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EDITORIAL COMMENT

The ATHERO-AF Study

A Need to Optimize AF Management in an Environment of Medical Advancement*

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Atrial fibrillation (AF) is the most common cardiac arrhythmia with worldwide impact and high frequency with increasing age.[1] AF is associated with an increased incidence of stroke and systemic embolism (SSE), and mortality.[2] The ATHERO-AF prospective cohort study conducted by Menichelli et al[3] from the Sapienza University based in Rome, Italy, provides insight into the frequency and causes of hospitalization in a predominantly elderly population with AF. Understanding the causes of hospitalization creates the potential to lower hospitalization rates. The ATHERO-AF study enrolled 2,782 patients with AF, mean age 74.6 years, evenly divided by gender, with a mean follow-up of 31 months. The rate of all-cause hospitalization was 12.9% per year. The causes of hospitalization were classified as cardiac, respiratory, cancer, trauma, bleeding, cerebrovascular, infection, or surgery-related. Cardiac hospitalizations were defined as those not related to AF and were acute coronary syndromes, heart failure, systemic embolism, hypertensive urgency, requiring vascular/cardiac surgery, and then those that were AF-related. AF-related hospitalization was defined as recurrence of AF in patients with paroxysmal AF or high ventricular rate symptomatic AF episodes in patients with persistent/permanent AF. Cardiovascular-related hospitalizations for the full period of observation totaled 44.2%, of which 37.0% were AF-related.

Treating AF is directed at restoring and maintaining normal sinus rhythm at an optimal ventricular rate to reduce the risk of SSE and to optimize cardiac function by optimizing heart rate. The U.S. and European guidelines[4,5] emphasize achieving symptom relief rather than a strict numerical target. The U.S. guidelines aim for a resting heart rate of <110 beats/min in asymptomatic patients with stable ventricular function and <80 beats/min in symptomatic patients or those with left ventricular dysfunction. Heart rate control is usually achieved with beta-blockers and nondihydropyridine calcium channel blocker agents (verapamil/diltiazem). Antiarrhythmic medications with or without cardioversion and or AF ablation restore and maintain normal sinus rhythm.

An important focus of the ATHERO-AF study is evaluating the hospitalization risk of patients' prescribed medications for rate and rhythm control. Digoxin and beta blockers were not associated with an increased risk of AF-related or cardiovascular hospitalization. In contrast, verapamil/diltiazem use was associated with an increased risk of AF-related hospital admission (HR: 2.067; 95% CI: 1.117-3.825; $P = 0.021$) in patients with permanent/persistent AF. Class 1C antiarrhythmic agents, flecainide and propafenone (HR: 1.947; 95% CI: 1.069-3.548; $P = 0.029$), were associated with an increased risk of hospitalization in paroxysmal and persistent/permanent AF. Amiodarone (HR: 3.012; 95% CI: 1.835-4.943; $P < 0.001$) was associated with a significant increase in hospitalization risk in patients with persistent/permanent AF but not in patients with paroxysmal AF (HR: 1.045; 95% CI: 0.584-1.872; $P = 0.881$). These

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TABLE 1 Drug-Drug Interactions and DOAC Dosing

	Dabigatran[20,21]	Rivaroxaban[20,21]	Apixaban[20,21]	Edoxaban[20,21]
Usual dosing	150 mg twice daily	20 mg once daily	5 mg twice daily	60 mg once daily
Dose reduction (use with caution)	75 mg twice daily for patients with CrCl 30-50 mL/min and concomitantly prescribed P-gp inhibitors such as: • Dronedarone • Propafenone • Ranolazine • Amiodarone • SSRIs/SNRIs	Dose reduction is not required for patients prescribed a P-gp inhibitor.	2.5 mg twice daily in patients concomitantly prescribed CYP3A4 and P-gp inhibitors.	Dose reduction is not required for patients prescribed a P-gp inhibitor.
Avoid use	Avoid use with strong inducers of CYP3A4 and/or P-gp: • Rifampin • Carbamazepine • Phenobarbital • Phenytoin			
Contraindications	Exclude patients with ClCl <30 mL/min who are prescribed concomitant therapy with the P-gp inhibitors	Exclude patients with ClCl 15-30 mL/min who are prescribed p-gp and moderate CYP3A4 inhibitors or with normal kidney function prescribed both a strong CYP3A4 and P-gp inhibitors	Exclude patients prescribed with both strong CYP3A4 and P-gp inhibitors.	Exclude patients prescribed: • Antiplatelet agents (aspirin, clopidogrel, prasugrel, and ticagrelor) • SSRIs/SNRIs • Chronic NSAIDs

