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REVIEW

Management of Venous Thrombo-embolism: From Leeches to Novel Oral Anticoagulants

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Abstract

Venous thromboembolism (VTE) is one of the three major cardiovascular causes of death, but the history of venous thrombosis in miniature illustrates the development of medicine itself. Anticoagulation therapy has a long history. It started with leeches and passed through heparin, warfarin and low molecular weight heparin (LMWH). The development of the novel oral anticoagulants (NOACs) has marked the beginning of a new era in the treatment of VTE. Dabigatran, Rivaroxaban and Apixaban has been approved for different indications of anticoagulation which include non valvualr atrial fibrillation, venous thromboembolism prophylaxis and treatment. Use of these agents requires expertise in managing the dose and their adjustment in special cases like renal insufficiency as these agents carry risk of bleeding and proper antidote is still being developed. Knowledge of NOACs is essential for all medical personal as these agents are the future of the anticoagulation and they are set to replace warfarin and LMWH on the long term.

Key Words: Venous thromboembolism (VTE), Thrombosis, Anticoagulation, Heparin, Warfarin, Low Molecular weight heparin (LMWH), Novel Oral Anticoagulants (NOACs), Atrial fibrillation (AF),

Epidemiology

Venous thromboembolism (VTE) is one of the three major cardiovascular causes of death, along with myocardial infarction and stroke. VTE is estimated to cause >500,000 deaths in Europe every year (1). In the US, the annual incidence of symptomatic VTE is estimated to exceed 600,000, with nearly 300,000 VTE-related deaths annually (1). Currently, VTE is considered the most common preventable cause of hospital death, and the third most common cause of all hospital-related deaths. Thus, there has been a tremendous need for healthcare policy makers to ensure that VTE prophylaxis guidelines are consistently implemented (2,3).

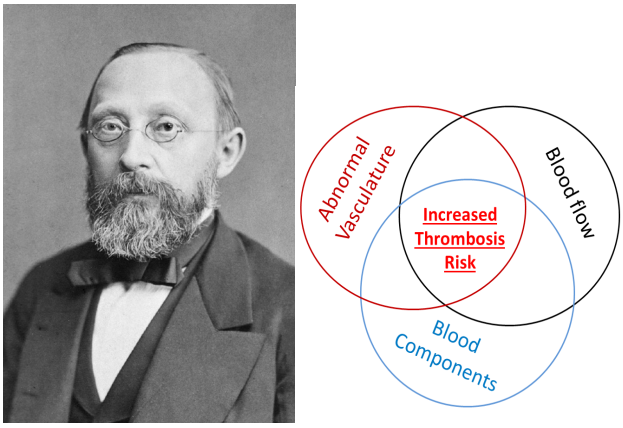

Figure 1. Virchow's Triad of Thrombogenesis, Source: Wolberg AS, Aleman MM, Leiderman K, Machlus KR. Procoagulant activity in hemostasis and thrombosis: Virchow's triad revisited. Anesth Analg. 2012;114(2): 275-85.

Figure 2. Progression of anticoagulation from biological means represented by a leech stuck to skin and releasing its saliva that contains a natural anticoagulant substance to the first pharmacological method with the discovery of heparin by a medical student Jay McLean (1890-1957).

Historical Background

The history of venous thrombosis in miniature illustrates the development of medicine itself (4). It goes as far back as 2650 B.C. when the Chinese physician Huang Ti noted that coagulation within the feet causes pain and chills (5). In 17th century, Wiseman described the increased risk of thrombosis in pregnancy and cancer (6). At that time, deep venous thrombosis (DVT) of the iliofemoral veins in post-partum women was termed "milk leg" as the leg resembled a thin bag of skin filled with milk, taunt, shiny, smooth with white or mottled skin and dilated veins. It was believed that milk from the breasts fell to the leg, and even was thought of as "milk metastasis". It took till 1784, when Charles White demonstrated that "milk leg" was actually caused by clots obstructing the veins (5,6). Just over 70 years later in 1856, Rudolf Ludwig Karl Virchow proposed the predisposition to venous thrombosis and he attributed this to three factors (7). These factors, often termed "Virchow triad", are stasis, vascular damage and hypercoagulability (Figure 1). Virchow was also the first to connect the local DVT with the distant pulmonary embolism (PE). Hence, both DVT and PE are currently referred collectively as venous thromboembolism (VTE).

