Original article
Hospitalized patients with atrial fibrillation compared to those included in recent trials on novel oral anticoagulants: A population-based study

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Abstract
Background: Nonvalvular atrial fibrillation is associated with a substantial risk of stroke. Novel oral anticoagulants (NOACs) with predictable anticoagulant effect and no need for routine coagulation monitoring have recently shown good results when compared with warfarin in phase III clinical trials. Objective: To describe clinical features and pharmacological treatments of a population-based cohort of patients with nonvalvular atrial fibrillation and ascertain whether they are comparable with those included in the three main phase III clinical trials on NOACs.
Results: Of the 2,862,264 subjects considered for this study 13,360 patients (0.47%) were recently discharged from the hospital with a diagnosis of nonvalvular atrial fibrillation. Mean age was 76.3 (SD 10.7), 49.8% were men and 64.6% were ≥75 years of age. 50% of patients were treated with warfarin and 44.1% with antiplatelet agents. The proportion of patients on antplatelet therapy increased with age up to a rate of 54.3% in subjects ≥85 years. 92.9% of the studied cohort was on polypharmacy (mean 8 drugs/patient). Around 20% of the entire cohort was treated with amiodarone, a drug potentially interfering with NOACs, and 3.6% from a subgroup analysis had renal failure, which is an exclusion criterion in trials on NOACs. Conclusion: In patients recently discharged from the hospital with the diagnosis of nonvalvular AF, warfarin use decreases and aspirin treatment increases with patients’ age. These patients are older, more frequently female, and on multiple medications. The benefit of NOACs in these subjects needs to be confirmed in phase IV clinical studies.

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1. Introduction

Atrial fibrillation (AF), the most frequently observed sustained arrhythmia in clinical practice, affects 0.4–1.0% of the general population with a lower prevalence among subjects below the age of 60, increasing to 8% in those aged over 80 years [1]. AF is an independent risk factor for stroke; patients with AF have a four to five-fold higher risk for stroke than unaffected subjects [2,3]. The annual risk of stroke in untreated patients with AF is age-dependent, being 1% in the 50–59 age group, 3% in the 60–69 age group, 10% in the 70–79 age group, and 24% in patients aged 80 to 89 [2,4,5].

In a meta-analysis on vitamin K antagonists (VKAs) and aspirin for stroke prevention in patients with AF the occurrence of stroke decreased by 60% and 20%, respectively, compared to placebo or no treatment [6,7]. The magnitude of warfarin benefit increased with inherent risk of stroke. Despite the well-documented efficacy, VKAs are difficult to use for several reasons, including a narrow therapeutic window, the multiple food and drug interactions, the need for frequent monitoring, and the difficulty in maintaining a stable therapeutic INR and therefore for the bleeding complications, which are more common in elderly patients [8–11]. For all these reasons vitamin K antagonists are too often not given when indicated, despite the fact that international guidelines recommend their use, as a class I indication, in the large majority of patients with AF [1].

The promising results of the three phase III clinical trials (RE-LY, ROCKET AF and ARISTOTLE) on novel oral anticoagulants (dabigatran, rivaroxaban, apixaban, respectively) [12–14] as compared with warfarin challenge the use of classic oral anticoagulants as the new drugs are less likely to induce intracranial bleeding and need no routine laboratory testing. The apparently better safety profile and ease of use of NOACs will probably induce a wider use of antithrombotic agents in patients with AF. The question is whether the results obtained in clinical trials on NOACs are generalizable to hospitalized patients with AF.

The present study aims to describe clinical features and pharmacological treatments of a population-based cohort of Italian patients

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discharged from the hospital with a diagnosis of AF and to compare them with the patients included in the RE-LY, ROCKET AF and ARISTOTLE studies [12–14].

