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Influence of age on warfarin dose, anticoagulation control, and risk of hemorrhage

Running head: Influence of age on warfarin

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Keywords:

Age, warfarin dose, percent time in target range (PTTR), major hemorrhage

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Abstract

Objective: We assessed the influence of age on warfarin dose, percent time in target range (PTTR), and risk of major hemorrhage.

Design: Warfarin users recruited into a large prospective inception cohort study were categorized into three age groups: young (<50 years), middle-aged (50 -70 years), and elderly (>70 years). The influence of age on warfarin dose and PTTR was assessed using regression analysis and risk of major hemorrhage was assessed using the proportional hazards (PH) analysis. Models were adjusted for demographic, clinical and genetic factors.

Setting: Two outpatient anticoagulation clinics

Participants: 1498 anticoagulated patients

Outcomes: Warfarin dose (mg/day), PTTR, major hemorrhage

Results: Of the 1498 patients, 22.8% were young, 44.1% were middle-aged, and 33.1% were elderly. After accounting for clinical and genetic factors, compared to young warfarin users, warfarin dose requirements were 10.6% lower among the middle-aged and an additional 10.6% lower for the elderly. Compared to young patients, middle-aged and elderly patients spent more time in target INR range ($p<0.0001$), despite having fewer INR assessments ($p<0.0001$). Compared to young warfarin users, absolute risk for hemorrhage was marginally higher among middle-aged ($p=0.08$) and significantly higher among the elderly ($p=0.016$). Compared to young warfarin users, after adjustment, the relative risk of hemorrhage increased by 31% for each age category ($p=0.026$).

Conclusions: In a real-world setting, despite achieving better anticoagulation control, elderly patients had a higher risk of major hemorrhagic events. As the population ages and the candidacy for oral anticoagulation increases, strategies that mitigate the elevated risk of hemorrhage need to be identified.

Introduction

Oral anticoagulants are the main treatment modality for decreasing the risk of venous thromboembolism and thromboembolic events associated with atrial fibrillation.[1] Despite the introduction of non-vitamin K antagonists (DOACs), warfarin remains the most widely used oral anticoagulant in the US.[2, 3] Warfarin dosing has remained challenging because of its pronounced inter-individual variability, narrow therapeutic index, drug and dietary interactions,[4] and potential for over-anticoagulation leading to hemorrhagic complications.[5-7] Thus, despite being efficacious, warfarin is underutilized, [8, 9] due in part to fear of bleeding episodes.[10] Anticoagulation related bleeding is a frequent cause of adverse drug related hospitalizations in the US.[11]

Increasing age is an important predictor of dose and a non-modifiable risk factor for hemorrhage.[12-15] As the population ages, the need for anticoagulation is expected to increase with the rise in age-related comorbidities. For instance, the prevalence of atrial fibrillation (AF), the most common dysrhythmia, increases with age and is expected to reach 12.1 million by 2030.[16-18] Additionally, patients with AF are five times more likely to experience an ischemic stroke and twice as likely to die compared to patients without AF.[19, 20] Therefore, the need for safe and effective anticoagulation in an aging population is of paramount importance. To this end, we examined the effect of age on dose, anticoagulation control, and major hemorrhagic events in warfarin users after accounting for clinical and genetic variables.

Methods

Study Population

Participants (≥20 years old) initiating warfarin with the target international normalized ratio (INR) of 2.0-3.0 were enrolled at the beginning of treatment in an inception cohort under the approval of the Institutional Review Boards of the University of Alabama at Birmingham and Emory University. Patients requiring a target INR of 2.5-3.5 (e.g. mechanical heart valves) were excluded.[21, 22]

Clinical and Genetic Variables

Patients managed at two oral anticoagulant clinics were approached and consented for enrollment in the study. Patient history was collected through a structured interview form and included information on demographics, indications for therapy, comorbidities, and medications as previously reported.[21-23] Information on factors related to lifestyle and socio-economic status including smoking, alcohol use, physical activity, dietary vitamin K intake, education, annual household income, and medical insurance was also collected. Medical records were reviewed to verify the medical history of the patients.

Follow-up included monthly visits for up to two years from initiation of therapy. Information on factors that affect warfarin response were collected during these visits, and included INR, concurrent medications, dietary vitamin K intake, alcohol use, and physical activity. Medication information was verified by medical record review as before, with emphasis on drugs that alter warfarin response, including non-steroidal anti-inflammatory drugs, antiplatelet agents, and *CYP2C9* inhibitors, inducers, or substrates.

