Review

Catheter ablation for atrial fibrillation in the elderly

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Practice Points

- Atrial fibrillation is by far the most frequent sustained arrhythmia encountered in daily clinical routine. More than 5% in the patient age group over 65 years and more than 10% in the age group over 80 years are suffering from atrial fibrillation.
- The risk of ischemic neurologic events is increased fivefold if atrial fibrillation is present. Strokes related to atrial fibrillation are often complicated by severe disability or death.
- Ischemic neurologic events related to atrial fibrillation are significantly reduced by vitamin K antagonists and novel anticoagulants in patients of advanced age. While only a small increase in severe bleedings is observed, there is a significant overall benefit of oral anticoagulation if compared with antiplatelet agents in this patient age group.
- Invasive percutaneous catheter ablation with electrical pulmonary vein isolation is a valuable treatment modality for the older patient group, with few comorbidities if rhythm control is the preferred strategy and drug treatment has failed.
- The patient's age alone should not preclude from invasive rhythm control by electrical pulmonary vein isolation.

SUMMARY An important proportion of patients suffering from atrial fibrillation (AF) are in the patient age group over 65 years. Cardiac and noncardiac comorbidities are often present at this age and are challenging for pharmacological management. In the setting of hypertension, coronary artery disease, heart failure and left ventricular hypertrophy, specific antiarrhythmic drugs frequently fail due to adverse effects, proarrhythmic properties or impaired efficacy. Recently, catheter ablation became widely available as an effective therapy for symptomatic AF. However, a small number of elderly patients were enrolled in the large randomized trials,

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and international guidelines recommend a conservative strategy in elderly patients as the evidence-based data are limited. Nevertheless, our findings and the data of other groups show that ablation therapy is effective with acceptable risks for selected elderly patients even at octogenarian age, if AF is symptomatic despite pharmacological rate and rhythm control. For that reason, the fact of patient's age alone shouldn't be a factor to preclude patients from ablation procedure.

The majority of patients with sustained cardiac arrhythmias encountered in daily clinical practice have atrial fibrillation (AF) with an incidence and a prevalence that will increase significantly in the future. Neurological and systemic thromboembolic events and progressive heart failure contribute to the significant burden of morbidity and mortality in patients with AF. Age increases the prevalence of AF incrementally, especially at an octogenarian age **(Figure 1)**. Nearly 5% of 65 year olds and 10% of 80 year olds are diagnosed with AF. The median age of an AF patient is 75 years and 70% of the AF patients are 65–85 years of age [1]. Demographic calculations expect that the number of affected subjects will increase in the next 20–30 years by a factor of two to three due to the aging populations in Europe and North America.

The risk of ischemic neurologic events is increased by a factor of five in the presence of AF. This is often fatal or leads to severe disability. In octogenarian patients aged 80–89 years, the cause of stroke is AF in 25% of patients. Moreover, cerebrovascular events due to AF are associated with higher mortality and morbidity. A cornerstone in prevention of AF-related ischemic events is oral anticoagulation, but the practitioner managing octogenarian patients suffering from AF has to balance the risk for thromboembolic complications without anticoagulation against the bleeding rate of anticoagulant agents. The decision for anticoagulation can become a difficult task in the prevention of AF-related thromboembolic events in this elderly patient group. Furthermore, medical management is challenged by multiple comorbidities due to heart failure, hypertension, left ventricular hypertrophy, history of myocardial infarction, arteriosclerosis of coronary arteries and metabolic disorders. Patients with this background have more frequent thromboembolic events or drug-induced adverse side effects. A personalized and comprehensive management of this patient's age group based on the treating clinician's experience is essential.

