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Appropriateness of initial dose of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Non-Valvular Atrial Fibrillation in the United Kingdom: a Population-Based Observational Study using Primary Care Electronic Health Records

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Short title: Appropriate dosing of NOACs in the UK

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ABSTRACT

Objective: To evaluate the appropriateness of the initial prescribed daily dose of non-vitamin K antagonist oral anticoagulants (NOACs) according to label in patients with non-valvular atrial fibrillation (NVAF) in the United Kingdom (UK).

Design: Population-based cross-sectional study

Setting: United Kingdom (UK) primary care

Population: 30,467 patients with NVAF and a first prescription for apixaban, dabigatran or rivaroxaban between January 2011 and December 2016.

Main outcome measures: Percentage of patients prescribed NOAC dose according to the European Union [EU] labels (appropriately dosed), and not according to the EU labels (inappropriately dosed – including both underdosed and overdosed patients); percentage of patients prescribed an initial NOAC dose according to renal function status.

Results: A total of 15,252 (50.1%) patients started NOAC therapy on rivaroxaban, 10,834 (35.6%) on apixaban and 4381 (14.4%) on dabigatran. Among patients starting NOAC therapy on rivaroxaban, 17.3% were eligible to receive a reduced dose compared with 12.8% of patients starting on apixaban and 53.8% of patients starting on dabigatran. The majority of patients were prescribed an appropriate dose according to the EU labels: apixaban 74.9 %, dabigatran, 74.4%; rivaroxaban, 84.2%. Underdosing occurred in 21.6% (apixaban), 8.7% (dabigatran), 9.1% (rivaroxaban). Overdosing was more frequent for dabigatran (16.9%) than for rivaroxaban (6.6%) or apixaban (3.5%). There was a trend towards dose reduction with increasing renal impairment. Among patients with severe renal

impairment, the majority received a reduced dose NOAC: apixaban, 91.1%, dabigatran, 80.0%, rivaroxaban, 83.0%.

Conclusion: Between 2011 and 2016, the majority of patients starting NOAC therapy in UK primary care were prescribed a daily dose in line with the approved EU drug label. Underdosing was more than twice as common among patients starting on apixaban than those starting on dabigatran or rivaroxaban.

STRENGTHS AND LIMITATIONS OF THE STUDY

- Our study is the first to comprehensively evaluate the appropriateness of the initial prescribed daily dose of NOACs to patients with NVAF in the UK according to the approved EU drug labels, and the largest of its kind worldwide.
- Our large sample size was derived from two population-based data sources representative of the UK general population
- A small degree of misclassification for renal function and bodyweight may have occurred due to inaccuracies in data recording, which may have affected our findings for a small proportion of patients.
- Potential overdosing may have been overestimated because patients may have split a prescribed standard dose over more than one day.

INTRODUCTION

Recent years have seen a rapid increase in the proportion of patients with atrial fibrillation (AF) starting anticoagulant therapy with a non-vitamin K antagonist oral anticoagulant (NOAC), replacing use of vitamin K antagonists (VKAs) as leading oral anticoagulant (OAC) therapy, both in the United Kingdom (UK),[1-3] and elsewhere in Europe.[4-7] Decisions to prescribe standard or reduced dose NOACs are made on the basis of specific considerations such as age, weight, renal function, and use of specific concomitant medications. Descriptive data show that a high proportion of patients with AF initiating anticoagulant therapy with a NOAC are prescribed a reduced dose,[8-10] particularly in Europe,[8 9] with evidence to suggest that many of these patients do not satisfy the necessary dose reduction criteria as specified on the drug labels.[10-14] In Europe, studies describing the appropriate dosing of prescribed NOACs have been conducted in smaller cohorts[8 12-14] and/or limited to a particular drug,[8 14] and we are unaware of any conducted in patients with NVAF in the UK. Therefore, using routinely-collected primary care electronic health records (EHRs), we conducted a large population-based study to evaluate the level of appropriate prescribing (consistency with the approved drug label) of standard and reduced dose NOACs in over 30,000 patients with NVAF initiating therapy with a NOAC between 2011 and 2016. To our knowledge, our study is the largest of its kind among patients with AF in routine clinical practice worldwide.

METHODS

Data sources

We used data from The Heath Improvement Network (THIN) and the Clinical Practice Research Datalink (CPRD)-GOLD in the UK – two similarly structured validated databases of anonymized primary care EHRs representative of the UK demographic.[15-18] The databases

hold clinical and prescribing information entered by primary care practitioners (PCP) as part of routine patient care, and cover approximately 5% and 7% of the UK population, respectively. The study protocol were approved by independent Scientific Research Committees (reference SRC 17THIN014 for THIN, and ISAC 17_020R for CPRD).

Study population

We identified patients aged ≥18 years with a first recorded prescription (index date) for apixaban, dabigatran or rivaroxaban between 01 January 2011 and 31 December 2016. Patients were required to have been registered with a PCP for at least 1 year before their first NOAC prescription and have at least 1 year prescription history. We subsequently identified patients with NVAF as those with a record of AF any time before the index date or in the 2 weeks after, and with no record of heart valve replacement or mitral stenosis during this time. We excluded patients with a record of deep vein thrombosis, pulmonary embolism, or hip/knee replacement surgery in the 3 months before the index date because these could all have been alternative reasons for NOAC initiation. As some practices contribute data to both THIN and CPRD, we included all practices contributing to THIN and those exclusively contributing to CPRD. To identify and exclude duplicated practices, matching of anonymized patient characteristics was applied.[19 20]

NOAC study cohorts

Three mutually exclusive cohorts were identified based on the first prescribed NOAC (index NOAC), either dabigatran (a direct thrombin inhibitor), apixaban or rivaroxaban (both direct factor Xa inhibitors). Edoxaban – another direct factor Xa inhibitor – was only relatively recently approved by the EMA and recommended by NICE (June and September 2015,

respectively), therefore we anticipated prescribing levels would not be sufficiently high for robust analysis and thus excluded new users of edoxaban. Identification of the study cohorts is depicted in (**Supplementary Figure 1**.) Patients who were prescribed two different NOACs on the same day were excluded. Patients qualifying as a new user of more than one NOAC during the study period with different index dates (i.e. switchers), were assigned to the cohort of the first prescribed NOAC. Patients were categorised as OAC non-naïve if they had a prescription for any oral anticoagulant before their index NOAC (or a clinical entry implying previous use of any oral anticoagulant, warfarin monitoring or international normalized ratio >2), otherwise they were considered to be OAC-naive.

Renal function and other patient characteristics

We extracted data on the initial daily dose of the index NOAC, as well as patients' age, renal function and weight at the time of the index date, using the most recently recorded values. Patients' renal function was ascertained using the closest valid serum creatinine value to the index date (within the year before) to estimate glomerular filtration rate (eGFR) expressed as mL/min/1.73m^2 applying the Chronic Kidney Disease Epidemiology Collaboration equation,[21] but omitting ethnicity because this is not routinely recorded in UK primary care. Individuals with no valid serum creatinine measurement were assigned to a category 'unknown'. Information on lifestyle variables (smoking status and body mass index [BMI]) was collected, using the most recently recorded value/status before the index date. CHA_2DS_2Vasc score for stroke risk was calculated according to patients' recorded history of congestive heart failure, hypertension, age, diabetes mellitus and prior stroke/transient ischaemic attack (CHADS score was also calculated because this was assessed in the pivotal studies for the NOACs investigated in this study). HAS-BLED score for major bleeding risk

was calculated using recorded history of hypertension, renal disease, liver disease, stroke history, prior major bleeding or predisposition to bleeding, age >65 years, medication use predisposing to bleeding, and alcohol use. We also estimated frailty using an adaptation of a frailty index developed from data recorded in primary care databases,[22] and categorised patients as fit, mildly frail, moderately frail or severely frail.

Recommendations for NOAC dosing

We categorised patients as eligible for standard or reduced dose NOAC therapy or ineligible for NOAC therapy (i.e. contraindicated) based on all information in the approved European Union (EU) label for each respective NOAC, adapted to the information recorded in the databases (**Supplementary Table 1**). For the prevention of stroke and systemic embolism in adults with NVAF, the recommended standard dosages according to the EU labels are 5 mg twice daily for apixaban, 150 mg twice daily for dabigatran and 20 mg once daily for rivaroxaban; the recommended reduced dosages are 2.5 mg twice daily for apixaban, 110 mg twice daily for dabigatran and 15 mg once daily for rivaroxaban. Hereafter, for simplicity, we refer to these dosages as 'daily dose'. Dose reduction recommendations for rivaroxaban are based on renal function, while dose reduction for dabigatran considers renal function, age, concomitant medications and other comorbidities. For apixaban, at least two of the following criteria are to be met for dose reduction: □8□years, body weight □□□kg, serum creatinine □B□%□ Also, patients with renal impairment creatinine clearance 15-29 mL/min patients are recommended to receive the reduced dose of apixaban. We defined appropriate dosing as a patient being prescribed the correct recommended dose based on the approved EU label. Potential inappropriate dosing was

defined as a patient being prescribed a dose not in line with the EU label – this included both underdosed patients (prescribing of a reduced dose NOAC to patients eligible for a standard dose) and overdosed patients (prescribing of a higher dose than recommended or any dose when contraindicated).

Statistical analysis

Patient characteristics were described according to the daily dose of the index NOAC (standard or reduced), using frequency counts and percentages for quantitative variables, and means with standard deviation (SD) for continuous variables. For each NOAC cohort, we calculated the percentage of patients appropriately dosed, both overall and according to whether the daily dose of the index NOAC was a standard or reduced dose. To determine if NOAC prescription patterns were influenced by renal status alone, we further evaluated the initial daily dose prescribed according to renal function, categorised as normal (eGFR >50 mL/min/1.73 m^2), mild-to-moderate impairment (eGFR 30–50 mL/min/1.73 m^2) and severe impairment (eGFR<30 mL/min/1.73 m^2). All analyses were undertaken using STATA version 12.0.

Patient and public involvement

This was a descriptive study using routinely collected primary care data in the UK. There was no public or patient involvement in the conception of the research question, the design and implementation of the study, or the writing of the manuscript.

RESULTS

During the study period, there were a total of 30,467 new users of a NOAC with a record of NVAF and no other recent indication for anticoagulation; 10,834 (35.6%) started on apixaban, 4381 (14.4%) started on dabigatran, and 15,252 (50.1%) started on rivaroxaban.

Patient characteristics by daily dose at index NOAC prescription

Characteristics of the study cohorts stratified by the daily dose of the index NOAC prescription (standard or reduced) are shown in **Table 1**. The most common starting NOAC dose was the standard 10 mg for apixaban (65.2% of patients) and the standard 20 mg for rivaroxaban (79.3% of patients). For dabigatran, the standard dose of 300 mg was not the most commonly prescribed initial dose, being slightly less frequently prescribed than a reduced dose of 220 mg (46.1% vs. 47.2%)(see **Supplementary Table 2** for a complete breakdown of the initial NOAC dose prescribed). A reduced starting NOAC dose was used in the majority of patients with impaired renal function. Among patients receiving a standard dose, the apixaban cohort had the highest proportion of OAC-naïve patients (55.4% vs. 45% for dabigatran and 48.6% for rivaroxaban). Most patients prescribed a standard dose had normal renal function (apixaban, 75.4%; dabigatran 80.5%; rivaroxaban, 79.0%). The majority of patients prescribed a reduced dose were aged 70 years or older (apixaban, 93.6%; dabigatran, 88.4%; rivaroxaban, 91.4%), and were moderately or severely frail (apixaban, 70.2%; dabigatran, 61.7%; rivaroxaban, 74.0%). Bleeding risk (according to the HAS-BLED score) was similar between the three cohorts, and was higher among patients prescribed reduced NOAC doses (mean 2.0, SD 0.9) than among patients receiving standard doses (mean 1.6; SD 0.9). Approximately three quarters of the patients in each cohort who were prescribed a reduced dose had a high stroke risk index (CHA2DS2VASc score of [illegible]

Overall appropriateness of index NOAC daily dose

Figure 1 presents the percentage of patients appropriately dosed, underdosed and overdosed among all patients in each study cohort. The majority of patients (76.9%) starting NOAC therapy were prescribed an appropriate dose; 74.9% of patients on apixaban, 74.4%

on dabigatran and 84.2% on rivaroxaban. Underdosing was more frequent in the apixaban cohort (21.6% of patients) than in the dabigatran (8.7% of patients) and rivaroxaban (9.1%) cohorts. Overdosing, however, was more frequent in the dabigatran cohort (16.9%) than in the rivaroxaban (6.6%) or apixaban (3.5%) cohorts.

Appropriateness of NOAC prescription by eligibility to receive a standard or reduced dose

As shown in **Table 2**, the majority of patients in the apixaban and rivaroxaban cohorts were eligible to receive the standard treatment dose, 84.9% (9194/10,834) for apixaban and 82.7% (12,608/15,252) for rivaroxaban, while in the dabigatran cohort less than half (40.9%; 1790/4381) were eligible for the standard dose. The percentage of users eligible to receive the reduced treatment dose was 12.8% for apixaban, 53.8% for dabigatran and 17.3% for rivaroxaban. Among all patients eligible to receive a standard dose NOAC (N=23,591), the majority received the correct standard dose (82.3%); this percentage was highest for rivaroxaban (88.5%) followed by dabigatran (78.7%) and apixaban (74.5%). However, a quarter of apixaban patients (25.5%, 2344/9194) eligible to receive the recommended standard daily dose were prescribed a reduced dose, compared with 21.3% (381/1790) in the dabigatran cohort and 11.0% (1390/12,608) in the rivaroxaban cohort. Among patients inappropriately prescribed a reduced dose of apixaban (n=2344), 73.1% met only one dose-reduction criteria with the remaining meeting no dose-reduction criteria. Among patients eligible for reduced dosing, the majority correctly received a reduced dose: apixaban (91.0%), dabigatran (78.4%) and rivaroxaban (63.9%).