In addition to clinical data, patients were genotyped for warfarin-specific polymorphisms.[21, 22] Blood samples were collected during the enrollment visit, and DNA extracted using the Gentra PureGene system (Gentra Sys, Inc. Minneapolis, MN). *VKORC1* (rs9923231), *CYP2C9* [*2 (rs1799853), *3 (rs1057910)], *CYP4F2* (rs2108622), African American specific *CYP2C9* Single Nucleotide Polymorphisms (SNPs) [**5* (rs28371686), **6* (rs9332131), **11* (rs28371685)], and the *CYP2C* SNP rs12777823 were genotyped. [21-26]

Outcome definitions

Warfarin dose (mg/day; log transformed to attain normality) was defined as the average maintenance dose after the attainment of three consecutive INRs in target range measured at least 2 weeks apart, as previously defined.[24, 25, 27, 28]

Proportion of time spent in target range (PTTR) and quality of anticoagulation control: For each patient, PTTR was calculated as the percentage of interpolated INR values within the target range of 2.0–3.0 after attainment of first INR in target range using the Rosendaal linear interpolation method.[29] We also present proportion of time spent below (PTBR) and above (PTAR) target range.

Because PTTR is a recognized risk factor for hemorrhage, we categorized patients' quality of anticoagulation control based on cumulative PTTR in two ways. First, we considered PTTR ≥60% (vs. <60%) because this has been evaluated as a predictor of hemorrhage in warfarin users in recent clinical trials and has also been included in the recently proposed HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile INR (defined as PTTR<60%), Elderly, Drug consumption/alcohol abuse) score.[30] Second, as the effectiveness of warfarin compared to the newer oral anticoagulants is related to the level of PTTR achieved, we also categorized PTTR as poor anticoagulation control (PTTR <60%), good control (60≤PTTR<70), and excellent control (PTTR ≥70).[31-34]

Major Hemorrhage: As previously defined,[35] major hemorrhages included fatal bleeding; and/or symptomatic bleeding in a critical area or organ, such as intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular, or pericardial, or intramuscular with compartment syndrome; and/or bleeding with a fall in hemoglobin level of ≥2 gm/dL, or leading to transfusion of ≥2 units of whole blood or red cells. As the focus of this manuscript was to evaluate the association of age on risk of major hemorrhages, minor hemorrhages (mild nosebleeds, microscopic hematuria, mild bruising, and mild hemorrhoidal bleeding) were not included in the analysis. During the 2-year follow-up, for all major hemorrhagic complications, the complication site (e.g. endoscopy of gastrointestinal tract), severity of the event (e.g. requiring transfusion, surgical intervention), and laboratory findings (e.g. INR, hemoglobin/hematocrit) at the time of the event were objectively documented. Isolated sub-therapeutic or supra-therapeutic INRs in the absence of evidence of bleeding were not classified as events. The Alabama Center for Health Statistics was queried to verify cause of death for all deceased to ensure inclusion of deaths due to hemorrhagic complications. All

complications were adjudicated independently by the Medical Director of the Anticoagulation Clinic. Only medically documented, adjudicated events were included in the analyses, as previously reported.[27, 36-38]

Statistical Analyses

Analysis of variance was used to assess group differences for continuous variables and chi-square for categorical variables. All SNPs were tested for the Hardy-Weinberg Equilibrium assumption by calculating the allele as well as genotype frequencies and using a chi-square exact test.

First, we evaluated the univariate association of age with warfarin dose, PTTR, and risk of hemorrhage. These results informed the age-categorization for subsequent adjusted analyses as young (<50), middle-aged (50-70) and elderly (>70). We then evaluated the effect of age (young, middle-aged, elderly) on warfarin dose and PTTR using multivariable linear regression analysis. The influence of age on the risk of major hemorrhage was assessed using the counting process format in the proportional hazards (PH) model. The models were adjusted for demographic [i.e. gender, race, body mass index (BMI)], lifestyle (i.e. smoking), clinical comorbid conditions [i.e. kidney impairment (categorized as estimated glomerular filtration rate eGFR >60, 30-59, <30ml/min/1.73 m^2)], medication use (i.e. antiplatelet), or genetic (i.e. *CYP2C9, CYP4F2, VKORC1* and rs12777823) factors. We included factors that showed significant differences in prevalence by age in our cohort and retained these factors in the model at a nominal p-value of $\leq$0.2. All analyses were performed using SAS version 9.3 at a non-directional alpha level of 0.05.

