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Review

Prophylaxis and treatment of deep vein thrombosis in general surgery

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Abstract

Background: Patients undergoing general surgery present an inherent risk of deep vein thrombosis (DVT). Evidence-based strategies for prevention and treatment of DVT should be continuously upgraded on the basis of good-quality recent trials.

Data sources: Articles were identified using MEDLINE, EMBASE, and the Cochrane Library databases (January 1980 to July 2003). Randomized clinical trials and meta-analyses in which different prophylactic and treatment methods were compared for general surgery patients were selected.

Conclusions: In general surgery, low–molecular weight heparins (LMWHs) are relied upon more and more for prophylaxis and initial anticoagulant treatment of DVT, because of their multiple advantages in efficacy, safety, and convenience in handling. For cost-effective reasons, full-dose vitamin K antagonists are still preferred as the standard long-term anticoagulation method, while LMWHs represent the exception. Long-term use of low-intensity warfarin should be considered a new standard of care for the management of venous thrombosis. Compared to LMWH, the new anticoagulant molecules fondaparinux and ximelagatran seem to have similar efficacy in the treatment of venous thromboembolism, but they have a 2-fold increased efficacy in its prophylaxis. Clinical implementation of these new anticoagulant molecules depends on their cost-effectiveness; however, they have the potential to become the treatment of choice in the next decade. Thrombolysis has an unacceptable risk of hemorrhagic complications when used in the treatment of postoperative DVT. Furthermore, there are no data to prove that thrombolysis reduces the incidence of postthrombotic syndrome (PTS), despite early and complete recanalization achieved by thrombolysis. Surgical thrombectomy is only meant to decompress the venous hypertension consecutive to massive thrombosis (phlegmasia cerulea dolens) and thus to avoid venous gangrene. Other mechanical percutaneous thrombectomy devices are under evaluation. In selected cases, a combination treatment consisting of locoregional thrombolysis of the crurofemoral venous axis and mechanical thrombectomy of the pelvic venous axis achieves high rates of complete desobliteration.

Keywords: Deep vein thrombosis; General Surgery; Prophylaxis; Treatment

Deep vein thrombosis (DVT) is a common risk in medicine. Data from 9 studies published since 1976 with a combined population of about 19 million persons showed for the primary cases of DVT, for all indications and for all ages, an incidence of 50 per 100,000. DVT occurred rarely below 20 years but increased with age, so that in people over 70, the rate was 200 per 100,000. The incidence was about the same in men and women. The causes of DVT were attributed to cancer or previous hospital admission for about a quarter to a third of cases, respectively. About 40% of cases of DVT had no known cause [1].

Especially for patients who undergo surgical procedures, the risk of developing a thrombotic complication is clearly increased. The high number of complications such as DVT or consecutive pulmonary embolism and the fatal outcome of patients without treatment could be easily remedied with simple and low-cost administration of sufficient prophylaxis or treatment of thrombosis. Therefore, the prevention and treatment of DVT represents a medical topic of high clinical interest.

Prophylaxis of DVT

The appropriate use of prophylaxis is based on the knowledge of specific risk factors for DVT. More than other types of patients, the surgical patient accumulates risk factors from every side of the Virchow triad. The risk of DVT for surgical patients depends on the type of surgery, the

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Table 1
Type of surgery as a risk factor for DVT

Type of surgery	Incidence of DVT
Orthopedic surgery	50%–60%
Oncologic surgery	29%
General surgery	25%
Neurosurgery	22%
Gynecologic surgery	16%
Urologic surgery*	5%

* Data from preponderent prostatectomies and pelvic lymphadenectomies.

presence of clinical risk factors, and the presence of congenital or acquired thrombophilic disorders [2].

Without prophylaxis, the highest risk of DVT occurs with orthopedic surgery (50% to 60%) [3–10], whereas with general surgery there is a 25% risk (Table 1). This percentage also reflects a variable amount of cancer patients, for whom separately taken the risk will be even greater (29%) [11].

