



Real-world characteristics of hospitalized frail elderly patients with atrial fibrillation: can we improve the current prescription of anticoagulants?

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Abstract

Background In elderly patients, especially those older than 80 years, atrial fibrillation (AF) is associated with an almost 25% increased risk of stroke. Stroke prophylaxis with anticoagulants is therefore highly recommended. The prevalence of factors that have been associated with a lower rate of prescription and adherence to anticoagulant therapy in these patients is little known. The objective of this study was to explore the clinical characteristics of elderly subjects, with and without AF, consecutively admitted to an acute geriatric unit, discussing factors that may decrease the persistence on stroke prophylaxis therapy. We also highlight possible strategies to overcome the barriers conditioning the current underuse of oral anticoagulants in this segment of the population. **Methods** A retrospective observational study was performed on a cohort of elderly patients with and without AF admitted to the Acute Geriatric Unit of San Gerardo Hospital (Monza, Italy). **Results** Compared to patients without AF ($n = 1216$), those with AF ($n = 403$) had a higher Charlson Comorbidity Index (3 vs. 2, $P < 0.001$), number of administered drugs (4 vs. 3, $P < 0.001$), rate of heart failure (36.5% vs. 12%, $P < 0.001$) and chronic kidney disease (20.6 vs. 13.2, $P < 0.001$). Many patients with AF were frail (54%) or pre-frail (29%). **Conclusions** Elderly patients with AF have higher rates of conditions that affect adherence to traditional anticoagulant therapy (vitamin K antagonists, VKA). New direct oral anticoagulants (DOAs) can help overcome this problem. In order to prescribe the most appropriate VKA or DOAs, with the best efficacy/safety profile and the highest compliance, a comprehensive geriatric assessment should always accompany the scores for thrombotic and hemorrhagic risk stratification.

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1 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and its prevalence increases with age.^[1–3] The number of patients with AF is expected to increase twofold in the next few decades.^[1,4] AF is strongly associated with increased mortality and risk of ischemic stroke at all ages,^[5–7] and especially between the ages of 80 and 89 years, an increase of almost 25% in the risk of ischemic strokes can be attributable to this arrhythmia.^[8] Indeed, being ≥ 75 years old per se is considered a major risk factor in stroke risk stratification schemes, accounting for two points in the new CHA₂DS₂-VASc scoring system.^[9]

Vitamin K antagonist (VKA) warfarin is classically considered as the mainstay for stroke prophylaxis, but it has

several limitations and adverse effects such as a narrow therapeutic window, and increased risk of bleeding and intracranial hemorrhage,^[10] with advancing age identified as a determinant for the risk of bleeding.^[11,12] Therapy with warfarin therefore requires frequent and regular evaluations of the patient and of its coagulation parameters, in order to maintain the target international normalized ratio.^[13–16] This can be an impediment for several elderly patients, particularly those with a history of previous strokes and physical limitations. The same patients are often affected by comorbidities that require the administration of several other drugs, and that can pharmacologically interact with each other. In addition, elderly patients are frailer than other adults and may present cognitive dysfunctions that lead to functional dependency. These factors, along with VKA limitations, lead to a suboptimal persistence on VKA,^[17,18] and have prompted pharmacological research for safer and easier-to-administer alternatives. These efforts have resulted in clinical trials and the regulatory approval of new direct thrombin inhibitor and direct factor Xa inhibitors, referred to as direct oral anticoagulants (DOAs).^[19,20]

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Recent international guidelines have recommended the use of DOAs in patients with a history of AF,^[21,22] since they overcome the main limitations of VKA. The main advantages of DOAs include more predictable pharmacological profiles, reduced risk of intracranial bleeding, and fewer interactions with other drugs or dietary components.^[23] In addition, some DOAs can be administered once a day, thus favoring a better compliance in elderly patients and their caregivers (often appointed to manage it). Some DOAs are also less affected by common comorbidities such as renal insufficiency.^[24] For all these reasons, DOAs are less likely to be discontinued, thus improving the patient's prognosis and quality of life, and diminishing their hospitalization rate.

