Medication regimen complexity and risk of bleeding in people who initiate oral anticoagulants for atrial fibrillation: a population-based study

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Abstract

Background

Oral anticoagulants (OACs) are high-risk medications often used in older people with complex medication regimens. This study was the first to assess the association between overall regimen complexity and bleeding in people with atrial fibrillation (AF) initiating OACs.

Methods

Patients diagnosed with AF who initiated an OAC (warfarin, dabigatran, rivaroxaban, apixaban) between 2010-2016 were identified from the Hong Kong Clinical Database and Reporting System. Each patient's Medication Regimen Complexity Index (MRCI) score was computed. Baseline characteristics were balanced using inverse probability of treatment weighting. People were followed until a first hospitalisation for bleeding (intracranial haemorrhage, gastrointestinal bleeding or other bleeding), and censored at discontinuation of the index OAC, death or end of the follow-up period, whichever occurred first. Cox regression was used to estimate hazard ratios (HR) between MRCI quartiles and bleeding during initiation and all follow-up.

Results

There were 19,292 OAC initiators (n=9,092 warfarin, n=10,200 direct oral anticoagulants) with a mean (standard deviation) age at initiation of 73.9 (11.0) years. More complex medication regimens were associated with an increased risk of bleeding (MRCI>14.0-22.00: aHR 1.17, 95%CI 0.93-1.49; MRCI>22.0-32.5: aHR 1.32, 95%CI 1.06-1.66; MRCI>32.5: aHR 1.45, 95%CI 1.13-1.87, compared to MRCI≤14). No significant association between MRCI and bleeding risk was observed during the initial 30-, 60- or 90-days of treatment.

Conclusion

In this cohort study of people with AF initiating an OAC, a more complex medication regimen was associated with higher bleeding risk over periods longer than 90 days. Further prospective studies are needed to assess whether MRCI should be considered in OAC prescribing.

Keywords

Medication regimen complexity; anticoagulant; atrial fibrillation; bleeding; adverse drug event; warfarin

Introduction

Older people with atrial fibrillation (AF) commonly use multiple medications for multimorbidity.[1-6] A US study of people 75 years or older found that use of five or more medications was associated with an increased risk of major bleeding (HR 1.16, 95% CI 1.12-1.20).[4] Bleeding risk is a major concern for people using warfarin and direct oral anticoagulants (DOACs), which are indicated to reduce ischaemic stroke risk in older adults with AF. Polypharmacy has been associated with increased bleeding risk for people using warfarin, rivaroxaban, and apixaban,[7,8] but polypharmacy did not change the comparative efficacy or safety between warfarin and DOACs.[3,9]

Medication regimen complexity is a concept that includes not only the number of medications, but also the frequency of administration, different formulations and specific dosing instructions (e.g. split tablets, take with food).[10] While the use of multiple medications (polypharmacy) is strongly correlated with medication regimen complexity, other aspects of complexity such as specific dosing instructions have been independently associated with outcomes such as medication adherence.[11,12] Complex medication regimens have been associated with medication non-adherence in older adults,[1,13] and there is evidence that regimen complexity is an independent predictor of clinical outcomes such as hospitalisation.[13,14] Medication regimen complexity has been suggested to be a better overall predictor of mortality than polypharmacy.[15]

Warfarin is a typical example of a medication that is complex to administer due to variable dosing, multiple tablet strengths, need for international normalized ratio monitoring, and drug-drug and drug-food interactions.[16,17] In contrast, DOACs have standard dosing regimens and require less intensive monitoring. However, people with AF using any OAC often have

complex regimens; almost three-quarters take medications at least twice daily.[18] However, current risk assessment scores used to inform prescribing do not consider medication regimen factors.[22,23] Medication regimen complexity could be a more informative factor to consider, compared to polypharmacy, in multifaceted decisions to initiate OACs, which include balancing of stroke and bleeding risk.[19]

No previous studies have investigated the association between overall medication regimen complexity and bleeding risk among people initiating OACs. Prescription claims data suggest that OAC use is increasing in people aged 65 years and older, including in vulnerable population such as those with dementia in Australia and in the United Kingdom (UK).[20,21] The objective of this study was to evaluate the association between overall medication regimen complexity and bleeding risk in people with AF who initiate OACs.

