

Guideline for the surgical treatment of atrial fibrillation

Joel Dunning^{a,*}, Myura Nagendran^b, Ottavio R. Alfieri^c, Stefano Elia^d, A. Pieter Kappetein^e, Ulf Lockowandt^f,
George E. Sarris^g and Phillippe H. Kolh^h, On behalf of the EACTS Clinical Guidelines Committee

^a Department of Cardiothoracic Surgery, James Cook University Hospital, Middlesbrough, UK

^b John Radcliffe Hospital, University of Oxford, Oxford, UK

^c Division of Cardiac Surgery, Ospedale San Raffaele, Milan, Italy

^d Department of Experimental Medicine and Surgery, General Thoracic Surgery, University Tor Vergata, Rome, Italy

^e Thoraxcenter, Erasmus MC, Rotterdam, Netherlands

^f Department of Cardiothoracic Surgery, Karolinska University Hospital, Stockholm, Sweden

^g Department of Pediatric and Congenital Heart Surgery, Mitera Children's and Hygeia Hospitals, Athens, Greece

^h Department of Cardiothoracic Surgery, University Hospital of Liège, Liège, Belgium

* Corresponding author. Department of Cardiothoracic Surgery, James Cook University Hospital, Middlesbrough, UK. Tel: +44-7801548122; fax: +44-1642854613; e-mail: joeldunning@doctors.org.uk (J. Dunning).

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and its prevalence is ~1–2% of the general population, but higher with increasing age and in patients with concomitant heart disease. The Cox-maze III procedure was a groundbreaking development and remains the surgical intervention with the highest cure rate, but due to its technical difficulty alternative techniques have been developed to create the lesions sets. The field is fast moving and there are now multiple energy sources, multiple potential lesion sets and even multiple guidelines addressing the issues surrounding the surgical treatment of AF both for patients undergoing this concomitantly with other cardiac surgical procedures and also as stand-alone procedures either via sternotomy or via videothoracoscopic techniques. The aim of this document is to bring together all major guidelines in this area into one resource for clinicians interested in surgery for AF. Where we felt that guidance was lacking, we also reviewed the evidence and provided summaries in those areas. We conclude that AF surgery is an effective intervention for patients with all types of AF undergoing concomitant cardiac surgery to reduce the incidence of AF, as demonstrated in multiple randomized studies. There is some evidence that this translates into reduced stroke risk, reduced heart failure risk and longer survival. In addition, symptomatic patients with AF may be considered for surgery after failed catheter intervention or even as an alternative to catheter intervention where either catheter ablation is contraindicated or by patient choice.

Keywords: Cardiac surgery • Guideline • Atrial fibrillation • Ablation • Cox-maze • Maze

INTRODUCTION

Atrial fibrillation (AF) occurs in 1–2% of the general population and is the most common sustained cardiac arrhythmia [1, 2]. The incidence of AF increases with age and patients have a 5 times higher risk of stroke and a 3 times higher risk of congestive heart failure. The long-term sequelae of AF include death, stroke, increased hospitalization and a reduction in quality of life. Antiarrhythmic drugs form the mainstay of medical treatment but unfortunately suffer from significant recurrence rates in many cases [3]. Catheter-based ablation provides a minimally invasive alternative, although its variable efficacy has prompted some to suggest that it may be most appropriate for selected groups of patients such as those with paroxysmal AF [4]. The Cox-maze III procedure remains the surgical treatment with the highest cure rates (over 90%) but the challenging technical nature of the traditional cut-and-sew technique limited its mainstream uptake. The Cox-maze IV procedure aimed to address this issue by making use of alternative energy sources to replace incisions with ablation lines [5].

Guideline development for the medical treatment of AF has been highly active in recent years, with the American College of Cardiology and American Heart Association (ACC/AHA) and Heart Rhythm Society (HRS) jointly publishing two major recent updates to their 2006 guideline [6, 7], the American College of Chest Physicians (ACCP) published its ninth version of Antithrombotic Therapy for AF in 2012 [8], the Canadian Cardiovascular has updated their guidance [9] and the European Society of Cardiology (ESC) has updated their guidelines in 2012 [2, 10]. Also, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) and the ACCF, AHA and HRS intend to completely rewrite their AF Guidelines in the near future. Guidelines for the new oral anticoagulants as alternatives to warfarin for AF have also been published [11].

This guideline will present and summarize the evidence for surgically based atrial ablation procedures with a view to allowing cardiac surgeons to make more informed decisions with regard to the surgical options for AF. We hope to bring together a brief summary of the available published guidelines and provide evidence summaries in some areas where guidelines were lacking.

SCOPE OF THE GUIDELINE

This guideline covers the surgical treatment of AF during concomitant cardiac surgery and as a stand-alone procedure. It includes different modalities for delivery of the energy used to carry out the ablative lesions. Also addressed is cessation of anticoagulation following the procedure, impact of left atrial (LA) size on atrial ablation surgery success and the efficacy of LA reduction during surgery. Specifically excluded is the medical prophylaxis and treatment of de novo AF that occurs following cardiac or thoracic surgery, and catheter-based interventions which are covered in other guidelines [2, 10].

We fully support and will highlight recommendations from guidelines written by partner European organizations including the ESC [10], their working group on thrombosis [12] and the European Heart Rhythm Association (HRS/EHRA/ESC guideline) [13, 14].

METHODOLOGY OF THE GUIDELINE

This guideline comprises several novel aspects of methodology in its derivation. Many guidelines are based on a single systematic review and multiple clinical questions are then answered on the basis of the papers found from this one review. In contrast, we felt that it was important to perform a full literature review for every single question addressed in order to maximize the robustness of the guideline. We used a structured systematic review protocol named 'Best Evidence Topics' to construct each review, where the search strategy, results of the search and a full appraisal of all papers are published in a structured format. Of note the quality of the included papers varies according to the question asked, so for some questions only large-cohort studies were included but for some reviews, especially when questions of safety were addressed, small studies or even case reports were included if they raised important issues. The details of this protocol are described in the Interactive Cardiovascular and Thoracic Surgery (ICVTS) [15].

Guidelines often fall short of expectations due to a failure to consult those clinicians who are most likely to use them. For this guideline, all the literature reviews have already been published in full in the ICVTS. Topics were published online and clinicians were able to post comments on them over a 2-month period. These comments were then published together with the full paper in the ICVTS and are now available to all readers in full text online at www.icvts.org.

LEVELS OF EVIDENCE AND GRADING OF RECOMMENDATIONS

We support the recommendations for formulating and issuing Guidelines and Expert Consensus Documents, which can be found on the European Society of Cardiology website (<http://www.escardio.org>) and search for recommendations for guidelines production) and which have been used previously in formulating EACTS guidelines [16].

In brief, with regard to grading the level of evidence derived from published papers:

- (i) Level of evidence A: data derived from multiple randomized clinical trials or meta-analyses.
 - (ii) Level of evidence B: data derived from a single randomized clinical trial or large non-randomized trials.
 - (iii) Level of evidence C: consensus of opinion of the experts and/or small studies, retrospective studies, registries.
- Then once recommendations are made, they are classed by the strength of their recommendation:
- (i) Class I: evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
 - (ii) Class II: conflicting evidence for and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.
 - (iii) Class IIa: weight of evidence/opinion is in favour of usefulness/efficacy.
 - (iv) Class IIb: usefulness/efficacy is less well established by evidence/opinion.
 - (v) Class III: evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

DEFINITIONS OF ATRIAL FIBRILLATION

For the purposes of this guideline, we adopt the definitions used by the ESC for AF. This statement is in accordance with the 2006 guidelines on AF published by the ACC/AHA/ESC 2006 guidelines and their subsequent updates [10, 17] and there is further information on definitions of AF published by the Society of Thoracic Surgery (STS) guidelines for reporting data and outcomes for the surgical treatment in AF [18].

AF is a supraventricular arrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. On electrocardiogram (ECG), AF is manifested by the replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in size, shape and timing, associated with an irregular, frequently rapid ventricular response when atrioventricular conduction is intact.