Appropriateness of NOAC prescription among patients prescribed a standard or reduced dose

Among patients starting NOAC therapy on a standard daily dose, the prescription was appropriate for the vast majority of those in the apixaban cohort (97.0%) and rivaroxaban cohort (92.3%), but for fewer patients in the dabigatran cohort (69.8%) (**Supplementary Figure 2**). Among patients starting NOAC therapy on a reduced dose, this was appropriate in only 33.4% of patients in the apixaban cohort compared with 78.2% of the dabigatran cohort and 54.7% of the rivaroxaban cohort (**Supplementary Figure 2)**.

Dosing by degree of renal impairment

The daily dose of the index NOAC prescription according to renal function is shown in **Figure 2** (approximately 1 in 8 patients in each cohort had unknown renal function). In all three cohorts, there was a trend towards dose reduction with increasing renal impairment. Among patients with severe renal impairment (eGFR<30 mL/min /1.73 m^2), most were prescribed a reduced daily dose: apixaban (91.1%, [illegible] dabigatran (80.0%, [illegible] mg) and rivaroxaban (83.0%, 15 mg). However, reduced doses were also prescribed to patients with no evidence of renal impairment, especially among the dabigatran cohort (50.1%, 1634/3259; mostly 220 mg/day) followed by apixaban (26.7% (1968/7291; nearly all 5 mg/day), and least frequently for rivaroxaban (10.3%, 1105/10,699; mostly 15 mg/day) users.

NOAC daily dose over time

As shown in **Supplementary Table 3**, among patients with at least 6 months of follow-up and still prescribed a NOAC at 6 months, the vast majority were prescribed the same dose of

the index NOAC at 6 months (95.4% for apixaban, 93.7% for dabigatran and 94.5% for rivaroxaban). Among patients whose were underdosed at the index date and who also had at least 6 months of follow-up, the majority still received an underdosed prescription 6 months after their initial underdosed prescription: apixaban 90.2%, dabigatran 82.0% and rivaroxaban 84.6%.

DISCUSSION

Between 2011 and 2016, the majority of patients with NVAF starting therapy with a NOAC in UK primary care were prescribed an appropriate daily dose based on the approved EU label, according to the information recorded in THIN and CPRD-GOLD. However, notable differences were seen in the level of underdosing between individual NOACs, being more than twice as frequent among patients starting treatment on apixaban compared with those starting on dabigatran or rivaroxaban.

Our study is the first to comprehensively evaluate the appropriateness of the initial prescribed daily dose of NOACs to patients with NVAF in the UK according to the approved EU drug labels, and the largest of its kind worldwide. Also, we are unaware of other studies that have compared levels of potential underdosing and overdosing between individual NOACs. The large sample from two population-based data sources representative of the UK general population is a key strength, as is the fact that all medications prescribed by the PCP will have been captured because they are automatically recorded upon issue. In terms of our study's limitations, we evaluated the dose of the first NOAC prescription issued in primary care and not subsequent prescriptions; however, the majority of patients had continued on the same dose of the index NOAC 6 months after treatment initiation. A small

degree of misclassification for renal function and bodyweight may have occurred due to inaccuracies in data recording, which may have affected our findings for a small proportion of patients. Also, potential overdosing may have been overestimated because patients may have split a prescribed standard dose over more than one day.

Potential underdosing of NOACs has been reported in moderate-to-large studies from the US,[10 11] as well as in smaller studies from Europe and North America.[12-14] Using data from 7925 patients with AF in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II) registry, Steinberg *et al*,[10] reported that 57% (734/1289) of patients prescribed a reduced dose NOAC did not fulfill the Food and Drug Administration's (FDAs) recommended criteria for dose reduction. A larger administrative claims database study of 14,865 patients with AF initiating NOAC treatment reported a much lower level of underdosing with 13.3% (1781/13,392) of patients with no renal indication for dose reduction receiving a reduced dose;[11] although other criteria for dose reduction were not assessed. In our analyses, the percentage of patients receiving a reduced dose differed between the individual NOACs, occurring more than twice as frequently among patients prescribed apixaban or dabigatran than those prescribed rivaroxaban, possibly reflecting the additional criteria for dose reduction for the former two NOACs. Studies from Europe have been small but also suggest that underdosing may be more prevalent for apixaban than rivaroxaban. In Germany, Bucholtz *et al*[8] found that among 268 patients with NVAF starting reduced dose apixaban therapy in 2016, 60.8% did not meet labelling criteria for dose reduction, while in a study of 899 patients with NVAF starting rivaroxaban therapy in the Netherlands, Pisters *et al*[14] reported that 3.1% received a label-discordant dose. In the US, Yao *et al*[11] found that 43% of patients with a renal indication for NOAC dose reduction did

not receive a reduced dose, while Steinberg *et al*[10] found that 32% of NVAF patients eligible for dose reduction according to the FDA approved drug labels received a standard dose NOAC. This is similar to the level of potential rivaroxaban overdosing in our study. Whether differences in levels of inappropriate prescribing between studies relates to differences between study populations or completeness of data in the information sources is unclear, but patients in our study were on average 4 years older than those in the ORBIT-II registry (75 vs. 71 years) and previous gastrointestinal bleeding was more frequent (14% vs. 4%).

Inappropriate dosing of NOACs has concerning clinical implications because patients may not receive the benefits of the recommended NOAC dose in protecting against stroke and systemic embolism. Data from the ORBIT-II registry suggest that patients receiving an inappropriately reduced NOAC dose have less favourable outcomes in terms of thromboembolic events and death.[10] Yao *et al*[11] found that among apixaban-treated patients with no renal justification for dose reduction, those receiving the reduced dose had a significantly higher risk of stroke with no significant change in the risk of bleeding when compared with those receiving the standard dose. Reasons why PCPs prescribe reduced NOAC doses to patients with no justification for dose reduction are unclear. It is possible that NOAC-related bleeding may be more concerning to physicians than reduced stroke prophylaxis. Although, contrary to expectations, Steinberg *et al*[10] found that patients inappropriately prescribed a reduced dose of a NOAC were significantly younger and had lower bleeding scores than those appropriately dose-reduced. In our study, we saw a trend of dose reduction with worsening renal function. In addition, the majority of patients started on a reduced dose NOAC were moderately or severely frail. It is therefore possible that some PCPs are exercising caution among patients with renal function values close to

the qualifying cut-offs and/or among frail individuals. For apixaban, being close to the cut-offs for age and bodyweight could also influence prescribing In the study by Bucholtz *et al*[8] there were 163 apixaban patients who received a reduced dose despite being eligible for the higher dose, and among these a substantial percentage met either only one (57.1%) or no (42.9%) dose-reduction criteria, with these patients more often having ages, weights and serum creatinine levels close to the cut-off values compared with patients prescribed an appropriate dose. In our study, the majority (73.1%) of patients inappropriately prescribed a reduced dose of apixaban met only one dose reduction criteria. Our findings also pointed to some potential overdosing of NOACs, and as shown by others to increase bleeding risk.[11] Notwithstanding our study's limitation in assessing overdosing, the possibility of overdosing prescribing habits among some UK PCPs cannot be excluded.

Our findings underscore the importance of monitoring the prescribing of NOACs in the post-marketing period. Further research is warranted into reasons for the inappropriate prescribing of reduced and standard dose NOACs in UK primary care, the impact this has on risks of clinical outcomes, including stroke, systemic embolism and major bleeding in this setting, and ways to improve levels of correct dosing to ensure patients receive maximum benefit from treatment.

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Competing interests: PV, YB, KS-W and BS are employees of Bayer AG (Germany), the funder of the study; GB is an employee of Bayer AB, (Stockholm, Sweden); LR and SF are employees of Bayer PLC (Reading, UK). KS-W declares Bayer stocks; LR and SF declare shares in Bayer. LAGR, MM-P and AR work for the Spanish Centre for Pharmacoepidemiologic Research (Madrid, Spain), which has received research funding from Bayer AG. LAGR also declares honoraria for serving on advisory boards for Bayer AG.

Author contributions: LR and SF developed the concept for the research study. LR, SF, LAGR, AR, GB, PV, KS and YB planned the study. AR, MM-P and LAGR conducted the study. All authors interpreted the data, reviewed drafts of the manuscript, and approved the final version of the article for publication.

Data sharing: Data are available from the corresponding author upon reasonable request.

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Table 1. Baseline characteristics of the cohort of 30,467 new users of NOACs with NVAF and no other recent indication, stratified by dose of first NOAC prescription (standard or reduced dose).

	Apixaban (N=10,834)		Dabigatran (N=4381)		Rivaroxaban (N=15,252)*	
	Standard dose (n=7061; 65.2%)	Reduced dose (n= 3773; 34.8%)	Standard dose (n=2018; 46.1%)	Reduced dose (n=2363; 53.9%)	Standard dose (n=12,091; 79.3%)	Reduced dose (n=3081; 20.2%)
Sex						
Male	4271 (60.5)	1488 (39.4)	1380 (68.4)	1143 (48.4)	7042 (58.2)	1289 (41.8)
Female	2790 (39.5)	2285 (60.6)	638 (31.6)	1220 (51.6)	5049 (41.8)	1792 (58.2)
Age (years)						
<60	833 (11.8)	63 (1.7)	380 (18.8)	73 (3.1)	1233 (10.2)	66 (2.1)
60–69	1903 (27.0)	177 (4.7)	726 (36.0)	202 (8.5)	2696 (22.3)	199 (6.5)
70–79	2860 (40.5)	676 (17.9)	842 (41.7)	699 (29.6)	4400 (36.4)	715 (23.2)
≥80	1465 (20.7)	2857 (75.7)	70 (3.5)	1389 (58.8)	3762 (31.1)	2101 (68.2)
Mean age (SD)	71.4 (10.2)	82.8 (7.8)	67.2 (9.1)	79.7 (8.5)	73.6 (10.6)	81.8 (8.5)
OAC naïve status						
Naïve	3915 (55.4)	1859 (49.3)	909 (45.0)	918 (38.8)	5881 (48.6)	1295 (42.0)
Non-naïve	3146 (44.6)	1914 (50.7)	1109 (55.0)	1445 (61.2)	6210 (51.4)	1786 (58.0)
Year of first NOAC prescription						
2011–13	184 (2.6)	107 (2.8)	968 (48.0)	1206 (51.0)	1492 (12.3)	479 (15.5)
2014–16	6877 (97.4)	3666 (97.2)	1050 (52.0)	1157 (49.0)	10,599 (87.7)	2602 (84.5)
BMI						
10–19 (underweight)	117 (1.7)	331 (8.8)	35 (1.7)	139 (5.9)	434 (3.6)	212 (6.9)
20–24 (healthy weight)	1322 (18.7)	1201 (31.8)	343 (17.0)	665 (28.1)	2679 (22.2)	875 (28.4)
25–29 (overweight)	2599 (36.8)	1228 (32.5)	735 (36.4)	866 (36.6)	4230 (35.0)	1035 (33.6)
≥30(obese)	2766 (39.2)	836 (22.2)	809 (40.1)	593 (25.1)	4291 (35.5)	847 (27.5)
Unknown	257 (3.6)	177 (4.7)	96 (4.8)	100 (4.2)	457 (3.8)	112 (3.6)
Smoking						
Non-smoker	2851 (40.4)	1683 (44.6)	784 (38.9)	1015 (43.0)	4876 (40.3)	1282 (41.6)
Smoker	605 (8.6)	221 (5.9)	178 (8.8)	126 (5.3)	1015 (8.4)	182 (5.9)
Ex-smoker	3598 (51.0)	1865 (49.4)	1052 (52.1)	1221 (51.7)	6190 (51.2)	1617 (52.5)
Unknown	7 (0.1)	4 (0.1)	4 (0.2)	1 (0.0)	10 (0.1)	0 (0.0)

	Apixaban (N=10,834)		Dabigatran (N=4381)		Rivaroxaban (N=15,252)*	
	Standard dose (n=7061; 65.2%)	Reduced dose (n= 3773; 34.8%)	Standard dose (n=2018; 46.1%)	Reduced dose (n=2363; 53.9%)	Standard dose (n=12,091; 79.3%)	Reduced dose (n=3081; 20.2%)
Alcohol (units/week)						
None	1356 (19.2)	1129 (29.9)	244 (12.1)	526 (22.3)	2244 (18.6)	827 (26.8)
1–9	3044 (43.1)	1663 (44.1)	857 (42.5)	1128 (47.7)	5501 (45.5)	1448 (47.0)
10–20	1316 (18.6)	390 (10.3)	422 (20.9)	315 (13.3)	1975 (16.3)	316 (10.3)
21–41	470 (6.7)	128 (3.4)	219 (10.9)	99 (4.2)	821 (6.8)	95 (3.1)
O	227 (3.2)	48 (1.3)	92 (4.6)	45 (1.9)	354 (2.9)	50 (1.6)
Unknown	648 (9.2)	415 (11.0)	184 (9.1)	250 (10.6)	1196 (9.9)	345 (11.2)
History of CVD						
IHD	1939 (27.5)	1309 (34.7)	416 (20.6)	735 (31.1)	3014 (24.9)	1098 (35.6)
Heart failure	1080 (15.3)	847 (22.4)	268 (13.3)	469 (19.8)	1709 (14.1)	791 (25.7)
Hypertension	4464 (63.2)	2762 (73.2)	1192 (59.1)	1691 (71.6)	7888 (65.2)	2338 (75.9)
Ischaemic stroke	990 (14.0)	774 (20.5)	254 (12.6)	435 (18.4)	1567 (13.0)	553 (17.9)
History of bleeding disorders						
Intracranial bleeding	96 (1.4)	108 (2.9)	20 (1.0)	51 (2.2)	139 (1.1)	52 (1.7)
GI bleeding	957 (13.6)	573 (15.2)	232 (11.5)	349 (14.8)	1609 (13.3)	440 (14.3)
Urogenital bleeding	877 (12.4)	517 (13.7)	214 (10.6)	309 (13.1)	1629 (13.5)	449 (14.6)
eGFR (CKD-EPI) /min/1.73 m²						
>50	5323 (75.4)	1968 (52.2)	1625 (80.5)	1634 (69.1)	9547 (79.0)	1105 (35.9)
30–50	694 (9.8)	1125 (29.8)	110 (5.5)	464 (19.6)	892 (7.4)	1475 (47.9)
<30	25 (0.4)	255 (6.8)	4 (0.2)	16 (0.7)	46 (0.4)	223 (7.2)
Unknown	1019 (14.4)	425 (11.3)	279 (13.8)	249 (10.5)	1606 (13.3)	278 (9.0)
Frailty index						
Fit	1306 (18.5)	191 (5.1)	517 (25.6)	201 (8.5)	2120 (17.5)	133 (4.3)
Mild frailty	2839 (40.2)	933 (24.7)	918 (45.5)	706 (29.9)	4624 (38.2)	668 (21.7)
Moderate frailty	1978 (28.0)	1395 (37.0)	448 (22.2)	833 (35.3)	3522 (29.1)	1182 (38.4)
Severe frailty	938 (13.3)	1254 (33.2)	135 (6.7)	623 (26.4)	1825 (15.1)	1098 (35.6)

