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SYSTEMATIC REVIEW

Direct oral anticoagulants for stroke prevention in patients with atrial fibrillation: meta-analysis by geographic region with a focus on European patients

Correspondence Dr Antonio Gómez-Outes, Division of Pharmacology and Clinical Drug Evaluation, Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Campezo 1, 28022 Madrid (Spain). Tel.: +034 9182 25751; Fax: +034 9182 25161; E-mail: agomezo@aemps.es

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Antonio Gómez-Outes[1], Ana-Isabel Terleira-Fernández[2,3], Gonzalo Calvo-Rojas[4], M. Luisa Suárez-Gea[1] and Emilio Vargas-Castrillón[2,3]

[1]Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Madrid, Spain, [2]Hospital Clínico San Carlos, Madrid, Spain, [3]Universidad Complutense, Madrid, Spain, and [4]Hospital Clinic, Barcelona, Spain

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AIMS

To analyse clinical outcomes with direct oral anticoagulants in patients with atrial fibrillation according to geographic region.

METHODS

We systematically searched MEDLINE, CENTRAL, websites of regulatory agencies, clinical trials registers and conference proceedings for randomized controlled trials of direct oral anticoagulants (DOAC: dabigatran, rivaroxaban, apixaban or edoxaban) against warfarin for prophylaxis of stroke and systemic embolic events (SEE) in patients with atrial fibrillation (AF). Two investigators independently extracted data. Relative risks of stroke and SEE as well as major bleeding depending on geographic region were estimated using a random effect meta-analysis.

RESULTS

Five trials in 72 963 patients were analysed; 32 089 (44%) patients were recruited in Europe (Western Europe: 13 676; Eastern Europe: 18 413). We found significant subgroup differences for stroke/SEE depending on the geographic region (interaction $P = 0.003$; I^2 88.5%), with a neutral effect of the DOAC *vs.* warfarin in Europe [relative risk (RR) 0.97, 95% confidence interval (CI) 0.85–1.11, I^2 0%] and a significant reduction of stroke/SEE in other regions including North America, Latin America and Asia-Pacific/other (RR 0.72, 95% CI 0.63–0.83, I^2 33%). There was a similar reduction in risk of major bleeding in Europe (RR 0.82, 95% CI 0.73–0.92, I^2 0%) and in other regions (RR 0.86, 95% CI 0.72–1.02, I^2 78%).

CONCLUSION

The DOAC did not provide additional benefit in reducing the risk of stroke/SEE compared with warfarin in European patients with AF, but were generally associated with a lower bleeding tendency than warfarin regardless of geographic region.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Dabigatran, rivaroxaban, apixaban and edoxaban are direct-acting oral anticoagulants (DOAC) licensed for stroke prevention in atrial fibrillation.
- Pivotal trials in atrial fibrillation included a heterogeneous population from worldwide regions with different standards of care.
- It is uncertain whether there are regional differences in the effect of the DOAC on stroke and major bleeding in comparison with warfarin.

WHAT THIS STUDY ADDS

- Our meta-analysis shows significant differences in the relative efficacy of the DOAC versus warfarin depending on geographic region.
- Compared with warfarin, the novel compounds did not reduce the risk of stroke and systemic embolism in European patients, but were generally associated with a lower bleeding tendency than warfarin in Europe and other regions.
- Geographic differences found in our meta-analysis appear mainly related to regional variations in stroke rates with warfarin.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the developed world, being associated with a five-fold risk of stroke and higher mortality [1]. Warfarin and other vitamin K antagonists (VKA) are highly effective treatments in reducing the risk of stroke, but their management remains problematic due to their narrow therapeutic index and variability in drug exposure, necessitating routine coagulation monitoring [international normalized ratio (INR)], clinical surveillance and continuous patient education.

In recent years, several direct-acting oral anticoagulants (DOAC) (dabigatran, rivaroxaban, apixaban and edoxaban) [2], also referred to in the literature as "novel anticoagulants" or "non-vitamin K antagonist oral anticoagulants" (NOAC) and "target-specific oral anticoagulants" (TSOAC), have been developed to overcome some of these limitations. The pivotal studies that support the use of DOAC for prevention of stroke and systemic embolic events (SEE) in AF have encompassed a heterogeneous population from worldwide regions with different standards of medical care. Globally, these studies have shown a benefit of DOAC compared with warfarin in reducing stroke/SEE, as well as intracranial bleeding (ICB) and mortality [3]. The assessment of the "transferability" of multinational trials to specific countries or regions [4] is a hot issue that may have important consequences for the cost-effectiveness analyses and recommendations for use that are usually based on the global results of these pivotal studies. Several subanalyses and reviews of results in Asian patients *vs*. non-Asians have been published recently [5]. In Asia, the DOAC seems to provide the highest clinical benefit compared with warfarin. However, no comprehensive review of disaggregated results in other geographic regions is currently available.

We systematically reviewed and meta-analysed data from randomized controlled trials of the DOAC for prophylaxis against stroke/SEE in patients with AF according to geographic region to assess if the overall study results can be transferred to the European population. We made direct comparisons between the DOAC and warfarin on the clinical outcomes of stroke/SEE and major bleeding depending on geographic region.

Methods

Eligibility criteria

We considered randomized controlled trials comparing any of the approved new oral anticoagulants (rivaroxaban, dabigatran, apixaban and edoxaban) with warfarin in patients with AF at risk of stroke/SEE and at least one year follow-up.

The doses tested in the experimental arms had to correspond to the doses approved for the DOAC in this indication [2]. We included the dabigatran low dose (110 mg twice daily) in addition to the dabigatran high dose (150 mg twice daily), because the low dose is recommended in a significant proportion of the target population (patients ≥80 yr, concomitant verapamil or high risk of bleeding) [2], and no differences in efficacy between the high and low dabigatran dose have been observed in the long term [6]. However, we excluded the edoxaban low dose in the base case analysis (30 mg once daily, reduced to 15 mg in patients with presumed increased exposure), because it has not been approved for use in Europe and North America in this indication.

