BMJ Open

Comparative effectiveness of novel oral anticoagulants in UK patients with non-valvular atrial fibrillation and chronic kidney disease: a matched cohort study

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To cite: Loo SY, Coulombe J, Dell'Aniello S, *et al*. Comparative effectiveness of novel oral anticoagulants in UK patients with non-valvular atrial fibrillation and chronic kidney disease: a matched cohort study. *BMJ Open* 2018;**8**:e019638. doi:10.1136/bmjopen-2017-019638

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-019638).

Received 14 September 2017
Revised 6 November 2017
Accepted 22 November 2017

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ABSTRACT

Objectives To evaluate the effectiveness and safety of novel oral anticoagulants (NOACs) compared with vitamin K antagonists (VKAs) among patients with non-valvular atrial fibrillation (NVAF), particularly those with chronic kidney disease (CKD).

Design Population-based matched cohort study.

Setting Over 670 primary care practices in the UK, contributing to the Clinical Practice Research Datalink.

Participants Up to 6818 adult patients newly treated with NOACs between 2011 and 2016, matched 1:1 to new users of VKAs on age, sex and high-dimensional propensity score.

Interventions Current exposure to NOACs compared with current exposure to VKAs.

Main outcome measures HRs of ischaemic stroke and systemic embolism (SE), major bleeding, gastrointestinal (GI) bleeding, intracranial bleeding, myocardial infarction and all-cause mortality.

Results In as-treated analyses, the rates of ischaemic stroke/SE were similar between NOACs and VKAs (HR 0.94; 95% CI 0.62 to 1.42), as were the rates of major bleeding (HR 0.86; 95% CI 0.56 to 1.33). NOACs also significantly increased the risk of GI bleeding (HR 1.78; 95% CI 1.27 to 2.48). In patients with NVAF and CKD, NOACs and VKAs remained comparable with respect to the risk of ischaemic stroke/SE (HR 0.79; 95% CI 0.40 to 1.58) and major bleeding (HR 0.88; 95% CI 0.47 to 1.62), with no difference in the risk of GI bleeding (HR 0.99; 95% CI 0.63 to 1.55). Similar results were obtained in on-treatment analyses using a time-dependent exposure definition.

Conclusions Our results suggest that in the UK primary care, NOACs are overall effective and safe alternatives to VKAs, among patients with NVAF altogether, as well as in patients with NVAF and CKD.

Strengths and limitations of this study

- ► We matched new novel oral anticoagulant (NOAC) and new vitamin K antagonist (VKA) users on age, sex and high-dimensional propensity scores, thereby reducing the potential for residual confounding.
- ► Using the UK's Clinical Practice Research Datalink, we evaluated the effectiveness and safety of NOACs in a study population that is representative of the UK population.
- ► Exposure to NOACs and to VKAs was determined based on issued prescriptions and not on prescriptions actually filled or taken by patients, thus introducing the potential for exposure misclassification.
- ► NOACs were evaluated as a class, and we were not able to conduct analyses stratified by individual NOACs due to insufficient power.

INTRODUCTION

Patients with non-valvular atrial fibrillation (NVAF) experience an estimated fivefold increased risk of ischaemic stroke.[1] Consequently, these patients require treatment with oral anticoagulants (OACs) such as vitamin K antagonists (VKAs), which have been shown to reduce the risk of stroke by approximately 60% compared with placebo, in randomised controlled trials (RCTs).[2] Although effective, VKA therapy may be challenging due to bleeding concerns, as well as the need for close and routine monitoring.[3 4]

In the UK, novel oral anticoagulants (NOACs) were licensed for stroke prevention in NVAF in August 2011. Based on the results of RCTs, these medications have generally been accepted as effective and safe alternatives to VKAs,[5] and these conclusions have been echoed in several observational studies evaluating NOACs in routine clinical practice.[6–9] In contrast, the effectiveness and safety of NOACs has been less extensively explored in subgroups of more vulnerable patients with NVAF. In particular, those with chronic kidney disease (CKD) experience an increased risk of ischaemic stroke and adverse bleeding events.[10] However, few observational studies have compared NOAC and VKA treatment in patients with CKD, and there is room to explore the clinical utility of these medications in such at-risk subgroups.

The objective of this study was to assess the effectiveness and safety of NOACs compared with VKAs in a cohort of patients with NVAF from a primary care setting in the UK, with a particular focus on patients with CKD.

