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REVIEW

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Atrial fibrillation management in older heart failure patients: a complex clinical problem

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ABSTRACT

Background: Atrial fibrillation (AF) and heart failure (HF), two problems of growing prevalence as a consequence of the ageing population, are associated with high morbidity, mortality, and healthcare costs. AF and HF also share common risk factors and pathophysiologic processes such as hypertension, diabetes mellitus, ischemic heart disease, and valvular heart disease often occur together. Although elderly patients with both HF and AF are affected by worse symptoms and poorer prognosis, there is a paucity of data on appropriate management of these patients.
Methods: PubMed was searched for studies on AF and older patients using the terms atrial fibrillation, elderly, heart failure, cognitive impairment, frailty, stroke, and anticoagulants.
Results: The clinical picture of HF patients with AF is complex and heterogeneous with a higher prevalence of frailty, cognitive impairment, and disability. Because of the association of mental and physical impairment to non-administration of oral anticoagulants (OACs), screening for these simple variables in clinical practice may allow better strategies for intervention in this high-risk population. Since novel direct OACs (NOACs) have a more favorable risk-benefit profile, they may be preferable to vitamin K antagonists (VKAs) in many frail elderly patients, especially those at higher risk of falls. Moreover, NOACs are simple to administer and monitor and may be associated with better adherence and safety in patients with cognitive deficits and mobility impairments.
Conclusions: Large multicenter longitudinal studies are needed to examine the effects of VKAs and NOACs on long-term cognitive function and frailty; future studies should include geriatric conditions.

Keywords: Atrial fibrillation, Cognitive impairments, Elderly, Frailty, Heart failure, Oral anticoagulants

Background

Atrial fibrillation (AF) is a global healthcare problem, currently affecting 2.5% of the population worldwide, its prevalence steeply increases with age (1), ranging from 9% between 76-85 years to >10% over 85 years (2) and it is expected to increase in the future (1). Although not directly life threatening, AF affects quality of life as a direct cause of left ventricular dysfunction (LVD), heart failure (HF), hospitalizations, disability, cognitive impairment (CI), and stroke.

The annual incidence of stroke in people with AF is approximately 5%, which is 2 to 7 times higher than the average rate of stroke in the general population, depending on the presence of other risk factors and age, ranging from 1.5% in patients aged 50 to 59 years to 23.5% in patients aged 80 to 89 years (3). Strokes associated with AF are mostly cardioembolic, tend to be more severe, and result in longer hospital stays and greater disability than atherothromobotic strokes not associated with AF, with an average mortality risk that is two-fold higher (4).

Similar to AF, HF is a significant and growing epidemic and its prevalence increases with age. AF and HF share several common risk factors and pathophysiologic processes such as hypertension, diabetes mellitus, ischemic heart disease, and valvular heart disease. Beyond sharing predisposing factors, AF and HF are closely intertwined, with each disease predisposing to the other. When present in combination, AF and HF portend a worse prognosis than either condition alone, with a four-fold increased risk of systemic thromboembolism events per year, while asymptomatic LVD is predictive of developing AF (5). In Framingham Heart Study participants with new-onset AF, 37% had HF and conversely, 57% individuals with new HF had AF (6).

General aspects

Several comorbidities are associated with AF, such as hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, CI, cerebrovascular disease. The symptoms

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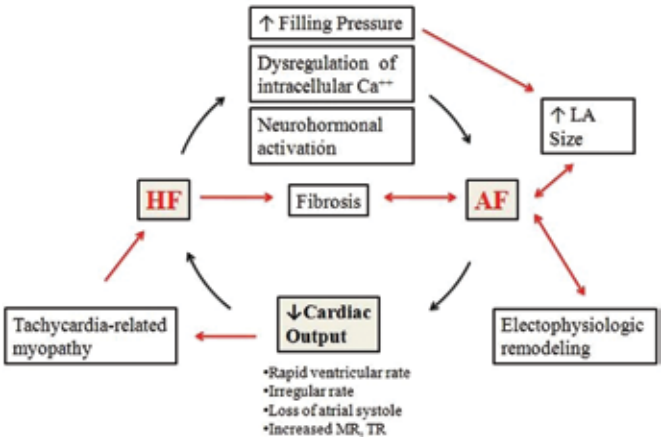

Fig. 1 - Common pathophysiological mechanisms and interactions between atrial fibrillation (AF) and heart failure (HF). LA = left atrium; MR = mitral regurgitation; TR = tricuspid regurgitation.

of AF vary widely between patients and range from none to severe and functionally disabling. The most common symptoms are palpitations (42%-55%), fatigue (15%-49%), dyspnea (24%-49%), and angina (10%-20%) (7). Only 12%-25% of patients are asymptomatic (7), more commonly elderly patients; asymptomatic or minimally symptomatic AF patients are not prompted to seek medical care and can initially be seen with a thromboembolic complication such as stroke or HF.

