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ORIGINAL ARTICLE

Safety of off-label dose reduction of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

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Aim: To investigate the effects of off-label non-vitamin K oral anticoagulant (NOAC) dose reduction compared with on-label standard dosing in atrial fibrillation (AF) patients in routine care.

Methods: Population-based cohort study using data from the United Kingdom Clinical Practice Research Datalink, comparing adults with non-valvular AF receiving an off-label reduced NOAC dose to patients receiving an on-label standard dose. Outcomes were ischaemic stroke, major/non-major bleeding and mortality. Inverse probability of treatment weighting and inverse probability of censoring weighting on the propensity score were applied to adjust for confounding and informative censoring.

Results: Off-label dose reduction occurred in 2466 patients (8.0%), compared with 18 108 (58.5%) on-label standard-dose users. Median age was 80 years (interquartile range [IQR] 73.0-86.0) versus 72 years (IQR 66-78), respectively. Incidence rates were higher in the off-label dose reduction group compared to the on-label standard dose group, for ischaemic stroke (0.94 *vs* 0.70 per 100 person years), major bleeding (1.48 *vs* 0.83), non-major bleeding (6.78 *vs* 6.16) and mortality (10.12 *vs* 3.72). Adjusted analyses resulted in a hazard ratio of 0.95 (95% confidence interval [CI] 0.57-1.60) for ischaemic stroke, 0.88 (95% CI 0.57-1.35) for major bleeding, 0.81 (95% CI 0.67-0.98) for non-major bleeding and 1.34 (95% CI 1.12-1.61) for mortality.

Conclusion: In this large population-based study, the hazards for ischaemic stroke *and* major bleeding were low, and similar in AF patients receiving an off-label reduced NOAC dose compared with on-label standard dose users, while non-major bleeding risk appeared to be lower and mortality risk higher. Caution towards prescribing an off-label reduced NOAC dose is therefore required.

KEYWORDS
anticoagulation, atrial fibrillation, non-vitamin K antagonist oral anticoagulants, off-label dose reduction

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1 | INTRODUCTION

Non-vitamin K oral anticoagulants (NOACs, or direct acting oral anticoagulants, DOACs) play a central role in anticoagulant treatment for stroke prevention in patients with non-valvular atrial fibrillation (AF). The lower risk of intracranial bleeding, as well as the practical advantages of NOACs over vitamin K antagonists (VKA), including a fixed dose, no need for International Normalized Ratio (INR) monitoring and fewer food and drug interactions, likely explain the observed increase in the proportion of patients receiving anticoagulant therapy.[1–3] Although this reduces the concern for "undertreatment" (ie, receiving no anticoagulant therapy at all),[4] new concerns have emerged about "underdosing" or off-label dose reduction: patients receiving an NOAC dose lower than recommended in the guidelines.[5,6]

Previous studies reporting on the prevalence of off-label NOAC dose reduction have shown variable results, with estimates between 8% and 39%.[7] More importantly, there is limited high-quality data on the effects on health outcomes in AF patients with an off-label reduced dose compared to AF patients with an on-label standard dose, and this was also not explicitly part of the landmark phase 3 randomized controlled trials. Several studies that have been performed in this field compared patients with an off-label reduced dose to all on-label dosed patients, both on-label standard dose and on-label reduced dose. From a clinical perspective this comparison is less relevant, as clinicians want to know if they can safely reduce an NOAC dose in patients with an anticipated high bleeding risk but without an official indication for dose reduction (thus when guidelines recommend prescribing a standard dose).[8–10] Few large studies compare off-label reduced dosing to on-label standard dosing, and are heterogeneous in terms of setting (predominantly Asia or USA), NOAC(s) investigated, outcomes and confounding adjustment methods used.[11–16] Therefore, it is not yet established whether off-label reduction of NOAC dose in patients with AF indeed prevents bleeding complications and whether this affects the effectiveness of preventing strokes.

Our aim was to investigate the occurrence of ischaemic stroke, major bleeding, non-major bleeding and death of off-label NOAC dose reduction compared to on-label standard dosing in AF patients treated in routine care.

What is already known about this subject

- Off-label non-vitamin K oral anticoagulants (NOAC) dose reduction, that is, receiving a reduced NOAC dose without a clear indication, is estimated to occur in 8-39% of AF patients, often in an attempt to reduce bleeding risk in more vulnerable patient subgroups.
- It is not yet known, however, whether off-label NOAC dose reduction in patients with AF indeed prevents such bleeding complications, or whether this puts patients at an unnecessary risk of ischaemic stroke or mortality.

What this study adds

- Off-label reduced-dose NOACs were prescribed more often in older, more vulnerable patients with comorbidity, a high-risk population for both thromboembolic events and bleeding.
- Yet, after adjusting for these differences, no major differences in the risk of ischaemic stroke and major bleeding were observed between off-label reduced-dose users compared to on-label standard-dose users. Non-major bleeding risk was lower, but mortality risk was higher among patients receiving an off-label reduced NOAC dose.
- Off-label NOAC dose reduction is unlikely to benefit patients when aiming to reduce major bleeding risk and appears to be associated with an as yet unexplained higher mortality risk, thus caution towards prescribing an off-label reduced NOAC dose is still warranted.