Traditional Anticoagulants

Anticoagulation therapy has a long history. In 1884, John B. Haycraft discovered Hirudine. A substance found in the saliva of leeches "Hirudo medicinalis", that has anti-coagulant effects. Interestingly the use of medicinal leeches can be dated back all the way to ancient Egypt (9) (Figure 2). Jay Mclean (Figure 2) accidentally discovered Heparin when he was a medical student in 1915 (2). Warfarin, the currently prescribed oral anticoagulant word wide, was initially introduced in 1948 as a pesticide against rats and mice, then was found to be effective and safe as anticoagulant in 1950s (10). The injectable forms of anticoagulants include unfractionated heparin (UFH), low molecular weight heparin (LMWH) and Fondaparinux and they work by inhibiting the activity of factor Xa indirectly through binding to circulating antithrombin III. The oral forms are vitamin K antagonists (VKAs), including warfarin, phenprocoumon and acenocoumarol (11).

These anticoagulants have some drawbacks that created the necessity to develop new agents. UFH needs monitoring and dose adjustment due to varied responses among individuals. It is also associated with a risk of heparin-induced thrombocytopenia (HIT) (12). LMWHs are as well associated with a risk of HIT that is lower in comparison

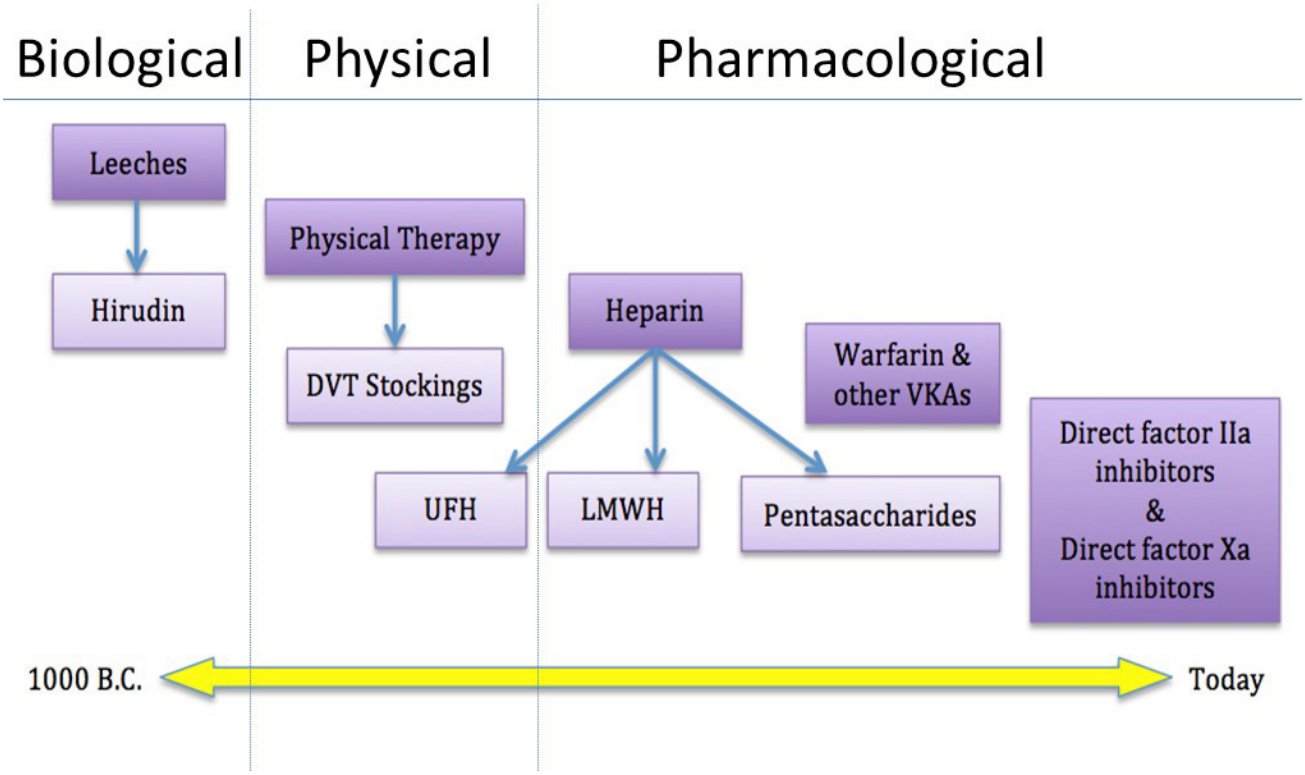

Figure 3. The progress of antithrombosis through ages from biological, to physical and pharmacological means. DVT= Deep vein Thrombosis; UFH: Unfractionated heparin; LMWH: Low molecular weight heparin. Modified from Antithrombosis through the ages Source: T Sylvia Haas (2012) the Stony Road to Anticoagulation, London: Andrew Ward