Among many clinical risk factors, age over 40 years, previous venous thromboembolism, obesity, varices, and estrogen use are especially relevant for surgical patients [11].

Within the thrombophilic disorders, factor V Leiden (activated protein C) is the most common hereditary blood coagulation disorder, present in 5% of the caucasian population and 1.2% of the African-American population, and induces a 5 to 80 times increase of the relative risk for venous thrombosis compared to the general population [12] (Table 2). The prothrombin 20210 mutation is the second most common inherited clotting abnormality: more common than protein S and C deficiency and antithrombin deficiency combined. About 2% of the general population is heterozygous. It is only a mild risk factor for clots, but together with other risk factors (such as oral contraceptive use, surgery, trauma, high blood pressure, obesity, smoking, etc.) or combined with other clotting disorders (like factor V Leiden), the risk of clotting increases dramatically.

In the last years, the approach to the problem has become increasingly evidence-based and some relevant medical professional societies worldwide have formulated recommendations and clinical practice guidelines. According to the incidence of DVT among surgical patients, 4 levels of risk emerged (Table 3) and appropriate prevention strategies were developed for each.

Table 2
Relative risk of DVT for the most common thrombophilic disorders

Relative risk of DVT	Thrombophilic disorders
Factor V Leiden (activated protein C resistance)	× 5–80
Prothrombin 20210 mutation	× 3
Protein C and S deficiency	× 7
Antithrombin deficiency	× 5
Hyperhomocysteinemia	× 2–4
Antiphospholipid antibody syndrome	× 1–2

Table 3
Thromboembolic risk stratification for surgery patients

Low risk	Uncomplicated surgery in patients aged <40 years with minimal immobility postoperatively and no risk factors
Moderate risk	Any surgery in patients aged 40–60 years, major surgery in patients <40 years and no other risk factors, minor surgery in patients with 1 or more risk factors
High risk	Surgery in patients aged >60 years, major surgery in patients aged 40–60 years with 1 or more risk factors
Very high risk	Major surgery in patients aged >40 years with previous venous thromboembolism, cancer or known hypercoagulable state, major orthopedic surgery, elective neurosurgery, multiple trauma, or acute spinal cord injury

Methods of prophylaxis

While some of the methods proved modestly effective (e.g., aspirin), until recently the use of heparins appeared to provide the maximum risk reduction. Five trials assessed the use of aspirin compared to placebo, showing a relative risk reduction of only 20%. The use of graded compression elastic stockings as the only prophylactic method has a 44% risk reduction. However, low-dose unfractionated heparin (LDUH) and low–molecular weight heparin (LMWH) are the most effective therapies in reducing the incidence of DVT, providing a 68% to 76% risk reduction. LMWH and LDUH appear to be equally effective in preventing DVT in general surgery patients. As to their side effects, some studies have reported significantly fewer wound hematomas and bleeding complications with LMWH [14–16], while other well-designed trials have shown that LMWH causes more bleeding than LDUH [17,18]. The discrepant findings appear to be related to dosage; there is a clear dose-response effect of LMWH on bleeding complications (and probably also on the efficacy of prophylaxis). Higher doses of LMWH (>3400 anti–factor Xa units daily) in comparison to LDUH (5,000 U, 2 or 3 times daily) are associated with more bleeding [19]. In contrast, lower doses of LMWH (<3400 anti-Xa units daily) are equivalent to LDUH in preventing venous thromboembolism (VTE) in moderate-risk patients and have a lower rate of bleeding complications [19,20]. While 1 meta-analysis could not discern superior efficacy of higher doses of LMWH [19], individual studies in high-risk general surgery patients suggest that this may be the case [21–23]. Although intermittent pneumatic compression (IPC) showed an important risk reduction of 88%, it must be noted that this result comes from several small, older studies [24,25]. In trials comparing IPC with LDUH, both therapies produced similar reductions in DVT [26–28].

