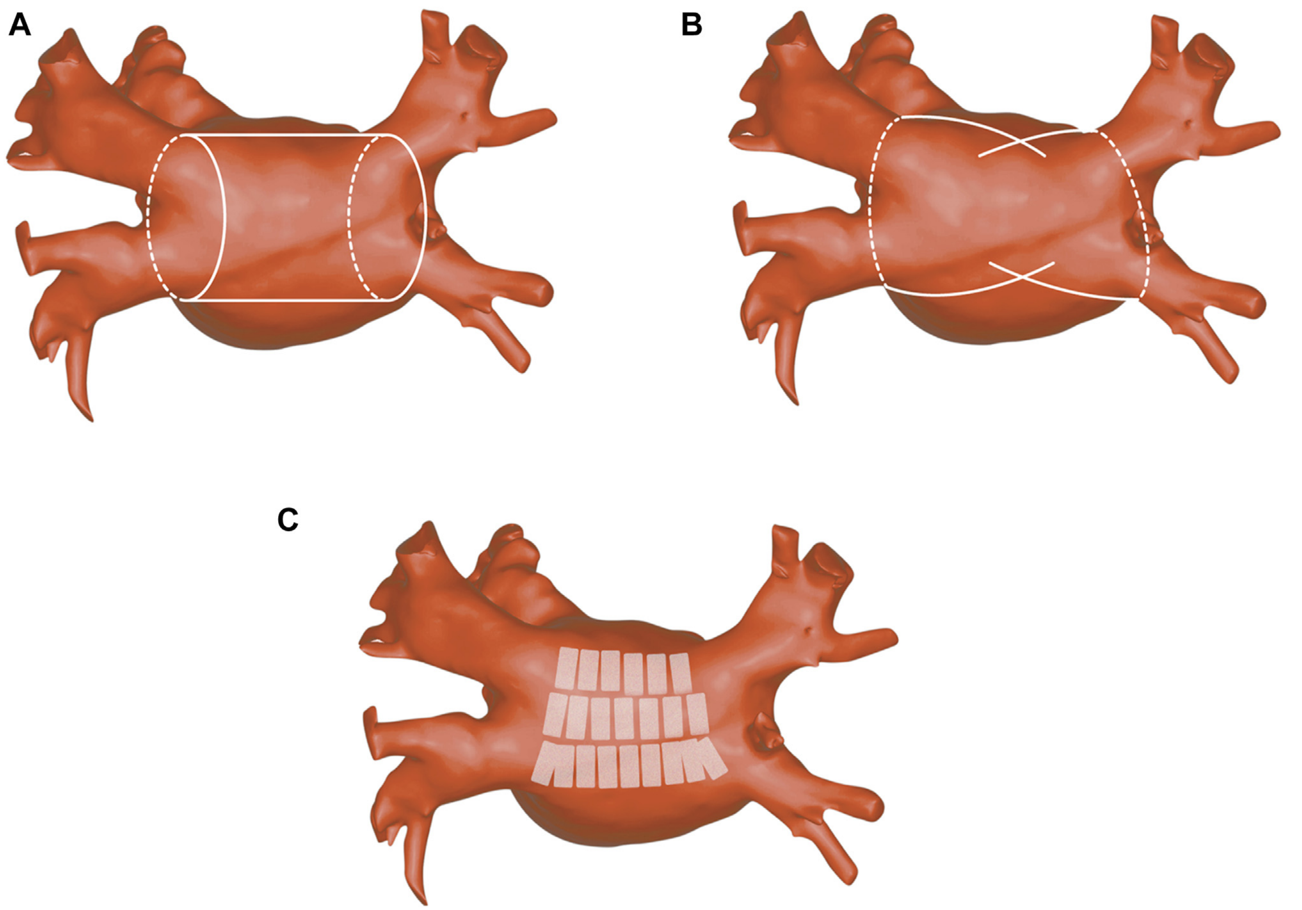


Figure 15
Posterior view of the left atrium showing epicardial lesion sets during thoracoscopic surgical AF ablation: pulmonary vein isolation with connecting roof and inferior lines (panel A), en-bloc pulmonary vein and posterior wall isolation using the Cardioblate Gemini-S (Medtronic Inc., Minneapolis, MN) RF ablation system (panel B) and posterior wall ablation using the convergent approach (panel C).

Minneapolis, MN) RF ablation system by performing two clamp lesions from the right and left side that overlap in the middle of the posterior wall (Figure 15).

Additional ablation lesions may be deployed, such as circular lesion of the SVC, linear lesion connecting both caval veins and mitral isthmus line. Endocardial touch-up ablation to achieve bidirectional block can be delivered in the same or subsequent stage with catheter ablation. Furthermore, in patients with prior history or intraprocedural induction of CTI-dependent flutter, the CTI is ablated endocardially.