With regard to the differing types of AF, these are further defined as:

- (i) *First diagnosed AF*: every patient who presents with AF for the first time is considered a patient with first diagnosed AF, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms.
- (ii) *Paroxysmal AF* is self-terminating, usually within 48 h. Although AF paroxysms may continue for up to 7 days, the 48-h time point is clinically important—after this the likelihood of spontaneous conversion is low and anticoagulation must be considered.
- (iii) *Persistent AF* is present when an AF episode either lasts >7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion.
- (iv) *Long-standing persistent AF* has lasted for ≥ 1 year when it is decided to adopt a rhythm control strategy.
- (v) *Permanent AF* is said to exist when the presence of the arrhythmia is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF. Should a rhythm control strategy be adopted (such as consideration of AF surgery), the arrhythmia is redesignated as 'long-standing persistent AF'.

As an additional note on nomenclature, the 2012 HRS/EHRA/ESC guidelines remind us that the term maze procedure is

appropriately used only to refer to the lesion set of the Cox-maze III. Less extensive lesion sets should not be referred to as a 'Maze' procedure. In general, surgical ablation procedures for AF can be grouped into three different groups: (i) a full Cox-maze lesion set, (ii) LA lesion sets and (iii) pulmonary vein isolation (PVI).

INDICATIONS FOR INTERVENTION FOR ATRIAL FIBRILLATION

The 2012 HRS/EHRA/ESC guidelines provided a comprehensive summary of the indication for the surgical ablation of AF (Table 1). They grade these recommendations and also break these recommendations into two groups, patients undergoing concomitant surgical ablation together with other cardiac surgery and patients undergoing stand-alone surgical ablation. These guidelines are given in Table 1.

The major indication for intervention is for patients who are symptomatic with their AF. The guidelines do not recommend intervention simply to avoid administration of anticoagulation. Providing intervention for other reasons including quality of life, decreased stroke risk, decreased heart failure risk and increased

survival have all been suggested in the literature in multiple large-cohort studies and also in some randomized studies.

They recommend intervention as an acceptable treatment in symptomatic patients undergoing cardiac surgery, for all categories of AF including long-standing persistent AF and that this may be performed even before initiation of antiarrhythmic drug therapy. The guidelines conclude that more extensive lesion sets in concomitant surgery are more effective than PVI. In the left atrium (LA), a mitral isthmus lesion should be added to PVI where possible and a biatrial procedure should be considered in symptomatic patients and patients with long-standing persistent AF.

For patients considering stand-alone AF surgery, the evidence is less clear. Surgery should be for symptomatic patients only and the patients should be refractory or intolerant of at least one Class 1 or Class 3 antiarrhythmic medication. Surgery may be performed in all categories of AF including paroxysmal, persistent and long-standing persistent AF and may be performed after failed catheter ablation or as an alternative to catheter ablation either due to contraindications or due to patient choice.

CESSATION OF ANTICOAGULATION

Evidence was sought to determine whether anticoagulation may be discontinued following successful surgical or catheter-based interventions without exposing the patient to an unacceptable risk of thromboembolic stroke. The search is fully documented in Ref. [19], together with a summary of all identified papers. We identified 177 papers from the presented search strategy. From these, 14 papers represented the best evidence on the topic.

Themistoclakis *et al.* [20] reported on the only large (albeit non-randomized) trial comparing warfarin discontinuation with continuation in patients following surgical correction of AF. The trial included 3355 patients who had undergone PVI, and the results reported a lower rate of ischaemic stroke in the discontinuation group ($P = 0.06$). However, selection bias resulted in the continuation group comprising the majority of patients who remained in AF, confounding the results. Nevertheless, the low absolute stroke rate in the warfarin discontinuation group (0.07% over 28 ± 13 months) suggests that discontinuation of warfarin at 3-month post-PVI is safe.

Smaller studies support Themistoclakis' conclusions. Pappone *et al.* [21] reported an annual stroke rate of 0.4% in a cohort of 589 PVI patients who discontinued warfarin 3 months postoperatively (provided they remained free of AF). The median follow-up was 900 days. Corrado *et al.* [22] reported no thromboembolic events (TEs) over a mean follow-up of 16 months in a cohort of 138 high-risk patients who stopped warfarin 5–6 months after undergoing PVI. Similarly, Bunch *et al.* [23] also recorded no strokes in a 327-day study following 123 patients undergoing irrigated catheter tip ablation who were maintained on aspirin monotherapy.

In a non-randomized retrospective study, Cox *et al.* [24] reported just one late stroke in 306 patients over a mean follow-up of longer than 3 years. All of these patients remained free of AF throughout, and the majority discontinued warfarin at 3-month post-procedure.

Oral *et al.* [25] and Nademanee *et al.* [26] looked at patients discontinuing warfarin 3 months after LA ablation. The annual stroke rates in these studies were 0 and 0.4%, respectively. However, in Nademanee's study, patients only discontinued warfarin if they had remained free of AF throughout the immediate 3 postoperative months, and in fact, in those who suffered recurrence of AF and remained on warfarin, the annual stroke rate was higher, at 2%.

Table 1: 2012 HRS/EHRA/ESC Guidelines indications for the surgical ablation of AF

Indications for concomitant surgical ablation of AF		
Symptomatic AF refractory or intolerant to at least one Class 1 or 3 antiarrhythmic medication		
Paroxysmal: surgical ablation is reasonable for patients undergoing surgery for other indications	IIa	C
Persistent: surgical ablation is reasonable for patients undergoing surgery for other indications	IIa	C
Long-standing persistent: surgical ablation is reasonable for patients undergoing surgery for other indications	IIa	C
Symptomatic AF prior to initiation of antiarrhythmic drug therapy with a Class 1 or 3 antiarrhythmic agent		
Paroxysmal: surgical ablation is reasonable for patients undergoing surgery for other indications	IIa	C
Persistent: surgical ablation is reasonable for patients undergoing surgery for other indications	IIa	C
Long-standing persistent: surgical ablation may be considered for patients undergoing surgery for other indications	IIb	C
Indications for stand-alone surgical ablation of AF		
Symptomatic AF refractory or intolerant to at least one Class 1 or 3 antiarrhythmic medication		
Paroxysmal: stand-alone surgical ablation may be considered for patients who have not failed catheter ablation but prefer a surgical approach	IIb	C
Paroxysmal: stand-alone surgical ablation may be considered for patients who have failed one or more attempts at catheter ablation	IIb	C
Persistent: stand-alone surgical ablation may be considered for patients who have not failed catheter ablation but prefer a surgical approach	IIb	C
Persistent: stand-alone surgical ablation may be considered for patients who have failed one or more attempts at catheter ablation	IIb	C
Long-standing persistent: stand-alone surgical ablation may be considered for patients who have not failed catheter ablation but prefer a surgical approach	IIb	C
Long-standing persistent: stand-alone surgical ablation may be considered for patients who have failed one or more attempts at catheter ablation	IIb	C

The evidence for warfarin discontinuation following non-rhythm-correcting, left atrial appendage (LAA) occlusion strategies is less convincing. In a randomized controlled trial, Holmes *et al.* [27] reported the risk of ischaemic stroke off warfarin, following LAA occlusion using the WATCHMAN device (Atritech, Inc., Plymouth, MN, USA), as being just 2.2 per 100 patient-years. This was non-significantly greater than in the control arm of patients on standard warfarin therapy alone (1.6 per 100 patient-years), but was still a very low rate. This study has been criticized, however, as one-third of the patients had a CHADS2 score of only 1 and therefore were at low risk of stroke at study entry. However, Sick *et al.* [28] demonstrated similarly encouraging results, reporting no strokes and only two transient ischaemic attacks (TIAs) over a 2-year follow-up period in 55 patients discontinuing warfarin following WATCHMAN implantation.

Multiple non-randomized studies have looked at stroke rates in patients maintained on antiplatelet therapy alone following PLAATO device LAA occlusion [29, 30]. These reported a relatively low incidence of stroke of 0–3.8% per annum.

In fact, the only study found that describes a high incidence of TE in patients taken off warfarin is that reported by Almahameed *et al.* [31]. This study reported a 15% incidence of TE over a mean 3.6-year follow-up of just 40 patients who were taken off warfarin following concomitant LAA amputation and mitral valve surgery. However, the incidence of TE was 10% in the control arm individuals remaining on warfarin—much higher than in similar studies. Thus, it appears likely that the mitral valve itself was a major embolic source, contributing to the spuriously high TE rate in this study.

There is a body of low-quality evidence showing that warfarin discontinuation following AF surgery might be safe. The annual stroke risk following AF ablation surgery undertaken in isolation in patients in whom warfarin is discontinued is low. The current literature review puts the annual stroke risk at 0–0.4% in such patients, compiled from studies with a cumulative 10 000 patient-years of the follow-up, where warfarin was discontinued at a mean of 3.9 months (range 0–8 months) post-procedure.