Clinical features and pathophysiologic pathways include the loss of atrial contraction, which can decrease cardiac output by up to 25% (8), atrioventricular dyssynchrony, and rapid and irregular ventricular rates, which result in negative consequences on diastolic and systolic function, as well as increased myocardial oxygen demands and an increased risk of tachicardiomyopathy (Fig. 1).

On the other hand, activation of the renin-angiotensin-aldosterone system (RAAS) and maladaptive physiological changes lead to increased left ventricular filling pressure (LVFP); increased LVFP is transmitted to the left atrium, causing fibrosis and increasing atrial stretch, which will finally lead to conduction abnormalities and proarrhythmic remodeling of the atrial chamber (9). Elevated atrial pressure is further increased when secondary mitral regurgitation develops along with LV remodeling (Fig. 1).

Rate versus rhythm control in HF patients with AF

Despite evidence from registries and study subsets suggesting adverse outcomes with HF and prevalent AF, the benefit of a rhythm control strategy versus rate control has never been established. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) (10) and the Atrial Fibrillation in Congestive Heart Failure (AF-CHF) (11) trials demonstrated similar all-cause HF incidence, hospitalization, and overall mortality in both rhythm control and rate control groups, although only 23% of patients in AFFIRM had clinical HF, so generalization of the results to the HF population should be made with caution. There are several reasons to explain the lack of improvement of survival with rhythm control, including imperfect effectiveness of normal sinus rhythm maintenance and adverse effects of current pharmacological therapy. Moreover, the Rate Control Efficacy in Permanent Atrial Fibrillation (RACE II) trial showed no differences in functional outcomes, hospital admissions, or symptoms in patients with AF treated to a more lenient heart rate regime (<110 beats/min resting heart rate) versus a stricter rate control (<80 beats/min resting heart rate) (12).

Catheter ablation has been shown to significantly improve freedom from AF in patients who have failed antiarrhythmic drugs, but there is a lack of evidence of its feasibility in older HF patients, as most patients included in trials were relatively young, with little co-morbidity, and normal to mildly reduced left ventricular ejection fraction (LVEF) (13).

Thromboembolic risk and oral anticoagulation therapy

Different studies have shown that oral anticoagulants (OACs) are much more effective than antiplatelet therapy in reducing the risk of stroke, particularly in elderly patients (14, 15). An analysis of the Atrial Fibrillation Investigators database, including 8932 patients from 12 trials, showed that with increasing age the relative efficacy of antiplatelet therapy to prevent ischemic stroke appears to decrease, whereas it does not change for OACs. Because stroke risk increases with age, the absolute benefit of OACs increases as patients get older, despite a significantly increased risk of serious bleeding (16). However, despite benefits, studies have shown that OACs are underused in AF, especially in older patients (17), due to uncertainty concerning the risk of stroke and the risk of bleeding.

There are several reasons for physicians to withhold therapy with OACs in older patients, including frailty, a high prevalence of chronic diseases and comorbidities, polypharmacy, adverse drug reactions, and changes in pharmacokinetics and pharmacodynamics. Risk of falls is also perceived as a reasonable factor for withholding OACs as it may increase the risk of intracranial bleeding, but it has been demonstrated that it should not prevent treatment in elderly patients with AF. Nevertheless, despite patients with many comorbidities and polypharmacotherapy being less commonly represented in clinical trials, these frail elderly patients for whom decisions regarding anticoagulation are a matter of concern are a significant proportion of the patients seen by physicians in their everyday practice.

