Advances in Venous Arterial Thrombosis

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

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Sylvia Haas

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Complexity of Venous Thromboembolism Risk in the Medically Ill Population

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Venous thromboembolism (VTE) is a complex disease associated with a broad range of both temporary (exposing) and permanent (predisposing) risk factors. In surgical patients, the onset of the exposing risk can be clearly determined. By contrast, in medical patients, the disease may have been present for an extended period of time, and hence the development of VTE may be advanced at the time of admission. Not only do most hospitalized patients possess at least one VTE risk factor, but the effects of combined risk factors tend to be cumulative. The MEDENOX, PREVENT, and ARTEMIS studies showed statistically significant reductions in VTE in patients who were treated with enoxaparin, dalteparin, and fondaparinux, respectively, compared with placebo. The patients in these studies were all acutely ill, hospitalized medical patients who were at risk for VTE during hospitalization, including patients with congestive heart failure, acute respiratory failure, infections, or inflammatory diseases. They demonstrated relative risk reductions of 47–63% with pharmacological prophylaxis of 6–14 days. VTE can occur because of a failure to administer prophylaxis, administering prophylaxis that is not optimally effective, or failure to continue prophylaxis throughout the period of increased risk. Efforts to increase utilization of prophylaxis in patients who are at risk, and to prolong prophylaxis beyond hospitalization, would benefit from the availability of agents that are effective and safe for long-term prophylaxis in acutely ill medical patients. However, data from the Computerized Registry of Patients with VTE indicate that the bleeding risk in medical patients may be higher than that in surgical patients. Hence, prolongation of pharmacological prophylaxis in acutely ill medical patients may be a challenge. Adv Venous Arterial Thromb 2011;1(3):81–6.

Venous thromboembolism (VTE) is an important healthcare problem as it leads to significant morbidity, mortality, and use of resources [1,2]. Among medical patients who do not receive thromboprophylaxis, the incidence of confirmed hospital-acquired deep vein thrombosis (DVT) is 10–20% [3], and death from hospital-acquired pulmonary embolism (PE) is markedly more common in medical patients than in surgical patients [4].

In addition to their disease-related risks, almost all patients who are admitted to hospital have at least one additional risk factor for VTE [5–11]. Among acutely ill medical patients, patient-related risk factors include increasing age, previous VTE, chronic medication use, chronic disease, pregnancy/postpartum, and obesity, whereas treatment-related risk factors include immobility and central venous catheterization [5–8]. This review will focus on the differences in VTE risk in surgical and medical patients, the classification and characterization of VTE risk in hospitalized and non-hospitalized acutely ill medical patients, and the lessons learnt from VTE prevention studies with short-term and extended use of pharmacological prophylaxis.

Differences in VTE risk between surgical and medical patients

PE and fatal bleeding in surgical and medical patients

The Computerized Registry of Patients with VTE (El Registro Informatizado de Pacientes con Enfermedad TromboEmbólica; RIETE) is a computerized registry coordinated by S&H Medical Science Service (Madrid, Spain) that lists patients with objectively confirmed, symptomatic, acute VTE. Clinical characteristics, details of anticoagulant therapy, and outcomes of all enrolled immobilized medical and surgical patients (postoperative) with acute VTE were analyzed. Of 6160 patients
who were enrolled up to December 2003, 756 (12%) were acutely ill medical patients who had been immobile for ≥4 days, and 884 (14%) were surgical patients who developed VTE within 2 months of surgical intervention. Only 28% of acutely ill medical patients had received thromboprophylaxis, compared with 67% of surgical patients. During the 3-month follow-up period, both fatal PE and fatal bleeding occurred more frequently in acutely ill medical patients than in the surgical patients. These data demonstrate a difference in clinical outcome for surgical and medical patients who are treated for acute VTE, with a more aggressive natural history and higher bleeding risk in medical patients. Because of the higher bleeding risk in medical patients than in surgical patients, pharmacological prophylaxis in acutely ill medical patients may be a challenge [4].

**Onset of VTE in surgical and medical patients**

The onset of VTE in medical patients is less clear than in surgical patients. In surgical patients, the onset of thrombus formation is mainly triggered by intraoperative hypercoagulability induced by surgery, which can last over a longer period of time. We investigated patients undergoing total hip replacement surgery by transesophageal ultrasound, and severe transatrial embolic events were observed during the insertion of the femoral component of the prosthesis. This intravasation of fat and bone-marrow particles was associated with an immediate onset of hypercoagulability demonstrated by a significant intraoperative increase of thrombin/antithrombin complexes [9].

It is difficult to assess the onset of VTE in acutely ill medical patients as >2% of medically ill patients have asymptomatic DVT upon admission to hospital [10,11]. Lawall et al. screened 617 patients admitted to the department of internal medicine at their hospital by compression ultrasound, and, in 16 of these acutely ill medical patients, DVT was found in the lower limbs [10]. Oger et al. found that 5.5% of patients who were hospitalized in a medical unit had an asymptomatic DVT of the lower limbs on admission, and their findings also suggest that the frequency is higher among patients aged >80 years [11]. Therefore, pharmacological VTE prophylaxis may be insufficient in many medical patients. Acutely ill medical patients with thrombosis already present upon hospitalization may require higher doses of anticoagulation therapy in order to treat thrombosis rather than as a preventative measure.

**VTE risk factors in surgical and medical patients**

In principle, the VTE risk factors in surgical and medical patients can be divided into exposing and predisposing factors (summarized in Figure 1) [12]. What both types of risk factor have in common is that they lead to or are associated with hypercoagulability. The exposing risk is attributable to the type of surgery or type of illness, which may provoke VTE, whereas the predisposing risk factors relate to permanent patient characteristics. Depending on the acuteness of disease, there may be an overlap of exposition and predisposition in medical patients. For example, cancer may provoke VTE in its active phase, which means that patients who are admitted to hospital because of their malignant disease are at high risk of thromboembolic complications. In patients who are admitted to hospital with other acute medical illnesses, a history of cancer may increase the VTE risk, alongside other predisposing risk factors.

In order to facilitate risk assessment in medical patients, the current author’s group drafted a two-dimensional VTE risk score that included the most important exposing and predisposing risk factors (Figure 2) [13]. According to evidence from clinical trials, the significance of each exposing risk factor was weighted using a score from 1 to 3; 3 points were assigned to factors such as ischemic stroke with paresis, acutely decompensated chronic obstructive pulmonary disease, acute myocardial infarction, New York Heart Association (NYHA) stage III/IV heart failure, sepsis, active cancer, or acute infection/inflammation with strict bed-rest. Acute infection/inflammation without strict bed-rest was assigned 2 points, and central venous catheterization 1 point. Corresponding categorization of risk was performed for the predisposing risk factors, as shown in Figure 2. The combination of exposing and predisposing risk factors reflects the individual risk of a patient.

A working group in Boston (MA, USA) developed a computer-alert program using eight common risk factors to determine each hospitalized patient’s risk profile for VTE [14]. Each risk factor was weighted according to a point scale: the major risk factors of cancer, prior VTE, and hypercoagulability were assigned a score of 3; the intermediate risk factor of major surgery was assigned a score of 2; and the minor risk factors of advanced age, obesity, bed-rest, and the use of hormone-replacement therapy or oral contraceptives were assigned...
Spyropoulos et al. assessed the incidence of VTE in the observational IMPROVE (International Medical Prevention Registry on VTE) study and derived VTE risk assessment scores at admission and associative VTE scores during hospitalization [15]. Data from 15 156 medical patients were analyzed to determine the cumulative incidence of clinically observed VTE over 3 months after admission. Multiple regression analysis identified factors associated with VTE risk. Of the 184 patients who developed symptomatic VTE, 76 had PE and 67 had lower-extremity DVT. Cumulative VTE incidence was 1.0%; 45% of events occurred after discharge. Factors that were independently associated with VTE were previous VTE, known thrombophilia, cancer, age >60 years, lower-limb paralysis, immobilization ≥7 days, and admission to an intensive care unit or coronary care unit. Points were assigned to each factor identified to give a total risk score for each patient. At admission, 67% of patients had a score ≥1. During hospitalization, 31% had a score ≥2; for a score of 2 or 3, the observed VTE risk was 1.5% compared with 5.7% for a score ≥4. During hospitalization, a score ≥2 was associated with higher overall and VTE-related mortality risks. The authors concluded that weighted VTE risk scores derived from four clinical risk factors that are present at hospital admission (previous VTE, known thrombophilia, cancer, and age >60 years) can predict VTE risk in acutely ill hospitalized medical patients. Scores derived from the seven clinical factors (listed above) during hospitalization may help to further understand symptomatic VTE risk [15].

**Figure 2. Two-dimensional VTE risk assessment model [13].**

COPD: chronic obstructive pulmonary disease; HRT: hormone replacement therapy; NYHA: New York Heart Association; VTE: venous thromboembolism. Modified from [13].
Classification and characterization of VTE risk in hospitalized and non-hospitalized medically ill patients

Many risk factors for VTE in hospitalized medical patients may also be present in medical outpatients. Several years ago, we performed a cross-sectional observational study that was designed to assess awareness of the risk of VTE in immobilized, acutely ill medical outpatients among German physicians [16]. This prospective study involved 1210 medical patients who were acutely confined to bed at home. Physicians performed a subjective assessment of VTE risk, which was rated on a 10-point scale (1 = very low risk, 10 = very high risk). The risk of VTE was also assessed retrospectively using a scorecard that was developed for use in hospitalized medical patients. Of the 1210 patients, 198 (16%) had risk scores of 0–4, 319 (26%) had scores of 5 or 6, and 693 (57%) had scores of ≥7.

In acutely ill medical patients, the underlying condition often remains active when the patient is discharged from hospital, and their mobility often remains restricted. With the continued push to discharge patients as early as possible, one might suppose that the risk of VTE is ongoing even after discharge, but there are few contemporary data that fully characterize out-of-hospital risk. We conducted a cross-sectional registry study, STATUS (Evaluation of the disease severity status of acute ill medical patients in hospital and at home) to compare the VTE risk in both inpatients and outpatients during routine care [17].

Datasets of 429 acutely ill medical patients who were treated in hospital and 349 outpatients (evaluated during a visit to their homes) were analyzed.

More patients in the outpatient setting (41.6%) were aged >80 years than in the inpatient setting (22.7%), and obesity was seen more frequently in hospitalized (28.5%) than non-hospitalized (19.5%) patients. The type of acute medical illnesses was different between the outpatients and inpatients, as shown in Figure 3.

There was a higher degree of immobilization in hospitalized patients, with 28.2% defined as completely bedridden compared with 18.3% of non-hospitalized patients. However, the duration of immobilization was longer at home, with 40.4% of outpatients immobilized for ≥ 5 days compared with 31.2% of hospitalized patients. Comorbidity was probably responsible for this increased duration of immobilization at home, with a comorbidity rate of 26.6% in outpatients compared with 13.5% in inpatients (Table 1).

According to our risk assessment score (Figure 2) [13], more patients in the hospital setting had a high exposing VTE risk because of their underlying diseases (56.1%) than outpatients (23.8%), although more outpatients than inpatients were found to have high predisposing VTE risk (9.3% vs. 12.3%). Regarding the exposing and predisposing risk combined, more patients in the outpatient setting fell into the category of high risk (48.5%) than inpatients (53.6%) [17]. It can be concluded from the STATUS registry that the total VTE risk in the outpatient setting is at least comparable with that of hospitalized patients. However, high levels of risk arising...
from the type of disease (exposing risk) is more frequently seen in hospitalized patients, whereas the risk attributable to patient-related risk factors (predisposing risk) is higher in the outpatient setting.

**Lessons from VTE prevention studies with short-term and extended use of pharmacological prophylaxis**

Hypercoagulability in patients undergoing major orthopedic surgery may continue beyond hospital discharge, thereby leading to continued thrombosis risk for several weeks. This has been shown by Dahl et al. who described an intraoperative increase in the levels of markers of activated coagulation that persisted over 5 weeks and may have been responsible for late development of VTE after hip replacement surgery [18,19]. Extended thromboprophylaxis after discharge from hospital has been shown to reduce both asymptomatic and symptomatic VTE in patients undergoing major orthopedic surgery [20,21]; based on these findings, current practice guidelines recommend extended thromboprophylaxis in such patients [22]. For acutely ill medical patients who are admitted to hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors (including active cancer, previous VTE, sepsis, acute neurological disease, or inflammatory bowel disease), thromboprophylaxis with low-molecular-weight heparin, low-dose unfractionated heparin, or the indirect Factor Xa inhibitor fondaparinux is recommended by the American College of Chest Physicians [22]. This recommendation is mainly based on three prior placebo-controlled trials in hospitalized medical patients who received enoxaparin [23], dalteparin [24], or fondaparinux [25]. In these studies, a 6–14 day course of low-dose thromboprophylaxis was compared with placebo in acutely ill medical patients. These studies (MEDENOX [Prophylaxis of Medical Patients with Enoxaparin], PREVENT [Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial], and ARTEMIS [Arixtra for Thromboembolism Prevention in Medical Indications Study], respectively) had in common that patients with congestive heart failure (NYHA stage III/IV), acute or chronic respiratory disease, acute infectious disease, or rheumatological diseases were eligible to participate. All three studies showed a significant reduction in VTE with anticoagulant prophylaxis without an increase in the risk of major bleeding. However, in contrast to surgical patients, the benefit of long-term prophylaxis in these medical patients is less clear.