METHODS

Data source

The UK's Clinical Practice Research Datalink (CPRD) is one of the largest databases of primary care electronic medical records, and details patient demographic characteristics and lifestyle habits, in addition to their clinical history. CPRD prescriptions are recorded using Gemscript codes which are based on the UK's Dictionary of Medicines and Devices,[11] while the READ classification scheme is used to record data on medical diagnoses, procedures and services.[12] The information is documented by general practitioners (GPs) from over 670 medical practices, which collectively represent over 7% of the total UK population.[13] GP-issued drug prescriptions are automatically transcribed into patients' computerised file, and the database therefore contains comprehensive patient prescription data. Thus, the CPRD has been used extensively for pharmacoepidemiological studies of drug effectiveness and safety,[14 15] and the validity and representativeness of its data have previously been confirmed.[13 16–18]

Study population

We identified all CPRD patients aged 18 or older with a first ever diagnosis for atrial fibrillation (AF). At the time of diagnosis, those with less than 12 months of valid and up to standard records were excluded, as were patients with valvular AF, hyperthyroidism and/or a prior history of OAC use. Within this population, we selected all new users of NOACs or VKAs who received their first prescription between 1 August 2011, when NOACs were first approved for the treatment of NVAF, and 30 September 2016. The date of first prescription was considered the date of cohort entry, and follow-up ended at the earliest of 30 September 2016, occurrence of the outcome of interest or the date of the patient's death or transfer out of the practice.

Exposure definition

We identified all OACs available in the UK between 2011 and 2016. The NOACs of interest included dabigatran, rivaroxaban, apixaban and edoxaban, and the VKAs included warfarin, acenocoumarin and phenindione. Continuous exposure was defined starting from the date of first prescription, for the intended duration of the prescription, plus the duration of any overlapping and successive prescriptions of the same OAC class. The duration of each prescription was extended by a grace period of 7 days to account for residual anticoagulation effects and delays between prescription refills. In primary as-treated analyses, patients were censored after treatment switching (NOAC to VKA or vice versa) or treatment discontinuation. In secondary analyses, exposure was defined as a time-dependent variable, and each day of follow-up was classified as exposed to either NOACs or VKAs, both or neither.

Outcome definition

The primary effectiveness outcome was a composite of ischaemic stroke and systemic embolism (SE). Safety outcomes of interest included major bleeding, intracranial bleeding, gastrointestinal (GI) bleeding, myocardial infarction (MI) and all-cause mortality. Major bleeding was defined as any bleeding requiring hospitalisation or transfusion, any bleeding resulting in death or any bleeding in a critical organ. All outcomes were identified over the course of follow-up through the identification of corresponding READ codes in patients' electronic files.

Statistical analyses

New users of NOACs were matched 1:1 to new users of VKAs on age, sex and high-dimensional propensity score (hd-PS), using callipers of 0.2 SD of the propensity score logit.[19] Briefly, using all data from within the year prior to cohort entry, hd-PS were calculated for each patient as the probability of being exposed to NOACs, based on the 500 covariates that were most likely to bias the exposure–outcome association. Thus, for each patient, a separate hd-PS was calculated for each outcome of interest. Age, sex and time between AF diagnosis and first prescription were forced into all hd-PS models. After matching, Poisson regression was used to calculate the rates of event occurrence, and Cox regression was used to compute the HR of events, comparing exposure to NOACs versus VKAs. The proportional hazards assumption was verified graphically by plotting the log(-log(survival)) function versus the log(time) function,[20] and using the Wald χ^2 test to evaluate trends in the HR over time. In primary analyses, OAC exposure was defined using an as-treated approach, and in secondary analyses, using a time-dependent approach, as described above. In addition to hd-PS matching, all Cox models were adjusted for antiplatelet use, hypertension, diabetes and CKD as time-dependent covariates. These analyses were also conducted in subgroups of patients defined by age (<75 and ≥75 years), sex, CKD status, CKD stage, as well as by CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, ischaemic stroke/transient ischaemic attack (TIA), vascular disease, age 65–74 years and sex)[21] and modified HAS-BLED (hypertension, abnormal renal and/or liver function, ischaemic stroke/TIA, bleeding, age >65 years, antiplatelet/non-steroidal anti-inflammatory drug use or alcohol abuse)[22] scores at cohort entry.

For stratified analyses by CKD status, patients were identified as having CKD if they had one of the following in the year prior to their first OAC prescription: (1) a diagnosis for CKD; (2) a kidney transplantation; (3) at least two sessions of dialysis; (4) at least two values for glomerular filtration rate (GFR) or estimated GFR (eGFR) <90 mL/min/1.73 m^2 and recorded at least 3 months apart; (5) at least one session of dialysis and one value for GFR/

eGFR <90 mL/min/1.73 m^2, recorded at least 3 months apart; (6) at least two diagnoses for renal impairments not specified as chronic or acute and recorded at least 3 months apart; or (7) at least one diagnosis for a renal impairment not specified as chronic or acute, and one session of dialysis or one value for GFR/eGFR <90 mL/min/1.73 m^2, recorded at least 3 months apart. eGFR values were calculated based on serum creatinine results using the CKD-EPI creatinine equation,[23] in accordance with recommendations from the UK's National Institute for Health and Care Excellence.[24]

Several sensitivity analyses were conducted to verify the robustness of our results. First, in as-treated analyses, the exposure window was extended by an additional 30 days after treatment switching or discontinuation, in order to account for potential informative censoring. Second, the grace period between prescriptions was increased to 15 and to 30 days so as to assess the impact of potential exposure misclassification. Third, we evaluated the effectiveness and safety of NOACs using an intention-to-treat analysis. Finally, primary analyses were repeated in the full cohort, trimmed to exclude patients with an hd-PS below and above the 5th and 95th percentile of scores, respectively, and with models adjusted for covariates measured at cohort entry, rather than using hd-PS matching.

