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How to reverse bleeding in patients on direct oral anticoagulants?

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Abstract
The direct oral anticoagulants (DOACs), or non-vitamin K antagonist oral anticoagulants (NOACs), including dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, edoxaban, and betrixaban, which inhibit coagulation factor Xa, are associated with similar or lower risk of bleeding compared with warfarin. The need for reversal of their anticoagulant effect may occur in patients with life-threatening bleeding or those requiring urgent surgery. Currently, the only specific reversal agent for dabigatran, idarucizumab is widely available, while andexanet alfa, which reverses factor Xa inhibitors, was approved in the US in May 2018. Ciraparantag, which has been designed to reverse all DOACs and other anticoagulants is being investigated in clinical trials. In the absence of licensed reversal agents for the oral factor Xa inhibitors, prothrombin complex concentrates are suggested in patients with life-threatening bleeding. Vitamin K and fresh frozen plasma should not be used to reverse DOACs. This review presents the current evidence regarding bleeding risk on DOACs and the reversal strategies to provide guidance on the management of patients treated with DOACs who experience serious bleeding.

Introduction

Non-vitamin K antagonist oral anticoagulants, or target-specific oral anticoagulants (TSOACs), which directly inhibit coagulation factor (F) Xa (rivaroxaban, apixaban, edoxaban, and betrixaban) or thrombin (dabigatran), are increasingly used worldwide. The International Society on Thrombosis and Haemostasis (ISTH) has recommended using the term direct oral anticoagulants (DOACs), which will be used in the present review [1]. The DOACs have common characteristics:

- They are all oral.
- They all have rapid absorption and their profile is very similar to a low-molecular-weight heparin in
• Compared to other oral anticoagulants, particularly warfarin, they have remarkably short half-lives (about 12 hours).
• They have no off-target toxicity. There is no increased risk of leukemia, liver failure or other adverse reactions, and any allergic reactions to the DOACs are caused by the dye used in the tablet or capsule, not by the compound itself.

The phase 3 trials evaluating the efficacy and safety of the DOACs in patients with nonvalvular atrial fibrillation (AF) for the prevention of stroke and systemic embolism [2-6] and the treatment and prevention of venous thromboembolism (VTE) [7-10] have demonstrated that DOACs have a favorable risk-benefit profile in comparison with a vitamin K antagonist (VKA), warfarin. However, there are indications in which all physicians will continue to use warfarin for the foreseeable future, most notably in patients with mechanical heart valves and patients with “high risk” antiphospholipid antibody syndrome [11].

**Bleeding risk in patients on DOACs**

There is compelling evidence that DOACs are as effective in reducing thromboembolic events as warfarin, but they are safer with respect to major and fatal bleeding, in particular intracranial hemorrhage [12,13]. All large clinical studies of DOACs were conducted without specific antidotes being available.

Clinical registries and large retrospective database studies, including an FDA analysis on >134 000 Medicare patients with AF and Danish nation-wide analyses, demonstrate results consistent results with those in randomized controlled trials (RCTs) [14-18].

