

# Managing atrial fibrillation in the very elderly patient: challenges and solutions

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**Abstract:** Atrial fibrillation (AF) is the most common arrhythmia affecting elderly patients. Management and treatment of AF in this rapidly growing population of older patients involve a comprehensive assessment that includes comorbidities, functional, and social status. The cornerstone in therapy of AF is thromboembolic protection. Anticoagulation therapy has evolved, using conventional or newer medications. Percutaneous left atrial appendage closure is a new invasive procedure evolving as an alternative to systematic anticoagulation therapy. Rate or rhythm control leads to relief in symptoms, fewer hospitalizations, and an improvement in quality of life. Invasive methods, such as catheter ablation, are the new frontier of treatment in maintaining an even sinus rhythm in this particular population.

**Keywords:** elderly, atrial fibrillation, anticoagulation, drugs, catheter ablation

## Introduction

Atrial fibrillation (AF) prevalence increases with age, making it the most common arrhythmia in patients older than 65 years. For patients older than 80 years, the corresponding rate is approximately 10%.<sup>1</sup> Furthermore, 70% of individuals with AF are between the age of 65 and 85 years.<sup>2</sup> The prevalence of AF is increasing in parallel to the aging of the population.<sup>3</sup> AF itself cannot be considered directly life threatening, but it is undoubtedly related to an increased risk of death. In the Framingham cohort, the total mortality odds ratio was 1.5 for male and 1.9 for female patients with AF, even after adjustment for age and other risk factors.<sup>4</sup> In addition, the morbidity of the elderly patients suffering from AF is of considerable importance, because these patients exhibit increased and, often, long hospitalizations due to heart failure, strokes, need for pacemaker implantations, and adverse effects related to antiarrhythmic therapy. Even though this arrhythmia has been acknowledged since the ancient civilizations of China, Egypt, and Greece,<sup>5</sup> and its treatment and management remain a challenge to the modern day physician. Recent breakthroughs in drug therapy and invasive techniques have opened new horizons in the field of AF. Elderly patients who were previously excluded from trials are now actively participating in various studies, thus giving medical science new solutions concerning the management and treatment of this age group. This review highlights the management of AF in the very elderly patients.

## Classification of AF

AF is classified as paroxysmal, persistent, longstanding persistent, and permanent.<sup>6</sup> Paroxysmal AF is defined as recurrent AF (two episodes) that terminates spontane-

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ously within 7 days. Episodes of AF of 48 hours duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes. Persistent AF is defined as continuous AF that is sustained beyond 7 days. Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after 48 hours of AF, but prior to 7 days, should also be classified as persistent AF episodes. Longstanding persistent AF is defined as continuous AF of greater than 12 months duration. The term permanent AF is not appropriate in the context of patients undergoing catheter or surgical ablation of AF, as it refers to a group of patients for which a decision has been made not to restore or maintain sinus rhythm by any means, including catheter or surgical ablation. If a patient previously classified as having permanent AF is to undergo catheter or surgical ablation, the AF should be reclassified.

## Pathophysiology of AF

Aging heart, characterized by myocardial fibrosis and atrial dilation, is a proper soil for AF to flourish. AF creates electrical and structural remodeling in the atria by shortening, mismatching, and lengthening the effective refractory period (increase of dispersion), depressing the intra-atrial conduction, and depriving its contractile function. Thus, "AF begets AF".<sup>7</sup> Structural heart disease enforces atrial chamber abnormality, and this explains the higher prevalence of AF in patients with underlying cardiovascular conditions.<sup>8,9</sup> Such conditions are valvular heart disease, hypertension, ischemic cardiomyopathy, dilated cardiomyopathy, and hypertrophic cardiomyopathy. Other less common causes are restrictive cardiomyopathies such as amyloidosis, constrictive pericarditis, cardiac tumors, and severe pulmonary hypertension.<sup>10</sup> Obstructive sleep apnea and obesity are independent risk factors for AF.<sup>11,12</sup> The electrical and structural remodeling determines the perpetuation of AF and the progression from paroxysmal to persistent and permanent forms. The longer one waits to initiate a rhythm treatment strategy, the more difficult it is to regain sinus rhythm.

