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Characteristics of warfarin under-prescription in older adults with atrial fibrillation

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ABSTRACT

Background: The prevalence of atrial fibrillation (AF) and atrial flutter (AFl) increases with age. Under-prescription of anticoagulants in older adults can lead to increased morbidity and mortality. We analyzed warfarin prescription patterns in older adults.

Methods: In this observational single-center study, we analyzed 2179 consecutive patients with admission diagnosis of AF or AFl. Patients were divided into "older" (≥ 75 years old) and "younger" (<75 years old) groups. Prescription patterns of warfarin were analyzed. Patients discharged from the hospital on a non-warfarin anticoagulation were excluded.

Results: Of the 1988 patients analyzed, 46.9% were ≥75 years old, of which 50.8% were prescribed warfarin. There was no association between mean CHA_2DS_2-VASc score and warfarin prescription on discharge (OR = 1.06 (95% CI 0.93–1.21), p = 0.388) in the older group. After adjusting for hypertension, renal function, and Black race, warfarin prescription in older adults was independently associated with lower aspirin prescription rates (OR = 0.57 (95% CI 0.43–0.75), p < 0.001), lower body mass index (OR = 1.03 (95% CI 1.01–1.06), p = 0.018), and lower hemoglobin levels (OR = 1.11 (95% CI 1.04–1.19), p = 0.002).

Conclusions: In our study, older adults (≥75 years old) with AF and AFl tended to have lower rates of warfarin prescription despite higher CHA_2DS_2-VASc score and higher risk of thromboembolic events. Anemia, lower body weight, and aspirin use were characteristics associated with warfarin under-prescription.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting 2.7–6.1 million Americans [1,2]. Its prevalence increases with age; 12% in ages 75–84, and 23.9% in ages 80–84 [3–6]. It is an independent risk factor for all-cause mortality, cardiovascular mortality, hospitalization, stroke, dementia, and heart failure [7–15]. In patients with AF, age over 75 years is one of the strongest independent risk factors for thromboembolic events, such as stroke [16]. The CHA_2DS_2-VASc score (congestive heart failure, hypertension, age 65–74, age ≥ 75 [2 points], diabetes, stroke [2 points], and vascular disease) signifies benefit of anticoagulation in AF or atrial flutter (AFl) for a score of ≥2 [17]. Anticoagulation also decreases morbidity and mortality rates associated with stroke [7,18]. When compared to antiplatelet therapy, anticoagulation decreases the risk of stroke with similar bleeding risk [19]. Despite the proven benefit and low risk of bleeding with falls, anticoagulants remain underutilized in the old adults (≥75 years old) [20–25]. Despite the advent of direct oral anticoagulants (DOAC), warfarin is still prescribed more frequently (i.e. among medically underserved populations) than DOACs and is solely

Abbreviations: AF, atrial fibrillation; AFl, atrial flutter; DOAC, direct oral anticoagulants; INR, international normalized ratio; OR, odds ratio; IQR, intraquartile range; BMI, body mass index.