The objective of this study was thus to explore the clinical characteristics of elderly patients, with and without AF, consecutively admitted to an Acute Geriatric Unit (AGU), discussing factors that can decrease the persistence on stroke prophylaxis therapy. We then highlight possible strategies to overcome the barriers conditioning the current underuse of oral anticoagulants in clinical practice, especially among the elderly.^[25–28]

2 Methods

2.1 Patients

This is a retrospective observational study conducted between September 1, 2012 and February 28, 2014 in the AGU of San Gerardo University Hospital (Monza, Italy). The population included 1619 consecutive patients, mostly admitted from the emergency department. Inclusion criteria were age ≥ 65 years, and diagnosis of persistent or permanent non-valvular AF obtained from medical records and confirmed according to an electrocardiogram performed within the previous 24 months. We excluded patients who had AF due to co-occurring acute illness, and those who died during hospitalization.

All patients gave their informed consent for the study which was conducted in accordance with the guidelines proposed in the Declaration of Helsinki. Informed consent for the anonymous use of clinical data was obtained from all patients during the hospitalization at San Gerardo Hospital. The informed consent is archived with the hospital charts at San Gerardo Hospital in Monza, Italy. A formal consent of participation is not required for this retrospective study. The Ethics Committee of the University of Milano-Bicocca (Italy) approved the study design.

2.1.1 Geriatric assessment

A comprehensive geriatric assessment (CGA) was ad-

ministered on the day of admission, including socio-demographic characteristics (age, sex, and living conditions), biochemical parameters (C-reactive protein, albumin, urea and creatinine serum levels), the main diagnosis of hospitalization, comorbidity (Charlson Comorbidity Index, CCI),^[29] and the current therapeutic plan.

2.1.2 Functional status assessment

We also assessed the functional status using Katz's activities of daily living score (ADL)^[30] and the New Mobility Score (NMS),^[31] and the nutritional status through the Mini-Nutritional Assessment Short Form (MNA-SF).^[32] The information was obtained directly from the patient's interview or (if impossible) surrogate interview referring to one month before the current hospitalization.

2.1.3 Dementia assessment

Dementia was established on admission referring to the DSM-IV-TR criteria.^[33] Any patient with a cognitive impairment, recognized and documented by the clinical case notes at least six months prior to hospitalization, was also considered as affected by dementia.^[34,35]

2.1.4 Polypharmacy assessment

Polypharmacy was defined as the co-occurring consumption of > 5 drugs.

2.1.5 Frailty assessment

Frailty was established according to the criteria proposed by Robinson, *et al.*^[36,37] with minimal variations. To each of the following characteristics was assigned one frailty trait: impaired cognition (Mini-Cog ≤ 3),^[38] recent falls (one or more falls in the previous six months), impaired mobility (NMS ≤ 6), anemia due to a chronic disease (hematocrit $< 35\%$), functional dependence in one or more ADL, poor nutrition (MNA-SF ≤ 8 or a serum albumin level below 3.4 g/dL) and comorbidity (CCI ≥ 3). Patients were divided into three groups according to the total number of frailty traits: non-frail (0–1), pre-frail (2–3), and frail (4–7).

2.2 Statistics

Statistical analysis was carried out with the SPSS statistical package (SPSS, version 22, Chicago, IL). Mean \pm SD were calculated, and quartiles were used for the description of continuous variables. The differences between patients with and without AF were analyzed by Student's *t*-test for variables with a normal distribution. For non-normally distributed variables, we adopted the Mann-Whitney *U* test. A *P*-value of 0.001 was considered as the cut-off for statistical significance.

3 Results

The analysis of our total cohort of 1619 patients showed that 403 (24.9%) were affected by AF. The rest ($n = 1216$) constituted the group of patients without AF.

