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Review

# Atrial fibrillation in the elderly: a risk factor beyond stroke

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ABSTRACT

Atrial fibrillation (AF) represents the most common arrhythmia worldwide and its prevalence exponentially increases with age. It is related to increased risk of ischemic stroke or systemic embolism, which determines a significant burden of morbidity and mortality, as widely documented in the literature. AF also constitutes a risk factor for other less investigated conditions, such as heart failure, pulmonary embolism, impairment in physical performance, reduced quality of life, development of disability, mood disorders and cognitive impairment up to dementia. In the elderly population, the management of AF and its complications is particularly complex due to the heterogeneity of the ageing process, the lack of specific evidence-based recommendations, as well as the high grade of comorbidity and disability characterizing the over 65 years aged people. In the present review, we aim to summarize the pieces of the most updated evidence on AF complications beyond stoke, mainly focusing on the elderly population.

## 1. Introduction

Atrial Fibrillation (AF) represents the most common arrhythmia worldwide, affecting about 2% of the general population (Chugh et al., 2014). In the next decades, due to population aging, improvement in diagnosis, management and therapies, AF prevalence will likely increase, outlining a global epidemic with even more significant impact on public health systems (Zoni-Berisso et al., 2014). Similarly to the majority of cardiovascular pathologies, AF prevalence increases with age, accounting from less than 0.5 % of the population younger than 50 years up to 10 %–17 % of people aged 80 years and older (Bencivenga et al., 2017). According to the "Expert consensus of the French Society of Geriatrics and Gerontology and the French Society of Cardiology", which has analysed the prevalence of AF stratified by age and sex in studies published from 1991 to 2011 in different countries, 70 % of patients with AF are over 75 years old, thus suggesting this arrhythmia to be a pathology almost exclusively of the elderly (Hanon et al., 2013).

AF can induce the formation of atrial thrombi and systemic embolism; therefore, it is often associated with a high number of complications. Among them, embolic stroke is undoubtedly the main one: the risk of stroke increases by almost fivefold in patients suffering this arrhythmia (Wolf et al., 1991). Aging is an independent risk factor for stroke in AF patients (Van Staa et al., 2011); indeed the $CHA_2DS_2$-VASc score, recommended for thromboembolic risk stratification according to the most recent European Society of Cardiology (ESC) guidelines for the management of AF, attributes 1 point for age between 65 and 74 years and even 2 points for age ≥75 years, the same as history of previous stroke or thromboembolism (Kirchhof et al., 2016). Furthermore, the presence of other concurrent conditions substantially enhances the risk of stroke and these are amplified in the characterization of the elderly patient: the high number of comorbidities, the increased risk of complications, the intrinsic vulnerability, the frequent lack of specific evidence-based indications, especially for the frail elderly. These features make the therapeutic management of this population particularly insidious, primarily if associated with specific acute or chronic disorders (Fohtung and Rich, 2016).

Beyond stroke, AF represents a risk factor for several other clinically relevant conditions, that can strongly impact on the health status of elderly patients: heart failure (HF), pulmonary embolism (PE), impairment in physical performance, reduced quality of life (QoL) and development of disability, mood disorders and cognitive impairment up to dementia (Fig. 1). The association between AF and these conditions/

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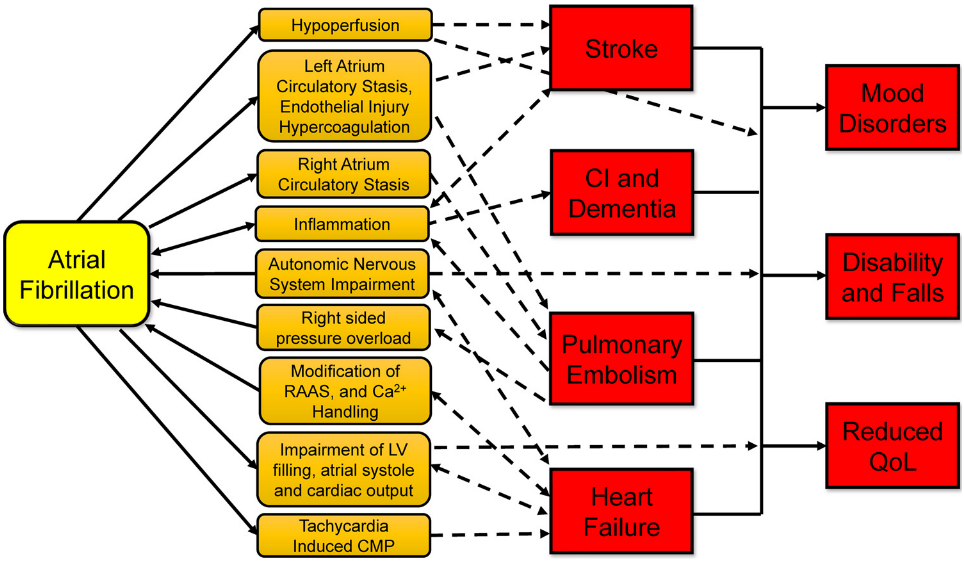


**Fig. 1.** Atrial fibrillarion as risk factor: an intricate relationship.
AF constitutes a well-documented risk factor for stroke and other less investigated conditions. Although the lack of a specific cause-effect relationship, many widely accepted theories emerged on potential mechanisms linking AF with heart failure, pulmonary embolism, impairment in physical performance, reduced quality of life and development of disability, mood disorders, and cognitive impairment up to dementia.
AF: Atrial Fibrillation; CI: Cognitive impairment; CMP: Cardiomyopathy; LV: Left Ventricular; QoL: Quality of Life; RAAS: Renin Angiotensin Aldosterone System.

pathologies in the elderly has been mainly highlighted by small observational, cross-sectional or longitudinal studies or data derived from registries, whereas more scientifically rigorous studies, such as trials, are not available (Table 1). Further, AF is associated with a countless number of both cardiovascular-related (i.e., hypertension, diabetes, ischemic heart diseases, cardiomyopathies) and non-cardiovascular-related diseases (i.e., respiratory disorders and cancer) for which the boundary between epidemiological association and cause-effect relationship with AF is not entirely defined (Lloyd-Jones et al., 2004; Gómez-Outes et al., 2017). In the present manuscript, the authors aim to summarize the evidence on the non-stroke AF complications, primarily focusing on the elderly.

## 2. AF and heart failure

As widely hypothesized in the past decades, AF and HF are emerging as new epidemics of this century (Anter et al., 2009): the prevalence of HF is projected to increase by almost 50 %, and the incidence of AF is predicted to double by 2030 (Chugh et al., 2014; Carlisle et al., 2019). The relationship between AF and HF is bidirectional; indeed, AF can be considered a cause of HF onset and worsening, otherwise, HF may trigger the development of AF. The notion that AF and HF are strongly correlated is mostly accepted, and it finds a first pathophysiological explanation in the several shared predisposing risk factors: hypertension, diabetes, obesity, coronary artery disease, sleep breathing disorders, smoking and renal impairment (Kotecha and Piccini, 2015). Furthermore, AF can promote the development of HF and also constitute a trigger for HF decompensation, through several pathophysiological pathways: a) impairment of left ventricular filling due to loss of atrial systole, which in turn reduces stroke volume and cardiac output; b) shorter diastolic filling time determined by increased resting heart rate and amplified chronotropic response to exercise, that results in further reduction of cardiac output; c) variable timing of diastole, with the decrease in left ventricle (LV) filling during short cycles not being compensated by an adequate increase during longer ones; d) tachycardia-induced cardiomyopathy, whose incidence, according to retrospective studies or reports performed on subjects with AF, is estimated to range from 25 % to 50 % (Edner et al., 1995; Redfield et al., 2000; Nerheim et al., 2004; Donghua et al., 2013). Notably, it has been suggested that aging facilitates the development of tachycardia-induced cardiomyopathy since the time from AF diagnosis to the presentation of LV dysfunction is shorter among older patients (Kim et al., 2019).

However, HF may trigger the development of AF through several mechanisms, including: neurohormonal dysregulation, altered $Ca^{2+}$ handling and elevation of cardiac filling pressure. It is well established that adrenergic and renin-angiotensin-aldosterone system (RAAS) hyperactivity in HF leads to increased LV filling pressures and afterload, which in turn enhances left atrial stretch and fibrosis, supporting anisotropic conduction which facilitates AF onset and persistence (Li et al., 2001). HF-related altered $Ca^{2+}$ handling represents another potential mechanism associated with impaired after-depolarizations, generating a pro-arrhythmic substrate. The intertwined pathogenesis and the common predisposing factors between AF and HF make it challenging to distinguish whether one entity exacerbates the other, or they are different manifestations of the same underlying mechanism.