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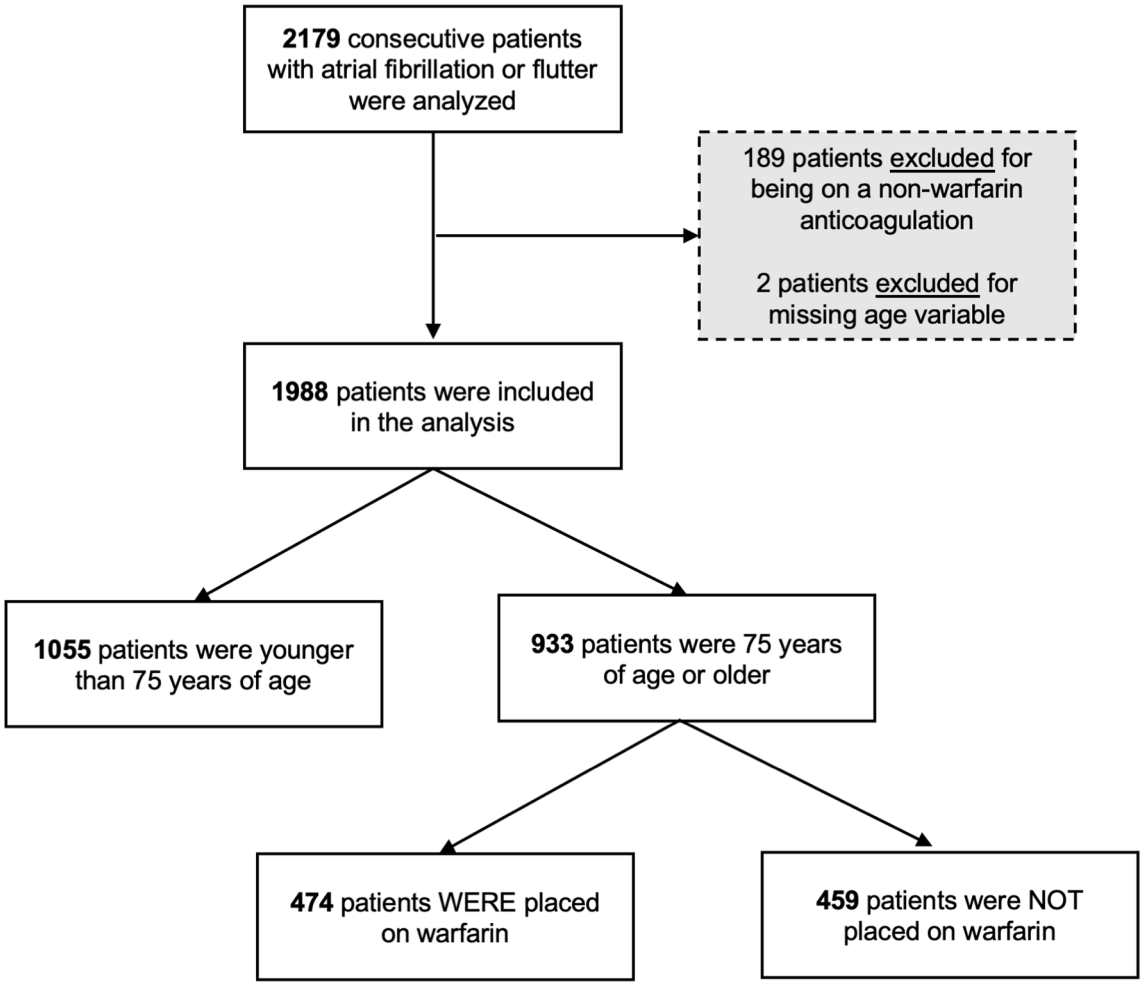

Fig. 1. Flow diagram with patient selection, exclusion criteria, and division by age and anticoagulation status.

indicated in conditions such as valvular atrial fibrillation [26,27]. The aim of our study was to examine the characteristics of older adults (herein defined as ≥75 years old) with AF or AFl who are and are not discharged from the hospital on warfarin.

2. Methods

2.1. Patient population

We analyzed a registry of 2179 consecutive patients with AF or AFl admitted to St Luke's Roosevelt Hospital Center, New York between September 2006 and April 2014. The study was approved by the institutional review board and informed consent for participation in anonymous data collection was waived. The study protocol met the requirements of the Declaration of Helsinki and was performed in compliance with human-studies guidelines. Informed consent was obtained from all patients.

Because warfarin is still widely prescribed, (i.e. valvular AF, affordability among underinsured), those discharged on a non-warfarin anticoagulation (i.e. DOACs) (189 patients) were excluded from the analysis. Those with missing age variable (2 patients) were also excluded from the data analysis. The remaining 1988 patients were divided into the "older group" (≥75 years old) and the "younger group" (<75 years old). Because age over 75 years is an independent risk factor for thromboembolic events, it was chosen as a cut-off between the two groups [16]. The older group was subdivided into those who were (*Warfarin* group) and were not discharged on warfarin (*Non-warfarin* group) (Fig. 1).

2.2. Statistical analysis

Continuous variables are expressed as the mean ± standard deviation for normally distributed or median (interquartile range) for not normally distributed continuous variables. Normality for all continuous variables was tested using the Shapiro–Wilk test. Patient groups were compared using Student's *t*-test or Wilcoxon's rank-sum test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. The selection of variables for multivariate logistic regression, which revealed determinants for warfarin underprescription, was based on bivariate statistical significance and published literature. Statistical significance was established as $\alpha = 0.05$, statistical analysis was performed using a standard statistical software package (R version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria).