	Apixaban (N=10,834)		Dabigatran (N=4381)		Rivaroxaban (N=15,252)*	
	Standard dose (n=7061; 65.2%)	**Reduced dose (n= 3773; 34.8%)**	**Standard dose (n=2018; 46.1%)**	**Reduced dose (n=2363; 53.9%)**	**Standard dose (n=12,091; 79.3%)**	**Reduced dose (n=3081; 20.2%)**
CHA_2DS_2VASc score						
0	42 (6.0)	25 (0.7)	220 (10.9)	32 (1.4)	608 (5.0)	23 (0.7)
1	675 (9.6)	52 (1.4)	260 (12.9)	76 (3.2)	1107 (9.2)	68 (2.2)
2	1425 (20.2)	252 (6.7)	517 (25.6)	222 (9.4)	2182 (18.0)	199 (6.5)
3	1564 (22.1)	623 (16.5)	418 (20.7)	475 (20.1)	2681 (22.2)	507 (16.5)
O	2971 (42.1)	2821 (74.8)	603 (29.9)	1558 (65.9)	5513 (45.6)	2284 (74.1)
Mean (SD)	3.2 (1.8)	4.6 (1.6)	2.7 (1.7)	4.2 (1.7)	3.4 (1.8)	4.6 (1.6)
CHADS score						
0	1127 (16.0)	103 (2.7)	480 (23.8)	114 (4.8)	1696 (14.0)	103 (3.3)
1	2119 (30.0)	595 (15.8)	681 (33.7)	448 (19.0)	3440 (28.5)	452 (14.7)
2	1929 (27.3)	1259 (33.4)	468 (23.2)	786 (33.3)	3596 (29.7)	1044 (33.9)
O	1886 (26.7)	1816 (48.1)	389 (19.3)	1015 (43.0)	3359 (27.8)	1482 (48.1)
Mean (SD)	1.8 (1.3)	2.6 (1.3)	1.5 (1.2)	1.9 (1.3)	1.9 (1.3)	2.6 (1.3)
HAS-BLED score						
0	814 (11.5)	46 (1.2)	312 (15.5)	49 (2.1)	1224 (10.1)	54 (1.8)
1	2437 (34.5)	1163 (30.8)	704 (34.9)	721 (30.5)	4460 (36.9)	938 (30.4)
2	2510 (35.5)	1514 (40.1)	699 (34.6)	1005 (42.5)	4467 (36.9)	1305 (42.4)
3	1089 (15.4)	789 (20.9)	263 (13.0)	470 (19.9)	1612 (13.3)	596 (19.3)
O	211 (3.0)	261 (6.9)	40 (2.0)	118 (5.0)	328 (2.7)	188 (6.1)
Mean (SD)	1.6 (1.0)	2.0 (1.0)	1.6 (0.9)	2.0 (0.9)	1.6 (0.9)	2.0 (0.9)
Medications†						
Antiplatelets	3250 (46.0)	1844 (48.9)	993 (49.2)	1285 (54.4)	5299 (43.8)	1519 (49.3)
Antiarrhythmics	1074 (15.2)	467 (12.4)	403 (20.0)	425 (18.0)	1764 (14.6)	403 (13.1)
Antihypertensives	6114 (86.6)	3400 (90.1)	1743 (86.4)	2147(90.9)	10,591 (87.6)	2860 (92.8)

*80 patients starting therapy on rivaroxaban were prescribed an initial daily dose higher than standard daily dose (>20 mg day) and are not included in the table.†Prescription in the year before the first NOAC prescription.

BMI, body mass index; CVD, cardiovascular disease; CKD-EPI, Chronic Kidney Disease Epidemiology; eGFR, estimated glomerular filtration; GI, gastrointestinal; IHD, ischaemic heart disease; NOACs, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; SD, standard deviation.

Table 2. Prescribing of recommended daily dose of index NOAC (first NOAC prescription) by eligibility according to the EU label.

Daily dose of index NOAC prescribed	Dosing eligibility			
	Standard dose	**Reduced dose**	**Contra-indicated**	**Total (overall eligibility)**
APIXABAN	**N=9194**	**N=1385**	**N=255**	**N=10,834**
Recommended	6850 (74.5)	1260 (91.0)	NA	8110 (74.9)
Lower than recommended	2344 (25.5)	0 (0)	NA	2344 (21.6)
Higher than recommended	0 (0)	125 (9.0)	NA	125 (1.1)
Prescribed a NOAC when contraindicated	NA	NA	255 (100)	255 (2.4)
DABIGATRAN	**N=1790**	**N=2357**	**N=234**	**N=4381**
Recommended	1409 (78.7)	1849 (78.4)	NA	3258 (74.4)
Lower than recommended	381 (21.3)	0 (0)	NA	381 (8.7)
Higher than recommended	0 (0)	508 (21.6)	NA	508 (11.6)
Prescribed a NOAC when contraindicated	NA	NA	234 (100)	234 (5.3)
RIVAROXABAN	**N=12,607**	**N=2638**	**N=7**	**N=15,252**
Recommended	11,162 (88.5)	1687 (63.9)	NA	12,849 (84.2)
Lower than recommended	1389 (11.0)	0 (0)	NA	1389 (9.1)
Higher than recommended	56 (0.40)	951 (36.1)	NA	1007 (6.6)
Prescribed a NOAC when contraindicated	NA	NA	7 (100)	7 (0.05)

Data are n (column %).

EU, European Union; NOAC, non-vitamin K antagonist oral anticoagulants

FIGURE LEGENDS

Figure 1. Overall dose appropriateness of index NOAC daily dose (first prescribed NOAC).

NOAC, non-vitamin K antagonist oral anticoagulant.

Figure 2. Daily dose at index prescription by degree of renal impairment* for (**A**) new users of apixaban, (**B**) new users of dabigatran and (**C**) new users of rivaroxaban, in patients with NVAF and no other recent indication. *Note*: Renal function was unknown in 13.6% of the apixaban cohort, 12.3% of the dabigatran cohort and 13.0% of the rivaroxaban cohort.

*Estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.

eGFR, estimated glomerular filtration rate; NVAF, non-valvular atrial fibrillation

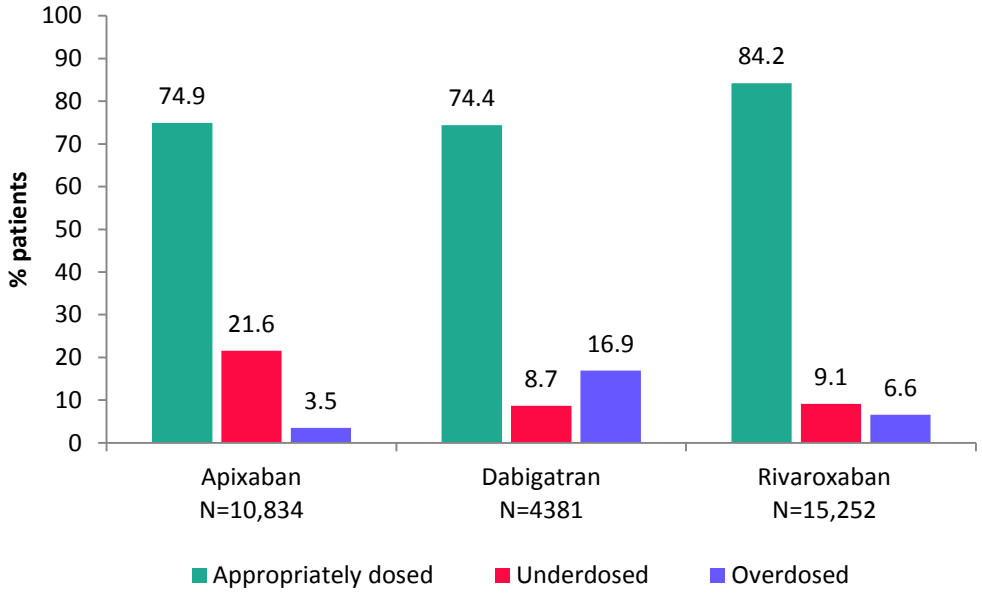
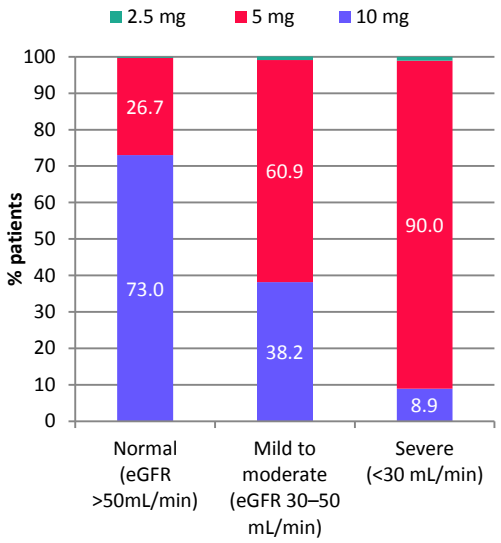


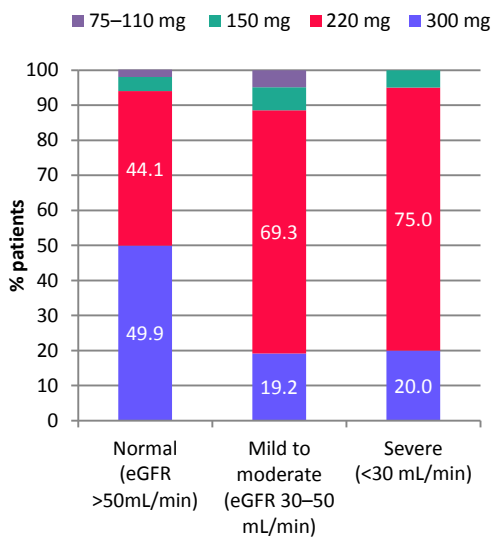
Figure 1. Overall dose appropriateness of index NOAC daily dose (first prescribed NOAC).

NOAC, non-vitamin K antagonist oral anticoagulant.

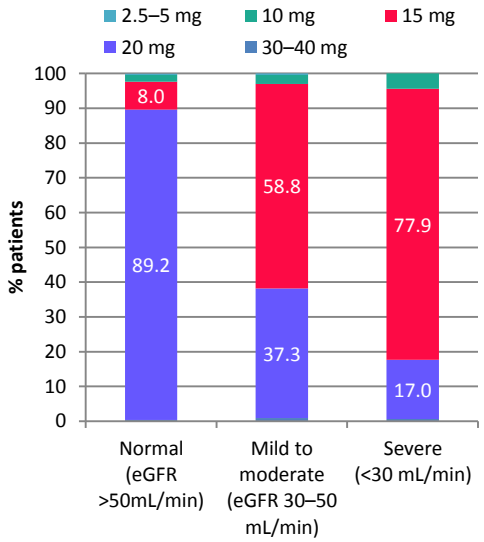
A. Apixaban



B. Dabigatran



C. Rivaroxaban



Supplementary Table 1. Recommended dosing criteria and contraindications for each NOAC (for the prevention of stroke and systemic embolism in patients with NVAF) that were applied in the study.

NOAC	Reduced dosing criteria	Contraindications
Apixaban[a] **standard or normal recommended daily dose = 10 mg**	2.5 mg taken orally twice daily in patients with NVAF and ≥ 2 of the following: • age ≥ 80 years • body weight ≤ 60 kg • serum creatinine ≥ 1.5 mg/dL (133 micromole/L). Or, severe renal impairment (CrCL 15–29 mL/min)	*Note*: In patients with CrCL < 15 ml/min or undergoing dialysis, there is no clinical experience therefore apixaban is not recommended.
Dabigatran[b] **standard or normal recommended daily dose = 300mg**	• age ≥ 80 years • concomitant use of verapamil Reduction for consideration when[d]: • patients between 75–80 years • patients with moderate renal impairment (CrCL 30–50 mL/min • patients with gastritis oesophagitis or gastrooesophagel reflux.	• Severe renal impairment (CrCL < 30ml/min) *Note*: Dabigatran is also not recommended in patients with hepatic impairment or liver disease
Rivaroxaban[c] **standard or normal recommended daily dose = 20mg**	In patients with moderate/severe renal impairment (CrCL 15–49 ml/min)	• Severe renal impairment (creatinine clearance < 15 ml/min)

Sources from which our modified criteria were obtained.

[a]Eliquis. Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf. Accessed 7 September 2018.

[b]Pradaxa. Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf

[c]Xarelto. Pradaxa. Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf

[d]Patients meeting at least one of these criteria were considered eligible for dose reduction in our study.

CrCL, creatinine clearance; NVAF, non-valvular atrial fibrillation

Supplementary Table 2. Frequency distribution of the daily dose of index NOAC prescription.

