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BRIEF REPORT

Comparing mortality in patients with atrial fibrillation who are receiving a direct-acting oral anticoagulant or warfarin: a meta-analysis of randomized trials

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Summary. *Background:* In patients with non-valvular atrial fibrillation (AF), direct-acting oral anticoagulants (DOACs) are at least non-inferior to warfarin for the prevention of stroke and systemic embolism. The main objective of this study was to obtain reliable and precise estimates for all-cause mortality, vascular mortality and bleeding mortality in patients with AF receiving a DOAC or warfarin for stroke prevention. *Methods:* A meta-analysis was performed on phase 3 randomized trials that compared a DOAC with warfarin for stroke prevention in AF. Published data were pooled by use of the DerSimonian random-effect model, with REVMAN 5.2 and COMPREHENSIVE META ANALYSIS software version 2. The results were presented as risk ratios (RRs), absolute risk reduction (ARR), and number-needed-to-treat (NNT). *Results:* A total of 71 683 patients were included in this meta-analysis from four randomized controlled trials (median patient follow-up: 1.8–2.8 years) that compared a DOAC with warfarin for stroke prevention in AF. As compared with warfarin, DOACs significantly reduced all-cause mortality (RR 0.89, 95% confidence interval [CI] 0.85–0.94; ARR 0.76%, 95% CI 0.39–1.13%; NNT = 132), vascular mortality (RR 0.88, 95% CI 0.82–0.94; ARR 0.53%, 95% CI 0.23–0.83%; NNT = 189), and bleeding mortality (RR 0.54, 95% CI 0.44–0.67; ARR 0.32%, 95% CI 0.21–0.43%; NNT = 313). *Conclusion:* As compared with warfarin therapy for stroke prevention in patients with AF, DOACs significantly reduce all-cause mortality, vascular mortality, and bleeding mortality. This mortality benefit appears to be driven by the reduction in vascular-related and bleeding-related mortality, which, in turn, may be related to the reduction in intracranial bleeding.

Keywords: anticoagulants; atrial fibrillation; hemorrhage; mortality; warfarin.

Introduction

Warfarin, when administered to achieve an International Normalized Ratio (INR) of 2.0–3.0, has established efficacy for stroke prevention in patients with non-valvular atrial fibrillation (AF), but its use is hampered by the need for periodic laboratory monitoring and dose adjustments, and multiple potential drug and food interactions [1]. Direct-acting oral anticoagulants (DOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban, are all at least as efficacious and safe as warfarin in non-valvular AF for stroke prevention, based on data from randomized trials [2–5] and related meta-analyses [6,7], are easier to administer, as there is no need for laboratory monitoring or dose adjustment [8], and are recommended by practice guidelines for this indication [9–12].

Nonetheless, clinicians may question whether there is a compelling therapeutic advantage of using a DOAC rather than warfarin in patients with AF. This uncertainty is understandable, given that studies have assessed the effects of DOACs on multiple and overlapping clinical outcomes, which include ischemic stroke, hemorrhagic stroke, stroke and systemic embolism, major bleeding, and intracranial bleeding. Moreover, the benefits of DOACs for such outcomes are expressed, typically, as relative risk reductions. An alternative approach to reporting the impact of a treatment benefit is absolute risk reduction (ARR) which, in turn, determines the number-needed-to-treat (NNT) to prevent an adverse outcome.

Given these considerations, the objective of this study was to compare the effect of DOACs with that of warfarin for stroke prevention in AF on mortality – a simple and

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unequivocal outcome – and to quantify the effect of DOACs on mortality based on NNT. Secondarily, we explored the cause of mortality in such patients on the basis of an assessment of vascular-related and bleeding-related mortality and intracranial bleeding.

Methods

We searched the www.clinicaltrials.gov and PubMed electronic databases from the 1 January 2009 to 30 November 2013 to identify phase 3 randomized trials comparing a DOAC with warfarin in patients with non-valvular AF. To be included, trials had to meet all of the following criteria: randomized studies, inclusion of patients with AF, comparison of a DOAC with warfarin therapy given for at least 1 year, and reporting of at least one of the following outcomes – all-cause mortality, vascular mortality, bleeding mortality, and intracranial bleeding. Two physician reviewers (A.L. and J.D.) determined whether trials met inclusion criteria, with disagreements being resolved by joint review and consensus. The main outcomes of interest were: all-cause mortality; vascular mortality; bleeding mortality; and intracranial bleeding.