The EXCLAIM (Extended Prophylaxis for VTE in Acutely Ill Medical Patients with Prolonged Immobilization) study evaluated the efficacy and safety of extended-duration enoxaparin thromboprophylaxis in acutely ill medical patients. In this trial, 5968 medically ill patients were given open-label enoxaparin (40 mg once daily) for an average of 10 days prior to randomization to either continued prophylaxis with enoxaparin or to receive placebo injection for an additional 28 days. Compared with placebo, extended prophylaxis significantly reduced the rate of VTE from 4.0% to 2.5%. However, compared with placebo, extended enoxaparin

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CI: confidence interval.
prophylaxis significantly increased the rate of major bleeding from 0.3% to 0.8% [26]. Thus, the net clinical benefit is not sufficient to recommend extended duration of low-molecular-weight heparin prophylaxis for all acutely ill medical patients. Further studies are required to identify high-risk subgroups of acutely ill medical patients in whom the benefit of extended VTE prophylaxis outweighs the risk of bleeding.

**Conclusion**

VTE has long been regarded as a complication that is mainly associated with surgical procedures. However, more recent data have demonstrated that the risk of VTE in medical patients is comparable to that in surgical patients who are at moderate risk for VTE. Based on solid evidence derived from clinical trials in hospitalized patients, pharmacological prophylaxis has become clinical routine in some countries for patients who are at VTE risk while they are in hospital; however, the optimal duration of prophylaxis is still unknown. Various VTE risk assessment models have been developed to improve patient care in hospital, but additional studies are required to determine the validity of their use in non-hospitalized patients and to answer the question of which patients may benefit from prophylaxis beyond hospital stay.

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

**Disclosure**

The author has no competing financial interests to disclose.

**References**


Several new anticoagulant drugs are currently being developed for the treatment of established venous thromboembolism (VTE) and the prevention of this disorder in medical patients. These drugs are direct inhibitors of Factor Xa or direct thrombin inhibitors; they can be administered orally, have minimal interactions with food and other drugs, and can be administered at fixed dosages without monitoring. They have been tested for the prevention of VTE after major orthopedic surgery, and some have already gained approval for this indication in many countries. Rivaroxaban, dabigatran, apixaban, and edoxaban have been or are currently being tested for the treatment or prevention of VTE in medical patients in large Phase III studies. Rivaroxaban has been proven to be noninferior to standard therapy for the treatment of deep venous thrombosis in the EINSTEIN study, and dabigatran, given after a short course of heparin, has been shown to be noninferior to warfarin for the treatment of VTE in the RE-COVER study. Rivaroxaban and dabigatran have been found to be more effective than placebo for the secondary prevention of VTE in patients who have received anticoagulants for 3–12 months, and dabigatran has been shown to be noninferior to warfarin in similar patient groups. Rivaroxaban is currently being tested for the treatment of acute pulmonary embolism, and dabigatran is being evaluated for the treatment of acute VTE. Studies are evaluating the efficacy and safety of apixaban and edoxaban for the treatment of VTE, and two large trials have recently been completed with apixaban and rivaroxaban in the prevention of VTE in medical patients. Available results and the design of these studies are reviewed in this article. Adv Venous Arterial Thromb 2011;1(3):87–95.
thrombocytopenia with the use of LMWH, the need for frequent monitoring and dose adaptation of VKAs, and the numerous interactions between VKAs and drugs and food. In everyday clinical practice, VKAs are one of the drugs associated with the highest number of adverse events and drug-related deaths as reported to health authorities [9]. The development of new anticoagulants that are administered orally without the need for monitoring or dose-adjustment is welcome, even if they do not prove to be more effective or safer than the current therapies in the setting of randomized, controlled trials.

Several new anticoagulants are currently being developed for the prevention and both initial and long-term treatment of VTE, for the prevention of thromboembolism in patients with atrial fibrillation (AF), and for the treatment of acute coronary events (Table 1). Some of these drugs have already been marketed for the prevention of VTE after major orthopedic surgery in many countries. This article will focus on the recently published results with new oral drugs in the acute and long-term treatment of VTE, as well as on ongoing studies on the prevention of VTE in medical patients (summarized in Table 2). These drugs are not yet approved by regulatory authorities for these indications.

**Rivaroxaban**

Rivaroxaban is a direct selective inhibitor of Factor Xa. Rivaroxaban has an oral bioavailability of 80%, a half-life of 7–11 h (5–9 h in the young and 11–13 h in the elderly), and is cleared by the kidneys and the gut.

Rivaroxaban is metabolized through multiple cytochrome P450 (CYP450) pathways, primarily through CYP3A4/3A5 and, to a lesser extent, CYP2J2. Ketoconazole and ritonavir significantly increase the blood concentration of rivaroxaban, and its use is contraindicated in patients who are receiving these drugs. Potent CYP3A4 inducers such as rifampicin and anticonvulsants such as phenytoin, carbamazepine, and phenobarbital can reduce the blood concentration of rivaroxaban, and it should be used with caution in those who are receiving these drugs [10].

**Phase II studies in patients with DVT**

In the first Phase II study, rivaroxaban, given as 10–30 mg twice daily, was compared with enoxaparin followed by warfarin (dosed to give an international normalized ratio [INR] 2–3) over 12 weeks in a study involving 613 patients with proximal DVT. The incidence of the primary efficacy outcome (defined as improvement in thrombotic burden and lack of recurrent thrombosis) was not significantly different between patients who were treated with rivaroxaban (43.8–59.2%) or enoxaparin (45.9%). Major bleeding was observed in the rivaroxaban group at an incidence of 1.7–3.3%; no major bleeding was observed in the enoxaparin group [11].

In a similar 12-week trial, 543 patients with acute DVT were randomized to rivaroxaban 20–40 mg once daily or LMWH followed by a VKA [12]. The primary efficacy outcome of symptomatic VTE or asymptomatic deterioration in thrombotic burden occurred in 5.4–6.6% of rivaroxaban-treated subjects compared with 9.9% of the active control group. The incidence of major and clinically relevant non-major bleeding ranged between 2.2% and 6.0% in the rivaroxaban groups and was 8.3% in the comparator group [12]. Thus, efficacy and safety appeared to be similar among the three doses of rivaroxaban and the once daily 20 mg dosage was selected as maintenance dose in the Phase III trials.

**Phase III studies in the treatment of VTE**

The EINSTEIN (Evaluating Oral, Direct Factor Xa Inhibitor Rivaroxaban in Patients with Acute Symptomatic DVT or PE) program is designed to evaluate the efficacy and safety of rivaroxaban in the treatment of patients with VTE. The EINSTEIN program consists of three randomized trials of rivaroxaban – one for the treatment of acute DVT (EINSTEIN-DVT), one for the treatment of acute PE (EINSTEIN-PE), and one for continued treatment in patients who have received 6–12 months of anticoagulant treatment for acute DVT or PE (EINSTEIN-Extension).

**The EINSTEIN-DVT study**

The EINSTEIN-DVT study was an open-label, randomized, event-driven, noninferiority study that compared oral rivaroxaban alone with subcutaneous enoxaparin followed by a VKA for 3 months, 6 months, or 12 months in patients with acute, symptomatic proximal DVT without symptomatic PE [13]. The main exclusion criteria were the following: creatinine clearance <30 mL/min; clinically significant liver disease; active bleeding or a high risk of bleeding; childbearing potential without proper contraceptive measures; pregnancy or breastfeeding; concomitant use of potent CYP450/3A4 inhibitors

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<td>Apixaban</td>
<td>Anti-Factor Xa</td>
<td>50–80%</td>
<td>12 h</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Anti-Factor Xa</td>
<td>45%</td>
<td>10 h</td>
</tr>
</tbody>
</table>

*After multiple doses; †unchanged drug or active metabolites; ‡50% unchanged drug and 50% inactive metabolites; ††40% unchanged drug and 60% inactive metabolites; **70% unchanged drug and 30% inactive metabolites; †‡40% unchanged drug and 60% inactive metabolites; †¶40% unchanged drug and 60% inactive metabolites; †††40% unchanged drug and 60% inactive metabolites.
A total of 1731 patients were assigned to rivaroxaban during the treatment period versus 138 patients receiving standard therapy, compared with 49 (2.9%) of those who received rivaroxaban during the treatment period compared with 49 (2.9%) of those who received standard therapy, respectively [13]. Major or clinically significant bleeding occurred in 139 patients (8.1%) who were allocated to rivaroxaban during the treatment period versus 138 patients (8.1%) in the control group (HR 0.97, 95% CI 0.76–1.22; p=0.77). The secondary outcome of net clinical benefit, defined as recurrent VTE or major bleeding, occurred in 51 patients (3.0%) who received rivaroxaban and in 73 (4.2%) of the patients who were given standard therapy for noninferiority; Table 3). Major or clinically significant bleeding occurred in 139 patients (8.1%) who were allocated to rivaroxaban during the treatment period versus 138 patients (8.1%) in the control group (HR 0.97, 95% CI 0.76–1.22; p=0.77). The secondary outcome of net clinical benefit, defined as recurrent VTE or major bleeding, occurred in 51 (2.9%) of those who received standard therapy. Serious adverse events occurred in 201 (12.0%) and 238 (13.6%) patients in the rivaroxaban and control groups, respectively [13].

EINSTEIN-DVT shows that rivaroxaban as a single agent is as effective and safe as LMWH followed by a VKA, for both the acute and long-term treatment of DVT. This result is

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Study acronym</th>
<th>Comparator</th>
<th>Patients</th>
<th>Status</th>
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<tr>
<td>Apixaban</td>
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<td>Enoxaparin</td>
<td>&gt;6500</td>
<td>Completed</td>
</tr>
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<td>Apixaban</td>
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<td>Warfarin</td>
<td>4800*</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Dabigatran</td>
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<td>RE-COVER I</td>
<td>Warfarin</td>
<td>2539</td>
<td>Published</td>
</tr>
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</tr>
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<td>Dabigatran</td>
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<td>RE-SONATE</td>
<td>Placebo</td>
<td>1343</td>
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<td>RE-MEDY</td>
<td>Warfarin</td>
<td>2856</td>
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</tr>
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<td>Edoxaban</td>
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<td>Warfarin</td>
<td>7500*</td>
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</tr>
<tr>
<td>Rivaroxaban</td>
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<td>EINSTEIN-DVT</td>
<td>Enoxaparin and warfarin</td>
<td>3449</td>
<td>Published</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Treatment of acute PE</td>
<td>EINSTEIN-PE</td>
<td>Enoxaparin and warfarin</td>
<td>4800*</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Rivaroxaban</td>
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<td>EINSTEIN-Extension</td>
<td>Placebo</td>
<td>1197</td>
<td>Published</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Prevention of VTE in medical patients</td>
<td>MAGELLAN</td>
<td>Enoxaparin</td>
<td>8101</td>
<td>Completed</td>
</tr>
</tbody>
</table>

A total of 1731 patients were assigned to rivaroxaban and 1718 to standard therapy. In the rivaroxaban and control groups, the mean age was 55.8±16.4 years and 56.4±16.3 years, respectively; the proportion of patients weighing >100 kg was 14.2% and 14.3%; 60.9% and 63.0% had an unprovoked DVT; 6.8% and 5.2% had active cancer; and 19.4% and 19.2% had previous VTE. Treatment with LMWH or fondaparinux was given before randomization and for a period not exceeding 2 days to 73.0% and 71.0% of the patients given rivaroxaban and standard therapy, respectively. Treatment duration was 3 months in 12.0% and 11.8%, 6 months in 62.6% and 63.0%, and 12 months in 25.4% and 25.1% of the respective treatment groups. In the patients who were allocated to standard therapy, the INR was in the therapeutic range (2.0–3.0) for 57.7% of the time, >3.0 for 16.2% of the time, and <2.0 for 24.4% of the time.

“In EINSTEIN-DVT, recurrent VTE occurred in 2.1% of patients given rivaroxaban vs. 3.0% on standard therapy”
reinforced by the high quality of the INR control in the patients who were given standard therapy. Although the characteristics of the patients enrolled in the EINSTEIN-DVT study are similar to those in other studies, the patients are slightly younger and the proportion of patients with cancer is much lower than in recent registries [14,15].

The EINSTEIN-PE study

The EINSTEIN-PE study is an ongoing open-label, randomized, event-driven, noninferiority study that is comparing oral rivaroxaban alone with subcutaneous enoxaparin followed by a VKA for 3 months, 6 months, or 12 months in patients with acute, symptomatic PE. The main exclusion criteria, treatment regimens (dose and duration), and outcomes are similar to those of the DVT study. Overall, >4800 patients have been included in the study; the recruitment is completed and the results will be disclosed in 2012 (Clinicaltrials.gov identification number NCT00439777).

The EINSTEIN-Extension study

The rate of recurrent VTE after stopping anticoagulant treatment for VTE is estimated at 7.8% per 100 patient-years [16]. Rivaroxaban has been evaluated as a treatment for recurrent VTE with the aim of reducing the long-term recurrence of VTE in patients who had been treated for 6–12 months with a VKA or rivaroxaban.

The EINSTEIN-Extension study was a double-blind, randomized, controlled, multicenter study that compared rivaroxaban with placebo in patients with confirmed symptomatic DVT or PE who had been treated for 6 months or 12 months with a VKA or rivaroxaban [13]. Patients were eligible if they had objectively confirmed symptomatic DVT or PE and had been treated for 6–12 months with acenocoumarol, warfarin, or rivaroxaban, and if there was equipoise with respect to the need for continued anticoagulation according to the treating physician. Exclusion criteria were the same as in EINSTEIN-DVT. Patients received either rivaroxaban 20 mg once daily or matching placebo for an intended duration of 6 months or 12 months, which was chosen by the treating physician at the time of randomization. The primary efficacy outcome was symptomatic, recurrent VTE. The principal safety outcome was major bleeding.

