Heart type fatty acid binding protein

An overlooked cardiac biomarker

Goel, Harsh; Melot, Joshua; Krinock, Matthew D; Kumar, Ashish; Nadar, Sunil K; Lip, Gregory Y H

Published in:
Annals of Medicine

DOI (link to publication from Publisher):
10.1080/07853890.2020.1800075

Publication date:
2020

Document Version
Accepted author manuscript, peer reviewed version

Journal Pre-proof

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PII: S1547-5271(20)30678-0

DOI: https://doi.org/10.1016/j.hrthm.2020.07.022

Reference: HRTHM 8489

To appear in: *Heart Rhythm*

Received Date: 2 June 2020

Revised Date: 15 July 2020

Accepted Date: 15 July 2020

Please cite this article as: Chan Y-H, Chao T-F, Chen S-W, Lee H-F, Yeh Y-H, Huang Y-C, Chang S-H, Kuo C-T, Lip GYH, Chen S-A, Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Clinical Outcomes in Asian Patients with Atrial Fibrillation, *Heart Rhythm* (2020), doi: https://doi.org/10.1016/j.hrthm.2020.07.022.

Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Clinical Outcomes in Asian Patients with Atrial Fibrillation

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Running title: Off-label dosing of NOACs and clinical outcomes

Total word count: 4,973

Conflict of interest: The authors have no conflicts to disclose.

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Abstract

Background: Prescriptions of off-label dosing non-vitamin K antagonist oral anticoagulants (NOACs) are common for Asian patients with atrial fibrillation (AF).

Objective: To investigate the associations between inappropriate dosing of NOACs and clinical outcomes.

Methods: We used medical data from a multi-center healthcare system in Taiwan including 2,068, 5,135, 2,589, 1,483, and 2,342 AF patients taking dabigatran, rivaroxaban, apixaban, edoxaban and warfarin, respectively. The risks of ischemic stroke/systemic embolism (IS/SE) and major bleeding of patients treated with under-dosing or over-dosing NOACs were compared to on-label dosing NOACs and warfarin.

Results: Around 27% and 5% of AF patients were treated with under-dosing and over-dosing NOACs, respectively. Compared to on-label dosing**,** under-dosing NOACs were associated with a significantly higher risk of IS/SE (aHR 1.59, 95%CI 1.25-2.02; *P*<.001), while over-dosing NOACs were associated with a significantly higher risk of major bleeding (aHR 2.01, 95%CI 1.13-3.56; *P*=0.017). Compared to warfarin, the four on-label dosing NOACs were all associated with a comparable risk of IS/SE and a significantly lower risk of major bleeding, while under-dosing NOACs were associated with a higher risk of IS/SE (aHR 1.46; *P*=0.012).

Conclusions: Around 3 in 10 Asian AF patients were treated with off-label dosing NOACs in daily practice. Compared to on-label dosing, underdosing was associated with a higher risk of IS/SE, while overdosing was associated with a higher risk of major bleeding. Even for Asian AF patients at a higher risk of bleeding, NOACs should still be prescribed at the dosing following clinical trial criteria and guideline recommendations.

Key words: atrial fibrillation, NOACs, Asian; dosing, outcomes

Introduction

Stroke prevention is central to the managements of patients with atrial fibrillation (AF), and long-term use of oral anticoagulants (OACs) effectively reduces the risk of stroke.[1] The non-vitamin K antagonist oral anticoagulants (NOACs) provide an alternative option to the vitamin K antagonists (VKA, eg.warfarin) and are becoming the preferred choice for stroke prevention in guidelines.[2,3]

Since routine monitoring of drug concentration is not necessary for NOACs, the selection of appropriate dose of NOACs according to the dosage criteria defined in randomized controlled trials (RCTs) is very important. Nevertheless, prescriptions of off-label dosing NOACs remained as a major problem in the daily practice. In a previous report from the United States, around 9.4% of AF patients received off-label under-dosed NOACs, which was associated with a worse clinical outcome.[4] Since the Asian population is associated with a higher bleeding risk such as intracranial hemorrhage (ICH),[5] physicians generally tend to prescribe low-dose NOACs for Asian AF patients in daily clinical practice. In Taiwan, full-dosed dabigatran (150mg twice daily), rivaroxaban (20mg per day) and apixaban (5mg twice daily) were prescribed in only 12%, 6% and 38% of AF patients, respectively.[6] Despite the high prescription rates of low-dosed NOACs, NOACs were still associated with a comparable or even lower risk of ischemic stroke/systemic embolism (IS/SE) compared to warfarin in some real-world data from Asian cohorts.[7,8] These findings raise a question about whether there should be a lower dose of NOACs, so-called “Asian dose”, for Asian AF patients. Since information about renal function and body weight was usually not available in prior real-world studies, the actual percentages of these low-dose NOACs that were actually “off-label low-dose” and their associations with clinical outcomes remains unknown.

In the present study, we aimed to compare the clinical outcomes of AF patients treated with on-label or off-label dosing NOACs. We hypothesized that inappropriate dosing of NOACs without following individual labeling dosage recommendations may be associated with worse clinical outcomes in Asian AF patients.

Methods

The study is based on data from the Chang Gung Research Database provided by Chang Gung Memorial Hospital. The interpretation and conclusions contained herein do not represent the position of Chang Gung Memorial Hospital (CGMH). We conducted the retrospective observational study by using the patients' data from the CGMH Medical System. The CGMH Medical system composed of 3 major teaching hospitals and 4 tertiary care medical centers with a total of 10,050 beds and admits around 280,000 patients per year, and is the largest healthcare provider in Taiwan. In 2015, the emergent and outpatient department visits to CGMH Medical system were 500,000 and 8,500,000, respectively, approximately 1/10 of the Taiwanese medical service annually. The advantage of CGMH medical database is that each patient's detailed chart record, diagnosis, laboratory, and imaging data are available. The personal information and identification number of each patient are encrypted and de-identified by using a consistent encrypting procedure; therefore, informed consent was waived for this study. Our study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (201802075B0).

