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Does the presence of diabetes mellitus confer an increased risk of stroke in patients with atrial fibrillation on direct oral anticoagulants? A systematic review and meta-analysis

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Abstract

Background There is limited data on clinical outcomes in high risk groups such as patients with diabetes mellitus (DM) with atrial fibrillation (AF) on direct-acting oral anticoagulants (DOACs).

Design Using a systematic review and meta-analysis of published studies, we aimed to determine the risk of stroke and other clinical outcomes in patients with AF on DOACs, with or without DM.

Methods Observational cohort studies reporting clinical outcomes in patients with AF on DOACs, with or without DM were identified from MEDLINE, Embase, Web of Science, the Cochrane Library, and search of bibliographies to April 2020. Summary measures of effect were relative risks with 95% confidence intervals (CIs).

Results Eight studies comprising of 4 observational cohorts (n=76,260 participants) and 4 randomised controlled trials (RCTs) (n=71,683 participants) were included. In RCTs, DOACs compared with warfarin reduced the risk of the composite outcome of stroke and systemic embolism, CVD death and intracranial bleeding in patients with DM: RRs (95% CIs) of 0.75 (0.62-0.90), 0.84 (0.72-0.97), and 0.57 (0.40-0.81) respectively. The corresponding estimates for patients without DM were 0.81 (0.68-0.96), 0.93 (0.80-1.08), and 0.47 (0.31-0.70) respectively. There was no evidence of interactions between DM status and effects of DOACs. The absolute reduction in clinical outcomes with DOACs compared to warfarin was greater in DM than without DM. Regardless of treatment strategy, interventional and observational evidence indicate that patients with DM had higher rates of stroke or systemic embolism, mortality and major bleeding compared to patients without DM.

Conclusions Patients with AF and DM have increased risk of vascular events, which is reduced with the use of DOACs. The use of DOACs should be considered as an option in reducing the risk of stroke in these populations.

Systematic review registration: PROSPERO 2020: CRD42020157196

Keywords: direct oral anticoagulants; atrial fibrillation; diabetes mellitus; stroke; bleeding

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia globally and is associated with increased morbidity and mortality and reduced quality of life.[1,2] Atrial fibrillation is a significant contributor (about 5-fold increased risk) to embolic stroke.[3] Until recently, vitamin K antagonists (VKAs) (eg, warfarin) have been used as the treatment of choice

for stroke prevention in AF. However, though they result in significant reduction in stroke, systemic embolism and all-cause mortality,[4] they have many limitations which include increased risk of major bleeding events,[5,6] several dietary and drug interactions and the need for frequent monitoring and dose-adjustment. Since 2009, several new oral anticoagulants – direct oral anticoagulants (DOACs) – have been developed and approved for use by regulatory authorities.[7-10] The DOACs (comprising dabigatran, rivaroxaban, apixaban and edoxaban) have several advantages over VKAs, such as rapid onset, fewer drug interactions, good safety profile (lower rates of bleeding) and simplified treatment without the need for coagulation monitoring.[11]

Over the last decade, the use of DOACs has increased substantially because of their efficacy in stroke or systemic embolism prevention in AF among the general population.[12-14] However, the effectiveness of DOACs in high risk populations such as those with diabetes mellitus (DM), established atherosclerotic disease and end-stage kidney disease is controversial. The pivotal trials that were the basis for the approval of the DOACs did not specifically enrol these high-risk populations.[7-10] Cardiovascular complications are the leading cause of morbidity and death in individuals with DM[15] and DM is known to increase the risk of AF by about 40% compared to individuals without DM.[16] With increasing life expectancy and prevalence of DM, complications and deaths attributable to DM will also increase, especially if there is no concomitant improvement in management strategies.[17] In patients with AF, DM is associated with a higher risk of stroke and systemic embolism; hence the majority of these patients require longer-term anticoagulation.[18] Adverse and severe vascular outcomes in patients with DM are attributable to the creation of a prothrombotic environment;[19] DM is associated with several abnormalities in the haemostasis system and these include abnormalities in coagulation, altered platelet function, hypofibrinolysis and endothelial dysfunction.[19,20]

Whether DM affects the activity of DOACs hence subsequently affecting their efficacy and safety, is not well known. In a pilot study of 65 patients with non-valvular AF who were treated with dabigatran, rivaroxaban or apixaban, no differences in the activity of DOACs according to DM status were observed.[21] There is sparse data on clinical outcomes in patients with AF on DOACs with concomitant DM; whether DOACs have similar benefits on reducing stroke and other clinical outcomes in patients with and without DM is uncertain. In order to summarise the existing evidence, we conducted a systematic review and meta-analysis of published studies to determine the risk of stroke and other clinical outcomes in patients with AF on DOACs, with or without DM. We also sought to explore any gaps in the existing evidence on the relative benefits of DOACs vs warfarin in people with and without diabetes.

Methods

Data sources and search strategy

This review was conducted in accordance with PRISMA and MOOSE guidelines[22,23] (**Appendices 1-2**) using a pre-defined protocol which was registered with the PROSPERO International prospective register of systematic reviews (CRD42020157196). We systematically searched MEDLINE, Embase, Web of Science and The Cochrane library for studies reporting on clinical outcomes in patients with atrial fibrillation on DOACs, with or without DM from inception till 15 April 2020. The computer-based searches combined free and MeSH terms related to population (e.g., "atrial fibrillation", "direct oral anticoagulants", "dabigatran", "rivaroxaban", "apixaban", "edoxaban"), exposure (e.g., "diabetes mellitus"), and outcome (e.g., "stroke"). The search was restricted to human studies reported in any language. Study design filters were applied. The detailed search strategy is reported in **Appendix 3**. The titles and abstracts of retrieved citations were initially screened independently by 2 reviewers (MA and SS) for potential eligibility. Disagreements were resolved by a third reviewer (SKK). After selection of potential eligible abstracts, their full texts were acquired for further evaluation. Reference lists of relevant articles were manually scanned to identify additional articles missed by the initial search. Finally, the "Cited Reference Search" function in Web of Science was used to check for eligible studies missed by the search.

Study selection and eligibility criteria

We included population-based cohort studies and RCTs which reported on clinical outcomes in patients with atrial fibrillation on DOACs, with or without DM. The following studies were excluded: (i) cross-sectional and clinical case studies; (iii) observational studies which had no appropriate control group; and (iii) studies conducted in non-population-based samples. The primary outcome was any stroke event (first or recurrent stroke, stroke subtypes and transient ischaemic stroke). Secondary outcomes, where reported, included all-cause mortality, major bleeding complications, (including gastrointestinal and cerebrovascular haemorrhage), and venous thromboembolism (VTE). No limits were placed on the study follow-up duration.

Data extraction

A pre-designed data extraction form was used to extract information on patient characteristics (inclduing, average age, sex, percentage of males); location of study; number of patients enrolled and randomised; exposure and control groups; study design characteristics such as randomisation, allocation concealment; treatment comparisons and dosages; duration of treatment or follow-up; nature of outcome and their counts; and risk ratios. End point definitions employed

those reported by the individual studies. To assess the methodological quality of observational cohort studies, we used the nine-star Newcastle-Ottawa Scale (NOS),[24] a validated tool for assessing the quality of non-randomised studies. NOS measures the quality of evidence from a score of zero to nine, based on three pre-defined domains including: (i) selection of participants; (ii) comparability; and (iii) ascertainment of outcomes of interest. The Cochrane Collaboration's risk of bias tool[25] was used to assess potential sources of bias for the RCTs.

