ORIGINAL RESEARCH

Predictors of new oral anticoagulant drug initiation as opposed to warfarin in elderly adults: a retrospective observational study in Southern Italy

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Aim: The aim of this study was to assess the predictive role of age, gender, and number and type of co-treatments for new oral anticoagulant (NOAC) vs warfarin prescription in elderly patients naïve for the aforementioned drugs.

Materials and methods: Data collected in the period from January 1, 2014, to December 31, 2014, in Caserta Local Health Unit administrative databases (Campania Region, Italy) were screened to identify new users of oral anticoagulants (OACs) who were 75 years or older and whose OAC prescriptions amounted to >90 days of treatment. Age, gender, and number and type of concomitant medications at the time of first OAC dispensation were retrieved. Multivariable logistic regression analysis was used to assess the role of the aforementioned predictors for NOAC initiation as opposed to warfarin.

Results: Overall, 2,132 incident users of OAC were identified, of whom 967 met all inclusion criteria. In all, 490 subjects (50.7%) received an NOAC and 477 (49.3%) received warfarin. Age >75 years was positively associated with lower odds of NOAC initiation (OR: 0.969, 95% CI: 0.941–0.998, P=0.038). Similarly, multiple concomitant medication was negatively associated with NOAC initiation compared to warfarin (OR [five to nine drugs] group: 0.607, 95% CI: 0.432–0.852, P=0.004; OR [ten+ drugs] group: 0.372, 95% CI: 0.244–0.567, P<0.001). Prior exposure to platelet aggregation inhibitor drugs was associated with the initiation of NOACs (OR: 3.474, 95% CI: 2.610–4.625).

Conclusion: Age and multiple co-medication were negatively associated with NOAC initiation.

Keywords: retrospective databases, real-world data, atrial fibrillation, oral anticoagulation, drug utilization

Introduction

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia, and its prevalence increased progressively with age.[1–3] AF prevalence was estimated to be less than 0.1% in the population aged <55 years and rise to over 8% in those aged >80 years.[4] Patients with AF have a fivefold higher risk of stroke, which increases with age, reaching 23.5% between 80 and 89 years of age.[5] Vitamin K antagonists (VKAs) have been historically used to reduce cardiovascular risk associated with AF especially for stroke prophylaxis.[6] However, recently, a new therapeutic alternative to VKA was introduced, the new oral anticoagulants (NOACs). NOACs include both direct thrombin inhibitors (dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). Dabigatran and rivaroxaban were authorized by European Medicine Agency (EMA) in 2008 and became available on the Italian market in 2013.

Apixaban was approved by EMA in 2011 and became available for use in clinical practice in Italy in January 2014, while edoxaban was the last NOAC that obtained the marketing authorization by EMA in June 2015. Initially, in 2010, the Italian Medicine Agency (*Agenzia Italiana del Farmaco*, AIFA) allowed the use of NOACs only for the prophylaxis of venous thromboembolism after hip replacement surgery and knee surgery. However, since 2013, AIFA has extended the authorization also for reducing cardiovascular risk in non-valvular AF. In terms of stroke and systemic thromboembolism prevention, dabigatran, apixaban, rivaroxaban, and edoxaban demonstrated at least non-inferiority to warfarin.[7] Moreover, NOACs, when compared to VKA, provided a more reliable anticoagulation effect with a limited drug–drug and drug–food interactions, especially in frail population, such as elderly patients.[8,9] Considering these advantages, European guidelines for the management of AF recommended the initiation of an NOAC instead of warfarin in non-valvular AF.[7] However, to date, previous studies suggested that VKA tends to be underutilized especially in the elderly patients with AF.[10] Considering that little is known on the widespread activity of NOACs as therapeutic alternative in patients with AF, and even less is known on the predictors leading to their choice in clinical practice, this study aimed to fill this gap by investigating the use of NOACs and predictors of its initiation, as opposed to warfarin, in elderly patients with AF.