Table 1 shows a comparison of the demographic characteristics and prevalence of the analyzed comorbid conditions between the groups. Age did not differ significantly between patients with and without AF (84.6 ± 6.2 vs. 83.9 ± 6.9 years, $P = 0.102$), and females were equally represented in both groups (non-AF = 59.8%; AF = 59.6%, $P = 0.934$). The Median CCI was higher in patients with AF [3; interquartile range (IQR): 2–4], than those without AF (2; IQR: 1–4). Patients with AF had a significantly higher rate of heart failure (HF), chronic kidney disease (CKD, from stage 3A), and multi-morbidity (defined as being affected by more than three pathologies) compared to patients without AF ($P < 0.001$). In addition, the median number of drugs consumed by patients with AF was significantly higher (4; IQR: 3–6) than non-affected patients (3; IQR: 2–5). The prevalence of chronic obstructive pulmonary disease (COPD) and cerebrovascular disease was not significantly different between the study groups.

Figure 1 shows the comorbidities observed in patients with AF. The five most prevalent conditions were HF (36.5%), dementia (31.3%), COPD (24.3%), diabetes mellitus (25.8%), and CKD (20.6%). According to Robinson's criteria, 57 patients (14.1%) were categorized as non-frail (score 0–1), 115 (28.6%) as pre-frail (score 2–3), and 231 (57.3%) as frail (score ≥ 4) (Figure 2).

4 Discussion

The clinical management of AF, especially for older pa-

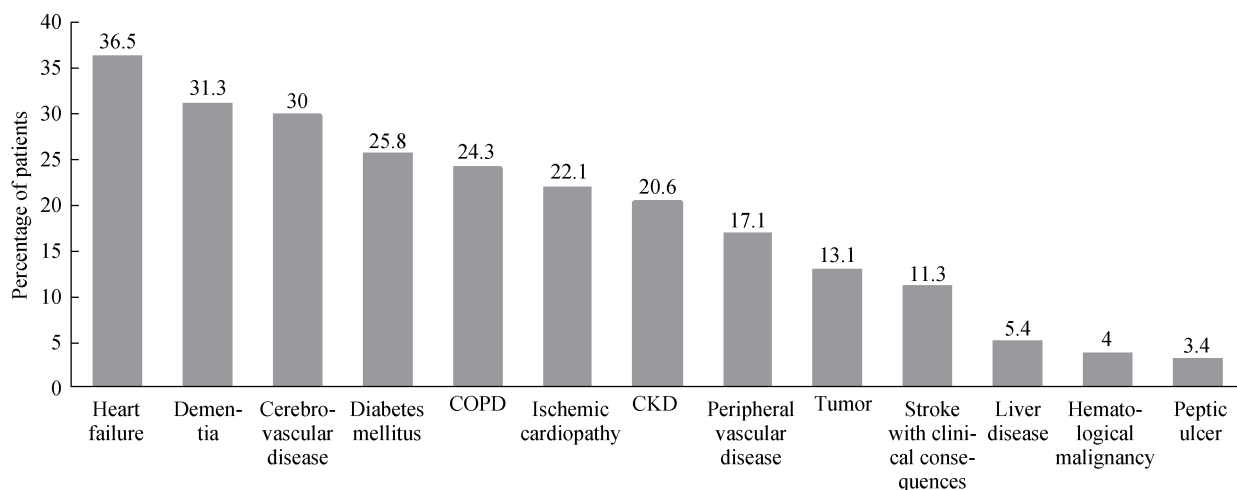


Figure 1. Comorbidities in patients with atrial fibrillation (from September 2012 to February 2014), CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease.

tients, should always consider anticoagulant therapy as a priority, since the cardio-embolic risk is at its highest level in this segment of the population. However, in this scenario, the prescription of VKA does not fulfill the above-mentioned goal. This emerged in particular from studies conducted in real-world settings.

