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Deep vein thrombosis and novel oral anticoagulants: a clinical review

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Abstract. – Deep vein thrombosis (DVT) is a common disease associated with high rates of mortality and significant morbidity. The diagnostic approach of DVT has evolved over the years. Algorithmical use of pretest probability, D-Dimer testing and ultrasonography allow safe and accurate investigation of DVT. The anticoagulation therapy, used to treat DVT, includes vitamin K antagonists (VKAs) and low-molecular-weight heparin (LMWH) or unfractionated heparin (UF). The duration of anticoagulation therapy depends on the cause of DVT and patient's clinical profile. Although these conventional therapies are effective, narrow therapeutic index, need for frequent monitoring and various food-drug interactions cause difficulties for patients. In recent decades, new oral anticoagulants have been developed. These drugs focus directly on inhibiting either Factor Xa (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran). In contrast to warfarin, these new agents have shorter half-life, fewer drug or food interactions, no necessity for a close monitoring and ease of administration. This review summarizes current knowledge about deep vein thrombosis and new treatment aspects with novel oral anticoagulants.

Key Words:
Deep venous thrombosis, DVT, Warfarin, Heparin, New oral anticoagulants, Factor Xa inhibitors, Thrombin inhibitors.

Introduction

Deep vein thrombosis (DVT) is a condition in which a thrombus forms in a deep vein, predominantly in legs (such as the femoral vein or calf veins). DVT is the third most common cardiovascular disease with an annual incidence of about 108 in 100.000 people[1]. Males have higher age-adjusted rates of venous thromboembolism than females[2]. The incidence increases sharply after age 40[3]. Local damage to intima, venous stasis and hypercoagulability are major predisposing factors[4]. Clinical examination and patient history in patients suspected of DVT are not reliable for diagnosis. Therefore, highly sensitive and specific diagnostic tests are required to be performed. Complications from a blood clot in a deep leg vein can include pulmonary embolism, post-phlebitic syndrome (PPS) and even death. Additionally, there is an elevated risk of a recurrent episode in patients who have a first episode of venous thromboembolism (VTE)[5]. Anticoagulants are crucial drugs for prevention and treatment of thromboembolic diseases. The anticoagulant therapy lowers the risk of recurrent venous thromboembolism; however, it increases the risk of bleeding. Until recently, the only available oral anticoagulants were the vitamin K antagonists and heparins. Even though these anticoagulants have been used for many decades, they fail to fulfill the ideal anticoagulant characteristics (Table I). New oral anticoagulants targeting thrombin or factor Xa, including Dabigatran etexilate (Pradaxa®), Rivaroxaban (Xarelto®), and Apixaban (Eliquis®), have been developed and introduced in clinical practice. This review summarizes the current approach to diagnosis and therapy of deep vein thrombosis.

Diagnosis

Signs and Symptoms

Typical signs and symptoms of DVT include swelling of the lower extremity, pain or tenderness, warmth and increased protuberance of veins and various special signs named for the de-

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Table I. Basic characteristics of an ideal anticoagulant.

Less monitoring
Availability of an antidote
Fixed dosing
Oral administration
Rapid onset
Minimal food and drug interactions
Wide therapeutic window
Predictable pharmacokinetics

scriber. Although special clinical signs such as Pratt signs, Bisgaard sign or Payr sign are highly sensitive for DVT, the accuracy still remains at only 50% approximately[6].

Clinical Prediction Rules

Since single signs, symptoms or risk factors are inadequate for determining likelihood or making a risk stratification, various clinical prediction rules have been developed. The foremost commonly known and used model was developed by Wells et al[7]. This model includes 9 clinical features and stratifies patients into 3 pre-test probabilities: low, moderate, high. A systematic review involving 14 studies showed an improved diagnostic accuracy when clinical probability is estimated before diagnostic tests[8]. Wells et al[7] also showed that it was safe and rational to use a single normal result of a noninvasive test to exclude DVT in the low-probability group, and abnormal results of an ultrasound to rule in DVT in the high-probability group. For patients with moderate pretest probability, the strategy shown to be safe was abnormal results of an ultrasound scan to rule in DVT and normal results of an ultrasound scan on 2 tests, 1 week apart, to rule out DVT[3]. The calculation of pretest probability is the first step in the clinical assessment. Combination of pretest probability with non-invasive diagnostic tests was shown to improve the diagnostic process and decrease costs[7].