However, several studies have highlighted the high prevalence of HF in the AF population. The Renfrew/Paisley Study reported in 15406 middle-aged men and women that AF was associated with a 3 fold increased risk for incident HF (3.4, 95 % CI: 1.7–6.8), higher than stroke incidence (2.5, 95 % CI: 1.3–4.8) and cardiovascular events (1.8, 95 % CI: 1.3–2.5) during a 20 years follow-up. AF was independently associated with overall mortality, and the association between AF and cardiovascular events was more pronounced in women (Stewart et al., 2002). In a cohort of elderly patients (over 65 years old) with abnormal LV relaxation, diastolic dysfunction was associated with the development of AF and chronic HF. Indeed, about 18 % of patients developed these complications during a mean follow-up of 4 years. Furthermore, history of myocardial infarction, diabetes, LV hypertrophy, left atrial enlargement and aging constituted independent predictors of adverse outcomes. Although an evident trend toward increased risk of AF and/or HF in women, this did not reach statistical significance (Tsang et al., 2004).

According to the real-life global survey international registry, HF prevalence within AF subtypes was: 33 % in paroxysmal, 44 % in persistent, and 56 % in permanent AF patients (Chiang et al., 2012). Another study, including one-third of elderly patients (75 years and older), reported a prevalence of HF in different AF subtype ranging from 4.6 % for paroxysmal AF to 19.7 % for permanent AF. Furthermore, in elderly patients with AF, HF with preserved ejection fraction (HFpEF) was the most frequent HF phenotype, representing 55.2 % of the whole population (Fumagalli et al., 2015). During the last years, the increased knowledge in HFpEF diagnosis and pathophysiology was paralleled by a rise in the proportion of patients being ”newly” diagnosed with HFpEF, leading to a significant modification in HF epidemiology. In a large, multicentric cohort study, including 23644 patients with HF, McManus and colleagues evaluated the association of preexisting or incident AF with clinically relevant outcomes. The frequency

**Table 1**
Main articles reporting the relationship between AF and non-stroke complications.

| First Author, year | Study Design | Study population | Aims | Results |
|---|---|---|---|---|
| *atrial Fibrillation and Heart Failure* | | | | |
| Stewart et al., 2002 | Prospective | 15406 patients, 7052 M, 8354 F, 45–64 yo; 100 patients with AF | AF effect on long term (20 years) outcomes | AF is an independent predictor of CV events [HR 3.0 in. F (2.1–4.2) and 1.8 in. M (1.3–2.5)]; stroke [HR 3.2 in. F (1.0–5.0), and 2.5 in. M (1.3–4.8)]; HF [HR 3.4 in. F (1.9–6.2), 3.4 in. M (1.7–6.8)]. |
| Tsang et al., 2004 | Retrospective | 569 patients over 65 yo with abnormal LV relaxation. 60 % F. | AF and HF risk and outcome during a follow-up of 4.0 ± 2.7 years. | 36 patients developed AF, 50 CHF, 19 AF and CHF; Age, myocardial infarction, diabetes mellitus, LV hypertrophy, and LA volume were predictors of AF and CHF in patients with abnormal diastolic relaxation. |
| Chiang et al., 2012 | Large-scale, cross-sectional international survey | 9816 AF patients | AF clinical characteristics in a real-life study | 2606 (26.5 %) paroxysmal, 2341 (23.8 %) persistent, and 4869 (49.6 %) permanent AF. HF prevalence (32.9 %, paroxysmal, 44.3 % persistent, 55.6 % permanent AF) |
| Fummagalli S et al 2015 | Prospective | 3119 AF patients; 33.7 % over 75 yo; mean age, 815 years; 50.6 % F | Age-related differences in presentation, treatment, and outcome of AF. | Elderly had more frequently (47.5 % vs. 41.1 %; $p < 0.0001$) non-self- terminating forms of AF. CHF present in 55 % of elderly. |
| McManus et al., 2013 | Retrospective Multiethnic Community-Based Cohort | 23644 HFpEF and HFrEF patients, 47.7 % F. | AF impact on HFpEF and HFrEF outcome | AF was present in 43.2 % of HFpEF and 32.4 % of HFrEF; Preexisting and incident AF were significantly associated with hospitalization for HF (HR 1.22, 95 % CI 1.15–1.29; HR 2.00, 95% CI 1.83–2.18, respectively), with similar results in those with HF-PEF or HF-REF. |
| Startipy U et al 2017 | Retrospective | 41446 HF patients, HFrEF 55.4 % HFmEF 21.5 % HFp EF 23.1 % | AF effect on HFpEF, HFrEF and HFmEF outcome | AF prevalence: 53 % in HFrEF; 60 % in HFmEF; 65 % in HFpEF. Age is independently associated with HF, HFpEF of 2.23 (95 % confidence interval [CI]: 1.98–2.51), in HFmrEF of 2.28 (95% CI: 1.98 − 2.62), and in HFrEF of 2.34 (95% CI: 2.15 − 2.55). F sex and myocardial infarction are inversely correlated with AF. |
| Kotecha et al., 2016 | Systematic Review and Meta-analysis | 45100 patients, HFrEF 48.5 %; 32.3 % F HFpEF 51.5 %; 58.9 % F | Outcome in AF patients with HFrEF and HFpEF | All-cause mortality was significantly higher in AF-HFrEF; risk ratio (RR) 1.24, 95 % CI 1.12 − 1.36, $p < 0.001$. (n = 45,100), with absolute death rates of 24% compared to 18% in AF-HFpEF over 2 years $p < 0.001$. (n = 45,100), with absolute death rates of 24% |
| Roddux V. et al 2017 | Systematic Review Meta-Analysis | 220928 patients 17.5 % AF 49.1 % F | CV mortality, myocardial infarction and HF risk in AF patients. | AF was associated with an increased risk of myocardial infarction: (RR) 1.54, 95 % (CI) 1.26 − 1.85), all-cause mortality (RR 1.95, 95% CI 1.50 − 2.54) and HF (RR 4.62, 95% CI 3.13 − 6.83). |
| Odutayo et al., 2017 | Systematic Review Meta-Analysis | 43549 AF patients | Mortality and cardiovascular disease risk associated with AF in CHF, stratified our analyses by AF timing and pattern. | Mortality risk for AF varied between incident and prevalent AF (RR 2.21, 95 % CI 1.96 − 2.49 vs relative risk 1.19, 95% CI 1.03 − 1.38, respectively; $P < .001$). The RR of mortality associated with incident AF in HFpEF was 1.86 (95% CI: 1.37 − 2.53). |
| Chamberlain et al., 2011 | Observational, Community based cohort | 1664 HF patients, 54.6 % F; 553 AF prior to HF 384 AF after HF | Outcome in AF and CHF patients | AF prior to HF had a 29 % increased risk of death, while AF after HF more than a 2-fold increased risk of death. |
| Savarese G. et al 2017 | Meta-Analysis | 55011 patients with AF, 52 % with HF; 36 % F. 27,518 on DOACs. | Efficacy and safety of DOACs in AF and HF | HF patients had reduced rates of overall and intracranial bleeding (RR: 0.86; 95 % CI: 0.81 to 0.91; $p < 0.01$) (RR: 0.74 95 % CI: 0.63 to 0.88; $p < 0.01$) but increased rates of all-cause and CV death (RR: 1.70 95 % CI: 1.31–2.19; $p < 0.01$); (RR: 2.05 95% CI: 1.66–2.55; $p < 0.01$). DOACs, compared with warfarin significantly reduced overall bleeding, regardless of the presence or absence of HF. |