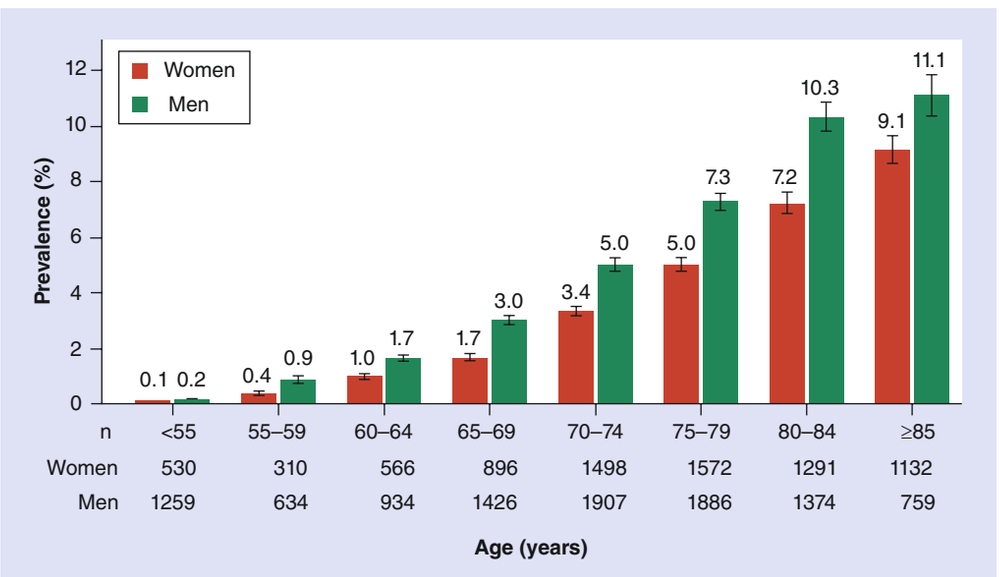

Figure 1. Prevalence of atrial fibrillation in the ATRIA cohort.
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In recent years, catheter ablation has become widely available as an effective therapy for symptomatic AF despite pharmacological antiarrhythmic therapy [2]. Techniques and experience with catheter ablation have markedly improved, resulting in improved results and a decreased rate of complications [3,4]. Therefore, referrals of patients with advanced age for catheter ablation of AF have markedly increased. However, only a small number of elderly patients were selected in trials comparing ablation procedure and drug therapy. The physician referring the patient for catheter ablation may be concerned that friable cardiac anatomies in the elderly patient population may pose a risk due to catheter manipulation, extended procedure duration and the comorbidities. Therefore, current recommendations stress that these considerations should be taken into account in the patient selection for AF catheter ablation, especially if the chance of a successful rhythm control is decreased by an important dilation of the atrial chambers or a long-standing history of AF [5]. Nevertheless, life expectancy is on the rise and the elderly are the fastest growing group of western populations. Catheter ablation will become an essential therapeutic option after failed medical drug therapy for the elderly patient population.

