Advances in Venous Arterial Thrombosis

Expert Commentary on Advances in the Prevention, Diagnosis, and Treatment of Venous and Arterial Thrombosis

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Venous Thromboembolism: The Magnitude of the Problem in Europe and the World

Alexander T Cohen, Mark Dobromirski, Shu-Ling Lin, and Jack O Wills
King’s College Hospital, London, UK

Venous thromboembolism (VTE), clinically presenting as deep venous thrombosis or pulmonary embolism (PE), remains a major cause of morbidity and mortality worldwide. Cohort studies have reported VTE incidence rates of approximately 100–200 cases per 100 000 patient-years. VTE is most likely to occur in the elderly, after surgery or trauma, in those with genetic predisposition, and in those with acute medical illness. PE causing death is found in approximately 10% of post mortem examinations, and the majority (60–75%) of these cases were not diagnosed prior to death, suggesting marked under-recognition. VTE events result in a significant health burden, necessitating prolonged anticoagulation therapy and conveying a substantial risk of post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension, and VTE recurrence. Mortality rates in the year after a VTE event reach 20–25%. *Adv Venous Arterial Thromb* 2011;1(2):39–45.

Deep venous thrombosis (DVT) and pulmonary embolism (PE), collectively termed venous thromboembolism (VTE), are a major cause of morbidity and mortality worldwide. Quantifying the disease burden has proven difficult, given that VTE is often clinically silent. Indeed, a significant majority of VTE diagnoses are likely missed [1]. This is evident from numerous post mortem studies identifying an abundance of VTE events that were clinically undiagnosed prior to death [2,3]. The present review summarizes relevant literature on the European and global disease burden of VTE.

**Etiology and risk factors**

Classically, VTE occurs as a result of interplay between venous stasis, hypercoagulability, and endothelial injury. While significant advances have been made in the identification of VTE risk factors since Virchow’s triad came into prominence in the medical vocabulary, the exact etiology remains poorly characterized. Ultimately, such causative factors must result in activation of the coagulation cascade for formation of a thrombus to result. In a recent review highlighting the role of tissue factor, Manly et al. described proposed pathophysiological mechanisms via which these factors may result in VTE [4]. Selected VTE risk factors are presented in Table 1.

**Age**

Age is one of the most well-established risk factors for VTE, and is associated with an exponential increase in VTE risk [5]. While decreasing mobility with age is likely a contributor, laboratory studies have confirmed significant changes in coagulation factor concentrations associated with age [6]. Higher rates of cancer probably further contribute to VTE incidence among the elderly [7]. While some have suggested gender as a risk factor, convincing evidence for a higher risk among women is lacking [8].

**Family history**

A family history of VTE is associated with a more than twofold increase in VTE risk [9,10]. Similarly, there is a well-recognized racial element, with white and black patients significantly more likely to experience VTE than Asian or Hispanic patients [11]. A range of specific candidate genes have been associated with VTE risk, most prominently the factor V Leiden mutation (see Table 1)
Surgery

Orthopedic surgery in particular has been investigated in detail with regard to VTE risk. Patients undergoing major orthopedic surgery of the pelvis, hip, or lower limbs are considered to be at high risk of thromboembolic complications [16]. The cause of this excess risk is likely multifactorial. Orthopedic surgery is associated with significant soft tissue and bone damage, requires immobilization beyond that seen with most surgeries, involves fracture hematomata that are associated with significant release of inflammatory mediators [17], and may involve the use of a tourniquet further prolonging venous stasis [18]. Specific orthopedic procedures carry different risks, with higher DVT rates in total knee arthroplasty (TKA) than total hip arthroplasty (THA), and patients with hip fractures representing one of the highest risk groups for PE. As such, reported incidence rates for individual operations vary widely. The incidence of DVT ranges 45–60% following THA and 40–80% after TKA [18]. Specific orthopedic procedures carry different risks, with higher DVT rates in total knee arthroplasty (TKA) than total hip arthroplasty (THA), and patients with hip fractures representing one of the highest risk groups for PE. As such, reported incidence rates for individual operations vary widely. The incidence of DVT ranges 45–60% following THA and 40–80% after TKA [18]. Fatal PE occurs in 0.7% of patients following TKA and 3.4–6% of patients following THA [19]. Up to 20% of early deaths following hip fracture have been attributed to PE [20]. As DVT preceding fatal PE is clinically unrecognized in most patients [16], routine pharmacological prophylaxis in major orthopedic surgery has become well established in clinical practice.

Major trauma

Major trauma, whether or not involving bone fracture, replicates many of the surgical factors predisposing patients to VTE: stasis, significant tissue injury, and a systemic inflammatory response. DVT has been identified in 58% of trauma patients at one major center [21]. The proportion of surgical patients at risk of VTE, as defined by the American College of Chest Physicians (ACCP) guidelines, was examined in the ENDORSE (Epidemiologic Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting) study. Among the 30,827 surgical patients included, a significant majority (64%) were deemed to be at risk of VTE [22]. ACCP-recommended VTE prophylaxis was administered to 59% of these at-risk patients [22].

Medical conditions

Some medical conditions are well known to confer a higher VTE risk. These tend to belong either to the spectrum of cardiovascular disease (ischemic heart disease, congestive heart failure [New York Heart Association (NYHA) class III or IV], stroke) or to the group of conditions associated with a systemic inflammatory response (acute respiratory disease, rheumatic disease, inflammatory bowel disease, infections) [23]. The pathophysiological rationale behind such associations is clear [24,25]. While earlier reports challenged the notion that arterial and venous thrombosis share common risk factors, evidence now suggests traditional risk factors for arterial thrombosis (hypertension, obesity, smoking, diabetes, hypercholesterolemia) do in fact predispose to VTE [26,27].

[12] However, the risk associated with having a first-degree relative with a history of VTE persists even in the absence of these known conditions, suggesting that the genetic factors affecting VTE risk remain incompletely characterized [9]. Given the limited clinical implications of identified thrombophilia, current guidelines do not recommend routine screening after the first episode of VTE [13]. UK guidelines recommend screening in women during pregnancy and in those taking hormonal therapy (including oral contraceptives) only if there is a past history or family history of VTE suggestive of inherited thrombophilia.

**Table 1. Risk factors for venous thromboembolism, with factors ranked by clinical significance [94].**

<table>
<thead>
<tr>
<th>Congenital factors</th>
<th>Acquired factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombin deficiency</td>
<td>Surgery*</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>Fracture (hip or leg)*</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>Major trauma*</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>Spinal cord injury*</td>
</tr>
<tr>
<td>Raised prothrombin levels</td>
<td>Cancer</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>Advanced age</td>
</tr>
<tr>
<td>Hyperfibrinogenemia</td>
<td>Acute medical illness</td>
</tr>
<tr>
<td>Raised Factor VIII levels</td>
<td>Varicose veins</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Hormone therapy</td>
</tr>
<tr>
<td>Obesity</td>
<td>Antiphospholipid antibody syndromes (including anticardiolipin antibodies)</td>
</tr>
<tr>
<td>Immobilization (including long-distance travel)</td>
<td>Central venous catheterization</td>
</tr>
<tr>
<td>Smoking</td>
<td>Cardiovascular risk factors (metabolic syndrome, hypertension, hyperlipidemia, hyperglycemia, hyperinsulinemia)</td>
</tr>
<tr>
<td>Dehydration</td>
<td></td>
</tr>
</tbody>
</table>

*Strong predisposing factors (odds ratio > 10).
Less common medical conditions linked to VTE include antiphospholipid syndrome, paroxysmal nocturnal hematuria, and Behçet’s disease [28–30].

More recent research has also highlighted the role of hypoxia as a predisposing factor to VTE. Localized hypoxia has been shown to increase the release of procoagulant factors [31]. This may contribute to the risk of VTE seen with conditions such as acute heart failure and chronic lung disease, which are not always associated with a systemic inflammatory response. Heart failure in particular has been shown to be linked to higher serum concentration of various procoagulant factors [32].

“Active malignancy can increase the VTE risk as much as fourfold, with VTE rates of up to 60% reported in active cancer patients”

The ENDORSE study also investigated medical patients at risk of VTE. Among 15 487 medical patients enrolled, 42% met the ACCP criteria for being at risk of VTE. Only 40% of those at-risk received ACCP-recommended prophylaxis [17]. Despite a lower proportion at risk, acutely ill medical patients have displayed higher mortality rates associated with PE, and these rates have proven difficult to reduce. Between 1966 and 2000, autopsy-detected fatal PE declined from 2.1% of surgical patients to 0.6%, a reduction of 71% [33]. During the same period, the decline noted among medical patients was from 4.0% of patients to 3.3%, a reduction of only 18% [33]. Multiple causes may account for this higher mortality rate. Acute medical illness is associated with a number of risk factors for VTE, including advanced age, immobilization, and other patient-related characteristics, as well as disease-related characteristics such as cancer, cardiac or respiratory failure, and infection [15]. Hospitalization itself is also a strong risk factor; a study investigating the risk factors behind the first occurrence of VTE in 625 patients showed that >60% of the VTE cases could be attributed to institutionalization, and 59% were associated with a medical condition treated inside or outside of hospital [34].

Cancer
The relationship between cancer and VTE, and the importance of preventing VTE in cancer patients, are well described [23,35]. The exact causal mechanisms at play are unclear. Many cancers, including tumors of the pancreas, lung, breast, stomach, and colon, have been associated with a prothrombotic state characterized by clotting factor abnormalities, endothelial dysfunction, and abnormal blood flow owing to increased viscosity or stasis [36]. Multiple tumor cells have been found to release microparticles containing significant quantities of tissue factor [37]. There is, however, great variation in the risk of VTE in different cancer types. Cancers of the pancreas, stomach, brain, and lung, and the presence of metastatic disease are associated with higher rates of VTE [38,39]. This relationship is of unambiguous clinical significance. Active malignancy can increase the risk of VTE as much as fourfold [40], with VTE rates of up to 60% reported in active cancer patients [41–44]. VTE is the most common complication, and the second most common cause of death in patients with active cancer [45,46].

In addition to reduced survival rates [47,48], VTE is associated with higher rates of both bleeding complications and VTE recurrence [49]. This has significant cost implications [50]. The attributable risk (absolute risk percentage) that cancer contributes to VTE is 18.0 (95% confidence interval 13.4–22.6) [34]. Conversely, patients with a new diagnosis of VTE have a substantially increased risk of receiving a subsequent new diagnosis of cancer [51]. A systemic review found that one in 17 patients with unexplained VTE will have an immediate malignant cause found, while one in 10 will be diagnosed with a malignancy within 1 year [52]. Based on this, they recommend that extensive screening for malignancy should be routine for patients with unexplained VTE. This is likely to be of greater yield in patients aged >50 years; in younger patients thrombophilia screening may be more likely to identify relevant pathology.

Estrogen
Excess estrogen appears to convey an increased risk of VTE. Studies confirm the presence of an increased VTE risk during pregnancy and among women taking hormone-replacement therapy, estrogen-containing oral contraceptive pills, or a selective estrogen receptor modulator [53,54]. An association with increased serum concentration of procoagulant factors has also been noted, but the molecular pathways remain incompletely understood [55].

Long-distance travel
Air travel exposes patients to stasis, hypoxia, a hypobaric environment, and dehydration; thus, it is plausibly an influence on VTE risk. A large cohort study reported a VTE incidence rate of 320 per 100 000 patient-years among subjects in the 8-week period after a flight exceeding 4 h, significantly higher than during periods without exposure to air travel [56]. This result is consistent with the results of a meta-analysis indicating a nearly threefold higher risk of VTE associated with air travel [57]. The majority of VTE incidents identified in clinical trials are asymptomatic calf DVTs, with uncertain clinical implications. PE after travel is exceedingly rare, occurring at a rate of 27 per million flights [58]. While simple measures such as hydration and frequent calf exercises are recommended during travel, routine use of thromboprophylaxis is not currently supported by evidence. Use of graduated compression stockings or a single dose of low-molecular-weight heparin may be considered for patients at heightened risk on an individual basis [15].
Prevalence, incidence, and attack rates

VTE is often clinically silent, and a significant number of diagnoses are missed [1]. Studies have shown that fewer than half of the patients with an autopsy diagnosis of PE had been diagnosed correctly prior to death [59]. Given these difficulties, retrospective analyses of VTE incidence are likely to underestimate the true disease burden. Table 2 presents published data on VTE incidence (inception cohorts or first time events) and attack (combined first time and recurrence) rates from selected published trials. A range of studies with general (hospital and community together), hospital only, and community only populations are presented in this table. Variation in event rates reflects methodological differences, biases (particularly diagnostic, coding, and ascertainment biases), and true variation.

“The VITAE study reported an estimated VTE attack rate of 243 per 100 000 person-years”

The VITAE (VTE Impact Assessment Group in Europe) study, performed by our group, utilized a robust statistical modified incidence-based model of VTE events in selected Western European nations, including hospital admission coding data from the UK and France and community event rates from the large French EPI-GETBO (Groupe d’Etude de la Thrombose de Bretagne Occidentale) study [60]. We reported an estimated VTE attack rate of 243 per 100 000 person-years. This included an attack rate of 148 per 100 000 patient-years for DVT and 95 per 100 000 patient-years for PE.

Western cohort studies have tended to report incidence rates in the range of 100–200 per 100 000 patient-years. The EPI-GETBO trial, a study following 342 000 subjects over a 1-year period, reported an annual VTE attack rate of 183 per 100 000 person-years [61]. US data have tended to reflect lower event rates. The large Worcester VTE study, analyzing cases among 477 800 subjects from Worcester, MA, USA, reported an attack rate of 128 per 100 000 patient-years [62]. A retrospective review from Minnesota (USA) suggested an incidence rate (thus excluding recurrent cases) of 117 per 100 000 patient-years [5]. A UK community-based cohort study reported an incidence rate of 74.5 per 100 000 patient-years [63]. Data regarding non-white populations are harder still to interpret; retrospective studies in Asian populations have consistently displayed a lower incidence of VTE, although with significant variability. Studies from Hong Kong, including hospital-based cases only, have reported incidence rates as low as 17–21 per 100 000 patient-years [64,65]. VTE rates reported in Korean and Taiwanese populations (14 per 100 000 patient-years and 16 per 100 000 patient-years, respectively) are similarly significantly below those found in white populations, although rapidly increasing rates over time suggest improving diagnostic yields may be affecting results [66,67]. Conversely, autopsy series in China report VTE rates much closer to those in white patients [68]. This racial variation in VTE rates suggests that some degree of caution is needed when applying incidence rates across ethnically diverse populations.

Table 2. VTE event rates from major published studies.

<table>
<thead>
<tr>
<th>Location [Ref]</th>
<th>VTE event rate per 100 000 patient years</th>
<th>DVT</th>
<th>Pulmonary embolism</th>
<th>Key methodological factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Europe [60]</td>
<td>243</td>
<td>148</td>
<td>95</td>
<td>Statistical model developed to estimate both diagnosed and undiagnosed attack rates in hospital and community</td>
</tr>
<tr>
<td>France [61]</td>
<td>183</td>
<td>124</td>
<td>63</td>
<td>Incidence rates, hospital, and community setting</td>
</tr>
<tr>
<td>Sweden [1]</td>
<td>160</td>
<td>160</td>
<td>-</td>
<td>Incidence figures include DVT events only, identified from positive phlebography results</td>
</tr>
<tr>
<td>USA [62]</td>
<td>128</td>
<td>111</td>
<td>31</td>
<td>Attack rates from medical records of all Worcester, MA, USA residents</td>
</tr>
<tr>
<td>USA [5]</td>
<td>117</td>
<td>48</td>
<td>69</td>
<td>Incidence rates from medical records of an inception cohort</td>
</tr>
<tr>
<td>Australia [95]</td>
<td>83</td>
<td>52</td>
<td>31</td>
<td>Incidence rates identified from multiple data sources</td>
</tr>
<tr>
<td>UK [63]</td>
<td>75</td>
<td>40</td>
<td>34</td>
<td>Incidence rates identified from community setting using general practitioner database</td>
</tr>
<tr>
<td>Hong Kong [64]</td>
<td>21</td>
<td>17</td>
<td>4</td>
<td>Incidence rates identified from hospital setting using public healthcare database</td>
</tr>
<tr>
<td>Hong Kong [65]</td>
<td>17</td>
<td>16</td>
<td>2</td>
<td>Incidence rates identified from hospital setting using multiple data sources</td>
</tr>
<tr>
<td>Taiwan [67]</td>
<td>16</td>
<td>-</td>
<td>-</td>
<td>Incidence rates identified from hospital setting from coding data</td>
</tr>
<tr>
<td>Korea [66]</td>
<td>14</td>
<td>5</td>
<td>7</td>
<td>Incidence rates identified from insurance claim database</td>
</tr>
</tbody>
</table>

DVT: deep venous thrombosis; VTE: venous thromboembolism.
The significant variation in reported event rates can be attributed to a number of factors. Primarily, our statistical model attempted to include undiagnosed cases, whereas the population-based studies could only include confirmed episodes of VTE. Given the extent of VTE underdiagnosis, we believe our approach is the most likely to represent the actual disease burden of VTE. Among the clinical trials, differences in the accuracy of clinical coding and clinical diagnosis across regions are difficult to reconcile. While ethnicity likely does influence VTE event rates, a range of data suggest the difference is not sufficient to explain the extremely wide discrepancies seen in these epidemiological studies [11]. There is also some evidence to support a decline in VTE incidence over recent years. A study of autopsies conducted from 1965 to 1990 indicated an almost three-fold reduction in VTE frequency over the 25-year period, with the most marked reduction occurring in surgical patients [33]. This is consistent with extensive and ongoing efforts to increase the use of thromboprophylaxis among hospitalized patients during that time period. However, large cohort studies show that significant risks remain in surgical patients [69].