However, if mitral valve surgery is performed concomitantly, stroke rates off warfarin can rise to up to 4.2% per annum, with mitral valve repair carrying a greater stroke risk than replacement.

The 2012 HRS/EHRA/ESC guidelines are also quite cautious on this issue. They do not recommend surgical intervention for AF only in order to discontinue warfarin or other oral anticoagulants. In addition, they do not recommend cessation of anticoagulants in patients postablation if their stroke risk is high as measured on CHADS2 scoring and they acknowledge the paucity of large-scale data in this new but growing population of patients postablation. If a patient is not high risk on CHADS2 and a significant continuous period of sinus rhythm has been demonstrated, they may have their warfarin changed for aspirin alone.

Recommendations

CESSATION OF ANTICOAGULATION FOLLOWING SUCCESSFUL SURGICAL OR CATHETER-BASED INTERVENTION

On the available evidence, we recommend cessation of anticoagulants at 3 months after established AF ablation procedures, if the patient is in sustained sinus rhythm, but only after first considering the stroke-risk profile of the individual patient and deeming it to be otherwise low.

Class IIa recommendation based on multiple retrospective studies (Level B).

Oral anticoagulation for ATRIAL FIBRILLATION

With the recent development of oral anticoagulants and their introduction into clinical practice, these are now a real alternative to warfarin in clinical practice for the prevention of stroke in AF.

The ESC working group on thrombosis published a state-of-the-art paper on this subject in April 2012 [12]. They summarized the results of the latest phase III clinical trials in this area, reporting that dabigatran etexilate 150 mg twice daily had been shown to reduce the rates of stroke/systemic embolism without any difference in major bleeding; dabigatran etexilate 110 mg twice daily had similar efficacy with decreased bleeding; apixaban 5 mg twice per day reduced stroke, systemic embolism and mortality as well as major bleeding; and rivaroxaban 20 mg four times per day was non-inferior to warfarin for stroke and systemic embolism without a difference in major bleeding. All these agents have been shown to reduce intracranial haemorrhage. Thus, these oral anticoagulants are a suitable alternative to warfarin in clinical practice. Caution should be taken in patients with a creatinine clearance of <50 ml/min, as reduced dosing is required. Also it is important to note that currently there are no reversal agents and fresh frozen plasma is only partially effective in reversal. In cases of uncontrolled bleeding unactivated or activated prothrombin complex concentrates or recombinant activated FVII may be helpful.

The National Institute of Health and Clinical Excellence in the UK also issued a technology appraisal of dabigatran in 2012 [11]. They conclude that dabigatran etexilate at a dose of 150 mg twice daily is superior to warfarin in terms of stroke prevention and is also cost-effective. They also remind us that the dose should be reduced to 110 mg twice daily in patients over the age of 80 due to the increased risk profile in this age group.

Recommendations

ORAL ANTICOAGULANTS FOR STROKE PREVENTION IN ATRIAL FIBRILLATION

On the available evidence, we recommend that the oral anticoagulants dabigatran, apixaban and rivaroxaban are suitable alternatives to warfarin for stroke prevention for patients requiring anticoagulation due to AF, based on clinical phase III trials and multiple international guidelines

Class Ia recommendation based on multicentre randomized controlled trials (Level A).

LEFT ATRIAL SIZE

Impact of preoperative left atrial size on ablation surgery success

Evidence was sought to determine what preoperative size of LA impairs ablation surgery success in terms of AF recurrence. The search is fully documented in Ref. [32] together with a summary of all identified papers. We identified 422 papers from the presented search strategy. From these, 12 papers represented the best evidence on the topic.

Kataoka *et al.* [33] looked at left atrial volume index (LAVI) as a predictor of maze failure. While they found no significant difference between sinus rhythm (SR) and AF groups in terms of left atrial diameter (LAD), multivariate analysis revealed LAVI as a predictor of AF recurrence—LAVI was significantly larger in the AF

group (122 ml/m² vs 81 ml/m², $P < 0.001$). They defined a cut-off value of 135 ml/m² that predicted whole population failure, i.e. 100% specific. The long-term outcomes are not reported.

Chaiyaroj *et al.* [34] found that at a 6-month follow-up, patients in SR were found to have had significantly smaller preoperative LAD compared with the AF group (54 mm vs 65 mm, $P < 0.001$). An adjusted odds ratio (OR) for persistent AF at 6 months was defined per mm increase in LAD: 1.65/mm (95% CI: 1.12–2.44, $P = 0.007$). The authors defined a cut-off point of highest accuracy for failure of surgical radiofrequency (RF) ablation >60 mm (100% sensitive, 73.6% specific). Risk of AF after the operation was three-fold greater with a preoperative LAD of >60 mm.

Chen *et al.* [35] reported that every 1 mm increase in LAD corresponded to a 12.7% increase in risk of persistent AF postoperatively. The risk of permanent AF after surgery was over 7-fold higher when the LAD >56.8 mm. In their population, a LAD of <56.8 mm corresponded to a reassuring success rate of RF maze procedure—93% remained in SR after a mean follow-up of 46.1 months.

Chen *et al.* [36] found LAD and left atrial area to be larger in the AF group. Multiple stepwise logistic regression analysis showed that only preoperative LAA was an independent determinant of sinus conversion by the RF maze procedure (OR 0.961, 95% CI: 0.935–0.988, $P = 0.005$). They concluded that a LAA of 56.25 cm² or a preoperative LAD of 57.8 mm could significantly and effectively discriminate between sinus converters and non-converters.

Kamata *et al.* [37] found that at a 1-year follow-up a larger preoperative LAD was associated with recurrent AF. The OR for postoperative SR restoration decreased gradually, with a statistically significant linear trend, in accordance with a larger preoperative LAD (suggesting a dose–response relationship). The OR for sinus conversion for LAD >65 mm was 0.21 (95% CI: 0.05–0.87).

Chen *et al.* [38] did not find LAD as a predictor of AF recurrence—in fact, no preoperative predictors were found. They did note, however, that a LAD of <48.3 mm was associated with a 100% sinus conversion rate.

Itoh *et al.* [39] looked at over 500 patients and found that sinus conversion at 10 years was significantly lower in patients with a preoperative LAD of >70 mm vs those with a LAD of <50 mm (52 vs 74%, $P < 0.001$).

Funatsu *et al.* [40] looked at 268 patients over a mean follow-up period of 3.8 years. The proportion of patients with a LAD of >70 mm was significantly larger in the cryothermic ablation based maze procedure group (20.9 vs 5.9%, $P = 0.0011$). The OR for failure when the LAD of >70 mm was 4.9 (95% CI: 2.8–13.1, $P = 0.0016$).

Kosakai *et al.* [41] found preoperative LAD to have been significantly larger in a modified maze failure group (66.6 vs 55.6 mm, $P < 0.001$).

Larger LA size was a predictor of failure in the surgical treatment of AF in 9 of 12 papers. Relatively few papers seek to define a useful cut-off point for LA size beyond which the risks of the procedure (such as bleeding, infection or stroke) outweigh the chance of sinus recovery. In studies that did try and define a cut-off value for sinus conversion, a LAVI of >135 ml/m² was reported to have 100% specificity and >60 mm 100% sensitivity for failure in the surgical treatment of AF, while a LAD of <48.3 mm was found to confer 100% sensitivity for sinus conversion.

Recommendations

LEFT ATRIAL SIZE AND ABLATION SURGERY SUCCESS

Since mean preoperative LAD in AF groups is consistently over 60 mm, caution should be exercised when offering these patients a surgical treatment for their AF. Furthermore, patients should be counseled as to their increased risk of failure based on their deviance from a diameter of 60 mm.

Class IIa recommendation based on multiple small retrospective studies (Level C).

Impact of left atrial reduction on ablation surgery success

Evidence was sought to determine the effect of atrial reduction on the success of surgical treatment of AF in terms of recurrence. The search is fully documented in Ref. [42] together with a summary of all identified papers. We identified 56 papers from the presented search strategy. From these, 8 papers represented the best evidence on the topic.

Wang *et al.* [43, 44] report on a relatively large number of patients with permanent AF who received the modified maze III RF ablation procedure. In one study [43], they randomized 322 patients to receive either the maze III procedure (control group; $n = 166$) or the maze III procedure plus a reduction plasty of the LA using a reef-imbricate suture technique, with aggressive postoperative pharmacological therapy (study group; $n = 166$). Restoration of sinus rhythm was significantly more frequent in the study group than in the control group at a 1-year follow-up (89.3 vs 67.2%; $P < 0.001$).