Statistical analysis

Relative risks (RRs) with 95% confidence intervals (CIs) were used as the summary measures of association across studies. Given that the outcomes were rare, reported HRs and ORs were assumed to approximate the same measure of RR following Cornfield's rare disease outcome assumption.[26] Fully-adjusted risk estimates were used if available, otherwise crude RRs were estimated from studies that provided raw counts. The inverse variance-weighted method was used to pool RRs using random-effects models to minimize the effect of heterogeneity.[27] Given the limited number of studies available for pooling in each comparison heterogeneity could not be quantified and explored. We employed random effects meta-regression to assess for interactions between DM status and the effect of DOACs.[28] We calculated the absolute risk reduction as the difference in risk between the control group (warfarin) and treatment group (DOAC). STATA release MP 16 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses. A narrative synthesis was performed for studies that could not be pooled.

Results

Study identification and selection

Figure 1 shows the flow of studies through the review. The search of relevant databases and manual scanning of reference lists of relevant studies identified 38 potentially relevant articles. After the initial screening of which was based on titles and abstracts, 13 articles remained for full text evaluation. Following detailed evaluation, 5 articles were excluded because (i) they were based on reviews (n=2); (ii) the outcome was not relevant (n=1); (iii) the intervention was not relevant (n=1); and (iv) duplicate study (n=1). The remaining 8 articles met the inclusion criteria and were included in the review.[29-36]

Study characteristics and quality

The 8 articles included in the review comprised of 4 observational cohort studies (n=76,260 participants) and 4 RCTs (71,683 participants) (**Table 1**). Of the 4 observational studies, 2 were conducted in only patients with DM and evaluated clinical outcomes comparing DOACs with warfarin;[29,34] whereas the other 2 evaluated clinical outcomes comparing patients on a DOAC (rivaroxaban) with or without DM.[35,36] Observational studies were based in USA, Japan and Taiwan; average age ranged from 70-76 years with average follow-up duration ranging from 1.0 to 2.5 years. Methodological quality of studies using the NOS score ranged from 5 to 8.

The 4 RCTs were post-hoc analyses of the pivotal trials that were the basis for the approval of the DOACs[7-10] and they evaluated efficacy and safety outcomes by DM status (DM vs no DM) and treatment groups in both patients with or without DM. Three of the trials were double-blinded and one was open-labelled. All trials were conducted in multiple countries and average follow-up durations ranged from 1.8 to 2.8 years. Using the Cochrane Collaboration tool, all trials demonstrated low risk of bias in the areas of random sequence generation, allocation concealment, blinding of outcome assessments, incomplete outcome data and selective reporting. Only one study reported a high risk of bias in blinding of participants & personnel. (**Appendix 4**). Detailed baseline characteristics of each study by intervention arms and DM status are reported in **Appendices 5-6.** The majority of patients recruited for the trials had persistent or permanent AF and were mostly on angiotensin converting enzyme inhibitors (ACEIs)/angiotensin-receptor blockers (ARBs) and β-blockers among other medications at time of randomization (**Appendix 5**). Three of the observational studies were based on patients with non-valvular AF (**Appendix 6**).

Outcomes by treatment groups and diabetes status

Interventional evidence

All-cause mortality **Figure 2** presents RRs (95% CIs) for efficacy and safety outcomes by treatment groups and DM status. Comparing DOACs with warfarin in patients with DM, there was no significant difference in risk of all-cause mortality (2 trials): RR (95% CIs) of 0.87 (0.75-1.02).

In patients without DM, DOAC compared with warfarin reduced the risk of all-cause mortality (2 trials): RR (95% CIs) of 0.89 (0.81-0.99).

Stroke In patients with DM, DOACs compared to warfarin reduced the risk of stroke or systemic embolism (3 trials) RR (95% CI) of 0.75 (0.62-0.90), with no statistically significant differences in risk of ischaemic stroke (2 trials) and haemorrhagic stroke: RRs (95% CIs) of 0.87 (0.68-1.13) and 0.34 (0.11-1.05) respectively (**Figure 2**).

In patients without DM, DOACs compared to warfarin reduced the risk of stroke or systemic embolism (3 trials) and haemorrhagic stroke (2 trials): RRs (95% CIs) of 0.81 (0.68-0.96) and 0.81 (0.68-0.96), with no statistically significant difference in risk of ischaemic stroke (2 trials) RR (95% CI) of 0.90 (0.67-1.21) (**Figure 2**).

CVD outcomes Comparing DOACs with warfarin in patients with DM, there was a decrease in the risk of CVD death (3 trials): RR (95% CIs) of 0.84 (0.72-0.97) with no statistically significant difference in risk of MI (2 trials): RR (95% CIs) of 0.88 (0.67-1.15) (**Figure 2**).

In patients without DM, DOAC compared with warfarin was not associated with a statistically significant difference in risk of CVD death (3 trials) and MI (2 trials): RRs (95% CIs) of 0.93 (0.80-1.08) and 0.94 (0.70-1.26) respectively (**Figure 2**).

There was no evidence of interactions between DM status and the effects of DOACs on all outcomes (*p*-value for meta-regression > 0.05 for all outcomes) (**Figure 3**).

Bleeding outcomes Comparing DOACs with warfarin in patients with DM, there was a decrease in the risk of intracranial bleeding (3 trials): RR (95% CIs) of 0.57 (0.40-0.81), with no statistically significant difference in risk of major bleeding (4 trials): RR (95% CIs) of 0.95 (0.82-1.10). Results from a single report showed a statistically significant reduction in the risk of any bleeding event comparing a DOAC with warfarin in DM (**Figure 2**).

In patients without DM, DOAC compared with warfarin reduced the risk of intracranial bleeding (3 trials): RR (95% CIs) of 0.47 (0.31-0.70), with no statistically significant difference in risk of major bleeding (4 trials): RR (95% CIs) of 0.83 (0.65-1.05). Results from a single report showed a statistically significant reduction in the risk of any bleeding comparing a DOAC with warfarin (**Figure 2**).

Absolute risk reduction Except for bleeding outcomes, the absolute risk reduction in all outcomes for DOAC compared with warfarin was greater among patients with DM than those without DM (**Table 2**).

Observational evidence

In pooled analysis of 2 observational studies[29,34] that were based on only patients with DM, there were no statistically significant differences in the risk of, all-cause mortality, ischemic stroke, MI, and major, intracranial or GIT bleeding comparing DOACs with warfarin (**Figure 4**). Results based on a single report showed a reduction in the risk of major adverse cardiac event (MACE).