Trial identification and data collection

We searched Medline and CENTRAL (up to July 2015), websites of regulatory agencies, clinical trial registries and relevant conference proceedings (Appendix S1). No language restrictions were applied. Two investigators (AG-O and AIT-F) independently and separately assessed trials for eligibility and extracted data. If a trial was covered in more than one report, we used the following hierarchy of data sources: public reports from regulatory authorities, peer reviewed articles, reports from the web-based repository for results of clinical studies and other sources. Finally, we contacted the main investigators to retrieve unpublished data from clinical trials (demographic characteristics and data on ICB and deaths by region). In case of no response, we sent a reminder to the main investigator after one week, with a copy to a Sponsor's representative (e.g., co-author(s) being employee(s) of the Sponsor).

Study characteristics and quality assessment

We collected data on patients' characteristics, numbers of patients evaluable for efficacy and safety, dosage used

in the experimental and control groups, duration of treatment and follow-up, inclusion and exclusion criteria. We assessed study quality using the Cochrane Collaboration's tool for assessing risk of bias in randomized studies [7]. Additionally, we used the Jadad scale to assess study quality [8].

Outcome measures

The pre-specified primary outcome was stroke/SEE. The pre-specified primary safety outcome was major bleeding. We also aimed to retrieve data on ICB and all-cause death as secondary outcomes whenever possible.

Quantitative data synthesis

We conducted this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations [9]. We used the intention-to-treat population for efficacy and safety whenever available. We calculated relative risks (RR) and their respective 95% confidence intervals (CI) for each study and for the pooled studies. Heterogeneity within subgroups and interaction between subgroups was assessed using the Cochran Q test and the Higgins I^2 test. A Cochran's Q $P < 0.05$ and $I^2 > 50\%$ within subgroups indicates significant heterogeneity, and between subgroups indicates statistically significant interaction (subgroup differences). We used the random effects model described by Der-Simonian and Laird [10] for the main analysis.

The base case was focused on the dichotomized comparison of RR of events in Europe *vs*. other regions. We also conducted a secondary analysis of the data in each of the regions defined within the trials (Western Europe, Eastern Europe, North America, Latin America and Asia-Pacific). We conducted sensitivity analyses taking into account different methodological issues that could influence the results of the meta-analysis: (a) geographic region definition (Western Europe instead of all Europe *vs*. other regions); (b) DOAC doses tested (not excluding the 30/15 mg edoxaban low dosing; excluding the 110 mg dabigatran dose); (c) statistical model (fixed effects instead of the random effects model); (d) type of measure (absolute risk or odds ratio instead of RR); (e) adjustment by exposure (events by patient-years instead of events by patients); (f) study location (only multinational studies instead of all studies); and (g) study quality (studies at low risk of bias instead of all studies). We also conducted a proportion meta-analysis within treatment groups to describe the average rate of events in each treatment group by trial and geographic region adjusted by exposure (per patient-year of follow-up on the basis of the mean reported follow-up). Rates of events were expressed per 100 patient-years (%/yr) to standardize different follow-up durations across studies.

Direct comparisons were carried out using the RevMan statistical software, version 5.1 (Nordic Cochrane Center). The descriptive analysis of event rates by treatment group and region was performed using StatsDirect software, version 2.8.0 (StatsDirect Ltd, Cheshire, United Kingdom).

Results

Study selection, design and methodology

The literature search identified 3784 articles, 356 of which related to clinical trials or protocols with rivaroxaban, dabigatran, apixaban or edoxaban (Figure 1). Of these, 11 were clinical trials in AF, and were selected for checking as full text. Five of the 11 studies were eligible for inclusion [11–15] and the remaining six were excluded because they were Phase II studies with insufficient follow-up or used aspirin as control rather than warfarin [16–21]. Additional data from included trials were obtained from Food and Drug Administration (FDA) reviews and in a subanalysis of dabigatran in AF [22–25].

The five studies comprised 72 963 patients (Table 1). Four of them were multinational studies that compared dabigatran [11], rivaroxaban [12], apixaban [13] and edoxaban [14] with warfarin in AF. The remaining trial corresponded to a Phase III study with rivaroxaban conducted in Japan only [15]. The risk of bias was low in three studies [12–14] and unclear in RE-LY due to lack of double-blinding [11], and J ROCKET due to no reporting of allocation concealment [15] (Appendix S2). For the same reasons, three studies scored five points in the Jadad scale [12–14] and the remaining two studies [11, 15] scored four points (Table 1).

Mean or median age ranged between 70 and 73 years (Table 2). There was predominance of men (range: 60–81%) and permanent/persistent AF (range: 67–83%). Mean thromboembolic risk ($CHADS_2$) ranged between 2.1 (RE-LY and ARISTOTLE) to 3.5 (ROCKET AF). History of prior stroke or transient ischemic attack ranged between 19% and 64%, and rate of VKA naive patients ranged from 10% to 50%.

A total of 32 089 patients (44%) were recruited in Europe, while 40 874 (56%) were recruited in other regions. For detailed information on the definitions of geographic regions and countries by trial as well as the pooling strategy by region, please see Appendix S3.