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**Table 1** (*continued*)

| First Author, year | Study Design | Study population | Aims | Results |
|---|---|---|---|---|
| Kotecha et al., 2017 | Meta-Analysis of RCT | 3043 AF and HF 14,166 Sinus Rythm; median age 65 years; 24 % F. | Prognostic importance of heart rate in patients with HFrEF | Beta-blockers reduce mortality in patients with HFrEF in sinus rhythm, HR: 0.73 vs. placebo; 95 % CI: 0.67 to 0.79; p < 0.001), regardless of baseline heart rate (interaction p = 0.35). Beta-blockers had no effect on mortality in patients with AF (HR: 0.96, 95 % CI: 0.81–1.12; p = 0.58) at any heart rate (interaction p = 0.48). |
| Caldeira et al., 2011 | Systematic Review and Meta-Analysis of RCT | 2486 AF and HF patients. | Effects of rate and rhythm control in patients with AF and HF. | Hospitalisations were less frequent in rate control than in rhythm control patients (RR 0.92; 95 % CI: 0.86 − 0.98; p = 0.008). Mortality and stroke/thromboembolic events were not significantly different in rate and rhythm control arms (RR 1.03; 95% CI: 0.90 − 1.17) and (RR 1.09; 95% CI: 0.61 − 1.96). |
| Zhu et al., 2016 | Systematic Review and Meta-Analysis of RCT | 143 AF and HF patients. | Effectiveness of restoring the sinus rhythm by catheter ablation relative to medical rate control for persistent AF patients with HF. | Catheter ablation improved LVEF, exercise capacity, and quality of life for persistent AF patients with HF compared with the medical rate control strategy :MD: 6.22 %; 95 % CI: 0.7 − 11.74, P = 0.03) and peak VO2 (MD: 2.81 mL/kg/min; 95% CI: 0.78 − 4.85, P = 0.007; Minnesota Living with Heart Failure Questionnaires scores (MD: -11.05; 95% CI: − 19.45 to − 2.66, P = 0.01). |
| Kelly et al., 2019 | Retrospective analysis from Get With The Guidelines-Heart Failure (GWTG-HF) registry data | 15682 AF and HF patients; median age 83; 65.8 % F; 1857 rhythm control; 13,825 rate control. | Outcomes in patients with HFpEF complicated by AF. | Rhythm control in patients aged 65 and older with heart failure with preserved ejection fraction and AF was associated with a lower risk of 1 year all-cause mortality. Adjusted HR, 0.86; 95 % CI, 0.75 − 0.98; *P* = 0.02. |
| *Atrial Fibrillation and Pulmonary Embolism* | | | | |
| Kukla et al., 2015 | Retrospective | 975 patients (59 % F) with AF; mean age 66 ± 15 yo (range 17–98) | RHT and AF prevalence and impact on survival and complications | AF and RHT in 16 patients (7%), mortality in patients with both AF and RHT 50 % vs 20 % in only AF, complications 40 % vs 22 % |
| Bikdeli et al., 2017 | Systematic review | 87063 patients with AF by 89 articles | Pathophysiological considerations, epidemiology, prognostic power, and potential impact of the association | Higher risk of PE in AF patients. Pooled analysis of 2 studies showed in AF patients and odds ratio of PE = 2.86 (95 % CI: 2.26–3.60) |
| Ng et al., 2016 | Retrospective | 1142 patients (55 % F) with PE; mean age 67.2 ± 16.6 yo | Prevalence and incidence of AF in patients with acute PE | Age-adjusted prevalence of AF 4672/100,000, (F 5358/100,000, M 4218/100,000). Age-adjusted incidence rate was 984/100,000 person-years (F 840/100,000 person-years, M 1167/100,000 person-years) |
| Tang et al., 2017 | Retrospective | 305 patients (≈53 % F) with PE and AF; age over 65 yo | CHADS2 score predicts prognosis of PE in patients with AF | CHADS2 and CHA2DS2-VASc scores were associated with adverse in-hospital outcome in patients with PE and AF. The combination of CHADS2 score ≥2 and sPESI ≥1 might help stratification of high-risk patients. |
| Guler et al., 2016 | Cross-sectional, retrospective, observational | 71 patients (F with No PE 38.5 %; F with PE 66.7 %) with persistent paroxysmal AF; No PE mean age 56.0 (26–83), PE mean age 66.0 yo (50–75) | Incidence and predictors of asymptomatic PE in patients undergoing AF ablation. | CHA2DS2-VASc scores were independent predictors of asymptomatic PE in patients undergoing AF ablation. |
| Hald et al., 2018 | Prospective | 29842 participants of the fourth and sixth surveys of the Tromsø study | Impact of AF on the cause-specific risks of PE and Ischemic Stroke | AF was related to higher risk of PE (HR, 10.88; 95 % CI, 6.23 − 18.89) and Ischemic Stroke (HR, 6.16; 95% CI, 4.47 − 8.48). When examining PE risk at different time points after AF diagnosis, the risk decreased over time and disappeared 3 years after onset of AF |
| *AF, physical performance and falls.* | | | | |
| Rienstra et al., 2013 | Cross-sectional prospective | 3609 participants (59 % F) of the Framingham Heart Study; mean age 73 ± 8 yo | Relation among physical disability (Rosow-Breslau Functional Health Scale), subjective health (self-reported) and incident AF | 24 % of patients suffered prevalent physical disability at baseline. 10-year age- and sex-adjusted incidence rate for AF was 13 %. Prevalent physical disability was related to incident AF (multivariable-adjusted HR 1.25; 95 %CI, 1.02–1.54) |

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**Table 1** (*continued*)

| First Author, year | Study Design | Study population | Aims | Results |
|---|---|---|---|---|
| Magnani et al., 2016 | Prospective | 2753 Health ABC participants (F 52 %); mean age 73.6 ± 2.9 yo | Association of incident AF and 4-year interval decline in physical performance | AF patients experienced a significantly greater 4-year physical performance battery decline than the ones without AF at age 70, 74, 78, and 82, with mean estimated decline ranging from -0.08 to -0.10 U (95 % CI -0.18 to -0.01) |
| Donoghue et al., 2014 | Prospective | 4525 Irish Longitudinal Study on Ageing (TILDA) participants (F 52.1 %); mean age 63.5 ± 8.9 yo | Association between AF and objectively measured mobility | AF was independently associated with lower usual gait speed in community-dwelling adults |
| Sanders et al., 2012 | Retrospective | 442 patients; median age of 81 yo | Association between AF and non-accidental falls. | The prevalence of history of AF was significantly higher in patients with non accidental fall when compared to patients with accidental fall (26 % vs 15 %). AF was an independent risk factor for non accidental fall in patients ≤81 years old (2.5 times greater) |
| Wong et al., 2017 | Retrospective | 113600 individuals (F 46.6 %); mean age 55.8 ± 19.7 yo | AF association with fracture risk | After adjusting for covariates, the association between a history of AF and incident hip fracture was statistically significant in both men (adjusted HR 1.97 [95 % CI 1.61–2.42]) and women (adjusted HR 2.08 [95 % CI 1.80–2.39]) |
| Hung et al., 2013 | Cross-sectional prospective | 401 geriatric subjects (F 24 %); mean age 82.2 ± 0.2 yo | Cardiovascular co-morbidities and medication associated with falls in older adults with AF. | Benzodiazepine use (OR 18.22, 95 % CI 2.71 − 122.38), a history of paroxysmal AF (OR 12.18, 95% CI 1.37 − 108.70) and hypertension (OR 9.49, 95% CI 1.19 − 75.57) were independent factors for falls in older adults with AF. Prevalence of falls or recurrent falls in AF subjects showed a linear relationship with the number of independent factors for falls. |
| Banerjee et al., 2014 | Retrospective | 7156 patients with non valvular AF; with prior history of falls (F 56.6 %) mean age 82.9 ± 8.9, with no prior history of falls (F 37.6 %) mean age 69.9 ± 15.1 | Risk of cardiovascular outcomes associated with prior history of falls in patients with AF. | Prior history of falls was 1.1 %. By Cox regression analyses for all AF patients with heart failure, the association for ischemic stroke/ thromboembolism (HR 1.71; 95 % CI, 1.04 − 2.83; P 1/4 .04) and all-cause mortality (HR 1.68; 95% CI, 1.07 − 2.62; P 1/4 .02) only remained significant. |
| Leibowitz et al., 2017 | Retrospective | 410 > 65 yo subjects underwent surgical repair of hip fracture (F 66.1 %); mean age 80 ± 7.8 yo | Newly diagnosed AF in subjects underwent hip fracture repair surgery was predictive for one-year mortality | Mortality in patients with new onset AF was higher than in the group without AF (60 % vs 19.5 %; p = 0.001) |
| *AF, disability and quality of life.* | | | | |
| Wallace et al., 2016 | Longitudinal prospective | 4046 subjects from the Cardiovascular Health Study (F 58.2 %); mean age 73 ± 5 yo | Associations between incident AF and disability-free survival / risk of disability | AF was associated with shorter disability-free survival and higher risk of ADL disability (HR 1.71, 95 % CI = 1.55 − 1.90 HR = 1.36, 95% CI = 1.18 − 1.58). |
| Ekerstad et al., 2018 | Clinical observational study | 408 elderly of the TREEE study; patients with AF (F 55.8 %) mean age 86.1 ± 5.1, patients without AF (F 56.9 %) mean age 85.3 ± 5.6 yo. | Prevalence of AF among hospitalized frail elderly patients | The prevalence of AF in hospitalized frail elderly population was 47 %. |
| Strømnes et al., 2019 | Systematic Review | 25 studies assessing sex differences in QoL in patients with AF (F 26 − 50%) | Sex differences in the QoL of patients with AF | Female AF patients report poorer QoL and were more symptomatic than male AF patients. |
| Freeman et al., 2015 | Observational, community-based prospective | 10087 adults who had AF (F 42.4 %); median age 75 (67 − 82) | Correlation between degree of AF symptoms severity and quality of life; the association between symptoms or quality of life with clinical outcomes (death, hospitalization, stroke, and major bleeding). | Inverse correlation between the EHRA AF symptom severity class and quality of life measured by the AFEQT. Patients with AF-related symptoms at baseline (EHRA ≥ 2) had a higher risk of hospitalization (adjusted hazard ratio 1.23 (95 % CI 1.15–1.31) |
| Thrall et al., 2006 | Systematic Review | 49 studies (528 patients) | Impact of AF on patients' QoL | Patients with AF showed significantly poorer QoL compared with healthy controls, the general population, and other patients with coronary heart disease |
| Wynn et al., 2015 | Prospective, multicenter randomized controlled trial | 146 patients with persistent AF of the SARA study (F 33 %); mean age 55 ± 9 yo | Quality of Life in AF patients undergoing catheter ablation | Catheter Ablation significantly improved QoL in persistent AF patients; medical therapy had no appreciable effect. |
| *AF, anxiety and mood disorders.* | | | | |
| Thrall et al., 2007 | Prospective | 101 AF patients (F 38.6 %); mean age 66.3 ± 11.0 yo | Prevalence and persistence of depression and anxiety in patients with AF, and their effect on future quality of life | AF patients presented depression (30 %), state anxiety (23 %), and trait anxiety (22 %). Depression was the strongest independent predictor of future QoL |

