Research Article

Direct Anticoagulants and Risk of Myocardial Infarction, a Multiple Treatment Network Meta-Analysis

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Abstract

We assessed the cardiovascular safety of long-term direct-acting oral anticoagulant (DOAC) treatment. A search of the medical literature was performed from inception until May 31, 2019. Inclusion criteria were (1) randomized trial that assessed the clinical efficacy and/or safety of 1 or more DOAC, (2) control group including oral anticoagulation and/or antiplatelet and/or placebo treatment, and (3) the incidence of acute coronary syndrome during follow-up was reported. Fixed-effect and random-effects models were applied. The analyzed outcomes were myocardial infarction (MI), major bleeding, and mortality. Twenty-eight randomized clinical trials (196 761 patients) were included. Rivaroxaban was associated with a 21% reduction in the relative risk of MI when compared to placebo (relative risk [RR]: 0.79 [95% credible interval, CrI: 0.65-0.94]) and a 31% reduction (RR: 0.70 [95% CrI: 0.53-0.89]) when compared to dabigatran. Apixaban resulted in 24% (RR: 0.76 [95% CrI: 0.58-0.99]) and vitamin K antagonists anticoagulation resulted in 19% (RR: 0.81 [95% CrI: 0.65-0.98]) risk reduction compared to dabigatran. The computed probability of being the first best choice of treatment was 61.8% for rivaroxaban. Cardiovascular safety shows considerable heterogeneity among oral anticoagulants. Treatment with rivaroxaban is associated with reduced rate of MI.

Keywords

myocardial infarction, non-vitamin k antagonist oral anticoagulants, network meta-analysis

Introduction

Ten years have passed since the approval of the first non-vitamin K antagonist oral anticoagulants. Direct oral anticoagulants (DOACs) have been proposed as an alternative term for this class of agents including oral direct thrombin inhibitors (DTIs) and activated factor X inhibitors (anti-Xa).[1] In several fields, compared to vitamin K antagonists (VKA), DOACs have been proven to have similar or higher efficacy in preventing ischemic events and similar or lower risk for major bleeding, bleeding-related case fatalities, and intracranial bleeding.[2,3] Furthermore, DOACs alleviate several problems associated with VKA use including the need for laboratory monitoring due to the narrow therapeutic window and drug/food interactions. [4] Consequently, DOACs have been widely adopted.[5]

Coronary heart disease (CHD) is the leading cause of death and disability having a major impact on both developing and developed nations.[6] The coagulation cascade plays an important role in the evolution of acute coronary syndrome (ACS) events.[7] Earlier analyses found that long-term treatment with VKAs, in monotherapy or in combination with aspirin, is superior to aspirin alone for secondary prevention after acute myocardial infarction (MI).[8]

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Importantly, DOACs showed dissimilar results regarding cardiovascular (CV) safety. Rivaroxaban showed favorable outcomes when combined with aspirin among patients with stable atherosclerotic disease, and it also reduced ischemic risk in ACS.[9,10] In contrast, signals from earlier studies have raised safety concerns regarding MI risk among dabigatran-treated patients, but dabigatran lowered the risk of major vascular complications among patients with myocardial injury after surgery.[11,12]

Direct comparative trials are not available to compare the risk of MI among DOAC-treated patients. Therefore, we performed a Bayesian multiple treatment network meta-analysis (NMA) of randomized clinical trials in order to summarize the data of DOAC trials and gain insight into CV safety.

Methods

A manual search of medical literature was performed in PubMed (MEDLINE), EMBASE, and Cochrane Trials from inception until May 31, 2019, for articles reporting randomized clinical trials with DOACs. No language restriction was used. The query included the following terms linked with Boolean operators: "pulmonary embolism," "atrial fibrillation," "thromboprophylaxis," "anticoagulation," "prevention," "rivaroxaban OR apixaban OR dabigatran OR edoxaban" (for detailed search history, refer to the Online Appendix).

In the analysis, we included trials that fulfilled the following criteria: (1) randomized clinical trials (RCTs) that assessed the clinical efficacy and/or safety of an anticoagulant protocol comprising either $\geq$1 of the approved and marketed DOACs, that is, dabigatran, rivaroxaban, apixaban, or edoxaban. (2) Having one or more control group with oral anticoagulation, antiplatelet treatment, or placebo. (3) Reporting the frequency of MI or the rate of ACS during the follow-up compliant with intention-to-treat analysis. Studies that aimed to compare merely the biological efficacy of the anticoagulant protocol and trials not reporting the frequency of MI were excluded. Nonrandomized studies, registries, and uncontrolled or cohort studies as well as reviews were disregarded. The review protocol was registered in the PROSPERO database a priori under the registration number of CRD42018103000.

All the relevant articles were combined in a reference manager software (EndNote X8; Clarivate Analytics, Philadelphia, PI) to remove duplicates by searching overlaps between titles, abstracts, authors, and publication year. After removing duplicates, we screened the articles by title, abstract, and full texts against our predefined eligibility criteria. Each phase was carried out by 2 independent investigators (P.K. and Z.S.) in duplicate, none of whom were blinded to publication data. Third-party (A.K.) arbitration resolved any discrepancies.

The following details were recorded for each study: study name, first author, year of publication, period of study, the applied doses of oral anticoagulant, number of patients, length of treatment period, length of follow-up, inclusion and exclusion criteria, protocol definitions of MI as well as patient and procedural characteristics including mean age, sex, and the following risk factors: diabetes, hypercholesterolemia, and hypertension.

The primary end point of the analysis was the frequency of MI. Overall mortality was defined as a secondary end point. As a safety measure, frequency of major bleeding complications was evaluated. Both MI and major bleeding were defined according to the internal definitions of the studies. If multiple major bleeding definitions were used, we extracted thrombolysis in myocardial infarction (TIMI) major bleeding and International Society on Thrombosis and Hemostasis major bleeding if available (Table 1). The data from intention to treat analyses were extracted. The end points of interest were collected until the longest follow-up available.

