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PHARMACOEPIDEMIOLOGY

Risk of major bleeding and stroke associated with the use of vitamin K antagonists, nonvitamin K antagonist oral anticoagulants and aspirin in patients with atrial fibrillation: a cohort study

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AIMS

Nonvitamin K antagonist oral anticoagulants (NOACs) are now available for the prevention of stroke in patients with atrial fibrillation (AF) as an alternative to vitamin K antagonists (VKA) and aspirin. The comparative effectiveness and safety in daily practice of these different drug classes is still unclear. The objective of this study was to evaluate the risk of major bleeding and stroke in AF patients using NOACs, VKAs or aspirin.

METHODS

A retrospective cohort study was conducted among AF patients using the UK Clinical Practice Research Datalink (March 2008–October 2014). New users of VKAs, NOACs and low dose aspirin were followed from the date of first prescription of an antithrombotic drug until the occurrence of stroke or major bleeding. Analyses were adjusted for a history of comorbidities and drug use with Cox regression analysis.

RESULTS

A total of 31 497 patients were eligible for the study. The hazard ratio (HR) of major bleeding was 2.07 [95% confidence interval (CI) 1.27–3.38] for NOACs compared with VKAs, which was mainly attributed by the increased risk of gastrointestinal bleeding (HR 2.63, 95% CI 1.50–4.62). This increased bleeding risk was restricted to women (HR 3.14, 95% CI 1.76–5.60). Aspirin showed a similar bleeding risk as VKAs. NOACs showed equal effectiveness as VKA in preventing ischaemic stroke (HR 1.22, 95% CI 0.67–2.19). VKAs were more effective than aspirin (HR 2.18, 95% CI 1.83–2.59).

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CONCLUSIONS

NOACs were associated with a higher risk on gastrointestinal bleeding, particularly in women. The use of NOACs in patients who are vulnerable for this type of bleeding should be carefully considered. NOACs and VKAs are equally effective in preventing stroke. Aspirin was not effective in the prevention of stroke in AF.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Randomized clinical trials show that nonvitamin K antagonist oral anticoagulants (NOACs) are at least as effective in the prevention of ischaemic stroke in atrial fibrillation as vitamin K antagonists (VKAs).
- There is no sound evidence for a preference starting either VKAs or NOACs.
- Asprin has no place in the prevention of ischaemic stroke in patients with atrial fibrillation.

WHAT THIS STUDY ADDS

- In UK general practice, it is confirmed that VKAs and NOACs are equally effective in the prevention of ischaemic stroke.
- Women have a higher risk on gastrointestinal bleeding when using NOACs compared to VKAs.
- Although aspirin is still commonly used in patient with atrial fibrillation in UK general practice, it is confirmed that is less effective and carries an equal bleeding risk compared to VKAs.

Tables of Links

TARGETS	
Enzymes [2]	COX-1
VKORC1	Thrombin
Coagulation factor X	

LIGANDS	
aspirin	rivaroxaban
dabigatran	warfarin

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

Introduction

Atrial fibrillation (AF) has a prevalence of 1–2% and is associated with a doubled rate of death and a 5-fold increased rate of stroke [3, 4]. Antithrombotic therapy such as vitamin K antagonists (VKAs), nonvitamin K antagonist oral anticoagulants (NOACs) and low dose aspirin are used treatment options for AF and can reduce stroke rates by up to 20%–60% [5–7]. The CHA_2DS_2-VASC risk score guides the choice of antithrombotic treatment using known risk factors for stroke: congestive heart failure, hypertension, age, diabetes, prior stroke or thromboembolism, vascular disease and female sex.

Studies have shown that NOACs may significantly reduce the risk of stroke and intracranial bleeding, when compared with warfarin [8–11]. In line with these findings the European guidelines now recommend using NOACs over VKAs for most patients with AF (2). The use of aspirin was used only in the treatment of patients at low risk for stroke, however, more recently it is advised that aspirin should be confined to those that refuse NOAC or VKA therapy.

While NOACs are effective in reducing stroke risk, the evidence remains inconclusive with respect to its risks of major and gastrointestinal bleeding [8, 9, 11–16]. This complicates the choice in antithrombotic therapy in daily practice as the harm–benefit ratio is uncertain in patients with higher baseline risks for bleeding. Furthermore, the risk of antithrombotic therapy in real world patients may differ from those in the randomized controlled trials (RCTs). Patients in RCTs using warfarin spent more time in the therapeutic range compared with patients monitored by community physicians [17]. Secondly, patients who are seen in everyday clinical practice have a different risk profile, as the patients in the trials were obligated to meet specific inclusion and exclusion criteria [18].

To investigate the safety and efficacy of NOACs compared with VKA in real-world patients, several observational studies have been conducted, but these were limited to the evaluation of dabigatran, and they were unable to statistically adjust for life style factors such as body mass index and smoking status [12–16].

The aim of this study was to evaluate the risk of major bleeding and stroke in AF patients using VKAs, NOACs and low dose aspirin in a UK general practice population.

Methods

Data source

We conducted a retrospective cohort study within the Clinical Practice Research Datalink (CPRD). This database contains computerized medical records of around 674 primary care practises in the UK, covering 11.3 million patients, representing 6.9% of the total UK population [19]. Data recorded in the CPRD include demographic information, laboratory tests, specialist referrals, hospital admissions, prescription details, and lifestyle variables such as body mass index (BMI), smoking, and alcohol consumption. Previous studies have shown a high validity of registration and high degrees of accuracy and completeness of these data have been shown for various diagnoses (including 85.3% for diagnoses related to the circulatory system and 87.4% for diagnoses related to the digestive system) and for smoking status [19–23].

Study population

The study population consisted of all patients aged ≥18 years with a first ever recorded diagnosis of AF during a patient's period of valid data collection. Only patients with follow-up time between 18th March 2008 (the date of market introduction of the NOACs) and 1 October 2014 were included. Within this cohort of AF patients, we identified new users of antithrombotic drugs: VKAs, NOACs and low dose (≤325 mg) aspirin. New users were defined as patients who had never been exposed previously to any one of the drugs of interest.

Exposure

Patients were followed from the start of antithrombotic treatment until the end of follow-up, death, or an outcome of interest, whichever date came first. The period of follow-up was divided into 30-day periods, starting with the index date. At the start date of each period, exposure to antithrombotic agents in the 30 days before was defined as current users and past users were defined as those who had discontinued their antithrombotic agents >30 days before the start of the interval. An example of exposure definition for a hypothetical patient is given in Figure 1. During follow-up, patients were able to move between current and past exposure groups. Patients were defined as current users of VKA only (warfarin, acenocoumarol and phenindione), NOAC only (dabigatran, rivaroxaban and apixaban), aspirin only, or mixed use of more than one of the three main study drugs. These groups were identified regardless of past use as it is expected that medications taken >30 days from an exposure period would no longer impact a patient's likelihood for the outcome. Patients could only contribute to one current user group during an interval. Among patients who were not considered current users, past use was defined as past VKA, NOAC, or aspirin use, and patients could contribute to more than one past user group in an interval.

