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ORIGINAL ARTICLE

Impact of double-blind vs. open study design on the observed treatment effects of new oral anticoagulants in atrial fibrillation: a meta-analysis

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Summary. *Background:* The prospective, randomized, open, blinded endpoint evaluation (PROBE) design has been proposed as a valid alternative to the double-blind (DB) design for trials comparing new oral anticoagulants (NOAs) with INR-adjusted vitamin K antagonists in patients with non-valvular atrial fibrillation (NVAF). *Objectives:* To determine whether the observed treatment effects of NOAs in patients with NVAF differ between PROBE/open-label trials and DB trials. *Methods:* All phase II or III trials were eligible. The main efficacy and safety outcomes were stroke/systemic embolism (SSE) and major bleeding, respectively. Other outcomes included ischemic SSE, hemorrhagic stroke, intracranial and extracranial bleeding, myocardial infarction, and all-cause and cardiovascular mortality. Interaction (Cochran's chi-squared test) between PROBE and DB designs was tested. *Results:* Thirteen studies (61 620 patients) were included. For SSE, a greater treatment effect of NOAs vs. INR-adjusted warfarin was observed in PROBE trials (RR 0.76, CI 0.65–0.89) compared with DB trials (RR 0.88, CI 0.78–0.98), but the interaction test was non-significant ($P = 0.16$). A significant 67% enhancement of treatment effect was found with PROBE/open-label trials compared with DB trials (interaction test, $P = 0.05$) for hemorrhagic stroke. No other interaction was significant. A non-significant interaction ($P = 0.07$) between oral direct thrombin inhibitors (RR 0.33; 0.22–0.51) and factor Xa inhibitors (RR 0.54; 0.40–0.72) was seen. No heterogeneity was found for any outcome. *Conclusions:* Our meta-analysis showed no significant interaction of study design for the main efficacy and safety outcomes. However, the non-significantly exaggerated reduction in SSE suggests interdependence of treatment effect and PROBE design, especially for hemorrhagic stroke.

Keywords: anticoagulants, atrial fibrillation, bias, meta-analysis, stroke.

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Introduction

Non-valvular atrial fibrillation (NVAF) is a major cause of ischemic stroke and systemic embolism and is consequently characterized by increased mortality and morbidity and higher costs of medical care [1,2]. Vitamin K antagonists (VKAs), principally warfarin, have been proven to be highly effective in preventing thromboembolic events in patients with paroxysmal, persistent or permanent NVAF [3]. In 29 randomized trials involving more than 28 000 patients pooled according to meta-analytic methods, adjusted-dose warfarin reduced the risk of stroke by 64% compared with the control and by 37% compared with aspirin, but at the cost of an increased risk of bleeding [3]. Furthermore, warfarin was associated with a 26% reduction in all-cause mortality in randomized, controlled trials when compared with no anticoagulation therapy in patients with NVAF [3].

New oral anticoagulants (NOAs), directly inhibiting thrombin or factor (F) Xa, have recently been developed. Their wide therapeutic windows permit the use of fixed doses without any need for monitoring [4,5]. These new drugs could potentially overcome the well-known limitations of VKAs, such as slow onset of action, need for regular monitoring of the international normalized ratio (INR) on blood samples, narrow therapeutic windows, marked inter-individual variations in drug metabolism, and multiple drug-drug and drug-food interactions, all of which lead to an increased risk of bleeding [6–8].

Different designs with respect to blinding of participants and researchers have been used to assess the efficacy and safety of NOAs, namely double-blind (DB), open-label, and prospective, randomized, open, blinded endpoint evaluation (PROBE) designs [9,10]. Several authors have presented evidence indicating an association between lack of blinding and over-optimistic estimates of treatment effects for subjectively assessed outcomes such as cardiovascular events [11,12]. However, the PROBE design has been debated as a valid alternative to the development of NOAs, as it improves the external validity of trials through the presence of an event adjudication committee, which guarantees the absence of information bias and the facilitation of patient recruitment, thereby enhancing sample representivity [13,14]. As a DB design of studies comparing VKAs with other anticoagulants necessitates a double-dummy strategy for INR monitoring, which is very difficult to perform, a demonstration that this design is not essential would be of great help in the development of NOAs. We performed a meta-analysis of all randomized NVAF trials to determine whether PROBE and open designs were associated with an enhancement of treatment effects in this clinical setting.

Methods

Inclusion criteria

The meta-analysis was performed according to a prospectively developed protocol (available upon request from the corresponding author), which prespecified the research objective, the search strategy, the study eligibility criteria, and the methods of data extraction and statistical analysis. All subgroup variables were defined before analysis.

All randomized, controlled trials conducted in patients with NVAF were eligible for inclusion in the present meta-analysis. Patients in the control group had to receive VKA and patients in the treated group had to receive an oral FXa or thrombin inhibitor. Double-blind and open-label trial designs with or without a blinded evaluation of outcomes were eligible. Studies were excluded if they concerned duplicate cohorts. Trials with short-term follow-ups (< 12 weeks) were excluded.