All statistical procedures were performed using SAS V.9.4.

RESULTS

We identified 176 731 adults registered in a CPRD practice and who were ever diagnosed with NVAF, among whom 155 953 with a first OAC prescription were eligible for study (figure 1). A total of 34 093 patients received their first prescription within the study period from 1 August 2011 to 30 September 2016, including 23 306 (68.36%) new users of VKAs and 10 787 (31.64%) new

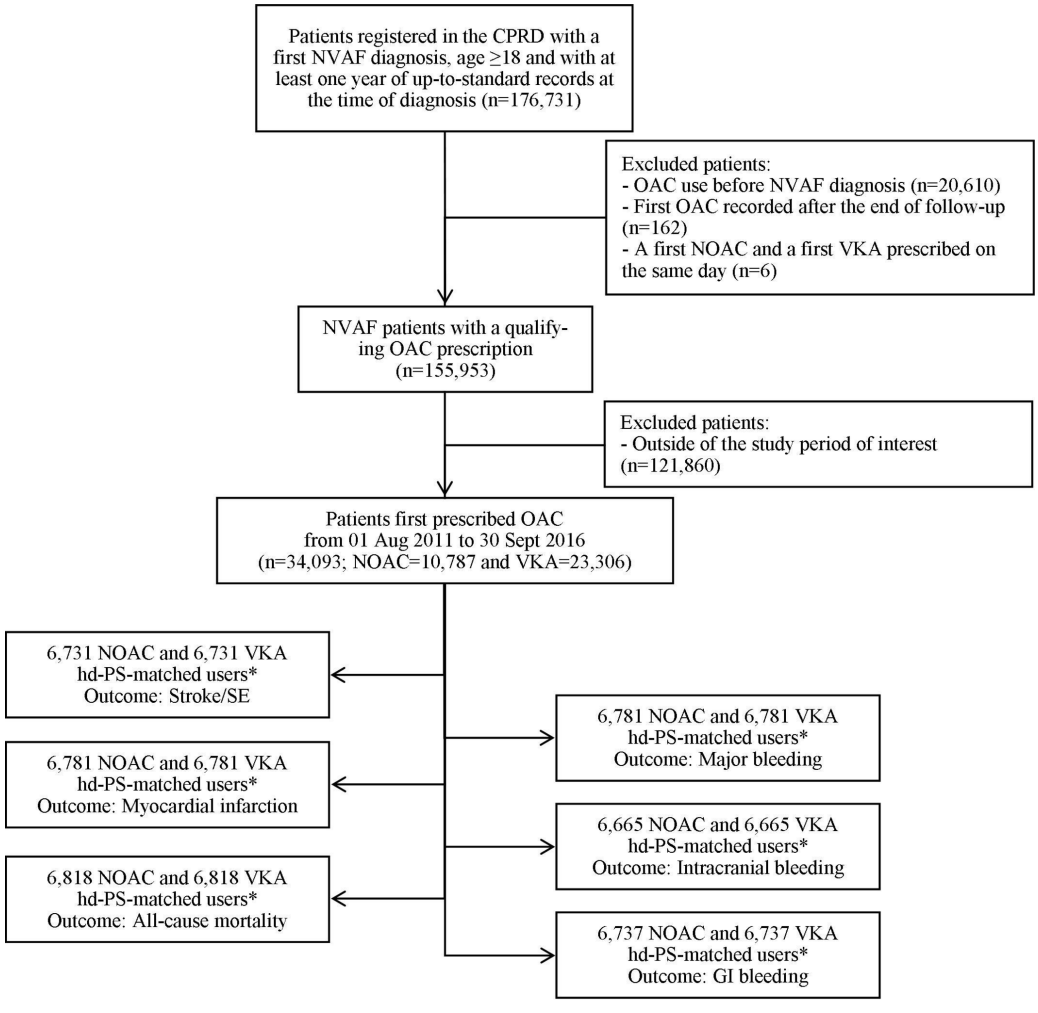

Figure 1 Cohort definition flow chart. CPRD, Clinical Practice Research Datalink; GI, gastrointestinal; hd-PS, high-dimensional propensity score; NOAC, novel oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant; VKA, vitamin K antagonist.

users of NOACs. Rivaroxaban comprised the majority of first ever NOAC prescriptions (52.11%), followed by apixaban (34.06%), dabigatran (13.61%) and edoxaban (0.22%).

