

Venice Chart International Consensus Document on Atrial Fibrillation Ablation

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Introduction

Over the past five years, the technique of catheter ablation for atrial fibrillation (AF) has evolved from being an experimental procedure to the most common ablation performed in many electrophysiology laboratories throughout the world.

Nevertheless, many aspects of the therapy are still controversial, from ablation techniques to procedural endpoints; patient management pre-, during, and postablation; hospital facilities; training requirements/competences; prevention and treatment of complications; and definition of success and long-term results. Consensus for these issues among the many physicians involved in the management of AF would be useful. With this in mind, the organizers of VeniceArrhythmias2007, an International Workshop that takes place every two years in Italy, have assembled world-recognized experts in the field to develop the present Venice Chart document, a synthesis of the consensus reached by these experts.

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*For the Venice Chart composition (Committees, members, and affiliations) see Appendix.

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Anatomy of Pulmonary Veins and Left Atrium

The pulmonary veins (PVs) and posterior left atrium (LA) play a critical role in the initiation and maintenance of AF; electrical isolation of the PVs forms the cornerstone for catheter ablation of AF. PV stenosis can result from inadvertent delivery of radiofrequency (RF) energy within a PV,^{1,2} but the risk of PV stenosis may be minimized and the success maximized by delivery of RF energy to the ostial portion and especially to the antrum of the PVs.¹⁻⁴ Understanding PV anatomy is also important in the development of balloon-based ablation technologies.⁵⁻⁸

Embryologic Considerations

The locations of the precursors of the conduction system are defined during embryological development of the heart by

the looping process of the heart tube.⁹ Specialized conduction tissue that is derived from the heart tube and is destined to have pacemaker activity has been found within the myocardial sleeves of the PVs.⁹ The presence of P cells, transitional cells, and Purkinje cells in the human PVs¹⁰ may provide an explanation for the electrical activity within the PVs.¹¹

PV Muscular Sleeves: Pathologic and Histologic Characteristics

The presence of myocardial muscle extensions (“sleeves”) covering the outside of PVs has been recognized for many years and regarded as part of the mechanism for regulating pulmonary venous flow. Myocardial muscle fibers extend from the LA into all the PVs to a length of 1–3 cm, with marked interindividual variability. The muscular sleeve is thickest at the proximal end of the PVs (1–1.5 mm), and it then tapers distally. Usually, the sleeve is thickest at the inferior wall of the superior PVs and at the superior wall of the inferior PVs.¹² Frequently, muscular fibers are found circumferentially around the entire LA–PV junction, but the muscular architecture is complex, with frequent segmental discontinuities and abrupt changes in fibre orientation.^{13,14} In addition, there are abundant adrenergic and cholinergic nerves in the ganglionated plexi in the PV vicinity.¹⁴ Preferential locations of these structures include the left superior PV at the junction with the atrial roof, the postero-inferior junction of the inferior PVs, and the anterior border of the right superior PV.

Electrophysiologic Characteristic Features of the PV Muscular Sleeves

Optical mapping techniques showed in canine atria that action potential duration was longer in the endocardium than epicardium of PVs.¹⁵ There was marked slowing of conduction in the proximal portion of the PVs as compared with the adjacent LA. During rapid atrial pacing, 2:1 conduction block into the veins was observed. The authors proposed that AF results from a focal trigger arising from within the PVs and is maintained as a rapid re-entrant circuit within the PVs. Hocini et al.¹⁶ examined the electrophysiologic characteris-

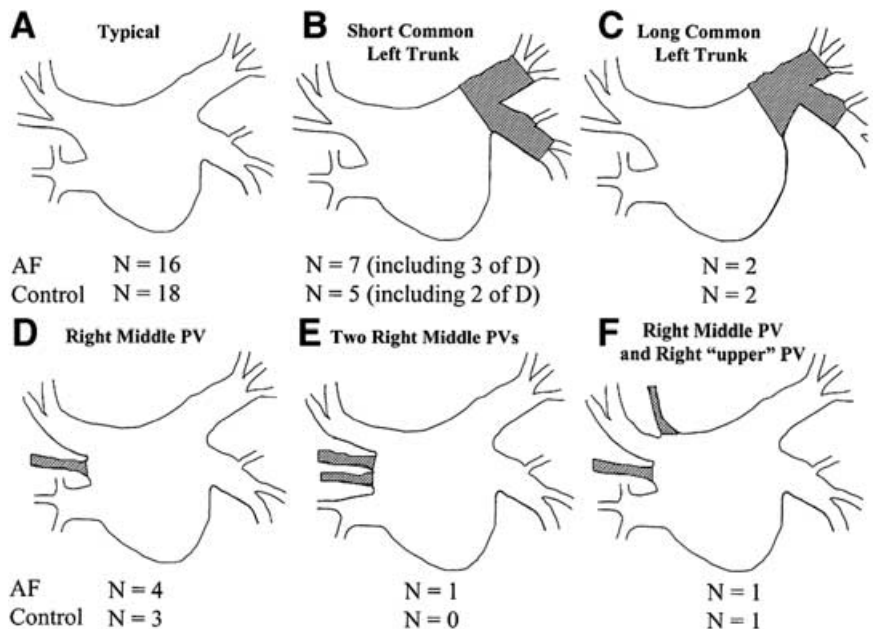
tics of the PVs in blood-perfused heart preparations using intracellular and extracellular recordings. Zones of conduction delay were found in all PVs, with fractionated signals noted in areas of slow conduction. Zones of slow conduction were correlated to sudden changes in histologic fiber orientation that could facilitate reentry. Kalifa et al.¹⁷ reported that as left atrial pressure was increased above 10 cm H₂O, the LA–PV junction became the source of dominant rotors, helping to explain the clinical link between AF and increased atrial pressure.

Anatomy of the LA and PVs

The major part of the LA, including the septal component, is relatively smooth-walled, whereas the appendage is rough with pectinate muscles. Seemingly uniform, the walls are composed of one to three or more overlapping layers of differently aligned myocardial fibers, with marked regional variations in thickness.¹⁸ The superior wall is thickest (3.5–6.5 mm),^{18,19} whereas the posterior wall is thin, especially between the superior PVs, explaining in part the risk of atrio-esophageal fistula when ablating in this area.²⁰

The transition between LA and PVs is smooth, without pronounced ridges. The veno-atrial junction is least distinct when the entrance of the PV is funnel-like. Anatomic studies and also studies using magnetic resonance (MR) imaging and computed tomography (CT) have reported significant variability in dimensions, shape, and branching patterns of the PVs.^{13,21–25} Typical PV anatomy, with four distinct PV ostia, is present in approximately 20% to 60% of subjects (Fig. 1).^{22–25} The orifices of the left PVs are located more superiorly than those of right PVs. The orifices of the right PVs are directly adjacent to the plane of the atrial septum. The right and the left superior PVs project forward and upward, while the right and left inferior PVs project backward and downward. The right superior PV lies just behind the superior vena cava or right atrium and the left PVs are positioned between the LA appendage and descending aorta. The orifice of the LA appendage lies in close proximity to the orifice of the left superior PV. The two orifices are separated by a fold in the atrial wall that appears like a ridge on the endocardial surface.²⁶ The PV orifices are oblong rather than round in

Figure 1. Branching pattern of PV anatomy in AF patients and controls (from Kato et al., 2003). Shaded portions indicate different parts from typical anatomy. A: Typical branching pattern. B: Short common left trunk C: Long common left trunk. D: Right middle PV. E: Two right middle PVs. F: Right middle PV and right “upper” PV. (Reproduced from Kato R, Lickfett L, Meininger G, Dickfeld T, Wu R, Juang G, Angkeow P, LaCorte J, Bluemke D, Berger R, Halperin H, Calkins H: Pulmonary vein anatomy in patients undergoing catheter ablation of atrial fibrillation: Lessons learned by use of magnetic resonance imaging. *Circulation* 2003;107:2004-2010, with permission.)



shape in both AF patients and controls, with the anterior–posterior diameter less than the superior–inferior diameter.²² Comparing the size of PV orifices, Kato et al. found no difference in AF patients, whereas the left inferior PV was smaller than the right inferior PV in normal controls.²² Overall, the PV size was larger in AF patients as compared with controls ($P < 0.05$).

AF can result in structural and electrical remodeling of the atrium,^{27–32} suggesting that AF can cause a rate-related atrial cardiomyopathy. Changes include molecular, cellular, and architectural alterations in the atrial myocardium, as well as electrophysiological perturbations.

Summary and Conclusion

Those involved in the field of catheter ablation of AF should have a clear understanding of the anatomy of the LA and PVs and their considerable variability among patients. It is desirable that MR or CT imaging be performed prior to AF ablation procedures.

Pathophysiology of AF

Two main theories on AF pathogenesis are ectopic focal activity and reentry, yet unifying theory is lacking. It is clear that the pathogenesis of AF is often multifaceted and the arrhythmia may develop in different pathologic conditions as well as in the normal heart. It is well recognized that increased atrial mass, decreased conduction velocity, and decreased atrial refractoriness with increased dispersion are all pro-fibrillatory factors. The onset and maintenance of AF, irrespective of the underlying mechanism, requires an event (trigger) that initiates the arrhythmia and the presence of a predisposing substrate that perpetuates it. Additional factors (e.g., inflammation or autonomic tone) may also cooperate as “modulators” in facilitating initiation or continuation of AF. Certain key points are summarized below.