Contrast Phlebography

Contrast phlebography is the definitive (gold standard) diagnostic test for DVT, but the use is limited in clinical practice being an invasive and labor-intensive test. The presence of an intraluminal filling defect is the primary criteria used to diagnose acute DVT. However, contrast phlebography remains the only available choice to rule-out DVT in asymptomatic patients).

D-Dimer Testing

D-Dimer is formed through the proteolytic action of plasmin on cross-linked fibrin. The D-Dimer test indicates whether or not there is activation of the fibrinolytic system. D-Dimer test has a sensitivity of approximately 95% and a negative predictive value (NPV) of nearly 100%. Thus, D-Dimer testing is a practical and valuable first line test to rule out DVT[10]. Despite its high sensitivity, the specificity is relatively low and elevated results may be the cause of miscellaneous pathological or physiological states such as trauma, inflammation, malignancy or pregnancy. A negative D-Dimer test in conjunction with a low pre-test probability score can exclude PE (pulmonary embolism) and may reduce unnecessary imaging procedures. The sensitivity of D-Dimer test was found 100% in detecting proximal DVT and 91% for all DVT cases[11]. Nevertheless, clinicians should be aware of the false negative results in patients with biochemically inactive DVT and small popliteal or calf DVT[12]. Accordingly, inclusion of D-Dimer testing into diagnostic algorithms simplifies the management of a patient presenting with suspected DVT.

Diagnostic Imaging

Venous ultrasonography is the most widely used imaging study for the diagnosis of DVT[13]. It is inexpensive, noninvasive and accurate diagnostic method. Compression ultrasonography (CUS), duplex US and color Doppler are both available diagnostic tools in DVT. Compression US (B-mode) has become the diagnostic modality of choice by radiologists for symptomatic DVT. Lack of compressibility is the main criterion to diagnose DVT (Figure 1). Compression US is typically performed on the proximal deep veins, whereas duplex US is generally used to investigate the calf and iliac veins. The mean specificity and sensitivity of venous ultrasonography for the diagnosis of symptomatic proximal DVT are 97% and 94%, respectively[14]. Therefore, high specificity allows clinicians to make the exact diagnosis without further tests. In addition, the use of compression US in the emergency department has been shown to reduce significantly the time to diagnosis.

Magnetic resonance direct thrombus imaging (MRDTI) is as well an appropriate choice for diagnosing DVT, especially in pregnant women and has high sensitivity[15]. Although this technique is noninvasive and does not require contrast agents, it is not routinely performed due to its inaccessibility and expensiveness.

