PHARMACOEPIDEMIOLOGY

Risk of myocardial infarction in patients with atrial fibrillation using vitamin K antagonists, aspirin or direct acting oral anticoagulants

Leo M. Stolk[1], Frank de Vries[1,2,3], Chiel Ebbelaar[3], Anthonius de Boer[3], Tom Schalekamp[3], Patrick Souverein[3], Arina ten Cate-Hoek[4] and Andrea M. Burden[1,3]

[1]Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre, Maastricht, the Netherlands, [2]MRC Life-course Epidemiology Unit, University of Southampton, Southampton, UK, [3]Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, the Netherlands, and [4]Department Internal Medicine, Maastricht University Medical Centre, Maastricht, the Netherlands

AIM

Direct-acting oral anticoagulants (DOACs) have become available for the prevention of stroke in patients with atrial fibrillation (AF). Conflicting results have been published on the risk of acute myocardial infarction (AMI) with the use of DOACs in comparison with vitamin K antagonists (VKAs). The objective of the present study was to evaluate the risk of AMI in patients with AF who are exposed to either VKAs, DOACs or low-dose ($<$ 325 mg) aspirin.

METHODS

We conducted a population-based cohort study using data from the Clinical Practice Research Datalink (2008–2014). The study population ($n = 30\,146$) consisted of all patients ≥18 years with a diagnosis of AF who were new users of VKAs, DOACs (rivaroxaban and dabigatran) or aspirin. Cox proportional hazards models were used to estimate the hazard ratio (HR) of AMI for users of DOACs or aspirin *vs.* VKA. Adjustments were made for age, gender, lifestyle, risk factors, comorbidity and other drugs.

RESULTS

The risk of AMI was doubled when we compared current use of DOACs with current use of VKAs [adjusted HR 2.11; 95% confidence interval (CI) 1.08, 4.12] and for current users of aspirin *vs.* current VKA users (adjusted HR 1.91; 95% CI 1.45, 2.51).

CONCLUSIONS

There is a twofold increase in the risk of AMI for users of DOACs, in comparison with VKAs, in AF therapy. In addition, the results suggested that in patients with AF, the incidence of AMI is higher during aspirin monotherapy than during the use of VKAs.

BJCP

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
- Direct-acting oral anticoagulants (DOACs) have become available for the prevention of stroke in patients with atrial fibrillation (AF).
- Conflicting results have been published on the risk of acute myocardial infarction (AMI) with the use of DOACs, especially with the IIa inhibitor dabigatran, in comparison with vitamin K antagonists (VKAs).

WHAT THIS STUDY ADDS
- This retrospective cohort study is the first to compare the risk of AMI with use of DOACs with that associated with VKA use.
- A twofold increase in the risk of AMI was found with use of the DOACs dabigatran and rivaroxaban, in comparison with the VKAs, in AF therapy.

Table of Links

LIGANDS	
Apixaban	Edoxaban
Dabigatran	Rivaroxaban

This Table lists key 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].

Introduction

Oral anticoagulant treatment with vitamin K antagonists (VKAs) has been the cornerstone for the prevention of stroke in patients with atrial fibrillation (AF) for decades. Since 2009, several new direct-acting oral anticoagulants (DOACs) have become available: a IIa inhibitor (dabigatran) and three Xa inhibitors (rivaroxaban, apixaban and edoxaban).

Large clinical trials [2–5] and meta-analyses [6–8] have shown that these agents are either non-inferior or, for some outcomes, possibly superior to warfarin in the prevention of stroke and thromboembolic events in patients with AF.

There has been much debate about the effect of DOACs on acute myocardial infarction (AMI) among patients with AF. The risk of AMI was significantly increased among dabigatran users in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial [2]. However, *post hoc* analysis of revised data from the RE-LY trial did not confirm this finding [9]. Moreover, two meta-analyses of randomized non-inferiority trials concluded that the use of dabigatran [10] or DOACs [11] was associated with an increased risk of AMI, while other meta-analyses have not identified an increased risk for dabigatran [12] or DOACs [6, 13]. Recently, an increased risk of AMI in AF patients treated with the anti-IIa DOAC, and not in patients treated with anti-Xa DOACs, was reported in a meta-analysis [14]. In a recent network meta-analysis, the odds found for AMI were worse with dabigatran when compared with VKA, rivaroxaban, apixaban and edoxaban [15].