In a second study [44], Wang *et al.* report on a subset of these patients ($n = 122$) with either an enlarged LA (ELA; 55–74 mm) or a giant LA (GLA; ≥ 75 mm) who all received the aggressive bilateral atrial reduction with a reef-imbricate technique as an adjunct to the Cox-maze III procedure. At the last follow-up (median 19 ± 16 months), sinus rhythm had been restored in 72 of 80 patients (90%) in the ELA group and in 21 of 36 (58%) in the GLA group.

Marui *et al.* [45] retrospectively analysed 74 patients with chronic AF and a LA diameter of ≥ 60 mm into two non-randomized groups, one of which received a maze procedure alone (control group; $n = 28$) and the other received a maze procedure plus LA reduction surgery using continuous horizontal mattress sutures to plicate the LA (study group, $n = 46$). At the mean follow-up (13.8 ± 5.9 months), the rate of sinus conversion was significantly better in the LA reduction group (39 of 46; 85%) than in the control group (19 of 28; 68%) ($P < 0.05$).

Marui *et al.* [46] retrospectively analysed data from 57 patients with chronic AF and an LA diameter of >60 mm in two non-randomized groups, of which one received a maze procedure (control group; $n = 25$) and the other received a maze procedure plus LA reduction surgery using continuous horizontal mattress sutures to plicate the LA (study group; $n = 32$). Sinus rhythm restoration at the 3-month follow-up was significantly greater in the volume reduction group (27 of 32; 84%) than in the control group (17 of 25; 68%) ($P < 0.05$).

Marui *et al.* [47] studied 80 patients with chronic AF, mitral valve disease and an ELA (diameter >60 mm) in two groups. One group underwent just a maze procedure (control group; $n = 36$), whereas the other received LA volume reduction using a plication

technique with continuous horizontal mattress sutures (study group; $n = 44$). Sinus rhythm restoration was significantly better in the volume reduction group at 12, 24 and 36 months of the follow-up ($P < 0.05$). It is important to note that it is unclear to what degree there was patient overlap in the 3 aforementioned studies by Marui *et al.* [45–47].

An ELA is a risk factor for failure of surgical treatment for AF, and various models of AF suggest that reducing atrial mass and/or diameter may help to abolish the re-entry circuits underlying AF.

Four of the 8 papers compared a volume reduction technique as an adjunct to the maze procedure with a maze procedure alone—all 4 papers reported that a reduction in atrial volume significantly increases restoration of sinus rhythm: 89.3 vs 67.2%, $P < 0.001$; 85 vs 68%, $P < 0.05$; 84 vs 68%, $P < 0.05$; 90 vs 69%, $P < 0.05$.

Three of 8 papers had no control group but reported good rates of sinus rhythm restoration at last follow-up—90, 92 and 89%, respectively—despite the study population including patients with atrial enlargement, a risk factor for procedure failure. One paper reported no benefit from an atrial reduction plasty in patients with an LA diameter of >70 mm.

The concerns we have in answering this clinical question are manifold: the majority of the available studies are retrospective and have a small population, most of the studies have short follow-up periods (usually ≤ 1 year) and 4 of 8 papers present no control group. There are also several important variations between studies, notably the aetiology of the AF, the type of procedure employed, the method of size reduction and the post-operative management.

Recommendations

LEFT ATRIAL SIZE REDUCTION AND ABLATION SURGERY SUCCESS

Overall, the evidence suggests that patients with an enlarged LA (≥ 55 mm) or giant LA (≥ 75 mm) who are at risk of failing to obtain sinus conversion after a standard maze procedure may derive benefit from concomitant atrial reduction surgery using either a tissue excision or a tissue plication technique. However, the evidence is not strong since the available papers are not readily comparable owing to substantial variations in the populations and procedures involved. We, therefore, emphasize the need for prospective randomized studies in this area. Class IIa recommendation based on multiple small retrospective studies (Level C).

ABLATIVE MODALITIES

Unipolar radiofrequency ablation

Evidence was sought to determine the effectiveness of unipolar RF ablation during concomitant cardiac surgery for returning the patient to sinus rhythm. The search is fully documented in Ref. [48] together with a summary of all identified papers. We identified 256 papers from the presented search strategy. From these, 9 papers represented the best evidence on the topic.

Myrdko *et al.* [49] conducted a prospective study in a cohort of 100 patients with permanent AF and severe mitral valve disease. The two groups had similar baseline characteristics and received mitral valve replacement alone or in combination with unipolar ablation. At discharge, 56% of patients in the RF group were in SR

compared with only 22% of controls and at a 1-year follow-up, the number in SR compared with controls was 54 vs 16%, respectively. Ablation, therefore, increased the chances of SR restoration ($P < 0.001$), whereas isolated mitral valve surgery alone was ineffective at restoring SR. Both groups were also considered for treatment with amiodarone postoperatively for 3 months and, if refractory, electrical cardioversion. The need for both of these measures was reduced in the RF group ($P < 0.05$), and in the case of resorting to cardioversion, success rates were much higher in the RF group ($P < 0.002$). Unsuccessful ablations were associated with patients who had severe heart failure and LADs [50] exceeding 60 mm (OR of 9.3 for ablation failure with LAD >60 mm vs 45 mm).

Johansson *et al.* [51] showed that similar positive conclusions could be drawn with patients undergoing coronary artery bypass graft (CABG) procedures. Their follow-up period was significantly longer, at 32 ± 11 months, and they conducted more intermediate checks, e.g. at 3 and 6 months. SR at 3 months was highly predictive of remaining in sinus for follow-up, the rates of which were 62% for the RF group and 33% for the non-RF group ($P = 0.03$). This study also showed that patients with paroxysmal or persistent AF had a better chance of regaining and maintaining SR than those with permanent AF ($P = 0.0004$). Additionally, a quality of life (QoL) assessment confirmed the benefits of SR restoration, noting improved general health ($P = 0.005$) and reduced bodily pain ($P = 0.002$).

Maltais *et al.* [50] conducted a retrospective study with a larger cohort to corroborate the above findings. At a 3-year follow-up, SR was present in 71% of the 293 patients. A variety of different surgeries were performed, and Khargi *et al.* [52] quantified the lack of significance between the type of surgery performed and success rates (71% for mitral and 79% for CABG/aortic surgery [$P = 0.262$]). Independent predictors of AF recurrence were LAD and also age. The addition of RF ablation to open-heart surgery did not cause any increase in mortality rates compared with undertaking the respective cardiac procedures alone. The superior success rates in this study may be attributed to the fact that the majority (151) of the patients had only paroxysmal AF prior to surgery. Jeanmart *et al.* [53] found a SR maintenance rate of 70% at a 17.4-month follow-up.

Beukema *et al.* [54] demonstrated very similar results, this time in a range of cardiac operations that included tricuspid valve surgery. Again, the above point regarding the type of AF is relevant—a 5-year follow-up showed that SR was present in a lower proportion of patients, only 52%, but all of whom had fulfilled the criteria for permanent AF.

Zangrillo *et al.* [55] took a different approach for analysing the effect of concomitant ablation in 142 patients undergoing mitral valve surgery. RF ablation did not significantly increase cardiac troponin release compared with isolated mitral surgery ($P = 0.7$).

Deneke *et al.* [56] demonstrated in a group of 222 patients that the extent of the ablation procedure (bilateral vs LA only) did not affect the success of sinus conversion rates—they were 74 and 83%, respectively ($P = 0.45$). Moreover, all the patients had permanent AF with a mean preoperative duration of 6 years. The very encouraging results of this study add further evidence to the benefits of undergoing concomitant surgery.

The success rate remained high for Khargi *et al.* [52] who also used a cohort of permanent AF patients. Seventy-one percent of mitral surgery and 79% of aortic/CABG patients remained in SR at 12 months. Deneke *et al.* [57] corroborated this and showed that even at a median 48-month follow-up, 69% of patients were still in SR. This contrasts with the study by Beukema *et al.* [54].

There is one caveat with all of the above studies. Evaluation of SR restoration was through 24 h holter ECG monitoring at out-patient clinics. This method can miss recurrent or asymptomatic AF, as patients were not monitored continuously throughout the follow-up period. In future, studies with longer periods of monitoring may pick up more episodes of recurrence, although one would imagine lower adherence rates for such measures.

