Peertechz

Medical Group

Journal of Cardiovascular Medicine and Cardiology

ISSN: 2455-2976 DOI CC By

Nabila Ferahta[1], Lukshe Kanagaratnam[2], Moustapha Dramé[2,3], Thomas Vogel[4], Pierre-Jacques Ambrosi[5] and Pierre-Olivier Lang[1,6]*

[1]Geriatric and rehabilitation geriatric division, University hospital of Lausanne, Lausanne, Switzerland
[2]Department of Research and Public Health, University hospitals of Reims, Reims, France
[3]EA-3797, Faculty of Medicine, University of Reims-Champagne-Ardenne, Reims, France
[4]Geriatric Department, University Hospital of Strasbourg, Strasbourg, France
[5]Department of Cardiology, La Timone Hospital, Aix-Marseille University, Marseille, France
[6]Health and Wellbeing academy, Anglia Ruskin University, Cambridge, United Kingdom

Dates: Received: 09 June, 2017; **Accepted:** 08 July, 2017; **Published:** 10 July, 2017

***Corresponding author:** Pierre Olivier Lang, Geriatric and Geriatric rehabilitation division, University Hospital of Lausanne (CHUV), Chemin de Mont Paisible 16, CH-1011 Lausanne, Switzerland, Tel: +41.(0)21.314.37.04; Fax: +41.(0)21.314.17.20; E-Mail: pierre-olivier.lang@chuv.ch

Keywords: Oral Anticoagulants; Factor Xa Inhibitor; Antivitamin K; Bleeding Events; Major Bleeding; Gastrointestinal Bleeding; Intracranial Haemorrhage; Atrial Fibrillation; Meta-Analysis

https://www.peertechz.com

Research Article

Bleeding Risk under Oral Factor Xa Inhibitors: Meta-analysis of the randomized comparison with Vitamin K Antagonists and Meta-Regression analysis

Abstract

Background: Randomized trials have shown that oral direct factor Xa inhibitors (ODIXa) offer potential advantages over vitamin K antagonists (VKAs). It is however unclear whether the magnitude of their benefit is similar at the current recommended doses.

Objective: We assessed bleeding risks and total mortality associated with ODIXa therapy compared to VKAs among patients with non-valvular atrial fibrillation or acute venous thromboembolic disease.

Methods: Medline, Embase and Cochrane library databases were searched to identify all randomized controlled trials comparing ODIXa to VKAs. The main outcomes were major bleeding, major and clinically relevant non-major (CRNM) bleeding, intracranial haemorrhage, gastrointestinal bleeding, total bleeding events and overall mortality. Pooled odds ratios were calculated with random effect model. Meta-regression was performed.

Results: The use of ODIXa was associated with a significant reduced-risk of major bleeding (OR, 0.72; 95% CI, 0.60-0.87), major and CNRM bleeding (OR, 0.72; 95% CI, 0.54-0.96), intracranial bleeding (OR, 0.48; 95% CI, 0.39-0.59) and total bleeding events (OR, 0.69; 95% CI, 0.60-0.80). No difference in risk of gastrointestinal bleeding was observed in NVAF. A linear association was found between a higher $CHADS_2$ and risk of major bleeding; increasing age and a high quality of warfarin monitoring (TTR) were also correlated with a higher risk of gastrointestinal bleeding on ODIXa.

Conclusions: ODIXa therapy was associated with a lower rate of bleedings complications and overall mortality. The gastrointestinal bleeding risk, which was globally similar, was however increasing in ODIXa groups with advancing age and greater quality of VKAs management.

Introduction

Adequate antithrombotic therapy with vitamin K antagonists (VKAs) significantly reduces the risk of stroke in patients with atrial fibrillation (AF) which were until recently the cornerstone of treatment in patients with an increased risk of thromboembolic complications. VKAs were thus our standard for oral anticoagulation for more than 50 years, with about 30 million prescriptions annually in the USA [1].

The increased bleeding risk common to anticoagulants ranges in severity from clinically manageable epistaxis to life-threatening intracranial hemorrhage. All those bleeding events are also one of the leading causes for emergency department (ED) visits and preventable costs [2]. In the USA, warfarin was incriminated in 17.3% of ED visits for adverse drug events in older adults, and about 90% of warfarin-related hospitalizations were attributed to unintentional overdose [3]. VKAs management was inappropriate in 48.7% (31% were not or under treated and 17.7% over treated) among hospitalized patients with AF [4].

The development of oral direct thrombin (DTI) and factor Xa inhibitors (ODIXa) have streamlined clinical care and evidence-based guidelines contributed to their rapid adoption [5]. Based on data from the IMS Health National Disease and Therapeutic Index, the prescription of direct oral anticoagulants (DOACs) was dramatically extended but matching the use of

Citation: Ferahta N, Kanagaratnam L, Dramé M, Vogel T, Ambrosi PJ, et al. (2017) Bleeding Risk under Oral Factor Xa Inhibitors: Meta-analysis of the randomized comparison with Vitamin K Antagonists and Meta-Regression analysis. J Cardiovasc Med Cardiol 4(3): 038-048. DOI: http://doi.org/10.17352/2455-2976.000048

VKAs and was associated with increased number AF patients receiving oral anticoagulants [5]. DOACs have more favorable pharmacological profile compared with VKAs (*i.e.* predictable effect, lack of frequent monitoring or re-dosing, fewer drug-drug and drug-food interaction) [6], and are therapeutically at least as effective [7-21]. When there is probably no doubt that DOACs represent a major step forward in the management of patients needing oral antithrombotic, better knowledge about risk of bleeding complications would certainly provide relevant insights into treatment outcomes. Despite the availability of predictive tools and evidence-based guidelines, many patients are still inappropriately treated for conditions that predispose to thromboembolic complications and debilitating strokes. Indeed, the fear of bleeding commonly leads physician to estimate systematically the risk of bleeding greater than the risk of stroke [22].

Meta-analyses have already attempted to assess the exact benefit and safety of DOACs [7-12,14-16,18,20,21,23-26]. Globally they all reported a lower risk of intracranial and major bleeding compared to warfarin or aspirin [7,8,10,11,14-16,19-21,26,27]. However, either they considered phase III studies only [7,10,13-16,19,21,24], or combined data from heterogeneous pharmacological classes (ODIXa and DTI) [7-14,16-21,25,28], leading to sub-group comparisons or sensitivity analyses [13,15,18,20,27]. Meta-analyses have also considered a limited number of ODIXa [7,9,12,14,17,19,24,26,29], in comparison with the current number of available molecules that would also have different safety profiles. Previous reports have also mixed different therapeutic indications [25].

The aim of the present meta-analysis was to estimate the safety profile of the five currently available ODIXa in terms of bleeding risk in patients with non-valvular (NV) AF, acute DVT, or PE compared to VKAs. The primary objective was to assess the risk of major bleeding when ODIXa was prescribed at recommended dose. Secondary objectives were composite outcomes of major bleeding and clinically relevant non-major bleeding (CRNM), intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), all bleeding events, and all-cause mortality. We also assessed the influence of potential modulators for all these outcomes through meta-regression analyses.

Materials and Methods

This meta-analysis was conducted and reported in accordance with the PRISMA statement [30].

Study selection

Design: Randomized controlled trials (RCTs) comparing the effect of one of the five currently available ODIXa (rivaroxaban, apixaban, edoxaban, betrixaban and darexaban) to VKAs in patients with NVAF, DVT, or PE were identified. Phase III and II dose-ranging clinical trials were considered. For the latter, only trials or trial arms testing doses that were finally approved, recommended, or considered for phase III studies were included. Double blind and open-label trials were included because dose monitoring of VKAs makes blind design very challenging.

Treatment: For ODIXa, standard daily dose (approved or recommended doses) were considered: apixaban 10 mg, betrixaban 80 mg, darexaban 120 mg, edoxaban 60 mg and rivaroxaban 20 mg or 15 mg twice day. Low-dose ODIXa were considered in case of renal insufficiency according to guidelines. For VKAs, all molecules were considered and therapeutic dosing was adjusted to a target international normalized ratio (INR) range of 1.5 to 3.0 according to study protocols (Table 1).