Among VTE events, DVT outnumbers PE in a ratio of roughly 2:1. Our statistical model of VTE in Western Europe (the VITA study) estimated that 61% of VTE events were due to DVT, while 39% were due to PE [60]. Again, this was relatively similar to the division reported in the French EPI-GETBO study (68% and 32% for DVT and PE, respectively), but differed significantly from that reported in the US (78% and 22%, respectively) [62] and in Hong Kong (87% and 12%, respectively) [65].

**Outcomes and recurrence rates**

**Mortality**

Prospective studies have generally identified short-term (under 6 months) mortality rates in the order of 5–10% following an initial DVT, and 15–20% following PE [63,70–72]. Mortality rates remain high beyond the immediate post-event period, with reported figures of approximately 20–25% at 1 year and 30–35% at 3 years after VTE [72].

The occurrence of PE, rather than DVT, is among the most important predictors of mortality. This is most prominent at 30 days post-event, but the difference persists as far as 3 years post-event [72]. The mortality risk is also increased by age, medical comorbidities (cancer, heart failure, infection, chronic obstructive pulmonary disease), and clinical condition at presentation (hypotension, tachypnea, acute right heart strain on echocardiography) [63,73,74].

Prospective studies are, however, unable to account for the significant mortality burden of undiagnosed VTE. Most autopsy series show that PE is the cause of death in 5–15% of patients, with a figure of around 10% most commonly reported [2,3,74]. A study including 46 cases of PE identified at autopsy revealed that only 30% of these were diagnosed *ante mortem* [2]. Gaspar et al. identified PE in 12% of all hospital autopsies of medical patients performed during a 23-year period, of whom only 46% had a clinical diagnosis of PE [3]. It is not easy to assess how many of these deaths are the agonal event in the natural history of severe comorbidities such as cancer and cardiorespiratory disease. While it may be that as many as 30% of these deaths are unavoidable, these studies confirm a significant preventable disease burden remains [3,74]. Our statistical model of VTE attempted to adjust for some of these discrepancies. We estimated that the combined mortality from sudden fatal PE, diagnosed and treated PE, and undiagnosed PE is equal to 32% [60].

**Post-thrombotic syndrome**

Post-thrombotic syndrome (PTS) describes a syndrome of chronic limb edema, pain, claudication, and skin ulceration that often follows DVT. The etiology is thought to involve both residual thrombus and valvular dysfunction, resulting in persistent venous hypertension and thus the clinical symptoms [75]. PTS complicates between one-quarter and one-half of DVT cases [76–80]. The risk is highest in the first year after an event, with reported rates ranging 7–17% [76,77]. The most important predictors of PTS are ileofemoral location of DVT, and DVT recurrence on the ipsilateral limb [76,77]. PTS has been shown to significantly impact quality of life [81], and treatment may involve not only compression stockings but also endovascular surgery if symptoms prove refractory [75].

**Recurrence**

The current standard of care following an initial VTE is anticoagulation for a length typically between 3 and 6 months. Despite this, recurrence rates remain high. The 1-year recurrence rate is typically reported to be in the 5% range [82–84], but rates as high as 15% are noted in older studies [76]. The annualized risk does not appear to decrease significantly, with cumulative 3-year recurrence rates reported in the 15–25% range [76,82,83]. These recurrences tend to be of the same form as the initial event; in one trial 86% of VTE recurrences after a PE were another PE [70]. A slight predominance of DVT recurrences (55%) occur in the ipsilateral limb [76].

As would be expected, patients who suffered VTE associated with persistent risk factors such as malignancy experience higher recurrence rates, while those who had transient VTE risk factors such as surgery or recent trauma were less likely to suffer recurrence [76]. Patients with unprovoked VTE in general have high rates of recurrence, suggesting an unrecognized persisting VTE risk factor [85]. Unlike the first VTE event, recurrence rates seem to differ with gender, with males significantly more likely to suffer a repeat event after unprovoked VTE [82]. The higher proportion of transient sex-specific risk factors, such as estrogen therapy, has been proposed as an explanation for this observation [86].
Chronic thromboembolic pulmonary hypertension

Chronic thromboembolic pulmonary hypertension (CTPH) occurs secondary to deposition of thrombi in the pulmonary vasculature. The hypertension results from persistent increases in pulmonary vascular resistance, and often leads to right heart failure. While relatively rare, this condition contributes significantly to the disease burden of VTE. Approximately 0.4–4% of patients with PE will eventually develop CTPH [87–90]. Without treatment, mortality at 1 year exceeds 50% for those with a mean pulmonary arterial pressure above 50 mmHg [91]. The treatment of choice, pulmonary thromboendarterectomy, involves cardiopulmonary bypass and itself represents a significant healthcare burden. This treatment is, however, unavailable to over half of CTPH patients [92]. Medical therapy has yet to demonstrate any survival advantage [93].

Conclusion

VTE remains a common medical condition, affecting a significant number of patients both in the community and in hospital. VTE frequently results in death, and is identified as a cause of death in roughly 10% of post mortem examinations. Treated VTE, furthermore, conveys an ongoing risk of recurrence, PTS, and CTPH. Given the preventable nature of VTE, increasing awareness of the true epidemiological burden is essential to design efficient and effective systems to reduce VTE events.

You can submit comments and questions on this article at:
www.venous-arterial-thrombosis.com

Disclosures

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Venous thromboembolism (VTE), i.e. deep venous thrombosis (DVT) and pulmonary embolism (PE), is an important healthcare problem. In particular, PE is the major preventable fatal complication in hospitalized patients worldwide. Without thromboprophylaxis, the incidence of objectively confirmed, hospital-acquired DVT is approximately 10–40% among medical and general surgical patients and 40–60% following major orthopedic surgery. A huge number of randomized controlled clinical trials have provided solid evidence that thromboprophylaxis reduces the incidence of DVT and PE. Unfortunately, despite these trials, a low rate of adherence to evidence-based thromboprophylaxis protocols compromises their benefit in daily practice. In this narrative review, the current pharmacological and non-pharmacological methods of thromboprophylaxis used in major orthopedic surgery are discussed. The VTE risk, evidence-based recommendations, benefits, and pitfalls of the current strategies and the potential future roles of new oral anticoagulants are highlighted. Oral administration, predictable anticoagulant responses, and low potential for drug–drug interactions render direct thrombin and Factor Xa inhibitors good candidates to replace low-molecular-weight heparin, fondaparinux, oral vitamin K antagonists, and unfractionated heparin for VTE prophylaxis. 


Venous thromboembolism (VTE), i.e. deep venous thrombosis (DVT) and pulmonary embolism (PE), is an important healthcare problem. In particular, PE is the major preventable fatal complication in hospitalized patients worldwide. Without thromboprophylaxis, the incidence of objectively confirmed, hospital-acquired DVT is approximately 10–40% among medical and general surgical patients and 40–60% following major orthopedic surgery (Table 1) [1,2]. Over the last 30 years, a large number of randomized controlled clinical trials have provided solid evidence that thromboprophylaxis reduces the incidence of DVT and PE, making PE the most common preventable cause of hospital death and reducing the incidence of PE the number one strategy to improve patient safety in hospitals [1,4]. Unfortunately, despite these trials demonstrating the benefit of thromboprophylaxis, a low rate of adherence to evidence-based thromboprophylaxis protocols compromises the benefits of this practice [5]. In the present narrative review, major clinical trials and established and guideline-recommended prophylaxis regimens for use in orthopedic surgery will be discussed.

VTE risk stratification

There are three general approaches to the stratification of VTE risk in surgical and medical patients [1,6]. One approach considers the risk of VTE in each patient, based on their individual predisposing factors and the risk associated with their current illness or procedure. Formal risk assessment models for VTE have been proposed to assist with this process [7]. However, these models are not used routinely by most clinicians, and some experts, as described in the latest edition of
Surgery, have at least a 40% risk of developing VTE without fracture surgery (HFS), classically defined as major orthopedic surgery [1]. In particular, patients undergoing total orthopedic patients have the highest VTE risk among all orthopedic surgery [1,6]. Has formed the basis for most randomized controlled trials on thromboprophylaxis [1,6]. In fact, group risk assignment involves implementation of group-specific thromboprophylaxis [1]. A second, simplified, risk assessment approach has been proposed to stratify surgical patients [1]. Four VTE risk levels have been identified based on the type of operation (minor, major), age (<40 years, 40–60 years, and >60 years), and the presence of additional risk factors (such as cancer or previous VTE) [1,6]. However, the uncertainty about the influence of each factor on overall risk, lack of definitions for minor and major surgery, and arbitrary cut-offs for age and duration of surgery are major drawbacks [1,6]. Partly as a result of these limitations, the individualized approach to thromboprophylaxis has not undergone rigorous clinical evaluation to date. A third approach involves implementation of group-specific thromboprophylaxis routinely for all patients who belong to each of the major target groups, for example patients undergoing major general surgery or major orthopedic surgery [1,6]. In fact, group risk assignment has formed the basis for most randomized controlled trials on thromboprophylaxis [1,6].

**Orthopedic surgery**

Orthopedic patients have the highest VTE risk among all surgical patients [1]. In particular, patients undergoing total hip arthroplasty (THA), total knee arthroplasty (TKA), and hip fracture surgery (HFS), classically defined as major orthopedic surgery, have at least a 40% risk of developing VTE without thromboprophylaxis (Table 2) [1]. Several concomitant risk factors contribute to increased VTE risk: stasis owing to continued reduced mobility, vein injury, prolonged impairment of venous function, surgery-associated hypercoagulability, and patient-related risk factors such as advanced age, obesity, and comorbidities.

Numerous randomized controlled trials have clearly demonstrated that thromboprophylaxis after orthopedic surgery effectively prevents VTE; it has reduced the rate of postoperative DVT by 60–70% and made fatal PE uncommon [1,5]. However, despite effective thromboprophylactic strategies, symptomatic VTE continues to be reported in 1.3–10% of patients within 5 months of surgery [8,9]. Most symptomatic VTE occurs after hospital discharge, and the risk continues to be high for at least 2 months after surgery [9]. Furthermore, VTE is the most common cause of readmission to hospital following THA [10]. In some patients with post-hospital discharge DVT, the thrombus is probably present early after surgery and, as thromboprophylaxis is discontinued, the silent DVT continues; conversely, a new thrombosis may develop during recovery in a rehabilitation center or at home [1,11,12].

**Table 1. Risk of objectively confirmed asymptomatic and symptomatic DVT [1].**

<table>
<thead>
<tr>
<th>Hospitalized patients</th>
<th>DVT risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical patients</td>
<td>10–20</td>
</tr>
<tr>
<td>General surgery</td>
<td>15–40</td>
</tr>
<tr>
<td>Stroke</td>
<td>20–50</td>
</tr>
<tr>
<td>Hip or knee arthroplasty, hip fracture surgery</td>
<td>40–60</td>
</tr>
<tr>
<td>Major trauma</td>
<td>40–80</td>
</tr>
<tr>
<td>Critical care patients</td>
<td>10–80</td>
</tr>
</tbody>
</table>

DVT: deep venous thrombosis.

**Table 2. Risk of objectively confirmed asymptomatic and symptomatic DVT and PE in major orthopedic surgery [1].**

<table>
<thead>
<tr>
<th>Surgery</th>
<th>DVT risk (%)</th>
<th>PE risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip arthroplasty</td>
<td>42–57</td>
<td>0.9–28</td>
</tr>
<tr>
<td>Knee arthroplasty</td>
<td>41–85</td>
<td>1.5–10</td>
</tr>
<tr>
<td>Hip fracture surgery</td>
<td>46–60</td>
<td>3–11</td>
</tr>
</tbody>
</table>

DVT: deep venous thrombosis; PE: pulmonary embolism.

the American College of Chest Physicians (ACCP) guidelines on antithrombotic and thrombolytic therapy, judge them to be of limited value because they have not been adequately validated, there is little formal understanding of how the various risk factors interact, and they do not simplify decision-making [1,6]. A second, simplified, risk assessment approach has been proposed to stratify surgical patients [1]. Four VTE risk levels have been identified based on the type of operation (minor, major), age (<40 years, 40–60 years, and >60 years), and the presence of additional risk factors (such as cancer or previous VTE) [1,6]. However, the uncertainty about the influence of each factor on overall risk, lack of definitions for minor and major surgery, and arbitrary cut-offs for age and duration of surgery are major drawbacks [1,6]. Partly as a result of these limitations, the individualized approach to thromboprophylaxis has not undergone rigorous clinical evaluation to date. A third approach involves implementation of group-specific thromboprophylaxis routinely for all patients who belong to each of the major target groups, for example patients undergoing major general surgery or major orthopedic surgery [1,6]. In fact, group risk assignment has formed the basis for most randomized controlled trials on thromboprophylaxis [1,6].
but this complication is rare when thromboprophylaxis is used [1]. For this reason, the routine use of thromboprophylaxis has been recommended for THA patients since the first edition of the ACCP guidelines [1].

Both pharmacological and non-pharmacological methods have been tested in THA patients. Pharmacological methods include unfractionated heparin (UFH), LMWH, fondaparinux, dose-adjusted oral VKAs (e.g. warfarin), and aspirin, while the non-pharmacological approaches include graduated compression stockings, intermittent pneumatic compression, and venous foot pumps.

LMWH has been the most intensively studied thromboprophylaxis option in THA patients, and provides highly effective and safe VTE thromboprophylaxis [1]. In Europe it is the preferred drug for this indication, and is therefore also the reference drug in all randomized controlled trials testing new anticoagulants for VTE prevention in orthopedic surgery [14–17].

"Patients undergoing THA, TKA, and HFS have at least a 40% risk of developing VTE without thromboprophylaxis"

The synthetic pentasaccharide fondaparinux selectively inhibits coagulation Factor Xa and has proven highly efficacious in the prevention of DVT among THA patients in two large randomized controlled trials [19,20]. As a result of its long half-life (approximately 18 h) and renal clearance, patients with renal dysfunction may have an accumulation of fondaparinux and thus be at greater risk of bleeding [1]. The safety of fondaparinux among patients receiving postoperative analgesia with an indwelling epidural catheter has also not been established [1].

Overall, LMWHs, and likely fondaparinux by indirect comparison, are more effective than VKAs in preventing asymptomatic and symptomatic in-hospital VTE, with a slight increase in surgical site bleeding and wound hematoma [1]. In particular, in the two fondaparinux randomized controlled trials, major bleeding occurred in 1.6% patients with enoxaparin and in 2.6% patients with fondaparinux [1,19,20].

Several non-pharmacological thromboprophylaxis methods have been studied [1]. While all of the mechanical thromboprophylaxis methods reduce the risk of DVT, their efficacy has generally been found to be lower than current anticoagulant-based thromboprophylaxis strategies, especially for preventing proximal DVT [1,18,21]. Moreover, they have been tested in a limited number of patients in unblinded trials [1]. Costs related to their purchase, storage, and maintenance, as well as to their proper fitting, and the intensive strategies required to ensure optimal compliance are major limitations to their routine use in clinical practice [1].

**TKA**

TKA is even more increasingly performed than THA: by 2030, it has been projected that the demand for primary TKA will grow 6.7-fold to 3.48 million procedures in the US [13]. The demand for TKA revisions is also expected to grow sixfold between 2005 and 2030 [13].

The risk of DVT without thromboprophylaxis is even higher after TKA than after THA (Table 2), but proximal DVT occurs less commonly after TKA and the period of increased risk of VTE after discharge is presumably shorter [1,22]. The efficacy and safety of pharmacological and non-pharmacological thromboprophylaxis methods are similar to the situation in THA [1]. Two meta-analyses of TKA studies have confirmed the superior efficacy of LMWH over both UFH and warfarin, with no significant difference in bleeding [23,24]. While LMWH prevents more venographic total DVTs and proximal DVTs than warfarin, starting LMWH within 12 h after surgery may be associated with a small increase in wound hematomas [1,23,24]. Even though adjusted-dose oral VKAs such as warfarin have been assessed in 12 randomized controlled trials following TKA with routine venography and are frequently used in the US, LMWH is the standard comparator in randomized controlled trials testing new drugs for VTE prevention in TKA and is the preferred treatment in Europe [1,16,17]. As in THA, the complex post-hospital discharge management of VKAs limits their use in Europe [1].

Fondaparinux, starting approximately 6 h after surgery, has been compared with LMWH in only one randomized controlled trial in patients undergoing TKA [25]. The rates of VTE and proximal DVT were more than halved using fondaparinux, but major bleeding was significantly more common in the fondaparinux group [25]. In a meta-analysis of the four Phase III clinical trials comparing fondaparinux and enoxaparin thromboprophylaxis in patients undergoing orthopedic surgery, major bleeding was significantly more common with fondaparinux when the first dose of fondaparinux was administered ≤6 h following surgery (but not if started later) [26].

Non-pharmacological methods are efficacious but less practical than pharmacological methods: poor compliance, patient intolerance, and their inability to be continued after hospital discharge limit their utility [1].