Substrate

Diseases associated with AF and the role of fibrosis

Although approximately 10% of AF patients have no evident cardiac disorder (so-called “lone” AF), the arrhythmia usually occurs in patients with structural heart disease.^{33,34} Hypertension, coronary heart disease, valvular heart disease, dilated cardiomyopathy, and heart failure are the most frequent pathological conditions associated with AF. Atrial enlargement is often present in patients with AF, although it is difficult to establish if it represents the cause or the consequence of the arrhythmia. Atrial fibrosis and loss of myocardial tissue are common findings in patients with AF. Fibrosis has an apparent, clear impact in facilitating AF by reducing the conduction velocity and possibly creating areas of conduction block. Fibrosis may be either a substrate for AF (due to coexisting heart disease) or a result of fibrillating atria and part of the so-called “structural remodeling.” It has been demonstrated that activation of the renin angiotensin system with increases in angiotensin II levels promotes formation of collagen. Therefore, pharmacological inhibition of this system could represent a novel approach to counteract development of fibrosis and recurrence of AF.^{35,36} This may explain the apparent benefit in the prevention of AF recently observed in many posthoc analyses of randomized controlled trials in

which ACE-inhibitors or angiotensin receptor blockers have been compared with placebo.³³

Genetic factors

It is now evident that lone AF may be caused by mutations of different genes controlling cardiac excitability, such as KCNQ1, KCNE2, KCNJ2, SCN5A, and KCNA5 (Table 1).^{37–42} The final effect of ion channel mutations leading to AF is that of reduced action potential duration. Consequently, carriers of genetic channelopathies have a short atrial refractory period that creates a vulnerable substrate for the development of AF. Interestingly, the evidence of somatic mutations (i.e., DNA mutations that occur after conception and are not passed on to children) in the connexin 40 encoding gene, may explain why many cases of lone AF may not present a familial distribution.⁴³ Defects in connexin 40 are expected to lead to increased propensity to AF through an impaired electrical coupling between cells and decreased atrial conduction velocity. Finally, one study⁴⁴ has also highlighted the role of mitochondrial DNA as a “dynamic” genetic factor, accumulating with aging, that predicts the occurrence of the arrhythmia.

Electrophysiological Mechanisms

General concepts

Increased automaticity, single and multiple circuit reentry can cause AF. These mechanisms are not mutually exclusive and are probably variable according to the underlying pathogenesis. For instance, it is conceivable that the mechanisms of AF in a patient with a KCNQ1 mutation and a structurally normal heart are different from those responsible for AF in a patient with dilated cardiomyopathy. Regardless, the onset and maintenance of the arrhythmia require both a trigger and a substrate.

Trigger and substrate

Recent observations have focused attention on the PVs as a source of ectopic activity determining AF.^{18,45,46} Other anatomical structures that may also provide ectopic beats causing AF are the superior vena cava, the vein of Marshall, the musculature of coronary sinus, and the posterior wall of LA. However, for AF to become sustained, the presence of an atrial substrate of sufficient mass capable of maintaining re-entrant circuits is necessary. The LA-PV junction and the posterior wall of LA are critical structures to this regard.

Role of the autonomic tone

The role of parasympathetic and sympathetic tone as initiators of AF has been extensively studied in the past. Vagal stimulation shortens refractory period and isoproterenol increases the automaticity and induces triggered activity. These findings suggest a potential role of both parasympathetic and sympathetic tone in the onset and perpetuation of AF. It has been shown that electrical stimulation of autonomic ganglia at the LA-PV junction can transform the PV focal electrical activity into AF.⁴⁷ Moreover, vagal denervation, obtained by delivering RF energy at the sites where autonomic ganglia are located, may have a beneficial effect in controlling AF.⁴⁸

TABLE 1
Pathophysiology of AF.

	Group	Factor/Disease	Proposed Mechanism
Substrate	Associated diseases causing atrial enlargement and fibrosis	Hypertension Valvular disease Coronary artery disease/heart failure	<ul style="list-style-type: none"> ● Increased pro-fibrotic factors (TGFbeta-1) ● Increased atrial stretch ● KCNQ1- ↑IKs current and ↓refractory period ● KCNE2- ↑IKr current and ↓refractory period ● KCNJ2- ↑IK1 current and ↓refractory period ● SCN5A- ↓INa current and ↓refractory period ● KCNA5- ↑IKur current and ↓refractory period ● GJA5 - impaired electrical conduction
	Genetic-mendelian disorders	Ion channels gene mutations	
Triggers	Genetic – somatic genetic defects	Connexin genes (mutations and promoter polymorphisms)	<ul style="list-style-type: none"> ● Impaired energy substrate production leading to cell death and fibrosis ● Triggered activity, increased automaticity and PVs-reentry due to short action potential
	Genetic – mitochondrial DNA*	mtDNA4977 (nt8224-13501 deletion)	
Modulating factors	Pulmonary veins abnormal excitability	Focal activity Reentry	<ul style="list-style-type: none"> ● Reduced refractory period ● Increased cell damage ● Impaired excitability favouring both initiation and maintenance of AF
	SNS/RAS** Inflammation Electrical remodelling	Increased parasympathetic tone and RAS pathway Increased C-reactive protein Reduced CaV1.2 (L-type calcium channel) expression Reduced NCX (Sodium calcium exchanger) expression Reduced Kv4.3 (transient outward current) expression Increased K ⁺ channel beta subunit expression (MinK and MiRp2) expression Increased expression of TWIK-1, two-pores K ⁺ channel	
	Structural remodeling	Impaired SR calcium handling (reduced Ca ²⁺ ATPase expression) leading to Ca ²⁺ overload Increased cell size Glycogen accumulation Myolysis Alterations of nuclear chromatin	<ul style="list-style-type: none"> ● Increase of fibrosis and heterogeneity of electrical properties

*Age-related accumulation of mutations and possible matrilineal transmission.

**SNS = sympathetic nervous system, RAS = renin-angiotensin system; SR = sarcoplasmic reticulum.

Structural and Electrical Remodeling

The process of AF self-perpetuation is called remodeling. Both structural and electrical remodeling can occur when AF profoundly impacts on the atrial tissue activating several pathways contributing to its maintenance^{27,28,49-52} (Table 1).

At macroscopic level, AF causes atrial dilatation, increased compliance, and reduced contractility. Ultrastructural changes of myocytes include increase in cell size, accumulation of glycogen, myolysis, alterations in connexin expression, changes in mitochondrial shape, and fragmentation of sarcoplasmic reticulum. Interestingly, such changes are not uniform throughout the atria and therefore, they may substantially contribute to electrical instability by creating further heterogeneity of the electrical properties.

Electrical remodeling parallels the structural abnormalities observed during AF. Progressive shortening and dispersion of refractory periods are the main changes occurring during AF.

Techniques and Technologies for AF Catheter Ablation

At present, multiple approaches have been developed for catheter ablation of AF that report similar success rates, particularly in patients with paroxysmal and persistent AF. The current techniques focus on the elimination of mechanisms involved in the initiation and maintenance of AF, which are

essentially represented by triggers and substrate (Fig. 2). It should be recognized that, although the techniques and end-points of AF catheter ablation may differ significantly among centers, the resulting lesion set may be similar. The different approaches proposed for catheter ablation of AF include PV isolation, electrogram-based ablation or complex fractionated atrial electrograms (CFAEs) ablation, linear lesions, autonomic ganglionated plexi ablation, and sequential ablation strategy. The PV isolation comprises segmental/ostial PV ablation, circumferential PV ablation, and circumferential/antral PV isolation.

PV Isolation

Segmental/Ostial PV isolation

A truly segmental PV isolation requires ablation inside the vein or very close to the output into the atrium.^{53,54} It is now appreciated that ablation in the PVs themselves needs to be avoided as much as possible. Consequently, the current emphasis is to ablate more atrially, which requires more extensive atrial ablation, often circumferential. A circular mapping catheter of variable diameter (15–25 mm) is inserted into the LA through a long introducer via the transseptal route, and is positioned sequentially at the ostia of the four PVs.⁵⁴ The ablation catheter is positioned at the ostium of the vein on the atrial side; a series of segmental lesions are then created until isolation of the vein can be demonstrated by disappearance

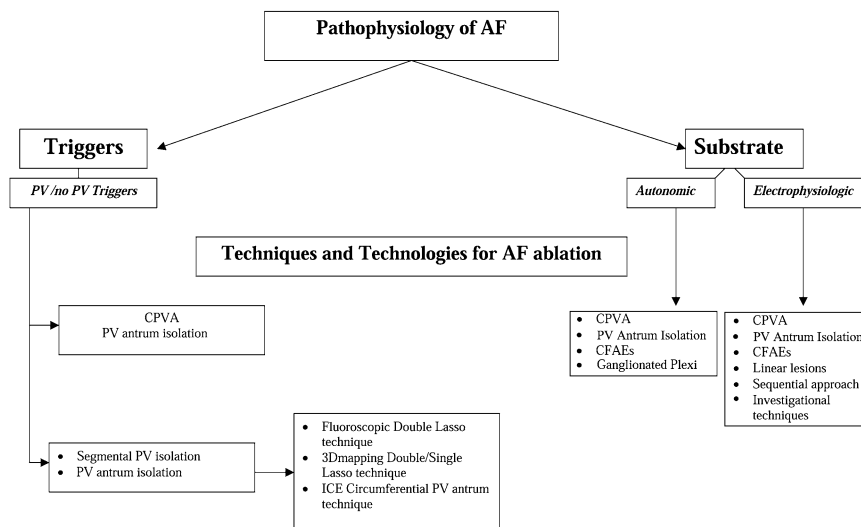


Figure 2. Schematic representation of pathophysiology of atrial fibrillation and of sites where the different atrial fibrillation ablation techniques impact.

of the venous potentials on the circular mapping catheter. Ablation can be carried out in sinus rhythm or during AF.