Search strategy, data extraction and quality assessment

A comprehensive systematic database search for manuscripts was conducted using MEDLINE, Embase, and Cochrane Central Register of controlled Trials *via* OVID from 1990 to January 2016. The search was subsequently updated to April 15, 2017. In order to identify unpublished data, abstract books from the congresses of the *International Society of Thrombosis and Hemostasis*, the *European Society of Cardiology*, the *American Heart Association*, the *American Society of Hematology*, and the *American College of Cardiology* were scrutinized as well as *www.clinicaltrial.gov* and *www.strokecenter.org*. Electronic databases were consulted with search keywords: « *apixaban* » [MeSH Terms] OR « *edoxaban* » [MeSH Terms] OR « *rivaroxaban*» [MeSH Terms] OR « *betrixaban*» [MeSH Terms] OR « *darexaban* » [MeSH Terms]. Articles were searched manually for potential inclusion; duplicates were immediately removed (Figure 1). Reference lists of articles retrieved, reviews articles, and position stands were reviewed for further references.

Two reviewers (NF and TV) independently assessed manuscripts for potential inclusion. Disagreements were first resolved through discussion and, when necessary, the opinion of a third reviewer (POL) was considered. Briefly, data were extracted according to study design, population's characteristics (total number, mean or median age, gender), treatment type (pharmaceutical component, clinical indication, dose, treatment duration, and follow-up), and the report of adverse events. The latter was defined as follows: "major bleeding", the combination of "major and clinically relevant non-major (CRNM) bleeding", "intracranial hemorrhage", "gastrointestinal bleeding", "total bleeding", and "all-cause mortality".

Once studies were collected based on a minimum quality threshold, defined as having met all inclusion criteria, a more detailed assessment was conducted according to the Cochrane Collaboration risk of bias assessment for potential bias [31].

Statistical analysis

Analyses were computed using R (version 3.1.2; R Foundation for Statistical Computing, Vienna, Austria). The significant threshold was set at $P=0.05$. Data from ODIXa were pooled to perform a comparison in a random effect model (Mantel-Haenszel method) for primary (major bleeding) and secondary objectives (major bleeding and CRNM, ICH, GIB, total bleeding events, and all-cause mortality). Results were expressed as Mantel–Haenszel pooled odds ratio (OR) and 95% confidence interval (CI). Heterogeneity between trials was assessed using the χ^2 (*Chi2*) test and I^2 statistic. The random effect model was considered independently of the existence of

Citation: Ferahta N, Kanagaratnam L, Dramé M, Vogel T, Ambrosi PJ, et al. (2017) Bleeding Risk under Oral Factor Xa Inhibitors: Meta-analysis of the randomized comparison with Vitamin K Antagonists and Meta-Regression analysis. J Cardiovasc Med Cardiol 4(3): 038-048. DOI: http://doi.org/10.17352/2455-2976.000048

Table 1: Baseline characteristics of included trials.

Study (year)	Indication	Study drug			Control drug			Duration (month)	Mean age (year)		ISTH Bleeding definition
		Drug	Dosage	N	VKA	INR	N		Drug	VKA	
Botticelli (2008)	VTE	Apixaban	5 mg BD	134	Warfarin Acenocoumarol Phenprocoumaron	2-3	128	3	59.0±17	59.0±16	+
Aristotle (2011)	AF	Apixaban	5 mg BiD	9120	Warfarin	2-3	9081	21.6*	69.1±9.6	69.0±9.7	+
Aristotle-J (2011)	AF	Apixaban	5 mg BiD	74	Warfarin	2-3	74	3	70.0±8.1	71.7±7.0	+
Amplify (2013)	VTE	Apixaban	10 mg BiD for 7 days then 5 mg BiD	2691	Warfarin	2-3	2704	6	57.2±16.0	56.7±16.0	+
Amplify-J (2015)	VTE	Apixaban	10 mg BiD for 7 days then 5 mg BiD	40	Warfarin	1.5-2.5	40	6	64.3±13.4	66.1±17.7	+
EDOX US-EU (2010)	AF	Edoxaban	60 mg QD	235	Warfarin	2-3	251	3	64.9±8.8	66.0±8.5	+
EDOX Asia (2010)	AF	Edoxaban	60 mg QD	80	Warfarin	2-3	75	3	65.9±7.7	64.5±9.5	-
EDOX Japan (2011)	AF	Edoxaban	60 mg QD	131	Warfarin	2-3	121	3	68.4	68.8	-
Engage AF-TIMI (2013)	AF	Edoxaban	60 mg QD	7035	Warfarin	2-3	7036	33.6*	70.6±9.5	70.5±9.5	+
Hokusai (2013)	VTE	Edoxaban	60 mg QD	4143	Warfarin	2-3	4149	12	55.7±16.3	55.9±16.2	+
Explore-Xa (2013)	AF	Betrixaban	80 mg QD	127	Warfarin	2-3	127	9	72.0±7.6	72.7±8.7	+
OPAL-1 (2010)	AF	Darexaban	120 mg OD	93	Warfarin	NA	94	3	67.0±9.6	67.0±9.4	NA
OPAL-2 (2014)	AF	Darexaban	120 mg OD	163	Warfarin	2-3	324	3	66.4	65.9	+
Einstein DVT (2008)	VTE	Rivaroxaban	15 mg BiD for 21 days then 20 mg QD	134	Warfarin Acenocoumarol Phenprocoumon Fluindione	2-3	137	3	55.8±16.4	56.4±16.3	+
Einstein DVT (2010)	VTE	Rivaroxaban	15 mg BiD for 21 days then 20 mg QD	1731	Warfarin Acenocoumarol	2-3	1718	12	57.9±7.3	57.5±7.2	+
Rocket-AF (2011)	AF	Rivaroxaban	20 mg QD	7111	Warfarin	2-3	7125	23.2*	71.0 (34-89)*	71.2 (43-90)*	-
Einstein PE (2012)	VTE	Rivaroxaban	15 mg BiD for 21 days then 20 mg QD	2420	Warfarin Acenocoumarol	2-3	2413	3	57.9±7.3	57.5±7.2	+
J-Einstein (2015)	VTE	Rivaroxaban	15 mg BiD then 15 mg QD	23	Warfarin	2-3	19	6	68.8±12.2	63.4±18.3	+

* Median value ; ISTH International Society on Thrombosis and Haemostasis; BiD Twice daily; QD Once daily; VKA Vitamin K antagonist; INR International normalized ratio; VTE Venous thromboembolism; AF Atrial fibrillation; NA Not available.

heterogeneity because we used pooled results of studies with different designs and patient's characteristics. Analyses were also stratified according to therapeutic indication and study phase. In addition, sensitivity analysis including meta-analysis of only phase III RCTs was performed.

Finally, meta-regressions by a random effect model were computed; the log OR for primary and secondary objectives were predicted according to the age, patient's time in therapeutic range (TTR) on VKAs, sex-ratio, heparin therapy duration when applied, $CHADS_2$ score, and the combined use of aspirin. Funnel plots asymmetries were considered (showing the standard errors and the effect size) to investigate publication bias.

Results

Study inclusion/exclusion

The process of study inclusion/exclusion is detailed in (Figure 1). Briefly, 20 RCTs were eligible for final inclusion; two were secondarily excluded because the dose of ODIXa was not

Citation: Ferahta N, Kanagaratnam L, Dramé M, Vogel T, Ambrosi PJ, et al. (2017) Bleeding Risk under Oral Factor Xa Inhibitors: Meta-analysis of the randomized comparison with Vitamin K Antagonists and Meta-Regression analysis. J Cardiovasc Med Cardiol 4(3): 038-048. DOI: http://doi.org/10.17352/2455-2976.000048

the one recommended for the therapeutic indications [32,33]. The 18 remaining [34-51] consisted of 5 RCTs reporting the effect of apixaban [34,36,43,45,46,52], 1 trial for betrixaban [41], 2 for darexaban [44,48], 5 for edoxaban [37,40,42,49,51], and 5 for rivaroxaban [35, 38, 39, 47, 50]. Fourteen RCTs have considered warfarin as VKA in control group and 4 studies authorized warfarin or another VKA [35, 36, 38, 39]. NVAF was the therapeutic indication in 10 RCTs [40-44, 46-49, 51], and DVT and PE in 8 [34-36, 38, 39, 45, 50]. Major and CRNM bleedings were defined according to the definition of the ISTH [53] in most RCTs (Table 1). No publication bias was detected according to funnel plot analysis. All studies were funded and/or supported by pharmaceutical companies.

Study quality

Globally, the assessment of the study quality [31] concluded that all 18 RCTs specified their inclusion criteria, randomly assigned groups, reported standard deviations or confidence intervals, and reported baseline participant's characteristics. None of all was at high risk of bias for random sequence generation or allocation concealment; however, the allocation concealment was not reported for 6 studies [40, 44, 45, 48, 49, 51] and missing data for 6 studies [36, 38, 45, 46, 49, 51]. Most studies had an open-label arm for VKAs.