**Optimal timing and duration of thromboprophylaxis**

There are two important questions to consider when planning VTE prophylaxis in major orthopedic surgery patients [27]. First, when should prophylaxis be initiated to optimize the risk–benefit profile of each drug? And second, how long are patients at increased risk of developing VTE and when should prophylaxis be stopped?
Whenever the anticoagulant agent, the balance between the benefits (prevention of VTE) and the risks (major bleeding and epidural hematoma) is the central consideration when deciding whether or not to provide pharmacological prophylaxis, and when deciding to start or stop the anticoagulants [27]. This balance depends on the pharmacological properties of each agent and the dosage given, the timing of administration, the type of surgery, and patient characteristics. For example, delaying the initiation of thromboprophylaxis with LMWHs postoperatively has been shown to result in suboptimal antithrombotic effectiveness [28,29]; however, commencing LMWHs too soon after surgery has been linked to an increased bleeding risk [30]. At present, two different thromboprophylaxis regimens prevail in Europe and North America, respectively. In Europe, LMWH thromboprophylaxis is generally started 10–12 h before surgery; usually the night before. In North America, thromboprophylaxis with LMWH usually commences 12–24 h after surgery to reduce the risk of intraoperative and early postoperative bleeding, and to simplify same-day hospital admission for elective surgery and decisions related to the method of anesthesia [1]. Of note, all studies using fondaparinux have started prophylaxis postoperatively [1]. These studies have shown that the incidence of major bleeding is significantly higher in patients who receive the first dose within 6 h of skin closure (3.2%), compared with waiting >6 h (2.1%) [31].

The optimal duration of thromboprophylaxis after major orthopedic surgery is still a topic of debate, and is currently being tested in randomized controlled trials of new oral anticoagulant drugs [15,27]. In general surgery, the duration of thromboprophylaxis traditionally corresponds to the average period of hospitalization, which is 10–14 days [1]. However, the physiological and hematological disturbances associated with major orthopedic surgery persist for longer than this period [1]. Four systematic reviews have found that post-hospital discharge thromboprophylaxis is both effective and safe in reducing VTE [32–35]. In particular, the relative risk reduction is approximately 60%, comparable with the in-hospital period. Patients who underwent THA tended to experience greater protection from symptomatic VTE using extended thromboprophylaxis than patients who underwent TKA. Consequently, patients at higher risk undoubtedly have a net benefit from extended prophylaxis. Although further studies are needed to define which orthopedic patients are at higher risk, factors that have been shown to predispose patients to VTE following major orthopedic surgery include a history of previous VTE, obesity, delayed mobilization, advanced age, and cancer [1,36].

The latest edition of the ACCP guidelines on VTE prevention recommends pharmacological thromboprophylaxis for THA and TKA as the first choice (Table 3) [1]. In particular, for patients undergoing elective THA or TKA they recommend one of the following three anticoagulant agents: LMWH, fondaparinux, or VKA (INR target 2.5, range 2.0–3.0; each Grade 1A). They recommend that patients undergoing THA, TKA, or HFS receive thromboprophylaxis for a minimum of 10 days (Grade 1A); for THA and HFS, they recommend continuing thromboprophylaxis for >10 days and for up to 35 days (Grade 1A) [1]. The ACCP further recommend against the use of aspirin, dextran, low-dose UFH, graduated compression stockings, or venous foot pumps as the sole method of thromboprophylaxis [1]. The ACCP recommendations are described here because they are the most renowned evidence-based guidelines in the field of thrombosis and hemostasis. However, other societies, such as the American Academy of Orthopedic Surgeons, have different recommendations because these guidelines are more practically based. This issue has been discussed in depth in the literature [44].

### Real life: open issues

The multinational Global Orthopedic Registry, which concluded enrollment in December 2004, showed that <90% of patients undergoing THA or TKA received some form of ACCP-recommended prophylaxis, and that 7 days after THA, 26% of patients were no longer receiving prophylaxis [37,38]. By day 28, only 46% of patients were still receiving prophylactic treatment [37,38]. This difference between guidelines and clinical

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**Table 3. American College of Chest Physicians guidelines, 8th edition, for thromboprophylaxis in orthopedic surgery [1].**

<table>
<thead>
<tr>
<th>First choice treatment</th>
<th>LMWH initiation</th>
<th>Duration</th>
<th>High risk of bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip arthroplasty</td>
<td>LMWH, fondaparinux, or adjusted-dose VKA (INR range 2.0–3.0)</td>
<td>Preoperatively or postoperatively</td>
<td>At least 10 days; recommendation to extend up to 35 days</td>
</tr>
<tr>
<td>Knee arthroplasty</td>
<td>LMWH, fondaparinux, or adjusted-dose VKA (INR range 2.0–3.0)</td>
<td>Preoperatively or postoperatively</td>
<td>At least 10 days; suggestion to extend up to 35 days</td>
</tr>
<tr>
<td>Hip fracture surgery</td>
<td>Fondaparinux, LMWH, adjusted-dose VKA (INR range 2.0–3.0), or UFH</td>
<td>Preoperatively or postoperatively</td>
<td>At least 10 days; recommendation to extend up to 35 days</td>
</tr>
</tbody>
</table>

Fondaparinux for LMWH initiation should be started either 6–8 h after surgery or the next day. INR: international normalized ratio; LMWH: low-molecular-weight heparin; UFH: unfractionated heparin; VKA: vitamin K antagonist.
practice can be explained in part by some of the limitations of the available anticoagulant drugs. LMWH and fondaparinux need subcutaneous administration, which may present a problem after the patient is discharged when the assistance of a healthcare professional may be required to administer the drug. Hospital stays are increasingly becoming shorter, and patients are at increased risk of not receiving an adequate duration of thromboprophylaxis. Furthermore, LMWH is associated with the risk of heparin-induced thrombocytopenia, which requires monitoring of the platelet count during treatment. Protamine sulfate is the only available antidote for parenteral antithrombotic drugs. Conversely, warfarin has an oral route of administration and anticoagulation can be easily reversed if needed. However, VKAs are less effective than LMWH, at least in TKA, and require regular monitoring to maintain an INR within the therapeutic range. In addition, the management of warfarin is complicated by several food and drug interactions, unpredictable pharmacological effects, and inter-patient variability [1].

**Possible answers: new oral anticoagulant drugs**

The ideal pharmacological thromboprophylaxis method would have the following characteristics: better efficacy and improved safety compared with current options, the availability of fixed doses, the absence of food or drug interactions, a rapid onset and offset of action, a more convenient route of administration including not requiring regular coagulation monitoring, and easy reversibility in case of bleeding or requirement for an urgent surgical procedure. Two new classes of oral anticoagulant drugs are already available on the market: direct Factor IIa inhibitors and direct Factor Xa inhibitors (Figure 1).

Direct Factor IIa inhibitors are a class of anticoagulants that bind selectively to thrombin and block its interaction with its substrates [39]. Older direct IIa inhibitors, such as recombinant hirudin, argatroban, or bivalirudin, are administered parenterally and are currently approved in specific settings [40]. Newer direct thrombin inhibitors have the advantage of being administered orally. Ximelagatran was the first of this new generation, but the drug was withdrawn from the world market in 2006 because of potential idiosyncratic severe (even lethal) hepatic toxicity [40]. Dabigatran etexilate, AZD0837, and MCC-977 are now under development [39,40]. Dabigatran etexilate has already been licensed in the European Union, Canada, and several other countries for the prevention of VTE in patients undergoing THA and TKA [41], with a recommended dose of 220 mg once-daily for all patients but those with moderate renal insufficiency (creatinine clearance between 30 and 50 mL/min) and the elderly (age >75 years), for whom the recommended dose is 150 mg once-daily [14].

Oral direct Factor Xa inhibitors are a class of anticoagulants that directly inhibit activated Factor X [40]. Other selective Factor Xa inhibitors, such as fondaparinux and idraparinux, are administered parenterally and act indirectly on Factor Xa [40]. Direct Factor Xa inhibitors are able to inhibit both free and prothrombinase-bound Factor Xa [7]. Several compounds are under different developing stages (such as edoxaban, betrixaban, LY517717, YM150) [40], but only rivaroxaban and apixaban are currently being marketed [42,43]. Rivaroxaban has been licensed in the European Union, Canada, and other countries for the prevention of VTE in patients undergoing THA and TKA [42]. The recommended dose is 10 mg once-daily [42]. The first dose should be administered between 6 h and 10 h postoperatively. A number of clinical trials are currently ongoing in other settings for both direct thrombin inhibitors and direct Factor Xa inhibitors.

Some characteristics of the new anticoagulants make them a major step towards an ideal anticoagulant. The oral route of administration is a major advantage over UFH, LMWH, and fondaparinux, in particular when treatment is administered for an extended period of time. The possibility of administering these drugs without the need for laboratory monitoring, thanks to their predictable pharmacokinetics and pharmacodynamics (including a rapid onset and offset of action), and their limited food–drug and drug–drug interactions, is a major advantage over UFH and the VKAs. In particular, there is a low propensity for drug–drug interactions with commonly used concomitant medication such as nonsteroidal anti-inflammatory drugs and acetyl salicylic acid.
Dosing is not adjusted based on coagulation parameters in individual patients and this has not been done in the clinical trials. Nevertheless, measurement of plasma concentrations might be of use, for example in emergency settings and suspected overdose cases. Even if we still do not have the ideal anticoagulant, findings of cost–benefit analyses should be taken into account. The favorable results of the first clinical trials support the potential of these new drugs to change current practice and the management of patients requiring VTE prophylaxis in the orthopedic setting and beyond.

Disclosures

The author has no competing financial interests to disclose.

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Since first publication of the direct anterior approach (DAA) technique over 5 years ago [1], surgery for total hip arthroplasty (THA) has changed around the globe. The MicroHip technique is unique, and when first introduced seemed “exotic” to many people, even though other existing approaches to the hip, such as those pioneered by Smith–Petersen and Hüter, are also anterior approaches. Awareness of the anterior approach has now completely changed. The MicroHip technique is becoming more and more popular [2], and many different DAA techniques have been published using different patient positions and technical methods, and different types of traction table.

The purpose of this article is to provide an update on the MicroHip technique. This approach has evolved over the past few years as a consequence of the number of procedures performed (>2500 procedures at this author’s institute alone).

The postoperative and perioperative treatment regimens have also changed. One of the most important changes has been the introduction of oral anticoagulants for thrombosis prophylaxis.

Many people are unaware that the MicroHip approach can be easily extended without the use of a complete Smith–Petersen approach. If the skin incision is extended in a Z shape we stay within the same interval, with a greatly extended vision. Care must be taken with regard to the anterior circumflex artery, which needs to be ligated in the extended version of this approach. On the proximal end it is better to extend straight up to the iliac crest and not extend the incision too far ventrally, because the lateral cutaneous femoral nerve could then be damaged. In cases where a femoral crack needs to be dealt with, this is possible by using a wire from a standard incision. To treat a severe femoral fracture, it is easier to use an extended skin incision but then convert it into a lateral femoral approach by “jumping” over the iliotibial band (ITB).
Patient selection

The DAA, or MicroHip, can be used in a wide range of indications, including in obese patients, and in all age groups. It is not implant-dependent so can be used for cement-free and cemented implants, although uncemented implants with a low shoulder profile such as the Corail® or TriLock® (DePuy) are the most suitable for this approach. When first using the MicroHip approach, patient selection is extremely important. It is key to build up an initial experience with simple cases, such as women with a normal body mass index (BMI) and a standard anatomy. It is recommended that the range of indications be gradually increased towards heavy muscular men with short femoral necks and varus hips. This is certainly the most difficult type of patient on which to perform THA using the MicroHip technique. There are no specific contraindications as long as the surgeon operates within his/her comfort zone.

Surgical procedure

Positioning and incision placement

The patient should be positioned in a lateral decubitus position, with the posterior foot part of the table removed. A strong support for the back of the patient is needed in order to prevent the pelvis from moving (Figure 1). The surgeon should stand in front of the patient; it is critical to have good access to the femur. Specific landmarks are used for the incision – in the author’s clinic, we draw a line from the middle of the anterior border of the greater trocanter to the anterior iliac crest. The distal 6–8 cm of this line are used for the incision (Figure 2A). As already mentioned, the length of the incision is not important. If the surgeon does not have a sufficient view, he or she can easily extend the standard incision (Figure 2B).

Superficial dissection

The subcutaneous tissue is dissected down to the level of the fascia. We can then access the border of the ITB, and the incision is placed on the very border of the ITB but 2–3 mm lateral to it, therefore within the ITB. This is for two reasons. Firstly, the border of the ITB is easier to suture when closing than the sometimes-fine fascia of the tensor muscle. Secondly, the superficial lateral nerve of the thigh can be avoided by proceeding with the blunt dissection of the tensor muscle from underneath the fascia.

The lateral cutaneous nerve may be close, but it always runs on the superficial side of the fascia. The first blunt retractor should be set on the lateral side of the femoral neck in order to move all of the musculature to the lateral side and give access to the femoral neck.

Deep dissection

The anterior neck is covered with a thin double layer of fascia containing the yellow fat pad in the middle. The reflected rectus tendon runs medially. A longitudinal incision of the superficial layer should be followed by a blunt dissection of the yellow fat pad, moving it medially together with the reflected rectus tendon and holding it in place with a second blunt retractor. The capsule should be incised in a T-shaped manner lateral to the insertion of the reflected rectus tendon; it is better to dissect the capsule from the intertrochanteric line in an inside-out technique to avoid the main branches of the circumflex artery (Figure 3). The ascending branch, which runs along the deeper surface of the tensor muscle, needs to be coagulated or ligated. The blunt retractors should be placed around the femoral neck and the osteotomy performed prior to dislocation of the femoral head. For dislocation, a corkscrew should be inserted into the lateral femoral neck and used to flip the femoral neck towards the surgeon. The corkscrew can then be repositioned into the longitudinal axis of the femoral neck and used to twist the head several times until it is completely loose. After removing the head there will be an excellent 360° view of the acetabulum, which can be further enhanced by adding a third double-bent.
Hohmann retractor at the lateral insertion of the transverse acetabular ligament (TAL), so as to distalize the femur. The TAL, which is an important local landmark for controlling version of the cup, should be identified. When implanting the cup, surgeons should be aware that in the lateral decubitus position the pelvis tends to adduct and, combined with the impact of version on radiographical inclination, this means the surgeon should aim for an operative inclination of approximately 35° in order to achieve a 45° angle on the postoperative anteroposterior radiograph.

For preparation of the femur, a blunt retractor should be placed over the tip of the greater trochanter before the leg is dropped behind the table (Figure 4). With this retractor the tensor muscle can be flipped over the greater trocanter at the same time as the trocanter can be moved with the tip of the retractor medially in order to prevent the femur from impinging against the lateral acetabular rim. In standard hips, no specific release is needed. If the hip is very stiff, we first perform a release of the posterior capsule followed by a release of the piriformis tendon and then a partial release of the tensor muscle from the anterior iliac crest.

Before broaching it should be ensured that a good overview of the femur is available in order to ascertain the correct entry point for the specific implant. The most common error is to start broaching in too medial a position so the broach will be in varus; this increases both the risk of undersizing and of cracking the calcar.

**Deep repair and closure**

After implantation, all that remains to be done is to close the capsule with a few stitches and a running suture to the fascia followed by skin closure. The procedure is then complete.

**5-Year results**

The 5-year results of MicroHip THA surgery, performed at the Orthopaedic Center Münsingen were compared with those of patients undergoing “conventional” (transgluteal approach) THA surgery. The comparison group was collect retrospectively from the same hospital and consultants. Initially, the study was to be single-blinded; however, because of the success of the technique, the study protocol was adapted and the prospective MicroHip group compared against a retrospective collective. The two groups of patients were comparable in terms of age and BMI. The thromboprophylaxis regimen was the same for both groups: low molecular-weight heparin (LMWH) was given up to day 4, and patients were then switched to warfarin using the standard protocol. Warfarin was continued for 3 months.

**Results**

In the MicroHip group, blood loss was decreased by 42% and hospital stay was reduced by 2.1 days (±0.6 days) compared with the conventional surgery group, with no change in variables other than operative technique. Cup inclination was 45.6° (±3.4°) in the conventional surgery group and 44.8° (±3.7°) in the MicroHip group. The dislocation rate was lower in the MicroHip group (0.4% compared with 3.5% in the conventional surgery group).

Gait analysis (excluding patients with additional joint problems) showed no significant difference between the operated and the non-operated leg at 5 years in 98.8% of the MicroHip group. In addition, the Harris Hip score, which is a conservative scoring system, showed a significantly better result for those patients undergoing the MicroHip technique compared with those who underwent conventional surgery (Figure 5). The Harris Hip score for the MicroHip group was 91.35 (vs. 78.3 in the conventional surgery group) at 3 months and 94.48 (vs. 82.4 in the conventional surgery group) at 1 year. At 5 years, the difference in Harris Hip score remained significant between the two groups (p<0.001).
Complications, VTE rates, and thromboprophylaxis

There was no superficial or deep infection in either group, despite a higher infection rate for smaller incisions being suggested in the literature. This shows that by handling the soft tissue with care, there is no increase in infection rate for surgical procedures using small incisions.

Neurological complications were more frequent in the conventional surgery group (four vs. none in the MicroHip group), with the majority being dysfunctions of the sciatic nerve. There were no significant neurological problems seen in the MicroHip group, and in particular there was no neuropraxis of the femoral nerve. This had been a cause for concern as the leg was taken into a hyperextended position for implantation of the femoral component, thereby applying tension to the femoral nerve.

A difference in thrombosis risk was noted between the groups. There were two pulmonary embolisms in the conventional surgery group versus none in the MicroHip group. There was one clinically relevant deep vein thrombosis in the MicroHip group compared with three in the conventional surgery group. We suggest the below factors contribute to a decrease in the risk of venous thromboembolism (VTE):

- Trauma of the soft tissue was much less in the MicroHip group. Despite the positioning on the operating table, hyperextension of the leg is a physiological position and therefore trauma to the blood vessels is less.
- Because of the tissue-sparing procedure, patients undergoing the MicroHip technique experience much lower levels of pain, rehabilitation is quick, and return to normal gait is achieved within a short time frame.

