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Running title: Atrial fibrillation in older persons

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ABSTRACT

INTRODUCTION: Atrial fibrillation (AF) is the most common cardiac sustained arrhythmia, whose incidence and prevalence increase with age, representing a significant burden for health services in western countries. Older people contribute to the vast majority of patients affected from AF.

EVIDENCE ACQUISITION: Although oral anticoagulant therapy represents the cornerstone for the prevention of ischemic stroke and its disabling consequences, several other interventions – including left atrial appendage occlusion (LAAO), catheter ablation (CA) of AF, and rhythm control strategy (RCS) – have proved to be potentially effective in reducing the incidence of AF-associated clinical complications. Scientific literature focused on the three items will be discussed.

EVIDENCE SYNTHESIS: Practical treatment of older AF patients is presented, including approach and management of patients with geriatric syndromes, selection of the most appropriate individualized drug treatment, clinical indications and potential clinical benefit of LAAO and CA in selected older AF patients.

CONCLUSIONS: Older people carry the greatest burden of AF in real world practice. Within a shared decision making process, the patient centered approach need to be put in the context of a comprehensive assessment, in order to gain maximal net clinical benefit and avoid futility or harm.

Key words: atrial fibrillation, older patients, oral anticoagulants, left atrial appendage occlusion, AF catheter ablation

TEXT

INTRODUCTION

Atrial fibrillation (AF) is one of the most common form of cardiac arrhythmia. Both incidence and prevalence of this disorder increase with advancing age, representing a significant medical burden for health services in most western countries [1]. The currently estimated prevalence of AF in adults is between 2% and 4%, and a 2.3-fold rise is expected, owing to extended longevity in the general population and intensifying search for undiagnosed AF [2]. Indeed, prevalence of AF has been reported to be around 10% among persons aged 80 years and over in the general population [3]. Patients with AF have an increased risk of ischemic stroke, which is approximately 5-fold higher than the general population, with an incidence of approximately 5% per year. In addition, as AF-related cardioembolic strokes are associated with higher mortality and morbidity than other strokes, the need for more effective stroke prevention in these patients should be emphasized [4,5]. Atrial fibrillation poses significant burden to patients, physicians, and healthcare systems globally. The complexity of AF requires a multifaceted, holistic, and multidisciplinary approach to the management of AF patients. Recent European Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in proposing the best management strategies for an individual patient with AF [2]. The Atrial Fibrillation Better Care (ABC) approach in the 2020 European Society of Cardiology (ESC) AF Guidelines is a continuum of this approach, with the goal to further improve the structured management of AF patients, promote patient values, and finally improve patient outcomes. In this review we will discuss some common clinical uncertainties in the management of AF in older persons, dealing with the following issues: 1) practical use of oral anticoagulants; 2) percutaneous left atrial appendage occlusion; 3) catheter ablation of AF.

METHODS

Scientific literature focused on the three items discussed (use of oral anticoagulant therapy, percutaneous left atrial appendage occlusion and catheter ablation of AF) in older persons published in the last 8 years was retrieved by the authors (MB, FV, PA, GI, EB) from the MEDLINE database entering these terms and using the terms "atrial fibrillation", OR "new oral anticoagulants" OR "direct oral anticoagulants", OR "aged" OR "elderly"

OR “older” as keywords. Reviews, recommendations and expert opinions, as well as clinical trials and large observational studies in English published until December 2020 were systematically analyzed and included according to their relevance to the objective. Additional references were obtained from the reference list of the selected full-text manuscripts.

ORAL ANTICOAGULANT THERAPY (OAT) IN OLDER AF PATIENTS

Current European guidelines recommend oral anticoagulant therapy (OAT) with direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) irrespective of age for patients with AF and a CHA_2DS_2-VASc score ≥2 in men and ≥3 in women, and without contraindications to DOACs (mechanical prosthetic valves or moderate-to-severe mitral valve stenosis) [6,7]. Phase III DOAC randomized clinical trials (RCTs) enrolled a significant proportion of older subjects, and consistently demonstrated a greater net clinical benefit compared to VKAs also in persons aged 75 years and over, who account for the largest proportion of AF patients [8-10].

Geriatric syndromes in AF older patients

However, despite consistent evidence of clinical benefit and increasing prescription of these drugs [11], they are still widely underused, particularly in the oldest patients [12,13]. Some uncertainties in DOACs use in older patients might arise from the concern that the significant proportion of older persons enrolled in DOACs RCTs might not be fully representative of real world (RW) patients. However, with the inherent limitations of the observational design, real world studies confirm a greater net clinical benefit of DOACs compared with VKAs also in older patients, with an apparent better safety profile for apixaban and low dose dabigatran [14-18].