Outcomes

The primary outcome of interest was major bleeding. Secondary outcomes were gastrointestinal bleeding, intracranial bleeding, stroke, ischaemic stroke and haemorrhagic stroke. The UK Read code system was used to define outcomes. Major bleeding was defined as a bleeding at a critical site or organ and the selected Read-codes were reviewed by a clinician for relevancy. The codes used for defining the primary outcome can be found in Appendix 1.

Potential confounders

Potential confounders considered in this study were based on literature review. The presence of a covariate was assessed by reviewing the computerized medical records for any record of a covariate. For each outcome, sex, BMI, smoking status and alcohol status were considered at baseline and age at the start of each interval. The following covariates were evaluated prior to the start of each interval for bleeding outcomes: oesophagitis, gastritis, cerebrovascular disease and malignancies. The use of the following prescription drugs in the 6 months before an interval were considered: statins, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II (ATII) blockers, diuretics, β-blockers, antiplatelet drugs (excluding aspirin), anticoagulant drugs (excluding VKAs and NOACs), antiarrhythmic drugs, nitrates, antidiabetic drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), systemic glucocorticoids, selective serotonin reuptake inhibitors (SSRIs). Proton-pump inhibitors and histamine 2 receptor antagonists were assessed in the 3 months before an interval. For stroke, covariates included history of congestive heart failure, hypertension, cerebrovascular disease, ischaemic heart disease, peripheral

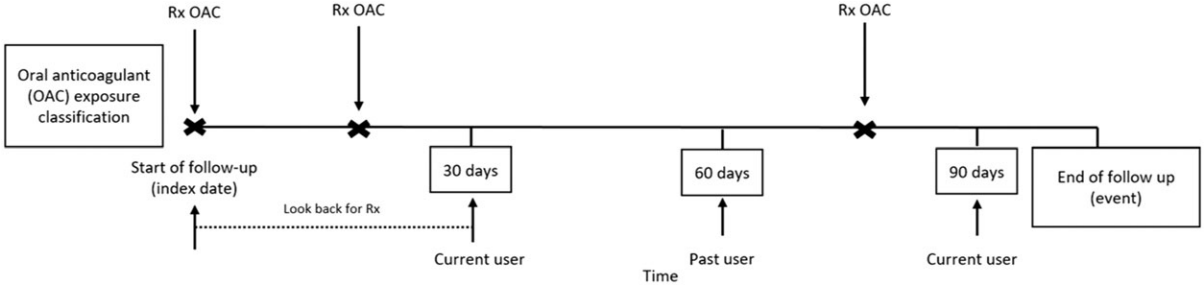

Figure 1

Diagram of exposure definition demonstrating a hypothetical case example of a patient classified as oral anticoagulants user at time of a stroke or bleeding event

artery disease, acute or chronic renal failure. Prescriptions in the 6 months prior were also considered for stroke: statins, calcium channel blockers, ACE-inhibitors, ATII-blockers, diuretics, β-blockers, clonidine, monoxide, doxazosin, antipsychotics, SSRIs, NSAIDs, antiplatelet drugs, anticoagulant drugs, antiarrhythmic drugs, nitrates, antidiabetic drugs and insulin.

Statistical analysis

The outcomes of interest were incident first-ever events; patients with a history of the outcome were excluded. Baseline characteristics were summarized as means and standard deviations or proportions where appropriate. Crude incidence rates of outcomes within 1 year per 1000 person-years were calculated. Cox proportional hazard regression analysis estimated the adjusted hazard ratios (HR) using the SAS 9.2 PHREG procedure. Potential confounders were included in the final model if they independently changed the β-coefficient for current use with the outcome of interest by at least 5%, or when a consensus about inclusion existed within the team of researchers, supported by clinical evidence from the literature. Current use of VKAs served as the reference group and was used to compare to the other exposure groups (current use of NOAC only, aspirin only, mixed use and past use). Analyses were stratified by sex and the CHA_2DS_2-VASC risk score. Missing data were dealt with by including an indicator for missingness in the model.

Patient involvement

For this study, we did not actively involve patients.

Results

We identified 31 497 patients with an AF diagnosis and a first-ever prescription of antithrombotic therapy. Figure 2 shows the study flowchart.

Baseline characteristics are presented in Table 1. At the index date, 16 094 (51.1%) patients were prescribed aspirin, 13 643 (43.3%) VKAs, 1306 (4.1%) NOACs, and 453 (1.4%) a mix of these agents. In the NOACs group 28.5% of patients were using dabigatran and 71.5% rivaroxaban. None were using apixaban. The mean duration of follow-up was shorter for users of NOACs (1.0 years) than for users of VKAs (2.7 years) or aspirin (2.8 years). Age, BMI, smoking status and alcohol use did not differ much between exposure groups at baseline. Users of NOACs (18.9%) had more often a history of cerebrovascular disease as compared with users of VKAs (13.4%) or low dose aspirin (6.1%). Appendix 2 shows baseline characteristics of the two cohorts excluding history of the respective outcomes, stroke or major bleed.

The incidence rate for major bleeding per 1000 person-years was 10.6 for current NOAC use, 5.8 for current VKA use, 7.5 for current aspirin use and 8.2 for current mixed use (Table 2). A 2-fold increased risk of major bleeding was found with current use of NOACs [adjusted hazard ratio (HR) 2.08; 95% confidence interval (CI) 1.28–3.40], which dropped after discontinuation (HR 1.13; 95% CI 0.42–3.05). Current use of aspirin did not have an increased risk of major bleeding (HR 1.05; 95% CI 0.84–1.32), as compared with current use of VKAs. The doubled risk of major bleeding with current users of NOACS was largely explained by an increased risk for gastrointestinal bleeding (HR 2.63; 95% CI 1.50–4.60) for current NOAC users as compared with current VKA users. No difference was found for the occurrence of intracranial

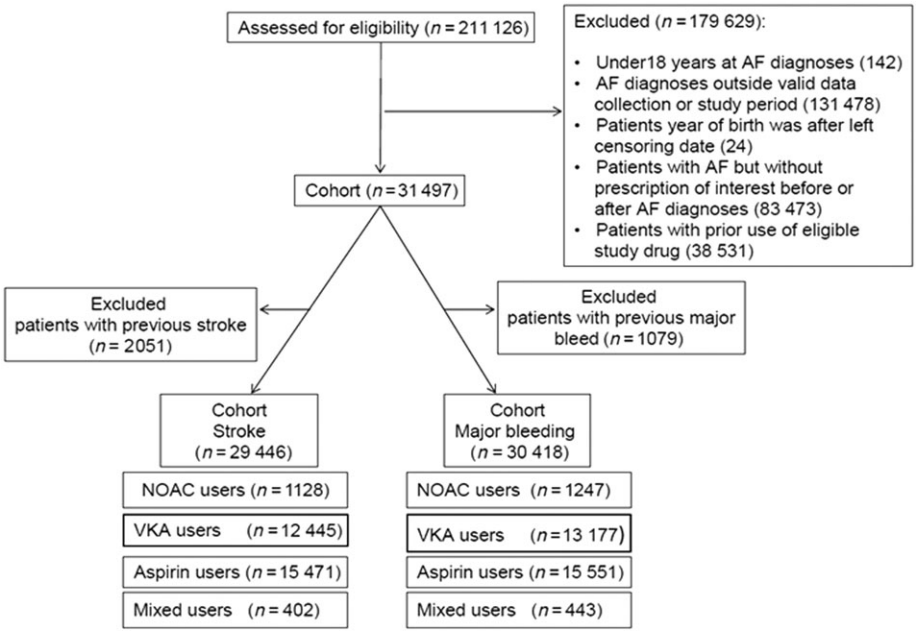

Figure 2
Flow diagram of cohort assembly

Table 1

Baseline characteristics for users of NOACs, VKAs, aspirin or mixed users at the index date