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**Table 1** (*continued*)

| First Author, year | Study Design | Study population | Aims | Results |
|---|---|---|---|---|
| Rewiuk et al., 2018 | Clinical multicenter observational study | 4049 AF subject enrolled in the PolSenior project (F 48 %); mean age 78.1 ± 8.3 yo | Prevalence of depression in Polish community-dwelling older patients with a history of AF. | After adjustment for age, gender and marital status AF was the second strongest cardiovascular risk factor of depression occurrence (OR = 1.69; 95 %CI: 1.43–2.00). After full adjustment for comorbidities, number of medications, and significant geriatric dysfunctions, AF remained the only cardiovascular comorbidity correlating with depression occurrence (OR = 1.35, 95 %CI: 1.10–1.67), beside stroke |
| Wändell et al., 2016 | Retrospective | 12283 AF subjects (F 46.2 %); mean age 74.4 ± 10 | Effects of depression and anxiety on all-cause mortality in patients with AF. | 30 % increased mortality risk in men with AF and concomitant depression compared to their counterparts without depression. Among women, the association between depression or anxiety and all-cause mortality was weaker and not statistically significant. |
| von Eisenhart Rothe et al., 2014 | Controlled retrospective | 702 AF patients of the ANTIPAF and Flec-SL trials (F 34.5 %); mean age 64.16 ± 13 | Assessment of depressed mood frequency in persistent or paroxysmal AF and identification of cases of major depressive disorder in AF | Depressed mood was more severe in patients with persistent AF than in patients with paroxysmal AF (OR confounder controlled model = 1.44; 95 %CI: 1.13 − 1.75). |
| Hu and Lin, 2019 | Retrospective | 88259 patients with AF (F 43.5 %) and 88,259 without AF (F 44.5 %); with AF mean age 72.7 ± 13.4, without AF 72.4 ± 14.2 | Incidence of suicide attempt in a Taiwanese population following admission for AF, adjusted for competing risks and comorbidities. | Incidence of suicide attempt after AF significantly increased in the following 10 years. |
| *AF and cognitive impairment.* | | | | |
| Bunch et al., 2010 | Retrospective | 37025 patients by the Intermountain Heart Collaborative Study database (F 39.9 %); mean age 60.6 ± 17.9 yo | Verification of the independent risk of AF and AD. The impact of AF in those subsequently diagnosed with AD and other dementia types on risk of mortality. | 27 % developed AF and 4.1 % developed dementia during the 5-year follow-up. AF was independently associated with risk of all forms of dementia. The highest risk of AD was in the younger AF group. The presence of AF in all dementia subtypes identified patients at higher risk of mortality, most prominent in the youngest population. |
| Singh-Manoux et al., 2017 | Prospective | 414 AF patients of the Whitehall II study (15.7 %); mean age 58.8 ± 5.9 | Potential dose-response association of duration of exposure to AF on cognitive decline, and whether stroke and coronary heart disease subsequent to AF mediated this association. | AF was associated with a 6.22 times increased risk of stroke (95 % CI: 4.74, 8.16) and its association with dementia was not fully explained by stroke. AF increased risk of coronary artery disease (HR = 5.29; 95 % CI: 4.50, 6.22) and CVD (HR = 5.74; 95 % CI: 4.95, 6.65). The association between AF and dementia was present in those with CVD (HR = 1.79; 95 % CI: 1.04, 3.08) but not in those free of CVD (HR = 1.29; 95 % CI: 0.74, 2.24). |
| Chen et al., 2014 | cross-sectional study | 1906 participants of the U.S. community-based ARIC study (F 52.9 %); mean age 76.9 ± 5.2 yo | AF association with lower cognitive function | Persistent but not paroxysmal AF is associated with lower cognitive function in community-dwelling elderly individuals |

AD: Alzheimer's disease; ADL: activities of daily living; AF: atrial fibrillation; AFEQT: Atrial Fibrillation Effect on QualiTy-of-Life; CHF: Chronic Heart Failure; CV: Cardiovascular; CVD: Cardiovascular Disease; CI: confidence interval; DOACs: Direct Oral Anticoagulants; EHRA: European Heart Rhythm Association; F: female; Health ABC: Health, Aging, and Body Composition; HF: Heart Failure; HFmEF: Heart Failure with midrange Ejection Fraction; HFrEF: Heart Failure with Reduced Ejection Fraction; HFpEF: Heart Failure with Preserved Ejection Fraction; HR: hazard ratio; OR: odds ratio; LA: left atria; LVEF : Left Ventricular Ejection Fraction; PE: pulmonary embolism; QoL: quality of life; RHT: right heart thrombi; RR: Relative Risk; MD: Mean Difference; sPESI: simplified pulmonary embolism severity index; yo: years old.

of pre-existing AF was higher in HFpEF than in HFeEF (43.2 % vs. 31.4 %, respectively), while incident AF resulted higher in HFrEF than in HFpEF (10.5 % vs. 9.5 %, respectively). During a median follow-up of 1.8 years, incident and pre-existing AF independently predicted morbidity and mortality both in HFpEF and HFrEF patients. It is essential to underline that more than half of the population (53.9 %) was represented by over 75 years old patients (McManus et al., 2013). Further studies to explore differences among HF categories in the clinical setting of AF are still needed, considering some conflicting results reported in the scientific literature (Kotecha et al., 2016).

Several clinical trials and epidemiological studies confirmed the relevant impact of AF on cardiac mortality in HF patients, accordingly, a recent meta-analysis reported the association between AF and the risk of developing HF to be independent of the coronary status (Ruddox et al., 2017). AF frequently constitutes an incident condition in chronic HF patients and the time of arrhythmia onset importantly impacts the survival rate (Odutayo et al., 2017). In particular, when an arrhythmia occurs after HF diagnosis, AF exerts a worse prognostic impact, with a risk of death more than doubled than that observed in HF patients without AF. The reasons behind this phenomenon are not completely known: besides the above-reported theories linking AF and HF, it is possible to speculate on the role exerted by medications (e.g., drugs for heart rate control), fluid status, or HF etiology (Chamberlain et al., 2011). Thus, AF onset may constitute an indirect sign of HF progression (Hohendanner et al., 2018).

