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Comparative effectiveness and safety of direct oral anticoagulants versus warfarin in UK patients with atrial fibrillation and type 2 diabetes: A retrospective cohort study

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Abstract

Purpose: To estimate the effectiveness and safety of direct oral anticoagulants (DOACs) compared with warfarin in AF patients with type 2 diabetes (T2DM).

Methods: A retrospective cohort study was designed, using the UK Clinical Practice Research Datalink (August 2011–June 2018). Participants were 1-year naïve users of DOACs or warfarin, followed from the date of first prescription of an oral anticoagulant until the end of the study period, death, discontinuation of treatment, switching to another anticoagulant, or an outcome of interest, whichever came first. Cox regression analysis was performed to estimate the hazard ratio (HR) adjusted for potential confounders.

Results: A total of 8555 patients were identified. No significant differences were found between DOACs and warfarin in the risk of stroke (adjusted HR 1.15; 95% CI 0.82–1.60), ischemic and unspecified stroke (adjusted HR 1.23; 95% CI 0.86–1.76) or haemorrhagic stroke (adjusted HR 0.75; 95% CI 0.30–1.85), and myocardial infarction (adjusted HR 1.39;95% CI 0.99–1.97). DOAC and warfarin users were comparable with respect to risk of major bleed (adjusted HR 0.83; 95% CI 0.68–1.03), intracranial bleeding (HR 0.66; 95% CI 0.34–1.30), gastrointestinal bleeding (HR 0.88; 95% CI 0.60–1.30), and bleeding on other clinically relevant sites (HR 0.89; 95% CI 0.60–1.31). In the subgroup analyses stratified by gender and diabetes severity, the risk for stroke and bleeding remained consistent.

Conclusion: DOACs are effective and safe alternatives to warfarin for the prevention of stroke in AF patients with T2DM.

KEYWORDS
anticoagulants, atrial fibrillation, bleeding, diabetes mellitus, stroke

1 | INTRODUCTION

Atrial fibrillation (AF) has an estimated prevalence of approximately 1.5%–2% in the developed world, and is associated with a five-fold risk of stroke and higher mortality.[1,2] Diabetes Mellitus (DM) is one of the most common comorbidities in AF patients, with type 2 diabetes (T2DM) accounting for the majority (about 90%) of DM cases.[3] Various studies have suggested DM as an independent risk factor for atrial fibrillation,[4-7] haemorrhagic and ischemic stroke,[3,8] and for bleeding events.[9-11]

In August 2011, the first direct oral anticoagulant (DOAC), dabigatran, was approved by the EMA for stroke prevention in AF patients, based on the results from RCTs showing that DOACs, compared to warfarin, a vitamin K antagonist (VKA), significantly reduce the risk of stroke and intracranial bleeding.[12] Several observational studies have been conducted with results in line with findings from clinical trials.[13-15] Thus, current guidelines recommend DOACs over warfarin for most patients with AF, including patients with T2DM.[16]

Participants with diabetes constituted a substantial proportion of the four randomized trials, and pre-specified post hoc analyses of individual trials showed that the efficacy and safety of DOACs versus warfarin extends to patients with both AF and diabetes regarding the main outcome measures.[17-19] Furthermore, a study level meta-analysis of the four DOACs by Patti et al. showed no significant interaction between diabetes and the benefit–risk ratio of DOACs in patients with AF.[20]

However, results from well controlled RCTs should be duplicated in a real-world setting,[21] and the evidence on DOACs' effectiveness and safety in diabetic patients from clinical practices is still limited. Therefore, we aimed to provide a real-world assessment of the effectiveness and safety of DOACs in patients with AF and T2DM in the UK general practice population, to offer clinicians a more comprehensive understanding of DOACs as a therapeutic option for patients with both conditions.

Key Points

- Diabetes is associated with an increased risk of stroke and bleeding.
- Post-hoc analysis of clinical trials show that the effectiveness and safety of direct oral anticoagulants (DOACs) extend to patients with atrial fibrillation (AF) and diabetes.
- The effect of diabetes severity on the benefits and risks of DOACs is unknown.
- Real-life data on effectiveness and safety of DOACs in diabetic patients is scarce.
- Our retrospective cohort study shows that DOACs are effective and safe alternatives to warfarin for the prevention of stroke in AF patients with type 2 diabetes, and the effectiveness and safety is irrespective to diabetes severity.

2 | METHODS

2.1 | Data source

We performed a retrospective cohort study using the Clinical Practice Research Datalink (CPRD). This database is one of the largest databases of primary care electronic medical records, including around 674 primary care practices in the UK, covering 11.3 million patients, and representing 6.9% of the total UK population.[22] It includes details on demographic information, hospital admissions, prescription details, laboratory tests, specialist referrals, and lifestyle variables such as body mass index (BMI), smoking, and alcohol consumption. Several studies have been conducted showing a high validity of registration, high degrees of accuracy and completeness of data for various diagnoses (including 85.3% for diagnoses related to the circulatory system and 87.4% for diagnoses related to the digestive system) and for smoking status.[22-26]

Approval of the study protocol was granted by the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory Agency (protocol 19_225).

2.2 | Study population

The study population consisted of all patients aged ≥18 years with first ever recorded diagnosis of AF during a patient's period of valid data collection. Only patients with follow-up time between 1st August 2011, when the first DOAC was approved by EMA for stroke prevention in AF patients, and 20 June 2018 were included. Within this cohort of AF patients, we identified naïve users of an oral anticoagulant (OAC). Naïve users were defined as patients who had not been exposed to either a DOAC or warfarin within 1 year prior to their first prescription during the follow up period. Patients were included only once. Thus, restarting an OAC after a discontinuation period was not included in the patient's follow up time.

Among OAC-naïve AF patients, we identified patients with T2DM based on diagnostic Read codes. Problems with miscoding and misclassification of diabetes in CPRD are well known.[27,28] Therefore, we attempted to create a list of diagnostic codes to identify patients with T2DM, and remove other forms of diabetes. To exclude patients with type 1 diabetes, Read codes were not used as there are known problems with coding errors.[29] Instead, we excluded patients with an age at diagnosis <35 years, or patients only treated with insulin, patients who were prescribed insulin as their first treatment or within 1 year of diagnosis.[30] Figure 1 shows the inclusion and exclusion criteria to identify T2DM patients. The final inclusion and exclusion Read codes for T2DM are shown in Appendix A (Tables A1 and A2).

Index date was defined as the date of first OAC prescription within the follow up period, and patients without a diagnostic code for AF and T2DM prior to index date were excluded from the study cohort.

Medical codes inclusion list:

- Included medcodes with the word "diab" in the description field
- Removed medcodes:
  - Diabetes is inferred but not clearly stated (e.g., 'seen in diabetic clinic', 'referral to diabetologist', 'monitoring')
  - Codes with keyword family history, pre-diabetes, remission and diabetes resolved

Medical codes exclusion list:

Medcodes that include the word "diab" and other forms of diabetes (e.g., 'steroid-induced', 'gestational', 'juvenile' or 'maturity onset diabetes of the young')

Exclusion criteria for patients with T1DM:

Age at diagnosis <35 years
Only treated with insulin
First therapy was insulin
Prescribed insulin within 1 year of diagnosis

FIGURE 1 Type 2 diabetes mellitus (T2DM) patients inclusion and exclusion criteria

2.3 | Exposure

The DOACs of interest included dabigatran, rivaroxaban, apixaban and edoxaban. Patients were followed from index date until the end of follow-up period, death, discontinuation of medication of interest, treatment switching (DOACs to warfarin and vice versa) or an outcome of interest, whichever date came first. We defined discontinuation of treatment as not claiming a new prescription for more than 180 days after the start of a last prescription.

In this definition, a gap of maximum 180 days was allowed between two successive prescriptions to provide a broad reflection of imperfect adherence observed in clinical practice.

2.4 | Outcomes

Main effectiveness outcome was defined as a composite of ischaemic stroke, unspecified stroke and haemorrhagic stroke. The secondary effectiveness outcome was myocardial infarction (MI).

The main safety outcome was major bleeding, defined as a composite of intracranial bleeding, gastrointestinal (GI) bleeding, and bleeding on other clinically relevant sites (including haemoptysis, post-menopausal bleeding, ocular bleeding, bleeding with anemia and hemarthrosis).

The UK Read code system was used to define outcomes. The selected Read codes were reviewed by a clinician for relevance. The codes used for defining the outcomes can be found in the Appendix B.

2.5 | Covariates

As treatment allocation was not randomly, adjustment for baseline covariates was required. We selected baseline covariates based on the corresponding Read codes, registered prior to or at the index date.

Baseline covariates were age, gender, most recent BMI, smoking status and stage four and five chronic kidney disease (CKD). CKD was identified based on Read codes or test results (eGFR <30 ml/min).

For stroke outcomes, we additionally adjusted for comorbidities from the CHA_2DS_2-VASc score (congestive heart failure, hypertension, peripheral vascular disease, previous stroke, previous MI),[31] and prescriptions of the following drugs were evaluated in the 6 months prior to index date: aspirin, antiplatelet drugs, statins, calcium channel blockers, ACE-inhibitors, angiotensin II receptor blockers, diuretics, β-blockers, selective serotonin reuptake inhibitors (SSRIs) and nonsteroidal anti-inflammatory drugs (NSAIDs).

For bleeding outcomes, we additionally adjusted for comorbidities from the HAS-BLED score (hypertension, moderate to severe liver disease, previous stroke, previous bleed, alcohol abuse, concomitant drug use),[32] gastritis, malignancies and anemia. Prescriptions of the following drugs were also evaluated in the 6 months prior to index date: aspirin, antiplatelet drugs, NSAIDs, and SSRIs. Proton-pump inhibitors and histamine 2 receptor antagonists were assessed in the 3 months before index date.

2.6 | Effect modification

To study the effect of diabetes severity on the outcomes, severity levels were identified based on antidiabetic therapy. Patients who were not receiving antidiabetic prescriptions or were only on metformin were considered as non-severely diabetic, and patient with prescription codes for second line antidiabetics or insulin were identified as severely diabetic.

2.7 | Statistical analysis

Baseline characteristics were summarized as means and standard deviations or proportions where appropriate. We calculated crude incidence rates of outcomes within 1 year per 100 person-years as the number of events divided by person time.

