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# Atrial Fibrillation and Stroke: The Evolving Role of Rhythm Control

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## Opinion statement

Atrial fibrillation (AF) remains a major risk factor for stroke. Unfortunately, clinical trials have failed to demonstrate that a strategy of rhythm control—therapy to maintain normal sinus rhythm (NSR)—reduces stroke risk. The apparent lack of benefit of rhythm control likely reflects the difficulty in maintaining NSR using currently available therapies. However, there are signals from several trials that the presence of NSR is indeed beneficial and associated with better outcomes related to stroke and mortality. Most electrophysiologists feel that as rhythm control strategies continue to improve, the crucial link between rhythm control and stroke reduction will finally be demonstrated. Therefore, AF specialists tend to be aggressive in their attempts to maintain NSR, especially in patients who have symptomatic AF. A step-wise approach from antiarrhythmic drugs to catheter ablation to cardiac surgery is generally used. In select patients, catheter ablation or cardiac surgery may supersede antiarrhythmic drugs. The choice depends on the type of AF, concurrent heart disease, drug toxicity profiles, procedural risks, and patient preferences. Regardless of strategy, given the limited effectiveness of currently available rhythm control therapies, oral anticoagulation is still recommended for stroke prophylaxis in AF patients with other stroke risk factors. Major challenges in atrial fibrillation management include selecting patients most likely to benefit from rhythm control, choosing specific antiarrhythmic drugs or procedures to achieve rhythm control, long-term monitoring to gauge the efficacy of rhythm control, and determining which (if any) patients may safely discontinue anticoagulation if long-term NSR is achieved.

### Keywords

Atrial Fibrillation; Stroke; Rhythm Control; Antiarrhythmic Drugs; Catheter Ablation; Maze Surgery; Anticoagulation

## Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the United States, affecting up to 5 million people [1]. The burden of AF is expected to rise three-fold by 2050 to an estimated 12–16 million Americans [2]. The most feared consequence of AF is stroke due to thromboembolism; AF leads to a five-fold increase in stroke risk and an overall stroke rate of 5% per year [3]. Since AF is commonly silent and undiagnosed, the impact of AF on stroke is almost certainly underestimated.

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Despite the undisputed link between AF and stroke, efforts to maintain normal sinus rhythm (NSR) have not been shown to reduce thromboembolic events. Among several large clinical trials comparing a “rate control” to a “rhythm control” strategy, stroke and thromboembolic events were similar regardless of assigned treatment arm. [4–8]. In fact, most embolic events in the rhythm control arms of the AFFIRM and RACE trials occurred after warfarin was stopped or when the INR < 2.0, highlighting the importance of continued anticoagulation regardless of AF treatment strategy and underscoring the inefficacy of a strategy using antiarrhythmic drugs (AADs) alone in reducing stroke risk [4, 5].

However, there are several reasons for the apparent failure of rhythm control in these trials. Most importantly, rhythm control as attempted with AADs does not actually maintain NSR very effectively. In AFFIRM, the prevalence of NSR in the rhythm control arm was only 63% at five years. RACE was more disappointing; only 39% of patients in the rhythm control group had NSR after a mean follow-up of 2.3 years. Of note, these estimates were derived from intermittent EKG monitoring alone. Observational studies using intermittent EKG and Holter monitoring show that despite cardioversion and antiarrhythmic drugs, the recurrence rate of AF is 35–60% at one year [9, 10]. Using more intensive, continuous monitoring over 18 months, the recurrence rate is even higher at 88% [11]. Given the fact that most AF is asymptomatic and that intermittent monitoring alone is inadequate in assessing AF burden, the estimates of AF control in the major trials of rate versus rhythm control likely represent a vast overestimate of the efficacy of AAD therapy [12]. Additionally, episodes of AF lasting only hours have been shown to be associated with increased stroke risk in several trials, signifying that even a moderate reduction in AF burden may not be enough to ameliorate the event rate [13–17]. Furthermore, most trials report significant crossover from rhythm control to rate control; in AFFIRM, for example, the crossover rate was 17% at one year and 38% at five years due to either the inability to maintain NSR or drug intolerance [4]. Finally, while the major etiology of stroke in AF is thromboembolism from the left atrium, structural and functional alterations in the left atrium may also predispose the AF patient to stroke even if NSR is maintained. Factors independent of rhythm control, including endothelial dysfunction, inflammation, platelet activation, and hypercoagulability, are increasingly recognized as important contributors to stroke risk in AF and may persist even if NSR is maintained [18–20].