CYP3A4 = cytochrome P450; DOAC = direct oral anti-coagulant; NSAID = nonsteroidal anti-inflammatory drug; P-gp = P-glycoprotein; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor.

results align with publications in which antiarrhythmic drugs did not offer a survival advantage over rate control.[6,7] This study suggests a need to optimize the use of antiarrhythmic agents.

A limitation of the ATHERO-AF study was the failure to include the impact of interventions, eg, electrical cardioversion and catheter ablation. Catheter ablation reduces AF recurrence and improves quality of life, favorably affecting hospitalization rates.[8]

Anticoagulation contributes to hospitalization rates. Warfarin[9] and direct oral anticoagulant (DOAC) particularly as demonstrated in comparisons against warfarin, minimize the risk of SSE very effectively.[10-13] The U.S. and European guidelines emphasize DOAC dosing relative to kidney function.[10-13] The exception in the United States is the reduced dose of dabigatran 75 mg twice a day, which was approved based on pharmacokinetic data, later validated in renally impaired patients,[14] and retrospectively evaluated,[15] thus creating a need to evaluate dabigatran 75 mg twice a day prospectively. In the ATHERO-AF study, patients prescribed DOACs had a reduced risk of cardiovascular events (HR: 0.586; $P < 0.001$) and AF-related hospitalizations (HR: 0.318; $P < 0.001$), highlighting the advantages of DOACs over vitamin-K antagonists (VKAs).[10-13] The DOACs, dabigatran 150 mg twice a day and apixaban 5 and 2.5 mg twice a day, were superior to warfarin,[11,13] while rivaroxaban and edoxaban were noninferior.[12,16] All DOACs had much lower rates of neurological bleeds.[11-13,16] DOACs, except for apixaban, had higher non-neurological bleed rates compared to warfarin.[11] The lower hospitalization in the ATHERO-AF study in patients prescribed DOACs compared to VKA are limited by the failure to report the time in therapeutic range for the VKA group. Another limitation of ATHERO-AF is using the HASBLED score to predict hospitalization. Higher HASBLED score is correlated with higher cardiovascular hospitalization rate. The HASBLED score was developed in patients prescribed a VKA and never validated for DOAC use. Subsequently, a DOAC score was developed as a better predictor of bleeding than the HASBLED score in patients with AF prescribed a DOAC.[17,18] It would be interesting to correlate the DOAC score with the hospitalization risk.

Drug interactions involving antiarrhythmic drugs and other medications used in elderly patients with AF and polypharmacy need evaluation.[19] Warfarin has multiple drug interactions.[9] Drug interactions with DOACs are less frequent but include the use of concomitant P-glycoprotein inducers or CYP3A4 inducers (**Table 1**).

Control of blood pressure, diabetes, and the definition of type of cancer are important omissions when evaluating admission rates.

In conclusion, the ATHERO-AF study highlights several areas for further research. There is a need for

randomized controlled trials to validate the observational findings by optimizing medication use and alternative treatment strategies (**Table 1**).

The ATHERO-AF study provides insights regarding a personalized approach to AF management. Future research should validate the findings in the current environment of major medical advances that have prolonged life.

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Dr Ezekowitz is a LIBREXIA-AFIB trial (A Study of Milvexian Versus Apixaban in Participants With Atrial Fibrillation) national leader; his role is limited to finding supporting sites for other investigators to enroll patients; and he is also a consultant for Alta Thera, Pharmaceuticals, Johnson and Johnson, and the Sharpe Strumia Foundation of Bryn Mawr Hospital. The Sharpe Strumia Foundation of Bryn Mawr Hospital provided support to cover administrative expenses related to the development of the editorial. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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