Cox proportional hazard regression analysis was used to estimate the adjusted hazard ratio (aHR) of events with warfarin as the primary reference. The proportional hazards assumption was tested on the basis of Schoenfeld residuals and was valid for all outcomes.[33]

To estimate the effect of continuous treatment, a per-protocol analysis approach was applied, and time at risk was calculated from the index date until censoring at the first incidence of an event of interest, death, discontinuation of treatment, switching or the end of the study period. To account for baseline differences, we adjusted the models for the aforementioned covariates.

Stratified analyses were performed based on gender, and anti-diabetic treatment as a proxy for diabetes severity.

Missing data on BMI was dealt with by median imputation. All statistical procedures were performed using R version 3.5.0.

2.8 | Sensitivity analysis

Several sensitivity analyses were performed to ensure robustness of our study results.

First, we performed a propensity-score (PS) matched analysis as an alternative method to adjust for imbalances in baseline covariates, where DOACs users were matched 1:1 to users of warfarin without replacement, using greedy nearest neighbor method and calipers of 0.25 of the standard deviation of the logit of the PS.[34,35] PSs for DOAC exposure were estimated using a binary logistic regression, which included the same covariates as the Cox model. To assess the success of the matching procedure, we measured mean standardized differences in observed covariates between the matched groups after matching, using a threshold of 0.1 to indicate imbalance. After matching, a Cox regression was used to compute the HR of events, comparing exposure to DOACs versus warfarin.

Second, we repeated the analysis and changed the definition of discontinuation to 90 and to 60 days after the start of a last prescription of an OAC. Third, we applied an intention-to-treat analysis, comparing the hazard rates based on the exposure status at baseline, without censoring at discontinuation or switching. Finally, we repeated the analysis in all patients diagnosed with AF, including both patients with and without T2DM, and performed a stratified analysis per diabetes status to evaluate whether there is an interaction between diabetes status and the benefits and risks of DOACs.

3 | RESULTS

We identified 8555 treatment naïve AF and T2DM patients registered in CPRD during the study period. Figure 2 shows the flowchart of patient selection.

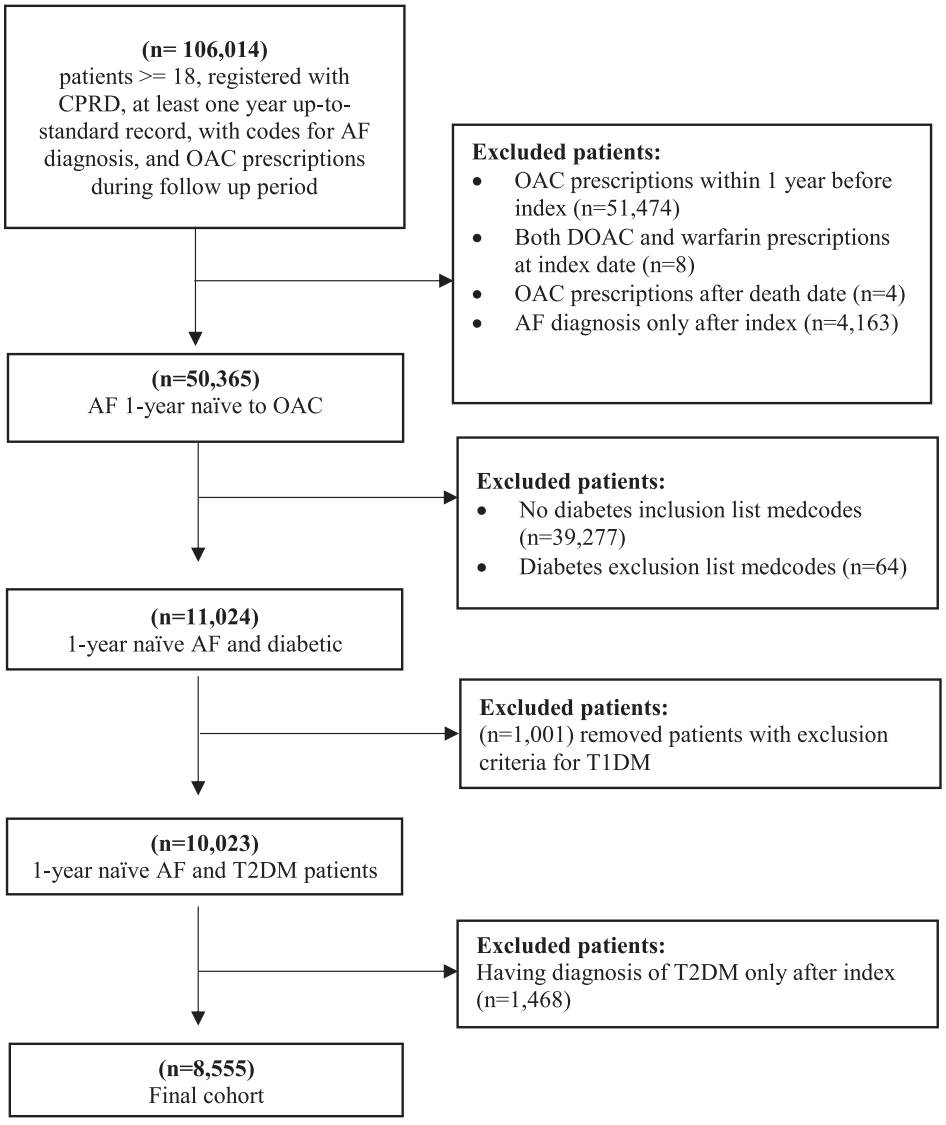

FIGURE 2 Cohort definition flow chart. AF, atrial fibrillation; CPRD, Clinical Practice Research Datalink; DOAC, direct oral anticoagulant; OAC, oral anti-coagulant; OAD, oral anti-diabetics; T2DM, type 2 diabetes mellitus

TABLE 1 Baseline characteristics of DOAC and warfarin users. Summary of patients' characteristics at baseline

Characteristic	DOACs *n* = 3437 (40.18%)	Warfarin *n* = 5118 (59.82%)
Age at index (mean, SD)	76.07 (9.66%)	75.05 (9.19%)
Female	1328 (38.64%)	1966 (38.41%)
Current smoker	297 (8.64%)	422 (8.25%)
BMI (mean, SD)	30.95 (6.76)	31.32 (6.65)
Missing	24 (0.70%)	22 (0.43%)
History of comorbidities		
Heart failure	564 (16.41%)	941 (18.39%)
Hypertension	2633 (76.61%)	3994 (78.04%)
Peripheral vascular disease	230 (6.69%)	344 (6.72%)
Ischaemic heart disease	1106 (32.18%)	1853 (36.21%)
Alcohol abuse	438 (12.74%)	495 (9.67%)
Mild liver disease	123 (3.58%)	119 (2.33%)
Moderate to severe liver disease	9 (0.26%)	7 (0.14%)
Severe CKD	33 (0.96%)	106 (2.07%)
Gastritis	788 (22.93%)	1057 (20.65%)
Myocardial infarction	931 (27.09%)	1513 (29.56%)
Previous stroke	455 (13.24%)	579 (11.31%)
Previous major bleed	710 (20.66%)	1015 (19.83%)
GI bleed	460 (13.38%)	655 (12.80%)
Anemia	131 (3.81%)	207 (4.04%)
Cancer	131 (3.81%)	200 (3.91%)
History of co-medication		
6 months before index		
Aspirin	1882 (54.76%)	3665 (65.75%)
Other anti-platelets	676 (19.67%)	991 (19.36%)
Dual anti-platelet therapy	311 (9.05%)	614 (12.00%)
ACE inhibitors	1857 (54.03%)	3188 (62.29%)
Angiotensin II receptor antagonists	927 (26.97%)	1444 (28.21%)
Calcium channel blockers	1644 (47.83%)	2669 (52.15%)
B blockers	2551 (74.22%)	3891 (76.03%)
Diuretics	2112 (61.45%)	3618 (70.69%)
Statins	2747 (79.92%)	4339 (84.78%)
All NSAIDs	176 (5.12%)	354 (6.92%)
SSRIs	513 (14.93%)	878 (17.16%)
3 months before index		
H2RA	287 (8.35%)	470 (9.18%)
PPIs	1915 (55.72%)	2953 (57.70%)
Diabetes severity: History of antidiabetic treatment before index		
Only Metformin or diet	1886 (54.87%)	2692 (52.60%)
Second line oral antidiabetics/Insulin	1551 (45.13%)	2426 (47.40%)
CHA2DS2-VASc score		
Mean (SD)	4.18 (1.52)	4.12 (1.49)
Distribution — no. (%)		
1	89 (2.59%)	157 (3.07%)
2	396 (11.52%)	570 (11.14%)
≥3	2952 (85.89%)	4391 (85.80%)
Modified HAS-BLED score[a]		
Mean (SD)	2.90 (1.08)	2.93 (1.03)
Distribution — no. (%)		
0	44 (1.28%)	47 (0.92%)
1	259 (7.54%)	326 (6.37%)
2	905 (26.33%)	1294 (25.28%)
≥3	2229 (64.85%)	3451 (67.43%)

Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; GI, gastrointestinal; H2RA, histamine 2 receptor antagonists; NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; SD, standard deviation; SSRIs, selective serotonin reuptake inhibitors.
[a]INR values were not included.

Baseline characteristics are presented in Table 1. At the index date 3437 (40.2%) patients were prescribed a DOAC, and 5118 (59.8%) warfarin. The mean duration of follow-up was shorter for users of DOACs (1.39 and 1.37 years for main stroke and bleeding outcomes, respectively), than for users of warfarin (2.1 and 2.03 years).

In the DOACs group, the average prescription fill rate (i.e., number of days covered divided by the number of prescriptions) was 32.5 days, and the majority of patients was prescribed rivaroxaban (45.4%), followed by apixaban (43.7%), dabigatran (9.4%) and edoxaban (1.5%). (For more information about the proportion of patients that filled each dose of the DOACs, see Appendix C, Table C1).

History of comorbidities did not differ much between exposure groups for most covariates at baseline. Users of warfarin (65.8%) were more often using aspirin at baseline compared to users of DOACs (54.8%), and history of severe kidney disease and diuretic prescriptions were more often present in warfarin users (2.1% and 70.7%) compared to DOAC users (1.0% and 61.5%). Of the DOAC users, 54.9% of the patients had no antidiabetic prescriptions or were treated with metformin alone before index date, as compared to 52.6% in the warfarin group, and 45.1% of DOACs users had prescriptions for second line oral antidiabetics/insulin before index date, as compared to 47.4% in the warfarin group.