Methods

Study design and data source

A population-based cohort study was undertaken using electronic health records from the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority. The Hospital Authority is the sole comprehensive public-funded population-wide healthcare provider to Hong Kong's population of over seven million people.[24] Electronic health records, including demographics, date of hospital admission and discharge, diagnoses, procedures, laboratory tests, and medication prescription records, are centralized in the Hospital Authority system and regularly audited. The records cover all patient consultations with the Hospital Authority, including inpatient, discharge and outpatient clinic visits. All medications that are prescribed at any consultation are captured. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM were used

for identifying diagnoses and cause of death respectively in CDARS. Deidentified data were extracted. CDARS has demonstrated high coding accuracy, with positive predictive values over 90% for diagnosis records for AF, intracranial haemorrhage, gastrointestinal bleeding, and ischaemic stroke.[25,26] CDARS has been extensively used to study the outcome of oral anticoagulant use.[27,28] This study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW13-468) and registered with the Monash University Human Research Ethics Committee. Informed consent was not required for the use of de-identified data in the absence of patient contact.

Population

People aged 18 years or older with a diagnosis of AF (ICD-9-CM code 427.3) between 1 January 2010 and 31 December 2016 were included. Individuals with a diagnosis of valvular disease, hyperthyroidism and those who underwent valve replacement at or prior to their AF diagnosis were excluded using the ICD-9-CM codes listed in Supplementary Table 1.

The index date was defined as the first day of a prescription of an OAC (warfarin, dabigatran, rivaroxaban, apixaban) following the first recorded AF diagnosis. Warfarin and dabigatran were captured from 2010, rivaroxaban from 2012 and apixaban from 2013. Edoxaban was first licensed in Hong Kong in May 2016, so it was not included in this study. Medication names were used to identify OACs from electronic prescription records. To select new users of OAC, people with any prescription of an OAC within 180 days before index date were excluded.

Exposure

Medication regimen complexity was quantified using the validated 65-item Medication Regimen Complexity Index (MRCI). This is the most widely used measure of overall medication regimen complexity.[10,29] The MRCI assigns weights for each medication in the regimen across three domains of formulation, dose frequency, and special instructions.[10] The points were then summed for the total MRCI score. Therefore, while MRCI does not explicitly measure number of medications, the score does reflect it. Fields extracted from CDARS used to calculate MRCI included prescription start and end date, medication name, route, medication strength, dosage, medication frequency, and unit of measurement of the medication (e.g. millilitres). The MRCI score on the index date was calculated for each person. Prescriptions were included if the person's index date fell in the duration on and between the prescription start and end dates. Vaccines were excluded. Information on special administration instructions were deduced from records where possible, such as splitting tablets or taking the medication with food. There are no widely accepted cut-offs for MRCI scores considered to be "high" or "low".[30,31] The population was divided into quartiles based on MRCI scores (quartiles 1-4 (Q1-4), with 1 being the lowest and 4 being the highest MRCI scores). This approach to categorization of MRCI has been used in previous studies.[32-36]

Primary and secondary outcomes

The primary outcome was defined as the first episode following index date for any hospitalisation with a diagnosis of intracranial haemorrhage (ICH), gastrointestinal bleeding (GIB), other bleeding. Other bleeding was defined as including hemopericardium, hemoptysis and haemorrhage from the kidney, throat, or vagina, epistaxis, hemarthrosis, hematuria and metrorrhagia (Supplementary Table 1). We examined outcomes occurring in the first 30-, 60-, and 90-days, and through the entire follow-up period, with follow-up

occurring from the index date until the first occurrence of any outcome of interest, end of study period (31 December 2017), death, switching to another oral anticoagulant, or discontinuation of the index oral anticoagulant. Discontinuation of therapy was defined as a gap greater than 10 days between the end of one prescription and the start of the next prescription. The mean gap for OAC prescriptions was five days. To capture most of the continuous users, we doubled this period and kept it short enough to get a reliable estimate for the 30-day follow-up. Secondary outcomes were the first episodes of ICH and GIB, and all-cause mortality.

Statistical analysis

Baseline characteristics were expressed as means (standard deviation [SD]) for continuous variables and as frequencies (percentages) for categorical variables. Incidence rates were calculated by dividing the number of events over follow up time. Cumulative incidence of any bleed over time and all-cause mortality were depicted using Kaplan-Meier curves.