2. Materials and methods

2.1. Prescription database

The ARNO database is a population-oriented database for drug use in Italy [15]. The system has been active since 1988 and run by Centro Universitario di Calcolo dell’Italia Nord-Orientale, a National interuniversity consortium, with the purpose of providing a friendly and efficient database that collects and monitors the prescriptions for nearly 11 million inhabitants (as of November 2012). The database stores all prescriptions reimbursed by the National Health Service to individuals living in the area covered by the local health units. The system merges information regarding prescriptions, population, geographical areas, and hospital admissions into a single database. For hospital admissions, it stores International Classification of Diseases, Ninth Revision (ICD-9) codes for all admissions to public and private hospitals located in the areas covered by the local health units. It is updated monthly and available through the Internet, and accessible to authorized users with different levels of information. The present analysis used data from 11 Italian local health units in four regions (Abruzzo, Puglia, Toscana, Veneto), covering a population of 3,428,000 inhabitants, of whom 2,862,264 aged ≥ 18 years.

2.2. Study participants

The study group consisted of male and female patients aged ≥ 18 years discharged from the hospital with a primary or secondary diagnosis of nonvalvular AF (ICD-9 diagnostic code 427.31).

Hospitalizations due to ischemic stroke (ICD-9 diagnostic codes 434, 436), transient ischemic attack (ICD-9 diagnostic code: 435), and renal failure (ICD-9 diagnostic codes: 403, 584, 585, 586) were also evaluated.

Prescribed drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system and the following groups were included: VKAs (ATC group B01AA), antiplatelet agents and other antithrombotic drugs (ATC group B01AC), ARB-inhibitors (ATC groups C09C and C09D), ACE-inhibitors (ATC groups C09A and C09B), β-blockers (ATC group C07), amiodarone (ATC group C01BD01), verapamil (ATC group C08DA01), statins (ATC groups C10AA and C10BA02), proton-pump inhibitors (ATC group A02BC), H2-receptor antagonists (ATC group A02BA), and antidiaebetics (ATC group A10). All these agents are fully reimbursed by the Italian National Health Service.

The study period was from January 1, 2007 to December 31, 2008. The accrual period was from January 1, 2007 to December 31, 2007 with a follow-up period of one year.

3. Results

During 2007, out of the 2,862,264 screened subjects, 13,360 patients (0.47%) were discharged from the hospital with a diagnosis of nonvalvular AF. The prevalence of AF in this cohort ranges from 0.03% among subjects aged <55 years and reaches 3.52% after 85 years.

The prevalence of VKA use among the 2,862,264 screened subjects is 1.5% and ranges from 0.15% among subjects aged <55 years, increases until 8.35% among patients aged 75–84 and slightly decreases among those aged >85 years (6.77%). Considering that AF affects 45% of naive patients taking VKAs [16] the prevalence of this condition in the screened cohort is 0.68% and more than two thirds of these subjects were discharged from the hospital with a diagnosis of nonvalvular AF. Fig. 1 shows the prevalence of antithrombotic treatments according to age. Half of the overall ARNO cohort received warfarin, 44.1% antiplatelet agents, and 17.3% no antithrombotic treatment. The highest prevalence of VKAs was among subjects aged 65–74 years and the lowest after 85 years. The prevalence of antiplatelet agent use increased with age and nearly half of the patients aged ≥85 years received this therapy.

3.1. Characteristics of patients in the ARNO cohort as compared to those of patients randomized in the RE-LY, ROCKET AF and ARISTOTLE trials

3.1.1. Age and gender

The main ARNO cohort was fairly older compared to participants in the RE-LY (mean age 76.3 ± 10.7 vs. 71.5 ± 8.7), ROCKET AF (median age 79 [interquartile range 71–84] vs. 73 [interquartile range 65–78]) and ARISTOTLE (median age 79 [interquartile range 71–84] vs. 70 [interquartile range 63–76]) trials.

Fig. 2 shows the prevalence of patients ≥75 years in the overall ARNO cohort vs. RE-LY, ROCKET and ARISTOTLE studies. A total of 63.2% of the cohort was aged ≥75 years (21.7% of them ≥85 years), while patients of this age hardly reached 40% in the trial setting.