Direct oral anticoagulants in older AF patients

Novel direct OACs (NOACs) have been extensively investigated across multiple randomized trials in AF. All studies have demonstrated at least non-inferiority when compared with traditional vitamin K antagonists (VKAs) with no increase in stroke risk or bleeding (Tab. I). All of these trials enrolled relatively large proportions of elderly (31.2-43.7%) and HF patients (32%-63%), with only small interstudy discrepancies in the criteria for diagnosis of HF.

Detailed subgroup analysis in the major NOAC trials showed similar benefit in the subgroups with HF with reduced (HFrEF) and preserved LVEF (HFpEF) compared to the total study population (18-21). For example, an analysis from the Apixaban for Reduction in Stroke and Other Thromboembolic

TABLE I - Characteristics of the populations enrolled in NOAC studies

	RE-LY (18)	Rocket AF (19)	Aristotle (20)	Engage (21)
Drug	Dabigatran 150 mg bid	Rivaroxaban 20 mg od	Apixaban 5 mg bid	Edoxaban 60 mg od
$CHADS_2$ score				
Mean	2.2	3.48	2.1	2.8
≥3, % (n)	32.6	87.0 (12287)	30.2	-
4-6, % (n)	-	44.0 (6131)	-	22.9
Previous TIA/stroke, %	20.3	54.9	19.2	28.1
Hypertension, %	78.9	90.3	87.3	93.7
Diabetes, %	23.1	40.4	25	36.4
Heart failure, %	31.8	62.6	35.5	58.2
Age >75, %	40	43.7	31.2	40.5
ASA use, %	39.0	37.0	31.3	29.4

ASA = aspirin; bid = twice daily; $CHADS_2$ = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke or transient ischemic attack; od = once daily; NOAC = novel direct oral anticoagulant; TIA = transient ischemic attack.

Events in Atrial Fibrillation (ARISTOTLE) study compared patients with LVEF <40% to those with LVEF >40%, and found no difference in the risk of embolic events in warfarin-treated patients, nor in subsequent reduction of risk with apixaban (22).

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (23, 24) included patients with a mean $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke or transient ischemic attack) score of 2.2 and a mean age of 71.5 years. More than one-third of study patients were older than 75 years. There was a significant treatment-by-age interaction for major bleeding. In patients aged ≥75 years, dabigatran 150 mg twice daily (bid) resulted in a similar reduction in stroke and systemic thromboembolism compared with warfarin (1.4%/year vs. 2.1%/year, hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.66-1.17; p = 0.81). However, when compared with warfarin, dabigatran 150 mg bid was associated with a trend toward more major bleeding in patients ≥75 years (5.1%/year vs. 4.3%/year, p = 0.07); in the same subgroup of patients, dabigatran 110 mg bid resulted in a similar major bleeding rate compared with warfarin (4.43%/year vs. 4.37%/year, p = 0.89).

The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) included patients with a mean $CHADS_2$ score of 3.5 and a median age of 73 years with 62.1% prevalence of HF (19). In patients aged ≥75 years, rivaroxaban resulted in a similar reduction in stroke and systemic thromboembolism compared with warfarin (2.3%/year vs. 2.8%/year, HR 0.80; 95% CI, 0.63-1.02; p = 0.3). There was no treatment-by-age interaction for major bleeding, with similar rates of bleeding with rivaroxaban and warfarin in each age stratum, despite a not significant trend toward more major bleeding in patients ≥75 years (4.8%/year vs. 4.4%/year, HR 1.1; 95% CI, 0.92-1.34; p = 0.3).

The ARISTOTLE trial included patients with mean $CHADS_2$ score of 2.1 and a median age of 70 years. The dose of apixaban, 5 mg bid, was reduced to 2.5 mg bid in patients with two of the following characteristics: age ≥80 years, weight ≤60 kg, and creatinine ≥1.5 mg/dL (20). In patients aged 75 years, apixaban resulted in a higher reduction in stroke and systemic thromboembolism compared with warfarin (1.56%/year vs. 2.19%/year, HR 0.71; 95% CI, 0.53-0.95). Apixaban was associated with a lower risk of major bleeding in both patients <75 years (1.99%/year vs. 2.82%/year, HR 0.71; 95% CI, 0.56-0.80) and in patients aged 75 years (3.33%/year vs. 5.19%/year, HR 0.64; 95% CI, 0.52-0.79) when compared with warfarin (25). Apixaban was also associated with greater efficacy and safety with increasing age in all major end-points of the study suggesting a significant net clinical benefit in the elderly population. Moreover, no significant interaction with apixaban dose (i.e. 2.5 vs. 5.0 mg) was found with respect to treatment effect on major outcomes (25) (Fig. 2).

