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Direct Oral Anticoagulants & Vitamin K Antagonists In Venous Thromboembolisim

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Abstract

Direct oral anticoagulants (DOACs) have quickly emerged as a good attractive alternatives to the vitamin K antagonist in the long-standing standard of care in anticoagulation . DOACs are used to prevent and treat a variety of cardiovascular diseases and venous thromboembolism. DOACs have emerged as leading therapeutic alternatives that provide both clinicians and patients with more effective, safe, and convenient treatment options in thromboembolic settings since their initial approval in 2010. With the growing role of DOACs, clinicians must make increasingly complex decisions about the appropriate agent, duration of treatment, and use in special populations. Direct oral anticoagulants (DOACs) dabigatran, rivaroxaban, apixaban, and edoxaban are anticoagulation medications used to prevent and treat the thrombosis in a variety of cardiovascular settings. DOACs are divided into two groups: oral direct factor Xa inhibitors (such as rivaroxaban, apixaban, and edoxaban) and direct thrombin inhibitors (ie, dabigatran). DOACs are relatively new agents that have demonstrated superiority or non inferiority to prior standards of care, anticoagulation with vitamin K antagonists (VKA; ie, warfarin), or low molecular weight heparins (LMWHs), in reducing the risk of thromboembolic complications with similar or reduced bleeding risk. DOACs have fewer monitoring requirements, less frequent follow-up more immediate drug onset and fewer drug and food interactions when compared to VKAs. As a result, DOAC prescriptions surpass warfarin prescriptions.

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a main cause of morbidity and mortality worldwide, affecting approximately one in 1000 adults annually and increasing in incidence from 0.05 % at the age of 45 to 0.5 % at the age of 80 years.[(1)(2)(3)]

After coronary artery disease and cerebrovascular disease, VTE is the third most common cardiovascular condition. and has a significant socioeconomic effect. [(3)] VTE is 100 times more common in hospitalized patients than in the general population and an objectively

diagnosed DVT can be found in up to 80% of high-risk surgical and medical patients who are not on thromboprophylaxis.[1][4]

Fatal PE, the most serious complication of VTE, occurs in 0.01% of low-risk surgical patients to 5% of hospitalized medical patients with multiple risk factors and is currently considered the most common avoidable cause of hospital death .[4][5] VTE is associated with a high risk of recurrence after a first event, with approximately 10% of patients experiencing a recurrence within 1 year of discontinuing anticoagulant therapy and up to 30% experiencing a recurrence within 10 years.[6][7] Furthermore, VTE is linked to long-term clinically significant complications such as post-thrombotic syndrome and chronic pulmonary hypertension.

As a result, VTE may be classified as both an acute and chronic condition and its management represents a major medical challenge.[8] In general, subcutaneous low-molecular-weight heparins (LMWHs) as well as fondaparinux, recommend for treatment of acute VTE followed by vitamin K antagonists (VKAs) (i.e. warfarin, acenocoumarol or phenprocoumon).[9][10] However, both anticoagulants have a number of important limitations. While LMWHs may be inconvenient for patients because these drugs need subcutaneous administration, Because of their complex pharmacokinetics and pharmacodynamics, oral VKAs are often related to haemorrhagic accidents, necessitating regular coagulation monitoring and dose adjustments. There are several interactions with other medications and foods.[9][10]

To overcome these problems , a new class of anticoagulant drugs has been developed with the aim of being at least as efficacious but with a more practical profile (i.e. oral administration and no laboratory monitoring) than traditional anticoagulants.[11] These anticoagulants, which are direct and target-specific inhibitors acting at the level of specific steps of the coagulation system, include the thrombin inhibitor dabigatran etexilate and the activated factor X (FXa) inhibitors rivaroxaban, apixaban and edoxaban (table 1 for their pharmacological features).[12][13][14]

Dabigatran, rivaroxaban, and apixaban are currently approved in the European Union (EU) and the United States for the treatment and prevention of VTE in patients undergoing orthopaedic surgery. Edoxaban is currently approved in Japan for the prevention of VTE after major orthopaedic surgery, as well as the acute treatment and secondary prevention of VTE in the EU and the United States .All of these drugs are also accepted for the prevention of stroke and thromboembolism in patients with nonvalvular atrial fibrillation in the EU and the United States.