LAA exclusion should also be performed in all patients during minimally invasive surgical AF ablation to reduce thromboembolic risk (section 12.4). Through an incision at the 3rd to 4th intercostal space, or via a completely thoracoscopic approach, the surgeon can easily reach the LAA and exclude it. LAA exclusion must be performed at the very base of the structure, as to avoid leaving behind residual stump. Incomplete removal of LAA is associated with increased risk of local thrombus formation and embolization.

Since the thoracoscopic surgical AF ablation lesions are exclusively epicardial, one can perform the procedure without the need for anticoagulation during and after the procedure. Therefore, stand-alone thoracoscopic surgical AF ablation is the best option for patients who have bleeding diathesis (particularly central nervous system bleeds) precluding the anticoagulation needed during and after endocardial catheter ablation. Additional suitable patient subsets include those without the ability to achieve LA access endocardially (large atrial septal occlusion device, interrupted inferior vena cava), or those with LAA thrombus.

12.3.2.2 Hybrid Convergent procedure. The hybrid Convergent procedure was first described in 2009 and clinical outcomes published in 2010 by Kiser et al.[1433] Since then, the employment of this technique has been reported in numerous studies and subsequent modifications have been developed to maximize safety and clinical outcomes [221,1425–1432,1434–1438]. This is a minimally invasive, closed-chest procedure performed on the beating heart that combines epicardial radiofrequency ablation focused on the LA posterior wall followed by complementary endocardial catheter ablation. Epicardial ablation is performed under endoscopic visualization using a closed-irrigation, unipolar RF catheter device (EPi-Sense Guided Coagulation System with Visitrax, AtriCure, Inc.). The device is inserted via a small subxiphoid incision using a pericardioscopic cannula (SUBTLE, AtriCure, Inc.) to reach the LA posterior wall and is maneuvered in the pericardial space using the cannula and endoscope. During ablation, epicardial tissue is suctioned by vacuum onto the RF coil on one side of the device such that RF energy is only applied towards the heart, and thus stabilizes the device on the atrium and optimizes energy delivery. Each lesion is created by a 90-second application of alternating current via an impedance-based power control algorithm with a maximum output of 30 Watts. Lesions are overlapped across the entire LA posterior wall to promote contiguity, and thus minimize gaps. The epicardial stage aims to debulk as much of the LA posterior wall as can be accessed and is limited at the superior margin of the lesion set by the oblique sinus (section 3.8). Posterior segments of the PV ostia/antra may also be reached and ablated in most cases (Figure 15). The endocardial component supplements the epicardial lesions around the pericardial reflections and any incompletely ablated posterior wall areas and addresses any remaining gaps between the PV and the posterior wall lesion set ensuring electrical isolation of the PVs. The endocardial component can also include a CTI line and additional substrate modification. A key difference between thoracoscopic ablation and the hybrid Convergent procedure is that PVI is performed epicardially using bipolar RF clamps in the former while in the latter it is achieved endocardially with catheter ablation.

Single and multi-center studies have reported 66% to 95% freedom from atrial tachyarrhythmias at one year following the hybrid Convergent procedure [221,1425–1428,1430,1432,1439], with 52% to 81% arrhythmia-free survival without the use of AADs [1425,1427–1429,1439]. RCT data are reported in detail in section 12.3.3. Gained experience with hybrid Convergent ablation has identified potential adverse events that can be mitigated. Thermal injury to the esophagus can be avoided by careful device orientation, esophageal temperature monitoring, and prophylactic irrigation of the pericardial space. Late pericardial effusion due to Dressler's syndrome and cardiac tamponade can be prevented by pericardial drains [1427,1436] and prophylactic medications (colchicine, steroids and/or NSAIDs) [1440,1441]. Timely diagnosis of pericardial effusion is facilitated by patient education on symptoms, and transthoracic echo surveillance at approximately 2-4 weeks [1440]. Complications can arise from both epicardial and endocardial procedures, but greater experience has been associated with reduced procedural complications [1438].

Several energy sources and variant lesion sets (apart from PVI and LA posterior wall ablation) have been incorporated in Convergent endocardial ablation workflows. One large study reported the use of endocardial cryoballoon in hybrid Convergent procedures with favorable safety and efficacy [1442]. The availability of PFA can improve safety and durability of endocardial lesions delivered at the posterior wall and thus potentially increase success rates. Given the likely role of LAA in persistent AF pathophysiology, [829] limited studies have also combined the hybrid Convergent approach with transthoracic epicardial placement of a clip or stapled excision of the LAA reporting favorable initial results [1443–1446].

12.3.3 Clinical evidence – comparison of catheter and surgical ablation

Several RCTs have compared efficacy and safety of surgical ablation (minimally invasive or hybrid) with catheter ablation in mostly persistent and long-standing persistent AF patients. Existing data and pertinent advice are reported below.