To account for confounding and indication bias between exposure groups, inverse probability of treatment weighted approach was applied. Propensity scores were estimated using logistic regression based on age (continuous), sex, oral anticoagulant, index year, medical history of myocardial infarction, congestive heart failure, hypertension, diabetes, cancer, chronic obstructive pulmonary disease (COPD), ischaemic stroke/transient ischaemic attack/systemic embolism, vascular disease, renal disease, or prior bleed; recent use (<90 days prior to index date) of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta blocker, amiodarone, dronedarone, aspirin, clopidogrel, non-steroidal anti-inflammatory drugs (NSAIDs), histamine type-2-receptor antagonist, calcium channel blocker, statins, selective serotonin re-uptake inhibitor (SSRI)/selective noradrenaline re-uptake inhibitor (SNRI) and oral corticosteroids; and CHADS2-VASc and HAS-BLED score (continuous). In Hong

Kong, most low-dose aspirin and NSAID use is recorded in CDARS. Ticagrelor and prasugrel were not included as variables due to low use (n=30 and n=3, respectively). The covariates identified by ICD-9-CM were listed in the supplementary table 1. Balance between baseline characteristics in exposure groups was assessed using standardized mean differences, with differences <0.2 considered balanced.

Cox proportional hazard regression was used to estimate cause specific hazard ratios (HR) and their confidence intervals (CI). Characteristics with a standardised mean difference >0.1 after weighting were also further adjusted for in the Cox model. Subgroup analyses were conducted to investigate the effect of MRCI within age groups (<80 and 80 years or older) and type of OAC (warfarin and NOACs). Analyses were conducted in R v 3.6.3 (Comprehensive R Archive Network) with RStudio v 1.2.5042.

Results

Baseline characteristics

Of 71,630 people identified with AF, there were 19,292 new users of an OAC with a mean (SD) age at initiation of 73.9 (11.0) years (Figure 1). The median follow-up was 501 (IQR 119-1040) days. MRCI scores ranged from 1.5-129.5; while the mean (SD) MRCI score was 24.82 (14.62). Quartile cut-offs were identified as MRCI scores ≤14 (26.2%), >14.0-22.0 (25.3%), >22.0-32.5 (24.1%), and >32.5 (24.4%) (Table 1). People with the most complex medication regimens had more comorbidities. The mean (SD) Charlson Comorbidity Index (CCI) increased with increasing complexity quartile, from 0.8 (1.1) in Q1, 1.3 (1.4) in Q2, 1.7 (1.5) in Q3, and 2.5 (1.9) in the highest complexity Q4. The mean (SD) number of medications prescribed also increased with increasing complexity quartile, from 4.7 (1.6) in Q1, 7.6 (1.6) in Q2, 10.2 (1.9) in Q3, and 15.0 (3.7) in Q4.

Bleeding outcomes

A total of 2,494 people experienced a bleeding event during follow-up. The highest medication complexity quartile (Q4) had the most people experience any bleed (n=717, 15.2%) (Table 2). Rate of all-cause mortality was also highest in quartile 4. Q2 had the highest number of ICHs (n=140, 3.0%), while Q4 had the highest number of GIBs (n=318, 6.7%). The crude incidence rate of bleeding was highest in the first 30 days after OAC initiation for all levels of medication regimen complexity.

People with the higher complexity scores had a higher risk of bleeding outcomes compared with people with the lowest complexity scores (aHR 1.32, 95% CI 1.06-1.66 for Q3 and aHR 1.45, 95% CI 1.13-1.87 for Q4), after balancing baseline characteristics (Table 3). For the follow-up periods of 30-, 60- and 90-days after OAC initiation, MRCI was not associated with the risk of bleeding. When analysed by type of bleed, MRCI was not associated with higher risk of ICHs (aHR 1.05, 95% CI 0.55-1.99 for Q2; aHR 1.29, 95% CI 0.68-2.42 for Q3; aHR 1.09, 95% CI 0.54-2.17 for Q4). People with higher complexity scores had a higher risk for GIB (aHR 1.51, 95% CI 1.13-2.01 for Q3; aHR 1.76 95% CI 1.27-2.45 for Q4).

Subgroup analyses

In subgroup analyses by age, MRCI was significantly associated with an increased risk of bleeding for people <80 years across all higher complexity quartiles (Q2-4) (Figure 2). Results for people aged 80 years or older were not significant. In analyses between OACs, high MRCI score (Q4) was associated with increased risk of bleeding in people who initiated warfarin (HR 1.50, 95% CI 1.06-2.12) and people who initiated DOACs (HR 1.43, 95% CI 1.02-1.99).