Cohorts characteristics

The 18 RCTs totalized 70,871 patients assigned to either ODIXa (n =35,364) or VKAs (n =35,507); the mean sample age ranged from 55.7 ± 16.3 to 73.3 ± 8.5 years according to trials. Study and cohort characteristics are summarized in (Table 1). Briefly, AF cohorts were significantly older than those with DVT or PE; the sex ratio was similar across the trials analyzed.

Study cohorts were also relatively healthy independent living adults with a reduced number of additional stable chronic conditions (commonly hypertension, diabetes, renal impairment). For AF studies, mean $CHADS_2$ scores were reported ranging from 1.8 to 3.5. In overall, the mean TTR was between 45.1 to 80.3% for warfarin. As showed in (Table 1), the follow-up was 3 or 6 months in VTE studies, and 3 to 40 months for NVAF RCTs. Patients enrolled, were for 49.9% treated with ODIXa. When indicated, combining anticoagulant therapy with antiplatelet agent (for the most aspirin) was allowed in all 18 RCTs.

Meta-analysis on risk of bleeding

The use of ODIXa was associated with a significant reduced-risk of major bleeding (OR, 0.72; 95% CI, 0.60-0.87) (Figure 2), of major and CRNM bleeding (OR, 0.72; 95% CI, 0.54-0.96) (Figure 3), ICH (OR, 0.48; 95% CI, 0.39-0.59) (Figure 4), and of total bleeding events (OR, 0.69; 95% CI, 0.60-0.80), whatever the therapeutic indication (NVAF or acute venous thromboembolic disease). Systematically, a more prominent effect was measured with apixaban, in comparison with VKAs, for major bleeding (OR, 0.46; 95% CI, 0.23-0.91), major and CRNM bleeding (OR, 0.50; 95% CI, 0.33-0.76), and total bleedings (OR, 0.61; 95% CI, 0.47-0.79). Apixaban was

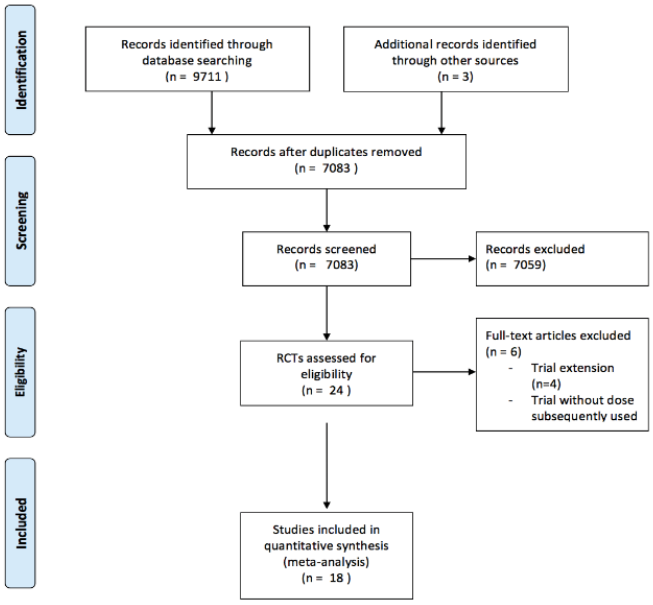

Figure 1: Flow chart describing systematic research and study selection process.

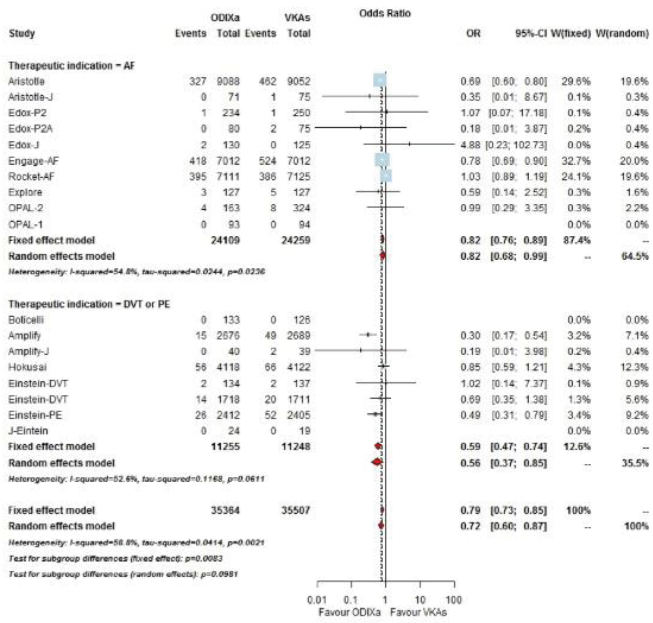

Figure 2: Forest plot for risk of major Bleeding in patient with ODIXa versus VKAs.

associated with a lower risk of major and CRNM bleeding compared to warfarin. However, there was no significant difference detected in odds of major, major and CRNM bleeding occurring on betrixaban, darexaban and rivaroxaban *vs*. VKAs, and on edoxaban with respect to primary outcome. The risk of GIB with ODIXa was not significantly different from that with VKAs in NVAF, but significantly lower in venous thromboembolic disease (OR, 0.39; 95% CI, 0.18-0.85; *P=0.02*) (Figure 5).

Meta-analysis on risk of all-cause death

Standard-dose ODIXa significantly reduced the risk of all-cause death (OR, 0.88; 95% CI, 0.81-0.96) compared to VKAs

Citation: Ferahta N, Kanagaratnam L, Dramé M, Vogel T, Ambrosi PJ, et al. (2017) Bleeding Risk under Oral Factor Xa Inhibitors: Meta-analysis of the randomized comparison with Vitamin K Antagonists and Meta-Regression analysis. J Cardiovasc Med Cardiol 4(3): 038-048. DOI: http://doi.org/10.17352/2455-2976.000048

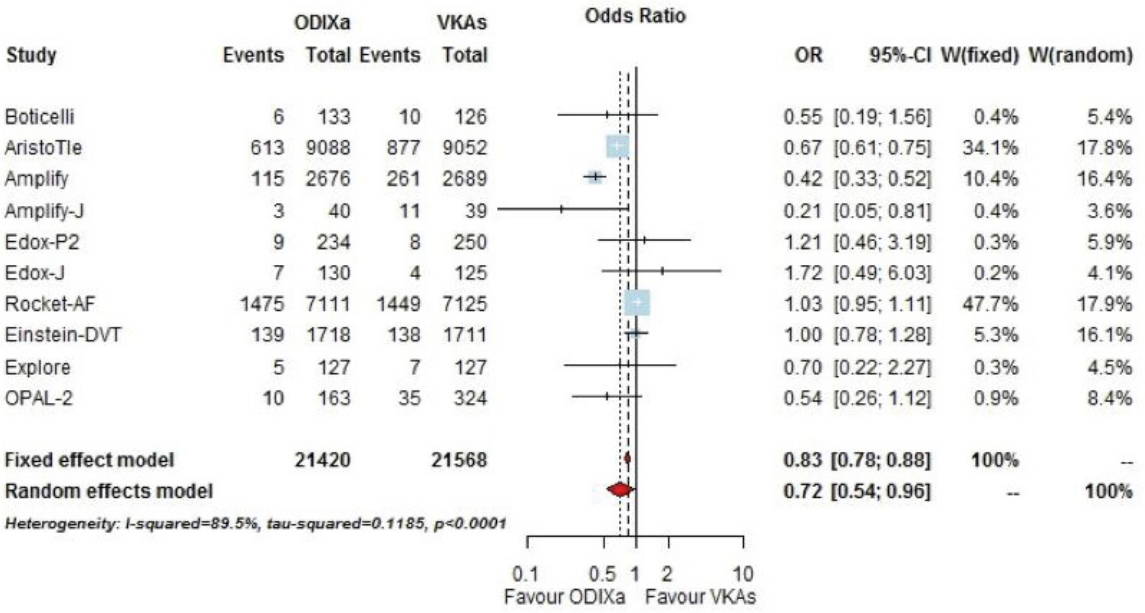

Figure 3: Forest plot for risk of major and CRNM bleeding in patients with ODIXa versus VKAs.