The incident rates for main stroke outcome in DOAC and warfarin users were 1.23 and 1.00 events per 100 persons years, respectively, (adjusted HR 1.15; 95% CI 0.82–1.60) (Table 2).

No significant differences were found in the risk of ischemic and unspecified stroke (adjusted HR 1.23; 95% CI 0.86–1.76) or haemorrhagic stroke (adjusted HR 0.75; 95% CI 0.30–1.85) (Table 2).

TABLE 2 Main analysis of the effectiveness and safety outcomes of DOACs compared to warfarin

Effectiveness outcomes (mean follow-up = 1.81 years, SD = 1.51)				
Outcome	**OAC exposure**	**Number of events (%)**	**Incidence rate per 100 person/years**	**Adjusted HR (95% CI)[a]**
Any stroke	Warfarin	107 (2.09%)	1	1.00 reference
	DOAC	59 (1.72%)	1.23	1.15 (0.82–1.60)
Ischaemic and unspecified stroke	Warfarin	90 (1.76%)	0.84	1.00 reference
	DOAC	52 (1.51%)	1.09	1.23 (0.86–1.76)
Haemorrhagic stroke	Warfarin	17 (0.33%)	0.16	1.00 reference
	DOAC	7 (0.20%)	0.15	0.75 (0.30–1.85)
Myocardial infarction	Warfarin	98 (1.91%)	0.91	1.00 reference
	DOAC	54 (1.57%)	1.12	1.39 (0.99–1.97)
Safety outcomes (mean follow-up = 1.77 years, SD = 1.49)				
Outcome	**OAC exposure**	**Number of events (%)**	**Incidence rate per 100 person/years**	**Adjusted HR (95% CI)[b]**
Major bleed	Warfarin	310 (6.06%)	2.98	1.00 reference
	DOAC	129 (3.75%)	2.73	0.83 (0.68–1.03)
GI bleeding	Warfarin	183 (3,58%)	1.76	1.00 reference
	DOAC	81 (2.36%)	1.72	0.88 (0.60–1.30)
Intracranial bleeding	Warfarin	33 (0.64%)	0.32	1.00 reference
	DOAC	12 (0.35%)	0.25	0.66 (0.34–1.30)
Bleeding on other sites	Warfarin	94 (1.84%)	0.9	1.00 reference
	DOAC	38 (1.11%)	0.8	0.89 (0.60–1.31)

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; OAC, oral anticoagulant; HR, hazard ratio; GI, gastrointestinal.

[a]Adjusted for age, gender, most recent body mass index (BMI), smoking status, chronic kidney disease, congestive heart failure, hypertension, peripheral vascular disease, previous stroke, previous myocardial infarction, aspirin, antiplatelet drugs, statins, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, β-blockers, selective serotonin reuptake inhibitors (SSRIs), and nonsteroidal anti-inflammatory drugs (NSAIDs).

[b]Adjusted for age, gender, most recent BMI, smoking status, chronic kidney disease, hypertension, moderate to severe liver disease, previous stroke, previous bleed, alcohol abuse, gastritis, cancer, anaemia, aspirin, antiplatelet drugs, NSAIDs, SSRIs, Proton-pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RA).

For the secondary effectiveness outcome, there was no significant difference in the risk of MI (adjusted HR 1,39;95% CI 0.99–2.97).

The incidence rate for major bleeding outcome per 100 person-years was 2.73 for DOAC users, and 2.98 for warfarin users, (adjusted HR 0.83; 95% CI 0.68–1.03) (Table 2).

No substantial differences were observed between DOAC and warfarin users with respect to intracranial bleeding (HR 0.66, 95% CI 0.34–1.30), GI bleeding (HR 0.88; 95% CI 0.60–1.30), and bleeding on other clinically relevant sites (HR 0.89; 95% CI 0.60–1.31). (Table 2).

In the subgroup analyses stratified by gender and diabetes severity, results of main stroke and bleeding outcomes remained consistent. (Table 3).

In the PS matched analysis, all covariates had a standardized difference of <0.1 after matching, and no imbalance was observed (Appendix C, Table C2). Results also remained consistent in the sensitivity analyses with PS matched analysis (Appendix C, Table C3), 90 and 60 days discontinuation definition (Appendix C, Tables C4 and C5) and intention-to-treat analysis (Appendix C, Table C6).

In the analysis of the full AF cohort, the results from patients without T2DM were comparable to patients with T2DM (adjusted HR 0.92;95% CI 0.78–1.07 and 0.96; 95% CI 0.88–1.06) for main stroke and major bleeding outcomes respectively, and no significant interaction per diabetes status was observed. (see Appendix C, Table C7).

4 | DISCUSSION

In this comparative effectiveness and safety study, we found that DOACs were as effective as warfarin in reducing the risk of stroke in primary care patients with AF and T2DM. The rates of major, intracranial, GI bleeding and bleeds on other sites were also similar in DOAC and warfarin patients. The overall effectiveness and safety of DOACs compared to warfarin remained similar in subgroups defined by diabetes severity. In addition, the results on major bleeding and stroke were comparable between patients with and without diabetes.

The evidence on DOACs' effectiveness and safety in patients with both AF and T2DM in the clinical practice is scarce. Our results

TABLE 3 Stratified analysis of the effectiveness and safety outcomes of DOACs compared with Warfarin

HRs for any stroke outcome stratified per diabetes severity			
	Crude HR (95% CL)	**Adjusted HR (95% CL)[a]**	**P interaction**
Only metformin or no medication	1.17 (0.76—1.79)	1.17 (0.76—1.82)	0.685
Second line OAD/Insulin	1.17 (0.70—1.93)	1.14 (0.68—1.91)	
Female	0.77 (0.55–1.07)	0.81 (0.57—1.14)	
HRs for major bleeding outcome stratified per diabetes severity			
	Crude HR (95% CL)	**Adjusted HR (95% CL)[b]**	**P interaction**
Only metformin or no medication	0.87 (0.66–1.15)	0,89 (0.67–1.18)	0.525
Second line OAD/Insulin	0.78 (0.57–1.06)	0,78 (0.57–1.06)	
HRs for any stroke outcome stratified per gender			
	Crude HR (95% CL)	**Adjusted HR (95% CL)[a]**	**P interaction**
Male	1.05 (0.68–1.61)	1.02 (0.66–1.60)	0.338
Female	1.36 (0.82–2.24)	1.29 (0.77–2.15)	
HRs for major bleeding outcome stratified per gender			
	Crude HR (95% CL)	**Adjusted HR (95% CL)[b]**	**P interaction**
Male	0.87 (0.66–1.13)	0.86 (0.65–1.12)	0.494
Female	0.77 (0.55–1.07)	0.81 (0.57–1.14)	

Abbreviations: CI, confidence interval; HR, hazard ratio; OAD, oral antidiabetic.

[a]Adjusted for age, gender, most recent body mass index (BMI), smoking status, chronic kidney disease, congestive heart failure, hypertension, peripheral vascular disease, previous stroke, previous myocardial infarction, aspirin, antiplatelet drugs, statins, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, β-blockers, selective serotonin reuptake inhibitors (SSRIs), and nonsteroidal anti-inflammatory drugs (NSAIDs).

[b]Adjusted for age, gender, most recent BMI, smoking status, chronic kidney disease, hypertension, moderate to severe liver disease, previous stroke, previous bleed, alcohol abuse, gastritis, cancer, anaemia, aspirin, antiplatelet drugs, NSAIDs, SSRIs, Proton-pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RA).

on risks of stroke, MI and major bleeding are in line with a large meta-analysis of RCTs of the four DOACs in which the rates associated with DOACs were overall comparable to warfarin, and no significant interaction was shown between diabetes and rates of stroke and major bleeding.[12]

In a meta-analysis of RCTs of DOACs in the subgroup of diabetic patients by Patti et al, the prevention of thromboembolic and major bleeding complications by DOACs compared with warfarin was irrespective of diabetes status.[20]

Our findings of similar risks of stroke in patients taking apixaban or rivaroxaban compared to warfarin are not in line with a large observational study in patients with AF and diabetes by Lip et al., were apixaban and rivaroxaban were associated with a lower risk of stroke compared to warfarin.[36]

Contradictory results have been shown for bleeding risks in diabetic patients with AF treated with individual DOACs. Our cohort mostly included users of rivaroxaban and apixaban. In the ARISTOTLE trial comparing apixaban and warfarin, diabetes was independently associated with an increased risk of bleeding events, and the reduction in bleeding with apixaban appeared to be less in diabetic patients compared with non-diabetics.[11] In the study by Lip et al., the risk of major bleeding was significantly lower in apixaban users compared to warfarin among patients with AF and diabetes.[36]

In the ROCKET-AF trial comparing rivaroxaban and warfarin, no significant interaction was observed between diabetes and the risk of bleeding.[37] Moreover, no interaction between diabetes status and the benefits of DOACs was found for the risk of major bleeding, or intracranial bleeding in the meta-analysis by Patti et al.,[20] and the result was consistent with two observational studies assessing the benefits and risks of rivaroxaban in patients with AF and diabetes.[36,38]

4.1 | Strengths

Current evidence on DOACs in diabetic patients is mainly derived from post-hoc analyses of clinical trials, and patients with severe chronic kidney disease were excluded, thus excluding patients with diabetic nephropathy who are at increased risk of bleeding and cardiovascular events. In our study, we included all AF and T2DM patients with different diabetes severity and treatment intensity levels, providing a well-defined and representative cohort of patients with AF and T2DM in the UK.

Despite the potential impact of patients' compliance to their prescribed treatment on our study, we obtained consistent results in the intention to treat analysis and sensitivity analyses using different discontinuation definitions.

4.2 | Limitations

This study has several limitations. Confounding by indication is a major concern in observational study designs. In the sensitivity analysis, we matched patients on baseline characteristics to minimize differences in the distribution of potential confounders between exposure groups, and the main effectiveness and safety results remained unchanged. However, residual confounding may still persist given the observational nature of this study.

The results on bleeding risks depends on the definition of the outcome, which explains the differences of results across studies. In clinical trials, major bleed was defined according to the International Society of Thrombosis and Hemostasis (ISTH).[39] In our study, we used Read codes to select bleeding events, thus classification of events as major bleeds may be influenced by investigator-based definitions. In addition, we did not have data on INR values nor on type of AF (paroxysmal or persistent) available in our study.