Gomes, *et al.*^[39] had reported that persistence on VKA is suboptimal, with rates of discontinuation higher than 60% five years following therapy initiation. They found that the factors predicting poor persistence with warfarin were younger age, male gender, and estimated lower stroke risk.^[39] In addition, in patients aged ≥ 80 years, the risk of stopping warfarin in the first year after prescription was significantly higher than in patients younger than 80 years of age.^[18] Discontinuation was mainly attributable

Table 1. Clinical characteristics of 1619 patient with and without AF.

	Without AF ($n = 1216$)	With AF ($n = 403$)	<i>P</i> value
Age, yrs	83.9 ± 6.9	84.6 ± 6.2	0.102
Female	727 (59.8%)	240 (59.6%)	0.934
Charlson comorbidity index	2 (1–4)	3 (2–4)	< 0.001
Comorbidities			
Heart failure	146 (12.0%)	147 (36.5%)	< 0.001
COPD	233 (19.2%)	98 (24.3%)	0.026
CKD (from stage 3A)	160 (13.2%)	83 (20.6%)	< 0.001
Cerebrovascular disease	275 (22.6%)	121 (30.0%)	0.003
Multimorbidity (> 3 diseases)	350 (28.8%)	286 (71.0%)	< 0.001
Number of medications	3 (2–5)	4 (3–6)	< 0.001

Data are presented as mean \pm SD, n (%) or median (IQR). AF: atrial fibrillation; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; IQR: interquartile range.

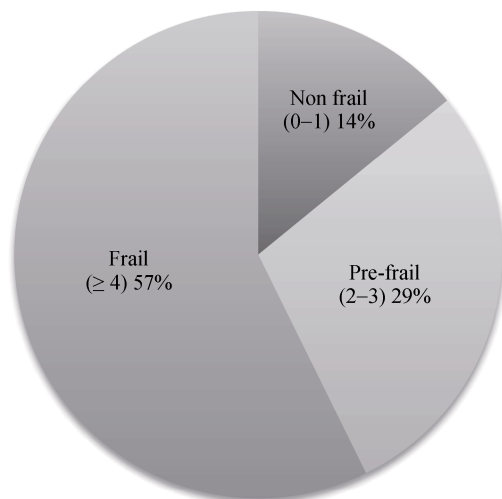


Figure 2. Assessment of frailty (percentage) in 403 consecutive patients with atrial fibrillation (from September 2012 to February 2014). The Robinson Frailty Score^[36] is reported in parentheses.

to safety concerns,^[18] which specifically include frailty and risk of falls, high bleeding risk, and hospitalizations for bleeding, plus cardiovascular and non-cardiovascular events.^[40]

The recent introduction of DOAs provides a valid alternative to VKA for a more inclusive prescription policy. However, in clinical trials regarding DOAs, patients ≥ 75 years represent a minority, with percentages varying from 27% to 44%.^[41-44]

In our study, which compared the clinical characteristics of consecutive patients older than 80 years with and without AF, admitted in an AGU, we found that patients with AF had a significantly higher CCI, number of administered drugs, and rate of HF and CKD. These factors may potentially affect the prescription rate of VKA and the persistence on anticoagulation therapy due to drug interactions, safety concerns, and difficulties in the management of polypharmacy.

With reference to CKD, CCI, and polypharmacy, our findings are in line with a recent paper on 1384 hospitalized patients from the REPOSI study.^[45] This study found that dementia and CKD were highly prevalent and determined an increased risk of mortality among 321 subjects with concomitant AF.^[45] Compared to non-AF subjects, patients with AF presented significantly more comorbidities [Cumulative Illness Rating Scale (CIRS),^[46] both Comorbidity and Severity index], and a higher number of drugs. Prescription of anticoagulants was suboptimal ($< 50\%$), and physicians were less likely to prescribe VKA to patients with advanced age and severe disability.^[45]