Table 1
Characteristics of patients with atrial fibrillation and flutter.

	Overall N = 1988	Younger Group (< 75 years) N = 1055	Older Group (≥ 75 years) N = 933	P value
Baseline Characteristics				
Age	71.8 (14.4)	60.9 (10.5)	84.1 (5.8)	**<0.001**
Male sex - no. (%)	1019 (51.3)	683 (64.7)	336 (36.0)	**<0.001**
BMI - (kg/m2)	26.8 [24.0, 30.4]	26.9 [25.8, 33.0]	26.4 [22.0, 27.0]	**<0.001**
CHA_2DS_2-VASc	4.54 (1.65)	3.62 (1.50)	5.58 (1.11)	**<0.001**
Past Medical History - no. (%)				
Hypertension	1546 (77.8)	779 (73.8)	767 (82.2)	**<0.001**
Diabetes	542 (27.3)	308 (29.2)	234 (25.1)	0.045
Hyperlipidemia	808 (40.6)	414 (39.2)	394 (42.2)	0.189
Myocardial infarction	264 (13.3)	130 (12.3)	134 (14.4)	0.203
Coronary artery disease	467 (23.5)	231 (21.9)	236 (25.3)	0.083
Congestive heart failure	667 (33.6)	331 (31.4)	336 (36.0)	**0.031**
First episode of AF	760 (38.2)	409 (38.8)	351 (37.6)	0.611
Smoking Status - no. (%)				
Non-smoker	1152 (57.9)	572 (54.2)	580 (62.2)	**<0.001**
Current smoker	239 (12.0)	187 (17.7)	52 (5.6)	
Former smoker	585 (29.4)	291 (27.6)	294 (31.5)	
Prior Procedural History - no. (%)				
Percutaneous coronary intervention	265 (13.3)	153 (14.5)	112 (12.0)	0.117
Coronary artery bypass braft	183 (9.2)	77 (7.3)	106 (11.4)	**0.002**
Home Medications - no. (%)				
Aspirin	907 (45.6)	461 (43.7)	446 (47.8)	0.089
Beta blockers	1127 (56.7)	588 (55.7)	539 (57.8)	0.419
Clopidogrel	180 (9.1)	87 (8.2)	93 (10.0)	0.221
ACEI/ARB	852 (42.9)	451 (42.7)	401 (43.0)	1
Diuretic	746 (37.5)	369 (35.0)	377 (40.4)	**0.018**
Digoxin	223 (11.2)	102 (9.7)	121 (13.0)	0.025
Spironolactone	78 (3.9)	39 (3.7)	39 (4.2)	0.676
Statins	796 (40.0)	374 (35.5)	422 (45.2)	**<0.001**
Insulin	151 (7.6)	84 (8.0)	67 (7.2)	0.553
Antiarrhythmic	153 (7.7)	110 (10.4)	43 (4.6)	**<0.001**
Anticoagulation	634 (31.9)	365 (34.6)	269 (28.8)	**0.007**
Discharge Medications - no. (%)				
Aspirin	1246 (62.7)	655 (62.1)	591 (63.3)	0.602
Beta blockers	1366 (68.7)	720 (68.2)	646 (69.2)	0.678
Digoxin	382 (19.2)	185 (17.5)	197 (21.1)	**0.049**
Rate and rhythm control	316 (15.9)	209 (19.8)	107 (11.5)	**<0.001**
Rate control alone	1462 (73.5)	733 (69.5)	729 (78.1)	**<0.001**
Antiarrhythmic	343 (17.3)	231 (21.9)	112 (12.0)	**<0.001**
Antiplatelets	1249 (62.8)	656 (62.2)	593 (63.6)	0.585
Warfarin	1118 (56.2)	643 (60.9)	474 (50.8)	**<0.001**

Values represent mean ± standard deviation, median [IQR 25th–75th percentiles] or number (%). Bold values indicate statistical significance ($p < 0.05$). BMI = body mass index; ACEI = angiotensin converting enzyme inhibitor; ARB = aldosterone receptor blocker.