Demographic characteristics by region were available from the RE-LY study (kindly provided by the Sponsor after request) and collected for the ROCKET-AF study from a secondary

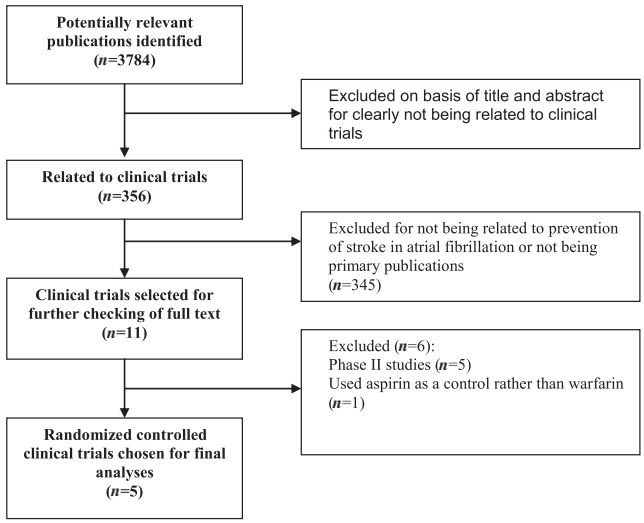


Figure 1
Study identification, selection and exclusions

Table 1

Characteristics of trials included in the systematic review

Characteristic	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF	J ROCKET
N Randomized*	18 113	14 264	18 201	21 105	1280
ITT patients*	18 113	14 171	18 201	21 026	1280
Safety patients	18 113	14 236	18 201	21 026	1278
Patient-years	31 273	22 493	30 943	46 888	1718
Experimental drug	Dabigatran 150 mg and 110 mg twice daily	Rivaroxaban 20 mg once daily†	Apixaban 5 mg twice daily†	Edoxaban 60 mg and 30 mg once daily†	Rivaroxaban 15 mg once daily†
Exposure, mean (yrs)	1.69–1.71	1.57	1.72	2.21–2.26	1.37
Control drug	Warfarin‡	Warfarin‡	Warfarin‡	Warfarin‡	Warfarin‡
Exposure, mean (yrs)	1.78	1.59	1.68	2–22	1.32
TTR (%), mean	64.4	55.2	62.2	65	65
Median follow-up (yrs)	2	1.9	1.8	2.8	1.3
Trial phase	III	III	III	III	III
Design	Open-label PROBE	Double-blind	Double-blind	Double-blind	Double-blind
Non-inferiority margin	1.46	1.46	1.44	1.38	2.00§
Main efficacy outcome	Stroke or SEE	Stroke or SEE	Stroke or SEE	Stroke or SEE	Stroke or SEE
Main safety outcome	Major bleeding	Clinically relevant bleeding	Major bleeding	Major bleeding	Clinically relevant bleeding
Pre-specified subgroup analysis by region?	Yes	Yes	Yes	Yes	No
Randomization stratified by centre/geographic region?	NA	Yes	Yes	No	No
Risk of bias (Cochrane)	Unclear	Low	Low	Low	Unclear
Jadad Score	4	5	5	5	4

NA, not available; PROBE, Prospective, randomized, open-label, blinded-endpoint. *Randomized patients in RE-LY, J ROCKET and ARISTOTLE; ITT to site notification in ROCKET AF; mITT on-treatment in ENGAGE. †Dose-reduction was applied in patients with CrCl 15–50 ml min^{-1} (rivaroxaban: from 20 mg to 15 mg in ROCKET AF; from 15 mg to 10 mg in J ROCKET), in patients with at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg or serum creatinine ≥ 1.5 mg dl^{-1} (apixaban: from 5 mg to 2.5 mg twice daily) and in patients with a CrCl 30–50 ml min^{-1}, a body weight ≤ 60 kg or concomitant potent P-gp inhibitors (edoxaban: from 60 mg to 30 mg once daily in the high dosing group; from 30 mg to 15 mg once daily in the low dosing group). ‡Dose adjusted to an international normalized ratio (INR) between 2 and 3, once daily. §Non-inferiority was focused on efficacy in all studies with the exception of J ROCKET, in which non-inferiority was focused on clinically relevant bleeding.

publication of the study [26] (Appendix S4). Patients recruited in Europe and North America had a much higher mean body weight than patients recruited in Latin America and Asia. History of prior stroke or transient ischemic attack (TIA) at study enrolment was more frequent among Asian patients, while VKA-experienced patients were more frequent in Western Europe and North America. Highest mean percentage time in therapeutic INR range (TTR) was reported in Western Europe (69%) and lowest in Asia (53–55%) (Appendix S5).

Descriptive analysis of event rates

Pooled stroke/SEE rates with the DOAC were the lowest in North America (1.3%/yr) and the highest in Asia (2.1%/yr) (Table 3). Pooled stroke/SEE with warfarin ranged from 1.4%/yr in Western Europe to 2.9%/yr in Asia. There was also variability across trials, with the highest stroke rates in both treatment arms observed in ROCKET AF.

Pooled major bleeding rates with the DOACs showed variability across regions, ranging from 1.7%/yr in Eastern Europe to 4.7%/yr in North America. The same trend, though less pronounced, was apparent in the warfarin arm, with major bleeding rates ranging from 2.1%/yr in Eastern Europe to 4.6%/yr in North America. There was variability in major bleeding rates across trials, being more pronounced within the DOAC groups than within the warfarin groups (Table 3).

Rates of ICB and deaths by region were not available from the literature search and were requested from the main investigators of the studies. A positive response was obtained from the main investigator of the RE-LY trial (Dr. Connolly) who delegated to the Sponsor who kindly provided the data (Appendix S5). Asian patients had the highest rate of ICB (1.1%/yr) and patients from Latin America had the highest mortality rates (6.2%/yr) with warfarin, while European patients had the lowest rates of both ICB (0.6% yr) and mortality (3.8%/yr) with warfarin.

Primary efficacy outcome: stroke and systemic embolism

We found significant subgroup differences for stroke/SEE depending on the geographic region (P for interaction = 0.003; I^2 = 88.5%) with a neutral effect of the DOAC *vs*. warfarin in Europe (RR 0.97; 95% CI 0.85–1.11; I^2 0%) and a significant reduction of stroke/SEE in other regions (RR 0.72; 95% CI 0.63–0.83; I^2 33%) (Figure 2).