Warfarin is not convenient for prophylaxis, because its onset of action is delayed and it also requires frequent

Table 4
Evidence-based use of antithrombotic prophylaxis in general surgery

Low risk	Early mobilization LDUH (5000 IU 12 hourly starting 2 hours before surgery) or LMWH (<3400 anti-Xa IU daily)
Moderate risk	or ES (compression elastic stockings) or IPC (intermittent pneumatic compression) LMWH (>3400 anti-Xa IU daily) plus ES or
High risk	LDUF (5000 IU eight hourly starting two hours before surgery) plus ES or IPC if anticoagulation contraindicated Perioperative warfarin (INR 2-3)
Very high risk	or LMWH (>3400 anti-Xa IU daily) plus ES

Adapted by Turpie from the 6th ACCP guidelines [29].

laboratory monitoring to maintain an adequate international normalized ratio (INR) of 2 to 3.

Prevention strategies

Different patient risk groups have to be treated with different strategies. While in low-risk patients no specific prophylaxis is needed, high-risk patients benefit from a combination of heparins (LDUH or LMWH) and IPC or elastic stockings (Table 4). Patients with low risk undergoing general surgery do not need specific prophylaxis other than early mobilization. In moderate-risk patients, fixed LDUH (5000 IU every 12 hours) or LMWH (3400 anti-Xa units or equivalent) once daily is sufficient. Higher doses of LMWH (>3400 IU anti-Xa daily) should be reserved for high-risk general surgery and orthopedic operations. Compression elastic stockings and IPC may protect high-risk patients when used with anticoagulants. They are also effective when used alone in moderate-risk patients in whom anticoagulants are contraindicated [29]. IPCs are probably more effective than graduated compression stockings or LDUH in patients at moderate to high risk [30]. Knee-length stockings are equally effective, less expensive, more likely to fit correctly, and better tolerated by patients than thigh-length stockings [31].

Efficiency of prophylaxis in colorectal surgery

Colorectal surgery represents a major field of general surgery and implies a higher risk of thromboembolic complications than other surgical procedures. A recent Cochrane review, a meta-analysis of 19 studies from 1974 to 1999, compared the incidence of postoperative thromboembolism after colorectal surgery using different prophylactic methods focusing on various heparins and mechanical methods (IPC, compression elastic stockings) and their combinations [32]. The review found that unfractionated heparin (UFH) gives better prophylaxis against DVT and/or pulmonary embolism compared with no treatment or placebo, with an overall odds ratio of 0.35. In addition, LMWH seems better than no treatment or placebo in preventing DVT (odds ratio 0.17). Meanwhile, the 2 heparins were found equally effective in preventing DVT. Furthermore, when adding elastic stockings to LMWH, the efficacy of prophylaxis increased dramatically (4 times).

Recommended prophylaxis in general surgery

The conclusion in our surgical department is that both UFH and LMWH can be used as effective prophylaxis against postoperative thromboembolic complications after general surgery. The optimal prophylaxis in general surgery seems to be the combination of graded compression stockings and LMWH.

Treatment of DVT

The combination of UFH or LMWH and oral anticoagulants is currently the treatment of choice for most patients with VTE. Oral anticoagulants are started at the same time and heparin is discontinued after at least 5 days, when the INR for the prothrombin time reaches the therapeutic range between 2.0 and 3.0. Nevertheless, many aspects of initial and long-term anticoagulation are subject to present and further assessment.

Initial anticoagulation

The most important questions to be answered regard the type of heparin to be used (UFH or LMWH), the posology of LMWH, the feasibility of outpatient treatment using LMWH, and the eventual differences between LMWHs. Relevant answers can be obtained only by using an evidence-based approach that seeks to synthesize the findings from relevant good-quality studies.

UFH or LMWH?