Data sources and searches

We searched Medline (PubMed) and Embase up to October 2012 using sensitive methods and employing the keywords: rivaroxaban, apixaban, betrixaban, edoxaban (DU-176b), eribaxaban, ximelagatran, dabigatran (BIBR1048), LY 517717, darexaban (YM150), letaxaban, AZD0837, TTP889, RB006, MCC977 and TAK442 [15,16]. Search terms included combinations of free text and medical subject headings (MeSH or Emtree). The complete search strategies may be requested from the authors. We also reviewed the citations of the retrieved studies, reviews and meta-analyses obtained by searches of PubMed and Embase. Unpublished and ongoing trials were sought in clinical trial repositories, including those of the National Institute of Health, the National Research Register, Current Controlled Trials, Meta-Embol and Trials Central. We also searched the Internet using the keywords listed above, including websites dedicated to the dissemination of clinical trial results, such as TheHeart.org and the US Food and Drug Administration web site, as well as the web sites maintained by the drug manufacturers and product information sheets.

Unpublished studies were included in the meta-analysis if the design had been previously published in detail and the patient characteristics, follow-up and main results had been presented at international congresses. No restrictions with regard to language or small population size were applied. All qualifying studies were assessed for adequate blinding of randomization, completeness of follow-up, and objectivity of the outcome assessment. Phase II trials were included if an arm corresponding to the dose of interest was selected in a subsequent phase III trial. When an abstract in congress proceedings and a full paper referred to the same trial, only the full article was included in the analysis. When two or more papers reported the same study (for example one for the protocol, a second for the results and a third for additional safety data), we included all that were useful for our purpose.

Outcomes

The main outcomes were the composite of stroke and systemic embolism (SSE; main efficacy outcome), major bleeding (main safety outcome) as defined by the International Society on Thrombosis and Haemostasis [17], intracranial bleeding, and all-cause and cardiovascular mortality. Other outcomes included ischemic stroke and systemic embolism separately, hemorrhagic stroke, myocardial infarction, and extracranial bleeding (including hemorrhagic stroke).

Data extraction

Studies were selected and data extracted from publications by two reviewers independently (JCL and CC). A

2 × 2 table was constructed for each study to compute the relative risk. If the data required to complete this table were missing or incomplete, the hazard ratio and its confidence interval were extracted and directly included in the pooled results [18]. Data regarding inclusion criteria, proportion of VKA-naive patients, proportion of patients with a CHADS2 score < 2, treatments, pharmacological class of study drugs, duration of follow-up, type of design (DB vs. PROBE or open-label), study phase (II or III) and randomization procedure were extracted from each individual study. The risk of bias was assessed by the Cochrane Collaboration's tool [19]. The results obtained for the intention-to-treat population were used for the main analyses. Disagreements were resolved by consensus. When the trial evaluated different dosages of the NOA and therefore allowed more than one comparison with the VKA arm, we divided the number of events and the number of participants in the VKA arm accordingly so that each was counted only once.

Statistical analysis

The relative risks (RRs) or hazard ratios were weighted by the inverse of their variance and combined using the logarithm of RR method according to a fixed-effects model with EasyMA 2.0 [20,21]. The heterogeneity between studies was assessed using Cochran's chi-squared test and I^2 [22]. We retained heterogeneity at $P < 0.10$. In the event of unexplained heterogeneity, the results were pooled according to a random-effects model. Interaction was systematically tested for PROBE or open-label vs. DB design and pharmacological class and was considered as significant at $P < 0.10$. Combined effect estimates were also calculated separately for trials with and without a DB design. We used the logistic regression models described previously to estimate RR ratios, comparing treatment effects in trials with and without a DB design [23]. Enhancement of the treatment effect, in terms of RR ratio, was determined by dividing the RR values obtained in PROBE trials by those obtained in DB trials. For example, a RR ratio of 1.3 would imply that the estimates of treatment effect were enhanced by 30% in trials with a PROBE or open-label design compared with trials with a DB design. We derived 95% confidence intervals (CIs) using robust standard errors allowing for heterogeneity between meta-analyses [23].

Results

Literature search and study selection

We identified 1151 references through electronic searches and 17 references by manual searches and contacts with experts (Fig. 1). Among these, 13 studies (including 61 620 patients) were eligible for analysis [9,10,24–35]. The funnel plot showed an asymmetry around the point estimate due to the lack of expected phase II studies in the bottom right-hand quadrant (Fig. 2). This asymmetry was due to the intrinsic properties of phase II studies, which are designed with the aim of selecting the dose with the best safety and efficacy profile and excluding doses showing adverse profiles. Patient characteristics are shown in Table 1 and study designs, methodological features and patient characteristics in Tables 2 and 3. The risk of bias according to the Cochrane Collaboration's tool mainly reflected the lack of blinding (Table 3). Random sequence generation was not reported in one small phase III study [34] and two phase II studies [31,32], and allocation concealment was not reported in one small phase III study [34] and four phase II studies [27,31–33]. Patient inclusion criteria were based on various combinations of the known risk factors for thromboembolism included in the CHADS2 score and consequently the proportion of patients with a CHADS2 score < 2 differed greatly from study to study, ranging from 0 to 47%. The proportion of VKA-naive patients ranged from 10 to 64%. Four trials had a DB design [9,25,26,34], three were open-label studies [28,31,32] and the other six had a PROBE design (Table 2).