Pharmacological rhythm management in the elderly

Several randomized prospective studies comparing the clinical outcome of AF patients undergoing pharmacological rhythm control against rate control showed no significant difference between both strategies in terms of stroke, hospitalization and mortality, although the clear relationship between AF and cardiovascular events was shown [6–8]. However, subgroup analyses and outcome data of the ATHENA study demonstrated that AF-induced complications are reduced by carefully restored and stabilized normal sinus rhythm [9]. This randomized prospective trial assessed the clinical outcome of 4628 AF patients who underwent a treatment with dronedarone in terms of hospitalization rate and survival. The mean age of the patient study group was 71.6 years, while 42% of the patients were at least 75 years of age. Cardiovascular hospitalization rate and mortality were not significantly different whether the patient's age was above or below 75 years (hazard ratio: 0.76 vs 0.75). In the PALLAS study, the impact on outcome of dronedarone was assessed in patients with permanent AF lasting longer than 6 months and presenting with cardiovascular risk factors [10]. This trial had to be aborted prematurely due to an increase in cardiovascular events and mortality in the dronedarone treated arm compared with placebo. The characteristics of the patient population in both the ATHENA and PALLAS trials differ significantly and may contribute to the differences in outcome. Patients included in the PALLAS trials had to be in permanent AF and had a higher burden of cardiovascular risk factors compared with the patient selection in ATHENA. For that reason, dronedarone is contraindicated in patients with permanent AF, current or history of congestive heart failure (New York Heart Association class III/IV), left ventricular dysfunction and significant cardiovascular risk factors (e.g., postmyocardial infarction). The major trials comparing rhythm against rate control are the RACE trial, the AFFIRM trial and the AF-CHF trial; the patients' mean age were 68.0, 69.7 and 66.0 years, respectively [6,8,11]. The patient population over 65 years of age is not well represented in these studies. There is no trial available that has assessed specific drug therapy particularly in the patient age group beyond 65, 70 and 80 years [12]. The AFFIRM trial described a decreased survival in elderly patients (n = 3091) aged over 65 years who underwent a rhythm control strategy by antiarrhythmic agents compared with the patients with a rate control strategy only [11]. There are smaller studies, including the PIAF [13], STAF [14] and HOT CAFÉ [7] trials, which reported that rate control strategy is not inferior to rhythm control strategy. The recommendations of the European Society of Cardiology about AF management propose a primary rate control strategy in the elderly patients with AF and, if this management fails, a rhythm control strategy for maintenance of sinus rhythm [15]. β-blockers, nondihydropyridine calcium channel blockers and digoxin are recommended and widely prescribed for control of rapid ventricular rate response in patients with AF [16]. Digoxin is recommended if impairment of the left ventricular function is present, but the treating physician should be careful with regard to potential drug toxicity in patients at advanced age with

frequent concomitant decreased renal function and polypharmacy. Previous recommendations target a resting heart rate of less than 80 beats per minute. However, a recent randomized trial demonstrated no clinical benefit of a strict versus a lenient rate control targeting heart rates at rest of approximately 115 beats per min in terms of clinical cardiovascular events [17]. Specific antiarrhythmic drugs with the purpose of restoring and maintaining normal sinus rhythm should be evaluated in elderly patients, if they are still having symptoms despite optimal control of ventricular rate response. The treating physician making the choice of a specific antiarrhythmic agent should consider drug-related proarrhythmic risks, drug interactions and comorbidities in patients at an advanced age (Table 1). Class Ic antiarrhythmic agents, flecainide and propafenone, demonstrated a decreased survival in patients with coronary artery disease [18]. The class III antiarrhythmic drugs, sotalol and dofetilide, should not be used in patients with compromised renal function. Amiodarone is by far the antiarrhythmic drug with the greatest impact on sinus rhythm maintenance and is safe for patients with heart failure and coronary artery disease. However, the chronic use of amiodarone mandates regular check-up to prevent extracardiac toxicity on thyroidea, liver and lungs. For that reason, amiodarone should be reserved for use if other antiarrhythmic agents have failed or cannot be used because contraindications are present.

Catheter ablation of AF in the elderly

Percutaneous catheter ablation for AF has been developed on the understanding of pathophysiology of ectopic focal beats originating in the pulmonary veins and triggering AF [2]. The ablation procedure consists of the application of continuous circumferential ablation lines around the pulmonary vein ostia in order to disconnect the electrical conduction between the pulmonary veins and left atrium [19,20]. The rates of maintaining sinus rhythm are between 70 and 90% in high-volume and experienced institutions. Nevertheless, the available data and results are derived from trials having selected and enrolled patients aged younger than 65 years and not presenting heart disease or significant comorbidities. Percutaneous catheter ablation procedure is less effective in patients with chronic than paroxysmal AF. Furthermore, the procedure is associated with an increased hazard ratio for complications in the elderly patient group who have important structural heart disease [21,22].