Several observational cohort studies have compared the risk of AMI associated with use of the IIa inhibitor dabigatran with that associated with use of VKAs but the results have been conflicting. One study identified a higher risk of AMI with dabigatran compared with warfarin in prior VKA users

[16], while others found a lower risk [17–19] or no difference [20]. In a recent phase IV study following the 1-year safety of patients using rivaroxaban, no increased risk of AMI was observed [21]. The Xa inhibitors, which were registered later than the inhibitors, are being used increasingly. However, up until now, there have been no cohort studies comparing the risk of AMI associated with the Xa inhibitors with that associated with VKAs. Therefore, the aim of the present study was to determine the risk of AMI in real-world patients with AF, using three different classes of antithrombotic agent – DOACs (both IIa and Xa inhibitors), VKAs and aspirin.

Methods

Data source

We used data from the Clinical Practice Research Datalink (CPRD, www.cprd.com). The CRPD is the world's largest primary care database and contains the medical records of 674 primary care practices in the UK, representing 6.9% of the total population. Data recorded in the CPRD include demographic information, prescription details, laboratory tests, specialist referrals, hospital admissions, diagnoses and lifestyle variables such as body mass index (BMI), smoking and alcohol consumption. CPRD data have been shown to have high validity and completeness [22].

Study population

The study population consisted of all patients ≥18 years of age with a CRPD datalink read code for their first diagnosis of AF during a patient's period of valid data collection. The index date for the start of follow-up was the date of the first prescription for VKA, DOAC or low-dose (<325 mg) aspirin.

Patients with prior AMI or with previous exposure to the drugs of interest were excluded. This was a new user design, with cohort entry defined as the date of first prescription identified between 18 March 2008 and 30 June 2014. Patients were followed from the index date to the end of data collection, date of transfer of the patient out of the practice, death or the first record of AMI recorded in the CPRD, whichever came first.

Exposure

Patient follow-up time was divided into 30-day intervals in order to classify exposure time-dependently (Figure 1). In the UK, the median prescription length is 28 days. At the start of each 30-day period, we identified if a patient had had exposure to an eligible antithrombotic agent based on the start date of a prescription. Patients were defined as current users if they had a prescription in the 30 days before the start of a 30-day interval. If there were no prescriptions during this period, they were classified as a past user. All patients were current users of one of the eligible study drugs at the index date, and categorized into mutually exclusive exposure groups (VKAs, DOACs, aspirin or, if more than one treatment was used, they were classified as mixed users of more than one of the three main study drugs). The current user groups were categorized regardless of past use. Thus, a patient could have past use of a VKA but be a current user of a DOAC. Among patients who were not current users, past use was defined as past VKA, DOAC or aspirin use, and patients could contribute to more than one past user group in an interval. Thus, past user groups were not mutually exclusive.

Outcome

The primary outcome of interest was AMI [ST-segment elevation myocardial infarction (STEMI) or non-STEMI], defined using the UK Read code system.

Other variables

Potential confounders/risk factors were selected from the literature [23, 24]. The presence of risk factors for AMI was assessed by reviewing the computerized medical records for any such factors prior to the start of an interval. The following potential confounders were determined at baseline: gender, BMI, smoking status and alcohol use. Assessment of lifestyle variables (BMI, alcohol use and smoking status) were determined at the index date, and the most recent assessment of each, as recorded by the general practitioner (GP), was used. These variables were determined optionally by the GP, and a missing variable was created to account for those patients without a recording prior to their index date.

All of the other potential confounders that were considered in the present study were determined time-dependently (i.e. at the start of each interval). These included: history of congestive heart failure, cerebrovascular disease, coronary artery disease, peripheral artery disease, ischaemic heart disease, acute or chronic renal failure, liver dysfunction or cancer. The following drug prescriptions, based on the start date in the 6 months prior to the start of an interval, were considered as potential confounders: lipid-lowering drugs; antihypertensive agents such as calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II (ATII) blockers, diuretics, beta-blockers; antiplatelet drugs such as clopidogrel, prasugrel, ticagrelor, dipyridamole, concomitant use of other anticoagulant drugs (low-molecular-weight heparin or heparin), aspirin at analgesic dosages ($\geq$325 mg); cardiovascular drugs such as antiarrhythmic drugs, isosorbides; antidiabetic drugs and insulin; analgesics such as cyclooxygenase-2 inhibitors and naproxen; strong cytochrome P450 (CYP) 3A4/P-glycoprotein (P-gp) inhibitors (azole antimycotics, protease inhibitors); Strong CYP3A4/P-gp inducers (carbamazepine, rifampicin).