There were other limitations of the major clinical trials that prevent the results from being extrapolated to the entire spectrum of AF patients. Both RACE and AFFIRM enrolled older patients (average age 68–70 years). Perhaps younger patients would have benefited more from a rhythm control strategy given the reduced lifetime exposure to AF and the increased comorbidities seen in the aging population. In AFFIRM, the use of AADs led to increased mortality while the presence of NSR (regardless of assigned treatment arm) was associated with reduced mortality, suggesting that NSR may be beneficial if there was a safer and more effective way of achieving this goal. Also, both RACE and AFFIRM allowed anticoagulation to be discontinued four weeks after NSR was documented, leading some to believe that perhaps the combination of anticoagulation and rhythm control would have led to better outcomes than either strategy alone.

Despite the results of the major clinical trials, there is compelling evidence that rhythm control may actually be beneficial beyond symptom relief in AF. Two sub-studies of the AFFIRM trial support this notion. In one, stroke events were strongly associated with the presence of AF, regardless of a rate or rhythm control strategy [21]. In another, NSR was associated with better survival and a 60% reduction in stroke risk; to account for the high crossover rate between treatment arms, this sub-study used an actual treatment analysis instead of an intention-to-treat analysis [22]. A sub-study of the DIAMOND trial, a study of the AAD dofetilide, echoed these results; the presence of NSR regardless of treatment

strategy was associated with better survival [23]. Furthermore, a recent observational study of 57,000 Canadian patients with AF showed that rhythm control therapy was associated with lower rates of stroke and transient ischemic attacks compared with rate control therapy [24]. These findings are not limited to rhythm control using AADs. Pappone et al performed a retrospective cohort study comparing a catheter ablation strategy to AADs and demonstrated that AF ablation reduced stroke and mortality over a median follow up of 900 days [25]. Thus, NSR appears to be beneficial in terms of stroke and survival, though there are two possible explanations for this finding. The first is that NSR itself reduces stroke risk. The second is that those patients in whom NSR can be maintained with either drugs or ablation are inherently less prone to stroke. Two important ongoing trials, Early Treatment of Atrial Fibrillation for Stroke Prevention (EAST; ClinicalTrials.gov NCT01288352) and Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA; ClinicalTrials.gov NCT00911508), will contribute randomized control data to this important question. EAST will compare early rhythm control using AADs and catheter ablation with usual care on a composite outcome that includes death and stroke. The goal of CABANA is to establish the appropriate roles of medical (AADs or rate control drugs) and ablation therapy for AF; patients randomized to ablation or medical therapy will be compared across several endpoints including death and stroke.

While the evidence base for rhythm control is mounting, significant challenges remain. The various rhythm control options have limited efficacy and important side effects and risks. The unreliable symptoms of AF, the high burden of asymptomatic AF, and the limited sensitivity of external monitoring represent important hurdles to detecting AF and judging effective rhythm control. There is also uncertainty surrounding the threshold for AF duration and risk of stroke. These limitations are being addressed in ongoing research, but at present, rhythm control is only indicated for symptom control of AF and can neither be recommended as a stand-alone strategy for stroke prevention nor as a means to discontinue anticoagulation [26]. Thus far, long-term oral anticoagulation is the only proven strategy to reduce stroke risk and remains the gold standard for stroke prophylaxis in AF patients with other stroke risk factors, regardless of a rate or rhythm control strategy [27, 28].

## TREATMENT

### ANTICOAGULATION

- Oral anticoagulation is the foundation of AF stroke prophylaxis in current practice, whether or not rhythm control is attempted. The decision to anticoagulate is based on a patient-by-patient assessment of stroke risk in the context of other clinical risk factors. For non-valvular AF, the dominant risk stratification tool is the CHADS2 score, which incorporates Congestive heart failure, Hypertension, Age over 75 years, Diabetes, and prior Stroke or transient ischemic attack [29]. Aspirin therapy is recommended for a CHADS2 score of 0, systemic anticoagulation is recommended for a CHADS2 score of 2 or higher, and either option is reasonable for a CHADS2 score of 1.
- For valvular AF—related to either rheumatic disease or prosthetic heart valves—anticoagulation is indicated regardless of other stroke risk factors. Importantly, only warfarin is recommended in patients with valvular AF; at present, the newer anticoagulants lack sufficient data in this patient population.
- The efficacy of oral anticoagulation is well established. A large meta-analysis of patients with non-valvular AF showed that warfarin reduced stroke by 64% [28]. The newer anticoagulants were shown to have similar (rivaroxaban) or superior (dabigatran and apixaban) efficacy compared with warfarin [30–32].