Recently, our group reported the clinical result of 45 consecutively enrolled patients aged 65 years or more with symptomatic paroxysmal and persistent AF undergoing catheter ablation for rhythm control [23]. Important structural heart disease was not documented in any of these elderly patients. Anatomical circumferential isolation of the pulmonary vein was performed in all patients, who presented mostly with paroxysmal AF. The ablation

Table 1. Antiarrhythmic drugs for atrial fibrillation.

Drug	Considerations for the elderly patients
Class Ic antiarrhythmic agents (flecainide and propafenone)	▪ Contraindicated in CAD, impaired systolic left ventricular function (proarrhythmia) and insufficiency of the kidneys ▪ Caution in the presence of pre-existing prolongation of the infranodal conduction system ▪ Dose reduction if QRS duration change >25% (proarrhythmia) ▪ Combination with atrioventricular nodal-slowing drugs mandatory to avoid rapid ventricular rate response if AF converts into atrial flutter
Sotalol	▪ Not recommended in patients with important left ventricular hypertrophy and/or reduced left ventricular function. Caution in females, in bradycardic, hypokalemic (malnutrition) patients, in presence of long QT interval and renal insufficiency (risk of proarrhythmia i.e., Torsades de Pointes, ventricular tachycardia) ▪ QT-interval monitoring at therapy initiation or dose increase (corrected QT-interval not >500 ms)
Dronedarone	▪ Contraindicated in NYHA class III–IV or recent (last 4 weeks) decompensated heart failure insufficiency of kidneys
Amiodarone	▪ ECG-monitoring required if combined with other drugs prolonging QT-interval and decompensated heart failure present. Dose reduction of vitamin K antagonists and of digoxin/digitoxin. Risk of bradycardia with concomitant atrioventricular node-slowing drugs. Regular monitoring of extracardiac adverse effects (thyroidea, lungs, eye and liver) mandatory

AF: Atrial fibrillation; CAD: Coronary artery disease; NYHA: New York Heart Association.

was obtained by radiofrequency energy and facilitated by a 3D electroanatomical mapping system (Figure 2) [24]. Our collected data demonstrated that the ablation procedure can be offered to and undertaken in patients aged over 65 years with comparable results of sinus rhythm maintenance and safety compared with the results in patients at a younger age (Table 2). Catheter ablation confers a successful sinus rhythm restoration and maintenance in 80% of this patient selection who have a mean age of 69 years. The strategy and technique of the procedure was the same in this elderly patient group as for younger patients. The older patients were exposed to the same types of complications inherent to the invasive procedure as the younger patients. The indication of catheter ablation in this elderly patient group was based on similar criteria for inclusion and exclusion. Zado *et al.* reported comparable results and complication rates in patients aged 65 years and more [25]. In a study by Tan *et al.* patients over the age of 80 years were less likely to undergo a redo procedure, but the rates of success and complication were not different in patients aged over 80 years than in those aged 60–69 years (success rates of 70 vs 74%) [26]. The patient's outcome was assessed by regular ECGs and 72 h Holter recordings, while the mean follow-up time in this cohort was 18 months. Similarly, the trial published by Bunch *et al.* demonstrated that the risk of periprocedural adverse events in patients aged 80 years and older is not elevated [27]. In another observational multicenter analysis Liu *et al.* reported a very small, but significant decrease of sinus rhythm maintenance rate in a large Chinese cohort of 2970 patients aged 60 years or more compared with younger patients (77.3 vs 79.3%, respectively) and no difference of complication rates after a follow-up of 6.7 months [28]. However, all of the results on efficacy and safety of catheter ablation in the elderly population are obtained from observational cohort trials with small patient numbers and short follow-up periods. Trials with a prospective and randomized design analyzing the outcome of ablation compared with conservative medical drug therapy are necessary to answer questions on best practice and strategy in the AF patients aged 65 years and older. Invasive ablation procedures should be evaluated as a valuable therapy for the elderly patient with symptomatic AF after rate and rhythm control by pharmacological agents have failed. Age alone should not be a criterion to exclude patients from undergoing percutaneous AF ablation procedure. A decision-making tree for the management of

