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INDICATION OF ORAL ANTICOAGULANTS IN VENOUS THROMBO EMBOLISM

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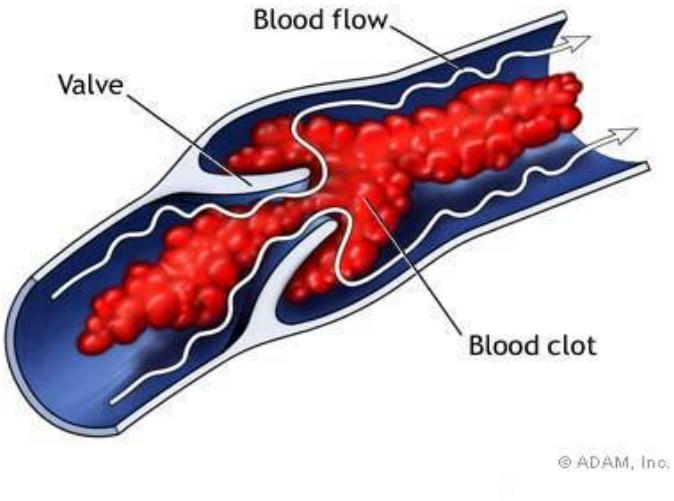
ABSTRACT

Venous thromboembolism (VTE) is a disease that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). It is a common, lethal disorder that affects hospitalized and non-hospitalized patients, recurs frequently, is often overlooked, and results in long-term complications including chronic thromboembolic pulmonary hypertension (CTPH) and the post-thrombotic syndrome (PTS). Venous thromboembolism, comprising deep vein thrombosis and pulmonary embolism, is one of the leading causes of mortality and morbidity. Venous thromboembolism is the third most common illness after acute coronary syndrome and stroke. DVTs are most common in adults over age 60. Evidence supports the use of heparin in surgical patients whom have a high risk of thrombosis to reduce the risk of DVTs.

KEYWORDS: Venous thromboembolism (VTE) risk of DVTs.

INTRODUCTION

A venous thrombosis is a blood clot (thrombus) that forms within a vein. Thrombosis is a term for a blood clot occurring inside a blood vessel.



Classification

- **Superficial venous thromboses**can cause discomfort but generally do not cause serious consequences, unlike the deep venous thromboses (DVTs) that form in the deep veins of the legs or in the pelvic veins.
- **Systemic embolisms** of venous origin can occur in patients with an atrialor ventricular septal defect, through which an embolus may pass into the arterial system.
- **A venous thrombosis** which results from vein inflammation is a thrombophlebitis.

Risk Factors for DVT/PE

ACQUIRED	INHERITED	MIXED
Older age Major surgery and orthopedic surgery Cancers, most particularly pancreatic, but not cancers of the lip, oral cavity, and pharynx Immobilization, as in orthopedic casts the sitting position, and travel, particularly by air Pregnancy and the postpartum period	Antithrombin deficiency Protein S deficiency (type I) Factor V Leiden Prothrombin G20210 Dysfibrinogenemia Non O-blood type	Lofree protein S Activated protein C resistance High factor VIII levels Hyperhomocysteinemia High fibrinogen levels High factor IX levels High factor XI levels

Drug Induced Venous Thromboembolism

- An increasing number of reports suggest a link between venous thromboembolism (VTE) and the use of antipsychotics.
- To better understand this association the available body of evidence has been critically scrutinised.

- Relevant articles were identified in the databases Scopus and PubMed. Several observational studies using different methodologies show an increased risk of VTE in psychiatric patients.
- This elevated risk seems to be related to the use of antipsychotic medication and in particular to the use of clozapine and low-potency first-generation drugs.
- Many studies investigating the association have, however, methodological limitations. The biological mechanisms involved in the pathogenesis of this possible adverse reaction are largely unknown but several hypotheses have been suggested such as drug-induced sedation, obesity, increased levels of antiphospholipid antibodies, enhanced platelet aggregation, hyperhomocysteinemia and hyperprolactinemia.
- The association may also be related to underlying risk factors present in psychotic patients. Physicians need to be aware of this possible adverse drug reaction.
- Although supporting evidence has not been published they should consider discontinuing or switching the antipsychotic treatment in patients experiencing VTE
- In addition, although data is lacking, the threshold for considering prophylactic antithrombotic treatment should be low when risk situations for VTE arise, such as immobilisation, surgery and so on.

Prevention

Evidence supports the use of heparin in surgical patients whom have a high risk of thrombosis to reduce the risk of DVTs; however, the effect on PEs or overall mortality is not known.