Study cohort

The flowchart of study design and patient enrollment is shown in **Figure 1**. The CGMH medical database was retrospectively searched for patients ≥ 20 years in whom new-onset AF was diagnosed from January 1st, 2010 to September 30st, 2018 (n = 53,852). There were 15,841 patients treated with OACs after June 1st, 2012. Patients with a diagnosis of pulmonary embolism or deep venous thrombosis (n = 73), post valvular surgery (n = 215), mitral stenosis (n = 19), or end stage renal disease (n = 94) were excluded from the present study. Besides, patients whose information about body weight and serum creatinine were not available within 6 months before the dates when OACs were prescribed were also excluded

(n = 1,823). Finally, a total of 2,068, 5,135, 2,589, 1,483, and 2,342 AF patients treated with dabigatran, rivaroxaban, apixaban, edoxaban and warfarin, respectively, constituted the study population.

Eligibility and dosage adjustment of NOACs

In the present study, the definitions of eligibility and dosage adjustment criteria of four NOACs are summarized in **Table 1**. Patients treated with NOACs were defined as "off-label underdosing", "on-label dosing", and "off-label overdosing" generally based on the dosage reduction criteria of pivotal NOACs randomized trials and recommendations of international society guidelines.[9-14] Of note, there were no prospective dose-reduction criteria for patients treated with dabigatran in the RE-LY study.[9] However, dabigatran 110 mg bid was suggested for patients aged ≥ 80 years, age 75-80 years with a high risk of bleeding or concomitant use of verapamil based on the prior study and expert opinions.[14-16] For rivaroxaban, Taiwan Food and Drug Administration (FDA) approved either standard-dose regimen (20mg/day for patients with a creatinine clearance rate [CCr] ≥50 ml/min and 15mg/day for those with a CCr <50 ml/min), following the ROCKET AF dosage criteria, or low-dose regimen (15mg/day for patients with a CCr ≥50 ml/min and 10mg/day for those with a CCr <50 ml/min), following the J-ROCKET AF dosage criteria, for stroke prevention in AF patients.[10,11] Therefore, patients following either ROCKET-AF or J-ROCKET AF dosage criteria for rivaroxaban were defined as on-label dosing in the present study. In case of apixaban, if 2 of 3 criteria (age ≥80 years, body weight ≤60 kg, and measured serum creatinine ≥1.5 mg/dl) were met, the dosage of apixaban was reduced from 5 mg bid to 2.5 mg bid.[12] For patients with a CCr between 15-30 ml/min, apixaban 2.5 mg bid was recommended.[14] For edoxaban, if any of 3 criteria (body weight ≤ 60 kg, CCr <50 ml/min, and concomitant use of P-glycoprotein inhibitor) was met, the daily dose of edoxaban was

reduced from 60mg to 30 mg.[13] The off-label over-dosing was defined as the prescriptions of NOACs at the full dose even when patients met the dosage reduction criteria mentioned above. Conversely, the off-label under-dosing was defined as the prescriptions of NOACs at the reduced dose even when patients did not meet the dosage reduction criteria. Of note, prescriptions of dabigatran for patients with a CCr <30 ml/min or use of rivaroxaban, apixaban and edoxaban for patients with a CCr <15 ml/min were defined as overdosing in our study.[14]

Study outcomes

We reported the clinical outcomes of IS/SE and major bleeding for AF patients treated with NOACs. All study outcomes were defined on the basis of the first discharge diagnosis to avoid misclassification. The major bleeding events were defined as the total number of hospitalized events of ICH, gastrointestinal bleeding, and other sites of critical bleeding. The follow-up period was defined as the duration from the drug index date until the occurrence of study outcomes, mortality, or until the end date of the study period (September 30th, 2018), whichever came first. The risks of clinical events of underdosing and overdosing groups were compared to that of on-label dosing group. Besides, the risks of clinical events of NOACs in each dosing groups were compared to that of warfarin.

Statistical analysis

Data are presented as the mean value (standard deviation [SD]) for continuous variables and proportions for categorical variables. Differences between continuous values were assessed using the unpaired two-tailed *t*-test or one-way analysis of variance (ANOVA) when the comparisons of 3 groups were performed. Differences between nominal variables were compared by the chi-squared test. The rates of clinical events were assessed using the Cox

regression analysis. The proportional hazards assumption was tested using Schoenfeld residual test which showed no non-proportionality. All statistical significances were set at a $p < 0.05$.

Results

The clinical characteristics of study population are shown in **Table 2**. There were 7,764 (68.9%), 2,999 (26.6%), and 512 (4.5%) patients treated with on-label dosing, off-label under dosing, and off-label over-dosing NOACs, respectively. Compared to on-label dosing group, patients receiving under-dosing NOACs were younger with a lower mean CHA_2DS_2-VASc and HAS-BLED scores, while patients receiving over-dosing NOACs were older and had higher CHA_2DS_2-VASc and HAS-BLED scores. The CCr was higher in under-dosing and lower in over-dosing groups compared to on-label dosing one. Baseline medications were not significantly different among three groups, except for a higher prescription rate of verapamil in the over-dosing group.

The proportions of different dosing groups of 4 NOACs are shown in **Figure 2**. The highest rate of on-label dosing was observed for rivaroxaban (81%), followed by edoxaban (67%), apixaban (65%) and dabigatran (44%). For all NOACs, the percentages of underdosing (17%-48%) were higher than overdosing (2-10%). **Supplemental Figure 1** shows the percentages of patients receiving on-label dosing, under-dosing and over-dosing NOACs in different groups stratified by age, CHA_2DS_2-VASc and HAS-BLED scores. Generally, underdosing was more common among younger patients and those having a CHA_2DS_2-VASc score <4, whereas over-dosing NOACs, except for edoxaban, were more common for elderly patients. Baseline characteristics of patients treated with each NOACs are summarized in **Supplemental Tables 1 to 4**.

Clinical outcomes of patients treated with off-label dosing vs. on-label dosing NOACs

Overall, those 2,999 patients taking under-dosing NOACs were associated with a significantly higher risk of IS/SE (adjusted hazard ratio [aHR] 1.59, 95% confidence interval

[CI] 1.25-2.02; *P* < .001) and a similar risk of major bleeding (aHR 0.80, 95% CI 0.50-1.27; *P* = 0.337) compared to 7,764 patients taking on-label dosing NOACs, after the adjustment for age, gender, CHA_2DS_2-VASc score, HAS-BLED score and CCr (**Figure 3A**). Of note, patients taking off-label under-dosing rivaroxaban (n = 858) and apixaban (n = 799) were associated with a significantly higher risk of IS/SE than those treated with on-label dosing rivaroxaban (n = 4,191) and apixaban (n = 1,677).