Moreover, geriatric syndromes such as frailty, cognitive impairment and functional dependence, which have been demonstrated to influence physicians’ decision about DOACs use in older persons [19,20], were not considered in RW studies as well as in DOACs trials. Although cardiologists usually recognize frailty based on the presence of a mix of problems of motility, cognition, nutrition and inappropriate loss of body weight and muscle mass [21], there are two basic conceptualizations of frailty. The frailty “phenotype” is based on the presence of at least three of five criteria – slow gait speed, low physical activity, unintentional weight loss, self-reported exhaustion, and muscle weakness – and is associated with worsening mobility and disability, hospitalizations, and mortality over 7 years in community-dwelling older persons [22]. This “frailty phenotype”, which should not be confused with disability or comorbidity, may also be identified using other tools, such as the Simplified Fried test, the Short Physical Performance Battery (SPPB), the 5 meter gait speed, the Study of Osteoporotic Fractures (SOF) index and the simple Frail Scale [23]. On the other side, the Frailty Index [24] is a 70-item form based on the accumulation of deficits (including functional limitations and disabilities, cognitive and sensory impairment, psycho-social variables and number of diseases), whose score is associated with increased short term risk of institutionalization, mortality and hospitalization. The 7-point Clinical Frailty Scale (a semi-quantitative eye-ball global judgment of frailty or vulnerability) was shown to be highly correlated with the Frailty Index and significantly associated with increased risk of death and entry into an institution [25]. The Multidimensional Prognostic Index (MPI) (including information on functional basic and instrumental activities of daily living, cognitive and nutritional status, comorbidities, medications, and social support network) has also been demonstrated to be predictive of mortality and adverse clinical outcomes [26,27]. In summary, the “frailty phenotype” based tools identify patients at risk of disability, but not of short term mortality, whereas high scores in the Frailty Index, Clinical Frailty Scale and MPI identify patients with poor health status and increased risk of mortality. Despite inherent limitations according to different frailty tools adopted, frail older patients with AF are less likely to receive an appropriate anticoagulant prescription and, at the same time, are at greater risk of embolic stroke and death [28,29]. The lack of evidence to guide optimal care for patients with AF and frailty might in part explain the gap between current guidelines and clinical practice in the management of these patients [29]. On the basis of current evidence there is general agreement that the “frailty phenotype” should not be an exclusion criterion to anticoagulate, since these patients are at increased risk of stroke and have been shown to benefit from OAC [30].

Predisposition to falls is common in frail patients and is often perceived as an important issue in starting DOACs [21,31,32]. However, patients on OAT at high risk of falls did not consistently have a significantly increased risk of major bleedings (MBs) [33-35]. Current guidelines do not require fall risk estimation in candidates to OAT, and the risk of fall per se should not be considered a contraindication to the use of DOAC [2,6,7].

Many older adults have both cognitive impairment or overt dementia and AF. Although AF is a recognized risk factor for later occurrence of cognitive impairment and dementia

[36], dementia is a well-recognized risk factor for under-use of OAT [12]. A retrospective cohort study of 2572 older patients with AF (73% aged ≥75 years) showed that after diagnosis of dementia, those who persisted on OAT had lower rates of stroke and all-cause mortality, with no significant differences in risk of MBs [37]. Although cognitive impairment and frailty were associated with increased risk of death and reduced probability of receiving OAT among older AF patients enrolled in the ORBIT-AF registry [38], there was no interaction between OAT use and cognitive impairment or frailty in their association with mortality, major bleeding and a composite end-point of stroke, systemic thromboembolism, myocardial infarction and cardiovascular death [38]. Whereas cognitive impairment at mild-to moderate stage should not be viewed as a general contraindication to DOAC therapy, especially if well-managed from a logistic point of view, in states of poor physical functioning, limited life-expectancy and high risk for competing causes of death there may be limited benefit from OAT [6,7].

Persistent uncertainties about OAT use in older AF patients

Despite recent studies reinforced the evidence of net clinical benefit of OAT, including DOACs, in extremely older community-dwelling persons (aged ≥85 years) [39], prescription of OAT to older AF patients is often a troublesome decision, involving a global evaluation of health, residual life-expectancy, functional and cognitive status, rather than a simple addition of variables within cardio-embolic and bleeding risk scales [9]. It is likely that sometimes physicians perceive OAT as "futile" or potentially harmful in patients with multi-morbidity and short life-expectancy, and, moreover, cost-effectiveness considerations might affect decision about DOACs prescription in these patients. Indeed, when considering OAT with DOACs in older persons, the high risk of competing cardiovascular and non-cardiovascular causes of death in this population should be considered. In fact, while the adjusted overall mortality in landmark phase III DOAC trials was 4.72%/year, with cardiac death contributing for 46% of deaths [40], all-cause mortality in real-world older patients are definitely higher, with difference in cause-specific mortality. In a population-based, retrospective cohort study of a nationally representative sample of fee-for-service Medicare beneficiaries 65 years or older with incident atrial fibrillation diagnosed between 1999 and 2007, including 186 461 patients with AF and no recent hospitalizations for heart failure, myocardial infarction, stroke, or gastrointestinal hemorrhage, mortality was the most frequent major clinical events (19.5% at 1 year; 48.8% at 5 years), with an incidence which was 7-fold higher than that of ischemic stroke. In this sample, the risk of all-cause mortality was further increased in in-patients compared with out-patients [41]. In the ORBIT-AF registry, older patients not on OAT experienced higher mortality rates (7.42 vs 5.78%, p=0.006) over a 2.5 years follow-up without significant differences in thromboembolic event rates, compared with patients receiving OAT [42]. Data from the Galician Healthcare Service showed that among patients aged 80 years and older (45.6% of those with AF) two-year all-cause mortality was higher than in younger counterparts (27.8% vs 8.05%, p<0.001), as well as thromboembolic and hemorrhagic events (2.03% vs 0.9%, p<0.01 and 2.5% vs 1.7%, p=0.01, respectively) [43]. In two studies including hospital discharged older AF patients (mean age over 80 years) we documented high mortality rates, mainly for non-cardiovascular causes, which were about two-fold higher in untreated patients, reflecting the higher proportion of poor health status in these latter patients [44, 45]. A recent systematic review and meta-regression analysis demonstrated that in older AF patients DOACs are superior to warfarin for stroke/thromboembolism prevention, with reduced risk of MB, thereby reinforcing the evidence that DOACs should be preferred for stroke prevention in older AF patients [46]. However, some older AF patients are at risk of increased short-term all-cause mortality, thereby diluting the undisputable benefit of DOACs. Unfortunately, by now there are not validated methods to identify those few older patients who, because of their poor general health and/or functional status, are expected not to have a net clinical benefit from anticoagulation [30].