We report the risk ratios (RRs), ARRs and NNTs for all-cause, vascular and bleeding mortality. Pooled estimates were obtained by use of the DerSimonian and Laird random-effects method, and the results are expressed as RRs and ARRs with their corresponding 95% confidence intervals (CIs) [13]. Heterogeneity assessment was performed with the I^2 index and chi-square test. Egger's regression intercept was used to address small study effects. The risk of bias within studies was assessed with the Cochrane Collaboration tool [14]. Calculations were performed with REVMAN version 5.2 and COMPREHENSIVE METAANALYSIS software version 2.

Results and discussion

We identified four trials [2–5,15], totalling 71 683 patients, which contributed to the analysis of the following outcomes: all-cause mortality (71 562 patients); vascular mortality (71 562 patients); bleeding mortality (71 515 patients); and intracranial bleeding (71 515 patients). The ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials were double-blinded, double-dummy trials with computer-generated sham INRs. The RE-LY trial was open-label with warfarin but double-blind for the dose of dabigatran. Approximately two-thirds of patients were male, and the median age of patients in these trials was between 70 years and 73 years. The median patient follow-up durations for the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials were 2.0, 1.9, 1.8 and 2.8 years, respectively.

The assessment of reviewer agreement at the level of study selection from full-text articles with Cohen's weighted kappa was 1.0 (standard deviation = 0). The mortality outcomes were independently adjudicated, and causes of death were determined on the basis of, where available, death certificates, autopsy results, and related clinical information. In the ARISTOTLE and ENGAGE AF-TIMI 48 trials, where the vascular mortality outcome was not available, data on death from cardiovascular causes were used instead.

In patients with non-valvular AF, DOAC therapy was associated with significant reductions in all-cause mortality (RR 0.89, 95% CI 0.85–0.94, $P < 0.0001$; ARR 0.76%, 95% CI 0.39–1.13%, $P < 0.0001$; NNT = 132; Table 1 and Fig. 1A), vascular mortality (RR 0.88, 95% CI 0.82–0.94, $P < 0.0001$; ARR 0.53%, 95% CI 0.23–0.83%, $P = 0.0006$; NNT = 189; Table 1 and Fig. 1B), and bleeding mortality (RR 0.54, 95% CI 0.44–0.67, $P < 0.0001$; ARR 0.32%, 95% CI 0.21–0.43%, $P < 0.0001$; NNT = 313; Table 1 and Fig. 1C). There was no significant heterogeneity among these outcomes. In a subgroup analysis according to the DOAC dose regimens (standard dose or low dose), there was no significant heterogeneity among these outcomes except for the outcome for intracranial bleeding with a low-dose regimen (Table S1). Nevertheless, Egger's regression intercept test showed that all of the estimates for the four outcomes went in the same direction, albeit with only four trials. Finally, the assessment of the risk of bias within studies by use of the Cochrane Collaboration tool showed that there was

Table 1 Summary of efficacy and safety outcomes in the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials

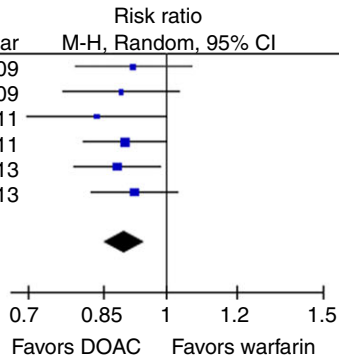
Outcomes	Events (DOAC vs. warfarin)	Risk ratios (95% CI), *P*-value	Risk difference (95% CI), *P*-value	ARR (%)	NNT
All-cause mortality	3205/42 341 vs. 2245/29 221	0.89 (0.85–0.94), < 0.0001*	− 0.0076 (− 0.0113 to − 0.0039), < 0.0001	0.76	132
Vascular mortality	2098/42 341 vs. 1465/29 221	0.88 (0.82–0.94), < 0.0001†	− 0.0053 (− 0.0083 to − 0.0023), 0.0006	0.53	189
Bleeding mortality	165/42 304 vs. 208/29 211	0.54 (0.44–0.67), < 0.0001‡	− 0.0032 (− 0.0043 to − 0.0021), < 0.0001	0.32	313
Intracranial bleeding	272/42 304 vs. 425/29 211	0.42 (0.34–0.53), < 0.0001§	− 0.0085 (− 0.0110 to − 0.0060), < 0.0001	0.85	118