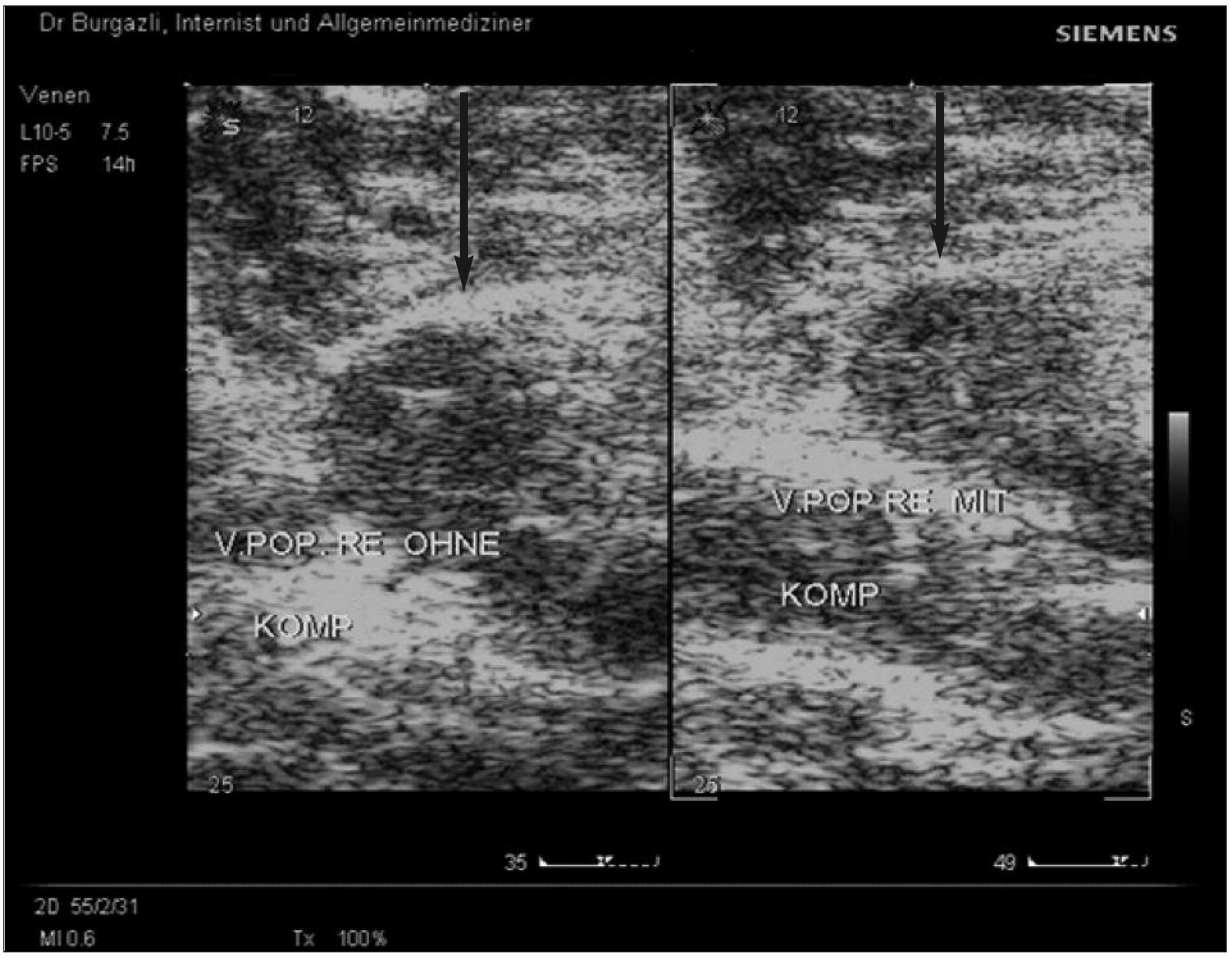

Figure 1. Compression ultrasonography (CUS). Left arrow shows vein before the compression. Right arrow shows compressed view of the vein.

Treatment

Conventional Anticoagulation Treatment

The primary goal of treatment of DVT is prevention of early and late complications of venous thrombosis and posttraumatic syndromes. Anticoagulation is the most commonly chosen treatment option. The initial treatment regimen often involves either unfractionated heparin (UFH) or low molecular weight (LMW) heparin. Achieving the targeted therapeutic ratio in the first 24 hours has been associated with high efficacy of treatment[16-18]. UFH is usually administered via continuous intravenous infusion. The activated partial thromboplastin time (APTT) is a common choice in monitoring. Because the bioavailability of subcutaneous UFH is less than that of intravenous heparin, larger initial doses of subcutaneous heparin are needed to achieve a therapeutic anticoagulant effect. There are well known limitations of UFH such as thrombocytopenia, osteoporosis and various pharmacokinetic limitations. Numerous studies have demonstrated potential advantages of LMWH over UF[19]. Low molecular weight heparins are derived from unfractionated heparin trough depolarization. LMWH is more effective than UFH for the initial treatment of VTE. Use of LMWH was shown to significantly reduce the occurrence of major hemorrhage during initial treatment and overall mortality at follow up[20]. Thus, the current standard of care is to administer weight- adjusted LMW heparin once daily, for first 5-7 days. Since LMW heparin is predominantly excreted by the kidneys, unfractionated heparin should be used in patients with significant renal dysfunction. A study compared effectiveness of low-molecular-weight heparin versus unfractionated heparin for thromboembolism prophylaxis showed similar effectiveness and

cost, but LMWH was associated with fewer complications[21]. LMWH therapy is monitored by the anti-factor Xa assay via measuring anti-factor Xa activity.

After treatment with heparin for several days, the long-term treatment is maintained by oral anticoagulants (warfarin) for weeks to months. An adjusted-dose of warfarin is more effective than low-dose heparin in preventing recurrent venous thromboembolism[22]. Although warfarin is a potentially hazardous drug, causing intracranial bleeding in nearly 0.1%-0.5% and major bleeding in 1%-2% of people treated during each year, people suffer from DVT can benefit from long term treatment[23]. However, heparin treatment requires frequent monitoring. The treatment duration depends on the patients' clinical condition and parameters. 6 to 12 weeks of warfarin treatment is sufficient for post-surgical or transient immobilization, 6 weeks for symptomatic calf DVT and by 3 months of treatment for proximal DVT[23,24]. On the other hand, long term treatment more than 6 months may be required for idiopathic or recurrent DVT.