Statistical analyses

Crude incidence rates of outcome were calculated and represented as events per 1000 person-years. Cox proportional hazards models (SAS 9.2, PHREG procedure, SAS Institute, SAS campus drive Care, North Carolina 27513) estimated the risk of AMI with the use of DOACs, aspirin or mixed use vs. VKAs.
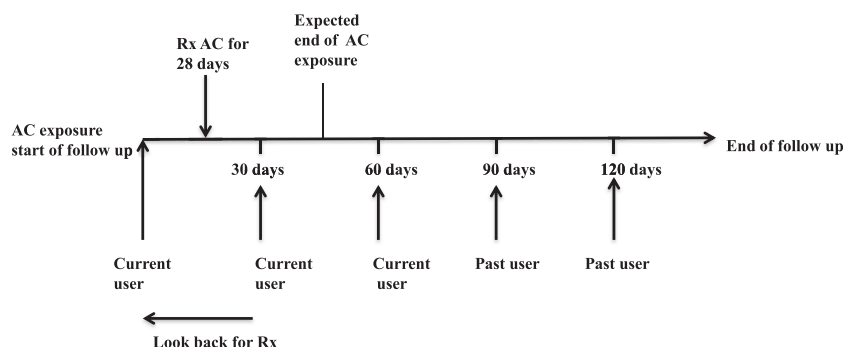
Figure 1

Diagram of exposure definition demonstrating a hypothetical patient case. The classification of exposure is identified at the start of every 30-day period and is as follows: current use (patient with exposure in the previous 30 days from the start of a 30-day interval) or past use (patients whose last exposure was >30 days from the start of a 30-day interval). Note that all patients were current users of one of the eligible ACs at the start of follow-up. AC, anticoagulant; Rx, prescription

Potential confounders were included if they independently changed the beta-coefficient for current anticoagulant exposure by at least 5%. In all analyses, current users of VKAs were used as the reference group. Sensitivity analyses were performed according to gender and to the CHA_2DS_2-VASc score, a clinical prediction rule for estimating risk of stroke in AF patients. This score was calculated at baseline and time-dependently (at the start of each period). CHA_2DS_2-VASc score groups were defined as: high (CHA_2DS_2-VASc score ≥ 4), medium (CHA_2DS_2-VASc score >1 and <4) or low (CHA_2DS_2-VASc score ≤ 1). In the case of missing data, an indicator was included in the statistical analysis.

Scientific approval

The study protocol was approved by the Independent Scientific Advisory Committee for the Medicines and Healthcare products Regulatory Agency database research, protocol number 14_121.

Results

Study population and follow-up

Following the inclusion and exclusion criteria, we identified 30 146 new users (Table 1) of DOACs ($n = 1266$), VKAs ($n = 13 098$), low-dose aspirin ($n = 15 400$) or mixed users ($n = 382$) at the index date. The DOACs were rivaroxaban (71.6%) and dabigatran (28.4%).

The characteristics of the study population are presented in Table 2. The follow-up time was about 1 year for DOAC and about 3 years for VKA or low-dose aspirin users. The mean age was approximately 72 years and 50–60% were male. There was a balanced division of CHA_2DS_2-VASc score categories among the three groups of DOAC, VKA and low-

Table 1

Study flow

		Number of patients
	All patients	**211 126**
	Reasons for exclusion:	
a	Age <18 years at index date	**142**
b	AF diagnosis outside valid data collection or study time	**131 487**
c	Patient's year of birth was after censoring date	**24**
d	Patients with AF but without prescription of interest before or after AF diagnosis	**83 473**
e	Patients with prior use of eligible study drug	**38 531**
	Excluded for one of the reasons above (a–e)	**179 629**
	Cohort	**31 497**
	Excluded patients with AMI prior to index date	**1351**
	Final study cohort	**30 146**

AF, atrial fibrillation; AMI, acute myocardial infarction

dose aspirin users: 25% had a low score (≤ 1), 25–30% a high score (≥ 4) and the remainder a medium score (>1 and <4). This distribution of antithrombotic use was not in line with the guidelines for use of antithrombotic agents for stroke prevention in AF [25, 26].

Current or past antithrombotic use and risk of AMI

Table 3 shows that the risk of AMI was doubled when we compared current use of DOACs with current use of VKAs [adjusted hazard ratio (adj HR) 2.11; 95% confidence interval (CI) 1.08, 4.12]. A similar increase was observed among current users of aspirin *vs.* current VKA users (adj HR 1.91; 95% CI 1.45, 2.51). The risk of AMI was increased when we compared past use of aspirin with current VKA use (Table 3).