In contrast, those 512 patients taking off-label over-dosing NOACS were associated with a significantly higher risk of major bleeding (aHR 2.01, 95% CI 1.13-3.56; *P* = 0.017) and a similar risk of IS/SE (aHR 1.24, 95% CI 0.74-2.07; *P* = 0.415) than patients taking on-label dosing NOACs (**Figure 3B**). Over-dosing rivaroxaban (n = 86) was associated with a significantly higher risk of IS/SE (aHR 2.53, 95% CI 1.17-5.45; *P* = 0.018) and major bleeding (aHR 3.06, 95% CI 1.10-8.49; *P* = 0.032) compared to on-label dosing (n = 4,191).

Among patients receiving on-label dosing rivaroxaban (n = 4,191), 1,354 and 2,837 of them followed the ROCKET-AF and J-ROCKET AF dosing criteria, respectively. Off-label dosing rivaroxaban was associated with a higher risk of IS/SE or major bleeding compared to ROCKEK-AF (**Supplemental Figure 2A**) or J-ROCKET AF (**Supplemental Figure 2B**) dosing regimen. These findings were generally consistent to the results of the main analysis which pooled ROCKET-AF and J-ROCKET AF dosing together as the on-label dosing group.

Subgroup analysis

Supplemental Figure 3 shows the comparisons of off-label underdosing and on-label dosing in different subgroups of patients. Consistent with the results of principal analysis, patients treated with off-label under-dosing NOACs were associated with a higher risk of

ISS/E but a comparable risk of major bleeding than those treated with on-label dosing across all subgroups (all P_{int} >0.05). **Supplemental Figure 4** shows the comparisons of off-label overdosing and on-label dosing in different subgroups of patients. The increased risk of major bleeding for off-label over-dosing compared to on-label dosing was observed in different subgroups (all P_{int} >0.05).

Different NOAC dosing groups compared to warfarin

The clinical characteristics of patients taking NOACs and warfarin are shown in **Supplemental Table 5**. Those patients treated with NOACs (n = 11,275) were older, had more co-morbidities and higher mean CHA_2DS_2-VASc and HAS-BLED scores compared to the warfarin group (n = 2,342). Patients taking four on-label dosing NOACs were all associated with a comparable risk of IS/SE and a significantly lower risk of major bleeding compared to those receiving warfarin (**Figure 4A**). In contrast, patients treated with off-label under-dosing NOACs, especially for rivaroxaban (aHR 1.92, 95%CI 1.28-2.87; *P* = 0.002) and apixaban (aHR 1.71, 95%CI: 1.10-2.66; *P* = 0.017), were associated with a significantly higher risk of IS/SE than those treated with warfarin (**Figure 4B**). Patients treated with off-label over-dosing NOACs were associated with a comparable risk of IS/SE (aHR 1.13, 95%CI 0.66-1.93; *P* = 0.663) and major bleeding (aHR 1.07, 95%CI 0.60-1.90; *P* = 0.814) compared to those treated with warfarin (**Figure 4C**).

Discussion

In the present study, we investigated the associations between inappropriate dosing of four NOACs and clinical outcomes of Asian AF population in daily practice. Our principal findings are as follows: (i) around 27% and 5% of patients were treated with off-label under-dosing and overdoing NOACs, respectively; (ii) compared to on-label dosing NOACs, off-label under-dosing NOACs were associated with a significantly higher risk of IS/SE, whereas off-label overdosing NOACs were associated with a significantly higher risk of major bleeding; and (iii) compared to warfarin, all four on-label dosing NOACs were associated with a comparable risk of IS/SE and a lower risk of major bleeding, whereas underdoing was associated with a higher risk of IS/SE. These results highlighted the importance of prescriptions of NOACs at the on-label dosing even for Asians AF patients who were more prone to bleeding.

Prevalence of off-label dosing NOACs

Although there are various registry and administrative studies investigating the effectiveness and safety of NOACs for AF stroke prevention in real-world practice, a key and fundamental limitation is the inability to calculate CCr due to the absence of data about body weight and serum creatinine in most datasets, making it difficult to distinguish whether patients were actually treated with an appropriate dosing NOAC or not. Until now, there have been few clinical studies evaluating the impacts of inappropriate dosing of NOACs in AF patients.

In the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) study, around 13% of patients received NOACs at an inappropriate dosing (underdoing in 9.4% and overdosing in 3.4%) which were associated with an increased risk

of clinical events.[4] Yao et al. studied 14,865 AF patients treated with apixaban, dabigatran, or rivaroxaban.[17] Among the 1,473 patients with a renal indication for dose reduction, 43% were overdosed, which was associated with a higher risk of major bleeding but no significant difference in risk of stroke. Among the 13,392 patients with no renal indication for dose reduction, 13% were potentially underdosed. This underdosing was associated with a higher risk of stroke but no significant difference in risk of major bleeding in apixaban-treated patients. Compared to these 2 studies from the United States, the percentage (32%) of off-label dosing, mainly due to underdosing (27%), was higher in our study including Chinese AF patients. This reflects how physicians tended to prescribe low-dosed NOACs, even against the standard labeling, for Asian AF patients probably due to the concern of the higher risk of bleeding for Asians and the lack of data regarding this issue.

Off-label dosing NOACs and clinical outcomes

Similar to previous studies of non-Asians,[4,17] we showed that underdosing NOACs were associated with an 59% and 46% increased risk of IS/SE compared to on-label dosing NOACs and warfarin, respectively. Of note, the underdoing was not associated with a significantly lower risk of major bleeding compared to on-label dosing NOACs, the reason why they were often prescribed. The increased risk of IS/SE for underdoing NOACs was particularly evident for rivaroxaban and apixaban. Our data are consistent with the previous study by Yao et al. showing that under-dosed apixaban in patients without severe renal impairment was associated with a nearly 5-fold increased risk of stroke but without a reduction of major bleeding when compared to those taking on-label dosing apixaban.[17] For rivaroxaban, the off-label underdosing (10mg/day for patients with a CCr >50 min/day) defined in our study was associated with a 2-fold increased risk of IS/SE compared to on-label dosing and warfarin, and therefore, should be avoided.