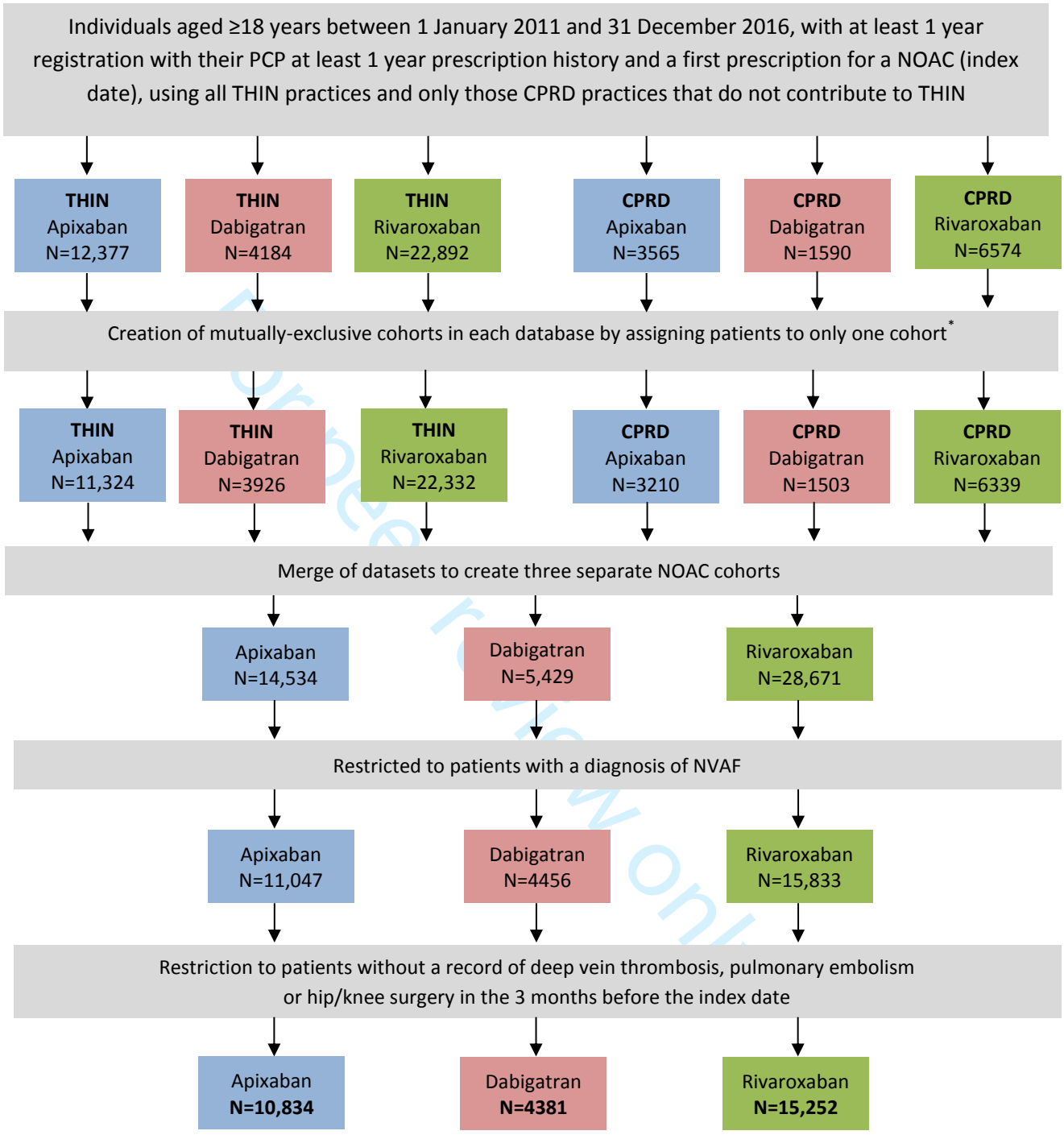
Daily dose of index NOAC prescription	No. of patients	% of patients
Apixaban	**10,834**	
2.5 mg	53	0.5
5 mg	3720	34.3
10 mg (standard)	7061	65.2
Dabigatran	**4381**	
75–110 mg	101	2.3
150 mg	196	4.5
220 mg	2066	47.2
300 mg (standard)	2018	46.1
Rivaroxaban	**15,252**	
2.5–5 mg	50	0.3
10 mg	340	2.2
15 mg	2691	17.6
20 mg (standard)	12,091	79.3
30–40 mg	80	0.5

NOAC, non-vitamin K antagonist oral anticoagulant

Supplementary Table 3. Daily dose of NOAC 6 months after the index date among patients with at least 6 months follow-up and still using a NOAC at 6 months.

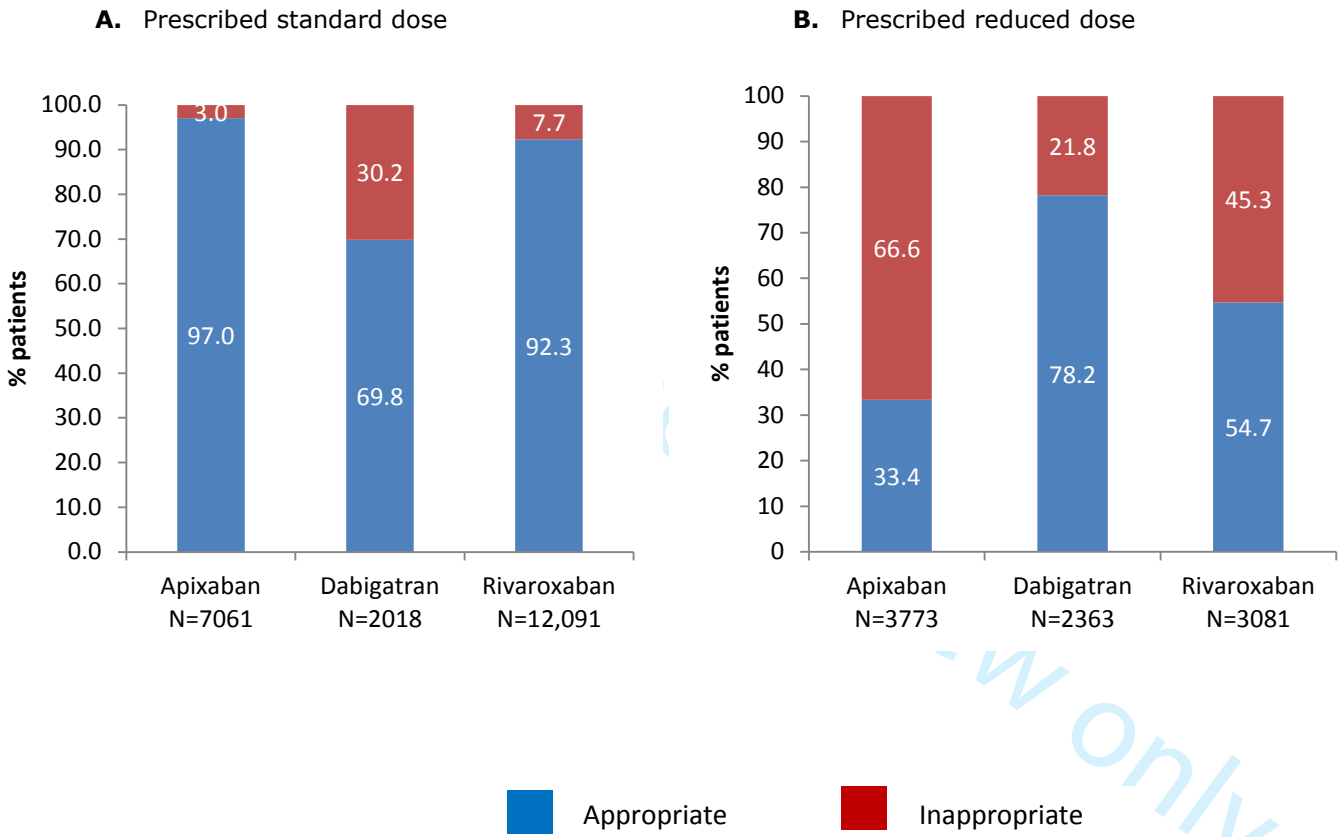
	Daily dose 6 months after the index date					
	Lower dose than the index NOAC prescription		Same dose than the index NOAC prescription		Higher dose than the index NOAC prescription	
	n	%	n	%	n	%
Apixaban (N=6783)	119	1.8	6471	95.4	193	2.8
Dabigatran (2874)	74	2.6	2692	93.7	108	3.8
Rivaroxaban (10,068)	377	3.7	9511	94.5	180	1.8

NOAC, non-vitamin K antagonist oral anticoagulant



Supplementary Figure 1. Flowchart depicting identification of the three NOAC study cohorts from THIN and the CPRD. *Mutually exclusive cohorts were created by excluding patients who were prescribed two different NOACs on the same day and by assigning patients to the cohort of the first prescribed NOAC.

CPRD, Clinical Practice Research Datalink; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; PCP, primary care practitioner; THIN, The Health Improvement Network.



Supplementary Figure 2: Appropriateness of daily dose of index NOAC among patients with non-valvular atrial fibrillation who were prescribed (**A**) a standard dose and (**B**) a reduced dose.
NOAC, non-vitamin K antagonist oral anticoagulant

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2 and 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5 and 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6 to 8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6 to 8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8 to 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7 to 8
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9 and Suppl Fig 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Suppl Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	10 to 13, Fig 1, Fig 2 and Suppl Fig 2

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Appropriateness of initial dose of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Non-Valvular Atrial Fibrillation in the United Kingdom: a Population-Based Observational Study using Primary Care Electronic Health Records

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Appropriateness of initial dose of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Non-Valvular Atrial Fibrillation in the United Kingdom: a Population-Based Observational Study using Primary Care Electronic Health Records

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Short title: Appropriate dosing of NOACs in the UK

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ABSTRACT

Objective: To evaluate the appropriateness of the initial prescribed daily dose of non-vitamin K antagonist oral anticoagulants (NOACs) according to label in patients with non-valvular atrial fibrillation (NVAF) in the United Kingdom (UK).

Design: Population-based cross-sectional study

Setting: UK primary care

Population: 30,467 patients with NVAF and a first prescription for apixaban, dabigatran or rivaroxaban between January 2011 and December 2016.

Main outcome measures: Percentage of patients prescribed NOAC dose according to the European Union [EU] labels (appropriately dosed), and not according to the EU labels (inappropriately dosed – including both underdosed and overdosed patients); percentage of patients prescribed an initial NOAC dose according to renal function status.

Results: A total of 15,252 (50.1%) patients started NOAC therapy on rivaroxaban, 10,834 (35.6%) on apixaban and 4381 (14.4%) on dabigatran. Among patients starting NOAC therapy on rivaroxaban, 17.3% were eligible to receive a reduced dose compared with 12.8% of patients starting on apixaban and 53.8% of patients starting on dabigatran. The majority of patients were prescribed an appropriate dose according to the EU labels: apixaban 74.9 %, dabigatran, 74.4%; rivaroxaban, 84.2%. Underdosing occurred in 21.6% (apixaban), 8.7% (dabigatran), 9.1% (rivaroxaban). Overdosing was more frequent for dabigatran (16.9%) than for rivaroxaban (6.6%) or apixaban (3.5%). There was a trend towards dose reduction with increasing renal impairment. Among patients with severe renal

impairment, the majority received a reduced dose NOAC: apixaban, 91.1%, dabigatran, 80.0%, rivaroxaban, 83.0%.

Conclusion: Between 2011 and 2016, the majority of patients starting NOAC therapy in UK primary care were prescribed a daily dose in line with the approved EU drug label. Underdosing was more than twice as common among patients starting on apixaban than those starting on dabigatran or rivaroxaban. Research into the patient characteristics that may influence inappropriate underdosing of NOACs in UK primary care is warranted.

STRENGTHS AND LIMITATIONS OF THE STUDY

- Our study is the first to comprehensively evaluate the appropriateness of the initial prescribed daily dose of NOACs to patients with NVAF in the UK according to the approved EU drug labels, and the largest of its kind worldwide.
- Our large sample size was derived from two population-based data sources representative of the UK general population, both of which contained data on bodyweight
- A potential limitation of study is that a small degree of misclassification for renal function and bodyweight may have occurred due to inaccuracies in data recording, which may have affected our findings for a small proportion of patients.
- Potential overdosing may have been overestimated because patients may have split a prescribed standard dose over more than one day.

INTRODUCTION

Recent years have seen a rapid increase in the proportion of patients with atrial fibrillation (AF) starting anticoagulant therapy with a non-vitamin K antagonist oral anticoagulant (NOAC), replacing use of vitamin K antagonists (VKAs) as leading oral anticoagulant (OAC) therapy, both in the United Kingdom (UK),[1-3] and elsewhere in Europe.[4-7] Decisions to prescribe standard or reduced dose NOACs are made on the basis of specific considerations such as age, weight, renal function, and use of specific concomitant medications. Descriptive data show that a high proportion of patients with AF initiating anticoagulant therapy with a NOAC are prescribed a reduced dose,[4 8-10] particularly in Europe,[8 9] with evidence to suggest that many of these patients do not satisfy the necessary dose reduction criteria as specified on the drug labels.[10-15] In Europe, studies describing the appropriate dosing of prescribed NOACs have been conducted in smaller cohorts[8 12-14] and/or limited to a particular drug,[8 14] and we are unaware of any conducted in patients with NVAF in the UK. Therefore, using routinely-collected primary care electronic health records (EHRs), we conducted a large population-based study with the aim of evaluating the level of appropriate prescribing (consistency with the approved drug label) of standard and reduced dose NOACs in over 30,000 patients with NVAF initiating therapy with a NOAC between 2011 and 2016. To our knowledge, our study is the largest of its kind among patients with AF in routine clinical practice worldwide.

METHODS

Data sources

We used data from The Heath Improvement Network (THIN) and the Clinical Practice Research Datalink (CPRD)-GOLD in the UK – two similarly structured validated databases of

anonymized primary care EHRs representative of the UK demographic.[16-19] The databases hold clinical and prescribing information entered by general practitioners (GPs) as part of routine patient care, and cover approximately 5% and 7% of the UK population, respectively. The study protocol were approved by independent Scientific Research Committees (reference SRC 17THIN014 for THIN, and ISAC 17_020R for CPRD). Data collection for THIN was approved by the South East Multicentre Research Ethics Committee in 2003 and individual studies using THIN data do not require separate ethical approval if only anonymized THIN data is used. Similarly, the CPRD has been granted generic ethics approval for individual studies that make use of only anonymised data.