Role of the funding source

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Results

Of the 1498 patients (48% women, 44% African American) included in the analysis, 341 (23%) were below the age of 50 years (young), 661 (44%) were between the ages of 50 and 70 years (middle-aged) and 496 (33%) were more than 70 years of age (elderly). Participant characteristics by age groups are shown in **Table 1**.

Compared to young warfarin users, the middle-aged and elderly patients had lower warfarin dose requirements ($p<0.0001$) and lower eGFR ($p<0.0001$). When compared to younger and middle-aged groups, the elderly group consisted of a significantly higher proportion of women ($p=0.048$) and European Americans ($p<0.0001$), and were more likely to be on warfarin due to atrial fibrillation ($p<0.0001$). The younger patients were more likely to be African American and be on warfarin for venous thromboembolism ($p<0.0001$). The prevalence of hypertension ($p<0.0001$), hyperlipidemia ($p<0.0001$), diabetes ($p<0.0001$), and heart failure ($p=0.0026$) increased with age. The elderly had the highest prevalence of stage 3 chronic kidney disease (CKD) (eGFR 30 -59ml/min/1.73m2) and the lowest prevalence of end stage renal disease (eGFR<30 ml/min/1.73m2). Similarly, the concurrent use of statins ($p<0.0001$), antiplatelet agents ($p<0.0001$), and amiodarone ($p=0.001$) was highest among the elderly. The assumption of Hardy Weinberg Equilibrium was met for all SNPs ($p>0.20$). The prevalence of genetic factors known to influence warfarin response did not vary by age group

except for the *VKORC1* (p<0.0001) and *CYP2C9*3* variants (p=0.01), which were more prevalent in the elderly.

After accounting for clinical and genetic factors, compared to young patients, warfarin dose requirements were 10.6% lower among the middle-aged and an additional 10.6% lower for the elderly patients. Gender did not influence warfarin dose requirements. Warfarin dose requirements were lower among patients possessing *CYP2C9*, *VKORC1* and rs12777823 variant, among African Americans, in patients with CKD, congestive heart failure (CHF) and those on concurrent amiodarone therapy. On the other hand, higher BMI, venous thromboembolism and possession of the *CYP4F2* variant were associated with higher warfarin dose requirements. The final dosing algorithm by age after incorporating clinical and genetic factors is presented in **Table 2**.

Overall PTTR in the study cohort was 52.4% (±22.5%). Young patients spent more time below range (PTBR, p<0.0001) compared to the middle-aged and elderly **(Table 3, Figure 1a).** Compared to young patients, middle-aged and elderly patients spent more time in target INR range (p<0.0001), despite having fewer INR assessments per month (1.78 ± 1.52 vs. 1.35 ± 1.19 vs. 1.24 ± 1.74 visit/month, p<0.0001). Patients achieving a PTTR≥ 60% over the treatment period are considered to have good anticoagulation control and those achieving a PTTR≥ 70% are considered to have excellent anticoagulation control. Young warfarin users were less likely to achieve these metrics for anticoagulation control compared to the middle-aged (p<0.0001) and elderly (p<0.0001) warfarin users (**Table 3, Figure 1b**).

Over 2050 person-years of follow-up, 173 major hemorrhagic events were encountered [incidence rate (IR): 8.44; 95% CI: 7.25-9.77]. Major hemorrhages by site included gastrointestinal (n=104), genitourinary (n=22), retroperitoneal (n=7), intracranial

bleeds (n=15), hemoptysis (n=5), and hematomas (n=20). Incidence rates were lowest in the young warfarin users and highest among the elderly (**Table 3**). Compared to young warfarin users, the incidence rate ratio (IRR) of hemorrhage was marginally higher among middle-aged (IRR: 1.5; 95% CI 0.95-2.56; p=0.08) and significantly higher among the elderly (IRR: 1.8; 95% CI 1.12-3.0; p=0.016).