Materials and methods
Data source
Based on data availability, we retrieved anonymized data stored in Caserta Local Health Unit (LHU) administrative databases from January 1, 2014, to December 31, 2014. For reimbursement purposes, Caserta LHU administrative databases contain demographical information (ie, age, gender, and date of death), hospital contact, and drugs redeemed/supplied from pharmacies/local health authority in the catchment area of Caserta (Campania Region, Italy) which covers a population of approximately 1 million inhabitants. For each redeemed/supplied prescription information on the active ingredient, dose, formulation, the number of packages, the date of dispensation, drug price, and the Anatomical Therapeutic Chemical (ATC) classification system code were available.[11] In the aforementioned databases, all information was linked through a unique and anonymous personal identification code. These data sources have been previously used for pharmacoepidemiological and drug utilization study purposes.[12–19]
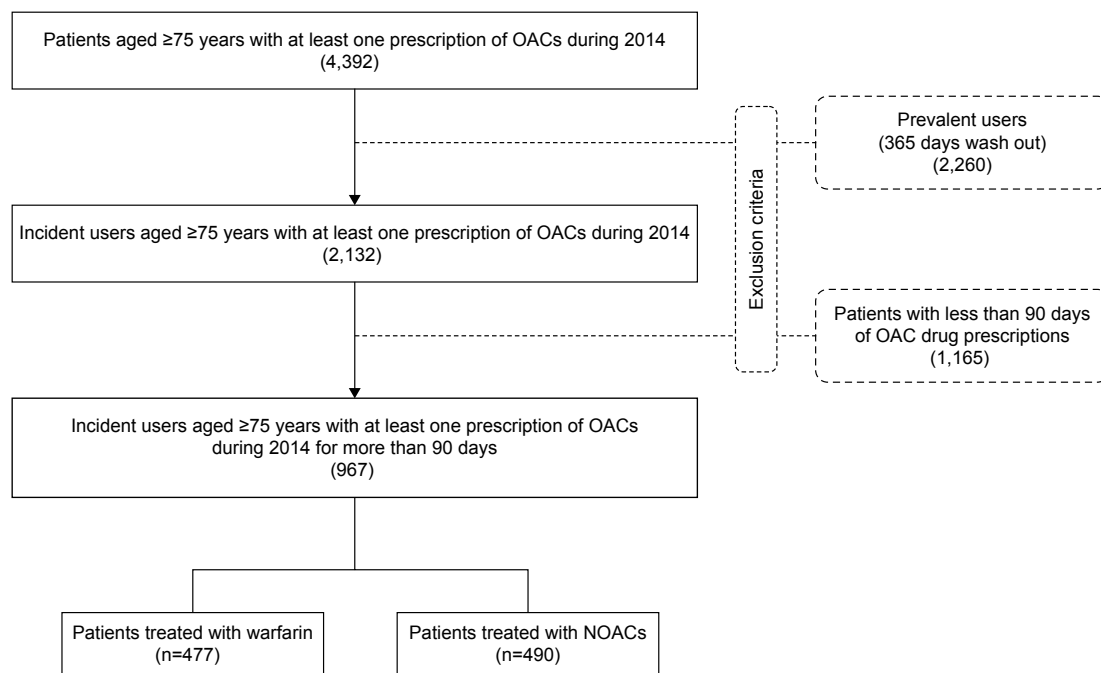
Study population
The study population consisted of all subjects aged 75 years or older receiving at least one prescription of warfarin or NOAC in the period from January 1, 2014, to December 31, 2014. We defined a subject as receiving a warfarin prescription if he/she redeemed a prescription with a drug having ATC code B01AA03. On the other hand, we defined NOAC users as those subjects redeeming prescriptions of dabigatran (ATC code: B01AE07), rivaroxaban (ATC code: B01AF01), and apixaban (ATC code: B01AF02). The date of the first redemption of such prescriptions was used as the index date for each subject. From this preliminary population, we identified our study population that is composed of naïve users of warfarin or NOACs. We defined a subject as naïve for warfarin or NOACs if he/she did not redeem prescriptions of these drugs within 365 days prior to index date. Because information on the medical needs leading to a prescription of warfarin or NOACs was not available, to assume AF as the indication of use for such drugs, we restricted the analysis to subjects whose pharmacy prescriptions amounted to ≥90 days of anticoagulation (90 or more days between first and last OAC prescription dates). Figure 1 shows the flowchart of the study.