Circumferential PV ablation

Circumferential PV ablation using three-dimensional (3-D) electroanatomical mapping was initially described by Papapone et al.,^{55,56} and has been performed in more than 10,000 patients worldwide.⁵⁷⁻⁵⁹ Initially, the lesion set was limited to wide (>0.5 cm outside PV ostia) circumferential lesions around and outside the PV ostia, but over time it was modified with wider (1–2 cm outside PV ostia) circumferential lesions, additional posterior lines connecting the PVs, the mitral isthmus line, and abolition of the evoked vagal reflexes, in order to increase the amount of substrate included in the ablation schema and in order to prevent recurrences of atrial tachycardia.^{48,60} Successful lesion creation at each point is considered to have taken place when the local bipolar voltage has decreased by 90% or to less than 0.05 mV. The same ablation schema, which takes one hour in most cases, can be used when ablating paroxysmal, persistent, and long-lasting AF, as quite similar results have been reported for all different AF types in one large case series and two randomized studies. A low complication rate has been reported with this technique. The most serious complication, atrio-esophageal fistula, can also occur with other ablation techniques.

Circumferential/Antral PV isolation

Circumferential PV isolation can be monitored by various tools, according to operator preference. Selective pulmonary venography is widely used to define the relevant anatomy. Intracardiac echocardiography (ICE) can localize catheter position and define anatomy, as well as monitor microbubble formation, which may be a prelude for “popping” and tissue overheating. Computerized mapping and navigation techniques (Carto, NavX, etc.) help define anatomy and catheter guidance. These techniques can be made more anatomically accurate by registration with other imaging techniques, such as MR or CT imaging. The critical goal for any technique is to ensure that the lesion is made outside the PVs. Single/double circular mapping catheters have been widely used to guide the placement of ablation lesions.⁶¹

One or two circular mapping catheters are placed within the ipsilateral superior and inferior PVs or within the su-

perior and inferior branches of a common PV during RF delivery. RF is applied until the maximal local electrogram amplitude decreases by $\geq 90\%$. RF ablation is performed 0.5 to 1.0 cm outside the PV ostia, as defined by angiography, MR or CR imaging. The endpoint is absence or dissociation of all PV potentials documented by lasso catheter(s) within the ipsilateral superior and inferior PVs. Some investigators have extended the PV isolation concept to include ablation of the “PV antrum.”⁶² The antrum includes the entire posterior wall and extends anteriorly to the right PVs. Recently, combining spectral mapping with PV antrum isolation has been reported to improve AF ablation success in patient with persistent long-lasting AF.⁶³

Electrogram-Based Ablation or Complex Fractionated Atrial Electrograms (CFAEs) Ablation

Recently, it has been recognized that during sustained AF, ablation of areas showing CFAEs can cure AF.⁶⁴ CFAEs can be defined as (1) fractionated electrograms that are composed of ≥ 2 deflections and/or have a perturbation of the baseline with continuous deflection of a prolonged low voltage activation complex or (2) atrial electrograms with a very short cycle length (<120 msec) with or without multiple potentials. When compared with the rest of the atria, sites where CFAEs are recorded have a shorter cycle length. The distribution of CFAEs in the right and left atria is quite variable. Mapping is always done during AF to improve the accuracy of CFAEs mapping and software with algorithms that enable association of the anatomical shell of both atria with areas of CFAEs has been created. The incremental benefit of this software over visual inspection remains to be established. When the areas with CFAEs are completely eliminated but the arrhythmia continues as organized atrial flutter or atrial tachycardia, atrial tachyarrhythmias are mapped and ablated.

Linear Lesions

Linear lesions have been reported to be associated with conversion of AF either directly to sinus rhythm or to atrial tachycardia, further demonstrating that such lesions may at least in some patients deeply modify the substrate for AF.^{65,66} In many patients, conversion to atrial macrore-entry is observed during the ablation process and its elimination is an obligatory step on the way to sinus rhythm. This is

particularly true for the recent approaches combining multiple ablation strategies for AF ablation that are almost always associated with transformation of AF into atrial tachycardia. Most of these atrial tachycardias are macrore-entrant and require long linear lesions to be treated. This situation is often observed during the index procedure or during follow-up. Linear lesions have been suggested to prevent these tachycardias. However, this strategy may be counter-productive, as linear lesions may themselves be proarrhythmic, especially if incomplete.⁶⁷

Linear lesions are generally deployed at the LA roof and/or at the mitral isthmus.^{68,69} Lesion creation remains challenging and the use of irrigated-tip ablation catheters is suggested to ensure optimal efficacy and safety. The goal of linear lesions is the achievement of bidirectional block.

Autonomic Ganglionated Plexi Ablation

Recent clinical data suggest a potential role for ganglionated plexi ablation, especially in patients with paroxysmal AF. Left atrial ganglionated plexi may be localized at the time of ablation using high-frequency stimulation (cycle length 50 msec, 12 V, 1–10 msec pulse width) delivered by a mapping catheter in the LA. Based on previous experience by Pappone et al.,⁴⁸ four major left atrial ganglionated plexi have been recently identified in patients with AF. The ganglionated plexi are usually located within areas of CFAEs during AF. For ablation, RF current (20–35 watts) can be applied at each site of positive vagal response to high-frequency stimulation. High-frequency stimulation is repeated and additional RF applications can be applied until the vagal response to high-frequency stimulation is eliminated. The vagal response can be eliminated at almost all ganglionated plexi sites (usually 2–10 RF applications) unless ablation is limited due to close proximity to the esophagus.

Sequential Ablation Strategy

A stepwise or tailored approach has been recently developed in patients with long-lasting persistent AF with different sequences that target multiple atrial areas.^{70–72} The end point of the sequential ablation strategy is termination of AF. This can be achieved either by passing directly from AF to sinus rhythm or, more commonly, to atrial tachycardia that is then mapped and ablated. Once sinus rhythm has been restored, PV isolation and linear lesions are checked for completeness and areas re-ablated if needed. It should be emphasized that this approach represents an extensive procedure associated

with significant risks and requires careful and individualized risk-benefit assessment.

Future Technologies

New ablation technologies are currently under intense experimental and clinical investigation. Alternative energy sources include cryoenergy, high-focused ultrasound, and laser energy. For all three energy sources, balloon-based ablation systems have been developed. These balloon-based systems aim at the induction of circular lesions around the PVs on an atrial level. Currently, clinical experience is too limited to judge reliably on the efficacy risk profile of these new ablation technologies.

New software algorithms have been developed to support the various methods of image integration (from MR or CT) and to improve further the image registration process. In addition, real-time catheter-based imaging systems for on-line 3-D cardiac chamber reconstruction based on ICE technology are currently under investigation.

Endpoints of Catheter Ablation for AF

The goal of catheter ablation is trigger elimination and substrate modification using the least amount of ablation necessary. Various ablation strategies and targets used solo or in combination have been adopted for the ablation of AF. It appears that particularly in persistent and long-lasting AF, the placement of additional lines of ablation, as well as targeting CFAEs in addition to standard PV isolation, may add to the overall success rate of the procedure.

Principal procedural endpoints may depend on the type of AF and include completion of a predetermined lesion set⁷¹; termination of AF during ablation⁷⁰; and noninducibility of AF following ablation.^{72,73} There is still debate surrounding the predictive value of AF termination or noninducibility as endpoints for the procedure.

In patients with paroxysmal AF, it is possible that the termination of AF during ablation is coincidental. In these patients, noninducibility seems to be associated with an improved outcome^{73,74} during the follow-up. However, there is no current consensus on the definition of noninducibility and the induction protocol used. Furthermore, the termination or noninducibility of AF might only identify a subgroup of patients who have less severe AF disease and are therefore more likely to have a successful outcome. In patients with persistent and long-lasting AF, the procedural endpoint is also unclear. Although restoration of sinus rhythm by ablation, without

TABLE 2
Endpoints of Catheter Ablation for AF

Ablation Technique	Ablation Site	Ablation End-Points
Segmental/ostial PV isolation	PV ostium	Complete elimination or dissociation of PV potentials
Circumferential PV isolation	1–2 cm outside PV ostium	Abatement of local bipolar voltage by 90% or <0.05 mV within the encircled areas
Antral PV isolation	PV antrum	Complete elimination of PV potentials with isolation of all PVs and posterior wall
CFAEs ablation	LA areas where CFAEs are recorded	Complete elimination of CFAEs Interruption of AF? Non inducibility of AF?
Linear lesions	LA roof and mitral isthmus	Creation and demonstration of line of complete block
Autonomic GP ablation	Zones where GP are located around PVs	Abolition of vagal reflexes induced by HFS

PV = pulmonary vein; CFAEs = complex fractionated atrial electrograms; LA = left atrium; AF = atrial fibrillation; GP = ganglionated plexi; HFS = high frequency stimulation.

the use of antiarrhythmic drugs or direct current cardioversion, appears an intuitively ideal endpoint, this is not always achievable and the proof of superior outcome still not proven. In the interim, completion of a predetermined lesion set incorporating PV isolation and LA ablation remains the basic procedure.

Verification of ablation lesion sets is important to prevent proarrhythmias or late procedural failure from arrhythmia recurrence. The ablation endpoints of the principal ablation approaches previously discussed are summarized below.

PV Isolation

There is increasing consensus that electrical PV isolation is the optimal endpoint for ablation targeting the LA-PV junction.⁷⁵ The most objective procedural endpoint is absence or dissociation of PV potentials recorded from circular mapping catheter.^{61,62,76,77} After circumferential PV ablation, reduction of local bipolar amplitude of $\leq 90\%$ or 0.05 mV inside the encircled area has been suggested as a suitable endpoint in order to avoid the necessity for a circular mapping catheter.⁵⁵ Exit block into the LA can also be proven with pacing maneuvers from inside the PV, but this is not routinely applied. This is due to the technical difficulty of ensuring pacing capture of the muscle sleeves inside the vein without far-field capture of the left or right atrium. The role of intravenous adenosine as an adjunct to prove permanent abolition of PV conduction has been suggested.