2 | METHODS

2.1 | Study design and data source

We performed a large population-based cohort study using primary care data from the United Kingdom Clinical Practice Research Datalink (CPRD). The CPRD GOLD database contains data from electronic healthcare records of over 11.3 million patients (6.9% of the UK population) treated in primary care practices in the United Kingdom.[17] CPRD has been widely used for epidemiological research and its validity and representativeness of the general UK population is well-established.[18,19] The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA Database Research (protocol number 18_241R). The manuscript was written according to the STROBE Statement for cohort studies.[20]

2.2 | Study population

We selected all adult patients (≥18 years) registered in a CPRD practice with a first prescription of a NOAC during the study period between January 1, 2010 and July, 1 2018. The date of the first NOAC prescription during the study period was set as the index date. Patients needed to be enrolled in the database at least 12 months prior to the index date to ensure that valid baseline data were available. Only NOAC users with a record of non-valvular AF before the index date or within 3 months after the index date were included. Patients did not have to be OAC naïve, as patients who previously used a VKA (ie, switchers) before starting the NOAC were also included. We excluded patients with a CHA_2DS_2-VASc score of 0 or

1 who either had a diagnosis of a deep vein thrombosis or pulmonary embolism in the 3 months around the index date, or a hip or knee replacement together with a reduced NOAC dose in the 3 months around the index date, as these patients likely used the NOAC (and a non-standard dose accordingly) for a different indication than stroke prevention in AF. Patients with an estimated eGFR below 15 were also excluded, as NOACs are contraindicated in these patients. Finally, patients who started an on-label reduced dose (ie, a reduced dose in the presence of a clear indication, according to the Summary of Product Characteristics [SmPC]) or an off-label standard dose (a standard dose where the dose should have been reduced) were excluded from the analyses. Patients were followed up until they reached the outcome of interest, died, switched to a different NOAC or dosage, discontinued the NOAC, moved out of the CPRD practice or until the last day of valid, available data (whichever occurred first).

2.3 | Exposure

The criteria of the SmPC of the four different NOACs were used to define which patients used an off-label reduced dose and are shown in Table 1.[21–24] For example, when a patient used a reduced dose of **rivaroxaban** but had a creatinine clearance of 55 mL/min/1.73 m^2, this was regarded as an off-label reduced dose. For **dabigatran**, dose reduction in the presence of one or more of the subjective criteria (shown in italics in Table 1) was considered as on-label dose reduction except for "other increased bleeding risk2, which could not be determined in our dataset.

Treatment episodes were constructed according to the method of Gardarsdottir et al to define current use and past use of NOACs.[25] A so-called permissible gap time, or grace period, of 60 days between the theoretical end date of a prescription and the next prescription was allowed for, as patients may have had tablets left due to non-adherence or temporary discontinuation around invasive medical procedures. The grace period only accounted for gaps *between* subsequent prescriptions and was not applied at the end of a current use period. In case an off-label reduced first prescription was changed to an on-label standard dose within 7 days after the index date, we reclassified the exposure of the first prescription to on-label standard dose, to disregard incorrect prescriptions that were corrected (eg, by pharmacists), as in these cases it is unlikely that the physician truly intended to prescribe a reduced dose.

Exposure to an on-label standard dose or off-label reduced dose was treated as fixed by censoring follow-up time when the exposure changed, so if the NOAC dose or type changed when the on/off-label status changed (eg, when renal function declined and an indication for dose reduction appeared) or when NOAC treatment was discontinued. When we examined the data after NOAC discontinuation, it appeared that a considerable number of major bleeding events occurred shortly after the presumed end of a current use period, suggesting a higher incidence rate for major bleeding in the period immediately following discontinuation than during exposure to NOAC. This is highly improbable and is most likely explained by exposure misclassification at the time of the recorded outcome. Therefore, similar to our previous study using the CPRD database, for all analyses, we decided post hoc to reclassify the first 30 days after apparent discontinuation to exposure to the last NOAC used (ie, a "last measurement carried forward" approach).[26]

The available serum creatinine levels were used to calculate the estimated glomerular filtration rate (eGFR) based on the Chronic Kidney Disease Epidemiology (CKD-EPI) equation.[27] After disregarding values of outdated creatinine levels and body weight measured more

TABLE 1 Criteria for dose reduction per NOAC according to the SmPC for the indication of stroke prevention in non-valvular atrial fibrillation[21–24]