Outcomes by diabetes status

Interventional evidence

Figure 5 presents results of efficacy and safety outcomes comparing patients with DM to those without irrespective of treatment strategy (DOAC or warfarin). Patients with DM compared with no DM were at increased risk of stroke or systemic embolism (3 trials), ischemic stroke (3 trials), CVD death (3 trials), all-cause mortality (2 trials), major bleeding (3 trials) and GIT bleeding (2 trials): RRs (95% CIs) of 1.18 (1.02-1.38), 1.23 (1.02-1.47), 1.43 (1.21-1.67), 1.38 (1.21-1.58), 1.28 (1.13-1.46), and 1.35 (1.17-1.57) respectively. There were no significant differences in the risk of stroke (2 trials), systemic embolism (2 trials), haemorrhagic stroke (3 trials), or intracranial bleeding (4 trials). Results based on single reports showed that patients with DM were at increased risk of MACE, MI or any bleeding.

Observational evidence

Two studies based on only patients treated with a DOAC compared clinical outcomes with or without DM.[35,36] In pooled analysis, patients with DM had an increased risk of major bleeding RR (95% CI) of 1.56 (1.40-1.74) (**Appendix 7**). Results based on a single report showed no significant difference in the risk of the composite outcome of stroke, systemic embolism or MI.

Discussion

In this systematic review and meta-analysis from available RCTs and observational cohort studies, we have evaluated efficacy and safety outcomes in patients with AF on DOACs, with or without DM. Results from interventional studies show that DOACs compared with warfarin similarly reduced the risk of the composite outcome of stroke and systemic embolism in both groups of patients with and without DM. There was also a similar reduction in risk of intracranial bleeding in both populations. Furthermore, there was a decrease in the risk of CVD death in patients with DM, but this was not evident in patients without DM. Formal analyses showed no significant differences in the magnitude of effect for any outcome between patients with or without DM. Furthermore, the absolute reduction in clinical outcomes with

DOACs compared to warfarin was greater in DM than without DM. On efficacy and safety outcomes based on DM status, interventional and observational evidence indicate that patients with DM had higher rates of stroke or systemic embolism, mortality and major bleeding compared to patients without DM regardless of the treatment choice (DOAC or warfarin).

In a previous meta-analysis of the 4 pivotal trials that were the basis for the approval of the DOACs,[7-10] the authors sought to assess whether differences in patient and trial characteristics affected efficacy and safety outcomes.[14]It was noted that the benefits of DOACs in reducing the risk of stroke or systemic embolism and major bleeding was consistent across irrespective of DM status. In a more recent review which was also based on the 4 pivotal trials, Patti and colleagues also demonstrated that the efficacy and safety of DOACs in patients with AF were comparable to warfarin irrespective of DM status.[37] Both reviews evaluated outcomes by treatment groups and diabetes status and some of our findings concur with these results. However, we have also shown based on absolute risk reduction estimates that absolute reduction in clinical outcomes with DOACs compared to warfarin was greater in patients with DM than those without DM. Furthermore, on evaluation of clinical outcomes based on DM status irrespective of the treatment group, findings from both interventional and observational evidence suggest that patients with DM had higher rates of adverse events relative to patients without DM regardless of being treated with a DOAC or warfarin. Evidence based on observational data also suggested that bleeding rates were still higher in patients with DM even if they were DOAC treatment only.

Diabetes mellitus is associated with a higher risk of arteriothrombotic and thromboembolic events, which is mediated by a prothrombotic environment[19] created by the multiple pathological processes involved in this condition.[19,20] There are abnormalities in coagulation, altered platelet function, hypofibrinolysis and endothelial dysfunction.[19,20] Furthermore, compared to those without DM, patients with DM have a higher prevalence of cardiovascular risk factors (comorbidities) such as hypertension, hyperglycaemia, obesity, dyslipidaemia and kidney disease, which have a cumulative effect on atherosclerosis progression and subsequently on the risk of thromboembolic events. Additionally, in people with DM, there is an increased risk of bleeding which has been attributed to hyperglycaemia induced vascular leakage and direct microangiopathy.[38,39] Consistently, our meta-analysis has shown that patients with DM are at increased risk of vascular events and mortality compared with their non-DM counterparts, irrespective of whether treatment is a DOAC or warfarin. Though our results showed similar risk reduction using DOACs compared to warfarin regardless of DM status, there was a greater absolute benefit for patients with DM. It has been shown that DOACs and warfarin have similar pharmacokinetic and pharmacodynamic properties when stratified by DM status, and these have

been suggested to explain the similar efficacy and safety profile of DOACs relative to warfarin irrespective of the presence or absence of DM.[33] In light of the current findings and the distinct advantages of DOACs over VKAs such as lower bleeding rates, rapid onset, fewer drug interactions, and no need for coagulation monitoring, it appears the DOACs have a more favourable risk-benefit profile in patients with DM. In patients with AF, oral anticoagulant therapy is recommended for patients with elevated CHA_2DS_2-VASc score[18,40] (a major contributor to an individual's stroke risk stratification and accepted by both European and North American society guidelines as an established tool to guide stroke prevention anti-thrombotic treatment in people with AF[18,40]). This means that patients with DM aged 65 years or more or the presence of another risk factor should be considered for oral anticoagulation.[18] However, due to concerns of serious bleeding and the need for long-term monitoring with VKAs, only half of eligible patients receive therapy.[41] The DOACs seem to have potential superior efficacy over VKAs and should be considered in patients with DM when not contraindicated. Furthermore, given that vascular risk in individual patients with DM varies depending on the duration of DM and development of complications, antithrombotic treatment needs to be tailored individually. Despite the generally favourable pharmacological profile of DOACs and lower risk of drug interactions,[42-45] issues regarding the use of DOACs in patients with DM and AF should be a cause for concern. First, there is very limited data regarding potential interactions between DOACs and antidiabetic agents.[46] Second, is the issue of administering DOACs to AF patients with DM and kidney disease; it appears there is insufficient data to guide recommendations.[46] Given that patients with DM are more likely to have kidney dysfunction, the decision to administer long-term anticoagulation needs to be carefully considered. Though apixaban and edoxaban appear to be safe in patients with severe kidney impairment and could be used in these patients,[46] there is a need for specific studies that evaluate the efficacy and safety of DOACs in patients with diabetic kidney disease. Finally, there are no large definitive studies that have specifically examined the effect of DM on the efficacy, safety and plasma activity of DOACs.[46] Most of the evidence on the efficacy and safety of DOACS in patients with AF and DM appear to be derived from subanalyses of phase III clinical trials. There is need for further research on these pertinent issues.

Strengths and limitations

The current review has several strengths which deserve mention. Compared to the two previous reviews, we evaluated clinical outcomes by treatment group and diabetes status as well as by diabetes status irrespective of the treatment group. Our review was prespecified to include all observational study designs as well as RCTs published on the topic; therefore, our search strategy was very detailed and spanned several databases. To minimise selective reporting, we evaluated a

comprehensive panel of efficacy and safety outcomes as reported by the individual studies. Limitations of the current review were mostly inherent and these included the limited number of studies for both designs, which precluded the ability to perform subgroup analyses and the fact that the results of included trials were based on post-hoc analyses of studies designed for the wider population. Given that patients with DM represent a specific population group, large definitive trials targeted at this patient groups are warranted.

Conclusions

In conclusion, both interventional and observation evidence suggest that the favourable risk-benefit profile of DOACs in patients with AF extend to those with DM. The use of DOACs should be considered as options in reducing the risk of stroke and other adverse vascular events in these high-risk populations.