A systematic review by Chai-Adisaksopha et al. [19], which comprised 12 RCTs (VTE, n=7 and AF, n=5) involving 102 607 patients (Table 1), was the first meta-analysis to examine the impact of bleeding complications of DOACs compared with the VKAs in patients with VTE or AF. Patients were treated for 1.6 to 2.0 years in most of the AF trials, while the duration of VTE trials was between 3 to 12 months. The average age was from 70 to 73 years in the AF trials and 54 to 57 years in the VTE trials [19]. It has been confirmed that intracerebral bleeding, the most feared hemorrhagic adverse event in patients receiving oral anticoagulants, is reduced by >50% while using the DOACs compared with warfarin. Intracranial bleeding represents 8.7% of all major bleeding episodes in VKA users and results in a 46% to 55% mortality rate [20, 21].
Patients with AF or VTE on DOACs have been found to have a lower risk of overall major bleeding (relative risk [RR] 0.72, number needed to treat [NNT] 156), fatal bleeding (RR 0.53, NNT 454), clinically relevant nonmajor bleeding (RR 0.78, NNT 99), and all bleeding (RR 0.76, NNT 18) [19]. Interestingly, Chai-Adisaksopha et al. [19] did not observe an increased risk of gastrointestinal (GI) bleeding (RR 0.94 [95% CI, 0.88-1.34] (Table 1) in contrast to a few published systemic reviews in which DOACs were compared with standard care [12,22]. The increase in the risk of GI bleeding were observed in the RCTs evaluating dabigatran and rivaroxaban in AF patients [4,2]. In the RE-LY trial dabigatran 150 mg bid (but not dabigatran 110 mg bid) increased risk of major GI bleeding compared with warfarin (RR 1.50 [95% CI, 1.19-1.89]) [2], whereas in the ROCKET-AF rivaroxaban 20 mg once daily increased this risk by 1% (3.2% vs 2.2%) [4]. The mechanism underlying DOAC-associated GI bleeding is likely the presence of the active drugs in the GI tract which precipitates bleeding from vulnerable lesions [23]. The discrepancy of the findings of various systematic reviews might be explained from the difference of the population and the comparators used.

There is consensus that the best way to treat bleeding in a patient on an anticoagulant is to avoid having a bleed, and this can be achieved by using the medications with the lowest risk of bleeding. Warfarin is known to have the highest risk of major bleeding, therefore a DOAC should be used in many patients at high bleeding risk.

Similarly, a very common cause of avoidable bleeding is coincident use of aspirin and a DOAC or warfarin. Concomitant administration of antiplatelet drugs and nonsteroidal anti-inflammatory drugs (NSAID) should be avoided when possible. Most patients who are on warfarin and aspirin do not need aspirin. In a patient who is receiving any form of oral anticoagulant and any form of antiplatelet agent the most important thing in prevention of bleeding is to consider whether they need to be on dual antithrombotic therapy and be confident in discontinuing one of the antithrombotic drug if it is not indicated. The current ESC guidelines recommend that oral anticoagulation alone, not combination therapy with aspirin or another antiplatelets agent, be administered in AF patients with stable coronary artery disease, who did not experience an acute coronary syndrome and/or coronary intervention in the previous 12 months [24, 25].

**Specific strategies to reverse anticoagulant effects of the DOACs**

In decision making regarding all clinical problems, good quality evidence is of particular value. Unfortunately, in the field of reversing anticoagulants, including DOACs, there is no level 1A
evidence and there essentially never will be such evidence.

**Idarucizumab** is a humanized monoclonal antibody fragment which is a specific reversal agent for dabigatran. It binds with 350 times higher affinity than thrombin to free and thrombin-bound dabigatran within minutes of its administration [26]. This reaction is irreversible [27]. Idarucizumab is primarily eliminated renally [28, 29] and the drug exposure is increased in patients with impaired renal function, which is consistent with higher dabigatran concentrations in such patients. In phase I and II clinical trials, reversal of anticoagulant effects of dabigatran by idarucizumab in a dose-dependent manner has been convincingly demonstrated based on measurements of activated partial thromboplastin Time (APTT), thrombin time (TT), diluted TT (dTT), ecarin clotting time, and activated clotting time (ACT) in healthy volunteers and in subjects with reduced creatinine clearance [28, 30, 31].

No effects on coagulation parameters were observed when idarucizumab was administered in subjects not taking dabigatran [28].

Idarucizumab was approved in the USA by the Food and Drug Administration in October 2015 and in Europe one month later. It has become the standard of care for the reversal of dabigatran when it is available [32-34].

The RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran) study was a phase 3, prospective, cohort study designed to show the safety and efficacy of idarucizumab (administered as two consecutive rapid 2.5 g intravenous boluses) in dabigatran-treated patients who present with uncontrolled or life-threatening bleeding (group A) or nonbleeding patients who require emergent surgery or invasive procedure (group B). The primary outcome of the RE-VERSE AD study was maximum percentage reversal of the anticoagulant effect of dabigatran expressed using dTT and ecarin clotting time performed in a central laboratory. Results of the RE-VERSE AD study were published twice in the *New England Journal of Medicine*, i.e. an interim analysis of the first 90 patients (51 with uncontrolled, life-threatening bleeding [group A] and 39 undergoing urgent surgery or an invasive procedure [group B]) in 2015 [35] and the final analysis of 503 patients (n=301 [group A] and n=202 [group B]) in 2017 [28].

Most participants (95.7%) from 39 countries were treated with dabigatran to prevent AF-associated stroke. The median age of participants was 78 years. The efficacy analysis included 461 patients with prolonged dTT or elevated ecarin clotting time and the median maximum percent reversal was 100% within four hours following idarucizumab administration. The median time to cessation of bleeding in bleeding patients was 2.5 hours. The median time to initiation of procedure in patients requiring surgery was 1.6 hours, and hemostasis was assessed as normal in 93.4% of the
participants. The 30-day mortality rate was 13.5% in group A and 12.6% in group B with most deaths occurring within five days after enrollment.

Of note, nine participants received an additional dose of idarucizumab due to recurrent bleeding or the need for a second urgent procedure, which was related to recurrent prolongation of clotting time due to redistribution of unbound dabigatran from the extravascular to the intravascular compartment.

The RE-VERSE AD study demonstrated the utility of idarucizumab in two groups of patients: those with life-threatening bleeding, in whom very good efficacy in terms of clinical hemostasis was shown; and those going for urgent surgery, in whom excellent efficacy around the time of surgery was demonstrated.

There is a concern that a person reversed from an anticoagulant might suffer from thrombotic complications. In the RE-VERSE AD trial 35 thrombotic events occurred in 31 patients of the almost 500 at 90 days. Restart time varied with a median time of 4.1 days in patients with life-threatening bleeding compared to a much shorter time of 1.4 days in those requiring urgent surgery [36]. Although the half-lives of dabigatran and idarucizumab are prolonged in patients with renal impairment, the adjustment of timing of re-initiation of dabigatran is not necessary. Almost two-thirds of patients had not had their anticoagulants restarted at the time of their thrombotic event. Thus, another key take-home message is that reversed patients must be started back on anticoagulants if they do not have a very high risk of bleeding.

**Andexanet alpha** is a very specific reversal agent which binds with high affinity to not only direct FXa inhibitors, but also low-molecular-weight heparins and fondaparinux, indirect FXa inhibitors [37]. Andexanet alpha is a modified human recombinant FXa decoy protein that lacks catalytical activity following replacement of an active-site serine with alanine and with removal of the membrane-binding domain, which precludes this protein to participate in the formation of the prothrombinase complex [37, 38].

In vitro andexanet alpha has been shown to correct increased anti-FXa activity caused by all 4 DOACs acting as FXa inhibitors, namely rivaroxaban, apixaban, edoxaban, and betrixaban [38, 39]. Moreover, in animal bleeding models andexanet alpha has been demonstrated to decrease blood loss and restore hemostasis [40-42]. In phase 2 studies, andexanet demonstrated a rapid, dose-dependent reversal of anticoagulant effects (anti-FXa activity, unbound FXa concentrations, restoration of thrombin potential) in healthy volunteers who received apixaban, rivaroxaban, or enoxaparin [39, 43-45]. Because of its pharmacodynamic half-life of 1-hour, andexanet has been evaluated both as a
bolus, and a bolus followed by an infusion anti-FXa activity returning to placebo levels within 2 hours of completion of dosing.