Oral direct antithrombin inhibitors were assessed in six studies [10,26–28,30,31] and oral direct FXa inhibitors in seven studies [9,24,25,29,32–34] (Tables 2 and 4). A reduced dose of the NOA was used in patients with renal failure in two trials (apixaban 2.5 mg and rivaroxaban 15 mg) and in Japanese patients in one trial (rivaroxaban 15 mg) [9,25,34]. All studies used adjusted-dose warfarin (target INR, 2.0–3.0) as the control, except for three trials in Japan in which the targeted INR was lower in patients aged > 70 years [32–34]. Depending on the study, the INR was in the therapeutic range for 45–83% of the treatment period (Table 1).

Assessment of the impact of study design on the results

Stroke and systemic embolism A greater treatment effect was observed in trials with a PROBE/open-label design, showing a 24% relative risk reduction (nine trials including 37 665 patients; RR, 0.76; CI, 0.65–0.89), than in trials with a DB design, indicating a 12% relative risk reduction (four trials including 23 955 patients; RR, 0.88; CI, 0.78–0.98). The interaction test was not significant ($P = 0.16$), indicating a non-significant enhancement of the treatment effect by 16% (CI −5; + 41%; Fig. 3).

Major bleeding and intracranial bleeding We found no interaction with respect to major bleeding. The interaction tests showed a non-significant enhancement of the treatment effect (+33%, CI −9; + 92%) in trials with a PROBE/open-label design (RR, 0.40; CI, 0.30; 0.54) compared with those with a DB design (RR, 0.52; CI, 0.43; 0.66; interaction test; $P = 0.16$; Fig. 3) for intracranial