Characteristic	NOAC-users (*n* = 1306)	VKA-users (*n* = 13 643)	Aspirin-users (*n* = 16 094)	Mixed users (*n* = 454)
Follow up, years (SD)	0.95 (0.63)	2.71 (1.86)	2.84 (1.87)	2.94 (1.97)
Number of women	589 (45.1%)	6283 (46.1%)	8008 (49.8%)	163 (35.9%)
Age				
Mean (years, SD)	72.6 (12.6)	72.1 (11.9)	73.6 (12.7)	72.2 (10.6)
18–49	59 (4.5%)	673 (4.9%)	665 (4.1%)	14 (3.1%)
50–59	159 (12.2%)	1288 (9.4%)	1454 (9.0%)	39 (8.6%)
60–69	258 (19.8%)	3017 (22.1%)	3662 (22.8%)	119 (26.2%)
70–79	419 (32.1%)	4663 (34.2%)	4408 (27.4%)	163 (35.9%)
80+	411 (31.5%)	4002 (29.3%)	5905 (36.7%)	119 (26.2%)
CHA_2DS_2-VASc				
Mean	2.6	2.6	2.5	2.6
0–1	25.0%	24.6%	27.2%	22.7%
2	20.7%	21.0%	21.1%	23.4%
3–10	54.3%	54.5%	51.8%	54.0%
BMI (kg/m^2)				
Mean (SD)	27.9 (6.2)	28.7 (6.3)	27.8 (6.2)	28.9 (6.6)
< 20	82 (6.3%)	543 (4.0%)	963 (6.0%)	21 (4.6%)
20–25	334 (25.6%)	3165 (23.2%)	4134 (25.7%)	96 (21.2%)
25–30	420 (32.2%)	4629 (33.9%)	5318 (33.0%)	155 (34.1%)
30–35	248 (19.0%)	2672 (19.6%)	2754 (17.1%)	91 (20.0%)
>35	142 (10.9%)	1800 (13.2%)	1659 (10.3%)	60 (13.2%)
Missing	80 (6.1%)	834 (6.1%)	1266 (7.9%)	31 (6.8%)
Smoking status				
Never	566 (43.3%)	5659 (41.5%)	7074 (44.0%)	173 (38.1%)
Current	105 (8.0%)	1230 (9.0%)	1548 (9.6%)	54 (11.9%)
Ex	628 (48.1%)	6691 (49.0%)	7391 (45.9%)	225 (49.6%)
Missing	7 (0.5%)	63 (0.5%)	81 (0.5%)	<5
Alcohol status				
Yes	905 (69.3%)	9513 (69.7%)	11 002 (68.4%)	313 (68.9%)
No	288 (22.1)	3158 (23.2%)	3794 (23.6%)	100 (22.0%)
Missing	113 (8.7)	972 (7.1%)	1298 (8.1%)	41 (9.0%)
History of comorbidities				
Acute renal failure	7 (0.5%)	65 (0.5%)	120 (0.8%)	<5
Cerebrovascular disease	247 (18.9%)	1822 (13.4%)	988 (6.1%)	73 (16.1%)
Chronic renal failure	7 (0.5%)	157 (1.2%)	158 (1.0%)	<5
Congestive heart failure	98 (7.5%)	1396 (10.2%)	961 (6.0%)	68 (15.0%)
Gastritis	82 (6.3%)	849 (6.2%)	933 (5.8%)	18 (4.0%)
GI bleeding	42 (3.2%)	374 (4.7%)	410 (2.6%)	7 (1.5%)
Hypertension	713 (54.6%)	7323 (53.7%)	8048 (50.0%)	233 (51.3%)

(*continues*)

Table 1

(Continued)

Characteristic	NOAC-users (*n* = 1306)	VKA-users (*n* = 13 643)	Aspirin-users (*n* = 16 094)	Mixed users (*n* = 454)
Ischaemic heart disease	111 (8.5%)	1461 (10.7%)	1499 (9.3%)	115 (25.3%)
Liver disease	<5	15 (0.1%)	35 (0.2%)	<5
Oesophagitis	126 (9.6%)	1179 (8.6%)	1298 (8.1%)	34 (7.5%)
Cancer	15 (1.2%)	125 (0.9%)	122 (0.8%)	<5
Peripheral artery disease	72 (5.5%)	712 (5.2%)	661 (4.1%)	26 (5.7%)
History of medication use (6 months before index date)				
Antiarrhythmic drugs	81 (6.2%)	907 (6.7%)	679 (4.2%)	13 (2.9%)
Anticoagulant drugs	17 (1.3%)	209 (1.5%)	65 (0.4%)	0 (0.0%)
Antidiabetic drugs (including insulin)	102 (7.8%)	1058 (7.8%)	911 (5.7%)	38 (8.4%)
Antihypertensive drugs	342 (26.2%)	3849 (28.2%)	3574 (22.2%)	104 (22.9%)
Antiplatelet drugs	9 (0.7%)	207 (1.5%)	95 (0.6%)	<5
NSAIDs	143 (11.0%)	1597 (11.7%)	2107 (13.1%)	60 (13.2%)
SSRIs	91 (7.0%)	800 (5.9%)	1073 (6.7%)	17 (3.7%)
Statins	394 (30.2%)	4083 (29.9%)	3385 (21.0%)	113 (24.9%)
Glucocorticoids	127 (9.7%)	1342 (9.8%)	1278 (7.9%)	32 (7.1%)
History of medication use (3 months before index date)				
H2 receptor-antagonists	32 (2.5%)	324 (2.4%)	306 (1.9%)	13 (2.9%)
PPIs	360 (27.6%)	3334 (24.4%)	3542 (22.0%)	84 (18.5%)

NOAC, nonvitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; SD, standard deviation; BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; H2, histamine 2; PPIs, proton pump inhibitors, GI, gastrointestinal.

bleeding in current users of NOACs as compared with current use of VKAs (HR 1.39; 95% CI 0.55–3.52).

Table 3 shows that there was no difference in the risks of ischaemic and haemorrhagic stroke between current use of NOAC and VKA (HR 1.22, 95% CI 0.67–2.19 and HR 1.56, 95% CI 0.61–3.99, respectively). The risk of ischaemic stroke was doubled with current use of low dose aspirin compared with current use of VKAs (HR 2.18; 95% CI 1.72–2.39). A higher risk was also found for past use of low dose aspirin compared with current use of VKA (HR 1.65; 95% CI 1.38–1.97).