## Warfarin

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| **Standard dosage** | 2–10 mg daily (highly individualized) |
| **Contraindications** | Absolute: Active bleeding, pregnancy (except if mechanical heart valve). |
| | Relative: Elevated bleeding risk, high likelihood of non-compliance |
| **Main drug interactions** | Quinolones, macrolides, penicillins, antifungals, amiodarone, digoxin, NSAIDs |
| **Main side effects** | Bleeding, skin/tissue necrosis (rare), teratogenicity |
| **Special points** | Vitamin K antagonist (inhibits factors II, VII, IX, X, protein C and S). |
| | Most established anticoagulant on the market. |
| | Monitoring and dose adjustment based on frequent INR measurement (target 2.0 to 3.0). |
| | No dose adjustment required for hepatic or renal impairment. |
| | Important interactions with several medications and vitamin K rich foods. |
| | Patients need education regarding bleeding prevention and consistent dietary habits. |
| | Anticoagulation can be reversed acutely with vitamin K and fresh frozen plasma. |
| **Cost/cost-effectiveness** | Generic (approximate cost $14–25 per month). Requires periodic blood draws. |

## Dabigatran

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| **Standard dosage** | 150 mg twice daily |
| | 75 mg twice daily (if creatinine clearance 15–30) |
| **Contraindications** | Absolute: Active bleeding, renal impairment (creatinine clearance < 15) |
| | Relative: Elevated bleeding risk, high-risk activities (extreme sports, certain occupations) |
| **Main drug interactions** | Carbamazepine, cyclosporine, dronedarone, antifungals, quinidine, verapamil, rifampin |
| **Main side effects** | Bleeding, dyspepsia/gastritis |
| **Special points** | Direct thrombin inhibitor. |
| | Similar safety and superior efficacy compared with warfarin [30]. |
| | No INR monitoring required. |
| | Limited interaction with medication and food. |
| | Patients need education regarding bleeding prevention. |
| | No effective method to rapidly reverse anticoagulation effect. |
| **Cost/cost-effectiveness** | Non-generic (approximate cost $246 per month). Periodic blood draws not required. |

## Rivaroxaban

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| **Standard dosage** | 20 mg once daily |
| | 15 mg once daily (if creatinine clearance 15–50) |
| **Contraindications** | Absolute: Active bleeding, renal impairment (creatinine clearance < 15) |
| | Relative: Elevated bleeding risk, high-risk activities (extreme sports, certain occupations) |
| **Main drug interactions** | Amiodarone, diltiazem, verapamil, macrolides, cyclosporine, dronedarone, antifungals, phenytoin, rifampin |
| **Main side effects** | Bleeding, elevated liver function tests, thrombocytopenia, pruritus |
| **Special points** | Factor Xa inhibitor. |
| | Comparable safety and efficacy to warfarin [31]. |
| | No INR monitoring required. |
| | Limited interaction with medication and food. |
| | Must be taken with evening meal to achieve effective absorption. |
| | Patients need education regarding bleeding prevention. |
| | No effective method to rapidly reverse anticoagulation effect. |

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| **Cost/cost-effectiveness** | Non-generic (approximate cost $246 per month). Periodic blood draws not required. |

### Apixaban

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| **Standard dosage** | 5 mg twice daily |
| | 2.5 mg twice daily (if any two of the following: age ≥ 80 years, weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL) |
| **Contraindications** | Absolute: Active bleeding, renal impairment (creatinine clearance < 15) |
| | Relative: Elevated bleeding risk, high-risk activities (extreme sports, certain occupations) |
| **Main drug interactions** | Antifungals, macrolides, rifampin, carbamazepine, phenytoin |
| **Main side effects** | Bleeding |
| **Special points** | Factor Xa inhibitor. |
| | Superior safety and efficacy compared with warfarin [32]. |
| | No INR monitoring required. |
| | Limited interaction with medication and food. |
| | Can be administered with or without food. |
| | Patients need education regarding bleeding prevention. |
| | No effective method to rapidly reverse anticoagulation effect. |
| **Cost/cost-effectiveness** | Non-generic (approximate cost $250 per month). Periodic blood draws not required. |

## RHYTHM CONTROL

- The goal of rhythm control is to reduce the burden of symptomatic AF, both the number of episodes and the duration of episodes. Ideally, rhythm control would result in complete maintenance of NSR. This goal is challenged by the modest efficacy of the various treatment options, the risks of the treatment options (both medication toxicities and procedural risks), and, at present, the lack of randomized control data showing a definitive link between the treatment options and stroke reduction.