3. Results

In our study, the older group included 933 patients (46.9%) and the younger group included 1055 patients. When compared to the younger group, those in the older group tended to be female, had lower body weight, and a diagnosis of heart failure and coronary artery disease. Within the older group, only 474 (50.8%) patients were prescribed warfarin on hospital discharge compared to 643 (60.9%) patients in the younger group. Table 1 summarizes clinical characteristics of the groups.

The younger group had higher rates of warfarin prescription as CHA_2DS_2-VASc score increased ($p < 0.001$). However, the older group had no statistically significant difference between CHA_2DS_2-VASc score and warfarin prescription on discharge ($p = 0.16$). (Fig. 2). Table 2 summarizes the clinical characteristics in the older group that were and were not discharged on warfarin. Within the non-warfarin group, only 14.6% were on home anticoagulation at baseline compared to 42.6% who were on anticoagulation at baseline within the warfarin group ($p < 0.001$). Those discharged on warfarin, were also more likely to be prescribed a rhythm control agent.

In the multivariate analysis, after adjusting for hypertension, renal function, and Black race, warfarin prescription in older adults was independently associated with lower rates of aspirin prescription (OR = 0.57 (95% CI 0.43–0.75), $p < 0.001$), lower body mass index (BMI) (OR = 1.03 (95% CI 1.01–1.06), $p = 0.018$), and relative anemia (normal ≥13.5 g/dL in males, ≥ 12 g/dL in females) (OR = 1.11 (95% CI 1.04–1.19), $p = 0.002$). Additionally, there was no difference between mean CHA_2DS_2-VASc score and warfarin prescription (OR = 1.06 (95% CI 0.93–1.21), $p = 0.388$)) in the older group (Fig. 3).

4. Discussion

In this observational study, patients under 75 years of age with AF or AFl were more likely to be prescribed warfarin as indicated by their CHA_2DS_2-VASc score. However, those 75 and older were less likely to be discharged on warfarin irrespective of their CHA_2DS_2-VASc score (mean 5.6 ± 1.1). Similarly, a retrospective study with over 41,000 Medicare beneficiaries with AF reported warfarin prescription rates decreased significantly with advancing age and multiple comorbidities [28]. In our study, the older group was also more likely to have lower BMI, relative anemia, and to be discharged on aspirin therapy. One possible explanation is that physicians are hesitant to prescribe anticoagulation when perceived harm of anticoagulation outweighs benefit. Another plausible explanation is patient preference and shared decision-making to withhold anticoagulation. Despite this potential hesitancy, withholding anticoagulation confers with it a substantial risk of ischemic stroke [35].

4.1. Antiplatelet medications and anticoagulation

Our study demonstrated that those with higher rates of active aspirin prescription were less likely to be discharged on warfarin. This is likely given the perceived risk of severe hemorrhage outweighing anticoagulation benefits. However, there is evidence that risk of ischemic stroke without anticoagulation outweighs risk of intracranial bleeding on anticoagulation [29]. Additionally, antiplatelet therapy does not have a reduced risk of bleeding compared to warfarin, and when compared to warfarin, it was suboptimal for stroke prevention [30]. Thus, careful assessment of benefits and risks, along with shared decision making, are necessary for optimal care of older patients with AF or AFl.

4.2. Anemia and anticoagulation

The prevalence of anemia in AF increases with age [31]. In our study, multivariate analysis showed that older adults who were more anemic were less likely to be discharged on warfarin. In a prospective multicenter trial of 929 patients, those with AF and anemia had higher mortality, more thrombotic events, and more minor bleeding events [32]. Similarly, a Japanese prospective observational study of 4169 AF patients found increased incidences of major bleeding, heart failure hospitalizations, and mortality as severity of anemia increased regardless of anticoagulation use [33]. In another prospective group trial, anemia was found to be a significant risk factor for bleeding regardless