When stratified by gender, an increased risk of AMI was observed among current users of aspirin both in men (adj HR 1.60; 95% CI 1.10, 2.33) and women (adj HR 2.33; 95% CI 1.55, 3.50). No other exposures were significantly associated with AMI (Table 4).

We also stratified current users by CHA_2DS_2-VASc score at the index date. When stratified for high score (≥ 4) compared with current VKAs users, a significant increase in AMI risk was observed in current aspirin users (adj HR 2.21; 95% CI 1.37, 3.55), while among patients with a medium score (>1 and <4), we identified an increased risk in current users of DOACs (adj HR 2.67; 95% CI 1.11, 6.40) and aspirin (adj HR 1.82; 95% CI 1.23, 2.68). More results are shown in Table 5.

Discussion

The study showed that, among patients with AF, the risk of AMI was doubled for current users of DOACs and aspirin *vs.* current users of VKAs. The higher risk of AMI was also significant for past users of aspirin *vs.* VKAs. After stratification for gender, the risk remained significant only for users of aspirin. After stratification for stroke risk by CHA_2DS_2-VASc score, the risk of AMI remained significantly increased for high risk (score ≥ 4) aspirin users and medium risk (score >1 and <4) DOAC and aspirin users compared with current users of VKAs.

Our results differed from the randomized controlled Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial with rivaroxaban *vs.* warfarin (risk of AMI: HR 0.81; 95% 0.63, 1.06) [3] but were in line with the randomized controlled RE-LY trial with dabigatran *vs.* warfarin (risk of AMI: HR 1.38; 95% CI 1.0, 1.91) [2]. A major weakness of these clinical trials is their limited external validity. They do not reflect a real-life population, as patients with AF currently using these drugs have a different risk profile to patients seen in daily clinical practice. A recent study showed that about two-thirds (51–68%) of the patients with AF recommended for anticoagulation in the UK, identified by the Clinical Practice Research Datalink, met the inclusion criteria of the randomized controlled trials for DOACs [27]. With age and gender being equal, we also observed important differences in a number of characteristics of the population in the

Table 2

Baseline characteristics of patients with atrial fibrillation and new users of DOACs, VKAs or low-dose aspirin

Characteristic	Exposure to antithrombotics			
	DOACs	VKAs	ASPIRIN	Mixed
Number	1266	13 098	15 400	382
Mean follow-up years (SD)	0.95(0.62)	2.72(1.86)	2.86(1.87)	2.99(1.96)
Females (%)	573(45.3)	6078(46.4)	7690(49.9)	151(39.5)
Age				
Mean age at index date, years (SD)	72(12.6)	72(12)	73(12.7)	73(10.6)
<65 y %	24.7	23.9	24.1	19.4
65-74 y %	27.4	28.6	25.5	33.8
>75 y %	47.9	47.6	50.4	46.9
BMI mean at index date (SD)	28(6.2)	29(6.3)	28(6.2)	29(6.7)
Smoking status				
Never, %	43.6	41.9	44.3	41.9
Current, %	8.1	8.9	9.6	11.5
Previous, %	47.8	48.8	45.6	46.1
Alcohol				
Yes, %	69.6	69.9	68.6	69.1
No, %	21.7	23	23.3	20.7
CHA_2DS_2-VASC score (mean ± SD)	2.6(1.5)	2.6(1.5)	2.4(1.4)	2.6(1.4)
Low, %	25.5	25.4	26.1	24.6
Medium, %	45.1	46.1	46	47.9
High, %	29.4	28.4	25.8	27.5
History of disease				
Congestive heart failure, %	6.9	9.6	5.3	13.3
Acute renal failure, %	0.47	0.48	0.72	0.26
Chronic renal failure, %	0.32	1.12	0.92	0.26
Liver disease, %	0.16	0.11	0.23	0.26
Cancer, %	1.18	0.93	0.73	0.26
Cerebrovascular disease, %	18.5	12.8	5.8	17.5
Peripheral artery disease, %	5.29	4.83	3.82	5.24
Ischaemic heart disease, %	5.77	7.05	5.27	11.26
Drug use 6 months prior to index date				
Antidiabetic drugs, %	7.7	7.4	5.4	7.3
ACE inhibitors, %	25.8	27.6	21.8	19.9
Antiarrhythmic drugs, %	6.24	6.51	4.1	2.36
Anticoagulant drugs, %	1.34	1.53	0.38	0.00
Antiplatelet drugs, %	0.47	1.30	0.51	0.00
ATII-blockers, %	12.16	12.15	9.81	10.99
Beta-blockers, %	39.57	34.46	22.44	24.35
Calcium channel blockers, %	28.91	27.78	24.09	24.61
Diuretics, %	29.94	36.35	31.01	30.10