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Conflict of interest

The Authors declare that there is no conflict of interest

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Figure 1. Selection of studies included in the meta-analysis

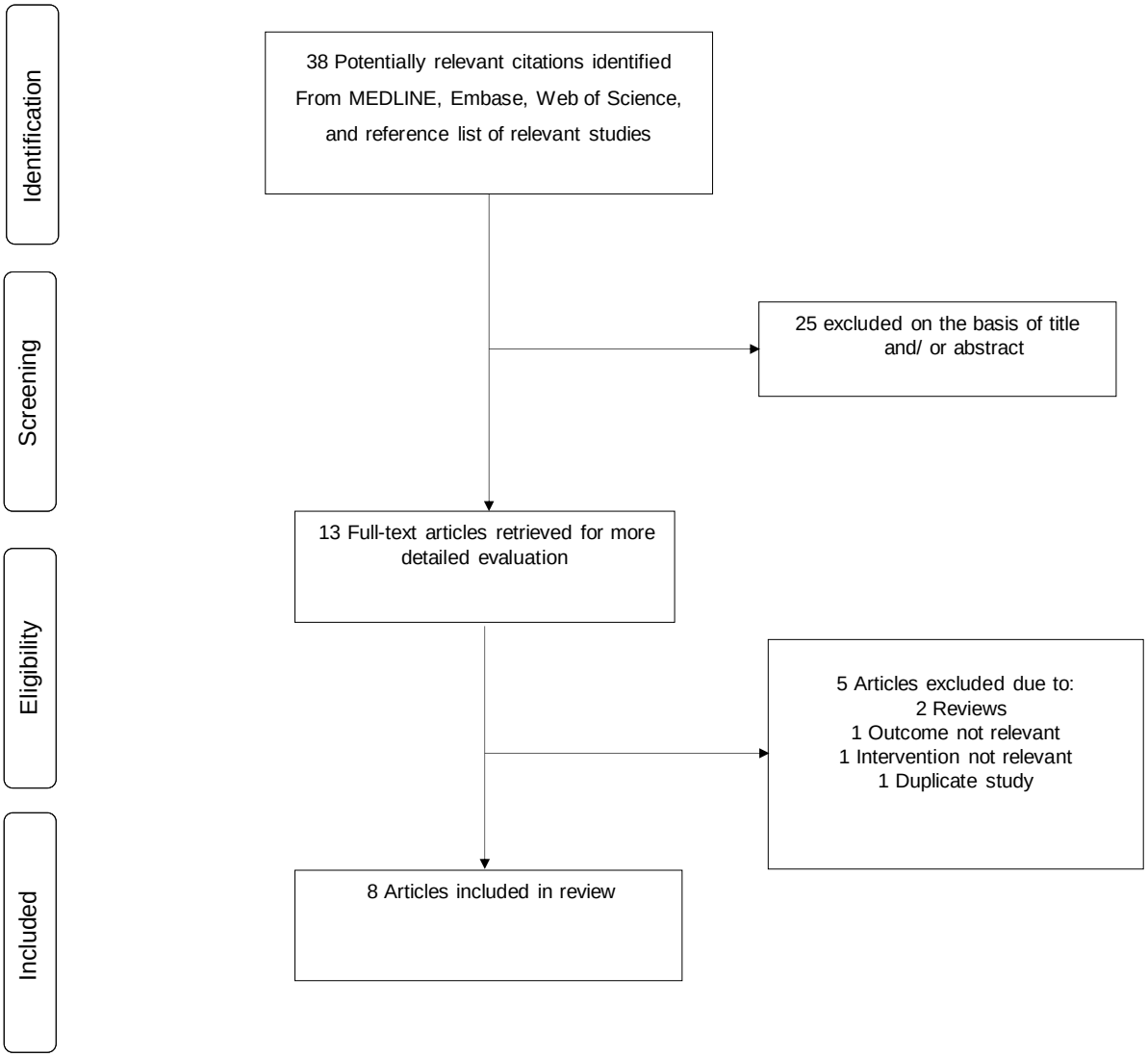
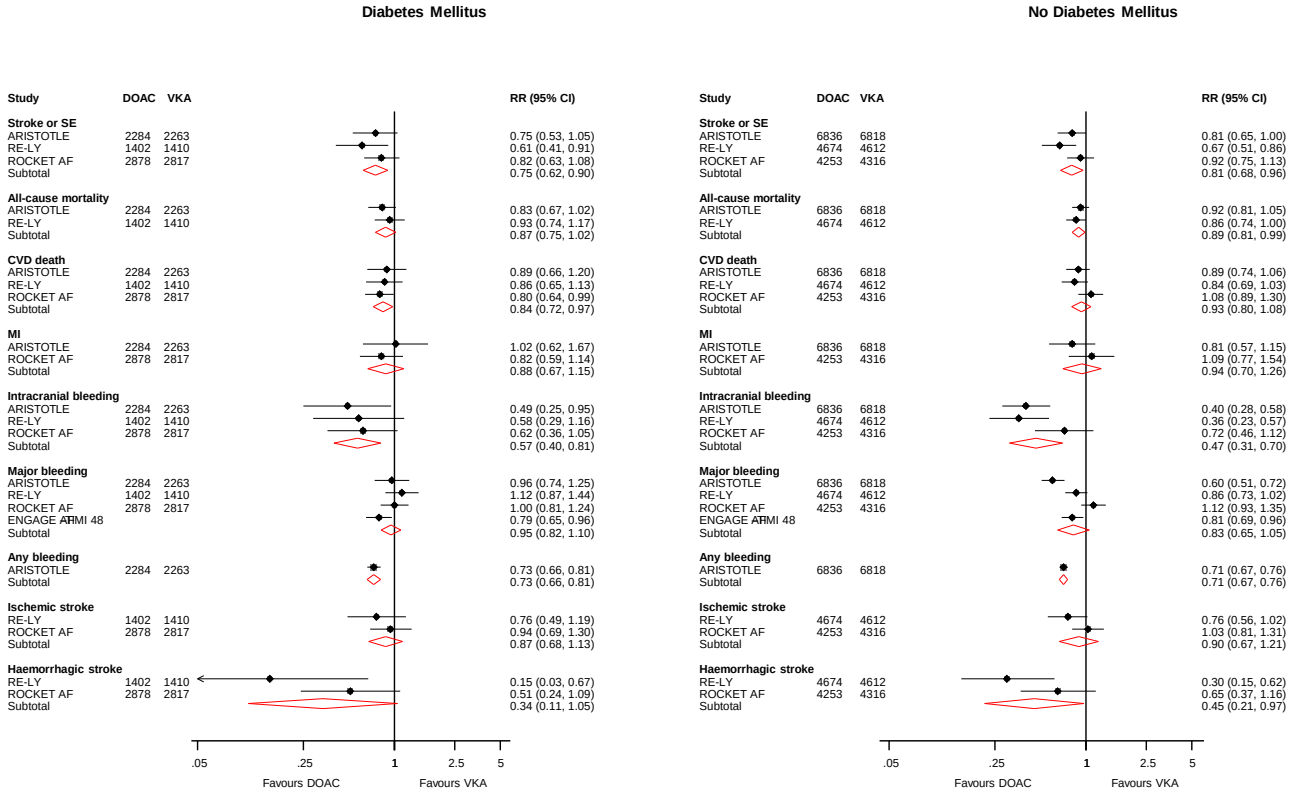
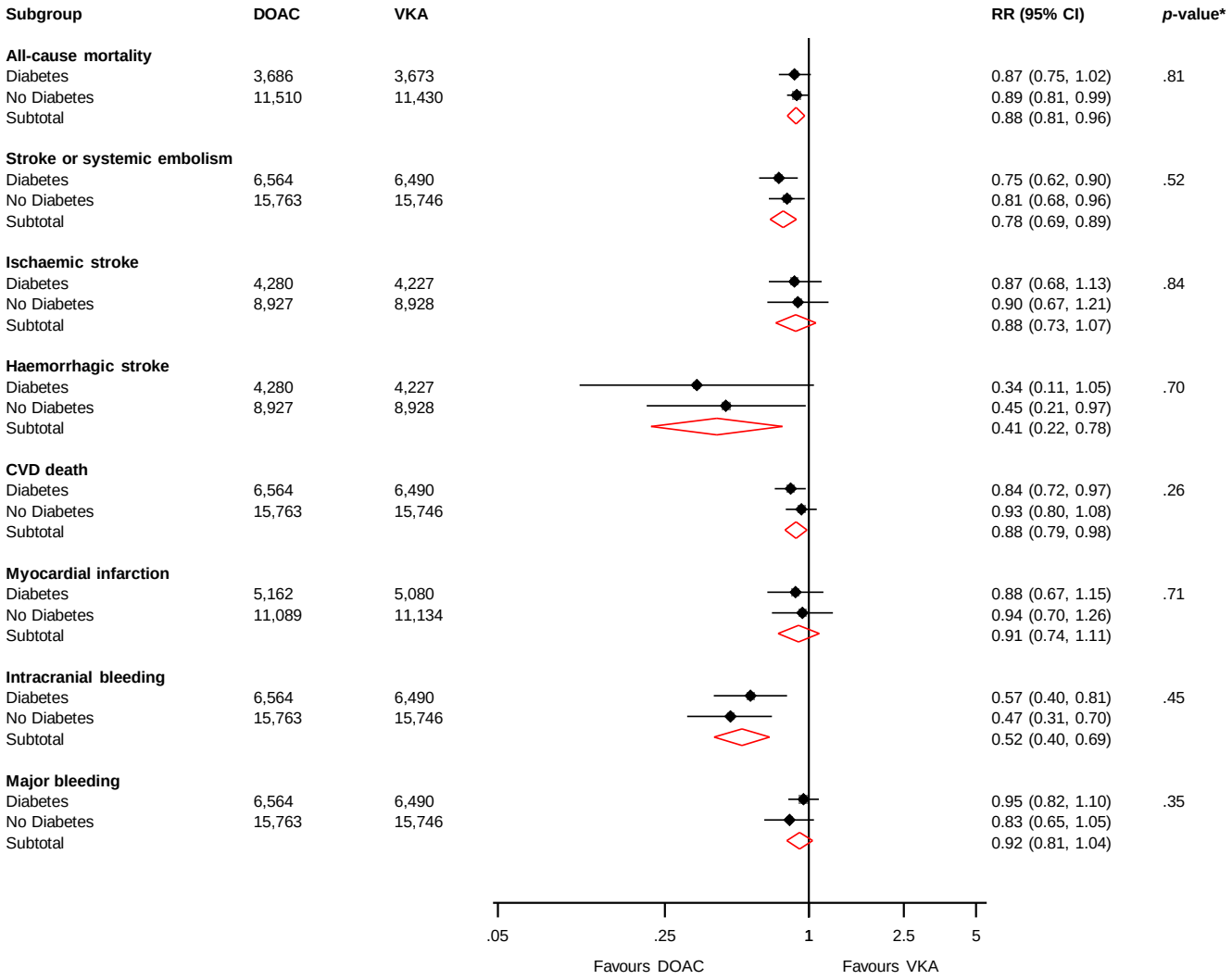