Study covariates
For each subject, we retrieved information on age, gender, and co-treatment in the 12-month period prior to the index date. Specifically, we evaluated the number of co-prescribed medications within 365 days prior to index date and the exposure to specific co-treatments: drugs platelet aggregation inhibitor (PAI) excluding heparin (ATC: B01AC), anti-inflammatory and antirheumatic products (ATC: M01A), and proton pump inhibitor (PPI; ATC: A02B). Moreover, AF drugs such as digitalis glycosides (ATC: C01AA), antiarrhythmics class Ia (ATC: C01BA), antiarrhythmics class Ic (ATC: C01BC), antiarrhythmics class III (ATC: C01BD), strophanthus glycosides (ATC: C01AC), other cardiac glycosides (ATC: C01AX), nonselective beta-blocking agents (ATC: C07AA), selective beta-blocking agents (ATC: C07AB), and alpha and beta-blocking agents (ATC: C07AG) were also evaluated. Finally, selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor (SSRI/SNRI; ATC: N06A) was evaluated. The number of co-prescribed drugs was categorized as follows: 0–4 drugs, 5–9 drugs, and ≥10 drugs.

Outcomes
The study outcomes are the OR of receiving an NOAC prescription as opposed to a warfarin prescription among

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┌──────────────────────────────────────────────────────────────┐
│ Patients aged ≥75 years with at least one prescription of OACs │
│ during 2014                                                    │
│ (4,392)                                                        │
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                                                    ┌────────────────────────────┐
                                                    │ Prevalent users            │
                                                    │ (365 days wash out)        │
                                                    │ (2,260)                    │
                                                    └────────────────────────────┘
┌──────────────────────────────────────────────────────────────┐
│ Incident users aged ≥75 years with at least one prescription   │
│ of OACs during 2014                                            │
│ (2,132)                                                        │
└──────────────────────────────────────────────────────────────┘
                                                    ┌────────────────────────────┐
                                                    │ Patients with less than 90  │
                                                    │ days of OAC drug            │
                                                    │ prescriptions               │
                                                    │ (1,165)                    │
                                                    └────────────────────────────┘
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│ Incident users aged ≥75 years with at least one prescription   │
│ of OACs during 2014 for more than 90 days                      │
│ (967)                                                          │
└──────────────────────────────────────────────────────────────┘

┌──────────────────────────┐        ┌──────────────────────────┐
│ Patients treated with     │        │ Patients treated with      │
│ warfarin                  │        │ NOACs                      │
│ (n=477)                   │        │ (n=490)                    │
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Figure 1 Patient selection flowchart.
Abbreviations: NOACs, new oral anticoagulants; OACs, oral anticoagulants.

genders, ages (expressed as unitary increase), and patients exposed to specific co-treatments.

Statistical analysis

Baseline characteristics of the study cohort were presented separately for NOACs and warfarin. Continuous variables were presented as mean ± SD, and differences between two therapy groups were compared using the Student's unpaired t-test. Categorical variables were presented as numbers (percentages) and were compared across therapy groups by chi-squared test. Univariate and multivariate logistic regression models were conducted to identify whether study covariates were predictors of NOAC initiation as opposed to warfarin. In the multivariate model, all the potential predictors were entered that were significant at the $P<0.25$ in the univariate analysis. All analyses were performed using SPSS software version 17.1 for Windows (IBM Corporation, Armonk, NY, USA). A P-value of <0.05 was considered as statistical significance.