## Diagnosis of AF

A single 12-lead electrocardiogram (ECG) is more than enough to set the diagnosis of AF. Because the elderly patients are often asymptomatic, AF is frequently a random finding.<sup>13</sup> If AF is suspected, repeated ECGs or ambulatory monitoring is advised. In the case of first-diagnosed AF, diagnostic evaluation should further continue with chest X-ray, transthoracic, or transesophageal echocardiography and blood tests, including thyroid hormones.<sup>14</sup>

## Management and treatment

The goals in the treatment and management of AF are, first, to prevent thromboembolic episodes, mainly strokes, which leads to a considerable reduction in mortality, and second, to improve the quality of life, by reducing the symptoms and hospitalizations. The first goal is achieved using anticoagulant therapy, and the second is achieved through rhythm or rate control. Newer techniques such as catheter ablation are rapidly establishing their role in treatment.

### Anticoagulation therapy in elderly patients

Elderly patients should be administered anticoagulation therapy for AF. Both CHADS<sub>2</sub> and the newer CHA<sub>2</sub>DS<sub>2</sub>-VASc scores<sup>15,16</sup> emphasize the importance of increased age in the evaluation of thromboembolic risk. Patients with CHADS<sub>2</sub>  $\geq 2$  should receive oral anticoagulation (OAC).<sup>15</sup> Patients with score 1 are subject to the physician's opinion to receive anticoagulants or aspirin. Using the newer CHA<sub>2</sub>DS<sub>2</sub>-VASc score, all patients older than 75 years should receive OAC, unless there is a strong contraindication.<sup>16</sup> The ATRIA<sup>1</sup> and BAFTA<sup>17</sup> studies have shown that elderly patients with AF benefited by the use of anticoagulation therapy. OACs have reduced the thromboembolic risk in these patients when compared to aspirin.<sup>1,17</sup> The OACs used in these studies were vitamin K antagonists (VKAs), especially warfarin. Maintaining an international normalized ratio (INR) between 2.0 and 3.0 is the target for thromboembolic protection. INR values more than 3.0 have not shown any advantage; on the other hand, they raised the risk of bleeding. The revised guidelines by Japanese Circulation Society (JCS) suggest a target INR of 1.6–2.6 for patients with nonvalvular AF and aged  $\geq 70$ .<sup>18</sup> INR should be monitored regularly, even if the patient is stable, and every one of them must keep an INR diary. VKAs were traditionally and incorrectly underused in the elderly patients by the physicians, fearing that this subgroup of patients would be eventually neglected and that INR monitoring would be skipped. Elderly patients are prone to injuries and falls, and thus the fear of bleeding is considerable in them. The HAS-BLED<sup>19</sup> and HEMMORR2HAGES<sup>20</sup> scores are valuable tools in evaluating these patients' bleeding risk. VKAs are connected to serum albumin. In the elderly patients, serum albumin levels often drop dramatically due to inflammation or malnutrition and lack of protein in their diets.<sup>21</sup> VKA overdose is frequent in these situations and hence INR should be monitored closely, every 15–21 days.

Novel oral anticoagulants (NOACs), on the contrary, do not require INR monitoring and are rapidly getting popular