Results stratified by sex (Table 4) showed that the risk of major bleed in NOAC users was elevated in women (HR 3.14, 95% CI 1.76–5.60) but not in men (HR 0.94, 95% CI 0.34–2.59). Table 5 shows the results stratified by CHA_2DS_2-VASc risk score. Current NOAC users with a high stroke risk (CHA_2DS_2-VASc >3) had a higher risk of major bleeding compared with current VKA users with a high stroke risk (HR 2.62, 95% CI 1.41–4.87). Across all risk categories, current low dose aspirin use showed an increased risk for ischaemic stroke compared with current VKA use.

Discussion

This study showed a tw2o-fold increase in the risk of major bleeding with current NOAC use compared with current VKA use. This was largely explained by the increase in gastrointestinal bleeding risk; there was no difference in intracranial haemorrhage risk. The increased risk of gastrointestinal bleeding diminished after NOAC discontinuation, as expected. NOACs were equally effective as VKA in the prevention of ischaemic stroke, whereas aspirin was less effective. Our results further suggest that the increased risk for bleeding for NOAC users was restricted to women.

Our main finding of an increased risk of major bleed is not in line with a large meta-analysis from four phase III randomized trials of four different NOACs (dabigatran, rivaroxaban, apixaban, edoxaban) [10]. This study showed that the risk of major bleeding was lower compared with warfarin. A 52% decreased risk for intracranial haemorrhage was found with the usage of NOACs compared with warfarin, although the risk of gastrointestinal bleeding was found to be increased with 25%, which is in line with the results from the current study. Patients who were prone to bleeding were excluded from the clinical trials. Although we have excluded patients with a history of a major bleeding event, we did not exclude patients with other comorbidities (e.g. renal failure, malignancies, gastritis) or concomitant medication (NSAIDs, SSRIs) that increases the risk of bleeding, which might have selected patients with a different baseline risk. In contrast to the trials, we excluded patients with prior events of interest and therefore our results are not directly comparable with the results from the trials.

Table 2

Risk of bleeding outcomes in NOAC, aspirin, and mixed users compared with VKA users

Outcome	Number of events	Incidence rate per 1000 person-years	Age/sex adjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Major bleeding				
Current (≤30 days before index date)				
VKA only use	167	5.78	Reference	Reference
NOAC only use	19	10.63	2.07 (1.27–3.38)	2.08 (1.28–3.40)
Aspirin only use	140	7.51	1.05 (0.84–1.32)	1.05 (0.84–1.32)
Mixed use	9	8.16	1.37 (0.70–2.68)	1.37 (0.70–2.68)
Past (>30 days before index date)				
VKA use	123	6.47	1.23 (0.98–1.54)	1.23 (0.98–1.54)
NOAC use	<5	**	1.13 (0.42–3.06)	1.13 (0.42–3.05)
Aspirin use	130	5.91	0.93 (0.74–1.16)	0.94 (0.75–1.17)
GI bleeding				
Current (≤30 days before index date)				
VKA only use	107	3.68	Reference	Reference
NOAC only use	15	7.73	2.63 (1.50–4.62)	2.63 (1.50–4.60)
Aspirin only use	103	5.29	1.18 (0.89–1.55)	1.17 (0.89–1.54)
Mixed use	7	6.31	1.67 (0.77–3.59)	1.63 (0.76–3.50)
Past (>30 days before index date)				
VKA use	73	3.61	1.11 (0.83–1.48)	1.11 (0.83–1.48)
NOAC use	<5	**	0.91 (0.22–3.71)	0.90 (0.22–3.67)
Aspirin use	85	3.65	1.00 (0.76–1.33)	1.01 (0.77–1.34)
Intracranial bleeding				
Current (≤30 days before index date)				
VKA only use	62	2.09	Reference	Reference
NOAC only use	5	2.53	1.39 (0.55–3.53)	1.42 (0.56–3.61)
Aspirin only use	38	1.91	0.80 (0.53–1.20)	0.80 (0.53–1.20)
Mixed use	<5	***	0.85 (0.21–3.47)	0.87 (0.21–3.56)
Past (>30 days before index date)				
VKA use	53	2.56	1.41 (0.99–2.00)	1.41 (0.99–2.00)
NOAC use	<5	***	1.37 (0.33–5.62)	1.37 (0.33–5.64)
Aspirin use	50	2.10	0.87 (0.61–1.24)	0.87 (0.61–1.24)

CI, confidence interval; GI, gastrointestinal; VKA, vitamin K antagonist; NOAC, non-vitamin K antagonist oral anticoagulant; ATII, angiotensin II; NSAID, nonsteroidal anti-inflammatory drug; H2, histamine 2; PPI, proton pump inhibitor; SSRI, selective serotonin receptor inhibitor.
*Adjusted for age, sex, body mass index, alcohol status, smoking status, anticoagulants, antiplatelets, cerebrovascular disease, PPIs.
**Suppressed due to fewer than five patients (ISAC regulations).

Several observational studies have been carried out that assessed the bleeding risk of NOACs compared with warfarin. A study using US Medicare data compared dabigatran with warfarin and found results that were partially in line with our findings. In this study, an increase in gastrointestinal bleeding was found as well (HR 1.28, 95% CI 1.14–1.44), but a decrease in intracranial bleeding (HR 0.34, 95% CI 0.26–0.46) was shown [16]. No difference for gastrointestinal bleeding was found in a study using Optum Labs Data Warehouse data (a different claims database) in the USA [14]. Similar to the current study, the two observational studies mentioned above used a new user design. By excluding all previous users, the effects of switching and long-term use are reduced. However, in this study we not only identified new users of NOACs and VKAs, but additionally we excluded patients who had used aspirin before. Also the in- or exclusion of prior events of the outcome might be a reason for differences in bleeding risks.

Table 3

Risk of stroke outcomes in NOAC, aspirin and mixed users compared with VKA users

Outcome	Number of events	Incidence rate per 1000 person-years	Age/sex adjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Stroke				
Current (≤30 days before index date)				
VKA only use	181	6.72	Reference	Reference
NOAC only use	15	8.81	1.37 (0.81–2.33)	1.38 (0.81–2.35)
Aspirin only use	342	17.85	1.99 (1.69–2.36)	2.03 (1.72–2.39)
Mixed use	16	15.62	1.98 (1.19–3.29)	2.04 (1.23–3.39)
Past (>30 days)				
VKA use	195	10.15	1.11 (0.93–1.32)	1.10 (0.92–1.31)
NOAC use	8	10.36	1.37 (0.68–2.78)	1.37 (0.68–2.78)
Aspirin use	276	12.19	1.53 (1.29–1.81)	1.54 (1.30–1.82)
Haemorrhagic stroke				
Current (≤30 days before index date)				
VKA only use	57	1.92	Reference	Reference
NOAC only use	5	2.53	1.54 (0.60–3.93)	1.56 (0.61–3.99)
Aspirin only use	38	1.91	0.87 (0.58–1.31)	0.87 (0.58–1.31)
Mixed use	<5	**	0.94 (0.23–3.84)	0.95 (0.23–3.89)
Past (>30 days before index date)				
VKA use	49	2.37	1.37 (0.95–1.97)	1.37 (0.95–1.97)
NOAC use	<5	**	1.50 (0.36–6.18)	1.50 (0.36–6.18)
Aspirin use	47	1.97	0.89 (0.62–1.30)	0.89 (0.62–1.29)
Ischaemic stroke				
Current (≤30 days before index date)				
VKA only use	156	5.76	Reference	Reference
NOAC only use	12	7.00	1.20 (0.67–2.17)	1.22 (0.67–2.19)
Aspirin only use	327	16.95	2.13 (1.79–2.54)	2.18 (1.83–2.59)
Mixed use	15	14.58	2.09 (1.24–3.53)	2.16 (1.28–3.64)
Past (>30 days befor index date)				
VKA use	170	8.79	1.04 (0.86–1.26)	1.03 (0.86–1.25)
NOAC use	6	7.68	1.10 (0.49–2.49)	1.10 (0.49–2.48)
Aspirin use	256	11.22	1.63 (1.37–1.95)	1.65 (1.38–1.97)