(*continues*)

Table 2

(Continued)

Characteristic	Exposure to antithrombotics			
	DOACs	VKAs	ASPIRIN	Mixed
Insulin, %	1.42	1.37	0.95	1.57
Statins, %	29.30	28.52	20.23	23.56
Strong CYP3A4 inducers, %	0.16	0.34	0.28	0.79
Azol CYP3A4 inhibitors, %	0.55	0.56	0.60	0.26
Protease/NNRTI CYP3A4 inhibitors, %	0.0	0.0	0.0	0.0
Isosorbides, %	0.79	1.05	0.69	0.79
Naproxen + COX2 inhibitors, %	6.0	3.44	3.43	3.93

CHA_2DS_2-VASC score, stroke risk: low ≤ 1; medium >1 and <4; high ≥ 4. Patients were classified as mixed users if they used more than one of the three study drugsACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; ATII, angiotensin II; BMI, body mass index; COX, cyclooxygenase; CYP, cytochrome P450; DOAC, direct-acting oral anticoagulant; NNRTI, non-nucleoside reverse-transcriptase inhibitor; SD, standard deviation; VKA, vitamin K antagonist

Table 3

Risk of AMI in DOAC, aspirin and mixed users compared with current VKA users

Exposure	Number of AMIs	IR/1000 PY	Age-/gender-adjusted HR (95% CI)	Adjusted HR final (95% CI)
Current VKA	81	2.90	reference	reference
Current DOAC	10	5.00	2.10 (1.08, 4.10)[a]	2.11 (1.08, 4.12)[a]
Current aspirin	114	6.05	1.84 (1.40, 2.42)[a]	1.91 (1.45, 2.51)[a]
Current mixed	5	5.27	1.80 (0.73, 4.42)	1.69 (0.69, 4.16)
Past VKA	74	3.69	1.05 (0.79, 1.39)	1.01 (0.76, 1.35)
Past DOAC	<5[b]	3.52	1.21 (0.38, 3.83)	1.21 (0.38, 3.84)
Past aspirin	106	4.62	1.62 (1.23, 2.12)[a]	1.69 (1.29, 2.22)[a]

Patients were classified as mixed users if they used more than one of the three study drugs. Current use: exposure to antithrombotic agents was based on use in the 30 days before the start date of each 30-day period; past use: discontinuation of treatment for > 31 days. Adjusted for the following variables: age, gender, BMI, alcohol status, smoking status, antihypertensive use, congestive heart failure, statin useAMI, acute myocardial infarction; CI, confidence interval; DOAC, direct-acting oral anticoagulant; HR, hazard ratio; IR, incident rate; PY, per year; VKA, vitamin K antagonist
[a]Statistically significant difference compared with past VKA use, according to the Wald test ($P < 0.05$)
[b]Cells supressed due to <5 events

clinical trials compared with our patient population: about 17% of patients had prior AMI (both in the RE-LY and ROCKET-AF studies) while we excluded prior AMI; more patients had congestive heart failure (about 60% and 32% in the RE-LY and ROCKET-AF studies, respectively) while this was the case in 5–10% of our patients; 20% and 35% of patients, respectively, used concurrent aspirin while our patients did not; and patients in this study populations had a different stroke risk (CHA_2DS_2, a clinical prediction rule for estimating stroke risk in AF patients, score 3.5 and 21. respectively), compared with a CHA_2DS_2-VASc score of 2.4–2.6 in our study. Moreover, the time that patients on warfarin spent in the therapeutic range was different, or unknown, in these studies: 64% of the time in the RE-LY study, 55% of the time in the ROCKET-AF study and not known in the present study.

In addition, the results from cohort studies may be driven by the selection that is made with regard to patients and the prescription of anticoagulant medication. The published cohort studies investigating the same topic, from the USA and Denmark, all compared dabigatran with warfarin [16–20]. By contrast, our patients used mainly rivaroxaban (71.6%), the most frequently used DOAC in the UK, with only 28.4% using dabigatran. Apart from the difference with regard to the DOACs used, there was also a difference in patient selection between our cohort and the other cohort studies. Our results on the increase in AMI risk associated with DOACs *vs.* VKAs were in line with those in the observational study of Larssen *et al.* [16], although in their study patients were prior VKA users, while all of our patients were new users. Moreover, 24% of the patients in their study had suffered prior AMI. Our results were not in line with