After adjusting for race, gender, BMI, hypertension, chronic kidney disease, PTTR (<60 vs. ≥60%), genetic factors, concurrent antiplatelet, amiodarone and statin therapy, the risk of hemorrhage increased by 31% for each age category (HR= 1.31 95% CI 1.03-1.66; p=0.026; **Figure 1c**) when compared to young warfarin users. In addition to older age, African American race (HR= 1.49 95% CI 1.02-2.17; p=0.04), concomitant antiplatelet therapy (HR= 1.64; 95% CI 1.14-2.36; p=0.008), hypertension (HR= 1.70; 95% CI 1.07-2.71; p=0.025), CKD (HR= 1.49; 95% CI 1.15-1.96; p<0.0001), PTTR<60% (HR= 2.27; 95% CI 1.51-3.42; p<0.0001), and possession of *CYP2C9*3* variant (HR=1.7; 95% CI 1.0- 2.9; p=0.05) were associated with an increased risk of hemorrhage.

Discussion

We present a comprehensive look at warfarin response among young (<50), middle-aged (50-70), and elderly (>70) warfarin users from a large prospective cohort study. We demonstrate that middle-aged patients need a 10% warfarin dose reduction and the elderly need an additional 10% warfarin dose reduction after accounting for clinical and genetic factors. Assessment of anticoagulation control (PTTR) showed that middle-aged and elderly patients have better anticoagulation control as compared to young warfarin users, and a higher proportion of these patients also achieve good (PTTR>60%) and excellent control (PTTR>70%). Furthermore, evaluation of the age-hemorrhage association indicated that elderly patients have a higher risk of major hemorrhage despite achieving better anticoagulation control.

Our study found a significant inverse association between age and warfarin dose, a finding that is consistent with existing literature.[12-15] Warfarin dose reductions in prior studies have ranged from 8% to 21% per decade of life, whereas evaluation of age on a continuous scale has been shown to result in a weekly warfarin dose decrease of 0.4 mg per year of aging.[12-15] Thus, older patients are more sensitive to warfarin compared to younger patients. Age related changes in drug response are multifactorial with decline in clearance, albumin binding, or renal excretion contributing to pharmacokinetic changes.[38-40] Moreover, the increase in comorbid conditions and concomitant medication use in the elderly may influence warfarin response in complex ways through drug-drug and drug-disease interactions. This is illustrated by the multitude of factors that influence warfarin dosing, several of which are now included in the warfarin dosing algorithm.

Several factors significantly associated with warfarin dose in the current study are also part of the commonly used warfarin dosing algorithm listed above and have been established as important predictors of warfarin dose and response. Our own research group has previously reported on the associations of kidney function,[25] left ventricular systolic dysfunction,[41] and the *CYP2C9*,[21, 22] *VKORC1*,[22, 23] and *CYP4F2* [27] variants with warfarin dose. We also recently evaluated the differential effect of self-reported race on warfarin, reporting on the variable effect of genetic and non-genetic factors on warfarin dose and hemorrhage by race.[28, 36] However, the effect of age on warfarin dose was similar across race groups in our study. [32]

Age is also an important predictor of bleeding outcomes among warfarin users, and has been incorporated into several bleeding risk scores.[30, 42-44] However, comparison of the different scores show variability in classification across risk categories and only modest improvements in the ability to predict bleeding outcomes.[45, 46] Moreover, the age cut-off across these models are not consistent, making it difficult to establish a fixed age threshold

for assessing bleeding risk. The recent evaluation by Senoo et al. demonstrated that the HAS-BLED score performed better compared to the ATRIA or ORBIT scores because it incorporates PTTR.[50] A significant body of evidence exists which supports that poor anticoagulation control (PTTR<60%) is a predictor for hemorrhage among warfarin users.[31-34] Moreover, PTTR≥60% is widely recognized as the accepted quality metric for anticoagulation management services and is incorporated into risk prediction rules. The consistency of the influence of PTTR on risk of hemorrhage was also demonstrated in the recent DOAC clinical trials.[34, 47] For instance, compared to dabigatran (150 mg dose), the risk of hemorrhage was higher for warfarin users with PTTR <57%, similar among warfarin users with PTTR 57-72%, and lower among those with PTTR>72%.[34] In our study, older patients had significantly higher PTTR compared to younger patients but also had a higher risk of major hemorrhagic events despite attaining better anticoagulation control. Sanden et al. demonstrated that at very high PTTR (>70), where almost all patients have achieved therapeutic INR of 2.0-3.0, PTTR was not correlated to warfarin-related complications in patients with AF.[48] In this scenario, it is possible that factors other than PTTR such as poor hypertension control may be responsible for the high hemorrhagic risk. Another possible explanation may be age-related frailty where the deterioration in normal bodily functions play a role in precipitating adverse outcomes.[49,50] Although aiming for a lower INR target range (1.6 to 2.6) in patients over the age of 70 may reduce the bleeding risk,[51, 52] it may also limit effectiveness.[53] Based on current evidence, the benefits of warfarin therapy (INR 2-3) still outweigh the risks even in elderly patients.[8, 54]