Use of DOACs in older AF patients

Medical history and comorbidities may drive the choice of a particular DOAC in older patients. Several DOACs rankings [47-49] and expert opinions have been published to assist physicians to fit the best DOAC according to individual patient's characteristics [50-53]. Apixaban has been suggested as a reasonable first choice both in older patients and in subjects with chronic renal failure [47,52,53]. The recently updated 2019 American Geriatrics Society Beers criteria recommend a cautious use of dabigatran and rivaroxaban in AF patients aged ≥75 years because of greater risk of gastrointestinal bleeding [54]. In a recent report from the Fit-fOR-The-Aged (FORTA) classification (evaluating benefit, risk and appropriateness of drugs for older patients in everyday clinical settings), apixaban was labelled A among OATs, meaning it was seen as the drug with the most favorable risk/benefit ratio in older patients [55].

In RW clinical practice use of reduced-dose DOACs and inappropriate off-label DOAC under-dosing, particularly of apixaban and rivaroxaban, are quite common, mainly in the oldest patients and with poor health status [56-59]. In a recent review [60], we demonstrated that several conditions, including advanced age, female gender, fear of bleeding and/or previous bleeding, history of chronic kidney disease and polypharmacy, are associated with oral Factor Xa Inhibitors (FXaIs) underdosing, supporting the hypothesis that a substantial proportion of these prescriptions may be voluntary rather than casual. However, the vast majority of bleedings occurs within well-conducted OAT, and appears to be associated with patient's characteristics (e.g., advanced age, comorbidity, anemia, previous bleedings, concomitant therapy with antiplatelet drugs or non-steroidal anti-inflammatory drugs) and underlying gastrointestinal pathology, rather than with OAT intensity. Indeed, in FXaI RCTs, the rates of MB were consistently higher among patients treated with reduced dose (RD) rather than in those treated with full dose (FD). Moreover, correct use of RD had reassuringly the same efficacy and safety as FD FXaIs compared with warfarin. Real-life studies do not provide evidence of a sizeable net clinical benefit by using off-label RD FXaIs, but rather suggest an increased risk of adverse events, including hospitalizations for cardiovascular causes and stroke, particularly in patients on underdosed apixaban. Current evidence should discourage FXaIs underdosing and support their prescription according to drug-specific dosing guidelines for the most patients.

Conclusions

The availability of DOACs has dramatically increased the proportion of older AF patients receiving appropriate OAT. Because of their potential for clinical benefit, DOACs should be recommended for "fit and robust" older subjects, as well as for persons with the frailty phenotype, irrespective of age; risk of falls, cognitive impairment without functional limitations, and mild disability should not be regarded as contraindications to DOAC use in these patients. However, as for many other preventive therapies, at the moment there is no evidence of a net clinical benefit from OAT in older patients with advanced dementia, and/or with loss of functional independence, and/or short life expectancy [30]. Hopefully, further studies will provide information in this setting of patients. Individual selection of DOAC and use of recommended appropriate dose, careful clinical surveillance, periodic review of co-medications, and minimization of bleeding risk are mandatory in these patients.

