Outcomes of Non–Vitamin K Antagonist Oral Anticoagulants versus Warfarin in Patients with Atrial Fibrillation and Diabetes Mellitus: A Systematic Review of Randomized Controlled Trials and Observational Studies

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INTRODUCTION

- Approximately 15% of people with diabetes mellitus (DM) develop atrial fibrillation (AF), and overall, 30% of patients with AF have DM[1]
- Concomitant DM increases the risk of unfavorable outcomes among patients with AF, such as experiencing a stroke[2]
- Current practice guidelines provide few recommendations regarding disease management for patients with both AF and DM[3]
- The beneficial effect of non-vitamin K antagonist oral anticoagulants (NOACs) vs warfarin on both stroke and bleeding prevention within this population was established in a meta-analysis on randomized controlled trials[2]
  - However, comparisons between NOACs via meta-analyses may not be appropriate, due to heterogeneity between studies

OBJECTIVE

- To identify differences between primary studies of NOACs vs warfarin in patients with AF and DM to support interpretation of results across studies

METHODS

- A systematic search of PubMed was performed using the search terms: ((atrial fibrillation) **AND** (diabetes mellitus)) **AND** ((non-vitamin K antagonist oral anticoagulant) **OR** (NOAC) **OR** (direct oral anticoagulant) **OR** (DOAC) **OR** (new oral anticoagulant) **OR** (novel oral anticoagulant) **OR** (oral thrombin inhibitor) **OR** (factor Xa inhibitor) **OR** (factor IIa inhibitor) **OR** (dabigatran) **OR** (rivaroxaban) **OR** (apixaban) **OR** (edoxaban))
  - Studies that occurred in the last 10 years and published in English were included
  - Books, documentaries, case reports, commentaries, editorials, guidelines, meta-analyses (except those that included primary studies), and systematic reviews were excluded
- After reviewing the abstracts, additional inclusion criteria were included
  - Patients with AF and DM receiving any NOAC (apixaban, dabigatran, edoxaban, and rivaroxaban) as the intervention and warfarin as the comparator
  - Comparative efficacy (or effectiveness in real-world studies), defined as rates of stroke/systemic embolic events (SEEs), and safety, defined as major bleeding per International Society on Thrombosis and Haemostasis (ISTH), were the outcomes
  - Additionally, focus was placed on ex-US observational studies where edoxaban was available for comparison

RESULTS

- The systematic search from PubMed yielded a total of 215 studies; of these, 4 randomized controlled trials (RCTs) and 5 observational studies comparing NOACs vs warfarin in patients with AF and DM were identified (**Figure 1**)

Randomized controlled trials

- Baseline demographics and clinical characteristics were different among the 4 RCTs (**Table 1**)
- Three out of 4 trials reported mean CHA_2DS_2VASc (congestive heart failure, hypertension, age [≥75], diabetes, previous stroke/transient ischemic attack, vascular disease, age [65–74], sex [female]) score, suggesting the risk of stroke, and only 1 study reported a HAS-BLED (hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, elderly, drug/alcohol use) score, which is normally used as a predictor for risk of major bleeding in patients with AF[8]
- Among the 4 RCTs, NOACs were noninferior in preventing stroke/SEE, intracranial hemorrhage (ICH), and cardiovascular (CV) death compared to warfarin in patients with AF and DM[4-7]
- While all NOACs demonstrated at least comparable or better efficacy and safety vs warfarin overall, a meta-analysis of the 4 RCTs showed:
  - Edoxaban 60 mg (ENGAGE AF-TIMI 48 trial) was the only NOAC to reduce major bleeding (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.65–0.96; **Figure 2A**) in patients with AF and DM vs warfarin[2]
    - This reduction in major bleeding risk seen with edoxaban over warfarin was not affected by the presence of DM
  - Dabigatran 150 mg (RE-LY trial) was the only NOAC to substantially reduce the risk for stroke/SEE vs warfarin in patients with AF and DM (HR, 0.61; 95% CI, 0.41–0.91; **Figure 2B**)
- Relevant covariates in the meta-regression analyses for the RCTs included age, sex, kidney function, hypertension, heart failure, and CHA_2DS_2VASc scores

Observational studies

- The 5 observational studies had differences in study designs and definitions for stroke and bleeding risks (**Table 1**)[9-13]
- Only 1 study adopted the ISTH definition for major bleeding, and ICH, a component of the ISTH definition for major bleeding, was included as a separate endpoint in 4 studies[13]
- Baseline stroke risk, as measured by CHA_2DS_2VASc score, ranged from 4.1 to 4.4; the score was not available from 1 study
- Of the 5 observational studies, 2 studies provided true HAS-BLED scores and 1 study only provided a modified HAS-BLED score (ie, without the international normalized ratio)
- Even though the definition of effectiveness and safety differ across studies, NOACs were better than or comparable to warfarin in terms of effectiveness and safety in patients with AF and DM (**Figure 3**)[9-13]
- For the observational studies, either matching/weighting using propensity score was applied to adjust for covariates and balance between groups (NOACs vs warfarin)