Figure 2. Risk of stroke outcomes and other efficacy and safety outcomes by treatment groups and diabetes status in randomised controlled trials



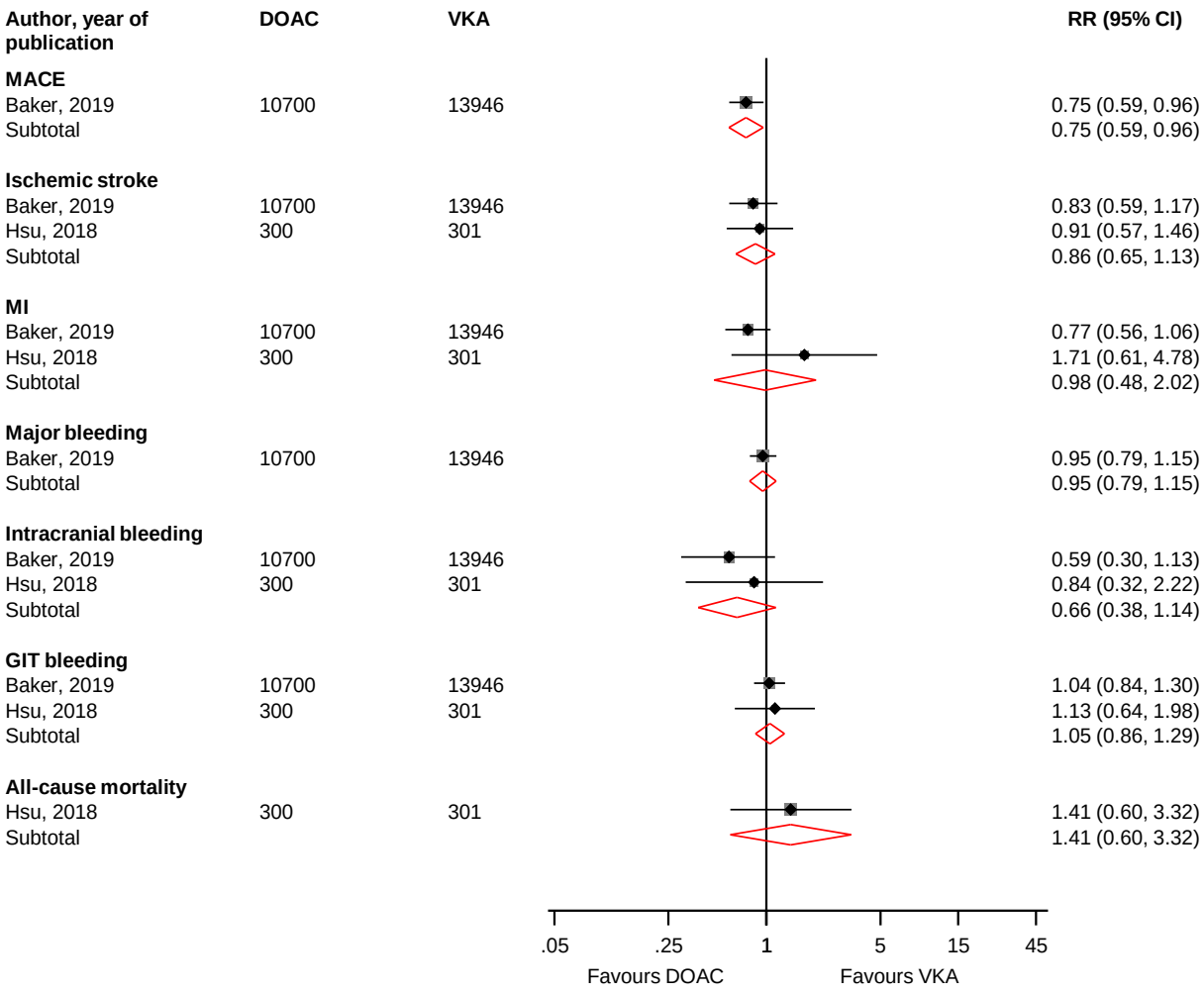
CI, confidence interval (bars); CVD, cardiovascular disease; DOAC, direct oral anticoagulants; GIT, gastrointestinal; MACE, major adverse cardiac events; MI, myocardial infarction; RR, relative risk; SE, systemic embolism; VKA, vitamin K antagonist