The analysis was repeated for the five disaggregated regions (Western Europe, Eastern Europe, North America, Latin America, Asia-Pacific), and subgroup differences still remained

Table 2

Characteristics of patients

Characteristic	Drug, trial				
	Dabigatran RE-LY	Rivaroxaban ROCKET AF	Apixaban ARISTOTLE	Edoxaban ENGAGE AF	Rivaroxaban J ROCKET
Randomized	18 113	14 264	18 201	21 105	1280
Age (years)	72 (mean)	73 (median)	70 (median)	72 (median)	71 (mean)
Male gender (%)	64	60	65	62	81
Atrial fibrillation type					
Permanent/persistent (%)	67	81	83	75	NA
Paroxysmal (%)	33	18	17	25	NA
$CHADS_2$ score (mean)	2.1	3.5	2.1	2.8	3.3
Prior stroke/TIA (%)	20	55	19	28	64
VKA naive (%)	50	37	43	41	10
Region*					
Europe, *n* (%)	6770 (38)	7596 (53)	7343 (40)	10 380 (49)	0 (0)
Western Europe	4651 (26)	2096 (15)	3693 (20)	3236 (15)	—
Eastern Europe	2119 (12)	5500 (38)	3650 (20)	7144 (34)	—
Other regions, *n* (%)	11 343 (62)	6668 (47)	10 858 (60)	10 725 (51)	1280 (100)
North America	6533 (36)	2681 (19)	4474 (25)	4681 (22)	—
Latin America	956 (5)	1878 (13)	3468 (19)	2661 (13)	—
Asia Pacific, other	3854 (21)	2109 (15)	2916 (16)	3383 (16)	1280 (100)

NA, not available. *The distribution by region corresponds to randomized patients. Calculation of numbers of patients enrolled in Western and Eastern Europe in ARISTOTLE was made based on patients enrolled by countries (see Supplementary Appendix).

statistically significant (P for interaction = 0.02; I^2 65.3%) (Figure 2). Across European sub-regions, the point estimate for the RR of stroke tended to favour warfarin in Western Europe, particularly in ARISTOTLE and ENGAGE, and to slightly favour the DOAC in Eastern Europe, without statistically significant differences between the DOAC and warfarin. DOAC significantly reduced the RR of stroke/SEE in other regions, with a more pronounced effect in Asia and Latin America.

Primary safety outcome: major bleeding

There was a similar reduction in risk of major bleeding in Europe (RR 0.82; 95% CI 0.73–0.92) and in other regions (RR 0.86, 95% CI 0.72–1.02) (P for interaction = 0.66; I^2 0%) (Figure 3). However, there was evidence of statistical heterogeneity within other regions (P = 0.001; I^2 78%) (Figure 3).

In Western Europe, the RR of bleeding was lower in ARISTOTLE and in ENGAGE than in the other studies. In other regions, the heterogeneity was mainly due to the increase in major bleeding observed in North America in the ROCKET-AF study (see also the discussion for potential explanations) and, to a lesser extent, by the high relative reduction in risk of major bleeding (47%) reported in Asian patients in ARISTOTLE (Figure 3).

Sensitivity analyses

All the ten sensitivity analyses conducted to explore the geographic differences in the effect on stroke/SEE showed statistically significant results (Appendix S6) that were consistent with the primary analysis. Geographic differences were apparent regardless of included/excluded doses of the DOAC, European region definition, statistical model, adjustment by exposure, effect measure, exclusion of studies conducted in a single region (J ROCKET) and exclusion of studies at uncertain risk of bias (RE-LY and J ROCKET).

Consistent with the primary analysis of major bleeding, none of the ten sensitivity analyses showed geographic differences in the effect on major bleeding (Appendix S6).

Absolute difference in events per 1000 patients treated per year in the various regional subgroups

There were no significant differences between the DOAC and warfarin in stroke/SEE events per 1000 patient-years in Europe (Dif.: 0 events; 95% CI −2 to 2) (Table 4). On the contrary, significant reductions in stroke/SEE were found in other regions (Table 4), ranging between four events avoided in North America, six events avoided in Latin America and nine events avoided in Asia per 1000 patient-years.

The DOAC significantly avoided four major bleeding events per 1000 patient-years in comparison with warfarin in Europe. The reduction in bleeding events was particularly high in Asia and Latin America, in which the DOAC avoided 11 and 7 additional major bleedings per 1000 patient-years compared with warfarin, respectively (Table 4). Finally, rivaroxaban tended to increase the number of major bleeding events compared with warfarin in North America (potential explanations are included in the Discussion).

Selective outcome reporting, dissemination bias and missing data

Subgroups by geographic region for the main efficacy and safety outcomes were pre-specified in the protocols and

Table 3

Descriptive analysis of events by trial and region and adjusted event rates per 100 patients per year