Electrogram-Based Ablation or CFAEs Ablation

The local endpoint indicating when the RF should be discontinued is unclear. Endpoints for ablation at sites of CFAEs include: (1) complete elimination of the areas with CFAEs; (2) conversion of AF to normal sinus rhythm for both paroxysmal AF and persistent/long-lasting AF patients; and (3) noninducibility of AF in paroxysmal AF patients. The ablation typically begins at the sites where CFAEs have the shortest interval. Such sites are unfortunately ubiquitous in persistent AF. It is not known whether ablation of all such sites is necessary or if it is possible to target specific locations and thereby limit the extent of unnecessary ablation and resultant tissue damage. Irrespective of electrogram complexity, ablation all along some structures like the coronary sinus, left appendage, and septum may also have an impact on AF perpetuation.

Importantly, after “defragmentation” and prior ablation (PV isolation and possibly linear lesions), electrograms may become discrete or organized, allowing a dominant rate (frequency) and specific activation sequence to be identified. In such situations, parameters other than fragmentations may be used. Local high-frequency activity or focal and centrifugal spread of activation or sites with temporal gradient between two bipoles of conventional mapping catheter (representing local circuit or “rotor”) are potentials target for ablation.⁷⁸

Linear Lesions

In patients with persistent AF, the use of adjunctive linear ablation, for example at level of LA roof and mitral isthmus, have been associated with higher success rates.^{59,73,79} Even after termination of ablation-induced macro-reentry tachycardia, the endpoint should be complete linear lesions^{69,80-82} because incomplete lesions are associated with recurrence of atrial arrhythmias.^{8,83} The electrophysiological endpoint

should therefore be demonstration of bidirectional line of block. Conduction block at the LA roof or mitral isthmus can be readily assessed in a manner analogous to that used for the cavotricuspid isthmus—a corridor of double potentials and demonstration of activation moving towards the line of block on both sides—representing an unequivocal endpoint.⁸¹ A complete LA roof line may be demonstrated by activation progressing in a caudalcranial direction on the posterior wall during left appendage pacing.⁶⁹ A complete mitral isthmus line may be demonstrated by an inversion of coronary sinus activation sequence from distal-proximal to proximal-distal during pacing from the left appendage.⁸

Autonomic Ganglionated Plexi Ablation

Autonomic ganglionated plexi are present in epicardial fat pads and can be identified by high-frequency stimulation (HFS). They are often clustered around the PVs. HFS at these sites leads to induction of AF and/or bradycardia or AV block due to increased vagal tone. Abolition of inducible vagal reflexes has been proposed as an endpoint of ablation on the basis of experimental data.⁴⁷ It is unclear whether ganglionated plexi should be specifically targeted, given that these sites may be concomitantly ablated in the course of above described ablation targets.

Coronary Sinus and Other Thoracic Veins Ablation

Similar to triggers arising from the muscle sleeves surrounding the PVs, rapid atrial activity from the musculature of the coronary sinus may be a driver for persistent or long-lasting AF. The same electrogram-based approach as discussed above can be applied to the coronary sinus. Ablation endpoints include organization of coronary sinus activity and slowing of local rate. Total elimination of coronary sinus activity does not appear to be necessary.

Other potential triggers, such as superior vena cava and persistent left superior vena cava can be electrically isolated by ablation technique and endpoints similar to PV isolation. Abnormal activity from the vein of Marshall can be eliminated from the opposite LA endocardium and uncommonly requires direct catheterization from within the coronary sinus.

Patient Management Pre and Postablation

Hospital Facilities, Training Requirements/Competences

Equipment

Although biplane fluoroscopy is desirable, a single-plane fluoroscopy system capable of angulated views and road map images is adequate. The ability to measure and evaluate intracardiac pressures is necessary. The competence and experience to perform emergency needle pericardiocentesis must be promptly available. Rapid anticoagulation efficacy testing, such as ACT, must also be possible. Anesthesiology availability is desirable in order to manage procedural sedation/general anesthesia and provide resuscitatory support when required. Cardiac surgery should be promptly accessible to perform emergency surgical procedures as needed. Urgent bedside echocardiographic examination in the EP lab must be available primarily for diagnosing pericardial tamponade. In-hospital transthoracic and transesophageal

TABLE 3
Questionnaire on Training (49 answers)

Question no. 1: How many ablation procedures on substrates other than AF should the trainee perform before he can enter the AF training program?					
0–50	51–100	101–200			>200
12%	26%	36%			26%
Question no. 2: How many AF ablation procedures should the trainee attend before he can enter the AF training program?					
0–20	21–40	41–60	61–80	81–100	>100
14%	40%	31%	7%	7%	–
Question no. 3: How many AF ablation procedures should the trainee assist before he can start the AF program on his own?					
0–20	21–40	41–60	61–80	81–100	>100
7%	36%	26%	7%	21%	2%
Question no. 4: How many AF ablation procedures should the trainee perform under guidance before he can start the AF program on his own?					
0–10	11–20	21–30	31–40	41–50	>50
5%	14%	19%	10%	36%	17%

AF = atrial fibrillation.

echocardiography echo expertise is necessary. ICE is useful but is not mandatory.

Personnel

The medical personnel must be appropriately trained before starting AF ablation. An ad-hoc questionnaire was expressly prepared for this consensus document and sent to all Venice Chart members to have their opinion about training requirements for physicians who want to perform AF ablation. As evidenced by the answers reported in Table 3, the Venice Chart members believe that the attending/supervising physician must have independently performed from 50 to more than 200 procedures on substrates other than AF and attended more than 20 AF ablation procedures before he or she can enter the AF training program. Moreover, the attending/supervising physician must have assisted at least 20 AF ablation procedures and performed more than 20 AF ablation procedures under guidance before he or she can start the AF program on his or her own. Competence in managing pericardial tamponade in the interventional setting is necessary. The EP medical, nursing, and technical support staff must have adequate experience, especially in the management of 1) lines placed within the left side of the circulation, 2) a heavily sedated patient for long periods, and 3) bedside anticoagulation testing within the EP lab.

Preablation Management

Anticoagulation

An effective anticoagulation therapy is often necessary before an ablation procedure for AF. The modalities and duration of preablation anticoagulation therapy are reported in detail later.

Other drugs

Drug treatment for nonarrhythmic indications is generally continued. There is no consensus with regard to discontinuing antiarrhythmic drugs, although to avoid confounding ablation effects with antiarrhythmic drug effects, all antiarrhythmic drugs except amiodarone should be discontinued at least four half-lives in advance. However, if symptomatic arrhythmias demand, effective antiarrhythmic drugs may be continued.

Transesophageal echocardiogram (TEE)

A preablation TEE is used to rule out the presence of a LA thrombus, and should be considered a supplementary and backup strategy to continuous effective anticoagulation leading up to the ablation procedure. It should be performed shortly before the ablation procedure and without an intervening window in effective anticoagulation. In many EP laboratories, TEE is performed only in patients presenting in AF and without coumadin.

TABLE 4
Recommendations for Anticoagulation Therapy in Patients Undergoing AF Ablation

- 1) Preablation anticoagulation strategy
 - Patients with CHADS₂ score ≥ 1 and those with CHADS₂ score 0 and persistent AF require oral anticoagulation with warfarin with at least 3 weeks of documented INRs 2–3. They should undergo bridging with i.v. heparin or subcutaneous LMWH before ablation
 - Patients with CHADS₂ score 0 and paroxysmal AF may be treated either with warfarin or aspirin 75–325 mg/day
 - Patients in AF at the time of procedure should undergo TEE the same day or the day before ablation to rule out the presence of left atrium thrombus
- 2) Anticoagulation strategy during ablation procedure
 - I.v. heparin is given during the ablation procedure to all patients. Anticoagulation is started immediately after left atrial access is completed
 - Heparin is administered as an initial bolus dose of 100–140 IU/kg followed by an infusion of 15–18 IU/kg/hour and/or by additional boluses
 - The ACT target should be at least 250 seconds up to 350–400 seconds
 - Heparin infusion is discontinued in all patients after removal of catheters from the left atrium
- 3) Postablation anticoagulation strategy
 - Warfarin is restarted in all patients the same evening of the ablation procedure or next morning. Subcutaneous LMWH or i.v. heparin is often given as bridging therapy until INR is ≥ 2 . Warfarin is continued for at least 3–6 months
 - After this period no universal recommendations exist. It is suggested for most individuals with a CHADS₂ score of ≥ 2 to continue long-term warfarin treatment with a targeted INR of 2–3. For the others decision should be taken individually.

AF = atrial fibrillation; INR = international normalized ratio; LMWH = low molecular weight heparin; ACT = activated clotting time; TEE = transesophageal echocardiography.

Other imaging studies

Imaging to define the cardiac substrate could include establishing the presence and extent of coronary artery disease (if present) and left ventricular size and function. A transthoracic echocardiogram before the procedure is useful and allows measurement of chamber size and ejection fraction while a chest X-ray may be useful to document kyphoscoliosis. A MR or contrast enhanced spiral CT scan is obtained both as a baseline for comparison and for formulating an ablation strategy with variable PV anatomy.⁸⁵ In some labs, the ablation is performed with MR or CT image integration and in such situations, the underlying rhythm and ventricular rate are both important in order to make effective use of the 3-D images.⁸⁶

Postprocedural Management

The immediate postprocedural management consists of continuing and maintaining anticoagulation, maintaining hemostasis at puncture sites, and supportive treatment. Vagal episodes remedied by fluid infusion and/or atropine are not uncommon; however, pericardial tamponade must be excluded in patients with postprocedural hypotension. Pericarditic discomfort may occur during the first 3–5 days, sometimes accompanied by a mild and self-limited febrile syndrome. Aspirin is usually sufficient treatment, although uncommonly, continuing symptoms and a nonresolving pericardial effusion may require the administration of systemic steroids. The later occurrence (6–10 days postablation) of a febrile state with or without neurological symptoms should prompt suspicion of an atrio-esophageal fistula and lead to a contrast-enhanced spiral CT to exclude the diagnosis.