CONCLUSIONS

NOACs are better than or at least comparable to warfarin in patients with AF and DM in both clinical-trial and real-world settings

Differences in study design and the lack of appropriate covariate adjustment and standardized outcome measures made the comparison between NOACs across different studies difficult

Appropriate covariate adjustment and standardized outcome measures are needed in future studies to make a comparison between NOACs across different studies possible

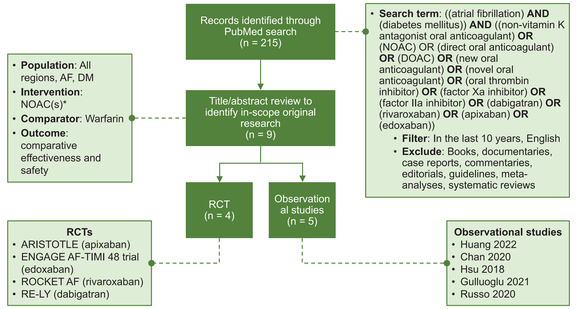
There is a clear distinction in each study when assessing risk of bleeding and safety outcomes.

However, whether analyzed separately or as a group, NOACs are better than or at least comparable to warfarin in patients with AF and DM.

FIGURES AND TABLES

Poster Code: CO4

Figure 1. Systematic review of efficacy and safety of NOACs vs warfarin in patients with AF and DM



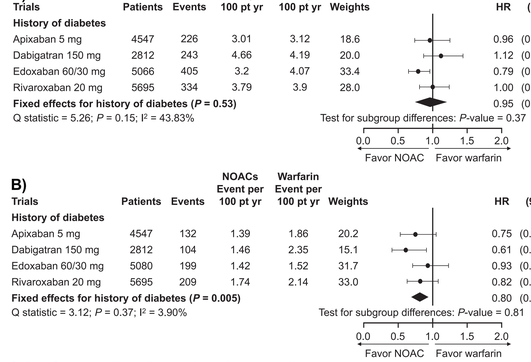
*NOACs included were apixaban, dabigatran, edoxaban, and rivaroxaban.
AF, atrial fibrillation; DM, diabetes mellitus; DOAC, direct oral anticoagulant; NOAC, non–vitamin K oral anticoagulant; RCT, randomized controlled trial.

Table 1. Four randomized controlled trials assessing efficacy and safety of NOACs vs warfarin in patients with AF and DM[4-7]

Study	Bansilal 2015	Plitt 2020	Ezekowitz 2015	Brambatti 2015
Region	All regions	All regions	All regions	All regions
Cohort identification	AF and DM or on glucose-lowering medication at randomization	AF and DM at randomization	AF at randomization; DM defined by site investigator according to local guidelines	AF and DM at randomization
Approach to balance between groups/ covariates adjustment	• Wilcoxon rank-sum test • Cox model • PS matching	• Wilcoxon rank-sum test • Cox model	• Wilcoxon rank-sum test • Cox model	• Cox model
Number of patients	Rivaroxaban (2878) vs warfarin (2817)	Edoxaban (2559) vs warfarin (2521)	Apixaban (2284) vs warfarin (2263)	Dabigatran (2811) vs warfarin (1410)
Mean CHA_2DS_2VASc score	NA	4.6	4.2	4.4
Mean HAS-BLED score	NA	NA	1.9	NA
NOAC dose reduction available at randomization	Yes	Yes	No	Yes
ISTH-defined MB	No	Yes	Yes	No
ICH	Yes	Yes	Yes	Yes

AF, atrial fibrillation; CHA_2DS_2VASc, congestive heart failure, hypertension, age (≥75), diabetes, previous stroke/transient ischemic attack, vascular disease, age (65–74), sex (female); DM, diabetes mellitus; HAS-BLED, hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, elderly, drug/alcohol use; ICH, intracranial hemorrhage; ISTH, International Society on Thrombosis and Haemostasis; MB, major bleeding; NA, not applicable; NOAC, non-vitamin K oral anticoagulant; PS, propensity score.