Although this is a large prospective inception cohort study, we recognize its limitations. It was neither feasible nor possible to control for all potential confounders such as over-the-counter medication use, episodic use of antibiotics, dietary vitamin K intake, rare genetic variants, and gene-

gene, gene-environmental interactions. Given the efficacy of warfarin, the incidence of thromboembolic events among patients on warfarin in our cohort was low. As a result, we were unable to assess the benefit vs. risk of warfarin across the three age categories. However, anticoagulation control can serve as a practical surrogate for the actual thromboembolic events as it is always the goal for any anticoagulation therapy to attain target INR. All patients in our study were able to achieve a target INR of 2.0-3.0, however, this prevented us from assessing whether a lower INR range would result in a lower risk of hemorrhage. Finally, as in all observational studies, caution in ascribing the observed effects as causal is prudent.

Conclusion

Despite achieving better anticoagulation control, elderly patients on warfarin had a higher risk of major hemorrhagic events as compared to younger patients. Strategies to mitigate the hemorrhagic risk while maintaining the risk reduction in thromboembolic events are needed. As the population ages and the candidacy for oral anticoagulation increases, identifying reliable strategies that enable protection against adverse bleeding events would be impactful.

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Table 1. Characteristics of the participants categorized by age

Footnote to table 1: SD: Standard Deviation
[a]All eGFR are based on National Kidney Foundation staging using the Modification of Diet in Renal Disease Study equation. Patients were categorized into 3 categories: GFR ≥60 (no CKD or mild CKD stage 1 and 2), GFR=30-59 (moderate CKD; stage 3) and GFR<30 (severe CKD; stage 4 and 5).
[b]Statins included any of the HMG-COA reductase inhibitors.
[c]Concurrent antiplatelet agents included aspirin, clopidogrel, and dipyridamole as mono or dual therapy.
[d]Genotype information was not available in 93 patients for *CYP2C9,* 45 patients for *VKORC1*, 197 for *CYP4F2* and 198 for rs12777823 as these samples had not been genotyped. The *VKORC1* variant *(-1639 C>T)* includes 'TT or CT', *CYP4F2* variant includes 'AG or AA', and rs12777823 variant includes 'AG or GG'.

Table 2. Warfarin dose requirements by age (<50, 50-70, and >70 years) after accounting for clinical and genetic factors

Footnote to table 2: CI: confidence intervals, BMI: Body Mass Index
[a]The referent is a white male, 50 years or younger with BMI centered at 25 kg/m2, without chronic kidney disease, venous thromboembolism or heart failure (left ventricular ejection fraction <55%), not on concurrent Amiodarone or statin therapy, with wild-type genotype for *CYP2C9, VKORC1*, *CYP4F2,* and rs12777823.

Table 3. Influence of age (<50, 50-70, and >70 years) on indices of anticoagulation control, and incidence of hemorrhage

Footnote to table 3: PTBR: Percent Time spent Below target INR Range, PTTR: Percent Time spent in Target INR Range, PTAR: Percent Time spent Above Target INR Range, CI: confidence intervals.