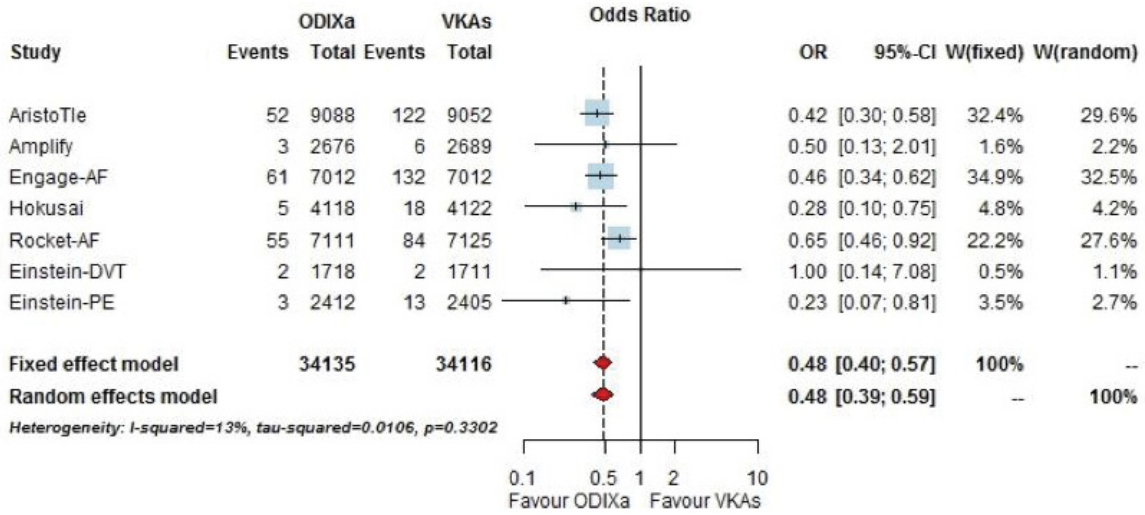

Figure 4: Forest plot of risk of intracranial hemorrhage in patients with ODIXa versus VKAs.

(Figure 6). The reduction risk was however not statistically different (*P= 0.6041*) when analysis was adjusted on the therapeutic indication (NVAF and venous thromboembolic disease. A significant reduction was measured for apixaban (OR, 0.88; 95% CI, 0.79-0.99) only.

Meta-regression analysis

Meta-regression analyses showed no significant impact of age, sex-ratio, TTR, combination with antiplatelet agent and heparin therapy duration on risk of major bleeding, major and CRNM bleeding, ICH, total bleeding and total mortality events (all $P > 0.05$). A significant correlation with $CHADS_2$ score was identified; higher score was associated with increased risk of major bleeding (*P=0.002*) in NVAF patients receiving ODIXa. For risk of gastrointestinal bleeding under ODIXa, results showed the same significant linear correlation with increasing age *(P=0.003)* and a higher TTR *(P=0.006)* (Figure 7).

Sensitivity analysis

The sensitivity analysis with removal of phase II dose-ranging studies showed parallel results to the primary analyses.

Discussion

To better assess the clinical benefit of ODIXa, we carried out a systematic review of the literature and meta-analysis of large phase II and phase III RCTs. Our pragmatic approach (recommended doses) provides results mimicking real-world

Citation: Ferahta N, Kanagaratnam L, Dramé M, Vogel T, Ambrosi PJ, et al. (2017) Bleeding Risk under Oral Factor Xa Inhibitors: Meta-analysis of the randomized comparison with Vitamin K Antagonists and Meta-Regression analysis. J Cardiovasc Med Cardiol 4(3): 038-048. DOI: http://doi.org/10.17352/2455-2976.000048

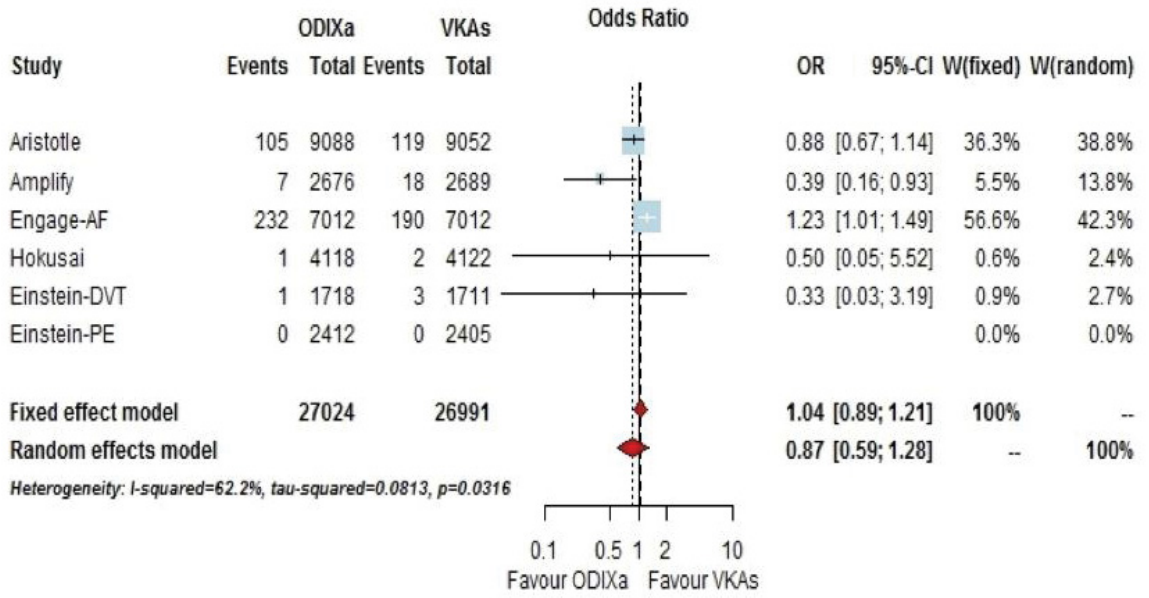

Figure 5: Forest plot for risk of gastrointestinal bleeding in patients on ODIXa versus VKAs.

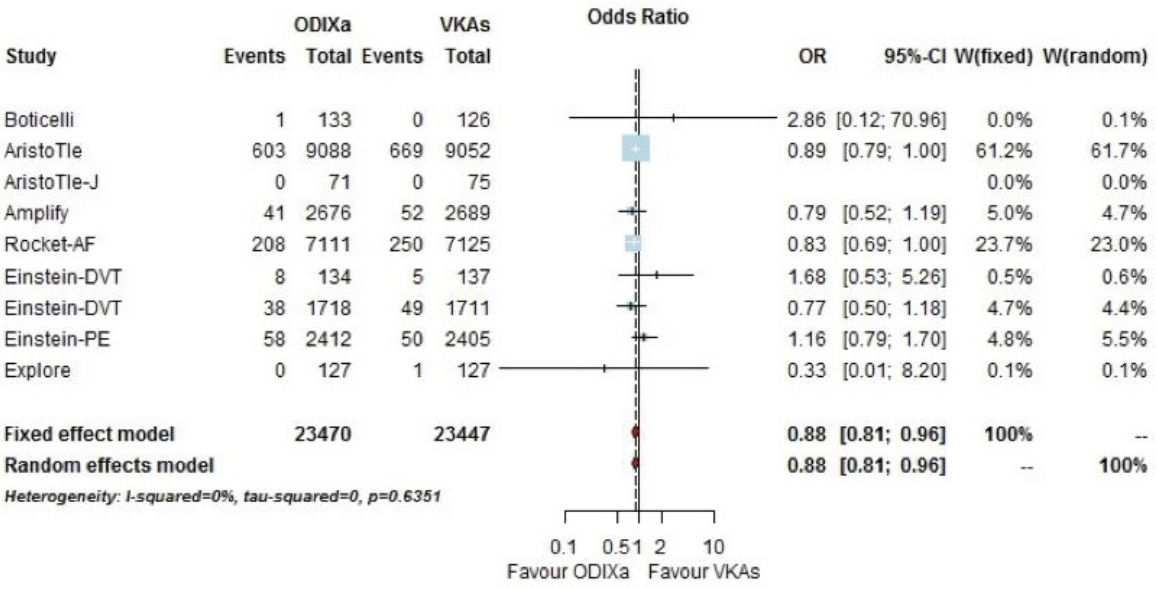

Figure 6: Forest plot of risk of global mortality in patients with ODIXa versus VKAs.

data and gives raise to five major clinical implications suitable for the clinical practice.