Interestingly, we did not observe a higher risk of IS/SE for patients treated with underdoing dabigatran or edoxaban. Dabigatran 110 mg twice daily was the only low-dosed NOAC without any specified dosage criteria which was compared to warfarin in the randomized trial.[9] Lee et al. analyzed 1,834 non-valvular AF patients treated with warfarin, dabigatran 150 mg, and dabigatran 110 mg,[18] and the dabigatran 110 mg group was further classified as off-label or on-label dosing following European labeling.[15] The results indicate that both on-label and off-label dabigatran 110 mg displayed a comparable efficacy and a lower risk of major bleeding compared to warfarin.[18] Our results were consistent with above studies showing that even the guideline-discordant use of dabigatran 110 mg demonstrated a similar efficacy compared to on-label dosing dabigatran or warfarin. However, further prospective studies are necessary to evaluate the optimal dosage of dabigatran in Asian AF patients.

In case of edoxaban, our results indicated that off-label under-dosing edoxaban was not associated with a significantly higher risk of IS/SE compared to on-label dosing edoxaban (aHR 1.43, 95% CI 0.53-3.89) or warfarin (aHR 1.53, 95% CI 0.64-3.65). However, our results should not be interpreted as off-label underdosing edoxaban could be prescribed for Asian AF patients since the non-significant increase in risk of IS/SE may be because of the relatively small sample size of edoxaban users in our study. Furthermore, even with on-label dosing edoxaban, the risk of major bleeding was not higher than off-label underdosing edoxaban and still significantly lower than warfarin (aHR 0.39, 95% CI 0.15-0.99). Therefore, off-label low-dosing edoxaban should generally not be considered for the Asian AF population.

Limitations

There are several limitations of the present study. First, the present study is a retrospective study, and therefore, the results from the individual NOAC may be confounded by the bias of prescriptions (e.g., a perceived risk may result in conscious avoidance in use of specific NOAC in specific patient populations). Second, our study was performed in an intention to treat design**,** and did not take the changes of dosages of NOACs which may result in different categorizations of patients into considerations. Third, there was no universal and pre-specified algorithm for the measurements of body weight and serum creatinine due to the retrospective and observational study design. Although we have excluded patients without information of body weight and serum creatinine within 6 months before the prescriptions of OACs, there was only 69% of patients whose data were measured within 3 months of NOAC prescriptions. Lastly, the Chang Gung Research Database we used in the present study were based on the closed CGMH Medical System without external link to protect each patient's privacy. Therefore, data from other medical care systems outside CGMH were not available, and underestimations of medical activities for some patients were possible. However, CGMH database represented 1/10 of the whole Taiwanese medical service and included data about laboratory examinations. Its large sample size and available data of body weight and CCr enabled us to investigate the issue about off-label dosing NOACs.

Conclusion

Around 3 in 10 Asian AF patients were treated with off-label dosing NOACs in daily practice. Compared to on-label NOAC dosing, underdosing was associated with a higher risk of IS/SE without a lower risk of major bleeding while overdosing was associated with a higher risk of major bleeding without a lower risk of IS/SE. Even for Asian AF patients at a higher risk of bleeding, NOACs should still be prescribed at the dosing following clinical trial criteria and guideline recommendations.

Acknowledgments

The authors thank the statistical assistance and wish to acknowledge the support of the Maintenance Project of the Center for Big Data Analytics and Statistics (Grant CLRPG3D0045) at Chang Gung Memorial Hospital for study design and monitor, data analysis and interpretation.

Sources of Funding

This study was supported by grants 105-2628-B-182A-003-MY3 from the Ministry of Science and Technology and grants CMRPG3E1681, CMRPG3E1682, CMRPG3E1683, and CORPG3G0351 from Chang Gung Memorial Hospital, Linkou, Taiwan.

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Figure Legends

Figure 1 A flowchart of patient enrollment. A total of 2,068, 5,135, 2,589, 1,483, and 2,342 AF patients treated with dabigatran, rivaroxaban, apixaban, edoxaban and warfarin, respectively, have constituted the study population.

AF = atrial fibrillation; NOACs = non-vitamin K antagonist oral anticoagulants; OACs = oral anticoagulants

Figure 2 Proportions of different dosing groups of 4 NOACs. Overall, around 69%, 27% and 5% of patients were treated with on-label dosing, off-label under dosing, and off-label over-dosing NOACs, respectively. For all NOACs, the percentages of underdosing (17%-48%) were higher than overdosing (2-10%).

NOACs = non-vitamin K antagonist oral anticoagulants

Figure 3 Clinical outcomes of patients treated with off-label dosing vs. on-label dosing NOACs. Compared to on-label dosing**,** under-dosing NOACs were associated with a significantly higher risk of IS/SE and a similar risk of major bleeding (**Figure 3A**), while over-dosing NOACS were associated with a significantly higher risk of major bleeding and a similar risk of IS/SE (**Figure 3B**).

*Adjustment for age, gender, CHA_2DS_2-VASc score, HAS-BLED score and CCr

aHR = adjusted hazard ratio; CCr = creatinine clearance rate; CI = confidence interval; IS/SE = ischemic stroke/systemic embolism; NOACs = non-vitamin K antagonist oral anticoagulant

Figure 4 Clinical outcomes of NOACs in different dosing groups compared to warfarin. Patients taking four on-label dosing NOACs were all associated with a comparable risk of IS/SE and a significantly lower risk of major bleeding compared to those receiving warfarin

(**Figure 4A**). In contrast, patients treated with off-label under-dosing NOACs were associated with a significantly higher risk of IS/SE than those treated with warfarin (**Figure 4B**). Patients treated with off-label over-dosing NOACs were associated with a comparable risk of IS/SE and major bleeding compared to those treated with warfarin (**Figure 4C**).

*Adjustment for age, gender, CHA_2DS_2-VASc score, HAS-BLED score and CCr

Abbreviations were the same as Figure 3.