PERCUTANEOUS LEFT ATRIAL APPENDAGE OCCLUSION FOR THE PREVENTION OF STROKE IN OLDER AF PATIENTS

The left atrial appendage (LAA) in the pathogenesis of thrombus

The thrombogenesis in AF is multifactorial and includes Virchow's triad which, through endothelial and endocardial damage or dysfunction, abnormal blood stasis, and altered hemostasis, platelet function and fibrinolysis, promotes the onset of thrombosis [5,61-62]. These changes are most evident in the left atrial appendage (LAA), where a remarkably low blood flow velocity plays a very important role in promoting thrombus formation. The LAA, which is the remnant of the embryonic left atrium, is a tubular blind-ended structure with several lobes and variable morphology, in contrast to the wide triangular shape of the right atrial appendage [62-65]. Unlike the right atrium, pectinate muscles are located within the LAA and do not extend into the remaining parts of the left atrium. Several forms and variants of the LAA have been described, with 1-4 lobes and 4 prevailing morphologies, called "windsock", "cauliflower", "cactus-like" and "chicken wing" [63]. Its complex structure with areas of relatively low flow velocity predisposes to stasis, mainly during AF when blood flow velocity is further reduced, as can be visualized on transthoracic or, better, transoesophageal echocardiographic examination (TOE) with evidence of spontaneous contrast (smoke effect) or on pulsed wave Doppler during AF paroxysms [63-67]. Because of these predisposing situations, it has been shown that in patients with non-valvular AF, about 91% of thrombi develop in the LAA as opposed to 57% only in patients with rheumatic AF [63,68]. In fact, literature data show that the presence of thrombi or a reduced peak flow rate in the LAA are independent predictors of increased thromboembolic risk [63,68], as well as stroke recurrence among patients with non-valvular AF. However, a recent analysis has shown that while in valvular AF more than half of the thrombi were in the left atrial cavity even in patients with non-valvular AF and a history of stroke, the chances of developing a thrombus in the left atrial cavity compared to LAA were up to 45% in the case of missed anticoagulation or ventricular dysfunction [69].

In NVAF patients with a CHA_2DS_2-VASc score ≥2 for men and ≥3 for women, DOAC use is a class I recommendation for primary and secondary prevention of cerebral and systemic embolisms [7] with consistent greater clinical benefit over warfarin also in older patients [9,70]. LAA occlusion may be considered (Class IIb; Level of Evidence B) for stroke prevention in patients with AF and contra-indications to long-term use of OAT [6].

LAA Occluders in Clinical Trials

In recent decades, there has been a progressive development of transcutaneous LAA occlusion (LAAO) techniques along with an increasing availability of different LAAO devices, although many of them yet unapproved [71]. Therefore, most of current evidence is based on the WATCHMAN LAA occluder (Boston Scientific, Marlborough, Massachusetts), the most extensively used in RCTs and observational studies (Table I).

Over the past decade, two RCTs using the WATCHMAN device, PROTECT AF (WATCHMAN Left Atrial Appendage Closure Device for Embolic Protection in Patients with Atrial Fibrillation) and PREVAIL (Prospective Randomized Evaluation of the WATCHMAN Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation versus Long-Term Warfarin Therapy) [72,73] as well as registry data on patients with various LAA closure devices have demonstrated excellent safety and efficacy compared with the use of VKAs [74-76]. A recent meta-analysis demonstrated that the WATCHMAN device was non-inferior to VKAs for the prevention of stroke and systemic thromboembolism and with a significantly lower risk of hemorrhagic stroke, nonprocedure-related MB, and mortality at 5 years follow-up [77]. However, patients enrolled in these RCTs and registries received VKA-based OAT for 6 weeks to facilitate endothelialization of the device. As a consequence, the WATCHMAN device received FDA regulatory approval in the United States for use only in patients eligible for short-term OAT, thereby excluding access to this device for patients with absolute contraindications to OAT. In contrast, ESC guidelines recommend the use of percutaneous LAA closure in patients with AF and prior life-threatening bleeding or contraindications to long-term OAT (Class IIb; Level of Evidence B) [6] using dual antiplatelet therapy (DAPT) with aspirin and clopidogrel in the postprocedural period. Currently, there are no randomized data to support this recommendation, and most of the evidence comes from prospective single-center and multicenter observational registries including the WATCHMAN and Amplatzer Occlusion Device (St. Jude Medical, Minneapolis, Minnesota) [74, 78-80].

In the prospective multicenter EWOLUTION Registry (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology), including approximately 72% of patients ineligible for OAT, the post-implantation antithrombotic strategy was highly variable including use of single and dual antiplatelet therapy and VKAs. The rate of stroke observed in the entire cohort was only 1.3%/year, and the combined end-point of ischemic stroke, transient ischemic attack (TIA), and systemic embolism was 2%/year: these rates correspond to a risk reduction of 83% and 80%, respectively, compared with that expected in untreated patients. [79-81]. Notably, these rates of ischemic and bleeding events are similar to those observed in the combined PROTECT AF and PREVAIL RCT data [77], where the WATCHMAN group received combination therapy of aspirin 81 mg daily and warfarin (target INR, 2-3) for 45 days followed by DAPT (aspirin 81 mg daily+clopidogrel 75 mg daily) for 4.5 months, and then lifetime aspirin 81 mg daily. Despite, the growing body of RW evidence on the use of single or DAPT after LAAO, the appropriate postprocedural antithrombotic regimen is not well defined and clouded by device-related thrombus (DRT), leakage, and bleeding events. In the EWOLUTION Registry, the rate of DRT, despite the highly variable antithrombotic strategy, was 4.1%/year, substantially superimposed on that of the ASAP trial and similar to the 3.7%/year observed in the combined analysis of the 4 prospective WATCHMAN FDA clinical trials (PROTECT AF, PREVAIL, CAP, and CAP-2) in which the warfarin/DAPT regimen was used [82].