Anticoagulation, rate and/or rhythm control represent current cornerstones of AF treatment, whose management is particularly complex in elderly patients with concomitant HF. According to current guidelines, suggesting the use of $CHA_2DS_2$-VASc score to assess the thromboembolic risk in AF patients, almost all elderly patients with concomitant AF and HF receive an indication for antithrombotic therapy unless specific contraindications (Kirchhof et al., 2016). Many trials have demonstrated that direct oral anticoagulants (DOACs) ensure equivalent efficacy at reducing stroke events with superior safety, in terms of lower risk of bleeding, compared to Vitamin K antagonists. Further, DOACs do not require routine International Normalized Ratio (INR) monitoring, which is needed to check the therapeutic range in patients treated with warfarin, while dosing of DOAC is based on clinical and laboratory data (Thomas et al., 2017). For all the above-mentioned reasons, DOACs are frequently prescribed in elderly HF patients with AF (Hohendanner et al., 2018). From a recent meta-analysis comparing DOACs with warfarin, it emerged that the non-vitamin K antagonists reduced embolic events and bleeding, with no differences related to HF presence (Savarese et al., 2016). Moreover, it is essential to mention that left atrial appendage closure represents as a valid alternative approach in AF patients suffering high bleeding risk (Kirchhof et al., 2016). The decision of whether to target a rhythm or rate-control strategy frequently represents a challenging issue in elderly HF patients. In consideration of the efficacy of HF-related mortality, beta-blockers constitute the gold standard treatment to achieve rate control if concomitant AF is present, while digoxin and amiodarone represent alternatives burdened by a higher risk of side effects (Kirchhof et al., 2016; Ponikowski et al., 2016). Alongside the importance of heart rate control to decrease sympathetic tone, reduce oxygen consumption and allow adequate diastolic filling time (Kotecha et al., 2017; Komici et al., 2018), the pathophysiological assumption of rhythm control therapy for AF in HF patients is intuitive, especially in the elderly. Indeed, the contribution of atrial contraction to ventricular filling becomes particularly relevant in the elderly population to support an adequate cardiac output, as widely demonstrated by several investigations (Ionescu-Ittu et al., 2012).

Following current guidelines, the therapeutic armamentarium of antiarrhythmic approaches to treat AF in HF patients is limited to electrical cardioversion, amiodarone, or catheter-based pulmonary vein isolation, due to specific contra-indications of the other class IC/class III drugs in patients with structural heart disease (Kirchhof et al., 2016; Ponikowski et al., 2016). The positive impact of rhythm control strategies on mortality has also been confirmed in HF patients, despite no significant difference with rate control approaches has emerged (Caldeira et al., 2011). Although rate control therapies have been associated with reduced hospitalization rates compared to rhythm control (Caldeira et al., 2011), recent data indicate that the latter strategy is particularly useful when obtained through catheter ablation, whose application can reduce HF-related mortality and hospitalizations, independently from the potential EF increase in HFrEF patients (Merchant and Delurgio, 2014; Zhu et al., 2016). Further, retrospective data from the Get With The Guidelines-Heart Failure (GWTG-HF) registry revealed rhythm control to be associated with reduced risk of 1-year all-cause mortality in patients with AF and HFpEF aged 65 years and older when compared to rate control approaches (Kelly et al., 2019).

Based on the above-mentioned data, it is evident that whether HF patients more benefit from a rhythm or rate-control approach remains unclear. In the absence of additional data on specific populations, including the frail elderly patients, the decision on the most appropriate strategy may be based on the risk/benefit balance assessed in every single patient (Mene-Afejuku et al., 2018).

Another relevant issue is represented by the impact of HF therapies on AF onset and progression. Based on available scientific evidence, current guidelines recommend the use of drugs inhibiting RAAS for AF prevention in HF (Kirchhof et al., 2016). Although beta-blockers constitute a cornerstone of the pharmacological approach in HFrEF, these drugs seem to lose their ability to reduce mortality if concomitant AF is present (Kotecha et al., 2017). Inconclusive results have been obtained from studies exploring the role of other drugs recommended for the management of HFrEF (including diuretics, digoxin, mineralocorticoid receptor antagonists, statins) on new AF onset or outcomes. In this scenario, it is evident that these therapies still warrant further investigation in this specific setting, especially in the elderly population (Hohendanner et al., 2018). To date, no studies on the new HF therapeutic option sacubritril/valsartan are available to take over any role on the onset or progression of AF.

As previously described, HFpEF is the most prevalent HF phenotype among elderly and AF represents one of the most frequent concomitant comorbidity (Bencivenga et al., 2017), moreover, atrial remodeling constitutes a hallmark of HFpEF, independently associated with increased hospitalization and mortality rates (Rossi et al., 2014). Since currently no therapy has revealed to be effective in the management of HFpEF patients, and RAAS inhibitors, statins and mineralocorticoid receptor antagonists did not prove to be effective at reducing the occurrence of AF in the presence of atrial remodeling (Woods and Olgin, 2014), there is a particular interest in the scientific community to research for active drugs in this HF subtype.

## 3. AF and pulmonary embolism

Although being considered two different entities without an established pathophysiological link, several pieces of evidence support an association between PE and AF (Flegel, 1999). In a retrospective observational study on a thousand of patients with acute PE, AF has emerged as frequent coexisting morbidity, with an impact on mortality, not rarely associated with the evidence of right-sided cardiac thrombi. Further, AF patients with evidence of thrombus in right-sided heart showed significantly higher mortality (Kukla et al., 2015). Despite several clinical cases of PE in AF elderly patients have reported the echocardiographic finding of thrombus in the right atrium, it has not been adequately identified as the ascertained pathophysiological mechanism of PE in AF (Bălăceanu, 2011; Valiton et al., 2017; Ptaszynska-Kopczynska et al., 2019). However, the most accepted mechanistic link between AF and PE identifies in right atrium blood flow reduction, related to the absence of atria contractions, the trigger that induces clot formation with consequent potential embolization to the pulmonary vascular bed, similarly to systemic embolization determined by thrombus formation in the left atrium (Flegel, 1999). The coexistence of an atrial septal defect in patients with AF, although less frequent (Ishihara et al., 2002), may represent another contributing mechanism. Finally, PE-related increase in right-heart pressures and systemic inflammatory status may facilitate AF occurrence (Kline et al., 2009). A recent metaanalysis concluded that a strong relationship between AF and PE exists, suggesting the direction of this association to be more indicative for AF as a risk factor for PE than the opposite, although the two conditions share numerous common risk factors (Bikdeli et al., 2017). Another retrospective study on 1142 PE patients revealed age as an independent predictor for the subsequent incidence of AF, together with congestive heart failure, diabetes, and obstructive sleep apnoea; interestingly, all the mentioned comorbidities represent well known AF risk factors (Ng et al., 2016). Accordingly, $CHADS_2$ score provides information for risk stratification in patients with PE and AF, predicting the worse in-hospital outcome (Tang et al., 2017), and the $CHA_2DS_2$-VASc score can also forecast asymptomatic PE in AF patients undergoing ablation (Guler et al., 2016). Further, paroxysmal AF in elderly patients has been related to PE even in the absence of deep vein thrombosis (Morella et al., 2018). In a recent study on nearly 30000 patients enrolled in the fourth, fifth and sixth Tromso study surveys (Hald et al., 2018), from 1994 to 2012, the authors evaluated the incident cases of AF, detecting those who subsequently developed either stroke or PE as first event: in the first 6 months from AF diagnosis, patients showed a 6-fold increased risk of stroke; this data tends to a reduction in the following years, always remaining significant. Similarly, AF patients showed a strong risk of PE, about 10 times superior to those without atrial arrhythmia in the first 6 months; the significant risk decreased over time, fading after about 3 years. As the totality of the evidences in this scientific field, the group of people that developed AF was significantly older than the one of patients which did not experience this rhythm disorder (Hald et al., 2018).

## 4. AF, physical performance and falls

AF accelerates age-related impairment in walking speed, strength, balance and coordination (Magnani et al., 2016). A significant association between AF and physical disability, assessed with Rosow-Breslau Functional Health Scale, already emerged from the Framingham Heart Study (Rienstra et al., 2013). A recent prospective cohort study in community-dwelling elderly patients conducted 4-year interval (from the age of 70 to 82 years) evaluations of physical performance, assessing the Health ABC physical performance battery, grip strength, 2-minute walk distance, and 400-meter walking time. As expected, overall physical performance declined with age and, importantly, incident AF was independently related to a significantly greater decline in all the physical performance tests, with an average of 20 s slower at the 400-meter walk compared to the elderly without rhythm irregularity (Magnani et al., 2016). Similar results have also been obtained assessing mobility through other performance tests, as the Timed Up-and-Go (TUG) test (Donoghue et al., 2014). Physical performance depends on the complex interaction of several functions, mainly involving the cardiovascular, respiratory and musculoskeletal systems. Apart from reduced physical performance due to thromboembolic stroke, the relationship between AF and physical activity is particularly complex due to the presence of many concomitant conditions (e.g., HF, obesity, structural heart diseases) that virtually affect both physical performance and cardiac rhythm. However, it has been hypothesized that AF may cause a reduction in exercise performance mainly through cardiac stroke volume reduction as a consequence of left ventricular systolic dysfunction, impairment of diastolic filling and dyssynchrony in atrioventricular hemodynamic (Rienstra et al., 2012) Alteration of physical performance in the elderly is closely related to an increased risk of falls, one of the most serious and feared events in this population, burdened with frequent fatal complications. Apart from a small number of evidence (Wallace et al., 2017), AF represents an ascertained independent risk factor for non-accidental falls (Sanders et al., 2012; Wong et al., 2017), which can be influenced by the presence of concomitant conditions and therapies, especially in the older patients (Hung et al., 2013). Further, a study on a cohort of 7000 AF patients emphasized that prior history of falls is independently associated with increased risk of stroke/thromboembolism, bleeding and mortality, thus resulting more clinically relevant than estimating the current falling risk (Banerjee et al., 2014).