Up to 6818 new users of NOACs were matched 1:1 to new users of VKAs on age, sex and hd-PS, and overall, covariates were well balanced within all matched groups (table 1). The rates of ischaemic stroke/SE were 1.4 (95% CI 1.3 to 1.5) and 1.9 (95% CI 1.7 to 2.1) events per 100 persons per year among matched new users of NOACs and VKAs, respectively. New users of NOACs also experienced an overall rate of 1.3 (95% CI 1.2 to 1.4) major bleeding events per 100 persons per year, compared with 1.7 (95% CI 1.5 to 1.8) in new users of VKAs. In as-treated analyses, the rates of ischaemic stroke/SE were similar between NOACs and VKAs (HR 0.94; 95% CI 0.62 to 1.42), as were the rates of major bleeding (HR 0.86; 95% CI 0.56 to 1.33) (table 2). NOACs significantly increased the risk of GI bleeding, and tended to decrease the risk of intracranial bleeding, although with wide CIs around the point estimate. The risk of mortality was slightly higher with NOACs compared with VKAs, and there was no difference between OACs with respect to the risk of MI.

Within our cohort of new users, we identified 13 706 patients (40.20%) who were diagnosed with CKD prior to receiving their first OAC prescription. Over 80% of these had mild or moderate CKD (stages 2 and 3), and the distribution of CKD severity was retained after matching on hd-PS (online supplementary table 1). Within groups of up to 2664 matched pairs, the rates of ischaemic stroke/SE in NOAC and VKA users were 1.2 (95% CI 1.1 to 1.4) and 1.9 (95% CI 1.6 to 2.1) events per 100 persons per year, respectively, (HR 0.79; 95% CI 0.40 to 1.58) (table 2). The rate of major bleeding was 1.7 (95% CI 1.5 to 2.0) per 100 persons per year among new users of NOACs, compared with 2.1 (95% CI 1.8 to 2.4) among new users of VKAs (HR 0.88; 95% CI 0.47 to 1.62). No substantial differences were observed between NOAC and VKA users with respect to other outcomes, including GI bleeding. These treatment effects were stable among mild and moderate patients with CKD (data not shown). It was not possible to evaluate those with a higher CKD stage, owing to the small number of patients.

Results were consistent in on-treatment analyses using a time-dependent exposure definition (table 3). Results of the primary analyses were also unchanged in subgroup analyses of the full NVAF cohort, stratified by age and sex (data not shown). In patients at high risk of stroke (CHA_2DS_2-VASc ≥2), the rates of ischaemic stroke/SE were similar between NOACs and VKAs (HR 0.83; 95% CI 0.53 to 1.24). Likewise, we observed no significant difference in the rates of major bleeding among new users at high risk of bleeding (modified HAS-BLED >2) (HR 0.77; 95% CI 0.42 to 1.40).

In sensitivity analyses extending the exposure window by 30 days after continuous exposure, we observed no difference in mortality comparing NOACs to VKAs, however, NOACs remained associated with a higher risk of GI bleeding among patients with NVAF altogether (HR 1.47; 95% CI 1.09 to 2.00) (table 4). The as-treated results were virtually unchanged when increasing the grace period between prescriptions to 15 and to 30 days (data not shown). The effectiveness and safety of NOACs were also comparable to VKAs with respect to ischaemic stroke/SE and major bleeding in intention-to-treat analyses, as well as in analyses using a standard covariate adjustment technique to address confounding (data not shown).

DISCUSSION

In this population-based study, we found that NOACs were as effective as VKAs in reducing the risk of ischaemic stroke/SE in primary care patients with NVAF. While the rates of major bleeding were also similar overall, compared with VKAs, NOACs were associated with a non-significantly lower risk of intracranial bleeding, as well as a higher risk of GI bleeding. We observed no difference between OACs in the risk of MI and all-cause mortality. The effectiveness and safety of NOACs remained similar to VKAs in patients with CKD, as well as in subgroups defined by patient age, sex and HAS-BLED and CHA_2DS_2-VASc scores.

Our results are in line with RCTs in which the rates of ischaemic stroke, major bleeding and MI associated with NOACs were overall comparable to warfarin.[5] Several observational studies also showed that individual NOACs were similar, if not better than warfarin in the prevention of thromboembolic events in patients with AF.[6–9] Moreover, rates of major bleeding were comparable to warfarin for dabigatran and rivaroxaban in other studies of routine clinical practice.[8 25 26] In clinical trials, all NOACs reduced the risk of intracranial bleeding compared with warfarin,[27–30] as shown in our results and other observational studies.[9 25] Conversely, the association between NOACs and GI bleeding varied between individual NOACs in RCTs.[27–30] The increased risk that we observed is consistent with the results of the ROCKET AF trial on rivaroxaban,[29] which constituted the majority of new NOAC prescriptions in our cohort. Several observational studies have also shown an increased risk of GI bleeds associated with dabigatran and rivaroxaban.[6 7 31] Indeed, it has been suggested that the low bioavailability of dabigatran and the high dosing of rivaroxaban may increase GI bleeding due to a higher concentration of active metabolites in the intestinal tract, in which VKAs are not active.[32] In contrast, apixaban has consistently been associated with a lower risk of most forms of bleeding in the few studies available to date.[9 27] Therefore, the heightened risk of GI bleeds that we observed might have been primarily attributable to rivaroxaban and dabigatran.