Approximately 1 year ago, the thromboprophylaxis regimen in this author’s center was changed to rivaroxaban. The introduction of rivaroxaban thromboprophylaxis increased the efficiency of the unit because of its ease of application without the need for monitoring. A high patient volume coupled with a shorter hospital stay not only reduces costs but also increases patient safety. No difference in VTE rates with rivaroxaban compared with the LMWH/warfarin regimen have been observed, but this specific question has not yet been studied.

Conclusions

The main advantages of the MicroHip technique are avoidance of the hip deltoid in an internervous plane, therefore rehabilitation is quick and outcomes have been shown to be superior to a standard transgluteal approach, even after 5 years. In the lateral decubitus position hardly any release is needed, blood loss is minimized, and no specific tools such as an extension table are involved. Therefore, not only does the surgeon have an excellent view of the acetabulum and femur, he/she also has full control over the procedure. Analysis of the 5-year results using the MicroHip technique clearly show advantages of a soft-tissue-sparing DAA over a conventional standard lateral or transgluteal approach.

The MicroHip technique is, however, a completely different procedure from any standard approach, and thus requires specific training and education of surgeons in order to protect patients from unnecessary risks.

For further information please visit www.do-surgery.com or www.ozm.com.

Disclosures

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References


You can submit comments and questions on this article at: www.venous-arterial-thrombosis.com
Effect of elevated left ventricular diastolic filling pressure on the frequency of left atrial appendage thrombus in patients with nonvalvular atrial fibrillation

Iwakura K, Okamura A, Koyama Y et al.

The present work investigated the relationship between the ratio of early transmitral flow velocity to mitral annular velocity, and incidence of left atrial appendage thrombus in atrial fibrillation patients. The results show that diastolic dysfunction may in part contribute to left atrial appendage thrombosis.

The association of increased risk of stroke and left ventricular (LV) systolic and diastolic dysfunction is well established in the atrial fibrillation (AF) setting. In the present study, the authors investigated the relationship between the ratio of early transmitral flow velocity (E) to mitral annular velocity (e'; E/e'), an echocardiographic marker of LV diastolic filling pressures, and the incidence of left atrial appendage (LAA) thrombus in patients with AF.

The study was a retrospective, case–control study that enrolled 376 patients with paroxysmal or persistent AF, excluding those with New York Heart Association class IV heart failure and AF related to rheumatic heart disease, mitral stenosis, or mitral valve surgery. LAA thrombi were observed in 28 patients (7.4%) on transesophageal echocardiogram. E/e' was significantly higher in patients with LAA thrombi than in those without thrombus (18.3±9.3 vs. 11.4±5.9; p<0.0001). Receiver operator curve analysis demonstrated that 12.8 was the optimal cut-off value of E/e', with a moderate ability (75% sensitivity and 74.4% specificity) for predicting LAA thrombus. An E/e' ratio of ≥13 was significantly and independently associated with LAA thrombus (odds ratio 3.50, 95% confidence interval [CI] 1.22–10.61; p=0.02) in addition to LA size and presence of low ejection fraction in a multiple logistic regression model.

The findings of the present study show that diastolic dysfunction may, at least in part, contribute to LAA thrombosis; this may have future clinical implications as the treatment of diastolic dysfunction could decrease the risk of stroke in the high-risk AF population. However, careful interpretation of the results is warranted, as the present study was designed retrospectively and E/e' measurement in AF rhythm is problematic. Furthermore, a low percentage of patients were on anticoagulation therapy, and patients who presented with an LAA thrombus had an international normalized ratio (INR) of <2, which was also marginally lower than the INR in patients without or LAA thrombus (p=0.08). Finally, multiple logistic regression analysis was not thoroughly investigated since an interaction effect could very well exist between E/e' and LA size, and additionally total CHADS2 score (a clinical score for estimating the risk of stroke in non-rheumatic AF) was not included as a potential confounder.

The golden hour of prehospital reperfusion with triple antiplatelet therapy: a sub-analysis from the Ongoing Tirofiban in Myocardial Evaluation 2 (On-TIME 2) trial early initiation of triple antiplatelet therapy

Heestermans T, van ’t Hof AW, ten Berg JM et al.

The authors of the present study evaluated whether the lytic effect of glycoprotein IIb/IIIa inhibitors in ST-elevation myocardial infarction is time-dependent. The results suggest that this is indeed the case and that there
is an additive effect of tirofiban and dual antiplatelet pretreatment prior to percutaneous coronary intervention.

Previous studies in ST-elevation myocardial infarction (STEMI) patients have shown the advantage of performing primary percutaneous coronary intervention (PCI) after pretreatment with antiplatelet therapy alone (without lytic therapy), or a combination of antiplatelet and lytic therapy. The difference in clinical endpoints was mainly driven by more hemorrhagic events with the latter treatment strategy. Furthermore, conflicting results have been reported regarding the efficacy of pretreatment with glycoprotein IIb/IIIa inhibitors on vessel patency in STEMI patients undergoing PCI.

The present study is a subanalysis of the On-TIME 2 (Ongoing Tirofiban in Myocardial Evaluation 2) trial, which aimed to evaluate whether the lytic effect of glycoprotein IIb/IIIa inhibitors is time-dependent. The On-TIME 2 trial included 1398 consecutive STEMI patients referred for primary PCI. Patients were randomized to dual (500 mg aspirin and 600 mg clopidogrel) or triple antiplatelet (500 mg aspirin, 600 mg clopidogrel, and tirofiban 25 μg/kg bolus and 0.15 μg/kg per min maintenance infusion for 18 h) pretreatment. The primary outcome of this subanalysis was initial patency of the infarct-related vessel assessed using TIMI flow criteria (percentage of TIMI 3 flow or TIMI 2 or 3 flow) and ST-segment resolution (STR; complete ≥70%, partial 30–70%, and no resolution <30%) before PCI according to time from symptom onset to the first medical contact. The time from symptom onset to the first medical contact was analyzed as quartiles (0–45 min, 46–76 min, 77–149 min, and ≥150 min). The effect of the additional treatment with tirofiban as compared with control pretreatment (only aspirin and clopidogrel) on complete STR before angiography was apparent only in the first quartile of symptom duration (29.1% vs. 17.2%; p=0.02). The effect on initial patency compared with control pretreatment was again only apparent in the first quartile of symptom duration (TIMI 3: 30.7% vs. 21.4%, p=0.06; TIMI 2 or 3: 52.8% vs. 40.3%, p=0.03). The authors found no significant interactions between randomization (to additional treatment with tirofiban or control group) and the quartiles of time between symptom onset and diagnosis with respect to complete STR, TIMI 3 flow, or TIMI 2 or 3 flow. The incidence of TIMI major bleeding did not differ significantly between tirofiban and the control group in all four quartiles of time to symptom duration.

The findings of the present study suggest an additive effect of tirofiban with dual antiplatelet pretreatment on reperfusion shortly after symptom onset with a higher initial patency and STR. The greatest efficacy was observed in patients with early initiation of tirofiban (within approximately 1 h of chest pain onset). Several aspects of this analysis merit careful consideration, including the fact that the time-dependent impact on the association between the two different treatment strategies and outcomes was only partly supported by interaction analysis. More importantly, these findings should be interpreted as a post hoc analysis, and should be viewed only as hypothesis-generating.

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Intracoronary versus intravenous administration of abciximab in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with thrombus aspiration: the comparison of intracoronary versus intravenous abciximab administration during emergency reperfusion of ST-segment elevation myocardial infarction (CICERO) trial


The authors of the present study investigated whether intracoronary administration of abciximab is superior to intravenous administration for improvement of myocardial reperfusion in ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention with thrombus aspiration. Conflicting results regarding myocardial perfusion and neutral results regarding clinical endpoints were found. Recently, the implementation of adjunctive mechanical therapies during primary percutaneous coronary intervention (PCI) such as manual thrombus aspiration, which reduces thrombus burden at the local level, has improved myocardial reperfusion and clinical outcome in ST-elevation myocardial infarction (STEMI) patients. Similarly, adjunctive pharmacological therapies such as glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors are expected to further improve clinical outcome when administered in an intracoronary manner, resulting in higher local drug concentration. The present study therefore investigated whether intracoronary administration of abciximab is superior to intravenous administration in improving myocardial reperfusion in STEMI patients undergoing primary PCI with thrombus aspiration.

The study was designed as a single-center, prospective, randomized, open-label trial. The primary endpoint was
the incidence of restored myocardial reperfusion, defined as complete ST-segment resolution (STR). Secondary endpoints of myocardial reperfusion included myocardial blush grade and residual ST-segment deviation. Other secondary endpoints included post-procedural thrombolysis in myocardial infarction (TIMI) flow and angiographically visible distal embolization, enzymatic infarct size, all-cause mortality, and major adverse cardiac events (a combined endpoint of cardiac mortality, reinfarction, and target vessel revascularization) at 30 days.

A total of 271 STEMI patients were randomized to intracoronary use, and 263 patients to intravenous use of GP IIb/IIIa inhibitors. The primary endpoint of complete STR was achieved in 64% of the intracoronary group and 62% of the intravenous group (p=0.562). Concordantly, there were no differences in the distributions of residual ST-segment deviation (p=0.662), post-procedural TIMI grade 3 flow (p=0.261), and post-procedural distal embolization (p=0.635) between the intracoronary and intravenous groups. Only infarct size was smaller (by 30%, as assessed by serial measurements of creatine kinase; p=0.008) and incidence of myocardial blush grade 2/3 was higher (p=0.022) in the intracoronary group than in the intravenous group. Finally, all-cause mortality (p=0.524) and incidence of major adverse cardiac events (p=0.786) were not different between the two groups.

The present study reports conflicting results regarding myocardial perfusion and neutral results regarding clinical endpoints. The use of GP IIb/IIIa inhibitors on top of thrombus aspiration, sample size, only bolus, and timing of dosage of GP IIb/IIIa inhibitors may explain the reported discrepancies. Larger, adequately-powered studies with longer follow-up are needed to clarify the discrepancy between the findings of the present study and those of previous studies that reported angiographic and clinical benefits.

It has been well established that patients with idiopathic venous thromboembolism (VTE) are at a higher risk of being subsequently diagnosed with cancer than the general population (estimated incidence 10% within 12 months of diagnosis). The question arises whether more extensive screening at diagnosis of pulmonary embolism or deep vein thrombosis would lead to earlier cancer diagnosis and an improved prognosis. The authors of this study show that extensive cancer screening utilizing mammography and abdominal and chest computed tomography (CT) scanning results in a low diagnostic yield and, therefore, cannot be recommended in clinical practice.

This was a prospective, concurrently controlled cohort study that included 630 patients from 10 Dutch teaching hospitals with objectively confirmed first VTE who had no known risk factor such as recent fracture, surgery, immobility for more than 6 days, thrombocytosis (>1000 × 10^9 cells/mL), severe dehydration, pregnancy or puerperium, recently started oral contraceptives, or presence of a known malignancy. Dependent on the participating hospital, patients were allocated to a limited cancer screening group consisting of physical examination, and determination of erythrocyte sedimentation rate, whole blood count with leukocyte differentiation, creatinine, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase and calcium, and a chest X-ray, or an extensive cancer screening cohort, with additional mammography and abdominal and chest CT scans. The outcomes were incidence of cancer, and cancer-related and overall mortality.

At baseline, malignancy was diagnosed in 12 of 342 patients (3.5%) in the extensive screening group compared with seven of 288 (2.54%) in the limited screening group. After a median of 2.5 years follow-up, cancer had been diagnosed in 3.7% and 5.0%, respectively (p=non-significant). In the extensive screening group, 26 patients (7.6%) died compared with 24 (8.3%) in the limited screening group, resulting in a non-significant survival benefit in the extensively screened patients (adjusted hazard ratio 1.22, 95% confidence interval 0.69–2.2).

Importantly, the study was discontinued because at interim analysis it was concluded that the assumptions on which the original sample size to detect a survival benefit of extensive screening was based represented an underestimation of the real numbers required, and the newly calculated sample size indicated the need for more than 10 000 patients. Therefore, the study was grossly underpowered to detect a potential survival benefit. Nonetheless, the low yield of extensive screening and lack of survival benefit do not support routine extensive screening for cancer in patients with a first idiopathic VTE event.
Cancer and venous thromboembolism (VTE) are known to be associated. This study sought to establish whether the site of VTE is associated with underlying cancer, with the results showing that arm and intra-abdominal VTE, and bilateral leg VTE, may be related to active cancer.

The association between active cancer and venous thromboembolism (VTE) is well established. The incidence of cancer is higher in patients with recurrent thromboembolism, and, conversely, active cancer increases the occurrence of VTE by five- to six-fold. Until recently, there has been no consensus regarding screening for an underlying active cancer after an episode of idiopathic VTE. Furthermore, there is a paucity of data regarding location of VTE and active cancer. The present study therefore assessed whether underlying cancer is associated with particular VTE locations.

The authors designed their study as a retrospective longitudinal, observational, case–control study. The study population consisted of 1599 cases presenting with objective VTE during a 17-year period (1984–2000). For the following reasons, 56 cases were excluded: the VTE was associated with an indwelling catheter or permanent pacemaker, the VTE was of unknown site, and because of a final diagnosis of chronic thromboembolic disease. Gastrointestinal and urogenital cancers were the more frequently encountered active forms of cancers. The principal finding of the study was that active cancer was associated with three VTE locations. Specifically, active cancer was strongly associated with arm or intra-abdominal VTE, and intra-abdominal VTE alone, compared with leg VTE or pulmonary embolism; furthermore, there was an association between active cancer and bilateral leg VTE, compared with unilateral leg VTE. Interestingly, this latter association persisted after adjustment for age, gender, body mass index, and other independent VTE risk factors such as hospitalization, neurological disease associated with immobility, varicose veins, prior superficial thrombosis, and nursing home residency. However, no association was observed between pulmonary embolism with or without VTE and active cancer when compared with unilateral leg VTE only.

These findings may have clinical implications as they suggest that patients presenting with arm, intra-abdominal, or bilateral leg VTE should be screened for active cancer. However, certain limitations should be noted. Firstly, the association between active cancer location and VTE was not assessed with screening cost-effectiveness in mind. Moreover, the present analysis was not adjusted for coagulation disorders or for other systemic diseases that may precipitate thromboembolism. Finally, the generalizability of the results may be limited as the current diagnostic testing methods for active cancer may have changed since the analysis of the present study cohort (1984–2000).

Cancer and its medical and surgical treatment are well-defined risk factors for venous thromboembolism (VTE). However, the decision of when to offer VTE prophylaxis to cancer patients is often difficult in clinical practice, since it may be affected by various comorbidities and clinical scenarios.

Abdel-Razeq and colleagues searched their hospital database for all discharge diagnoses of cancer with deep-vein thrombosis between 2004 and 2008. They looked at the prophylaxis rates for all patients as well as for subgroups in relation to recent hospitalization, duration of cancer diagnosis, and number of coexisting risk factors. The results showed the majority of venous thromboembolism events occurred in cancer patients who were not offered prophylactic treatment, with only a minority of events associated with prophylaxis failure.

Cancer and its medical and surgical treatment are well-defined risk factors for venous thromboembolism (VTE). However, the decision of when to offer VTE prophylaxis to cancer patients is often difficult in clinical practice, since it may be affected by various comorbidities and clinical scenarios.
difficult, and will depend on individual patient factors such as bleeding propensity and hematological findings.

In summary, in this retrospective observational series the majority of VTE events occurred in cancer patients who were not offered prophylactic treatment, with only a minority associated with prophylaxis failure. In the absence of guidelines, the potential benefits of VTE prophylaxis should be weighed against the risk of complications for each individual patient.

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Prediction of venous thromboembolism in cancer patients


In this prospective observational study of patients with newly diagnosed cancer or progression of disease after remission, the authors propose a venous thromboembolism (VTE) risk stratification model consisting of clinical and standard laboratory parameters plus biomarkers. The cumulative probability of VTE was highest in those with the highest score.

Patients with active malignancy – i.e. cancer with ongoing treatment, treatment within the previous 6 months, or in the palliative stages – are at an increased risk of symptomatic venous thromboembolism (VTE). This frequent complication occurs in up to 20% of patients and is associated with poor survival. Therefore, identification of patients at a very high risk of VTE might enable the treating physician to establish preventative treatment measures and would, therefore, be of great clinical value. The authors of this prospective observational cohort study of patients with newly diagnosed cancer or progression of disease after remission propose a risk stratification model consisting of clinical and standard laboratory parameters with the addition of biomarkers.

In a sample of 819 patients with newly diagnosed cancer or progression of disease after remission they assessed soluble P-selectin (sP-selectin) and D-dimer blood levels to complete their expanded risk scoring model [1]. The same authors have previously shown that both sP-selectin and D-dimer independently predict VTE in cancer patients [2,3].

Of 819 patients, 61 (7.4%) experienced VTE during a median follow-up of 656 days. In the expanded risk model, the cumulative VTE probability after 6 months in patients with the highest score (25 points) was 35.0%. In those with an intermediate score (score ≤ 25) the probability was 10.3%, and this was only 1.0% in patients with a very low score (0 points). Future prospective outcome studies are needed to confirm the validity of the suggested risk stratification and, in addition, to study the hopefully positive effects of treatment measures based on this score.