Table 1. Definitions of eligibility and dosage adjustments of NOACs

	On-label dosing	Off-label under-dosing	Off-label over-dosing
Dabigatran	dabigatran 110 mg bid if any of three criteria was met: - age ≥80 years - age 75-80 years with a high risk of bleeding - concomitant use of verapamil OR dabigatran 150 mg bid if none of the dosage reduction criteria was met	dabigatran 110 mg bid for patients without any dosage reduction criteria	dabigatran 150 mg bid if any dosage reduction criteria was met OR use of dabigatran if CCr <30 ml/min
Rivaroxaban	rivaroxaban 20 mg (ROCKET-AF) or 15 mg (J-ROCKET AF) qd if CCr ≥50 ml/min OR rivaroxaban 15 mg (ROCKET-AF) or 10 mg (J-ROCKET AF) qd if CCr <50 ml/min	rivaroxaban 10 mg qd if CCr ≥50 ml/min	rivaroxaban 20 mg qd if CCr <50 ml/min OR use of rivaroxaban if CCr <15 ml/min
Apixaban	apixaban 2.5 mg bid if ≥ 2 of 3 criteria were met - aged ≥80 years - serum creatinine ≥1.5 mg/dl - body weight ≤60 kg OR apixaban 2.5 mg bid if CCr between 15-30 ml/min OR	apixaban 2.5 mg bid if the dosage reduction criteria were not met	apixaban 5 mg bid for patients who met the dosage reduction criteria OR use of apixaban if CCr <15 ml/min

	apixaban 5 mg bid if the dosage reduction criteria were not met		
Edoxaban	edoxaban 30 mg qd if any of three criteria was met: - body weight ≤60 kg - CCr <50 ml/min - use of P-glycoprotein inhibitor OR edoxaban 60 mg qd if none of the dosage reduction criteria was met	edoxaban 30 mg qd for patients who did not meet the dosage reduction criteria OR use of edoxaban 15 mg qd	edoxaban 60 mg qd for patients who met the dosage reduction criteria OR use of edoxaban if CCr <15 ml/min

CCr = creatinine clearance rate

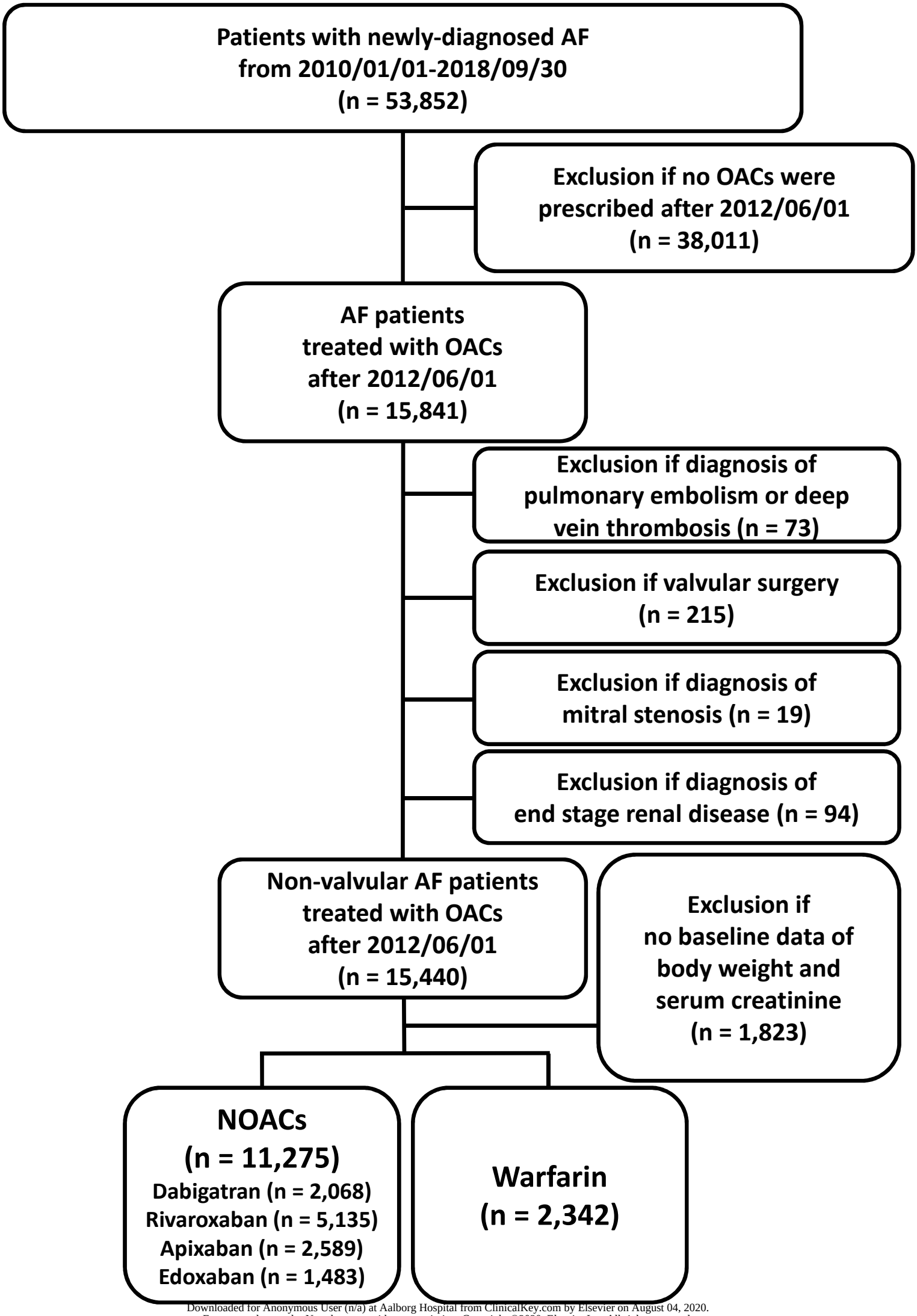
Table 2. Baseline characteristics of AF patients treated with NOACs

	Overall (n = 11,275)	**On label dose (n = 7,764)**	**Off-label under-dosing (n = 2,999)**	**Off-label over-dosing (n = 512)**	***P value* (ANOVA)**
Baseline characteristics					
Age, yrs	74.21±10.40	74.87±10.63	71.70±9.41	78.90±9.23	**<.001**
Female, n (%)	4684 (42%)	3281 (42%)	1132 (38%)	271 (53%)	**<.001**
Body weight, kg	65.44±14.23	64.81±14.32	68.45±13.32	57.37±13.72	**<.001**
CHA_2DS_2-VASc score	3.49±1.60	3.57±1.61	3.21±1.54	3.89±1.51	**<.001**
HAS-BLED score	2.77±1.23	2.80±1.22	2.67±1.23	2.93±1.19	**<.001**
Past medical history, n (%)					
Chronic lung disease	3264 (29%)	2299 (30%)	802 (37%)	163 (32%)	**0.004**
Chronic liver disease	2205 (20%)	1510 (19%)	606 (20%)	89 (17%)	0.301
Congestive heart failure	1205 (11%)	882 (11%)	275 (9%)	48 (9%)	**0.003**
Hypertension	8464 (75%)	5891 (76%)	2182 (73%)	391 (76%)	**0.003**
Hyperlipidemia	4816 (43%)	3332 (43%)	1270 (42%)	214 (42%)	0.761
Diabetes mellitus	3855 (34%)	2700 (35%)	981 (33%)	174 (34%)	0.128
Previous stroke	1973 (17%)	1391 (18%)	493 (16%)	89 (17%)	0.195
Ischemic heart disease	1345 (12%)	903 (12%)	381 (13%)	61 (12%)	0.305
Gout	1797 (16%)	1284 (17%)	423 (14%)	90 (18%)	**0.005**
Malignancy	1792 (16%)	1236 (16%)	458 (15%)	98 (19%)	0.086