Discussion

To our knowledge, this is the first study to investigate the association between medication regimen complexity and bleeding risk in people with AF initiating OACs. Our results are concordant with preliminary findings that suggested MRCI was associated with 12-month medication-related hospitalization in people with heart failure and AF.[37] However, that study did not find a significant association between MRCI and all-cause hospitalization.[37] Increasing rates of multimorbidity in people with AF mean that people who initiate OACs have increasingly complex medication regimens.[38] Widely used bleeding risk assessment tools such as HAS-BLED do not consider the overall complexity of a person's medication regimen.[22]

As expected since medication regimen complexity and polypharmacy covary, our findings are consistent with secondary analyses of the landmark randomised trials (ROCKET-AF and ARISTOTLE) that demonstrate polypharmacy is associated with increased bleeding risk for people using warfarin, rivaroxaban, and apixaban over a longer follow up period (up to 36 months).[7,8] In ARISTOTLE, polypharmacy was associated with increased GIB but not ICH,[8] which was also the case for MRCI and OACs in the present study. While MRCI does not explicitly include a medication count, the score accumulates for each medication, and inherently reflects the number of medications in a regimen. However, regimens with the same number of medications can vary considerably in MRCI score and complex medication regimens may be simplified without deprescribing, or changing the therapeutic intent of the regimen, for example by consolidating administration times or medication formulations.Advinha 2014, Chen 2018 This is of particular relevance in the oral anticoagulant category, within the context of the choice between warfarin, a typically complex medication to administer, and DOACs, which offer standard dosing (both of which contribute the same

magnitude to polypharmacy). Given the potentially different management strategies, it may be appropriate to use both MRCI and polypharmacy to assess patient complexity when initiating OACs.

In our subgroup analysis, both warfarin and DOACs had the same trend of only the most complex medication regimens being significantly associated with increased risk of bleeding. This is similar to recent studies that found that polypharmacy did not increase the relative risk of bleeding between DOACs and warfarin.[3,9] This was somewhat unexpected, given the benefit to patients of the DOACs' fixed regimen. Regimen complexity may affect an individual's ability to correctly self-manage and administer medications.[40] A comparison of persistence and discontinuation between once-daily rivaroxaban and twice-daily dabigatran showed people using rivaroxaban were 11% less likely to become non-persistent (have large gaps between prescription refills) and 29% less likely to discontinue therapy.[41] A Turkish study compared people receiving once-daily and twice-daily DOACs, and did not find a difference in bleeds, despite finding lower adherence in people in the twice-daily dosing group.[42] A proposed mechanism was the smaller pharmacokinetic risk of medication dose errors (missing a dose or taking an extra dose) for DOACs with twice-daily regimens compared to once-daily regimens.[42] However, the presence of three or more additional medical conditions was an independent risk factor for bleeding.[42] This suggest that clinicians should consider patient-related factors, rather than the medication characteristics, in the choice of OAC.

Perceived risk of bleeding and physician's judgement of a patients' ability to adhere with their treatment regimen can be a barrier to prescribing of OACs, particularly in older people.[43] While the incidence of major bleeding increases with age,[44] current evidence

suggests that, even for older people, OAC use has a net clinical benefit,[45] and DOACs appear to have a favourable safety profile compared to warfarin.[44,46,47] Our study suggests that MRCI was not significantly associated with an increased risk of bleeding for people aged 80 years or older across all higher complexity quartiles (Q2-4) (Figure 2). This suggests that for this population, presence of medication complexity should not hinder the use of oral anticoagulants.