Figure 3. Comparisons of magnitudes of effect by diabetes status in randomised controlled trials using meta-regression analyses



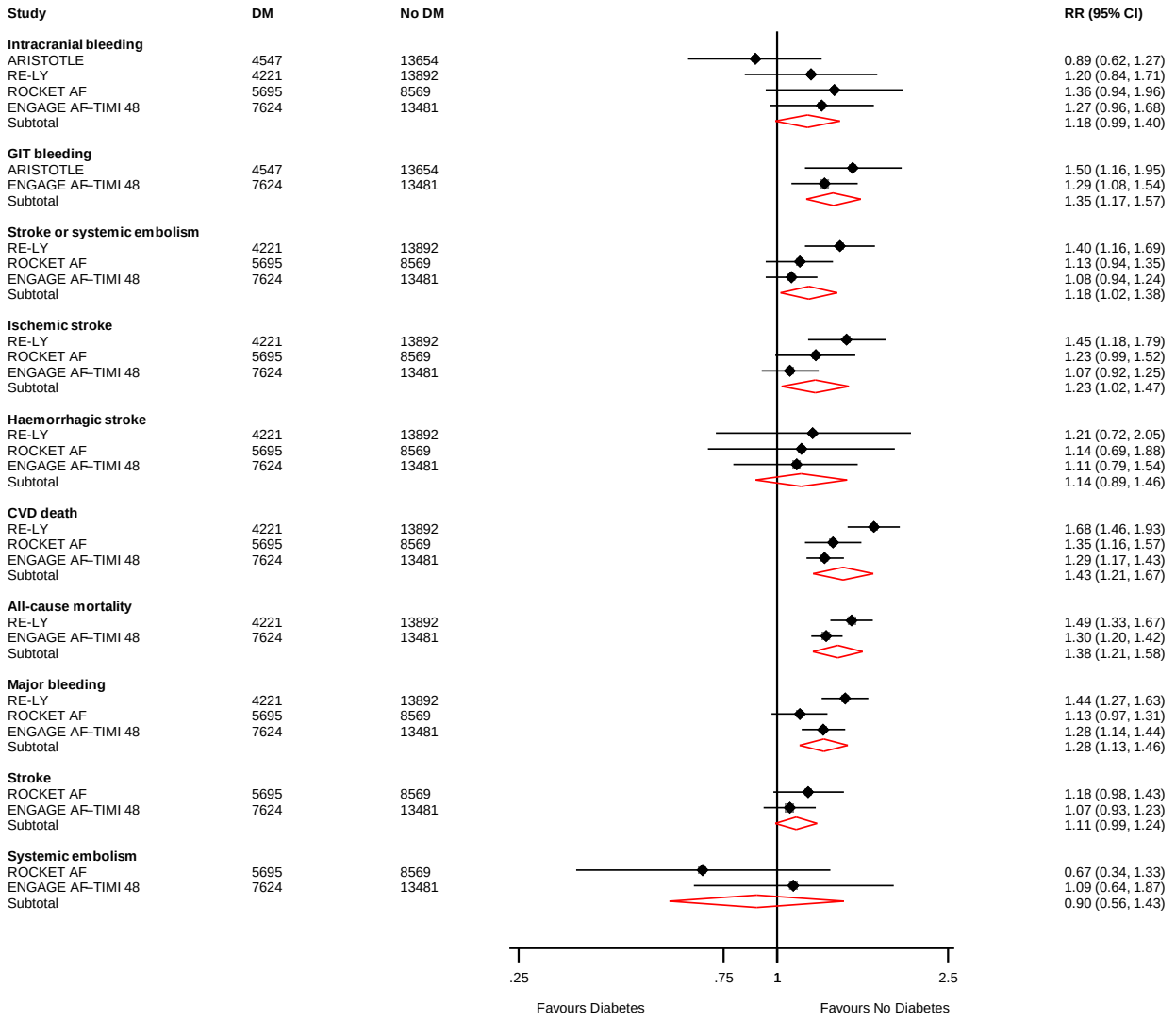
CI, confidence interval (bars); CVD, cardiovascular disease; DOAC, direct oral anticoagulants; VKA, vitamin K antagonist; *, p-value for meta-regression

Figure 4. Efficacy and safety outcomes by treatment groups in patients with diabetes in observational studies



CI, confidence interval (bars); DOAC, direct oral anticoagulants; GIT, gastrointestinal; MACE, major adverse cardiac events; MI, myocardial infarction; RR, relative risk; VKA, vitamin K antagonist

Figure 5. Efficacy and safety outcomes by diabetes status irrespective of treatment strategy in randomised controlled trials



CI, confidence interval (bars); CVD, cardiovascular disease; GIT, gastrointestinal; RR, relative risk

SUPPLEMENTARY MATERIAL

Appendix 1	PRISMA checklist
Appendix 2	MOOSE checklist
Appendix 3	MEDLINE literature search strategy
Appendix 4	Assessment of risk of bias
Appendix 5	Baseline characteristics of intervention studies by intervention and diabetes status
Appendix 6	Baseline characteristics of observational cohort studies by intervention and diabetes status
Appendix 7	Efficacy and safety outcomes by diabetes status in observational studies of DOAC

Appendix 1: PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Introduction
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	Introduction
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	Methods
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	Methods
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	Methods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Appendix 2
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	Methods
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	Methods
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	Methods
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Methods
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	Methods
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	Methods
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	Methods
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	Methods
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	Results, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	Results, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	Results, Appendix 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Results, Figures 2-4;
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	Not applicable
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	Not applicable
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	Discussion
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	Discussion
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	Page 18

Appendix 2. MOOSE checklist

Does the presence of diabetes mellitus confer an increased risk of stroke in patients with atrial fibrillation on direct oral anticoagulants? A systematic review