Table 4

Risk of AMI in DOAC, aspirin and mixed users compared with VKA users, stratified by gender

Exposure	Number of AMIs	IR/1000 PY	Age-adjusted HR (95% CI)	Adjusted HR final (95% CI)
Females				
Current VKA	35	2.59	reference	reference
Current DOAC	5	5.36	2.24 (0.86, 5.82)	2.23 (0.86, 5.79)
Current aspirin	62	6.30	2.28 (1.52, 3.42)[b]	2.33 (1.55, 3.50)[b]
Current mixed	<5[c]	2.58[c]	1.06 (0.15, 7.71)	0.99 (0.14, 7.19)
Males				
Current VKA	46	3.01	reference	reference
Current DOAC	5	5.03	2.04 (0.80, 5.21)	2.10 (0.82, 5.39)
Current aspirin	52	5.78	1.55 (1.07, 2.26)[b]	1.60 (1.10, 2.33)[b]
Current mixed	<5[c]	7.12	2.09 (0.76, 5.76)	1.93 (0.70, 5.34)

Patients were classified as mixed users if more than one of the three study drugs was used. Current use: exposure to antithrombotic agents was based on use in the 30 days before the start date of each 30-day period. [11]AMI, acute myocardial infarction; CI, confidence interval; DOAC, direct-acting oral anticoagulant; HR, hazard ratio; IR, incident rate; PY, per year, VKA, vitamin K antagonist
[b]Statistically significant difference compared with past VKA use, according to the Wald test ($P < 0.05$)
[c]Cells supressed due to <5 events

Table 5

Risk of AMI in DOAC, aspirin and mixed users compared with VKA users, stratified by CHA_2DS_2-VASc score

Exposure	Number of AMIs	IR/1000 PY	Age-/gender-adjusted HR (95% CI)	Adjusted HR final (95% CI)
High CHA_2DS_2-VASc score				
Current VKA	27	3.51	reference	reference
Current DOAC[b]	<5	5.50	1.76 (0.52, 5.94)	1.77 (0.52, 5.97)
Current aspirin	43	8.43	2.14 (1.33, 3.44)[a]	2.21 (1.37, 3.55)[a]
Current mixed[b]	<5	8.43	2.22 (0.53, 9.28)	2.14 (0.51, 8.96)
Medium CHA2DS2-VASc score				
Current VKA	43	3.05	reference	reference
Current DOAC	6	6.75	2.58 (1.08, 6.17)[a]	2.67 (1.11, 6.40)[a]
Current aspirin	55	6.41	1.80 (1.22, 2.66)[a]	1.82 (1.23, 2.68)[a]
Current mixed	< 5[b]	6.51	2.08 (0.65, 6.67)	1.95 (0.61, 6.25)
Low CHA_2DS_2-VASc score				
Current VKA	11	1.52	reference	reference
Current DOAC	<5[b]	2.03	1.34 (0.17, 10.51)	1.38 (0.18, 10.80)
Current aspirin	16	1.95	1.86 (0.92, 3.77)	1.82 (0.89, 3.71)

CHA_2DS_2-VASC score, stroke risk: low ≤ 1; medium >1 and <4; high ≥ 4. Patients were classified as mixed users if they used more than one of the three study drugs. Current use: exposure to antithrombotic agents was based on use in the 30 days before the start date of each 30-day period. Adjusted for the following variables: age, sex, BMI, alcohol status, smoking status, antihypertensive use, congestive heart failure, statin use
AMI, acute myocardial infarction; CI, confidence interval; DOAC, direct-acting oral anticoagulant; HR, hazard ratio; IR, incident rate; PY per year; VKA, vitamin K antagonist
[a]Statistically significant difference compared with past VKA use, according to the Wald test ($P < 0.05$)
[b]Cells supressed due to <5 events

those of Lauffenburger et al. [18], who reported a lower risk of AMI in Medicare patients taking dabigatran; however, both age (lower) and stroke risk (higher) were substantially different from those in our population and some patients in their study had suffered prior AMI. Compared with the present study, Villines et al. [17] reported a lower risk of

AMI in non-Medicare patients with no economic barriers to care; their patients were older and had a higher stroke risk compared with our study, and about 20% of them had coronary artery disease. Compared with the present results, Larsen *et al.* [19] reported a lower risk of AMI in VKA-naïve patients; the differences between their study and ours were: >10% of their patients had had a prior AMI and they had a much lower stroke risk. Our results were also not in line with the study by Graham *et al.* [20], who reported no difference between DOACs and VKAs in the risk of AMI; patients in their study were substantially older than those in the present study and 17% were also using antiplatelet drugs.