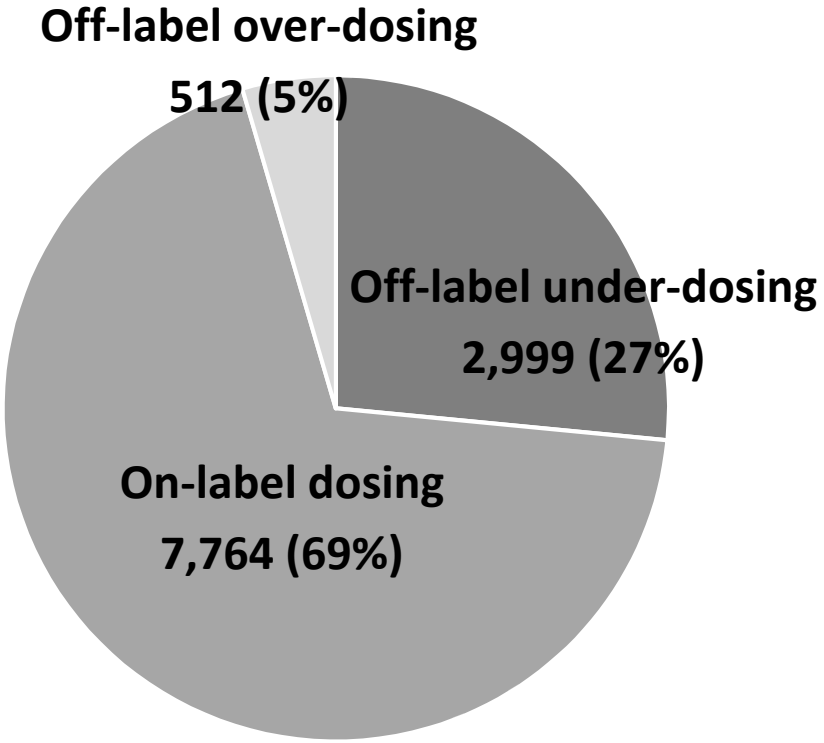
Baseline laboratory data					
Hemoglobin, g/dl	12.95±2.15	12.88±2.15	13.25±2.07	12.31±2.30	**<.001**
Platelet, x 1000/Ul	202.63±73.46	202.08±70.04	204.96±74.07	197.61±76.07	0.083
Creatinine clearance, ml/min	60.89±29.12	58.75±29.64	69.73±25.87	41.65±23.17	**<.001**
ALT, U/L	31.09±83.85	30.51±87.69	31.86±66.42	35.32±110.38	0.417
Baseline medications, n (%)					
Use of NSAIDs	1543 (14%)	1043 (13%)	417 (14%)	83 (16%)	0.192
Use of ACEI/ARB	6151 (55%)	4279 (55%)	1606 (54%)	266 (52%)	0.166
Use of loop diuretics	3247 (29%)	2320 (30%)	767 (26%)	160 (31%)	**<.001**
Use of amiodarone	2399 (21%)	1609 (21%)	683 (23%)	107 (21%)	0.065
Use of dronedarone	410 (4%)	270 (3%)	123 (4%)	17 (3%)	0.279
Use of quinidine	0(0%)	8 (0%)	1 (0%)	1 (0%)	0.392
Use of beta-blocker	6582 (58%)	4492 (58%)	1794 (60%)	296 (58%)	0.174
Use of diltiazem	2145 (19%)	1484 (19%)	563 (19%)	98 (19%)	0.919
Use of verapamil	494 (4%)	375 (5%)	68 (2%)	51 (10%)	**<.001**
Use of digoxin	1811 (16%)	1279 (16%)	457 (15%)*	75 (15%)*†	0.198
Use of statin	3687 (33%)	2539 (33%)	993 (33%)	155 (33%)	0.449

ACEI = angiotensin-converting-enzyme inhibitor; AF = atrial fibrillation; ALT = alanine aminotransferase; ARB = angiotensin II receptor antagonists; CHA_2DS_2-VASc = congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65 to 74 years, female; HAS-BLED = hypertension, abnormal renal or liver function, stroke, bleeding history, labile INR, age 65 years or older, and antiplatelet drug or alcohol use; NOAC = non-vitamin K antagonist oral anticoagulant; NSAIDs = non-steroidal