Criteria		Brief description of how the criteria were handled in the review
Reporting of background		
√	Problem definition	There is limited data on clinical outcomes in high risk groups such as patients with diabetes mellitus (DM) with atrial fibrillation (AF) on direct-acting oral anticoagulants (DOACs).
√	Hypothesis statement	DOACs may have similar benefits on reducing stroke and other clinical outcomes in AF patients with and without DM
√	Description of study outcomes	Stroke outcomes, other vascular endpoints and safety endpoints
√	Type of exposure	Diabetes and no diabetes
√	Type of study designs used	Prospective cohort studies
√	Study population	Adult general populations with AF on DOAC treatment, with or without DM
Reporting of search strategy should include		
√	Qualifications of searchers	Setor K. Kunutsor, PhD; Samuel Seidu, MD
√	Search strategy, including time period included in the synthesis and keywords	Time period: from inception to 15 April 2020 The detailed search strategy can be found in Appendix 3
√	Databases and registries searched	MEDLINE, Embase, Web of Science and The Cochrane Library
√	Search software used, name and version, including special features	OvidSP was used to search Embase and MEDLINE EndNote X9 used to manage references
√	Use of hand searching	We searched bibliographies of retrieved papers
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list for excluded studies are available on request.
√	Method of addressing articles published in languages other than English	Not applicable
√	Method of handling abstracts and unpublished studies	Not applicable
√	Description of any contact with authors	None
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, and outcome.
√	Assessment of confounding	We assessed confounding by ranking individual studies on the basis of different adjustment levels and performed sub-group analyses to evaluate differences in the overall estimates according to levels of adjustment.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed based on the nine-star Newcastle–Ottawa Scale using pre-defined criteria namely: population representativeness, comparability (adjustment of confounders), ascertainment of outcome. Sensitivity analyses by several quality indicators such as study size, duration of follow-up, and adjustment factors.
√	Assessment of heterogeneity	Not done because of limited number of studies
√	Description of statistical methods in sufficient detail to be replicated	Described in methods section
√	Provision of appropriate tables and graphics	Table 1; Figures 1-4; Appendix 5
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figure 2-4
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Not applicable
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates
Reporting of discussion should include		
√	Quantitative assessment of bias	The systematic review is limited in scope, as it involves published data. Individual participant data is needed. Limitations have been discussed.
√	Justification for exclusion	All studies were excluded based on the pre-defined inclusion criteria in methods section.
√	Assessment of quality of included studies	Brief discussion included in 'Methods' section

Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Discussion
√	Generalization of the conclusions	Discussed in the context of the results.
√	Guidelines for future research	We recommend individual participant data meta-analysis
√	Disclosure of funding source	In “Acknowledgement” section

Appendix 3: MEDLINE literature search strategy

Relevant studies published from inception to 15 April 2020 (date last searched), were identified through electronic searches not limited to the English language using MEDLINE, Embase, Web of Science, and Cochrane databases. Electronic searches were supplemented by scanning reference lists of articles identified for all relevant studies (including review articles), and by hand searching of relevant journals. The computer-based searches combined free and MeSH terms related to population (e.g., “atrial fibrillation”, “direct oral anticoagulants”, “dabigatran”, “rivaroxaban”, “apixaban”, “edoxaban”), exposure (e.g., “diabetes mellitus”), and outcome (e.g., “stroke”) in humans without any language restrictions.

1 exp Atrial Fibrillation/ (54138)
2 direct oral anticoagulant.mp. (729)
3 exp Dabigatran/ (3026)
4 exp Rivaroxaban/ (3102)
5 apixaban.mp. (3408)
6 edoxaban.mp. (1410)
7 exp Diabetes Mellitus, Type 2/ (130483)
8 2 or 3 or 4 or 5 or 6 (8027)
9 1 and 7 and 8 (7)

Each part was specifically translated for searching alternative databases.

Appendix 4: Assessment of risk of bias

	Random sequence generation	*Allocation concealment*	*Blinding of participants & personnel*	*Blinding of outcome assessments*	*Incomplete outcome data*	*Selective reporting*	*Other bias*
ARISTOTLE	+	+	+	+	+	+	+
RE-LY	+	+	-	+	+	+	?
ROCKET AF	+	+	+	+	+	+	+
ENGAGE AF–TIMI 48	+	+	+	+	+	+	+

+	**Low risk of bias**
?	**Unclear risk of bias**
-	**High risk of bias**

Appendix 5. Baseline characteristics of intervention studies by intervention and diabetes status

	ARISTOTLE				RE-LY		ROCKET AF				ENGAGE AF–TIMI 48	
	Diabetes		No diabetes		Diabetes	No diabetes	Diabetes		No diabetes		Diabetes	No diabetes
	Apixaban	Warfarin	Apixaban	Warfarin			Rivaroxaban	Warfarin	Rivaroxaban	Warfarin		
No. of patients	2,284	2,263	6,836	6,818	4,221	13,892	2,878	2,817	4,253	4,316	7,624	13,481
Age (years)	69.0	69.0	70.0	70.0	70.9	71.7	71.0	71.0	74.0	74.0	70.0	73.0
% Males	64.4	65.7	64.6	64.7	65.8	62.9	60.8	60.5	60	60.2	63.5	61.0
Type of AF (%)												
Paroxysmal	14.1	14.9	15.4	15.8	32.9	31.7	16.5	15.9	18.1	19.0	26.4	24.9
Persistent	-	-	-	-	32.9	0	81.9	82.6	80.6	79.6	-	-
Persistent or permanent	85.9	85.1	84.6	84.2	34.1	35.5	-	-	-	-	-	-
Newly diagnosed	-	-	-	-	-	-	1.6	1.6	1.3	1.3	-	-
Medications (%)												
ACEI or ARB	77.3	77.4	70.4	69.1	-	-	81.5	81.0	69.9	69.1	68.8	64.2
Amiodarone	10.3	9.6	11.6	12.3	-	-	-	-	-	-	10.5	12.6
B-Blocker	66.2	64.7	64.2	63.2	-	-	66.4	68.2	63.1	63.3	-	-
Aspirin	34.4	33.8	30.3	29.5	-	-	38.7	39.6	37.9	38.1	31.5	28.0
Clopidogrel	2.2	2.1	1.8	1.8	-	-	-	-	-	-	-	-
Digoxin	35.3	34.9	31.6	31.8	-	-	-	-	-	-	-	-
CCA	36.3	37.7	28.7	29.5	-	-	31.9	31.6	25.9	24.4	-	-
Statin	55.6	54.9	37.2	37.2	-	-	-	-	-	-	-	-
NSAID	9.3	10.5	8.1	7.9	-	-	-	-	-	-	-	-
Gastric antacid drugs	21.2	22.1	18.0	17.5	-	-	-	-	-	-	-	-
VKA	-	-	-	-	-	-	65.0	65.6	60.5	60.6	-	-
Diuretic	-	-	-	-	-	-	66.7	67.4	55.1	53.9	-	-
Thienopyridine	-	-	-	-	-	-	-	-	-	-	2.7	2.1

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CCA, calcium channel blocker; NSAID, Non-steroidal anti-inflammatory drug; VKA, vitamin K antagonist

Trial abbreviations: ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ENGAGE AF–TIMI 48, Effective aNticoaGulation with factor Xa next GEneration in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48; RE-LY, Randomized Evaluation of Long Term Anticoagulant Therapy