Type of NOAC	Standard dose	Reduced dose	Criteria for dose reduction
Dabigatran	150 mg bd	110 mg bd	Age ≥80 years Verapamil Consider dose reduction in case of - Age 75-80 years - CrCl 30-50 mL/min/1.73 m^2 - Gastritis/esophagitis/GERD - Other increased bleeding risk
Rivaroxaban	20 mg od	15 mg od	CrCl 15-49 mL/min/1.73 m^2
Apixaban	5 mg bd	2.5 mg bd	CrCl 15-29 mL/min/1.73 m^2, or Two or more of the following criteria: - Age ≥80 years - Serum creatinine ≥1.5 mg/dL (133 μmol/L) - Body weight ≤60 kg
Edoxaban	60 mg od	30 mg od	CrCl 15-50 mL/min/1.73 m^2 Body weight ≤60 kg Ciclosporin, ketoconazole, dronedarone or erythromycin

Abbreviations: bd, twice a day; CrCl, creatinine clearance; od, once daily; GERD, gastro-oesophageal reflux disease; SmPC, summary of product characteristics.

than 5 years before the index date, missing creatinine values were assumed to be normal, as the fact that it was missing in these patients likely indicates no suspicion of renal insufficiency and hence no indication for dose reduction. For the same reason, we assumed the body weight to be over 60 kg in case of missing data for body weight.

2.4 | Outcomes

Outcomes of interest were ischaemic stroke, major bleeding, non-major bleeding and all-cause mortality. Ischaemic strokes registered during the first month of NOAC use were excluded (ie, a so-called blanking or quarantine period)[28] because in those cases an ischaemic stroke is probably the first presentation of AF, when the anticoagulant had not yet been initiated. Hence, due to the possibility of late registration of the stroke in the GP registry, counting these strokes as an outcome event during anticoagulation treatment could induce misclassification.[28]

Major bleeding was defined as a symptomatic bleeding in one of the following critical areas or organs: intracranial, intraspinal, retroperitoneal, intraocular, gastrointestinal, intra-articular or intrathoracic. This definition was chosen because the definition of major bleeding recommended by the International Society on Thrombosis and Haemostasis[29] is difficult to use because of missing information about haemoglobin levels or blood transfusions in CPRD data. Non-major bleeding was defined according to the remaining Read codes on bleeding events that were not included in the definition of major bleeding. Lists of the Read codes defining each outcome are provided in Supporting Information Appendix S1. For all-cause mortality, we used the death date as recorded in CPRD. No linkage to death registration data from the Office of National Statistics was available for this study, but the reliability of death registration in CPRD GOLD has been previously verified.[30]

2.5 | Statistical analysis

Incidence rates of the outcomes with 95% confidence intervals (CIs) were calculated as the number of events per 100 person-years. When comparing patients with an off-label reduced NOAC dose to patients with an on-label standard dose, we used inverse probability of treatment weighting (IPTW) to adjust for confounding. We calculated propensity scores (PSs) for the probability of being treated with an off-label reduced NOAC dose conditional on 39 predefined potential confounders, using logistic regression, and used the PS to calculate the weights used in IPTW (in which patients with higher PSs received larger weights).[31] For an overview of the 39 potential confounders that were included in the PS model, see Supporting Information Appendix S2.

Two IPTW approaches were used. Usually, observational studies use IPTW to obtain marginal effect estimates, or the average treatment effect in the population (ATE). The ATE analysis answers the question "What, on average, would have happened if *all* patients with an indication for an on-label standard dose received an off-label reduced dose?", that is, targeting the counterfactual randomized clinical trial scenario in which *all patients* eligible for a standard dose were randomized towards either the reduced dose or the standard dose. However, we were primarily interested in the estimates of the treatment effect among patients for whom a clinician ultimately decides to prescribe an off-label reduced dose, the so-called average treatment effect in the treated (ATT).[31,32] The ATT analysis answers the question "What, on average, would have happened if patients who were treated with an off-label reduced dose had been given the standard dose?", that is, targeting the theoretical, but clinically highly relevant, scenario in which patients for whom the clinician reduced the dose were randomized towards either the reduced dose or the standard dose. For all our analyses, both the IPTW-ATE and IPTW-ATT estimates were provided, but from a clinical perspective we considered the IPTW-ATT-analyses as our main analyses. In the calculation of ATE weights, the treated (off-label reduced) get a weight of 1/PS and the untreated (on-label standard dose) get a weight of $1/(1-PS)$. In calculating ATT weights, the weights for the treated (off-label reduced) are all set to 1 and the weights for the untreated (on-label standard dose) are $PS/(1-PS)$ instead of $1/(1-PS)$.[31,33]

PS weights were truncated at the 99th percentile to prevent extreme weights. The comparability of the treatment groups was assessed by examining the overlap between the density plots of the PSs of each group. Covariate balance before and after applying IPTW weights was assessed by calculating standardized mean differences (SMDs) for all covariates and by plotting boxplots for continuous covariates.[31]

To mitigate bias that may occur due to informative (ie, non-random) censoring, we applied inverse probability of censoring weighting (IPCW) by calculating the propensity score (probability) for becoming censored. The same variables were included in the IPCW PS as for IPTW because they could potentially be associated with switching treatment regimen, resulting in censoring. The weights of IPCW were multiplied with the IPTW weights (either ATT or ATE) in Cox regression models. The results obtained when applying only IPTW without IPCW are shown in Supporting Information Appendix S4.