even among the elderly. NOACS currently used in clinical practice include dabigatran which is a direct thrombin inhibitor, and rivaroxaban, apixaban, and edoxaban which are direct factor Xa inhibitors. Dabigatran at a dosage of 110 mg twice daily showed a reduced cerebral hemorrhage risk in the patients over 75 years old, but still maintained a smaller risk for thromboembolic events versus warfarin. However, at a dose of 150 mg twice daily, the risk of major bleeding was higher compared to VKAs and was found to increase with age.<sup>22</sup> Due to its renal elimination, dabigatran should be handled cautiously in patients with renal impairment and should be strongly contraindicated if creatinine clearance is below 30 mL/min.<sup>23</sup> Rivaroxaban in patients over 75 years old has shown noninferiority in comparison to warfarin in thromboembolic protection, as seen in the ROCKET-AF trial. Patients receiving rivaroxaban presented less intracranial hemorrhages and fatal bleeding.<sup>24</sup> These results applied even in the subgroup with moderate renal failure (clearance 30–49 mL/min). In such patients, the dosage of 15 mg once per day is suggested. Rivaroxaban is also contraindicated if creatinine clearance is below 30 mL/min. The AVERROES trial, which compared apixaban versus aspirin in patients who could not receive VKAs, was stopped because it showed clear superiority for apixaban.<sup>25</sup> Apixaban, administered 5 mg twice daily, was compared to warfarin in the ARISTOTLE trial. In the subgroup of patients over 75 years old, apixaban was more beneficial than warfarin in terms of thromboembolic protection and major bleeding events.<sup>26</sup> The dosage of 2.5 mg twice daily was administered to patients with two of the three following criteria: age  $\geq 80$  years, weight  $\leq 60$  kg, and serum creatinine  $\geq 133$   $\mu\text{mol/L}$ . Apixaban must not be administered in patients displaying creatinine clearance less than 30 mL/min. Edoxaban is administered once daily and has a renal excretion of 50%. In the Engage AF TIMI 48 trial, patients over 75 years of age receiving edoxaban in the highest dosage presented a reduction in strokes and other thromboembolic events, but also an increase in major bleeding events. On the other hand, the subgroup over 75 years old receiving low-dose edoxaban showed results similar to the warfarin group.<sup>27</sup> A recent meta-analysis showed that NOACS, compared to warfarin, lead to a significant reduction in strokes, intracranial hemorrhages, mortality, and comparable major bleeding events.<sup>28</sup> Their safety and relative efficiency have been consistent throughout a wide range of age groups including the elderly. They have fewer interactions with other drugs, they do not interact with food as VKAs do, and they present a rapid onset of action. However, they are related to a rise in gastrointestinal bleedings, their

cost is considerable, and their effects are still difficult to reverse.<sup>28</sup>

OAC therapy in elderly patients with AF and coronary artery disease (CAD) is challenging. In patients 75 years or older with AF after an acute coronary syndrome and revascularization, triple antithrombotic therapy (aspirin, clopidogrel plus oral anticoagulant) for a minimum of 4 weeks and up to a maximum of 6 months should be administered. Because of the high risk of bleeding in the elderly, the duration of this therapy should not last more than 4 weeks, and bare metal stent should be selected. Afterward, patients will continue treatment with dual therapy (antiplatelet agent plus oral anticoagulant) for 1 year. In such a case, clopidogrel plus VKA seems to have a better hemorrhagic profile than clopidogrel plus acetylsalicylic acid plus VKA, with no inferiority to stent thrombosis.<sup>29</sup> Patients 75 years or older with AF with stable CAD who underwent revascularization should receive triple therapy for 2–4 weeks and proceed to dual therapy for 1–12 months. Bare metal stenting should be preferred in such a case also. In patients without a revascularization procedure, a single treatment with VKAs or NOAC seems to be sufficient. It should be noted that newer antiplatelets are not yet approved in triple therapy and prasugrel is contraindicated in patients aged 75 and over.<sup>29</sup>

## Percutaneous left atrial appendage closure

As mentioned earlier, many patients, particularly the elderly, cannot tolerate or even refuse to receive chronic anticoagulation therapy. As an alternative to systemic anticoagulation, a new invasive procedure has been evolved, the percutaneous left atrial appendage (LAA) closure. Approximately 90% of the left atrial thrombi originate from the LAA, and its successful occlusion can significantly reduce the thromboembolic risk. Patients with nonvalvular AF, at high stroke risk and contraindications for OACs are possible candidates for this technique.<sup>30</sup> Contraindications to anticoagulants among others include acute clinically significant bleeding, gastrointestinal diseases such as esophageal varices, insufficiently treated neoplasms, peptic ulcer within last 3 months, decompensated liver disease or deranged baseline clotting screening, and hematological disorders such as unexplained and untreated anemia, myelodysplastic syndrome, and severe thrombocytopenia. Additional contraindications are vascular diseases or malformations, previous history of intracranial hemorrhage, and a high probability of injuries and traumas such as epilepsy, frequently noted in the elderly.<sup>30,31</sup>