12.3.3.1 Paroxysmal AF. Randomized controlled clinical trial data evaluating the efficacy of any type of standalone surgical AF ablation in paroxysmal AF patients are limited. The FAST trial was a head-to-head randomized comparison of catheter ablation versus epicardial thoracoscopic surgery (bipolar RF ablation without standardized procedural workflow) in a total of 124 patients who had drug-refractory, symptomatic AF (66% paroxysmal AF) with prior failed catheter ablation or at high risk for failure (dilated LA) [1362]. The primary efficacy study end point (freedom from atrial tachyarrhythmias >30 seconds off AADs at 12-month follow-up) was significantly higher in the surgical as compared to the catheter ablation group (66% vs 37%, p=0.002). In the subgroup analysis, surgical ablation showed superior efficacy in the paroxysmal but not in the persistent AF patient subgroup. The adverse event rate at 12 months was significantly higher in the surgical ablation group mainly due to increased procedural complications. After a mean follow-up period of 7.0 years from randomization, atrial tachyarrhythmia recurrence was still significantly lower with surgical ablation (56%) compared with catheter ablation (87%), without any difference in the primary clinical composite endpoint (death, myocardial infarction, or cerebrovascular event)[1363]. In a smaller RCT of 64 patients with previous failed catheter ablation (59% paroxysmal AF), minimally invasive surgical ablation (thoracoscopic approach using bipolar RF clamp and targeting PVI, posterior box isolation and GP ablation) resulted in a significantly lower atrial tachyarrhythmia recurrence at 12 months of follow-up as documented by ICM, with an associated significant increase in serious adverse events as compared to catheter ablation [1364].

Only one RCT has compared minimally invasive surgical ablation (thoracoscopic approach using irrigated bipolar RF clamp and targeting PVI only with adjunctive LAA ligation) to catheter ablation as primary invasive AF treatment. The study included 52 patients with drug-refractory paroxysmal or early persistent (< 3 months duration) AF with ICM for rhythm assessment during follow-up. Single procedure arrhythmia-free survival off AADs after 2 years was similar in the catheter ablation as compared to the surgical ablation group (56% vs 29%, respectively, p=0.059), while a greater proportion of patients in the catheter ablation group had a low AF burden (<0.5%) at 2 years. Procedure-related major complications occurred more often with the surgical than with the catheter ablation approach (20.8% vs 0%, p=0.029)[1365].

In paroxysmal AF patients, the primary therapeutic target for any type of ablation strategy remains PVI. The following factors have been taken into account when determining the role of stand-alone surgical or hybrid ablation in symptomatic paroxysmal AF patients: (a) paucity of RCT data in paroxysmal AF patients, (b) discrepancy in reported rhythm outcome benefit when compared to catheter ablation (c) consistent reporting of higher complication rate with surgical ablation compared to catheter ablation, (d) lack of pathophysiological evidence to support ablation targets beyond PVI in paroxysmal AF patients that may be achieved more efficiently with surgical approaches, (e) efficiency of catheter ablation in achieving durable PVI while ensuring reduced hospital stay and more rapid patient recovery.

12.3.3.2 Persistent and longstanding persistent AF. Several RCTs have evaluated the role of minimally invasive surgical or hybrid ablation in comparison to catheter ablation in symptomatic patients with persistent or long-standing persistent AF as primary ablative therapy.

In the CASA-AF trial, 120 patients with symptomatic long-standing persistent AF without prior ablation were randomized to surgical ablation (thoracoscopic approach using bipolar RF clamp and targeting PVI, posterior box isolation and GP ablation) or catheter ablation (PVI, posterior box isolation, CTI and mitral isthmus line) [1447]. At 12 months, 26% of patients in the surgical ablation arm and 28% of patients in the catheter ablation arm were free from atrial tachyarrhythmias, off AADs, after a single procedure as documented by invasive cardiac rhythm monitoring ($p = 0.84$). A similar percentage of patients experienced an arrhythmia burden reduction of $\geq$75% as well as procedure-related serious complications within 30 days of the intervention in both compared arms. Surgical ablation was associated with significantly higher costs and fewer quality-adjusted life-years than catheter ablation. Based on the study findings, the authors concluded that they found no evidence to suggest standalone thoracoscopic surgical ablation as first-line invasive therapy in patients with symptomatic long-standing persistent AF refractory to AADs.

In the CONVERGE trial, 153 patients with symptomatic persistent or long-lasting persistent AF (mean duration 4.4±4.7 years) were randomized 2:1 to undergo PVI plus PWI with a hybrid thoracoscopic/endocardial approach (99 patients) or PVI plus roof line (no PWI) plus CTI line using a percutaneous, fully endocardial approach (50 patients). There was a significantly higher 12-month freedom from AF in the absence of new or increased dosage of previously failed or intolerant AADs (primary endpoint) in the hybrid arm compared with the endocardial arm (68% vs 50%; $p=0.036$)[219]. However, there was a higher major adverse event rate of 7.8% in the hybrid group compared with a 0% incidence in the endocardial group. The reported efficacy superiority of the hybrid as compared to the catheter ablation approach should be acknowledged in the context of relevant limitations such as the non-uniform ablation targets in compared groups (no empirical PWI in the catheter ablation group) and comparison of a hybrid (epicardial / endocardial) double approach versus a single catheter ablation.