Moreover, the event rates are lower than those seen in clinical trials. Therefore, the statistically non-significant results could be due to the small number of events, thus the lack of statistical power to show a difference between the two exposure groups.

Furthermore, diabetes severity and its effect on the risk of stroke could be better evaluated when considering the duration of disease and levels of HbA1c.[40] However, we did not include these measures in our analysis; instead, we only stratified patients according to antidiabetic treatment as a proxy for severity. Further studies incorporating disease duration and HbA1c levels could give better estimates of the impact of diabetes severity on the comparative effectiveness and safety of DOACs versus warfarin.

Finally, due to limited number of observed events, we were not able to study individual DOACs and different dosages.

In conclusion, our study results suggest that DOACs are effective and safe alternatives to warfarin for the prevention of stroke in AF patients with T2DM in daily practice, and supports the current available information obtained from RCTs subgroups analyses.

ETHICAL STATEMENT

The study design was reviewed and approved by ISAC (ISAC protocol number 19_225).

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CONFLICT OF INTEREST

All authors have completed the Pharmacoepidemiology and Drug Safety Conflict of Interest (COI) disclosure forms, and declare: Mr. Komen received personal fees from Boehringer Ingelheim, outside the submitted work. Other authors disclose no conflicts.

AUTHOR CONTRIBUTIONS

Fatma Rustem Gulluoglu was involved in the conception and design of the study, statistical analysis and interpretation of data, drafting and critical revision of the manuscript. Patrick C. Souverein was involved in the conception and design of the study, acquisition of data and critical revision of the manuscript. Hendrika A. van den Ham was involved in the conception and design of the study and critical revision of the manuscript. Anthonius de Boer was involved in the conception and design of the study, critical revision of the manuscript and supervision. Joris Komen was involved in conception and design of the study, statistical analysis and interpretation of the data, critical revision of the manuscript and supervision.

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APPENDIX A.

TABLE A1 Diabetes inclusion list

Medcode	Readcode	Description
506	C100112	Non-insulin dependent diabetes mellitus
711	C10..00	Diabetes mellitus
758	C10F.00	Type 2 diabetes mellitus
1038	C100011	Insulin dependent diabetes mellitus
1407	C10FJ00	Insulin treated Type 2 diabetes mellitus
1549	C10E.00	Type 1 diabetes mellitus
1647	C108.00	Insulin dependent diabetes mellitus
1682	C101.00	Diabetes mellitus with ketoacidosis
2475	C104.11	Diabetic nephropathy
4513	C109.00	Non-insulin dependent diabetes mellitus
5884	C109.11	NIDDM – Non-insulin dependent diabetes mellitus
6509	C108700	Insulin dependent diabetes mellitus with retinopathy
6791	C108800	Insulin dependent diabetes mellitus – poor control
7563	66A3.00	Diabetic on diet only
8403	C109700	Non-insulin dependent diabetes mellitus – poor control
8842	66A5.00	Diabetic on insulin
9835	2BBL.00	O/E – diabetic maculopathy present both eyes
9881	M271200	Mixed diabetic ulcer – foot
10099	F420300	Advanced diabetic maculopathy
10418	C10ED00	Type 1 diabetes mellitus with nephropathy
10642	ZC2C800	Dietary advice for diabetes mellitus
10659	F464000	Diabetic cataract
10692	C10EM00	Type 1 diabetes mellitus with ketoacidosis
10755	F420600	Non proliferative diabetic retinopathy
11018	8HBG.00	Diabetic retinopathy 12 month review
11129	2BBQ.00	O/E – left eye background diabetic retinopathy
11433	2BBP.00	O/E – right eye background diabetic retinopathy
11599	7276.00	Pan retinal photocoagulation for diabetes
11626	F420z00	Diabetic retinopathy NOS
11663	M271100	Neuropathic diabetic ulcer – foot
11848	C314.11	Renal diabetes
12213	8BL2.00	Patient on maximal tolerated therapy for diabetes
12455	C10E.11	Type I diabetes mellitus
12640	C10FC00	Type 2 diabetes mellitus with nephropathy
12736	C10F500	Type 2 diabetes mellitus with gangrene
13078	13AC.00	Diabetic weight reducing diet
13097	2BBT.00	O/E – right eye proliferative diabetic retinopathy
13099	2BBR.00	O/E – right eye preproliferative diabetic retinopathy
13100	2BBJ.00	O/E – no right diabetic retinopathy
13101	2BBV.00	O/E – left eye proliferative diabetic retinopathy
13102	2BBW.00	O/E – right eye diabetic maculopathy
13103	2BBS.00	O/E – left eye preproliferative diabetic retinopathy
13104	2BBK.00	O/E – no left diabetic retinopathy

TABLE A1 (Continued)

Medcode	Readcode	Description
13108	2BBX.00	O/E – left eye diabetic maculopathy
14050	42c..00	HbA1 – diabetic control
14803	C100100	Diabetes mellitus, adult onset, no mention of complication
15690	C103.00	Diabetes mellitus with ketoacidotic coma
16230	C106.00	Diabetes mellitus with neurological manifestation
16502	C104.00	Diabetes mellitus with renal manifestation
17067	F171100	Autonomic neuropathy due to diabetes
17095	2G5A.00	O/E – Right diabetic foot at risk
17247	F35z000	Diabetic mononeuritis NOS
17262	C109600	Non-insulin-dependent diabetes mellitus with retinopathy
17313	F440700	Diabetic iritis
17545	C108F11	Type I diabetes mellitus with diabetic cataract
17858	C108.12	Type 1 diabetes mellitus
17859	C109.12	Type 2 diabetes mellitus
18056	2G5C.00	Foot abnormality – diabetes related
18142	N030000	Diabetic cheiroarthropathy
18143	C109G11	Type II diabetes mellitus with arthropathy
18209	C109012	Type 2 diabetes mellitus with renal complications
18219	C109.13	Type II diabetes mellitus
18230	C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
18264	C109J12	Insulin treated Type II diabetes mellitus
18278	C109J00	Insulin treated Type 2 diabetes mellitus
18387	C10E700	Type 1 diabetes mellitus with retinopathy
18390	C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
18425	C10FB00	Type 2 diabetes mellitus with polyneuropathy
18496	C10F600	Type 2 diabetes mellitus with retinopathy
18505	C108.11	IDDM-Insulin dependent diabetes mellitus
18642	C10EH00	Type 1 diabetes mellitus with arthropathy
18662	8HBH.00	Diabetic retinopathy 6 month review
18683	C10E500	Type 1 diabetes mellitus with ulcer
18777	C10F000	Type 2 diabetes mellitus with renal complications
21482	C102.00	Diabetes mellitus with hyperosmolar coma
21983	C108012	Type 1 diabetes mellitus with renal complications
22573	C106z00	Diabetes mellitus NOS with neurological manifestation
22871	C10EP00	Type 1 diabetes mellitus with exudative maculopathy
22884	C10F.11	Type II diabetes mellitus
22967	2BBF.00	Retinal abnormality – diabetes related
24327	M271000	Ischaemic ulcer diabetic foot
24423	C108.13	Type I diabetes mellitus
24458	C109711	Type II diabetes mellitus – poor control
24571	F372200	Asymptomatic diabetic neuropathy
24693	C109G00	Non-insulin dependent diabetes mellitus with arthropathy
24694	C108B00	Insulin dependent diabetes mellitus with mononeuropathy
24836	C109C12	Type 2 diabetes mellitus with nephropathy
25041	ZC2CA00	Dietary advice for type II diabetes
25591	C10FQ00	Type 2 diabetes mellitus with exudative maculopathy

(Continues)

TABLE A1 (Continued)

Medcode	Readcode	Description
25627	C10F700	Type 2 diabetes mellitus – poor control
26054	C10FL00	Type 2 diabetes mellitus with persistent proteinuria
26664	2G5B.00	O/E – Left diabetic foot at risk
26666	2G5E.00	O/E – Right diabetic foot at low risk
26667	2G5I.00	O/E – Left diabetic foot at low risk
26855	C108400	Unstable insulin dependent diabetes mellitus
27891	N030100	Diabetic Charcot arthropathy
27921	2G51000	Foot abnormality – diabetes related
28769	66AV.00	Diabetic on insulin and oral treatment
28873	66Ai.00	Diabetic 6 month review
29979	C109900	Non-insulin-dependent diabetes mellitus without complication
30294	C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
30323	C10EK00	Type 1 diabetes mellitus with persistent proteinuria
30477	F420700	High risk proliferative diabetic retinopathy
31053	R054300	[D]Widespread diabetic foot gangrene
31156	2G5J.00	O/E – Left diabetic foot at moderate risk
31157	2G5F.00	O/E – Right diabetic foot at moderate risk
31171	2G5G.00	O/E – Right diabetic foot at high risk
31172	2G5K.00	O/E – Left diabetic foot at high risk
31790	F372.00	Polyneuropathy in diabetes
32359	ZRbH.00	Perceived control of insulin-dependent diabetes
32403	C107.11	Diabetes mellitus with gangrene
32556	C107.12	Diabetes with gangrene
32627	C10FN00	Type 2 diabetes mellitus with ketoacidosis
33254	C105.00	Diabetes mellitus with ophthalmic manifestation
33807	C107200	Diabetes mellitus, adult with gangrene
34152	G73y000	Diabetic peripheral angiopathy
34268	C10F200	Type 2 diabetes mellitus with neurological complications
34283	C105z00	Diabetes mellitus NOS with ophthalmic manifestation
34450	C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
34912	C109400	Non-insulin dependent diabetes mellitus with ulcer
35105	C104100	Diabetes mellitus, adult onset, with renal manifestation
35107	C104z00	Diabetes mellitus with nephropathy NOS
35116	2G5L.00	O/E – Left diabetic foot – ulcerated
35288	C10E800	Type 1 diabetes mellitus – poor control
35316	2G5H.00	O/E – Right diabetic foot – ulcerated
35385	C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
35399	C107.00	Diabetes mellitus with peripheral circulatory disorder
35785	F372100	Chronic painful diabetic neuropathy
36633	C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
36695	C10D.00	Diabetes mellitus autosomal dominant type 2
37315	F3y0.00	Diabetic mononeuropathy
37648	C109J11	Insulin treated non-insulin dependent diabetes mellitus
37806	C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
38161	C108711	Type I diabetes mellitus with retinopathy
38986	C100.00	Diabetes mellitus with no mention of complication

TABLE A1 (Continued)