- In hospitalized non-surgical patients, heparin results in an almost statistically significant decrease in mortality and may decrease the risk of PE and DVT, but it increases major bleeding events yielding little or no overall clinical benefit[-] It does not appear however to decrease the rate of symptomatic DVTs.
- In hospitalized non-surgical stroke patients, mechanical measures (compression stockings) resulted in skin damage and no clinical improvement[-] Data on the effectiveness of compression stockings among hospitalized non-surgical patients without stroke is scarce.
- A 2011 clinical guideline from the American College of Physicians (ACP) gave three strong recommendations with moderate quality evidence on VTE prevention in non-surgical patients: that hospitalized patients be assessed for their risk of thromboembolism and bleeding before prophylaxis (prevention); that heparin or a related drug is used if

potential benefits are thought to outweigh potential harms; and that graduated compression stockings not be used.

- As an ACP policy implication, the guideline stated a lack of support for any performance measures that incentivize physicians to apply universal prophylaxis without regard to the risks. Despite development of various practice guidelines for prevention of VTE, they remain underused in most countries.
- To prevent thrombus extension, decrease of the risk of recurrent thrombosis and subsequent death in patient with VTE pharmacological approaches can be administered.

Conventional Anticoagulant Treatment *Three Stages*

1. **Acute Treatment**(≥5 days)—to stabilize the thrombus, prevent extension and possibly subsequent fatal pulmonary embolism
2. **Secondary Prevention** of recurrent venous thromboembolism (≥3 months)
3. **Long-Term Maintenance Treatment**(>months/indefinite). With the currently available agents, immediate anticoagulation can only be achieved with parenteral anticoagulants (such as unfractionated heparin, low molecular weight heparin, or fondaparinux).

Potential Role of New Oral Anticoagulants

Most patients with deep vein thrombosis are treated at home, and this outpatient treatment increases the need for a safe, effective, single oral anticoagulant that can be administered at a fixed dose. New oral anticoagulants exhibit many characteristics of the 'ideal anticoagulant.' They are administered orally at fixed doses, have a rapid onset of action, predictable pharmacokinetics and pharmacodynamics, and minimal food–drug or drug–drug interactions. Therefore, there is no need for routine coagulation monitoring or dose adjustment. Adopting the novel oral agents for the treatment of venous thromboembolism will considerably simplify the treatment strategy, as one oral regimen will be sufficient for the whole treatment duration, without the need for bridging therapy from a parenteral anticoagulant in the acute treatment phase (even though this option has not been used in all phase III studies in this indication).

A singledrug therapy would provide great convenience both within and out of the hospital setting; this single-drug approach was used in both the EINSTEIN (rivaroxaban) and the AMPLIFY (apixaban) studies. In the phase III EINSTEIN DVT/PE studies, intensified treatment in the first 3 weeks (15 mg bid) is utilized, and this initial dose regimen is to ensure

adequate treatment is achieved during this acute period. This is then followed by a once daily regimen for the rest of the treatment period without routine coagulation monitoring and dose adjustment (unlike warfarin). A similar approach is used in the AMPLIFY program with the direct Factor Xa inhibitor apixaban, but the drug is given at 5 mg bid and intensified treatment is given during the first 7 days (10 mg bid). In the edoxaban and dabigatran etexilate programs, an initial period of at least 5 days with a parenteral low molecular weight heparin administration is mandatory. It should be noted that the design of the ongoing trials for the treatment of venous thromboembolism are different, which may impact the use of the different new drugs, as shown it.

Although double-blind designs are considered optimal for phase III randomized trials in general, this paradigm may distort one of the fundamental objectives of phase III studies, i.e. to compare a new regimen with the existing standard under realistic clinical conditions. This becomes especially problematic when the best current therapy is complicated by the need for monitoring and dose adjustments. According to Büller et al., with adequate controls to minimize bias, open-label phase III studies may provide more accurate assessments than trials that adhere to a double-blind design, because they would apply in actual clinical practice, but these views are not shared by all made a strong casefor a double-blind design in spite of the many challenges. The available clinical studies have established non-inferiority oreven superiority of several regimens of the new oral agents compared with conventional therapy. The new oral anticoagulants are also associated with similar or lower bleeding rates incomparison with conventional anticoagulants (such as enoxaparin and warfarin).For example, there was no significant difference in the rate of major bleeding in all the completed phase III studies for the prevention and treatment of venous thromboembolism between the new agents and conventional therapy. In addition, there was no indication of sustained hepatoxicity associated with the new oral anticoagulants within the trial periods in these studies (unlike ximelagatran).