Study population

We identified patients aged ≥18 years with a first recorded prescription (index date) for apixaban, dabigatran or rivaroxaban between 01 January 2011 and 31 December 2016. Patients were required to have been registered with a GP for at least 1 year before their first NOAC prescription and have at least 1 year prescription history. We subsequently identified patients with NVAF as those with a record of AF any time before the index date or in the 2 weeks after, and with no record of heart valve replacement or mitral stenosis during this time. We excluded patients with a record of deep vein thrombosis, pulmonary embolism, or hip/knee replacement surgery in the 3 months before the index date because these could all have been alternative reasons for NOAC initiation. As some practices contribute data to both THIN and CPRD, we included all practices contributing to THIN and those exclusively contributing to CPRD. To identify and exclude duplicated practices, matching of anonymized patient characteristics was applied.[20 21]

NOAC study cohorts

Three mutually exclusive cohorts were identified based on the first prescribed NOAC (index NOAC) for stroke prevention in AF, either dabigatran (a direct thrombin inhibitor), apixaban or rivaroxaban (both direct factor Xa inhibitors). Edoxaban – another direct factor Xa inhibitor – was only relatively recently approved by the EMA and recommended by NICE (June and September 2015, respectively), therefore we anticipated prescribing levels would not be sufficiently high for robust analysis and thus excluded new users of edoxaban. Identification of the study cohorts is depicted in (**Supplementary Figure 1**.) Patients who were prescribed two different NOACs on the same day were excluded. Patients qualifying as a new user of more than one NOAC during the study period with different index dates (i.e. switchers), were assigned to the cohort of the first prescribed NOAC. Patients were categorised as OAC non-naïve if they had a prescription for any oral anticoagulant before their index NOAC (or a clinical entry implying previous use of any oral anticoagulant, warfarin monitoring or international normalized ratio >2), otherwise they were considered to be OAC-naive.

Renal function and other patient characteristics

We calculated the daily dose of the index NOAC based on the product instructions (quantity, pack size, number of tablets and posology) for the first recorded NOAC prescription. We also extracted information on patients' age, renal function and weight at the time of the index date, using the most recently recorded values. Patients' renal function was ascertained using the closest valid serum creatinine value to the index date (within the year before) to estimate glomerular filtration rate (eGFR) expressed as mL/min/1.73m^2 applying the Chronic Kidney Disease Epidemiology Collaboration equation,[22] but omitting ethnicity because this is

not routinely recorded in UK primary care. Individuals with no valid serum creatinine measurement were assigned to a category 'unknown'. Information on lifestyle variables (smoking status and body mass index [BMI]) was collected, using the most recently recorded value/status before the index date. CHA_2DS_2Vasc score for stroke risk was calculated according to patients' recorded history of congestive heart failure, hypertension, age, diabetes mellitus and prior stroke/transient ischaemic attack (CHADS score was also calculated because this was assessed in the pivotal studies for the NOACs investigated in this study). HAS-BLED score for major bleeding risk was calculated using recorded history of hypertension, renal disease, liver disease, stroke history, prior major bleeding or predisposition to bleeding, age >65 years, medication use predisposing to bleeding, and alcohol use. We also estimated frailty using an adaptation of a frailty index developed from data recorded in primary care databases,[23] and categorised patients as fit, mildly frail, moderately frail or severely frail.

Recommendations for NOAC dosing

We categorised patients as eligible for standard or reduced dose NOAC therapy or ineligible for NOAC therapy (i.e. contraindicated) based on all information in the approved European Union (EU) label for each respective NOAC, adapted to the information recorded in the databases (**Supplementary Table 1**). For the prevention of stroke and systemic embolism in adults with NVAF, the recommended standard dosages according to the EU labels are 5 mg twice daily for apixaban, 150 mg twice daily for dabigatran and 20 mg once daily for rivaroxaban; the recommended reduced dosages are 2.5 mg twice daily for apixaban, 110 mg twice daily for dabigatran and 15 mg once daily for rivaroxaban. Hereafter, for

simplicity, we refer to these dosages as 'daily dose'. Dose reduction recommendations for rivaroxaban are based on renal function, while dose reduction for dabigatran considers renal function, age, concomitant medications and other comorbidities. For apixaban, at least two of the following criteria are to be met for dose reduction: ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5mg/dL. Also, patients with renal impairment creatinine clearance 15-29 mL/min patients are recommended to receive the reduced dose of apixaban. We therefore defined appropriate dosing as a patient being prescribed the correct recommended dose based on the approved EU label. Potential inappropriate dosing was defined as a patient being prescribed a dose not in line with the EU label – this included both underdosed patients (prescribing of a reduced dose NOAC to patients eligible for a standard dose) and overdosed patients (prescribing of a higher dose than recommended or any dose when contraindicated).

Statistical analysis

Patient characteristics were described according to the daily dose of the index NOAC (standard or reduced), using frequency counts and percentages for quantitative variables, and means with standard deviation (SD) for continuous variables. For each NOAC cohort, we calculated the percentage of patients appropriately dosed, both overall and according to whether the daily dose of the index NOAC was a standard or reduced dose. For this calculation, patients with missing data on renal function were assumed to have normal renal function, and those with missing data on weight (when analysing apixaban dosing) were assumed to have a weight above 60 kg. To determine if NOAC prescription patterns were influenced by renal status alone, we further evaluated the initial daily dose prescribed according to renal function, categorised as normal (eGFR >50 mL/min/1.73 m^2), mild-to-

moderate impairment (eGFR 30–50 mL/min/1.73 m^2) and severe impairment (eGFR<30 mL/min/1.73 m^2). All analyses were undertaken using STATA version 12.0.

Patient and public involvement

This was a descriptive study using routinely collected primary care data in the UK. There was no public or patient involvement in the conception of the research question, the design and implementation of the study, or the writing of the manuscript.

RESULTS

During the study period, there were a total of 30,467 new users of a NOAC with a record of NVAF and no other recent indication for anticoagulation; 10,834 (35.6%) started on apixaban, 4381 (14.4%) started on dabigatran, and 15,252 (50.1%) started on rivaroxaban.

Patient characteristics by daily dose at index NOAC prescription

Characteristics of the study cohorts stratified by the total daily dose of the index NOAC prescription (standard or reduced) are shown in **Table 1**, and the frequency distribution of the daily dose of the index NOAC prescription is shown in **Supplementary Table 2.**

A reduced NOAC dose was prescribed in the majority of patients with impaired renal function. Among patients receiving a standard dose, the apixaban cohort had the highest proportion of OAC-naïve patients (55.4% vs. 45% for dabigatran and 48.6% for rivaroxaban). Most patients prescribed a standard dose had normal renal function. Among patients prescribed a reduced dose NOAC, the majority were aged 70 years or older and were moderately or severely frail. Bleeding risk (according to the HAS-BLED score) was similar between the three cohorts, and was higher among patients prescribed reduced NOAC doses (mean 2.0, SD 0.9) than among patients receiving standard doses (mean 1.6; SD 0.9).

Approximately three quarters of the patients in each cohort who were prescribed a reduced dose had a high stroke risk index (CHA2DS2VASc score of ≥4).

Overall appropriateness of index NOAC daily dose

Characteristics of patients appropriately or inappropriately dosed in accordance with the drug label can be found in **Supplementary Table 3**. The percentage of patients appropriately dosed, underdosed and overdosed among all patients in each study cohort **is shown in Figure 1**. The majority of patients (76.9%) starting NOAC therapy were prescribed an appropriate dose; 74.9% of patients on apixaban, 74.4% on dabigatran and 84.2% on rivaroxaban. Underdosing was more frequent in the apixaban cohort (21.6% of patients) than in the dabigatran (8.7% of patients) and rivaroxaban (9.1%) cohorts. Overdosing was more frequent in the dabigatran cohort (16.9%) than in the rivaroxaban (6.6%) or apixaban (3.5%) cohorts. Little difference was seen in the level of appropriate prescribing when analyses were stratified by whether patients had previously been prescribed a vitamin K antagonist (non-naïve) or not (naïve)(**Supplementary Tables 4a** to **4d**).

Appropriateness of NOAC prescription by eligibility to receive a standard or reduced dose

As shown in **Table 2**, the majority of patients in the apixaban and rivaroxaban cohorts were eligible to receive the standard treatment dose, 84.9% (9194/10,834) for apixaban and 82.7% (12,608/15,252) for rivaroxaban, while in the dabigatran cohort less than half (40.9%; 1790/4381) were eligible for the standard dose. The percentage of users eligible to receive the reduced treatment dose was 12.8% for apixaban, 53.8% for dabigatran and 17.3% for rivaroxaban. Among all patients eligible to receive a standard dose NOAC (N=23,591), the majority received the correct standard dose (82.3%); this percentage was highest for

rivaroxaban (88.5%) followed by dabigatran (78.7%) and apixaban (74.5%). However, a quarter of apixaban patients (25.5%, 2344/9194) eligible to receive the recommended standard daily dose were prescribed a reduced dose, compared with 21.3% (381/1790) in the dabigatran cohort and 11.0% (1390/12,608) in the rivaroxaban cohort. Among patients inappropriately prescribed a reduced dose of apixaban (n=2344), 73.1% met only one dose-reduction criteria with the remaining meeting no dose-reduction criteria. Among patients eligible for reduced dosing, the majority correctly received a reduced dose: apixaban (91.0%), dabigatran (78.4%) and rivaroxaban (63.9%).

Appropriateness of NOAC prescription among patients prescribed a standard or reduced dose

Among patients starting NOAC therapy on a standard daily dose, the prescription was appropriate for the vast majority of those in the apixaban cohort (97.0%) and rivaroxaban cohort (92.3%), but for fewer patients in the dabigatran cohort (69.8%) (**Supplementary Figure 2**). Among patients starting NOAC therapy on a reduced dose, this was appropriate in only 33.4% of patients in the apixaban cohort compared with 78.2% of the dabigatran cohort and 54.7% of the rivaroxaban cohort (**Supplementary Figure 2)**.

Dosing by degree of renal impairment

The daily dose of the index NOAC prescription according to renal function is shown in **Figure 2** (approximately 1 in 8 patients in each cohort had unknown renal function). In all three cohorts, there was a trend towards dose reduction with increasing renal impairment. Among patients with severe renal impairment (eGFR<30 mL/min /1.73 m^2), most were

prescribed a reduced daily dose: apixaban (91.1%, ≤5mg), dabigatran (80.0%, ≤200 mg) and rivaroxaban (83.0%, 15 mg). However, reduced doses were also prescribed to patients with no evidence of renal impairment, especially among the dabigatran cohort (50.1%, 1634/3259; mostly 220 mg/day) followed by apixaban (26.7% (1968/7291; nearly all 5 mg/day), and least frequently for rivaroxaban (10.3%, 1105/10,699; mostly 15 mg/day) users.

NOAC daily dose over time

As shown in **Supplementary Table 5**, among patients with at least 6 months of follow-up and a continuous user of a NOAC at 6 months (i.e. no gaps of more than 30 days between the end of supply of one prescription and the start of the next), the vast majority were prescribed the same dose of the index NOAC at 6 months (95.4% for apixaban, 93.7% for dabigatran and 94.5% for rivaroxaban). Among patients whose were underdosed at the index date and who also had at least 6 months of follow-up, the majority still received an underdosed prescription 6 months after their initial underdosed prescription: apixaban 90.2%, dabigatran 82.0% and rivaroxaban 84.6%. Baseline doses of the index NOAC among patients who were, or who were not, continuous users of a NOAC at 6 months are shown in **Supplementary Table 6**).

DISCUSSION

Between 2011 and 2016, the majority of patients with NVAF starting therapy with a NOAC in UK primary care were prescribed an appropriate daily dose based on the approved EU label, according to the information recorded in THIN and CPRD-GOLD. However, notable differences were seen in the level of underdosing between individual NOACs, being more

than twice as frequent among patients starting treatment on apixaban compared with those starting on dabigatran or rivaroxaban.

Our study is the first to comprehensively evaluate the appropriateness of the initial prescribed daily dose of NOACs to patients with NVAF in the UK according to the approved EU drug labels, and the largest of its kind worldwide. Also, few other studies have compared levels of potential underdosing and overdosing between individual NOACs. The large sample from two population-based data sources representative of the UK general population is a key strength, as is the fact that all medications prescribed by the GP will have been captured because they are automatically recorded upon issue. Another strength is that, unlike other healthcare databases, THIN and CPRD-GOLD contain data on all criteria, including bodyweight, required to make an accurate assessment of appropriate NOAC dosing. In terms of our study's limitations, we evaluated the dose of the first NOAC prescription issued in primary care and not subsequent prescriptions; however, the majority of patients had continued on the same dose of the index NOAC 6 months after treatment initiation. Additionally, although the very first NOAC prescription may have been issued in secondary care and this will not have been captured in the primary care databases, we believe it is unlikely that the first NOAC prescription issued in primary care would be a different dose to that issued by a specialist with the relevant expertise. A small degree of misclassification for renal function and bodyweight may have occurred due to inaccuracies in data recording, which may have affected our findings for a small proportion of patients. Also, potential overdosing may have been overestimated because patients may have split a prescribed standard dose over more than one day, and likewise potential underdosing may have occurred if patients were instructed to spread out their prescribed medication, although we feel this is unlikely.