In none of these observational studies, or in our study, was the extent of the therapeutic range of anticoagulation with VKAs (the gold standard), known and therefore we do not know the extent to which suboptimal anticoagulation with VKAs influenced the results.

We identified a similar increased risk of AMI among current and past aspirin users in comparison with VKAs. This was an interesting finding as, to our knowledge, there have been no previous reports of increased AMI among AF patients receiving aspirin. Previous AF guidelines have recommended aspirin for thromboprophylaxis for those not considered to be at high risk of AMI [25, 26]. In contrast with these guidelines, we observed that many of the medium- or high-risk patients in our population (CHA_2DS_2-VASc score >1; $CHADS_2$ score ≥2) were treated with aspirin monotherapy, and that many low-risk patients were treated with VKAs or DOACs. This pattern of inadequate anticoagulation of AF patients has been reported previously by several authors (e.g. Ben Freedman *et al.* [28]). The usefulness of aspirin in AF has also been called into question [28], and new guidelines no longer include this agent [26, 29].

In addition to those already identified, a couple of additional limitations should be mentioned. Regrettably, the number of events was not sufficient to analyse separately the risk of AMI associated with dabigatran and with rivaroxaban. We therefore were unable to differentiate between the impact of anti-IIa *vs.* anti-Xa oral anticoagulants. Our results were different to those of the meta-analysis by Loffredo *et al.* [14], who found that myocardial infarction significantly increased with patients treated with the anti-IIa DOAC and not with the anti-Xa DOACs. We had no information about possible comedication with over-the-counter drugs (such as nonprescription aspirin).

Although we were able to include lifestyle factors that are important for AMI, we note that there were some limitations to these data. BMI, alcohol intake and smoking status are not always recorded by the GP, so we did not have complete information for all patients. However, we included an indicator variable for missingness, to ensure that all patients were included in the final model. Moreover, we acknowledge that alcohol intake and smoking status can be underestimated. However, we did not observe significant differences across the exposure groups, and therefore do not believe that this would have had a large impact on our final conclusions.

Our study had several strengths. Our study used population-based data, resulting in high external validity. All participants were extensively clinically characterized, which allowed us to take a large number of potential confounders into account. We used a new-user design, exposure to covariates was taken into account time-dependently and we excluded patients with prior AMI. Our study was the first to report on the risk of AMI associated with DOACs in comparison with VKAs, including both the Xa inhibitor rivaroxaban and the IIa inhibitor dabigatran, and of the risk of aspirin *vs.* VKAs in patients with AF.

In regard to the possible pharmacological mechanism involved, it seems possible that VKAs have an effect on the pathological conditions affecting angina pectoris and therefore also have a protective effect against AMI [30]. DOACs (at least rivaroxaban) and aspirin therefore might have a lesser protective effect against AMI compared with VKAs. It has previously been established that VKAs have a protective effect against AMI, but the results of the present study strongly suggest that this is not a class effect of 'oral anticoagulants'.

In conclusion, our cohort study identified a twofold increase in the risk of AMI when using DOACs, rivaroxaban or dabigatran, in comparison with VKAs, in AF therapy in real-world patients. In addition, our results showed that in AF patients, the risk of AMI with current use of aspirin as monotherapy is higher than with current use of VKAs. VKAs probably have greater beneficial effects on AMI than DOACs. Ongoing research is needed as the use of DOACs increases in the population.

Competing Interests

Contributors

A.B. performed statistical analysis; F.V. handled supervision; A.B. acquired the data; L.S., A.B., F.V., C.E., A.d.B., T.S., P.S. and A.C. conceived and designed the research; L.S. drafted the manuscript; F.V., A.B., C.E., A.d.B., T.S., P.S. and A.C. made critical revision of the manuscript for key intellectual content.

References

1 Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP, *et al.* The IUPHAR/BPS guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucleic Acids Res 2016; 44 (Database Issue): D1054–D1068.

2 Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139–51.

3 Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883–91.

4 Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, *et al.* Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981–92.

5 Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, *et al.* Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369: 2093–104.

6 Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation 2012; 126: 2381–91.

7 Ntaios G, Papavasileiou V, Diener HC, Makaritsis K, Michel P. Nonvitamin-K-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a systematic review and meta-analysis of randomized controlled trials. Stroke 2012; 43: 3298–304.

8 Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, *et al.* Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014; 383: 955–62.