Characteristic	Type of direct oral anticoagulant, trial events (%/year)					Total* %/year
	Dabigatran RE-LY	Rivaroxaban ROCKET AF	Apixaban ARISTOTLE	Edoxaban ENGAGE AF	Rivaroxaban J ROCKET	
Stroke/SEE						
Direct oral anticoagulants						
Europe pooled, n (%)	111 (1.4)	140 (2.4)	75 (1.2)	104 (1.4)	—	1.6 (1.1–2.1)
Western Europe	80 (1.5)	40 (2.4)	30 (0.9)	37 (1.6)	—	1.6 (1.1–2.1)
Eastern Europe	31 (1.3)	100 (2.4)	45 (1.4)	67 (1.3)	—	1.6 (1.1–2.1)
Other regions pooled, n (%)	206 (1.6)	129 (2.5)	137 (1.5)	78 (1.0)	22 (2.5)	1.7 (1.2–2.2)
North America	103 (1.4)	47 (2.2)	42 (1.1)	23 (0.7)	—	1.3 (0.8–1.9)
Latin America	15 (1.4)	37 (2.5)	43 (1.4)	20 (1.0)	—	1.6 (1.0–2.2)
Asia Pacific, other	88 (2.0)	45 (2.7)	52 (2.1)	35 (1.4)	22 (2.5)	2.1 (1.7–2.5)
Warfarin						
Europe pooled, n (%)	58 (1.4)	157 (2.6)	77 (1.2)	93 (1.2)	—	1.6 (1.0–2.3)
Western Europe	45 (1.6)	43 (2.6)	25 (0.8)	25 (1.1)	—	1.4 (0.8–2.2)
Eastern Europe	13 (1.0)	114 (2.6)	52 (1.7)	68 (1.3)	—	1.7 (1.0–2.4)
Other regions pooled, n (%)	144 (2.1)	149 (2.8)	188 (2.1)	139 (1.8)	26 (3.1)	2.3 (1.9–2.7)
North America	67 (1.7)	50 (2.3)	56 (1.5)	42 (1.2)	—	1.7 (1.3–2.1)
Latin America	9 (1.6)	45 (3.0)	52 (1.8)	42 (2.1)	—	2.2 (1.6–2.8)
Asia Pacific, other	68 (3.0)	54 (3.2)	80 (3.2)	55 (2.2)	26 (3.1)	2.9 (2.5–3.4)
Major bleeding						
Direct oral anticoagulants						
Europe pooled, n (%)	180 (2.3)	137 (2.3)	110 (1.7)	150 (2.0)	—	2.1 (1.8–2.4)
Western Europe	131 (2.5)	49 (3.0)	74 (2.3)	71 (3.0)	—	2.6 (2.3–3.0)
Eastern Europe	49 (2.0)	88 (2.0)	36 (1.1)	79 (1.5)	—	1.7 (1.3–2.1)
Other regions pooled, n (%)	561 (4.4)	258 (4.9)	217 (2.3)	268 (3.4)	23 (2.6)	3.5 (2.6–4.6)
North America	403 (5.4)	149 (7.1)	106 (2.7)	135 (3.9)	—	4.7 (3.1–6.5)
Latin America	26 (2.4)	46 (3.1)	60 (2.0)	48 (2.5)	—	2.5 (2.0–3.0)
Asia Pacific, other	132 (3.0)	63 (2.9)	51 (2.0)	85 (3.4)	23 (2.6)	3.0 (2.4–3.6)
Warfarin						
Europe pooled, n (%)	104 (2.6)	153 (2.5)	135 (2.2)	206 (2.7)	—	2.5 (2.3–2.7)
Western Europe	80 (2.9)	69 (4.1)	77 (2.5)	86 (3.6)	—	3.2 (2.6–4.0)
Eastern Europe	24 (1.9)	84 (1.9)	58 (1.9)	120 (2.3)	—	2.1 (1.8–2.3)
Other regions pooled, n (%)	317 (4.7)	233 (4.4)	327 (3.6)	318 (4.0)	27 (3.2)	4.1 (3.6–4.6)
North America	209 (5.4)	111 (5.2)	137 (3.7)	152 (4.4)	—	4.6 (3.9–5.5)
Latin America	17 (3.0)	41 (2.7)	94 (3.2)	67 (3.4)	—	3.2 (2.8–3.6)
Asia Pacific, other	91 (4.0)	81 (4.8)	96 (3.9)	99 (4.0)	27 (3.2)	4.1 (3.7–4.5)

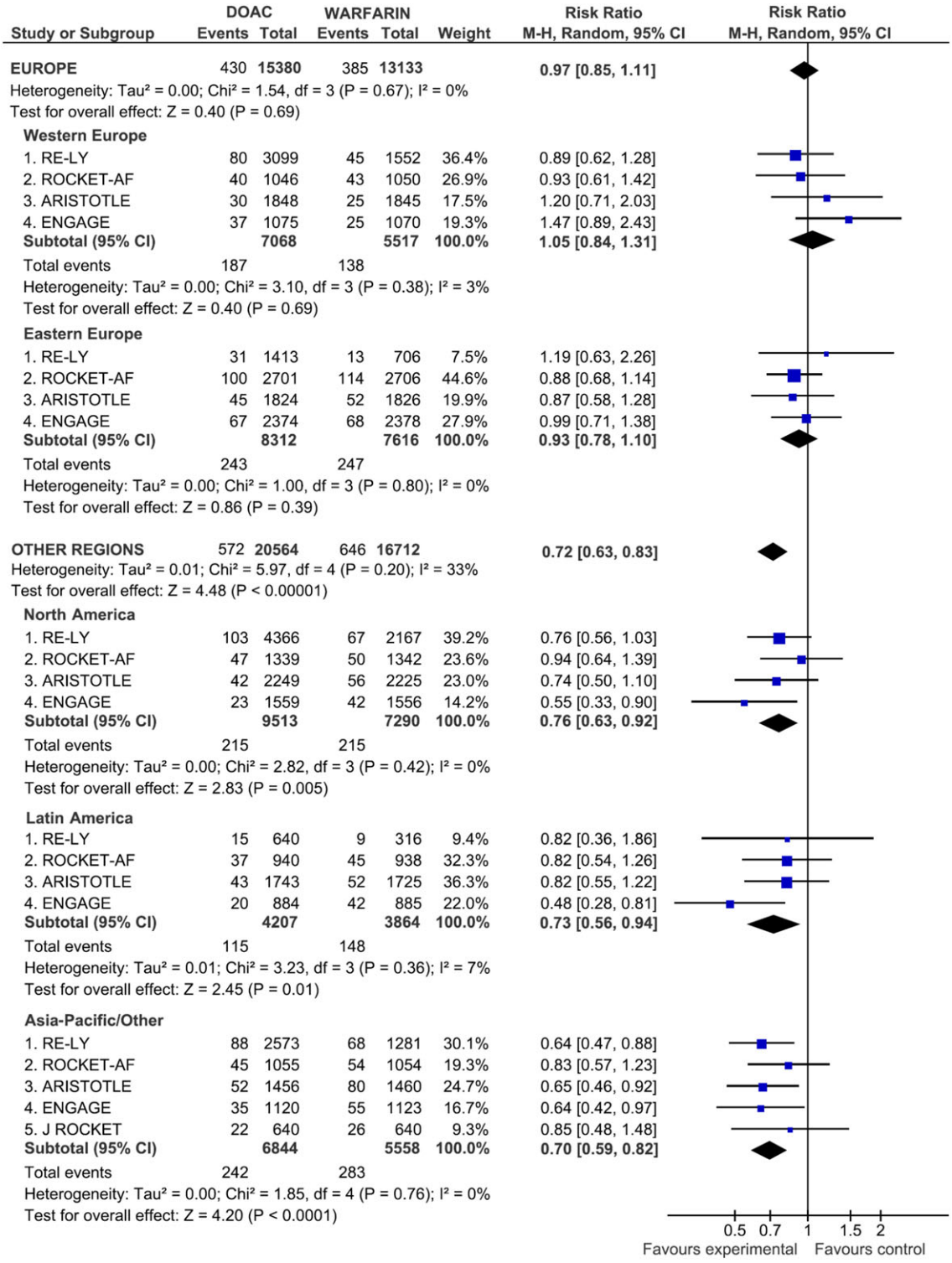
SEE, systemic embolic events. *Proportion meta-analysis, random effects model, StatsDirect software.