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction (ENGAGE-TIMI) 48 trial included patients with a mean $CHADS_2$ score of 2.8 and a median age of 72 years (21). The edoxaban dose was reduced by half in patients with reduced renal function (30-50 mL/min), weight ≤60 kg, or with concomitant use of verapamil, quinidine, or dronedarone. Edoxaban 60 mg daily was associated with a lower risk of major bleeding among patients aged <75 years compared with warfarin, and similar rates among those aged ≥75 years (edoxaban 60 mg; 4%/year vs. 4.8%/year, absolute risk reduction 0.8% and edoxaban 30 mg; 2.3%/year vs. 4.8%/year, absolute risk reduction 2.6%) (26).

Barco et al (27) reviewed the risks and benefits of NOACs compared with VKAs in elderly subgroups of patients enrolled in phase 3 randomized trials. The results confirmed that the favorable balance between risks and benefits of NOACs is preserved in the elderly population. The absolute risk reductions are higher in elderly than in younger patients due to the higher absolute risks. Although interpretations of subgroup analyses should always be made with caution, the proportion of patients aged ≥75 years was consistently over 40%, which

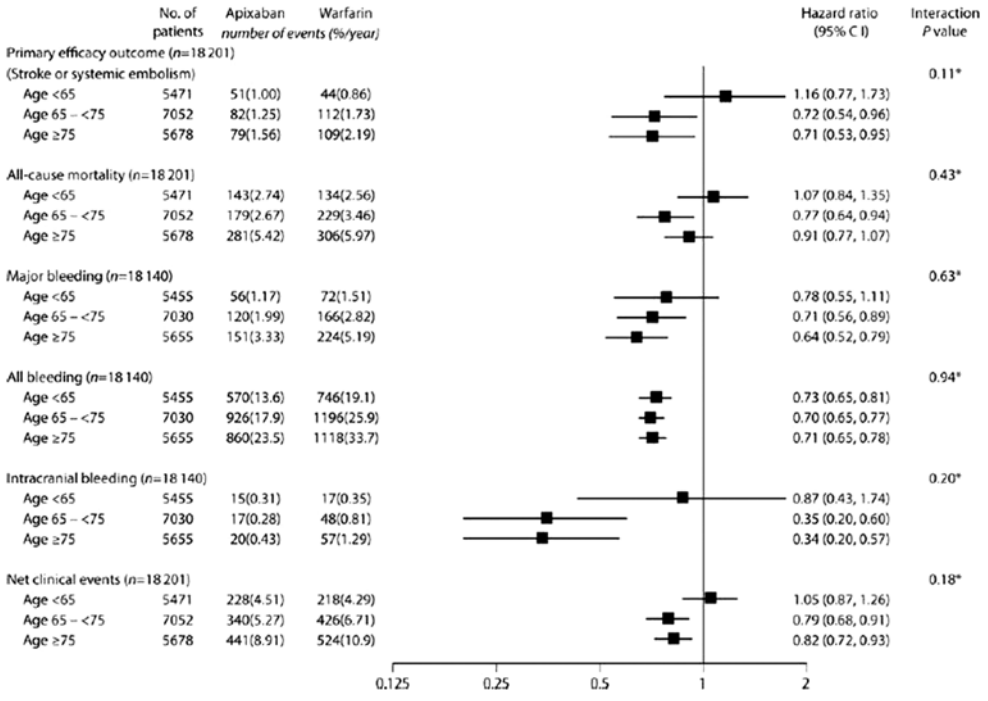

Fig. 2 - The effect of apixaban versus warfarin on major study outcomes according to age in the ARISTOTLE study. *Interaction p values are based on continuous age. Modified from (25): Halvorsen S, Atar D, Yang H, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. Eur Heart J. 2014;35(28):1864-1872, by permission of Oxford University Press.