Table 1: Characteristics of the participants categorized by age

Characteristics	Age < 50	Age 50-70	Age >70
	n=341	n=661	n=496
	Mean ± SD	Mean ± SD	Mean ± SD
Mean Age	38.6 ± 8.1	60.0 ± 5.7	77.8 ± 5.6
Body mass index (BMI)	30.8 ± 8.5	31.3 ± 8.0	28.3 ± 6.1
Hematocrit, %	36.7 ± 13.3	37.1 ± 6.7	37.2 ± 6.5
Glomerular filtration rate (eGFR)	80.1 ± 38.2	67.5 ± 28.2	61.1 ± 21.6
Dose (mg/day)	6.8 ± 2.8	5.7 ± 2.4	4.6 ± 2.0
	N (%)	N (%)	
Female	172 (50.4%)	297 (44.9%)	257 (51.8%)
Race			
European American	138 (40.5%)	353 (53.4%)	337 (67.9%)
African American	197 (57.8%)	302 (45.9%)	156 (31.5%)
Other	6 (1.7%)	6 (0.7%)	3 (0.6%)
Indication for Warfarin therapy			
Venous thromboembolism	231 (67.7%)	283 (42.8%)	140 (28.2%)
Atrial Fibrillation	38 (11.1%)	267 (40.4%)	315 (63.5%)
Stroke / Transient Ischaemic Attack	21 (6.2%)	33 (5.0%)	25 (5.0%)
Other	51 (17.9%)	77 (11.6%)	15 (3.0%)
Comorbid conditions			
Hypertension	146 (44.4%)	470 (71.5%)	376 (76.0%)
Hyperlipidemia	66 (20.1%)	352 (55.6%)	298 (60.2%)
Diabetes Mellitus	63 (19.1%)	254 (38.9%)	159 (32.1%)
Congestive Heart Failure	68 (20.2%)	186 (28.3%)	122 (24.6%)
Chronic Kidney Disease[a]			
eGFR ≥60ml/min/1.73m2	255 (75.2%)	430 (65.5%)	247 (50.2%)
eGFR 30 -59ml/min/1.73m2	45 (13.3%)	160 (24.4%)	217 (44.1%)
eGFR < 30 ml/min/1.73m2	39 (11.5%)	217 (44.1%)	28 (5.7%)
Concurrent medications			
Statins[b]	95 (28.2%)	412 (62.7%)	308 (62.2%)
Antiplatelet agents[c]	133 (36.5%)	418 (63.6%)	338 (68.3%)
Amiodarone	17 (5.0%)	76 (11.6%)	62 (12.5%)
Genetic factors[d]			
*CYP2C9 *2* variant	39 (13.6%)	94 (16.7%)	75 (17.9%)
*CYP2C9 *3* variant	15 (5.2%)	41 (7.3%)	47 (11.2%)
*CYP2C9*5 or *6 or *11*	8 (2.8%)	8 (1.4%)	3 (0.7%)
VKORC1 (-1639C/T)			
Wild-type	198 (66.9%)	336 (59.1%)	217 (50.1%)
Variant	98 (33.1%)	232 (40.9%)	216 (49.9%)
CYP4F2 variant	90 (32.5%)	193 (35.2%)	170 (41.5%)
rs12777823	101 (36.5%)	186 (34.0%)	152 (37.0%)

Table 2: Warfarin dose requirements by age (<50, 50-70, >70 years) accounting for the effect of genetic and clinical factors

Variable	Effect on Warfarin Dose (95% CI)		
	Dose (mg/day)	% Dose Change	P-value
White male < 50 years[a]	8.1 (7.5 to 8.8)		
50-70 years	7.2 (6.3 to 8.3)	-10.6 (-15.8 to -5.2)	0.0002
> 70 years	7.2 (6.3 to 8.3)	-10.6 (-15.1 to -5.9)	<0.0001
African American	7.6 (6.6 to 8.7)	-6.2 (-11.3 to -0.9)	0.02
Female	7.9 (6.9 to 9.0)	-2.2 (-6.9 to 2.8)	0.39
BMI centered at 25 kg/m2	9.0 (8.1 to 10)	11.3 (8.7 to 14.0)	<0.0001
Chronic Kidney disease	7.5 (6.7 to 8.5)	-6.8 (-9.9 to -3.6)	<0.0001
Venous thromboembolism	8.4 (7.4 to 9.6)	4.3 (-0.7 to 9.6)	0.09
Congestive Heart Failure	7.6 (6.6 to 8.7)	-6.6 (-11.5 to -1.5)	0.012
Concurrent amiodarone use	6.4 (5.5 to 7.5)	-20.6 (-26.1 to -14.6)	<0.0001
Statin Use	7.8 (6.8 to 8.8)	-4.0 (-8.4 to 0.6)	0.08
CYP2C9 *2	6.6 (5.8 to 7.6)	-18.3 (-22.7 to -13.6)	<0.0001
CYP2C9 *3	6.8 (4.5 to 6.2)	-34.7 (-39.5 to -29.6)	<0.0001
*CYP2C9 *5 or *6 or *11*	6.0 (5.2 to 8.7)	-16.5 (-29.8 to -0.6)	0.04
VKORC1	8.4 (5.3 to 6.7)	-26.1 (-28.8 to -23.3)	<0.0001
CYP4F2	6.0 (7.4 to 9.5)	3.7 (-0.3 to 7.8)	0.07
rs12777823	7.4 (6.5 to 8.4)	-8.6 (-12.7 to -4.2)	0.0001