New Oral Anticoagulants

In the past decades, new oral anticoagulants have been developed. These drugs focus directly on inhibiting either Factor Xa (such as rivaroxaban, apixaban or edoxaban) or thrombin (dabigatran). In contrast to conventional long term treatment choice of DVT, these agents have shorter half-life, fever drug interactions, no necessity for a frequent monitoring and ease of administration. Table II summarizes the comparative pharmacology of anticoagulants.

Dabigatran etexilate (Pradaxa®), a direct thrombin inhibitor, is a prodrug activated by plasma esterases and has a half-life between 14-17 hours. It is eliminated mostly by kidneys; therefore, use of dabigatran in patients with severe renal dysfunction can cause accumulation[26-28]. It is recommended to be administered orally twice daily. A randomized and double blinded study in which oral dabigatran and warfarin were compared in a long term treatment of DTV, dabigatran was found as equally effective and safe as warfarin. Dyspepsia was observed more frequently in patients treated with dabigatran[29]. Dabigatran is approved by the EMEA for the prevention of VTE after total knee or hip replacement[26]. In the RE-NOVATE study, 3494 patients administered either dabigatran or enoxaparin after knee arthroplasty[30]. Median treatment duration was 33 days. Dabigatran was equally effective with enoxaparin in prevention of VTE incidence and VTE related deaths. Similarly, the RE-MODEL study compared 150 or 220 mg oral dabigatran with 40 mg subcutaneous enoxaparin and outcomes of both drugs were in same efficacy and safety profile[31]. A pooled analysis of RE-MODEL, RE-NOVATE and RE-MOBILIZE trials oral dabigatran in doses of 150 or 220 mg were shown as effective as 40 mg or 30 mg subcutaneously given enoxaparin in reducing the risk of major VTE and VTE-related mortality after hip or knee arthroplasty and had a similar bleeding profile[32]. Another randomized, double-blind and noninferiority trial investigated the efficacy of dabigatran versus warfarin in the treatment of acute VTE for 6 months. A fixed dose of dabigatran was as effective as warfarin without requiring laboratory monitoring[29].

Rivaroxaban (Xarelto®) which has been approved in European Union Member Countries, is an FXa inhibitor with a half-life of 7-11 hours. It is metabolized by kidney and eliminated unchanged via kidneys[26]. Therefore, rivaroxaban is contraindicated in patients with liver disease asso-

Table II. Pharmacodynamic characteristics of the anticoagulants. Reproduced with the permission of Jeffrey et al[25].

Characteristics	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Target	VKORC1	Thrombin	Factor Xa	Factor Xa
Prodrug	No	Yes	No	No
Bioavailability	100%	6%	60%-80%*	60%
Dosing	OD	BID (OD)	BID (OD)	BID
Time to peak effect	4-5 d	1-3 h	2-4 h	1-2 h
Half-life	40 h	8-15 h	7-11 h	12 h
Renal clearance	None	80%	33%	25%
Monitoring	Yes	No	No	No
Interactions	Multiple	P-gp	3A4/P-gp	3A4/P-gp

BID indicates twice daily; OD: once daily; P-gp: P-glycoprotein; VKORC1: C1 subunit of the vitamin K epoxide reductase enzyme; 3A4: cytochrome P450 3A4 enzyme. *Bioavailability of rivaroxaban decreases as the dose is increased because of poor drug solubility; with OD doses of 20 and 10 mg, the bioavailabilities are 60% and 80%, respec-tively.

ciated with coagulapathy. Phase II studies comparing rivaroxaban with enoxaparin, demonstrated an acceptable safety and efficacy similar to enoxaparin in the prevention of DVT[33,34]. In a pooled analysis of three phase III RECORD trials, a significant 2-fold lower risk of symptomatic VTE plus all-cause mortality was observed among patients treated with rivaroxaban compared with enoxaparin[35]. On the other hand, clinically relevant bleedings was significantly higher in patients received rivaroxaban. In addition, no significant differences were shown in secondary bleeding rates. Phase III EINSTEIN-DVT study in which 3449 patients treated with either 3 weeks oral rivaroxaban alone (15 mg bid) and followed by 20 mg daily subcutaneous enoxaparin or vitamin K antagonist for 3, 6 or 12 month, showed a statistically significant efficacy of rivaroxaban with respect to primary outcome. Bleeding outcomes were found to be similar between groups[36]. Also, an extended prophylaxis with 10 mg of rivaroxaban once daily for 3 weeks resulted as effective as bemiparin in knee arthroscopy thromboprophylaxis[37].