A total of 1197 patients were enrolled in the study; 602 were randomized to rivaroxaban and 595 to placebo. Approximately 28% and 27% of patients had been treated with rivaroxaban for 6–12 months as part of the EINSTEIN-DVT or EINSTEIN-PE studies; 71% and 73% of patients had been treated with a VKA for 6–12 months in the rivaroxaban and placebo groups, respectively, as part of the EINSTEIN study or were referred from usual care. The mean age of the patients in the rivaroxaban and placebo groups was 58.2±15.6 years and 58.4±16 years, respectively; bodyweight exceeded 100 kg in 14.1% and 14.6% of patients; VTE was unprovoked in 73.1% and 74.2% of patients; 4.7% and 4.4% of patients had active cancer; 17.9% and 14.1% of patients had previous VTE; and the intended treatment duration was 6 months for 59.8% and 60.1% of patients, and 12 months for 40.2% and 39.9% of patients, respectively.

Recurrent VTE occurred in eight patients (1.3%) who were given rivaroxaban during the treatment period compared with 42 patients (7.1%) who received placebo (p<0.001; Table 3). Four patients (0.7%) given rivaroxaban experienced major bleeding.

<table>
<thead>
<tr>
<th>Study acronym</th>
<th>Study arms</th>
<th>Number of patients</th>
<th>Rate of VTE (%)</th>
<th>HR (95% CI)</th>
<th>Rate of major bleeding (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-COVER I</td>
<td>Dabigatran</td>
<td>1273</td>
<td>2.4</td>
<td>1.10 (0.65–1.84)</td>
<td>1.6</td>
<td>0.82 (0.45–1.48)</td>
</tr>
<tr>
<td></td>
<td>LMWH plus warfarin</td>
<td>1266</td>
<td>2.1</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-SONATE</td>
<td>Dabigatran</td>
<td>681</td>
<td>0.4</td>
<td>0.08 (0.02–0.25)</td>
<td>0.39</td>
<td>p=0.5*</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>662</td>
<td>5.6</td>
<td></td>
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<tr>
<td>RE-MEDY</td>
<td>Dabigatran</td>
<td>1430</td>
<td>1.8</td>
<td>1.44 (0.78–2.64)</td>
<td>0.9</td>
<td>0.52 (0.27–1.01)</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>1426</td>
<td>1.3</td>
<td></td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>Rivaroxaban</td>
<td>1731</td>
<td>2.1</td>
<td>0.65 (0.33–1.30)</td>
<td>0.8</td>
<td>0.65 (0.33–1.30)</td>
</tr>
<tr>
<td></td>
<td>LMWH plus warfarin</td>
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<td>3.0</td>
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</tr>
<tr>
<td>EINSTEIN-Extension</td>
<td>Rivaroxaban</td>
<td>602</td>
<td>1.3</td>
<td>0.18 (0.09–0.39)</td>
<td>0.7</td>
<td>p=0.11*</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>594</td>
<td>7.1</td>
<td></td>
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</tr>
</tbody>
</table>

bleeding as compared with none in the control group (p=0.11). The primary safety outcome of major or clinically significant bleeding occurred in 36 patients (6.0%) in the rivaroxaban group during the treatment period versus seven patients (1.2%) in the control group (HR 5.19, 95% CI 2.3–11.7; p<0.001) [13].

In summary, in patients with predominantly unprovoked VTE who were treated for 6 months or 12 months, rivaroxaban reduced the rate of recurrent VTE by 82%, with an increase in clinically significant but not major bleedings.

Studies of the prevention of VTE in medically ill patients

The MAGELLAN study

The recently completed MAGELLAN (Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of VTE in Hospitalized Medically Ill Patients Comparing Rivaroxaban with Enoxaparin) study was a randomized, double-blind, placebo-controlled study comparing rivaroxaban 10 mg once daily for 35 days with subcutaneous enoxaparin 40 mg once daily for 10 days in hospitalized medically ill patients (n=8101) who are at risk for VTE (Clinicaltrials.gov identification number NCT00571649). Patients included in the study were aged ≥40 years, at risk of VTE events, and were hospitalized for the following acute medical conditions: New York Heart Association class III or IV heart failure; active cancer; acute ischemic stroke; acute infectious and inflammatory diseases, including acute rheumatic diseases; acute respiratory insufficiency; additional risk factors for VTE, including reduced mobility.

The main exclusion criteria were conditions that contraindicate the use of antithrombotic therapy with the LMWH enoxaparin; conditions that may increase the risk of bleeding, including intracranial hemorrhage; requirement for drugs or procedures that may interfere with the study treatment; and concomitant conditions or diseases that may increase the risk of study subjects or interfere with the study outcome.

Patients in the rivaroxaban group were given rivaroxaban 10 mg once daily for 35 days and subcutaneous placebo for 10 days, whereas patients in the enoxaparin group were given 40 mg enoxaparin administered subcutaneously for 10 days and an oral placebo for 35 days. The primary outcome measures were the composite of VTE and death at days 10 and 35. The primary safety measure was the composite of major and non-major clinically relevant bleeding observed not later than 2 days after the intake of the last dose of double-blinded study medication. Rivaroxaban was found to be noninferior to enoxaparin at 10 days and superior to enoxaparin at day 35. Preliminary study results were presented in part during the American College of Cardiology's meeting in April 2011 (April 2–5, 2011, New Orleans, LA, USA), but were not detailed in the meeting abstract.

Dabigatran

Dabigatran is a selective and reversible direct thrombin inhibitor. It is hydrophilic and lacks oral bioavailability because of the basic moiety of the molecule. However, this basic moiety has been reversibly masked, leading to the development of the prodrug dabigatran etexilate, which has sufficient oral bioavailability. Dabigatran etexilate is hydrolyzed to dabigatran in liver microsomes. Maximum plasma concentrations of dabigatran are obtained 75–90 min after oral intake of dabigatran etexilate. Approximately 85% of the drug is recovered in the urine as unchanged dabigatran. The terminal half-life is approximately 7–9 h after a single dose; this is dose-dependently prolonged after multiple-dosing, ranging from 7–17 h. The area under the curve is approximately two-fold greater in healthy volunteers aged ≥65 years than in younger subjects after twice-daily dosing. A reduction in the daily dose from 220 mg to 150 mg is recommended in patients with moderate renal impairment (creatinine clearance rate of 30–50 mL/min) and its use is contraindicated in patients with severe renal insufficiency (creatinine clearance rate of <30 mL/min). Dabigatran inhibits CYP2E1 and CYP3A4 activity at supertherapeutic doses and has moderate affinity to the major human efflux transporter P-glycoprotein. Amiodarone, verapamil, ketoconazole, and clarithromycin increase the concentration of dabigatran; caution should be used when these drugs and dabigatran are co-administered [17]. Rifampicin decreases the concentration of dabigatran and the co-administration of the two drugs should be avoided [10]. Pantoprazole also decreases the concentration of dabigatran in the blood because of the increase in the gastric pH with the proton pump inhibitor [17].

Phase II studies

There have been no Phase II studies specifically evaluating dabigatran in the treatment of patients with VTE. However, dabigatran has been compared with warfarin in patients with AF [18]. In the PETRO (Stroke Prevention in Patients With AF by Treatment With Dabigatran, With and Without Aspirin, Compared to Warfarin) trial, 502 patients with AF were randomly assigned to dabigatran etexilate given twice daily at doses of 100–600 mg/day alone or in combination with salicylic acid (81 mg or 325 mg), or warfarin as active comparator. The primary safety outcome of major bleeding was exclusively noted in four patients who were treated with the highest dabigatran dose in combination with salicylic acid. None of the patients receiving dabigatran alone experienced major bleeding. Thromboembolic events occurred in two patients receiving the lowest dabigatran dose [18].

Phase III studies in the treatment of VTE

The RE-COVER study

Dabigatran has been compared with warfarin in patients with symptomatic VTE in the RE-COVER (Efficacy and Safety of
Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic VTE study. The RE-COVER study was a double-blind, double-dummy, noninferiority, randomized trial that compared 6 months of treatment with dabigatran at a fixed dose of 150 mg twice daily with dose-adjusted warfarin therapy, after initial parenteral anticoagulation in patients with symptomatic VTE [19].

Patients who had acute, symptomatic, objectively verified proximal DVT of the legs or PE and for whom 6 months of anticoagulant therapy was considered to be appropriate were included in the study. The main exclusion criteria were as follows: PE with hemodynamic instability or requiring thrombolytic therapy; recent unstable cardiovascular disease; a high risk of bleeding; liver disease with an aminotransferase level that was two times the local upper limit of the normal range; an estimated creatinine clearance rate of <30 mL/min; a life-expectancy of <6 months; pregnancy or risk of becoming pregnant; a requirement for long-term antiplatelet therapy (≤100 mg of acetylsalicylic acid daily was acceptable).

“In RE-COVER, recurrent VTE occurred in 2.4% of patients receiving dabigatran vs. 2.1% receiving warfarin”

Patients were assigned to receive a fixed dose of dabigatran orally (150 mg twice daily; n=1273) or warfarin (n=1266). All patients were initially given an approved parenteral anticoagulant (generally unfractionated heparin or LMWH). Warfarin or a warfarin-like placebo was started on the day of randomization and was adjusted to achieve either a true INR or a sham INR of 2–3. Dabigatran or a dabigatran-like placebo was started once the parenteral anticoagulant had been given for ≥5 days and the true or sham INR was ≥2.0 on 2 consecutive days. Active dabigatran and warfarin-like placebo or active warfarin and dabigatran-like placebo were then given for 6 months. The primary efficacy outcome was the composite of symptomatic VTE or death associated with VTE in the 6 months after random assignment. The main safety outcomes were major and clinically significant non-major bleeding. Dabigatran was considered to be noninferior to warfarin if the upper boundary of the 95% CI for the HR was <2.75 and the upper boundary of the 95% CI for the difference in risk was <3.6%.

The mean age of the patients in the dabigatran and warfarin (placebo) groups was 55.0±15.8 years and 54.4±16.2 years, respectively; mean bodyweight was 85.5±19.2 kg and 84.2±18.3 kg; 69.1% and 68.6% of patients had DVT only, whereas 21.2% and 21.4% had isolated PE, and 9.5% and 9.8% had combined PE and DVT; 5.0% and 4.5% had active cancer; and 25.7% and 25.4% had previous VTE, respectively. In the patients who were allocated to warfarin, the INR was in the therapeutic range (2.0–3.0) for 59.9% of the time.

Recurrent VTE occurred in 30 patients (2.4%) who were given dabigatran during the treatment period compared with 27 patients (2.1%) who received warfarin (p<0.001 for noninferiority; Table 3). Major bleeding occurred in 20 patients (1.6%) allocated to the dabigatran group during the treatment period versus 24 patients (1.9%) in the control group. Major or clinically significant bleeding occurred in 71 patients (5.6%) in the dabigatran group compared with 111 patients (8.8%) in the warfarin group (HR 0.63, 95% CI 0.47–0.84; p=0.002). A total of 21 patients (1.6%) who were treated with dabigatran died before the end of the intended treatment period versus 21 patients (1.7%) who received warfarin. Serious adverse events occurred in 165 (13.0%) and 150 patients (11.8%) in the dabigatran and control groups, respectively. The proportion of patients with abnormal liver function tests was low in both groups and did not differ significantly between groups [19].

The RE-COVER study shows that dabigatran given after a short course of parenteral anticoagulation is as effective and safe as warfarin for the long-term treatment of VTE, including proximal DVT and PE. This result is particularly encouraging given the high quality of the INR control in the patients given warfarin and the double-blind methodology used in this study. As in the EINSTEIN study, the characteristics of the patients in the RE-COVER study are similar to those in previous trials in patients with VTE, but the patients were slightly younger and the proportion of patients with cancer was much lower than in recent registries [14].

The RE-COVER 2 study

At the request of the US Food and Drug Administration (FDA), a second trial with dabigatran has been conducted in patients with acute VTE. The RE-COVER 2 study (Clinicaltrials.gov identifier NCT00680186) has essentially the same design as the original RE-COVER study. Patient recruitment has been completed, and a total of 2589 patients have been included in the study. The results are expected to be published in the near future.

Long-term prevention of VTE

Dabigatran has been compared with placebo and warfarin for the long-term secondary prevention of VTE after 6 months of anticoagulant treatment in two separate studies.

The RE-SONATE study

The RE-SONATE (Twice-Daily Oral Direct Thrombin Inhibitor Dabigatran Etxetilate in the Long-Term Prevention of Recurrent Symptomatic VTE) study was a multicenter, double-blind, randomized trial comparing dabigatran etexilate and placebo for the long-term prevention of recurrent symptomatic VTE in patients with symptomatic VTE who completed 6–18 months of treatment with a VKA (Clinicaltrials.gov identifier NCT00558259) [20]. Adult patients with confirmed
symptomatic PE or proximal DVT of the leg(s) who had been treated for 6–18 months with therapeutic dosages (intended INR of 2–3) of an oral VKA or RE-COVER study medication up to the time of screening were included. The main exclusion criteria were as follows: indication for VKA other than DVT and/or PE; need for long-term anticoagulant treatment for the index VTE; active liver disease; levels of alanine aminotransferase (ALT) more than three-times the upper limit of normal range; creatinine clearance rate <30 mL/min; active bleeding or at high risk for bleeding; life expectancy <6 months; pregnancy or breastfeeding.

Patients in the dabigatran group were given oral dabigatran 150 mg twice daily for 6 months, and patients in the control group were given matching placebo. The main study outcome was symptomatic recurrent VTE (i.e. the composite of recurrent DVT or fatal or non-fatal PE during the intended treatment period). The principal safety outcome was major bleeding during the intended treatment period [20].