A few studies found no increased risk of GI bleeding associated with rivaroxaban and/or dabigatran, as compared with warfarin.[33–35] These conflicting conclusions may be partially explained by different definitions of bleeding events, which can vary substantially when considering their degree of severity. The International Society on Thrombosis and Haemostasis (ISTH) has

Table 1 Baseline characteristics of new users of NOACs and VKAs, matched on hd-PS to evaluate the risk of ischaemic stroke/SE

	All patients with NVAF		Patients with NVAF and CKD	
	NOAC (n=6731)	VKA (n=6731)	NOAC (n=2596)	VKA (n=2596)
Age, mean years (SD)	74.91 (10.29)	74.91 (10.29)	77.62 (8.49)	77.62 (8.49)
18–55	284 (4.2)	284 (4.2)	20 (0.8)	20 (0.8)
55–64	706 (10.5)	706 (10.5)	159 (6.1)	159 (6.1)
65–74	2041 (30.3)	2041 (30.3)	698 (26.9)	698 (26.9)
75–84	2471 (36.7)	2471 (36.7)	1142 (44.0)	1142 (44.0)
≥85	1229 (18.3)	1229 (18.3)	577 (22.2)	577 (22.2)
Sex				
Men	3720 (55.3)	3720 (55.3)	1376 (53.0)	1376 (53.0)
Women	3011 (44.7)	3011 (44.7)	1220 (47.0)	1220 (47.0)
Comorbidities and risk factors				
Congestive heart failure	544 (8.1)	547 (8.1)	265 (10.2)	290 (11.2)
Coronary artery disease	739 (11.0)	721 (10.7)	376 (14.5)	371 (14.3)
Peripheral vascular disease	60 (0.9)	57 (0.8)	25 (1.0)	25 (1.0)
Hypertension	4815 (71.5)	4706 (69.9)	2104 (81.0)	2116 (81.5)
Ischaemic stroke/TIA/SE	782 (11.6)	739 (11.0)	277 (10.7)	244 (9.4)
Venous thromboembolism	131 (1.9)	152 (2.3)	51 (2.0)	66 (2.5)
CKD	2684 (39.9)	2508 (37.3)	2596 (100.0)	2596 (100.0)
Diabetes	1228 (18.2)	1191 (17.7)	720 (27.7)	746 (28.7)
Bleeding	328 (4.9)	288 (4.3)	144 (5.5)	126 (4.9)
Hyperlipidaemia	3829 (56.9)	3586 (53.3)	1691 (65.1)	1618 (62.3)
Cancer	322 (4.8)	287 (4.3)	138 (5.3)	130 (5.0)
COPD	512 (7.6)	545 (8.1)	237 (9.1)	226 (8.7)
Liver disease	19 (0.3)	15 (0.2)	7 (0.3)	7 (0.3)
Alcohol abuse	115 (1.7)	80 (1.2)	40 (1.5)	34 (1.3)
Obesity				
Obese	1899 (28.2)	1828 (27.2)	823 (31.7)	820 (31.6)
Not obese	3137 (46.6)	3138 (46.6)	1344 (51.8)	1325 (51.0)
Unknown	1695 (25.2)	1765 (26.2)	429 (16.5)	451 (17.4)
Smoking				
Never	2467 (36.7)	2360 (35.1)	964 (37.1)	962 (37.1)
Ever	3355 (49.8)	3430 (51.0)	1363 (52.5)	1377 (53.0)
Unknown	909 (13.5)	941 (14.0)	269 (10.4)	257 (9.9)
Medications				
Amiodarone	218 (3.2)	215 (3.2)	80 (3.1)	71 (2.7)
Antidiabetic drugs	895 (13.3)	874 (13.0)	530 (20.4)	525 (20.2)
Cardioprotective drugs	6147 (91.3)	6049 (89.9)	2462 (94.8)	2466 (95.0)
ACE inhibitors	2616 (38.9)	2554 (37.9)	1181 (45.5)	1166 (44.9)
ARBs	1205 (17.9)	1129 (16.8)	596 (23.0)	584 (22.5)
Beta-blockers	4539 (67.4)	4488 (66.7)	1769 (68.1)	1795 (69.1)
Calcium-channel blockers	2571 (38.2)	2537 (37.7)	1133 (43.6)	1131 (43.6)
Loop diuretics	1751 (26.0)	1782 (26.5)	908 (35.0)	936 (36.1)
Thiazide diuretics	1353 (20.1)	1319 (19.6)	639 (24.6)	634 (24.4)
Antiplatelets	3832 (56.9)	3873 (57.5)	1681 (64.8)	1688 (65.0)