In our study, the incidence of bleeding was highest in the first 30 days following OAC initiation, consistent with previous studies that found that higher risk of bleeding within this period.[48-50] However, in adjusted analysis, MRCI score was not associated with bleeding within 90-days following OAC initiation. This could be because the additional risk associated with regimen complexity is small relative to the risk of bleeding due to other factors, such as prior bleeding, during this initial period. The increased risk of adverse drug events due to interactions or medication errors that arise from managing complex medication management may be more likely to materialize over a longer period of time.[51,52] Limited literacy, cognitive decline and multimorbidity were independent predictors of dosing errors over nine years.[52] Additionally, we estimated MRCI on the index date. Medication regimens may have changed throughout the follow up period. However, the decision to initiate an OAC is made on the index date and so assessing complexity at this time is consistent with how knowledge of bleeding risk would be used by clinicians in routine clinical practice.[53] A cohort study of people with AF found that over half had new comorbidities diagnosed during the follow-up.[38] Subsequent initiation or discontinuation of medications throughout the follow-up period, including those which would impact bleeding risk such as aspirin, were not considered in our analyses. This may be disproportionately the case for those with higher MRCI, who had higher prevalence of prior myocardial infarction, vascular disease, stroke and diabetes.

While MRCI is a 65-item tool, making it impractical to manually calculate in practice, automated calculation in electronic health systems is feasible using existing data if it is found to be a useful tool.[39] The use of electronic medical records, and the potential of the data they generate to be used to improve patient care, is on the rise. More research is needed to determine whether the MRCI is a useful tool to implement in such a manner, and whether it could be particularly beneficial in certain settings. Our results contribute to the evidence base towards answering this question.

Strengths and limitations

This study used large real-world population-based data and investigated validated clinical outcomes.[24,50] A strength of this study was the large sample size. We used a validated scale to calculate the MRCI score, so our results can be compared to other studies that have used the MRCI to quantify complexity.[14,15,31,34,35] The distribution of MRCI scores appear to vary in different populations internationally, although the source of medication regimen data may explain some of the differences.

While the electronic medical records used in this study have been used in previous research, there are limitations in the data. It is difficult to get an overall impression of a person's health, in particular how social determinants interact with the information we have. For example, the level of social support available to assist medication administration and management is unknown. Early or undiagnosed cognitive impairment or dementia would also not have been recorded. While strength and directions were available for medications, the fields were not always complete, making it difficult to detect if patients received appropriate dosing of DOACs. Both under- and over-dosing are of concern with all OACs. Results from

our population-based study should be interpreted in context of individual patients, by clinicians who have access to such information. For example, MRCI could be used as a risk assessment tool to inform patient complexity in comprehensive geriatric assessments.

Our calculation of MRCI was conservative. Only prescriptions current on the index date were included, however, prescription durations for many chronic medications were long and so would likely have been captured. Similar to other studies using electronic medical records, complementary and alternative medications and any non-prescribed over-the-counter medications were not captured in CDARS and so were not included. Furthermore, electronic medical records cannot measure adherence to OACs. Non-adherence to OACs has been associated with lower risk of bleeding.[54] Additional patient-specific administration instructions, such as crushing tablets to aid swallowing difficulties, may have been counselled but not recorded. These factors may have contributed to an underestimation of complexity. There may be residual confounding despite a rigorous approach to balance known and measured factors. Finally, the relationship between MRCI and bleeding may not be causal. Further prospective studies are needed to confirm these results and to assess whether MRCI should be included in clinical decision-making.

Conclusion

Higher medication regimen complexity is associated with increased bleeding risk over treatment periods longer than 90 days among people with AF. Both warfarin and DOACs showed the same trend in bleeding risk. MRCI was not significantly associated with an increased risk of bleeding for people aged 80 years or older. Our findings suggest that simplifying medication regimen complexity might be considered for patients initiating OACs.

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EYHC, JZ, JI, JEB and EWC contributed to the concept and design of the study. All authors contributed to the acquisition, analysis or interpretation of data. EYHC drafted the manuscript, all authors critically revised the manuscript for important intellectual content. EYHC and JZ had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest and financial disclosures

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Table 1: Baseline characteristics, mean (SD) unless specified						
	Q1 (n=5,060)	**Q2 (n=4,876)**	**Q3 (n=4,643)**	**Q4 (n=4,713)**	**SMD[a]**	**Adj SMD[a]**
Definition (MRCI)	0-14.0	>14.0-22.0	>22.0-32.5	>32.5		
Follow up, days	764 (719)	734 (685)	653 (646)	548 (582)		
Age, years	70.4 (11.6)	73.2 (10.8)	75.2 (10.3)	77.1 (10.0)	0.6200	0.0350
Female, n (%)	2182 (43)	2335 (48)	2352 (51)	2430 (52)	0.1692	0.0482
Oral anticoagulant, n (%)						
Warfarin	2256 (44.6)	2192 (45.0)	2182 (47.0)	2462 (52.2)	0.1536	0.0441
Dabigatran	1508 (29.8)	1478 (30.3)	1304 (28.1)	1063 (22.6)	0.1738	0.0088
Rivaroxaban	897 (17.7)	776 (15.9)	712 (15.3)	678 (14.4)	0.0916	0.0308
Apixaban	399 (7.9)	430 (8.8)	445 (9.6)	510 (10.8)	0.1013	0.0577
Baseline medical conditions, n (%)						