“Recurrent VTE occurred in 0.4% of patients given dabigatran vs. 5.6% given placebo in the RE-SONATE study”

The study has been completed and preliminary data presented in part during the last International Society on Thrombosis and Haemostasis (ISTH) meeting (Kyoto, Japan, 28–30 July 2011). Recurrent VTE occurred in three (0.4%) of 681 patients who were treated with dabigatran and 37 (5.6%) of 662 patients who were treated with placebo (p<0.0001; Table 3). There were two patients with major bleeds (0.39%) who were treated with dabigatran, whereas none occurred in the placebo group (p=0.5). Clinically relevant bleeding occurred in 36 patients (5.3%) who were treated with dabigatran and in 12 patients (1.8%) who received placebo (HR 2.9, 95% CI 1.5–5.6; p=0.001). Cardiovascular events were observed in three patients (0.4%) in the dabigatran group compared with two patients (0.3%) in the placebo group. In the on-treatment safety analysis, there were no deaths in the dabigatran group and one unexplained death in the placebo group, and there were 30 severe adverse events in each of the two treatment groups [20].

The RE-MEDY study

The RE-MEDY (Secondary Prevention of VTE) study was a multicenter, international, randomized, double-blind trial (Clinicaltrials.gov identifier NCT00329238). The general aim of the study was to determine the comparative safety and efficacy of dabigatran etexilate and warfarin for the secondary prevention of symptomatic VTE in patients who had been treated for 3–6 months for acute symptomatic VTE [21].

Patients with objectively confirmed acute symptomatic DVT or PE who were diagnosed 3–6 months prior to screening and who had been successfully treated with standard doses of an approved anticoagulant for 3–6 months were included if they did not have any of the following exclusion criteria: symptomatic DVT or PE at screening; interruption of anticoagulant therapy for ≥2 weeks during the 3–6 months of treatment for the prior VTE; excessive risk of bleeding; elevated levels of ALT or aspartate aminotransferase (AST) to more than two-times the upper limit of normal range; severe renal impairment (estimated creatinine clearance rate ≤30 mL/min).

Patients who were randomized to the dabigatran group were given oral dabigatran etexilate 150 mg twice daily for 6–36 months and warfarin-like placebo adjusted to sham INR measurements. Patients in the active control group were given warfarin adjusted to obtain an INR value between 2 and 3 and dabigatran-like placebo twice daily for 6–36 months. The primary outcome measure was the composite of recurrent symptomatic VTE and deaths related to VTE during the treatment period.

The results were presented in part during the 2011 ISTH meeting. Recurrent VTE occurred in 26 (1.8%) of 1430 patients who were treated with dabigatran and 18 (1.3%) of 1426 patients who received warfarin (p=0.03 for the pre-specified noninferiority margin; Table 3). There were 13 major bleeds (0.9%) in patients who received dabigatran compared with 25 (1.8%) in patients who received warfarin. Any bleeding occurred in 277 patients (19%) who were treated with dabigatran versus 353 patients (26%) who received warfarin (HR 0.71, 95% CI 0.61–0.83). Acute coronary syndromes were observed in 13 patients (0.9%) following treatment with dabigatran and in three patients (0.2%) following treatment with warfarin (p=0.02). There were 17 deaths in the dabigatran group and 19 deaths in the warfarin group; other adverse events were also similar between the two groups [21].

Apixaban

Apixaban is a selective and reversible direct inhibitor of Factor Xa. Maximal plasma concentration is obtained within 50–120 min. The half-life of apixaban is approximately 12 h and it is excreted mainly unchanged in feces (75%). Apixaban is predominantly metabolized by CYP3A4; concomitant administration of potent CYP3A4 inhibitors or inducers may affect apixaban concentration [10]. Ketoconazole increases the blood concentration of apixaban and caution is needed when the two drugs are used concomitantly. Rifampicin reduces the blood concentration of apixaban and it should not be used concomitantly [10].

Phase II studies for the treatment of VTE

Apixaban has been evaluated for the treatment of established DVT in the Botticelli DVT Phase II study [22]. A total of 520 patients were randomized to three once- or twice-daily
doses of apixaban (10–20 mg/day) or heparin treatment followed by VKA given over 3 months. Symptomatic VTE or deterioration of thrombotic burden dose-independently occurred at a similar frequency of 4.7% in patients who were given apixaban and 4.2% in the control group. The incidence of major and clinically relevant non-major bleeding did not differ between apixaban-treated subjects (7.3%) and patients who were given control treatment (7.9%). No alterations in the concentrations of liver transaminases or bilirubin in plasma were observed [22].

**Phase III studies in VTE**

**The ADOPT study**

The ADOPT (Study of Apixaban for the Prevention of Thrombosis-related Events in Patients with Acute Medical Illness) study is a recently completed multicenter, randomized double-blind trial that compared the safety and efficacy of apixaban and enoxaparin for preventing VTE in acutely ill medical patients during and after hospitalization (Clinicaltrials.gov identifier NCT00457002). Men and non-pregnant, non-breastfeeding women aged ≥40 years who were hospitalized with congestive heart failure or acute respiratory failure, infection (without septic shock), acute rheumatic disorder, or inflammatory bowel disease were included in the study. The main exclusion criteria were as follows: hospitalization for VTE; active bleeding or at high risk of bleeding; inability to take oral medication; the presence of diseases requiring ongoing treatment with anticoagulants or antiplatelet therapies other than aspirin at a dose ≤165 mg/day.

Patients in the experimental arm were given apixaban 2.5 mg orally twice daily for 30 days and enoxaparin-like placebo given subcutaneously once daily for 6–14 days; patients in the active control group were given enoxaparin 40 mg once daily subcutaneously for 6–14 days and apixaban-like placebo twice daily for 30 days. The primary outcome measure was the composite of VTE and VTE-related death during 30 days of double-blind treatment. Secondary outcome measures include all-cause death, major bleeding, and clinically relevant non-major bleeding during 30 days of double-blind treatment.

The study enrollment is completed, and >6500 patients have been included in the study. The results are expected in late 2011 or 2012.

**The AMPLIFY study**

The AMPLIFY (Apixaban After the Initial Management of PE And DVT With First-Line Therapy) study is a multicenter, randomized, controlled, double-blind trial designed to evaluate the effects of apixaban in preventing VTE recurrence or death in patients with DVT or PE (Clinicaltrials.gov identifier NCT00643201). Patients aged ≥18 years with a confirmed episode of symptomatic DVT or PE are eligible for this study. The main exclusion criteria are as follows: contraindication for enoxaparin or warfarin; active bleeding or high risk for serious bleeding; short life-expectancy; uncontrolled high blood pressure; significantly impaired kidney or liver function.

Patients who are allocated to the experimental group will be given oral apixaban 10 mg twice daily for 7 days followed by oral apixaban 5 mg twice daily for 6 months. In this group, patients will be given enoxaparin-like placebo subcutaneously twice daily until the sham INR is >2 and warfarin-like placebo adjusted to sham INR 2–3. Patients in the active control group will be given subcutaneous enoxaparin 1 mg/kg twice daily until the INR is >2 and warfarin adjusted to INR (2–3); in this group, patients will be given apixaban-like placebo twice daily for 6 months. The primary outcome measure is recurrent VTE or death during study treatment. The secondary outcome measure is bleeding during study treatment. The recruitment of >4800 patients is foreseen and the study completion date is expected to be December 2012.

**Edoxaban**

Edoxaban is a selective and reversible direct Factor Xa inhibitor. Oral bioavailability is estimated at 45%, and plasma half-life is estimated to be between 9 h and 11 h. Edoxaban is excreted in the feces (35%) and urine (65%), 40% as unchanged drug and 60% as inactive metabolites. Edoxaban is a substrate for CYP3A4 and for P-glycoprotein [10].

**Phase III studies in the treatment of VTE**

**The HOKUSAI study**

The HOKUSAI (Comparative Investigation of LMWH/Edoxaban Tosylate [DU176] Versus [LMW] Heparin/Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots) study is a multicenter, randomized, controlled, double-blind trial evaluating heparin and edoxaban tosylate versus heparin and warfarin for the prevention of VTE recurrence in patients with acute symptomatic DVT or PE (Clinicaltrials.gov identifier NCT00986154). Adult patients with acute symptomatic proximal DVT and/or symptomatic PE confirmed by appropriate diagnostic imaging are currently being recruited for the study. The main exclusion criteria are as follows: thrombectomy; insertion of a caval filter; use of a fibrinolytic agent to treat the current episode of DVT and/or PE; >48 h treatment with anticoagulant therapy prior to randomization; calculated creatinine clearance rate <30 mL/min; significant liver disease (such as acute hepatitis, chronic active hepatitis, or cirrhosis) or ALT levels two-times the upper limit of normal; total bilirubin 1.5-times the upper limit of normal; patients with active cancer for whom long-term treatment with LMWH is anticipated; active bleeding or high risk for bleeding contraindicating treatment with heparin or warfarin; chronic treatment with non-aspirin nonsteroidal anti-inflammatory drugs; treatment with aspirin at a dosage of
>100 mg/day or dual antiplatelet therapy; concurrent treatment with potent P-glycoprotein inhibitors.

Patients in the experimental group are to be given heparin or LMWH at therapeutic dosage and warfarin-like placebo until the sham INR is >2; heparin treatment will then be stopped and edoxaban 60 mg once daily given along with warfarin-like placebo for 3 months, 6 months, or 12 months. In the active comparator group, patients will receive heparin or LMWH at therapeutic dosage and warfarin until the INR is >2; heparin treatment will then be stopped and edoxaban-like placebo given once daily along with warfarin adjusted to obtain an INR of 2–3, for 3 months, 6 months, or 12 months. The principal study outcome is symptomatic recurrent VTE (i.e. the composite of DVT, non-fatality PE, and fatal PE during the treatment period). Secondary outcome measures are the composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality; and clinically relevant bleeding (i.e. major or clinically relevant non-major bleeding) occurring during treatment. Recruitment of the study participants is ongoing, and approximately 7500 patients will be included.

**Conclusion and future perspectives**

Current anticoagulant treatment of VTE is limited by the need of parenteral administration for heparin derivatives, and the need for drug monitoring and the risk of drug interactions for VKAs. New oral anticoagulants given at fixed dosages without the need for monitoring are currently being investigated for primary prevention, treatment, and secondary prevention of VTE. The initial results are encouraging – the new drugs have been shown to be noninferior to the current anticoagulants in the treatment of established VTE. If these results are confirmed in the ongoing trials, these drugs will probably take the lead in the treatment of VTE. Will it be the end of warfarin? It is premature to answer this question yet. Initial results, obtained on selected patients, need to be confirmed in the elderly and in some subgroups such as cancer patients, especially with regard to bleeding complications. We also need reliable tests in the event of bleeding, recurrence, or in the case of urgent surgery. Although new oral drugs will be easier to use than the current ones, the short half-life and the absence of monitoring may cause problems in cases of poor compliance. Patient and physician education will probably also be a major issue with the use of these drugs in everyday clinical practice.

**Disclosures**

The author declares the following competing interests: uncompensated advisory membership for Bayer, Leo Pharma, and Sanofi-Aventis; research grants from Boehringer Ingelheim and Leo Pharma; travel grants from Boehringer Ingelheim and Leo Pharma; study investigator for Bayer, Deschi Sankyo, Leo Pharma, and Sanofi-Aventis.

**References**

New Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation: An Update

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Stroke prevention is important in the management of patients with atrial fibrillation (AF). Current guidelines recommend oral anticoagulation therapy in patients who are at moderate-to-high risk of stroke. Until recently, the only available oral anticoagulation therapies have been vitamin K antagonists (VKAs) such as warfarin. Unfortunately, VKAs have wide variability in their actions, drug and food interactions, and a need for regular monitoring and dose adjustment. As a result, the utility of these drugs has remained inadequate. Novel oral therapies, such as direct thrombin inhibitors and direct Factor Xa inhibitors, have been developed and have overcome many of the limitations of VKAs. Several large clinical trials (RE-LY, ROCKET-AF, ARISTOTLE, and AVERROES) have demonstrated that these new therapies (dabigatran etexilate, rivaroxaban, and apixaban) can potentially replace VKAs altogether. This article provides an update on new oral anticoagulants for stroke prevention in patients with AF.


Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. Stroke and thromboembolism occur more frequently in patients with AF and cause substantial morbidity and mortality [1–3]. AF-related strokes are associated with worse disability and longer hospital stays, and an increased mortality rate, compared with strokes that are attributable to other causes [4–7]. Hence, prevention of stroke is vital in the management of patients with AF. Current guidelines recommend oral anticoagulation therapy in patients who are identified as being at moderate-to-high risk of stroke [8,9].

Until recently, the only available oral anticoagulants have been the vitamin K antagonists (VKAs), such as warfarin or phenindione. VKAs have been shown to be very effective at reducing the risk of stroke and thromboembolism [10], particularly in older patients [11]. Unfortunately, their utility remains inadequate [9,12,13], and just over half of patients who are eligible for warfarin actually receive the drug [14]. This may partly be due to the many disadvantages of VKAs, including such factors as [15,16]:

- Inter- and intra-individual variability.
- The need for regular monitoring and dose adjustment.
- The increased risk of bleeding.
- The potential for drug and food interactions.

Furthermore, many studies show that patients who receive warfarin remain in the therapeutic range only approximately 50–60% of the time [17–19].

Over the years, novel therapies have been developed to try and overcome the limitations of VKAs, and it is hoped they may improve the use of oral anticoagulation therapy and, ultimately, reduce the risk of stroke in patients with AF. This article provides an update on new oral anticoagulants for stroke prevention in AF.