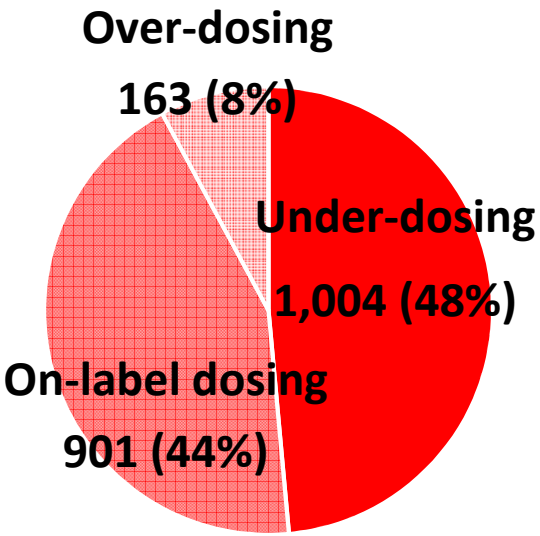
anti-inflammatory drugs



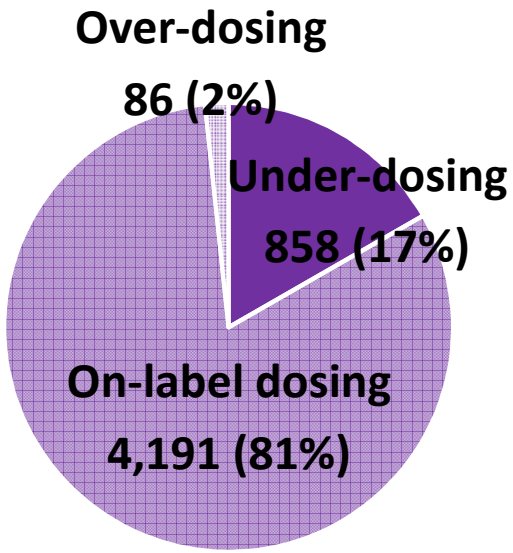
All NOACs
11,275



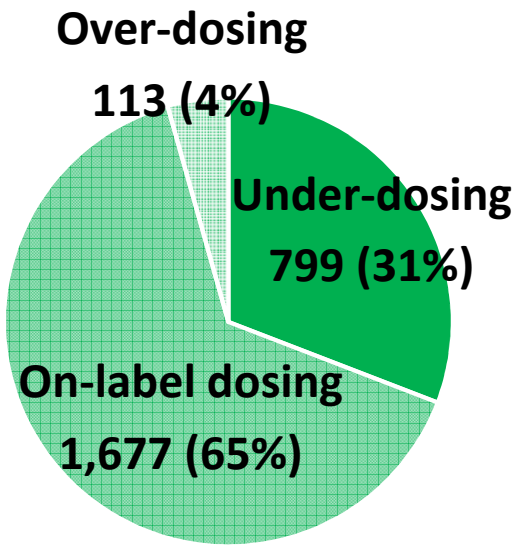
Dabigatran
2,068



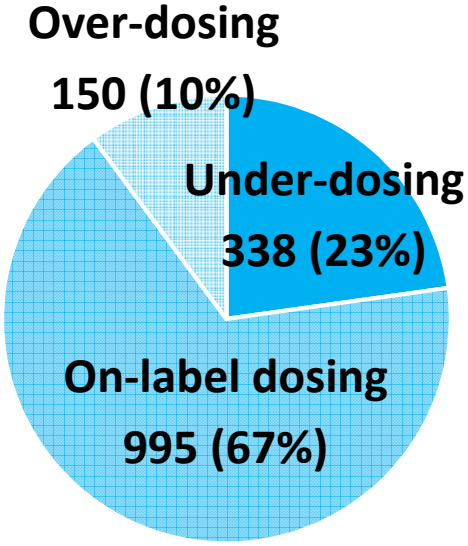
Rivaroxaban
5,135



Apixaban
2,589

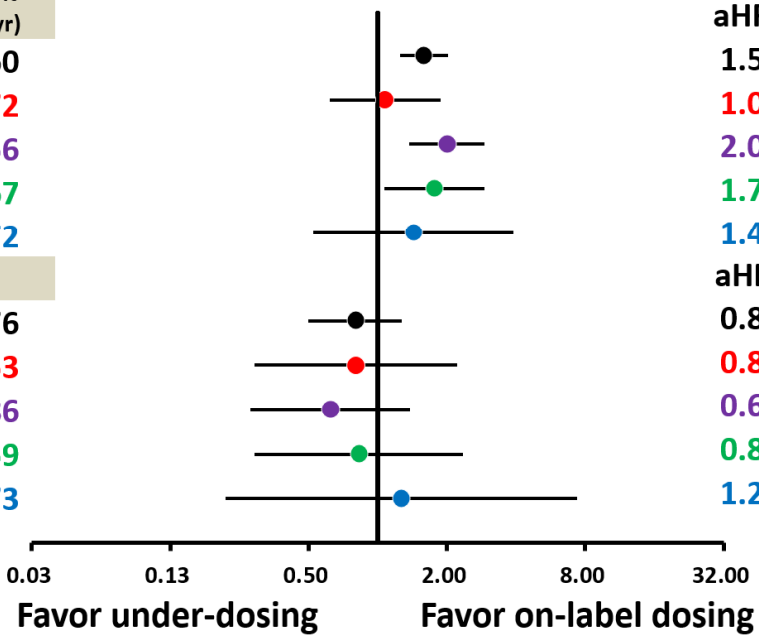


Edoxaban
1,483



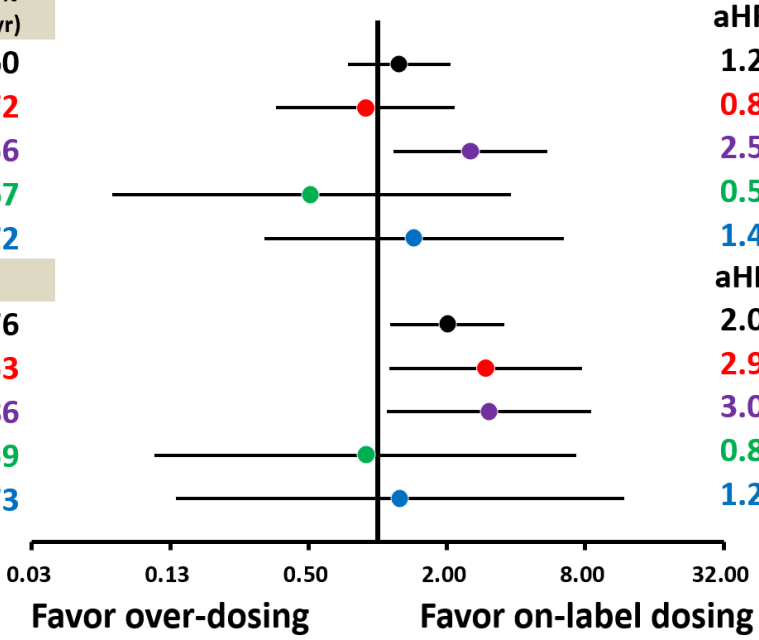
A. Off-label under-dosing vs. On-label dosing

IS/SE	Under Event (%/yr)	On label Event (%/yr)	aHR*	95% CI	*P* value
All NOACs	2.20	1.60	1.59	[1.25-2.02]	<.001
Dabigatran	2.04	1.72	1.07	[0.62-1.87]	0.800
Rivaroxaban	2.68	1.56	2.00	[1.37-2.92]	<.001
Apixaban	2.89	1.67	1.76	[1.07-2.91]	0.026
Edoxaban	2.04	1.72	1.43	[0.53-3.89]	0.484
Major bleeding			aHR*	95% CI	*P* value
All NOACs	0.46	0.76	0.80	[0.50-1.27]	0.337
Dabigatran	0.41	0.53	0.80	[0.29-2.21]	0.662
Rivaroxaban	0.45	0.86	0.62	[0.28-1.38]	0.243
Apixaban	0.53	0.59	0.83	[0.29-2.34]	0.722
Edoxaban	0.68	0.73	1.27	[0.22-7.40]	0.796