Table 1. Pharmacokinetics and Current Dosing Guidelines for New Oral Anticoagulation Agents

	Dabigatran	Rivaroxaban	Apixaban
Route of administration	Oral twice daily	Oral once daily	Oral twice daily
Bioavailability (%)	65	80	66
Time to maximal concentration (Tmax) (h)	1.25	2-4	1-3
Half-life (h)	12-14	5-13	8-15
Renal excretion (%)	80	66	25
Plasma protein binding (%)	35	90	87
Dosing for atrial fibrillation with normal renal function	150 mg BID	20 mg QD	5 mg BID
Dosing for atrial fibrillation: renal dysfunction	75-110 mg BID*	15 mg QD** with CrCL 15–50ml/min	2.5 mg BID
DVT prophylaxis	220 mg QD	10 mg QD†	2.5 mg BID
DVT prophylaxis with Renal dysfunction	150 mg QD (Not approved in the United States for this indication)	Avoid with CrCL < 30ml/min	-

** For Apixaban, no data available for use with CrCL < 15 ml/min or on dialysis.*
† For hip and knee surgery. BID = twice a day; CrCL = creatinine clearance; QD = daily.

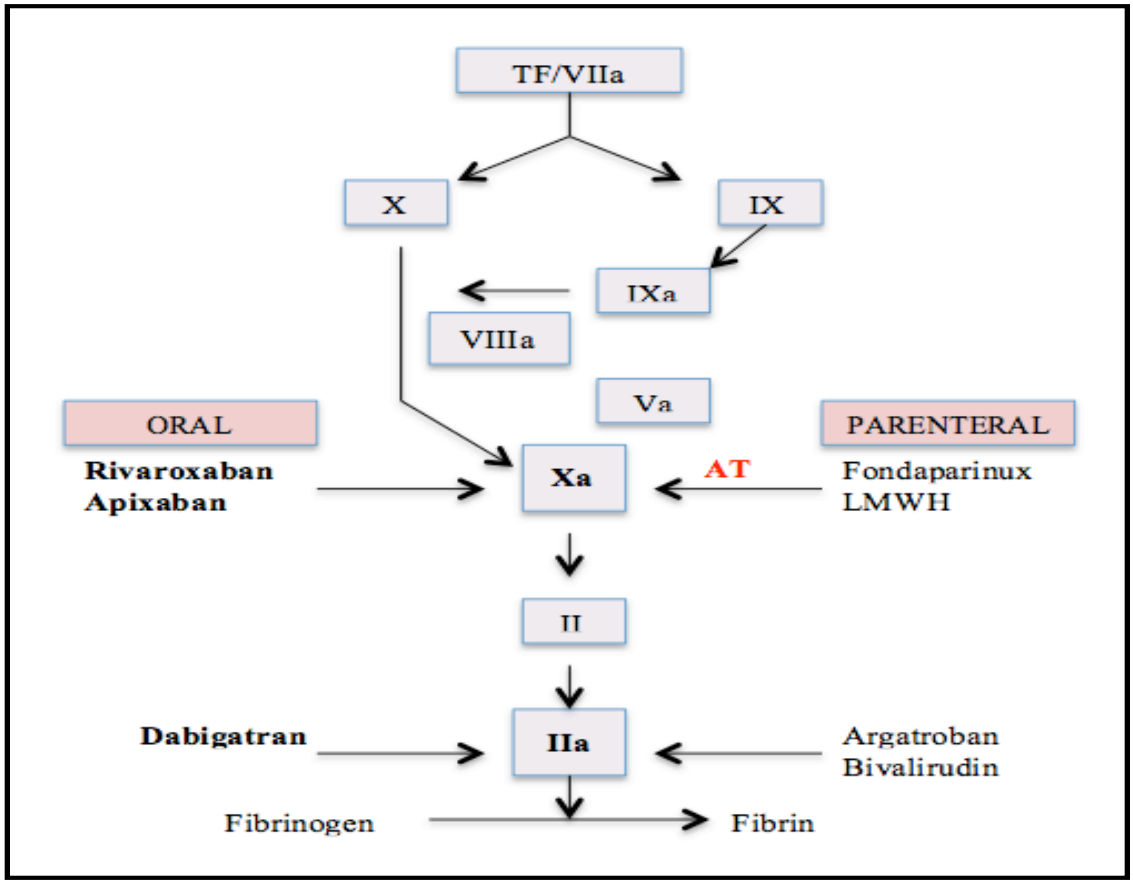

Figure 4. Sites of action of anticoagulation agents. The NOACs act by directly inhibiting thrombin independent of antithrombin (Dabigatran) or by directly inhibiting factor Xa (Rivaroxaban and Apixaban)

Table 2. Outlines of the practical management of patients with bleeding on novel anticoagulant agents depending on the severity of the bleeding

Severity of Bleeding	Therapeutic Measures
Mild bleeding	Delay next dose or discontinue treatment as feasible.
Moderate-severe bleeding	Symptomatic treatment. Mechanical compression. Surgical intervention. Fluid replacement and hemodynamic support. Blood products transfusion. Oral charcoal application if Dabigatran was ingested <2 h before. Hemodialysis (for Dabigatran)
Life-threatening bleeding	Same strategies as applied in moderate-severe bleeding, PLUS: hemodynamic and hemostatic resuscitation, consideration of prothrombin complex concentrates (PCCs), charcoal filtration

with UFH (12). Oral VKAs, on the other hand, are far more problematic in clinical use due to their narrow therapeutic window, variable dose response and multiple food–drug and drug–drug interactions (13).

Novel Oral Anti-Coagulants for treatment of VTE:

The development of the NOACs has marked the beginning of a new era in the treatment of VTE (Figure 4). These oral anticoagulants are specifically directed against thrombin or factor Xa, and they surpass the limitations of the standard therapy such as the need for injections and laboratory monitoring for dose adjustment (14) (Figure 5). Moreover, the new oral anticoagulants have a predictable anticoagulant effect, a rapid onset and offset of action with peak effect reached within two to four hours, overcoming the need for a parenteral anticoagulant in the initial treatment of VTE (15). Dabigatran is a reversible direct thrombin (or factor II) inhibitor that works independent of antithrombin cofactor level (16). The pharmacokinetics of Dabigatran is shown in table 1. In comparison to other NOACs, Dabigatran has a low protein binding, which makes it dialyzable (16). Based on the results of the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) study, Dabigatran is licensed for stroke prevention in patients with non-valvular atrial fibrillation in United States, Canada, Europe and Japan (16,17). This study aimed to demonstrate the efficacy and safety of Dabigatran for stroke and systemic embolisim prevention in patients with non-valvular atrial fibrillation (16). It concluded that Dabigatran is as effective (110 mg BID) or more effective (150 mg BID) than warfarin in preventing stroke or systemic embolism, and both regimens decreased the likelihood of intracranial bleeding by more than one-half compared with warfarin (17,18) The RE-LY study also showed a dose-dependent increase in the incidence of GI bleeding (10). Dabigatran is approved for VTE prevention in adult patients undergoing total hip or total knee replacement surgery in Europe and Canada, but not in United States (16). Another target for NOACs is factor Xa, a rate-limiting factor in the coagulation cascade. Direct oral factor Xa inhibitors include Rivaroxaban, Apixaban and Edoxaban, and all are working independently of antithrombin cofactor (16). Rivaroxaban has a high bioavailability of about 80% but, in contrast to Dabigatran, is highly bound to plasma proteins, mainly albumin, with ranges between 92% and 95%, making it undialyzable (16,20). Two thirds of Rivaroxaban dose is metabolized in the liver via cytochrome P450, half of which is eliminated through the kidneys and half through the faecal route (21). One third of the dose is excreted unchanged in the urine (21). Table 1 shows the pharmacokinetics of Rivaroxaban. The antithrombotic effect of Rivaroxaban is dose-dependent (20).