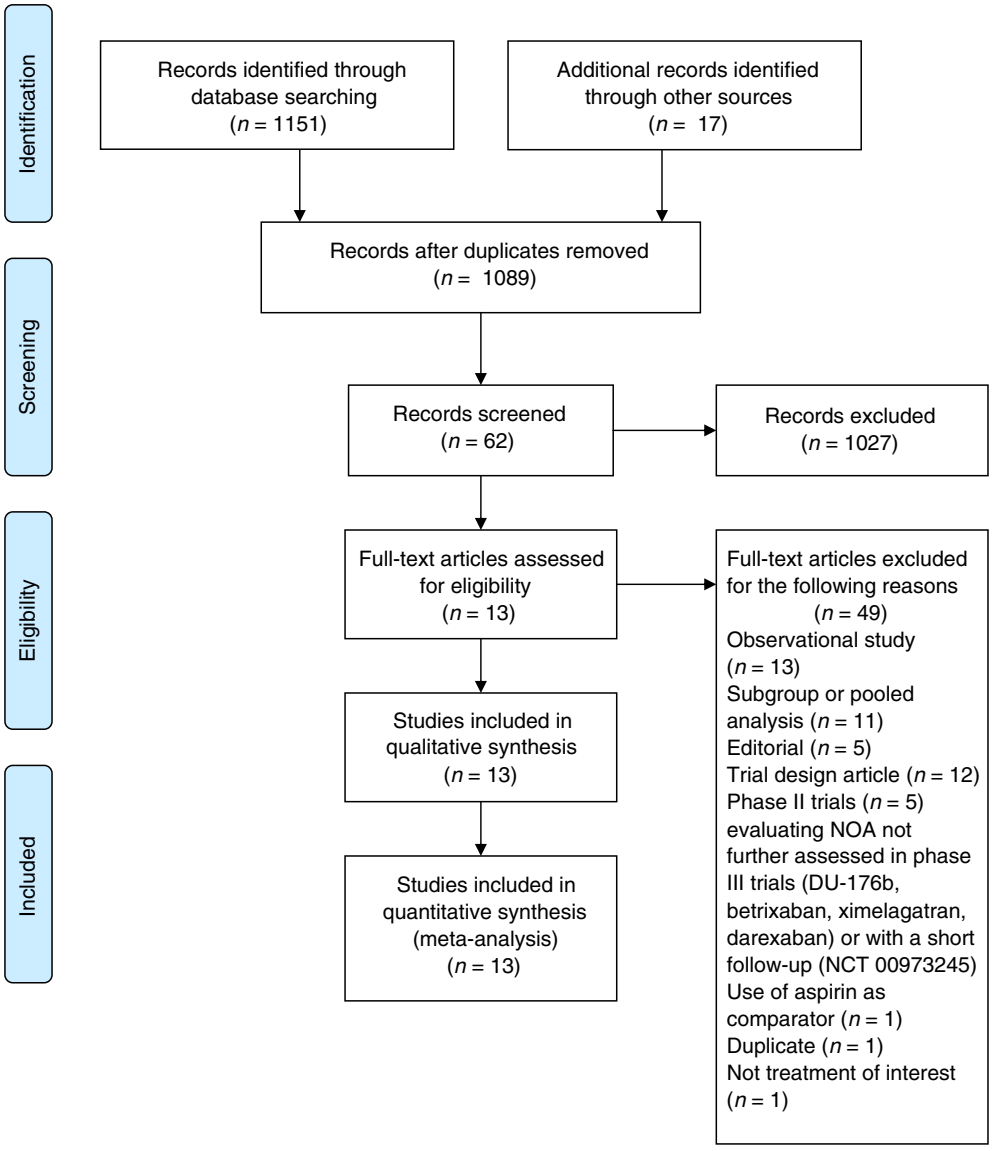

Fig. 1. Flow chart of trial selection.

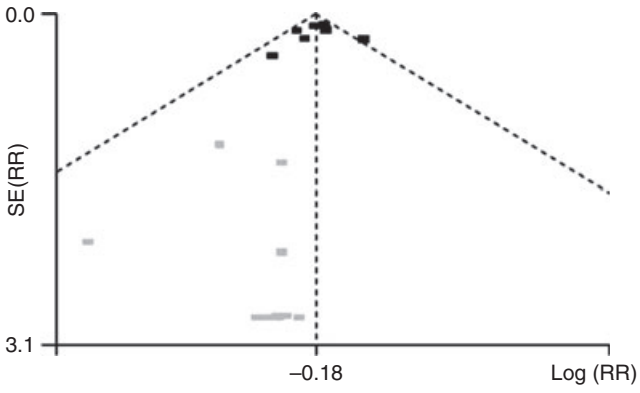

Fig. 2. Funnel plot of primary efficacy outcome (stroke or systemic embolism). Grey squares indicate phase II study arms and black squares phase III study arms. RR, relative risk; SE (log RR), standard error of relative risk.

Table 1 Patient characteristics in each trial included in the meta-analysis

Trial, year	Mean age (yr)	Men (%)	VKA-naive patients (%)	Patients with CHADS2 < 2 (%)	Lost to follow-up (%)	TTR (%)
SPORTIF III, 2003	70	69	27	30	1.3	66
SPORTIF V, 2005	72	69	16	26	0.6	68
NCT 01136408, 2007	68	88	NR	NR	NR	NR
PETRO, 2007	70	82	NR	NR	0	57
Lip *et al.* 2009	69	68	29	30	0	58
RE-LY, 2009	71	64	50	32	0.1	64
Weitz *et al.* 2010	65	62	64	0	0	NR
ROCKET, 2011	73	60	37	0	0.01	55
ARISTOTLE, 2011	70	65	43	34	2.1	62
ARISTOTLE-J, 2011	70	83	15	43	0	NR
Chung *et al.* 2011	65	65	48	47	0.8	45
J-ROCKET-AF, 2012	71	81	10	0	1.5	65
Yamashita *et al.* 2012	69	82	15	NR	NR	73 for pts aged < 70 yrs; 83 for pts aged ≥ 70 yrs

Pts, patients; NR, not reported; TTR, time during which the INR was in the therapeutic range; yr, years.

bleeding. This result was not associated with an interaction concerning pharmacological class (Fig. 4).

Cardiovascular mortality and all-cause mortality No interaction was concluded for these outcomes.

Other outcomes Interaction was evident with respect to the risk of hemorrhagic stroke, which was reduced to a greater extent in trials with a PROBE/open-label design (RR, 0.33; CI, 0.21–0.50) than in those with a DB design (RR, 0.55; CI, 0.41–0.73; interaction test; $P = 0.05$; Fig. 3). The test for interaction was also significant for pharmacological class ($P = 0.07$; Fig. 4). With respect to myocardial infarction, the subgroup analysis according to study design (PROBE/open-label vs. DB) revealed a significant interaction ($P < 0.0001$), DB trials showing a reduction in the risk of myocardial infarction (RR, 0.82; CI, 0.69–0.98) whereas PROBE/open-label trials indicated a significant increase (RR, 1.37; CI, 1.07–1.75). The test of interaction between these two trial subsets was significant ($P < 0.0001$) and corresponded to a RR enhancement of −35% (CI, −15; −49%; Fig. 3). In addition, the risk of myocardial infarction was reduced by oral direct FXa inhibitors (RR, 0.85; CI, 0.70–1.03) compared with VKA, the decrease in risk being less pronounced in the case of thrombin inhibitors (RR, 1.20; CI, 0.96–1.50) with a significant interaction effect ($P = 0.02$; Fig. 4). No interaction was found for ischemic stroke/systemic embolism or extracranial bleeding.