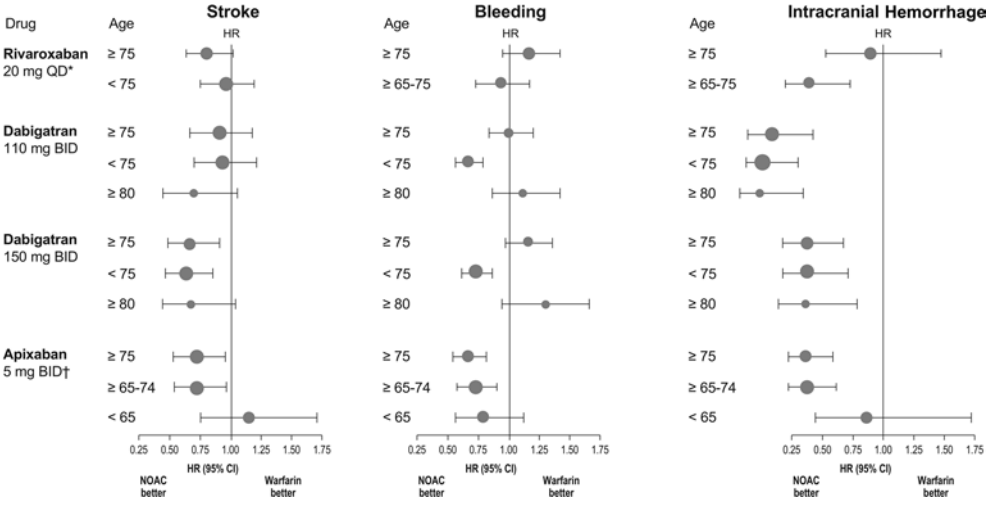

Fig. 3 - Primary efficacy outcome of stroke or systemic embolism, major bleeding and intracranial hemorrhage in phase 3 randomized controlled trials comparing a NOAC with vitamin K antagonists in patients with atrial fibrillation according to age. BID = twice daily; HR = hazard ratio; NOAC = novel direct oral anticoagulant; QD = once daily. Modified from (27): Best Pract Res Clin Haematol, Vol. 26, No. 2, Barco S, Cheung YW, Eikelboom JW, Coppens M. New oral anticoagulants in elderly patients, pp. 215-224, Copyright (2013), with permission from Elsevier.

provides considerable power to explore age subgroups (27) (Fig. 3).

As reduced LVEF is independently associated with stroke, the combination of HF with AF increases significantly the risk of stroke compared with AF alone. Although no trials have investigated this specific population, indirect sub-group data from the NOACs randomized trial suggest that the effect of anticoagulation for AF is similar in patients with concomitant HF (15, 18-21), and NOACs are particularly attractive in these patients due to more favorable net clinical benefit compared to VKA therapy.

In conclusion, in patients aged ≥75 years with HF, NOACs have a favorable risk-benefit profile compared with warfarin for prevention of stroke and systemic thromboembolism.

Frailty and cognitive dysfunction as markers of complexity in older patients with AF

In advanced age, global health status results from a complex and dynamic interaction between different areas: the changes related to 'normal' ageing, disease severity, comorbid conditions, and social and environmental factors (28). The three main geriatric conditions, frailty, comorbidity, and disability, are frequent in older HF and AF patients (28). Disability is defined as difficulty or dependency in carrying out activities essential to independent living, including essential roles, tasks needed for self-care and living independently at home.

Frailty is common in older people and is clinically recognized as a syndrome of loss of reserves that enhances

vulnerability to stressors (e.g. acute illnesses, hospitalizations, medical procedures), thus increasing the risk for major events and disability. Because it reflects biological rather than chronological age, frailty may explain substantial heterogeneity in clinical outcomes within older patients (29, 30). Multiple physiological factors are thought to be involved in the development of frailty, including dysregulation of the immune, hormonal, and endocrine systems. Notably, cardiovascular diseases and frailty share several commonalities, particularly a consistent correlation with the upregulation of inflammatory cytokines. Frailty can be evaluated in many ways and several multi-item indices have been proposed for diagnosis of frailty (31, 32). In contrast to multi-item frailty scales, 4-meter gait speed, and to a lesser extent handgrip strength, has been advocated as a single-item measure of frailty that often outperforms more elaborate and time-consuming scales. Chaudhry et al (33) showed that in HF patients slow gait speed and weak grip strength were powerful predictors of hospitalizations, and in a recent study, we found that slow gait speed is independently associated with death, hospitalization for HF, and all-cause hospitalization in older HF patients (34).