First, practitioners have to pay close attention to polypharmacy when they initiate a treatment with ODIXa. When compared to VKAs in the present meta-analysis, ODIXa were associated with lower risks of major bleeding, CRNM, ICH, total bleeding events, and all-cause mortality. This was measured whatever the length of the initial heparin therapy and the therapeutic indication. This is consistent with other meta-analysis [7, 8, 14-16, 18, 20, 24, 26, 28]. The specific modes of action of these drugs and/or the lesser frequency of drug-drug or food-drug interactions are often suggested as an explanation. Indeed, VKAs have direct inhibitory effects on factors II, VII, IX unlike ODIXa that specifically targets the factor Xa. Recently, it has been showed that ODIXa were substrates of P-glycoprotein (P-gp) that is an efflux transporter. It is found, as an example, in the blood-brain barrier. Thus, differences of tissue distribution could explain, at least in part, the difference in bleeding rates measured between ODIXa and VKAs. Among cardiovascular drugs, many are P-gp substrate or inhibitor and can be considered in AF patients. As an example, amiodarone or verapamil have been observed to have clinically relevant interactions with ODIXa and subsequently may increase the anticoagulant plasma concentrations [54]. Gschwind *et al* have found that P-gp inhibitors did not affect significantly

Citation: Ferahta N, Kanagaratnam L, Dramé M, Vogel T, Ambrosi PJ, et al. (2017) Bleeding Risk under Oral Factor Xa Inhibitors: Meta-analysis of the randomized comparison with Vitamin K Antagonists and Meta-Regression analysis. J Cardiovasc Med Cardiol 4(3): 038-048. DOI: http://doi.org/10.17352/2455-2976.000048

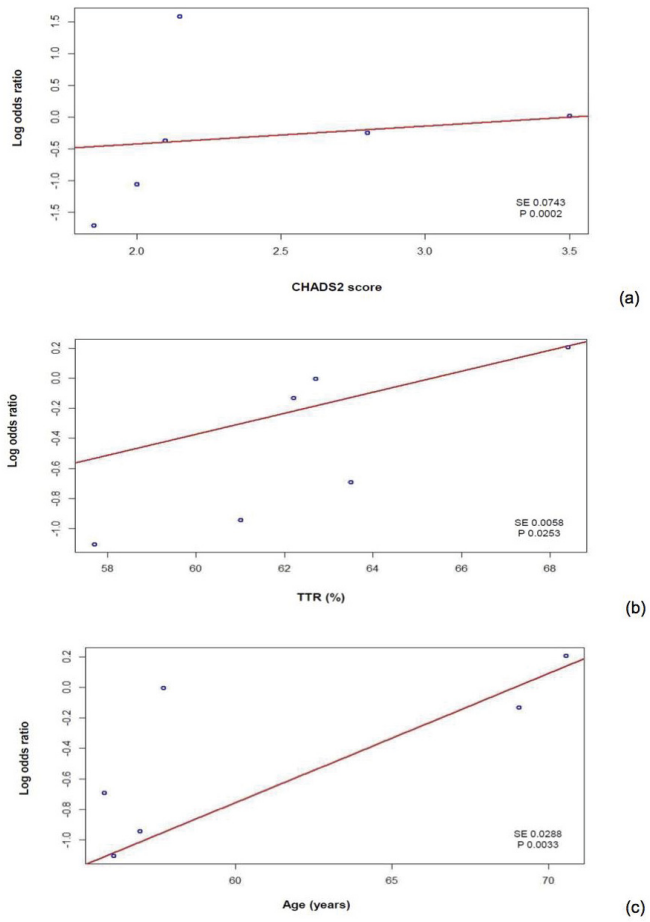

Figure 7: Major bleeding and regression on $CHADS_2$ score (a); gastrointestinal bleeding and regression on TTR (b) and age (c).

the transport of warfarin but might potentiate the ODIXa anticoagulant effect [55,56]. So clinicians have to pay close attention to polypharmacy when they initiate a treatment with ODIXa.

Second, based on our findings, another caution in prescribing ODIXa is the lost of benefit of ODIXa over VKAs when the warfarin treatment is properly balanced within therapeutic range (*i.e.*, TTR). Indeed, this above described benefits of ODIXa can be directly influenced by the quality of warfarin therapy. In multicenter RCTs, greater relative benefits of ODIXa were systematically reported when the INR management was poor [57]. On average, the TTR across the 18 RCTs of this meta-analysis ranged between 45.1 to 80.3%. A retrospective analysis of 3, 587 AF patients reported that one-third with the poorest INR control (*i.e.*, 48% of TTR) had twice the rate of stroke, myocardial infarction, major bleeding, and death as did the one-third with the best control (*i.e.* TTR ≥ 83%) [58]. TTR ≥ 75% were commonly reported with warfarin treatment in real-life [59], revealing TTR during RCTs qualitatively disappointing with an over-estimation of the real benefits of ODIXa. This confirms, not only that patients on warfarin with INR stable in therapeutic range should stay on it because in that case ODIXa do not appear as a better alternative [60] but also in older patients without any concomitant physical and medical problems that may increase the interactions and risks associated with warfarin (i.e., concurrent medication or disease states that increase bleeding risk or interfere with anticoagulation control, a problem with drug compliance or attendance for monitoring) [61]. Even we confirmed that the risk of major bleeding under ODIXa was greater with higher $CHADS_2$ score so common stroke risk factors and comorbid conditions increase the risk of major bleeding under ODIXa [62].

Third, in the line with one previous report [12], and real-word data [63], while the risk of ICH was lowered when taking ODIXa compared to VKAs, a particular attention should be paid on older and frail patients. Of all types of bleeding events, ICH is the most devastating and disabling complication but also the most feared adverse events of anticoagulants [64,65]. ICH are however less frequent than GIB which represent the most common bleeding site, with an age-standardized incidence rate of 5.8 per 1000 person-year [66], (i.e., an approximately three-fold increased risk as compared with the general population [67]. When the current recommendations include low bodyweight and impaired renal clearance as criteria in addition to age for dose adaptation in older patients, the lack of proper clinical evidence on the use of ODIXa in the frail older patients raises concerns on whether these recommendations apply for this particular group.

Fourth, in the assessment of the risk of GIB, physicians have to pay attention that the patients receiving ODIXa in every day practice are dramatically different from those enrolled in RCTs. Consistent with many registries [68-71], and real-world studies, on ODIXa [70, 72-74], the risk of GIB is described as being lower as or at least similar to that for warfarin. In the present meta-analysis, globally the risk of GIB with ODIXa was not significantly different from that with VKAs in NVAF, but lower in DTV or PE. Among all five ODIXa, apixaban was associated with a lower risk of GIB compared with VKA [34]. Similarly, this was the conclusion of a recent large population-based study retrospectively conducted on administrative claims data from the OptumLabs Data Warehouse of privately insured individuals and Medicare Advantage enrollees [75]. Three matched-pair cohorts were created from patients with NVAF who were exposed to dabigatran, rivaroxaban, or apixaban during a period of 4 years and 5 months (data on rivaroxaban vs dabigatran for 31,574 patients, data on apixaban vs dabigatran for 13,084 patients, and data on apixaban vs rivaroxaban for 13,130 patients). Higher rate of GIB events occurred with rivaroxaban than with dabigatran (2.74 *vs.* 2.02/100 patient-years; hazard ratio – HR, 1.20; 95% confidence interval, 1.00–1.45) ; fewer with apixaban than with dabigatran (1.38 *vs.* 2.73/100 patient-years; HR. 0.39; 95% CI, 0.27–0.58) ; and fewer GIB events also occurred with apixaban than with rivaroxaban (1.34 *vs.* 3.54/100 patient-years; HR, 0.33; 95% CI, 0.22–0.49). Thus, apixaban has the lowest risk and rivaroxaban the highest and comparing apixaban with rivaroxaban and with dabigatran, the number needed to harm was 45 and 74, respectively. This was also observed in other real-word studies [73,76]. In the line with this comment, the meta-regression analysis has also shown that the older age was an independent risk factor of GIB [61]. This was also measured in the two large

Citation: Ferahta N, Kanagaratnam L, Dramé M, Vogel T, Ambrosi PJ, et al. (2017) Bleeding Risk under Oral Factor Xa Inhibitors: Meta-analysis of the randomized comparison with Vitamin K Antagonists and Meta-Regression analysis. J Cardiovasc Med Cardiol 4(3): 038-048. DOI: http://doi.org/10.17352/2455-2976.000048

population-based studies conducted by Abrahams *et al* [71,75]. Among all the ODIXa, authors reported that apixaban had the fewest GIB events in patients ≥75 years of age and finally had the most favorable gastrointestinal safety profile among all age groups [75]. Similarly, in a recent systematic review and meta-analysis assessing the efficacy and safety of four DOAC (apixaban, dabigatran, edoxaban and rivaroxaban) in patients aged 75 years or older with NVAF or DVT, DOAC demonstrated the same or greater efficacy that VKA but no statistically significant difference in safety outcomes [77]. In addition, in RCTs, methodological reasons related to characteristics of patients at baseline, such as age and $CHADS_2$ score, may also explain the described benefit of ODIXa over VKAs. In ROCKET-AF [47], the mean age was higher and none of patients had a $CHADS_2$ score ≤1 compared those enrolled in Abraham et *al.* population-based study [71], in which the risk of GIB under DOACs was similar to that for warfarin. Most RCTs excluded patients at higher risk of bleeding. It however important to note that in ROCKET-AF [47], despite higher $CHADS_2$ score, major bleeding were consistently similar to VKAs regardless of the $CHADS_2$ score and age. Hence, the relationship between rivaroxaban and bleeding risk compared to VKA is systematic and not specific to higher risk subgroups as subsequently confirmed by real-word studies [73,75].