Fig. 3 presents the gender distribution in the overall ARNO cohort vs. the study population in the three randomized clinical trials (RCT). The proportion of women in the study setting did not reach 40%, while they accounted for half of the patients with nonvalvular AF in daily practice (57.2% of patients ≥75 years were female).

3.1.2. Drug treatments other than antithrombotic drugs

The use of amiodarone, statins and proton pump inhibitors somehow differs between patients discharged from the hospital with a diagnosis of AF and those randomized in the NOAC clinical trials. The use of amiodarone in the main ARNO cohort nearly doubled that in the RE-LY and ARISTOTLE studies (20.2% in the overall ARNO cohort vs. 10.7% in RE-LY and 11.3% in ARISTOTLE).

Statin use among hospitalized patients with AF was roughly half that seen in the trials (24.3% in the overall ARNO cohort vs. 44.4% in RE-LY, 43.1% in ROCKET-AF, and 45.0% in ARISTOTLE).

Approximately two thirds of the cohort were given proton-pump inhibitors as compared with one fifth in the RCTs (65.3% in the overall ARNO cohort vs. 17.7% in RE-LY, and 18.4% in ARISTOTLE).

Nearly all patients in the overall ARNO cohort were on multiple medications, as 92.9% of them were treated with ≥3 drugs (mean 8 drugs per patient; range 1–28).

3.1.3. Renal failure, previous cerebral ischemia, diabetes, and hypertension

For a sub-group of the overall ARNO cohort (i.e. 7994 subjects belonging to seven of the 11 local health units participating in the study and representing 59.8% of the overall ARNO cohort), information on hospitalization due to severe stroke, and/or renal failure within 12 months before accrual was also available.

Age and gender distribution of this sub-group was similar to the overall ARNO cohort (mean age 77 ± 10.6 in the sub-group vs. 76.3 ± 10.7 in the overall ARNO cohort; female prevalence 49.2% vs. 50.2%, respectively).

A total of 3.6% of hospitalized patients with AF were hospitalized for renal failure in the 12 months before hospitalization due to AF, which means that 288 out of 7994 subjects hospitalized for AF would not have been suitable for the therapy with the new anticoagulants.

Similarly, 176 subjects from the same sub-group were hospitalized for severe stroke in the same period. These patients would also meet the exclusion criteria for both the RE-LY and ROCKET-AF studies.

For the same sub-group of the overall ARNO cohort information on other co-morbidities such as diabetes and hypertension was also available. The prevalence of diabetes (17.7%) is slightly lower than
that in clinical trials and that of hypertension (76.9%) is close to that reported for patients included in the RCTs.

4. Discussion

To the best of our knowledge this is the first study comparing a large cohort of patients discharged from the hospital with a diagnosis of nonvalvular AF with patients included in the recent NOAC RCTs. The study population does not represent the whole “real world” setting. Many patients with AF are community patients receiving treatment without need for hospitalization. However, the mean prevalence in general population accounts for about 1%; data from ATRIA study reported that AF prevalence accounts for 0.95% in North America [17] and 0.87% in the study of Scottish Murphy [18]. In another more recent study in the United States of America, its prevalence was 1.12% [19]. Thus hospitalized patients with AF (0.47%) account for nearly half of patients with AF in the general population.

Despite the fact that the use of VKAs is mandatory and that the magnitude of benefit increases with age [7–10,20], half of the ARNO cohort did not receive VKA therapy and the same can be said for patients aged ≥85 years, whose risk is higher due to age and co-morbidities. The underutilization of VKAs in the elderly is partially compensated by the use of aspirin, with nearly half of patients ≥85 years undergoing this treatment. These findings seem in line with other studies [8,9], which reflect the reluctance of clinicians in giving VKAs to elderly patients due to the potential bleeding complications which are more common in this population. This attitude is in contrast with the clear evidence that VKAs are superior to aspirin in this setting too, with no difference in major bleeding (or intracranial hemorrhage) in the elderly [21–23]. Recently it was reported that the benefits in stroke prevention and cerebral bleeding with dabigatran versus warfarin are preserved in those in the 9th decade compared to those younger except for major bleeding where, compared to warfarin, there is no difference using a lower dosage of dabigatran (110 mg bid) and an increase bleeding rate using 150 mg bid. of dabigatran [24]. Therefore a dose reduction should be considered for dabigatran in the very old population and this strategy might be applied to all the new oral anticoagulants.