Medcode	Readcode	Description
39070	C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
39317	C106100	Diabetes mellitus, adult onset, + neurological manifestation
39809	C108J00	Insulin dependent diab mell with neuropathic arthropathy
40401	C109500	Non-insulin dependent diabetes mellitus with gangrene
40837	C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
41049	C108712	Type 1 diabetes mellitus with retinopathy
41389	C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
41716	C108C00	Insulin dependent diabetes mellitus with polyneuropathy
42505	C101z00	Diabetes mellitus NOS with ketoacidosis
42729	C108E11	Type I diabetes mellitus with hypoglycaemic coma
42762	C109612	Type 2 diabetes mellitus with retinopathy
42831	C10E200	Type 1 diabetes mellitus with neurological complications
43139	C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
43227	C10F311	Type II diabetes mellitus with multiple complications
43453	C10C.00	Diabetes mellitus autosomal dominant
43785	C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
43857	C10M.00	Lipoatrophic diabetes mellitus
43921	C10E400	Unstable type 1 diabetes mellitus
44033	F345000	Diabetic mononeuritis multiplex
44260	C108F00	Insulin dependent diabetes mellitus with diabetic cataract
44440	C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
44443	C108500	Insulin dependent diabetes mellitus with ulcer
44779	C109E12	Type 2 diabetes mellitus with diabetic cataract
44982	C10FE00	Type 2 diabetes mellitus with diabetic cataract
45276	C10E312	Insulin dependent diabetes mellitus with multiple complications
45467	C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
45491	C10z.00	Diabetes mellitus with unspecified complication
45913	C109712	Type 2 diabetes mellitus – poor control
45914	C108812	Type 1 diabetes mellitus – poor control
45919	C109212	Type 2 diabetes mellitus with neurological complications
46150	C109512	Type 2 diabetes mellitus with gangrene
46301	C10EC00	Type 1 diabetes mellitus with polyneuropathy
46850	C108811	Type I diabetes mellitus – poor control
46917	C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
46963	C108000	Insulin-dependent diabetes mellitus with renal complications
47144	2BBM.00	O/E – diabetic maculopathy absent both eyes
47315	C10F711	Type II diabetes mellitus – poor control
47321	C10F100	Type 2 diabetes mellitus with ophthalmic complications
47328	2BBk.00	O/E – right eye stable treated prolif diabetic retinopathy
47409	C109B11	Type II diabetes mellitus with polyneuropathy
47582	C10E000	Type 1 diabetes mellitus with renal complications
47584	F420500	Advanced diabetic retinal disease
47649	C10E100	Type 1 diabetes mellitus with ophthalmic complications

(Continues)

TABLE A1 (Continued)

Medcode	Readcode	Description
47650	C10E300	Type 1 diabetes mellitus with multiple complications
47816	C109H11	Type II diabetes mellitus with neuropathic arthropathy
47954	C10F900	Type 2 diabetes mellitus without complication
48078	F372000	Acute painful diabetic neuropathy
48192	C109E11	Type II diabetes mellitus with diabetic cataract
49074	C10F400	Type 2 diabetes mellitus with ulcer
49146	C108211	Type I diabetes mellitus with neurological complications
49276	C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
49554	C10EF00	Type 1 diabetes mellitus with diabetic cataract
49640	2G5W.00	O/E – left chronic diabetic foot ulcer
49655	C10F611	Type II diabetes mellitus with retinopathy
49869	C109G12	Type 2 diabetes mellitus with arthropathy
49949	C10E411	Unstable type I diabetes mellitus
50225	C109011	Type II diabetes mellitus with renal complications
50429	C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
50527	C10FB11	Type II diabetes mellitus with polyneuropathy
50609	L180600	Pre-existing diabetes mellitus, non-insulin-dependent
50813	C109A11	Type II diabetes mellitus with mononeuropathy
50960	L180500	Pre-existing diabetes mellitus, insulin-dependent
50972	C100z00	Diabetes mellitus NOS with no mention of complication
51261	C10E.12	Insulin dependent diabetes mellitus
51756	C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
51957	C108511	Type I diabetes mellitus with ulcer
52104	C108300	Insulin dependent diabetes mellitus with multiple complication
52212	Cyu2.00	[X]Diabetes mellitus
52283	C108200	Insulin-dependent diabetes mellitus with neurological comps
52303	C109000	Non-insulin-dependent diabetes mellitus with renal comps
53392	C10F911	Type II diabetes mellitus without complication
54008	C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
54600	C10E412	Unstable insulin dependent diabetes mellitus
54856	C101100	Diabetes mellitus, adult onset, with ketoacidosis
54899	C109F11	Type II diabetes mellitus with peripheral angiopathy
55075	C109411	Type II diabetes mellitus with ulcer
55239	C10EQ00	Type 1 diabetes mellitus with gastroparesis
55842	C109200	Non-insulin-dependent diabetes mellitus with neuro comps
56268	C109D11	Type II diabetes mellitus with hypoglycaemic coma
56448	C108A00	Insulin-dependent diabetes without complication
57278	C10F011	Type II diabetes mellitus with renal complications
57333	N030011	Diabetic cheiropathy
57621	C108D00	Insulin dependent diabetes mellitus with nephropathy
58604	C109611	Type II diabetes mellitus with retinopathy
59253	C10FG00	Type 2 diabetes mellitus with arthropathy
59365	C109C00	Non-insulin dependent diabetes mellitus with nephropathy
59725	C109111	Type II diabetes mellitus with ophthalmic complications

TABLE A1 (Continued)

Medcode	Readcode	Description
59991	C10D.11	Maturity onset diabetes in youth type 2
60107	C108411	Unstable type I diabetes mellitus
60208	C108J11	Type I diabetes mellitus with neuropathic arthropathy
60499	C108600	Insulin dependent diabetes mellitus with gangrene
60699	C109F12	Type 2 diabetes mellitus with peripheral angiopathy
60796	C10FL11	Type II diabetes mellitus with persistent proteinuria
61071	C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
61344	C108011	Type I diabetes mellitus with renal complications
61829	C108212	Type 1 diabetes mellitus with neurological complications
62107	C109511	Type II diabetes mellitus with gangrene
62146	C109300	Non-insulin-dependent diabetes mellitus with multiple comps
62209	C10EM11	Type I diabetes mellitus with ketoacidosis
62352	C108H11	Type I diabetes mellitus with arthropathy
62613	C10EA11	Type I diabetes mellitus without complication
62674	C10FA00	Type 2 diabetes mellitus with mononeuropathy
63357	C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
63690	C10FR00	Type 2 diabetes mellitus with gastroparesis
63762	C10z100	Diabetes mellitus, adult onset, + unspecified complication
64357	C10zz00	Diabetes mellitus NOS with unspecified complication
1323	F420.00	Diabetic retinopathy
1684	66A4.00	Diabetic on oral treatment
2340	F381311	Diabetic amyotrophy
2342	F372.12	Diabetic neuropathy
2471	K01x100	Nephrotic syndrome in diabetes mellitus
2478	66AJ100	Brittle diabetes
2986	F420200	Preproliferative diabetic retinopathy
3286	F420100	Proliferative diabetic retinopathy
3837	F420400	Diabetic maculopathy
5002	F372.11	Diabetic polyneuropathy
7069	F420000	Background diabetic retinopathy
7328	M037200	Cellulitis in diabetic foot
7795	C106.12	Diabetes mellitus with neuropathy
9013	66AJ.11	Unstable diabetes
11471	8B3l.00	Diabetes medication review
16491	C106.13	Diabetes mellitus with polyneuropathy
24363	8A13.00	Diabetic stabilization
39420	F381300	Myasthenic syndrome due to diabetic amyotrophy
47341	8A12.00	Diabetic crisis monitoring
52630	2Bbo.00	O/E – sight threatening diabetic retinopathy
53634	R054200	[D]Gangrene of toe in diabetic
55431	L180X00	Pre-existing diabetes mellitus, unspecified
59903	C106.11	Diabetic amyotrophy
61670	889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
64446	C108G00	Insulin dependent diab mell with peripheral angiopathy
64449	C108z00	Unspecified diabetes mellitus with multiple complications
64571	C109C11	Type II diabetes mellitus with nephropathy

(Continues)

TABLE A1 (Continued)

Medcode	Readcode	Description
64668	C10FJ11	Insulin treated Type II diabetes mellitus
65025	C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
65062	C103z00	Diabetes mellitus NOS with ketoacidotic coma
65267	C10F300	Type 2 diabetes mellitus with multiple complications
65616	C108H00	Insulin dependent diabetes mellitus with arthropathy
65704	C109412	Type 2 diabetes mellitus with ulcer
66145	C10EN11	Type I diabetes mellitus with ketoacidotic coma
66872	C108D11	Type I diabetes mellitus with nephropathy
66965	C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
67905	C109211	Type II diabetes mellitus with neurological complications
68105	C10EB00	Type 1 diabetes mellitus with mononeuropathy
68390	C108512	Type 1 diabetes mellitus with ulcer
68843	C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
69278	C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
69676	C10EA00	Type 1 diabetes mellitus without complication
69993	C10E600	Type 1 diabetes mellitus with gangrene
70316	C109112	Type 2 diabetes mellitus with ophthalmic complications
70766	C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
72320	C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
72345	C102z00	Diabetes mellitus NOS with hyperosmolar coma
72702	C10E812	Insulin dependent diabetes mellitus – poor control
83532	66Ao.00	Diabetes type 2 review
85660	66An.00	Diabetes type 1 review
85991	C10FM11	Type II diabetes mellitus with persistent microalbuminuria
91646	C10F411	Type II diabetes mellitus with ulcer
91942	C10E311	Type I diabetes mellitus with multiple complications
91943	C10EC11	Type I diabetes mellitus with polyneuropathy
93468	C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
93727	C10FE11	Type II diabetes mellitus with diabetic cataract
93875	C10E712	Insulin dependent diabetes mellitus with retinopathy
93878	C10E511	Type I diabetes mellitus with ulcer
95343	C10E711	Type I diabetes mellitus with retinopathy
95351	C10FA11	Type II diabetes mellitus with mononeuropathy
95992	C108A11	Type I diabetes mellitus without complication
97474	C108412	Unstable type 1 diabetes mellitus
97894	C10EP11	Type I diabetes mellitus with exudative maculopathy
98071	C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
98616	C10F211	Type II diabetes mellitus with neurological complications
98704	C10E512	Insulin dependent diabetes mellitus with ulcer
98723	C10FD11	Type II diabetes mellitus with hypoglycaemic coma
99231	C108B11	Type I diabetes mellitus with mononeuropathy
99311	C10E111	Type I diabetes mellitus with ophthalmic complications
99716	C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
99719	C10EA12	Insulin-dependent diabetes without complication
100292	Cyu2300	[X]Unspecified diabetes mellitus with renal complications