We used IPTW/IPCW-weighted Cox proportional hazards regression with robust sandwich variance estimation to calculated hazard ratios (HRs) and 95% CIs for the comparative treatment effect, using each set of IPTW weights (ATT and ATE), multiplied by IPCW weights. Unadjusted HRs were estimated using unweighted Cox regression. The proportional hazards assumption was assessed visually by plotting scaled Schoenfeld residuals.[34] All analyses were performed using *R* version 3.6.0.[35]

Four sensitivity analyses were done for the outcome ischaemic stroke (see Supporting Information Appendix S5): a complete case analysis for renal function, a complete case analysis for body weight, an analysis excluding patients with a record of AF in the 3 months after the index date and an analysis excluding patients with a history of VKA use (so including only OAC-naïve patients).

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.

3 | RESULTS

3.1 | Descriptives

We identified 31 788 AF patients who initiated a NOAC during the study period. A flowchart showing the numbers of excluded patients is given in Figure 1. After applying the exclusion criteria, we included 2466 patients (8.0%) who received an off-label reduced dose and 18 108 patients (58.5%) who received an on-label standard dose in our analyses. Off-label dose reduction occurred in 5.8% of dabigatran users (n = 206), 6.2% of **apixaban** users (n = 774), 9.9% of rivaroxaban users (n = 1417) and 11.9% of **edoxaban** users (n = 69). Patients receiving an on-label reduced dose (6496 patients, 21.0%) and patients receiving an off-label non-reduced dose (3863 patients, 12.5%) were excluded from the analyses. Baseline characteristics are shown in Table 2. Patients in the off-label reduced-dose group were older than patients in the on-label standard-dose group (median age 80 *vs* 72) and almost all comorbidities were more prevalent among the off-label reduced-dose patients, in particular history of major bleeding, non-major bleeding, ischaemic stroke or transient ischaemic