### Diet and lifestyle

- Primary prevention of AF is an important strategy to reduce stroke risk. This includes adequate prevention and management of coronary artery disease, diabetes mellitus, hypertension, dyslipidemia, congestive heart failure, and valvular heart disease, all of which can lead to structural heart disease and the development of atrial fibrillation. Obesity and sleep apnea are also important and potentially modifiable AF risk factors.
- General strategies to prevent heart disease and AF include regular exercise, weight control, sodium and saturated fat restriction, avoidance of tobacco products, and age-appropriate screening for diabetes mellitus, hypertension, and dyslipidemia.
- Since advanced age alone represents a major risk factor for AF, the above preventive measures cannot be expected to eliminate AF risk in all individuals.

### Pharmacologic treatment

- AADs, the traditional mainstay of AF rhythm control, have had no success in terms of stroke prevention across all the major clinical trials.
- The efficacy of AADs for the maintenance of NSR is dependent on both the drug and the “type” of AF (i.e., paroxysmal, persistent, or long-standing persistent).

- Success rates for flecainide and propafenone have been reported to be 77% and 75%, respectively, the maintenance of NSR or fewer episodes of paroxysmal AF at one year [33].
- Rhythm control in AFFIRM, predominantly using sotalol and amiodarone, achieved NSR only 63% of the time [21]. In CTAF, amiodarone had a 65% success rate in maintaining NSR at 20 months whereas sotalol and propafenone had 37% success rates [34]. In SAFE-T, the rate of NSR at one year was better for amiodarone and sotalol (52% and 32%) than for placebo (13%) [35].
- For dofetilide, SAFIRE-D and EMERALD reported success rates of 58% and 66% for the maintenance of NSR at one year [36, 37].
- Dronedarone echoes the modest efficacy of the other AADs. In the pooled results of EURODIS and ADONIS, 67% of patients on dronedarone and 77.5% of patients on placebo had a recurrence of AF at one year [38].
- Several non-randomized studies of amiodarone show efficacy rates between 53% and 79% during a 15 to 27 month follow-up period, with amiodarone being less effective in patients with AF for over one year or enlarged left atria [39–41].

## Flecainide

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| **Standard dosage** | 50–300 mg/day divided every 8–12 hours |
| **Contraindications** | Absolute: Coronary artery disease or structural heart disease (left ventricular systolic dysfunction, left ventricular hypertrophy, valvular disease), based on the results of the CAST trial [42] |
| | Relative: Significant bradycardia, significant renal impairment |
| **Main drug interactions** | Macrolides, quinolones, antifungals, protease inhibitors (risk of QT prolongation and proarrhythmia) |
| **Main side effects** | Bradycardia, worsening of heart failure, drug-induced atrial and ventricular arrhythmias, organization of atrial fibrillation into 1:1 atrial flutter |
| **Special points** | Class IC agent (sodium channel blocker). |
| | Generally prescribed with an AV nodal blocker (beta blocker, non-dihydropyridine calcium channel blocker) to prevent 1:1 atrial flutter. |
| | Generally requires a screening stress test and echocardiogram to rule out coronary artery disease and structural heart disease. |
| | Rest and/or exercise electrocardiogram within 1–2 weeks of drug initiation to screen for QRS widening (a sign of drug toxicity and risk of proarrhythmia). |
| **Cost/cost-effectiveness** | Generic (approximate cost $58–115 per month). Can be initiated on an outpatient basis. |

## Propafenone

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| **Standard dosage** | 150–300 mg every 8 hours (immediate-release form) |
| | 225–425 mg every 12 hours (extended-release form) |
| **Contraindications** | Absolute: Coronary artery disease or structural heart disease (left ventricular systolic dysfunction, left ventricular hypertrophy, valvular disease), based on the results of the Propafenone Multicenter Study [43] and an extrapolation of the results of the CAST trial [42] |
| | Relative: Significant bradycardia, significant hepatic impairment |
| **Main drug interactions** | Macrolides, quinolones, antifungals, protease inhibitors, antipsychotics (risk of QT prolongation and proarrhythmia) |
| **Main side effects** | Bradycardia, worsening of heart failure, drug-induced atrial and ventricular arrhythmias, organization of atrial fibrillation into 1:1 atrial flutter |