TABLE A1 (Continued)

Medcode	Readcode	Description
100770	C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
100964	C10F111	Type II diabetes mellitus with ophthalmic complications
101311	C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
101728	66As.00	Diabetic on subcutaneous treatment
101735	C10E212	Insulin-dependent diabetes mellitus with neurological comps
101801	66At100	Type II diabetic dietary review
101881	2BBr.00	Impaired vision due to diabetic retinopathy
102112	C10E611	Type I diabetes mellitus with gangrene
102163	C10ED12	Insulin dependent diabetes mellitus with nephropathy
102201	C10FC11	Type II diabetes mellitus with nephropathy
102434	66Au.00	Diabetic erectile dysfunction review
102611	66At111	Type 2 diabetic dietary review
102620	C10EL11	Type I diabetes mellitus with persistent microalbuminuria
102704	66At000	Type I diabetic dietary review
102740	C108112	Type 1 diabetes mellitus with ophthalmic complications
102946	C10E012	Insulin-dependent diabetes mellitus with renal complications
103902	C10FG11	Type II diabetes mellitus with arthropathy
104323	C10F511	Type II diabetes mellitus with gangrene
104639	C10FF11	Type II diabetes mellitus with peripheral angiopathy
105302	K08yA00	Proteinuric diabetic nephropathy
105337	C10E811	Type I diabetes mellitus – poor control
105784	C109912	Type 2 diabetes mellitus without complication
106061	C10FP11	Type II diabetes mellitus with ketoacidotic coma
106360	K27y700	Erectile dysfunction due to diabetes mellitus
106528	C10FN11	Type II diabetes mellitus with ketoacidosis
107701	C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus
107881	K08yA11	Clinical diabetic nephropathy
108005	C109312	Type 2 diabetes mellitus with multiple complications
108007	C108311	Type I diabetes mellitus with multiple complications
108724	C10EQ11	Type I diabetes mellitus with gastroparesis
109051	C10E612	Insulin dependent diabetes mellitus with gangrene
109103	C109911	Type II diabetes mellitus without complication
109197	C10FH11	Type II diabetes mellitus with neuropathic arthropathy
109837	C10E011	Type I diabetes mellitus with renal complications
109865	C109B12	Type 2 diabetes mellitus with polyneuropathy
109878	ZC2C911	Diet advice for insulin-dependent diabetes
110344	66o2.00	Diabetic on non-insulin injectable medication
110379	66o5.00	Diabetic on oral treatment and glucagon-like peptide 1
110400	C108F12	Type 1 diabetes mellitus with diabetic cataract
111106	C108A12	Type 1 diabetes mellitus without complication
111483	66o6.00	Diabetic on insulin and glucagon-like peptide 1
111798	C10FQ11	Type II diabetes mellitus with exudative maculopathy
112365	Lyu2900	[X]Pre-existing diabetes mellitus, unspecified

TABLE A2 Diabetes exclusion list

Medcode	Readcode	Description
1045	C135.00	Diabetes insipidus
2471	K01x100	Nephrotic syndrome in diabetes mellitus
2664	L180900	Gestational diabetes mellitus
8446	L180811	Gestational diabetes mellitus
10098	C10yy00	Other specified diabetes mellitus with other spec comps
10278	L180800	Diabetes mellitus arising in pregnancy
11359	L180.00	Diabetes mellitus during pregnancy/childbirth/puerperium
11551	C10B.00	Diabetes mellitus induced by steroids
13279	C104y00	Other specified diabetes mellitus with renal complications
16946	13L4.11	Diabetic child
21472	Q441.00	Neonatal diabetes mellitus
22487	C10N.00	Secondary diabetes mellitus
23479	C350011	Bronzed diabetes
24490	C100000	Diabetes mellitus, juvenile type, no mention of complication
26108	C10B000	Steroid induced diabetes mellitus without complication
30310	K081.00	Nephrogenic diabetes insipidus
30970	Q44B.00	Syndrome of infant of mother with gestational diabetes
32193	C11y000	Steroid induced diabetes
32999	Q440.00	"Infant of a diabetic mother" syndrome
33343	C10y.00	Diabetes mellitus with other specified manifestation
33969	C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
34639	L180100	Diabetes mellitus during pregnancy - baby delivered
38617	C101y00	Other specified diabetes mellitus with ketoacidosis
39420	F381300	Myasthenic syndrome due to diabetic amyotrophy
40023	C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
40682	C10E900	Type 1 diabetes mellitus maturity onset
41686	Cyu2000	[X]Other specified diabetes mellitus
42567	C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
46290	C108y00	Other specified diabetes mellitus with multiple comps
46624	C10C.11	Maturity onset diabetes in youth
47377	C105y00	Other specified diabetes mellitus with ophthalmic complication
49559	L180300	Diabetes mellitus during pregnancy - baby not yet delivered
50064	Q44y100	Transitory metabolic disturbance-infant pre-diabetic mother
51697	C10G.00	Secondary pancreatic diabetes mellitus
52236	C10A.00	Malnutrition-related diabetes mellitus with ketoacidosis

TABLE A2 (Continued)

Medcode	Readcode	Description
53200	C101000	Diabetes mellitus, juvenile type, with ketoacidosis
59288	C103y00	Other specified diabetes mellitus with coma
60046	C135.12	Diabetes insipidus - pituitary
61122	C10H.00	Diabetes mellitus induced by non-steroid drugs
61523	C106y00	Other specified diabetes mellitus with neurological comps
63017	C108911	Type I diabetes mellitus maturity onset
63371	C10y100	Diabetes mellitus, adult, + other specified manifestation
64283	C10zy00	Other specified diabetes mellitus with unspecified comps
66675	C10A000	Malnutrition-related diabetes mellitus with coma
67853	C106000	Diabetes mellitus, juvenile, + neurological manifestation
68792	C10z000	Diabetes mellitus, juvenile type, + unspecified complication
69748	C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
70448	C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
70821	C10yz00	Diabetes mellitus NOS with other specified manifestation
93380	C10N100	Cystic fibrosis related diabetes mellitus
93922	C104000	Diabetes mellitus, juvenile type, with renal manifestation
94383	C10N000	Secondary diabetes mellitus without complication
95636	C10ER00	Latent autoimmune diabetes mellitus in adult
96235	C10E911	Type I diabetes mellitus maturity onset
96506	C10G000	Secondary pancreatic diabetes mellitus without complication
96823	L180400	Diabetes mellitus in pueperium - baby previously delivered
97446	C108912	Type 1 diabetes mellitus maturity onset
98392	C10C.12	Maturity onset diabetes in youth type 1
100347	C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
101172	C135000	Cranial diabetes insipidus
102435	8CE0000	Gestational diabetes information leaflet given
104588	66Ay.00	Gestational diabetes mellitus annual review
106927	PKyP.00	Diab insipidus,diab mell,optic atrophy and deafness
108013	ZC2CB00	Dietary advice for gestational diabetes
109133	L180700	Pre-existing malnutrition-related diabetes mellitus
110481	K081000	Acquired nephrogenic diabetes insipidus
110997	C10y000	Diabetes mellitus, juvenile, + other specified manifestation
112402	C107y00	Other specified diabetes mellitus with periph circ comps

APPENDIX B.

Codes used for stroke outcomes

Medcode	readcode	Description
569	G64..12	Infarction - cerebral
1298	G66..11	CVA unspecified
1469	G66..00	Stroke and cerebrovascular accident unspecified
1786	G60..00	Subarachnoid haemorrhage
2417	G65..13	Vertebro-basilar insufficiency
3149	G64z.00	Cerebral infarction NOS
3535	G61z.00	Intracerebral haemorrhage NOS
5051	G61..00	Intracerebral haemorrhage
5185	G64z111	Lateral medullary syndrome
5268	G650.11	Insufficiency - basilar artery
5363	G64..11	CVA - cerebral artery occlusion
5602	G64z.12	Cerebellar infarction
6116	G66..13	CVA - Cerebrovascular accident unspecified
6155	G64..13	Stroke due to cerebral arterial occlusion
6253	G66..12	Stroke unspecified
6960	G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
7780	G667.00	Left sided CVA
7912	G614.00	Pontine haemorrhage
8443	G663.00	Brain stem stroke syndrome
8837	G64..00	Cerebral arterial occlusion
9696	G604.00	Subarachnoid haemorrhage from posterior communicating artery
9985	G64z200	Left sided cerebral infarction
10504	G64z300	Right sided cerebral infarction
12833	G668.00	Right sided CVA
13564	G613.00	Cerebellar haemorrhage
15019	G641.00	Cerebral embolism
15252	G64z.11	Brainstem infarction NOS
16517	G640.00	Cerebral thrombosis
17322	G664.00	Cerebellar stroke syndrome
17326	G60X.00	Subarachnoid haemorrh from intracranial artery, unspecified
18604	G61..12	Stroke due to intracerebral haemorrhage
18689	G660.00	Middle cerebral artery syndrome
19201	G61X100	Right sided intracerebral haemorrhage, unspecified
19260	G662.00	Posterior cerebral artery syndrome
19280	G661.00	Anterior cerebral artery syndrome
19412	G602.00	Subarachnoid haemorrhage from middle cerebral artery
20284	G62z.00	Intracranial haemorrhage NOS
21118	G651000	Vertebro-basilar artery syndrome
23580	G60z.00	Subarachnoid haemorrhage NOS
23942	G650.00	Basilar artery syndrome

