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.

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).

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.

2.2 | 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 criteria 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 hemorrhaxis).

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 CHA2DS2-VASc score (congestive heart failure, hypertension, peripheral vascular disease, previous stroke, previous MI), 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), 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.

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.\textsuperscript{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.
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).

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### 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%)               |

### TABLE 1  
(Continued)

| Characteristic                  | DOACs n = 3437 (40.18%) | Warfarin n = 5118 (59.82%) |
|--------------------------------|--------------------------|-----------------------------|
| **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*       |                          |                             |
| 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.

*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).
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).

**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)* |
|---|---|---|---|---|---|
| **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)** |
|---|---|---|---|---|---|
| **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.

*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).

**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.\(^\text{12}\)

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.\(^\text{20}\)

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., where apixaban and rivaroxaban were associated with a lower risk of stroke compared to warfarin.\(^\text{36}\)

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.\(^\text{11}\) 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.\(^\text{36}\)

In the ROCKET-AF trial comparing rivaroxaban and warfarin, no significant interaction was observed between diabetes and the risk of bleeding.\(^\text{37}\) 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.,\(^\text{20}\) and the result was consistent with two observational studies assessing the benefits and risks of rivaroxaban in patients with AF and diabetes.\(^\text{36,38}\)

### 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.

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

| Strata                        | Crude HR (95% CL) | Adjusted HR (95% CL) | P interaction |
|------------------------------|------------------|----------------------|---------------|
| **HRs for any stroke outcome stratified per diabetes severity** |                  |                      |               |
| 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** |                  |                      |               |
| 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** |                  |                      |               |
| 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** |                  |                      |               |
| 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.

\(^\text{a}\)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, antplatelet 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).

\(^\text{b}\)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, antplatelet drugs, NSAIDs, SSRIs, Proton-pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RA).
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). 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. 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...0  | Diabetes mellitus |
| 758     | C10F.00  | Type 2 diabetes mellitus |
| 1038    | C100111  | 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 |
| 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   | F35z00   | 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 chiroarthropathy |
| 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  | IDDDM-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)
| Medcode | Readcode | Description |
|---------|----------|-------------|
| 25627   | C10F700  | Type 2 diabetes mellitus – poor control |
| 26054   | C10FL00  | Type 2 diabetes mellitus with persistent proteinuria |
| 26664   | 2GSB.00  | O/E – Left diabetic foot at risk |
| 26666   | 2GSE.00  | O/E – Right diabetic foot at low risk |
| 26667   | 2GSI.00  | O/E – Left diabetic foot at low risk |
| 26855   | C108400  | Unstable insulin dependent diabetes mellitus |
| 27891   | N030100  | Diabetic Charcot arthropathy |
| 27921   | 2G51000  | O/E – 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   | 2GSJ.00  | O/E – Left diabetic foot at moderate risk |
| 31157   | 2GSF.00  | O/E – Right diabetic foot at moderate risk |
| 31171   | 2GSG.00  | O/E – Right diabetic foot at high risk |
| 31172   | 2GSK.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   | C105s00  | 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 |
| 35116   | C104z00  | Diabetes mellitus with nephropathy NOS |
| 3516    | 2GSL.00  | O/E – Left diabetic foot – ulcerated |
| 35288   | C10E800  | Type 1 diabetes mellitus – poor control |
| 35316   | 2GSH.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   | C109Y11  | Insulin treated non-insulin dependent diabetes mellitus |
| 38806   | C10FF00  | Type 2 diabetes mellitus with peripheral angiopathy |
| 38161   | C108711  | Type 1 diabetes mellitus with retinopathy |
| 38986   | C100.00  | Diabetes mellitus with no mention of complication |
| 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 mononeuropatis 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   | C10F000  | 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)
| 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 complications |
| 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 ophthalmic complications |
| 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   | C108200    | Insulin-dependent diabetes mellitus with neurological complications |
| 52283   | C109000    | Non-insulin-dependent diabetes mellitus with renal complications |
| 52303   | C10F911    | Type II diabetes mellitus without complication    |
| 53392   | C10EJ00    | Type I diabetes mellitus with neuropathic arthropathy |
| 54008   | 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 complications |
| 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 |
| 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 complications |
| 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   | C10x100    | 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   | 8B31.00    | 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 diabetes mell with peripheral angiopathy|
| 64449   | C108z00    | Unspecified diabetes mellitus with multiple complications |
| 64571   | C109C11    | Type II diabetes mellitus with nephropathy            |
### 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 comp |
| 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 |
| 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  | 2Br0.00  | 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  | C10B112  | Type 1 diabetes mellitus with ophthalmic complications         |
| 102946  | C10EO12  | Insulin-dependent diabetes mellitus with renal complications   |
| 103902  | C10FG11  | Type II diabetes mellitus with arthropathy                    |
| 104323  | C10FS11  | 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  | C10EO11  | 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                |
| 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 specified complications |
| 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 complications |
| 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 |
| 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 comp |
| 63017   | C108911  | Type I diabetes mellitus maturity onset |
| 63371   | C10y100  | Diabetes mellitus, adult, + other specified manifestation |
| 64283   | C10zy00  | Other specified diabetes mellitus with unspecified complications |
| 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   | C10N000  | Secondary diabetes mellitus without complication |
| 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 puerperium - baby previously delivered |
| 97446   | C108912  | Type I diabetes mellitus maturity onset |
| 98392   | C10C.12  | Maturity onset diabetes in youth type 1 |
| 100347  | C10A500  | Malnutrition-related diabetes mellitus with periph circ complctn |
| 101172  | C135000  | Cranial diabetes insipidus |
| 102435  | BCE0000  | 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 comp |

**TABLE A2** (Continued)
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 arterial 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 accident 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 haemorrhage 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  | Vertebrobasilar 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 cerebrovascular 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 stenosis/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 haemorrhage 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    | J68z00   | 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   | G62r.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   | J10100     | 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 haemorrhage                                    |
| 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   | J13yy00  | 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

| 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

|            | Crude HR (95% CL) | Adjusted HR (95% CL) |
|------------|-------------------|----------------------|
| 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)     |

### TABLE C3

Cox hazard ratios with 60 days discontinuation definition

|            | Crude HR (95% CL) | Adjusted HR (95% CL) |
|------------|-------------------|----------------------|
| 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)     |

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

| 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 (55.82%)       | 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) | Adjusted HR (95% CL) |
|-------------------------------------------------|--------------|----------------------|
| Any stroke                                     | 1.53 (0.97–2.43) | 1.06 (0.80–1.41) |
| Ischaemic stroke - unspec                       | 1.56 (0.96–2.52) | 1.14 (0.85–1.54) |
| Haemorrhagic stroke                             | 1.33 (0.30–5.96) | 0.70 (0.31–1.59) |
| Myocardial infarction                           | 1.15 (0.72–1.82) | 0.98 (0.72–1.34) |

| 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) |
|---------------------------------------------------------------------------|------------------|---------------------|
| 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) |
|---------------------------------------------------------------------------|------------------|---------------------|
| 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.

*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).

*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.
### Cox hazard ratios for DOACs compared to warfarin for any stroke stratified per diabetes status

|                | Crude HR (95% CL) | Adjusted HR (95% CL) | 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) | 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)     |               |

*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).

*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).