Continued

Table 1 Continued

	All patients with NVAF		Patients with NVAF and CKD	
	NOAC (n=6731)	VKA (n=6731)	NOAC (n=2596)	VKA (n=2596)
Antipsychotic drugs	390 (5.8)	378 (5.6)	165 (6.4)	185 (7.1)
H_2 receptor antagonists	284 (4.2)	290 (4.3)	143 (5.5)	144 (5.5)
HRT*	160 (5.3)	154 (5.1)	54 (4.4)	62 (5.1)
Lipid lowering drugs	3805 (56.5)	3560 (52.9)	1682 (64.8)	1610 (62.0)
NSAIDs	988 (14.7)	1004 (14.9)	366 (14.1)	392 (15.1)
Proton pump inhibitors	2960 (44.0)	2924 (43.4)	1330 (51.2)	1294 (49.8)
$CHADS_2$				
0	802 (11.9)	882 (13.1)	139 (5.4)	139 (5.4)
1	2033 (30.2)	2011 (29.9)	595 (22.9)	593 (22.8)
≥2	3896 (57.9)	3838 (57.0)	1862 (71.7)	1864 (71.8)
CHA_2DS_2-VASc				
0	215 (3.2)	249 (3.7)	17 (0.7)	11 (0.4)
1	638 (9.5)	669 (9.9)	114 (4.4)	136 (5.2)
≥2	5878 (87.3)	5813 (86.4)	2465 (95.0)	2449 (94.3)
HAS-BLED				
≤2	1470 (21.8)	1545 (23.0)	43 (1.7)	55 (2.1)
>2	5261 (78.2)	5186 (77.0)	2553 (98.3)	2541 (97.9)

All values are expressed as n (%), unless otherwise specified.
*HRT was identified in women only.
ACE, angiotensin-converting-enzyme; ARBs, angiotensin II receptor blockers; $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, ischaemic stroke/ TIA, and vascular disease; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, ischaemic stroke/TIA, vascular disease, age 65–74 years and sex; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; modified HAS-BLED, hypertension, abnormal renal and/or liver function, ischaemic stroke/TIA, bleeding, age >65 years, antiplatelet/NSAID use or alcohol abuse; hd-PS, high-dimensional propensity score; HRT, hormone replacement therapy; NOAC, novel oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug; NVAF, non-valvular atrial fibrillation; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

developed a standard definition for major bleeds,[36] however, this was intended for clinical studies, and some healthcare databases, including the CPRD, may not contain all of the required information to identify the stipulated criteria. Thus, in observational studies such as this, the classification of events as major bleeds may be influenced by investigator-based definitions. The inconsistent results may also be partly explained by limitations in study design, such as the inclusion of prevalent users, the use of intention-to-treat analyses only, and/or the potential for immortal time bias. Finally, different study populations resulting from different exclusion criteria may have also contributed to these conflicting findings.

There is limited evidence regarding NOACs' effectiveness and safety in patients with NVAF and CKD. In accordance with our results, subgroup analyses of RCTs have suggested that NOACs are as effective as VKAs in reducing the risk of stroke, and further do not increase the risk of bleeds within this population.[27 29 30] These conclusions are generally consistent with studies of routine clinical practice, however, most of these evaluated the comparative effectiveness and safety of dabigatran only.[6 37–39] One nested case–control study of elderly patients with CKD found that neither dabigatran nor rivaroxaban increased the risk of major haemorrhage compared with warfarin.[40] Similarly, a recent cohort study found no difference in the rate of major bleeds, and a significant decrease in the rate of ischaemic stroke associated with rivaroxaban compared with warfarin, in patients with impaired renal function.[41] Our cohort was mostly composed of news users of rivaroxaban and, to a lesser extent, of apixaban. Therefore, our results contribute evidence towards the effectiveness and safety of rivaroxaban and apixaban, which have been less extensively studied compared with dabigatran among patients with NVAF and CKD. However, given the limited evidence, future observational studies would help to further assess the safety of the various NOACs within this population, particularly those with a more severe CKD stage.