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POST-THROMBOTIC SYNDROME

Six-month exercise training program to treat post-thrombotic syndrome: a randomized controlled two-centre trial


In this pilot study, the authors investigated the feasibility of a 6-month exercise training program in treating post-thrombotic syndrome. Patients participating in the training program experienced significantly improved venous-diseases-specific quality of life and non-significantly improved severity of post-thrombotic syndrome. Further trials are now required to confirm these results.

Chronic post-thrombotic syndrome (PTS) develops in up to every second patient with lower-limb deep venous thrombosis (DVT). Walking exercise is an important treatment approach in patients with peripheral arterial disease and symptoms of claudication, and may be helpful in improving PTS.

Kahn and colleagues conducted a randomized pilot trial to assess the feasibility of a 6-month exercise training program
for the treatment of PTS. A total of 43 patients with unilateral symptomatic DVT were randomized to receive control treatment (n=22) or a 6-month supervised exercise training program (n=21) consisting of strengthening, stretching, and aerobic training aimed at improving leg strength, flexibility, and cardiovascular fitness. The training regimen was performed three times per week during the first 2 weeks, twice per week in week 3, once per week in week 4, and once per month thereafter. The control group received a standardized, 1 h educational slide presentation on PTS followed by telephone follow-up at 1, 2, 4, and 5 months to inquire about well-being and leg-related symptoms. The primary outcomes were change in venous-diseases-specific quality of life, assessed using the Venous Insufficiency Epidemiological and Economic Study Quality of Life (VEINES-QOL) questionnaire, and PTS severity, assessed using the Villalta scale, at 6 months. Leg strength, leg flexibility, and exercise capacity were also assessed.

Three patients withdrew from the exercise program between baseline and 3 months. At 6 months, exercise training was associated with significant improvements in VEINES-QOL score (mean change 6.0 in exercise group vs. 1.4 in control group, 95% CI 0.5–8.7; p=0.027) and non-significant improvements in Villalta score (mean change −3.6 in exercise group vs. −1.6 in control group, 95% CI −4.6 to 0.6; p=0.14). Exercise training was also associated with significant improvements in leg strength and some aspects of flexibility, but not in exercise capacity.

The authors conclude that exercise training may improve PTS. These findings, however, should be evaluated in a larger multicenter randomized trial. Although the dropout rate was low compared with rates in patients with peripheral arterial disease undergoing exercise training, it may be interesting to evaluate whether a training program that requires less time is equally effective.

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Predictors of the post-thrombotic syndrome with non-invasive venous examinations in patients 6 weeks after a first episode of deep vein thrombosis


This prospective observational cohort study was performed to determine predictors of post-thrombotic syndrome following deep venous thrombosis. Male sex, age >50 years, proximal localization of the thrombus at entry, residual proximal thrombosis, and superficial valvular reflux at 6 weeks seem to be the most important prognostic factors.

Post-thrombotic syndrome (PTS) is the term used to describe the debilitating signs and symptoms that may complicate deep venous thrombosis (DVT), which include aching or cramping pain, heaviness, itching or tingling, edema, skin discoloration, and ulcers on the affected extremities. The precise underlying pathophysiological mechanism causing PTS is unknown, but damage to venous valves, increased valvular reflux, and persistent venous obstruction resulting from incomplete thrombus clearance have all been shown to result in high walking venous pressure and alterations in the skin microcirculation. As a result of the high prevalence and clinical burden of PTS (33–50%), early identification of patients at high risk for the development of this syndrome is relevant. The current authors performed a prospective observational cohort study with the intention of assessing potential predictors of PTS.

A total of 111 consecutive patients with an echocardiographically objectivated first episode of DVT were followed for 2 years. Using non-invasive venous examination, residual thrombosis, valvular reflux, calf muscle pump function, and venous outflow resistance were measured after a period of 6 weeks, 3 months, 6 months, 1 year, and 2 years. The cumulative incidence of PTS was 46% at 3 months after study inclusion and did not increase further. Univariate analysis revealed proximal vein thrombosis, high thrombosis score, high superficial or popliteal reflux score, poor calf muscle function, and high venous outflow resistance as significant predictors of PTS 1 year after diagnosis. In contrast, varicose veins at diagnosis, body mass index, and idiopathic DVT (thrombosis occurring in the absence of clear risk factors) were not associated with the development of PTS. Risk ratio calculations for the other time points were not reported. A multivariate logistic regression model including the overall thrombosis score and overall valvular reflux together with sex, age, thrombosis localization, and the absence of venous thromboembolism risk factors resulted in a high area under the receiver operator curve of 0.79 (95% CI 0.70–0.88), indicating high prognostic value.

In their discussion, the authors stress the importance of implementing a non-invasive follow-up examination with duplex scanning 6 weeks after diagnosis in order to identify patients at high risk of PTS. In addition, and applied to symptomatic patients, this can aid in correctly differentiating between symptomatic recurrent thrombosis and residual thrombosis with PTS because of the distinct treatment consequences.
Factors predicting development of post-thrombotic syndrome in patients with a first episode of deep vein thrombosis: preliminary report


The authors of the present work investigated indicative parameters linked to the progression of post-thrombotic syndrome (PTS) in patients with a first episode of deep venous thrombosis (DVT) detected sonographically. The results confirmed the suspected predictors of disease progression in these patients, and demonstrated that symptomatic PTS occurs in more than one in five patients with a first episode of DVT.

Post-thrombotic syndrome (PTS) is a common late sequela of deep venous thrombosis (DVT). Its clinical symptoms include lower-extremity pain, heaviness, and swelling, and specific skin alterations such as eczema, hyperpigmentation, and ulceration. To date, the factors associated with the development of PTS have only been roughly defined. This might be because the physicians who initially diagnose DVT are often different from those who diagnose PTS in the long-term follow-up of these patients.

In the current study, Yamaki and colleagues investigated indicative parameters reflecting the progression of PTS in patients with a first, sonographically verified DVT episode. Besides assessment of risk factors such as age, sex, body mass index, presence of active cancer, congestive heart disease, hormone replacement therapy, immobilization, surgery, previous history of DVT, and renal failure, the authors categorized clinical manifestations of PTS in line with the CEAP (clinical, etiological, anatomical, and pathophysiological) classification. Moreover, venous occlusion, reflux, and reflux parameters were scrutinized at 6-month follow-up.

Of 121 patients analyzed, 25 (21%) developed PTS during a mean follow-up of 66 months. At initial presentation, the presence of iliofemoral DVT (odds ratio [OR] 3.4, 95% CI 1.4–8.6) was an independent predictor of PTS. At 6 months, venous occlusion combined with reflux (OR 4.4, 95% CI 2.9–20.7), peak reflux velocity >29.7 cm/s (OR 13.7, 95% CI 4.1–45.7), and mean reflux velocity >8.6 cm/s (OR 4.4, 95% CI 1.5–12.9) in the popliteal vein were independently associated with PTS.

This study confirms predictors of disease progression and shows that symptomatic PTS occurs in approximately one in five patients with a first episode of DVT. The only risk factors identified previously for PTS were ipsilateral recurrence of DVT and increased body mass index. Considering that iliofemoral DVT was a strong predictor of PTS in the current study, it is reasonable to further scrutinize endovascular clot removal technologies in patients with proximal DVT (reviewed in [1]; discussed here on p64–5) before this technology is investigated in further distal pathologies.


MANAGEMENT AND TREATMENT

Effect of early or delayed administration of warfarin on thrombosis in pulmonary thromboembolism


The authors of the present study investigated whether early warfarin treatment, if started simultaneously with unfractionated heparin prior to reaching the activated partial thromboplastin time therapeutic level, causes increased coagulation risk among patients with pulmonary embolism. The results suggest that the suppressor effect of warfarin on protein C and S in the early period of anticoagulation did not increase the risk of clot formation.

It is known that oral anticoagulation therapy with warfarin has an early suppressor effect on the activity of anticoagulant proteins C and S before its inhibitory effect on vitamin K-dependent coagulation factors. It is unclear whether or not there is an increased risk for hypercoagulability secondary to inactivation of proteins C and S in patients receiving early oral warfarin therapy. Using thromboelastography, the present study investigated whether early warfarin treatment started simultaneously with unfractionated heparin (UFH) before reaching the activated partial thromboplastin time therapeutic level caused increased coagulation risk among pulmonary embolism (PE) patients.

A total of 16 PE patients were allocated to early treatment (warfarin and UFH simultaneously) while 17 PE patients were allocated to delayed treatment (UFH followed by warfarin 1–3 days later). Protein C levels were suppressed in the group of patients on early treatment with maximal suppression observed during the first 24 h. However, the fluctuation of protein C concentration did not differ over time within each group. No suppression of protein S levels was observed. Thromboelastography revealed that neither the internal nor the external coagulation pathway was significantly different between the two groups.
The results of the present study suggest that the suppressor effect of warfarin on protein C and S in the early period of treatment did not aggravate the risk of clot formation as assessed by thromboelastography in PE patients in whom warfarin was started simultaneously with UFH. Among the weaknesses of this study is the small study population, failure to account for multiple comparisons p-value adjustment, and not adjusting for possible confounders (i.e. underlying causes of PE). The clinical implications of the present study should be confirmed in larger studies with “hard” clinical endpoints.

Statins have an early antiplatelet effect in patients with acute myocardial infarction


The current authors explored the antiplatelet effects of statins in ST-elevation myocardial infarction, and suggest that statins have an early antiplatelet effect.

Statins (or 3-hydroxy-3-methyl-glutaryl coenzyme A [HMG-CoA] reductase inhibitors) are a class of drug used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. It has been shown that statins improve survival in patients with myocardial infarction (MI) because of this effect and, in addition, because of several pleomorphic properties, including a suggested antiplatelet effect. In the current study, the antiplatelet effects of statins in ST-elevation MI (STEMI) were further explored.

The study included 120 patients with STEMI, diagnosed by specific electrocardiogram characteristics and elevated troponin I levels, who underwent primary angioplasty within 12 h of symptom onset and who were not treated with statins before. All patients received aspirin, clopidogrel, and eptifibatide treatment according to the latest international guidelines. In addition, 80 patients received statin treatment from day 1 while the remaining 40 patients did not. Except for slightly higher smoking exposure in patients who were not treated with statins, the two groups had comparable baseline characteristics. Blood samples were drawn prior to percutaneous coronary intervention and 72 h later. From these blood samples, ex vivo platelet reactivity was studied by conventional aggregometry and aggregometry under flow conditions (Impact R). Measures of platelet reactivity under flow conditions included signifying platelet aggregation, aggregate size, and surface coverage.

From their data, the authors report reduced platelet deposition under flow conditions as measured by surface coverage from admission to 72 h later among statin-treated patients (19±28% reduction; p<0.01), while this was unchanged in non-statin-treated patients. This effect remained after correction for potential confounders such as patient characteristics, lipid profile, and type of statin administered.

The authors, therefore, conclude that in acute MI patients, statins have an early antiplatelet effect, independent to that afforded by standard antiplatelet therapy. Importantly, as the authors discuss, this was not a randomized trial and thus the adjudication to the study groups is likely to have been subject to bias. Consequently, the results reported in this article should be interpreted with great caution. Further trials should be performed to establish the antiplatelet effect of statins in this and other patient cohorts and evaluate the potential benefit of early start with statin therapy in patients with MI.

Oral rivaroxaban for symptomatic venous thromboembolism


Outpatient management of deep venous thrombosis or pulmonary embolism is hampered by the requirement for initial parenteral administration of heparin and an oral vitamin K antagonist, with the latter constrained by mandatory monitoring and dose adjustments because of variations in anticoagulant effect. The direct Factor Xa inhibitor rivaroxaban has been suggested as an alternative agent. The results of this trial indicate that rivaroxaban represents a simple and single-drug approach for the short-term and continued treatment of patients with deep vein thromboembolism.

Deep venous thrombosis (DVT) and pulmonary embolism are common disorders, with around 1–2 cases per 1000 persons per year in the general population. The standard treatment is currently limited by the need for initial parenteral administration of heparin combined with oral administration of a vitamin K antagonist. The latter requires regular laboratory monitoring and dose adjustments, and may be associated with fluctuations in its anticoagulatory effect. The direct Factor Xa inhibitor rivaroxaban may represent a simpler, fixed-dose regimen for the treatment of acute DVT and for continued treatment following DVT or pulmonary embolism.

In the current study, the EINSTEIN investigators randomized 3449 patients with acute DVT to either subcutaneous enoxaparin plus a vitamin K antagonist (control group) or oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) for 3, 6, or 12 months. Both
patients and physicians were blinded to the study medication. The primary efficacy outcome was recurrent venous thromboembolism (VTE), and the primary safety outcome was major bleeding or clinically relevant non-major bleeding.

Rivaroxaban was non-inferior to enoxaparin–vitamin K antagonist in terms of efficacy (recurrent VTE in 2.1% vs. 3.0% of patients, respectively, 95% confidence interval 0.44–1.04; p<0.001). Moreover, major bleeding or clinically relevant non-major bleeding occurred in 8.1% of patients in both treatment groups.

A second double-blind randomized superiority study was performed in parallel to the trial described above. Here, rivaroxaban 20 mg once daily was compared with placebo for an additional 6 or 12 months in 1197 patients who had completed 6–12 months of VTE treatment. The primary efficacy outcome was recurrent VTE, while the primary safety endpoint was major bleeding. Rivaroxaban had superior efficacy (recurrent VTE in 1.3% vs. 7.1% of patients, relative risk reduction 82%) and there was no difference between the two groups in terms of bleeding complications.

The authors conclude that rivaroxaban offers a simple single-drug approach, without the need for continuous monitoring, in the short-term and continued treatment of VTE patients.

Alternatives to warfarin have been awaited for a long time and the results of the EINSTEIN study indicate that rivaroxaban has the potential to significantly improve anticoagulant therapy for VTE patients by combining appropriate effectiveness with a favorable safety profile and adherence-enhancing administration. In addition, the reversibility of the drug effect and the ability to measure the anticoagulant effect are interesting features that further add to the above-illustrated benefits of oral Factor Xa inhibitors.

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**Modest response in translation to home management of deep venous thrombosis**


This work investigated the impact of studies showing the safety and efficacy of outpatient treatment of deep venous thrombosis on current clinical practice. The results indicate that there has been only a 21% decrease in hospitalizations. It therefore appears that adoption of clinical study results into clinical practice may occur over a long timescale.

The first trial to show that outpatient treatment of deep venous thrombosis (DVT) is safe and effective was published in 1996, and several trials have since confirmed this finding. To investigate the impact of these results on clinical practice, Stein and colleagues tracked the timeline of evidence for the outpatient treatment of DVT patients. The authors used the National Hospital Discharge Survey to determine the number of patients with a principal diagnosis of DVT discharged from short-stay hospitals in the US between 1979 and 2006. The proportion of patients managed on an outpatient basis began to rise after the first publication concerning home treatment of DVT and continued to increase over the years, but the total proportion of patients assigned to home therapy remained very modest (21–25%). Eleven years after the scientific demonstration of the effectiveness and safety of outpatient treatment for DVT, there was only a 21% decrease in hospitalizations in this nationwide registry.

This study indicates that a long time span may be required before clinical study results are adopted into clinical practice. The factors responsible for this delay might range from the hesitancy of treating physicians to implement study findings in clinical practice, to local issues related to reimbursement or a lack of awareness about clinical trial results and guidelines.

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**Catheter-directed thrombolysis of lower limb thrombosis**


This work adds to the limited number of reviews on the methods, safety, and clinical efficacy of endovascular treatment for suprapopliteal deep venous thrombosis (DVT). Findings suggest iliofemoral DVT can be treated with endovascular therapy using catheter-directed thrombolysis or mechanical thrombectomy. However, the extent to which the incidence of post-thrombotic syndrome can be lowered by active endovascular treatment will need to be investigated in further trials.

Thrombotic occlusion of lower-limb veins has traditionally been treated with anticoagulation and compression stockings. Significant late complications in patients undergoing conservative treatment include venous stasis ulcers, which occur in up to 15% of patients. Substantial refinements in dedicated catheter technologies have recently improved endovascular options for the treatment of deep venous thrombosis (DVT). The scientific body of evidence with regard to the clinical benefits of endovascular clot removal after lower limb thrombosis has begun to accumulate.

In the current article, Pianta and Thomson review the methods, safety, and clinical efficacy of endovascular treatment for suprapopliteal DVT. Endovascular options for lower-limb DVT include catheter-directed thrombolysis, pulse-spray lysis,
and the use of various mechanical embolectomy devices. Catheter-directed thrombolysis involves application of the lytic agent directly at the site of thrombosis. The pulse-spray technique was developed to increase penetration of the lytic agent into the thrombus. In contrast, mechanical devices have the potential to lower the thrombus burden by allowing interventional removal of the clot.

To date, academic scrutiny of the above-mentioned techniques has been scarce. One randomized study on endovascular intervention plus anticoagulation versus anticoagulation alone [1] was reviewed in the previous issue of this journal (Adv Venous Arterial Thrombosis 2011;1[1]:31). In addition, various single-arm trials assessing pharmacomechanical thrombolysis have reported high technical success and low complication rates. Considering that the clinical endpoint definitions applied in the published literature exhibit vast heterogeneity, a direct comparison of study data is currently very challenging.

Reviewing the available data, Pianta and Thomson conclude that iliofemoral DVT can be safely and successfully treated by endovascular therapy using catheter-directed thrombolysis and/or mechanical thrombectomy. The extent to which the incidence of post-thrombotic syndrome can be lowered by active endovascular treatment will have to be determined in randomized trials. The ATTRACT (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis) trial started enrollment in 2009 and is still recruiting participants. In addition, the ULTIMA (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism) study, which is also recruiting, will investigate the clinical utility of ultrasound-enhanced local thrombolysis in patients with pulmonary embolism.