Results

Overall, 4,392 subjects aged 75 years or older, with at least one prescription of OAC drugs, were identified from January 1, 2014, to December 31, 2014. Among these subjects, 967 out of 4,392 (22.01%) were naïve and treated for at least 90 days with OACs (Figure 1). The characteristics of the study population are summarized in Table 1. The mean age (SD) of the study population was 81.5 years (4.5 years), and the female gender (61.4%) was predominant. In all, 490 (50.7%) out of the 967 patients were exposed to NOACs and 477 (49.3%) to warfarin. Among the 490 patients treated with NOACs, more than half (58.6%) received rivaroxaban, 22.4% apixaban, and 19.0% dabigatran. A significantly lower number of subjects received PAI among warfarin users if compared to NOAC users ($P<0.001$). The number of patients receiving AF drugs, NSAIDs, and SSRI/SNRI was comparable between patients exposed to NOAC therapy vs those exposed to warfarin. The number of co-prescribed drugs was comparable between NOAC and warfarin patients ($P=0.076$).

Predictors of NOAC initiation

Increasing age was significantly associated with a lower odds of NOAC initiation: for each 1-year increase in age, patients were about 3% less likely to receive an NOAC (OR: 0.969, 95% CI: 0.941–0.998, $P=0.038$; Table 2 and Figure 2). As the number of co-prescribed medicines increased, an increased likelihood of receiving warfarin as opposed to NOACs was observed. In particular, subjects exposed to five to nine drugs and those exposed to ten+ drugs were 39% and 63% less likely to receive an NOAC (OR [five to nine drugs] group: 0.607, 95% CI: 0.432–0.852, $P=0.004$; OR [ten+ drugs] group: 0.372, 95% CI: 0.244–0.567, $P<0.001$). The strongest predictors of NOAC initiation were the previous exposure to

Table 1 Descriptive statistics of the study population (N=967)

	NOACs (n=490)	Warfarin (n=477)	Overall (N=967)	*P*-value
Gender (female)	289 (59.0%)	305 (63.9%)	594 (61.4%)	0.113
Age (mean ± SD)	81.3±4.5	81.6±4.5	81.5±4.5	0.217
Age group				0.517
75–79 years	193 (39.4%)	177 (37.1%)	370 (38.3%)	
80–84 years	176 (35.9%)	167 (35.0%)	343 (35.5%)	
85+ years	121 (24.7%)	133 (27.9%)	254 (26.3%)	
Receiving PAI	273 (55.7%)	150 (31.4%)	423 (43.7%)	<0.001*
Receiving AF drugs	378 (77.1%)	372 (78.0%)	750 (77.6%)	0.753
Receiving NSAIDs	221 (45.1%)	220 (46.1%)	441 (45.6%)	0.750
Receiving J02A	15 (3.1%)	13 (2.7%)	28 (2.9%)	0.755
Receiving PPI	369 (75.3%)	367 (76.9%)	736 (76.1%)	0.552
Receiving SSRI/SNRI	74 (15.1%)	72 (15.1%)	146 (15.1%)	0.997
Number of co-prescribed medicines				0.076
0–4	118 (24.1%)	92 (19.3%)	210 (21.7%)	
5–9	272 (55.5%)	264 (55.3%)	536 (55.4%)	
10–14	100 (20.4%)	121 (25.4%)	221 (22.9%)	

Note: *P-value of <0.05 was considered statistically significant.
Abbreviations: AF, atrial fibrillation; J02A, antimycotics for systemic use; NOACs, new oral anticoagulants; PAI, platelet aggregation inhibitor; PPI, proton pump inhibitor; SSRI/SNRI, selective serotonin reuptake inhibitor/serotonin norepinephrine reuptake inhibitor.

PAI which was three times more likely to use an NOAC as opposed to warfarin (OR: 3.474, 95% CI: 2.610–4.625).

Ethics statement

All procedures performed in this study were in accordance with the current national law from Italian Medicines Agency.[45] The manuscript does not contain clinical studies, and all patients' data were fully anonymized. For this type of study, formal consent is not required. Permission to use anonymized data for the present study was granted by the responsible authority, Caserta LHU, Regione Campania.