Discussion

The aim of this meta-analysis was to determine whether open designs with or without blinded outcome assessments were associated with an enhancement of the treatment effects compared with double-blind designs in randomized trials evaluating NOA in patients with NVAF. Our meta-analysis showed a non-significant enhancement with respect to the main efficacy outcome. The PROBE design may influence the results by a 16% enhancement of the observed reduction in the risk of SSE compared with the DB design. This point estimate is consistent with a previous estimate of 17% derived from a meta-analysis of blinded/unblinded randomized trials in pediatric and obstetrical settings [36]. The lack of statistical significance may be due to a lack of power in detecting a significant interdependence of treatment effect and PROBE study design. The interaction test is known to suffer from lack of power even in a meta-analysis combining the results from many studies, as previously reported [37]. Only meta-epidemiological approaches encompassing more than 1000 trials can achieve statistical significance [11].

Other authors have already highlighted the potential biases introduced by the PROBE design [11,38]. In a trial comparing rosiglitazone with a combination of metformin and sulphonylurea in type 2 diabetes, an FDA review revealed a differential assessment of outcomes, resulting from under-reporting of events occurring in the active arm to the blinded endpoint committee, compared with those occurring in the control arm, leading to spurious underestimation of the rate of myocardial infarction [38]. Robust outcomes, such as all-cause mortality, were less likely to be influenced by reporting bias [11]. Our meta-analysis showed no impact of the PROBE study design on the reported risk of cardiovascular and all-cause mortality. Nevertheless, the other potential biases that could lead to enhancement of the treatment effect with the PROBE design in comparison to the double-blind design are less well known. Apart from reporting bias, the lack of blinding of investigators might potentially lead to an imbalance between patients receiving VKAs or NOAs

Table 2 Characteristics of the studies included

Trial, year	Design	NOA class	NOA treatment	Randomization method	ITT	Mean follow-up (months)	Timing of endpoint (ITT)
SPORTIF III, 2003	Phase III PROBE	Thrombin inhibitor	Ximelagatran 36 mg bid	Computer-generated and centralized (IVRS)	Death, SSE, myocardial infarction	17.4	3 months after MI, bleeding, SSE
SPORTIF V, 2005	Phase III Double-blind	Thrombin inhibitor	Ximelagatran 36 mg bid	Computer-generated and centralized (IVRS)	Death, SSE	20.0	3 months after MI, bleeding, SSE
NCT 01136408, 2007*	Phase II Open	Thrombin inhibitor	Dabigatran 110 mg bid Dabigatran 150 mg bid	NR	NR	3	NR
PETRO, 2007	Phase II PROBE	Thrombin inhibitor	Dabigatran 150 mg bid	Dose stratification	Per protocol	3.0	12-week follow-up visit
Lip *et al*. 2009	Phase II Open	Thrombin inhibitor	AZD0737 300 mg od	Computer-generated and centralized (IVRS) – stratification according to prior VKA status	NR	5.0	NR
RE-LY, 2009	Phase III PROBE	Thrombin inhibitor	Dabigatran 110 mg bid Dabigatran 150 mg bid	Computer-generated and centralized (IVRS)	All outcomes	24.0	NR
Weitz *et al*. 2010	Phase II PROBE	Factor Xa inhibitor	Edoxaban 30 mg od Edoxaban 60 mg od	Computer-generated and centralized (IVRS)	NR	4.0	End of follow-up
ROCKET, 2011	Phase III Double-blind	Factor Xa inhibitor	Rivaroxaban 20 mg od†	Computer-generated and centralized (IVRS)	SSE	23.2	Switch to open label-treatment with conventional anticoagulants
ARISTOTLE, 2011	Phase III Double-blind	Factor Xa inhibitor	Apixaban 5 mg bid†	Computer-generated and centralized (IVRS) – stratification according to investigative site and prior VKA status	All outcomes	21.6	Efficacy outcomes: cut-off date Safety outcomes: 2 days after last dose received
ARISTOTLE-J, 2011	Phase II PROBE	Factor Xa inhibitor	Apixaban 2.5 or 5 mg bid	NR	Per protocol	3	End of follow-up
Chung *et al*. 2011	Phase II PROBE	Factor Xa inhibitor	Edoxaban 30 mg od Edoxaban 60 mg od	Computer-generated and centralized (IVRS)	All outcomes	3	End of follow-up
J-ROCKET-AF, 2012	Phase III Double-blind	Factor Xa inhibitor	Rivaroxaban 15 mg od	NR	SSE	5.8	12-week follow-up visit
Yamashita *et al*. 2012	Phase II Open	Factor Xa inhibitor	Edoxaban 30 mg od Edoxaban 60 mg od	Stratification according to prior VKA status	Per protocol	3	8-week follow-up visit

Bid, twice daily; ITT, intention-to-treat analysis; IVRS, interactive voice-response system; NR, not reported; od, once daily; PROBE, prospective, randomized, open, blinded-endpoint; SSE, stroke and systemic embolism. *Additional data were provided by the trial investigators. †Doses were reduced in patients with renal failure.