Congestive heart failure	682 (13.5)	1072 (22.0)	1336 (28.8)	1956 (41.5)	0.6534	0.0434
Hypertension	1868 (36.9)	2460 (50.5)	2620 (56.4)	3115 (66.1)	0.5978	0.0471
Diabetes mellitus	445 (8.8)	896 (18.4)	1345 (29.0)	1775 (37.7)	0.7049	0.0377
Prior ischemic stroke or TIA or systemic embolism	1188 (23.5)	1486 (30.5)	1552 (33.4)	1547 (32.8)	0.2178	0.0235
Vascular disease	446 (8.8)	875 (17.9)	1249 (26.9)	1809 (38.4)	0.7275	0.0393
Myocardial infarction	94 (1.9)	225 (4.6)	434 (9.4)	722 (15.3)	0.5118	0.0616
COPD	119 (2.4)	195 (4.0)	314 (6.8)	1089 (23.1)	0.7552	0.0221
Renal disease	118 (2.3)	295 (6.1)	439 (9.5)	886 (18.8)	0.5841	0.0761
Cancer	304 (6.0)	373 (7.7)	340 (7.3)	461 (9.8)	0.1478	0.0346
Prior bleed	576 (11.4)	733 (15.0)	834 (18.0)	1215 (25.8)	0.3823	0.1021
Medications prescribed in the 90 days prior to index date, n (%)						
ACEI/ARB	1520 (30.0)	2340 (48.0)	2637 (56.8)	3008 (63.8)	0.6984	0.0268
Beta blocker	2623 (51.8)	3130 (64.2)	3103 (66.8)	2937 (62.3)	0.3100	0.0416
Calcium channel blocker	2251 (44.5)	2834 (58.1)	2886 (62.2)	3360 (71.3)	0.5559	0.0260

Amiodarone	324 (6.4)	502 (10.3)	688 (14.8)	957 (20.3)	0.4190	0.1726
Dronedarone	68 (1.3)	40 (0.8)	33 (0.7)	25 (0.5)	0.0886	0.1116
Aspirin	3274 (64.7)	3699 (75.9)	3664 (78.9)	3880 (82.3)	0.4144	0.0589
Clopidogrel	250 (4.9)	373 (7.6)	455 (9.8)	614 (13.0)	0.2862	0.1179
Dipyridamole	29 (0.6)	59 (1.2)	101 (2.2)	135 (2.9)	0.1774	0.0493
NSAID	216 (4.2)	297 (6.1)	363 (7.8)	497 (10.5)	0.2441	0.0296
H2RA	2491 (49.2)	2795 (57.3)	2746 (59.1)	2818 (59.8)	0.2138	0.0452
Proton pump inhibitor	875 (17.3)	1212 (24.9)	1531 (33.0)	2169 (46.0)	0.6427	0.0756
Statin	1808 (35.7)	2514 (51.6)	2765 (59.6)	2831 (60.1)	0.4967	0.0454
SSRI/SNRI	50 (1.0)	107 (2.2)	178 (3.8)	267 (5.7)	0.2675	0.0414
Oral corticosteroid	82 (1.6)	162 (3.3)	319 (6.9)	1066 (22.6)	0.7838	0.0567
Spironolactone	63 (1.3)	117 (2.4)	137 (3.0)	239 (5.1)	0.2281	0.0249
Risk scores						
CHAD2S2-VASc	2.67 (1.59)	3.46 (1.75)	3.99 (1.80)	4.54 (1.82)	1.0726	0.0383
HAS-BLED	2.16 (1.14)	2.65 (1.20)	2.90 (1.20)	3.26 (1.22)	0.9291	0.0574

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, age 65–74 years, prior stroke/transient ischemic attack/systemic embolism (doubled), vascular disease, and sex category (female); HAS-BLED, hypertension, abnormal liver or kidney function, stroke history, bleeding history, labile international normalized ratio [not included], elderly [age >65 years], drug, and alcohol use; H2RA, histamine type-2-receptor antagonist; MRCI, medication regimen complexity index; NSAIDs, non-steroidal anti-inflammatory drugs; SMD, standardised mean difference; SNRIs, selective noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TIA, transient ischemic attack. Note. [a]maximum standardised pairwise difference, crude and adjusted using inverse probability of treatment weighting with no truncation.