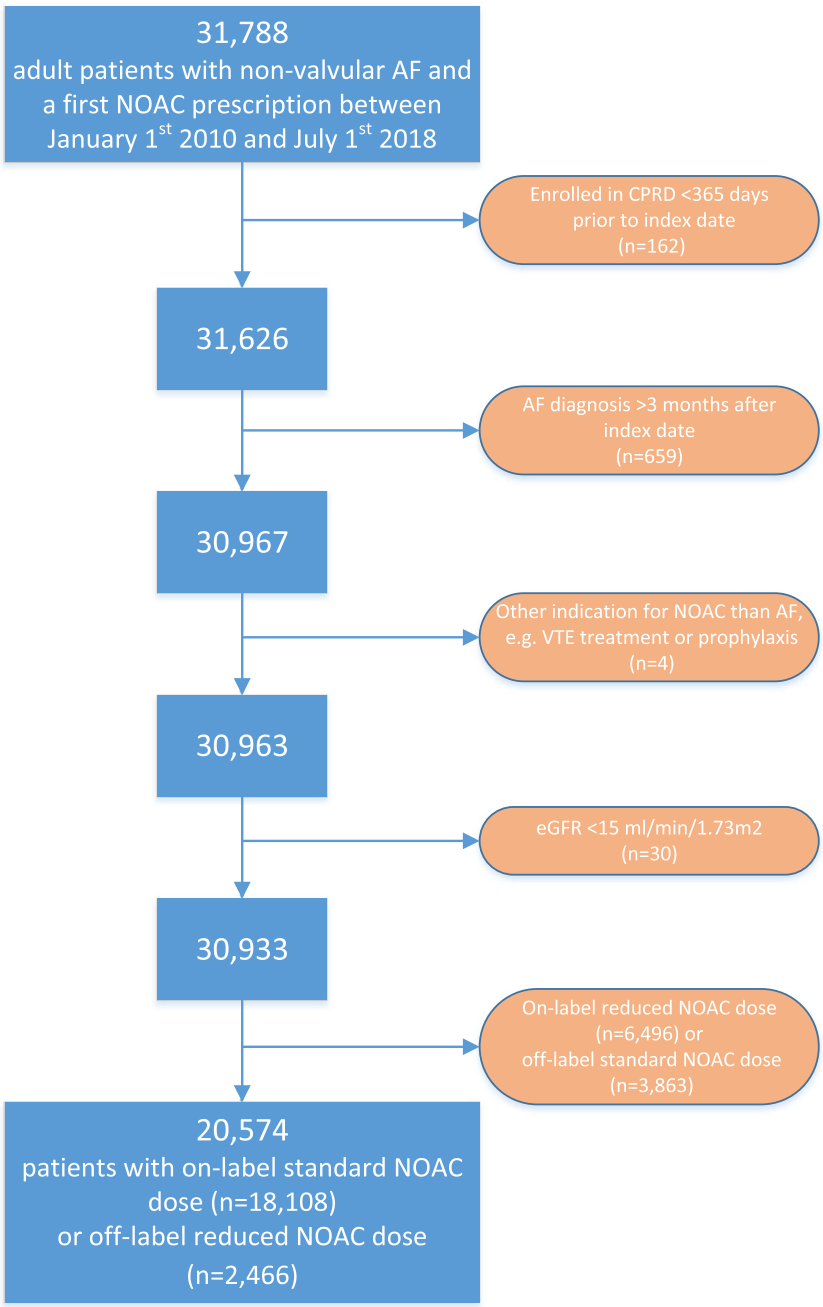

FIGURE 1 Flowchart showing the numbers of excluded patients. AF, atrial fibrillation; CPRD, Clinical Practice Research Datalink; eGFR, estimated glomerular filtration rate; NOAC, non-vitamin K oral anticoagulant; VTE, venous thromboembolism

TABLE 2 Baseline characteristics

	Off-label reduced dose (n = 2466)	On-label standard dose (n = 18 108)
Age in years, median (IQR)	80 (73.0-86.0)	72.0 (66.0-78.0)
Female sex	1134 (46.0)	6857 (37.9)
Dabigatran	206 (8.4)	926 (5.1)
Apixaban	774 (31.4)	6237 (34.4)
Rivaroxaban	1417 (57.5)	10 578 (58.4)
Edoxaban	69 (2.8)	367 (2.0)
Previous VKA use	952 (38.6)	6181 (34.1)
eGFR in mL/min per 1.73 m^2, median (IQR)	61.5 (51.3-76.6)	76.3 (64.7-87.4)
Creatinine in μmol/L, median (IQR)	88.0 (74.0-109.0)	81.0 (70.0-93.0)
Missing creatinine level	49 (2.0)	596 (3.3)
Weight in kg, median (IQR)	76.8 (65.0-90.0)	85.0 (73.0-99.0)
Missing weight	388 (15.7)	3039 (16.8)
Comorbidities/risk factors		
History of major bleeding	196 (7.9)	847 (4.7)
History of non-major bleeding	910 (36.9)	5563 (30.7)
History of ischaemic stroke or TIA	597 (24.2)	3213 (17.7)
History of VTE	109 (4.4)	671 (3.7)
Hypertension	1653 (67.0)	10 590 (58.5)
Heart failure	451 (18.3)	2292 (12.7)
Ischaemic heart disease	768 (31.1)	3921 (21.7)
History of chronic kidney disease	852 (34.5)	2319 (12.8)
Diabetes	567 (23.0)	3434 (19.0)
Presence of malignancy	100 (4.1)	691 (3.8)
Anaemia	<5 (0.1)	14 (0.1)
Peptic ulcer disease	190 (7.7)	1068 (5.9)
Liver disease	42 (1.7)	391 (2.2)
Medication use		
Concomitant antiplatelet therapy	366 (14.8)	1740 (9.6)
Non-steroidal anti-inflammatory drugs	68 (2.8)	735 (4.1)
Corticosteroids	292 (11.8)	1778 (9.8)
SSRI	224 (9.1)	1642 (9.1)
CYP3A4/P-gp inhibitors	294 (11.9)	1785 (9.9)
CYP3A4/P-gp inducers	19 (0.8)	80 (0.4)
Diuretics	1139 (46.2)	5818 (32.1)
ACE inhibitors/ARB	1307 (53.0)	8919 (49.3)
Calcium channel blockers	823 (33.4)	5725 (31.6)
Digoxin	358 (14.5)	1669 (9.2)
Statins	1330 (53.9)	9276 (51.2)
Proton pump inhibitors	1047 (42.5)	6898 (38.1)

Note: All values are expressed as n (%), unless otherwise specified.
Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; IQR, interquartile range; P-gp, P-glycoprotein; SSRI, selective serotonin reuptake inhibitor; TIA, transient ischaemic attack; VKA, vitamin K antagonist; VTE, venous thromboembolism.

attack, venous thromboembolism and hypertension. Renal function was lower among off-label reduced-dose patients compared to the on-label standard-dose group (eGFR 61.5 *vs* 76.3 mL/min per 1.73m^2, respectively). Information on recent creatinine level was missing for 645 patients (3.1%) and recent body weight was missing for 3427 patients (16.7%).

3.2 | Outcomes

During follow-up, 6717 out of 20 574 patients (33% of all patients, 51% in the off-label reduced-dose group and 30% in the on-label standard-dose group) were censored when their exposure changed (ie, by discontinuing the NOAC, switching from one NOAC to another, changing NOAC dose, or when a dose reduction criterion appeared which changed the status of on/off-label use), yet until censoring contributed to follow-up time for the current analyses. In total, the 20 574 included patients contributed to 23 516 person-years of follow-up, with a median follow-up time of 285 days per patient (10.2 months). Unadjusted and adjusted hazard ratios are presented in Table 3 and Figure 2. After IPTW, all potential confounders among the weighted samples appeared to be well balanced, with standardized mean differences ≤ 0.099. Visual assessment of density plots and boxplots showed good balance (see Supporting Information Appendix S3). As can be seen in Supporting Information Appendix S5, similar results compared with the results described below were observed in all of the sensitivity analyses.