Fall represents a geriatric syndrome, whose risk and occurrence is influenced by intrinsic (related to patients' health status) and extrinsic (the main one constituted by the environment) factors (Tinetti, 2003). The above mentioned possible mechanisms explaining the link between AF and physical performance may also apply to the risk of falling. Moreover, it has also been reported a potential role exerted by bradycardia after AF-induced high ventricular response, which may turn into a long pause and possibly asystole, leading to syncope and/or subsequent fall. Similarly, falls may also occur as a consequence of paroxysmal AF or be related to the high prevalence of sinus node disease among elderly patients with AF (Maurer and Bloomfield, 2002). Finally, AF seems to negatively act on the baroreflex, aggravating the risk of orthostatic hypotension. All the above-mentioned mechanisms/conditions are exponentially worsened by the use of chronotropic or antihypertensive drugs, highly prevalent in the elderly AF patients (Sanders et al., 2012).

Regarding hip fracture, which constitutes a frequent consequence of falls in older people, one-year mortality in elderly patients undergone surgical repair was significantly superior in patients with postoperative AF and the result was not influenced by medical therapeutic management (Leibowitz et al., 2017). As mentioned above, the delicate balance between the risk of stroke without anticoagulation and the risk of bleeding with anticoagulation poses a relevant clinical challenge in choosing the most appropriate therapeutic approach, which is further complicated by the risk of falls. Despite for the majority of elderly patients the benefits of the antithrombotic therapy may exceed the risks of complications, including major bleeding events, as ascertainable with the use of the scores suggested by the guidelines, the decision-making process should be discussed for each person and shared with the patients and the relatives/caregivers because of the tremendous heterogeneity of the older population, regarding the number and severity of concomitant diseases and the dissimilarity in the social support (Hagerty and Rich, 2017; Bencivenga et al., 2018). It is essential to underline that almost all the main clinical trials have excluded older people who were frail or at high fall risk. As a general consideration, the exaggerated perception of the bleeding risk in the elderly often leads both patients and doctors to desist from using anticoagulant therapy. In this scenario, an important issue is related to the risks of falls and bleeding, which represent the most frequent justifications reported by physicians for non-prescribing anticoagulant therapy in AF (Hylek et al., 2006). Contrarywise, it has been demonstrated that, even in very elderly patients with AF at increased risk of accidental fall, the possibility of developing a traumatic intracranial haemorrhage is negligible compared to the risk of experiencing a stroke (Man-Son-Hing et al., 1999).

In this context, the growing interest of the scientific community in the comparison among the various available anticoagulant agents for the management of thromboembolic risk in AF patients provides minimal but consistent support. Analyses from the recent ARISTOTELE and ENGAGE AF–TIMI48 trials seem to suggest a superiority in terms of efficacy and safety for the DOACs compared to vitamin K antagonist for AF patients at risk or with history of falls, although confirming the worse outcomes, including the risk of major bleeding and death, observed in this vulnerable population (Steffel et al., 2016; Rao et al., 2018). Once again, it is necessary to highlight that the best possible approach should be the development of intensive interventions to reduce fall risk in elderly patients with AF, rather than to give up a proven efficacy therapy like anticoagulants (Hylek and Ko, 2016).

## 5. AF, disability and quality of life

A great heterogeneity in pathophysiological processes characterizes aging: interpersonal variability in age-related decline of body reserve and occurrence of different degrees of comorbidity result in various phenotypes ranging from frailty to successful healthy aging (Cosco et al., 2015). Disability is determined by the gap created between the demands of the environment and the capability of every single person (Evans, 1997), enormously impacting on the QoL of both patients and caregivers (Motl and McAuley, 2010). As mentioned above, AF complications, especially stroke, determine different patterns of disability in surviving patients, greatly affecting their QoL. Many research groups have studied the relationship between AF and disability, often assessing the degree of dependence of older people in terms of activities of daily living (ADL), both basic ADL exploring any difficulty in bathing, dressing, eating, using the toilet, moving out of a bed or chair, and instrumental ADL (IADL), as ability to perform actions with tools such as drugs, telephone, money, home furnishings. The QoL has also been investigated in this clinical setting, although with different non-standardized tools (Reynolds et al., 2008).

A prospective study on healthy people (without AF, disability, history of stroke or HF) aged 65 years or more has demonstrated incident AF, within 7 years of follow-up, to be associated with reduced disability-free survival, even after adjustment for incident stroke and HF (Wallace et al., 2016). The degree of dependence also influences the therapeutic management of AF: many evidence reports underutilization of anticoagulants in older people with impaired ADL and IADL, although evidence of comparable or superior thromboembolic risk than autonomous AF patients (Blich and Gross, 2004; Ekerstad et al., 2018). Interestingly, a recent systematic review of the literature regarding gender differences in the QoL of AF patients described a trend of lower scores in female, but it is still not clear if the causes of the observed dissimilarity may be ascribed to the rhythm disorder or specific characteristics of the study population (Strømnes et al., 2019). The analysis of the data on more than 10000 AF patients, recruited within the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF), revealed symptoms severity, assessed through the European Heart Rhythm Association (EHRA) classification system, to be related with QoL estimated by the Atrial Fibrillation Effect on Quality-of-Life (AFEQT) questionnaire (Freeman et al., 2015). Regardless of the employed methodology, the QoL impairment in AF patients emerged from different studies, including large trials, and it was also indirectly confirmed by the evidence of a significant score improvement through effective rate or rhythm-control therapies (Thrall et al., 2006). Accordingly, catheter ablation has been shown to improve QoL, as well as physical performance and plasma BNP levels, in patients with persistent AF (Wynn et al., 2015; Yagishita et al., 2017).

## 6. AF, anxiety and mood disorders

Mood disorders are prevalent in late life and they are associated with adverse outcomes, due to multifactorial factors, both neurobiological and psychosocial, related to concomitant comorbidities and the onset of cognitive deficits, which lead to adverse outcomes, including suicide and mortality risks (da C. L. Valiengo et al., 2016). Approximately, one on three AF patients suffers anxiety and/or depression, with significant impact on QoL (Thrall et al., 2007). The idea of anxiety acting as a trigger for AF has been tested in several researches, which have supposed an arrhythmogenic substrate in the modulation of autonomic nervous system as the pathophysiological mechanism, together with a possible role played by the increased systemic inflammatory status in creating a fertile substrate for alterations of the heart rhythm (Severino et al., 2019).

The higher prevalence of depression in AF elderly patients has been also identified in a study on 5000 community-dwelling Polish AF patients, aged 65 years or more, independently from disabilities, comorbidities (including the history of stroke), or demographic factors (Rewiuk et al., 2018). A cohort study on more than 12000 Swedish primary care AF patients highlighted the augmented all-cause mortality risk among adults with depression (Wändell et al., 2016). Accordingly, depression has been linked to the risk of sudden cardiac death, major ventricular events and AF recurrence, thus allowing to speculate on a possible role of rhythm abnormalities in the relationship between mood disorders and mortality, independently from other cardiovascular diseases (Shi et al., 2017). Despite comparable symptom burdens, persistent AF patients seem to suffer from a higher depressive mood than people with paroxysmal AF (von Eisenhart Rothe et al., 2014). Moreover, mood disorders also increase the risk for AF recurrence after electrical cardioversion: similarly to the anxiety, a possible mechanism underlying the reported relationship may be an enhanced adrenergic tone and a potential pro-inflammatory state (Lange and Herrmann-Lingen, 2007). Restoration of sinus rhythm seems to reduce anxiety and depression symptoms, as demonstrated by a small prospective study that reported catheter ablation to be more effective than antiarrhythmic drugs in improving mood disorders and QoL in patients with paroxysmal AF. Regarding antithrombotic therapies, it has been suggested that dabigatran may reduce morbidity and mortality of AF patients related to anxiety and depression, also improving the QoL, compared with warfarin (Sang et al., 2013). This scenario emphasizes the need for evaluating mood disorders in patients with AF and to adopt a correct therapeutic approach, even considering frequently reported complications, such as the increased bleeding risk in concomitant therapy with oral anticoagulants and serotonin or serotonin/norepinephrine reuptake inhibitors (Cochran et al., 2011). Furthermore, cardiovascular comorbidities pose challenge in the therapeutic management of AF patients with mood disorders, given the superimposable adverse effects of some effective drugs, such as amiodarone and serotonin/norepinephrine reuptake inhibitors in prolonging QT interval, or diuretics causing hypokalaemia and QT prolongation (Alagiakrishnan et al., 2019).