Potential underdosing of NOACs has been reported in moderate-to-large studies from the US,[10 11] as well as in smaller studies from Europe, North America[12-14] and Israel,[15] with findings indicative of variation in the level of inappropriate NOAC dosing between countries. Using data from 7925 patients with AF in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II) registry, Steinberg *et al*,[10] reported that 57% (734/1289) of patients prescribed a reduced dose NOAC did not fulfill the Food and Drug Administration's (FDAs) recommended criteria for dose reduction. A larger administrative claims database study of 14,865 patients with AF initiating NOAC treatment reported a much lower level of underdosing with 13.3% (1781/13,392) of patients with no renal indication for dose reduction receiving a reduced dose;[11] although other criteria for dose reduction were not assessed. A large administrative healthcare database study in Israel reported very high levels of inappropriate prescribing of low-dose NOACs, occurring in 84% of patients prescribed reduced dose dabigatran, 68% of those prescribed reduced dosed apixaban and 78.5% of those prescribed reduced dose rivaroxaban. It is unclear what factors might underlie the marked difference in findings between studies yet it is clear that inappropriate underdosing is not uncommon. In our analyses, the percentage of patients receiving a reduced dose differed between the individual NOACs, occurring more than twice as frequently among patients prescribed apixaban or dabigatran than those prescribed rivaroxaban. One can speculate that this finding may reflect the criteria for dose reduction for the former two NOACs with respect to apixaban and dabigatran although it was not possible to substantiate this with the current study design. Studies from Europe have been small but also suggest that underdosing may be more prevalent for apixaban than rivaroxaban. In Germany, Bucholtz *et al*[8] found that among 268 patients with NVAF starting

reduced dose apixaban therapy in 2016, 60.8% did not meet labelling criteria for dose reduction, while in a study of 899 patients with NVAF starting rivaroxaban therapy in the Netherlands, Pisters *et al*[14] reported that 3.1% received a label-discordant dose. In the US, Yao *et al*[11] found that 43% of patients with a renal indication for NOAC dose reduction did not receive a reduced dose, while Steinberg *et al*[10] found that 32% of NVAF patients eligible for dose reduction according to the FDA approved drug labels received a standard dose NOAC. This is similar to the level of potential rivaroxaban overdosing in our study. Whether differences in levels of inappropriate prescribing between studies relates to differences between study populations or completeness of data in the information sources is unclear, but patients in our study were on average 4 years older than those in the ORBIT-II registry (75 vs. 71 years) and previous gastrointestinal bleeding was more frequent (14% vs. 4%).

Inappropriate dosing of NOACs has concerning clinical implications because patients may not receive the benefits of the recommended NOAC dose in protecting against stroke and systemic embolism. Data from the ORBIT-II registry suggest that patients receiving an inappropriately reduced NOAC dose have less favourable outcomes in terms of thromboembolic events and death.[10] Yao *et al*[11] found that among apixaban-treated patients with no renal justification for dose reduction, those receiving the reduced dose had a significantly higher risk of stroke with no significant change in the risk of bleeding when compared with those receiving the standard dose. Reasons why GPs prescribe reduced NOAC doses to patients with no justification for dose reduction are unclear. It is possible that NOAC-related bleeding may be more concerning to physicians than reduced stroke prophylaxis. Although, contrary to expectations, Steinberg *et al*[10] found that patients inappropriately prescribed a reduced dose of a NOAC were significantly younger and had

lower bleeding scores than those appropriately dose-reduced. In our study, we saw a trend of dose reduction with worsening renal function. In addition, the majority of patients started on a reduced dose NOAC were moderately or severely frail. It is therefore possible that some GPs are exercising caution among patients with renal function values close to the qualifying cut-offs and/or among frail individuals. For apixaban, being close to the cut-offs for age and bodyweight could also influence prescribing In the study by Bucholtz *et al*[8] there were 163 apixaban patients who received a reduced dose despite being eligible for the higher dose, and among these a substantial percentage met either only one (57.1%) or no (42.9%) dose-reduction criteria, with these patients more often having ages, weights and serum creatinine levels close to the cut-off values compared with patients prescribed an appropriate dose. In our study, the majority (73.1%) of patients inappropriately prescribed a reduced dose of apixaban met only one dose reduction criteria. Our findings also pointed to some potential overdosing of NOACs, and as shown by others to increase bleeding risk.[11] Notwithstanding our study's limitation in assessing overdosing, the possibility of overdosing prescribing habits among some UK GPs cannot be excluded.

Our findings underscore the importance of monitoring the prescribing of NOACs in the post-marketing period. Research is warranted into reasons for the inappropriate prescribing of reduced and standard dose NOACs in UK primary care, and the patient characteristics that may influence this. Additionally, research is needed into the impact that inappropriate dosing of NOACs has on risks of clinical outcomes, including stroke, systemic embolism and major bleeding in this setting, and ways to improve levels of correct dosing to ensure patients receive maximum benefit from treatment.

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Competing interests: PV, YB, KS-W and BS are employees of Bayer AG (Germany), the funder of the study; GB is an employee of Bayer AB, (Stockholm, Sweden); LR and SF are employees of Bayer PLC (Reading, UK). KS-W declares Bayer stocks; LR and SF declare shares in Bayer. LAGR, MM-P and AR work for the Spanish Centre for Pharmacoepidemiologic Research (Madrid, Spain), which has received research funding from Bayer AG. LAGR also declares honoraria for serving on advisory boards for Bayer AG.

Author contributions: LR and SF developed the concept for the research study. LR, SF, LAGR, AR, GB, PV, KS-W and YB planned the study. AR, MM-P and LAGR conducted the study. All authors (LAGR, AR, MM-P, LR, SF, GB, PV, KS-W, YB and BS) interpreted the data, reviewed drafts of the manuscript, and approved the final version of the article for publication.

Data sharing: Data are available from the corresponding author upon reasonable request.

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Table 1. Baseline characteristics of the cohort of 30,467 new users of NOACs with NVAF and no other recent indication, stratified by dose of first NOAC prescription (standard or reduced dose).

	Apixaban (N=10,834)		Dabigatran (N=4381)		Rivaroxaban (N=15,252)*	
	Standard dose (n=7061; 65.2%)	Reduced dose (n= 3773; 34.8%)	Standard dose (n=2018; 46.1%)	Reduced dose (n=2363; 53.9%)	Standard dose (n=12,091; 79.3%)	Reduced dose (n=3081; 20.2%)
Sex						
Male	4271 (60.5)	1488 (39.4)	1380 (68.4)	1143 (48.4)	7042 (58.2)	1289 (41.8)
Female	2790 (39.5)	2285 (60.6)	638 (31.6)	1220 (51.6)	5049 (41.8)	1792 (58.2)
Age (years)						
<60	833 (11.8)	63 (1.7)	380 (18.8)	73 (3.1)	1233 (10.2)	66 (2.1)
60–69	1903 (27.0)	177 (4.7)	726 (36.0)	202 (8.5)	2696 (22.3)	199 (6.5)
70–79	2860 (40.5)	676 (17.9)	842 (41.7)	699 (29.6)	4400 (36.4)	715 (23.2)
≥80	1465 (20.7)	2857 (75.7)	70 (3.5)	1389 (58.8)	3762 (31.1)	2101 (68.2)
Mean age (SD)	71.4 (10.2)	82.8 (7.8)	67.2 (9.1)	79.7 (8.5)	73.6 (10.6)	81.8 (8.5)
OAC naïve status						
Naïve	3915 (55.4)	1859 (49.3)	909 (45.0)	918 (38.8)	5881 (48.6)	1295 (42.0)
Non-naïve	3146 (44.6)	1914 (50.7)	1109 (55.0)	1445 (61.2)	6210 (51.4)	1786 (58.0)
Year of first NOAC prescription						
2011–13	184 (2.6)	107 (2.8)	968 (48.0)	1206 (51.0)	1492 (12.3)	479 (15.5)
2014–16	6877 (97.4)	3666 (97.2)	1050 (52.0)	1157 (49.0)	10,599 (87.7)	2602 (84.5)
BMI						
10–19 (underweight)	117 (1.7)	331 (8.8)	35 (1.7)	139 (5.9)	434 (3.6)	212 (6.9)
20–24 (healthy weight)	1322 (18.7)	1201 (31.8)	343 (17.0)	665 (28.1)	2679 (22.2)	875 (28.4)
25–29 (overweight)	2599 (36.8)	1228 (32.5)	735 (36.4)	866 (36.6)	4230 (35.0)	1035 (33.6)
≥30 (obese)	2766 (39.2)	836 (22.2)	809 (40.1)	593 (25.1)	4291 (35.5)	847 (27.5)
Unknown	257 (3.6)	177 (4.7)	96 (4.8)	100 (4.2)	457 (3.8)	112 (3.6)
Smoking						
Non-smoker	2851 (40.4)	1683 (44.6)	784 (38.9)	1015 (43.0)	4876 (40.3)	1282 (41.6)
Smoker	605 (8.6)	221 (5.9)	178 (8.8)	126 (5.3)	1015 (8.4)	182 (5.9)
Ex-smoker	3598 (51.0)	1865 (49.4)	1052 (52.1)	1221 (51.7)	6190 (51.2)	1617 (52.5)
Unknown	7 (0.1)	4 (0.1)	4 (0.2)	1 (0.0)	10 (0.1)	0 (0.0)

	Apixaban (N=10,834)		Dabigatran (N=4381)		Rivaroxaban (N=15,252)*	
	Standard dose (n=7061; 65.2%)	**Reduced dose (n= 3773; 34.8%)**	**Standard dose (n=2018; 46.1%)**	**Reduced dose (n=2363; 53.9%)**	**Standard dose (n=12,091; 79.3%)**	**Reduced dose (n=3081; 20.2%)**
Alcohol (units/week)						
None	1356 (19.2)	1129 (29.9)	244 (12.1)	526 (22.3)	2244 (18.6)	827 (26.8)
1–9	3044 (43.1)	1663 (44.1)	857 (42.5)	1128 (47.7)	5501 (45.5)	1448 (47.0)
10–20	1316 (18.6)	390 (10.3)	422 (20.9)	315 (13.3)	1975 (16.3)	316 (10.3)
21–41	470 (6.7)	128 (3.4)	219 (10.9)	99 (4.2)	821 (6.8)	95 (3.1)
≥42	227 (3.2)	48 (1.3)	92 (4.6)	45 (1.9)	354 (2.9)	50 (1.6)
Unknown	648 (9.2)	415 (11.0)	184 (9.1)	250 (10.6)	1196 (9.9)	345 (11.2)
History of CVD						
IHD	1939 (27.5)	1309 (34.7)	416 (20.6)	735 (31.1)	3014 (24.9)	1098 (35.6)
Heart failure	1080 (15.3)	847 (22.4)	268 (13.3)	469 (19.8)	1709 (14.1)	791 (25.7)
Hypertension	4464 (63.2)	2762 (73.2)	1192 (59.1)	1691 (71.6)	7888 (65.2)	2338 (75.9)
Ischaemic stroke	990 (14.0)	774 (20.5)	254 (12.6)	435 (18.4)	1567 (13.0)	553 (17.9)
History of bleeding disorders						
Intracranial bleeding	96 (1.4)	108 (2.9)	20 (1.0)	51 (2.2)	139 (1.1)	52 (1.7)
GI bleeding	957 (13.6)	573 (15.2)	232 (11.5)	349 (14.8)	1609 (13.3)	440 (14.3)
Urogenital bleeding	877 (12.4)	517 (13.7)	214 (10.6)	309 (13.1)	1629 (13.5)	449 (14.6)
eGFR (CKD-EPI) /min/1.73 m²						
>50	5323 (75.4)	1968 (52.2)	1625 (80.5)	1634 (69.1)	9547 (79.0)	1105 (35.9)
30–50	694 (9.8)	1125 (29.8)	110 (5.5)	464 (19.6)	892 (7.4)	1475 (47.9)
<30	25 (0.4)	255 (6.8)	4 (0.2)	16 (0.7)	46 (0.4)	223 (7.2)
Unknown	1019 (14.4)	425 (11.3)	279 (13.8)	249 (10.5)	1606 (13.3)	278 (9.0)
Frailty index						
Fit	1306 (18.5)	191 (5.1)	517 (25.6)	201 (8.5)	2120 (17.5)	133 (4.3)
Mild frailty	2839 (40.2)	933 (24.7)	918 (45.5)	706 (29.9)	4624 (38.2)	668 (21.7)
Moderate frailty	1978 (28.0)	1395 (37.0)	448 (22.2)	833 (35.3)	3522 (29.1)	1182 (38.4)
Severe frailty	938 (13.3)	1254 (33.2)	135 (6.7)	623 (26.4)	1825 (15.1)	1098 (35.6)

	Apixaban (N=10,834)		Dabigatran (N=4381)		Rivaroxaban (N=15,252)*	
	Standard dose (n=7061; 65.2%)	**Reduced dose (n= 3773; 34.8%)**	**Standard dose (n=2018; 46.1%)**	**Reduced dose (n=2363; 53.9%)**	**Standard dose (n=12,091; 79.3%)**	**Reduced dose (n=3081; 20.2%)**
CHA_2DS_2VASc score						
0	42 (6.0)	25 (0.7)	220 (10.9)	32 (1.4)	608 (5.0)	23 (0.7)
1	675 (9.6)	52 (1.4)	260 (12.9)	76 (3.2)	1107 (9.2)	68 (2.2)
2	1425 (20.2)	252 (6.7)	517 (25.6)	222 (9.4)	2182 (18.0)	199 (6.5)
3	1564 (22.1)	623 (16.5)	418 (20.7)	475 (20.1)	2681 (22.2)	507 (16.5)
≥4	2971 (42.1)	2821 (74.8)	603 (29.9)	1558 (65.9)	5513 (45.6)	2284 (74.1)
Mean (SD)	3.2 (1.8)	4.6 (1.6)	2.7 (1.7)	4.2 (1.7)	3.4 (1.8)	4.6 (1.6)
CHADS score						
0	1127 (16.0)	103 (2.7)	480 (23.8)	114 (4.8)	1696 (14.0)	103 (3.3)
1	2119 (30.0)	595 (15.8)	681 (33.7)	448 (19.0)	3440 (28.5)	452 (14.7)
2	1929 (27.3)	1259 (33.4)	468 (23.2)	786 (33.3)	3596 (29.7)	1044 (33.9)
≥3	1886 (26.7)	1816 (48.1)	389 (19.3)	1015 (43.0)	3359 (27.8)	1482 (48.1)
Mean (SD)	1.8 (1.3)	2.6 (1.3)	1.5 (1.2)	1.9 (1.3)	1.9 (1.3)	2.6 (1.3)
HAS-BLED score						
0	814 (11.5)	46 (1.2)	312 (15.5)	49 (2.1)	1224 (10.1)	54 (1.8)
1	2437 (34.5)	1163 (30.8)	704 (34.9)	721 (30.5)	4460 (36.9)	938 (30.4)
2	2510 (35.5)	1514 (40.1)	699 (34.6)	1005 (42.5)	4467 (36.9)	1305 (42.4)
3	1089 (15.4)	789 (20.9)	263 (13.0)	470 (19.9)	1612 (13.3)	596 (19.3)
≥4	211 (3.0)	261 (6.9)	40 (2.0)	118 (5.0)	328 (2.7)	188 (6.1)
Mean (SD)	1.6 (1.0)	2.0 (1.0)	1.6 (0.9)	2.0 (0.9)	1.6 (0.9)	2.0 (0.9)
Medications†						
Antiplatelets	3250 (46.0)	1844 (48.9)	993 (49.2)	1285 (54.4)	5299 (43.8)	1519 (49.3)
Antiarrhythmics	1074 (15.2)	467 (12.4)	403 (20.0)	425 (18.0)	1764 (14.6)	403 (13.1)
Antihypertensives	6114 (86.6)	3400 (90.1)	1743 (86.4)	2147(90.9)	10,591 (87.6)	2860 (92.8)

*80 patients starting therapy on rivaroxaban were prescribed an initial daily dose higher than standard daily dose (>20 mg day) and are not included in the table.†Prescription in the year before the first NOAC prescription.