A high risk of MB is typically the most common reason why patients receive LAAO [63,66]. The nonprocedural MB rate in the EWOLUTION study was 2.7%, with the lowest rates (1.1%) in patients with early discontinuation of DAPT (≤105 days) when compared with those who continued DAPT beyond that limit (3.5%) with no significant difference in the combined end point of systemic thromboembolism, TIA, and DRT between groups [79-81]. Furthermore, the benefit of LAAO in reducing stroke and MBs was also observed in high-risk subgroups, such as patients with CHA_2DS_2-VASc score ≥3 and history of stroke, TIA, MB, or hemorrhagic stroke. These findings strongly raise the question regarding the initial transition with OAT post-WATCHMAN closure of LAA and whether the current recommended strategy provides an additional incremental benefit over DAPT alone. Larger studies are needed to better define the role and duration of DAPT in the post-LAAO phase.

Since the vast majority of RCTs with LAAO were initiated before the widespread use of DOACs, the need to compare LAAO procedures with respect to the use of DOACs is becoming increasingly compelling. Compared with warfarin, DOACs are certainly easier to use and are associated with a greater clinical net benefit even in older subjects [9,30,70]. Transcatheter LAAO performs similarly to DOACs in RCTs against warfarin, showing a significant reduction in intracranial hemorrhage, with no statistically significant increase in ischemic stroke and a possible reduction in all-cause mortality [77,83]. In addition, LAAO has been shown to be associated with a reduction in the risk of gastrointestinal hemorrhage [84]. The prospective, randomized, noninferiority PRAGUE-17 study aimed to compare transcatheter LAAO with DOAC therapy in 402 patients (mean age 73 years) [85]. Enrollment criteria were based on failure of DOAC treatment, significant prior bleeding, or a combination of high thromboembolic risk and high bleeding risk. Patients were randomly assigned to DOAC (mostly apixaban) or LAAO therapy. The primary endpoint was a composite outcome that included both safety and efficacy and periprocedural complications. During a 20 months period of observation, the PRAGUE-17 data demonstrated non-inferiority of LAAO compared with DOACs, with a similar rate of all-cause stroke and a lower rate of bleeding in patients receiving LAAO. Despite the numerical and methodological limitations, PRAGUE-17 has certainly the merit of reinforcing the role of LAAO in patients at high risk of bleeding or failure of drug treatment, even in the era of DOACs. Hopefully, incoming studies will provide more substantial and convincing data on the use of LAAO in subjects over 80 years old.

Clinical considerations for older AF patients

The mean age of the patients involved in the aforementioned RCTs and registries was slightly above 70 years and, although almost half of the patients enrolled were aged >75 years (Table I), there are no subanalyses related to this age group. In any case, the few data in the literature on octogenarian subjects do not show age-related differences in terms of both efficacy and safety. Even the risk of periprocedural complications does not seem to increase in relation to the age of patients showing, over time, a progressive reduction in incidence as a function of the physiological learning curve of the operators related to the greater diffusion of this technique. Recent data from the prospective observational Left-Atrium-Appendage Occluder Registry Germany, including a total of 638 patients (402, 63%, aged ≥75 years), reported similar high procedural success rate in both groups (97.6%), without significant differences of adverse events between older and younger patients. At one year follow-up, all-cause mortality was higher in patients aged ≥75 compared with younger group (13.0% vs 7.8%, p=0.04), mainly due to non-cardiovascular causes (10.6% vs 6.0%) [86].

It is also interesting to point out that there are currently no data in the literature that analyze the weight of common conditions in the elderly such as frailty syndrome, comorbidities, polypharmacy in relation to the use of LAAO devices. The evaluation of the risk/benefit ratio of LAAO in the elderly based on the above determinants is of paramount relevance to assess the possible futility of this procedure in relation to both the estimated residual life expectancy as well as the quality of life, and the residual thrombo-embolic risk related to specific comorbidities. In fact, it is known that several diseases such as heart failure with severe ejection fraction impairment are associated with an increased risk of occurrence of thrombus outside the LAA, as already described by the meta-analysis of Mahajan et al [69] that showed, in patients with non-valvular AF, a prevalence of atrial thrombi outside the LAA of 11%, which doubled in older patients. Therefore, although at present potential candidates for LAAO are those with absolute or relative contraindications to OAT, or patients at high risk of recurrent ischemic stroke, severe renal dysfunction, severe gastrointestinal bleeding, in older patients, pending specific trials, it is useful that the assessment of the risk-benefit ratio is done, for each individual case by a multidisciplinary team involving the patient and care givers.