Use of the CPRD provided several advantages for our study. First, we were able to evaluate the comparative effectiveness and safety of NOACs in a well defined and representative cohort of patients with NVAF in the UK. Second, we classified treatment exposure using comprehensive CPRD prescription data, which is automatically transcribed into patients' electronic records by the clinician at the time of prescribing, therefore avoiding recall bias. Although we were not able to assess

Table 2 As-treated analyses of the comparative effectiveness and safety of NOACs

		All patients with NVAF			Patients with NVAF and CKD		
Outcome	Drug exposure	Events	Person-time in years	Adjusted* HR (95% CI)	Events	Person-time in years	Adjusted† HR (95% CI)
Ischaemic stroke/SE	VKA	44	2341.07	1.00 (reference)	17	913.13	1.00 (reference)
	NOAC	47	3379.05	0.94 (0.62 to 1.42)	16	1303.89	0.79 (0.40 to 1.58)
Major bleeding	VKA	40	2389.38	1.00 (reference)	19	899.66	1.00 (reference)
	NOAC	44	3391.36	0.86 (0.56 to 1.33)	23	1321.58	0.88 (0.47 to 1.62)
Intracranial bleeding	VKA	10	2337.03	1.00 (reference)	<5‡	904.46	1.00 (reference)
	NOAC	6	3359.16	0.51 (0.18 to 1.44)	<5‡	1325.62	0.73 (0.10 to 5.28)
GI bleeding	VKA	51	2346.59	1.00 (reference)	34	896.15	1.00 (reference)
	NOAC	116	3351.07	1.78 (1.27 to 2.48)	43	1302.43	0.99 (0.63 to 1.55)
Myocardial infarction	VKA	25	2388.46	1.00 (reference)	12	929.92	1.00 (reference)
	NOAC	28	3399.32	0.94 (0.54 to 1.63)	14	1323.15	0.98 (0.45 to 2.14)
Death	VKA	88	2411.62	1.00 (reference)	44	939.43	1.00 (reference)
	NOAC	144	3433.39	1.20 (0.92 to 1.58)	79	1343.47	1.34 (0.92 to 1.94)

*Adjusted for hypertension, diabetes, antiplatelet use and CKD, as time-dependent covariates.
†Adjusted for hypertension, diabetes and antiplatelet use, as time-dependent covariates.
‡Cells with less than five events were suppressed owing to privacy restrictions, in accordance with CPRD policy.
CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; GI, gastrointestinal; NOAC, novel oral anticoagulant; NVAF, non-valvular atrial fibrillation; SE, systemic embolism; VKA, vitamin K antagonist.

patients' compliance to their prescribed treatment, we obtained consistent results when evaluating the potential for exposure misclassification using different exposure definitions, as well as in various sensitivity analyses. Several limitations also have to be considered in our study. First, observational studies are susceptible to residual confounding, however, in matching on hd-PS, we were able to minimise imbalances in the distribution of covariates between exposure groups. Furthermore, hd-PS were calculated using the entirety of available CPRD data, and may have therefore incorporated proxies for unmeasured confounders. Second, owing

Table 3 On-treatment analyses of the comparative effectiveness and safety of NOACs using a time-dependent exposure definition

		All patients with NVAF			Patients with NVAF and CKD		
Outcome	Drug exposure*	Events	Person-time in years	Adjusted† HR (95% CI)	Events	Person-time in years	Adjusted‡ HR (95% CI)
Ischaemic stroke/SE	VKA	91	7652.58	1.00 (reference)	33	3005.67	1.00 (reference)
	NOAC	90	8387.21	0.93 (0.70 to 1.25)	38	3285.07	1.07 (0.67 to 1.71)
Major bleeding	VKA	101	7884.40	1.00 (reference)	47	2940.65	1.00 (reference)
	NOAC	115	8502.21	1.06 (0.81 to 1.38)	58	3294.41	1.10 (0.75 to 1.62)
Intracranial bleeding	VKA	21	7584.61	1.00 (reference)	10	2992.39	1.00 (reference)
	NOAC	19	8382.86	0.84 (0.45 to 1.57)	7	3333.11	0.62 (0.24 to 1.64)
GI bleeding	VKA	161	7592.96	1.00 (reference)	80	2928.80	1.00 (reference)
	NOAC	228	8301.75	1.30 (1.06 to 1.59)	98	3266.84	1.11 (0.83 to 1.49)
Myocardial infarction	VKA	52	7803.54	1.00 (reference)	25	3029.20	1.00 (reference)
	NOAC	48	8498.77	0.87 (0.59 to 1.30)	23	3328.41	0.86 (0.49 to 1.52)
Death	VKA	245	7812.37	1.00 (reference)	131	3100.51	1.00 (reference)
	NOAC	348	8574.31	1.25 (1.06 to 1.47)	180	3387.33	1.24 (0.99 to 1.55)

*Regression models also included simultaneous exposure to both VKA and NOAC and exposure to neither VKA nor NOAC.
†Adjusted for hypertension, diabetes, antiplatelet use and CKD, as time-dependent covariates.
‡Adjusted for hypertension, diabetes and antiplatelet use, as time-dependent covariates.
CKD, chronic kidney disease; GI, gastrointestinal; NOAC, novel oral anticoagulant; NVAF, non-valvular atrial fibrillation; SE, systemic embolism; VKA, vitamin K antagonist.