The relationship between frailty and AF is also complex. Fumagalli et al (35) have suggested that AF may be a marker of frailty in the elderly, and Marzona et al (36) have reported a loss of independence in performing activities of daily living in a follow-up study of AF elderly patients.

Cognitive impairment is also frequent in older HF and AF patients; both HF and AF represent risk factors for significant cognitive decline, through a multitude of pathways including a hypercoagulable and proinflammatory state, thromboembolic events, cerebral microinfarcts and microbleeds, cerebral hypoperfusion with consequent chronic hypoxic injury secondary to impaired cerebrovascular reactivity, reduced cardiac output combined with hypotension, and cycle length beat-to-beat variability (37).

The Mini Mental Status Examination (MMSE) is the most commonly used cognitive function test. Scores <24 are suggestive of dementia, but the MMSE has a low sensitivity for mild CI. The Montreal Cognitive Assessment (MoCA) was developed as a screening tool for early cognitive decline, and was found to have a sensitivity of 90% in identifying mild CI compared with a sensitivity of only 18% with the MMSE (38).

Vascular CI, as seen in AF patients with stroke and transient ischemic attack, is associated with deficits in executive function, attention, and speed of information processing more than other domains, and MoCA has been shown to be superior to the MMSE in identifying CI.

In older patients, previous stroke is associated with a two-fold increase in the risk of developing dementia, but AF is thought to play a role in cognitive decline beyond stroke; it is less clear whether this association is directly related to AF itself or to an aging population with multiple comorbidities (39).

In a subgroup of patients of the Cardiovascular Health Study (mean age >65 years), Thacker et al (40) found that MMSE scores declined faster after incident AF compared with no prior AF; the 5-year decline in mean MMSE score from age 80 to age 85 was -6.4 points for participants without a history of AF, but was -10.3 points for participants experiencing incident AF at age 80.

A similar link among AF, CI, and disability can be found in HF patients. Recently, Alosco et al (41) examined the associations among AF, cognitive function, and cerebral perfusion in 187 patients with HF and found that HF patients with AF exhibited worse global cognition, memory, and cerebral blood flow velocity and that decreased cerebral blood flow velocity predicted worse cognition in multiple domains in these patients, but not in those with heart failure and no AF.

In a cohort of patients with newly diagnosed HF from the Cardiovascular Health Study (mean age 78.7 years), 23% subsequently developed disability. Factors independently associated with disability included impaired gait speed (HR 2.29, 95% CI 1.34-3.90); impaired cognition (HR 1.87, 95% CI 1.14-3.05); and depressive symptoms (HR 1.72, 95% CI 1.04-2.83), suggesting that geriatric variables affect prognosis and quality of life in older HF patients (42).

In a recent observational survey, we studied the relation between AF, CI, frailty and disability in 331 elderly HF patients aged >70 years (mean 78 ± 6; range 70-93; 43% women) (43). CI was defined by a corrected MMSE score <24. Gait speed was used as a marker of frailty and measured on a 4-meter distance at usual pace. Ninety-eight patients (30%) had AF at enrollment and 20 (6%) had a history of paroxysmal/persistent AF. AF patients were more frequently women with severe valvular disease, preserved LVEF, and less frequently on beta-blockers. A cMMSE <24 was present in 19.6% of patients and a Geriatric Depression Scale (GDS)-15 score >6 in 51.4%. Patients who had AF performed significantly worse on the cMMSE than those who had not. Gait speed was significantly reduced in AF patients (Tab. II). Furthermore, AF was significantly associated with disability in either basic or instrumental activities of daily living (Fig. 3). On multivariable analyses, AF emerged as independently related to CI (odds ratio [OR] 1.909, [1.072-3.397]; p = 0.028), and to reduced gait speed (OR 4.366 [2.104-9.060]; p<0.001).

The effects of OAC on cognitive decline, excluding stroke reduction, has not been well established (37). Available data on the benefits of VKAs are controversial (44), and there is no consensus on the effects of this therapy on cognitive function among patients with AF. In some studies, the use of OACs did not affect cognitive decline while others found a trend toward an association. Data from the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W) found that among AF patients with a mean $CHADS_2$ score of 2 on warfarin, cognitive dysfunction was associated with lower time in therapeutic range (TTR) of anticoagulation, suggesting that maintaining therapeutic anticoagulation may reduce cognitive decline. There are no studies examining the cognitive effects of the NOACs (dabigatran, rivaroxaban, and apixaban); however, because they mitigate the challenges of TTR, there has been speculation that they may be able to slow or reverse cognitive decline among AF patients.