Recommendations

USE OF UNIPOLAR RADIOFREQUENCY ABLATION

In patients undergoing cardiac surgery, concomitant unipolar RF ablation to treat AF is effective at restoring SR. Success rates range from 54 to 83% at a medium-term follow-up of at least 12 months. Furthermore, the procedure is safe in terms of contributing no significant additional risks. Higher degrees of success are associated with paroxysmal or persistent AF, younger age and those with smaller LAD. The type of cardiac surgery does not affect the success rates. Class IIa recommendation based on multiple small prospective and retrospective studies (Level C).

Bipolar radiofrequency ablation

Evidence was sought to determine the effectiveness of bipolar RF ablation during concomitant cardiac surgery for returning the patient to sinus rhythm. The search is fully documented in Ref. [58] together with a summary of all identified papers. We identified 263 papers from the presented search strategy. From these, 13 papers represented the best evidence on the topic.

Chiappini *et al.* [59] performed a meta-analysis that identified 6 non-randomized studies that included 451 AF patients undergoing cardiac surgery with concomitant RF ablation. Overall survival rate was 97.1% with 76% freedom from AF at a mean follow-up period of 13.8 months.

Srivastava *et al.* [60] and Von Oppell *et al.* [61] conducted randomized control trials. Srivastava *et al.* [62] compared biatrial [biatrial maze (BAM)], LA and PVI procedures with a control group. The bipolar RF procedures elicited a good success rate (over 50%) of SR maintenance at 6 months. The SR conversion rate for BAM, left atrial maze and PVI was highly significant compared with the control group ($P = 0.001$), but there was no significant difference between BAM and PVI. The average extra cross-clamp time required was ~5–7 min for the bipolar RF procedures.

Von Oppell *et al.* [61] compared groups undergoing Cardioblate RF ablation and concomitant surgery vs cardiac surgery alone in patients with persistent or permanent AF. Cardioblate ablation was significantly better at restoring SR at 1 year (75 vs 39%, $P = 0.019$). An average 30 min extra was required both for bypass and for cross-clamp for Cardioblate operations. After performing the first 6 cases with bipolar only ablation, the authors state that it was difficult to ensure a confluent ablation line between the left pulmonary veins and the mitral valve annulus and the tricuspid valve annulus with the bipolar device alone without potentially injuring coronary arteries. Subsequently, a monopolar pen was used for these lines.

Raman *et al.* [63] and Benussi *et al.* [64] both studied the use of Cobra RF ablation on AF patients undergoing concomitant cardiac surgery. Raman *et al.* studied 132 patients with all forms of AF across 20 centres and found an 84% SR maintenance rate at 3 months (72 of 87), 90% at 6 months (45 of 50) and 100% at 12

months (however, $n = 12$). These operations required a 12–14 min extra cross-clamp time.

Comparatively, Benussi *et al.* [64] studied 90 patients with AF that was permanent or refractory to antiarrhythmics and showed 79% maintained in SR at 3 months, 87% at 6 months and 89% at 1 year. Although the success rate appears high, the poor follow-up rates (<50% at 12 months) make conclusions drawn from these success rates potentially unreliable. In their 2010 paper [65], 13 patients undergoing concomitant mitral surgery and bipolar ablation had additional wires placed on the pulmonary vein and LA. All the patients achieved intraoperative conduction block, and 11 had complete conduction block at 3 weeks.

Onorati *et al.* [66] focused on heart failure patients undergoing mitral surgery and RF ablation. SR prevalence was good at 74, 64 and 64% at 6, 12 and 18 months, respectively. They showed restoring SR was associated with improving heart failure. Freedom from congestive heart failure was 94% in SR patients compared with 69% for AF patients ($P = 0.018$). The New York Heart Association class was also ameliorated for those in SR compared with AF at 6 months (1.4 vs 2.7) and 18 months (1.2 vs 1.9; $P < 0.0001$).

Martin-Suarez *et al.* [67] retrospectively compared Cobra endocardial and epicardial monopolar RF ablation with bipolar ablation. Overall incidence of SR at the end of the follow-up was higher using endocardial monopolar ablation or the bipolar RF ablation compared with the epicardial monopolar ablation ($P = 0.01$). Overall freedom from AF was significantly higher using bipolar ablation than that in either monopolar endocardial or epicardial ablation ($P = 0.01$).

Gillinov *et al.* [68] employed Atricure (West Chester, OH, USA) bipolar RF ablation in patients with permanent, persistent and paroxysmal AF undergoing concomitant cardiac surgery. AF recurrence was assessed using the ECG follow-up at 1, 3, 6 and 12 months. Prevalence of AF peaked at 38% 2 weeks postoperatively. By 6 months, prevalence decreased to 13% before increasing to 16% at 1 year. Comparatively, Geidel *et al.* [69] used either Cobra monopolar or Atricure bipolar RF ablation solely on patients with permanent AF and employed longer follow-up but had similar results. At 3 and 30 months SR conversion rate was 73 and 77%, respectively. Survival was 96% at 30 months. Both ablation and total procedure times were shorter with bipolar compared with monopolar ablation. The authors strongly recommend bipolar RF due to shorter procedure time, ability to avoid performing a standard left atriotomy and a greater guarantee of transmural ablation.

Three papers [64, 68, 69] utilized logistic regression analysis to demonstrate that permanent AF ($P < 0.0001$), longer preoperative AF duration ($P = 0.005$) and larger preoperative LA size ($P = 0.018$) are predictive of postoperative AF recurrence.

Tekumit *et al.* [70] found SR conversion rates of 75, 78 and 79% at 3, 6 and 12 months, respectively. They concluded that LA bipolar RF ablation did not add significantly to cardiopulmonary bypass time and had no major complications from the procedure itself. They further suggested that a partial lesion as opposed to the traditional Cox-maze III complete lesion could still be effective at treating AF. Benussi *et al.* [71] further found that performing the mitral line with bipolar RF ablation is safe and cost-effective. They compared their bipolar only RF ablation group to a control group that had the mitral line carried out using unipolar RF ablation. There was no significant difference in SR recovery rate but there was a major cost difference (per patient cost of ablation devices was €2403 in the control group vs €1245 in the study group; $P < 0.0001$).

Lin *et al.* [72] conducted a prospective trial in which patients were randomized to either undergo microwave (MW) ($n = 94$) or

RF [30] ($n = 93$) ablation. At all follow-up time points ranging from discharge to 24 months, there was a significant difference in the numbers of patients remaining in SR that favoured RF over MW ablation. The authors stated that the uncertainty in transmural and continuity of the lesions might have contributed to the inferior success rates of MW relative to RF ablation.

Recommendations

USE OF BIPOLAR RADIOFREQUENCY ABLATION

Bipolar RF ablation has a higher success rate in restoring SR as an adjunct to cardiac surgery compared with no ablation for at least 1 year. On average, this requires 15 min additional cross-clamp time. While one prospective trial has provided evidence for an advantage of using bipolar RF ablation over MW energy, there is limited evidence to suggest superiority of bipolar RF ablation over unipolar energy as yet.

Class I recommendation based on three randomized trials and multiple small prospective and retrospective studies (Level A).

Cryoablation

Evidence was sought to determine the effectiveness of cryoablation during concomitant cardiac surgery for returning the patient to sinus rhythm. The search is fully documented in Ref. [73] together with a summary of all identified papers. We identified 291 papers from the presented search strategy. From these, 10 papers represented the best evidence on the topic.

The PRAGUE 12 trial is a landmark trial in AF surgery [74]. In this randomized multicentre trial, patients undergoing coronary and/or valve surgery with AF were randomized to surgical ablation of the LA or no treatment for AF. Two hundred and twenty-four were randomized and in the ablation group 96% had treatment with an argon-based cryoprobe. Left and right pulmonary veins were isolated separately, and then a connecting lesion, a mitral annulus lesion and a lesion to the LAA were performed and the appendage removed. At 1 year SR was 60% in the treated group and 36% in the untreated group. In terms of clinical outcomes, mortality and stroke were similar in the two groups. The study concluded that there were no clinical benefits at 1 year in AF surgery but the patients will be followed up for 5 more years. Of note, no entrance or exit blocks were assessed in this study.