Fifth, specific pharmacological and safety profiles of ODIXa are extended well beyond the risk of GIB. Indeed, while all five ODIXa have the same mechanism of action and results are consistent across molecules regardless of indication it is important to note that some start diverging in different population (e.g. NVAF vs. DVT or PE). This has been previously presented with apixaban and rivaroxaban for gastrointestinal safety [73,75,76]. Recently, in a systematic review and meta-analysis assessing the efficacy and safety of DOAC in adults aged 75 years or over [77]. Interestingly, in NVAF patients, when major or CRNM were considered, apixaban showed a statistically significant odds reduction compared with rivaroxaban (OR 0.57, 95 CI 0.45–0.73). The latter was associated with higher odds ratios for bleeding compared with edoxaban doses (OR 0.71, 95% CI 0.57–0.89). Indirect comparison of ODIXa for the composite endpoint recurrent DVT or DVT-related death did not show any statistical difference. However, edoxaban showed a statistically significant higher odds ratio for bleeding when compared with apixaban (OR 3.58, 95% CI 1.13–11.40) and rivaroxaban (OR 2.94, 95% CI 1.22–7.08). Whereas only direct comparative studies will really help to detect possible profile differences among ODIXa, some explanations can be found in intrinsic ODIXa pharmacological characteristics. In a recent study the potency using drug-related parameters (i.e., molecular weight, bioavailability, protein-biding rate, inhibitory constant and dosage) was considered to compare ODIXa dosage and intensity [78]. The relatives potencies were different, with that of apixaban higher than edoxaban and nearly twice that of rivaroxaban. These results suggest that rivaroxaban and apixaban differ in regard to anticoagulation type, as the former shows persistent and the latter intermittent anticoagulation.

Whilst the provision of interesting and important results throughout the exploration of the available literature this meta-analysis has five major limitations. First, it has been conducted on aggregated published data from randomised controlled trials, instead of individual patient data, which can be a potential source of bias. Second, it did not include unpublished data. Third, the wide heterogeneity observed within study populations, design, durations of follow-up, and definitions of bleeding events across the 18 RCTs, could have confounded our findings. In order to limit inter-trial heterogeneity all the pooled analyses were computed with a random effect model that is more appropriate to consider than a fixed effect model in this situation. Indirect comparisons by startifying analyses according to therapeutic indication (NVAF and DVT or PE) and study phase have been conducted. In addition, in order to further explore the heterogeneity for phase III RCTs sensitivity analysis was performed. However, we cannot exclude the possibility that some of the differences in trial design and baseline characteristics of participants might have an impact on our results. The open label study design also appears to overestimate safety of ODIXa [79], and it was not possible to exclude a reporting bias regarding the safety outcome. Fourth, the lack of randomized controlled head-to-head comparisons between the five available ODIXa has also limited our conclusion. Fifth, we are aware that the population included in the randomised controlled trials is not always totally representative of everyday practice. Thus, the extrapolation of the results of the RCTs to the entire patient population is also restricted, as the strict design yields information suitable to a relatively narrow spectrum of patients. Not all the patients are exposed to the same risk of bleeding when taking ODIXa. Thus, vulnerable populations (i.e., older, frail, polymedicated, and multimorbid patients) were generally under- or not represented; so the impact of older age and underlying conditions such as impaired kidney function, malignancy, prior stroke or bleeding events, and potential drug-drug interaction on bleeding risks were not reported due to non-availability of data in most of RCTs [80]. Consequently, caution is also needed to apply the conclusions of this meta-analysis to these very high-risk groups and may lead to the decision of not prescribing the ODIXa or to adapt the dose of this family medication for which, finally, we still have a limited experience and no registered antidote yet.

Conclusion

Pooled analysis from RCTs concludes that the risks of major, CRNM bleeding, and more particularly ICH are reduced under ODIXa compared with VKA. It was measured higher CHADS2 score as predictor of major bleeding risk under ODIXa and GIB risk was increased with advancing age and greater quality of VKAs monitoring. More accurate safety data was however lacking among polymedicated patients and those with multiple comorbid conditions, frailer and older patients and should be provided through clinical trials specifically designed for these vulnerable population.

References

1. Wysowski DK, Nourjah P, Swartz L (2007) Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. Arch Intern Med 167: 1414-1419. Link: https://goo.gl/c9m97C

Citation: Ferahta N, Kanagaratnam L, Dramé M, Vogel T, Ambrosi PJ, et al. (2017) Bleeding Risk under Oral Factor Xa Inhibitors: Meta-analysis of the randomized comparison with Vitamin K Antagonists and Meta-Regression analysis. J Cardiovasc Med Cardiol 4(3): 038-048. DOI: http://doi.org/10.17352/2455-2976.000048

2. Classen DC, Jaser L, Budnitz DS (2010) Adverse drug events among hospitalized Medicare patients: epidemiology and national estimates from a new approach to surveillance. Jt Comm J Qual Patient Saf 36: 12-21. Link: https://goo.gl/aoyJNs

3. Budnitz DS, Lovegrove MC, Shehab N, Richards CL (2011) Emergency Hospitalizations for Adverse Drug Events in Older Americans. New England Journal of Medicine 365: 2002-2012. Link: https://goo.gl/HM8AH4

4. Berti D, Moors E, Moons P, Heidbuchel H (2015) Prevalence and antithrombotic management of atrial fibrillation in hospitalised patients. Heart 101: 884-893. Link: https://goo.gl/hLQXN1

5. Barnes GD, Lucas E, Alexander GC, Goldberger ZD (2015) National Trends in Ambulatory Oral Anticoagulant Use. Am J Med 128: 1300-1305. Link: https://goo.gl/enXuVK

6. Yeh CH, Fredenburgh JC, Weitz JI (2012) Oral direct factor Xa inhibitors. Circ Res 111: 1069-1078. Link: https://goo.gl/av8QHs

7. Del-Carpio Munoz F, Gharacholou SM, Munger TM, Friedman PA, Asirvatham SJ, et al. (2016) Meta-Analysis of Renal Function on the Safety and Efficacy of Novel Oral Anticoagulants for Atrial Fibrillation. Am J Cardiol 117: 69-75. Link: https://goo.gl/v8JujY

8. Dentali F, Riva N, Crowther M, Turpie AGG, Lip GYH, et al. (2012) Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation 126: 2381-2391. Link: https://goo.gl/HKWPaX

9. Fox BD, Kahn SR, Langleben D, Eisenberg MJ, Shimony A (2012) Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-analysis of randomised controlled trials. BMJ 345: e7498. Link: https://goo.gl/UB5qmX

10. Fu W, Guo H, Guo J, Lin K, Wang H, et al. (2014) Relative efficacy and safety of direct oral anticoagulants in patients with atrial fibrillation by network meta-analysis. J Cardiovasc Med (Hagerstown) 15: 873-879. Link: https://goo.gl/cXem8f

11. Koifman E, Lipinski MJ, Escarcega RO, Didier R, Kiramijyan S, et al. (2016) Comparison of Watchman device with new oral anti-coagulants in patients with atrial fibrillation: A network meta-analysis. Int J Cardiol 205: 17-22. Link: https://goo.gl/qJrTL2