UFH has been used for more than 50 years as an effective anticoagulant for the treatment of VTE. However, LMWHs have recently emerged as more convenient, safe, and effective alternatives. The most important limitations of UFH are the unpredictable anticoagulant response, heparin resistance, heparin-induced thrombocytopenia, and osteopenia.

By way of contrast, LMWH poses some important advantages (Table 5). The longer plasma half-life enables a reduced number of daily administrations (once or twice). The anticoagulant response (anti-Xa U/mL) observed with a

Table 5
Clinical advantages of the reduced binding of LMWH to different structures

Less binding to:	Clinical advantages
Macrophage and endothelial cell surfaces	Longer plasma half-life enhances administration at greater intervals of time
Plasma proteins	More predictable dose-response relationship avoids the need for laboratory monitoring
Thrombin	Reduced anti-IIa to anti-Xa ratio means less risk for bleeding for the same anticoagulant effect
Platelets and platelet factor-4	Smaller incidence of immune heparin-induced thrombocytopenia
Osteoblasts	Smaller incidence of osteoporosis

given dose of LMWH was highly correlated with body weight. Thus, LMWH is effective in most patients when given in weight-based doses (anti-Xa U/kg body weight) and there is no need for subsequent laboratory monitoring or dose adjustment. The reduced anti–factor II-a (thrombin) activity is the theoretical premise for a reduced incidence of bleeding. The incidence of heparin-induced thrombocytopenia is 3.5% with UFH but only 0.6% with LMWH because of its reduced binding to platelet factor-4 [33]. The occurrence of heparin-induced osteoporosis appeared to be strictly related to the length of treatment (more than 4 to 5 months) and the dosage (≥15,000 U daily), but the pathogenesis is poorly understood. It has been suggested that heparin could cause an increase in bone resorption by increasing the number of differentiated osteoclasts and by enhancing the activity of individual osteoclasts. In any case, LMWHs cause less osteoporosis. The reduced number of daily administrations without the need for monitoring and the decreased incidence of bleeding with the use of LMWH offer the potential for home therapy or early hospital discharge [34–37].

Although these advantages of LMWH over UFH are important, surgeons are primarily interested in the immediate effectiveness of treatment, particularly in the reduction of recurrent thrombosis. Important evidence has been published from randomized controlled trials by the American-Canadian Thrombosis Study [38], the studies of Koopman et al [39] and Levine et al [40] in 1996, and further from recent meta-analyses from Gould (1999) [41], Dolovich (2000) [42], and the American College of Chest Physicians (ACCP) (2001) [43].

The American-Canadian Thrombosis Study, a multicenter randomized trial performed in 1992, determined that LWMH given subcutaneously once daily, without laboratory monitoring, is as effective and safe as continuous intravenous UFH (monitored using the activated partial thromboplastin time) for the initial treatment of patients with acute proximal vein thrombosis [38]. Koopman et al, in a randomized controlled trial from 1996, found no significant differences between in-hospital administration of UFH and at-home administration of LMWH as regards recurrent thromboembolism, major bleeding, and death. Nevertheless, they demonstrated a 67% reduction in hospital days in the LMWH group [39]. The same results were found by Levine et al in a 1996 trial, which also found that LMWH can be used as safely and effectively as UFH to treat patients with proximal DVT [40]. Gould et al performed a meta-analysis of 11 randomized studies comparing UFH and LMWH for the treatment of DVT or pulmonary embolism and found that LMWH appeared at least as effective and safe as heparin [41]. One of the most methodically accurate meta-analyses was performed by Dolovich et al (2000) [42]. These authors assessed more than 4000 patients in 13 studies comparing UFH to 5 different LMWHs. Regarding the incidence of recurrent VTE, pulmonary embolism, and major and minor bleeding, no differences were found, confirming again that LMWHs are at least as effective as UFH. Furthermore, there was a significant decrease in total mortality in favor of LMWH for which no explanation could be provided.