Table 3 Assessment of the risk of bias according to the Cochrane Collaboration's tool

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
SPORTIF III, 2003	+	+	–	+	+	+
SPORTIF V, 2005	+	+	+	+	+	+
NCT 01136408, 2007	?	?	–	–	?	+
PETRO, 2007	+	?	–	+	+	+
Lip *et al.* 2009	+	+	–	–	+	+
RE-LY, 2009	+	+	–	+	+	+
Weitz *et al.* 2010	+	+	–	+	+	+
ROCKET, 2011	+	+	+	+	+	+
ARISTOTLE, 2011	+	+	+	+	+	+
ARISTOTLE-J, 2011	+	?	–	+	+	+
Chung *et al.* 2011	+	+	–	+	+	+
J-ROCKET-AF, 2012	?	?	+	+	+	+
Yamashita *et al.* 2012	?	?	–	–	–	+

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

Table 4 Trial results

Trial name, Year	Group	Patients (*n*)	Stroke/SE	Ischemic stroke/SE	Hemorrhagic stroke	MB	Intracranial bleeding	All-cause mortality	Cardiovascular mortality	AMI
SPORTIF III, 2003	X 36 mg bid	1704	40	36	4	29	10	78	40	24
	VKA	1703	56	48	9	41	13	79	33	13
SPORTIF V, 2005	X 36 mg bid	1960	51	51	2	70	7	116	NR	26
	VKA	1962	37	37	2	93	9	123	NR	37
NCT 01136408, 2007	D 110 bid	46	0	0	0	0	0	0	0	0
	D 150 bid	58	0	0	0	1	0	0	0	0
	VKA	62	1	1	0	1	0	0	0	0
PETRO, 2007	D 150 mg bid	166	0	0	0	0	0	NR	NR	NR
	VKA	70	0	0	0	0	0	NR	NR	NR
Lip *et al.* 2009	AZD0737	151	0	0	0	0	0	0	0	1
	VKA	318	1	1	0	2	0	2	0	1
RE-LY, 2009	D 110 mg	6015	183	170	14	322	27	446	289	98
	D 150 mg	6076	134	124	12	399	36	438	274	97
	VKA	6022	202	156	45	421	87	487	317	75
Weitz *et al.* 2010	E 30 mg od	235	1	0	0	0	NR	NR	2	2
	E 60 mg od	234	1	0	0	1	NR	NR	0	2
	VKA	250	3	3	0	1	NR	NR	2	0
ROCKET, 2010	R 15 or 20 mg od	7081	269	154	29	395	55	208	170	101
	VKA	7090	306	183	50	386	84	250	193	126
ARISTOTLE, 2011	A 2.5 or 5 mg	9120	212	177	40	327	52	603	0.89 (0.76–1.04)	90
	VKA	9081	265	192	78	462	122	669		102
ARISTOTLE-J 2011	2.5 mg bid	74	0	0	0	0	0	0	0	0
	5 mg bid	74	0	0	0	0	0	0	0	0
	VKA	74	3	2	1	1	1	0	0	0
Chung *et al.*, 2011	E 30 mg od	79	0	0	0	0	0	0	0	0
	E 60 mg od	80	0	0	0	0	0	1	1	0
	VKA	75	0	0	0	2	0	1	0	0
J-ROCKET-AF, 2012	R 10 or 15 mg od	640	22	8	3	26	4	7	6	3
	VKA	640	26	18	4	30	10	5	2	1
Yamashita *et al.*, 2012	E 30 mg od	130	0	0	0	0	0	0	0	0
	E 60 mg od	130	0	0	0	2	1	1	0	0
	VKA	125	0	0	0	0	0	1	0	0

A, apixaban; AMI, acute myocardial infarction; bid, twice daily; D, dabigatran; E, edoxaban; MB, major bleeding; NOA, new oral anticoagulant; NR, not reported; od, once daily; R, rivaroxaban; SE, systemic embolism; VKA, vitamin K antagonist; X, ximelagatran.