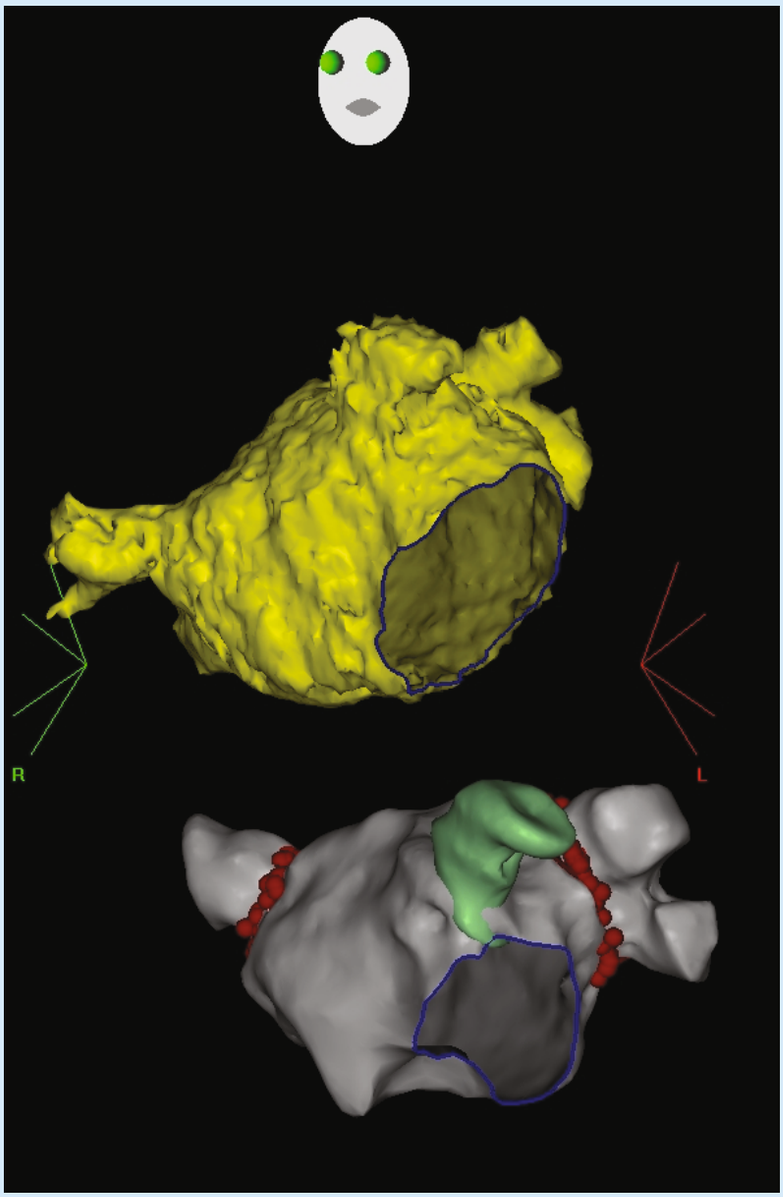

Figure 2. 3D electro-anatomical map of the left atrium (gray) and the left atrial appendage (green) in a left anterior oblique projection with circumferential ablation (red points) around ipsilateral pulmonary veins. (A) Using a 3D reconstruction of the MRI of the left atrium (yellow) and **(B)** an electro-anatomical mapping system (CARTO Biosense Webster Inc.,CA, USA).
Please see color figure online at www.futuremedicine.com/doi/full/10.2217/CPR.13.23

Table 2. Catheter ablation of atrial fibrillation in the elderly.