Finally, it should not be underestimated the evidence of a trend to increased incidence of suicide attempt in AF patients (Hu and Lin, 2019), even taking into consideration the significant reduction in suicide ideation and severe psychological distress obtained with effective arrhythmia ablation, thus suggesting AF to constitute itself a risk factor (Walters et al., 2018).

## 7. AF and cognitive impairment

Cognitive impairment and dementia represent a significant public health burden worldwide with high prevalence ranging from 2% in Africa to over 8% in South America. In 2010 more than 35 million people were living with dementia, and this estimate is expected to double every 20 years up to exceed 115 million in 2050 (Prince et al., 2013). Several prospective epidemiological studies have extensively explored the main features of dementia, in particular regarding the risk factors involved in its pathogenesis. Beside non-modifiable ones, especially age and genetics, lifestyle plays a key role in the onset and progression of cognitive impairment; further, several cardio-cerebrovascular and metabolic diseases have been linked to dementia, including obesity, arterial hypertension, diabetes and dyslipidaemia, which in turn account for 30 % of the risk of cognitive decline (Femminella et al., 2017; Da Silva et al., 2019). Given the growing evidence on the association between cognitive impairment and AF and the frequent under-diagnosis of paroxysmal AF in the elderly suffering dementia, the European, Asian, American and South American Heart Rhythm Association Societies have recently published an expert consensus on arrhythmias and cognitive function, mainly focused on AF (Dagres et al., 2018).

The decline in cognitive function undoubtedly constitutes one of the most studied non-stroke AF complications: from several studies investigating the mentioned relationship, it emerges that the development of cognitive impairment in patients with AF occurs in association with stroke and the presence of subclinical cerebral infarctions, but also in patients without evidence of cerebrovascular alterations. A study on nearly 40000 participants, aged 60 years or over, has prospectively analyzed the incidence of dementia concerning AF: the arrhythmia resulted independently associated with both vascular dementia and Alzheimer's disease (Bunch et al., 2010). It is well known that the risk for stroke is higher in AF patients; moreover, a history of previous stroke increases the risk of recurrence of cerebrovascular events facilitating the development of cognitive impairment. Interestingly, a metanalysis investigating the association between AF and cognitive decline highlighted that patients suffering of atrial arrhythmias are burdened with up to 40 % greater risk of developing cognitive deficits, independently of stroke (Kalantarian et al., 2013). Accordingly, in a large study confirming the strong relationship between stroke and dementia, AF has demonstrated to accelerate cognitive impairment, even in groups of younger patients at intrinsic lower incidence of rhythm disturbance; in the same study, AF was also related to increased development of cognitive decline in non-stroke patients (Singh-Manoux et al., 2017), although it remains unclear whether differences exist between patients with paroxysmal and permanent AF (Gaita et al., 2013; Chen et al., 2016).

Several hypotheses have been formulated regarding the pathophysiological mechanisms involved in the association between AF and dementia: the most accredited one is represented by silent embolism, repetitive microbleeds and clots, with the development of subclinical small cerebral areas of ischemia or infarction. Hitherward, extensive literature, providing data on morphological brain imaging, demonstrates a significant association between silent cerebral infarctions and AF in stroke-free patients (Chen et al., 2014; Kalantarian et al., 2014). Another potential explanation may be found in the reduction of the cardiac output, due to the variability of the R-R interval and to the high ventricular frequency, which is frequent in the elderly with AF (Cacciatore et al., 2012). This thesis is also supported by the evidence of hippocampal atrophy in AF patients, determined by impairment of cerebral perfusion, being the hippocampus a high perfusion-sensitive structure of the brain (Dagres et al., 2018). Indeed, a cross-sectional analysis of the AGES-Reykjavik Study, in which over 4000 dementia-free patients underwent brain magnetic resonance, showed reduced brain volume in AF patients, especially non-paroxysmal, compared to participants with sinus rhythm (Stefansdottir et al., 2013). Further, people with persistent AF suffered a reduction in total cerebral flow and cerebral perfusion, compared to patients without rhythm disturbance or with paroxysmal AF (Gardarsdottir et al., 2018). Finally, being oxidative stress, inflammation and endothelial dysfunction documented risk factors of both Alzheimer's disease and AF, it is possible to speculate on a causal role played by systemic inflammatory status, elicited and accelerated by concomitant conditions such as metabolic syndrome and sedentary lifestyle (Bunch et al., 2019).

In this scenario, the previously mentioned consensus document recommends the physicians dealing with AF patients to be able to promptly recognize neurological deficits, through screening tests and cognitive assessment, despite nowadays this indication lacks of evidence derived from trials (Dagres et al., 2018). In a Swedish retrospective registry study on a large population with a long follow-up, patients treated with anticoagulant showed significantly lower risk of developing dementia than those untreated at baseline (Friberg and Rosenqvist, 2018). Comparisons between warfarin and DOACs on dementia-free AF participants resulted in a significant advantage for the second ones (Jacobs et al., 2016; Cheng et al., 2018). Indeed, the consensus document suggests to prefer DOACs for the prevention of stroke and cognitive disorders in AF (Dagres et al., 2018). The impact of catheter ablation on cognitive impairment is still debated: although evidence showing higher incidence of silent brain infarcts and subsequent accelerated cognitive decline in patients undergoing catheter ablation compared to medical therapy (Merchant and Delurgio, 2014), a study conducted on an extremely large population of patients with AF who underwent ablation or medical therapy indicates that the incidence of cognitive decline is lower in the ablation arm (Xiaoxi et al., 2018). Several ongoing trials aim to evaluate the effects of different therapeutic pharmacological and non-pharmacological approaches on cognitive function in AF patients; the results will allow to better understand the relationship between AF and cognitive decline and to summarize the efficacy of interventions to prevent dementia development (Dagres et al., 2018).

## 8. The gender-oriented perspective

While women are underrepresented in randomized clinical trials (RCTs) (Corbi et al., 2019), a vast body of evidence is available on sex-specific differences in AF incidence, prevalence, risk factors, clinical presentation and outcomes (Lip et al., 2014; Linde et al., 2018; Kloosterman et al., 2019). Differences in a gender-oriented perspective are also available on AF as risk factors beyond stroke.

In a community-based sample comprising 202417 person-years, Schnabel and collaborators showed that 1544 individuals (n = 821 men, n = 723 women) experienced new-onset AF. Women with AF were older and tended to show a more advantageous risk factor profile, except for a worse blood pressure profile despite the prescription of a higher proportion of hypertensive medications (Schnabel et al., 2015). In the EuroHeart survey 2007, Dagres and colleagues reported that, compared to males, females with AF were older, more comorbid, suffered a worse quality of life and more frequently presented HFpEF (Dagres et al., 2007). The Euro Observational Research Programme on Atrial Fibrillation (EORP-AF) Pilot registry confirmed the latter reports with females being older, more symptomatic and more frequently affected by non-ischaemic HF and HFpEF. Moreover, EORP-AF reported that, although more symptomatic than males, females also received less antiarrhythmic therapy, which often consisted of rate control medications. Furthermore, women were at higher overall stroke risk (although prior stroke history was more common in males), and oral anticoagulation was used in a higher proportion of females (95.3 % vs. 76.2 %) (Lip et al., 2014).