Recently, the HARTCAP-AF trial randomized 41 symptomatic, ablation-naive patients with persistent or long-standing persistent AF to an epicardial surgical ablation performed thoracoscopically (bipolar RF ablation) with occlusion/removal of the LAA combined with percutaneous endocardial ablation (one-stage) versus percutaneous endocardial catheter ablation, with optional repeated catheter ablation(s)[1448]. Hybrid ablation resulted in significantly more patients in SR off AADs at 12 months of follow-up compared with catheter ablation (89% vs 41%, $P = 0.002$), without increasing the number of serious adverse events (21% vs 14%, $P = 0.685$).

The recent, multicenter CEASE-AF trial randomized a total of 154 patients with drug refractory, symptomatic persistent or long-standing persistent AF in a 2:1 ratio to either a staged hybrid ablation or catheter ablation with potential repeat ablation which was not considered a primary effectiveness failure. The hybrid ablation procedure included thoracoscopic RF ablation (PVI, posterior wall isolation) and LAA exclusion with second stage endocardial catheter ablation performed 3 to 6 months later. In the catheter ablation arm, PVI was mandatory while additional ablation was left to physician's discretion (only 40.2% received posterior wall ablation). Only 11.5% of patients in the endocardial ablation arm underwent a second catheter ablation procedure. The primary efficacy endpoint (freedom from AF/AFL/AT > 30 seconds off all class I/III AADs except those at doses previously failed) was significantly higher in the hybrid group as compared to the catheter ablation group (71.6% versus 39.2%, $p<0.001$) with similar major complication rates [1449].

There is no RCT directly comparing minimally invasive epicardial surgical ablation alone versus hybrid ablation. A systematic meta-analysis of 41 studies (published until November 2016) reporting outcomes of these two types of ablation strategies in a total of 2737 patients concluded that single-procedure survival free from atrial tachyarrhythmias without AADs was similar between epicardial-alone and hybrid approaches both at 12 months (epicardial alone 72% vs hybrid 63%) and at 24 months (69% and 57% respectively). Interestingly, hybrid ablation was associated with higher rate of major complications, while transdiaphragmatic access and use of unipolar RF was associated with lower success rates as compared to thoracoscopic access and bipolar RF respectively [1450].

A limitation of hybrid AF ablation that restrains its wider applicability is the higher rate of complications compared to percutaneous catheter ablation. This is not surprising given the added complexity and duration of combining surgical and catheter-based procedures, particularly when done at the same session. The reported rate of procedural related serious adverse events in the abovementioned RCTs as well as in observational studies is usually in the range of 8-20% [1447,1448,1451,1452]. These findings emphasize the importance of assembling an experienced multidisciplinary hybrid team consisting of a cardiologist, electrophysiologist and surgeon as discussed above. Patients should be informed of the risks and benefits of a hybrid versus a percutaneous ablation approach prior to undergoing an AF ablation procedure. Continued advances in ablation technologies, surgical and catheter-based approaches are anticipated to further improve patient outcome and reduce complications from hybrid ablation procedures.

12.4 Left atrial appendage exclusion

The LAA is the site of thrombus location in 90% of nonrheumatic AF patients with stroke and is a well-documented target for stroke reduction in patients with AF [1453]. Multiple percutaneous and surgical techniques have been proposed for LAA elimination. Recent evidence supports the value of percutaneous LAA occlusion devices as an alternative to anticoagulants in AF patients [1454,1455]. Surgical management of the LAA has an established role for stroke risk reduction in AF patients as a part of surgical/hybrid AF ablation, as an adjunct to concomitant cardiac surgery and, more rarely, as a standalone treatment. Early evaluation of the Cox maze III procedure suggested a reduction in late stroke after surgery[1456,1457]. Other retrospective series subsequently suggested a lower-than-expected incidence of late neurologic events after a Cox maze procedure, independent of the preoperative CHA_2DS_2VASc score or long-term warfarin use [1458,1459]. The reduction in stroke has been attributed to both a combination of SR restoration and LAA elimination.

Historically, the most common techniques for exclusion of the LAA have been internal ligation, excision, or stapling at the base [1460–1463]. Unfortunately, the efficacy of internal ligation and stapled excision or exclusion have been poor in late follow up [1464–1466]. While surgical excision has been shown to be effective, there has been concern for bleeding complications, especially in elderly patients with friable tissue. A more recent technique has been the use of external clips placed either under direct visualization or thoracoscopically at the base of the appendage (AtriClip, AtriCure, Inc.) [1467–1471]. The first AtriClip exclusion device was FDA approved in 2009 for the occlusion of the LAA in patients undergoing other open cardiac surgical procedures. In a large prospective non-randomized trial, the EXCLUDE trial, 60 of 61 patients had a successful LAA exclusion at the 3 month follow up with a first generation AtriClip device[1472]. Subsequently, the long-term results from a prospective device trial reported that all 36 patients were without stroke and there was 100% LAA occlusion confirmed by imaging at 3 years without thrombi, reperfusion, or residual neck stump of > 1 cm [1473]. In a recent larger series of 291 patients undergoing epicardial deployment of AtriClip device during open-heart surgery, the LAA was successfully excluded at 3 years in all patients [1474]. Furthermore, the subgroup of patients with LAA occlusion who discontinued OAC during follow-up had a 87.5% relative risk reduction in ischemic stroke as compared to the expected rate in patients with similar CHA_2DS_2VASc score [1474].