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**Mechanical thrombectomy of an infected deep venous thrombosis: a novel technique of source control in sepsis**


The authors describe a case of extensive septic thrombophlebitis with septic pulmonary emboli arising from a lower-limb deep venous thrombosis (DVT) in a 24-year-old man with a history of chronic intravenous drug abuse and recurrent lower-limb DVT. The patient was successfully managed in a minimally invasive manner utilizing mechanical extraction thrombectomy.

Septic thrombophlebitis and pulmonary emboli are life-threatening complications of deep venous thrombosis (DVT). The generally recommended treatment consists of broad-spectrum antibiotics, anticoagulation, and occasionally thrombolytic therapy. If these conservative approaches fail, surgical removal of the infected thrombus is a last resort. Considering the invasiveness of surgery, removal of the infected thrombus via endovascular means is an attractive treatment option.

Sulaiman and colleagues describe the case of a 24-year-old man with a history of chronic intravenous drug abuse and recurrent lower-limb DVT. The patient presented with a swollen leg, pleuritic chest pain, shortness of breath, and general malaise. Further investigation revealed multiple septic pulmonary emboli originating from a thrombus in the external iliac and femoropopliteal vein. The patient continued to deteriorate after systemic anticoagulation and parenteral antibiotics, entering septic shock.

The authors decided to perform percutaneous mechanical thrombectomy. A 6 Fr sheath was placed after puncture of the popliteal vein. Simultaneously, an infrarenal inferior vena cava filter was placed over a 10 Fr access through the left internal jugular vein. Mechanical thrombectomy was performed via the popliteal vein and effluent was removed for culture. The vein was then angioplastied. Subsequently, a large clot was noted in the inferior vena cava filter and the filter left in situ. The clinical course of the patient improved substantially 2 days after endovascular therapy.

This case demonstrates that DVT associated with septic shock may be treated in a minimally invasive manner utilizing endovascular means in selected patients in whom conservative measures alone do not lead to clinical improvement. Considering ongoing technical innovations, it is likely that endovascular treatment modalities will complement open surgical strategies in the near future.

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**PREGNANCY**

**Rate of wound complications with enoxaparin use among women at high risk for post partum thrombosis**


This investigation sought to estimate wound complications related to post-cesarean thromboprophylaxis with
enoxaparin. The findings suggest wound-related complications are greater in the enoxaparin-treated individuals compared with enoxaparin-naïve individuals regardless of cofounding factor such as age and weight.

Thromboprophylaxis during the post partum period is a known effective prevention for development of embolic events in women who are at a high risk of thromboembolism. However, to date, no adequately powered clinical trial of thromboprophylaxis after cesarean section is available to thoroughly evaluate the risk–benefit ratios. Therefore, the aim of the present study was to estimate the rate of wound complications associated with post-cesarean enoxaparin thromboprophylaxis. The study was designed as a retrospective, observational investigation in a cohort of 1677 pregnant women at moderate or high risk for thromboembolism (age >35 years and/or body mass index [BMI] >30 kg/m²) who underwent cesarean delivery.

Of the 1677 study participants, 653 (39%) received enoxaparin as thromboprophylaxis and 1024 (61%) did not. Data regarding post-delivery wound complications (wound separation, hematoma, or rehospitalization) were recorded for the first 3 months after cesarean delivery. More wound-related complications resulting in more hospitalizations were observed in the enoxaparin-treated group than in the enoxaparin-naïve group (composite endpoint 8.5% vs. 4.7%; p=0.002). Specifically, more wound separations (6.8% vs. 3.6%; p=0.003) and more frequent rehospitalizations (2.1% vs. 0.8%; p=0.017) were noted in the enoxaparin-treated group. Furthermore, in an adjusted analysis controlling for the confounding effects of maternal age, BMI, chronic hypertension, and pregestational diabetes mellitus, an independent association was observed between enoxaparin use and wound complications (composite endpoint odds ratio [OR] 1.69, 95% confidence interval [CI] 1.12–2.56; p=0.01); this was mainly driven by rates of wound separation (OR 1.66, 95% CI 1.03–2.66; p=0.04). Finally, an interaction effect was noted between enoxaparin use and BMI regarding study outcome; that is, the rate of wound separation was higher in the enoxaparin-treated group only among the morbidly obese patients (BMI >35 kg/m²).

The findings of the present study may have a clinical application, as they identify a higher rate of wound complications associated with enoxaparin use post-cesarean delivery, especially in severely obese women. However, there are several potential weaknesses in this study that need to be addressed. Firstly, it was not sufficiently powered to detect significant differences in thromboembolic events; therefore, a risk–benefit analysis cannot be performed. Secondly, no information is given regarding the grounds on which enoxaparin was not prescribed in women who were otherwise indicated to receive such a treatment. Furthermore, the reported follow-up interval data were only documented for 64% of the cases. Finally, no specific data are given regarding the incidence of other thromboembolic precipitative factors (such as previous thromboembolism, history of abortions, or coagulation disorders), rendering a selection bias possible.

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### STROKE PREVENTION IN ATRIAL FIBRILLATION

**Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation**


The authors of the present work extracted data from trials of anticoagulant therapy in order to estimate the cost-effectiveness of dabigatran compared with warfarin for the prevention of stroke in atrial fibrillation patients. The results show that for patients aged ≥65 years at increased risk for stroke, dabigatran may be a cost-effective alternative to warfarin. However, this will be dependent on local pricing.

Atrial fibrillation (AF) is the second most common cardiovascular disease condition in the US and affects at least 2.5 million US citizens. AF patients who are not treated with anticoagulation have an annual stroke incidence of 4.5%. Thus, AF accounts for 15% of the 700,000 annual strokes in the US, resulting in annual direct and indirect costs of nearly US$58 billion.

The multicenter RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial reported that dabigatran, an oral direct thrombin inhibitor, at a dose of 110 mg twice daily, was associated with very similar rates of stroke and systemic embolism to warfarin, but lower rates of major hemorrhage. Dabigatran 150 mg twice daily was also associated with lower rates of stroke and systemic embolism than warfarin, but had similar rates of major hemorrhage. Thus, dabigatran is the first direct thrombin inhibitor with proven comparable potency in terms of stroke prevention in AF patients.

Freeman and colleagues extracted data from the RE-LY trial and other anticoagulation studies to estimate the cost-effectiveness of dabigatran 110 mg twice daily compared with warfarin (targeted international normalized ratio 2–3) for stroke prevention in AF patients aged ≥65 years, based on prices in the UK. Outcome measures included quality-adjusted life years (QALYs) and costs (in 2008 US$).
The quality-adjusted life expectancy was 10.28 QALYs with warfarin and 10.70 QALYs with dabigatran. Total costs were US$143 193 for warfarin and US$164 576 for dabigatran. Thus, the authors concluded that dabigatran may be a cost-effective alternative to warfarin in AF patients aged ≥65 years at increased risk for stroke, depending on the scheduled pricing in the US.

It should be noted, however, that the event rates used to calculate cost-effectiveness in the present study were derived from a single trial and extrapolated to 35-year follow-up from clinical trials with approximately a 2-year follow-up. Moreover, prices will vary between countries, thereby calling into doubt the generalizability of the study findings. Further studies are required to assess the cost-effectiveness of this novel anticoagulant drug.

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Clinical signs in the diagnosis of deep vein thrombosis


Many clinical signs are known to be associated with deep venous thrombosis (DVT). The present study sought to investigate the clinical importance of 15 of these signs, with the results suggesting a modified Well’s score could be of use for the diagnosis of DVT.

Deep venous thrombosis (DVT) is a common disease that may be associated with life-threatening conditions such as pulmonary embolism. It is therefore important to make the correct diagnosis even if no technical laboratory equipment is available. More than 15 different clinical signs are considered disease-specific for the presence of DVT. To date, however, the actual clinical importance of these individual clinical signs for the diagnosis of DVT has not been examined extensively. The diagnostic performance of 15 different clinical signs of DVT was assessed in the present study, which was designed as a prospective, case-control observational, double-blind investigation.

A total of 204 patients with suspected DVT were recruited. DVT was confirmed in 62 patients. Several clinical signs such as swelling of extremities, cyanosis, pain in the extremities, Payr’s sign, Homan’s sign, and others, were assessed, giving a total of 15 different clinical signs. The negative predictive value (NPV) of the signs ranged from 69–83% with “muscle hardening” having the highest NPV. The positive predictive value (PPV) was lower and ranged from 30–55% with the “cyanotic discoloration” sign having the highest PPV. Multivariable modeling showed that combining different clinical signs yielded a greater diagnostic accuracy with “muscle hardening”, “Meyer’s sign”, and “swelling of the ankle” being the most influential variables. Incorporating these two clinical variables, muscle hardening and Meyer’s sign, as well as their absence, into Well’s score for DVT further improved the diagnostic performance of the established model.

The findings may have a clinical application as they suggest a modified Well’s score may have utility for the diagnosis of DVT. However, certain issues should be taken into account before interpreting the results of the present study. Firstly, the study population was rather small for a complex diagnostic model. Secondly, although the study was double blind, no data are reported regarding the reproducibility of the clinical signs under investigation between clinicians. Finally, reclassification analysis and classification regression-tree analysis would be required in order to prove the additive predictive value of the proposed modified Well’s score for DVT.

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The diagnostic yield of D-dimer in relation to time from symptom onset in patients evaluated for venous thromboembolism in the emergency medicine department


The present study sought to establish whether the diagnostic yield of D-dimer level testing is related to the onset time of venous thromboembolism symptoms. The results show that the diagnostic efficacy of D-dimer level assessment is lost after 1 week from symptom onset.

The assessment of D-dimer levels in the evaluation of patients suspected of having acute venous thromboembolism (VTE) is an established clinical practice. However, the association of its diagnostic yield with the time-onset of symptoms has not been assessed adequately. The present study was a retrospective, observational case–control study that recruited 734 patients presenting with symptoms and signs of possible VTE. In each of the study patients, D-dimer levels were assessed, and also an objective test to identify/eliminate pulmonary embolism (PE) or deep venous thrombosis (DVT) was performed. The authors included only patients for whom data regarding the time of onset (in days) of symptoms that were relevant for the appearance of the thrombotic event were available. Of this cohort, a positive objective test for either DVT or PE, or both, was noted in 197
individuals. The other 557 patients who had a negative objective test (no DVT or PE) were considered as controls. No difference was noted between patients and controls regarding background disorders except for a higher prevalence of malignancies in the patients as opposed to the controls. A clear decline in the predictive ability of D-dimer levels was evident from day 6 onwards after symptoms onset in a receiver operating curve analysis.

The finding of the present study that the D-dimer concentrations lose their diagnostic potential after 1 week from the onset of symptoms may have clinical implications regarding their diagnostic use. The time from onset of symptoms employed in previous studies may explain the observed variation in reported sensitivities and specificities between these numerous VTE studies. Nonetheless, there are several limitations that must be taken into account before interpretation of the results of the present study. Firstly, the study was retrospective in nature and thus there was no unified questionnaire used regarding symptom onset. Secondly, the time-frame analysis conducted was subject to restrictions in terms of determining the variation of events over time. Finally, and more importantly, the exclusion of patients who presented with suspected VTE and who had a negative D-dimer test and were subsequently discharged without having an objective test, is highly suggestive of a selection bias that may have influenced the results.

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**RISK STRATIFICATION**

**Low vegetable intake is strongly associated with venous thromboembolism in Thai population**


This case–control study was performed to study the effects of dietary and behavioral factors that may contribute to the occurrence of venous thromboembolism (VTE). Interestingly, the authors conclude from their data that low vegetable consumption is significantly associated with symptomatic VTE.

This case–control study was conducted to study the effects of dietary and behavioral factors that may contribute to the occurrence of venous thromboembolism (VTE) in a Thai population. Cases were patients aged >15 years (mean age 57 years, 70% female) with objectively confirmed deep venous thrombosis of the legs or pulmonary embolism. Of 473 potential candidates, 296 were excluded based on predefined criteria, including underlying malignancy, previous arterial cardiovascular disease, antiphospholipid syndrome, and failure to provide informed consent. Age-matched and sex-matched controls (mean age 53 years, 70% female) were recruited as part of national health surveys and had no underlying disease. In total, 97 cases and 195 controls were selected for the study.

In addition to the assessment of extended baseline characteristics, all cases and controls were presented with a food frequency questionnaire. In a univariate analysis, cases consumed significantly fewer vegetables, fish, and spicy food than controls, with odds ratios [ORs] for VTE of 3.74 (95% confidence interval [CI] 2.2–6.3), 2.05 (95% CI 1.2–3.4), and 2.30 (95% CI 1.3–4.1), respectively. Moreover, VTE was associated with more established risk factors such as estrogen use and obesity. Upon multivariate analysis, low vegetable consumption (OR 3.74, 95% CI 1.9–7.6), female hormones (OR 5.8, 95% CI 1.5–22), and body mass index were found to be independently associated with VTE.

Although several methodological issues including patient selection, data gathering, and extended correction for potential confounders, can be raised, which would complicate correct interpretation of the presented data, the outcome is nonetheless interesting and deserves future study to further and more accurately establish the association between dietary factors and VTE in Thai as well as Western patients.

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**Usefulness of computed tomographic pulmonary angiography in the risk stratification of acute pulmonary thromboembolism. Comparison with cardiac biomarkers**


This study shows that, in addition to high sensitivity and specificity for the diagnosis of acute pulmonary embolism (PE), computed tomography pulmonary angiography is useful for risk stratification of patients with established PE by assessing embolus load and right ventricular function.

This study was the imaging test of choice in patients suspected of acute pulmonary embolism (PE) with an indication for CTPA, i.e. likely clinical pretest probability and/or elevated D-dimer blood concentration.
According to this study, in addition to high sensitivity and specificity for the diagnosis of acute PE, CTPA is useful in the risk stratification of patients with established PE via assessing embolus load and right ventricular function. The latter was previously shown to be an important marker of clinical outcome after PE [1].

In total, 80 consecutive patients with CTPA-proven PE were stratified for the presence of right ventricular dysfunction on transthoracic echocardiography. In 49 patients with and 31 patients without right ventricular dysfunction, several CTPA variables were assessed and compared: the ratio of right to left ventricular dimension, CT index of pulmonary artery clot load, contrast reflux to the inferior vena cava, and ventricular septal bowing. In addition, N-terminal-pro-brain-type natriuretic peptide, troponin, and high sensitivity C-reactive protein, all established prognostic relevant biomarkers in PE patients, were measured. The authors describe clear differences between CT variables in the patients with and without echocardiographic right ventricular dysfunction: increased right to left ventricular dimension ratio, high clot load, and contrast reflux were significantly more prevalent in the right ventricular dysfunction group. Furthermore, the same CT parameters showed clear positive correlation with all three measured biomarkers.

With these results, CTPA appears to be useful not only in the diagnosis, but also in the risk stratification of patients with PE. This might prove particularly useful when selecting PE patients without CT signs of right ventricular dysfunction, and thus favorable prognosis, for outpatient treatment. Nonetheless, although several retrospective and prospective cohort studies have shown the potential patient and cost benefits of outpatient treatment, randomized controlled clinical trials to prove the safety of such a strategy are lacking. Consequently, at this time outpatient treatment of patients with acute PE cannot yet be recommended.


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**Incidence and predictors of intracranial hemorrhage after minor head trauma in patients taking anticoagulant and antiplatelet medication**


In this study, the authors investigated whether computed tomography (CT) of the head was justified in minor head trauma patients on clopidogrel or warfarin. The results suggest that loss of consciousness is a predictor for positive CT findings.

Minor head trauma is one of the most common causes for accident and emergency department visits. The number of patients taking antiplatelet, anticoagulation, or a combination of both therapies, is increasing, especially among elderly patients who are at an increased risk of fall. The indications for head computed tomography (CT) in trauma patients, particularly those suffering from minor head injuries and on antithrombotic treatment, are still being debated. The present study was a retrospective, observational investigation of the diagnostic yield of head CT for intracranial hemorrhage in patients suffering minor head trauma who had a score of 15 on the Glasgow Coma Scale (GCS) and who were on clopidogrel or warfarin.

A total of 141 patients, mean age 79 years, were included in the study. In all, 84 patients were being anticoagulated with warfarin, 21 were receiving combination therapy (warfarin and aspirin, n=18; warfarin and clopidogrel, n=2; or warfarin, clopidogrel, and aspirin, n=1), and 36 patients were on antiplatelet therapy (clopidogrel, n=15; clopidogrel and aspirin, n=21). A total of 41 (29%) patients were diagnosed with intracranial hemorrhage. Of these, 19 patients had subdural hematoma, 14 had subarachnoid hemorrhage, five had cerebral contusions, and three suffered multiple types of intracranial hemorrhage. The frequency of a positive CT finding with regards to anticoagulation, antiplatelet, or combined therapy was 27%, 41%, or 14%, respectively, with differences between these frequencies not reaching statistical significance. Among various presenting characteristics such as age, gender, presenting international normalized ratio and partial thromboplastin time, external evidence of injury above the shoulders, and type of medication (warfarin, aspirin, or clopidogrel), only loss of consciousness (LOC) was a predictor for a positive CT result.