BMI, body mass index; CVD, cardiovascular disease; CKD-EPI, Chronic Kidney Disease Epidemiology; eGFR, estimated glomerular filtration; GI, gastrointestinal; IHD, ischaemic heart disease; NOACs, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; SD, standard deviation.

Table 2. Prescribing of recommended daily dose of index NOAC (first NOAC prescription) by eligibility according to the EU label.

Daily dose of index NOAC prescribed	Dosing eligibility			
	Standard dose	Reduced dose	Contra-indicated	Total (overall eligibility)
APIXABAN	**N=9194**	**N=1385**	**N=255**	**N=10,834**
Recommended	6850 (74.5)	1260 (91.0)	NA	8110 (74.9)
Lower than recommended	2344 (25.5)	0 (0)	NA	2344 (21.6)
Higher than recommended	0 (0)	125 (9.0)	NA	125 (1.1)
Prescribed a NOAC when contraindicated	NA	NA	255 (100)	255 (2.4)
DABIGATRAN	**N=1790**	**N=2357**	**N=234**	**N=4381**
Recommended	1409 (78.7)	1849 (78.4)	NA	3258 (74.4)
Lower than recommended	381 (21.3)	0 (0)	NA	381 (8.7)
Higher than recommended	0 (0)	508 (21.6)	NA	508 (11.6)
Prescribed a NOAC when contraindicated	NA	NA	234 (100)	234 (5.3)
RIVAROXABAN	**N=12,607**	**N=2638**	**N=7**	**N=15,252**
Recommended	11,162 (88.5)	1687 (63.9)	NA	12,849 (84.2)
Lower than recommended	1389 (11.0)	0 (0)	NA	1389 (9.1)
Higher than recommended	56 (0.40)	951 (36.1)	NA	1007 (6.6)
Prescribed a NOAC when contraindicated	NA	NA	7 (100)	7 (0.05)

Data are n (column %).

EU, European Union; NOAC, non-vitamin K antagonist oral anticoagulants

FIGURE LEGENDS

Figure 1. Overall dose appropriateness of index NOAC daily dose (first prescribed NOAC).

NOAC, non-vitamin K antagonist oral anticoagulant.

Figure 2. Daily dose at index prescription by degree of renal impairment* for (**A**) new users of apixaban, (**B**) new users of dabigatran and (**C**) new users of rivaroxaban, in patients with NVAF and no other recent indication. *Note*: Renal function was unknown in 13.6% of the apixaban cohort, 12.3% of the dabigatran cohort and 13.0% of the rivaroxaban cohort.

*Estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.

eGFR, estimated glomerular filtration rate; NVAF, non-valvular atrial fibrillation

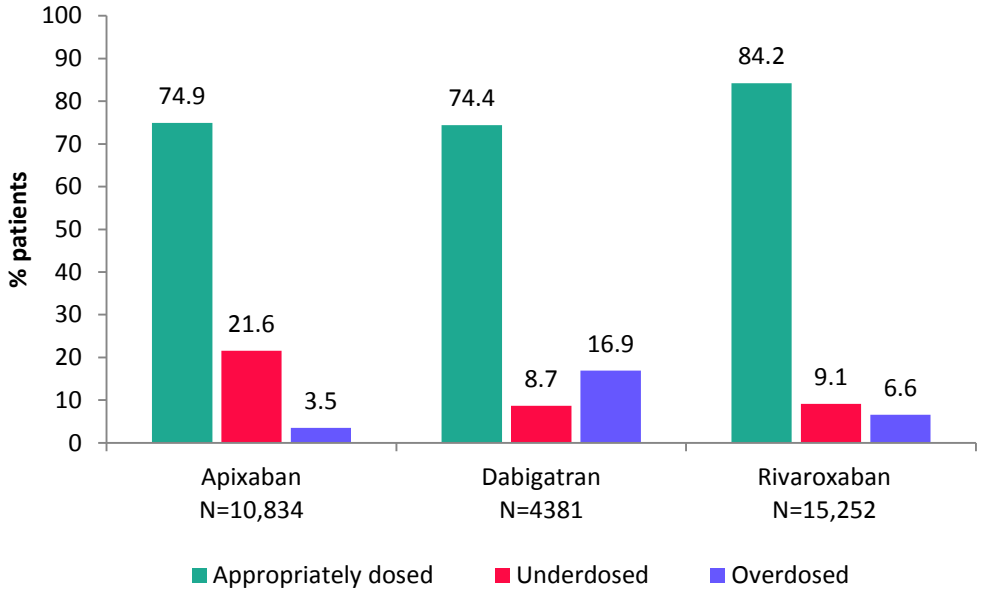
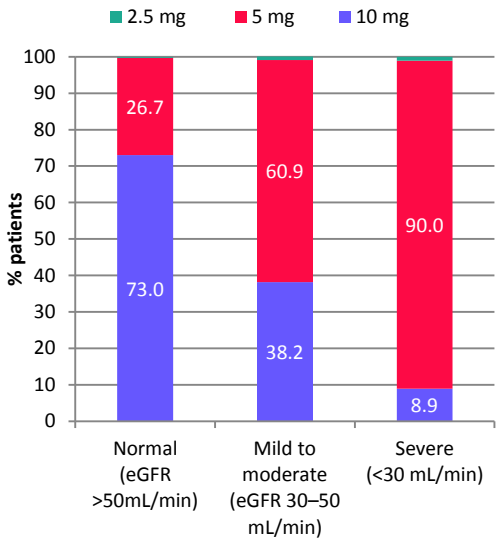


Figure 1. Overall dose appropriateness of index NOAC daily dose (first prescribed NOAC).

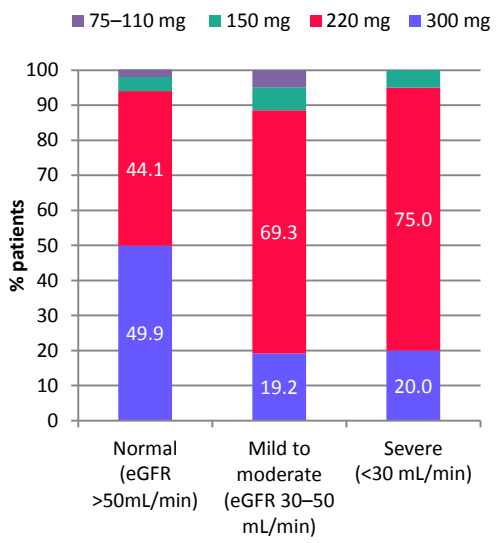
NOAC, non-vitamin K antagonist oral anticoagulant.

Note: Overdosed includes patients who received a higher dose than recommended plus patients who were contraindicated.