Since then, several iterations have been made with the most recent devices, Pro-V and FLEX-V AtriClip (AtriCure, Inc.), receiving FDA approval in 2016 and 2018 respectively. Several studies have established the safety and long term efficacy of stand-alone minimally invasive or thoracoscopic LAA occlusion with the AtriClip (AtriCure, Inc.) device in patients who either cannot be anticoagulated or who are not candidates for a transcatheter approach [1352–1357,1475,1476]. The role of concomitant surgical LAA occlusion, in addition to OAC use, is best supported by a large RCT on LAA occlusion (LAAOS III)[1358]. Over 4800 patients with AF undergoing cardiac surgery, were randomized to LAA occlusion (amputation, stapling, or suturing) or no treatment, and were followed for a mean period of 3.8 years, with 76.8% of the participants continuing their OAC treatement. At 3 years, there were significantly fewer strokes and systemic emboli in the occluded vs non-occluded cohorts (4.8% vs 7%, P= 0.001).

Section 13: Training and Institutional Requirements for Atrial Fibrillation Ablation

For patients to have safe and effective AF ablation treatment, clinicians need to be adequately trained and work in an institution with appropriate facilities and support. Before performing AF ablation, clinicians and institutions need to have formally assessed and recorded that they have the training, standard operating procedures and facilities to:

- Select appropriate patients for treatment
- Deliver the treatment in a safe and cost-effective way
- Manage common complications (e.g. postprocedural pain, hematoma)
- Manage or have arrangements to manage rare complications (e.g. cardiac perforation and tamponade, AEF, stroke)
- Ensure adequate patient follow-up
- Record and audit their results and outcomes
- Respond to incidents, errors and complications and modify their practice to reduce the probability of recurrence.

The cost, efficiency and access to catheter ablation is an important consideration. It is therefore unrealistic to expect every clinician and institution to provide the same level of facility and care. More complex cases with higher risk should be treated by clinicians with a greater level of experience and training, in institutions with greater support. Conversely, many lower risk patients undergoing simple PVI will not require the same level of support. As long as centers and clinicians can demonstrate that they are able to deliver all of these fundamental quality metrics outlined above, then it is reasonable for them to perform catheter ablation of AF.

13.1 Training requirements

AF ablation is not performed by a doctor or surgeon alone; it is a procedure involving a multidisciplinary team. Patients may interact with and depend on many of the clinicians in this team and therefore training, competence and access to facilities for all of these team members needs to be considered.

13.1.1 Appropriate selection of patients

Patients who are suitable for AF ablation are likely to be identified by clinicians who do not perform AF ablation, including specialist nurses. However, before being scheduled for a procedure, patients should have had the opportunity to meet a doctor who is competent to perform the procedure, with knowledge of the outcomes and other treatment options in order to allow the patient to make an informed decision. Patients should also understand any limitations of the facilities available to them and physicians should be able to advise patients when a more complex level of care is needed. The treatment options for AF, AF ablation and factors that influence outcomes are discussed in detail in previous sections. Trainees should have demonstrated similar knowledge and quality of consent as their supervisors before selecting and consenting patients independently. Clinical staff involved in preparing patients for their procedure should also be aware of clinical features that may give them an increased risk or poorer outcome from an ablation and members of the team like specialist nurses performing pre-admission assessment should be competent to identify such risk factors and alert the rest of the team.

13.1.2 Technical knowledge required

The doctor performing the procedure should have a thorough understanding and appropriate training (with formal documentation of this if appropriate) of:

- Current indications for AF ablation (section 4)
- Relevant anatomy (section 3)
- Advantages and disadvantages of different technologies and techniques for AF ablation (section 6 and section 8)
- Success rates for ablation in different patient groups (section 8 and section 10)
- Appropriate postoperative management and follow up of patients (section 9)
- Prevention, clinical presentation and management of procedural complications (section 11)

Physicians should also have been through a formal and documented training program with their progress logged and signed off by an appropriate supervisor. They should have demonstrated a knowledge of the areas required and competence to perform independently:

- Achieve venous access (including use of vascular ultrasound)
- Perform transseptal puncture
- Identify and isolate the PVs (including validating PVI on electrophysiological tracings and performing differential pacing maneuvers)
- Be competent in using and interpreting 3D mapping systems
- Understand biophysics of RF, cryothermy and other energy sources, energy selection and application
- Achieve hemostasis postprocedure; this may include use of figure-of-8 sutures and/or vascular closure devices
- Identify and drain a pericardial effusion

AF ablation now comes in several forms which range from PVI to complex AT ablation. It is recognized that some clinicians may work in a service that just performs PVI with single-shot technologies and refers patients with rhythms other than AF to other electrophysiologists. The writing group suggests that all physicians involved in AF ablation, even when focusing on single-shot PVI, should also have attained basic competence in mapping and ablation procedures that are required for treatment of coexistent arrhythmias e.g. typical AFl, atypical AFl or SVT. In case of non-availability of 3D mapping systems, patients with AT post AF ablation should be referred to appropriately equipped institutions.