3.2.1 | Ischaemic stroke

During follow-up, 21 ischaemic stroke events occurred in the off-label reduced-dose group versus 159 in the on-label standard-dose group (Incidence rate 1.04 and 0.74 per 100 person-years, respectively). In the analysis using the IPTW-ATT weights, the adjusted HR was 0.95 (95% CI 0.57-1.60). In the IPTW-ATE analysis, the adjusted HR was 1.04 (95% CI 0.63-1.71).

3.2.2 | Major bleeding

For major bleeding, we observed 30 events in the off-label reduced-dose group and 180 events in the on-label standard-dose group. The incidence rate for major bleeding was higher in the off-label reduced-dose group compared to the on-label standard-dose group (Incidence rate 1.48 and 0.83 per 100 person-years, respectively). After applying IPTW-ATT, the adjusted HR indicated no difference between the off-label reduced-dose group compared to the on-label standard-dose group (adjusted HR-ATT 0.88, 95% CI 0.57-1.35). In the IPTW-ATE analysis the adjusted HR was 0.92 (95% CI 0.59-1.45).

3.2.3 | Non-major bleeding

Non-major bleeding occurred in 132 patients (5.3%) in the off-label reduced-dose group, compared with 1259 patients (7.0%) in the on-label standard-dose group (Incide 6.78 and 6.16 per 100 person-years, respectively). The IPTW-ATT and IPTW-ATE analyses both showed a statistically significant reduction in non-major bleeding risk among patients receiving an off-label reduced dose (HR-ATT 0.81, 95% CI 0.67-0.98; HR-ATE 0.72, 95% CI 0.57-0.91).

TABLE 3 Primary and secondary outcomes for off-label reduced dose *vs* on-label standard dose

	Off-label reduced dose (n = 2466)			On-label standard dose (n = 18 108)			Off-label reduced dose *vs* on-label standard dose		
	n events	Total follow-up (py)	Event rate per 100 py	n events	Total follow-up (py)	Event rate per 100 py	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI) ATT	Adjusted HR[b] (95% CI) ATE
Ischaemic stroke	21	2016.6	1.04 (0.66-1.57)	159	21499.8	0.74 (0.63-0.86)	1.32 (0.84-2.09)	0.95 (0.57-1.60)	1.04 (0.63-1.71)
Major bleeding	30	2027.2	1.48 (1.02-2.09)	180	21579.6	0.83 (0.72-0.96)	1.63 (1.11-2.41)	0.88 (0.57-1.35)	0.92 (0.59-1.45)
Non-major bleeding	132	1947.8	6.78 (5.69-8.01)	1259	20452.3	6.16 (5.82-6.50)	1.02 (0.86-1.23)	0.81 (0.67-0.98)	0.72 (0.57-0.91)
All-cause mortality	206	2035.2	10.12 (8.81-11.58)	807	21664.7	3.72 (3.48-3.99)	2.57 (2.20-3.00)	1.34 (1.12-1.61)	1.56 (1.28-1.91)

Abbreviations: ATT, average treatment effect in the treated; ATE, average treatment effect; CI, confidence interval; HR, hazard ratio; Py, person-years.

[a]Adjusted hazard ratios after inverse probability of treatment weighting (IPTW) and inverse probability of censoring weighting (IPCW) using the propensity score with the IPTW-ATT weights multiplied by the IPCW weights, yielding the average treatment effect among the treated (ATT).

[b]Adjusted hazard ratios after IPTW and IPCW using the propensity score with the IPTW-ATE weights multiplied by the IPCW weights, yielding the average treatment effect (ATE) for the whole study population.

	Off−label reduced dose *Event rate (n)*	On−label standard dose *Event rate (n)*	Adjusted HR ATT *(95% CI)*
Ischaemic stroke	1.04 (21)	0.74 (159)	0.95 (0.57−1.60)
Major bleeding	1.48 (30)	0.83 (180)	0.88 (0.57−1.35)
Non−major bleeding	6.78 (132)	6.16 (1259)	0.81 (0.67−0.98)
All−cause mortality	10.12 (206)	3.72 (807)	1.34 (1.12−1.61)

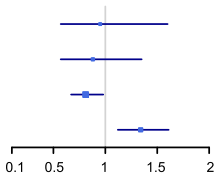

FIGURE 2 Forest plot showing the main results comparing off-label dose reduction to on-label standard dosing. Event rates are incidence rates per 100 person-years. ATT, average treatment effect among the treated

3.2.4 | All-cause mortality

In the off-label reduced-dose group 206 patients died, compared with 807 patients in the on-label standard-dose group (Incidence rate 10.12 and 3.72, respectively). After adjustment for confounders, both the IPTW-ATT and the IPTW-ATE showed a statistically significant increased risk of mortality of 34% and 56%, respectively, in patients treated with an off-label reduced NOAC dose (HR-ATT 1.34, 95% CI 1.12-1.61; HR-ATE 1.56, 95% CI 1.28-1.91).