Analyses of subgroups, heterogeneity, as well as assessment of bias were performed using the Cochrane Review Manager version 5.3. software.[15] Degree of inconsistency among studies was quantified by means of I2. Cochrane Q heterogeneity test (χ^2) was also performed. These data were reported as percentage of the I2 together with the P value of the χ^2 test. The likelihood of publication bias was visually assessed by generating a funnel plot for the primary end point. The risk of MI was analyzed in a hierarchical Bayesian mixed-treatment comparison meta-analysis. The Bayesian analysis allows the combination of existing knowledge with new information according to established rules of probability.[16] Substantive prior knowledge can thereby be included in any Bayesian analysis by choice of initial (predata) distribution. We wanted our final (posterior) distribution to reflect the information in our data set only and not to be influenced by our choice of initial (prior) distribution. Therefore, "noninformative" prior distributions were used throughout so that the data from the trials dominated the final inferences. The RCT data were then added via the Bayes rule to produce posterior distributions. Treatment effects are reported as risk ratio with 95% associated credible interval (CrI), which is a Bayesian analog of the 95% confidence interval from traditional meta-analyses. Inferences were calculated with a Gibbs sampler algorithm as implemented through WinBUGS software (version 1.4.3; MRC Biostatistics Unit, Cambridge, United Kingdom).[17] To ensure convergence, 3 Markov Monte Carlo chains were run. Data input and graphical output were performed using the NetMetaXL interface.[18] Inferences based on random effects models are presented. The choice of random-effects model was made based on the consideration that the true preventive effect of anticoagulant treatment may vary from study to study influenced by heterogeneity of the included trials. Random-effects model accounts better for interstudy differences; furthermore, it results in wider credible intervals and thus provides more conservative and robust results. To supplement the information of random-effects modeling, fixed-effects models were also built and analyzed as sensitivity test. Subgroup analyses were performed by building networks of studies performed in the same risk groups as well as according to MI definitions (see Online Appendix). Meta-regression analyses were performed using the Open Meta-analyst software (Brown University, RI).[19]

Table 1. Study Characteristics of the Included Trials.[a]

Study name/First Author (Publication year)	Period of Study	Study Drug (Total Daily Dose, mg)	Comparator Drug	Patients Number	Follow-Up, months	Inclusion Criteria	MI Definition	MB Definition
AMPLIFY/G. Agnelli (2013)	2008-2013	Apixaban (20 first 7 days, 10)	Warfarin	5395	7	Confirmed symptomatic proximal DVT or PE	2≥ of the followings: symptoms; ECG abnormalities, elevated cardiac biomarkers	Based on ISTH MB
APPRAISE-2/J. H. Alexander (2011)	2009-2011	Apixaban (10)	Placebo	7392	8	ACS within 7 days	2≥ of the followings: symptoms; ECG abnormalities, elevated cardiac biomarkers	Based on TIMI MB
ARISTOTLE/C.B. Granger (2011)	2006-2011	Apixaban (10)	Warfarin	18 201	21.6	AF or flutter, ≥1 RF for stroke	IRCE	Based on TIMI MB
ATLAS ACS 2-TIMI 51/J. L. Mega (2012)	2008-2011	Rivaroxaban (5/10)	Placebo	15 342	13.1	ASA or DAPT, ACS	IRCE	Based on TIMI MB
AUGUSTUS/R. D. Lopes (2019)	2015-2018	Apixaban (10/5)	Warfarin	4614	6	NVAF, stable or unstable CAD treated with PCI	IRCE	Based on ISTH MB
AVERROES/S. J. Connolly (2011)	2007-2010	Apixaban (10/5)	ASA(81-324 mg)	5599	13.2	≥50 years, documented AF within prior 6 months	IRCE	Based on ISTH MB
COMPASS/J. W. Eikelboom (2017)	2013-2017	Rivaroxaban (5) + ASA/rivaroxaban (10)	ASA (100 mg)	27 395	23	CAD or PAD	Compatible with UDMI 2012	Based on ISTH MB
COMMANDER HF/F. Zannad (2018)	2013-2017	Rivaroxaban (5)	Placebo	5022	21.1	Chronic HF, EF<40% CAD, and elevated plasma concentrations of natriuretic peptide	Compatible with UDMI 2012	Based on ISTH MB
EINSTEIN-CHOICE/J. I. Weitz (2017)	2014-2016	Rivaroxaban (20/10)	ASA (100 mg)	3365	12+1	Confirmed, symptomatic proximal DVT or PE	Compatible with UDMI 2012	Based on ISTH MB
EINSTEIN-DVT/R. Bauersachs (2010)	2007-2010	Rivaroxaban (30 3 weeks, 20)	Warfarin/ acenocoumarol	3429	12	Symptomatic, recurrent DVT or nonfatal or fatal PE	IRCE	Based on ISTH MB
EINSTEIN-PE/H. R. Büller (2012)	2007-2011	Rivaroxaban (30 3 weeks, 20)	Warfarin/ acenocoumarol	4832	12	Symptomatic PE with or without symptomatic DVT	IRCE	Based on ISTH MB
EMANATE/M. D. Ezekowitz (2018)	2014-2017	Apixaban (10/5)	Warfarin	1500	1.2/2.4	Elective electrical or pharmacological cardioversion	IRCE	Based on ISTH MB
ENGAGE AF—TIMI 48/R. P. Giugliano (2013)	2008-2013	Edoxaban (60/30)	Warfarin	21,105	33.2	AF, a CHADS2 score of ≥2	IRCE	Based on ISTH MB
ENSURE-AF/A. Goette (2016)	2014-2016	Edoxaban (60/30)	Warfarin	2199	1/1.63+1	Ongoing AF lasting at least 48 hours but ≤12 months, elective ECV	IRCE	Based on ISTH MB
Hokusai-VTE/Hokusai investigators (2013)	2009-2013	Edoxaban (60/30)	Warfarin	8240	12	Confirmed DVT and/or symptomatic PE	Compatible with UDMI 2012	Based on ISTH MB
J-ROCKET AF/M. Hori (2012)	2007-2009	Rivaroxaban (15)	Warfarin	1280	30+1	AF; prior ischemic stroke, TIA or non-CNS systemic embolism or ≥2 RF for stroke	2≥ of the followings: symptoms; ECG abnormalities, elevated cardiac biomarkers	Based on ISTH MB