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| **Special points** | Class IC agent (sodium channel blocker) with mild beta blocking activity. |
| | Can be used in patients with renal impairment. |
| | Generally prescribed with an AV nodal blocker (beta blocker, non-dihydropyridine calcium channel blocker) to prevent 1:1 atrial flutter. |
| | Generally requires a screening stress test and echocardiogram to rule out coronary artery disease and structural heart disease. |
| | Rest and/or exercise electrocardiogram within 1–2 weeks of drug initiation to screen for QRS widening (a sign of drug toxicity and risk of proarrhythmia). |
| **Cost/cost-effectiveness** | Generic (approximate cost $100–200 per month). Can be initiated on an outpatient basis. |

## Sotalol

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| **Standard dosage** | 80–160 mg every 12 hours |
| **Contraindications** | Absolute: Prolonged QT interval, significant bradycardia/heart block |
| | Relative: Congestive heart failure, significant left ventricular hypertrophy, significant renal impairment |
| **Main drug interactions** | Macrolides, quinolones, phenothiazines, antifungals (risk of QT prolongation) |
| **Main side effects** | Bradycardia, heart block, QT prolongation leading to torsade de pointes |
| **Special points** | Class III agent (potassium channel blocker) with significant beta-blocking activity. Not as effective for converting AF, but useful to maintain NSR. |
| | Not as effective for converting AF, but useful to maintain NSR. |
| | Especially useful in patients with ischemic heart disease. |
| **Cost/cost-effectiveness** | Generic (approximate cost $24 per month). First 5 doses generally administered inpatient to monitor QT interval, but variability in clinical practice. |

## Dofetilide

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| **Standard dosage** | 250–500 mg every 12 hours |
| **Contraindications** | Absolute: Prolonged QT interval, significant renal impairment |
| | Relative: Significant bradycardia, hypokalemia, hypomagnesemia |
| **Main drug interactions** | Thiazide diuretics, macrolides, antifungals, phenothiazines, quinolones, verapamil (risk of QT prolongation) |
| **Main side effects** | QT prolongation and torsade de pointes/ventricular arrhythmias |
| **Special points** | Class III agent (potassium channel blocker). |
| | Especially useful in patients with heart failure. |
| | Prescribing rights restricted to authorized users. |
| **Cost/cost-effectiveness** | Non-generic (approximate cost $245 per month). First 5 doses must be administered inpatient with careful monitoring of QT interval. |

## Dronedarone

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| **Standard dosage** | 400 mg twice daily |
| **Contraindications** | Absolute: Symptomatic congestive heart failure and recent decompensation requiring hospitalization [44], NYHA Class IV heart failure [44], permanent AF [45] |
| | Relative: Significant bradycardia/AV block, prolonged QT, hypokalemia, hypomagnesemia, significant hepatic impairment |
| **Main drug interactions** | Drugs which are metabolized via CYP3A4 and CYP2D6 enzymes including warfarin and dabigatran (dronedarone is a moderate inhibitor of these enzymes) |
| **Main side effects** | Worsening heart failure, QT prolongation, bradycardia, diarrhea/GI upset |
| **Special points** | Primarily a Class III agent (potassium channel blocker) but crosses all four classes. |
| | Especially useful in patients with left ventricular hypertrophy. |
| | Consider monitoring liver function tests especially during first 6 months. |
| **Cost/cost-effectiveness** | Non-generic (approximate cost $276 per month). Can be initiated on an outpatient basis. |