Polypharmacy and interactions

Polymedication is common in patients with AF, particularly in the elderly population. In a Danish observational study, 53% of AF patients took more than five drugs/day (45), while an analysis of the ROCKET AF study showed that 36% of patients were on 0 to 4 medications, 51% were on 5 to 9,

TABLE II - Comprehensive Geriatric Assessment variables according to the presence of atrial fibrillation

Variable n, (%)	All n = 331 (100%)	Atrial fibrillation n = 98 (29.6%)	No atrial fibrillation n = 233 (70.4%)	p value
Education ≤5 years	204 (61.6)	67 (68.4)	137 (58.8)	0.065
Living alone	80 (24.2)	28 (28.6)	52 (22.3)	0.142
Frailty (gait speed <1 m/s)	243 (73.4)	87 (88.8)	156 (67.0)	0.0001
Transportation IADL dependence	129 (39.0)	45 (45.9)	84 (36.1)	0.06
Drug IADL dependence	65 (19.6)	28 (28.6)	37 (15.9)	0.007
cMMSE ≤24	65 (19.6)	27 (27.8)	38 (16.3)	0.015
GDS-15 ≥6	170 (51.4)	55 (56.1)	115 (49.4)	0.158

BADL = basic activities of daily living; GDS-15 = 15-item geriatric depression scale; IADL = instrumental activities of daily living; MMSE = mini mental state examination. Modified with permission from (43): Pulignano G, Del Sindaco D, Tinti MD, et al; IMAGE-HF Study Investigators. Atrial fibrillation, cognitive impairment, frailty and disability in older heart failure patients. J Cardiovasc Med (Hagerstown). 2016;17(8):616-623.

13% were on ≥10; patients taking ≥10 medications daily were older and showed a trend toward a higher bleeding risk (HR 1.46, 95% CI [1.29-1.64], p = 0.81) (46).

HF also requires complex medication regimens due to the multiple therapeutic targets that exist and the need for routine symptomatic management; most studies have found medication non-adherence rates between 40% and 60% in patients with HF (47). Having multiple conditions also decreases self-efficacy in performing specific self-care tasks such as medication taking (48). Polymedication and complexity of treatment are also associated with poorer medication adherence and poor compliance.

It is well known that many medications interfere with dose response to VKAs; amiodarone, antibiotics such as quinolones and macrolides, antifungal agents, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, omeprazole, and lipid-lowering agents are just some of the drugs that should be used with caution. Although NOACs are less prone to drug interactions, P-glycoprotein and cytochrome P450 3A4 inhibitors like verapamil, amiodarone, rifampicin, antiretrovirals, and azole antimycotics should be prohibited or used with great caution.

Chronic kidney disease and AF in the elderly

Kidney function declines with age and chronic kidney disease (CKD) is common in patients with AF, and increases both the risk of thromboembolic and bleeding events (49). The efficacy of OAC therapy for stroke prevention has been demonstrated in patients with moderate CKD, but a prospective cohort study reported that patients with severe CKD (estimated glomerular filtration rate [eGFR] <30 mL/min per 1.73 kg/m^2) had less TTR (international normalized ratio [INR] 2-3), had a higher risk of over-anticoagulation (INR >4), and required lower warfarin dosing when compared with patients with eGFR >30 mL/min per 1.73 kg/m^2 (50).

VKAs are associated with increased calcification of renal and other arteries; vascular calcification, arterial damage, and decline in renal function may be triggered by the inhibition of the vitamin K-dependent protein matrix gamma-carboxyglutamic acid (Gla/MGP) by VK (51). Therefore, VKAs may accelerate vascular end-organ damage, including renal dysfunction. Böhm et al (52) analyzed changes in GFR during long-term treatment with warfarin or dabigatran in patients enrolled in the RE-LY trial. After an average of 30 months, the mean decline in GFR was significantly greater with warfarin compared with dabigatran 110 and 150 mg bid.