(continued)

Table 1. (continued)

Study name/First Author (Publication year)	Period of Study	Study Drug (Total Daily Dose, mg)	Comparator Drug	Patients Number	Follow-Up, months	Inclusion Criteria	MI Definition	MB Definition
MANAGE/Manage investigators (2018)	2013-2018	Dabigatran (220)	Placebo	1754	16	Undergone noncardiac surgery, MINS	IRCE	Based on ISTH MB
NAVIGATE ESUS/R. G. Hart (2018)	2014-2018	Rivaroxaban (15)	ASA (100 mg)	7213	15	ESUS, within 7 days and 6 months before screening	IRCE	Based on ISTH MB
PIONEER AF-PCI/C.M. Gibson (2016)	2013-2016	Rivaroxaban (10-15/5)	Warfarin	2214	12	PCI with stent placement, history of AF	IRCE	Based on TIMI MB
RE-COVER II/S. Schulman (2014)	2008-2011	Dabigatran (300)	Warfarin	2568	6+1	Symptomatic, confirmed proximal DVT of the legs, or PE	IRCE	Based on ISTH MB
RE-COVER/S. Schulman (2009)	2006-2009	Dabigatran (300)	Warfarin	2539	6+1	Acute, symptomatic, proximal DVT or PE	IRCE	Based on ISTH MB
RE-DUAL/C. P. Cannon (2017)	2014-2017	Dabigatran (300/220)	Warfarin	2725	14	NVAF, stable or unstable CAD treated with PCI	Compatible with UDMI 2012	Based on TIMI MB
RE-LY/S. J. Connolly (2009)	2005-2009	Dabigatran (300/220)	Warfarin	18 113	24	AF and risk of stroke	IRCE	Based on ISTH MB
RE-MEDY/S. Schulman (2013)	2006-2011	Dabigatran (300)	Warfarin	2856	36	Symptomatic, proximal DVT or PE, previously treated with AC	IRCE	Based on ISTH MB
RE-SONATE/S. Schilman (2013)	2007-2011	Dabigatran (300)	Placebo	1343	12	Symptomatic, proximal DVT or PE, previously treated with AC	IRCE	Based on ISTH MB
RE-SPECT ESUS/H. C. Diener (2019)	2014-2018	Dabigatran (300/220)	ASA (100)	5390	19	ESUS within 3 months before screening	IRCE	Based on ISTH MB
ROCKET AF/M. R. Patel (2011)	2006-2010	Rivaroxaban (20/15)	Warfarin	14 236	23.6	AF; prior ischemic stroke, TIA or non-CNS systemic embolism or $\geq$2 RF for stroke	2$\geq$ of the followings: symptoms; ECG abnormalities, elevated cardiac biomarkers	Based on ISTH MB
X-VeRT/R. Cappato (2014)	2012-2014	Rivaroxaban (20/15)	Warfarin/ acenocoumarol	1504	1.5/2.68+1	Elective electrical or pharmacological cardioversion	IRCE	Based on ISTH MB

Abbreviations: AC, anticoagulation; ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, aspirin; ATLAS ACS 2–TIMI 51, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51; CAD, coronary artery disease; CNS, central nervous system; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; DAPT, dual antiplatelet therapy; DVT, deep vein thrombosis; ECG, Electrocardiography; ESUS, embolic stroke of undetermined source; GI, gastrointestinal; HF, heart failure; IRCE, Investigator reported clinical event; ISTH, International Society of Thrombosis and Haemostasis; LA, left atrial; LMWH, low-molecular-weight heparin; MB, major bleeding; MANAGE, Management of Myocardial Injury After Noncardiac Surgery; MI, myocardial infarction; MINS, myocardial injury after noncardiac surgery; MS, mitral stenosis; NA, not available; NVAF, nonvalvular atrial fibrillation; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PE, pulmonary embolism; RE-LY, Randomized Evaluation of Long Term Anticoagulant Therapy with Dabigatran Etexilate; RF, risk factor; STD, ST depression; STE, ST elevation; TIA, transient ischemic attack; TIMI, Thrombolysis in Myocardial Infarction; UDMI, universal definition of myocardial infarction;[13,14] URL, upper rate limit; VKA, vitamin K antagonist.

[a] For resolution of study acronyms please refer to the Supplementary data.