Table 3: Influence of age (categorized as <50; 50-70; ≥70 years) on indices of anticoagulation control, and incidence of hemorrhage

Characteristics	Age < 50 (n=341)	Age 50-70 (n=661)	Age >70 (n=496)
PTBR (INR <2)	37.8 ± 28.4	26.6 ± 26.6	24.3 ± 19.8
PTTR (INR 2-3)	44.6 ± 23.8	52.7 ± 55.3	57.2 ± 20.5
PTAR (INR >3)	15.4 ± 17.6	19.2 ± 20.9	17.7 ± 15.9
Number of patients (%) achieving good anticoagulation control			
Poor (PTTR<60)	250 (73.3%)	394 (59.6%)	257 (51.8%)
Good (PTTR≥60<70)	40 (11.7%)	117 (17.7%)	104 (21.0%)
Excellent (PTTR>70)	51 (15.0%)	150 (22.7%)	135 (27.2%)
Major hemorrhage			
Number of events	20	78	75
Follow-up (years)	363.1	925.3	761.5
Incidence (95% CI)	5.5 [3.5, 8.4]	8.4 [6.7, 10.5]	9.8 [7.8, 12.3]

Figure legends

Figure 1a. Percent time spent below, in, and above target INR range of 2.0-3.0 by warfarin users across the three age groups.

Figure 1b. Proportion of patients achieving poor, good, and excellent anticoagulation control by warfarin users across the three age groups.

Figure 1c. Time to major hemorrhage across the three age groups.
Estimated survival curve from Cox proportional hazards model adjusted for race, gender, BMI, hypertension, chronic kidney disease, PTTR (<60% vs. ≥60%), concurrent antiplatelet, amiodarone and statin medications, and *CYP2C9* genotype (note: y axis starts at 0.5)

Figure 1a.