Rhythm outcome

Estimating the burden of AF, both symptomatic and asymptomatic, is the key to determining the outcome of the procedure. The ideal outcome would be a zero residual burden with no atrial flutter or atrial tachycardia. The absence of symptoms may not correspond to the stable restoration of sinus rhythm, perhaps due to ablation-induced denervation, or because of the absence of symptoms at baseline. The accuracy of estimating AF burden depends chiefly upon the duration of ECG recording.⁵⁹ Many labs use a clinical definition of successful ablation to mean the absence of symptomatic tachycardia, as well as the absence of documented AF during periodic follow-up visits as well as on periodic 24–48-hour Holter recordings, typically at one, three, and six months after the ablation. An event recorder may be used to evaluate symptoms not elucidated by the above tests. However, extending the duration of Holter tracings to seven days has been shown to enhance the sensitivity of detecting recurrent AF.⁵⁹ Another approach has been to monitor periodic, even daily, trans-telephonic ECG recordings supplemented by ECG transmission during symptomatic episodes, although the correlation to AF burden may be difficult to determine.⁸⁷ Finally, more and more implanted devices have sufficient memory and accurate arrhythmia recognition software to provide probably the most accurate measurement of AF burden possible, but of course, only in a limited patient population.⁸⁸ From a clinical standpoint, when success is defined as the restoration of stable sinus rhythm, this automatically assumes the elimination

of (sustained) atrial tachycardias as well, whether re-entrant (flutters) or non-re-entrant.

Owing to the difficulty of clinically measuring the AF burden, the temporal evolution of arrhythmias in ablated patients has not been clearly determined. Although some groups have re-ablated patients as soon as they develop recurrent AF, others have advocated waiting for one to three months with or without adding antiarrhythmic treatment in the interim period. An early re-ablation may result (unnecessarily) in a higher incidence of local puncture site complications, a longer hospital stay, and, of course, the risks of a left-sided procedure. About 30–50% of patients with documented or symptomatic recurrences during the first three months after an AF ablation have no further AF or flutter even without further ablation. The role of continued antiarrhythmic drug treatment in such an evolution is not clear, particularly when amiodarone is used.

Antiarrhythmic therapy

Some continue antiarrhythmic drug therapy even after a presumably successful ablation, ostensibly to favor reverse remodeling and promote the maintenance of sinus rhythm. This may have the advantage of satisfactory arrhythmia control, but at the price of “hybrid” therapy—the risks and adverse effects of both the ablation as well as antiarrhythmic drug therapy—and possibly prevent determination of a true ablation outcome. Alternatively, antiarrhythmic drugs are stopped four half-lives before ablation and not restarted unless symptomatic or sustained recurrences occur, particularly for patients not willing to undergo an additional procedure or at a high risk of arrhythmia recurrence. There are no guidelines for discontinuing antiarrhythmic drug therapy: depending upon the risk of recurrence and the accuracy of determining residual AF burden, trial of discontinuation may be offered after three to six arrhythmia-free months.

Late surveillance

Echocardiographic monitoring is useful to detect improvement in left ventricular function and even reductions in LA size after ablation.^{89,90} In the light of the high rates of symptomatic PV stenosis/occlusion in the early days of ablation targeting the PVs, routine MR or CT imaging has been advocated at three to six months following the ablation. However, the availability of variable loop circular mapping catheters and 3-D imaging systems have allowed ablations to be placed on the atrial side of the PV ostia with significant reductions in PV stenosis rates. Further, about 80% of PV stenoses including most single PV occlusions⁹¹ are asymptomatic. Consequently, it is debatable whether to perform routine imaging with MR or CT, or to restrict it to patients with suggestive symptoms.

Lastly, in the absence of data on long-term outcome after AF ablation, it is advisable to maintain periodic surveillance for arrhythmia recurrence at six or 12 monthly intervals, even in supposedly “cured” patients.

Anticoagulation Issues

Thrombotic stroke is one of the most feared complications of catheter ablation to cure AF. Published series estimate the incidence of symptomatic thromboembolic events from 0–5%; screening for asymptomatic events with routine cerebral

imaging postablation suggests this problem may be more widespread.⁹² In registry data, the incidence of symptomatic thromboembolism was approximately 1%.⁹³ Few prospective randomized trial data are available regarding the optimum approach to reduce thromboembolic risk in the peri-ablation period. This section provides a consensus of the Venice Chart members based on available evidence.

Preablation Anticoagulation Strategy and the Role of TEE

All efforts should be made to minimize a thromboembolic event prior to ablation. To accomplish this goal, one needs to know the baseline risk for thromboembolic event. This depends on several factors, as summarized in the CHADS2 scoring system. Thus, a patient with a CHADS2 score of 2 or more requires oral warfarin therapy with at least three weeks of documented INRs 2–3, and should undergo bridging with iv heparin or subcutaneous low molecular weight heparin (LMWH) before ablation. We suggest the same strategy for patients with a CHADS2 score of 1. Patients with a CHADS2 score of 0 with persistent AF require the same anticoagulation protocol noted above, for they will undergo cardioversion at the time of ablation. However, there is no consensus on the need for preablation oral anticoagulation for patients with paroxysmal AF and a CHADS2 score of 0, and some experts use the protocol outlined above whereas others use aspirin 75–325 mg/day.

TEE is used prior to transseptal puncture to be sure that the LA is free of clots; if not, the study is cancelled for that day. A TEE is recommended for any patient presenting in AF who has not undergone oral anticoagulation therapy with bridging before ablation, but is optional in other patients. The TEE should be performed as close in timing before the ablation as possible, but certainly within one day of the procedure.

Anticoagulation Strategy During the Ablation Procedure

The direct cause(s) of thromboembolic events during LA ablation procedures is not clear. Thrombus can form on long intravascular sheaths, as demonstrated by ICE, particularly in patients with persistent AF, dilated atria, and spontaneous echo contrast.⁹⁴ RF lesions can induce endothelial disruption and char that may lead to thrombus formation.

Unfractionated heparin, delivered by weight- or time-based nomograms and/or monitored by frequent measurement of activated clotting time (ACT) is given during the ablation procedure. The target intensity of anticoagulation is not standardized among experienced investigators and may vary according to several factors, for example, patient age, type of ablation procedure and catheter used, and energy source. Several laboratories using ICE have shown that the incidence of sheath thrombus markedly decreased with an increase in target ACT from 250–300 to > 300 seconds.^{94,95}

Anticoagulation should be established after LA access is completed using an intravenous bolus dose of unfractionated heparin of 100–140 IU/kg, followed by an infusion of 15–18 IU/kg/hour or additional bolus to maintain an ACT target of at least 250, but up to 400 seconds. As sheath thrombus can occur immediately, many laboratories that use ICE establish anticoagulation prior to transseptal puncture. ACT measurements should be performed every 20–30 minutes and the heparin dose adjusted to the desired target ACT. Heparin infusion is discontinued after removal of catheters from the LA. Because thromboembolic events have been observed af-

ter the procedure but during the time interval associated with reversal of anticoagulation with protamine, some laboratories have abandoned this practice.

Postablation Anticoagulation Strategy

No universally accepted recommendations exist for the anticoagulation therapy after successful ablation of AF. Due to the high risk of thromboembolism in the early postprocedural period,⁹⁶ in the majority of centers maintenance warfarin therapy is restarted in all patients either the same evening of the ablation procedure or the next morning. In the initial period, LMWH (e.g., enoxaparin at a dosage of 0.5 to 1.0 mg/kg twice a day) is often given as bridging therapy by starting three to four hours after the ablation.^{62,97} Less frequently, heparin is administered intravenously until the day after the procedure, starting about three hours after sheath removal at a rate of 1,000 IU/hour.^{57,96} Thereafter, LMWH is administered until the international normalized ratio (INR) is ≥ 2 . Once the therapeutic INR is achieved, LMWH is stopped, whereas warfarin is continued for at least three months.

The anticoagulation strategy after the initial three months varies among laboratories, and few data are available to form a consensus on the best approach to adopt. Lacking any large randomized clinical trial data in postablation patients, it is suggested for most individuals with a CHADS2 score of ≥ 2 to continue long-term warfarin treatment with a targeted INR of 2–3. It should be noted that the level of INR may vary among different people, for example, Asians, and the dose used should be what is routine for that population to achieve appropriate anticoagulation. In selected patients without evidence of recurrent AF after three to six months, it may be possible to discontinue warfarin, but the safety of this approach requires further study. Some factors that might affect the decision to stop warfarin in this situation include LA size and the lesion set used for ablation. If warfarin is discontinued, aspirin (75–325 mg/day) should be started unless contraindicated. Patients with a CHADS2 score of 1 may be treated with aspirin or warfarin, and those without moderate risk factors are advised to take aspirin or nothing.

Role of Anticoagulation in Patients with Early Recurrences of AF

During the first three months after ablation, there is a relatively high expected incidence of AF. This time period is referred to as the “blinking period.” Such early recurrences of AF are often transient and are not necessarily predictive of long-term AF recurrences. Anticoagulation for AF that occurs after the blinking period follows the guidelines for risk of stroke as noted above. In this situation, warfarin is preferable for all patients with a CHADS2 score of 2 or more.