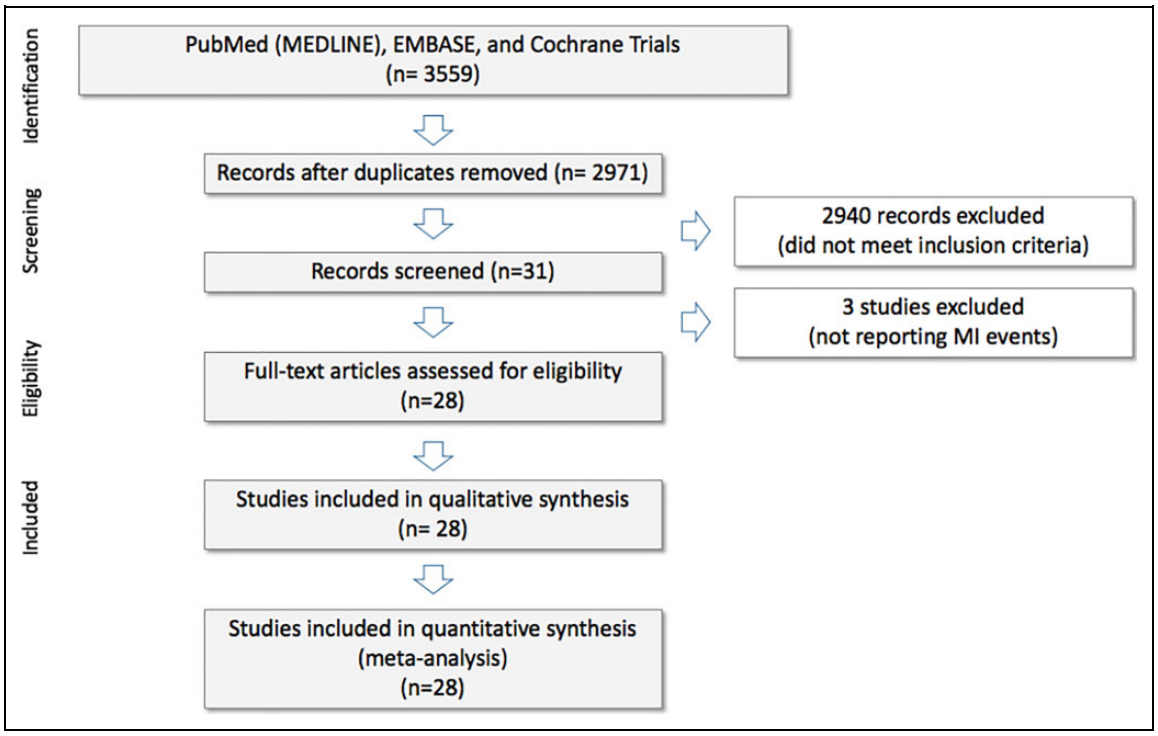

Figure 1. PRISMA flow diagram of the systematic review and source selection.

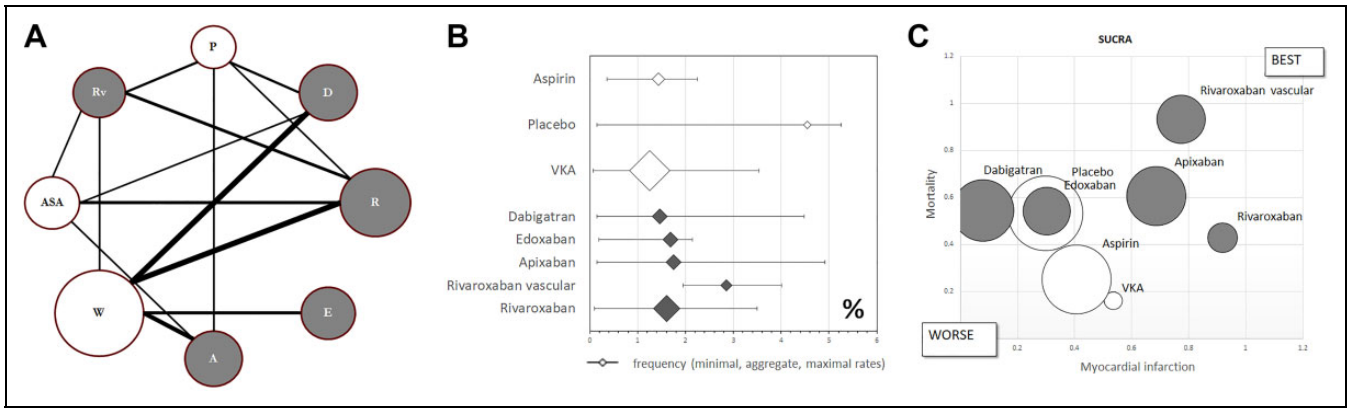

Figure 2. Study network, myocardial infarction frequencies, and ranking. A, Plot of the study network. Nodes show anticoagulation treatments being compared, and edges represent an available direct comparison between pairs of intervention. B, Rate of myocardial infarction according to the treatment groups. Whiskers depict minimal and maximal rates. The diamond depicts the aggregate rate, and its size is proportional to the number of patients treated with the particular intervention. C, Clustered ranking plot of the network. The plot is based on the cluster analysis of SUCRA curves, and the plot shows SUCRA values for the risk of myocardial infarction and mortality. Size of the circles is plotted based on the SUCRA values for major bleeding. AP indicates placebo; D, dabigatran; R, rivaroxaban; E, edoxaban; A, apixaban; W, warfarin; ASA, aspirin; Rv, rivaroxaban vascular dose; SUCRA, surface under the cumulative ranking.