HF is also frequently associated with AF, as in our set of

patients. This co-occurrence is known to worsen the overall prognosis,^[47] and a role may be played by a low compliance with overall pharmacological therapy, and anticoagulants in particular.^[47-49] Additionally, patients with CKD (20.6% in our sample) may experience problems while taking VKA due to possible anticoagulant instability requiring frequent monitoring and dose adjustments compared to subjects with preserved kidney function.^[50]

From a geriatric perspective, frailty represents a condition of high instability that negatively affects both prescription and maintenance of anticoagulation therapy.^[51,52] In our real-world acute care setting, it is not surprising that the vast majority (85.9%) of patients with AF were pre-frail or frail. Indeed, anticoagulation therapy is more complex and needs a tailored approach in frail patients, due to factors that may affect anticoagulation safety, such as comorbid conditions (HF, dementia, COPD, diabetes, CKD, etc.), risk of falls, malnutrition, and polypharmacy.^[53]

When considering elderly patients with AF, the choice between different anticoagulants should therefore take into account all the factors that could decrease treatment adherence. An effective anticoagulation should be personalized and combine efficacy at preventing stroke, safety-tolerability, and good adherence to the therapeutic regimen.^[54] The use of DOAs, as opposed to a conventional VKA treatment, can overcome some of these limitations. Among this group of agents, the drugs also differ in terms of once-daily or twice-daily dosing and metabolism, and the choice of the most appropriate candidate should be tailored to the individual patient. Comparing the main DOAs, rivaroxaban has a reduced renal elimination, thus allowing its use in CKD patients with creatinine clearance ≥ 15 mL/min. In addition, for patients at risk of discontinuation, single daily administration could be key for improved adherence, as it is the case for rivaroxaban,^[24] and the EHRA guidelines indeed suggest that once-per-day dosing may favor patient compliance.^[55-57] Recent studies have confirmed this, showing an association with a higher persistence on treatment compared to warfarin, which was crucial in the long run (less than 15% discontinuation of rivaroxaban after one year).^[58,59]

For dabigatran^[60] and apixaban,^[61] a reduction in dosage is required depending on age, renal impairment, concomitant use of inhibitors of CYP3A4 or P-gp, gastritis/esophagitis, and weight. It is worth noting that a dose adjustment of rivaroxaban is required only in the case of renal impairment.^[24]

In conclusion, despite the single-center design-already adopted by studies exploring frail subjects with AF and their use of anticoagulants-we believe that we have presented a

realistic picture of everyday clinical practice. Thus, we studied very elderly hospitalized patients with a diagnosis of permanent AF, multi-morbidity (mainly represented by acute HF) and with a high prevalence of functional limitation, ascribable overall to full-blown frailty. The AGU portrays a setting where hospitalization represents a double opportunity: first, to review and update the patterns of therapy; secondly, to potentially include in an anticoagulant scheme therapy subjects which were previously considered unsuitable because of adherence or safety issues, and consequently were often diverted to other antithrombotic therapy (i.e., anti-platelet) incorrectly considered as safer.^[62]

In conclusion, in this real-world setting, we found that patients with AF are also frequently affected by important comorbidities, take a higher number of drugs than non-AF subjects, and in the vast majority of cases are frail. Underuse of anticoagulants (VKA or DOAs) is almost never ascribable to a single geriatric condition or factor,^[63] but rather to a combination of barriers, such as physician- or health-care system-related aspects, and patient-caregiver concerns.

The adoption of scores for thrombotic and hemorrhagic risk stratification should be always accompanied by a CGA, which is the best tool to contextualize each older patient affected by AF and to assess their need for anticoagulation correctly. This must be carefully considered when prescribing a VKA or DOAs agent, in order to achieve the best efficacy/safety profile and the maximum possible compliance by the patient, always bearing in mind that these subjects carry the highest cardio-embolic risk.

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