Discussion

This study provides up-to-date information on the recent anticoagulation prescription behavior in elderly patients with AF in the catchment area of Caserta (Campania Region, Italy). In this regard, it should be emphasized that stroke prophylaxis among high-risk patients, eg, elderly, is clinically challenging, and data show that OAC treatm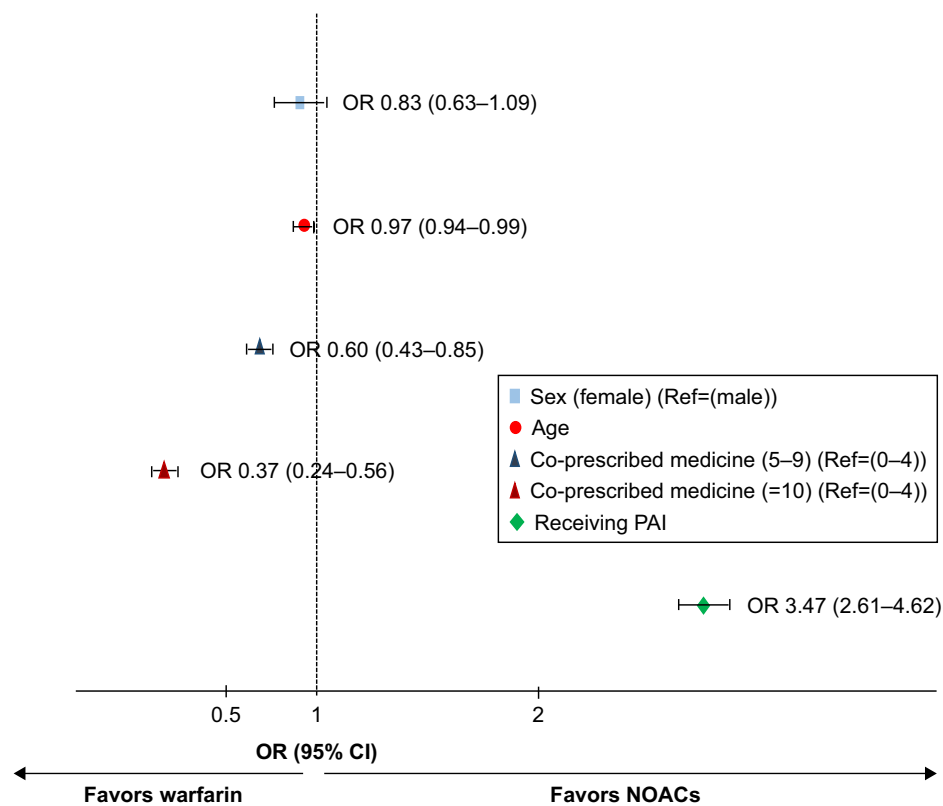ent is often underused.[20,21] The suboptimal OAC treatment of elderly patients has been increasingly explored in recent years as elderly patients are at particularly high risk of stroke, and prior studies have shown that OAC provides a net clinical benefit among elderly AF patients.[22,24] According to our findings, polypharmacy seems to drive the choice of VKA over NOAC. In fact, elderly patients with AF exposed to moderate polypharmacy (five to nine drugs) and extensive polypharmacy (ten+ drugs) were 39% and 63% less likely to receive an NOAC compared to warfarin users, respectively. This finding is in line with a retrospective study carried out in Ireland showing that

Table 2 Univariate and multivariate model predicting the initiation of NOACs vs warfarin

Characteristics	Unadjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Sex				
Male	Reference		Reference	
Female	0.811 (0.626–1.051)	0.113	0.830 (0.631–1.090)	0.180
Age (years)	0.982 (0.955–1.010)	0.217	0.969 (0.941–0.998)	0.038*
Receiving PAI				
No	Reference		Reference	
Yes	0.365 (0.280–0.474)	<0.001*	3.474 (2.610–4.625)	<0.001*
Number of co-prescribed medicines				
0–4	Reference		Reference	
5–9	0.803 (0.583–1.107)	0.181	0.607 (0.432–0.852)	0.004*
10+	0.644 (0.441–0.942)	0.023*	0.372 (0.244–0.567)	<0.001*

Notes: OR values higher than 1.0 indicate predictors of NOAC initiation as opposed to warfarin and vice versa. *P-value of <0.05 was considered statistically significant.
Abbreviations: NOACs, new oral anticoagulants; PAI, platelet aggregation inhibitor.