Medcode	readcode	Description
25615	G64z000	Brainstem infarction
26424	G64z400	Infarction of basal ganglia
27975	G641000	Cerebral infarction due to embolism of cerebral arteries
28314	G61X000	Left sided intracerebral haemorrhage, unspecified
29939	G600.00	Ruptured berry aneurysm
30045	G616.00	External capsule haemorrhage
30202	G617.00	Intracerebral haemorrhage, intraventricular
31060	G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
31595	G610.00	Cortical haemorrhage
31805	G62..00	Other and unspecified intracranial haemorrhage
33377	G651.00	Vertebral artery syndrome
33499	G665.00	Pure motor lacunar syndrome
34758	G641.11	Cerebral embolus
36717	G640000	Cerebral infarction due to thrombosis of cerebral arteries
39344	G676000	Cerebral infarction due cerebral venous thrombosis, nonpyogenic
40338	G611.00	Internal capsule haemorrhage
41910	G605.00	Subarachnoid haemorrhage from basilar artery
42331	G603.00	Subarachnoid haemorrhage from anterior communicating artery
46316	G612.00	Basal nucleus haemorrhage
47642	G64z100	Wallenberg syndrome
50594	G654.00	Multiple and bilateral precerebral artery syndromes
51767	G666.00	Pure sensory lacunar syndrome
53745	Gyu6400	[X]Other cerebral infarction
53810	Gyu6200	[X]Other intracerebral haemorrhage
55247	G65z000	Impending cerebral ischaemia
56007	G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
57315	G618.00	Intracerebral haemorrhage, multiple localized
57495	G63..11	Infarction - precerebral
60692	G606.00	Subarachnoid haemorrhage from vertebral artery
62342	G615.00	Bulbar haemorrhage
65745	Gyu6100	[X]Other subarachnoid haemorrhage
91627	Gyu6300	[X]Cerebral infarction due/unspecified occlusion or stenos/cerebral arteries
94482	Gyu6G00	[X]Cerebral infarct due unspecified occlusion/ stenos precerebral arteries
96630	Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
107440	G619.00	Lobar cerebral haemorrhage
108630	Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecified
108668	Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries

Codes used for major bleeding outcomes

Medcode	Readcode	Description
397	J681.00	Melaena
621	J573011	Rectal bleeding
1188	J680.00	Haematemesis
1201	F4K2800	Vitreous haemorrhage
1583	K5A1.00	Postmenopausal bleeding
1610	172..12	Haemoptysis - symptom
1642	J68z.11	GIB - Gastrointestinal bleeding
1786	G60..00	Subarachnoid haemorrhage
2044	J510900	Bleeding diverticulosis
2120	N091.00	Haemarthrosis
2150	J68z100	Intestinal haemorrhage NOS
2244	R063.00	[D]Haemoptysis
2629	F404500	Intra-ocular haemorrhage
2712	J680.11	Vomiting of blood
2743	D211.00	Acute posthaemorrhagic anaemia
2814	J12y100	Unspecified duodenal ulcer with haemorrhage
2883	S622.00	Closed traumatic subdural haemorrhage
3039	F42y500	Retinal haemorrhage NOS
3097	J68..00	Gastrointestinal haemorrhage
3535	G61z.00	Intracerebral haemorrhage NOS
3872	J573.11	Bleeding PR
4135	172..00	Blood in sputum - haemoptysis
4273	G621.00	Subdural haemorrhage - nontraumatic
4354	J68z200	Upper gastrointestinal haemorrhage
4636	J68zz00	Gastrointestinal tract haemorrhage NOS
5051	G61..00	Intracerebral haemorrhage
5682	S62..00	Cerebral haemorrhage following injury
6554	J573012	PRB - Rectal bleeding
6569	S62..13	Subdural haemorrhage following injury
6574	J573000	Rectal haemorrhage
6830	H51y200	Haemothorax
6960	G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage
7912	G614.00	Pontine haemorrhage
8181	S628.00	Traumatic subdural haemorrhage
9696	G604.00	Subarachnoid haemorrhage from posterior communicating artery
10779	F42y.11	Haemorrhage - retinal
11124	J110111	Bleeding acute gastric ulcer
12471	J68z.00	Gastrointestinal haemorrhage unspecified
13564	G613.00	Cerebellar haemorrhage
15464	F436000	Unspecified choroidal haemorrhage
15517	J68z000	Gastric haemorrhage NOS
16114	J10y000	Haemorrhage of oesophagus
17326	G60X.00	Subarachnoid haemorrh from intracranial artery, unspecified

Medcode	Readcode	Description
17734	G622.00	Subdural haematoma - nontraumatic
18001	J120100	Acute duodenal ulcer with haemorrhage
18411	S62A.00	Traumatic extradural haematoma
18604	G61..12	Stroke due to intracerebral haemorrhage
18625	J121111	Bleeding chronic duodenal ulcer
18912	G623.00	Subdural haemorrhage NOS
19201	G61X100	Right sided intracerebral haemorrhage, unspecified
19271	J573.00	Haemorrhage of rectum and anus
19412	G602.00	Subarachnoid haemorrhage from middle cerebral artery
20284	G62z.00	Intracranial haemorrhage NOS
21799	F4K7.00	Retrobulbar haemorrhage
23580	G60z.00	Subarachnoid haemorrhage NOS
24989	G850.00	Oesophageal varices with bleeding
27337	J56y000	Haemoperitoneum - nontraumatic
27661	S62..11	Extradural haemorrhage following injury
28077	S62..14	Traumatic cerebral haemorrhage
28314	G61X000	Left sided intracerebral haemorrhage, unspecified
28366	J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
28763	F436100	Expulsive choroidal haemorrhage
28765	F42y400	Subretinal haemorrhage
28807	S62..12	Subarachnoid haemorrhage following injury
29492	J150000	Acute haemorrhagic gastritis
29702	FyuH400	[X]Vitreous haemorrhage in diseases classified elsewhere
30045	G616.00	External capsule haemorrhage
30054	J110100	Acute gastric ulcer with haemorrhage
30202	G617.00	Intracerebral haemorrhage, intraventricular
31060	G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
31595	G610.00	Cortical haemorrhage
31805	G62..00	Other and unspecified intracranial haemorrhage
32446	J573100	Anal haemorrhage
33360	F4G3200	Exophthalmos due to orbital haemorrhage
33742	R063z00	[D]Haemoptysis NOS
35867	S630.12	Intracranial haematoma following injury
36178	G620.00	Extradural haemorrhage - nontraumatic
36583	J111111	Bleeding chronic gastric ulcer
37550	F436.00	Choroidal haemorrhage and rupture
38304	S620.00	Closed traumatic subarachnoid haemorrhage
38851	R048.00	[D]Throat haemorrhage
39015	F42y000	Preretinal heamorrhage
40338	G611.00	Internal capsule haemorrhage
41910	G605.00	Subarachnoid haemorrhage from basilar artery
42283	S63z.00	Other cerebral haemorrhage following injury NOS
42331	G603.00	Subarachnoid haemorrhage from anterior communicating artery
44637	J130100	Acute peptic ulcer with haemorrhage
45304	J130300	Acute peptic ulcer with haemorrhage and perforation

(Continues)

Medcode	Readcode	Description
45421	S624.00	Closed traumatic extradural haemorrhage
45929	D211.11	Normocytic anaemia following acute bleed
46316	G612.00	Basal nucleus haemorrhage
46479	J573z00	Haemorrhage of rectum and anus NOS
46545	S62z.00	Cerebral haemorrhage following injury NOS
46938	F42y100	Superficial retinal haemorrhage
48730	J120300	Acute duodenal ulcer with haemorrhage and perforation
48951	J121100	Chronic duodenal ulcer with haemorrhage
50097	K167.00	Haemorrhage into bladder wall
53126	J131100	Chronic peptic ulcer with haemorrhage
53810	Gyu6200	[X]Other intracerebral haemorrhage
53980	S629000	Traumatic subdural haematoma without open intracranial wound
55063	N091000	Haemarthrosis of unspecified site
56689	F404300	Haemophthalmos (excluding current injury)
57315	G618.00	Intracerebral haemorrhage, multiple localized
57958	J11y100	Unspecified gastric ulcer with haemorrhage
58545	S627.00	Traumatic subarachnoid haemorrhage
59812	F436z00	Choroidal haemorrhage or rupture NOS
60346	J14y100	Unspecified gastrojejunal ulcer with haemorrhage
60692	G606.00	Subarachnoid haemorrhage from vertebral artery
62342	G615.00	Bulbar haemorrhage
63582	J111100	Chronic gastric ulcer with haemorrhage
65745	Gyu6100	[X]Other subarachnoid haemorrhage
66907	F212.00	Acute and subacute haemorrhagic leukoencephalitis [Hurst]
70456	J13y100	Unspecified peptic ulcer with haemorrhage
71197	F437200	Haemorrhagic choroidal detachment
71253	F42y300	Deep retinal haemorrhage
71403	J110300	Acute gastric ulcer with haemorrhage and perforation
71881	J121300	Chronic duodenal ulcer with haemorrhage and perforation
71897	J111300	Chronic gastric ulcer with haemorrhage and perforation
73471	S625.00	Open traumatic extradural haemorrhage
93436	J12y300	Unspecified duodenal ulcer with haemorrhage and perforation
94397	J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation
96622	J13y300	Unspecified peptic ulcer with haemorrhage and perforation
96628	J140100	Acute gastrojejunal ulcer with haemorrhage
96677	S629100	Traumatic subdural haematoma with open intracranial wound
96756	G852000	Oesophageal varices with bleeding in diseases EC
106330	J140300	Acute gastrojejunal ulcer with haemorrhage and perforation
107548	1720.00	Massive haemoptysis
110244	J141300	Chronic gastrojejunal ulcer with haemorrhage and perforation

APPENDIX C.