reported in the publications or regulatory reviews of the large multicentre studies included in this meta-analysis. There were three trials with missing outcome data for secondary outcomes (intracranial bleeding and mortality) where we were unable to obtain the data from the authors.

Discussion

This systematic review and meta-analysis indicates that, although the DOAC have a positive benefit-risk balance for prevention of stroke/SEE, the extent of such benefit may differ between geographic regions according to differences in stroke rates with warfarin. Asia and Latin America were the regions in which the effect of the DOAC over warfarin on stroke/SEE was more relevant, while no significant reduction of stroke/SEE was apparent in Europe, which comprised approximately 32 000 patients and 59 000 patient-years in these trials. The robustness of the results is strongly supported by ten sensitivity analyses.

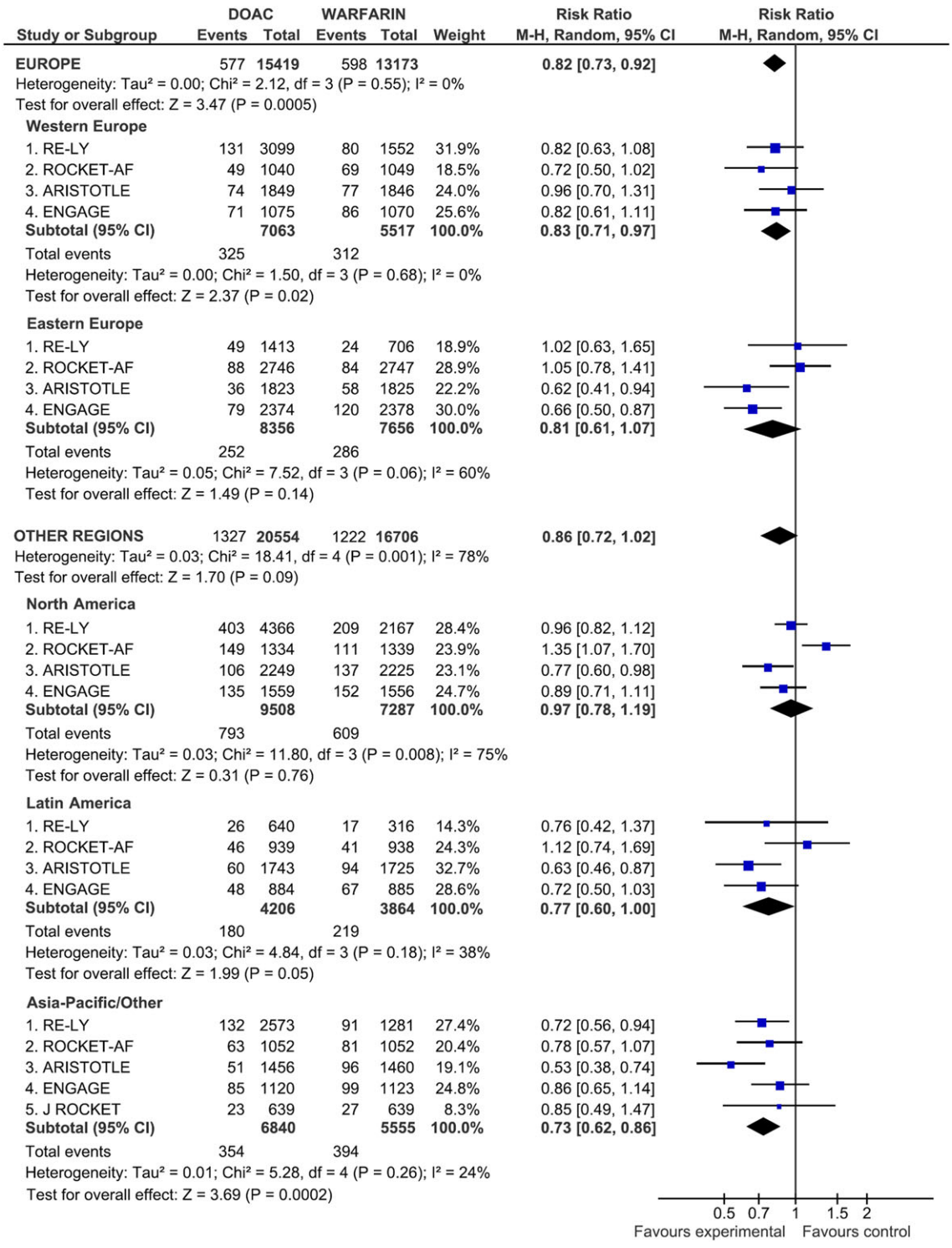
To the best of our knowledge, this is the first systematic review to explore the efficacy and safety of the DOAC in each of the geographical regions included in the Phase III clinical trials conducted with the new compounds for the prevention of stroke/SEE in patients with AF. A previous relevant meta-analysis reviewed the pivotal trials of the DOAC in AF [3], but did not analyse the efficacy and safety across