OR 0.83 (0.63–1.09)

OR 0.97 (0.94–0.99)

OR 0.60 (0.43–0.85)

OR 0.37 (0.24–0.56)

■ Sex (female) (Ref=(male))
● Age
▲ Co-prescribed medicine (5–9) (Ref=(0–4))
▲ Co-prescribed medicine (=10) (Ref=(0–4))
◆ Receiving PAI

OR 3.47 (2.61–4.62)

OR (95% CI)

Favors warfarin   Favors NOACs

Figure 2 Forest plot of predictors of NOAC vs warfarin initiation.
Abbreviations: NOACs, new oral anticoagulants; PAI, platelet aggregation inhibitor; Ref, reference.

multiple concomitant medications were negatively associated with NOAC initiation.[25] On the other hand, our findings are in contrast with other previous studies. Results of the study by Belen et al,[26] which investigated the reasons for a decline in VKA utilization, revealed that potential drug–drug interactions (DDIs) and diet were the most common reasons for choosing NOAC over VKA. According to Belen et al, further literature data demonstrated that, especially for elderly patients, NOACs represent a more suitable treatment option compared to warfarin due to a more predictable dosing, fewer DDIs, and reduced risk of intracranial bleeding.[27] In addition, a study by AbuDagga et al[28] reported that older age decreased the probability of initiating dabigatran, but their study ended in 2014, and rivaroxaban and apixaban data were absent. Nevertheless, our results showed that VKA treatment is still used and, in contrast to the NOACs, VKAs have the advantage of being suitable for patients with severe renal impairment (creatinine clearance ≤15 mL/min).[22] Still, a lack of knowledge on NOACs' DDIs may limit their tangible use, especially in elderly patients. As a matter of fact, despite their advantages over warfarin, NOACs carry a potential for DDIs, which could occur more frequently in elderly than in younger patients, due to the age-related higher prevalence of comorbidities and polymedication.[29] A recent review by Stöllberger[30] highlighted that several drugs, including acetylsalicylic acid, clopidogrel, ticagrelor, prasugrel, NSAIDs, and SSRIs/SNRIs, could interact with NOACs, increasing the risk of bleeding complications. Moreover, since NOACs are metabolized by the CYP/CYP450 isoenzymes 3A4 (CYP3A4) and 2J9 (CYP2J9), DDIs were also identified with drugs that affect the activity of such cytochrome isoenzymes. Furthermore, considering that NOACs are substrates for the drug ellux pump, P-glycoprotein (P-gp),drugs affecting the activity of P-gp, such as atorvastatin, clarithromycin, and diltiazem, can increase the risk of bleeding, thromboembolism, and further adverse events. Finally, it was found out that NOACs could influence the serum and tissue concentrations of immunosuppressant and analgesic drugs as well as that PPIs may affect NOAC bioavailability changing the gastric pH. A recent retrospective cohort study, which has evaluated, on more than 90,000 patients, the effects on major bleedings of co-exposure to NOACs and other drugs, revealed that the concurrent use of NOACs and amiodarone, fluconazole, rifampin, and phenytoin was associated with the increased risk of the main outcome.[31] However, considering that few