The aim of this review article, to know the efficacy of Direct Oral Anticoagulants, by using it in primary prophylaxis, acute treatment and secondary prevention of VTE. [(15)]

Review of Literature

In this article I focused on the medical literature for published studies on new oral anticoagulants for the treatment and prevention of VTE by comparing this new agents with conventional agents (LMWH/VKA) and see which more effective and associated with more adverse effects . The database was searched without regard to time and with the English language as a limitation. The Medical Subject used were “new oral anticoagulants”, “direct oral anticoagulants”, “apixaban”, “dabigatran”, “edoxaban”, “rivaroxaban”, “venous thromboembolism”, “deep vein thrombosis”, “pulmonary embolism”, “treatment” and “prevention”.

Direct oral anticoagulants

Apixaban

Apixaban is a reversible direct FXa antagonist that is rapidly absorbed after oral administration and has the lowest renal clearance (25%) of any direct oral anticoagulants as in **(table 1)**. [(34)]

Uses of Apixaban in Primary prophylaxis of VTE

An examination of trials for prevention of VTE after orthopaedic surgery (Apixaban Dosed Orally versus Anticoagulation with Enoxaparin).[16][17][18]

revealed that pixaban 2.5 mg twice daily was associated with a significant improvement in the rate of total VTE and all-cause mortality, as well as significantly lower risk of clinically relevant bleeding when compared to enoxaparin (LMWH).[40] In the ADOPT (Apixaban Dosing to Optimize Protection from Thrombosis) trial, extended prophylaxis with apixaban (2.5 mg twice daily for 30 days) was not superior to a shorter course of enoxaparin (40 mg for 6–4 days) but was associated with significantly more severe bleeding events .[19]

Use of Apixaban in Treatment of VTE

Apixaban was studied in 520 patients with symptomatic DVT in the trial at doses of 5 mg twice daily, 10 mg twice daily or 20 mg once daily and was compared to the standard therapy with LMWH followed by VKA .[19][20]

The findings of this dose-ranging study showed that all three regimens of apixaban had an efficacy and safety profile similar to that of LMWH/VKA in treated patients. Then, apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily for 6 months) was found the Apixaban similar to the conventional therapy with enoxaparin/warfarin for the treatment of acute VTE . Uesed apixaban in the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy trial in those 5385 patients and was associated with a reduction the bleeding complications.[21][22]

Dabigatran etexilate

Dabigatran etexilate is a direct thrombin inhibitor converted quickly to the active form. Dabigatran absorbed from the gastrointestinal tract. The plasma half-life of dabigatran is 12–14 h and its main route of elimination is the kidney, which accounts for 80% of drug clearance .[14]

Uses of Dabigatran in Primary prophylaxis of VTE

In this study they revealed that the dabigatran (150 or 220 mg twice daily) was at least as effective as enoxaparin for thromboprophylaxis after hip and knee replacement, with a similar incidence of bleeding complications (1.4% in the enoxaparin group versus 1.4% in the dabigatran 220 mg group and 1.1% in the dabigatran 150 mg group) .[(14)]

Uses of Dabigatran in Treatment of VTE

Dabigatran was compared with warfarin in this study for the treatment of acute VTE (primary outcome: 6-month incidence of recurrent symptomatic or fatal VTE). The study results of these two trials, which including 5109 patients, revealed that dabigatran was noninferior to warfarin for this primary efficacy end-point (observed incidence: 2.4% versus 2.2%; hazard ratio (HR) with a lower risk of bleeding complications.[(23)]

Dabigatran was also evaluated in the so-called extension studies which were designed to evaluate this drug in patients who had completed and stopped the traditional VKA treatment for the acute phase of VTE. In this trial, patients who had previously been treated for with VKA for 3-12 months were randomised to dabigatran (150 mg twice daily) or warfarin for an additional period of 6–36 months.[(24)] Recurrent VTE occurred at a similar rate in dabigatran-treated and warfarin-treated patients (1.8% versus 1.3%. while a lower rate of major bleeding was observed in the dabigatran group (0.9% versus 1.8%). In the other study dabigatran therapy (150 mg twice daily) was compared with placebo in patients with VTE who had discontinued standard VKA therapy after 6–18 months. Dabigatran reduced the rate of recurrent VTE when compared to the placebo over the next 6 months, (0.4% versus 5.6%), with a 0.3% rate of major bleeding versus no bleeding at all in the placebo group .