Figure 2. Risk of major bleeding (A) and stroke/SEE (B) in NOACs vs warfarin across meta-analyses on RCTs in patients with AF and DM[2]



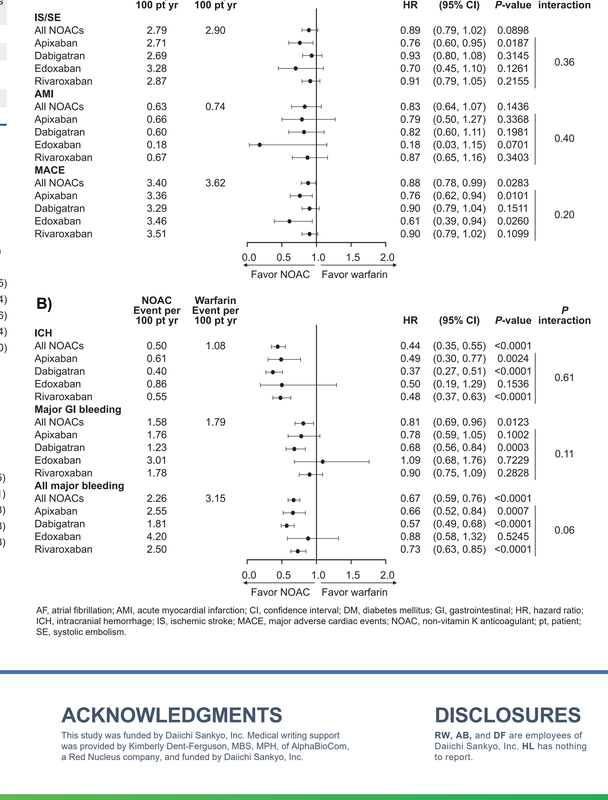
Cochrane Q statistic and Higgins' I² were used to test for between-trial heterogeneity.
AF, atrial fibrillation; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; NOAC, non–vitamin K oral anticoagulant; pt, patient; RCTs, randomized controlled trials, SEE, systemic embolism event.

Table 2. Five observational studies identified assessing efficacy and safety of NOACs vs warfarin in patients with AF and DM[9-13]

Study	Huang 2022	Chan 2020	Hsu 2018	Gulluoglu 2021	Russo 2020
Region	Asia (Taiwan)	Asia (Taiwan)	Asia (Taiwan)	EU (UK)	EU (Italy)
Data source	Claims	Claims	Claims	CPRD	Registry
Cohort identification	• Prevalent DM • Incident AF • Incident anticoagulant users	• Prevalent DM • Incident AF • Incident anticoagulant users; NOAC users could be exposed to warfarin	• Prevalent DM • Incident AF • Incident anticoagulant users	• Prevalent DM • Incident AF • Incident anticoagulant users	• AF and concomitant DM • Edoxaban once daily or VKA
Approach to balance between groups/covariates adjustment	• IPTW • PS matching • Cox model	• PS-stabilized weights	• PS matching	• Cox model • Stratified analyses • PS matching (sensitivity analysis)	• PS matching
Number of patients	NOACs (19,909) vs warfarin (10,300)	NOACs (20,967) vs warfarin (5812)	Rivaroxaban (300) vs warfarin (301); dabigatran (305) vs warfarin (305)	NOACs (3437) vs warfarin (5118)	Edoxaban (135) vs warfarin (135)
Mean CHA_2DS_2VASc score	4.3	4.4	NA	4.1	4.4
Mean HAS-BLED score	NA	3.06	NA	2.9 (without INR)	3.5
NOAC dose (% of patients on each NOAC on specified dose)	NA	• Rivaroxaban: 15/10 mg (95%) • Apixaban: 2.5 mg (66%) • Dabigatran: 110 mg (89%) • Edoxaban: 30 mg (68%)	• Rivaroxaban: 20 mg (12.5%) • Dabigatran: 150 mg (11.5%)	• Rivaroxaban: 20 mg (78%) • Apixaban: 5mg (70%) • Dabigatran: 110 mg (51%), 150 mg (48%) • Edoxaban: 60 mg (71%)	• Edoxaban: 60 mg (87%)
ISTH-defined MB	NA	No	NA	No	Yes
ICH	NA	Yes	Yes	Yes	Yes

AF, atrial fibrillation; CHA_2DS_2VASc, congestive heart failure, hypertension, age (≥75), diabetes, previous stroke/transient ischemic attack, vascular disease, age (65–74), sex (female); CPRD, Clinical Practice Research Datalink; DM, diabetes mellitus; HAS-BLED, hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, elderly, drug/alcohol use; ICH, intracranial hemorrhage; INR, international normalized ratio; IPTW, inverse probability treatment weighting; ISTH, International Society on Thrombosis and Haemostasis; MB, major bleeding; NA, not applicable; NOAC, non-vitamin K oral anticoagulant; PS, propensity score; VKA, vitamin K antagonist.

Figure 3. Hazard ratios of effectiveness (A) and safety (B) in observational studies of NOACs vs warfarin in patients with AF and DM[10]



AF, atrial fibrillation; AMI, acute myocardial infarction; CI, confidence interval; DM, diabetes mellitus; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial hemorrhage; IS, ischemic stroke; MACE, major adverse cardiac events; NOAC, non-vitamin K anticoagulant; pt, patient; SE, systolic embolism.

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DISCLOSURES

RW, AB, and **DF** are employees of Daiichi Sankyo, Inc. **HL** has nothing to report.