CATHETER ABLATION IN OLDER PATIENTS WITH AF

Catheter ablation (CA) is increasingly used for AF treatment since antiarrhythmic drugs have demonstrated a limited efficacy in maintaining stable sinus rhythm. Some RCTs comparing antiarrhythmic drugs for rhythm control with rate control did not demonstrate a benefit of one treatment strategy over the other [87]. However, very symptomatic patients were not enrolled. Very recently, the EAST-AFNET-4 RCT [88] demonstrated that AF patients (mean age 70 years) who were randomly assigned to early rhythm control (median time of 36 days after diagnosis) had a lower risk of death from cardiovascular causes, stroke, or heart failure hospitalization or acute coronary syndrome versus rate control (HR 0.79, 95% CI 0.66-0-94). Many observational and some small randomized studies investigated whether rhythm control therapy was more effective by utilizing antiarrhythmic drugs or AF CA and the results appear to be conflicting. However, some meta-analyses showed superiority of ablation in reducing episodes of recurrent AF and in improving quality of life [2,89], but many patients required two or more procedures. It should be stressed that in most studies the mean age of the patients was rather low, between 50 and 60 years, considering that the mean age of AF patients is approximately 75 years [2]. After single procedure, success was reported in 40-70% of the patients during a follow-up period of 12-24 months and the major risk factors for AF relapse were advanced age, long AF duration, the non-paroxysmal form of AF at baseline, structural heart disease, increased left atrial volume and the presence of comorbidities such as hypertension, obesity. renal dysfunction, and sleep apnea [2,89]. Prospective, registry-based data show that 4-15% of patients experience periprocedural complications, 1-7% of which are defined as major (mainly stroke/TIA, symptomatic pulmonary vein stenosis, pericardial tamponade, atrioesophageal fistula, phrenic nerve injury, retroperitoneal bleeding, femoral arteriovenous fistula) [2,89]. The periprocedural mortality is approximately 0.1% [2]. Radiofrequency and cryoballoon ablation seem to have similar efficacy and complication rates, even if some studies show lower complication rates with cryoballoon ablation [2,89].

In two recent RCTs [90,91], hard endpoints such as death and stroke were investigated, besides the incidence of AF recurrence and the impact on quality of life. In the CABANA trial [90,92], 2204 symptomatic patients (median age 68 years) with paroxysmal or persistent AF were randomized to CA versus medical therapy (antiarrhythmic drugs in 88% of patients). This trial showed that CA is associated with an improvement in quality of life, a reduction in cardiovascular hospitalization, and a lower AF recurrence rate than drug therapy (50% versus 69% at 3 years follow-up). However, CA did not reduce the primary composite outcome of death, stroke, serious bleeding, or cardiac arrest compared with medical therapy. Therefore, this large trial shows that for many patients ablation is not curative and has not a prognostic impact, but it reduces AF burden and improves symptoms. In another recent trial (CASTLE-AF) [91], selected patients with paroxysmal or persistent AF, heart failure, left ventricular ejection fraction ≤35% and an implanted defibrillator were randomized to AF ablation versus medical therapy (rate or rhythm control). The study enrolled 363 patients, and the mean age was rather low (64 years). AF ablation significantly reduced the risk of death and heart failure hospitalization by 40%. There was also a benefit in all-cause mortality, which was driven by a significantly lower rate of cardiovascular death in the ablation group. Furthermore, CA reduced AF burden and improved left ventricular ejection fraction. However, the generalizability of the CASTLE-AF trial has recently been evaluated in a large heart failure patient population and this analysis showed that only a small number of patients (about 8%) met the trial inclusion criteria [93]. In the 2020 European guidelines [2], CA is recommended for rhythm control after one failed or intolerant class I or III antiarrhythmic drug to improve symptoms in patients with paroxysmal or persistent AF without major risk factors for AF recurrence (class I, level of evidence A) and in patients with persistent AF with major risk factors for AF relapse (class I, level of evidence B). Moreover, CA should be considered in selected AF patients with heart failure with reduced ejection fraction to improve survival and reduce heart failure hospitalization (class IIa, level of evidence B).