Edoxaban

Edoxaban is a selective direct FXa inhibitor which has half-life of 8–10 h; renal secretion accounts for one- third of its elmentation.[(35)]

Uses of Edoxaban in Primary prophylaxis of VTE

Randomised trials comparing edoxaban to enoxaparin for thromboprophylaxis after total knee (Studying Thrombosis After Replacement Surgery) or hip replacement revealed that edoxaban efficacy was comparable or superior to enoxaparin, with a similar safety profile.[25][26]

Uses of Edoxaban in Treatment of VTE

In this study, 8292 patients with acute symptomatic VTE were randomly assigned to receive edoxaban (60 or 30 mg once daily) or warfarin which demonstrated that edoxaban was noninferior to warfarin standard therapy in terms of the primary outcome (i.e. recurrent symptomatic VTE), with a similar rate of major bleeding.[27]

Rivaroxaban

Rivaroxaban is a selective, direct factor Xa inhibitor with a half-life (7–11 h) and a high oral bioavailability (80%) that is partially excreted (66%) by the kidneys (table 1) .[36]

Uses of Rivaroxaban in Primary prophylaxis of VTE

In these studies compared oral rivaroxaban (10 mg once daily) with enoxaparin (40 mg once daily or 30 mg twice daily) for prevention of VTE after total hip replacement surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism or in knee arthroplasty.[28][29][30][31]

A pooled analysis of these trials found that rivaroxaban significantly reduced the incidence of composite VTE and all-cause mortality when compared to enoxaparin-based regimens, but there was no evidence of differences in bleeding events.[37]

Uses of Rivaroxaban in Treatment of VTE

Rivaroxaban was tested in patients with acute VTE using a, open-label, noninferiority design. Recently, a pooled analysis of the results of both studies including a total of 8282 patients showed that rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once

daily) was noninferior to standard therapy with enoxaparin/warfarin for prevention of recurrent VTE (observed incidence: 2.1% versus 2.3%). Major bleeding occurred with a lower frequency in the rivaroxaban group (Hazard Ratio 95%).[38]

In the EINSTEIN-Extension study VTE patients who had been treated with rivaroxaban or VKA for 6–12 months were randomly assigned to receive either rivaroxaban 20 mg once daily or placebo. Rivaroxaban reduced the incidence of symptomatic recurrent VTE more than placebo, with a nonsignificant increase in the incidence of major bleeding.[32][33][39][40][41]

characteristics	**Thrombin Inhibitor**	**Factor Xa Inhibitors**		
	Dabigatran	**Apixaban**	**Edoxaban**	**Rivaroxaban**
prodrug	**Yes**	**No**	**No**	**No**
Bioavailability	3-7%	50%	62%	80%
Time to peak Concentration in hours	1-3	1-3	1-3	2-4
Halaf Life	12-17	8-15	8-10	7-13
Renal clearance	80%	25%	35%	66%

Table 1: Pharmacological characteristics of the direct oral anticoagulants

Conclusion

Selective thrombin and FXa inhibitors are a new class of anticoagulant drugs, designed to overcome the unmet needs of current therapy. They are orally active, achieve maximum anticoagulant effects quickly after ingestion, have a short half-life after discontinuation, and

no need for routine laboratory monitoring or dose modification in the majority of clinical situations. These properties make these drugs easier to use and more desirable to patients and doctors than heparins Number of systematic reviews and meta-analyses published recently pooled data from randomised trials and made indirect comparisons. In comparison to standard therapies, they found that the four direct anticoagulants currently available have at least comparable efficacy for primary and secondary prevention of VTE recurrence and all-cause mortality. [42][43][44][45][46]

In terms of safety, the main question is whether direct anticoagulants cause fewer bleeding complications than traditional anticoagulants, particularly VKA antagonists. Overall, direct anticoagulants have been shown to cause less intracranial bleeding than traditional agents. whereas evidence of their superiority at other sites of bleeding is more unclear.[43] Despite this favorable scenario, a number of issues remain unresolved. Aside from the lack of antidotes, which is close to being resolved (the antidote for dabigatran was recently approved in the US and EU, and the antidote for FXa inhibitors is in an advanced stage of development), their use in specific categories of VTE patients, such as those with obesity, those on dual antiplatelet therapy, or with renal and/or liver dysfunction or cancer, is not settled. [47]

Some systematic reviews and meta-analyses conducted in cancer-related VTE patients enrolled in clinical trials suggest efficacy and safety in this clinical setting .[48][49][50][51] Regarding to the cost of these agents, the dabigatran was estimated to be cost-effective compared to warfarin in patients with atrial fibrillation at high risk of stroke in an economic analysis based on data from the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial. [52]

It's cost-effectiveness in a relatively short period of time (such as that encompassing most VTE treatments) has yet to be proven.

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