Blomström-Lundqvist *et al.* [75] performed a randomized controlled trial of prospective patients undergoing mitral valve repair surgery with concomitant AF. This study showed that the use of cryoablation during mitral valve surgery was significantly more effective at returning patients to SR than mitral valve surgery alone at a 12-month follow-up (73.3 vs 42.9%, respectively, $P = 0.013$). While there was a higher complication rate in the cryoablative group (vs those that had mitral valve surgery alone), this was not shown to have a significant impact on morbidity or mortality. The relatively small study size and lack of 24-h monitoring are limitations of this paper.

Kim *et al.* [76] retrospectively compared the effects of and cryoablative techniques during mitral valve repair operation. At a 5-year follow-up, it was shown that those who had undergone cryoablation had a higher (although non-significant) rate of SR conversion compared with the MW group (79.9 vs 61.3%, $P = 0.089$). Given that aortic cross-clamp time was longer in the cryoablative group and the fact that there were no significant differences in either 3- or 5-year survival rates between the groups,

this paper suggests that cryoablation may not be superior to alternative energy sources.

Itoh *et al.* [39] retrospectively analysed the use of cryoablation in comparison with two-different cut-and-sew maze techniques in patients undergoing mitral valve surgery. They showed that there was no significant difference between the patient groups with regard to AF recurrence at 3 months. However, 24-h monitoring was not implemented and thus paroxysmal AF may have been unaccounted for.

Ghavidel *et al.* [1] examined the use of cryoablation either in generating a Cox-maze III pattern or in PVI. They showed that there was no significant difference between the patterns in return to SR during a 12-month follow-up. Antiarrhythmic medication was continued in this trial for at least 6 months.

Funatsu *et al.* [40] found that 91.8% of patients were free from AF at discharge and 80.2% continued to be free at a 5-year follow-up. The results from this group showed a very high return to SR following cryoablation. This suggests that cryoablation is a stable intervention for the removal of AF. Limitations of the study included no indication as to the level of antiarrhythmic medication that was used in AF-free patients and lack of 24-h monitoring to detect paroxysmal AF.

Gammie *et al.* [77] reported a much lower level of SR conversion following cryoablation (60%) than Funatsu *et al.* [40]. A higher uptake of holter monitoring (75%) suggests that this study would have missed less paroxysmal AF. There was a clear distinction in results between those previously suffering from paroxysmal and continuous AF. Paroxysmal AF sufferers had a significantly higher rate of SR conversion (85 vs 47%, $P < 0.001$).

Kolek and Brat [78] and Mack *et al.* [79] reviewed the results of LA cryoablation. In agreement with Gammie *et al.* [77], Kolek and Brat showed a high rate of SR conversion in those suffering paroxysmal but not permanent AF after a 12-month follow-up (89.7 vs 61.9%, $P = 0.005$). However, at the 24-month follow-up, there was a significantly reduced proportion of patients remaining in SR (52.6%). Mack *et al.* [79] showed a similarly high conversion rate following cryoablation, but had a very low uptake of 24-h monitoring. They showed no difference between left atrial ablation and biatrial ablation.

Rahman *et al.* [80] found that freedom from AF at a 6-month follow-up was high (80%). However, 28% of these patients were on antiarrhythmic medication.

Paucity of Level 1 evidence was a major limitation to this analysis. All 9 papers were either small randomized controlled trials or prospective/retrospective studies with small sample sizes (57–521) and varied follow-up regimens. A lack of 24-h monitoring in 7 of the 9 studies prevents effective elucidation of the rate of paroxysmal AF following cryoablation. Only one study [75] suggested an increased complication rate from cryoablation, however, none suggested any negative impact on mortality or morbidity. Of the 9 studies 6 suggested that cryoablation is most successful in patients suffering from paroxysmal rather than permanent AF.

Recommendations

USE OF CRYOABLATION

Cryoablation during concomitant surgery is an acceptable intervention for the treatment of AF with acceptable SR conversion rates of between 60 and 82% at 12 months. Six of 9 studies suggested that cryoablation is most successful in patients suffering from paroxysmal rather than permanent AF. Class IIa recommendation based on one small randomized trial and multiple prospective and retrospective studies (Level B).

Microwave ablation

Evidence was sought to determine the effectiveness of MW ablation during concomitant cardiac surgery for returning the patient to sinus rhythm. The search is fully documented in Ref. [81] together with a summary of all identified papers. We identified 200 papers from the presented search strategy. From these, 11 papers represented the best evidence on the topic.

Paucity of Level 1 evidence (only one randomized trial [72] identified) was a major limitation to this analysis and many of the studies share similar methodological flaws. In several, patients were given antiarrhythmic medication or were cardioverted during the follow-up, making it difficult to determine whether MW ablation had cured AF. Evaluation of SR restoration was through 24–72 h holter ECG monitoring at outpatient clinics. This method can miss recurrent or asymptomatic AF, as patients were not monitored continuously throughout the follow-up period. Some studies also included patient populations with a mixture of permanent and paroxysmal AF. Furthermore, the follow-up time and preoperative AF duration of patients in many of the studies were often very variable.

Maessen *et al.* [82] reported that 87% of patients were in SR at a mean period of 6.4 months postoperation in a study of 24 patients. Wisser *et al.* [83] reported that 81% of the patients were free of AF at 12 months in a study of 23 patients, concluding that MW ablation gave results similar to those of RF ablation.

Kabbani *et al.* [84] reported that 74% of the patients were in SR at 6 months in a study of 84 patients. Additionally, preoperative LAD [50] seemed to be an important factor in the conversion to SR, with a mean diameter of 7.0 cm in non-responding patients compared with 5.7 cm in responding patients ($P < 0.001$).

Ahlsson *et al.* [85] reported that 74% of the patients were in SR at 12 months in a study of 20 patients. They also noted that all patients in SR at 6 months postoperatively displayed left and right A waves of velocity equivalent to those seen in patients in SR preoperatively. Thus, they suggest that MW ablation can restore SR in a majority of patients while also preserving atrial mechanical function.

Topkara *et al.* [86] reported that 67% of the patients were in SR at 1 year in a study of 85 patients. However, the mean follow-up was only 0.8 ± 0.6 years.

Knaut *et al.* [87] reported that 72% of the 42 patients who underwent MW ablation concomitant to isolated CABG were in SR at 12 months, compared with 63% of the 68 patients who underwent MW ablation concomitant to isolated mitral valve surgery. They concluded that MW ablation in combination with CABG or mitral valve surgery can be performed with comparable success rates.

Zembala *et al.* [88] reported 66% of the 42 patients in SR at a mean period of 7.3 months postoperatively and suggested that the risk of AF recurrence was significantly increased with a larger LAD (OR = 1.21, $P = 0.02$) and an increased duration of preoperative AF (OR = 2.14, $P = 0.03$).

Another study by Knaut *et al.* [89] reported 65% of the patients in SR at 1 year in a study of 96 patients. They also examined success rates between patients undergoing the ablation by 2 techniques (described in Table 1) and between patients undergoing ablation with CABG alone or CABG in combination with other procedures. They found a significant difference in success rates between CABG combined with the initial technique or combined with the box technique (52 vs 74%, respectively, $P = 0.0026$).

Knaut *et al.* [89] published a further study showing 62% of the patients in SR at 1 year in a study of 202 patients, although many of these patients were lost during the follow-up. The paper does not suggest why the attrition rate was so high. The Knaut group has published several papers investigating different factors affecting the rate of sinus conversion after MW ablation. It is important to note that it is unclear whether the patients used for their studies overlap.

Over longer periods of 3 and 5 years, Kim *et al.* [76] demonstrated an 80% and a 61% freedom from AF, respectively (without antiarrhythmic administration). Vicol *et al.* [62] showed that at a mean period of 5.37 years, only 39% of the patients who underwent ablation were in SR, a vastly lower proportion than noted in other studies assessing SR over shorter periods. They, therefore, concluded that MW ablation is not a reliable method of achieving long-term conversion to SR.

Lin *et al.* [72] conducted a prospective trial in which patients were randomized to undergo either MW ($n = 94$) or RF ($n = 93$) ablation. At all follow-up time points ranging from discharge to 24 months, there was a significant difference in the numbers of patients remaining in SR that favoured RF over MW ablation. The authors stated that the MW antenna in particular had to be repositioned two to three times to finish the circular lesion around the endocardial pulmonary veins. They postulated that the uncertainty in transmural and continuity of the lesions might have contributed to the inferior success rates of MW relative to RF ablation.