Apixaban (Eliquis®) is a direct FXa inhibitor with a high oral bioavailability. Its half-life is 12 hours and eliminated mainly through the cytochrome P450 CYP3A4/5 pathway[38,39] Risk-benefit balance was evaluated in ADVANCE-2 and ADVANCE-3 phase III studies. Pool analysis of these phase III trials showed superior efficacy of the treatment with apixaban at a dose of 2.5 mg twice daily compared to treatment with subcutaneously enoxaparin[40]. A randomized study compared the efficacy and safety of 5 mg of apixaban orally twice daily with 30 mg of enoxaparin subcutaneously in patients underwent total knee replacement. The study concluded that both treatments had similar efficacy and apixaban may have a favorable benefit-risk ratio as compared to LMW Heparins[41].

Edoxaban, a direct FXa inhibitor with a half-life of 8-10 hours, is rapidly absorbed and eliminated mostly by kidney[26] A Phase IIb randomized, double blinded and placebo-controlled study showed a significant preventive effect of edoxaban in patients who underwent a total knee arthroplasty[42]. Further studies assessing the efficacy of edoxaban in prevention of deep vein thrombosis are needed and being conducted.

Other Interventions

Although they are not commonly used, thrombolysis and inferior vena cava filters have been proposed in addition to anticoagulation. Although the thrombolytic therapy is advantageous in leading to earlier vein patency, it increases the risk of major hemorrhage including intracranial hemorrhage. Additionally, a benefit in terms of post-thrombic syndrome is unproven[43]. The indication for systemic thrombolytic therapy is massive iliofemoral DVT, which leads to phlegmasia cerulean dolens. The use of inferior vena cava filters is as well limited in clinical practice; however few indications such as absolute contraindication to anticoagulation, life-threatening hemorrhage on anticoagulation or failure of adequate anticoagulation exist. Thrombosis at the access site is a common complication of vena cava filter replacement[44]. The results of a study with a follow-up period of 8 years showed that vena-cava filters reduced the risk of pulmonary embolism but increased risk of deep-vein thrombosis. Collectively, it had no effect on survival. Therefore, it is an important reserve for clinicians; however, more studies with appropriate study designs are needed for widely use[45].

Discussion

Reversal of Anticoagulation

The main concern in patients receiving anticoagulant therapy is hemorrhagic complications. Pharmacology and management of the vitamin K antagonists and heparins are well defined and published in evidence-based guidelines[46]. Vitamin K is the specific antidote for the reversal of anticoagulant effect of VKAs. Nevertheless, the reversal agents recommended for the effects of VKAs have several safety and practical limitations. Analogously, the effects of UFH can be rapidly antagonized by an IV bolus of protamine or by other agents such as hexadimethrine and heparinase[47].

On the other side, no antibodies against factor Xa and thrombin inhibitors are currently available. In cases of mild to moderate bleeding, routine management involving stoppage of the inciting oral anticoagulant, mechanical compression, surgical or interventional therapy and hemodynamic stabilization will suffice. Using fresh frozen plasma, prothrombin complex concentrates, recombinant factor VIIa should be considered in severe bleeding. In patients receiving dabigatran, hemodialysis can be used to lower the drug level and activated charcoal may be given in 3 hours of oral anticoagulant intake to reduce gastrointestinal absorption[39,48,49]. However,

specific antidotes against these novel agents are under development and may become available in the future[50,51].

Cost-Effectiveness

The new oral anticoagulants are more expensive than warfarin and heparin. Although they are much cheaper, use of VKAs and heparin derivatives lead to additional costs arising from frequent INR monitoring. McCullagh et al[52] compared the cost-effectiveness of rivaroxaban and dabigatran etexilate with enoxaparin sodium in Irish patients who needed thrombophylaxis after total hip and total knee replacement. The study concluded that when both rivaroxaban and dabigatran etexilate are compared with enoxaparin sodium, rivaroxaban was the most cost-effective option after total hip or knee replacement. Another study[53], which compared the cost-effectiveness of oral direct factor Xa inhibitors with subcutaneous LMWH represented the new oral anticoagulants as an economically dominant strategy. A study[54] calculated the cost effectiveness of dabigatran etexilate to warfarin in stroke prevention indicated that the new anticoagulant is likely to be cost-effective alternative to warfarin. Yet, large and multicenter randomized controlled trials are needed to reduce the uncertainty. Despite the expensive costs of new oral anticoagulants, long term results of cost-effectiveness may seem economically dominant strategy.