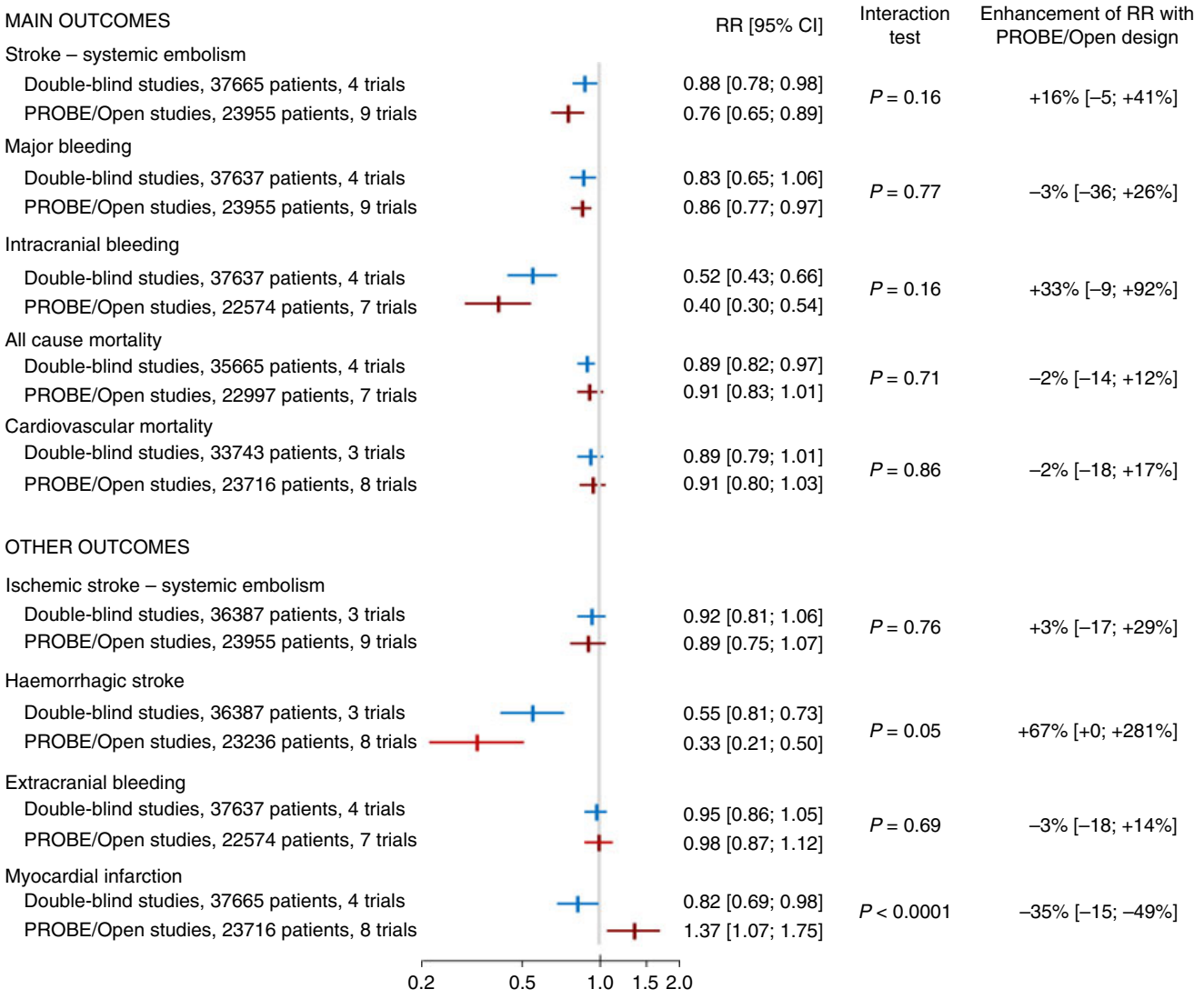

Fig. 3. Analysis of interaction between study design and treatment effect.

with regard to medical interventions such as invasive investigations or prescriptions (e.g. co-administration of antiplatelet agents) after randomization and result in confusion bias. The enrichment of our meta-analysis by publication of the results of ongoing trials may provide additional arguments to confirm or refute our assumptions.

Regarding safety, the PROBE design seems to influence the results by overestimating the observed reduction in the risk of intracranial hemorrhage by 33% and that of hemorrhagic stroke by 67% compared with the DB design, resulting in the consistent core benefit of these new drugs across all trials. Even though this observation concerning safety may result from a detection bias due to the lack of blinding of suspected outcome occurrence in PROBE/open studies (i.e. observer bias), we cannot rule out the impact of a confounding factor. Indeed, the large PROBE/open studies mainly assessed oral direct thrombin inhibitors whereas double-blind studies mainly assessed FXa inhibitors, and it is conceivable that the risk of intracranial bleeding differs between the two pharmacological classes. If the site of bleeding is related to the pharmacological class, it is impossible to know if the interaction is related to the study design or the type of drug evaluated. As for myocardial infarction [39], we cannot preclude a difference between thrombin and FXa inhibitors as regards the reduction of hemorrhagic stroke risk, with a greater risk reduction by oral direct thrombin inhibitors.

In conclusion, our meta-analysis did not show a significant interaction of study design on the main efficacy and safety outcomes. Nevertheless, the non-significant interaction seen on analysis of the effect of NOAs in reducing the risk of SSE suggests an interdependence of