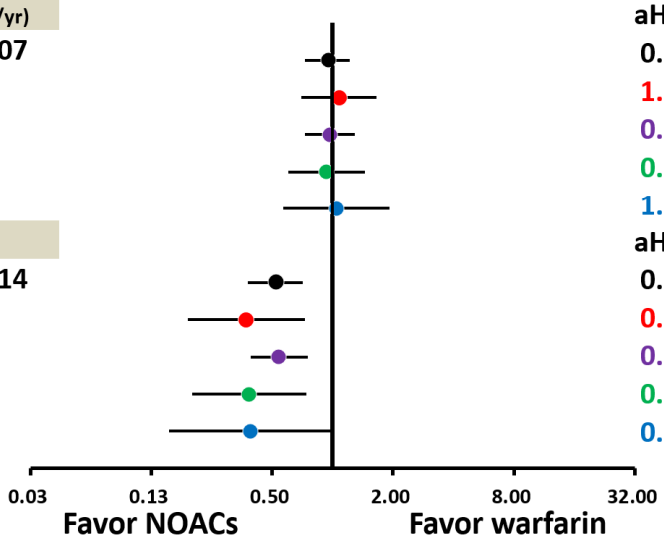
B. Off-label over-dosing vs. On-label dosing

IS/SE	Over Event (%/yr)	On label Event (%/yr)	aHR*	95% CI	*P* value
All NOACs	2.33	1.60	1.24	[0.74-2.07]	0.415
Dabigatran	1.48	1.72	0.89	[0.36-2.17]	0.790
Rivaroxaban	4.33	1.56	2.53	[1.17-5.45]	0.018
Apixaban	0.90	1.67	0.51	[0.07-3.80]	0.512
Edoxaban	1.77	1.72	1.44	[0.32-6.46]	0.633
Major bleeding			aHR*	95% CI	*P* value
All NOACs	2.01	0.76	2.01	[1.13-3.56]	0.017
Dabigatran	2.61	0.53	2.95	[1.12-7.77]	0.029
Rivaroxaban	2.44	0.86	3.06	[1.10-8.49]	0.032
Apixaban	0.89	0.59	0.89	[0.11-7.31]	0.911
Edoxaban	0.88	0.73	1.25	[0.13-11.82]	0.847



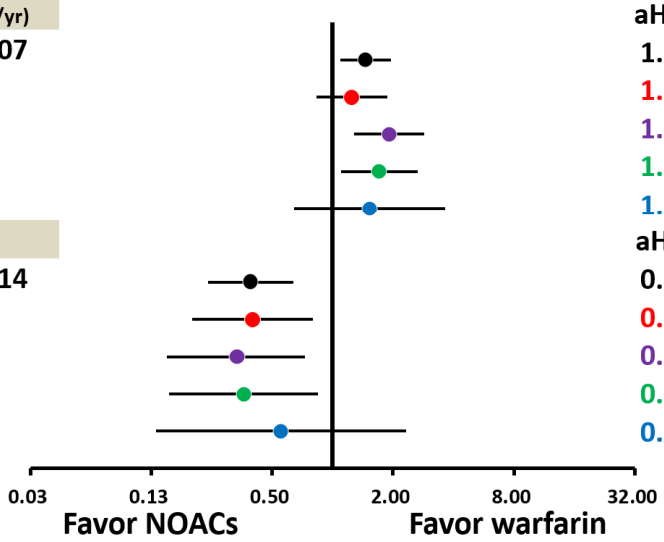
A. On-label dosing

IS/SE	On label Event (%/yr)	Warfarin Event (%/yr)	aHR*	95% CI	*P* value
All NOACs	1.60	2.07	0.95	[0.73-1.22]	0.668
Dabigatran	1.72		1.08	[0.70-1.65]	0.734
Rivaroxaban	1.56		0.97	[0.73-1.29]	0.833
Apixaban	1.67		0.93	[0.60-1.45]	0.760
Edoxaban	1.72		1.13	[0.27-4.08]	0.889
Major bleeding			aHR*	95% CI	*P* value
All NOACs	0.76	2.14	0.52	[0.38-0.71]	<.001
Dabigatran	0.53		0.37	[0.19-0.73]	0.004
Rivaroxaban	0.86		0.54	[0.39-0.75]	<.001
Apixaban	0.59		0.38	[0.20-0.74]	0.004
Edoxaban	0.73		0.39	[0.15-0.99]	0.047



B. Off-label under-dosing

IS/SE	Under Event (%/yr)	Warfarin Event (%/yr)	aHR*	95% CI	*P* value
All NOACs	2.20	2.07	1.46	[1.09-1.96]	0.012
Dabigatran	2.04		1.24	[0.83-1.87]	0.296
Rivaroxaban	2.68		1.92	[1.28-2.87]	0.002
Apixaban	2.89		1.71	[1.10-2.66]	0.017
Edoxaban	2.04		1.53	[0.64-3.65]	0.335
Major bleeding			aHR*	95% CI	*P* value
All NOACs	0.46	2.14	0.39	[0.24-0.64]	<.001
Dabigatran	0.41		0.40	[0.20-0.80]	0.009
Rivaroxaban	0.45		0.33	[0.15-0.73]	0.006
Apixaban	0.53		0.36	[0.15-0.85]	0.019
Edoxaban	0.68		0.55	[0.13-2.32]	0.418



C. Off-label over-dosing

IS/SE	Over Event (%/yr)	Warfarin Event (%/yr)	aHR*	95% CI	*P* value
All NOACs	2.33	2.07	1.13	[0.66-1.93]	0.663
Dabigatran	1.48		0.92	[0.40-2.14]	0.852
Rivaroxaban	4.33		2.53	[1.17-5.50]	0.019
Apixaban	0.90		0.43	[0.06-3.09]	0.398
Edoxaban	1.77		1.13	[0.27-4.08]	0.864
Major bleeding			aHR*	95% CI	*P* value
All NOACs	2.01	2.14	1.07	[0.60-1.90]	0.814
Dabigatran	2.61		1.16	[0.55-2.43]	0.696
Rivaroxaban	2.44		1.67	[0.61-4.59]	0.319
Apixaban	0.89		0.46	[0.06-3.32]	0.440
Edoxaban	0.88		0.58	[0.08-4.25]	0.597