ARR, absolute risk reduction; CI, confidence interval; DOAC, direct-acting oral anticoagulant; NNT, number-needed-to-treat. *Heterogeneity: $I^2 = 0\%$; $\chi^2 = 1.03$ ($P = 0.96$). Egger's regression intercept: − 1.08 (95% CI − 3.78 to 1.61); $P = 0.33$. †Heterogeneity: $I^2 = 0\%$; $\chi^2 = 0.40$ ($P = 1.00$). Egger's regression intercept: − 0.60 (95% CI − 1.39 to 2.59); $P = 0.45$. ‡Heterogeneity: $I^2 = 0\%$; $\chi^2 = 3.34$ ($P = 0.65$). Egger's regression intercept: − 0.47 (95% CI − 8.67 to 7.73); $P = 0.88$. §Heterogeneity: $I^2 = 53\%$; $\chi^2 = 10.55$ ($P = 0.06$). Egger's regression intercept: − 5.80 (95% CI − 16.53 to 4.94); $P = 0.21$.

A

Study or subgroup	Favors DOAC Events	Total	Favors warfarin Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
RE-LY (LD vs. W)	446	6015	243	3011	12.1%	0.92 (0.79–1.07)	2009
RE-LY (SD vs. W)	438	6076	244	3011	12.1%	0.89 (0.77–1.03)	2009
ROCKET AF	208	7061	250	7082	8.3%	0.83 (0.70–1.00)	2011
ARISTOTLE	603	9120	669	9081	24.2%	0.90 (0.81–1.00)	2011
ENGAGE AF-TIMI 48 (LD vs.. W)	737	7034	419	3518	21.4%	0.88 (0.79–0.98)	2013
ENGAGE AF-TIMI 48 (SD vs.. W)	773	7035	420	3518	21.9%	0.92 (0.82–1.03)	2013
Total (95% CI)		42 341		29 221	100.0%	0.89 (0.85–0.94)	
Total events	3205		2245				

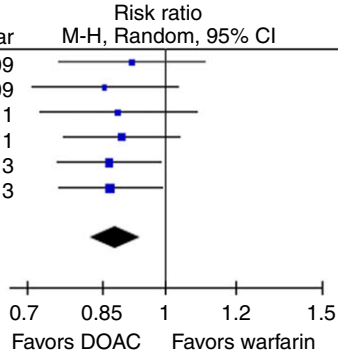
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.03$, d.f. = 5 ($P = 0.96$); $I^2 = 0\%$
Test for overall effect: $Z = 4.17$ ($P < 0.0001$)



B

Study or subgroup	Favors DOAC Events	Total	Favors warfarin Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
RE-LY (LD vs. W)	289	6015	158	3011	12.0%	0.92 (0.76–1.11)	2009
RE-LY (SD vs. W)	274	6076	159	3011	11.8%	0.85 (0.71–1.03)	2009
ROCKET AF	170	7061	193	7082	10.3%	0.88 (0.72–1.08)	2011
ARISTOTLE	308	9120	344	9081	18.8%	0.89 (0.77–1.04)	2011
ENGAGE AF-TIMI 48 (LD vs. W)	527	7034	305	3518	23.5%	0.86 (0.75–0.99)	2013
ENGAGE AF-TIMI 48 (SD vs. W)	530	7035	306	3518	23.6%	0.87 (0.76–0.99)	2013
Total (95% CI)		42 341		29 221	100.0%	0.88 (0.82–0.94)	
Total events	2098		1465				

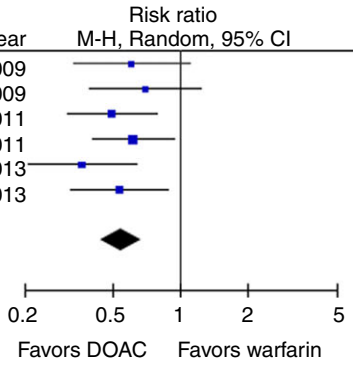
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.40$, d.f. = 5 ($P = 1.00$); $I^2 = 0\%$
Test for overall effect: $Z = 3.95$ ($P < 0.0001$)