## Amiodarone

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| **Standard dosage** | Initial load of 800–1600 mg/day for 1–3 weeks, followed by 200–600 mg/day |
| **Contraindications** | Significant bradycardia, pregnancy or breastfeeding, baseline pulmonary disease, baseline hepatic impairment, baseline thyroid disease |
| **Main drug interactions** | Drugs which are metabolized by CYP enzymes including warfarin (amiodarone is a potent inhibitor of CYP enzymes) and drugs which prolong the QT interval |
| **Main side effects** | Chronic interstitial pneumonitis, hyper- and hypothyroidism, hepatitis, corneal microdeposits, photosensitivity, skin discoloration, GI upset, QT prolongation and ventricular arrhythmias |
| **Special points** | Primarily a Class III agent (potassium channel blocker) but crosses all four classes. |
| | Considered the most effective AAD. |
| | Has the least cardiac toxicity but the most extra-cardiac toxicity. |
| | Generally safe in heart failure, structural heart disease, and coronary artery disease. |
| | Monitoring recommendations include thyroid function tests every 6 months, liver function tests every 6 months, eye examination yearly, pulmonary function tests/chest x-ray yearly. |
| **Cost/cost-effectiveness** | Generic (approximate cost $36 per month). Can be initiated on an outpatient basis. |

## Interventional procedures

- Catheter ablation of AF is being performed with increasing frequency since the initial descriptions of pulmonary vein electrophysiology in the 1990s [46–48]. The procedures primarily focus on the electrical isolation of the pulmonary veins (PVs) from the left atrium, thus eliminating potent AF triggers.
- Randomized control data suggest that ablation therapy is superior to AADs in maintaining NSR, specifically in patients failing at least one AAD [49]. However, success rates of catheter ablation as reported in the most recent consensus statement vary widely [26]. The single procedure success rate in patients with paroxysmal AF ranges from 38% to 78%, with most series reporting a single procedure efficacy of 60% or greater. For persistent AF, the single procedure success rate ranges from 22% to 45%, with most centers reporting an efficacy of 30% or less. Repeat ablation attempts are often required to achieve a better chance of success. The multiple procedure success rate in patients with paroxysmal AF ranges from 54% to 80%, with most series reporting an efficacy of 70% or greater. For persistent AF, the multiple procedure success rate ranges from 37% to 88%, with most centers reporting an efficacy of 50% or greater.
- The wide variation in success rates reflects differences in patient selection, ablation techniques, definitions of procedural success, and post-ablation monitoring. As a result, success rates in general may be overestimated. In a study using an AF-sensitive implantable cardiac monitor following ablation, one-year success rates of 68% for paroxysmal AF and 48% for persistent AF were observed [50]. Another concern is the longevity of success. From a series of 264 ablation patients who demonstrated >1 year of AF-free follow-up without AADs, the actuarial recurrence of AF at two years was 5.8% and dramatically increased to 26.5% at five years [51].
- Current guidelines recommend catheter ablation as second-line therapy after failure of at least one AAD. Patients with paroxysmal AF are generally better candidates for catheter ablation than those with persistent AF [26].
- Procedural-related strokes and long-term mechanical dysfunction of the left atrium following extensive ablation may partially offset the benefits of NSR achieved with this procedure.

## Catheter ablation

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| **Standard procedure** | Right heart catheterization via a femoral vein approach with subsequent trans-septal access to the left atrium and PVs. The cornerstone of AF ablation is the electrical isolation of the PVs. Other targets of ablation include focal triggers outside the veins (if identified), cavotricuspid isthmus (if typical atrial flutter is documented), complex fractionated atrial electrograms (areas of diseased myocardium which can perpetuate AF), and linear lines across the left atrium (left atrial roof, mitral isthmus, ligament of Marshall). Ablation is performed with either focal radiofrequency energy or cryothermal energy via a balloon catheter. Concomitant imaging modalities include left atrial angiography, intracardiac echocardiography, 3-dimensional electroanatomic mapping, and fluoroscopy. |
| **Contraindications** | Left atrial thrombus, inability to tolerate anticoagulation during and post-procedure for at least two months, poor cardiac reserve (critical coronary artery disease, decompensated heart failure, severe aortic stenosis, severe pulmonary hypertension), need for cardiac surgery for another reason during which surgical ablation/Maze can be performed |
| **Complications** | Minor: groin bleeding, hematoma, infection, pseudo-aneurysm (<1%)<br>Major: stroke or TIA (0–7%), PV stenosis (1.3%), phrenic nerve paralysis (<1%), cardiac tamponade/perforation (1.2–1.5%), aorto-esophageal fistula (0.1–0.25%), death (0.1%) |
| **Special points** | Pre-procedure cardiac CT or MRI to define PV anatomy.<br>Pre-procedure transesophageal echocardiography to rule out thrombus in high-risk patients (generally $CHADS_2$ score >2). |
| **Cost/cost-effectiveness** | One study formally analyzed the cost-effectiveness of catheter ablation compared to amiodarone therapy and a rate-control strategy, finding that the incremental costeffectiveness of catheter ablation varied widely ($28,700 to $98,900 per quality-adjusted life-year) depending on the age of the patient and the baseline risk of stroke [52]. Of note, the study assumed that successful ablation of AF eliminates the excess risk of stroke, which is yet to be proven in prospective studies. The limited data on cost-effectiveness suggests that catheter ablation of AF may be cost-effective in patients with one or more risk factors for stroke but not in patients without any risk factors. |