Vitamin K antagonists

Warfarin has been used as an oral anticoagulant since the 1950s; however, the mechanism of action was only discovered in 1978 [20]. Warfarin acts to reduce the effect of the vitamin K-dependent clotting factors, namely Factors II (thrombin), VII, IX, and X [21]. Precursors of these clotting factors are vitamin K-dependent proteins; warfarin modifies these precursors, leading to a reduction in the amount of vitamin K-dependent proteins that can be formed.

The therapeutic range for warfarin is between 2.0 and 3.5 units, where the patient is at the lowest risk of stroke and thromboembolism [22]. However, this range is large, and the patient may still be at risk of stroke outside this range. Moreover, the therapeutic range changes for some patients depending on their body weight, age, sex, and so on. This makes it difficult to maintain a patient in the therapeutic range.

Several large clinical trials (RE-LY, ROCKET-AF, ARISTOTLE, and AVERROES) have demonstrated that these new therapies (dabigatran etexilate, rivaroxaban, and apixaban) can potentially replace VKAs altogether. This article provides an update on new oral anticoagulants for stroke prevention in AF.
factors undergo carboxylation to allow them to function adequately. Carboxylation requires oxidation of vitamin K to form vitamin K epoxide, which can then be recycled back to the reduced form by the enzyme vitamin K epoxide reductase. Warfarin acts by inhibiting γ-carboxylation of the enzyme vitamin K epoxide reductase complex subunit (VKORC-1), thereby reducing the available stores of vitamin K and resulting in defective clotting factors [21]. Over a period of time, the previously produced functioning clotting factors will be degraded and the anticoagulation effect will become apparent. Peak concentrations of warfarin are reached approximately 90 min after administration, and the half-life is 36–42 h [21].

Warfarin has wide variability in its activity in the therapeutic dose range [22], and therefore requires dose-adjustment according to the international normalized ratio (INR), which in the context of stroke prevention in patients with AF should be maintained between 2 and 3 [15]. INRs outside of this range result in increased risk of stroke (INR <2), and bleeding (INR >3) [15,23]. The variability in efficacy with warfarin usage is thought to be due to mutations in the genes that encode cytochrome P450 and VKORC1 [23–25], as well as dietary and drug interactions [18,19].

Major bleeding is a recognized complication of warfarin therapy and the incidence is directly proportional to both the intensity of warfarin therapy [26] and the time spent at a high INR [27]. In certain instances the effects of warfarin may need to be reversed, such as prior to major surgery or in the event of significant bleeding. This can usually be achieved within 3–4 days by withholding warfarin. A more rapid reversal can be achieved by administering vitamin K (oral or intravenous) [28], fresh frozen plasma [29], prothrombin complex [30], or recombinant Factor VIIa [31]. The choice of antidote is dependent on the clinical situation.

New oral anticoagulants

Novel therapies have been developed to act at different stages of the clotting cascade (Figure 1) [32], namely the direct thrombin inhibitors (DTIs) and Factor Xa inhibitors (Table 1A and 1B).

Direct thrombin inhibitors

DTIs act by inhibiting Factor IIa (thrombin) to prevent formation of fibrin, blocking the common pathway in the coagulation cascade (Figure 1) [32,33].

Ximelagatran

Ximelagatran was the first oral direct thrombin inhibitor to be approved for clinical use in 2004 for thromboprophylaxis in patients undergoing hip surgery. However, it was withdrawn from the market in 2006 due to a significant number of patients with elevated plasma levels of liver enzymes, and numerous cases of acute liver failure [34].

Dabigatran

Dabigatran etexilate is an oral direct thrombin inhibitor, with a high affinity for thrombin and reversible binding [20]. It is converted from the produg to its active metabolite, dabigatran. It has a low bioavailability, estimated at 6%, and, consequently, high doses are required to maintain therapeutic plasma levels [35]. Peak concentrations are reached within 3 h of oral administration, and the half-life is 12–17 h. Dabigatran is mainly excreted renally (80%) and should therefore be used cautiously in patients with renal impairment. The mean half-life is prolonged in patients with moderate (creatinine clearance 30–50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment (18.4 h and 27.2 h, respectively) [36]. Its intestinal absorption is dependent on pH, and is reduced in patients who are taking proton pump inhibitors [35].

Unlike warfarin, dabigatran is metabolized independently of cytochrome P450 (CYP450) and is therefore safe in patients with moderate hepatic impairment [37]. Additionally, there is little drug and food interaction. The availability of dabigatran is dependent on P-glycoprotein, which binds to dabigatran within the gut, allowing excretion of the drug [35]. P-glycoprotein inhibitors, such as verapamil, amiodarone, quinidine, and ketoconazole, increase plasma concentrations of dabigatran. A reduced dose of dabigatran (110 mg twice daily) is recommended with verapamil and quinidine. Some caution may also be needed with amiodarone, and a lower dose may be prudent. Ketoconazole is contraindicated. Concomitant use...
of dabigatran with rifampicin, a P-glycoprotein inducer, should be avoided as the effect of dabigatran will be reduced. [35].

In certain situations the anticoagulant effect may need to be reversed, for example prior to major surgery. As the half-life of dabigatran is 12 h, omitting the dose for 24 h should be sufficient in patients with normal renal function. In patients with impaired renal function, an additional 24 h may be required. In contrast to warfarin, patients taking dabigatran do not require routine laboratory monitoring as it acts in a predictable manner. Laboratory testing may be needed prior to emergency surgery if drug failure is suspected or when life-threatening bleeding occurs. The thrombin time, partial thromboplastin time, and the ecarin clotting time can all provide qualitative assessment of the effect of dabigatran; however, the degree of effect cannot be reliably quantified [38].

Currently no specific antidote exists for dabigatran; although this is a drawback, the short half-life questions the need for a specific antidote. In cases of major bleeding, clinicians are recommended to withhold the drug to try and achieve adequate hemostasis, and to undertake supportive measures such as repeated blood transfusions until the effect of the dabigatran diminishes. In patients with severe or life-threatening bleeding, hemodialysis may be required [36]. A recent study has shown that, in contrast to warfarin, the serum concentration of prothrombin complex has no effect on the anticoagulant action of dabigatran [39]. The benefit of administering Factor VIIa is yet to be established [38].

The RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial of dabigatran etexilate was completed in 2009 (Table 1A and 1B) [40]. A total of 18 113 patients with

### Table 1A. Summary of the main clinical trials involving novel anticoagulants for stroke prevention in patients with non-valvular AF

<table>
<thead>
<tr>
<th>Drug characteristics</th>
<th>Dabigatran (RE-LY) [40]</th>
<th>Rivaroxaban (ROCKET AF) [58]</th>
<th>Apixaban (ARISTOTLE) [63]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug characteristics</strong></td>
<td>Oral direct thrombin inhibitor</td>
<td>Oral direct Factor Xa inhibitor</td>
<td>Oral direct Factor Xa inhibitor</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Oral direct thrombin inhibitor</td>
<td>Oral direct Factor Xa inhibitor</td>
<td>Oral direct Factor Xa inhibitor</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>6</td>
<td>60–80</td>
<td>50</td>
</tr>
<tr>
<td>Time to peak levels (h)</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>12–17</td>
<td>5–9 h in young, healthy individuals, 11–13 h in the elderly</td>
<td>9–14</td>
</tr>
<tr>
<td>Excretion</td>
<td>80% renal</td>
<td>66% liver, 33% renal</td>
<td>25% renal, 75% fecal</td>
</tr>
<tr>
<td>Dose</td>
<td>150 mg bid</td>
<td>20 mg qd</td>
<td>5 mg bid</td>
</tr>
<tr>
<td>Dose in patients with renal impairment</td>
<td>110 mg bid</td>
<td>15 mg qd (if creatinine clearance 30–49 mL/min)</td>
<td>2.5 mg bid</td>
</tr>
<tr>
<td>Special considerations</td>
<td>Intestinal absorption is pH-dependent and is reduced in patients who are taking proton pump inhibitors</td>
<td>Higher plasma levels expected in patients with renal or hepatic failure</td>
<td>Activity lower in fasted patients so should be taken after food</td>
</tr>
<tr>
<td></td>
<td>Higher plasma levels expected in patients with renal or hepatic failure</td>
<td>Increased risk of bleeding in patients who are taking verapamil, amiodarone, quinidine, or ketoconazole</td>
<td></td>
</tr>
<tr>
<td><strong>Study characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td>Randomized, open-label</td>
<td>Multicenter, randomized, double-blind, double-dummy</td>
<td>Randomized, controlled, double-blind, parallel arm</td>
</tr>
<tr>
<td>Number of patients</td>
<td>18 111</td>
<td>14 264</td>
<td>18 201</td>
</tr>
<tr>
<td>Follow-up period (months)</td>
<td>24</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Randomized groups</td>
<td>Dose-adjusted warfarin versus blinded doses of dabigatran (150 mg or 110 mg bid)</td>
<td>Dose-adjusted warfarin versus rivaroxaban 20 mg qd</td>
<td>Dose-adjusted warfarin versus apixaban 5 mg bid</td>
</tr>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (±SD or mIQR, years)</td>
<td>71.5±8.7</td>
<td>73 (65–78)</td>
<td>70 (63–76)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>63.6</td>
<td>61.3</td>
<td>64.5</td>
</tr>
<tr>
<td>Mean CHADS2 score</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; ARISTOTLE: Apixaban for the Prevention of Stroke in Subjects with AF; bid: twice daily; CHADS2: Cardiac Failure, Hypertension, Age, Diabetes, and Stroke (doubled); mIQR: median interquartile range; qd: once daily; RE-LY: Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET AF: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF; RR: relative risk; SD: standard deviation.
non-valvular AF were randomized into three treatment groups as follows:

- Dabigatran 110 mg twice daily.
- Dabigatran 150 mg twice daily.
- Dose-adjusted warfarin with target INR of 2–3.

Patients were blinded to the dose of dabigatran. The mean age of the patients was 71.5 years and the male:female ratio was almost 2:1 (63.6% male, 36.4% female). The mean CHADS₂ (Cardiac Failure, Hypertension, Age, Diabetes, and Stroke [Doubled]) score was 2.1. Approximately half of the patients had received long-term therapy with VKAs. The primary outcome measure was yearly rate of stroke or systemic embolic event, and was 1.53% per year in patients receiving dabigatran 110 mg, 1.11% per year in those who received dabigatran 150 mg, and 1.69% per year in those who received warfarin. Dabigatran 110 mg and 150 mg were found to be non-inferior to warfarin (p<0.001). Dabigatran 150 mg was superior to warfarin (relative risk [RR] 0.91, 95% confidence interval [CI] 0.53–0.82; p<0.001), although dabigatran 110 mg was not (RR 0.91, 95% CI 0.74–1.11; p=0.34). Rates of hemorrhagic stroke were higher in patients taking warfarin (0.38% per year) than in those taking dabigatran 110 mg (0.12% per year; RR 0.31, 95% CI 0.17–0.56; p<0.001) or 150 mg (0.10% per year; RR 0.26, 95% CI 0.14–0.49; p<0.001). Rates of major bleeding were higher in patients taking warfarin (3.36% per year) than in those taking dabigatran 110 mg (2.84% per year; RR 1.05, 95% CI 0.75–1.43; p=0.71) or 150 mg (2.84% per year; RR 1.05, 95% CI 0.75–1.43; p=0.71).

### Table 1B. Summary of the main clinical trials involving novel anticoagulants for stroke prevention in patients with non-valvular AF

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (RE-LY) [40]</th>
<th>Rivaroxaban (ROCKET AF) [58]</th>
<th>Apixaban (ARISTOTLE) [63]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Warfarin</td>
<td>Warfarin</td>
<td>Warfarin</td>
</tr>
<tr>
<td>(n=6015)</td>
<td>(n=6076)</td>
<td>(n=7133)</td>
<td>(n=9081)</td>
</tr>
<tr>
<td>Dose-adjusted</td>
<td>1.69</td>
<td>2.0 (0.88, 0.75–1.03; p&lt;0.001)</td>
<td>1.61 (0.79, 0.66–0.95; p&lt;0.001)</td>
</tr>
<tr>
<td>warfarin</td>
<td>(RR, 95% CI; p value)</td>
<td>[HR, 95% CI; p value]</td>
<td>[HR, 95% CI; p value]</td>
</tr>
<tr>
<td>target INR of 2–3</td>
<td>1.11 (0.86–1.40; p=0.35)</td>
<td>0.91 (0.66–0.95; p&lt;0.001)</td>
<td>0.91 (0.66–0.95; p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>1.53 (0.91–1.11; p for noninferiority &lt;0.001)</td>
<td>1.53 (0.66–0.95; p&lt;0.001)</td>
<td>1.53 (0.66–0.95; p&lt;0.001)</td>
</tr>
<tr>
<td>Stroke/systemic embolism</td>
<td>2.4 (intention-to-treat analysis)</td>
<td>2.1 (intention-to-treat analysis)</td>
<td>2.05 (0.77, 0.60–0.97; p=0.31)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.2 (0.86–1.40; p=0.35)</td>
<td>1.34 (1.11, 0.89–1.40; p=0.35)</td>
<td>1.34 (1.11, 0.89–1.40; p=0.35)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.38 (0.12–0.56; p&lt;0.001)</td>
<td>0.44 (0.26–0.59; p=0.24)</td>
<td>0.44 (0.26–0.59; p=0.24)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.36 (2.51–0.45)</td>
<td>3.4 (5.0, 4.7–9.3; p=0.02)</td>
<td>3.4 (5.0, 4.7–9.3; p=0.02)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.74 (0.23–0.31; p=0.003)</td>
<td>0.7 (0.67–0.93; p=0.03)</td>
<td>0.7 (0.67–0.93; p=0.03)</td>
</tr>
<tr>
<td>Extracranial bleeding</td>
<td>2.67 (2.84–1.07; p=0.001)</td>
<td>2.71 (0.80–1.01; p=0.001)</td>
<td>2.71 (0.80–1.01; p=0.001)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1.02 (1.51–1.19; p&lt;0.001)</td>
<td>1.12 (1.10, 0.86–1.41; p=0.43)</td>
<td>1.12 (1.10, 0.86–1.41; p=0.43)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.53 (0.72–1.35; p=0.07)</td>
<td>1.1 (0.81, 0.63–1.06; p=0.12)</td>
<td>1.1 (0.81, 0.63–1.06; p=0.12)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>4.13 (3.64–1.08; p=0.051)</td>
<td>2.2 (1.9–0.85; p=0.07)</td>
<td>2.2 (1.9–0.85; p=0.07)</td>
</tr>
</tbody>
</table>

Dabigatran has been found to be safe to use in patients undergoing cardioversion, with similar low rates of stroke 1-month post-cardioversion in patients taking warfarin (0.6%), dabigatran 110 mg twice daily (0.8%; p=0.71), and dabigatran 150 mg twice daily (0.3%; p=0.40) [42]. In this trial, 1983 cardioversions were performed in 1270 patients, making this the largest study to date of cardioversions in patients with AF. The study was not designed to assess the superiority of dabigatran over warfarin as this would require a far greater number of cardioversions to show significance, and a study of that size is unlikely to be performed. Nevertheless, the RE-LY study has shown that dabigatran is probably as safe and efficacious as warfarin in patients undergoing cardioversion.