13.1.3 Training of non-medical team members

The other members of the team performing ablation should have training appropriate to their roles. These roles may be varied but whatever their role, their training and competence should be recorded and assessed. Important roles fulfilled by non-medical members of the team may include:

- Selecting patients - understanding indications and characteristics adversely affecting outcomes of AF ablation
- Managing electrophysiology equipment
- Managing analgesia/sedation - appropriate and safe sedation training
- Assisting in management of life-threatening complications (e.g. tamponade) – training and rehearsal of procedures and use of equipment
- Performing patient follow-up
- Identification of complications or postablation arrhythmia recurrence

13.1.4 Completion of training

Numbers of procedures required to achieve competence are very difficult to define because different clinicians will progress at different rates. It is recommended that trainees should have completed a training program and their supervisor/trainer should be able to take responsibility for a trainee and confirm that the trainee is competent to perform the procedures they intend to undertake as an independent practitioner.

The writing group suggests that the minimum required practical experience with active participation, includes:

- 50 AF ablation procedures
- 20 CTI flutters
- 10 non-CTI dependent focal or reentrant tachycardias

These numbers are consistent with the 2015 ACC/AHA/HRS Advanced Training Statement on Clinical Cardiac Electrophysiology and the Level 2 EHRA Certified Electrophysiology Specialist requirements [1477]. Further skills and knowledge may be required depending on the practice of the trainee/physician.

13.1.5 Maintaining competence

It is well recognized that both physician and institution procedure volume is associated with improved patient outcomes. Even if physicians have received training for catheter ablation, it is important that they are performing these procedures regularly and continue a program of self-education to ensure that they are aware of the most current evidence and thinking on AF and its management.

Actual procedure numbers continue to be difficult to define because some clinicians will require longer training and more procedures to maintain their performance than others. Analysis of early practice suggested that individual and institutional volumes of <25 and <50 AF ablations per year respectively were associated with worse outcomes [298]. More recent evidence suggests that procedure numbers are less important for institutions using cryoballoon ablation, with studies failing to show a significant difference between high and low volume centers [297,1478]. The reality is probably more nuanced than simply a distinction between high and low volume centres because, although outcomes may not be statistically different, high-volume centers will manage more complex, high-risk cases [1479]. Therefore, we would recommend that rather than using procedure numbers as a crude assessment of competence, all centers performing AF ablation should be able to demonstrate their procedure outcomes and compliance with the recommendations in this consensus document.

There is evidence of improved performance with team-based simulations and loss of performance when this is discontinued [1480,1481]. It is therefore strongly suggested that all members of the ablation team take part in regular rehearsals or simulations to practice management of emergencies and rarely seen complications like pericardial effusion. This ensures that not only are all team members aware of the plan and their role in it, but also that the necessary equipment is available.

13.2 Institutional requirements

13.2.1 Staff

Institutions should have sufficient trained staff to provide pre-admission counselling, AF ablation and postoperative support and follow up. These roles should ideally not all be carried out by the physician performing the procedure, to ensure that other members of the team are appropriately trained to support patients in the absence of that physician. If an institution is not able to offer 24/7 care to patients, patients should be able to access care in the event of an emergency (even if it involves attending an emergency room) and know what those arrangements are. Staff should be aware of common complications after AF ablation and to triage them appropriately.

13.2.2 Equipment and facilities

AF ablation in selected patients can be performed safely in institutions without cardiothoracic surgical services [1236,1478]. In a retrospective, nonrandomized, propensity-matched analysis of Medicare beneficiaries aged 65 years and older, the presence or absence of on-site cardiothoracic surgery was not associated with 30-day rate of cardiac perforation, cardiothoracic surgery, rehospitalization, and death after AF ablation [1482]. However, in this study hospitals without cardiothoracic surgery accounted for just 2% of total ablations indicating that in the US, this remains uncommon. When AF ablation is performed in centres without cardiothoracic surgery services, it is recommended that transfer arrangements and checklists should be in place and patients should be aware of the potential need to be transferred to a cardiothoracic centre in case of emergency.

All institutions should have the following minimum equipment list to perform AF ablation:

- Ultrasound for vascular access
- Echocardiography, including TEE
- Fluoroscopic X-ray imaging
- 3-D mapping or a single-shot PV ablation technology
- Pericardial drainage equipment and anticoagulant reversal

Institutions performing AT ablation should have access to a 3D mapping technology.

