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 DTTI) [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 $\chi^2$ (Chi2) test and $I^2$ statistic. The random effect model was considered independently of the existence of...
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<sup>2</sup> 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

**Table 1:** Baseline characteristics of included trials.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Indication</th>
<th>Study drug</th>
<th>Control drug</th>
<th>Duration (month)</th>
<th>Mean age (year)</th>
<th>ISTH Bleeding definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottleci (2008)</td>
<td>VTE</td>
<td>Apixaban</td>
<td>Warfarin Acenocoumarol Phenprocoumon</td>
<td>2-3</td>
<td>128</td>
<td>3</td>
</tr>
<tr>
<td>Aristotle (2011)</td>
<td>AF</td>
<td>Apixaban</td>
<td>Warfarin</td>
<td>2-3</td>
<td>9081</td>
<td>21.6*</td>
</tr>
<tr>
<td>Aristotle-J (2011)</td>
<td>AF</td>
<td>Apixaban</td>
<td>Warfarin</td>
<td>2-3</td>
<td>74</td>
<td>3</td>
</tr>
<tr>
<td>Amplify (2013)</td>
<td>VTE</td>
<td>Apixaban</td>
<td>Warfarin</td>
<td>2-3</td>
<td>2704</td>
<td>6</td>
</tr>
<tr>
<td>Amplify-J (2015)</td>
<td>VTE</td>
<td>Apixaban</td>
<td>Warfarin</td>
<td>1.5-2.5</td>
<td>40</td>
<td>6</td>
</tr>
<tr>
<td>EDOX US-EU (2010)</td>
<td>AF</td>
<td>Edoxaban</td>
<td>Warfarin</td>
<td>2-3</td>
<td>251</td>
<td>3</td>
</tr>
<tr>
<td>EDOX Asia (2010)</td>
<td>AF</td>
<td>Edoxaban</td>
<td>Warfarin</td>
<td>2-3</td>
<td>75</td>
<td>3</td>
</tr>
<tr>
<td>EDOX Japan (2011)</td>
<td>AF</td>
<td>Edoxaban</td>
<td>Warfarin</td>
<td>2-3</td>
<td>121</td>
<td>3</td>
</tr>
<tr>
<td>Engage AF-TIMI (2013)</td>
<td>AF</td>
<td>Edoxaban</td>
<td>Warfarin</td>
<td>2-3</td>
<td>7036</td>
<td>33.6*</td>
</tr>
<tr>
<td>Hokusai (2013)</td>
<td>VTE</td>
<td>Edoxaban</td>
<td>Warfarin</td>
<td>2-3</td>
<td>4149</td>
<td>12</td>
</tr>
<tr>
<td>Explore-Xa (2013)</td>
<td>AF</td>
<td>Betrixaban</td>
<td>Warfarin</td>
<td>2-3</td>
<td>127</td>
<td>9</td>
</tr>
<tr>
<td>OPAL-1 (2010)</td>
<td>AF</td>
<td>Darexaban</td>
<td>Warfarin</td>
<td>2-3</td>
<td>94</td>
<td>3</td>
</tr>
<tr>
<td>OPAL-2 (2014)</td>
<td>AF</td>
<td>Darexaban</td>
<td>Warfarin</td>
<td>2-3</td>
<td>163</td>
<td>3</td>
</tr>
<tr>
<td>Einstein DVT (2008)</td>
<td>VTE</td>
<td>Rivaroxaban</td>
<td>Warfarin Acenocoumarol Phenprocoumon Flunidione</td>
<td>2-3</td>
<td>134</td>
<td>137</td>
</tr>
<tr>
<td>Einstein DVT (2010)</td>
<td>VTE</td>
<td>Rivaroxaban</td>
<td>Warfarin Acenocoumarol</td>
<td>2-3</td>
<td>1718</td>
<td>12</td>
</tr>
<tr>
<td>Rocket-AF (2011)</td>
<td>AF</td>
<td>Rivaroxaban</td>
<td>Warfarin</td>
<td>2-3</td>
<td>7125</td>
<td>23.2*</td>
</tr>
<tr>
<td>Einstein PE (2012)</td>
<td>VTE</td>
<td>Rivaroxaban</td>
<td>Warfarin Acenocoumarol</td>
<td>2-3</td>
<td>2420</td>
<td>3</td>
</tr>
<tr>
<td>J-Einstein (2015)</td>
<td>VTE</td>
<td>Rivaroxaban</td>
<td>Warfarin</td>
<td>2-3</td>
<td>19</td>
<td>6</td>
</tr>
</tbody>
</table>

* 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.
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 totaled 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 CHADS2 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 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.

(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 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
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
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 CHADS2 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-world 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% CI, 0.99–1.45); 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-world 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
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, 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 CHADS2 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 CHADS2 score, major bleeding were consistently similar to VKAs regardless of the CHADS 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-world 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 stratifying 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