The ACCP Consensus Conference from 2001 analyzed a large number of randomized controlled trials and meta-analyses performed from 1985 to 2000. Their recommendation was that patients with DVT or pulmonary embolism should be treated acutely with LMWH, UFH intravenously, or adjusted-dose subcutaneous heparin, making no difference between them concerning their efficiency and safety profiles. Nevertheless, because of advantages such as convenient dosing, facilitation of outpatient treatment, a potential of slightly less recurrent VTE, and survival benefit in patients with cancer, the ACCP recommended that clinicians should use LMWH over UFH [43].

Posology: once or twice daily administration of LMWH?

Besides a subgroup analysis in Dolovich's meta-analysis, another recent meta-analysis from van Dongen et al compared the once- versus twice-daily administration of different LMWHs for the initial treatment of VTE [44]. Both analyses found no significant differences regarding the recurrence of venous thromboemolism, major bleeding, or mortality between once- and twice-daily administration of several LMWHs.

In- or outpatient LMWH treatment?

A Cochrane Review by Schraibman et al in 2003 [45] included the 2 major trials mentioned above of Levine et al and Koopman et al and 1 smaller 2000 trial from Boccalon (2000) comparing home versus inpatient management of DVT. A total of 1101 patients were included in this review. Regarding the recurrence of VTE, minor or major bleeding, and death, no trial showed statistically significant differences between hospitalized and home-treated groups and pooling these results did not produce any significant differences. However, only Boccalon's study compared directly

home versus inpatient treatment using the same heparin, while the 2 other studies compared UFH in hospital to LMWH at home [45]. Further investigations are needed for clear evidence.

Differences between LMWHs

No studies have directly compared different LMWH compounds. Instead, a meta-regression was used by van der Heijden et al to find differences between different LMWH compounds: nadroparin (4 studies), tinzaparin (2 studies), enoxaparin (3 studies), dalteparin (3 studies), reviparin (2 studies) and certoparin (1 study). Interpretation of analyses comparing compounds was difficult and only one clinically relevant conclusion could be drawn: dalteparin appeared to be significantly less effective than other LMWH compounds but also was significantly less associated with major hemorrhage. The limited number of actual studies does not allow other firm conclusions about clinically relevant differences [46]. Recent meta-analysis confirms the lack of evidence to determine the therapeutic equivalence of LMWHs [47].

Long-term anticoagulation

VTE is today recognized as a chronic disease where the acute event is the validation of an underlying disposition (often hereditary) caused by supplemental risk factors. Since this disposition consists of a number of complex risk factors and therefore cannot be determined exactly, the correct attitude to prevent recurrences implies long-term anticoagulant therapy following initial treatment. Since 1960, warfarin has been used for long-term prevention of recurrences. With the development of the LMWHs the question was raised of what role there might be for long-term anticoagulation.

Vitamin K antagonists or LMWH?

A meta-analysis evaluated the efficacy and safety of long-term treatment of VTE with LMWH compared to vitamin K antagonists. The primary analysis concerned 7 trials and demonstrated no significant reduction in the risk of recurrent VTE but a significant difference in bleeding favoring LMWHs during the treatment. Six to 9 months after cessation of active treatment, there were no significant differences in recurrence and no bleeding at all in either group [48]. Van der Heijden et al concluded that LMWHs are as effective as vitamin K antagonists in the long-term prevention of symptomatic VTE after an episode of symptomatic DVT. Because of the higher costs of LMWH, vitamin K antagonists remain the treatment of choice for the majority of patients. Due to the decreased bleeding risk, LMWHs are possibly a safer alternative for patients in which monitoring (INR) is difficult or who present contraindications for vitamin K antagonists. This statement agrees with the major recommendation grade 1A of the ACCP (2001), based on 6 studies from 1979 to 1999 [43].