Results

Twenty-eight RCTs involving 196 761 (range: 1280-27 395) patients were analyzed (Figure 1). The main characteristics of these trials are shown in Table 1. Clinical characteristics of the included populations and procedural data of the trials are reported in Supplementary Table 1. Patients were recruited to the trials due to nonvalvular atrial fibrillation,[20-27] including those scheduled for elective cardioversion,[28-30] patients after embolic stroke of undetermined source,[31,32] patients treated for pulmonary embolism or deep vein thrombosis,[33-40] as well as cases at high risk for CHD[10,41,42] including ACS. According to the applied anticoagulants, study arms were grouped into 8 groups. The geometry of the network is depicted in Figure 2A. Dose of the anticoagulant was different and as follows: 150 mg twice daily and 110 mg twice daily for dabigatran, 5 mg once daily to 10 mg twice daily for apixaban, 30 mg once

Table 2. Indirect Comparisons of Different Oral Anticoagulants in a Network Meta-Analysis.[a]

Rivaroxaban				Treatment 1			
0.94 (0.76-1.15) 1.22 (1.04-1.45)[b] 1.82 (0.79-2.17)	Rivaroxaban vascular			Myocardial infarction Mortality Major bleeding	Treatment 2		
0.90 (0.68-1.18) 1.03 (0.87-1.25) 1.72 (0.97-3.13)	0.95 (0.70-1.29) 0.85 (0.69-1.07) 1.35 (0.66-2.70)	Apixaban					
0.88 (0.70-1.12) 0.92 (0.79-1.07) 0.90 (0.62-1.33)	0.93 (0.72-1.25) 0.75 (0.61-0.92)[b] 0.71 (0.39-1.22)	0.98 (0.76-1.31) 0.88 (0.76-1.02) 0.52 (0.31-0.88)[b]	VKA				
0.81 (0.61-1.01) 0.96 (0.82-1.14) 2.08 (0.23-3.57)	0.86 (0.64-1.09) 0.79 (0.66-0.95)[b] 1.61 (0.85-3.03)	0.90 (0.64-1.23) 0.93 (0.76-1.13) 1.21 (0.63-2.27)	0.92 (0.64-1.23) 1.05 (0.86-1.28) 2.27 (1.28-4.16)[b]	Aspirin			
0.79 (0.55-1.13) 1.00 (0.81-1.25) 1.28 (0.64-2.63)	0.84 (0.57-1.24) 0.82 (0.64-1.06) 1.00 (0.43-2.22)	0.88 (0.60-1.30) 0.97 (0.77-1.19) 0.74 (0.34-1.62)	0.90 (0.67-1.17) 1.01 (0.93-1.27) 1.41 (0.79-2.56)	0.97 (0.66-1.53) 1.04 (0.81-1.33) 0.62 (0.27-1.42)	Edoxaban		
0.79 (0.65-0.94)[b] 0.96 (0.79-1.16) 2.77 (1.54-5.00)[b]	0.84 (0.70-0.99) [b] 0.78 (0.63-0.97)[b] 2.13 (1.08-4.17)[b]	0.87 (0.67-1.11) 0.92 (0.75-1.12) 1.59 (0.84-3.03)	0.89 (0.66-1.14) 1.04 (0.86-1.27) 3.03 (1.75-6.67)[b]	0.97 (0.72-1.33) 0.99 (0.79-1.24) 1.33 (0.64-2.70)	1.00 (0.66-1.44) 0.96 (0.75-1.22) 2.13 (0.95-4.76)	Placebo	
0.70 (0.53-0.89)[b] 1.00 (0.82-1.21) 1.72 (1.05-2.94)[b]	0.80 (0.56-0.96)[b] 0.82 (0.65-1.03) 1.35 (0.71-2.56)	0.76 (0.58-0.99)[b] 0.96 (0.78-1.16) 1.01 (0.55-1.89)	0.81 (0.65-0.98)[b] 1.09 (0.94-1.23) 1.92 (1.32-2.86)[b]	0.87 (0.61-1.28) 1.03 (0.82-1.30) 0.84 (0.43-1.67)	0.89 (0.61-1.27) 1.00 (0.81-1.22) 1.35 (0.68-2.77)	0.90 (0.66-1.23) 1.04 (0.85-1.28) 0.63 (0.37-1.10)	Dabigatran

Abbreviation: VKA: vitamin K antagonist.
[a]League table shows the risk ratios (RR) and the 95% credible interval (CrI) of the different oral anticoagulants in a random effect model with vague prior for myocardial infarction (first line), mortality (second line), and major bleeding (third line). RR < 1 means that the top left treatment (Treatment 1) is better.
[b]The comparisons where the CrI did not overlap the line of equivalence.

daily and 60 mg once daily for edoxaban, while rivaroxaban dose ranged from 10 mg daily (once daily or twice daily) up to 30 mg daily except for 4 studies testing "rivaroxaban vascular" 2.5 mg twice-daily doses.[9,10,24,41] Control treatment arm was aspirin in 5, VKA in 18, and placebo in 5 trials. Study definitions of MI were discrepant (Table 1).[13,14]

Low-dose ($\leq$100/$\leq$165 mg daily) aspirin treatment was allowed in all studies. Combined antiplatelet therapy was allowed in 13 studies.[9,12,41,42,43,23-27,29,36,40] Analysis of bias showed high quality of the source information with low probability of possible bias. No obvious publication bias was found (Supplemental Figures 1 and 2).

In the included trials, 3554 MIs occurred in the VKA arm with lowest rate (1.25%) and in the placebo arms with the highest rate (4.55%; Figure 2B). Heterogeneity analysis showed consistent results within treatment groups (dabigatran I2: 26%, χ^2: $P = .23$ and I^2: 0%, χ^2: $P \geq .53$ for all other DOACs), while high heterogeneity was seen among DOAC subgroups (I2: 64.2%, χ^2: $P = .02$; Supplemental Figure 1). Exclusion of the Secondary Prevention of Venous Thrombo Embolism (RE-MEDY) or the Management of Myocardial Injury After Noncardiac Surgery (MANAGE) trial but none of the others corrected the I2 value in the dabigatran subgroup to zero (data not shown).