Results of two randomised, double-blind, placebo-controlled trials (ANNEXA [Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors trials]) performed in healthy volunteers aged 50 to 75 years who received apixaban (ANNEXA-A) and rivaroxaban (ANNEXA-R) were published [37]. Based on the phase 2 studies, a higher dose of andexanet was used for rivaroxaban than for apixaban because of higher plasma concentrations and a larger volume of distribution. For ANNEXA-A with apixaban, andexanet was given as a 400-mg intravenous bolus (30 mg/min) in part 1 and an 400-mg bolus followed by a continuous infusion of 4 mg/min for 120 minutes (480 mg total) in part 2. Corresponding doses in the ANNEXA-R with rivaroxaban were an 800-mg bolus and an 800-mg bolus followed by an infusion of 8 mg/min for 120 minutes (960 mg total) in part 1 and 2, respectively. The primary endpoint for the ANNEXA-A and -R studies was the maximum percent change in anti-FXa activity. Anti-FXa activity was rapidly (within 2–5 minutes) reduced by 92% to 94% with andexanet bolus with the reduction of 20% observed in the placebo group. Following a dose of andexanet there is a fall of anti-Xa activity followed by a slow return of the anticoagulant effect of FXa inhibitor over time. The reversal of anti-FXa activity persists for 120 minutes with a slow increase as early as after 15 minutes since the end of administration of this agent. Following a bolus of andexanet followed by an infusion persistent inhibition of FXa is achieved, as long as the infusion is continued.

Of note, andexanet alpha has a good safety profile without thromboembolic or other serious adverse events including no evidence for the generation of neutralizing antibodies against this agent or FX or FXa. Transient increases in markers of blood coagulation activation reported during the ANNEXA-A and ANNEXA-R trials (namely D-dimer and prothrombin fragments 1.2) in a subgroup of study participants have uncertain clinical relevance.

The ongoing ANNEXA-4 phase 3b to 4 study assesses the efficacy and safety of andexanet alpha in patients treated with FXa inhibitors with acute major bleeding, but not in those anticoagulated subjects who require emergency or urgent procedures, which is in contrast to the REVERSE-AD trial [36, 46].

At the present time, FXa inhibitors do not have reversal strategies in Europe or in Canada. On May 4th, 2018 andexanet alpha was approved in the United States. However, there are some caveats regarding andexanet alpha:

1. it will be available in very limited quantities for at least a year and then it will be more widely available only in the US;
2. the company estimates that it will cost about USD 25,000 for the lower dose and USD 50,000 for the higher dose, which effectively means that the vast majority of patients treated with
rivaroxaban or apixaban will never have access to it particularly outside the United States.

**Ciraparantag** is a small, water soluble, cationic synthetic molecule designed to specifically bind to unfractionated heparin, low-molecular-weight heparin, and DOACs, both thrombin and FXa inhibitors. This agent may be a universal antidote, however it is in an earlier stage of development. The mechanism of its inhibitory effects involves noncovalent hydrogen bonding and charge-charge interactions. Ciraparantag has been demonstrated to normalize clotting time within 10 to 30 minutes of administration. [47] Ciraparantag has been investigated as an antidote for edoxaban (60 mg) in in a double-blind, placebo-controlled study [48]. A single intravenous dose of ciraparantag (100 to 300 mg) reversed anticoagulant effects within 10 minutes and sustained for 24 hours in 80 healthy subjects. When administered to healthy subjects, ciraparantag is safe and well tolerated with minor, non-dose limiting adverse events such as periorbital and facial flushing and cool sensation [48].

**Non-specific reversal strategies**

The available Xa inhibitor reversal strategies rely on non-specific strategies of unknown effectiveness. PCCs are widely used in those strategies, but with no evidence of efficacy.

A prospective multicentre observational study, or a large case series, published in July 2017, described how physicians actually deal with bleeding on DOACs in the real world [49]. It demonstrated that reversal strategies are inconsistent with large variability in practice. Bleeds occurred in patients at an average age of almost 82 years. Looking at 460 bleeds that occurred in patients on DOACs, authors reported that almost 20% of those patients received vitamin K, which is useless in such clinical situations. It has absolutely no possibility of any effect, but was given probably because many of these patients had a prolonged INR due to rivaroxaban. Tranexamic acid, an antifibrinolytic agent effective in trauma or postpartum hemorrhages, acts a lysine analog that impairs plasminogen activation on fibrin. In patients on DOACs its efficacy is uncertain, however it might be used.