data from clinical practice are nowadays available on this topic, further data are strongly needed. Another interesting finding of our study is that the factor most strongly associated with NOAC initiation was the previous PAI utilization. In particular, patients receiving PAI medication were more than three times as likely to use an NOAC compared to warfarin (OR: 3.474, 95% CI: 2.610–4.625). These results could be explained considering that the concomitant use of PAI and OACs, also known as triple oral antithrombotic therapy (TOAT), is required in the specific group of patients affected by cardiovascular disease, usually AF which had drug-eluting stent implantation or acute coronary syndrome.[32] Therefore, in our opinion, the higher probability for patients receiving PAI medication to initiate an NOAC could be related to the easier management of therapy with NOAC compared to warfarin especially in terms of its bleeding risk. In our cohort, more than 50% of patients received a prescription of rivaroxaban, 22% of elderly patients were on apixaban, while dabigatran was adopted in about 19% of elderly patients. In this regard, we do not believe that this result could be associated with the different efficacy/safety differences among NOACs. In fact, the pivotal study for rivaroxaban, the multi-center, randomized, double-blind, double-dummy ROCKET AF trial, which compared once-daily oral rivaroxaban with dose-adjusted warfarin for the prevention of stroke and systemic embolism in patients with nonvascular AF who were at moderate to high risk for stroke, revealed that rivaroxaban was non-inferior to warfarin, with an annual rate of stroke and systemic embolism 2.12% vs 2.42% ($P<0.001$) reported with warfarin.[7] Safety results demonstrated that rivaroxaban was associated with a significant reduction in fatal bleeding (0.2% vs 0.5% per year, P=0.003) and cerebral hemorrhage (0.5% vs 0.7% per year, P=0.02). Since rivaroxaban is, for one-third, renally cleared, it is especially safe in patients with mild renal impairment (creatinine clearance 30–49 mL/min), which is one of the most frequent comorbidities in the elderly.[33] Similarly, the results of ARISTOTLE trial and its post hoc analyses found that apixaban had a lower relative risk of stroke or systemic embolism as well as major bleeding and death when compared to warfarin.[34,35] Moreover, a recent review by Diener et al[36] suggested apixaban as the first choice in AF patients older than 75 years. Although no comparable head-to-head randomized trial has examined the efficacy and safety between the NOACs yet, it is likely that the positive results from the ARISTOTLE trial might have influenced the rapidly increased uptake of apixaban compared to the other NOACs, in particular among elderly AF patients.[37] Finally, dabigatran was also associated with a notably lower relative risk of stroke or systemic embolism compared to warfarin, although it was related to an increased risk of gastrointestinal bleedings.[38] Notably, approximately 80% of dabigatran is eliminated by renal clearance, and a condition with impaired renal function is often found among elderly patients.[39] Data from the RE-LY trial showed that renal function was highly correlated with age, and plasma concentration of dabigatran increased with advancing age.[40]

Local policies should provide training and information to health care professionals to optimize health resources also implementing successful elements from other EU countries' activities.[41,42] Synergies between different actors involved in health care delivery can help achieve better results. Further studies are needed to improve our knowledge of the safety profile in a real-world setting.

Strengths and limitations
The main strength of our study is based on a data source with full coverage of the warfarin and NOAC prescriptions for a geographically defined, stable population, and we were able to account for multiple confounders such as age, gender, and co-medications.[10] However, the study also has potential limitations. Some predictive factors, such as comorbidities or previous cardiovascular events, have not been considered. Furthermore, as VKA administration may increase arterial stiffness (which is a predictor of cardiovascular risk), lack of information about diagnosis and stroke occurrence did not allow us to evaluate the advantage of NOAC use vs warfarin. Data reported in the study refer to 2014, and the current patterns regarding the use of NOACs could have changed meanwhile. Finally, doses of NOACs used have not been reported: further studies should be carried out for evaluating dosing regimens used in the real practice as reduced doses could be inappropriate and ineffective.

Conclusion
This study provides data on prescription of NOACs and warfarin from clinical practice in the Italian national territory. In a real-world setting, multiple co-medication may be associated with lower likelihood of NOAC initiation. This trend is more evident in patients with excessive polypharmacy (more than ten drugs) bringing significant implications for cost-effectiveness and outcome studies.

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Disclosure

The authors report no conflicts of interest in this work.

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