Rivaroxaban was associated with a relative risk (RR) reduction of 21% regarding MI when compared to placebo (RR: 0.79 [95% CrI: 0.65-0.94]) and a 31% reduction (RR: 0.70 [95% CrI: 0.53-0.89]) when compared to dabigatran. Apixaban resulted in 24% (RR: 0.76 [95% CrI: 0.58-0.99], and VKA resulted in 19% (RR: 0.81 [95% CrI: 0.65-0.98]) risk reduction compared with dabigatran. Furthermore, rivaroxaban in vascular dose resulted in 16% (RR: 0.70 [95% CrI: 0.70-0.99]) reduction compared with placebo, as well as 27% (RR 0.80 [95% CrI: 0.56-0.96] risk reduction compared to dabigatran (Table 2, Figure 3).

Leave-one-out analysis disregarding the data from the Randomized Evaluation of Long Term Anticoagulant Therapy with Dabigatran Etexilate (RE-LY) trial showed similar relations with lower MI risk with rivaroxaban than with placebo (0.78 [0.64-0.94]) and dabigatran as well (RR: 0.66 [0.49-0.89]; Supplemental Table 4).

The computed probability of being the first best choice of treatment was 61.8% for rivaroxaban, 17.4% for very low-dose rivaroxaban (5 mg daily), 14.2% for apixaban, 2.4% for VKAs, 3.0% for edoxaban, 1.1% for aspirin, and <0.1% for placebo and dabigatran in the network.

Ranking remained unaffected if data from the RE-LY trial were censored from the analysis. Ranking based on mortality and major bleeding result showed trends of similar ranks with MI and mortality, while trends of major bleeding showed opposite tendencies with lower ranking of bleeding at treatments with higher rankings in MI (Figure 2C). However, neither of these trends were significant at regression analyses of the surface under the cumulative ranking area values (R^2 for MI and mortality: 0.035, $P = .6577$ and R^2 for MI and major bleeding: 0.2963, $P = .1630$).

In univariate meta-regression analyses, the rate of MI showed positive association with the background risk and to the rate of antiplatelet use but not to the treatment duration. In

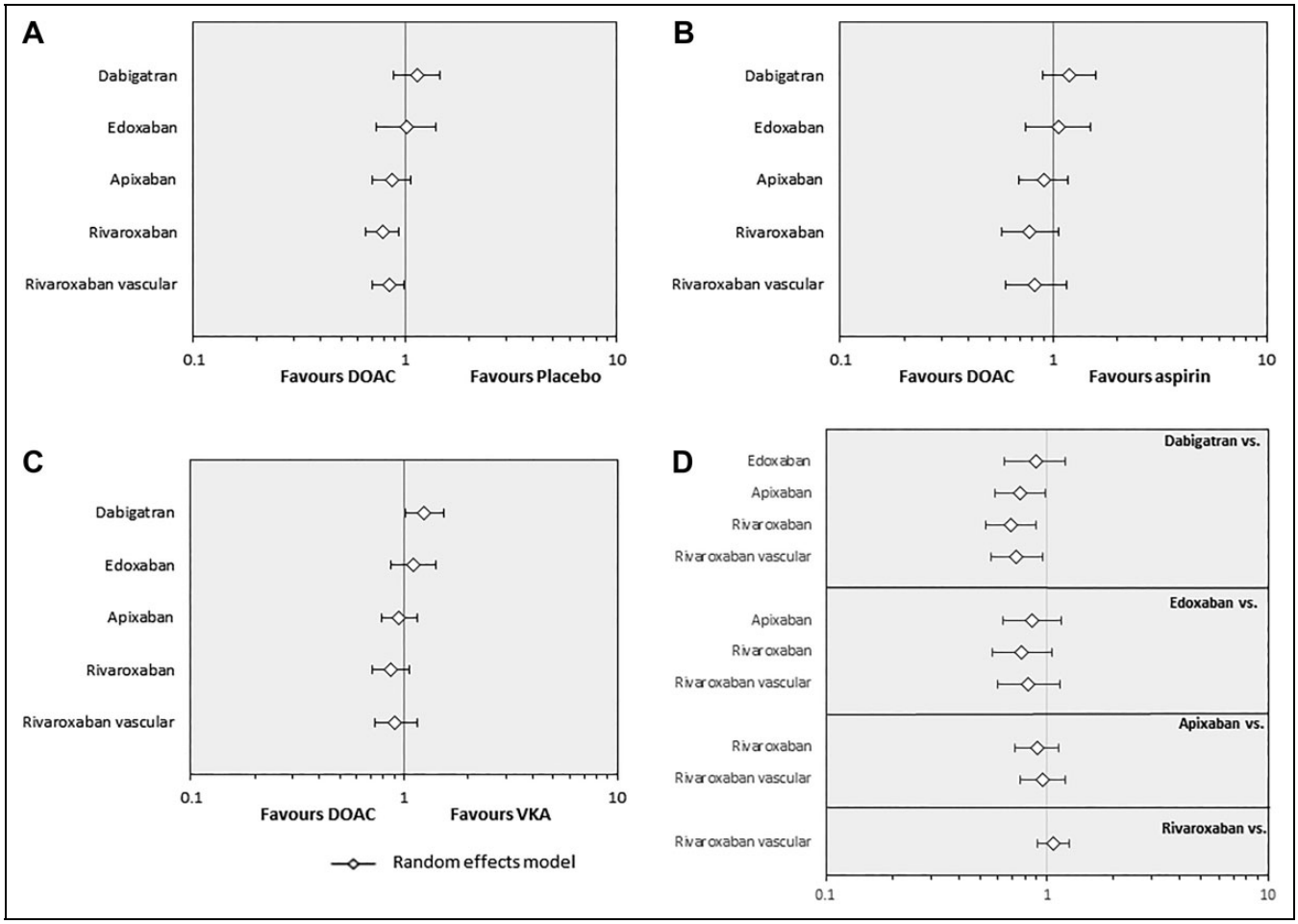

Figure 3. Forest plot of the relative risk of myocardial infarction. A, B, and C, The relation of the myocardial infarction risk of the DOAC treatments compared to the placebo and aspirin of vitamin K antagonist controls, respectively. D, Comparisons among the different DOAC groups. DOAC indicates direct oral anticoagulant; VKA, vitamin K antagonists.

multiple analysis background risk, prevailed as a significant determinant of the MI frequency ($P = .871$ for antiplatelet and $P < .001$ for the background risk). However, analyses of the RR against aspirin showed no association either with the antiplatelet use or with the background risk (Figure 4).