It is apparent that there is a large degree of heterogeneity in studies that address the success of MW ablation for AF during concomitant cardiac surgery, with patients' characteristics, for example type of AF, and patient management postoperatively, for example the administration of antiarrhythmics, being inconsistent. Of the 12 studies, 9 assessed SR at a mean period of 6–12 months and found postoperative success rates between 62 and 87%. One study looked at the medium range follow-up of 24 months with SR restoration at 71%. Two studies looked at the long-term follow-up (5 and 5.37 years) with SR restoration at 39 and 61%, respectively.

We also understand that currently there are no devices on the market offering MW ablation, due to these equivocal results.

Recommendations

USE OF MICROWAVE ABLATION

We conclude that MW ablation as an intervention for the treatment of AF during concomitant surgery is less effective on the limited available evidence. This is because the success rates in the longer term are less clear and the only randomized study to date has found outcomes inferior to those of RF-based ablation.

Class III recommendation based on one small randomized trial and multiple small prospective and retrospective studies (Level B).

High-intensity focused ultrasound

Evidence was sought for the effectiveness of high-intensity focused ultrasound (HIFU) during concomitant cardiac surgery for returning the patient to sinus rhythm. Altogether 7 papers were found that represented the best evidence on the topic.

Groh *et al.* [90, 91] reported the results of 129 patients. Freedom from AF was 86% at 18 months in a group where 51% had permanent AF. A circumferential lesion is created around the LA epicardium and many patients also received a mitral isthmus line.

McCarthy *et al.* [92] reported the results of 408 patients who had 5 types of ablation procedure including HIFU. They found a high rate of failure with HIFU and only 43% were free from AF, compared with 90% freedom from AF with the classic maze procedure, and 79% for LA maze procedure.

Schopka *et al.* [93] reported the results of 110 patients undergoing concomitant surgery. Sixty-two percent remained in sinus rhythm at 6 months and also at 12 months with no device complications reported.

Pozzoli *et al.* [94] assessed the exit block after ablation and on chest closure of 10 patients undergoing mitral surgery and HIFU PVI. None of the patients had complete isolation after the ablation or after surgery.

Klinkenberg *et al.* [95] reported the findings of 15 patients who had lone AF surgery with HIFU. At 6 months only 40% were in sinus rhythm and after a year only 4 patients were in SR. There was one late tamponade and one bleed requiring sternotomy.

Neven *et al.* [96] reported the findings of 28 patients who underwent HIFU. With the median 738-day follow-up 79% were free of AF; however, there was an atrio-oesophageal fistula, a pericardial effusion and 2 phrenic nerve palsies. Also there was 1 unexplained death.

A further oesophageal injury was reported by Prasertwitayakij *et al.* [97].

Recommendations

USE OF HIGH-FREQUENCY FOCUSED ULTRASOUND

We conclude that HIFU as an intervention for the treatment of AF during concomitant surgery is not currently recommended outside of clinical trials on the limited available evidence. This is because the success rates seem to be inferior to those of other devices and significant safety concerns have been reported.

Class III recommendation based on cohort studies (Level C).

EXCLUSION OF THE LEFT ATRIAL APPENDAGE

Evidence was sought to investigate whether patients with AF should have LAA exclusion in order to reduce their stroke risk. Of note, the search is not to look at the efficacy of the maze procedure by the addition of appendage exclusion. The search is fully documented in Ref. [98] together with a summary of all identified papers. We identified 310 papers from the presented search strategy. From these, 12 papers represented the best evidence on the topic.

There are two issues to address in this topic: whether the LAA is an important source of emboli in patients with AF and whether exclusion of the LAA reduces the incidence of thromboembolic events.

First, with regard to the LAA as the source of emboli, studies have concluded that ~90% of LA thrombi are located in the LAA [99], although this same study demonstrated it in only 50% of rheumatic patients. It has been concluded by many, therefore, that successful closure of the LAA should aid in reducing the risk of thromboembolic events in patients with AF [100]. Indeed, the ACC/AHA guidelines state that for recurrent and persistent AF in

patients who remain symptomatic with heart rate control and where antiarrhythmic medication is not tolerated or no longer effective, then LAA exclusion should be considered [17].

With regard to the second question as to whether exclusion reduces embolic events, Healey *et al.* [101] performed a randomized controlled clinical trial of 77 patients undergoing CABG surgery with 52 patients receiving LAA occlusion. Successful LAA occlusion was identified in only 66% of their study population, in whom it was attempted.

Perioperative thromboembolic events were recorded for 2 patients; 1 an intraoperative ischaemic stroke and the other a TIA. No thromboembolic events were recorded during the follow-up. Surveys were sent to all eligible patients for the study, but who chose not to participate and it showed that 12% self-reported a thromboembolic event (12 strokes and 13 TIAs).

During a 12-month period, Schneider *et al.* [102] examined 6 patients who received LAA closure at the time of mitral and/or aortic valve surgery. Postoperative TOE demonstrated successful closure in only 1 patient. One patient experienced a stroke 4 weeks postoperatively despite a high level of anticoagulation.

Bando *et al.* [103] examined 812 patients following mitral surgery of whom 55% had their LAA ligated. Seventy-two patients experienced a late stroke. Of the 72 patients, 65% had the LAA ligated. Of note, all patients had a mechanical mitral valve replacement.

In 2008, Kanderian *et al.* [104] examined 137 patients who underwent LAA closure. They demonstrated that only 55% of their patients had successful closure of the LAA. They reported that 52 patients had excision of the LAA (41 by scissors and 11 by a stapling device) and 85 received exclusion of the appendage of which 73 were by suture and 12 by stapler excision. It was found that successful occlusion occurred more often with excision of the LAA (73%) relative to suture and stapler excision (23 and 0%, respectively). Six of 55 patients with successful closure experienced a stroke or TIA compared with 12 of 82 patients who had unsuccessful LAA closure, which was not significant.

Garcia-Fernandez *et al.* [105] examined 205 patients undergoing mitral valve surgery of which 58 patients received LAA ligation. Successful ligation was present in 89.7%. Twenty-seven patients, 2 of whom had their LAA ligated, experienced thromboembolic complications; 19 patients had an ischaemic stroke, 5 patients had a peripheral arterial embolism and 3 patients experienced a TIA. Consequently, it was found that the occurrence of systemic emboli was more frequent among patients who had not received LAA ligation. Moreover, this study demonstrated that the absence of ligation of the LAA was an independent predictor of the occurrence of an embolic event following mitral valve surgery with an OR of 6.7. If the absence of effective ligation is incorporated into the model, the OR increased to 11.9.

Orszulak *et al.* [106] examined 285 patients undergoing mitral valve replacement. Ninety-two patients received operative ligation of the LAA. This study found an increased rate of late stroke in patients who had the LAA ligated.

In 2000, Johnson *et al.* [107] studied 437 patients who received exclusion of the LAA during open-heart surgery. Perioperative cerebrovascular accidents (CVAs) occurred in 21 patients despite no patients being identified by TOE to have intra-atrial clots. Seven patients developed a CVA postoperatively, 4 of whom were in AF, but no atrial clots were demonstrated on TOE.

Katz *et al.* [108] analysed 50 patients undergoing LAA ligation during mitral valve surgery. Incomplete ligation was detected in 36% of patients. Four patients with an incompletely ligated LAA

had thromboembolic phenomena (1 stroke; 1 TIA and 2 mesenteric emboli).

Almahameed *et al.* [31] studied 136 patients who underwent LAA ligation at the time of mitral valve surgery. Fourteen (12.3%) patients experienced thromboembolic events. They found a significantly increased rate of stroke in patients with LAA occlusion.

Fumoto *et al.* [109] studied 14 mongrel dogs implanted with the third-generation atrial exclusion device in their LAA. The right atrial appendage was stapled with commercial apparatus for comparison. LAA exclusion was complete and achieved without haemodynamic instability, and coronary angiography revealed that the left circumflex artery was patent in all cases.

Salzberg *et al.* [110, 111] have more recently reported effective occlusion of the LA appendage with a commercially available device specifically designed for this purpose, for intraoperative insertion.

Sick *et al.* [28] reported their experience with the WATCHMAN LAA occlusion device. The device was implanted into 75 patients, of whom 66 had successful implantation (88%). Complete closure of the LAA was observed in 93%. Three patients experienced device failure, 2 of whom were embolizations and 1 was a delivery system failure due to a fractured wire.

Kamohara *et al.* [112] analysed 10 mongrel dogs with the second-generation atrial exclusion device implanted at the base of the LAA. This was performed without complication in all dogs.