Future Trials on Anticoagulation in AF Ablation Patients

An overlying concern is the absence of long-term data in large numbers of patients following catheter ablation of AF. We need a perspective study not only on the incidence of recurrence of AF beyond the “blinking period,” but also on the incidence of stroke in the absence of anticoagulation therapy, especially in patients with risk factors for stroke. Data from relatively small studies suggest that the stroke incidence is low, but the incidence of AF recurrence, both manifest and asymptomatic, is uncertain. Future well-conducted randomized trials have to establish the best anticoagulation protocol

after ablation of AF, according to the clinical characteristics of the patients, especially their thromboembolic risk. Large-scale trial (>3,000) of patients with AF at risk for stroke should be considered. In this case, a trial of AF ablation with apparent success without anticoagulation versus standard therapy with anticoagulation might be contemplated. No trials are reasonable in patients at low stroke risk.

Periprocedural and Late Complications

Ablative therapy for AF is associated with significant risk. Recognition of common/unique complications related to AF ablation, their incidence, etiology, and techniques for prevention should help to minimize those risks and optimize the outcome of the ablation procedure. A reasonable estimate of risk in the general electrophysiology community has been suggested from a worldwide survey based on experience with over 8,000 patients undergoing catheter ablation for AF.⁹³ This section of the consensus document will address each of the major/unique complications related to the AF ablation procedure.

Cardiac Tamponade

Earlier surveys reported a 0.35–1.7% incidence of cardiac tamponade in an era before routine AF ablation procedures.^{98,99} Among 8,754 patients from the worldwide survey who underwent catheter ablation of AF between 1995 and 2002, peri-procedural cardiac tamponade occurred in 107 patients (1.2%).⁹³ A rate of 0.8–1% of cardiac tamponade has been confirmed in smaller series of patients who underwent catheter ablation of AF.^{56,100}

AF ablation involves LA mapping and ablation with access to the LA gained through one or multiple transseptal punctures. Tamponade risk related to transseptal puncture appears to be dependent on the experience with the technique. Monitoring tools, such as ICE or TEE with direct visualization of the transseptal puncture may help minimize risk related to experience. Direct echocardiographic imaging can identify unique anatomic variants, such as septal aneurysms, hypertrophic atrial septum, or thickened/fibrosed fossa ovalis that may increase technical difficulty.¹⁰¹ Of note, a recent multicenter survey on transseptal catheterization spanning 12 years¹⁰² reported a very low incidence of cardiac tamponade complicating LA catheterization performed for ablation of various arrhythmic substrates (five cardiac tamponade in 5,520 procedures; 0.1%).

In a series of 348 irrigated-tip AF ablations with complete PV isolation including LA linear ablation in 254 and cavo-tricuspid isthmus ablation in 265, 10 patients (2.9%) suffered cardiac tamponade during the procedure. All tamponade occurred during linear ablation attempting to create bidirectional conduction block in either the left or the right atrium. In eight out of 10 patients, cardiac tamponade was associated with “popping,” consistent with tissue disruption. A comparative analysis between patients with and without tamponade revealed that RF power was significantly higher in patients who developed tamponade (53 ± 4 vs 48 ± 7 W). The subsequent decision to limit power delivery to ≤ 42 W during linear ablation reduced the incidence of cardiac tamponade to 1% (four cardiac tamponade among the subsequent 398 procedures). A further power limitation to ≤ 40 W resulted in no cardiac tamponade in the next 167 AF ablations.¹⁰

Thus, although in some patients cardiac tamponade results from mechanical trauma from transseptal puncture or catheter manipulation, careful titration of RF power delivery seems to be very effective in reducing tissue boiling and endocardial rupture. Accordingly, this safety measure should currently be considered as a cornerstone in reducing the incidence of cardiac perforation and tamponade during RF catheter ablation.

Thromboembolic Events: See Previous Section

PV Stenosis

PV stenosis is a new clinical entity observed after RF catheter ablation of AF.^{1,104} The incidence was reported to be up to 40% when ablation targeted focal triggers inside the PVs.^{105,106} With the evolution of PV isolation techniques and ablation at the vein ostium or even more proximal to the veno-atrial junction, the incidence of severe stenosis has decreased to 0.5–2%.^{54–56,93,107} Minor degrees of stenosis may be anticipated if ablation is applied at the anterior margin of the left-sided veins, which abuts the left atrial appendage or the carina between ipsilateral PVs.

To reduce the risk of PV stenosis when ablation is performed near the PV ostium, the anatomy should be clearly defined. To localize the PV ostium and to avoid ablation inside the vein, angiography of the PVs, ICE, 3-D mapping systems with integration of MR or CT imaging anatomic information, and impedance measurements using the ablation catheter have been used.^{108–110} Intracardiac echo Doppler assessment of PV flow targeting a maximum flow of 100 mL/sec appears to be a useful guide to prevent significant stenosis.¹¹¹ Whatever monitoring/imaging technique is used, the decisive factor in avoiding PV stenosis seems to be a fundamental understanding of the anatomy of the LA, coupled with the ability to define further the anatomy and identify the location of lesion deployment. Avoidance of lesion placement within venous structure is critical.⁴

At selected sites, titration of energy delivery may avoid excessive tissue disruption and subsequent narrowing. The use of alternative energy delivery tools, such as balloon technology or energy sources for ablation like cryoenergy, ultrasound, or laser will need additional evaluation to determine if they may help to further reduce or even eliminate the risk of PV stenosis.

The clinical manifestation of PV stenosis may be quite insidious. Many people are asymptomatic if only single-vein stenosis is present.¹⁰⁶ The most frequent symptoms of PV stenosis are cough, dyspnea, hemoptysis, or recurrent and drug-resistant pneumonia.^{4,108,112} Symptoms may develop both early and/or late after the procedure, with most patients presenting within two to six months.⁴ To diagnose PV stenosis, TEE including Doppler measurements,¹¹³ V/Q lung scan,^{4,108} MR,¹¹⁴ or CT imaging⁴ may be used.

Significant PV stenosis in symptomatic patients should be treated by angioplasty and/or stenting.¹¹⁵ Angioplasty is associated with high restenosis rate of 45%, a problem not completely resolved by stenting.^{111,115} Surgical interventions may be considered, but because of the disappointing surgical results for congenital stenosis, surgery should be discouraged. In asymptomatic patients with two or more stenosed PVs, invasive therapy might be considered to prevent pulmonary hypertension during exercise.¹¹⁶ Whether patients with one stenosed PV and no or minimal clinical symptoms should be treated is not yet known. Regression, as well as progression

of PV stenosis to complete occlusion, has been observed during follow-up.^{106,114} Anticoagulation is typically maintained if severe stenosis is present to prevent acute thrombosis.

Phrenic Nerve Injury

The right phrenic nerve (PN) has a close anatomic relationship to the right superior PV and superior vena cava, as it runs along the lateral and postero-lateral wall of the right atrium and is vulnerable to collateral injury during endocardial RF delivery at or close to these structures.¹¹⁷⁻¹²¹ Experimental evidence has shown that the PN may be particularly susceptible to thermal injury.¹¹⁹ Permanent nerve damage may be preceded by transitory loss of function, opening a window for early recognition, and prevention by close monitoring.

Bai et al.¹²² reported 16 cases of right PN injury (81% during AF ablation and 19% during sinus node modification), with an estimated incidence around 0.1%. Most patients (88%) had persistent nerve damage, with only two presenting with transient loss of function. Nonetheless, recovery was documented in all cases after a mean of 7 ± 6 months of follow-up (range 3–28 months). Sacher et al.¹²³ reported 18 patients with PN injury during AF ablation of 3,755 consecutive patients (prevalence of 0.48%). Interestingly, two cases of left PN injury occurred during ablation of non-PV foci at the LA appendage roof. The remaining cases presented with right PN injury attributable to ablation lesions at the infero-anterior region of the right superior PV or the postero-septal superior vena cava. Complete recovery was documented in 66% after a mean of 4 ± 5 months after the index procedure. Partial recovery occurred in an additional 17% after 36 months of follow-up. PN injury appears to be clinically silent in the majority of cases, although symptoms may also depend on the previous existing lung condition. In fact, in the above mentioned series, 50%¹²² and 22%¹²³ were completely asymptomatic, with the majority of the remaining patients presenting with mild symptoms, such as dyspnea, cough, and weakness. However, some patients developed more severe lung complications, such as pneumonia, atelectasis, pleural effusion, and respiratory failure requiring mechanical support. One patient with persistent dyspnea required surgical plication of the paralyzed right diaphragm. The diagnosis of PN injury can be confirmed by fluoroscopy demonstrating the presence of unilateral diaphragmatic paralysis.

Despite the low prevalence and apparent benign course in most patients, prevention of persistent PN injury is possible by identification of PN location with high-output pacing and avoiding energy application in these regions.^{119,122,123} Such high-output pacing (≥ 30 mA, 2 msec) is recommended before energy delivery at or near the right superior PV, the superior vena cava, and the proximal LA appendage roof and, in case of diaphragmatic contraction, ablation should be avoided.

Atrio-Esophageal Fistula

Atrio-esophageal fistulas, esophageal damage, and perforation were first described following RF ablation on the posterior wall of the LA during open heart surgery in 2001. Ablation was performed endocardially with patients on cardio-pulmonary bypass. Patients presented with neurological deficits from air emboli, massive gastrointestinal bleeding, and septic shock on postoperative days 5–7.^{124,125} In

2004, the first descriptions of atrio-esophageal fistula formation following percutaneous RF catheter ablation were published.^{126,127} The patients in the published cases presented with nonspecific signs and symptoms including dysphagia, odynophagia, intermittent cardiac or neurologic ischemia (air emboli and/or vegetations), persistent fever, bacteremia, fungemia, and melena.¹²⁸ The manifestation of the fistula can occur weeks after the ablation procedure. Though atrio-esophageal fistula formation is apparently rare, it appears to be nearly universally fatal, and thus it has remained the subject of intense investigation.