CI, confidence interval VKA, vitamin K antagonist; NOAC, nonvitamin K antagonist oral anticoagulant; ACE, angiotensin converting enzyme; ATII, angiotensin II; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors. *Adjusted for age, sex, body mass index, alcohol status, smoking status, antidiabetics, ACE-inhibitors, antiplatelets, ATII antagonists, calcium channel blockers, cerebrovascular disease, hypertension, peripheral artery disease, statins.

**Suppressed due to fewer than five patients (ISAC regulations).

The results on major bleeding may strongly depend on the definition of this outcome, and this may explain some of the discrepancies in the current body of literature on this outcome. The most common definition of major bleeding is that of the International Society of Thrombosis and Haemostasis including bleeding at critical sites, need for transfusion of more than two units of blood and a fall in haemoglobin level of >20 g l^{-1} [24]. This definition, or a derivate of this definition, is used in the different trials comparing VKAs and NOACs [25–27]. In the current study, we used the Read coding system as opposed to the other observational studies that use ICD-9-CM (international classification of diseases, 9th revision, clinical modification) codes [14, 16], which might explain variation in results.

This study underlines that NOACs are equally effective in reducing ischaemic stroke as VKAs as is found in meta-

Table 4

Risk of major bleeding and ischaemic stroke in current NOAC and aspirin users compared with current VKA users stratified by sex

Exposure	Major bleeding			Stroke		
	Number of events	Incidence rate per 1000 person years	Adjusted HR (95% CI)*	Number of events	Incidence rate per 1000 person years	Adjusted HR (95% CI)**
Women						
Current (≤30 days before index date)						
VKA only use	82	6.08	Reference	87	6.94	Reference
NOAC only use	15	16.32	3.14 (1.76–5.60)	8	10.04	1.40 (0.77–2.56)
Aspirin only use	76	7.64	1.02 (0.74–1.40)	197	20.01	1.74 (1.42–2.14)
Mixed use	<5	***	1.14 (0.36–3.61)	11	28.16	2.38 (1.29–4.38)
Males						
Current (≤30 days before index date)						
VKA only use	85	5.54	Reference	94	6.52	Reference
NOAC only use	<5	***	0.94 (0.34–2.59)	7	7.73	1.45 (0.75–2.78)
Aspirin only use	64	6.89	1.08 (0.78–1.49)	145	15.57	1.91 (1.53–2.38)
Mixed use	6	8.84	1.52 (0.66–3.48)	5	7.89	1.00 (0.44–2.26)

CI, confidence interval VKA, vitamin K antagonist; NOAC, nonvitamin K antagonist oral anticoagulant; PPIs, proton pump inhibitors; ATII, angiotensin II ; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.
*Adjusted for age, sex, body mass index, alcohol status, smoking status, anticoagulants, antiplatelets, cerebrovascular disease, PPIs
**Adjusted for age, sex, body mass index, alcohol status, smoking status, antidiabetics ACE-inhibitors, antiplatelets, ATII antagonists, calcium channel blockers, cerebrovascular disease, hypertension, peripheral artery disease, statins.
***Suppressed due to <5 patients (ISAC regulations).

analyses of RCTs [10, 28]. Similar results were found in a study undertaken in new users of warfarin from the Danish registry [13]. The >2-fold increased risk of ischaemic stroke with aspirin use is in line with a Cochrane review that shows less frequent ischaemic stroke for oral anticoagulants (all VKAs) when compared with antiplatelet therapy in patients with nonvalvular AF without a history of stroke and transient ischaemic attack [29].

The higher risk of gastrointestinal bleeding might be explained by the pharmacokinetic in the case of dabigatran. Dabigatran exilate is a prodrug that is hydrolysed to the active drug by esterase. This leads to progressively high concentrations of the active drug during transit in the gastrointestinal tract. This local effect might aggravate bleeding in (pre-)existing diseased mucosa [28]. However, this explanation is not applicable for rivaroxaban, which accounts for most prescriptions in the NOAC group for this study.

The study by Graham *et al.* [16] identified a trend for a higher risk of gastrointestinal bleeding with dabigatran compared with warfarin in women aged 75–84 years and ≥85 years. This is confirmed in our study where we also found an increased risk in major bleed for women, but not in men. These results are not in line with the differences found for sex in RCTs [10, 30]. It has been shown that dabigatran concentrations were dependent on several demographic characteristics including, among others, female sex [31]. In women, concentrations of dabigatran were 30% higher compared with men and higher plasma concentrations were found to be related with a higher probability of major bleed. Further study should give more insight about the difference in benefit risk balance of antithrombotic agents for men and women.

In addition to those already identified, this study has several limitations. Benefit risk balance might be different for dabigatran and rivaroxaban and also across different dosages. This study lacked power to compare different NOACs or different dosages. Although we have adjusted the results for various risk factors, there might still be (unobserved) confounding. Despite the fact that the UK guidelines do not give a preference for either starting a NOAC or a VKA, we expect that these agents are prescribed to a selected group of people, which complicates comparison. Some misclassification of exposure might occur. If a patient starts a NOAC at day 1 of a specific month, it will take 29 days until this patient is classified as exposed in the next period. If they suffer a bleed on day 15, this will be wrongly attributed to nonexposure.

Despite the limitations, this study has several strengths, including inclusion of a diverse real-world population. We included all antithrombotic therapies used for AF in our investigation to provide a complete overview of efficacy and safety of these therapies. We have classified exposure in a time-dependent manner as well as confounders to minimize misclassification.