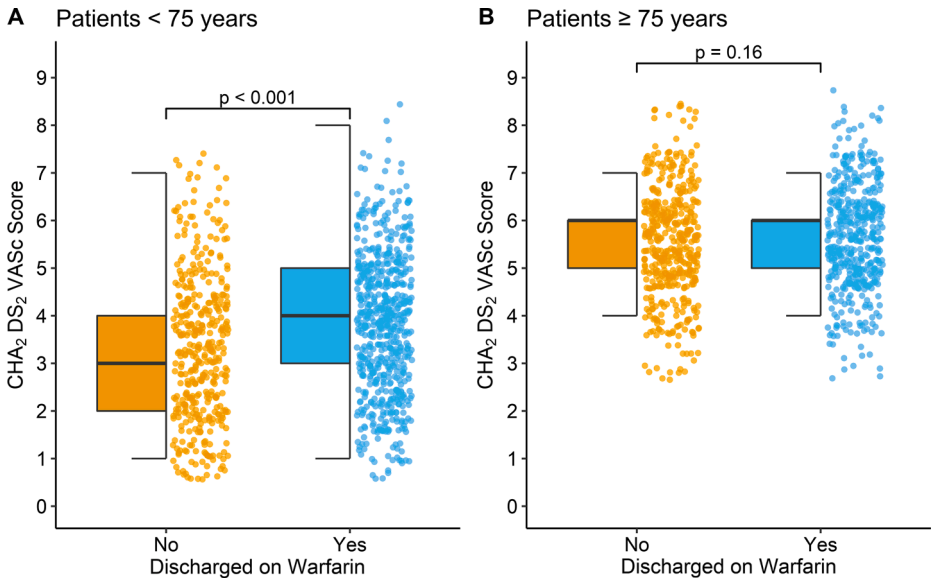

Fig. 2. The relationship between CHA_2DS_2-VASc Score and warfarin prescription on hospital discharge. In contrast to the younger group (A), there is no statistically significant difference between CHA_2DS_2-VASc score and being discharged on warfarin in the older group (B). Jitter was added to scatterplot to better visualize the data.

of when anticoagulation was initiated [34]. Because anemia is an independent risk factor for thromboembolic events and bleeding risk persists whether the patient is on warfarin or not [31], correction of underlying anemia and prescribing anticoagulation may reduce thromboembolic events. However, further studies are needed to confirm that anemia is a modifiable risk factor [31]. Although there are many confounding variables, such as underlying malignancy, that can explain why those with relative anemia were less likely to be anticoagulated, studies suggest that anemia should be promptly addressed as benefits of anticoagulation outweigh the risks of not anticoagulating those with AF.

4.3. Low weight and perceived frailty

Our study also showed that lower BMI was associated with warfarin under-prescription, perhaps implying that lower weight is a surrogate for perceived frailty that may discourage physicians from prescribing anticoagulation. Additional studies found warfarin lowered thromboembolic events in adults of ages 70–84 [35]. Several studies indicate that the risk of falls, rather than history of falls, is not a significant risk factor for bleeding and does not outweigh the benefit of thromboembolism prevention with anticoagulation [23–25]. Other cited reasons for withholding anticoagulation included cognitive disorders, non-adherence, history of previous bleeds, and alcoholism [23,36–39]. Still, even with a relative increased risk of fall and intracranial hemorrhage, those with multiple stroke risk factors would benefit from anticoagulation [40]. The European Society of Cardiology recommends that anticoagulation in the elderly population should be withheld only in the case of severe uncontrolled falls with examples such as epilepsy or advanced multisystem atrophy with backward falls [7].

4.4. Warfarin and direct-oral anticoagulants

Although DOACs are steadily increasing in prevalence, warfarin is prescribed more widely than apixaban and rivaroxaban according to Medical Expenditure Panel Survey released annually by the United States government in 2018 [26]. Given warfarin's low cost ($0.22 average spending per dose unit vs $7.45 for apixaban, $14.85 for rivaroxaban, and $6.21 for dabigatran), it is more accessible for uninsured and underinsured older patients with AF and AFl [41]. Additionally, reversal agents of warfarin are much more accessible. Internationally, particularly in low-to-middle income countries, unlike warfarin, DOACs are not placed on the national essential medicines lists, thus making it a less accessible for patients [42]. Until affordability and availability are addressed in these countries, warfarin will remain the popular anticoagulant [42]. Thus, further research into warfarin and its under-prescription is relevant for millions of people annually.