Interaction tests:
Europe vs. other regions: Cochran's Q test *P*-value = 0.003; Higgins $I^2 = 88.5\%$
Western Europe vs. Eastern Europe vs. North America vs. South America vs. Asia-Pacific/other: Cochran's Q test *P*-value = 0.02; Higgins $I^2 = 65.3\%$

Figure 2

Stroke/SEE in Europe (Western and Eastern Europe) and other regions (North America, South America, Asia-Pacific/Other)



Interaction tests:
Europe vs. other regions: Cochran's Q test *P*-value = 0.66; Higgins $I^2 = 0\%$
Western Europe vs. Eastern Europe vs. North America vs. South America vs. Asia-Pacific/other: Cochran's Q test *P*-value = 0.35; Higgins $I^2 = 9\%$

Figure 3

Major bleeding in Europe (Western and Eastern Europe) and other regions (North America, South America, Asia-Pacific/Other)

Table 4

Absolute difference in events per 1000 patients treated per year in the various regional subgroups*

Comparison	Stroke/SEE Risk difference (95%CI)	Major bleeding Risk difference (95%CI)
All Europe (*n* = 32 089)		
Dabigatran *vs.* warfarin	0 (−5 to 5)	−2 (−8 to 4)
Rivaroxaban *vs.* warfarin	−2 (−8 to 3)	−2 (−8 to 3)
Apixaban *vs.* warfarin	−1 (−4 to 3)	−4 (−9 to 0.4)
Edoxaban *vs.* warfarin	2 (−2 to 5)	−7 (−12 to −2)
All DOACs vs. warfarin	0 (−2 to 2)	−4 (−7 to − 2)
Western Europe (*n* = 13 676)		
Dabigatran *vs.* warfarin	−2 (−7 to 5)	−4 (−12 to 3)
Rivaroxaban *vs.* warfarin	−1 (−12 to 10)	−11 (−24 to 1)
Apixaban *vs.* warfarin	1 (−3 to 6)	−2 (−9 to 6)
Edoxaban *vs.* warfarin	5 (−1 to 12)	−6 (−17 to 4)
All DOACs vs. warfarin	1 (−1 to 4)	−5 (−10 to − 0.1)
Eastern Europe (*n* = 18 413)		
Dabigatran *vs.* warfarin	3 (−5 to 10)	1 (−8 to 11)
Rivaroxaban *vs.* warfarin	−3 (−10 to 4)	1 (−5 to 7)
Apixaban *vs.* warfarin	−3 (−9 to 4)	−7 (−14 to −1)
Edoxaban *vs.* warfarin	0 (−4 to 4)	−8 (−13 to −3)
All DOACs vs. warfarin	−1 (−4 to 2)	−4 (−9 to 1)
North-America (*n* = 18 369)		
Dabigatran *vs.* warfarin	−4 (−8 to 1)	0 (−9 to 9)
Rivaroxaban *vs.* warfarin	−1 (−10 to 8)	19 (5 to 34)
Apixaban *vs.* warfarin	−4 (−9 to 1)	−9 (−17 to −1)
Edoxaban *vs.* warfarin	−6 (−10 to −1)	−5 (−14 to 5)
All DOACs vs. warfarin	−4 (−7 to − 2)	0 (−10 to 10)
Latin-America (*n* = 8963)		
Dabigatran *vs.* warfarin	−2 (−15 to 10)	−6 (−23 to 11)
Rivaroxaban *vs.* warfarin	−5 (−17 to 7)	4 (−8 to 16)
Apixaban *vs.* warfarin	−4 (−10 to 3)	−12 (−21 to −4)
Edoxaban *vs.* warfarin	−11 (−19 to −3)	−10 (−20 to 1)
All DOACs vs. warfarin	−6 (−10 to − 2)	−7 (−14 to − 0.1)
Asia Pacific, other (*n* = 13 542)		
Dabigatran *vs.* warfarin	−10 (−18 to −2)	−10 (−20 to −0.2)
Rivaroxaban *vs.* warfarin†	−5 (−15 to 4)	−8 (−19 to 2)
Apixaban *vs.* warfarin	−12 (−21 to −3)	−19 (−28 to −9)
Edoxaban *vs.* warfarin	−8 (−15 to −1)	−5 (−16 to 5)
All DOACs vs. warfarin	−9 (−13 to − 5)	−11 (−16 to − 6)

CI, confidence interval; DOAC, direct oral anticoagulants; SEE, systemic embolic events. *Random effects model. The base case excludes the 30 mg/15 mg edoxaban dose. †Includes pooled data from ROCKET-AF (subgroup of Asian patients) and J ROCKET.

geographical regions. A relevant Cochrane review [27] focused only on two direct thrombin inhibitors [dabigatran (Pradaxa) and ximelagatran (Exanta; withdrawn from the market due to liver toxicity)], and did not include an analysis by geographic region. In addition, none of these reviews included a calculation of event rates corrected by exposure (events per 100 patients per year) that are important to ascertain the absolute differences between treatments and, therefore, the clinical relevance of the effect.

While there are benefits from trial globalization in terms of the worldwide evaluation of safety and efficacy, differences in degree of development, medical culture and standard of care raise important questions about the impact of the trial and the comparability of individual national/regional outcomes to the total international population [28]. Exploring the causes of heterogeneity across regions is a necessary exercise demanded by healthcare providers and may be informative for healthcare professionals and patients.