Fresh frozen plasma (FFP) is ineffective in patients bleeding on DOACs but was used in about 10% of patients reported by Xu Y et al. [49]. FFP may be used as a plasma volume expander in patients following transfusions, however its shortcomings are numerous and involve factors (limiting its effectiveness), has a higher risk of transfusion reactions, and acute heart failure especially in the elderly due to an increased volume load [50-53].

PCCs are plasma-derived products that contain 3 (factors II, IX, and X) or 4 (addition of factor VII) clotting factors in addition to variable amounts of heparin and the natural coagulation inhibitors
protein C and protein S, which are used among others to reverse anticoagulants effects of VKA in severely bleeding patients. Activated PPC, aPCC (known as factor VIII inhibitor bypassing activity) contains activated factor VII along with mainly nonactivated factors II, IX, and X. Animal studies have demonstrated that PCCs have variable ability to normalize anticoagulation parameters and to prevent or attenuate bleeding across the DOACs [53-60]. Three randomized, placebo-controlled studies have been performed in 12–93 healthy volunteers who received DOACs. They demonstrated that PCCs can reverse the anticoagulant effect of rivaroxaban and edoxaban with complete reversal with 50 U/kg and partial reversal with 25 U/kg, while no similar effect (no changes in TT, APTT, endogenous thrombin generation lag phase and ecarin clotting time) was observed in subjects on dabigatran [61-64]. In vitro studies in healthy volunteers demonstrated that aPCCs added to plasma containing DOACs have a more potent effect on coagulation parameters than PCCs alone [65, 66]. A dose of 50 U/kg of PCC or aPCC is recommend in patients treated with rivaroxaban or apixaban if life-threatening bleeding occurs.

Another therapeutic option in bleeding patients with DOACs is recombinant activated factor VII (rFVIIa, Novoseven). A few in vitro and ex vivo studies demonstrating variable efficacy of recombinant activated factor VII to reverse coagulation parameters attributable to DOACs [65, 66–73] have been published. There have been a few case reports of patients receiving this agent due to life-threatening bleeding, although there have been no clinical trials investigating this strategy. Based on limited experience a dose of 90 U/kg used in patients with acquired hemophilia A has been proposed to limit the most severe bleeding on DOACs [49].

Interestingly, reasonable non-specific strategies which might be used in emergency situations including PCC, aPCC or rVIIa, were all used in less than 20% of patients with serious bleeding on DOACs in the real-life study by Xu Y et al [49].

Experts suggest that hospitals should adopt anticoagulation reversal protocols developed by a multidisciplinary team involving intensivists, cardiologists, hematologists, surgeons, gastroenterologists, neurologists and others. Examples of such protocols are available for clinicians but they should be adopted to local circumstances [74]. By standardizing approaches to care, and minimizing the risk of missing key interventions, such studies are likely to improve care for patients with bleeding.

Examples of decision-making regarding bleeding patients on DOACs

Case no 1: A 79-year-old man with permanent AF receiving dabigatran 150 mg bid reported to the emergency department presenting with new hemiparesis and aphasia. Computed tomography
revealed subdural haemorrhage. His blood tests were as follows: INR of 1.1, APTT of 35 seconds and TT of 135 seconds (reference range below 30 seconds). The question is whether he should receive some form of reversal agent.

The decision was not to administer idarucizumab. The thrombin time of 135 seconds indicates that he still has some dabigatran in circulating blood, but the thrombin time goes up very quickly with dabigatran, so the level of 135 means he probably does not have very much of the drug in the system. And by the time he actually got the reversal agent administered he would probably have essentially no dabigatran left over.