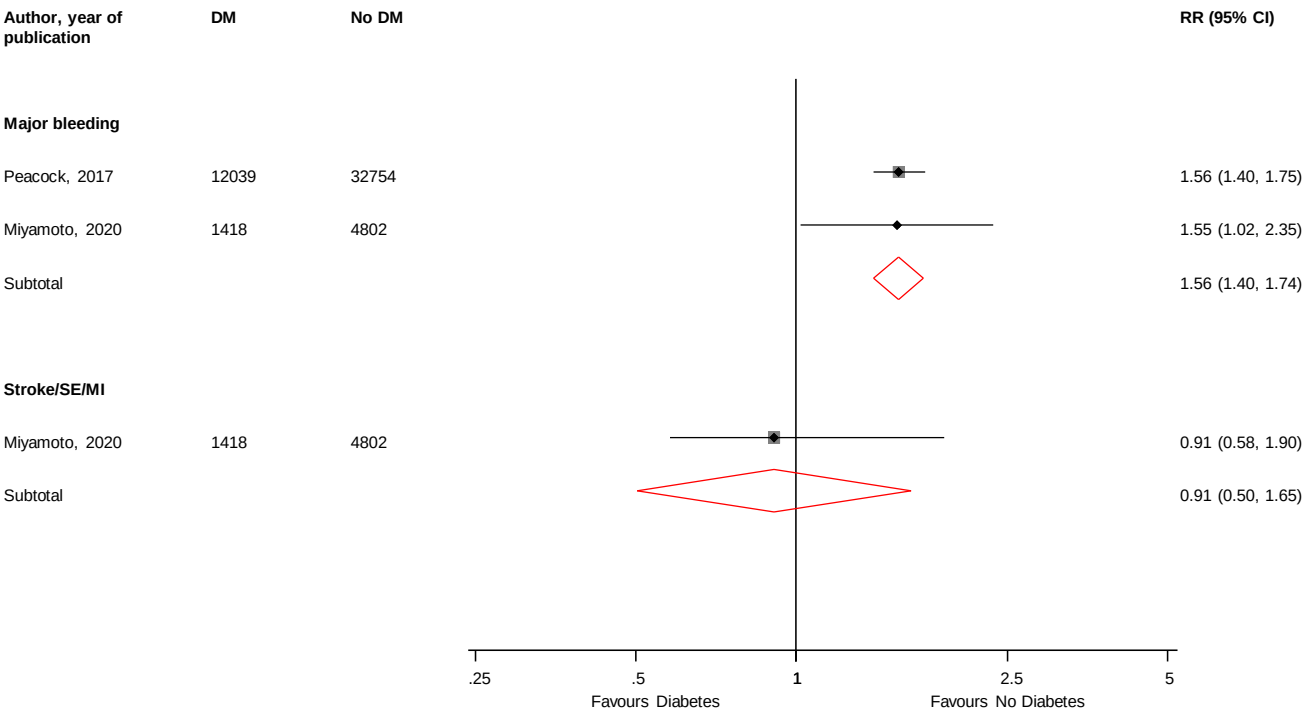
Appendix 6. Baseline characteristics of observational cohort studies by intervention and diabetes status

	Baker, 2019 Diabetes		Hsu, 2018 Diabetes			Peacock, 2017 Rivaroxaban		Miyamoto, 2020
	Rivaroxaban	**Warfarin**	**Dabigatran**	**Rivaroxaban**	**Warfarin**	**Diabetes**	**No diabetes**	**Overall population**
No. of patients	10,700	13,946	322	320	1,899	12,039	32,754	6,220
Age (years)	-	-	75.3	75.4	70.0	75.5	76.6	72.4
% Males	64.7	62.7	56.5	44.1	50.9	60.6	54.3	63.5
Type of AF (%)								
Paroxysmal	-	-	-	-	-	-	-	33.1
Persistent	-	-	-	-	-	-	-	36.1
Permanent	-	-	-	-	-	-	-	25.0
Persistent or permanent	-	-	-	-	-	-	-	-
Newly diagnosed	-	-	-	-	-	-	-	-
Non-valvular AF	100.0	100.0	100.0	100.0	100.0	100.0	100.0	-
Medications (%)								-
α-glucosidase inhibitors	0.3	0.3	-	-	-			-
Allopurinol						10.0	6.0	-
Amiodarone	5.5	5.4	-	-	-	15.2	14.6	-
Antibiotics	-	-	-	-	-	59.5	54.2	-
ACEI/ARB	69.7	69.1	-	-	-	-	-	-
B-Blocker	62.5	62.2	-	-	-	-	-	-
Cyclooxygenase-2 inhibitors	2.8	2.8	-	-	-	-	-	-
Dihydropyridine calcium channel blockers	30.0	29.7	-	-	-	-	-	-
Digoxin	7.4	7.6	-	-	-	-	-	-
Diltiazem	11.5	11.5	-	-	-	-	-	-
Dipeptidyl peptidase-4 inhibitors	9.9	9.8	37.3	39.4	20.7	-	-	-
Dronedarone	1.5	1.4	-	-	-	-	-	-
Glucagon-like peptide-1 analogues	3.9	3.8	-	-	-	-	-	-
Glucocorticoids						27.9	26.9	-
Histamine-2 receptor antagonists	5.1	5.0	-	-	-	8.8	7.3	-
Helicobacter pylori treatment	0.6	0.6	-	-	-	-	-	-
Hypnotics	7.0	6.9	-	-	-	-	-	-
Insulin	21.6	21.8	23.0	21.9	35.5	-	-	-
Loop diuretics	28.6	28.7				-	-	-
Metformin	45.0	44.2	53.1	49.1	48.8	-	-	-
Meglitinide	-	-	2.5	3.1	1.4	-	-	-
NSAIDs	19.4	19.1	-	-	-	28.5	23.4	-
Other anti-arrhythmic agents	6.5	6.2	-	-	-	-	-	-
Other lipid drugs	14.2	14.4	-	-	-	-	-	-
Other antidepressants	9.0	9.2	-	-	-	-	-	-
P2Y12 platelet inhibitors	16.2	16.1	-	-	-	15.6	10.0	4.6
Proton pump inhibitors	25.8	26.0	-	-	-	48.2	42.1	-
Sodium-glucose co-transporter-2 inhibitors	1.4	1.3	-	-	-	-	-	-
SSRIs or SNRIs	16.2	16.2	-	-	-	-	-	-

SSRIs	-	-	-	-	-	17.8	16.2	-
SNRIs	-	-	-	-	-	5.5	3.8	-
Statins	65.7	65.6	73.0	74.4	60.9	74.7	56.8	-
Sulphonylureas or glinides	27.0	27.1	51.6	47.2	56.5	-	-	-
Systemic corticosteroids	20.9	21.1	-	-	-	-	-	-
Thiazides	32.9	32.7	-	-	-	-	-	-
Thiazolidinediones	6.5	6.7	8.1	5.6	9.8	-	-	-
Warfarin inhibitors	72.8	72.4	-	-	-	-	-	-
Warfarin inducers	33.3	33.8	-	-	-	-	-	-
Verapamil	2.1	2.1	-	-	-	-	-	-

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CCA, calcium channel blocker; NSAID, Non-steroidal anti-inflammatory drug; SNRI, serotonin/norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VKA, vitamin K antagonist

Appendix 7: Efficacy and safety outcomes by diabetes status in observational studies of DOAC



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