Despite finding 5 clinical trials including one randomized controlled trial that studied ~1400 patients who underwent LAA occlusion, the results of these studies do not clearly show a benefit for appendage occlusion. Indeed of the 5 studies, only one showed a statistical benefit for LAA occlusion, with 3 giving neutral results and in fact one demonstrating a significantly increased risk. One reason for this may be the inability to achieve acceptably high rates of successful occlusion on TOE when attempting to perform this procedure. The highest success rate was only 93% but most studies reported only a 55–66% successful occlusion rate when attempting closure in a variety of methods including stapling, ligation and amputation. The best results were obtained using devices specifically designed for this purpose. Currently, the evidence is insufficient to support LAA occlusion and may indeed cause harm especially if incomplete exclusion occurs using suture or stapling techniques.

Recommendations

EXCLUSION OF THE LEFT ATRIAL APPENDAGE

We conclude that there has been no proven benefit of surgical LAA exclusion in terms of stroke reduction or mortality benefit. Indeed many papers have shown ineffective appendage occlusion and potentially increased risk due to poor technique. If exclusion is contemplated, devices designed for appendage exclusion should be used rather than a cut-and-sew or stapling technique.

Class IIa recommendation based on multiple cohort studies and one pilot randomized controlled trial (RCT) (Level B).

Lone atrial fibrillation surgery

The 2012 HRS/EHRA/ESC guideline [13, 14] recommend that lone AF surgery be performed in paroxysmal, persistent and long-standing AF in patients who prefer a surgical approach or who fail one or more attempts at catheter ablation.

Boersma and *et al.* [113] reported the first randomized trial comparing catheter ablation vs invasive surgical ablation performed from 2007 to 2011 in a hospital in the Netherlands and a hospital in Barcelona. Catheter ablation was performed using RF catheter ablation with three-dimensional mapping using NavX/CARTO. Surgical ablation was by VATS using the Atricure bipolar clamp, the 'coolrail' and the unipolar ablation pen. One hundred and twenty-four patients who had drug refractory AF (62% of whom also had previous failed catheter ablation) were randomized. The mean procedure time was 163 min in the catheter group and 188 min in the surgical group.

The primary endpoint was freedom from atrial arrhythmia, without antiarrhythmic medications at 12 months using holter monitoring. This was achieved in 36.5% in the catheter ablation group and 65.6% in the surgical ablation group ($P = 0.0022$). Also, the success rate allowing antiarrhythmic medications was 79% for surgery vs 43% in the catheter ablation group.

However, there was a significantly higher adverse incident rate in the surgical ablation rate, mainly driven by pneumothorax in 6, significant bleeding in 2 and pacemakers in 2 patients (34% rate in the surgical group). This compared with a groin haematoma in 4 in the catheter group. This randomized study concluded that surgical ablation was significantly superior to catheter ablation in terms of freedom of recurrence both with and without freedom from antiarrhythmic drugs.

Krul *et al.* [114] report their results in 31 patients who underwent thoracoscopic PVI using the Atricure bipolar ablation device and the unipolar ablation pen, ganglionic plexus ablation and periprocedural confirmation of ablation. They had an 86% freedom from AF without antiarrhythmics at 1 year (based on holter monitor follow-up). Three patients had a thoracotomy due to bleeding. Sixteen patients had paroxysmal AF, 45% previously had a catheter-based intervention and mean procedure time was 191 min. After block testing the left PV required additional lines in 33% and the right PV required additional lines in 58%.

La Meir *et al.* [115, 116] published a comparative study in lone AF surgery using a hybrid surgical and transcatheter approach. Sixteen patients underwent RF monopolar/monolateral ablation, whereas 35 had RF bipolar/bilateral thoracoscopic ablation. Assessment was by 7-day holter monitoring. In all groups the frequency of AF at 1 year was 13% for the monopolar group and 5% in the bipolar group. An interesting part of this study was the investigation of entrance or exit block after surgical creation. In the monopolar group, none of the 19 patients had a full block on testing after creating the epicardial box lesion. Seventeen had at least one pulmonary vein that was not isolated that required endocardial ablation to close. In the bipolar group 5 patients had gaps in their lesion lines and these required endocardial closure. These authors felt that the monopolar lone AF technique was unsatisfactory in their study.

Pison *et al.* [117] also reported their findings with VATS surgical ablation and transvenous catheter ablation. The surgical ablation was performed using the Atricure bipolar clamp, the coolrail and the Atricure pen. Twenty-six patients underwent this procedure, 42% of whom had persistent AF. During the surgical procedure, 23% of patients had lesions that were not transmural and required endocardial touch-up lesions. Freedom from AF was 93% in the paroxysmal group and 90% in the persistent group, and 2 patients underwent additional ablation procedures.

Weimar *et al.* [118] report their success with bilateral VATS surgical ablation in 89 patients using the Atricure bipolar clamp, and unipolar linear ablation. Sixty-five percent had persistent AF. They

assessed AF at 1 year using holter monitoring. The mean operative time was 180 min. Freedom from AF was 90%.

The above studies indicate the high level of success with stand-alone surgical ablation. The complication rate is higher but success from one randomized controlled trial (RCT) and several cohort studies is high not only after catheter-based interventions have failed but also as primary treatment.

Hybrid treatments also seem to hold promise for the future and the above studies indicate that these procedures have good success in identifying non-transmural areas from the epicardial ablation and allow completion of these lesion lines, although direct comparative studies have yet to be done.

In view of the high success rates of surgical ablation, in the same way that the heart team is successfully discussing coronary revascularization across Europe and the same heart teams are increasingly discussing treatment options in valve disease, we would advocate the advancement of heart teams with an interest in arrhythmia intervention where possible. This would allow patients to consider surgery as an alternative to primary catheter ablation in addition to the more common situation of surgery after failed primary catheter ablation.

Recommendations

STAND-ALONE SURGICAL ABLATION

We support the guidelines published by the HRS/EHRA/ESC in 2012 for stand-alone surgical ablation. Surgery may be considered for symptomatic patients refractory or intolerant of at least one antiarrhythmic medication. Surgery may be considered for patients who prefer surgery to catheter ablation or who have failed ablation in paroxysmal, persistent or long-standing AF.

Results of both catheter-based and surgically-based ablation should be discussed with the patient prior to their primary intervention for AF.

We support the concept of discussion of the relative merits of both approaches by a heart team with a special interest in ablative treatment where possible.

Class IIa recommendations based on one RCT and multiple cohort studies (Level B).

Reporting the results of surgery

The STS workforce on evidence-based surgery published an extensive document on the reporting of the results of surgery in AF [18]. They felt that the literature was in disarray when they published their guidelines and encourage the use of their reporting template for all subsequent studies. This should include reporting of regular interval ECG assessments and they encouraged more widespread [118] use of implantable recording devices to assess AF burden. Along with the HRS/EHRA/ESC guidelines, the STS workforce recommends that entrance and exit block should always be demonstrated intraoperatively and reported. The HRS/EHRA/ESC guidelines further recommend at least 1 year of the follow-up and a minimum of 24–72 h holter monitoring or alternatively trans-telephonic monitoring, 30-day auto-event triggered monitoring or outpatient telemetry.

We found a paucity of papers reporting the efficacy of entrance and exit blockade at the time of surgery, which is the reason why we have reported the results of most of the trials on the follow-up.

Recommendations

REPORTING THE RESULTS OF SURGERY

Entrance and exit block should routinely be tested after AF surgery to demonstrate the creation of effective lesion sets. The HRS/EHRA/ESC guidelines for reporting should be followed in any publication or reporting of the results of surgery. Class IIa recommendation based on consensus from multiple expert groups (Level C).

Limitations

There is a clear lack of large randomized studies comparing lesion sets and different energy sources in concomitant AF surgery. The present manuscript is based on large patient series and systematic reviews, with just a few randomized studies. This does mean that many of the results are open to interpretation and opinion and that consensus was required for many sections of this report. In the future, large registries, RCTs and accurate and uniform reporting of AF surgery together with entrance and exit block measurement will greatly assist in the creation of more definitive guidelines.

CONCLUSION

AF surgery is an effective intervention for patients with all types of AF undergoing concomitant cardiac surgery to reduce the incidence of AF in the future as shown in multiple randomized studies. There is some evidence that this translates into reduced stroke risk, reduced heart failure risk and longer survival. In addition, symptomatic patients with AF may be considered for lone AF surgery after failed catheter intervention or even as an alternative to catheter intervention where either catheter ablation is contraindicated or by patient choice.

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