As NOACs need no laboratory control and have caused significantly less intracranial bleeding as compared with warfarin, it is possible...
that physicians will be more confident in treating their patients with NOACs instead of aspirin. Are the results of the phase III NOAC trials applicable to the entire population of patients with nonvalvular AF? The answer is difficult, as features of hospitalized patients with AF are quite different from those presented by the subjects included in the clinical studies [12–14].

With nearly two thirds of subjects aged ≥75 years, hospitalized patients are much older than those included in the RE-LY, ROCKET AF and ARISTOTLE trials [12–14]. The under-representation of elderly in clinical trials is a matter of concern. An elderly patient with AF differs considerably from younger patients due to the fragile condition, multiple co-morbidities, including cardiovascular and non-cardiovascular diseases, and decreased renal and hepatic function. Of the individual components of the CHADS2 score, age ≥75 carries a worse prognosis for stroke and mortality than hypertension, diabetes, and heart failure [25].

Women are also underrepresented in the NOAC studies, although women and men are equally affected with AF in daily hospital practice and female are even predominant among hospitalized patients with AF aged ≥75 years. AF is associated with an increased risk of stroke, heart failure, and all-cause mortality, especially among women [26,27]. A report from the Euro Heart Survey on AF [28] documented that women with AF in European countries had more co-morbidities, a lower quality of life, and a higher risk of stroke than men. In addition, women have a greater risk of developing adverse drug reactions than men. In the Sportif V trial women were more prone to anticoagulant-related bleeding and to higher rate of thromboembolism due to more frequent interruption of anticoagulant therapy [29].

In spite of documented age- and gender-related differences, elderly patients and women are still underrepresented in RCTs and no analysis of the results by gender is reported.

Another important issue to be considered is the impact of polypharmacy in elderly patients with AF, as hypothetical interactions with drugs are likely to occur, based on the main mechanisms by which NOACs are metabolized and eliminated. The long term use of drugs for chronic disorders is common in the elderly and polypharmacy increases with age, particularly after the age of 70 and in women [30]. Thus, possible drug interactions increase in the patients described in this study as they are significantly older than those of NOAC clinical trials and women are largely more represented.

Looking at the treatments prescribed to the overall ARNO cohort, a matter of concern is the use of amiodarone in these patients, the prevalence of which doubled that seen in the phase III NOAC studies. Amiodarone is a P-glycoprotein inhibitor and, a single dose of 600 mg increases dabigatran AUC and Cmax by about 50% and 60%, respectively. The bioavailability of the other NOACs (rivaroxaban and apixaban) is also influenced by P-glycoprotein. In view of the long half-life of amiodarone the potential for drug interaction and the risk of bleeding may persist for weeks after its discontinuation. The European product monograph states that a reduction in the dose of dabigatran is recommended when it is co-administered with amiodarone [31,32].

Concerning possible drug-drug interactions verapamil, another P-glycoprotein inhibitor, should also be taken into consideration. Within the overall ARNO cohort, 1008 patients (8.3%) were treated with this active principle. When dabigatran (150 mg) is co-administered with oral verapamil, the Cmax and AUC of dabigatran increased (increase of Cmax by about 180% and AUC by about 150% in the case of an immediate release formulation of verapamil administered 1 h prior to dabigatran intake) but the magnitude of this change differs depending on timing of administration and formulation of verapamil. The European product monograph reports that no meaningful interaction is observed when the antihypertensive drug is given 2 h after dabigatran [31]. The over-prescription of proton-pump inhibitors among hospitalized patients with AF vs. the use reported in the NOAC trials could possibly be reduced with the use of the new anticoagulants as it can be explained with the large utilization of aspirin in these patients (nearly half of the overall ARNO cohort). On the other hand, the lower use of proton pump inhibitors in the phase III studies may account for the excess of dyspepsia (RE-LY) and gastro-intestinal bleeding (RE-LY and Rocket-AF) as compared to warfarin.