The introduction of the new oral anticoagulants may reduce the length of hospital stay, facilitating earlier discharge, particularly in patients who cannot or are unwilling to carry out subcutaneous injection themselves. Because the new oral agents do not require routine coagulation monitoring, adherence to guidelines is also expected to improve. Many physicians have concerns about the administration of vitamin K antagonists because they have a narrow therapeutic window and require routine coagulation monitoring and dose

adjustment. A meta-analysis showed that, in community-based practice in the US, patients with atrial fibrillation receiving warfarin treatment only spent 51% of their time within the therapeutic international normalized ratio range 2.0–3.0, leaving them at a risk of either thromboembolism or bleeding complications. The new oral anticoagulants may provide a better alternative to warfarin for stroke prevention in patients with atrial fibrillation because they do not require routine coagulation monitoring and dose adjustment. Both dabigatran etexilate (a direct thrombin inhibitor) and rivaroxaban (a direct Factor Xa inhibitor) havedemonstrated potential to replace warfarin in this indication. In addition, the new oral agents are expected to be more cost effective than the traditional anticoagulants, partly as a result of theiroral route of administration (versus parenteral administration) andthe lack of a need for routine coagulation monitoring.

A recent cost effectiveness analysis of rivaroxaban versus enoxaparin for the prevention of postsurgical venous thromboembolism in Canada showed that rivaroxaban was associated with improved health outcomes, lower incidence of symptomatic venous thromboembolism, and a lower cost per patient. Similarly, a cost-effectiveness model comparing rivaroxaban and dabigatran etexilate with enoxaparin as thromboprophylaxis after total hip and total knee replacement surgery in the Irish healthcare.

Setting indicated that both new agents had a lower overall cost thanenoxaparin, with rivaroxaban being the most cost-effective strategy in this setting. Potential limitations of these novel drugs do, however, exist. The lack of specific antidotes—in case immediate reversal is needed—is a theoretical rather than practical drawback, because the half-lives of the new oral agents are relatively short (compared with warfarin). Although routine monitoring is not required with these new anticoagulants, a simple assay for quantifying the activity or plasma levels of the drug would be useful in patients with a hemorrhagic o rthrombotic event, to determine whether patients are over- or under anticoagulated and/or how long the remaining anticoagulant effect is anticipated to last. Periodic coagulation testing, although cumbersome in most cases, may also be helpful to assess compliance even though this has never been demonstrated formally.

Both direct Factor Xa inhibitors and direct thrombin inhibitors have shown promising results in recent clinical studies, demonstrating that both Factor Xa and thrombin are viable targets for anticoagulant therapy. Therefore, we are now closer than ever to the ‘ideal anticoagulant’, and these new agents could improve the benefit–risk balance of extending anticoagulant

therapy beyond the usual, limited duration. Moreover, the single-drug approach for the whole treatment duration may revolutionize the therapeutic paradigm and is expected to improve overall clinical outcomes. The practice of medicine has changed dramatically in the 41 years since Barritt and Jordan published the first randomized clinical trial involving the treatment of pulmonary embolism.

Physicians are prepared to change their practice, but only when the recommended changes are based on properly designed clinical trials using clinically relevant end points. Arguably, the two most important advances in the treatment of venous thromboembolism have been the development of LMWH and the establishment of an optimal intensity for warfarin therapy. The first has increased the convenience of initial treatment and has reduced the risk for some side effects of heparin. The second has improved the safety of warfarin, thereby broadening its clinical use and benefiting many patients. Anticoagulants designed to target specific coagulation enzymes are being evaluated in clinical trials. However, if these new anticoagulants are to replace the very effective agents that are currently available, They will have to be more convenient, cost-effective, and safe. Despite the progress that has been made, several issues have yet to be resolved. The optimal duration of anticoagulation in various subgroups of patients with venous thrombosis has not been determined. It is not known whether less intense warfarin therapy, which would cause less bleeding, is effective in preventing recurrent venous thromboembolism.

Hereby i conclude my project by pointing out that from clinical experiments, it has been found out that newer oral anticoagulants are more effective in the treatment of venous thromboembolism. They are also cost-effective and easily available ones. They are having fewer side effects and contraindications as compared to other drugs. The increase in serum alanine aminotransferase is generally a symptomatic and reversible, regardless of whether ximelagatran treatment is continued or stopped. Although this phenomenon appears to be benign, more data on patients treated long-term are needed. Until this information is available, ximelagatran will need to be restricted to patients with normal or near normal hepatic function at baseline. Furthermore, it is likely that testing of liver function will need to be performed when initiating ximelagatran treatment and during the first 6 months of therapy. Although less problematic than the routine coagulation monitoring and dosage adjustments needed with vitamin K antagonists, the requirement for liver

function test monitoring may limit the convenience of ximelagatran. So the most applicable method of treatment of venous thromboembolism is by using oral anticoagulants.

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