Over the latest years, various percutaneous techniques and suitable devices have been used for LAA closure. Despite the promising long-term results, the initial device used for LAA closure (PLAATO, Medtronic, Mansfield, MA, USA) was pulled off the market.<sup>32</sup> In the PROTECT AF trial, the Watchman device (Boston Scientific, Marlborough, MA, USA) has been proven to be noninferior to warfarin regarding stroke risk, systematic embolism, and cardiovascular death and superior to warfarin for hemorrhagic stroke.<sup>33</sup> Then again, patients undergoing device implantation showed a four times higher complication risk, the most common risk being pericardial effusion. The mean age of the patients participating in the study was 71.7 years in the device arm and 72.7 years in the warfarin arm. In the PROTECT AF trial, the device arm received warfarin for 6 weeks after implantation.<sup>33</sup> After discontinuation of warfarin, clopidogrel and aspirin were administered for 6 months. Patients need to receive aspirin indefinitely. The ASAP study was designed to test the efficacy and safety of LAA closure in patients improper for warfarin administration.<sup>34</sup> Patients recruited for the study only received antiplatelet agent after implantation and had a mean age of  $72.5 \pm 7.4$  years. The main reason for warfarin ineligibility was history of hemorrhagic/bleeding tendencies. The ASAP study proved that LAA closure with the Watchman device could be safely performed without systemic OAC.<sup>34</sup> The Amplatzer Cardiac Plug (St Jude, Minneapolis, MN, USA) is a similar device with excellent results, but it has not been approved by the Food Drug Administration for LAA closure yet.<sup>35,36</sup> Implantation of the Lariat device (SentreHEART, Redwood City, CA, USA) requires closing a strangling noose around the LAA, advanced from the chest wall with a special sheath, after introducing a balloon in the LAA from the endocardium.<sup>37</sup> Newer devices, currently under investigation, are the Transcatheter Patch (Custom Medical Devices, Athens, Greece), AEGIS (AEGIS, Vancouver, Canada), and the Coherex WaveCrest (Coherex Medical, Salt Lake City, UT, USA).<sup>38</sup> Patients with AF at high stroke risk and with contraindications for OAC should be considered as candidates for LAA closure. Elderly patients often present these characteristics and could benefit from this novel therapy.

## Antiarrhythmic drugs in elderly patients

### Rate control

In the elderly patients, especially the asymptomatic ones, rate control is the first-line therapy.<sup>30</sup> As shown in the AFFIRM substudy,  $\beta$ -blockers are the most effective at achieving that goal.<sup>39</sup> Nondihydropyridine calcium channel

blockers (verapamil and diltiazem) can be administered as an alternative. Digoxin is recommended in acute heart failure,<sup>30</sup> but has been proven to be an independent risk factor for death in patients without heart failure and should be used cautiously in the elderly in whom renal function is delicate.<sup>40</sup> Amiodarone can also be used for rate control, but has considerable extracardiac side effects.<sup>41,42</sup> Strict rate control does not seem to improve morbidity and mortality,<sup>43</sup> and so appropriate use of these drugs is recommended in order to avoid excess bradycardia or atrioventricular block.