Duration of treatment with vitamin K antagonists

Based on studies through 2000, the ACCP also stated the necessary duration of the treatment with vitamin K antagonists, which targeted an INR of 2.5 (range 2.0 to 3.0). These recommendations (grade 1A) are subject to modification by individual characteristics, including patient preference, age, comorbidity, and likelihood of recurrence. For patients with a first episode of idiopathic VTE, a treatment duration of at least 6 months is recommended. In the presence of reversible or time-limited risk factors, the duration may be shorter but at least 3 months. In contrast, for continuing risk factors such as cancer or thrombophilic disorders, long-term anticoagulation should be 12 months or longer. The same recommendation applies for recurrent idiopathic VTE [43].

A 2003 systematic review evaluated the efficacy and safety of different treatment durations with vitamin K antagonists ranging from 1 month to 4 years. Six studies comparing treatment durations were included with a total of 2500 patients. Short period ranged from 1 to 6 months, while long period extended up to 27 months of treatment. In this additional period of treatment the recurrence of VTE significantly decreased to 1%, compared to 9% in the short-duration arm. Nonetheless, there was no significant difference in mortality. However, it should be noted that the complication of major bleeding increased significantly by more than 8 times. As the absolute risk of recurrent VTE decreases over time, the efficacy of prevention also decreases, while the risk of bleeding remains [49]. Because the risk of bleeding seems to be directly correlated with the dose of vitamin K antagonist, a logical way to obtain prolonged, harmless prevention is to lower the dosage to a limit where effectiveness is still not impaired.

Dosage of vitamin K antagonists

The problem of bleeding seems related to the dose of vitamin K antagonists. In 1982, Hull and colleagues reported that moderate-intensity anticoagulation (INR 2.0 to 3.0) was as effective as a higher intensity regimen (INR 3.0 to 4.5) but was associated with significantly less bleeding [50]. For this reason, for the past 20 years, a therapeutic INR range of 2.0 to 3.0 has been accepted as standard practice for warfarin therapy to prevent recurrent VTE.

However, there have been hints that we might be able to prescribe warfarin therapy in lower intensity without sacrificing efficacy. Testing the effectiveness of lower-intensity warfarin therapy for the primary prevention of VTE in high-risk women (who were receiving chemotherapy for metastatic breast cancer), Levine et al found that doses of warfarin adjusted to maintain an INR of 1.3 to 1.9 produced

a significant reduction of 85% in the rate of development of VTE without an increased risk of hemorrhage [51].

In 2003, Ridker et al reported the results of a new secondary-prevention trial that pushed the INR range even lower [52]. This randomized, double-blind trial (Prevention of Recurrent Venous Thromboembolism [PREVENT]) was designed to enroll 750 patients with documented idiopathic DVT or pulmonary embolism within the previous 2 years who had at least 3 uninterrupted months of treatment with full-dose warfarin. Based on interim findings showing a strong benefit for low-dose warfarin, the study was discontinued after half of the scheduled study duration. Patients were monitored for 2 years on average. The study demonstrated that long-term (2 to 4 years) and low-intensity (INR 1.5 to 2.0) warfarin therapy provided a risk reduction of 64% for recurrent DVT or pulmonary embolism, while the increase in major bleeding incidence was not significant. Ridker et al suggested that long-term low-intensity warfarin therapy should be considered a new standard of care for the management of venous thrombosis after stopping full-dose warfarin therapy [52].

Thrombolytic treatment

As the above-mentioned studies showed, anticoagulation is clearly effective for the prevention of recurrent VTE. But one should not forget that the long-term sequelae of DVT also include postthrombotic syndrome (PTS). The few studies that assessed PTS as an outcome achieved disappointing results. After 5 years, the incidence of mild to moderate PTS is about 28% and it increases further up to 36% after 12 years despite standard initial and long-term anticoagulation treatment [53].