4 | DISCUSSION

This large population-based cohort study showed that off-label dose reduction occurred infrequently in only 8.0% of AF patients treated with a NOAC and was most prevalent among edoxaban and rivaroxaban users. Physicians indeed appeared to opt for off-label dose reduction in older patients with more comorbidity, indicating that this is geared towards a higher risk population for thromboembolic events, bleeding and death, which is exemplified by the higher crude incidence rate for these outcomes in these patients. Still, for ischaemic stroke and major bleeding, absolute event rates were low, and after adjustment for baseline differences off-label dose reduction (compared with on-label standard dose) did not reduce this already low risk of major bleeding, nor did it increase the risk of ischaemic stroke. We did, however, observe a reduction in non-major bleeding. Yet for mortality, we observed an increased mortality risk of about 34% among patients receiving an off-label reduced dose.

4.1 | Strengths and limitations

When putting these results into perspective, several strengths and limitations should be considered. A great strength of this study is the large size, high generalizability and richness of the routine care data in the UK CPRD. To our knowledge, this is the largest and most detailed study evaluating the clinical impact of off-label NOAC dose reduction compared with on-label standard-dose users. The availability of clinical and laboratory measurements like weight and renal function creates the possibility of determining the prevalence of off-label dose reduction and its health effects on relevant patient outcomes for a large number of AF patients, in contrast to studies using claims databases, for example. We applied robust modelling techniques like IPTW to adjust for a large number of measured confounders, which permitted us to calculate the ATT. This added clinical relevance to this study, as a clinician would probably not consider off-label dose reduction in all patients, but more likely in old or frail patients who are suspected of a higher bleeding risk, and our adjusted ATT-analysis should be perceived to provide inferences exactly for that clinical scenario. By showing both the ATT and ATE, we found that the direction of effects was the same across analyses, and while the ATT estimate is more clinically relevant, the ATE estimates allow for comparison with the results of prior trials. Moreover, we have adjusted for possible informative censoring by applying IPCW. Our study is also the first to compare the occurrence of the outcome non-major bleeding in patients with an off-label reduced dose to patients with an on-label standard dose. This is a particularly relevant outcome as it occurs more often, and clinicians might prescribe an off-label reduced NOAC dose to patients with (a history or anticipated high risk of) frequently occurring non-major bleeding. In addition, we identified important signs of exposure misclassification and dealt with this through reclassification of the first 30 days after apparent discontinuation (ie, we carried the last exposure status forward).

Nevertheless, for full appreciation, a few issues deserve further attention. First, a limitation of our study is that we did not have data on the causes of death. This makes it difficult to explore if the observed increased mortality risk was due to fatal ischaemic stroke or other thrombotic events, for example, which could have strengthened the recommendation to be cautious with prescribing an off-label reduced NOAC dose. Due to this missing information we cannot rule out that at least part of the increased mortality risk is explained by residual confounding by indication. Possibly in part due to censoring, the median length of follow-up (10.2 months) was relatively short. Short follow-up, however, is a common phenomenon in observational studies on oral anticoagulant use, as the median length of follow-up varied between 3.6 months and 2 years in other studies.[11–13,15,16] Lastly, it is inherent to observational studies that exposure misclassification and confounding bias (especially residual confounding by indication) can never be completely eliminated. For example we assumed missing values for renal function and body weight to be normal, though this could have led to bias due to misclassification of prescriptions that were classified as off-label reduced. However, the proportion of patients with missing data on renal function and body weight was small (3.1% and 16.7%, respectively) and a complete case analysis did not alter the conclusions. Moreover, low body weight was only a dose reduction criterion for apixaban and edoxaban, and not necessarily a decisive criterion.

4.2 | Comparison with existing literature

Our results are in line with a large systematic review and meta-analysis including 148 909 patients from 10 observational studies.[8] This review observed no difference between patients being underdosed compared with patients using an on-label dose for the outcomes stroke and systemic embolism (HR 1.01, 95% CI 0.93-1.09) and major bleeding (HR 0.98, 95% CI 0.77-1.19). Similar to our study, an increased risk of death was observed in underdosed patients (HR 1.37, 95% CI 1.01-1.73). It has to be noted, however, that this meta-analysis compared off-label dose reduction to all on-label dosing (on-label standard dose but also on-label reduced dose), complicating the comparison to our study. Three smaller studies that compared off-label dose reduction to on-label standard dosing also observed no benefit of off-label dose reduction on bleeding, while ischaemic stroke or thromboembolism risk was similar[12,15] or even increased.[13] Two of these studies also evaluated mortality, both observing a similar increased mortality risk, thereby strengthening our inferences.[13,15]