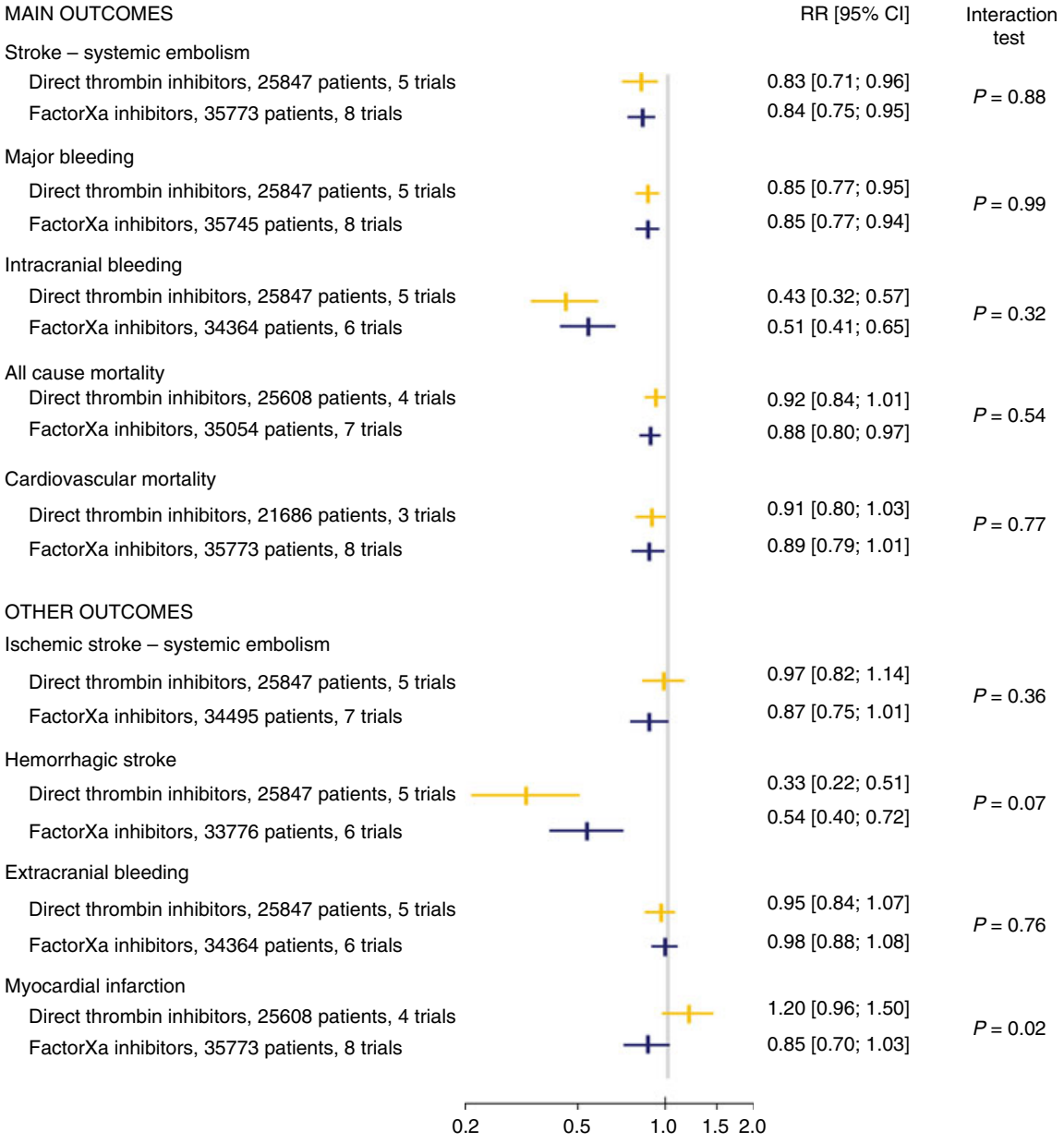

Fig. 4. Analysis of interaction between pharmacological class and treatment effect.

treatment effect and PROBE study design, especially with regard to hemorrhagic stroke risk, necessitating careful interpretation of trials using this design. However, we cannot rule out a difference in intracranial bleeding risk between the two pharmacological classes of NOAs.

Addendum

P. Mismetti, S. Laporte and M. Cucherat designed the study. J-C. Lega, C. Chapelle and T. Fassier contributed to data acquisition. J-C. Lega, S. Laporte and M. Cucherat were responsible for the statistical analyses. J-C. Lega, S. Laporte, L. Bertoletti and P. Mismetti interpreted data. J-C. Lega, S. Laporte and P. Mismetti planned and wrote the first draft of the paper, which was subsequently revised by all authors. All authors read and approved the final manuscript. J-C. Lega is guarantor.

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Disclosure of Conflict of Interest

J-C. Lega, P. Mismetti, M. Cucherat, T. Fassier, L. Bertoletti and C. Chapelle received no direct support for this study. S. Laporte received support from the Ministère de la Recherche through a grant from the Programme Hospitalier de Recherche Clinique (META EMBOL) in 2008. P. Mismetti and S. Laporte sit on advisory boards for Boehringer Ingelheim, BMS/Pfizer and Bayer, as well as Daichii Sankyo in the case of P. Mismetti. P. Mismetti has received honoraria from Sanofi-Aventis, GSK, Astra Zeneca, Merck Serono, Boehringer Ingelheim and Bayer. S. Laporte has received honoraria from Sanofi-Aventis, Merck Serono, Boehringer Ingelheim and Bayer. No other relationships or activities that could appear to have influenced the submitted work are declared. M. Cucherat has received research funding and speaking fees from, or acted as a consultant for, GSK, Bayer, Pfizer and BMS.

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