PTS is thought to be a result of the residual venous stenosis and damage to the venous valves, due to incomplete resolution of the thrombus. The inability of standard anticoagulation to provide complete recanalization in more than 50% of cases after 6 to 12 months [53] explains the high incidence of PTS after sole anticoagulation. The question arises if early and complete recanalization would reduce the incidence of PTS. One of the possibilities for early and complete vein patency is the use of thrombolytic therapy. This treatment was reviewed by Ng and Rivera in 1998, who showed that thrombolytic therapy was more effective than heparin at achieving early lysis of venous thrombi but was associated with a 3-fold risk of major bleeding [54]. Although thrombolytic therapy theoretically reduces the risk of the PTS, this potential benefit has not yet been demonstrated in a well-designed, prospective, randomized trial. Further trials are required to determine the true benefits of this approach.

Other studies have analyzed different treatments, comparing them to each other, as well as low and high doses of each agent and systemic or local administration of the drug; however, no significant differences in efficacy and safety were found.

There is also current interest in using catheter-directed local infusion of a thrombolytic agent to treat venous thrombosis [55,56], but the true benefits of this approach have not been demonstrated.

In conclusion, thrombolytic treatment is more hazardous than standard anticoagulation due to an elevated bleeding risk. Although the superiority of thrombolytic treatment could be measured by early vein patency, a directly positive effect for the incidence of PTS could not be determined. The different agents were equal and there were no differences found concerning the manner of administration or the potential role of catheter-directed therapy [53]. The ACCP recommends that the thrombolysis of DVT is indicated for patients with massive iliofemoral thrombosis and low risk to bleed. Thus, the indication for thrombolysis in surgical patients who develop postoperative thrombosis is difficult to determine.

Surgery

Surgical thrombectomy is a well-defined procedure in cases of severe pulmonary embolism [43], but it is rarely practiced as a routine procedure for DVT. Massive DVT with phlegmasia cerulea dolens or venous gangrene is an absolute indication for surgery. Surgical thrombectomy performed through a femoral venotomy allows instant decompression of the venous hypertension and thus avoids venous gangrene. However, because surgical thrombectomy cannot open the small venules that are affected in venous gangrene, it does not prevent valvular incompetence or postphlebitic syndrome. The incidence of postphlebitic syndrome may be as high as 94% among survivors, despite additional surgical procedures like arteriovenous fistula, designed to decrease the rethrombosis rate after thrombectomy. This is why the other indications are relative and only generally refer to acute (within 7 days) thrombosis involving the proximal venous trunks (caval, iliac, and common femoral veins) in individuals with a good health status and long life expectancy. In addition, this is why the number of thrombectomies is limited worldwide. Even in Germany, where the opinion is much in favor of thrombectomy, only 16% of DVT patients are offered a thrombectomy (while 18% are treated with fibrinolysis and 66% with standard anticoagulation) [57].

While thrombectomy was practiced as a surgical procedure for a long time, the current preference is that it be performed percutaneously by interventional radiologists. Some endoscopic devices that perform a hydrodynamic or mechanical thrombectomy have been recently developed (AngioJet [Possis Medical, Minneapolis, MN], Hydrolyser [Cordis Endovascular, Warren, NJ], Oasis [Boston Scientific/Medi-Tech, Natick, MA], and Amplatz Thrombectomy Device [Microvena, White Bear Lake, MN]). In vitro tests showed that all of the devices are efficient, with moderate differences in performance [58]. However, the clinical studies of Vedantham et al found only a 26% rate thrombus

Table 6
Trials assessing the new molecules fondaparinux and ximelagatran for prophylaxis and treatment of DVT

	Prophylaxis	Treatment
Fondaparinux	EPHESUS [63]*	REMBRANDT DVT‡
	PENTATHLON 2000 [64]*	
	PENTHIFRA*	MATISSE DVT‡
	PENTAMAKS*	
	APOLLO†	
	PEGASUS†	
Ximelagatran	Francis et al [67]*	THRIVE III§
	Colwell et al [68]*	
	METHRO III [69]*	
	EXPRESS [70]*	
	EXULT*	