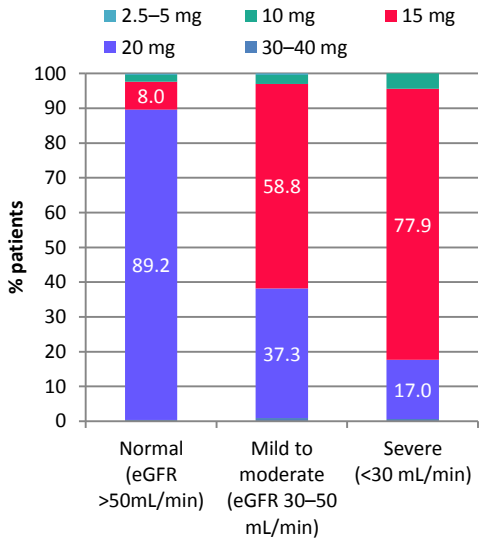
A. Apixaban

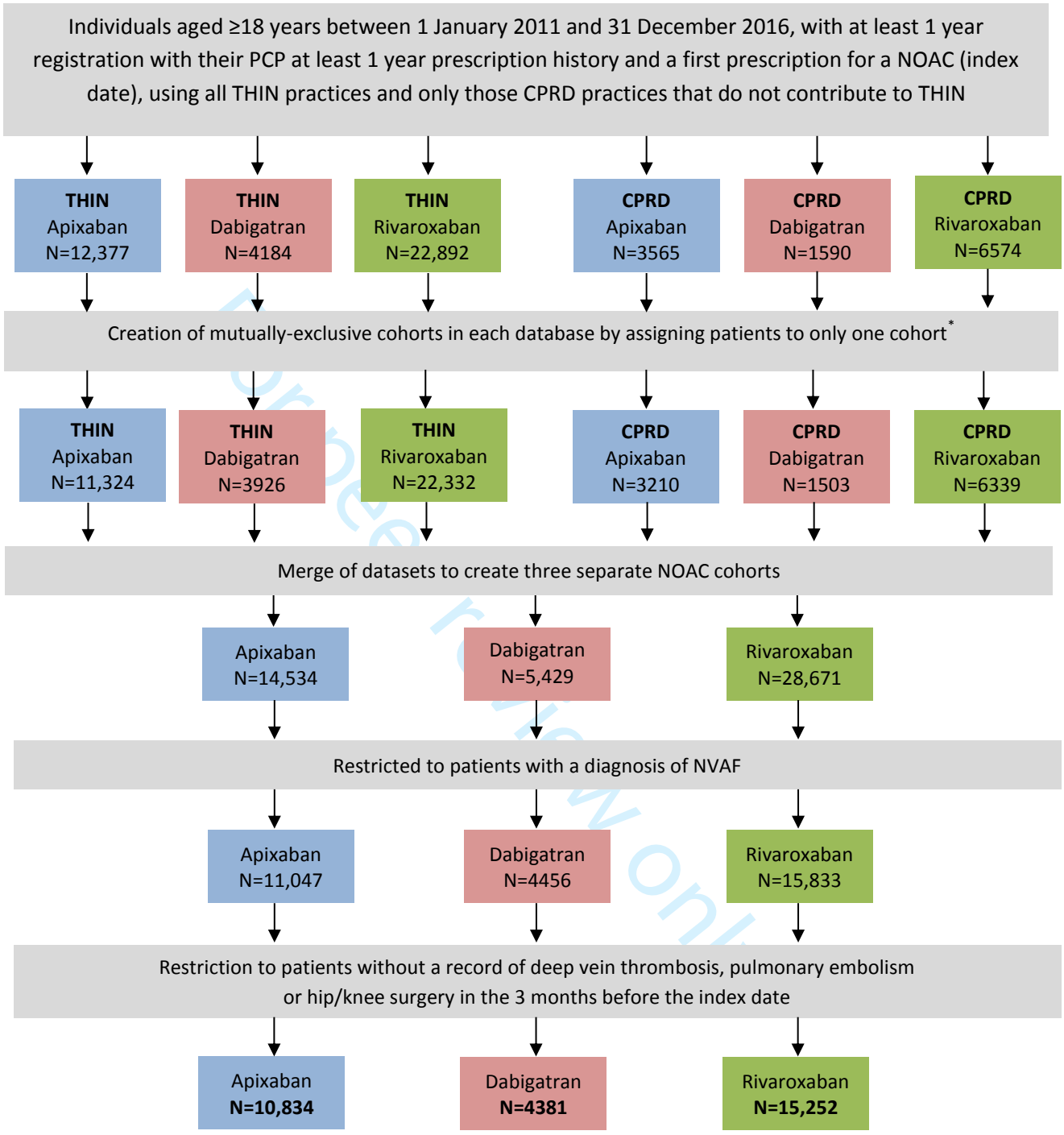


B. Dabigatran



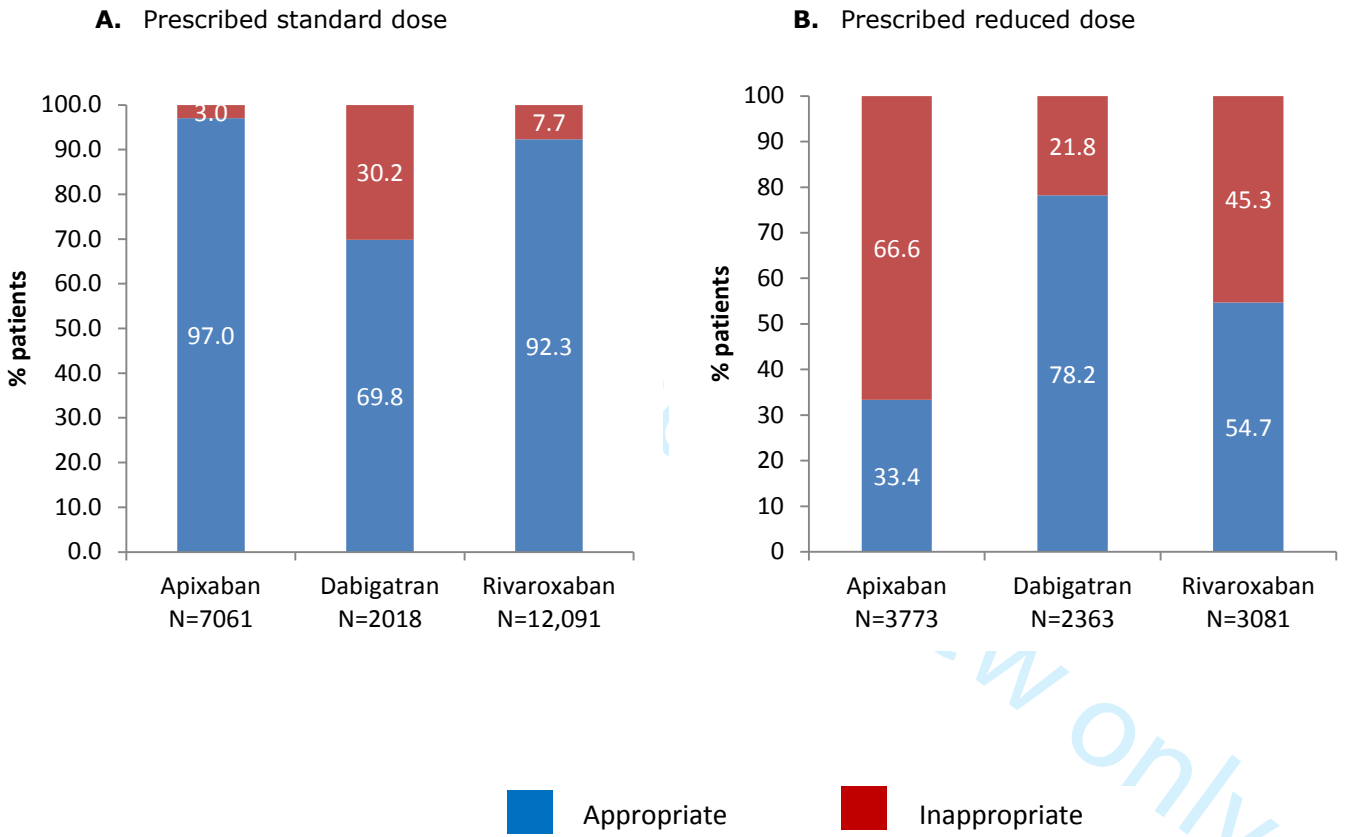
C. Rivaroxaban





Supplementary Figure 1. Flowchart depicting identification of the three NOAC study cohorts from THIN and the CPRD. *Mutually exclusive cohorts were created by excluding patients who were prescribed two different NOACs on the same day and by assigning patients to the cohort of the first prescribed NOAC.

CPRD, Clinical Practice Research Datalink; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; PCP, primary care practitioner; THIN, The Health Improvement Network.



Supplementary Figure 2: Appropriateness of daily dose of index NOAC among patients with non-valvular atrial fibrillation who were prescribed (**A**) a standard dose and (**B**) a reduced dose.
NOAC, non-vitamin K antagonist oral anticoagulant

Supplementary Table 1. Recommended dosing criteria and contraindications for each NOAC (for the prevention of stroke and systemic embolism in patients with NVAF) that were applied in the study.

NOAC	Reduced dosing criteria	Contraindications
Apixaban[a] **standard or normal recommended daily dose = 10 mg**	2.5 mg taken orally twice daily in patients with NVAF and ≥ 2 of the following: • age ≥ 80 years • body weight ≤ 60 kg • serum creatinine ≥ 1.5 mg/dL (133 micromole/L). Or, severe renal impairment (CrCL 15–29 mL/min)	*Note*: In patients with CrCL < 15 ml/min or undergoing dialysis, there is no clinical experience therefore apixaban is not recommended.
Dabigatran[b] **standard or normal recommended daily dose = 300mg**	• age ≥ 80 years • concomitant use of verapamil Reduction for consideration when[d]: • patients between 75–80 years • patients with moderate renal impairment (CrCL 30–50 mL/min • patients with gastritis oesophagitis or gastrooesophagel reflux.	• Severe renal impairment (CrCL < 30ml/min) *Note*: Dabigatran is also not recommended in patients with hepatic impairment or liver disease
Rivaroxaban[c] **standard or normal recommended daily dose = 20mg**	In patients with moderate/severe renal impairment (CrCL 15–49 ml/min)	• Severe renal impairment (creatinine clearance < 15 ml/min)

Sources from which our modified criteria were obtained.

[a]Eliquis. Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf. Accessed 7 September 2018.

[b]Pradaxa. Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf

[c]Xarelto. Pradaxa. Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf

[d]Patients meeting at least one of these criteria were considered eligible for dose reduction in our study.

CrCL, creatinine clearance; NVAF, non-valvular atrial fibrillation

Supplementary Table 2. Frequency distribution of the daily dose of index NOAC prescription among patients with NVAF.

Daily dose of index NOAC prescription	No. of patients	% of patients
Apixaban	**10,834**	
2.5 mg	53	0.5
5 mg	3720	34.3
10 mg (standard)	7061	65.2
Dabigatran	**4381**	
75–110 mg	101	2.3
150 mg	196	4.5
220 mg	2066	47.2
300 mg (standard)	2018	46.1
Rivaroxaban	**15,252**	
2.5–5 mg	50	0.3
10 mg	340	2.2
15 mg	2691	17.6
20 mg (standard)	12,091	79.3
30–40 mg	80	0.5

NOAC, non-vitamin K antagonist oral anticoagulant
NVAF, non-valvular atrial fibrillation

Supplementary Table 3. Baseline characteristics of patients with NVAF newly prescribed a NOAC according to whether they were appropriately dosed or inappropriately underdosed or overdosed.

	Appropriately dosed N=24,217		Inappropriately underdosed N=4114		Overdosed N=2136		Total N=30,467	
	n	%	n	%	n	%	n	%
Sex								
Male	13,687	56.5	1917	46.6	1052	49.3	16,656	54.7
Female	10,530	43.5	2197	53.4	1084	50.7	13,811	45.3
Age (years)								
<60	2411	10.0	175	4.3	68	3.2	2654	8.7
60–69	5244	21.7	455	11.1	218	10.2	5917	19.4
70–79	8273	34.2	1097	26.7	847	39.7	10,217	33.5
≥80	8289	34.2	2387	58.0	1003	47.0	11,679	38.3
OAC naïve status								
Naïve	11,924	49.2	2038	49.5	845	39.6	14,807	48.6
Non–naïve	12,293	50.8	2076	50.5	1291	60.4	15,660	51.4
Year of first NOAC prescription								
2011–2013	3413	14.1	513	12.5	527	24.7	4453	14.6
2014–2016	20,804	85.9	3601	87.5	1609	75.3	26,014	85.4
BMI, kg/m^2								
<20 (underweight)	5553	22.9	1047	25.4	502	23.5	7102	23.3
20–24 (healthy weight)	989	4.1	201	4.9	79	3.7	1269	4.2
25–29 (overweight)	8456	34.9	1530	37.2	739	34.6	10,725	35.2
≥30 (obese)	8296	34.3	1134	27.6	739	34.6	10,169	33.4
Missing	923	3.8	202	4.9	77	3.6	1202	3.9
Smoking								
Non-smoker	9904	40.9	1770	43.0	852	39.9	12,526	41.1
Smoker	1933	8.0	273	6.6	131	6.1	2337	7.7
Ex-smoker	12,359	51.0	2068	50.3	1151	53.9	15,578	51.1
Unknown	21	0.1	3	0.1	2	0.1	26	0.1
Alcohol (units/week)								
None	4780	19.7	1042	25.3	526	24.6	6348	20.8
1–9	10,870	44.9	1827	44.4	978	45.8	13,675	44.9
10–20	3968	16.4	517	12.6	260	12.2	4745	15.6
21–41	1541	6.4	180	4.4	115	5.4	1836	6.0
≥42	674	2.8	88	2.1	55	2.6	817	2.7
Unknown	2384	9.8	460	11.2	202	9.5	3046	10.0
CVD								
IHD								
Heart failure	3853	15.9	780	19.0	549	25.7	5182	17.0
Hypertension	15,920	65.7	2857	69.4	1617	75.7	20,394	66.9
Ischaemic stroke	3445	14.2	754	18.3	388	18.2	4587	15.1

	Appropriately dosed N=24,217		Inappropriately underdosed N=4114		Overdosed N=2136		Total N=30,467	
History of bleeding (GI, intracranial or urogenital)	6037	24.9	1135	27.6	609	28.5	7781	25.5
eGFR, ml/min/1.73m^2								
>50	17,707	73.1	2863	69.6	679	31.8	21,249	69.7
30–50	3017	12.5	590	14.3	1175	55.0	4782	15.7
<30	385	1.6	0	0.0	186	8.7	571	1.9
Missing	3108	12.8	661	16.1	96	4.5	3865	12.7
Frailty index								
Fit	4005	16.5	372	9.0	103	4.8	4480	14.7
Mild frailty	8912	36.8	1218	29.6	579	27.1	10,709	35.1
Moderate frailty	7140	29.5	1478	35.9	754	35.3	9372	30.8
Severe frailty	4160	17.2	1046	25.4	700	32.8	5906	19.4
CHA_2DS_2-VASc score								
≤2	7436	30.7	703	17.1	246	11.5	8385	27.5
3	5095	21.0	803	19.5	384	18.0	6282	20.6
≥4	11,686	48.3	2608	63.4	1506	70.5	15,800	51.9
HAS-BLED score								
0	10,841	44.8	1529	37.2	588	27.5	12,958	42.5
1–2	8962	37.0	1676	40.7	885	41.4	11,523	37.8
≥3	4414	18.2	909	22.1	663	31.0	5986	19.6

BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; OAC, oral anticoagulant; NOAC, non-vitamin K oral anticoagulant; NVAF, non-valvular atrial fibrillation; SD, standard deviation

Supplementary Table 4a. Appropriateness of the dose of the first NOAC prescription according to the EU drug label among patients with NVAF, stratified by previous use of an oral anticoagulant (naïve/non-naïve).

ALL NOACs	**Naïve patients N=14,807 (48.6%)**		**Non-naive N=15,660 (51.4%)**		**Total N=30,467**	
	n	**%**	**n**	**%**	**n**	**%**
Appropriate dose	11,924	80.5	12,293	78.5	24,217	79.5
Inappropriate dose	2883	19.5	3367	21.5	6250	20.5

EU, European Union; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation

Supplementary Table 4b. Appropriateness of the dose of the first apixaban prescription according to the EU drug label among patients with NVAF, stratified by previous use of an oral anticoagulant (naïve/non-naïve).

Apixaban	**Naïve patients N=5774 (53.3%)**		**Non-naive N=5060 (46.7%)**		**Total N=10,834**	
	n	**%**	**n**	**%**	**n**	**%**
Appropriate dose	4405	76.3	3705	73.2	8110	74.9
Inappropriate dose	1369	23.7	1355	26.8	2724	25.1

EU, European Union; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation

Supplementary Table 4c. Appropriateness of the dose of the first dabigatran prescription according to the EU drug label among patients with NVAF, stratified by previous use of an oral anticoagulant (naïve/non-naïve).

Dabigatran	**Naïve patients N=1827 (41.7%)**		**Non-naive N=2554 (58.3%)**		**Total N=4381**	
	n	**%**	**n**	**%**	**n**	**%**
Appropriate dose	1383	75.7	1875	73.4	3258	74.4
Inappropriate dose	444	24.3	679	26.6	1123	25.6

EU, European Union; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation

Supplementary Table 4d. Appropriateness of the dose of the first rivaroxaban prescription according to the EU drug label among patients with NVAF, stratified by previous use of an oral anticoagulant (naïve/non-naïve).

Rivaroxaban	**Naïve patients N=7206 (47.2%)**		**Non-naive N=8046 (52.8%)**		**Total N=15,252**	
	n	**%**	**n**	**%**	**n**	**%**
Appropriate dose	6136	85.2	6713	83.4	12849	84.2
Inappropriate dose	1070	14.8	1333	16.6	2403	15.8

EU, European Union; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation

Supplementary Table 5. Daily dose of NOAC 6 months after the index date among patients with NVAF with at least 6 months' follow-up and still using a NOAC at 6 months.

	Lower dose than the index NOAC prescription		Same dose than the index NOAC prescription		Higher dose than the index NOAC prescription		Patients with at least 6 months' follow-up and who were still prescribed a NOAC at 6 months	Total patients with NVAF in the study
	n	**%**	**n**	**%**	**n**	**%**		
Apixaban (N=6783)	129	1.9	6362	95.4	201	3.0	**6667**	**10,834**
Dabigatran (N=2874)	72	2.5	2648	93.7	107	3.8	**2827**	**4381**
Rivaroxaban (N=10,068)	325	3.3	9265	95.0	160	1.6	**9750**	**15,252**
							19,244	**30,467**

NOAC, non-vitamin K antagonist oral anticoagulant, NVAF, non-valvular atrial fibrillation

Supplementary Table 6. Dose of the index NOAC prescription among patients with and without a NOAC prescription at 6 months.

Index NOAC	Patients with at least 6 months of follow-up and still prescribed a NOAC at 6 months		Patients not prescribed a NOAC at 6 months (i.e. remaining patients)		TOTAL	
Apixaban	**N=6667**		**N=4167**		**N=10,834**	
	n	**%**	**n**	**%**	**n**	**%**
5 mg	2258	33.9	1515	36.4	3773	34.8
10 mg	4409	66.1	2652	63.6	7061	65.2
Dabigatran	**N=2827**		**N=1554**		**N=4381**	
	n	**%**	**n**	**%**	**n**	**%**
110 mg	63	2.2	38	2.4	101	2.3
150 mg	131	4.6	65	4.2	196	4.5
220 mg	1290	45.6	776	49.9	2066	47.2
300 mg	1343	47.5	675	43.4	2018	46.1
Rivaroxaban	**N=9750**		**N=5502**		**N=15,252**	
	n	**%**	**n**	**%**	**n**	**%**
10 mg	246	2.5	144	2.6	390	2.6
15 mg	1648	16.9	1043	19.0	2691	17.6
20 mg	7819	80.2	4272	77.6	12,091	79.3
≥30 mg	37	0.3	43	0.8	80	0.5

NOAC, non-vitamin K antagonist oral anticoagulant

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 and 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2 and 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5 and 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6 to 8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6 to 8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8 to 9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7 to 8
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9 and Suppl Fig 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	Suppl Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10 and Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	10 to 13, Fig 1, Fig 2 and Suppl Fig 2

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.