Effects of AF ablation in the elderly

In order to maintain sinus rhythm, antiarrhythmic drugs can be difficult to manage due to unpredictable metabolism in elderly patients and intolerance of side effects. However, even the success rate of AF CA may be affected by a higher degree of atrial myopathy in older individuals. Randomized trials comparing efficacy and safety of AF ablation versus medical therapy in the elderly with AF have not been carried out. Moreover, older patients were mostly excluded from RCTs and our knowledge on this issue is very limited. Therefore, we performed a systematic review on published data dealing with AF CA through the electronic database PubMed; bibliographies of retrieved articles, review articles and textbooks were evaluated. We searched English-only articles published during the last ten years (between January 2010 and September 2020) and included those involving a group (or subgroup) of ≥100 elderly patients with cutoff ≥65 years who underwent AF CA. Twelve non-randomized articles were eligible for this review [90,94-104]. In three studies the effects of AF ablation and medical therapy were compared [90,97,104]. Blandino et al [97] investigated 412 patients aged ≥70 years (mean age 75), admitted to two hospitals for persistent AF; 153 patients underwent radiofrequency AF ablation and 259 were treated with medications (rate or rhythm control). During a mean follow-up of 60 months, the success rate after single procedure was significantly higher in the ablation group (58% versus 43%, p=0.003) and it increased to 76% after multiple procedures, performed in 18% of patients. The periprocedural major complications rate was 6.7% and previous history of TIA/stroke was an independent predictor of post-ablation cerebral thromboembolic events. However, the rate of long-term adverse events was lower in the ablation group (7.7% versus 23.9%, p<0.001). Wang et al [104] investigated 1740 Chinese patients aged ≥65 years, admitted to four hospitals for AF, receiving either radiofrequency ablation or medical therapy. The propensity-matching algorithm produced 347 pairs of patients (mean age 71 years). The primary endpoint was a composite of all-cause death, non-fatal stroke and peripheral embolism and the patients in the ablation group were at significantly lower risk for these events compared with those treated conservatively (HR 0.40, 95% CI 0.19-0.85). These findings contrast with results of the large CABANA trial [90], wherein AF ablation did not reduce the primary composite outcome of death, stroke, serious bleeding, or cardiac arrest compared with medical therapy. However, when patients were stratified according to age, patients aged <65 years (n=766) might benefit from catheter ablation (HR 0.52, 95% CI 0.27-1.00) and in those aged 65-74 years (n=1130), the two treatments had similar effects (HR 0.84, 95% CI 0.57-1.23). On the contrary, in patients aged ≥75 years (n=308) there was a trend in favor of medical therapy (HR 1.46, 95% CI 0.80-2.67, p=0.07).

In the remaining nine studies [94-96,98-103] the effects of AF CA were investigated in older patients and in eight of these studies they were compared with those observed in younger ones. The main results are summarized in Table II. All the studies had a retrospective design. The age cutoff varied from ≥65 to ≥80 years. In eight studies the patients underwent radiofrequency ablation and in one [102] cryoballon ablation. Two studies were multicenter [101,103] and in the others only one or two centers were involved. In eight studies, success of the procedure was defined as a lack of atrial tachyarrhythmia recurrence and in two [94,100] as occurrence of infrequent relapse. In all the studies patients with symptomatic and drug refractory paroxysmal or persistent AF were enrolled. In three studies the prevalence of heart failure patients was not reported [95,101,103] and in the others it ranged between 6% and 17.8%. In one large study [103] the primary endpoint was periprocedural death, which was significantly higher in patients aged ≥80 years than in the younger ones (0.8% versus 0.2%, p<0.001). In the other studies the primary endpoints were periprocedural major complications rate and/or success rate. Incidence of major complications in the elderly patients enrolled in these studies ranged from 1% to 7.3%. In two studies [94100] the major complications rates increased with advancing age and in four [95,96,102,103] the differences were not statistically significant. Moser et al [101] reported a higher stroke rate in the older versus the younger cohort (1.3% versus 0.1%, p<0.01), whereas the other major complications did not statistically differ. The main predictors of major complications were kidney failure, anemia and chronic obstructive pulmonary disease [103]. The success rate was reported after both single procedure and multiple procedures in one study [96], only after single procedure in four studies [95,99,100,102] and only after multiple procedures in two studies [94,98]. After single procedure, success rates in older patients ranged from 44% to approximately 70% during a follow-up period of 18-25 months [95,96,100] and it seems to decrease to about 30% after 60 months [99]. In three studies [94,99,100] the success rates decreased with increasing age and in three [95,96,102] the differences were not statistically significant. After multiple procedures - performed in a percentage of patients variable from 20% to 44% - the success rates in the elderly appear to be high (approximately 80%). In two studies [94,100] the success rates of ablation were reported either without and with administration of antiarrhythmicdrugs, these latter increasing the efficacy by 50-80%. However, older patients required more antiarrhythmic therapy than younger ones in order to maintain sinus rhythm. A sub-analysis carried out by Nademanee et al [98] in 75 patients with implantable devices showed that ablation markedly reduced AF burden. In two studies, good AF control was associated with better survival [98,100].

In summary, despite uneven findings among these studies carried out in elderly patients, there is some evidence that 1) periprocedural major complications rates seem to increase in the elderly, but do not appear to be much higher than in younger patients; however, a periprocedural death rate of approximately 1%, observed in a large database dealing with octogenarians, appears to be very high; 2) success rates appear to be lower in older patients than in younger counterparts; however, CA seems to be superior to medical therapy in reducing episodes of recurrent AF and in improving quality of life; 3) older patients require more antiarrhythmic drugs after ablation than the younger ones in order to maintain sinus rhythm; 4) CA does not seem to reduce the risk of stroke and other cardiovascular events, even in presence of some contrasting results; 5) comorbidities are predictive of both major complications and lower success rate.