Another study suggested that the risk of stroke with dabigatran 110 mg twice daily (2.32% per year; RR 0.84, 95% CI 0.58–1.20) or 150 mg twice daily (2.07% per year; RR 0.75, 95% CI 0.52–1.08) is comparable to that with warfarin (2.78% per year) in patients with previous history of stroke or transient ischemic attacks [43]. Wallentin et al. confirmed that the benefits of dabigatran were consistent irrespective of the quality of INR control, and indeed greater in centers associated with poor INR control compared with those associated with good INR control [44]. Furthermore, the benefit of dabigatran has been found to be independent of renal function [45].

Rates of myocardial infarction were found to be numerically (although not significantly) higher in patients taking dabigatran compared with those taking warfarin – it has been postulated that this may be due to the protective effects of warfarin [46,47].

The RELY-ABLE (Long-Term Multi-Center Extension of Dabigatran Treatment in Patients with AF Who Completed the RE-LY Trial; clinicaltrials.gov identifier NCT00808067) study was expected to have completed data collection by August 2011. This study is being carried out to evaluate the long-term safety of dabigatran by following up patients from the original RE-LY trial.

Dabigatran was approved by the US Food and Drug Administration (FDA) in October 2010 for use in the prevention of stroke and venothromboembolism in adult patients with non-valvular AF [48]. The FDA approved its use only at the 150 mg twice daily dose, which caused controversy. Their reasoning was that the 150 mg twice daily dose provided the greatest benefit in stroke prevention and it may almost be considered unethical to approve the 110 mg twice daily dose as this does not provide as much benefit. Additionally, there was concern that given the choice clinicians may “over-use” the 110 mg dose, which causes less major bleeding.

The FDA approved dabigatran 75 mg twice daily for stroke prevention in patients with AF and severe renal impairment (creatinine clearance <30 mL/min). This was also felt to be controversial as the 75 mg twice daily dose had not been studied in the RE-LY trial, and the recommendation for this dose was based on the pharmacokinetics of dabigatran [49]. In October 2010, Health Canada approved the 150 mg and 110 mg twice daily doses for stroke prevention in patients with AF [50]. In August 2011, the European Medicines Agency (EMA) approved the use of dabigatran for stroke prevention in patients with AF at the 150 mg twice daily and 110 mg twice daily doses [51]. The 110 mg twice daily dose was targeted at patients aged >80 years or those with an increased risk of bleeding.

In summary, dabigatran 110 mg twice daily was found to be noninferior compared with warfarin for the prevention of stroke or systemic embolism, with lower rates of major hemorrhage; dabigatran 150 mg twice daily was found to be superior to warfarin in the prevention of strokes or systemic embolism, but with comparable rates of major hemorrhage. Dabigatran 150 mg twice daily is therefore the preferred dose to provide the greatest benefit in stroke prevention. Substudy analyses have shown dabigatran 150 mg twice daily to be safe in patients undergoing cardioversion.

Dabigatran 110 mg twice daily should be used in elderly patients (aged >80 years), those with an increased risk of
Direct Factor Xa inhibitors

Direct Factor Xa inhibitors act by inhibiting Factor Xa (Figure 1). This prevents the conversion of prothrombin to thrombin, which in turn prevents conversion of fibrinogen to fibrin. Direct Factor Xa inhibitors include rivaroxaban, apixaban, edoxaban, betrixaban, and darexaban.

Rivaroxaban

Rivaroxaban is an oral, direct Factor Xa inhibitor that acts by competitively and reversibly binding to Factor Xa, both in its free form and also within the prothrombinase complex [52]. It has a high oral bioavailability (60–80%), peak plasma concentrations are seen within 3 h of administration, and the half-life is between 5 h and 9 h in young and healthy individuals, 11 h and 13 h in the elderly [53]. Two-thirds of the agent is metabolized via the liver (CYP450-dependent) and one-third via the kidneys [53–55]. Higher plasma levels are therefore expected in patients with renal or hepatic failure. It is advised that in doses exceeding 15 mg, rivaroxaban should be taken after food as there is lower activity in fasted patients [56].

Similar to dabigatran, routine laboratory monitoring is not required; however, rivaroxaban’s effects can be determined by measuring the plasma prothrombin and activated partial thromboplastin time [57]. Specific laboratory assays for rivaroxaban are currently being investigated. To reverse the effects of rivaroxaban, omitting the dose for 24 h should be sufficient; rivaroxaban has a shorter half-life compared with dabigatran. Therefore, its effect would be expected to diminish in a shorter time. One recent study of healthy males has shown that administration of prothrombin complex concentrate can immediately and completely reverse the effects of rivaroxaban [39].

The ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF) was a multicenter, randomized, double-blind, double-dummy trial of 14 264 patients with non-valvular AF (Table 1A and 1B) [53]. Patients were randomized to receive rivaroxaban 20 mg once daily (or 15 mg once daily if creatinine clearance was between 30 mL/min and 49 mL/min) or dose-adjusted warfarin to maintain an INR between 2.0 and 3.0, and followed-up for a period of 40 months.

The median age (interquartile range) of the patients in the ROCKET AF trial was 73 years (65–78 years), with a male:female ratio of approximately 3:2 (61.3% male, 30.7% female). The mean CHADS2 score was 3.5. All of the patients were at moderate-to-high risk of stroke. Substantial rates of comorbidities were present in the patients – 90.5% had hypertension, 62.5% had heart failure, 40.0% had diabetes, and 54.8% had had a previous stroke, systemic embolism, or transient ischemic attack.

“In ROCKET AF, stroke and systemic embolism occurred at a yearly rate of 2.1% in patients taking rivaroxaban vs. 2.4% for warfarin”

The primary endpoint of stroke and systemic embolism, occurred in the intention-to-treat analysis at a rate of 2.1% per year in patients taking rivaroxaban compared with 2.4% per year for warfarin (hazard ratio [HR] 0.88, 95% CI 0.75–1.03; p for noninferiority <0.001). In the intention-to-treat analysis, rivaroxaban was not found to be superior to warfarin in prevention of stroke and systemic embolism. Superiority was achieved in the on-treatment per protocol analysis. Rates of major bleeding were comparable in patients taking rivaroxaban (3.6%) and warfarin (3.4%; p=0.58). However, rates of intracranial hemorrhage were significantly lower in the rivaroxaban group (0.5% per year) compared with the warfarin group (0.7% per year; HR 0.67, 95% CI 0.47–0.93; p=0.02). Importantly, rates of major bleeding from a gastrointestinal site were significantly greater in the rivaroxaban group (3.2%)
compared with those taking warfarin (2.2%; p<0.001). Rates of critical bleeding were significantly lower in patients taking rivaroxaban (0.8% per year) compared with warfarin (1.2% per year; HR 0.69, 95% CI 0.58–0.91; p=0.007). Rates of fatal bleeding were also significantly lower in patients taking rivaroxaban (0.2% per year) compared with warfarin (0.5% per year; HR 0.50, 95% CI 0.31–0.79; p=0.003). In contrast to dabigatran, rates of myocardial infarction were found to be numerically (although not significantly) lower in patients taking rivaroxaban compared with warfarin.

In a substudy analysis of the ROCKET AF trial, rivaroxaban was found to be noninferior to warfarin in patients with moderate renal impairment [59]. Of the 14,264 patients with AF who were randomized, 2950 (20.7%) had moderate renal impairment, with creatinine clearance rates of 30–49 mL/min. Rates of stroke or systemic embolism were similar for patients taking rivaroxaban 15 mg once daily (1.71% per year) compared with those who received dose-adjusted warfarin (2.16% per year; HR 0.79, 95% CI 0.66–0.96; p for noninferiority <0.001). There was no significant difference in the rates of major bleeding in patients taking rivaroxaban (4.49% per year) compared with those who were receiving warfarin (4.7% per year; HR 0.95, 95% CI 0.72–1.26; p=not significant). However, there was a higher rate of bleeding from a gastrointestinal site in patients who were receiving rivaroxaban (4.1%) compared with those who were receiving warfarin (2.6%; p=0.02). The results of the substudy largely echo the findings from the main trial. Additionally, the study also showed that patients with moderate renal impairment had higher risk of strokes or systemic embolism and bleeding complications.

In summary, rivaroxaban 20 mg once daily (15 mg once daily in patients with a creatinine clearance rate of 30–49 mL/min) was found to be noninferior to warfarin in the prevention of stroke and systemic emboli in patients with a moderate-to-high risk of stroke. The rates of major bleeding were similar in patients who were treated with rivaroxaban and those who received warfarin. However, the rates of major bleeding from a gastrointestinal site were higher in patients who were treated with rivaroxaban (3.2%) compared with those who received warfarin (2.2%; p<0.001), but rates of intracranial hemorrhage were lower (0.5% vs. 0.7% per year; HR 0.67, 95% CI 0.47–0.93; p=0.02).

Apixaban
Apixaban is an oral, direct Factor Xa inhibitor with reversible binding [20]. It has an oral bioavailability of 50% and peak plasma concentrations are reached 3 h after oral administration [60]. The half-life is between 9 h and 14 h. Apixaban is metabolized via the liver (CYP450-dependent). Approximately 25% is excreted renally and the remainder is excreted in feces [60]. Similar to rivaroxaban, apixaban binds free Factor Xa as well as Factor Xa that is bound within the prothrombinase complex [60].

As with dabigatran and rivaroxaban, routine laboratory monitoring of patients who are being treated with apixaban is not required. Current studies suggest that anti-Factor-Xa assays may be more accurate than prothrombin time assays in determining the anticoagulant effect of the drug [61]. No antidote currently exists for apixaban, although a novel recombinant protein is undergoing investigation [62].

The ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects with AF) study was a randomized, controlled, double-blind, parallel-arm trial designed to evaluate the efficacy and safety of apixaban in preventing stroke and systemic embolism in patients with non-valvular AF (Table 1A and 1B) [63]. In this trial, 18,201 patients with non-valvular AF were randomized to receive apixaban 5 mg twice daily (or 2.5 mg twice daily for patients with two of the following: aged ≥80 years, body weight ≤60 kg, or a serum creatinine of ≥1.5 mg/dL (≥133 µmol/L), or dose-adjusted warfarin to maintain an INR of 2–3. The median age (interquartile range) of the patients in the trial was 70 years (63–76 years), with a male:female ratio of almost 2:1 (male 64.5%, female 35.5%). The mean CHADS2 score was 2.1. Approximately 57% of patients had been previously treated with VKAs, and 19% had a prior history of stroke, systemic embolism, or transient ischemic attack. Patients were followed up for 40 months. Patients receiving warfarin were in the therapeutic range for a mean of 62.2% of the study duration.

“In ARISTOTLE, stroke or systemic embolism occurred less frequently in the apixaban compared with the warfarin group”

The primary outcome was stroke or systemic embolism, which occurred less frequently in the apixaban group (1.27% per year) compared with the warfarin group (1.60% per year; HR 0.79, 95% CI 0.66–0.95; p<0.001 for noninferiority, p=0.01 for superiority). Rates of major bleeding were lower in the apixaban group (2.13% per year) compared with the warfarin group (2.59% per year; HR 0.96, 95% CI 0.78–1.18; p=0.48). Rates of intracranial bleeding were significantly lower in patients who were treated with apixaban (0.33% per year) compared with those who received warfarin (0.80% per year; HR 0.42, 95% CI 0.30–0.58; p<0.001). Rates of adverse events were similar in both groups. This study also showed that rates of myocardial infarction were similar in patients taking apixaban and those receiving warfarin.

AVERROES (Apixaban vs. Acetylsalicylic Acid to Prevent Stroke in AF) was a double-blind, randomized, active-controlled study that was designed to evaluate apixaban compared with aspirin in patients who are unsuitable for therapy with a
VKA [64]. A total of 5600 patients with non-valvular AF and at least one risk factor were randomized to receive apixaban 5 mg twice daily (or 2.5 mg twice daily in selected patients) or aspirin (81–324 mg/day).