Case no 2: A 71-year-old man presents to the emergency department at 8:00 p.m. on a Saturday night with abdominal pain and hypotension. Imaging reveals a ruptured abdominal aortic aneurysm. He has non-valvular AF, arterial hypertension, dyslipidaemia, and a history of ischemic stroke one year ago. He takes apixaban 5 mg bid. His last dose of apixaban was taken approximately 12 hours ago. The surgeon calls the lab and wants proof that there is no anticoagulant effect present. The laboratory examination is as follows: haemoglobin is 10.2 g/dl, platelet count is 292 000/ul. The prothrombin time, INR and APTT are normal. The anti-Xa level is sent off, but the result is not available after 30 minutes which is the case in most hospitals worldwide. The question is whether this person has a discernible anticoagulant effect and if we should do something to intervene to reduce the risk of bleeding when he goes for surgery. An immediate decision is needed; vascular surgeon recommends emergent open repair, two hours is too long to wait. What strategy should be recommended?

One might think that the normal results of the coagulation tests indicate that the person does not have an anticoagulant effect, however apixaban does not produce any effect on most commonly available coagulation tests. Therefore, if a person is taking apixaban, the INR, prothrombin time, APTT, and thrombin time are all useless. If this person receiving apixaban has a ruptured abdominal aortic aneurysm, the surgery should performed surgery and the surgeon advised that the patient may have an enhanced risk of bleeding. Prothrombin complex concentrates are widely used to treat bleeding in patients taking DOACs, and they might be considered if the person bleeds excessively in the operating room. In all likelihood the patient is not going to have abnormal bleeding since the apixaban was taken 12 hours ago.

**Summary**
Reversal strategies in patients receiving DOACs depend on the anticoagulant involved, the location and severity of the bleeding, and/or the urgency of the invasive procedure. The available specific reversal agent for dabigatran, idarucizumab, is used infrequently for the reversal of DOACs, without increasing the underlying risk of thrombosis. Andexanet alpha to reverse FXa inhibitors has been approved by FDA recently. Evidence supporting non-specific reversal therapies including PCC, aPCC, or recombinant factor VIIa is still limited in terms of clinical outcome data. Administration of PCC or aPCC may be considered in addition to supportive measures for patients with severe or life-threatening bleeding.

Most importantly, the best way to treat a bleed related to a DOAC is to prevent it by using the right drug at the right dose in a right patient and withdrawing anticoagulation in patients without an indication for such therapy.
Table 1.
Bleeding risk in randomized controlled trials comparing the efficacy and safety of DOACs versus warfarin in patients with venous thromboembolism or atrial fibrillation.