13.2.3 Follow up and other requirements

Institutions should have arrangements for patient follow up. Follow up intervals and duration are discussed in section 9. Follow up does not always need to take place face to face. Digital ECG recording systems can facilitate remote phone or video consultation follow-up when the patient and the physician both feel this is appropriate. It is important that this follow up system should be used to record AF ablation outcomes. These results should be audited, and the institution have formal arrangements for identifying and responding to serious complications. The outcomes of physicians and their teams should be regularly reviewed and arrangements in place to identify and manage poor performance. Institutions should have a culture and system in place that encourages reporting of poor outcomes and responding to this by avoiding individual blame, rather, aiming to understand and correct the system failures that have led to poor performance and confirm that appropriate changes have resulted in improved outcomes.

If there is a regional or national audit database, centers should submit their data to those, including their complication rates.

Section 14: Areas for Future Research

There has been significant progress in the safety and efficacy of AF ablation as well as significant advances in the technologies used to perform ablation. However, many critical questions remain unanswered, especially as we enter a new era in energy delivery with the advent of PFA (Table 10).

14.1 Basic translational science

The importance of basic and translational research to better understand the mechanisms of AF should not be underestimated. It should be recognized that even after a century of research, the mechanisms of AF have not been fully elucidated, hampering our ability to develop better clinical tools for treating AF. The debate continues over the primacy of the multiple wavelet hypothesis versus focal sources of AF [1483]. While prior attempts to map with phase mapping and other technologies have not resulted in meaningful improvements in AF ablation, emerging technologies continue to

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Table 10 Unanswered questions in AF ablation

Topic	Questions
Basic / translational science	• What are the mechanisms of AF? • What are the best preclinical models of AF for understanding human disease?
Risk factor modification	• Treatment of which risk factors (i.e. OSA, obesity, hypertension, physical inactivity) improve outcome after AF ablation? • Does maintenance of risk factor modification reduce late AF recurrences? • Can pharmacologic prevention of remodeling/fibrosis improve long term freedom from AF after ablation?
Patient selection - Personalised management	• Can machine learning and artificial intelligence improve patient selection and downstream clinical outcomes? • Can we develop a personalized approach to AF ablation based on risk factors, AF duration and atrial substrate? • Do asymptomatic individuals benefit from catheter ablation, including reductions in cardiovascular adverse events?
Energy sources – ablation tools	• What are the optimal settings for cryothermy and radiofrequency ablation in different LA regions? • What are the optimal PFA settings for AF ablation (delivery design, dose)? • Does PFA improve long-term outcomes when compared with radiofrequency or cryoballoon ablation? • Does PFA improve the safety and efficacy of additional substrate modification? • Are there unrecognized safety concerns if more extensive PFA leads to greater proportions of atrial myocardium being ablated? • Can combined pulsed field and thermal ablation modalities improve AF ablation efficacy and safety?
Ablation strategies	• Can we prevent PV reconnection after PVI? • What is the optimal ablation approach of persistent AF? • Can ablation based upon computer simulations of the interactions between substrate and arrhythmia provide personalized ablation strategies and lesion sets that result in safer, more effective, and more efficient procedures? • Can we reproducibly map focal AF-drivers and does ablation of these focal sources lead to improved outcomes? • Which patients benefit from hybrid ablation? Are outcomes and safety improved compared to catheter ablation?
Endpoints and outcomes after ablation	• Can wearable technologies offer reliable monitoring of AF burden after AF ablation? • What is the optimal and most pragmatic efficacy endpoint for arrhythmia suppression after AF ablation?

offer promise. It is also possible that persistent AF has multiple mechanisms which may vary in different patients and substrates. Investigation into more personalized AF treatment strategies, based on clinical and electrophysiologic measurements, that minimize tissue destruction should be encouraged. Whether we can map AF in a way that leads to changes in ablation strategies with an impact on short-term and long-term outcomes perhaps remains one of the largest unanswered questions in AF ablation.

14.2 Risk factor modification

Recent evidence has highlighted the importance of risk factor modification for improving the outcome after AF ablation and preventing long term AF recurrences (section 5.1). Optimal strategies for maintaining weight loss and risk factor modification long term, and its effect on late AF recurrence should be investigated. Longer term (>10 year) outcome after ablation of AF should also be investigated to determine which patients benefit most from early intervention. It has also become apparent that an underlying fibrotic atrial myopathy underlies AF progression in many patients. Pharmacologic approaches to minimize the progression of atrial remodeling and fibrosis may be important for improving long term freedom from AF after ablation.

14.3 Patient selection – personalized management

A key step in AF ablation is optimization of patient selection. Several variables are predictive of ablation outcome (section 5.2.1). There have been significant advances in our understanding of left atrial substrate and its relation to ablation outcomes. The DECAAF study highlighted the value of MRI-detected fibrosis for predicting outcomes after ablation [103]. However, these findings have not been widely reproduced or employed. More recent studies have highlighted the promise of machine learning to predict outcomes following ablation [1484,1485]. Development of a personalized approach to identify optimal AF ablation candidates and predict procedural outcome is necessary to advance precision medicine approach in the care of AF patients.