5. Conclusion

Although there is ample evidence of the benefits of anticoagulation in older adults with AF and AFl, our study found that clinicians tend to under-prescribe anticoagulation regardless of their CHA_2DS_2-VASc score. Our study suggests that certain patterns associated with under-prescription include the presence of anemia, lower weight, and aspirin prescription. This may imply clinicians' hesitancy to anticoagulate when harm of anticoagulation is perceived to be higher than its benefit. Patterns of anticoagulation under-prescription can shed light on these patients who are already at a higher risk of thromboembolic events and have proven to benefit from therapeutic anticoagulation. And because warfarin is still the most widely prescribed anticoagulant, studies into its prescription characteristics continue to remain relevant. Additionally, warfarin remains the most affordable anticoagulant and thus accessible for the medically underserved. Careful assessment of benefits and risks, along with shared decision making, are necessary for optimal care of these older patients with AF or AFl.

5.1. Limitations

Our study has limitations. We analyzed a relatively small group of patients from a single center. Our study only included warfarin, thus the

Table 2
Characteristics of older patients (≥75 years of age) with atrial fibrillation and flutter.

	Overall N = 933	Non-Warfarin Group N = 459	Warfarin Group N = 474	P value
Baseline Characteristics				
Age	84.1 (5.8)	85.4 (6.1)	82.9 (5.2)	**<0.001**
Male sex - no. (%)	336 (36.0)	171 (37.3)	165 (34.8)	0.478
BMI	26.4 [22.0, 27.0]	26.0 [21.9, 26.8]	26.6 [22.5, 28.0]	**0.007**
CHA_2DS_2-VASc	5.58 (1.11)	5.52 (1.13)	5.64 (1.10)	0.099
Hemoglobin level (g/dL)	12.2 (2.1)	11.9 (2.2)	12.4 (1.9)	**<0.001**
Past Medical History - no. (%)				
Hypertension	767 (82.2)	364 (79.3)	403 (85.0)	**0.039**
Diabetes	234 (25.1)	116 (25.3)	118 (24.9)	0.923
Hyperlipidemia	394 (42.2)	190 (41.4)	204 (43.0)	0.7
Myocardial infarction	134 (14.4)	73 (15.9)	61 (12.9)	0.209
Coronary artery disease	236 (25.3)	118 (25.7)	118 (24.9)	0.803
Congestive heart failure	336 (36.0)	152 (33.1)	184 (38.8)	0.081
Smoking Status - no. (%)				0.228
Non-smoker	580 (62.2)	296 (64.5)	284 (59.9)	
Current smoker	52 (5.6)	26 (5.7)	26 (5.5)	
Former smoker	294 (31.5)	132 (28.8)	162 (34.2)	
Prior Procedural History - no. (%)				
Percutaneous coronary intervention	112 (12.0)	58 (12.6)	54 (11.4)	0.611
Coronary artery B\bypass graft	106 (11.4)	42 (9.2)	64 (13.5)	**0.049**
Home Medications - no. (%)				
Aspirin	446 (47.8)	241 (52.5)	205 (43.2)	**0.005**
Beta blockers	539 (57.8)	238 (51.9)	301 (63.5)	**0.001**
ACEI/ARB	401 (43.0)	180 (39.2)	221 (46.6)	**0.031**
Diuretic	377 (40.4)	169 (36.8)	208 (43.9)	0.038
Digoxin	121 (13.0)	51 (11.1)	70 (14.8)	0.118
Spironolactone	39 (4.2)	14 (3.1)	25 (5.3)	0.129
Statin	422 (45.2)	194 (42.3)	228 (48.1)	0.102
Insulin	67 (7.2)	31 (6.8)	36 (7.6)	0.725
Antiarrhythmic	43 (4.6)	19 (4.1)	24 (5.1)	0.61
Anticoagulation	269 (28.8)	67 (14.6)	202 (42.6)	**<0.001**
Discharge Medications - no (%)				
Aspirin	591 (63.3)	316 (68.8)	275 (58.0)	**<0.001**
Beta blockers	646 (69.2)	298 (64.9)	348 (73.4)	**0.011**
Digoxin	197 (21.1)	79 (17.2)	118 (24.9)	**0.005**
Rate and rhythm control	107 (11.5)	39 (8.5)	68 (14.3)	**0.007**
Rate control alone	729 (78.1)	356 (77.6)	373 (78.7)	0.735
Antiarrhythmic	112 (12.0)	42 (9.2)	70 (14.8)	**0.012**
Antiplatelets	593 (63.6)	317 (69.1)	276 (58.2)	**<0.001**
Warfarin	933 (100.0)	0 (0)	474 (100.0)	**<0.001**