This study adds to the information that is already available on real life use of the different antithrombotic agents. The usage of NOACs poses a greater risk on major bleeding, especially on gastrointestinal bleeding, compared with the usage of VKAs. The use of NOACs in patients who are

Table 5

Risk of major bleeding and ischaemic stroke in current NOAC and aspirin users compared with current VKA users stratified by CHA_2DS_2-VASC-score

	Major bleeding			Stroke		
Exposure	**Number of events**	**Incidence rate per 1000 person-years**	**Adjusted HR (95% CI)***	**Number of events**	**Incidence rate per 1000 person-years**	**Adjusted HR (95% CI)****
High CHA_2DS_2-VASC (>3)						
Current (≤30 days before index date)						
VKA only use	71	8.98	Reference	69	9.96	Reference
NOAC only use	13	24.10	2.62 (1.41–4.87)	9	21.22	1.86 (0.93–3.76)
Aspirin only use	58	10.87	0.96 (0.67–1.38)	132	25.88	1.79 (1.36–2.35)
Mixed use	<5	***	1.01 (0.32–3.23)	7	26.47	2.16 (1.00–4.66)
Medium CHA_2DS_2-VASC (2–3)						
Current (≤30 days before index date)						
VKA only use	75	5.34	Reference	82	6.16	Reference
NOAC only use	6	6.82	1.75 (0.75–4.09)	5	6.04	1.19 (0.48–2.95)
Aspirin only use	68	7.79	1.26 (0.90–1.75)	162	18.35	2.29 (1.78–2.93)
Mixed use	5	9.21	1.71 (0.69–4.23)	8	15.91	2.34 (1.14–4.81)
Low CHA_2DS_2-VASC (0–1)						
Current (≤30 days before index date)						
VKA only use	21	3.05	Reference	30	4.48	Reference
NOAC only use	0	0.00	-	<5	***	0.47 (0.06–3.42)
Aspirin only use	14	2.71	0.90 (0.46–1.77)	48	9.18	2.02 (1.34–3.07)
Mixed use	<5	***	1.02 (0.14–7.62)	<5	***	0.74 (0.10–5.37)

Abbreviations: CI, confidence interval VKA, vitamin K antagonist; NOAC, nonvitamin K antagonist oral anticoagulant; PPIs, proton pump inhibitors; ATII, angiotensin II inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.
NB: 0 counts for current NOAC users in the Low CHA_2DS_2-VASC stratum for the major bleed outcome. Current NOAC not included in this model.
*Adjusted for age, sex, body mass index, alcohol status, smoking status, anticoagulants, antiplatelets, cerebrovascular disease, PPIs
**Adjusted for age, sex, body mass index, alcohol status, smoking status, antidiabetics ACE-inhibitors, antiplatelets, ATII antagonists, calcium channel blockers, cerebrovascular disease, hypertension, peripheral artery disease, statin.
***Supressed due to <5 patients (ISAC regulations).

vulnerable for this type of bleeding should be carefully considered. Next to that, women might have a greater risk for bleeding events, which makes this group less suitable for the treatment with NOACs. Further studies should be performed that are designed to study effectiveness and safety in subgroups.

Competing Interests

The Division of Pharmacoepidemiology & Clinical Pharmacology employing authors Frank de Vries, Anthonius de Boer, Tjeerd van Staa, Hendrika van den Ham and Andrea Burden has received unrestricted funding from the Netherlands Organization for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), the Royal Dutch Pharmacists Association (KNMP), the private-public funded Top Institute Pharma (www.tipharma.nl), includes cofunding from universities, government, and industry), the EU Innovative Medicines Initiative (IMI), the EU 7th Framework Program (FP7), the Dutch Ministry of Health and industry (including GlaxoSmithKline, Pfizer, and others). Andrea Burden is supported by a Canadian Institutes of Health Research (CIHR) Post Doctoral Fellowship.

Author contributions

E.G., H.H., H.O., J.B., C.K., A.B., F.V. and A.B. conceived and designed the study. E.G., H.H. and A.B. collected the data, carried out the statistical analysis and drafted the manuscript. All authors analysed and interpreted the data and critically revised the manuscript for important intellectual content.

Appendix 1

Read codes for major bleed

Read code	Medical code	Clinical event	Read term
J680.00	1188	Bleeding	Haematemesis
J681.00	397	Bleeding	Melaena
J68z.11	1642	Bleeding	Gastrointestinal bleeding
J68.00	3097	Bleeding	Gastrointestinal haemorrhage
J680.11	2712	Bleeding	Vomiting of blood
J68z200	4354	Bleeding	Upper gastrointestinal haemorrhage
G850.00	24 989	Bleeding	Oesophageal varices with bleeding
J12y100	2814	Bleeding	Unspecified duodenal ulcer with haemorrhage
J68zz00	4636	Bleeding	Gastrointestinal tract haemorrhage NOS
J68z000	15 517	Bleeding	Gastric haemorrhage NOS
J120100	18 001	Bleeding	Acute duodenal ulcer with haemorrhage
J68z.00	12 471	Bleeding	Gastrointestinal haemorrhage unspecified
J68z100	2150	Bleeding	Intestinal haemorrhage NOS
J121111	18 625	Bleeding	Bleeding chronic duodenal ulcer
19E4.12	18 313	Bleeding	Complains of melaena
J110111	11 124	Bleeding	Bleeding acute gastric ulcer
1994.00	44 489	Bleeding	Vomiting blood – fresh
J110100	30 054	Bleeding	Acute gastric ulcer with haemorrhage
J121100	48 951	Bleeding	Chronic duodenal ulcer with haemorrhage
J10y000	16 114	Bleeding	Haemorrhage of oesophagus
4737.11	37 299	Bleeding	Melaena – on examination of faeces
J130100	44 637	Bleeding	Acute peptic ulcer with haemorrhage
J111100	63 582	Bleeding	Chronic gastric ulcer with haemorrhage
J111111	36 583	Bleeding	Bleeding chronic gastric ulcer
J11y100	57 958	Bleeding	Unspecified gastric ulcer with haemorrhage
J120300	48 730	Bleeding	Acute duodenal ulcer with haemorrhage and perforation
J131100	53 126	Bleeding	Chronic peptic ulcer with haemorrhage
J11yy00	94 397	Bleeding	Unspecified gastric ulcer; unspecified haemorrhage and/or perforation
J13y100	70 456	Bleeding	Unspecified peptic ulcer with haemorrhage
J110300	71 403	Bleeding	Acute gastric ulcer with haemorrhage and perforation
J111300	71 897	Bleeding	Chronic gastric ulcer with haemorrhage and perforation
J121300	71 881	Bleeding	Chronic duodenal ulcer with haemorrhage and perforation
J140100	96 628	Bleeding	Acute gastrojejunal ulcer with haemorrhage
J12y300	93 436	Bleeding	Unspecified duodenal ulcer with haemorrhage and perforation
J13y300	96 622	Bleeding	Unspecified peptic ulcer with haemorrhage and perforation
J140300	106 330	Bleeding	Acute gastrojejunal ulcer with haemorrhage and perforation
G60.00	1786	Bleeding	Subarachnoid haemorrhage
G61.00	5051	Bleeding	Intracerebral haemorrhage
G61.11	6960	Bleeding	Cerebrovascular accident due to intracerebral haemorrhage

(*continues*)

Appendix 1

(Continued)