The findings of the present study have potential clinical implications. The study suggests that in patients on antithrombotic therapy suffering minor head trauma, especially those with LOC despite a GCS score of 15, a head CT should be strongly considered. However, this study is inherent to certain limitations. According to the authors, a selection bias may have been present because the patients enrolled did not represent emergency trauma room “all comers” but rather patients likely suffering from a greater overall trauma. Furthermore, patients on aspirin alone or an antiplatelet drug other than clopidogrel were not included in the study, thus weakening the generalizability of the results. Finally, as acknowledged by the authors, their analysis was limited by the relatively small number of patients and by the retrospective study design.
Familial risk of venous thromboembolism: a nationwide cohort study


Sørensen et al. investigated the risk of venous thromboembolism (VTE) in siblings of patients with VTE, in order to study the influence of genetic factors on VTE development. A family history of VTE was found to be a potential risk factor for the condition.

It is well known that genetic factors contribute to an increased risk of venous thromboembolism (VTE). The majority of these factors are mutations and polymorphisms in genes coding for coagulation properties. Only a few, inadequately powered, studies have investigated familial aggregation to measure the extent of genetic disposition. The reported results of the aforementioned studies were also subject to various biases and were found to be inconclusive. The present study sought to estimate the relative risk of VTE in siblings of affected patients. The study was designed as a retrospective, case–control, nationwide (Denmark) cohort study.

The authors identified 19,599 patients with a first diagnosis of VTE from the years 1977 to 2009, with 30,179 siblings followed for 210,160 person-years. The authors estimated the standardized incidence ratio (SIR), corresponding to the number of cases among siblings divided by the number of expected cases according to the incidence rate in the general population. The overall incidence of VTE in the siblings of VTE cases was 2.2 cases per 1000 person-years compared with 0.7 cases per 1000 person-years in the general population. This translated to a three-fold increased risk (age-adjusted and sex-adjusted SIR of 3.08, 95% confidence interval 2.80–3.39). The risk did not differ substantially between gender or clinical presentation of the index event (pulmonary embolism vs. VTE).

The present study identifies family history as a potential risk factor for VTE, suggesting a genetic predisposition. However, familial clustering of environmental exposures, lifestyles, and behaviors may still have played a role in the increased risk of VTE among siblings of cases with a previous VTE. In addition, the present study did not study specific genetic factors such as antithrombin deficiency, protein C and S disorders, Factor V Leiden, and thrombin/prothrombin mutations, nor did it evaluate specific environmental factors such as obesity, smoking, prolonged travel, and shared acute illnesses. Another potential limitation is its retrospective nature, which relied on registry reported diagnoses that may not be sufficiently accurate. Finally, the clinical utility of the present findings is also debatable. To date, it is unclear whether testing for genetic factors among relatives with a history of DVT, or indeed taking preventative measures, will improve clinical outcomes.

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STENT THROMBOSIS

Multicenter randomized trial evaluating the efficacy of cilostazol on ischemic vascular complications after drug-eluting stent implantation for coronary heart disease: results of the CILON-T (Influence of Cilostazol-based Triple Antiplatelet Therapy on Ischemic Complication after Drug-eluting Stent Implantation) trial


Despite dual antiplatelet therapy, patients after percutaneous coronary intervention with application of drug-eluting stents (DESs) still suffer from in-stent stenosis, likely because of enduring high platelet reactivity. These authors found that triple platelet therapy including cilostazol, a selective inhibitor of type 3 phosphodiesterase, reduced platelet reactivity but did not show superiority in reducing the composite of ischemic events after DES implantation compared with standard antiplatelet therapy with aspirin and clopidogrel.

In order to study the effect of triple antiplatelet therapy using cilostazol in addition to the standard double platelet regimen in patients with drug-eluting stents (DESs) after percutaneous coronary intervention, the current authors performed an open-label randomized clinical trial including 960 patients with angina pectoris or a positive stress test, and native coronary artery lesions for which DES implantation was appropriate. Patients were recruited from five South Korean centers. After being randomly assigned to one of the two treatment arms, patients were followed for 6 months for a composite endpoint of adverse cardiovascular events, platelet reactivity, and therapy for side-effects including bleeding. Platelet reactivity was measured with the VerifyNow P2Y12 assay (Accumetrics,
San Diego, CA, USA) at discharge and 6 months after the index procedure. This assay uses ADP and prostaglandin E as agonists to induce platelet activation and ascertain the level of platelet function impaired by medication.

Although platelet reactivity in the triple therapy cohort was significantly lower than in the control group (p<0.001 for both baseline and follow-up measurements), this was not associated with an improvement in cardiovascular prognosis (8.5% vs. 9.2%, respectively, met the primary endpoint defined as composite of cardiac death, myocardial infarction, ischemic stroke, and target lesion revascularization; p=0.74) or an increased bleeding risk (0.4% vs. 0.2%; p=0.51). Interestingly, after Cox proportional hazard analysis, only platelet reactivity and length of primary coronary lesion were predictors of the primary outcome, while the use of cilostazol was not. The latter finding might be explained by the enduring high platelet reactivity in almost one-third of the patients in the triple therapy cohort. It is this hyporesponsive group of patients that perhaps represents the greatest challenge for future studies to improve the post-DES prognosis.

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The annual meeting of the Hemostasis and Thrombosis Research Society (HTRS) was held in Chicago, IL, USA, from April 28–30, 2011. There were 377 registered attendees and 38 speakers. Among the attendees was a substantial group of almost 100 nurses, who attended a pre-conference nurse-oriented program. There were presentations from invited speakers and two keynote speakers from Europe. Selected abstracts were delivered orally and there was also a well-attended poster section. This was the seventh annual meeting and the largest so far.

The HTRS began as an initiative by hemophilia physicians, both hematologists and pediatricians. This is still noticeable as many of those attending the meeting have a “hemorrhagic background”. However, at this year’s conference the presentations and posters not only dealt with hemophilia and other hemorrhagic disorders; there were also several sessions devoted to thrombotic disorders, including one on arterial disease, one on anticoagulant treatment, and another on thrombosis at rare sites (cerebral sinus, splanchnic vein, and retinal vein). The keynote lecture was on the Dutch MEGA (Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis) study, which is the largest trial undertaken on venous thrombosis worldwide.

A remarkable feature of the HTRS is its focus on young physicians and nurses. There were 50 abstracts submitted, with half of them from junior trainees and junior faculty members. HTRS covered the cost of travel for the top eight trainees with the best abstracts. This is in line with the mission of mentoring and encouraging trainees to use the meeting as an opportunity to “get their feet wet”. The small size of the meeting helps not only junior faculty to network with senior colleagues outside of their institution, but also led to animated discussions at many of the sessions. For nurses, one session of the half-day pre-conference meeting was dedicated to aging in hemophilia patients with a discussion of emerging problems such as osteoporosis and chronic viral infections; the second session was devoted to thrombotic nursing issues. In addition, the nurses held a breakfast meeting and a roundtable discussion at lunchtime. The outreach nature of the HTRS was also visible as the organizers made all presentations available to members on the internet.

Several presentations merit discussion. In a session titled “The Good, the Bad and the Slimy,” Jack Ansell (Lennox Hill Hospital, New York, NY, USA) gave an overview of the new synthetic oral anticoagulants, in which he reported on the drugs that have recently been or soon will be released for treatment and prophylaxis of venous thrombosis. He showed the results of several large-scale trials that have been published on these new drugs, and highlighted their advantages, notably the absence of monitoring that is required for vitamin K antagonists. He also addressed the drawbacks, including the absence of methods to reverse these drugs’ actions, as well as the remaining uncertainty regarding hemorrhagic risk.

Mrinal Patnaik (Mayo Clinic, Rochester, MN, USA) moved the audience into the realm of the slimy, and gave a highly entertaining presentation on herpetology (the science of amphibians and reptiles). Using many illustrations, he
discussed the various snake venoms, and their action on human coagulation. Snake venoms have been used for decades in coagulation assays, while more recently leeches’ venom (hirudin) has been developed as a recombinant direct thrombin inhibitor.

The session on unusual thromboses was extremely informative, and overviews on the incidence, prognosis, and management of these events were given. Robert McBane (Mayo Clinic, Rochester, MN, USA) presented on cerebral sinus thrombosis, Ayalew Tefferi (Mayo Clinic) on splanchnic vein thrombosis, and Michael Ip (University of Wisconsin–Madison, Madison, WI, USA) on retinal vein thrombosis. Although marked progress has been made in our understanding of these thrombotic disorders (e.g. the high prevalence of JAK2V617 mutation in patients with portal vein thrombosis and Budd–Chiari syndrome), the treatment of these rare thromboses still suffer from a paucity of data.

“The session on unusual thromboses was extremely informative, and overviews on the incidence, prognosis, and management of these events were given”

One of the sessions on the hemorrhagic side of the spectrum was devoted to studies on new products in hemophilia and rare bleeding disorders. Margaret Ragni (University of Pittsburgh, Pittsburgh, PA, USA) clearly outlined the problems that are facing us in the near future. Hemophilia is a rare disease, with a prevalence of around 1 per 10,000. Rare bleeding disorders (i.e. deficiencies of fibrinogen, Factor V, Factor X, and Factor XIII) have prevalences that are at least tenfold lower than hemophilia. Patents for the first generation of recombinant products for hemophilia will soon expire, which will open the market for concentrates from more manufacturers. Moreover, recombinant techniques allow the development of altered molecules that may have a longer-half life or reduced risk of inhibitor development. At the same time, concentrates will become available for rare bleeding disorders, some of which are still treated with plasma. The problem is how to clinically test the efficacy and safety of these products, as there are so few patients. This will require the use of innovative statistical methods and action, both from physicians and regulatory institutions to prioritize which products are studied. To put it bluntly, if the number of available patients allows only one product to be tested, and one offers no potential benefits over existing concentrates while another does, should not the first one be excluded from further clinical studies?

Charity Moore (University of Pittsburgh) presented an overview of innovative study designs and statistical methods that could help solve these issues, which to a large extent apply to all so-called orphan diseases. She discussed a variety of approaches, such as cross-over studies (including n=1 studies), sequential designs, and adaptive allocation. A major hurdle is that these methods will work well for questions of efficacy, but much less well for safety questions: for example, inhibitor development occurs in fewer patients than the effects of hemorrhage control, as side-effects are invariably more rare than intended effects, and are irreversible, so cannot be studied in cross-over designs. Val Bias, from the US National Hemophilia Foundation, presented the patient’s view on clinical trials of new concentrates. On the one hand, patients with hemophilia show a remarkable willingness to participate in such trials from an altruistic perspective. On the other hand, many are content with the product they use, and reluctant to face the risk of inhibitor development, which several have witnessed in their families or friends. What was missing in this session was a regulators’ perspective.

Both in Europe and the USA, new drugs can be licensed when they show efficacy that is equal or superior to existing products, and a risk profile that is not markedly inferior. While one may argue that this is contrary to progress in all medical fields, and stimulates the pharmaceutical industry to invest in best-selling “me-too” drugs, it will be an untenable practice for orphan drugs because of the paucity of patients available to test new products. As the near future may bring us concentrates that are truly superior to existing ones, I believe that including patients in trials of concentrates that do not have a clear superiority potential, thereby barring the investigation of potentially superior drugs, is unethical. Regulators may choose to recognize this, and not allow registration trials of “me-too” concentrates.

“The problem is how to clinically test the efficacy and safety of these products”

When there are several hundred physicians in one room, clinical sessions are always lively. This was certainly the case for the session titled “Case corner: bleeding disorder dilemmas”. In this session, Amy Shapiro (Indiana Hemophilia and Thrombosis Center, Indianapolis, IN, USA) discussed the work-up and treatment of acquired hemophilia (neutralizing antibodies directed towards coagulation factors in non-deficient individuals), Mark Reding (University of Minnesota, Minneapolis, MN, USA) spoke on the management of acute coronary syndrome in a patient with Von Willebrand’s disease, Honorio Benzon (Northwestern University Feinberg School of Medicine, Chicago, IL, USA) on the use of epidural catheters during delivery in women using heparin, Leonard Valentino (Rush University Medical Center, Chicago, IL, USA) reviewed radiosynovectomy in hemophilic arthropathy, and Nigel Key (University of North Carolina at Chapel Hill, Chapel Hill, NC, USA) joined the two sides of the hemostatis balance by discussing venous thrombosis prevention during major surgery in hemophilic patients.
The two keynote lectures were given by Erik Berntorp (Malmö Centre for Thrombosis and Haemostasis Malmö, Sweden), on immune tolerance therapy in hemophilia patients with inhibitors, and Frits Rosendaal (Leiden University Medical Center, Leiden, The Netherlands), on venous thrombosis etiology.

From the perspective of a foreigner, it is surprising that there is not, like in virtually all countries in Europe, a national society on thrombosis and hemostasis in the United States. There are many meetings on the subject in the US, such as Gordon Research Conferences, Arteriosclerosis, Thrombosis, and Vascular Biology meetings, and the Anticoagulation Forum, and several organizations have embraced hemostasis and thrombosis with an enthusiasm that has fluctuated over time, but generally the overall view is disjointed. Therefore, I approached Peter Kouides (Rochester, NY, USA), president of the HTRS, and posed the question whether the US is in need of a national society and whether the HTRS could fill the void. Dr Kouides said “Since we added 7 years ago thrombosis to our masthead and replaced hemophilia with hemostasis, I would like to think that we are filling that void with a tripartite mission focused on education, mentoring, and research”. I also asked him whether he planned to compete with existing national and international organizations, such as ASH, AHA, WFH, and ISTH, Dr Kouides said “There will always be local and national issues that will require a ‘grass roots’ approach. In this final year of my presidential tenure, I look forward to working with leaders of these organizations, including you, to decide what issues require an across the board response”. Finally, I asked him how he sees the future of research in the field in the USA; he replied “The present financial crisis in the US with the irrational and perverse response of many lawmakers who claim we can stimulate the economy by further cutting taxes and that in turn this would have to be offset by very sizable reductions in governmental funding for programs including clinical care (e.g. the dismantling of Medicare) and research (reduction of Centers for Disease Control and Prevention and National Heart, Lung, and Blood Institute funding) is a call to action for all of us, to advocate continued patient care and funding. Along those lines, next year our annual meeting will combine forces with at least eight other North American Hemostasis and Thrombosis organizations in the hope of increasing the power of advocacy. Such an alliance should be an excellent opportunity”.

Disclosure

Dr Rosendaal has no competing financial interests to disclose.
Thrombosis Management 2011: A Time for Change

Barcelona, Spain, June 17–18, 2011

Thrombosis Management 2011, supported by an unrestricted educational grant from Bayer, was attended by >700 delegates from 52 countries – a truly international audience. The plenary lectures focused on clinical outcomes, taking data from contemporary clinical trials with novel agents and putting them into context for real-life clinical practice.

**Acute coronary syndromes**

**Acute pharmacological management**

The accurate diagnosis of myocardial infarction (MI) is important for outcomes, and troponin is known to be a useful diagnostic marker in MI. However, as assays for troponin release have become more sensitive, the question has arisen as to whether these assays are indeed detecting real disease. Keith Fox (University of Edinburgh, Edinburgh, UK) presented data from his group that addressed this question. In a prospective, observational, single-center study, they found that lowering the diagnostic threshold of plasma troponin from 0.2 ng/mL to 0.05 ng/mL was associated with major reductions in morbidity and mortality rates [1].

At the meeting, Professor Fox discussed newer therapies such as prasugrel and ticagrelor, which have been associated with good efficacy in several major studies (e.g. TRITON-TIMI 38 [Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in MI 38] and PLATO [Platelet Inhibition and Patient Outcomes]) [2,3]. Despite these good efficacy data, Professor Fox noted increased bleeding events with the newer drugs and highlighted the importance of optimizing the balance between efficacy and safety. Individual patient risk stratification, he said, should be part of the decision-making process, recognizing the risks of bleeding. Strategies to reduce bleeding complications are as follows:

- Define the risk–benefit in each individual (risk score).
- Avoid over-dosing (use the lowest effective dose).
- Use radial rather than femoral vascular access.
- Avoid switching antithrombotic agents (unless proven) and double dosing.

**Secondary prevention**

Secondary prevention strategies in patients who have survived acute coronary syndromes (ACS) include smoking cessation, aspirin plus clopidogrel, β-blockade, lipid management (statins), and blood pressure management (angiotensin-converting enzyme inhibitors [ACEIs]). However, even with the optimal application of evidence-based strategies, ischemic events recur in >10% of patients in the first year after ACS. Freek Verheugt (University Medical Centre of Nijmegen, Nijmegen, The Netherlands) looked at the possible reasons behind this high event rate, initially focusing on stent thrombosis.

The CURRENT-OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions 7) trial compared standard with higher-dose clopidogrel (300-mg loading dose on day 1 followed by 75 mg once daily until day 30 vs. 600-mg loading dose followed by 150 mg once daily for 7 days then 75 mg once daily until day 30) [4]. The higher dose was associated with a significant reduction (15%) in death, MI, and stroke in the subgroup of patients who underwent percutaneous coronary intervention (PCI). One of the mechanisms of improvement was the nearly 50% reduction in stent thrombosis in the first 30 days with high-dose clopidogrel. TRITON-TIMI 38 reported similar results with prasugrel [2] as did PLATO with ticagrelor [5]. Of note, these drugs exert their effect in the short-term so should be given immediately (within early hours of) ACS onset.

These results indicate that clopidogrel, the current standard of care, will be supplanted by the stronger inhibitors prasugrel and ticagrelor in the near future. The choice of agent in an individual patient depends on the balance between the risk of stent thrombosis and the risk of bleeding. Research is continuing into new therapeutic targets and regimens.
Dr Verheugt also addressed the issue of coronary surgery after ACS. The PLATO trial in patients with ACS undergoing coronary artery bypass grafting (CABG) found an advantage for ticagrelor over clopidogrel in this setting, without an excess risk of CABG-related bleeding [6].