Values represent mean ± standard deviation, median [IQR 25th–75th percentiles] or number (%). Bold values indicate statistical significance ($p < 0.05$). BMI = body mass index; ACEI = angiotensin converting enzyme inhibitor; ARB = aldosterone receptor blocker.

generalizability is limited. Our study did not include history or risk of falls, frailty scores, history of major bleeds, bleeding risk scores, Charleston comorbidity index, or history of neurological and psychiatric conditions which may have added insight into warfarin underprescription among the older group. Unfortunately, due to lack of bleeding history, and liability of INR (international normalized ratio), we were unable to calculate the bleeding risk scores (i.e. HASBLED, ORBIT), to assess relationship between high bleeding risk and warfarin underprescription in relation to lower body weight, anemia, and aspirin use. Further prospective studies are needed to analyze these associations, and its relation to morbidity and mortality among the elderly.

CRediT authorship contribution statement

Sana Rashid: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Maciej Tysarowski:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jorge Naranjo:** Conceptualization, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. **Atharva Dhole:** Visualization, Writing – original draft, Writing – review & editing. **Luka Petrovic:** Writing – original draft, Writing – review & editing. **Emad F. Aziz:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

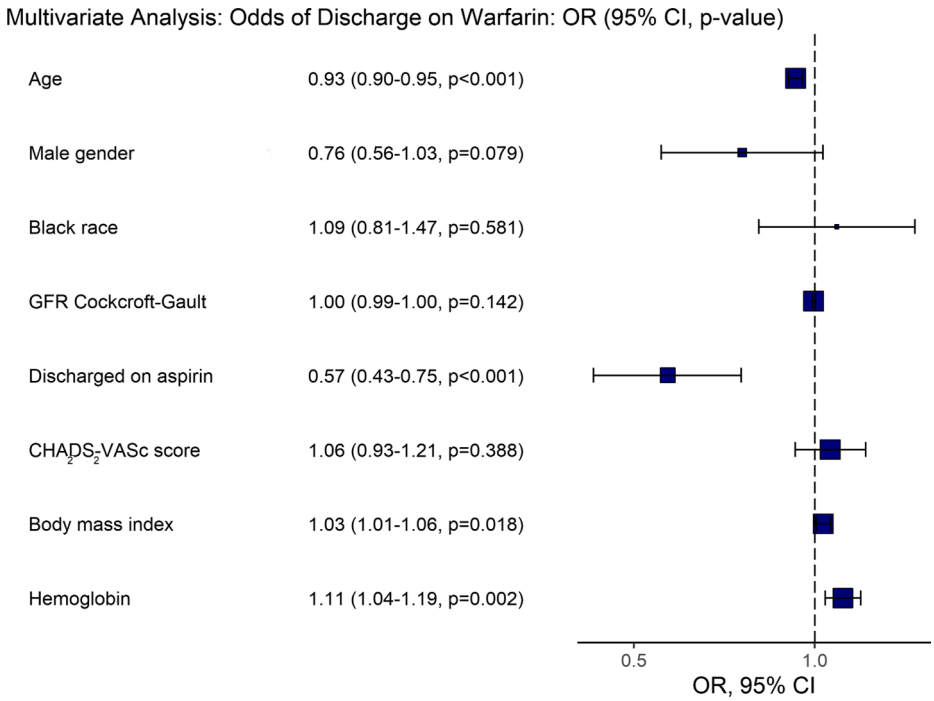

Fig. 3. Multivariate analysis assessing predictors of being discharged on warfarin in patients ⩾ 75 years old. After adjusting for hypertension, renal function, and Black race, warfarin prescription on hospital discharge was independently associated with lower aspirin prescription rates, lower body mass index, and lower hemoglobin levels.

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