G622.00	17 734	Bleeding	Subdural haematoma - nontraumatic
G623.00	18 912	Bleeding	Subdural haemorrhage NOS
G621.00	4273	Bleeding	Subdural haemorrhage - nontraumatic
G61z.00	3535	Bleeding	Intracerebral haemorrhage NOS
G61.12	18 604	Bleeding	Stroke due to intracerebral haemorrhage
G613.00	13 564	Bleeding	Cerebellar haemorrhage
S62.13	6569	Bleeding	Subdural haemorrhage following injury
S62A.00	18 411	Bleeding	Traumatic extradural haematoma
S622.00	2883	Bleeding	Closed traumatic subdural haemorrhage
G60z.00	23 580	Bleeding	Subarachnoid haemorrhage NOS
G617.00	30 202	Bleeding	Intracerebral haemorrhage, intraventricular
S62.00	5682	Bleeding	Cerebral haemorrhage following injury
G62z.00	20 284	Bleeding	Intracranial haemorrhage NOS
S62.11	27 661	Bleeding	Extradural haemorrhage following injury
G602.00	19 412	Bleeding	Subarachnoid haemorrhage from middle cerebral artery
G614.00	7912	Bleeding	Pontine haemorrhage
G61X000	28 314	Bleeding	Left sided intracerebral haemorrhage, unspecified
G611.00	40 338	Bleeding	Internal capsule haemorrhage
G60X.00	17 326	Bleeding	Subarachnoid haemorrhage from intracranial artery, unspecified
G620.00	36 178	Bleeding	Extradural haemorrhage - nontraumatic
G61X100	19 201	Bleeding	Right sided intracerebral haemorrhage, unspecified
G62.00	31 805	Bleeding	Other and unspecified intracranial haemorrhage
G603.00	42 331	Bleeding	Subarachnoid haemorrhage from anterior communicating artery
S62.12	28 807	Bleeding	Subarachnoid haemorrhage following injury
G610.00	31 595	Bleeding	Cortical haemorrhage
G612.00	46 316	Bleeding	Basal nucleus haemorrhage
S630.12	35 867	Bleeding	Intracranial haematoma following injury
G61X.00	31 060	Bleeding	Intracerebral haemorrhage in hemisphere, unspecified
S628.00	8181	Bleeding	Traumatic subdural haemorrhage
G604.00	9696	Bleeding	Subarachnoid haemorrhage from posterior communicating artery
G605.00	41 910	Bleeding	Subarachnoid haemorrhage from basilar artery
S62z.00	46 545	Bleeding	Cerebral haemorrhage following injury NOS
S62.14	28 077	Bleeding	Traumatic cerebral haemorrhage
S620.00	38 304	Bleeding	Closed traumatic subarachnoid haemorrhage
S624.00	45 421	Bleeding	Closed traumatic extradural haemorrhage
S627.00	58 545	Bleeding	Traumatic subarachnoid haemorrhage
G616.00	30 045	Bleeding	External capsule haemorrhage
G618.00	57 315	Bleeding	Intracerebral haemorrhage, multiple localized
Gyu6200	53 810	Bleeding	Other intracerebral haemorrhage
S629000	53 980	Bleeding	Traumatic subdural haematoma without open intracranial wound

(*continues*)

Appendix 1

(Continued)

G615.00	62 342	Bleeding	Bulbar haemorrhage
Gyu6100	65 745	Bleeding	Other subarachnoid haemorrhage
G606.00	60 692	Bleeding	Subarachnoid haemorrhage from vertebral artery
S625.00	73 471	Bleeding	Open traumatic extradural haemorrhage
S63z.00	42 283	Bleeding	Other cerebral haemorrhage following injury NOS
S629100	96 677	Bleeding	Traumatic subdural haematoma with open intracranial wound

Appendix 2

Baseline characteristics for users of NOACs, VKAs or aspirin at index date for the cohort with history of major bleed excluded and cohort with history of stroke excluded

Characteristic	Cohort outcome bleed				Cohort outcome stroke			
	NOAC-users (*n* = 1247)	VKA-users (*n* = 13 177)	Aspirin-users (*n* = 15 551)	Mixed-users (*n* = 443)	NOAC (*n* = 1128)	VKA (*n* = 12 445)	Aspirin (*n* = 15 471)	Mixed use (*n* = 402)
Follow-up (years, SD)	1.0 (0.6)	2.7 (1.9)	2.9 (1.9)	2.9 (2.0)	0.9 (0.6)	2.7 (1.9)	2.9 (1.9)	3.0 (2.0)
Number of women	566 (45.4%)	6073 (46.1%)	7753 (49.9%)	159 (35.9%)	501 (44.4%)	5683 (45.7%)	7665 (49.5%)	142 (35.3%)
Age								
Mean age at index date (years, SD)	72.4 (12.6)	71.9 (11.9)	73.5 (12.7)	72.2 (10.6)	72.0 (12.8)	71.7 (12.0)	73.4 (12.7)	71.8 (10.5)
18–49 years	59 (4.7%)	663 (5.0%)	654 (4.21%)	13 (2.9%)	54 (4.8%)	651 (5.2%)	661 (4.3%)	13 (3.2%)
50–59 years	155 (12.4%)	1263 (9.6%)	1421 (9.14%)	37 (8.4%)	148 (13.1%)	1231 (9.9%)	1428 (9.2%)	35 (8.7%)
60–69 years	252 (20.2%)	22 943 (22.3)	359 (23.1%)	117 (26.4%)	237 (21.0%)	2788 (22.4%)	3589 (23.2)%	110 (27.4%)
70–79 years	401 (32.2%)	4498 (34.1%)	4259 (27.4%)	160 (36.1%)	350 (31.0%)	4221 (33.9%)	4238 (27.4%)	143 (35.6%)
80+ years	380 (30.5%)	3810 (28.9%)	5627 (36.2%)	116 (26.2%)	339 (30.1%)	3554 (28.6%)	5555 (35.9%)	101 (25.1%)
BMI								
Mean BMI at index date (SD)	28.0 (6.2)	28.7 (6.3)	27.8 (6.2)	28.9 (6.5)	28.0 (6.2)	28.8 (6.4)	27.8 (6.2)	29.0 (6.6)
< 20 kg m^{-2}	77 (6.2%)	522 (4.0%)	925 (5.95%)	20 (4.5%)	70 (6.2%)	482 (3.9%)	926 (6.0%)	17 (4.2%)
20–25 kg m^{-2}	312 (25.0%)	3056 (23.2%)	3984 (25.6%)	94 (21.2%)	285 (25.3%)	2886 (23.2%)	3955 (25.6%)	83 (20.7%)
25–30 kg m^{-2}	403 (32.3%)	4468 (33.9%)	5149 (33.1%)	151 (34.1%)	364 (32.3%)	4200 (33.8%)	5134 (33.2%)	138 (34.3%)
30–35 kg m^{-2}	243 (19.5%)	2570 (19.5%)	2668 (17.2%)	90 (20.3%)	217 (19.2%)	2463 (19.8%)	2664 (17.2%)	81 (20.2%)
>35 kg m^{-2}	136 (10.9%)	1747 (13.3%)	1617 (10.4%)	59 (13.3%)	129 (11.4%)	1680 (13.5%)	1619 (10.5%)	56 (13.9%)
Missing	76 (6.1%)	814 (6.2%)	1208 (7.8%)	29 (6.5%)	63 (5.6%)	734 (5.9%)	1173 (7.58%)	27 (6.7%)
Smoking status								
Never	545 (43.7%)	5483 (41.6%)	6856 (44.1%)	168 (37.9%)	493 (43.7%)	5160 (41.5%)	6797 (43.9%)	154 (38.3%)
Current	97 (7.8%)	1191 (9.0%)	1493 (9.6%)	51 (11.5%)	93 (8.2%)	1124 (9.0%)	1495 (9.7%)	44 (11.0%)
Ex	598 (48.0%)	6440 (48.9%)	7126 (45.8%)	222 (50.1%)	537 (47.6%)	6106 (49.1%)	7105 (45.9%)	202 (50.3%)
Missing	7 (0.6%)	63 (0.5%)	76 (0.5%)	<5	5 (0.4%)	55 (0.4%)	74 (0.5%)	<5
Alcohol								
Yes	869 (69.7%)	9196 (69.8%)	10 650 (68.5%)	305 (68.8%)	795 (70.5%)	8755 (70.4%)	10 628 (68.7%)	277 (68.9%)
No	269 (21.6)	3034 (23.0%)	3646 (23.4%)	100 (22.6%)	240 (21.3%)	2835 (22.8%)	3612 (23.4%)	89 (22.1%)
Missing	109 (8.7%)	947 (7.2%)	1255 (8.1%)	38 (8.6%)	93 (8.2%)	855 (6.9%)	1231 (8.0%)	36 (9.0%)