The ATE analysis in our study allows for a direct comparison with the randomized trial RELY and ENGAGE AF-TIMI 48, which compared a lower dose regimen to a higher dose regimen of dabigatran and edoxaban, respectively.[36,37] In both trials, patients randomized to the higher dose regimen had a statistically significant lower risk of ischaemic stroke than patients randomized to the lower dose regimen (31% and 43% reductions, respectively). Major bleeding risk was higher in patients randomized to the higher dose regimen of dabigatran and edoxaban (16% and 36% relative risk increase, respectively). All-cause mortality was similar in higher-dose patients compared to lower-dose patients. We did not observe an increased risk of ischaemic stroke nor a reduced bleeding risk among patients receiving an off-label reduced dose in our data (although the numbers of events were small and did not allow for the analyses to be stratified per NOAC). Our results regarding mortality were also quite different from the trial data. While residual confounding in our study could explain at least part of these differences, we still have to consider the possibility that the safety profiles of different NOAC doses in routine care actually differ from the observations in randomized trials, as part of the observed mortality risk could be explained by an increased risk of fatal thromboembolic events. This is illustrated by the striking age difference between these trials and our data: the median age in the trials was 72 years (comparable to our on-label standard-dose group), while the median age of our off-label reduced-dose group was 80 years. It is therefore unlikely that the patients in whom a physician considers prescribing an off-label reduced dose (ie, older, frail patients with a presumed high bleeding risk) were sufficiently represented in these trials. That is why observational data, and especially our ATT analysis, are crucial and maybe even the best available way to investigate the safety of off-label dose reduction, despite the inherent limitations such as (residual) confounding by indication.

4.3 | Clinical implications and future considerations

Foremost, our study demonstrates that a relatively low number (8.0%) of patients in general practice receive an off-label reduced NOAC, which is lower than reported in many previous observational studies and certainly lower than the up to 40% of patients not receiving anticoagulants at all in previous decades.[4] Those patients using an off-label reduced NOAC dose are more frail, older and have a higher risk of bleeding and thromboembolic events compared to those using an on-label standard dose. This indicates that off-label dose reduction is likely not a random process but more a delicate balancing act—bleeding versus thrombosis—and thus a possible reflection of the perceived risk of bleeding by the prescribing physician. Second, in this relatively well-anticoagulated cohort, the risk of both stroke *and* major bleeding was low. As a consequence, we were not able to show any clear statistically significant difference between patient groups in both outcomes, therefore this illustrates that off-label dose reduction is unlikely to have a substantial impact on the occurrence of these already relatively rare outcomes. Nevertheless, we observed that reducing the NOAC dose without a clear indication does not increase the risk of stroke or attenuate the risk of major bleeding. This in turn makes it challenging to navigate the observed increased risk of mortality and decreased risk of non-major bleeding, and difficult to postulate clear recommendations regarding off-label dose reduction. Ultimately, new randomized clinical trials are needed for definitive answers on the impact of off-label dose reduction in older patients with AF, yet such trials likely will take years to perform and are thus unlikely to inform clinical practice soon, if performed at all. Until then, evidence from observational studies like ours is the only source of information available for clinicians on this topic, highlighting that off-label dose reduction is unlikely to have a substantial impact on stroke and major bleeding risk, while perhaps a reduction in non-major bleeding may be observed at the cost of an increased mortality risk (partly explained by residual confounding or perhaps by fatal thromboembolic events). Moreover, a perhaps more rewarding "intervention" to reduce bleeding risk would be managing "modifiable bleeding risk factors" as described by the ESC in the 2020 guidelines for the management of AF, for instance hypertension control, preventing concurrent use of NSAIDs or platelet inhibitors, and monitoring kidney function closely.[38] Nevertheless, such strategies aiming to eliminate these modifiable bleeding risk factors should also be investigated, for example in (cluster) randomized trials. Finally, as in our dataset the number of events was too small to allow for a stratified analysis per NOAC, further research in even larger or combined routine care datasets is warranted to investigate whether the effects of off-label dose reduction differ between NOACs, also focussing on specific causes of death to further explore our observed increased mortality risk in patients receiving an off-label reduced dose.

5 | CONCLUSION

In this large, population-based cohort study, off-label NOAC dose reduction occurred in only 8% of AF patients, predominantly those at high risk of bleeding. Risk of ischaemic stroke and major bleeding was low, with no apparent differences between off-label dose reduction and on-label standard dose users. On the other hand, we did observe a small reduction for non-major bleeding among patients receiving an off-label reduced dose. Nevertheless, given the observed increase in mortality and the limitations inherent to the observational nature of our data, caution is still required when considering off-label dose reduction.

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COMPETING INTERESTS

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CONTRIBUTORS

C.vdD., S.vD., G.J.G., P.S. and H.vdH. wrote the ISAC study protocol. P.S. prepared the dataset. C.vdD., R.P. and S.vD. performed the analyses. K.M., G.J.G. and A.H. advised on interpreting the results. C.vdD. wrote the first version of the manuscript. All authors participated in revising the manuscript.

DATA AVAILABILITY STATEMENT

The CPRD license agreement does not permit data sharing, but R scripts are available upon request.

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SUPPORTING INFORMATION

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