The use of statins is quite low in this study: this may reflect the unproven benefit in primary cardiovascular prevention in elderly patients and/or restrictions in getting these drugs free from the national health system. Patients with severe renal failure were excluded from all the three trials on new anticoagulants. According to our data 3.6% of hospitalized patients with AF cannot be treated with the new medications. Severe impairment of renal function is an important issue in the elderly, particularly in patients aged over 80 years, half of whom show a creatinine clearance ≤50 mL/min [33]. These frail patients should be carefully monitored for renal function over time if treated with NOACs with prevalent renal excretion.

The prevalence of diabetes in the sub-group of the overall ARNO cohort was assessed looking at the prescription data on antidiabetics. Each subject who received at least one package of glucose-lowering medications was considered a diabetic patient. This assumption is commonly utilized in pharmacoepidemiological studies using prescription databases [34]. Since no details concerning the disease were available, a slight underestimation of the disease prevalence in the ARNO cohort could be possible. However, this figure is consistent with previous national and international observational studies [35–37] and a randomized clinical trial performed among Italian ambulatory patients with AF [38]. The magnitude of the difference in the prevalence of diabetes between patients seen in the daily practice and those included into the three trials is unlikely to be explained by this potential limitation.

The prevalence of hypertension in the sub-group of the overall ARNO cohort was identified through analysis of therapies with at least four packs during 12 months of the following ATC codes: C02A, C02C, C03A, C03B, C03D, C03E, C07, C08C, C09A, C09B, C09C, and C09D (alone or combined). This assumption was previously utilized and validated [39] and is in line with the data reported in other observational studies performed on Italian patients with AF [33,36].

4.1. Strengths and limitations of the study

This population-based study includes data from a large cohort of subjects discharged from the hospital with a diagnosis of nonvalvular AF. The study dataset includes all the reimbursable prescriptions that were issued in 2008 by general practitioners and specialists to these patients and were subsequently collected by the patients in local pharmacies. Thus, the major strengths of the present study are the representativeness of the cohort and the reliability of the dispensing data.

This analysis is limited by its observational retrospective design, its focus on the hospital setting (while the majority of these subjects are outpatients, this study includes recently hospitalized patients, probably older in comparison with outpatients, with a higher number of drugs prescribed, and affected by conditions contraindicating the use of anticoagulants) and the incomplete clinical information on the included patients.

5. Conclusion

This study documents that patients discharged from the hospital with the diagnosis of nonvalvular AF are elderly people, with a higher prevalence of women among patients ≥75 years. Warfarin use decreases, aspirin treatment increases with age and nearly all
Learning points

- Patients discharged from the hospital with the diagnosis of nonvalvular AF are fairly different from those included into recent clinical trials; they are older, more frequently female and on multiple medications.

- Potentially dangerous drug–drug interactions in the treatment of these patients with NOACs, together with the high prevalence of renal failure, might be a relevant issue in daily practice, considering the lack of a lab test (INR) that, though extremely imprecise and not always sensible, can be a ringing bell and anyway a reason to monitor the patient; and 2) as far as we know, the absence of an antidote.

For all these reasons, while suggesting a role for NOACs in satisfying patients' needs that are still unmet so far, our study indicates that further phase IV studies are required to confirm the benefit and clarify the safety profile of novel oral anticoagulants in daily practice.

Italian horizon scanning group

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Conflict of interests

The authors state that they have no conflicts of interests.

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