Table 2: Incidence of bleeding events								
	Q1		**Q2**		**Q3**		**Q4**	
	Events	**Incidence/ 100 py**	**Events**	**Incidence/ 100 py**	**Events**	**Incidence/ 100 py**	**Events**	**Incidence/ 100 py**
All follow up – range (1-2,927 days), mean 685.8 days								
All bleeding	520	4.7	612	6.2	645	7.8	717	10.1
Intracranial bleed	95	0.8	140	1.3	139	1.5	128	1.6
GI bleed	183	1.6	225	2.2	266	3.0	317	4.2
Other bleeding	254	2.2	287	2.8	297	3.4	318	4.2
Mortality	265	2.4	398	4.1	476	5.7	915	12.9
Incidence of bleeding – 30 day follow up								
All bleeding	75	19.0	92	24.6	113	32.0	139	39.7
Intracranial bleed	12	3.0	30	8.0	34	9.5	36	10.2
GI bleed	25	6.3	32	8.5	37	10.4	50	14.1

Other bleeding	36	9.1	27	7.2	44	12.3	45	12.7
Mortality	17	0.2	23	0.2	45	0.5	147	2.1
Incidence of bleeding – 60 day follow up								
All bleeding	109	14.3	128	17.8	164	24.2	191	28.9
Intracranial bleed	14	1.8	34	4.7	43	6.3	43	6.4
GI bleed	38	4.9	46	6.3	56	8.2	72	10.7
Other bleeding	36	9.1	27	7.2	44	12.3	45	12.7
Mortality	26	0.2	47	0.5	74	0.9	238	3.4
Incidence of bleeding – 90 day follow up								
All bleeding	130	11.7	155	14.8	201	20.5	235	24.7
Intracranial bleed	16	1.4	41	3.9	50	5.0	46	4.7
GI bleed	45	4.0	51	4.8	71	7.1	89	9.2
Other bleeding	67	6.0	61	5.7	84	8.4	90	9.3
Mortality	36	0.3	62	0.6	104	1.3	293	4.1

Table 3: Association between MRCI quartile and bleeding over various follow up periods (compared to reference MRCI Q1)		
	Unadjusted HR (95%CI)	**Adjusted HR[a] (95%CI)**
All follow up		
Q1	1	1
Q2	1.14 (0.90-1.45)	1.17 (0.93-1.49)
Q3	1.27 (1.01-1.60)	1.32 (1.06-1.66)
Q4	1.43 (1.10-1.85)	1.45 (1.13-1.87)
30-day follow up		
Q1	1	1
Q2	0.89 (0.38-2.05)	1.00 (0.48-2.09)
Q3	1.08 (0.48-2.45)	1.25 (0.61-2.54)
Q4	1.07 (0.47-2.44)	1.15 (0.54-2.45)
60-day follow up		
Q1	1	1
Q2	0.88 (0.46-1.68)	0.99 (0.55-1.78)
Q3	1.13 (0.61-2.12)	1.28 (0.73-2.26)
Q4	1.17 (0.60-2.31)	1.27 (0.68-2.39)
90-day follow up		

Q1	1	1
Q2	0.89 (0.51-1.56)	0.98 (0.59-1.65)
Q3	1.16 (0.67-2.00)	1.30 (0.79-2.14)
Q4	1.28 (0.71-2.32)	1.37 (0.78-2.40)

MRCI: medication regimen complexity index. Note. [a]adjusted for Charlson Comorbidity Index score, prior bleeding, and recent use of amiodarone, dronedarone, or clopidogrel.

Figure 1. Study flowchart of participant selection

Figure 2. Unweighted Kaplan-Meier curve of A) first bleeding event and B) all-cause mortality

Table 1. Baseline characteristics, mean (SD) unless specified

Table 2. Incidence of bleeding events

Table 3. Association between MRCI quartile and bleeding over various follow up periods (compared to reference MRCI Q1)