DVT - Deep-Vein Thrombosis, AF - Atrial Fibrillation, PE - Pulmonary Embolism, NVAF – NonValvular Atrial Fibrillation, GI - gastrointestinal
†Median (minimum-maximum)
<table>
<thead>
<tr>
<th>Study (anticoagulation tested)</th>
<th>publication year</th>
<th>Indication for anticoagulation</th>
<th>Age of patients on DOAC/VKA</th>
<th>Major Bleeding (HR [95%CI])</th>
<th>Intracranial bleeding (HR [95%CI])</th>
<th>Major GI bleeding (HR [95%CI])</th>
<th>Fatal bleeding (HR [95%CI])</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER (dabigatran)</td>
<td>2009</td>
<td>Proximal DVT or PE</td>
<td>55.0±15.8/54.4±16.2</td>
<td>0.83 [0.46, 1.49]</td>
<td>0.14[0.01, 2.74]</td>
<td>1.79[0.60, 5.32]</td>
<td>0.99[0.06, 15.86]</td>
<td>75</td>
</tr>
<tr>
<td>RE-LY (dabigatran)</td>
<td>2009</td>
<td>AF ≥ 1 risk factors</td>
<td>71.4±8.6/71.6±8.6</td>
<td>0.88 [0.78, 0.98]</td>
<td>0.37 [0.27, 0.50]</td>
<td>1.30[1.07, 1.56]</td>
<td>0.65[0.43, 0.99]</td>
<td>2</td>
</tr>
<tr>
<td>RE-MEDY (dabigatran)</td>
<td>2013</td>
<td>Proximal DVT or PE</td>
<td>55.4±15.0/53.9±15.3</td>
<td>0.52[0.27, 1.01]</td>
<td>0.50[0.09, 2.72]</td>
<td>0.62[0.20, 1.90]</td>
<td>0.33[0.01, 8.15]</td>
<td>76</td>
</tr>
<tr>
<td>RE-COVER II (dabigatran)</td>
<td>2014</td>
<td>Proximal DVT or PE</td>
<td>54.7±16.2/55.1±16.3</td>
<td>0.69[0.36, 1.32]</td>
<td>1.01[0.14, 7.14]</td>
<td>0.60[0.22, 1.66]</td>
<td>0.34[0.01, 8.24]</td>
<td>10</td>
</tr>
<tr>
<td>ROCKET AF (rivaroxaban)</td>
<td>2012</td>
<td>NVAF, CHADS2 score ≥ 2</td>
<td>73(65-78)† / 73(65-78)‡</td>
<td>0.87[0.52, 1.45]</td>
<td>0.66[0.47, 0.92]</td>
<td>1.46[1.19, 1.78]</td>
<td>0.49[0.31, 0.78]</td>
<td>4</td>
</tr>
<tr>
<td>EINSTEIN-PE (rivaroxaban)</td>
<td>2012</td>
<td>Acute PE</td>
<td>57.9±7.3/57.5±7.2</td>
<td>0.50[0.31, 0.80]</td>
<td>0.25[0.07, 0.88]</td>
<td>Not reported</td>
<td>0.66[0.11, 3.97]</td>
<td>77</td>
</tr>
<tr>
<td>J-ROCKET AF (rivaroxaban)</td>
<td>2012</td>
<td>NVAF, ≥2 risk factors</td>
<td>71.0(34-89)† / 71.2(43-90)‡</td>
<td>0.87[0.52, 1.45]</td>
<td>0.50[0.17, 1.45]</td>
<td>0.50[0.19, 1.32]</td>
<td>0.33[0.03, 3.20]</td>
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<td>EINSTEIN-DVT</td>
<td>2010</td>
<td>Proximal DVT</td>
<td>55.8±16.4/</td>
<td>0.70[0.35, 1.28]</td>
<td>1.00[0.14, 7.06]</td>
<td>0.57[0.30, 1.08]</td>
<td>0.20 [0.02, 1.70]</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Comparator</td>
<td>Incidence</td>
<td>Odds Ratio</td>
<td>95% CI</td>
<td>p Value</td>
<td>p Value (intergroup)</td>
<td>p Value (intragroup)</td>
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<tr>
<td>ARISTOTEL E (apixaban)</td>
<td>2011</td>
<td>AF, ≥ 1 risk factors / 70(63-76)†</td>
<td>0.70/[0.61, 0.81]</td>
<td>0.42/[0.31, 0.59]</td>
<td>0.88/[0.65, 1.14]</td>
<td>0.62/[0.40, 0.94]</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>AMPLIFY (apixaban)</td>
<td>2013</td>
<td>Proximal DVT or PE / 57.2±16 / 57.2±16</td>
<td>0.31/[0.17, 0.55]</td>
<td>0.50/[0.13, 2.01]</td>
<td>0.39/[0.16, 0.93]</td>
<td>0.50/[0.05, 5.54]</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>ENGAGE-AF-TIMI-48 (edoxaban)</td>
<td>2013</td>
<td>AF, CHADS2 score ≥ 2 / 72(64-78)†</td>
<td>0.64/[0.57, 0.72]</td>
<td>0.39/[0.30, 0.50]</td>
<td>0.95/[0.80, 1.13]</td>
<td>0.45/[0.31, 0.65]</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>HOKUSAI-VTE (apixaban)</td>
<td>2013</td>
<td>Proximal DVT or PE / 55.7±16 / 55.9±16</td>
<td>0.85/[0.60, 1.21]</td>
<td>0.28/[0.10, 0.75]</td>
<td>Not reported</td>
<td>0.20/[0.04, 0.91]</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

References