Study (year)	Inclusion age (years)	Mean age (years)	Number of patients	Number of procedures	Paroxysmal AF (%)	Ablation strategy	Mean F/U (months)	Periprocedural complication rate (%)					Freedom of AF (%)	Ref.
								Pericardial tamponade	*Deep venous thrombosis*	*CVA/TIA*	*Retroperitoneal bleeding*	*Pseudoaneurysm/ AV fistula*		
Zado *et al.* (2008)	65–74	68 ± 3	185	228	62	PVI	27	0.4	0	0.8	0.4	2.7	84	[25]
	≥75	77 ± 2	32	34	53								86	
Tan *et al.* (2009)	≥80	84 ± 5	49	53	55	PVI	18	0.2	0.9	0.7	0.7	0.5	70	[26]
	70–79	75 ± 4	151	174	53								72	
	60–69	66 ± 4	177	209	51								74	
Bunch *et al.* (2010)	≥80	82 ± 2	35	35	46	PVI ± linear lesions	12	2.8	2.8	0	0	0	78	[27]
Haegeli *et al.* (2010)	≥65	69 ± 3.5	45	53	87	PVI ± linear lesions	6	1.9	0	0	0	0	74	[23]

AF: Atrial fibrillation; AV: atrioventricular; CVA: Cerebral vascular accident; F/U: Follow-up; PVI: Pulmonary vein isolation; TIA: Transient ischemic attack.

AF integrating different drug agents for rate and rhythm control by percutaneous ablation procedure is shown in **Figure 3**, adapted from the recommendations of the European Society of Cardiology [15]. However, an invasive ablation procedure should not be recommended in an elderly patient if the chance for a successful long-term result of the procedure would be compromized because of chronic long-standing AF. This clinical decision is made on an individual patient basis. Likewise, no first-line ablation treatment can be generally recommended in elderly AF patients.

There are no randomized, prospective studies available to date, showing that a successful ablation procedure translates into a stroke risk reduction warranting discontinuation of oral anticoagulation in any patient's age population. Large prospective, randomized intervention trials are now being undertaken and will hopefully address the question if an aggressive, comprehensive and early rhythm control therapy either by drugs or ablation procedure has a beneficial impact on overall cardiovascular morbidity and mortality [29].

Stroke prophylaxis

Oral vitamin K antagonists significantly decrease the hazard of stroke in elderly AF patients, as is clearly demonstrated in several randomized trials. The thromboembolic complication risk per year is estimated to be over 4% for the patient's age group over 75 years, mandating the prescription of oral anticoagulation agents, except if there is elevated risk for having a severe hemorrhage. Among the individual factors of the widely accepted CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke [doubled], vascular disease, age 65–74 and sex category [female]) the factor of age ≥75 years is associated with a prognosis for cerebrovascular events and survival significantly more compromized over the factors of hypertension, diabetes or congestive heart failure [15]. The rate for stroke is decreased by approximately two-thirds and the mortality by a third due to an intake of vitamin K antagonists (e.g., warfarin) [30]. However, vitamin K antagonists have a narrow therapeutic window, requiring regular monitoring and their use can be complicated by the associated hemorrhagic effects. Data derived from several trials have