Discussion

In this meta-analysis involving 196 761 patients, we found evidence that the choice of anticoagulant influences the risk of MI in anticoagulated patients. When risk of MI is taken into consideration, the probability of being the best choice of treatment is the highest for rivaroxaban administered in antithrombotic or vascular prevention dose regimen, while the lowest is for VKAs and the direct thrombin inhibitor, dabigatran.

Coagulation plays pivotal role in the development of CV events; thus, CV safety of these drugs is of paramount interest. Earlier analyses found favorable results for VKAs in the prevention after acute MI.[8] However, frequent bleeding complications and the narrow therapeutic window with the need for careful monitoring, in addition to drug and food interactions, limit the benefits.[44] In recent years, VKAs are progressively replaced by the specifically acting oral anticoagulants (DOACs) offering an easier and potentially safer option leading to a high number of patients exposed to these drugs. Moreover, improving safety and convenience of use raised the question as to whether DOACs reopen the field of CV prevention for anticoagulation.

Several recent trials supported this concept including the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial, where 2.5 mg rivaroxaban twice daily improved the CV outcomes compared to placebo. Despite the higher risk of bleeding, compared to placebo vascular dose rivaroxaban reduced the rate of death of CV origin (2.7% vs 4.1%, $P = .002$) and all other causes (2.9% vs 4.5%, $P = .002$).[9] More recently in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, low-dose rivaroxaban combined with aspirin was associated with a reduced risk of ischemic events and mortality among patients with established, stable atherosclerotic disease, compared to those receiving aspirin monotherapy. Although

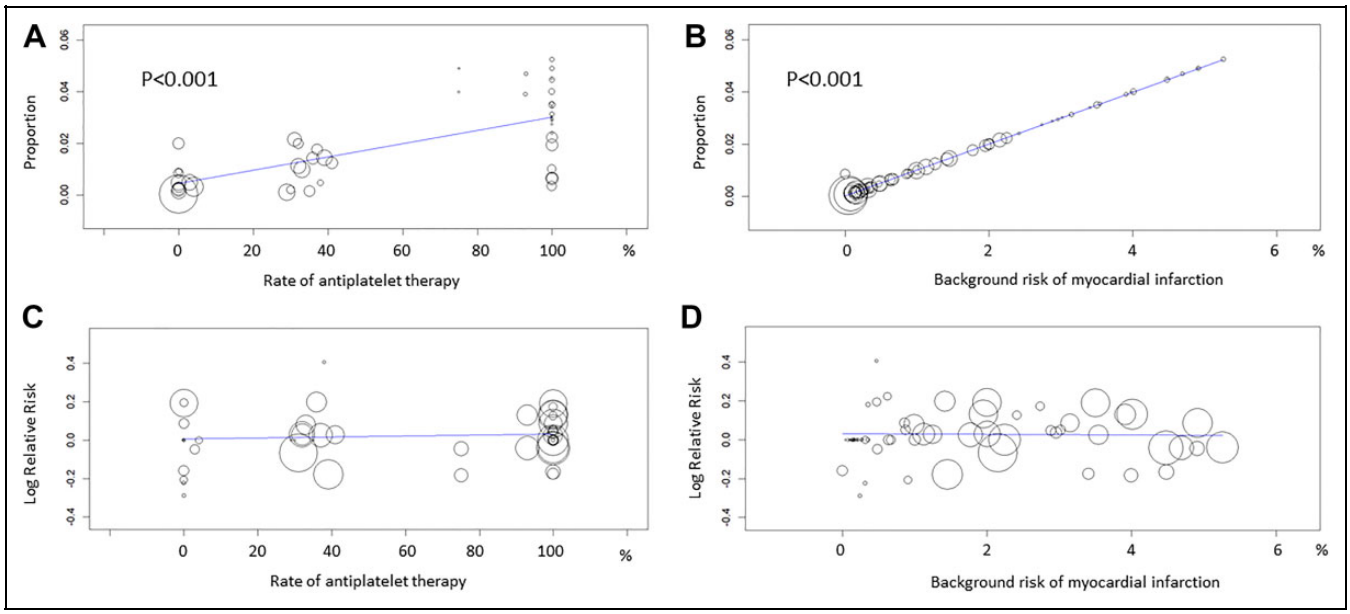

Figure 4. Meta-regression analyses. In univariate meta-regression analyses, the rate of myocardial infarction (MI) showed positive regression to the rate of antiplatelet use as well as to the background risk (A and B). Analyses of the risk ratio against aspirin showed no regression either to the antiplatelet use or to the background risk (C and D).

bleeding complications were also more common, the combined treatment with low-dose rivaroxaban resulted in superior net clinical benefit.[10] Furthermore, in the MANAGE trial among patients with myocardial injury after noncardiac surgery, twice-daily 110 mg dabigatran was tested against placebo and resulted in fewer major vascular events, while bleeding complications were similar in frequency ($P = .0115$ and $P = .76$, respectively).[12]