The mean age of the patients was 70 years, with a male:female ratio of approximately 3:2 (male 59%, female 41%). The mean CHADS2 score (± standard deviation) was 2.1 (±1.1). Approximately 40% of patients had previously received VKAs. The first formal interim analysis of efficacy found that primary outcome events had occurred approximately 50% less frequently in patients who received apixaban than in those who received aspirin. The data monitoring committee recommended that the trial be stopped early, and that all patients should receive open-label apixaban. The primary outcome of stroke or systemic embolism occurred less frequently in patients who were treated with apixaban (1.7% per year) compared with those who received aspirin (3.6% per year; RR reduction 0.48, 95% CI 0.34–0.67; p<0.001). Rates of major bleeding were similar in patients taking apixaban (1.6% per year) and warfarin (1.4% per year; RR 1.18, 95% CI 0.77–1.78; p=0.45), and rates of intracranial bleeding were also similar (0.5% per year for those receiving apixaban, 0.4% per year for those receiving aspirin; RR 1.19, 95% CI 0.53–2.66; p=0.43).

The AVERROES trial showed apixaban to be superior to aspirin for stroke prevention in patients with non-valvular AF; however, this should be placed into context. The European Society of Cardiology guidelines currently recommend oral anticoagulants in place of aspirin in patients with an intermediate risk of stroke, and no therapy in place of aspirin in patients with low risk of stroke [8].

In summary, apixaban 5 mg twice daily (2.5 mg twice daily in selected patients) was found to be superior to warfarin in the prevention of stroke or systemic embolism in patients with non-valvular AF; with lower rates of major bleeding (including intracranial bleeding) and a similar rate of adverse events. Furthermore, apixaban was found to be more effective than aspirin at stroke prevention in patients with non-valvular AF; with similar rates of major bleeding and intracranial hemorrhage. Of note, current guidelines do not encourage the use of aspirin for stroke prevention in AF [8].

### Other anticoagulants

Several drug therapies are currently undergoing evaluation for use in the prevention of stroke in patients with non-valvular AF (Table 2).

AZD-0837 is an extended-release oral direct thrombin inhibitor that has completed a Phase II trial [65]. AZD-0837 is rapidly metabolized to AR-H067657, which has a half-life of 9–14 h in healthy subjects [66,67]. AZD-0837 and its metabolites are excreted renally and fecally [68]. The extended-release formulation was designed to provide consistent plasma levels allowing for a stable anticoagulant effect with a once-daily dosing regimen. In the Phase II trial, 955 patients with non-valvular AF and at least one risk factor for stroke were randomized to receive a VKA (dose adjusted to achieve INR 2–3) or AZD-0837 at doses of 150 mg, 300 mg, and 450 mg once daily or 200 mg twice daily for a mean of 138–145 days. Total bleeding rates were similar or lower in all AZD-0837 groups compared with the VKA group, and there were fewer clinically relevant bleeding events in patients receiving AZD-0837 at the 150 mg and 300 mg once daily dose. D-dimer was used as a biomarker of thrombogenesis, and found to be lowered in patients naïve to VKA taking AZD-0837 in all groups. In patients who had previously taken a VKA, D-dimer levels started low and remained low in all AZD-0837 groups. Few strokes or systemic embolisms occurred during this study, and adverse events were similar in all groups. In the AZD-0837 groups the mean serum creatinine levels increased by approximately 10% from baseline and returned to baseline after withdrawal of the study drug. The findings of this study demonstrated that AZD-0837 was generally well tolerated and that a dose of 300 mg once daily provides similar suppression of thrombogenesis at a potentially lower bleeding risk compared with dose-adjusted VKA.

Tecarfarin (ATI-5923) is a structural analogue of warfarin that is not metabolized by the CYP450 system. It is thought to have less variability compared with warfarin, which may improve the time in the therapeutic range. It has completed a Phase II trial in

### Table 2. Novel oral anticoagulants currently under evaluation for stroke prevention in patients with atrial fibrillation.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Stage of testing (clinicaltrials.gov identifier)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD-0837</td>
<td>Oral extended-release direct thrombin inhibitor</td>
<td>Completed Phase II trial (NCT00684307)</td>
</tr>
<tr>
<td>ATI-5923 / Tecarfarin</td>
<td>Structural analogue of warfarin (thought to have less variability than warfarin)</td>
<td>Completed Phase II trial (NCT00431782)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Oral Factor Xa competitive inhibitor</td>
<td>Completed Phase II trial (NCT005004556)</td>
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<tr>
<td>Betrixaban</td>
<td>Oral Factor Xa competitive inhibitor</td>
<td>Completed Phase II trial (NCT00742859)</td>
</tr>
<tr>
<td>YM150 / Darexaban</td>
<td>Oral Factor Xa competitive inhibitor</td>
<td>Completed Phase II trial (NCT00938730) Further development has been discontinued</td>
</tr>
</tbody>
</table>
patients with AF [69]. Tecarfarin was found to be non-superior with regards to time in therapeutic range when compared with warfarin in patients who required chronic anticoagulation [70].

Edoxaban, an oral Factor Xa inhibitor, is currently undergoing a randomized, double-blind, double-dummy, multicenter trial to evaluate its safety and efficacy compared with warfarin in patients with non-valvular AF (ENGAGE AF TIMI 48; clinicaltrials.gov identifier NCT00781391). The 30 mg or 60 mg once daily dose is being compared with dose-adjusted warfarin in approximately 20 000 patients with AF.

Betrixaban and darexaban (YM150) are oral Factor Xa inhibitors that have completed Phase II trials in patients with non-valvular AF (EXPLORE-Xa and OPAL-2, respectively; clinicaltrials.gov identifiers NCT00742859 and NCT00938730). However, development of darexaban has been discontinued.

**Conclusion**

Novel anticoagulants have been shown to be at least as effective as warfarin in the prevention of stroke in patients with AF (Table 3). Furthermore, treatment with these drugs has been shown to result in similar rates of major bleeding and adequate safety profiles compared with warfarin. The oral DTIs and Factor Xa inhibitors overcome some of the limitations of warfarin therapy. For example, they have few food or drug interactions and do not require regular monitoring or dose adjustment, which is more convenient for patients and offers a cost saving to the health service. Although initially these anticoagulants will be relatively expensive, it is inevitable that competition will drive down the price. Until then, it is clear that cost will be a major drawback to the uptake of these novel agents.

Another limitation is the lack of antidote to reverse the effect of these anticoagulants. This may be problematic in patients who suffer major bleeding or who require urgent reversal of anticoagulation, for example prior to major surgery. However, the relatively short half-lives of these drugs compared with warfarin may offset this disadvantage, as the anticoagulant effect will be expected to diminish soon after the drug is withheld.

Reassuringly, it appears that clinicians may soon have a wider choice of anticoagulants that can be tailored to the individual needs of the patient. Dabigatran for stroke prevention in patients with AF appears to be superior to warfarin at the 150 mg dose. It is also safe to use in patients who are undergoing cardioversion, which is an important consideration for clinicians.

Rivaroxaban is noninferior to warfarin in the stricter “intention-to-treat” analysis, and superior in the “on-treatment” analysis. However, it should be noted that in the ROCKET AF trial the patients who were studied had substantial comorbidities and were at a higher risk of stroke compared with patients in RE-LY and ARISTOTLE. The mean CHADS² score of patients in the ROCKET AF trial was 3.5 compared with 2.1 in patients in the RE-LY and ARISTOTLE trials.

**Table 3. Summary of new oral anticoagulants for stroke prevention in patients with AF**

| RE-LY [40]                        | Dobigatran 150 mg twice daily is superior to warfarin in prevention of stroke in patients with AF, with similar rates of major bleeding
|                                  | Dobigatran 150 mg twice daily caused higher rates of major bleeding in patients aged ≥75 years compared with warfarin
|                                  | Dobigatran 110 mg twice daily is as effective as warfarin, but with lower rates of major bleeding
|                                  | Dobigatran 110 mg twice daily caused similar rates of major bleeding in patients aged ≥75 years compared with warfarin
|                                  | Dobigatran is safe to use in patients who are undergoing cardioversion
|                                  | Adverse effects of dabigatran include dyspepsia and higher rates of myocardial infarction
| ROCKET AF [58]                    | Rivaroxaban 20 mg daily is as effective as warfarin in stroke prevention in patients with moderate-to-high risk of stroke and comorbidities
|                                  | Rivaroxaban 20 mg daily results in similar rates of major bleeding as warfarin, with fewer intracranial bleeds but more gastrointestinal bleeds
| ARISTOTLE [63]                    | Apixaban 5 mg twice daily is superior to warfarin in stroke prevention
|                                  | Apixaban 5 mg twice daily causes less major bleeding and intracranial bleeding than warfarin
|                                  | Apixaban 5 mg twice daily has similar adverse effect profile to warfarin
| AVERROES [64]                      | Apixaban 5 mg twice daily is more effective at stroke prevention than aspirin
|                                  | Apixaban 5 mg twice daily results in similar rates of major bleeding and intracranial hemorrhage as aspirin

AF: atrial fibrillation; ARISTOTLE: Apixaban for the Prevention of Stroke in Subjects with AF; AVERROES: Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in AF; RE-LY: Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET AF: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF.
Rivaroxaban is a once-daily drug, which may be more suitable for patients in whom compliance is a concern, although it may not be suitable in patients who are at risk of gastrointestinal bleeding. Rivaroxaban is currently the only new agent with a possible antidote (prothrombin complex concentrate), which may allay some of the fears that clinicians have surrounding anticoagulant reversal.

Apixaban is superior to warfarin in both prevention of stroke and systemic embolism, and is also associated with a significant reduction in all-cause mortality and significantly lower rates of major bleeding, including intracranial bleeding.

Further head-to-head trials are needed to directly compare the effectiveness of these drugs. Nevertheless, the evidence clearly shows that dabigatran, rivaroxaban, and apixaban are all major contenders to replace warfarin (and, indeed, aspirin) for the prevention of stroke in patients with AF.

Disclosures
Professor Lip has served as a consultant for Astellas, AstraZeneca, Bayer, Biotronik, BMS/Pfizer, Boehringer Ingelheim Meds, Portola and Sanofi has been on the speaker’s bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi-Aventis. Dr Adlan has no competing financial interests to declare.

References


Outcomes and safety of antithrombotic treatment in patients aged 80 years or older with nonvalvular atrial fibrillation

Ruiz Ortiz M, Romo E, Mesa D et al. 

This study assessed the efficacy, under daily clinical practice conditions, of oral anticoagulation for patients aged ≥80 years with non-valvular atrial fibrillation. Patients were treated as per standard guidelines issued by scientific societies, and their progress monitored. All serious adverse events were logged according to patient group (oral anticoagulation vs. control). The findings suggest that oral anticoagulation is safe in this at-risk subgroup of older patients, and embolic event and mortality rates were lower than in controls.

The beneficial effect of antithrombotic treatment on mortality and morbidity in patients with atrial fibrillation (AF) is well established. However, the gain in terms of embolic episode prevention is frequently offset by hemorrhagic episodes. The aforementioned balance is of significant importance in subgroups of particularly frail patients, such as older individuals. Therefore, the aim of the present study was to evaluate the effectiveness and safety of oral anticoagulation as thromboembolic prophylaxis for patients aged ≥80 years with non-valvular AF in daily clinical practice.

The present study included 269 patients aged ≥80 years with non-valvular AF from the outpatients department of the study hospital. Of the 269 patients, 73% were aged 80–84 years, 21% were aged 85–89 years, and only 6% were aged ≥90 years. Patients with no contraindication for anticoagulation and with at least one additional thromboembolic risk factor(s) (other than age) were offered oral anticoagulation. Most patients received acenocoumarol; only a minority received warfarin. Patients with an absolute anticoagulation contraindication were treated with aspirin, other platelet aggregation inhibitors, or no antithrombotic treatment at the discretion of the responsible physician. As stated by the authors, sufficient time was spent explaining the benefits and risks of oral anticoagulation to the patients and their families to avoid treatment refusal.

Of the 269 patients included in the present study, 164 received oral anticoagulants (61%) and 105 (39%) did not. The patients prescribed oral anticoagulation were younger and presented with a greater frequency of hypertension and coronary heart disease, and had a greater CHADS$_2$ (Cardiac Failure, Hypertension, Age, Diabetes, and Stroke [doubled]) score, than the non-anticoagulated patients. Among non-anticoagulated patients, the majority received aspirin (37%). After 2.8±1.9 years of follow-up, the raw embolic event rate (per 100 patient-years) was significantly lower in the patients who had received oral anticoagulation (1.52% vs. 8.30%; p<0.01), with a non-significantly greater rate of bleeding events (3.03% vs. 1.25%; p=0.14). The combined embolic and hemorrhagic event rate (4.55% vs. 9.55%; p<0.01) and all-cause mortality (6.67% vs. 10.94%; p=0.04) was also lower in this subgroup. Those patients aged ≥85 years who had received oral anticoagulants showed a non-significant trend toward lower raw rates of embolic events and a greater risk of severe bleeding, with a neutral effect on the combined embolic and hemorrhagic event rate and all-cause mortality. On multivariate analysis, after adjusting for age, gender, CHADS$_2$ score, and coronary heart disease, oral anticoagulation independently predicted embolic events (HR 0.17; p<0.001) and all-cause mortality (HR 0.52; p<0.01). No association was observed between anticoagulant treatment and severe bleeding (HR 2.66; p=0.13).

The findings of the present study showed that oral anticoagulation is effective and safe in daily clinical practice, even in patients aged ≥80 years. However, the study is subject to certain limitations. Firstly, the duration of therapeutic international normalized ratio (INR) is not reported. Secondly, the relatively small study sample precludes subgroup analysis (i.e. within each CHADS$_2$ score stratum). Under the same notion,
findings regarding the advanced aged patients (≥85 years) should be interpreted with caution due to the very few events observed in this category. Furthermore, the newly published HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly [aged >65 years], Drugs/Alcohol Concomitantly) score was not utilized to draw clinically important conclusions regarding the risk of bleeding. Finally, a selection bias might be present as stated by the authors, since patients who were more ill and frail could not have been offered oral anticoagulation.