However, the inherent limitations of observational retrospective studies do not allow us to draw clear conclusions on the indications to AF CA in older subjects for several reasons: 1) different criteria to define success of the procedure, different patient selection criteria, different follow-up duration and different presentation of the results; 2) the studies have a retrospective design, with possible selection biases and confounders; 3) most studies are single-center (tertiary referral center) and the results cannot be generalized to other institutions; 4) in most studies it is not reported how many patients were treated with antiarrhythmic drugs after ablation; 5) the prevalence of frailty was not reported, but very likely only “robust” elderly patients were selected for the invasive treatment; 6) the impact of AF ablation on the risk of disability and cognitive decline, which are important endpoints in older patients, was not adequately investigated. With regard to this latter issue, evidence of reduced incidence of dementia in mainly adult or young-older AF patients who underwent CA were reported by recent papers [105-107].

Conclusions

AF ablation appears to be a promising treatment in older subjects, but the patient selection criteria need to be better defined. In the recent European guidelines [2] this issue is not discussed. In an expert consensus statement [89], the writing group recommends that "it is reasonable to use similar indications for AF ablation in selected older people with AF as in younger patients" (Class IIa, level of evidence B), but it is not discussed how the patients should be selected.

At present, we can only speculate that CA should be considered in older "robust" patients with symptomatic, drug-refractory, paroxysmal or persistent AF, without significant heart disease and comorbid conditions, without a very dilated left atrium and a long AF history, in order to reduce symptoms and improve quality of life. Prior to undergoing CA, it is important to confirm that the patient's symptoms result from AF and to assess their severity. At present, there are no data on the effects of CA in older patients with AF and heart failure with reduced ejection fraction.

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TABLES

Table I.— Main clinical trials for left atrial appendage closure with the Watchman device.

	PROTECT-AF	**PREVAIL**	**EWOLUTION**
Study Design	Randomized	Randomized	Registry
Randomization	2:1	2:1	NA
Control	Warfarin	Warfarin	NA
Number of Patients	707	407	1025
Age, mean±s.d.	72±8.9	74±7.4	73.4±9
Aged ≥75 years, %	43	54	50.8
CHA_2DS_2-VASc score, mean±s.d.	3.3±1.4	3.8±1.2	4.5±1.6
Stroke/TIA, %	18	28	30.5
Implant success, %	91	95	98.5
7-days severe peri-procedural events, %	8.7	4.2	2.7

Abbreviations: CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, prior stroke or transient ischemic attack (doubled), vascular disease, age 65–74, female sex; EWOLUTION = Registry on WATCHMAN Outcomes in Real-Life Utilization; PREVAIL = Evaluation of the WATCHMAN Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy; PROTECT-AF = Watchman Left Atrial Appendage Closure Technology for Embolic Protection in Patients With Atrial Fibrillation; s.d. = standard deviation; TIA = transient ischemic attack.

Table II – Main clinical trials for left atrial appendage closure with the Watchman device.

Author	**Patient number**	**Mean age** (yrs)	**Major complications** (%)	**Follow-up** (months)	**Success rates after single procedure** (%)	**Success rates after multiple procedures** (%)
Leong-Sit P [94]	308 ≥ 65 yrs 570 55-64 yrs 438 45-54 yrs 232 < 45 yrs	/ / / /	2.6% 2.0% 1.7% 0% p=0.01	~30	/ / / /	§ 53% ¶ 82% § 65% ¶ 88% § 68% ¶ 88% § 76% ¶ 87% p<0.001 NS
Tan HV [95]	49 ≥ 80 yrs 151 70-79 yrs 177 60-69 yrs	84 75 66	2% 2.6% 1.7% NS	18	70% 72% 74% NS	/ / / /
Santangeli P [96]	103 ≥ 80 yrs 2651 < 80 yrs	85 62	1% 0.9% NS	~18	69% 71% NS	87% /
Nademanee K [98]	261 ≥ 75 yrs	79	7.3%	36	/	83%
Bunch TJ [99]	46 ≥ 80 yrs 305 71-80 yrs 328 61-70 yrs 170 51-60 yrs 74 ≤ 50 yrs	83 74 66 56 43	/ / / / /	60	27% 32% 43% 52% 45% p=0.01	/ / / / /
Kautzner J [100]	394 ≥ 70 yrs 2803 < 70 yrs	73 57	5.3% 3.2% p=0.03	25	§ 44% ¶ 78% § 58% ¶ 83% p=0.0001p=0.01	/ /
Moser JM [101]	227 ≥ 75 yrs 4222 < 75 yrs	77 62	*1,3% # 4.4% *0.1% # 2.7% p<0.01 NS	/	/ /	/ /
Heeger CH [102]	104 ≥ 75 yrs 104 < 75 yrs	77 63	6.7% 6.7% NS	36	59% 49% NS	/
Romero J [103]	3482 ≥ 80 yrs 82.637 < 80yrs	83 60	3.6% ϕ 0.8% 2.8% ϕ 0.2% NS p<0.001	/	/ /	/ /

Abbreviations: yrs = years, NS: not significant

/ not reported, § without and ¶ with antiarrhythmic drugs administration after ablation,

*periprocedural stroke, # other major complications, ɸ periprocedural death