The benefit of oral anticoagulation with VKA is largely dependent on the quality of INR control as measured by the TTR [29, 30]. The quality of anticoagulation with VKA during pivotal studies with the DOAC greatly differed across trials, with the highest TTR reported in Western Europe, and the lowest TTR in centres in Asia and Latin America [26, 31].

These data are consistent with TTR reported across regions in worldwide AF registries [32] and meta-analyses [33]. A recent review of 55 studies on AF shows that patients in Europe have better INR control than those in other regions, as measured by the time spent with the INR in therapeutic range (67% in Europe and between 47% and 61% in other regions) [33], which is broadly consistent with the differences in mean TTR by geographic region reported in our meta-analysis (69% in Western Europe and between 53% and 66% in other regions; see Appendix S4). Therefore, regional differences in quality and organization of care [33], which could comprise among other factors a longer tradition of anticoagulation clinics with good INR control [34], are likely to explain why the relative efficacy of the DOAC *vs*. warfarin was substantially lower in Europe than in other regions. Current analysis of efficacy and safety in the European population is also fully consistent with a previous subgroup analysis that did not show a significant reduction in non-haemorrhagic stroke and SEE with the DOAC at centres that achieved a good quality of anticoagulation, defined as a centre-based TTR of more than 65% [35]. On the other hand, it is reassuring that the DOAC may be considered at least non-inferior to warfarin under the worst case circumstances (European centres and good control of anticoagulation).

With respect to bleeding, our meta-analysis showed a consistent overall reduction in risk of major bleeding across regions with most DOACs, with the more impressive risk reductions in major bleeding reported in Asia. A recent genetic substudy of ENGAGE-AF shows that 62% of Asian patients are sensitive responders to warfarin (defined by combinations of different *CYP2C9* and *VKORC1* genotype functional bins), compared with only 4% of the European population. Sensitive responders spent greater proportions of time over-anticoagulated and had a 31% increased risk of bleeding when compared with normal responders [36]. On the other hand, despite major bleeding risk being significantly reduced in most regions with the DOAC, there was an increase in major bleeding with rivaroxaban (ROCKET AF study) in North America, which was also responsible for the heterogeneity found in this outcome in other regions as compared to Europe. This could be chance finding, but the combination of a high rate of VKA-experienced patients, good TTR with warfarin and the higher prevalence of older patients and co-morbidities associated with higher bleeding rates (e.g., hypertension, anaemia) in North America may also have contributed to these differences [37]. This imbalance raises uncertainty about the real risk of bleeding with the DOAC in fragile populations in comparison with well-managed warfarin.

Finally, data on ICB and all-cause mortality by region could only be obtained from the RE-LY study, which showed a relatively low rate of ICB (0.6%/yr) and mortality (3.3 %/yr) with warfarin in Europe and a higher rate of ICB (1.1%/yr) and mortality (6.1%/yr) with warfarin in Asia and Latin America, respectively. A recent review of subanalyses in non-Asians *vs*. Asians indicates that the absolute reduction in risk of ICB in comparative pivotal studies with the DOAC and warfarin is much lower in non-Asians than in Asians [5]. As ICB rates with warfarin in Europe are approximately 0.4–0.5%/yr [38, 39], the 52% RR reduction with the DOAC seen in pivotal trials [3] would translate in Europe into approximately 0.2%/yr absolute risk reduction *vs*. warfarin. Within Europe, as in the overall study populations, there may be subpopulations in which the benefit of the DOACs with respect to ICB may be particularly relevant, like in those with a history of stroke/TIA and high bleeding risk [35]. With respect to mortality, considering the lack of differences in stroke rates in Europe between treatments and the relatively modest contribution of stroke to all-cause mortality in AF (10–13% of all deaths across pivotal studies) [11–14], it is not possible to conclude that DOACs would reduce stroke-related death in Europe. Whether some numerical benefit in haemorrhage-related deaths exists in Europe remains uncertain. This is far from indicating that European patients do not benefit from DOAC therapy, but is rather indicating that the quality of anticoagulation control differs across regions, as discussed previously.

Our review has several limitations. Firstly, it was based on subgroup analyses that have well-known limitations and are observational in their nature. However, subgroups by geographic region were pre-specified in all studies because it was clinically plausible to assume that medical practice and quality of anticoagulation with the control drug warfarin would differ between regions. Therefore, these secondary analyses may be used to illustrate applicability across regions. In addition, we choose a conservative threshold of significance ($P < 0.05$) to limit the risk of false positive results despite the lack of power of the interaction test, and the ten sensitivity analyses conducted were all significant. Secondly, the main comparison on our meta-analysis (Europe *vs*. other regions) was defined post-hoc. However, our secondary analysis was based on the regions that were pre-specified in the trials, and yielded similar results to the main analysis. An additional limitation is the absence of patient-level data that precludes investigating or adjusting for patient-level differences between regions.

In summary, our review shows significant regional differences in the extent of the benefit of the DOAC compared with warfarin for the prevention of stroke/SEE in patients with AF. The DOAC did not provide additional benefit in reducing the risk of stroke/SEE compared with warfarin in European patients. However, they were generally associated with a lower bleeding tendency than warfarin regardless of geographic region. These differences appear to be mainly related to differences in patient care of AF, thus resulting in different quality of anticoagulation with warfarin across regions. These regional differences are to be taken into account when interpreting the results from pivotal trials, as well as in the design and assumptions taken in pharmaco-economic analyses and indirect comparisons between the new compounds in specific regions and countries.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors

AGO, AITF, GCR, MLSG and EVC conceived and designed the study. AGO and AITF collected the data. AGO carried out the

statistical analysis and drafted the manuscript. EVC supervised the study. All authors analysed and interpreted the data and critically revised the manuscript for important intellectual content. The contents of this study are solely the responsibility of the authors and do not necessarily represent the official view of their institutions or any other party. AGO and EVC are the guarantors.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13005/suppinfo.

Appendix S1 Search strategy
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File S1 PRISMA statement