TABLE C1 Proportion of patients that filled each dose of DOAC

DOAC	Dosage	Number of patients per DOAC (%)
Rivaroxaban	2.5 mg	3 (0.19%)
	10 mg	27 (1.73%)
	15 mg	314 (20.13%)
	20 mg	1216 (77.95%)
Apixaban	2.5 mg	443 (29.51%)
	5 mg	1058 (70.49%)
Dabigatran	75 mg	4 (1.23%)
	110 mg	165 (50.93%)
	150 mg	155 (47.84%)
Edoxaban	30 mg	15 (28.85%)
	60 mg	37 (71.15%)

TABLE C2 Cox hazard ratios with 90 days discontinuation definition

Cox hazard ratios for DOACs compared to warfarin for stroke and MI endpoints		
	Crude HR (95% CL)	Adjusted HR (95% CL)[a]
Any stroke	1.18 (0.83–1.67)	1.15 (0.81–1.65)
Ischaemic and unspecified stroke	1.27 (0.87–1.86)	1.26 (0.85–1.85)
Haemorrhagic stroke	0.78 (0.32–1.92)	0.74 (0.30–1.86)
Myocardial infarction	1.11 (0.77–1.59)	1.44 (0.99–2.09)
Cox hazard ratios for DOACs compared to warfarin for major bleed endpoints		
	Crude HR (95% CL)	Adjusted HR (95% CL)[b]
Major bleed	0.82 (0.65–1.02)	0.81 (0.65–1.01)
Intracranial bleed	0.74 (0.38–1.47)	0.68 (0.34–1.36)
GI bleed	0.83 (0.63–1.10)	0.84 (0.63–1.12)
Bleeding on other sites	0.86 (0.57–1.30)	0.85 (0.56–1.28)

Abbreviations: CI, confidence interval; DOACs, direct oral anticoagulants; GI, gastrointestinal; HR, hazard ratio; MI, myocardial infarction.
[a]Adjusted for age, gender, most recent body mass index (BMI), smoking status, chronic kidney disease, congestive heart failure, hypertension, peripheral vascular disease, previous stroke, previous myocardial infarction, aspirin, antiplatelet drugs, statins, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, β-blockers, selective serotonin reuptake inhibitors (SSRIs), and nonsteroidal anti-inflammatory drugs (NSAIDs).
[b]Adjusted for age, gender, most recent BMI, smoking status, chronic kidney disease, hypertension, moderate to severe liver disease, previous stroke, previous bleed, alcohol abuse, gastritis, cancer, anemia, aspirin, antiplatelet drugs, NSAIDs, SSRIs, Proton-pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RA).

TABLE C3 Cox hazard ratios with 60 days discontinuation definition

Cox hazard ratios for DOACs compared to warfarin for stroke and MI endpoints		
	Crude HR (95% CL)	Adjusted HR (95% CL)[a]
Any stroke	1.21 (0.81–1.83)	1.17 (0.77–1.78)
Ischaemic and unspecified stroke	1.43 (0.91–2.23)	1.39 (0.88–2.19)
Haemorrhagic stroke	0.51 (0.16–1.59)	0.47 (0.15–1.51)
Myocardial infarction	1.15 (0.75–1.74)	1.51 (0.98–2.33)
Cox hazard ratios for DOACs compared to warfarin for major bleed endpoints		
	Crude HR (95% CL)	Adjusted HR (95% CL)[b]
Major bleed	0.81 (0.63–1.05)	0.79 (0.61–1.03)
Intracranial bleed	0.56 (0.24–1.34)	0.50 (0.21–1.20)
GI bleed	0.85 (0.62–1.17)	0.85 (0.62–1.17)
Bleeding on other sites	0.88 (0.54–1.43)	0.85 (0.52–1.39)

Abbreviations: CI, confidence interval; DOACs, direct oral anticoagulants; GI, gastrointestinal; HR, hazard ratio; MI, myocardial infarction.
[a]Adjusted for age, gender, most recent body mass index (BMI), smoking status, chronic kidney disease, congestive heart failure, hypertension, peripheral vascular disease, previous stroke, previous myocardial infarction, aspirin, antiplatelet drugs, statins, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, β-blockers, selective serotonin reuptake inhibitors (SSRIs), and nonsteroidal anti-inflammatory drugs (NSAIDs).
[b]Adjusted for age, gender, most recent BMI, smoking status, chronic kidney disease, hypertension, moderate to severe liver disease, previous stroke, previous bleed, alcohol abuse, gastritis, cancer, anemia, aspirin, antiplatelet drugs, NSAIDs, SSRIs, Proton-pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RA).

TABLE C4 Summary of patients' characteristics after propensity score matched analysis

Summary of patients' characteristics at baseline after propensity score matching			
Characteristic	**DOACs (*n* = 3437)**	**Warfarin (*n* = 3437)**	**SD Mean difference**
Age (mean) at index	76.07	75.96	0.011
Female	1328 (38.64%)	1345 (39.13%)	0.010
Current smoker	297 (8.64%)	275 (8.00%)	0.023
BMI (mean)	30.95	31.00	0.007
History of comorbidities			
Heart Failure	564 (16.41%)	568 (16.53%)	0.003
Hypertension	2633 (76.61%)	2647 (77.01%)	0.010
Peripheral vascular disease	230 (6.69%)	236 (6.87%)	0.007
Ischaemic heart disease	1106 (32.18%)	1139 (33.14%)	0.021
Alcohol abuse	438 (12.74%)	405 (11.78%)	0.029
Mild liver disease	123 (3.58%)	106 (3.08%)	0.027
Moderate to severe liver disease	9 (0.26%)	6 (0.17%)	0.017
Chronic kidney disease	33 (0.96%)	35 (1.02%)	0.006
Gastritis	788 (22.93%)	767 (22.32%)	0.015
Myocardial infarction	931 (27.09%)	965 (28.08%)	0.022
Any Stroke	455 (13.24%)	422 (12.28%)	0.028
Major bleed	710 (20.66%)	695 (20.22%)	0.011
Anemia	131 (3.81%)	124 (3.61%)	0.011
Cancer	131 (3.81%)	136 (3.90%)	0.008
History of co-medication			
6 months before index			
Aspirin	1882 (54.76%)	1953 (56.82%)	0.041
Other anti-platelets	676 (19.67%)	677 (19.70%)	0.001
ACE inhibitors	1857 (54.03%)	1891 (55.02%)	0.020
Angiotensin II receptor antagonists	927 (26.97%)	952 (27.70%)	0.016
Calcium channel blockers	1644 (47.83%)	1655 (48.15%)	0.006
B blockers	2551 (74.22%)	2564 (74.60%)	0.009
Diuretics	2112 (61.45%)	2160 (62.85%)	0.029
Statins	2747 (79.92%)	2784 (81.00%)	0.027
All NSAIDs	176 (5.12%)	174 (5.06%)	0.003
SSRIs	513 (14.93%)	492 (14.31%)	0.017
3 months before index			
H2RA	287 (8.35%)	303 (8.82%)	0.017
PPIs	1915 (55.72%)	1914 (55.69%)	0.001

Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; CKD, chronic kidney disease; DOAC, direct oral anticoagulant; GI, gastrointestinal; H2RA, histamine 2 receptor antagonists; NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; SD, standardized; SSRIs, selective serotonin reuptake inhibitors.

TABLE C5 Cox hazard ratios from propensity score matched analysis

Cox hazard ratios for DOACs compared to warfarin for stroke and MI endpoints	
	HR (95% CL)
Any stroke	1.53 (0.97–2.43)
Ischaemic stroke - unspec	1.56 (0.96–2.52)
Haemorrhagic stroke	1.33 (0.30–5.96)
Myocardial infarction	1.15 (0.72–1.82)
Cox hazard ratios for DOACs compared to warfarin for major bleed endpoints	
	HR (95% CL)
Major bleed	0.91 (0.70–1.20)
Intracranial bleed	0.78 (0.29–2.09)
GI bleed	0.91 (0.65–1.28)
Bleeding on other sites	1.04 (0.62–1.74)

Abbreviations: CI, confidence interval; DOACs, direct oral anticoagulants; GI, gastrointestinal; HR, hazard ratio; MI, myocardial infarction.

TABLE C6 Intention-to-treat analysis

Cox hazard ratios for DOACs compared to warfarin for stroke and MI endpoints		
	Crude HR (95% CL)	**Adjusted HR (95% CL)[a]**
Any stroke	1.06 (0.80–1.41)	1.05 (0.80–1.41)
Ischaemic and unspecified stroke	1.14 (0.85–1.54)	1.15 (0.84–1.55)
Haemorrhagic stroke	0.70 (0.31–1.59)	0.67 (0.30–1.54)
Myocardial infarction	0.98 (0.72–1.34)	1.29 (0.94–1.77)
Cox hazard ratios for DOACs compared to warfarin for major bleed endpoints		
	Crude HR (95% CL)	**Adjusted HR (95% CL)[b]**
Major bleed	0.80 (0.66–0.97)*	0.81 (0.67–0.99)*
Intracranial bleed	0.71 (0.38–1.30)	0.65 (0.35–1.20)
GI bleed	0.78 (0.61–0.99)	0.80 (0.62–1.02)
Bleeding on other sites	0.85 (0.60–1.21)	0.88 (0.62–1.25)

Abbreviations: DOACs, direct oral anticoagulants; MI, myocardial infarction; CI, confidence interval; HR, hazard ratio; GI, gastrointestinal.
[a]Adjusted for age, gender, most recent body mass index (BMI), smoking status, chronic kidney disease, congestive heart failure, hypertension, peripheral vascular disease, previous stroke, previous myocardial infarction, aspirin, antiplatelet drugs, statins, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, β-blockers, selective serotonin reuptake inhibitors (SSRIs), and nonsteroidal anti-inflammatory drugs (NSAIDs).
[b]Adjusted for age, gender, most recent BMI, smoking status, chronic kidney disease, hypertension, moderate to severe liver disease, previous stroke, previous bleed, alcohol abuse, gastritis, cancer, anemia, aspirin, antiplatelet drugs, NSAIDs, SSRIs, Proton-pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RA).
*p value <0.05.

TABLE C7 Analysis of NVAF patients stratified per diabetes status

Cox hazard ratios for DOACs compared to warfarin for any stroke stratified per diabetes status			
	Crude HR (95% CL)	**Adjusted HR (95% CL)[a]**	**P interaction**
Diabetic	1.17 (0.76–1.79)	1.15 (0.83–1.60)	0.366
Non diabetic	0.94 (0.81–1.10)	0.92 (0.78–1.07)	
Cox hazard ratios for DOACs compared to warfarin for major bleed stratified per diabetes status			
	Crude HR (95% CL)	**Adjusted HR (95% CL)[b]**	**P interaction**
Diabetic	0.83 (0.67–1.02)	0.83 (0.68–1.03)	0.228
Non diabetic	0.97 (0.89–1.06)	0.96 (0.88–1.06)	

[a]Adjusted for age, gender, most recent body mass index (BMI), smoking status, chronic kidney disease, congestive heart failure, hypertension, peripheral vascular disease, previous stroke, previous myocardial infarction, aspirin, antiplatelet drugs, statins, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, diuretics, β-blockers, selective serotonin reuptake inhibitors (SSRIs), and nonsteroidal anti-inflammatory drugs (NSAIDs).
[b]Adjusted for age, gender, most recent BMI, smoking status, chronic kidney disease, hypertension, moderate to severe liver disease, previous stroke, previous bleed, alcohol abuse, gastritis, cancer, anemia, aspirin, antiplatelet drugs, NSAIDs, SSRIs, Proton-pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RA).