shown that advanced age confers an incremental hazard ratio for warfarin-related bleeding complications and that the rate of major warfarin-associated bleedings events ranges between 0.3 and 10% per year in selected patient populations. Keeping the international normalized ratio (INR) between 2.0 and 3.0 optimizes the anticoagulation intensity [31]. Some doctors target INR numbers in the lower ranges in elderly patients, but it was shown that a given fixed and small dosage of warfarin or aiming INR values below <2.0 in patients at an advanced age confers an increased stroke risk with no protection against intracerebral bleeding [31]. If warfarin or phenprocoumon are not tolerated, antiplatelet therapy with acetylsalicylic acid confers some degree of prevention of the risk of stroke, but not with the same efficacy as vitamin K antagonists [32]. The prevention with acetylsalicylic acid is associated with a risk reduction for stroke by approximately 20%, but this net positive impact of antiplatelet therapy on cerebrovascular events seems to become smaller with aging and is not present anymore after patients are aged 77 years or over. The ACTIVE-W study found that warfarin alone was superior to the combination of clopidogrel and aspirin, while the rates of bleeding complications were similar [33]. Moreover, another prevention trial of AF-related complications comparing acetylsalicylic acid at a fixed dose of 300 mg against INR-adjusted oral anticoagulant agents in octogenarian patients reported that acetylsalicylic acid was discontinued more frequently than warfarin, in most cases due to gastrointestinal intolerance. The mean age of this patient population was 83.9 years. Novel oral anticoagulant drugs are available and are now approved for the indication in AF patients. Dabigatran, an oral direct inhibitor of thrombin, has been demonstrated in the randomized prospective RELY trial to be superior compared with warfarin by showing similar stroke rate reductions, but lower incidence of major bleeding complications [34]. This trial randomized 18,113 patients while the average age was 71 years. The pharmacokinetic properties of dabigatran were reproducible and predictable in healthy subjects aged over 65 years [35]. Other oral anticoagulation agents, direct factor Xa inhibitors (e.g., rivaroxaban and apixaban) have been approved for the prevention of thromboembolic complications

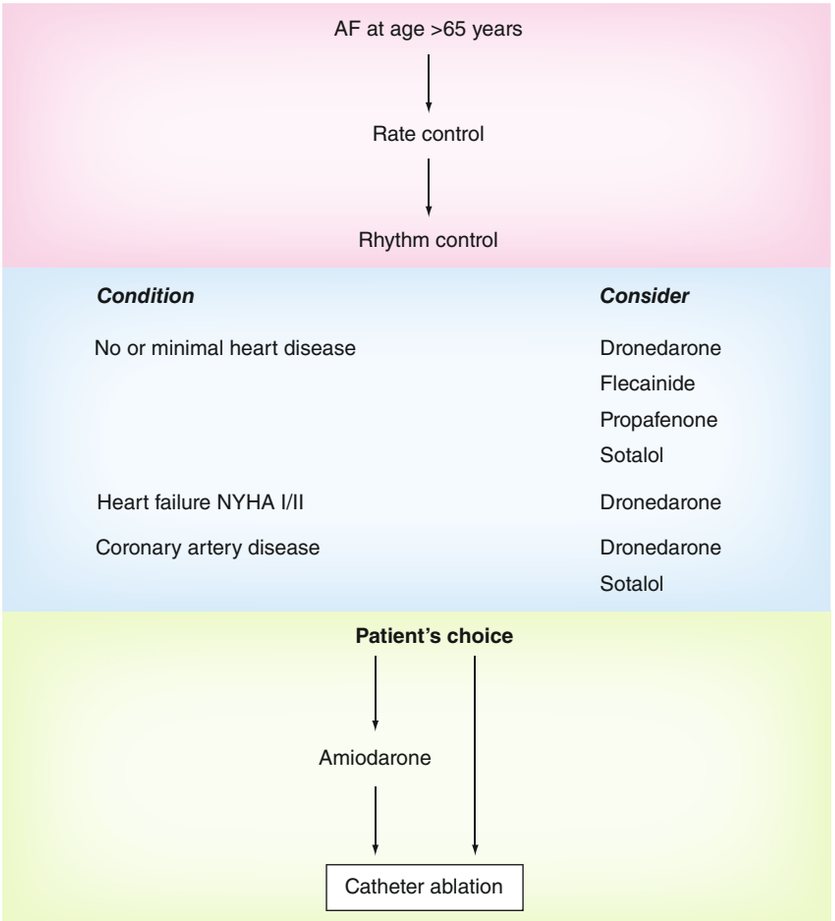

Figure 3. Overview and algorithm for the selection of the different treatment options for atrial fibrillation in elderly patients using drugs or ablation.
Adapted with permission from [15].