Evaluation of serial CT scans as well as ICE have documented the close proximity, often less than 0.5 cm, of the esophagus to the left atrial wall.¹²⁹⁻¹³¹ Some labs have also documented movement of the esophagus during an ablation procedure.¹³² 3-D mapping systems, including ESI-Ensite and Carto, the ingestion of radio-opaque contrast, and on-line ICE have all been used to image the esophagus before, during, and following ablation.¹³¹

Injury to the esophagus is presumed to be thermal in nature. Though some may argue that ablation in the region of the posterior LA wall is not safe and should be avoided, others believe that monitoring of esophageal location and/or temperature and avoidance of overheating the endocardial surface (microbubble formation) and/or low energy delivery for short duration offer safe options.¹²⁹ Because of the infrequent occurrence of atrio-esophageal fistula, there are currently no data that clearly place one approach superior to another, although esophageal fistula has been reported in patients in whom RF delivery was dictated by temperature monitoring.

Data, thus far, clearly demonstrate that atrio-esophageal fistula is characteristically a fatal complication. Surgical intervention to prevent fatality requires rapid and accurate recognition and diagnosis. Fever, malaise, leukocytosis, dysphagia, hematemesis, and neurological symptoms in patients with a recent catheter ablation procedure should raise suspicion of atrio-esophageal fistula. CT of the chest or head revealing intravascular air should immediately suggest a communication between the gastrointestinal tract and the vasculature. Currently, imaging techniques, such as MR or CT are recommended to diagnose an atrio-esophageal fistula. If a fistula is suspected, it is important that endoscopy is avoided because insufflation of the esophagus has been demonstrated to lead to massive air emboli through the fistula, leading to stroke and myocardial infarction.^{124,128} Though mortality of this complication is very high, previously published reports document survival following rapid surgical correction.¹²⁶ Stenting of the esophagus has also been reported to be effective.¹³³

Periesophageal Vagal Injury

A new extracardiac complication of AF ablation characterized by abdominal bloating and discomfort occurring within a few hours to two days after the procedure has recently been described.¹³⁴ The incidence of such adverse event was 1% in a series of 367 patients. This complication is probably due to LA RF energy delivery affecting the periesophageal vagal plexus. Upper gastro-intestinal investigation showed a pyloric spasm, gastric hypomotility, and a markedly prolonged gastric emptying time. To avoid this complication, the authors suggested using esophageal temperature monitoring and avoiding LA endocardium overlying the esophagus.

Moreover, identification of the esophageal vagal plexus and the titration of power, according to the myocardial thickness and surrounding structures, should be helpful.

Vascular Complications

Vascular complications can occur with any catheter-based procedure, but appear to be more common with ablation procedures targeting AF. These complications include large hematoma at the groin or neck sites of catheter insertion, pseudoaneurysm, arteriovenous fistula, or retroperitoneal bleeding. An incidence of femoral pseudoaneurysm and arteriovenous fistulae of 0.53% and 0.43%, respectively, has been reported, based on experience in more than 8,000 patients from a worldwide survey.⁹³

Large hematomas and retroperitoneal bleeding can almost always be managed conservatively. Anticoagulation may need to be held and transfusion may be necessary in selected patients. Echo-guided manual compression and percutaneous intervention are usually effective treatments of femoral pseudoaneurysms or arteriovenous fistula after ablation of AF, although direct surgical intervention may be necessary.¹³⁵ Minimizing vascular complications by careful vascular access, avoidance of large sheaths, and adequate vascular compression during states of persistent anticoagulation should be the norm.

Acute Coronary Artery Occlusion

Fortunately, coronary injury is an uncommon complication. Takahashi et al. described an incidence of 0.002% of circumflex artery occlusion in a large series of patients who underwent mitral isthmus ablation. In 71% of the study group, RF energy was delivered in the coronary sinus.¹³⁶

Air Emboli

Air emboli may enter the arterial system during sheath/catheter exchanges, aspiration, irrigation, or continuous infusion of sheaths.^{137,138} An air embolus often travels to the right coronary artery and mimics typical clinical presentations of acute inferior myocardial wall ischemia. If the procedure is performed under conscious sedation, the patient may complain of chest pain. There may also be ST elevation in the inferior ECG leads. Air embolus to the coronary arteries often resolves within several minutes without major complications and residual myocardial injury, although aggressive supportive measures may be required. If the signs suggestive of an embolus persist, coronary angiography and, if necessary, aspiration of the air from within the coronary artery should be considered. Air emboli may also travel to cerebral circulation and may lead to neurologic manifestations.

Air emboli are best prevented by proper attention to catheter and sheath technique. Caution should be exercised when exchanging the sheaths and catheters. The sheaths should routinely be flushed intermittently and also after each catheter withdrawal. If sheaths are continuously irrigated throughout the procedure, air bubbles should be avoided and automatic pumps capable of detecting air in the tubing should be used.

Catheter Entrapment in the Mitral Valve

A recent worldwide survey on AF ablation on 7,154 patients reported an incidence of 0.01% of valve damage.⁹³

Based on these data, several recommendations can be made to reduce the incidence of such a complication. First, an effort should be made to always position the circular part of the mapping catheter in the posterior LA during transseptal catheterization. Second, it is recommended to torque the catheter in a clockwise direction when leaving the transseptal sheath in order to avoid the tip of the catheter from becoming entrapped in anatomic structures that have a diameter less than that of the circular mapping catheter. Third, it is recommended to advance the catheter and/or the sheath over the catheter when such entrapment is observed with the initial withdrawal maneuvers. This may prevent a further tightening of the catheter loop and frequently frees up the tangled apparatus. Finally, early surgical extraction, which carries a small but unknown risk of thromboembolization, should be strongly considered before manual extraction in order to avoid mitral valve injury and preserve the mitral valve apparatus.

Organized Left Atrial Tachyarrhythmias after AF Ablation

Organized left atrial tachycardias and flutter are common in patients who have undergone left AF ablation with a reported incidence of ~3% to 50%.^{67,83,84,139-141} The variability in the frequency of occurrence postablation and the mechanism of the tachycardia appears to be clearly dependent upon the type of ablation procedure used. Centers utilizing wide area circumferential PV ablation combined with additional linear lesions in the LA report a higher prevalence of macro-entrant atypical flutters and an overall incidence of organized LA tachycardias that is three times that observed with only PV isolation procedures.^{67,83,84,139-141} This is especially true if no attempt is made to establish/confirm a line of bidirectional block.^{60,142} The macro-entrant circuit of atypical flutter typically moves around a large anatomic barrier, such as the mitral annulus or ipsilateral PVs, and typically incorporates a zone of slow conduction created by gaps in LA linear lesions. Occasionally, circuits can be defined around the fossa ovalis. Centers that utilize PV isolation alone have observed a low overall incidence of recurrent regular atrial tachycardias and these arrhythmias have been predominantly focal LA tachycardias originating from reconnected PVs.^{64,139,140}

Most of the regular LA tachycardias that occur after ablation will be manifest early in the postablation course. Patients are frequently symptomatic because they tend to demonstrate 2:1 AV conduction and a faster ventricular rate than observed in response to AF. Most of the tachycardias are resistant to drug therapy and a few may actually represent drug proarrhythmia. Despite the general poor response to medical therapy and frequent recurrence after cardioversion, attempts to temporize are still recommended. This is especially true given the fact that up to 50% of these tachycardias appear to resolve spontaneously during the "healing phase" postablation.⁸⁴ Because many tachycardias will persist after the two- to three-month blanking period and/or are recurrent and very symptomatic, repeat ablation procedures are appropriate.

The 12-lead ECG may be helpful in suggesting a focal source for the LA tachycardia from a reconnected PV. A superior and posterior location for the PVs creates inferiorly directed P waves with a positive precordial activation pattern.^{143,144} Importantly, right atrial flutter after extensive LA ablation can create atypical surface ECG patterns.¹⁴⁵ The ability to identify accurately the origin/path of regular

atrial tachycardias that occur after AF ablation is critically dependent on the use of detailed activation mapping primarily for focal atrial tachycardias and entrainment mapping techniques for large macrore-entrant rhythms.¹⁴⁶ Depending on the underlying mechanism, the ablation strategy may require either isolation of the reconnected PV segment (for focal tachycardias of PV origin) or may involve targeting the zone of slow conduction or a well defined anatomic isthmus for macrore-entrant flutter.^{81,139} Overall, ablation is quite effective for these arrhythmias, with reported long-term success rates in excess of 80%. The frequent occurrence of macrore-entrant rhythms associated with LA linear lesions has made it imperative that this lesion strategy should only be used when felt to be clinically necessary. In addition, documentation of bidirectional block using the appropriate stimulation techniques should be performed routinely to prevent this common complication.