C

Study or subgroup	Favors DOAC Events	Total	Favors warfarin Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
RE-LY (LD vs. W)	23	6015	19	3011	11.7%	0.61 (0.33–1.11)	2009
RE-LY (SD vs. W)	28	6076	20	3011	13.1%	0.69 (0.39–1.23)	2009
ROCKET AF	27	7111	55	7125	20.4%	0.49 (0.31–0.78)	2011
ARISTOTLE	34	9088	55	9052	23.6%	0.62 (0.40–0.94)	2011
ENGAGE AF-TIMI 48 (LD vs. W)	21	7002	29	3506	13.7%	0.36 (0.21–0.63)	2013
ENGAGE AF-TIMI 48 (SD vs. W)	32	7012	30	3506	17.4%	0.53 (0.32–0.88)	2013
Total (95% CI)		42 304		29 221	100.0%	0.54 (0.44–0.67)	
Total events	165		208				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.34$, d.f. = 5 ($P = 0.65$); $I^2 = 0\%$
Test for overall effect: $Z = 5.81$ ($P < 0.00001$)



D

Study or subgroup	Favors DOAC Events	Total	Favors warfarin Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year
RE-LY (LD vs. W)	27	6015	43	3011	13.0%	0.31 (0.19–0.51)	2009
RE-LY (SD vs. W)	36	6076	44	3011	14.4%	0.41 (0.26–0.63)	2009
ROCKET AF	55	7111	84	7125	18.6%	0.66 (0.47–0.92)	2011
ARISTOTLE	52	9088	122	9052	19.3%	0.42 (0.31–0.59)	2011
ENGAGE AF-TIMI 48 (LD vs. W)	41	7002	66	3506	16.4%	0.31 (0.21–0.46)	2013
ENGAGE AF-TIMI 48 (SD vs. W)	61	7012	66	3506	18.2%	0.46 (0.33–0.65)	2013
Total (95% CI)		42 304		29 211	100.0%	0.42 (0.34–0.53)	
Total events	272		425				

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 10.55$, d.f. = 5 ($P = 0.06$); $I^2 = 53\%$
Test for overall effect: $Z = 7.48$ ($P < 0.00001$)

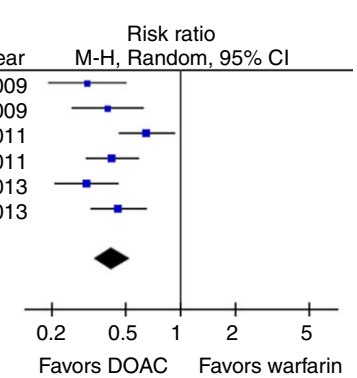


Fig. 1. Risk ratios in patients with non-valvular atrial fibrillation treated with direct-acting oral anticoagulant (DOAC) vs. warfarin. (A) All-cause mortality. (B) Vascular mortality. (C) Bleeding mortality. (D) Intracranial bleeding. CI, confidence interval; d.f., degrees of freedom; LD, low-dose DOAC; M-H, Mantel-Haenstel; SD, standard-dose DOAC; W, warfarin.

a low risk of bias for all key domains for the ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials. For the RE-LY trial, there was an unclear risk of bias for one key domain but, overall, a low risk of bias for all other key domains (Table 2 and Table S2).

Inferences can be made to explain the mortality benefit with DOAC therapy. In the setting of AF, DOACs (when considered collectively) do not reduce ischemic stroke or other cardiovascular outcomes as compared with warfarin, but reduce major bleeding and, especially, intracranial bleeding [6,7]. Indeed, the reduction in intracranial bleeding, as reported in other meta-analyses [6,7] and shown in Fig. 1D (RR 0.42, 95% CI 0.34–0.53, $P < 0.00001$; ARR 0.85%, 95% CI 0.60–1.10%, $P < 0.00001$; NNT = 118), is striking in terms of the magnitude of the risk reduction and the across-trial consistency of this finding. This may be an important factor that drives both vascular-related and bleeding-related mortality, and, more importantly, the overall mortality benefit with DOACs. This presumption is plausible, given the following considerations. A reduction in intracranial bleeding would have a greater impact on mortality than a reduction in extracranial bleeding, given the higher case-fatality rate of intracranial than extracranial bleeding (45–50% vs. 7–8%) [16–18]. In line with this reasoning, there is increasing recognition of bleeding as a determinant of overall mortality, whether directly or through the unintended development of thromboembolic consequences owing to anticoagulant interruption [15]. Moreover, a reduction in intracranial bleeding may reflect a lesser tendency for patients with ischemic stroke to develop hemorrhagic transformation, and may explain, in part, the reduction in vascular mortality with DOACs.