* In orthopedic surgery; †in general surgery; ‡initial anticoagulation in patients with symptomatic DVT; §secondary prevention of DVT and pulmonary embolism, following 6 months of standard anticoagulation.

removal when using mechanical thrombectomy alone compared to a substantial thrombus removal rate of 62% when using mechanical thrombectomy after pharmacologic thrombolytic agents had been administered [59]. Largiader et al favor combination treatment, which consists of a highly dosed locoregional thrombolysis of the valve-carrying crurofemoral axis and a mechanical thrombectomy of the valveless pelvic axis by Fogarty catheter. Used within 7 days, this method can result in complete desobliteration with maintained valve function in more than 80% of cases with acute leg and pelvic venous thrombosis [60].

Endovascular procedures also offer the possibility to introduce stents, which are required in 10% of cases because of stenoses.

New substances

A number of new antithrombotic agents have been developed or are currently being developed, including an oral direct thrombin inhibitor (ximelagatran), synthetic pentasaccharides with selective anti–factor Xa activity (e.g., fondaparinux), inhibitors of factor IX, factor VIIa, and tissue-factor inhibitors, and activated protein C. The new agents are promising, but their role in the prevention and treatment of VTE remains to be assessed in clinical trials that have been recently completed or are still ongoing (Table 6). Four major trials of the use of fondaparinux for prophylaxis in orthopedic surgery have been completed. The results showed a significant 50% risk reduction in VTE rates with fondaparinux compared to different doses of enoxaparin. Major bleeding did not differ among studies [61–64]. Two studies examining fondaparinux for treatment of VTE (REMBRANDT and MATISSE DVT) showed that there were no significant differences in the incidence of recurrent VTE or major bleeding. However, the administration of fondaparinux for prophylaxis is more convenient and the cost-effectiveness of treatment is not much higher than with enoxaparin [65].

Other studies investigated ximelagatran for prophylaxis in orthopedic surgery and showed a 46% relative risk reduction in total DVT rates when compared to dalteparin, 30% when compared to enoxaparin, and 25% when compared to warfarin [66–70]. As for the treatment, the THRIVE III trial found a significant risk reduction of recurrent VTE for ximelagatran as secondary prevention, following 6 months of standard anticoagulation compared to placebo. The treatment groups did not require monitoring and there were no statistically significant differences between the 2 groups with respect to the adverse event profile, including significant bleeding or death. Ongoing studies are evaluating indications for the use of ximelagatran for treatment of VTE, comparing ximelagatran to LMWH and warfarin [71].

Conclusion

In general surgery, LMWH is relied upon more and more for prophylaxis and initial anticoagulant treatment of DVT, because of its multiple advantages in efficacy, safety, and convenience in handling.

For cost-effective reasons, full-dose vitamin K antagonists are still preferred as the standard long-term anticoagulation method, while LMWHs represent the exception.

Long-term use of low-intensity warfarin should be considered a new standard of care for the management of venous thrombosis.

The new anticoagulant molecules fondaparinux and ximelagatran seem to have similar efficacy as LMWH for the treatment of VTE, but their efficacy in prophylaxis is increased 2-fold when compared with LMWH. Clinical implementation of these new anticoagulant molecules depends on their cost-effectiveness; however, they have the potential to become the treatment of choice in the next decade.

Thrombolysis has an unacceptable risk of hemorrhagic complications when used in the treatment of postoperative DVT. Furthermore, there are no data to prove that thrombolysis reduces the incidence of PTS, despite early and complete recanalization achieved by thrombolysis.

Surgical thrombectomy is only meant to decompress venous hypertension consecutive to massive thrombosis (phlegmasia coerulea dolens) and thus to avoid venous gangrene. Other mechanical percutaneous thrombectomy devices are under evaluation. In select cases, a combination treatment consisting of locoregional thrombolysis of the crurofemoral venous axis and mechanical thrombectomy of the pelvic venous axis achieves high rates of complete desobliteration.

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