## Surgery

- Surgery for atrial fibrillation, with a goal of permanent restoration of NSR, has been performed for over two decades.
- Prospective multicenter clinical trials are lacking to define the relative safety and efficacy of the different surgical tools and techniques. Among the published studies, surgical techniques, definitions of success, the type and frequency of follow-up, and post-surgical adjunctive treatments have varied widely. Not surprisingly, cure rates have also varied widely from 21% to 97%, with more intensive monitoring demonstrating lower than expected cure rates [26, 53].
- One surgical study showed a potential reduction in stroke risk, but it is unclear if this was driven by the restoration of NSR or the removal/exclusion of the left atrial appendage [54].
- Indications for AF surgery are in agreement between surgical society guidelines and electrophysiology guidelines, limiting AF surgery to a concomitant procedure for patients undergoing cardiac surgery for another reason (class II indication) [26, 55].

## Atrial fibrillation surgery

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| **Standard procedure** | The current gold standard is the Cox Maze III procedure, a “cut and sew” procedure that involves dividing and reconnecting the atria with the goal of compartmentalizing atrial tissue into segments too small to sustain AF [56].<br>The less complex Maze IV procedure, in which some “cut and sew” lesions are replaced with cryothermal or radiofrequency ablation, is rapidly replacing the Maze III in clinical practice [57].<br>Hybrid (catheter ablation plus surgery) and video thorascopic procedures are also in development [58, 59]. |
| **Contraindications** | Inability to tolerate cardiac surgery (high STS score, significant co-morbidities, poor functional status, deemed inoperable by an experienced cardiac surgeon) |

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| **Complications** | Based on stand-alone surgical AF ablation, the operative mortality rate is 0.8% and the major complications rate is 10% (renal failure, pericarditis, pneumothorax, pleural effusion, or re-operation for bleeding) |
| **Special points** | AF surgery generally includes the removal/exclusion of the left atrial appendage, which is felt to be an important modulator of stroke risk. |
| **Cost/cost-effectiveness** | Very expensive. |

### Emerging therapies

- As catheter ablation techniques improve, there is growing interest in establishing a more aggressive role for this procedure. Since ablation success rates drop dramatically for older patients with long-standing AF, it may be beneficial to ablate early in the course of AF prior to detrimental atrial remodeling, when the chance of success is highest. Two important trials, First Line Radiofrequency Ablation versus Antiarrhythmic Drugs for Atrial Fibrillation Treatment (RAAFT; ClinicalTrials.gov NCT00392054) and EAST, are currently underway to address this hypothesis of ablation as first-line therapy.
- Given the great difficulty in achieving success with rhythm control (defined as permanent restoration of NSR), an idea has emerged to focus instead on better detection of AF episodes using highly sensitive implantable cardiac rhythm devices that provide immediate feedback. With this information, it would be possible to administer anticoagulation only during episodes of AF, reducing the bleeding risk associated with chronic anticoagulation while still treating the risk of stroke due to AF. This strategy is now possible due to the emergence of new anticoagulants with rapid therapeutic onset. The Combined Use of Biotronik Home Monitoring and Predefined Anticoagulation to Reduce Stroke Risk trial (IMPACT; ClinicalTrials.gov NCT00559988) uses frequent home monitoring of patients with cardiac defibrillators and resynchronization devices to test this strategy while the Safety Study on Stopping Anticoagulation Medication in Patients with a History of Atrial Fibrillation trial (TACTIC AF; ClinicalTrials.gov NCT01650298) extends this effort to patients with permanent pacemakers. The Rhythm Evaluation for Anticoagulation with Continuous Monitoring trial is currently underway to test this novel strategy for stroke prevention in patients with implantable cardiac monitors (REACT COM; ClinicalTrials.gov NCT01706146).

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** Of major importance

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