Contrasting these recent results, there has been some question ever since the publication of one of the earliest DOAC phase 3 study, the RE-LY trial.[26] In this trial, 2 doses of dabigatran were shown to be either more effective in preventing stroke with a similar bleeding risk or safer than warfarin with similar prevention efficacy. Importantly, this study reflected that patients receiving anticoagulant treatment for atrial fibrillation remain at risk of MI and found an excessive risk of MI with dabigatran. There were numerically more MIs with both doses of dabigatran than with warfarin, and the difference reached statistical significance regarding the higher, 150 mg dose. However, a subsequent post hoc analysis revealed additional events of stroke, bleeding, and MI, and the revised results no longer showed a significant difference in MI.[45]

In the paucity of direct comparison randomized trials, several studies including prospective and retrospective registries attempted verification and characterization of the magnitude of the potential MI risk of dabigatran-treated patients. These studies, though subjected to several methodological shortcomings, especially an uncontrollable selection bias, could neither reliably support nor refute the importance of this signal.[46-48] Our extended review including a broad range of studies found that the data of randomized trials show important differences favoring the Xa inhibitor rivaroxaban and apixaban over dabigatran. This extends the earlier observations supporting that signal persists even after exclusion of the RE-LY data and reaches beyond the field of patients with atrial fibrillation.

Since the 2012 version of the European Society of Cardiology CV disease prevention guideline, the concept of primary and secondary prevention has been discouraged and replaced by the recognition that atherosclerosis is a continuous process.[49] The results of our analysis are consistent with the large body of evidence documenting the ability of anticoagulants to reduce ischemic events in patients with or without established CHD, including ACS.

Our analysis assessed the preventive potential of DOACs from 2 approaches. First, the inclusion of 5 placebo and 5 aspirin-controlled trials enables to relate this potential to established preventive therapy. Second, we found that the differences in the rate of MI in the study arms were explainable by the background risk of the included study populations rather than by the differences in the rate of antiplatelet treatment. The relative risks of the anticoagulant treatments compared to aspirin were independent from both the rate of antiplatelet treatment and background risk. Importantly, the subgroup analyses according to the clinical indications or the treatment length did not show a major influence on the results. These findings suggest that the preventive potential of DOACs is heterogeneous, correlates with that of aspirin and VKA, and is independent of the concomitant antiplatelet treatment.

The risk of MI with DOAC treatment has been assessed in earlier systematic reviews and meta-analyses. Besides that, these analyses did not include the results of some pivotal recent trials including the COMPASS, MANAGE, and AUGUSTUS

studies; they share some common limitations. These comprise inclusion of underpowered, dose-finding, phase 2 trials.[50-53] Only a few of them included trials with the recently approved edoxaban[53-55] but included trials with drugs that stopped development.[50,51,54,55] Some previous works restricted the analysis to trials related only to atrial fibrillation and or deep vein thrombosis/pulmonary embolism.[53-55] Some based their assumptions on the less robust fixed effect model that accounts for interstudy heterogeneity less adequately.[52,53]

Some limitations of our analysis should be discussed. The paucity of randomized trials comparing different DOAC agents was one of the main reasons for the choice of this analysis but represents also a limitation as the presented statistical inferences rely substantially on indirect comparisons. It is improbable that a specific trial with MI as an end point and aiming to perform a direct comparison of oral anticoagulants will ever be conducted; thus, analysis of the available data set remains the only option to shed light on these relationships.

Furthermore, safety and efficacy profiles of the anticoagulants may be dose dependent, and the variability in drug regimens might be a source of distortion. In fact, in trials testing >1 dose of DOACs, the rate of MI was different in some cases but similar in others. For example, 2.4% and 1.89% with 30 and 60 mg once-daily edoxaban in the Global Study to Assess the Safety and Effectiveness of Edoxaban vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation (ENGAGE AF—TIMI 48) trial, or 1.46% and 1.43% with 110 or 150 mg twice-daily dabigatran in the RE-LY trial among patients with AF, respectively.[21] However, in most of the remaining trials, the rather complicated schemes do not permit the study of dose–effect relationships. Thus, we decided to form our analysis groups based on DOAC exposure, with one exception regarding the distinction of the very low-dose rivaroxaban. Earlier studies with warfarin show that ischemic protection requires to reach a threshold of anticoagulation; above this limit, the rate of bleeding complications but not necessarily the preventive potential increases.[56] Acknowledging that this relation may apply to other means of anticoagulation, we handled "vascular dose" rivaroxaban as distinct treatment groups. Regarding VKA treatment, all but 3 included trials used warfarin in their VKA arms. In 3 trials, acenocoumarol was also allowed (see Table 1). Acknowledging that differences may exist in CV safety of the different VKAs due to the paucity of specific data, we could not differentiate among them. Furthermore, definition of MI slightly differed across studies, and none of them included trials had MI as an end point. Moreover, there are >1 publication regarding the rates of MI in the RE-LY trial.[26,45] This shows that even with meticulously conducted trials, the capture and adjudication of events may be incomplete. As data in the first publication reflected the results of the prospective event adjudication instead of a post hoc analysis, we used these in our analyses.[26] Furthermore, we performed sensitivity analyses that did not show important influence on the result.

Conclusions

Our comprehensive meta-analysis involving 28 RCTs and 196 761 patients has identified significant differences in CV safety among oral anticoagulants. Risk of MI is lowest with rivaroxaban, followed by apixaban and edoxaban, while it is the highest for VKA and dabigatran. Differences in risk of MI may influence the choice of treatment and may be considered in the development of personalized antithrombotic regimens.

Authors' Note

All authors contributed to (1) conception and design, or acquisition of data or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: András Komócsi: Lecture fees from Bayer Healthcare Pharmaceuticals, Eli Lilly, KRKA, MSD, Pfizer, Boehringer-Ingelheim and Abbot Vascular. Tamas Habon: Lecture fees from Bayer, Boehringer-Ingelheim, MSD, Novartis, Pfizer, Roche and Servier. The other authors have no potential conflict of interest.

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Supplemental Material

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