In terms of the clinical applicability of our findings, an NNT of 313 with DOACs (instead of warfarin) to prevent one bleeding-related death (over a 1.8–2.8-year treatment duration) should be considered at an individual level and a population level. To provide some perspective, an NNT of 400 with 7–10 days of anticoagulant therapy is required to prevent one fatal pulmonary embolism in hospitalized medical patients [19], and an NNT of 26 with ~ 1 year of β-blocker therapy is required to prevent one cardiovascular death in patients with heart failure [20]. Thus, at an individual level, the need to treat > 300 patients for at least 2 years with a DOAC instead of warfarin to prevent a single bleeding death may not appear compelling. On the other hand, at a population level, such a modest benefit is magnified, given the increasing prevalence of AF, estimated at 2.7–6.1 million in 2010 and expected to be 5.6–12 million in 2050 in the USA alone [21]. Of course, this formulation does not account for the morbidity benefit of DOACs, which collectively confer reductions in non-fatal stroke or systemic embolism and bleeding as compared with warfarin [7].

We acknowledge limitations of this meta-analysis and the interpretation of our findings. First, it is likely that most causes of death, whether vascular-related or bleeding-related, were not based on autopsy confirmation, given the low autopsy rates in current practice. Consequently, although it is likely that some deaths were misclassified, such misclassification would be balanced across DOAC or warfarin treatments in a randomized trial, and would not affect our findings. Similarly, although the thrombotic risk profiles of the patients were different among the trials ($CHADS_2$ scores of 2.1 in the RE-LY and ARISTOTLE trials, 2.8 in the ENGAGE-AF TIMI 48 trial, and 3.5 in the ROCKET-AF trial), these, too, would be balanced across treatments. Finally, there was a wide range of median time in therapeutic range (TTR) among warfarin-treated patients in the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials, with the lowest median TTR in the ROCKET-AF trial (58%) and the highest in the ENGAGE AF-TIMI 48 trial (68.4%). Although this might favor DOAC treatment in those trials with a worse TTR in warfarin-treated patients, this did not affect our findings, as the reduction in bleeding mortality was consistent across trials. Third, it is worth noting that the NNT derived from this meta-analysis is related to the absolute baseline risk, which may be different in a 'real-life' cohort. Finally, despite the apparent absence of significant heterogeneity, the I^2 and chi-square metrics are not powered to detect heterogeneity when there are few included studies. However, Egger's regression intercept test showed that all of the estimates for the four outcomes went in the same direction, despite the inclusion of only four trials in this meta-analysis. Therefore, taking these findings together, their direct extrapolation to the total population of patients with AF should be interpreted with caution.

Table 2 Summary of the assessment of the risk of bias within studies by use of the Cochrane Collaboration tool

	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE AF-TIMI 48
Random sequence generation	+	+	+	+
Allocation concealment	+	+	+	+
Blinding of participants and personnel	?	+	+	+
Blinding of outcome assessment	+	+	+	+
Incomplete outcome data	+	+	+	+
Selective reporting	+	+	+	+
Other sources of bias	+	+	+	+

+, low risk of bias; ?, unclear risk of bias; −, high risk of bias.

Conclusion

In summary, we found that, as compared with warfarin therapy for stroke prevention in AF, treatment with a DOAC reduces overall mortality. This mortality benefit appears to be driven by reductions in vascular-related and bleeding-related mortality, which, in turn, may be related to the observed reduction in intracranial bleeding.

Addendum

A. Liew and J. Douketis data collection, analysis, and interpretation. All authors made substantial contributions to the concept and design of the study, were involved in the writing and critical revision of the manuscript, and gave final approval of the version to be submitted.

Disclosure of Conflict of Interests

A. Liew has received educational and research support from AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Merck Sharpe & Dohme, Novo Nordisk, Novartis, Sanofi Aventis, and Medtronic. M. O'Donnell has received an unrestricted education grant and honoraria from Boehringer-Ingelheim, Pfizer, Bristol Myers Squibb, and Sanofi Aventis. J. Douketis was a consultant for Boehringer-Ingelheim, and served as a consultant during advisory board meetings (Sanofi-Aventis, AstraZeneca, Boehringer-Ingelheim, and Bristol Myers Squibb) relating to the development and clinical use of novel antiplatelet drugs (ticagrelor) and anticoagulant drugs (apixaban, semuloparin [not approved for clinical use], and dabigatran).

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Subgroup analysis (standard-dose vs. low-dose DOAC) of efficacy and safety outcomes in the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials.
Table S2. Assessment of the risk of bias within studies by use of the Cochrane Collaboration tool (including the support for judgement).
Appendix S1. PRISMA Checklist.
Appendix S2. PubMed search strategy.
Appendix S3. www.clinicaltrials.gov search strategy.

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