Adverse Impact on Atrial Contractility

Reverse remodeling of the left cardiac chambers have been reported after successful RF catheter ablation of paroxysmal and persistent AF.^{89,90,147,148} Independent of the technique applied—PV isolation guided by a circular mapping catheter,⁹⁰ proximal PV¹⁴⁷ or antral PV isolation guided by ICE and circular mapping catheter,⁸⁹ or circumferential PV ablation guided by a nonfluoroscopic system,¹⁴⁸—there was a significant decrease in LA diameters and volumes during follow-up. However, the consequences of RF ablation on the LA contractility are still somewhat inconsistent and appear to be directly related to the ablation procedure performed. In the PV isolation study, the authors observed no change in the LA active emptying fraction in patients with paroxysmal AF before and after ablation (mean of $30.5 \pm 13.5\%$). Otherwise, an increase in active emptying fraction from $5.5 \pm 3.6\%$ just after ablation to $21.8 \pm 11\%$ ($P < 0.05$) at 11 months was observed in patients with chronic AF.⁹⁰ In the studies using antral PV isolation guided by ICE, all echocardiographic parameters used as surrogates of LA contractile function showed an increase after RF ablation. The mean LA EF one day after ablation was $32 \pm 11\%$, compared with $54 \pm 18\%$ in the same patients at six months.¹⁴⁷ In patients undergoing cine electron-beam CT to assess LA EF, there was also a significant improvement in LA EF postantral PV isolation from $17 \pm 6\%$ to $22 \pm 5\%$ ($P = 0.01$).⁸⁹

In contrast, in the circumferential PV ablation study, patients undergoing LA contractile function evaluation by gated, multiphase, dynamic contrast-enhanced CT scans showed that LA EF was lower after circumferential PV ablation ($21\% \pm 8$ vs $32\% \pm 13$, $P = 0.003$). Furthermore, LA EF after catheter ablation was similar among patients with paroxysmal AF and those with chronic AF ($21\% \pm 8$ vs $23\% \pm 13$, $P = 0.7$) and LA EF after catheter ablation was lower in all patients with AF than in control subjects ($21\% \pm 10$ vs $47\% \pm 5$, $P < .001$).¹⁴⁸ It would appear that effects on LA function are clearly dependent on the extent of LA ablation. More prospective studies are needed to corroborate and clarify these important observations and to determine a possible relationship to thromboembolic risk.

Radiation Exposure During Catheter Ablation of AF

Catheter ablation of AF frequently requires the use of CT scan prior to the procedure and a long fluoroscopy time dur-

ing the procedure. Further complicating the issue is the fact that AF ablation procedures are often done in the obese patient, increasing the exposure to patient and operator. Very low frame rate pulsed fluoroscopy systems have become the norm to minimize radiation exposure. Skin radiation “burns” with proper operating equipment are currently extremely rare.^{149,150} Limiting cineangiography and avoidance of magnification are also suggested to reduce further exposure. Changing the angulation of fluoroscopic equipment may help to further reduce direct skin exposure when prolonged procedure and imaging times are required. Although single procedure exposure appears to represent a very low cancer risk, repeated procedures may indeed begin to produce a measurable risk increase and every effort should be made to minimize total exposure.¹⁵¹⁻¹⁵³ Electroanatomic and remote navigation systems that facilitate catheter placement and stability may help to reduce radiation exposure.

Short and Long-Term Efficacy

The acute and long-term efficacy of catheter ablation procedures for the treatment of AF is not, at the present time, easy to establish. In order to define the success rates of any given procedure, there must be a consistent approach to the technique, a well-accepted method of follow-up, and a strict definition of success. Unfortunately, the available literature is quite heterogeneous on these points.

There have been a variety of approaches reported for performing AF ablation. Although there has been some convergence in techniques, the technologies used, the exact endpoints of ablation, and intensity of patient follow-up continue to differ. Most centers report 12-month follow-up with recurrence based on patient reporting, routine ECGs, and Holter monitoring. Use of more meticulous methods of detecting AF (transtelephonic monitoring, loop recorders) may identify more AF, although there is some debate regarding the incidence of asymptomatic recurrence in previously highly symptomatic patients.^{154,155} Finally, even the definition of success has varied. Most studies use absence of AF as the gold standard, but some do not count very brief AF recurrences ($< 1-2$ minutes) as failures. Early recurrences occurring immediately after the procedure are also typically discounted, although the lengths of such “blinking periods” have varied (2–6 months). The literature is also divided on whether success should be defined in presence or absence of antiarrhythmic agents. These issues remain important challenges when interpreting efficacy of AF ablation from the current literature.

Early recurrences of AF are quite common within the first 2–3 months postablation. Studies suggest that the incidence of early AF recurrence ranges from 35–50%.^{156,157} Many patients who have early recurrences (30–50%) have no AF in the longer-term.^{156,157} Many studies thus describe an early “blinking period” of 2–3 months during which AF or atrial flutter are ignored, but some have suggested that atrial flutters may occur up to six months postablation without predicting long-term outcome.¹⁵⁸ Hypothesized mechanisms for early recurrences include transient postablation atrial inflammation and/or incomplete healing of the lesion sets. Most patients who have late AF recurrence have usually had recurrence within the first three months.¹⁵⁷ Many centers use temporary antiarrhythmic therapy for the first 2–3 months postablation to prevent early recurrences.

Reports of longer-term success rates have ranged from 45 to 95%. Part of this wide range is explained by the inclusion of earlier studies that used more limited ostial ablation of the PVs. A recent meta-analysis combined all reported results from studies employing a wide-circumferential approach encircling the PVs in 15,455 patients.¹⁵⁹ The overall success rate was 74% after >6 months follow-up in a wide range of patients. Ten percent of these patients were taking antiarrhythmic drugs. When recent single-center data from pioneering centers with greater experience are analyzed (total 1,039 patients), the off-drug success rate is 80.5% (follow-up six months–2.4 years).¹⁶⁰ Performing a second ablation procedure increases the chance of off-drug success in most studies by an additional 5–15%.¹⁶⁰ Whether >2 procedures provides benefit is not well known. Unfortunately, there is not much multicenter data at the present time to evaluate the outcome from AF ablation. A worldwide survey reported a 52% success rate off drugs, with an additional 23.9% partial success rate of patients on antiarrhythmics with follow-up of 11.6 months.⁹³ Very little data (single or multicenter) are available on the outcome of AF ablation beyond 12 months of follow-up. Pappone et al.,¹⁶¹ showed that most recurrences occurred within the first 12 months, with a small incidence of “late” failures (less than 3%).

Studies have shown that the mechanism for longer-term recurrence is linked to the recovery of electrical conduction between the PVs and the LA.¹⁶² Recurrence, particularly atrial flutter, may also be related to scars created by the initial ablation. Re-isolation of the PVs is quite often effective in treating recurrent AF or atrial flutter;¹⁶³ however, performance of additional linear lesions (mitral annulus, LA roof) may be required.⁸¹ The mechanism of very late recurrences may also involve development of non-PV triggers, particularly in the right atrium.⁶⁴

In general, the success rates of the ablation of AF are lower in cases of long-lasting AF than in those of paroxysmal or persistent AF. Two recent studies reported 74% and 95% success rates after one year^{97,165} in patients with long-lasting AF. However, many studies show success rates of 50–70% in nonparoxysmal AF and many have suggested the need for further adjuvant substrate modification in addition to PV isolation. Lower success rates have also been seen in patients with significant structural heart disease.¹⁵⁹ LA scarring is a major risk of procedural failure.¹⁶⁶ Other predictors of failure include extreme LA enlargement (>55 mm) and advanced age (>65 years).¹⁵⁷

The literature provides little data comparing ablation with the alternative of conventional drug therapy. In a nonrandomized, controlled study, Pappone et al. showed that ablation (n = 589) had less arrhythmia recurrence versus antiarrhythmic therapy over 2.4 years follow-up (22% vs 63%, P < 0.001).¹⁶¹ This benefit even translated into a lower number of strokes and improved survival (hazard ratio 0.46 vs medical therapy, P < 0.001). In the Radiofrequency Ablation of Atrial Fibrillation Trial (RAAFT) multicenter, prospective study, 70 previously untreated AF patients were randomized to ablation or to antiarrhythmic drugs as first line therapy.¹⁶⁷ Over 12 months, fewer symptomatic recurrences occurred in the ablation group (13% vs 63%, P < 0.001), with a lower incidence of hospitalization (9% vs 54%, P < 0.001). In the Catheter Ablation for the Cure of Atrial Fibrillation (CACAF) multicenter, prospective study, patients were randomized to ablation + antiarrhythmic drugs (n = 68) or to antiarrhythmic

mic drugs alone (n = 69).¹⁶⁸ After one year, the patients in the ablation group had a significantly lower incidence of arrhythmic recurrence than those of the control group (44% vs 91%, P < 0.001). In a randomized study by Oral et al., 146 patients with long-lasting AF were treated with amiodarone for six weeks before and three months after being randomly assigned either to circumferential PV ablation or to electrical cardioversion.¹⁶⁵ An intention-to-treat analysis revealed that 74% of the ablation-group patients and 58% of the controls were in sinus rhythm after one year (P = 0.05). Finally, in the Ablation for Paroxysmal Atrial Fibrillation (APAF) study, Pappone et al.,¹⁶⁹ compared AF ablation with antiarrhythmic drug therapy in 198 patients with paroxysmal AF. Ninety-three percent of subjects in the ablation group and 35 percent of those in the antiarrhythmic drug group were free of recurrent AF at one-year follow-up (P < 0.001). Moreover, AF ablation was associated with fewer cardiovascular hospitalizations (P < 0.01).

In summary, AF ablation appears to be an effective therapy over both the short- and longer-term, with an acceptably low incidence of complications. Limitations still exist as to the uniformity of the ablation technique, definition of success, and rigor of follow-up and these will need to be addressed in future studies. Multicenter, randomized data are still lacking, as are data on very long-term outcomes. AF ablation appears to be superior to conventional medical therapy, although larger studies are required, and whether superior arrhythmia prevention translates into reduced morbidity and mortality remains to be seen and should be the subject of future trials.

Appendix

Venice Chart Co-Chairmen

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