Food-Drug Interactions

Warfarin interacts with many commonly used drugs, and its metabolism varies between patients. A systemic review in which the drug interactions of warfarin were evaluated showed that 26 potential drugs and foods did interact with warfarin[55]. Many of these drug interactions increased warfarin's anticoagulant effect. The anticoagulant response of WKAs is influenced also by genetic polymorphisms that may modulate activity of CYP2C9. On the other hand, the metabolism of new oral anticoagulants is not affected by food and drug-drug interactions are uncommon[25]. Most common drug interactions occur with drugs that strongly inhibit both cytochrome P450 3A4 and P-glycoprotein, such as antimycotics; therefore, dabigatran requires caution and rivaroxaban is contraindicated in combination with these drugs[56] Patients receiving rivaroxaban and dabigatran should be monitored for altered response if CYP3A4 or P-gp inhibitors are added to or removed from their drug regimen. Patients with renal or hepatic dysfunction are likely to be sensitive to drug interaction-induced changes in elimination. However, one must take the fact that the clinical experiences and current publications about new oral anticoagulants are relatively less than conventional drugs into consideration before comparing interactions or side-effects.

Monitoring

Although there is no need for routine monitoring in patients receiving new agents, one potential problem is the inability to monitor their activity or drug levels particularly in emergency situations such as overdose or apparent bleeding. In addition, no antidote exists for these three drugs if reversal is indicated. Therefore, it is important to be able to quickly assess coagulation function in patients with overt bleeding. Patients receiving UFH, LMW heparin and warfarin are monitored with activated partial thromboplastin time (APTT), anti-Xa activity and INR respectively. Currently, no validated tests are available for new oral anticoagulants in case of major hemorrhage or apoplexia. Ecarin clotting time may be a reliable but not widely used assay to assess coagulation with dabigatran[50]. For rivaroxaban and apixaban, anti-factor Xa assays may be useful only in the future to monitor activity[57]. Patient knowledge of prevention and recognition of complications should be considered during follow up. Moreover, the agents frequently produce a predictable anticoagulant effect that they can be given in fixed doses without the need for routine coagulation laboratory monitoring[58].

Patient Selection and Contraindications

Special complications should be considered when using anticoagulants in certain patient groups, in patients with renal insufficiency, with poor compliance and with a high risk of gastrointestinal bleeding. The first step is to determine whether the patient is a candidate for one of the new oral agents or is suited for warfarin. Since compliance is the novel agents need at least 1 daily dose because of a very short half-life, patients who are noncompliant to warfarin should not to be switched to the new oral anticoagulants. Physicians should be also aware of the common side effects of these agents when prescribing especially to subpopulations. Dabigatran and rivaroxaban lead gastrointestinal bleeding more common than warfarin, particularly in patients over the age of 75. Therefore, dosage regimens can be changed or agents may be switched to warfarin for this patient

group[25]. Additionally, dyspepsia occurs in up to 10% patients receiving dabigatran, thus switching dabigatran to FXa inhibitors can be helpful for patients with certain gastrointestinal symptoms. Furthermore, new oral anticoagulants may be potentially useful in the management of patients with heparin-induced thrombocytopenia, a serious complication of heparin treatment.

Dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance (CrCl) < 30 ml/min), and rivaroxaban is not recommended when CrCl < 15 ml/min[50,59]. Therefore, renal functions are needed to be assessed in patients before starting these agents. Apixaban is contraindicated in people with severe hepatic impairment (Child-Pugh class C) and in people with hepatic disease associated with bleeding problems[60]. According to the safety announcement about Pradaxa (Dabigatran etexilate) released by FDA after the uncompleted RE-ALIGN trial, this trial was stopped because Pradaxa users were more likely to experience strokes, heart attacks, and blood clots forming on valves. Due to that reason, prescribing dabigatran to patients having prosthetic heart valves may lead to life-threatening consequences[61,62].

Conclusions

Deep vein thrombosis is an important cause of mortality and morbidity worldwide. Well established diagnostic algorithms and advanced tools simplify the diagnosis. Conventional therapy of DVT includes heparin, followed by a long term warfarin treatment. Although they have been used widely, they are far beyond the ideal anticoagulant. The new oral anticoagulants have potential to serve a more ideal and advantageous treatment option for DVT. These novel agents are not only safer than warfarin but also more effective. However, further randomized studies and reports are needed to strengthen the perception of these agents.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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