Rivaroxaban has been approved in the US, EU and Canada for the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery, at a fixed dose of 10 mg daily, starting when hemostasis is established (18,19). According to the RECORD trial, Rivaroxaban has been proven to be superior to enoxaparin in preventing VTE following total hip and knee replacement surgeries, without an increase in rates of bleeding (16,22). In 2011, Rivaroxaban has been approved for use in prevention of stroke and systemic embolism in adult patients with non-valvular AF (23,24). In November 2012, the U.S. FDA had approved it for the treatment of patients with DVT and PE and for long-term treatment to prevent recurrence (24). The EINSTEIN program is composed of three randomized trials of Rivaroxaban that are the Acute DVT Study, the Acute PE Study and the Continued Treatment Study. The program has concluded that oral Rivaroxaban can be given at a dose of 15 mg twice daily for the first 3 weeks, followed by 20 mg once daily afterwards. This was shown to provide an effective, safe, single-oral drug approach to the initial and continued treatment of venous thrombosis (14). Rivaroxaban is not recommended for patients with creatinine clearance (CrCl) less than 30 ml/min, and is contraindicated in patients with CrCl less than 15 ml/min. It is also contraindicated in those with hepatic impairment (Child-Pugh Class B and C with coagulopathy) (25). It is recommended for adults, as it was not tested on individuals less than 18 years of age (26), and it is not used in pregnant women. Rivaroxaban still doesn't have an antidote. Table 1 summarizes the current dosing and indications for some of the NOACs (16).

Preoperative Discontinuation of NOACs

The risk of bleeding versus venous thrombosis must be weighed carefully before discontinuing the anticoagulant (16). For Dabigatran, both the CrCl and the bleeding risk associated with the procedure determine the timing of its discontinuation (16). The recommended preoperative discontinuation of Dabigatran based on renal function (15). As for Rivaroxaban, renal impairment has a limited effect on its elimination and half-life. The Working Group on perioperative hemostasis and the French Study Group on thrombosis and hemostasis published recommendations on the perioperative management of NOACs (16, 27). For elective procedures with low bleeding risk, a therapeutic window of 48 hours (last administration 24 hours before

surgery, restart 24 hours after) is recommended (27), For elective procedures with moderate or high bleeding risk, they suggest stopping the oral anticoagulant 5 days before surgery to ensure complete elimination in all patients. Treatment should be resumed only when the risk of bleeding has been controlled (27). If the patient has a high thrombotic risk (e.g. has atrial fibrillation with a history of stroke), bridging with a therapeutic dose of either UFH or LMWH is recommended, and to be initiated 12 hours following the last dose of the oral anticoagulant (27). In case of an emergency, the procedure should be postponed for as long as possible (minimum of 1-2 half-lives) and non-specific anti-hemorrhagic agents, such as recombinant human activated factor VIIa or prothrombin complex concentrates (PCCs) should not be given for prophylactic reversal due to their uncertain benefit risk (27).

Management of bleeding secondary to NOACs

In cases of mild bleeding, discontinuing the oral anticoagulant or delaying the next dose is considered. The NOACs have short half-lives, so their anticoagulant effect rapidly decreases given the patient has a normal renal function (16). In cases of moderate to severe bleeding, standard therapeutic approaches should be followed after the immediate discontinuation of the oral anticoagulant. These include supportive care with volume resuscitation, hemodynamic support with vasoactive therapy, and transfusions of blood products and identification of bleeding source (16). If the oral anticoagulant was taken within 2 hours, administration of oral activated charcoal should be considered. Dabigatran can be eliminated by hemodialysis, while Rivaroxaban can't be dialyzed (16). In cases of life threatening bleeding, hemodynamic and hemostatic resuscitation must be achieved via the measures mentioned above. The use of either 3-factor or 4-factor prothrombin complex concentrates (PCCs) may be considered in cases of life threatening bleeding caused by Rivaroxaban but not Dabigatran (28). Activated PCCs as well can be used for Rivaroxaban induced bleeding as per current available efficacy data on humans (28). The use of recombinant activated factor aVII (Novoseven) should be reserved as a last resort due to the lack of pre-clinical or clinical data supporting its ability to reverse the anticoagulant effects of NOACs (28). Novoseven has been shown to decrease bleeding time in animal models, but human clinical outcome data are still lacking to determine its efficacy (16,29). Target-specific antidotes are in development and hold promise for NOACs reversal, but require further investigation (29). Table 2 summarizes the management strategies for bleeding in patients who have received the NOACs (16).

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