It is important to consider that different NOACs are eliminated via the kidneys to different degrees: 80% for dabigatran, 50% for edoxaban, 33% for rivaroxaban, and 27% for apixaban; this results in different plasma concentrations across the spectrum of creatinine clearance and underlies the advice to reduce the doses of each of the NOACs in patients with moderate CKD (53-57), and should be considered in the selection of the appropriate NOAC in the individual elderly patient. In a post-hoc analysis of the ARISTOTLE trial, where most patients aged ≥75 years (89%) had impaired renal function, Halvorsen et al (25) evaluated the occurrence of stroke or systemic embolism and major bleeding in relation to renal function and showed that the benefits of apixaban compared with warfarin were consistent across the range of eGFR, including in the elderly.

When considering dialysis patients, VKAs represent the most common approach for reducing the risk of stroke in this population. However, current evidence based on observational studies have provided conflicting results and clinicians are wary of their potential to increase the high risk of bleeding during dialysis. At the moment, none of NOACs can be safely prescribed in dialysis patients because of their potentially dangerous accumulation and the lack of sufficient experience (58).

Adherence

Adherence is crucial to achieve the optimal safety and efficacy of OAC therapy in AF patients. In fact, up to 40% of patients taking VKAs withdraw treatment after one year of therapy and up to 30% have suboptimal adherence (59). Reasons for poor adherence in the elderly include lack of support (e.g. caregiver), lack of disease knowledge, and confusion or physical difficulties associated with taking medicines and polypharmacy. In addition, a perceived high risk of falls or bleeding reduces the prescription rate of oral anticoagulation by general practitioners. OACs affect quality of life, requiring

frequent laboratory testing and attention to food and interactions, thus contributing to poor adherence.

A prospective study in 220 inpatients aged >70 years with AF reported that frail patients were less likely to receive warfarin than non-frail patients on admission and discharge, with a higher stroke risk over 6 months of follow-up (risk ratio 3.5, 95% CI 1.0-12.0, p<0.05) (60).

As most patients with AF are frail elderly with comorbid conditions, disability, and CI, treatment with OACs may present special challenges. AF is frequently associated with disability in either basic or instrumental activities of daily living, particularly in dependence in taking medications and use of transportation (43). These dependencies, combined with frailty and cognitive deficits, may increase the risk of falls with subsequent major injuries, need for surgery, and bleeding, and may seriously affect the patient's skills to safely manage OAC therapy.

Moreover, all of these conditions represent a risk factor for impaired self-care and low adherence, and, as a consequence, these patients may not take medications as prescribed and may be unaware of drug or food interactions, especially in the absence of a caregiver.

In an analysis of the ACTIVE-W study, low MMSE scores were correlated with a low TTR. Patients with scores <26 had more vascular events (6.7% vs. 3.6%/year) and more bleeding (9.6% vs. 7%/year). After controlling for TTR, MMSE no longer conferred increased risk, suggesting that if improved anticoagulation was provided, vascular events and bleeding would be reduced (61).

It is not clear if, in cases of suboptimal adherence, VKAs may be considered to be safer than NOACs because of their longer half-life and because of the planned frequent INR monitoring, helping to improve adherence through systematic laboratory control. Since recently introduced NOACs have a more favorable risk-benefit profile and a wide therapeutic window, a predictable anticoagulant effect, and few interactions with food and other medications, these drugs may be preferable to VKAs in many frail elderly patients, especially in those at higher risk of falls (23, 25). Furthermore, NOACs are very simple to administer and monitor and may be associated with better adherence and safety in patients with CI and mobility impairments.

Conclusions

The clinical picture of the older HF patient with AF is complex and heterogeneous with a higher prevalence of comorbidities, frailty, CI, and disability. The hypothetical mechanisms by which AF and HF may affect these conditions are multiple. However, because of the association of mental and physical impairment with non-administration of OACs, screening for simple geriatric variables in clinical practice may allow better strategies for intervention in this high-risk population. There is also a need for large multicenter longitudinal studies to examine the effects of VKAs and NOACs on long-term cognitive function and frailty. An individualized approach matching the particular NOAC to the individual patient, taking into consideration the risk of bleeding and other comorbidities, i.e. renal dysfunction, should be taken rather than a generalized "one drug fits all" approach in elderly adults.

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