9 Hohnloser SH, Oldgren J, Yang S, Wallentin L, Ezekowitz M, Reilly P, *et al.* Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (randomized evaluation of long-term anticoagulation therapy) trial. Circulation 2012; 125: 669–76.

10 Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med 2012; 172: 397–402.

11 Loffredo L, Perri L, Del Ben M, Angelico F, Violi F. New oral anticoagulants for the treatment of acute venous thromboembolism: are they safer than vitamin K antagonists? A meta-analysis of the interventional trials. Intern Emerg Med 2015; 10: 499–506.

12 Clemens A, Fraessdorf M, Friedman J. Cardiovascular outcomes during treatment with dabigatran: comprehensive analysis of individual subject data by treatment. Vasc Health Risk Manag 2013; 9: 599–615.

13 Artang R, Rome E, Nielsen JD, Vidaillet HJ. Meta-analysis of randomized controlled trials on risk of myocardial infarction from the use of oral direct thrombin inhibitors. Am J Cardiol 2013; 112: 1973–9.

14 Loffredo L, Perri L, Violi F. Myocardial infarction and atrial fibrillation: different impact of anti-IIa vs anti-Xa new oral anticoagulants: a meta-analysis of the interventional trials. Int J Cardiol 2015; 178: 8–9.

15 Tornyos A, Kehl D, D'Ascenzo F, Komocsi A. Risk of myocardial infarction in patients with long-term non-vitamin K antagonist oral anticoagulant treatment. Prog Cardiovasc Dis 2016; 58: 483–94.

16 Larsen TB, Rasmussen LH, Gorst-Rasmussen A, Skjoth F, Lane DA, Lip GY. Dabigatran and warfarin for secondary prevention of stroke in atrial fibrillation patients: a nationwide cohort study. Am J Med 2014; 127: 1172–8 e5.

17 Villines TC, Schnee J, Fraeman K, Siu K, Reynolds MW, Collins J, *et al.* Comparison of the safety and effectiveness of dabigatran and warfarin in non-valvular atrial fibrillation patients in a large healthcare system. Thromb Haemost 2015; 114: 1290–8.

18 Lauffenburger JC, Farley JF, Gehi AK, Rhoney DH, Brookhart MA, Fang G. Effectiveness and safety of dabigatran and warfarin in real-world US patients with non-valvular atrial fibrillation: a retrospective cohort study. J Am Heart Assoc 2015; 4: e001798.

19 Larsen TB, Rasmussen LH, Skjoth F, Due KM, Callreus T, Rosenzweig M, *et al.* Efficacy and safety of dabigatran etexilate and warfarin in 'real-world' patients with atrial fibrillation: a prospective nationwide cohort study. J Am Coll Cardiol 2013; 61: 2264–73.

20 Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M, *et al.* Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. Circulation 2015; 131: 157–64.

21 Camm AJ, Amarenco P, Haas S, Hess S, Kirchhof P, Kuhls S, *et al.* XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J 2016; 37: 1145–53.

22 Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, *et al.* Data resource profile: clinical practice research Datalink (CPRD). Int J Epidemiol 2015; 44: 827–36.

23 Davis EM, Packard KA, Knezevich JT, Campbell JA. New and emerging anticoagulant therapy for atrial fibrillation and acute coronary syndrome. Pharmacotherapy 2011; 31: 975–1016.

24 Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study. Lancet 2004; 364: 937–52.

25 Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, *et al.* ACC/AHA/ESC 2006 guidelines for the Management of Patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on practice guidelines and the European Society of Cardiology Committee for practice guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006; 114: e257–e354.

26 Lip GY, Lane DA. Stroke prevention in atrial fibrillation: a systematic review. JAMA 2015; 313: 1950–62.

27 Lee S, Monz BU, Clemens A, Brueckmann M, Lip GY. Representativeness of the dabigatran, apixaban and rivaroxaban clinical trial populations to real-world atrial fibrillation patients in the United Kingdom: a cross-sectional analysis using the general practice research database. BMJ Open 2012; 2: e001768.

28 Ben Freedman S, Gersh BJ, Lip GY. Misperceptions of aspirin efficacy and safety may perpetuate anticoagulant underutilization in atrial fibrillation. Eur Heart J 2015; 36: 653–6.

29 Jones C, Pollit V, Fitzmautice D, Cowan C. Updated NICE guideline: management of atrial fibrillation. Expert Rev. Cardiovasc Ther 2014; 12: 1037–40.

30 Knottenbelt C, Brennan PJ, Meade TW. Antithrombotic treatment and the incidence of angina pectoris. Arch Intern Med 2002; 162: 881–6.