12. Kundu A, Sen P, Sardar P, Chatterjee S, Kapoor A, et al. (2016) Intracranial hemorrhage with target specific oral anticoagulants in patients with atrial fibrillation: An updated meta-analysis of randomized controlled trials. Int J Cardiol 203: 1000-1002. Link: https://goo.gl/9Wo62c

13. Lega JC, Bertoletti L, Gremillet C, Boissier C, Mismetti P, et al. (2014) Consistency of safety profile of new oral anticoagulants in patients with renal failure. J Thromb Haemost 12: 337-343. Link: https://goo.gl/kqyb3X

14. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ (2012) Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. Am J Cardiol 110: 453-460. Link: https://goo.gl/UyKt4T

15. Nunes JPL, Rodrigues RP, Goncalves FR (2014) Comparative analysis and meta-analysis of major clinical trials with oral factor Xa inhibitors versus warfarin in atrial fibrillation. Open Heart 1: e000080. Link: https://goo.gl/d48Kg7

16. Providencia R, Grove EL, Husted S, Barra S, Boveda S, et al. (2014) A meta-analysis of phase III randomized controlled trials with novel oral anticoagulants in atrial fibrillation: comparisons between direct thrombin inhibitors vs. factor Xa inhibitors and different dosing regimens. Thromb Res 134: 1253-1264. Link: https://goo.gl/xFXpu7

17. Robertson L, Kesteven P, McCaslin JE (2015) Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism. Cochrane Database Syst Rev 12: CD010957. Link: https://goo.gl/4aswQi

18. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, et al. (2014) Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 383: 955-962. Link: https://goo.gl/9GcnuJ

19. Sardar P, Chatterjee S, Wu W-C, Lichstein E, Ghosh J, et al. (2013) New oral anticoagulants are not superior to warfarin in secondary prevention of stroke or transient ischemic attacks, but lower the risk of intracranial bleeding: insights from a meta-analysis and indirect treatment comparisons. PLoS One 8: e77694. Link: https://goo.gl/6rh9qh

20. Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M (2015) Efficacy and Harms of Direct Oral Anticoagulants in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention of Venous Thromboembolism: Systematic Review and Meta-Analysis. Circulation 132: 194-204. Link: https://goo.gl/uKSLFK

21. Verdecchia P, Angeli F, Bartolini C, De Filippo V, Aita A, et al. (2015) Safety and efficacy of non-vitamin K oral anticoagulants in non-valvular atrial fibrillation: a Bayesian meta-analysis approach. Expert Opin Drug Saf 14: 7-20. Link: https://goo.gl/XaT44T

22. Sen S, Dahlberg KW (2014) Physician's fear of anticoagulant therapy in nonvalvular atrial fibrillation. Am J Med Sci 348: 513-521. Link: https://goo.gl/RtWGnL

23. Garg J, Chaudhary R, Krishnamoorthy P, Palaniswamy C, Shah N, et al. (2016) Safety and efficacy of oral factor-Xa inhibitors versus Vitamin K antagonist in patients with non-valvular atrial fibrillation: Meta-analysis of phase II and III randomized controlled trials. Int J Cardiol 218: 235-239. Link: https://goo.gl/9C3kPz

24. Pathak R, Pandit A, Karmacharya P, Aryal MR, Ghimire S, et al.(2015) Meta-analysis on risk of bleeding with apixaban in patients with renal impairment. Am J Cardiol 115: 323-327. Link: https://goo.gl/pirPFY

25. Sardar P, Chatterjee S, Lavie CJ, Giri JS, Ghosh J, et al. (2015) Risk of major bleeding in different indications for new oral anticoagulants: insights from a meta-analysis of approved dosages from 50 randomized trials. Int J Cardiol 179: 279-287. Link: https://goo.gl/LJS1XS

26. Touma L, Filion KB, Atallah R, Eberg M, Eisenberg MJ (2015) A meta-analysis of randomized controlled trials of the risk of bleeding with apixaban versus vitamin K antagonists. Am J Cardiol 115: 533-541. Link: https://goo.gl/xWnaCL

27. Bruins Slot KMH, Berge E (2013) Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation. Cochrane Database Syst Rev 8: CD008980. Link: https://goo.gl/h5c6xM

28. Riva N, Dentali F, Permunian ET, Ageno W (2016) Major Bleeding and Case Fatality Rate with the Direct Oral Anticoagulants in Orthopedic Surgery: A Systematic Review and Meta-Analysis. Semin Thromb Hemost 42: 42-54. Link: https://goo.gl/GbCfTj

29. Diener H-C, Eikelboom J, Connolly SJ, Joyner CD, Hart RG, et al. (2012) Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. Lancet Neurol 11: 225-231. Link: https://goo.gl/kM7NHk

30. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, et al. (2015) The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and ExplanationsPRISMA Extension for Network Meta-analysis. Ann Intern Med 162: 777-784. Link: https://goo.gl/7L8PgT

31. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, et al. (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343: d5928. Link: https://goo.gl/nDj3sa

Citation: Ferahta N, Kanagaratnam L, Dramé M, Vogel T, Ambrosi PJ, et al. (2017) Bleeding Risk under Oral Factor Xa Inhibitors: Meta-analysis of the randomized comparison with Vitamin K Antagonists and Meta-Regression analysis. J Cardiovasc Med Cardiol 4(3): 038-048. DOI: http://doi.org/10.17352/2455-2976.000048

32. Agnelli G, Gallus A, Goldhaber SZ, Haas S, Huisman MV, et al. (2007) Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study. Circulation 116: 180-187. Link: https://goo.gl/xeqD1e

33. Hori M, Matsumoto M, Tanahashi N, Momomura S-i, Uchiyama S, et al. (2012) Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation – the J-ROCKET AF study –. Circ J 76: 2104-2111. Link: https://goo.gl/XBUaDK

34. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, et al. (2013) Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 369: 799-808. Link: https://goo.gl/QmTKh3

35. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, et al. (2010) Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 363: 2499-2510. Link: https://goo.gl/EuxwQy

36. Buller H, Deitchman D, Prins M, Segers A (2008) Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. J Thromb Haemost 6: 1313-1318. Link: https://goo.gl/mDQ961

37. Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, et al. (2013) Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 369: 1406-1415. Link: https://goo.gl/Wr942h

38. Buller HR, Lensing AWA, Prins MH, Agnelli G, Cohen A, et al. (2008) A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study. Blood 112: 2242-2247. Link: https://goo.gl/uueCTS

39. Buller HR, Prins MH, Lensin AWA, Decousus H, Jacobson BF, et al. (2012) Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 366: 1287-1297. Link: https://goo.gl/JWjqcj

40. Chung N, Jeon H-K, Lien L-M, Lai W-T, Tse H-F, et al. (2011) Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. Thromb Haemost 105: 535-544. Link: https://goo.gl/pCjBPQ

41. Connolly SJ, Eikelboom J, Dorian P, Hohnloser SH, et al. (2013) Betrixaban compared with warfarin in patients with atrial fibrillation: results of a phase 2, randomized, dose-ranging study (Explore-Xa). Eur Heart J 34: 1498-1505. Link: https://goo.gl/oZG8op

42. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, et al. (2013) Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 369: 2093-2104. Link: https://goo.gl/cAqa42

43. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, et al. (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 365: 981-992. Link: https://goo.gl/DqnJQb

44. Lip GYH, Halperin JL, Petersen P, Rodgers GM, Pall D, et al. (2015) A Phase II, double-blind, randomized, parallel group, dose-finding study of the safety and tolerability of darexaban compared with warfarin in patients with non-valvular atrial fibrillation: the oral factor Xa inhibitor for prophylaxis of stroke in atrial fibrillation study 2 (OPAL-2). J Thromb Haemost 13: 1405-1413. Link: https://goo.gl/drd3nk

45. Nakamura M, Nishikawa M, Komuro I, Kitajima I, Uetsuka Y, et al. (2015) Apixaban for the Treatment of Japanese Subjects With Acute Venous Thromboembolism (AMPLIFY-J Study). Circ J 79: 1230-1236. Link: https://goo.gl/KDRarf

46. Ogawa S, Shinohara Y, Kanmuri K (2011) Safety and efficacy of the oral direct factor xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation. The ARISTOTLE-J study. Circ J 75: 1852-1859. Link: https://goo.gl/pfKzpg

47. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, et al. (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 365: 883-891. Link: https://goo.gl/WHvZp7

48. Turpie AGG, Lip GYH, Minematsu K, Goto S, Renfurm RW, et al. (2010) Safety and tolerability of YM150 in subjects with non-valvular atrial fibrillation: a phase II study. European Society of Cardiology (ESC) Congress, Stockholm, Sweden. Link: https://goo.gl/eqGQaH