in AF patients after the beneficial outcomes were published in large prospective randomized trials [36,37]. Patients with advanced age receive an anticoagulation therapy less frequently than younger patients if needed and have more frequently have INR values <2.0. A prospective observational analysis showed that 783 AF patients with a median age of 75 years were in therapeutic range 71% of the time and that there was no difference for patient groups younger or older than 80 years [38]. The annual rate of major hemorrhage of patients aged over 80 years was 2.5%. Of note, less than half of eligible patients take oral anticoagulation. Surveys among physicians show that important criteria influencing the nonprescription of oral anticoagulant agents are increased risk for falling, bleeding history, noncompliance and dementia [39,40]. However, a statistical analysis calculated that a patient would have to have

300 falls in one year to reasonably recommend discontinuation of warfarin in an AF patient aged 65 years or more. Among the other risk factors for major hemorrhage complications of patients with AF are history of stroke, gastrointestinal hemorrhage, hypertension, concomitant antiplatelet use, presence of anemia, impaired renal function, cerebrovascular disease and/or malignancy, all of which may be encountered more often with age advancement. Therefore, physicians should be careful in the recommendation of oral anticoagulation in the elderly patient group. However, the single critierion of age should not restrain the use of oral anticoagulation therapy in elderly AF patients, because the potential net clinical benefit is greatest for patient groups with the highest stroke risk, which includes the oldest age category, as shown in a meta-analysis paper including the data of 11 randomized controlled studies [41,42]. For an optimal oral anticoagulation, INR measurements should remain in therapeutic ranges over 65% of the time (INR: 2–3) to avoid major anticoagulation-induced bleedings. The novel oral anticoagulation agents show net clinical benefits in terms of efficacy and safety compared with vitamin K antagonist agents. The implementation of these novel oral anticoagulants that do not require regular monitoring and dose-adjustment in daily routine will hopefully increase the proportion of elderly AF patients being appropriately protected by oral anticoagulation. Caution should be used with the novel oral anticoagulation agents if moderate renal insufficiency is present and the dose should be adjusted, accordingly.

Conclusion

Patients in the elderly age groups differ significantly from the younger age group as they have an increased incidence of AF, which is associated with a increased risk for thromboembolic events due to the presence of age and other cardiac and noncardiac comorbidities inherent to age advancement. Furthermore, adverse side effects of antiarrhythmic agents, such as proarrhythmic effects, are more frequently encountered in the elderly patient group. Nonrandomized, observational studies demonstrated that the ablation procedure can be offered and undertaken in patients aged over 65 years with comparable results of sinus rhythm maintenance and safety compared with the results in patients at a younger age. However, these studies involved small patient numbers and short follow-up periods. Nevertheless, invasive ablation procedures should be evaluated as a valuable therapy for elderly patients with symptomatic AF refractory to optimal drug treatment. Age alone should not be a criterion to exclude patients from undergoing percutaneous AF ablation procedures.

Future perspective

Percutaneous catheter ablation has become an established treatment of AF. Ablation techniques and strategies are being continuously improved as technologies supporting the procedure are in continuous progress and our understanding of the pathophysiological process of AF is increasing. The introduction of catheter navigation by electromagnetic steering systems will facilitate positioning of catheter tips within the area of interest and enhance the precision of lesion application. Developments of novel energy sources (e.g., laser energy) and catheter designs (e.g., balloon-based systems, multipolar circular irrigated catheter tips and the ability of contact force measurement of catheter–tissue interface) will facilitate and shorten the ablation procedure of AF. Periprocedural imaging of ablation lesion by cardiac magnetic resonance imaging will improve the lesion durability and decrease arrhythmia recurrence rates. These developments will further improve long-term efficacy and safety of the complex procedure of catheter ablation of AF. Large prospective, randomized intervention trials including elderly AF patients are now being undertaken and will address the question of whether an aggressive, comprehensive and early rhythm control therapy is beneficial to overall cardiovascular morbidity and mortality. As a consequence, more elderly patients with AF will benefit from catheter ablation.

Financial & competing interests disclosure

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