(*continues*)

Appendix 2

(Continued)

Characteristic	Cohort outcome bleed				Cohort outcome stroke			
	NOAC-users (*n* = 1247)	VKA-users (*n* = 13 177)	Aspirin-users (*n* = 15 551)	Mixed-users (*n* = 443)	NOAC (*n* = 1128)	VKA (*n* = 12 445)	Aspirin (*n* = 15 471)	Mixed use (*n* = 402)
CHA_2DS_2-VASc score								
Mean (SD)	2.6 (1.5)	2.6 (1.5)	2.5 (1.5)	2.6 (1.4)	2.4 (1.5%)	2.5 (1.5%)	2.5 (1.4%)	2.5 (1.4%)
Low	564 (45.2%)	6029 (45.8%)	7062 (45.4%)	219 (49.4%)	525 (46.5%)	5790 (46.5%)	7135 (46.1%)	205 (51.0%)
Medium	319 (25.6%)	3294 (25.0%)	4312 (27.7%)	101 (22.8%)	310 (27.5%)	3260 (26.2%)	4341 (28.1%)	97 (24.1%)
High	364 (29.2%)	3854 (29.2%)	4177 (26.9%)	123 (27.8%)	293 (26.0%)	3395 (27.3%)	3995 (25.8%)	100 (24.9%)
History of disease ever before								
Acute renal failure	7 (0.6%)	60 (0.5%)	110 (0.7%)	<5	5 (0.4%)	58 (0.5%)	114 (0.7%)	<5
Cerebrovascular disease	215 (17.2%)	1665 (12.6%)	814 (5.2%)	69 (15.6%)	69 (6.1%)	624 (5.0%)	365 (2.4%)	21 (5.2%)
Chronic renal failure	6 (0.5%)	150 (1.1%)	150 (1.0%)	<5	6 (0.5%)	134 (1.0%)	147 (1.0%)	<5
Congestive heart failure	90 (7.2%)	1333 (10.1%)	906 (5.8%)	66 (14.9%)	84 (7.5%)	1297 (10.4%)	890 (5.8%)	63 (15.7%)
Gastritis	74 (5.9%)	768 (5.8%)	866 (5.6%)	16 (3.6%)	67 (5.9%)	780 (6.3%)	892 (5.8%)	17 (4.2%)
GI-bleed	<5	<5	<5	<5	32 (2.8%)	328 (2.6%)	380 (2.5%)	6 (1.5%)
Hypertension	675 (54.1%)	7027 (53.3%)	7718 (49.6%)	227 (5.2%)	604 (53.6%)	6600 (53.0%)	7642 (49.4%)	205 (51.0%)
Liver disease	2 (0.2%)	15 (0.1%)	29 (0.2%)	1 (0.2%)	2 (0.2%)	14 (0.1%)	34 (0.2%)	0 (0.0%)
Cancer	11 (0.9%)	120 (0.9%)	114 (0.7%)	4 (0.9%)	15 (1.3%)	118 (1.0%)	118 (0.8%)	4 (1.0%)
Peripheral artery disease	64 (5.1%)	660 (5.0%)	612 (3.9%)	26 (5.9%)	61 (5.4%)	623 (5.0%)	613 (4.0%)	24 (6.0%)
Ischaemic heart disease	103 (8.3%)	1343 (10.2%)	1398 (9.0%)	111 (25.1%)	87 (7.7%)	1255 (10.1%)	1374 (8.9%)	105 (26.1%)
History of medication use (< 6 months before index date)								
Antiarrhythmic drugs	78 (6.3%)	866 (6.6%)	664 (4.3%)	13 (2.9%)	75 (6.7%)	845 (6.8%)	655 (4.2%)	12 (3.0%)
Anticoagulant drugs	16 (1.3%)	202 (1.5%)	63 (0.4%)	<5	16 (1.2%)	202 (1.5%)	63 (0.4%)	<5
Antidiabetic drugs	93 (7.5%)	1000 (7.6%)	876 (5.6%)	36 (8.1%)	82 (7.3%)	952 (7.7%)	852 (5.5%)	32 (8.0%)
Antihypertensive drugs	329 (26.3%)	3690 (28.0%)	3411 (21.9%)	102 (23.0%)	292 (25.9%)	3480 (28.0%)	3416 (22.1%)	98 (24.4%)
Antiplatelet drugs	9 (0.7%)	190 (1.4%)	90 (0.6%)	<5	4 (0.4%)	125 (1.0%)	63 (0.4%)	<5
Insulin	17 (1.4%)	203 (1.5%)	160 (1.0%)	10 (2.3%)	15 (1.3%)	187 (1.5%)	156 (1.0%)	9 (2.2%)
NSAID's	140 (11/2%)	1556 (11.8%)	2066 (13.3%)	60 (13.5%)	123 (10.9%)	1505 (12.1%)	2067 (13.4%)	55 (13.7%)
SSRI's	90 (7.2%)	761 (5.8%)	1018 (6.5%)	17 (3.8%)	80 (7.1%)	704 (5.7%)	1005 (6.5%)	15 (3.7%)
Statins	371 (29.8%)	3878 (29.4%)	3229 (20.8%)	110 (24.8%)	301 (26.7%)	3443 (27.7%)	3152 (20.4%)	100 (24.9%)
Glucocorticoids	121 (9.7%)	1297 (9.8%)	1226 (7.9%)	32 (7.2%)	118 (10.5%)	1245 (10.0%)	1235 (8.0%)	29 (7.2%)
History of medication use (<3 months before index date)								
H2 receptor-antagonists	30 (2.4%)	291 (2.2%)	291 (1.9%)	11 (2.5%)	22 (2.0%)	289 (2.3%)	282 (1.8%)	12 (3.0%)
PPI's	329 (26.4%)	3118 (23.7%)	3327 (21.4%)	81 (18.3%)	305 (27.0%)	3049 (24.5%)	3401 (22.0%)	75 (18.7%)

NOAC, nonvitamin K antagonist oral anticoagulant; VKA, vitamin K antagonist; SD, standard deviation; BMI, body mass index; NSAIDs, non-steroidal anti-inflammatory drugs; SSRI's, selective serotonin reuptake inhibitors; H2, histamine 2; PPI's, proton pump inhibitors, GI, gastrointestinal.

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