### Rhythm control

In an elderly patient with recurrences of AF despite receiving rhythm control medication, further attempts at restoring sinus rhythm are not suggested. Cardioversion, whether electrical or pharmaceutical, is related to serious side effects in the elderly and unless AF <48 hours, and OAC must be documented for at least 3 weeks. Electrical cardioversion requires anesthesia, while pharmaceutical cardioversion requires medication that has serious side effects and contraindications. Amiodarone is the safest choice in pharmaceutical cardioversion in the elderly. As featured in major studies, no significant difference in survival was found using rhythm or rate control in patients older than 65 years with at least one stroke risk factor.<sup>30,39,44</sup> While there is a wide range of antiarrhythmic agents used to maintain sinus rhythm, in the elderly, there are limitations because of their coexisting heart, renal, or hepatic diseases. Antiarrhythmic agents have been associated with serious adverse side effects, particularly the induction of proarrhythmia. Proarrhythmia, caused by class I and III agents, is manifested as a rise in ventricular ectopy, QT interval prolongation, polymorphic ventricular tachycardia (torsades de pointes), monomorphic ventricular tachycardia, or excess bradycardia. Studies have shown that quinidine, flecainide, sotalol, and dofetilide are the antiarrhythmics most prone to ventricular proarrhythmia.<sup>45,46</sup> Class I antiarrhythmic drugs are generally not recommended in the elderly. Class Ia agents, including quinidine, procainamide, and disopyramide, are not used anymore for the prevention of AF.<sup>42</sup> As observed in the CAST study,<sup>47</sup> flecainide, among other Ic drugs, increased mortality in comparison to placebo, in patients who suffered myocardial infarction. Therefore, flecainide and propafenone must be given to patients without structural heart disease. Administration of these drugs to the elderly must be performed cautiously, given the high probability of underlying CAD. When administered in outpatients, QRS duration must be monitored closely: QRS widening must not exceed 150% of the baseline QRS.<sup>6,15</sup> Exercise testing should be performed

1 or 2 weeks after initiation, as it may disclose QRS widening at high rates, or exercise-induced proarrhythmia.<sup>6,15,30,42</sup> In the case of CAD without heart failure, sotalol, dofetilide, amiodarone, and dronedarone (class III antiarrhythmic agents) can be used for maintaining sinus rhythm.<sup>6,15,30,42</sup> Dronedarone should be given cautiously to the elderly.<sup>48</sup> The PALLAS study has shown that dronedarone has been related to an increased risk of cardiovascular events in the following groups of patients: 1) 65 years or older with permanent AF and either CAD, previous stroke, or heart failure and 2) 75 years or older with hypertension and diabetes.<sup>48</sup> Patients with AF and heart failure or left ventricular dysfunction are limited to amiodarone and dofetilide. Those with substantial left ventricular hypertrophy (left ventricular wall thickness  $\geq 13$  mm) can only receive amiodarone.<sup>6,15</sup> When class III agents are administered, QTc interval must be monitored and must remain below 520 ms. In any case of antiarrhythmic drug use, follow-up must include measurement of serum creatinine, potassium, and magnesium regularly. Renal impairment can increase proarrhythmia and also requires dosage adjustment of dofetilide and sotalol.<sup>6,15,30,42</sup>

## Catheter ablation of AF in the elderly

Left atrial catheter ablation has lately proven to be a considerable therapeutic option in maintaining sinus rhythm in patients suffering from AF.<sup>49</sup> However, AF catheter ablation has not been yet commonly established in the elderly population.<sup>30</sup> Due to concerns about efficacy and safety of

this method, patients aged 75 years and over were previously excluded from many catheter ablation trials.<sup>50,51</sup> So far, the main volume of data concerning the safety and efficacy of left atrial ablation has been derived from studies and trials focused on younger patients without heart disease or comorbidities.<sup>52</sup> Catheter ablation is strongly contraindicated in patients with thrombus in the left atrium or in patients who cannot receive anticoagulation for at least 6–8 weeks after the procedure. In a large worldwide survey, major complications of catheter ablation, including death, cardiac tamponade, strokes, and transient ischemic attacks were reported in 4.5% of cases.<sup>53</sup> Then again, rate control strategy in the elderly may induce extreme bradycardia, while antiarrhythmic drugs used to achieve rhythm control are prone to proarrhythmia and drug interactions.