To date, patient selection and indications for ablation of AF have focused on those with symptoms and left ventricular systolic dysfunction. However, recent data supporting improved outcomes with early rhythm control in asymptomatic persons raise the question as to whether ablation may improve long-term outcomes in those without symptoms [332]. Determining whether ablation can improve outcomes in persons with asymptomatic AF will require relatively large randomized clinical trials.

14.4 Energy sources – ablation tools

In clinical practice across the world, cryothermy and RF remain the predominant modes of energy delivery for AF ablation. As both of these technologies develop, the best approach to lesion delivery still remains unclear. PFA has the potential to change that by providing safer and more efficient lesion delivery. Utilization of PFA is rapidly growing, and larger multicenter experiences are reassuring [653,1486]. Additional investigation will be required to determine if PFA results in similar or better long-term outcomes compared with cryoballoon and RF ablation [1487]. While PFA may reduce the risk of significant PN palsy, esophageal injury, and PV stenosis, does it permanently impair GP? If not, what are the implications for longer-term efficacy? [1488]. Does PFA perform as well on non-PV targets with similar safety or are there additional safety concerns as has been recently highlighted with coronary vasospasm [1489]. Finally, if PFA does provide more reliable and facile ablation, will easier ablation result in more atrial myocardium being ablated and thus increased risk for low-compliance complications of AF ablation such as stiff LA syndrome? Early data suggests that PFA does not engender changes that favor restrictive physiology [1198], but more data are needed, particularly in patients undergoing extensive substrate modification.

14.5 Ablation strategies

While PVI remains the gold standard for the treatment of paroxysmal AF, PV reconnection after ablation remains a common problem and the major reason for recurrence after ablation. Novel energy sources and approaches to minimize PV reconnection after ablation will be essential for determining the true effectiveness for durable PVI on freedom from AF. This is critical before other adjunctive strategies can be investigated.

Outcomes following ablation of persistent AF are suboptimal. Despite many clinical trials, no adjunctive ablation strategy has been shown to be consistently superior to PVI alone. Delineation of optimal method(s) for ablation of persistent AF beyond PVI remains a priority in future research in AF ablation. Advances in computational power and machine learning may also allow better characterization of the AF substrate and appropriate targets beyond PVI. Personalized computational modelling has been evaluated to help "personalize" ablation and predetermine ablation targets [1490]. Future studies will need to prospectively evaluate both clinical and machine learning risk stratification schemes and randomized studies will be needed to test personalized approaches to AF ablation. As with any new technology, reproducibility across centers will be essential.

The combined approach of hybrid ablation has shown some value for improved outcomes in patients with persistent AF and more advanced atrial substrates (section 12). However, the morbidity of such procedures is generally higher than catheter ablation and outcomes depend on surgical tools and experience. Studies to identify the best candidates, tools and approach to hybrid ablation are needed. Future studies should also compare catheter ablation to hybrid approaches, ideally involving similar lesion sets and follow-up. Hybrid approaches that involve two procedures (surgical ablation followed by catheter ablation) should ideally be compared to two catheter ablations. Furthermore, the optimal timing between different stages of the hybrid procedure should be investigated.

While interventional catheter-based approaches to treat AF dominate our current approach, noninvasive methods for treating AF will undoubtedly be developed in the future. Stereotactic body radiotherapy has been demonstrated to be effective for refractory VT and is growing in use [1491]. Stereotactic body radiotherapy has also been used in a pilot study to treat AF in humans [1492], and such techniques will only improve with safer targeting and radiation technology. Carbon and proton beam ablation may allow more accurate targeting and lower radiation dose to surrounding tissues [1493]. Further research into noninvasive ablation of AF should be encouraged.

14.6 Endpoints and outcomes after ablation

Testing different ablation strategies, evaluating the impact of new technologies, and accurately understanding the impact of ablation requires reporting and evaluation of standard, pragmatic, and meaningful measures of arrhythmia suppression. While it is generally agreed that 30-seconds of sustained atrial arrhythmia has limited value from a disease burden and patient-perspective, there still is no consensus on what the optimal efficacy endpoint should be for AF ablation (section 10.2). While AF burden may be an ideal measure [7], at present, it requires either extended monitoring to provide periodic samples of AF burden or an implanted device to measure truly continuous AF burden (section 10.3). However, this status quo may change as wearable technologies evolve (section 9.4) [1494, 1495]. A key goal for the field should be the identification of a universal, pragmatic, and meaningful efficacy endpoint for AF ablation that impacts outcome.

Measuring outcomes is also challenging in asymptomatic patients; while hard outcomes such as mortality and stroke would provide the strongest support for ablation in asymptomatic patients, other outcomes such as exercise tolerance and QoL improvements would be important to ascertain.

Supplementary material

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