Recently, the Get With the Guidelines—Heart Failure (GWTG-HF) Registry investigated 1561 H F subjects with concomitant AF. Women (n = 669) were older ($p < 0.001$), showed better cardiac systolic function ($p < 0.001$) and higher prevalence of hypertension ($p < 0.001$) compared to men. Although famele patients presented increased $CHADS_2$, the gender did not impact on the prescription of anticoagulat and antiarrhythmic medications before hospital admission. Moreover, women were less likely to suffer dizziness, lightheadedness, or syncope before hospitalization and they showed higher adherence to medications and diet recommendations. Despite significant differences in terms of clinical presentation, comorbidities and therapies, in-hospital mortality was similar between men and women. One of the main limitation of the study was represented by the lack of differentiation between systolic versus diastolic HF. However, this represents one of the first descriptive reports focusing on gender differences in patients with AF during their acute admission for HF. The authors summarized that women presenting with HF complicated by AF differ from men in patient characteristics, comorbidities and medical therapy, but both sex groups shared similar clinical presentation and in-hospital mortality rates (Daneshvar et al., 2018).

In a study investigating the impact of AF in determining PE, AF conferred a higher relative risk of developing PE in females (3.26) than in males (1.91) (Hald et al., 2018). Similar results were recently reported in a large registry-based study, in which the excess PE risk conferred by AF was significantly higher in women (Wang et al., 2015). In the clinical practice, the increased thromboembolic risk in women with AF has been acknowledged by the inclusion of female sex as an independent risk factor in the $CHA_2DS_2$-VASc score (Lip et al., 2010). To date, the clinical utility of the $CHA_2DS_2$-VASc score for PE prediction has only been assessed in a single registry-based study with limited follow-up. In this study, the PE risk was directly associated with the severity of the $CHA_2DS_2$-VASc score, with a power of prediction that was similar to that of stroke (Saliba and Rennert, 2014). Moreover, it is essential to underline that elderly females with non-valvular AF were unlikely to receive DOACs compared to males, in contrast with the female-dependent higher thromboembolic risk (Lane and Lip, 2009; Ciarambino et al., 2019).

In the Cardiovascular Health Study, examining the association of incident AF with the risk of subsequent fracture, Wallace and collaborators found a higher incidence of bone fractures in women than men, but confidence intervals were wide and this difference did not reach the statistical significance (Wallace et al., 2017). Recently, in an extensive population-based analysis of 113600 subjects, the research group guided by Wong demonstrated that both men and women with AF suffered an increased risk of subsequent hip fracture. It was observed a higher absolute risk of hip fracture in women with AF, although the relative risk attributable to AF appeared similar in both genders. Moreover, the association between AF and subsequent hip fracture appeared to remain significant even after adjusting for potential confounders such as age, comorbidities and medications (Wong et al., 2017). From the above-mentioned results, it could be assumed that women with AF may experience a higher incidence of disability. Roalfe and collaborators, by studying AF patients from the Birmingham Atrial Fibrillation Treatment of the Aged Study, reported that more women than men were in the oldest age category, and women had a higher prevalence of disabilities (60 % showed a Rankin score of 2 or more, as compared with 48 % of men). At multiple regression analysis, female gender, higher medication number and disability were independently associated with lower QoL scores in AF (Roalfe et al., 2012). However, as recently underlined, only a few studies support the impact of the female gender on QoL in the clinical setting of AF (Strømnes et al., 2019). Paquette and colleagues demonstrated a more significant impairment in QoL in female AF patients compared with age-matched men with AF (Paquette et al., 2000). Further, the Rate Control Versus Electrical Cardioversion and the Canadian Trial of Atrial Fibrillation studies showed that female AF patients experienced worse QoL than females without AF (Rienstra et al., 2005). Several studies report more anxiety and depression among women than men (Stordal et al., 2001; Rewiuk et al., 2018) with consequent poorer QoL (Ong et al., 2006). However, the sex difference in anxiety and depression prevalence could depend on the diagnostic methods used, and a symptom-based scale may yield higher scores in female than male patients (Stordal et al., 2001). Due to different assessment methods employed to measure anxiety and depression, it is difficult to know whether female AF patients are more prone to depression/anxiety or if women are merely more sensitive to symptoms (Strømnes et al., 2019).

Beyond anxiety and depression, cognitive impairment may also represent a consequence of AF. The gender differences in regards to this association are still debated. The Rotterdam Study reported a stronger association between AF and dementia in women than in men (Ott et al., 1997). The Mayo Clinic Study of Aging also reported a stronger association between cardiac diseases (including AF) and non-amnestic mild cognitive impairment in women than in men (Petersen et al., 2009). However, in the Women's Health Initiative Memory Study (Haring et al., 2016), AF was not associated with MCI or dementia in women aged 65–79 years. Therefore, sex-specific differences in the risk of cognitive impairment warrant further investigation (Madhavan et al., 2018).

Finally, it is also important to underline that the majority of the studies was not explicitly designed to explore the association of AF and its complications in elderly patients with a gender-oriented perspective.

## 9. Critical points and future perspectives

The present manuscript is the result of a review of the literature regarding the most frequent complications of AF other than stroke in the elderly population. The majority of the data derives from observational studies, which do not allow to definitively demonstrate a cause-effect relationship between AF and each explored condition. Herein the authors tried to mention and discuss only the widely accepted theories on potential mechanistic links, avoiding speculation on uncertain or less rigorous hypotheses, for which it was just possible to recognize a statistical association.

Along with epidemiologic and demographic transitions of the global population in the past decades, the scientific community has developed an increasing interest in the definition of aging, overcoming the concept of "chronological age", toward models and tools for assessing frailty in term of vulnerability and disability (Cesari et al., 2017). Nevertheless, this robust research interest does not significantly impact scientific progress. Indeed, older patients continue to be systematically underrepresented in clinical trials, whose exclusion criteria systematically oust those suffering from several comorbidities and high degrees of disabilities. This constitutes an obvious paradox, though the "real world" experience recognizes the elderly as the primary medications users (Hubbard et al., 2013), thus concurring to the lack of specific adequate evidence-based recommendations (Rehman, 2005; Ridda et al., 2008; Konrat et al., 2012; Hempenius et al., 2013; Sardar et al., 2014). Accordingly, current consensus and guidelines of scientific societies rarely provide specific recommendations for an appropriate approach to prevent and manage complications of AF in the elderly, especially in those burdened by multimorbidity. The main support that clinicians receive when visiting elderly patients is often limited to the inclusion, in risk scores validated in the general population, of the variables "chronological age" and other age-related conditions. It is evident how this age/disease-centered approach results inadequate to grasp the heterogeneity and complexity of the aging phenomenon, often preventing the clinician from discerning the enormous variety of possible phenotypes between the fit subject and the frail one.

Moreover, due to the interaction of both intrinsic features of ageing process (e.g., impairment in renal and cognitive systems, reduction in physical performance) and extrinsic factors (e.g., lower social support, environmental barriers, difficulties in accessing health care services) over 65 aged AF patients are more prone to be undertreated for their conditions or even develop iatrogenic complications, often due to inappropriate or overdosed prescriptions (Bencivenga et al., 2018).

The role of the geriatrician in this context is clearly prominent, constituting for specific training, the most suitable professional figure able to carry out a comprehensive multidimensional assessment to balance the benefits and risks associated with each clinical decision (Morley, 2020). Due to the high prevalence of elderly patients, geriatrics should also obtain a greater impact in scientific research of chronic diseases.

Furthermore, it is important to underline that one of the peculiarities of geriatric medicine is constituted by the management of the chronic nature of some clinical conditions. Frequently, as the case of disabilities, there is no therapy acting on the causes to reverse the situation, but it is only possible to act in preventive view to avoid/delay its onset (e.g., e lifestyle habits and psychological behavior, falls) or limit progression/complications (immobilization and pressure sores). Finally, taking into account the tremendous difficulty faced in studying elderly patients, the first step should be the establishment of multicenter data registers, in particular from geriatric centers. This would provide a large volume of "real world" data from daily clinical practice.

Moving toward the perspective of personalized medicine, biomedical research should mandatorily take greater account of the heterogeneity of the elderly, to construct evidence that allows physicians to no longer interpret the provided indications only based on their own experience.

## 10. Conclusions

AF represents a tremendous public health problem, with a high impact in terms of mortality and morbidity, due to complications, such as stroke and other less investigated conditions equally influencing the clinical status and survival of these patients. As typical in scientific literature, the geriatric population, whose management intrinsically results complex due to high heterogeneity in comorbidity, disability and socioeconomic conditions, is underrepresented in clinical trials. Thus, more robust studies would be desirable to better define the impact of AF on heart failure, pulmonary embolism, mood disorders, QoL, disability and cognitive impairment in elderly patients in order to better manage and treat the older population in which the atrial arrhythmia is more prevalent.

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## Declaration of Competing Interest

None.

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