Table 4 As-treated sensitivity analyses of the comparative effectiveness and safety of NOACs, with 30 days added to the end of the continuous use period to account for informative censoring

		All patients with NVAF			Patients with NVAF and CKD		
Outcome	Drug exposure	Events	Person-time in years	Adjusted* HR (95% CI)	Events	Person-time in years	Adjusted† HR (95% CI)
Ischaemic stroke/SE	VKA	48	2815.13	1.00 (reference)	18	1095.30	1.00 (reference)
	NOAC	50	3773.79	0.95 (0.64 to 1.42)	18	1455.21	0.90 (0.47 to 1.75)
Major bleeding	VKA	43	2869.60	1.00 (reference)	22	1082.23	1.00 (reference)
	NOAC	47	3790.54	0.92 (0.61 to 1.40)	24	1472.19	0.87 (0.48 to 1.56)
Intracranial bleeding	VKA	10	2808.32	1.00 (reference)	<5‡	1088.42	1.00 (reference)
	NOAC	7	3753.26	0.65 (0.24 to 1.74)	<5‡	1477.20	0.84 (0.12 to 6.07)
GI bleeding	VKA	67	2819.65	1.00 (reference)	44	1079.08	1.00 (reference)
	NOAC	117	3741.32	1.47 (1.09 to 2.00)	45	1454.48	0.88 (0.58 to 1.34)
Myocardial infarction	VKA	30	2867.63	1.00 (reference)	15	1112.88	1.00 (reference)
	NOAC	32	3796.18	0.95 (0.57 to 1.57)	15	1474.08	0.92 (0.44 to 1.90)
Death	VKA	152	2894.39	1.00 (reference)	70	1127.60	1.00 (reference)
	NOAC	195	3835.57	1.01 (0.82 to 1.25)	98	1498.09	1.14 (0.83 to 1.55)

*Adjusted for hypertension, diabetes, antiplatelet use and CKD, as time-dependent covariates.
†Adjusted for hypertension, diabete, and antiplatelet use, as time-dependent covariates.
‡Cells with less than five events were suppressed owing to privacy restrictions, in accordance with CPRD policy.
CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; GI, gastrointestinal; NOAC, novel oral anticoagulant; NVAF, non-valvular atrial fibrillation; SE, systemic embolism; VKA, vitamin K antagonist.

to the small number of observed outcome events, we obtained wide CIs around many of our point estimates. Although these preclude definitive conclusions, the consistency of our results using different definitions of exposure and their concordance with previous RCTs still allow for informative interpretations of our analyses. Third, we were unable to take into consideration certain laboratory tests which may not be systematically recorded in a primary care database such as the CPRD. For example, we did not include changes in haemoglobin in our definition of major bleeding, as stipulated by the ISTH. Nevertheless, we adhered to the ISTH definition in all other regards, and therefore, we expect any outcome misclassification resulting from this limitation to be slight. We were further unable to use time in therapeutic range to assess the degree of achieved anticoagulation among new users of VKAs; in addition, comparable information would have not been available for new users of NOAC. Finally, our cohort size did not allow for an analysis of individual NOACs.

To conclude, our results suggest that NOACs are overall effective and safe alternatives to VKAs for the prevention of ischaemic stroke/SE in NVAF, including NVAF patients with CKD. Nevertheless, despite our reasonably large cohort, we lack the statistical power to make a definitive conclusion. Moreover, the effectiveness and safety of these medications may vary from one NOAC to the next, and therefore, further large observational studies should be conducted to evaluate individual NOAC compared to VKAs. This would further inform clinicians as to the most appropriate treatment options for their patients.

Contributors SYL contributed to the study design, conducted statistical analyses, interpreted the data, wrote the first draft of the manuscript and revised the manuscript for important intellectual content. JC conducted supplementary statistical analyses, supervised the conduct of the statistical analyses, interpreted the data and revised the manuscript for important intellectual content. SD contributed to the study design, supervised the conduct of the statistical analyses, interpreted the data and revised the manuscript for important intellectual content. JMB contributed to the study design, interpreted the data and revised the manuscript for important intellectual content. SS contributed to the study design, interpreted the data and revised the manuscript for important intellectual content. CR conceived and designed the study, supervised the conduct of the statistical analyses, interpreted the data, revised the manuscript for important intellectual content and provided supervision and funding.

Funding This work was supported by the Canadian Institutes of Health Research (MOP-341510). SYL is the recipient of a Frederick Banting and Charles Best Canada Graduate Scholarship from the Canadian Institutes of Health Research.

Competing interests SS has received research grants, participated in advisory board meetings and/or was a speaker at conferences for Bayer, Boehringer-Ingelheim and Bristol-Myers-Squibb.

Patient consent Not required.

Ethics approval This study protocol (No: 16_271R) was approved by the Independent Scientific Advisory Committee of the CPRD and the Research Ethics Committee of the Jewish General Hospital (Montreal, Canada), and was made available to journal reviewers.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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