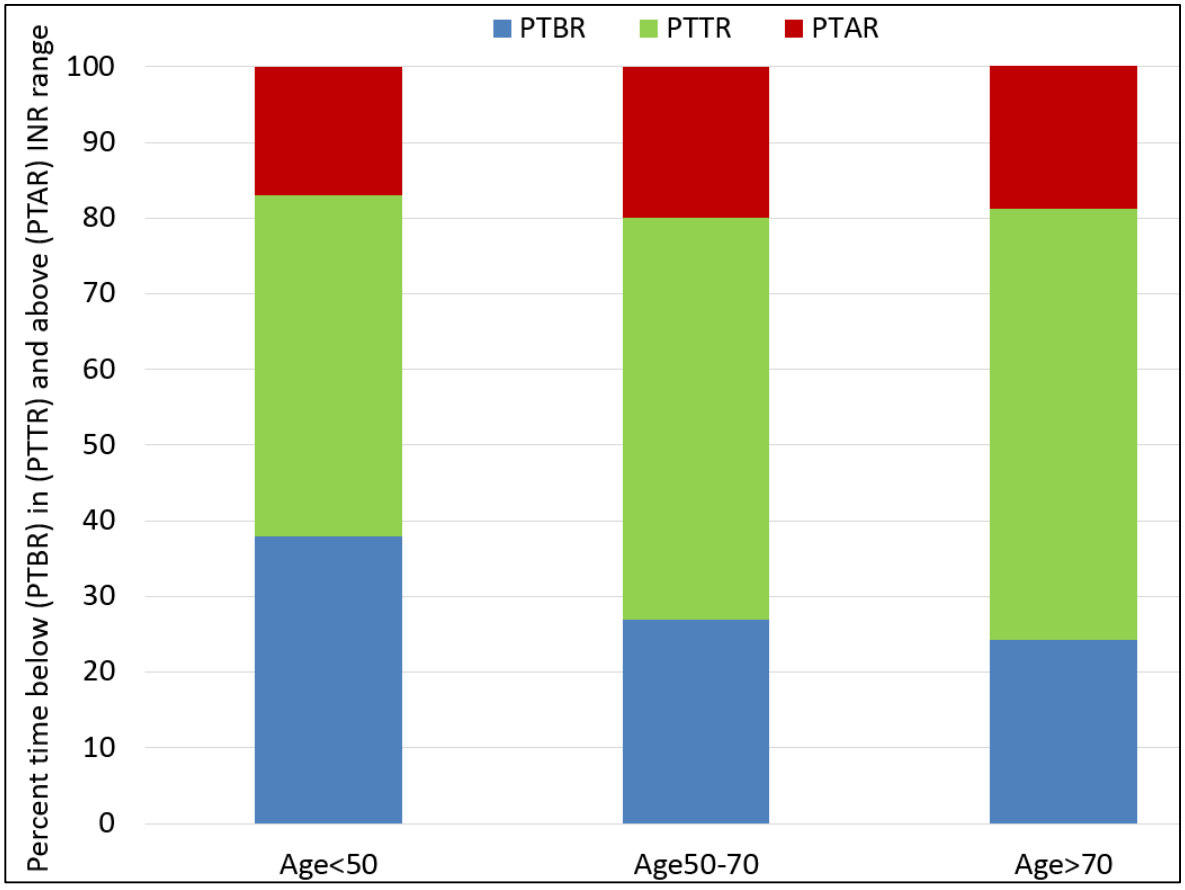

Figure 1b.

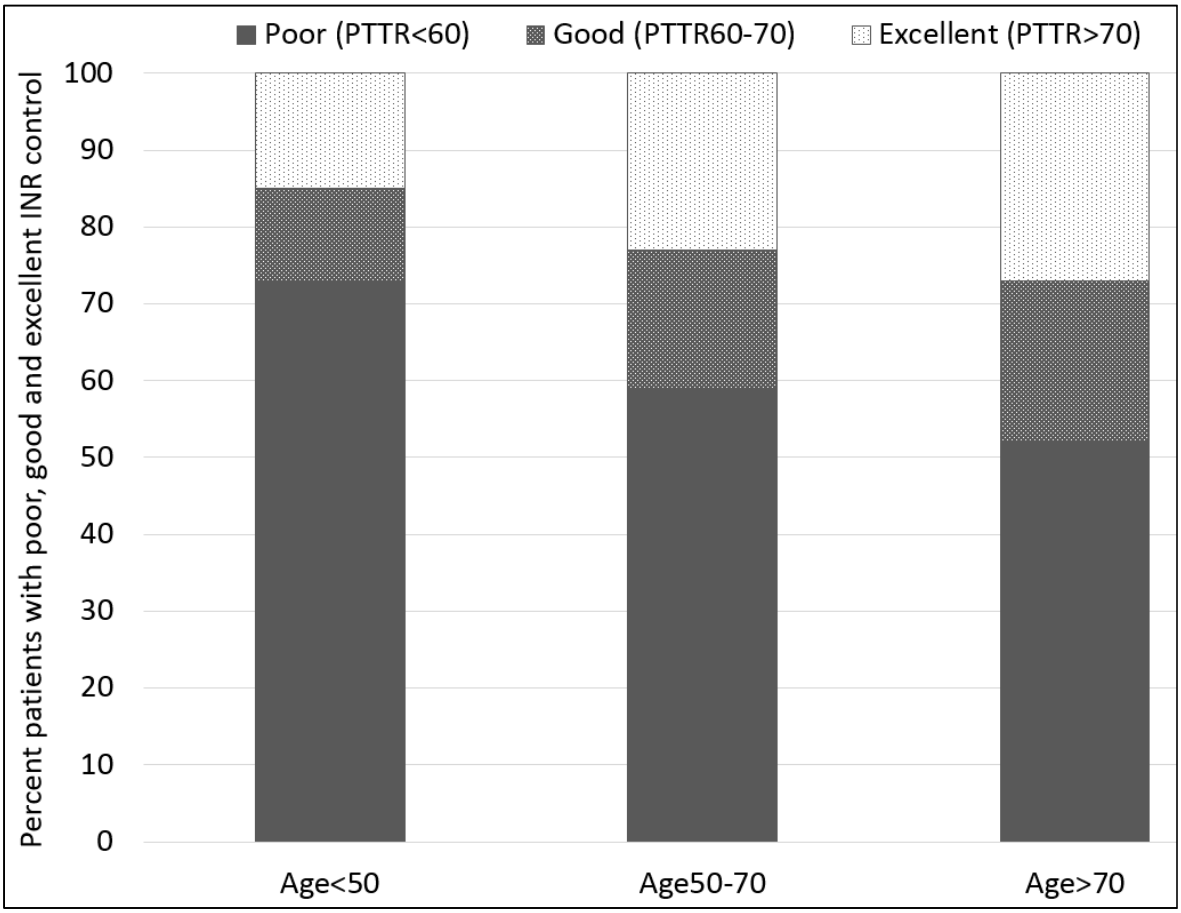

Figure 1c.