Evolution in AF ablation techniques and improved efficacy have given the elderly patients an alternative treatment for AF.<sup>54</sup> Recent studies, including our experience, have demonstrated similar rates of success and adverse events using radiofrequency catheter ablation between the elderly and younger patients.<sup>55–61</sup> Table 1 summarizes the main findings of these studies. There are some obvious disadvantages of this method. Some patients may relapse and so a second procedure will be required in order to maintain normal sinus rhythm.<sup>62</sup> Also, the need for anticoagulation<sup>63</sup> and detection of asymptomatic AF episodes<sup>61</sup> will have to be further evaluated. Cryoballoon ablation also seems to be a promising technique. The main advantage over radiofrequency ablation

**Table 1** Summary of studies addressing the role of catheter ablation of AF in the elderly patients

Study	Number of patients	Technique	AF type	Compared age groups (years)	Success rate (%)	Major complications in the elderly (%)
Zado et al <sup>55</sup>	32	PVI plus ablation of focal sources	PAF PersAF	<65	89	2.9
				65–74	84	
				>75	86	
Bhargava et al <sup>56</sup>	103	PVI	PAF PersAF PermAF	>60	82	3
				51–60	83	
				<50	85	
Kusumoto et al <sup>57</sup>	61	PVI	PAF PersAF	>75	61	0
				65–75	84	
Tan et al <sup>58</sup>	49	PVAI	PAF PersAF PermAF	>80	70	0.04
				70–79	72	
				60–69	74	
Bunch et al <sup>59</sup>	35	PVAI plus linear lesions	PAF PersAF	>80	75	0.057
				<80	78	
Liu et al <sup>60</sup>	2,970	PVAI	PAF PersAF PermAF	>60	77	4.53
				>60	79	
Lioni et al <sup>61</sup>	95	PVAI	PAF	$\geq 65$	58	3.2
				<65	67	

**Abbreviations:** AF, atrial fibrillation; PAF, paroxysmal atrial fibrillation; PersAF, persistent atrial fibrillation; PermAF, permanent atrial fibrillation; PVI, pulmonary vein isolation; PVAI, pulmonary vein antral isolation.

is the lower risk of pulmonary stenosis or esophageal injury. The most common complication of the latter technique is phrenic nerve palsy.<sup>64</sup>

Atrioventricular node (AVN) ablation and pacemaker implantation is a last resort treatment in the elderly patients, especially the highly symptomatic ones. As shown in the PABA-CHF study, left atrial catheter ablation was superior to AVN ablation with biventricular pacing in patients with heart failure who had drug-refractory AF.<sup>65</sup> Hsieh et al<sup>66</sup> compared the long-term results of elderly patients with medically refractory paroxysmal AF to either AVN ablation plus single-chamber pacemaker or catheter ablation of AF.<sup>66</sup> AF was better controlled in the group with AVN ablation and pacemaker implantation than in the group with AF ablation.<sup>66</sup> However, AVN ablation and pacemaker implantation was associated with a higher incidence of persistent AF and heart failure than catheter ablation of AF in the very long-term follow-up.

## Upstream therapies

Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins, and omega-3 polyunsaturated fatty acids have been related to a reduction in the relative risk in AF. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers display favorable effects on electrical and structural left atrial remodeling.<sup>67,68</sup> The use of statin seems to prevent the onset of AF after open heart surgery.<sup>69</sup> The positive results of statins are possibly mediated through their anti-inflammatory and antioxidant actions.<sup>69</sup> Polyunsaturated fatty acids have direct ion channel and anti-inflammatory effects. It is suggested that they can contribute to the prevention of AF when used in combination with an antiarrhythmic drug.<sup>70,71</sup>

## Conclusion

Over the past decades, novel medications and therapies have been administered to the elderly patients with AF. This subgroup of patients who were neglected and undertreated now occupy the center stage. Therapies must be tailored to elderly patients, with particular attention to structural heart disease and renal failure. Elderly patients are at increased risk for thromboembolic events. Thromboembolic protection is therefore of major importance in this population. Newer anticoagulants are increasing in popularity among the elderly patients without renal failure. Elderly patients with contraindications to OAC are possible candidates for percutaneous LAA closure. Left atrial catheter ablation should be considered in symptomatic elderly patients before AVN ablation and pacemaker implantation.

## Disclosure

The authors report no conflicts of interest in this work.

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