**Anticoagulants in secondary prevention**

Thrombin–platelet interaction plays a central role in arterial thrombus formation, providing a rationale for the use of anticoagulation for secondary prevention in ACS. Harald Darius (Vivantes Neukoelln Medical Centre, Berlin, Germany) presented data on the clinical efficacy of combined antiplatelet and anticoagulant treatment, which he described as “still not satisfying”.

Recent data on bleeding rates with triple therapy have been reported from the RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial, which looked at the prevention of stroke in atrial fibrillation (AF) patients [7]. Patients given triple therapy of an anticoagulant (warfarin or the direct thrombin inhibitor dabigatran) plus aspirin and clopidogrel experienced an average increase of 1.8% in severe bleeding or major bleeding complications versus anticoagulant alone.

“The clinical efficacy of combined antiplatelet and anti-coagulant treatment is still not satisfying”

Apixaban has been investigated in the APPRAISE-1 (Apixaban for Prevention of Acute Ischemic Events-1) and APPRAISE-2 trials [8]. Both trials were reportedly interrupted because of an increased rate of bleeding complications, mainly related to the administration of triple therapy (with aspirin and clopidogrel). The APPRAISE-2 results are expected to clarify the reason for the increase in the bleeding complication rate.

Rivaroxaban has been investigated in the dose-finding ATLAS-TIMI-46 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin Without Thienopyridine Therapy in Subjects with Acute Coronary Syndrome) study [9], which looked at rivaroxaban in combination with either single or dual antiplatelet therapy. Again, the total bleeding complication rate increased in a dose-dependent manner. Despite this, rivaroxaban was associated with a significant 1.6% reduction in the incidents of death, MI, and stroke. Research with rivaroxaban (2.5 mg and 5 mg twice daily) is continuing with the ATLAS-TIMI-51 trial. The results are expected to be reported in 2012.

Finally, Professor Darius presented his personal predictions for the next 5–10 years. He predicted that low- and intermediate-risk patients will be treated with a specific anticoagulant (e.g. rivaroxaban) and specific antiplatelet drug (e.g. ticagrelor), while very-high-risk patients will be treated with aspirin plus a reversible antiplatelet and specific anticoagulant.

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**Prevention of venous thromboembolism**

**Clinical trials in high-risk surgical patients**

A potential benefit for anticoagulant therapy in terms of reducing clinical thromboembolism and perioperative mortality was demonstrated >50 years ago, and studies since that time have proven the benefits of heparins and now oral agents in terms of a reduction in the frequency of both fatal pulmonary embolism (PE) and deep venous thrombosis (DVT).

Novel agents offer potential additional clinical advantages. Professor the Lord Kakkar (University College Hospital, London, UK) focused on trials of rivaroxaban, apixaban, and dabigatran. Rivaroxaban has had the largest evaluation in terms of a Phase III program looking at the prevention of venous thromboembolism (VTE) in patients undergoing elective hip or knee arthroplasty, with more than 12 000 patients randomized across four studies [10–13]. Rivaroxaban consistently showed superiority against enoxaparin for the combined primary efficacy endpoint in all four trials. In addition, pre-specified pooled analyses of three of the trials (>9500 patients) and of all four trials (>12 700 patients) showed a significant reduction in the frequency of VTE plus all-cause mortality in favor of patients randomized to rivaroxaban compared with enoxaparin [14,15]. Overall, rivaroxaban is associated with very convincing data that, Lord Kakkar said, “validate its efficacy and safety, demonstrating a substantial reduction in VTE with some small increase in bleeding”.

VTE is of increasing concern in the cancer population. In those undergoing laparotomy for malignant disease, in-hospital high-dose low-molecular-weight heparin (LMWH; 5000 IU) provided an important reduction in DVT frequency up to day 10 post-surgery, with no significant increase in bleeding [16]. The ENOXACAN II (Enoxaparin and Cancer II) trial has investigated the continuation of prophylaxis into the post-discharge period [16]. Extending prophylaxis for a further 21 days was associated with a 60% reduction in the risk of VTE, compared with in-hospital prophylaxis alone. This benefit was maintained for approximately 3 months after operation.

**Risk in the medically ill population**

In 2004, a study from the RIETE (Registro Informatizado de la Enfermedad Tromboembólica [Computerized Registry of Patients with VTE]) of over 6000 medical and surgical patients with clinically symptomatic VTE complications reported a higher mortality rate, fatal PE risk, and major bleeding rate in medical than in surgical patients [17]. This raises the question: what are the differences in VTE risk between surgical and medical patients?

Sylvia Haas (Technical University Munich, Munich, Germany) addressed this question. The first key difference, she said, is that the onset and duration of risk are less clear in medical than in surgical patients.
The second difference is that medical patients may have an accumulation of VTE risk factors upon hospitalization, and highly increased levels of C-reactive protein and other acute-phase proteins such as fibrinogen and Factor VIII. All three of these parameters have been clearly associated with VTE risk.

Third, bleeding risk (mucosal bleedings) is increased in medical patients, but identifying the bleeding risk can be challenging. The most recently validated score is HAS-BLED (Hypertension, Abnormal Renal or Liver function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio [INR], Elderly [>65 years], Drugs or Alcohol Concomitantly) [18], which was developed for patients with AF under warfarin therapy. It is hoped that some components of the HAS-BLED score (hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile INRs, age >65 years, and concomitant drugs) will be translated into the assessment of bleeding in the broader medical patient population. The components of the HAS-BLED score must now be prospectively evaluated in the medical patient population admitted to hospital.

Finally, acutely ill medical patients may have silent DVT upon admission to hospital.

Clinical trials in the medically ill

Most VTE-associated deaths are due to sudden PE, which is unpredictable, or occur after undiagnosed and untreated VTE, which can be managed with prophylaxis. “Prevention is the cornerstone,” said Alexander T Cohen (King’s College Hospital, London, UK).

Dr Cohen spoke about a number of safe and effective therapies that reduce death from PE: LDH, LMWH, and fondaparinux all have grade 1A evidence for the prevention of VTE in general medical patients [19]. He noted that the risk of VTE continues after the first 2 weeks. However, two studies of longer-term therapy in medical patients – EXCLAIM (Extended Clinical Prophylaxis in Acutely Ill Medical Patients) [20] and MAGELLAN (Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of VTE in Hospitalized Medically Ill Patients Comparing Rivaroxaban With Enoxaparin) [21] – have failed to show a clear benefit–risk advantage. In the MAGELLAN study, 8000 patients (mean age 71 years, median 11 days hospitalization) were randomized to 6–14 days of subcutaneous enoxaparin with oral placebo or 31–39 days of rivaroxaban with subcutaneous placebo. The primary efficacy outcomes were non-inferiority for rivaroxaban at day 10 and superiority at day 35. Rivaroxaban was non-inferior to enoxaparin at day 10 (p=0.0025) and superior to enoxaparin/placebo at day 35 (p=0.0211). There was a 23% reduction in VTE with rivaroxaban, with 19 VTE-related deaths in the rivaroxaban arm and 30 with enoxaparin. Patients experienced more bleeding in the rivaroxaban arm with a relative risk of approximately 2.5 for clinically relevant bleeding, similar to in the EXCLAIM study, although overall bleeding rates were low. Further analysis is ongoing to identify those patients who may derive benefit from thromboprophylaxis with rivaroxaban.

Thromboembolic stroke

Epidemiology, risk factors, and risk stratification

The prevalence of AF is unknown, with estimates in the USA ranging from 2.5 to 6.5 million affected people. It is clear, however, that AF will become far more common in the future, with estimates suggesting it will at least double by 2050 due to the rise in incidence of AF with age. AF increases the risk of death, heart failure, and stroke.

John Camm (St George’s University of London, London, UK) described the CHA_DS2-VASc (Cardiac Failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled] – Vascular Disease, Age 65–74, and Sex Category [Female]) system, which can be used to assess thromboembolic patient risk and has been validated in the Euro Heart Survey [22]. Bleeding risk can be assessed with several scores, including HEMORR_HAGES (Hepatic or renal disease, Ethanol abuse, Malignancy, Older age (>75 years), Reduced platelet count or function, Re-bleeding [Doubled], uncontrolled Hypertension, Anemia, Genetic factors, Excessive fall risk, and Stroke) and HAS-BLED.

Prof Camm then considered another question: how much AF justifies consideration for anticoagulation? “This is one of the most difficult questions faced by physicians”, he said.

Four large registries or trials have looked at patients with pacemakers to assess the precise burden of AF: TRENDS (A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics), ASSERT (Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial), IMPACT (The IMPACT of BIOTRONIK Home Monitoring Guided Anticoagulation on Stroke Risk in Patients With Implanted Dual-Chamber Defibrillators or Cardiac Resynchronization Therapy Devices), and the RATE Registry (Registry of Atrial Tachyarrhythmia/AF Episodes in the Cardiac Rhythm Management Device Population). TRENDS was inconclusive and IMPACT and the RATE Registry are expected to complete in 2014. ASSERT found that patients with ≥6 min of an atrial high-rate episode of >190 bpm had a 2.5-fold increased risk of stroke [23].

Other studies have identified additional factors associated with increased risk of stroke, including higher CHADS2 (Cardiac Failure, Hypertension, Age >75 years, Diabetes, and Stroke [Doubled]) score, left atrial abnormality, complex aortic plaque, and low ejection fraction. Short duration of AF or previous treatment with oral anticoagulants appear to lower the risk. The troponin level may identify at-risk patients,
and other risk factors such as C-reactive protein and brain natriuretic peptide have also been found to play major roles.

Prof Camm concluded with a recommendation from the ESC guidelines (class I, level A): antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those at low risk (lone AF, aged <65 years) or with contraindications.

Anticoagulants for the prevention of thromboembolic stroke in patients with AF

Manesh Patel (Duke University, Durham, NC, USA) described the major goals of therapy in patients with AF as being to decrease the risk of thrombosis and, in the ideal world, decrease the hemorrhagic risk. Today, he said, therapeutics are making meaningful contributions in both directions.

The RE-LY trial, which included over 18 000 patients worldwide, reported that in patients with AF and at least one risk factor for stroke, dabigatran 110 mg twice daily was associated with similar rates of stroke and systemic embolism to warfarin, but with lower rates of major hemorrhage [26]. Dabigatran 150 mg twice daily was associated with lower rates of stroke and systemic embolism than warfarin (34% relative risk reduction), but similar rates of major hemorrhage. Intracranial hemorrhage and hemorrhagic stroke were decreased with both doses of dabigatran.

The AVERROES (Apixaban versus Acetylsalicylic Acid to Prevent Strokes) trial investigated apixaban 5 mg twice daily versus aspirin in 5600 patients with AF and at least one risk factor for stroke who are unable to take a vitamin K antagonist (VKA). Apixaban statistically significantly reduced stroke compared with aspirin (p<0.001) [25]. In addition, the major bleeding rates were similar in the two groups.

Prof Patel described the ROCKET–AF (An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation) trial, which randomized >14 000 patients with AF and moderate to high risk for stroke to rivaroxaban 20 mg/day or warfarin [26]. The primary endpoint of non-inferiority in the protocol population was met, with event rates of 1.7 for rivaroxaban versus 2.2 for warfarin. The rates of clinically relevant bleeding were similar in both groups, with major hemorrhage rates of 3.6 and 3.5 per 100 patient-years in the rivaroxaban and warfarin groups, respectively. Intracranial hemorrhage was statistically significantly reduced with rivaroxaban with a hazard ratio of 0.67, and both fatal bleeding and bleeding into critical organs were also significantly reduced [26]. The group concluded that rivaroxaban is a proven alternative to warfarin for moderate- or high-risk patients with AF. “Rivaroxaban,” Prof Patel concluded, “provides a substantial way forward in these patients.”

In conclusion, Prof Patel said that evidence-based patient-specific decisions require consideration of three factors:

- Patient stroke risk.
- Patient bleeding risk.
- Dose/tolerability to anticoagulant.

Registry data and contemporary clinical practice

Despite good evidence that oral anticoagulants reduce the risk of stroke in patients with AF, there is strong evidence that these agents are underused or misused. Much of this evidence comes from registries, which aim to provide real-world information, as opposed to that from the selected populations enrolled in clinical trials.

Jean-Pierre Bassand (University of Franche-Comté, Besançon, France) noted that despite good evidence for their benefit, the use of VKAs has stayed relatively constant since the late 1990s, with around 60% of patients with documented AF being prescribed warfarin. Furthermore, the registries indicate that time on-target INR varies considerably, with about 50% of time spent off-target [27].

Registries to date have revealed gaps between the evidence and real-life management, particularly with regard to VKAs, and there remains a need for a large sample-size registry incorporating populations with all forms of AF and from all origins. GARFIELD (Global Anticoagulant Registry in the Field), which is targeting 50 000 patients, aims to meet this need. This will provide more information on real-life populations, giving a complete overview of AF, management of AF, prognosis, and much more.

VTE treatment

Henri Bounamaux (University Hospitals of Geneva and Faculty of Medicine, Geneva, Switzerland) provided a historical overview of the rationale for treatment of VTE, and summarized the improvements seen over the last five decades.

Novel agents for the management of VTE

While physicians have concerns regarding monitoring and dose adjustment with VKAs, these are in fact very effective agents that do reduce the risk of VTE. Therefore, most studies of new agents aim to establish non-inferior efficacy rather than superiority.

Harry R Büller (Academic Medical Center, Amsterdam, The Netherlands) discussed the explosion of compounds in this arena, most of which have been marketed for prevention of VTE in orthopedic surgery or AF, but are not yet available for the treatment of VTE.

Idrabiotaparinux is given as a subcutaneous injection once weekly in a fixed dose. It is long-acting but can be neutralized with avidin. Idrabiotaparinux appears to behave similarly to LMWH and VKAs in terms of efficacy, but with less bleeding than its non-biotinylated analog idraparinux [23]. Data from the Cassiopae study of more than 3000 people with PE was
presented as a late-breaking session at the International Society on Thrombosis and Haemostasis (ISTH) meeting in July [29].

Dabigatran etexilate has been investigated in the RECOVER (Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic VTE) study [30]. Dabigatran was non-inferior to warfarin in terms of efficacy, with rates of any VTE of 2.4% and 2.1%, respectively. In addition, it may be associated with less bleeding (including major bleeding), with rates of any bleeding of 5.6% and 8.8%, respectively. The RECOVER 2 study will add more data, which are expected to be presented later this year. Data from a further study, RE-SONATE (Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etxetilate in the Long Term Prevention of Recurrent Symptomatic VTE), which has compared extended-duration dabigatran with placebo, was also presented as a late-breaking session at the ISTH meeting in July [31].

The EINSTEIN DVT (Oral Rivaroxaban versus Standard Therapy in the Initial Treatment of Symptomatic Deep Vein Thrombosis and Long-Term Prevention of Recurrent VTE) study, which enrolled nearly 3500 patients, compared rivaroxaban 15 mg twice daily for 3 weeks, followed by 20 mg once daily, with standard treatment (enoxaparin/VKA) [32]. Recurrent VTE was seen in 3.0% of patients in the standard-treatment arm versus 2.1% in the rivaroxaban arm (HR 0.68, 95% CI 0.44–1.04). This met the non-inferiority endpoint (p<0.001 for non-inferiority; p=0.076 for superiority). A first major or clinically relevant non-major bleeding event was experienced by 8.1% of patients in both arms (HR 0.97, 95% CI 0.76–1.22; p=0.77).

In the extension study, EINSTEIN EXT, patients were continued on rivaroxaban 20 mg for 6 or 12 months. Overall, 7.1% of patients in the placebo arm versus 1.3% in the rivaroxaban arm experienced symptomatic recurrent VTE. This equates to a number needed to treat to prevent VTE of 15 – a figure Prof Büller described as “astonishingly low”. Major and clinically relevant non-major bleeding occurred in 1.2% of placebo patients versus 6.0% of those on rivaroxaban. Further studies, including the EINSTEIN PE study (due to report in March 2012), will help elucidate the role of rivaroxaban.

Prof Büller concluded with his thoughts for the future. “I think the investments we have made in trying to understand the coagulation system have paid off,” he said. “Those of you, including myself, who run anticoagulant clinics better start including myeloproliferative syndrome patients versus 6.0% of those on rivaroxaban. Further study, RE-SONATE (Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etxetilate in the Long Term Prevention of Recurrent Symptomatic VTE), which has compared extended-duration dabigatran with placebo, was also presented as a late-breaking session at the ISTH meeting in July [31].

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Prof Büller concluded with his thoughts for the future. “I think the investments we have made in trying to understand the coagulation system have paid off,” he said. “Those of you, including myself, who run anticoagulant clinics better start reorienting in what we are going to do in the future.”

Contemporary approaches to extended secondary prevention in patients with VTE

The optimal duration of anticoagulation in VTE – and selection of patients who require extended secondary prophylaxis – remain controversial and fascinating problems.

After stopping anticoagulation, patients with active cancer carry a particularly high risk of recurrent VTE, as do patients with chronic medical diseases requiring prolonged immobilization. Others at risk are those with multiple (idiopathic) VTE and antiphospholipid antibody syndrome. Although there is no conclusive evidence from randomized clinical trials, Paolo Prandoni (University of Padua, Padova, Italy) recommended that such patients should be treated with longer-term anticoagulation – consisting of LMWH in subtherapeutic doses in cancer patients, at least as long as the cancer is active – and all anticoagulants in the remaining situations.

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References


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