49. Weitz JI, Connolly SJ, Patel I, Salazar D, Rohatagi S, et al. (2010) Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Thromb Haemost 104: 633-641. Link: https://goo.gl/n3RJnt

50. Yamada N, Hirayama A, Maeda H, Sakagami S, Shikata H, et al. (2015) Oral rivaroxaban for Japanese patients with symptomatic venous thromboembolism - the J-EINSTEIN DVT and PE program. Thromb J 13: 2. Link: https://goo.gl/t8qEJg

51. Yamashita T, Koretsune Y, Yasaka M, Inoue H, Kawai Y, et al. (2012) Randomized, multicenter, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. Circ J 76: 1840-1847. Link: https://goo.gl/L4aC9m

52. Connolly SJ, Eikelboom J, Joyner C, Diener H-C, Hart R, et al. (2011) Apixaban in Patients with Atrial Fibrillation. N Engl J Med 364: 806-817. Link: https://goo.gl/NazGqQ

53. Schulman S, Kearon C (2005) Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 3: 692-694. Link: https://goo.gl/yg3ihn

54. Mendell J, Zahir H, Matsushima N, Noveck R, Lee F, et al. (2013) Drug-Drug Interaction Studies of Cardiovascular Drugs Involving P-Glycoprotein, an Efflux Transporter, on the Pharmacokinetics of Edoxaban, an Oral Factor Xa Inhibitor. Am J Cardiovasc Drugs 13: 331-342. Link: https://goo.gl/Hwv67J

55. Gschwind L, Rollason V, Daali Y, Bonnabry P, Dayer P, et al. (2013) Role of P-glycoprotein in the uptake/efflux transport of oral vitamin K antagonists and rivaroxaban through the Caco-2 cell model. Basic Clin Pharmacol Toxicol 113: 259-265. Link: https://goo.gl/wu5LMq

56. Mueck W, Kubitza D, Becka M (2013) Co-administration of rivaroxaban with drugs that share its elimination pathways: pharmacokinetic effects in healthy subjects. Br J Clin Pharmacol 76: 455-466. Link: https://goo.gl/5RZSsH

57. Witt DM, Delate T, Hylek EM, Clark NP, Crowther MA et al. (2013) Effect of warfarin on intracranial hemorrhage incidence and fatal outcomes. Thromb Res 132: 770-775. Link: https://goo.gl/ZLCwgY

58. White HD, Gruber M, Feyzi J, Kaatz S, Tse H-F, et al. (2007) Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. Arch Intern Med 167: 239- 245. Link: https://goo.gl/fY2ZPv

59. Bjorck F, Sanden P, Renlund H, Svensson PJ, Sjalander A (2015) Warfarin treatment quality is consistently high in both anticoagulation clinics and primary care setting in Sweden. Thromb Res 136: 216-220. Link: https://goo.gl/Y94ZY7

60. (2016) Which oral anticoagulant for atrial fibrillation?. JAMA 315: 2117-2118. Link: https://goo.gl/uPw4sW

61. Fitzmaurice DA, Blann AD, Lip GYH (2002) Bleeding risks of antithrombotic therapy. BMJ 325: 828-831. Link: https://goo.gl/Qpk9pP

62. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S (2007) Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation 115: 2689-2696. Link: https://goo.gl/1A6om1

63. Hecker J, Marten S, Keller L, Helmert S, Michalski F, et al. (2016) Effectiveness and safety of rivaroxaban therapy in daily-care patients with atrial fibrillation. Results from the Dresden NOAC Registry. Thromb Haemost 115: 939-949. Link: https://goo.gl/ivjMSC

Citation: Ferahta N, Kanagaratnam L, Dramé M, Vogel T, Ambrosi PJ, et al. (2017) Bleeding Risk under Oral Factor Xa Inhibitors: Meta-analysis of the randomized comparison with Vitamin K Antagonists and Meta-Regression analysis. J Cardiovasc Med Cardiol 4(3): 038-048. DOI: http://doi.org/10.17352/2455-2976.000048

64. Fang MC, Go AS, Chang Y, Hylek EM, Henault LE, et al. (2007) Death and disability from warfarin-associated intracranial and extracranial hemorrhages. Am J Med 120: 700-705. Link: https://goo.gl/nwPnd7

65. Hansen BM, Nilsson OG, Anderson H, Norrving B, Saveland H, et al. (2013) Long term (13 years) prognosis after primary intracerebral haemorrhage: a prospective population based study of long term mortality, prognostic factors and causes of death. J Neurol Neurosurg Psychiatry 84: 1150-1155. Link: https://goo.gl/1dyF9b

66. Hippisley-Cox J, Coupland C (2014) Predicting risk of upper gastrointestinal bleed and intracranial bleed with anticoagulants: cohort study to derive and validate the QBleed scores. BMJ 349: g4606. Link: https://goo.gl/DjQjny

67. Coleman CI, Sobieraj DM, Winkler S, Cutting P, Mediouni M, et al. (2012) Effect of pharmacological therapies for stroke prevention on major gastrointestinal bleeding in patients with atrial fibrillation. International journal of clinical practice 66: 53-63. Link: https://goo.gl/KDfnse

68. Kakkar AK, Mueller I, Bassand J-P, Fitzmaurice DA, Goldhaber SZ, et al. (2013) Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. PLoS One 8:e63479. Link: https://goo.gl/pzCuC2

69. Steinberg BA, Blanco RG, Ollis D, Kim S, Holmes DN, et al. (2014) Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II: rationale and design of the ORBIT-AF II registry. Am Heart J 168: 160-167. Link: https://goo.gl/EadZkw

70. Tamayo S, Frank Peacock W, Patel M, Sicignano N, Hopf KP, et al. (2015) Characterizing Major Bleeding in Patients With Nonvalvular Atrial Fibrillation: A Pharmacovigilance Study of 27 467 Patients Taking Rivaroxaban. Clin Cardiol 38: 63-68. Link: https://goo.gl/9SXrmQ

71. Abraham NS, Singh S, Alexander GC, Heien H, Haas LR, et al. (2015) Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. BMJ 350: h1857. Link: https://goo.gl/hUUXdU

72. Camm AJ, Amarenco P, Haas S, Hess S, Kirchhof P, et al.(2016) XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J 37: 1145-1153. Link: https://goo.gl/ULcraK

73. Yao X, Abraham NS, Sangaralingham LR, Bellolio MF, McBane RD, et al. (2016) Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation. JAHA 5: e003725. Link: https://goo.gl/Wd4w3Z

74. Ageno W, Mantovani LG, Haas S, Kreutz R, Monje D, et al. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. Lancet Haematol 3: e12-e21. Link:https://goo.gl/G4hgTD

75. Abraham NS, Noseworthy PA, Yao X, Sangaralingham LR, Shah ND (2017) Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population Based Study. Gastroenterology 152: 1014-1022.e1. Link: https://goo.gl/2S3eU6

76. Li XS, Deitelzweig S, Keshishian A, Hamilton M, Horblyuk R, et al. (2017) Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice. A propensity-matched analysis of 76,940 patients. Thromb Haemost 117: 1072-1082. Link: https://goo.gl/7XGZDF

77. Sadlon AH, Tsakiris DA (2016) Direct oral anticoagulants in the elderly: systematic review and meta-analysis of evidence, current and future directions. Swiss Med Wkly 146: w14356. Link: https://goo.gl/PR7zpW

78. Ieko M, Naitoh S, Yoshida M, Takahashi N (2016) Profiles of direct oral anticoagulants and clinical usage - dosage and dose regimen differences. J Intensive Care 4: 19. Link: https://goo.gl/ZuSN6n

79. Schulz KF, Chalmers I, Hayes RJ, Altman DG (1995) Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 273: 408-412. Link: https://goo.gl/fheto2

80. Topinkova E, Baeyens JP, Michel J-P, Lang P-O (2012) Evidence-based strategies for the optimization of pharmacotherapy in older people. Drugs Aging 29: 477-494. Link: https://goo.gl/5T2bCR

Citation: Ferahta N, Kanagaratnam L, Dramé M, Vogel T, Ambrosi PJ, et al. (2017) Bleeding Risk under Oral Factor Xa Inhibitors: Meta-analysis of the randomized comparison with Vitamin K Antagonists and Meta-Regression analysis. J Cardiovasc Med Cardiol 4(3): 038-048. DOI: http://doi.org/10.17352/2455-2976.000048