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Rivaroxaban versus warfarin in nonvalvular atrial fibrillation

Warfarin lowers the rate of ischemic stroke in patients with atrial fibrillation but requires frequent monitoring and adjustment of dosages. In this double-blind trial, the authors investigated whether rivaroxaban could provide a more consistent and predictable anticoagulation effect than warfarin. The results show that rivaroxaban was non-inferior to warfarin for prevention of stroke and systemic embolism. There was no significant difference between groups with regard to the risk of major bleeding; however, intracranial and fatal bleeding occurred less frequently in the rivaroxaban-treated group.

Atrial fibrillation (AF) is associated with a significantly elevated stroke risk and accounts for up to 15% of strokes in patients of all age groups. Administration of warfarin has been the cornerstone of stroke prevention in patients with AF considered at high stroke risk. While warfarin is highly effective for stroke prevention in this group of patients, food and drug interactions necessitate continuous coagulation monitoring and dose adjustments.

Rivaroxaban is an oral Factor Xa inhibitor that is associated with a more consistent and predictable anticoagulation effect compared with warfarin. ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke an Embolism Trial in Atrial Fibrillation) compared rivaroxaban once-daily with dose-adjusted warfarin for the prevention of stroke and systemic embolism in patients with non-valvular AF at moderate to high risk of stroke. Within this double-blind trial, a total of 14,264 patients were randomized to either rivaroxaban 20 mg daily or dose-adjusted warfarin. The primary endpoint within per protocol analysis was stroke or systemic embolism and was designed to scrutinize the non-inferiority of rivaroxaban to warfarin.

Within the per protocol population, the primary endpoint was noted in a total of 188 patients in the rivaroxaban arm (1.7% per year) and in 241 patients in the warfarin arm (2.2% per year). These differences were statistically significant (hazard ratio [HR] 0.79 in the rivaroxaban group, 95% confidence interval [CI] 0.66–0.96; p<0.001 for noninferiority). In the intention-to-treat analysis, however, no significant difference in the rates of the primary endpoint was observed (p=0.12 for superiority).

Major and non-major clinically relevant bleeding complications were not significantly different between the treatment groups: 14.9% per year in the rivaroxaban group and 14.5% in the warfarin group. However, both intracranial (0.5% vs. 0.7%, p=0.02) and fatal bleeding (0.2% vs. 0.5%; p=0.003) were observed significantly less frequently in the rivaroxaban group compared with the warfarin group. Thus, the authors conclude that in patients with AF, rivaroxaban is noninferior to the standard treatment, warfarin, for the prevention of stroke and embolism. While there was no between-group difference in the risk of major bleeding, intracranial bleeding and fatal bleeding were less frequently observed in patients randomized to rivaroxaban.

The results of this trial indicate that a novel orally available drug is equally effective without being associated with a higher bleeding probability, which is excellent news for AF patients. The ROCKET AF trial was the seventh in the rivaroxaban study program showing either superiority or noninferiority of this drug for various indications.

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Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial

In the present work, the authors compared bleeding risk of dabigatran 150 mg and 110 mg twice daily and warfarin when used for stroke prevention in patients at risk of atrial fibrillation as part of the RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) trial, a cohort of almost 20,000 patients. It was found that dabigatran 150 mg and 110 mg, when compared with warfarin, had lower risks of intracranial and extracranial
bleeding in patients aged <75 years. In patients aged ≥75 years, the risk of intracranial bleeding was also lower with dabigatran, but the risk of extracranial bleeding was similar or higher; this was true for both dose levels of dabigatran when compared with warfarin.

Dabigatran, a novel oral direct thrombin inhibitor, has recently been shown to be associated with similar risk of stroke and lower risk of major bleeding at doses of 110 mg twice daily, and with lower risk of stroke and similar risk of major bleeding at doses of 150 mg twice daily, compared with warfarin in patients with atrial fibrillation (AF) on long-term anticoagulation. The present study reported the safety results of both doses of dabigatran compared with warfarin for different types of major bleeding and also in key subgroups. According to the study design, major bleeding was defined as bleeding associated with a reduction in hemoglobin level of ≥2.0 g/dL, transfusion of at least two units of blood, or symptomatic bleeding into a critical area or organ. Life-threatening bleeding included fatal or symptomatic intracranial bleeding, bleeding associated with a hemoglobin decrease of ≥5.0 g/dL or requiring transfusion of at least four units of blood or inotropic agents, or bleeding necessitating surgery. Of interest, location of major bleeding – intracranial versus extracranial (gastrointestinal [GI] or non-GI) bleeding – was also studied.

Dabigatran 110 mg twice daily compared with warfarin was associated with a lower risk of major bleeding (2.37% vs. 3.57%; p=0.002), including life-threatening bleeding (1.24% vs. 1.85%; p=0.001); however, no difference was observed in extracranial bleeding (2.66% vs. 2.84%; p=0.420). Dabigatran 150 mg twice daily and warfarin, as expected, was associated with similar risks of major bleeding (3.31% vs. 3.57%; p=0.320). In contrast, dabigatran 150 mg twice daily was associated with more GI bleeding (1.85% vs. 1.25%; p<0.001) and less intracranial bleeding (0.32% vs. 0.76%; p<0.001) compared with warfarin. It is worth mentioning that dabigatran, although lacking an antidote, was not associated with increased surgical bleeding compared with warfarin.

Assessment of interactions between various baseline characteristics and treatment effects showed that only increasing age could modify the association of anticoagulation modality and bleeding events. Specifically, compared with warfarin, dabigatran was associated with a lower risk of major bleeding in patients aged <75 years (for both doses) whereas for patients aged ≥75 years, dabigatran was associated with a similar (for 110 mg dose) or a trend toward higher risk of major bleeding (150 mg dose; p for interaction <0.001 for both doses). The marked interaction between treatment and age was evident for extracranial bleeding but not for intracranial bleeding; the risk of intracranial bleeding was lower with both doses of dabigatran compared with warfarin, irrespective of age. The risk of bleeding also increased with decreasing creatinine clearance and with concomitant aspirin or combined antiplatelet use, but there were no significant interactions between creatinine clearance or concomitant aspirin and randomized treatment. Likewise, there were no significant interactions between sex, body weight, or concomitant use of amiodarone or proton pump inhibitors and randomized treatment.

The authors conclude that in patients aged <75 years, the higher dabigatran dose seems preferable because of the lower risk of stroke without any increase risk of bleeding; at older ages, however, the lower dabigatran dose might be considered a means to reduce the risk of bleeding in selected patients who are at high risk of bleeding. Furthermore, these data also highlight that dabigatran should be used with caution in patients with concomitant aspirin/dual antiplatelet therapy, or in patients with declining renal function.

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Stent Thrombosis

Frequency and predictors of stent thrombosis after percutaneous coronary intervention in acute myocardial infarction


The present study investigated potential predictors and occurrence of thrombosis as a result of stent use as part of the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. The findings suggest that thrombosis related to stent use is not a rare phenomenon in the 2 years following primary percutaneous coronary intervention in ST-segment elevation MI. It was also found that thrombosis appears to occur with similar frequency in cases of drug-eluting and bare-metal stent use, and with bivalirudin monotherapy versus heparin plus a glycoprotein platelet inhibitor.

Although the use of drug-eluting stents (DES) during percutaneous coronary intervention (PCI) in patients with stable coronary artery disease or acute coronary syndromes has reduced vessel restenosis, there is an increased risk of stent thrombosis. Therefore, the present study sought to evaluate the frequency and predictors of stent thrombosis occurring within the first 2 years after stent implantation in the setting of primary PCI in patients with ST-segment elevation myocardial infarction (STEMI).
The study enrolled patients with STEMI presenting within 12 h after the onset of symptoms. A total of 3602 patients were randomized to unfractionated heparin (UFH) plus a glycoprotein platelet inhibitor (GPI; n=1802) or bivalirudin monotherapy (n=1800). After angiography, 3006 patients were then randomized again to either DES (paclitaxel-eluting; n=2261) or to bare-metal stents (BMS; n=861). The patients were followed up to 2 years for early (≤30 days) or late (>30 days) stent thrombosis.

Definite or probable stent thrombosis within 2 years occurred in 137 patients (4.4%), including 28 acute events (within 24 h; 0.9%), 49 subacute events (>24 h to 30 days; 1.6%), 32 late events (>30 days to 1 year; 1.0%), and 33 very late events (>1 year; 1.1%). Compared with patients without stent thrombosis, those with stent thrombosis at any time-point within the 2-year follow-up period were younger and had a higher rate of insulin-treated diabetes mellitus, current smoking, prior MI, and prior PCI, and also had a higher baseline platelet count. With regard to periprocedural characteristics, lesions with stent thrombosis were more likely to be aneurysmal, to have a larger baseline thrombus burden, and to have a greater residual stenosis after the procedure. Stent thrombosis was also associated with a significantly higher prevalence of baseline and post-procedural Thrombolysis in MI (TIMI) flow grade 0/1. The type of stent implanted (DES vs. BMS) was not related to stent thrombosis during any time interval up to 2 years, including very late stent thrombosis. Regarding antithrombotic treatment, stent thrombosis within 2 years occurred with similar frequency in patients treated either with UFH plus a GPI or with bivalirudin monotherapy; however, acute stent thrombosis was more common with bivalirudin, whereas stent thrombosis after 24 h was more common with UFH plus a GPI.

Patients with stent thrombosis compared with those without stent thrombosis less frequently received a preprocedural loading dose of clopidogrel 600 mg. The high loading dose mainly impacted subacute thrombosis. Pre-randomization UFH was protective against the occurrence of cumulative stent thrombosis through 2 years, particularly against acute stent thrombosis. The predictors of stent thrombosis varied according to different time intervals. Independent predictors of early stent thrombosis were a higher baseline platelet count, insulin-treated diabetes mellitus, no administration of pre-randomization UFH, angiographic ulceration, a 600-mg loading dose of clopidogrel, and baseline TIMI grade 0/1 flow. Independent predictors of late and very late stent thrombosis (30 days to 2 years) were a higher baseline platelet count, current smoking, insulin-treated diabetes mellitus, and prior PCI.

In summary, the present study showed that stent thrombosis occurs relatively frequently within 2 years after primary PCI in STEMI, although with comparable rates with DES and BMS, and with bivalirudin monotherapy and UFH plus GPI combined therapy. More importantly, it was found that optimizing adjunct antithrombotic and antiplatelet therapy may reduce early stent thrombosis. However, the findings of the present study should be viewed with caution owing to certain limitations. As stated by the authors, the number of events was relatively low and therefore the study was not powered to completely exclude small differences in stent thrombosis between stent types or pharmacological regimens. Furthermore, not all multivariable correlates of stent thrombosis were identified, especially in each discrete time interval. Finally, it should be noted that pre-randomization heparin and loading dose of clopidogrel were not given in a randomized fashion but rather on the discretion of managing physicians.

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Usefulness of preprocedure high-sensitivity C-reactive protein to predict death, recurrent myocardial infarction, and stent thrombosis according to stent type in patients with ST-segment elevation myocardial infarction randomized to bare metal or drug-eluting stenting during primary percutaneous coronary intervention


This study showed that high-sensitivity C-reactive protein measured during primary percutaneous coronary intervention in patients suffering from ST-segment elevation myocardial infarction is predictive of adverse outcome. In addition, the presented findings suggest that the choice of either drug-eluting stent or bare-metal stent might be best made based on the inflammatory status of the patient.
and maintaining processes leading to these complications. The present study was a post hoc analysis of the DEDICATION (Drug Elution and Distal Protection in Acute MI) trial [1], a randomized controlled trial that was originally designed to evaluate whether implantation of a drug-eluting stent (DES) reduces neointimal proliferation in the infarct-related lesion, and thereby improves clinical outcome compared with bare-metal stents (BMS) in an unselected group of patients with STEMI. A total of 301 patients from one of the participating DEDICATION centers were included in the current analysis. In these patients, blood samples for high-sensitivity C-reactive protein (hs-CRP) measurement were drawn just before PCI was performed. As expected, hs-CRP proved to be an independent predictor of death and all non-fatal recurrent MIs (hazard ratio [HR] 2.7, 95% confidence interval [CI] 1.3–5.6) at a 36-month follow-up, as were age (HR 1.045 per year, 95% CI 1.016–1.075) and multivessel coronary disease (HR 2.1, 95% CI 1.4–3.2). Notably, when applying a clinical relevant hs-CRP cut-off of >2 mg/mL, significant differences for occurrence of death and recurrent myocardial infarction were seen: 4.8% for those with BMS and low hs-CRP, 11.9% in the DES and low hs-CRP (≤2 mg/L) group, 17.6% for those with DES and high hs-CRP, and 27.9% in the BMS and low hs-CRP group. These findings indicate that when selecting either BMS or DES for PCI in STEMI, the inflammatory status of the patient might be worth considering, since BMS seems to have the most favorable outcome in low-inflammatory patients, while DES is associated with favorable outcome in patients with high hs-CRP levels. Importantly, since this was a post hoc analysis and not the primary study outcome, several relevant biases might be present. Therefore, the results of this study cannot be extrapolated for use in daily practice before proper confirmation of the main findings is accomplished.


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Comparison of the diagnostic performance of the original and modified Wells score in inpatients and outpatients with suspected deep vein thrombosis


Wells scores (both original and modified) are commonly used for pretest probability assessment of deep vein thrombosis (DVT). The aim of the current study was to compare the predictive performance of both forms of the Wells score in consecutive inpatients and outpatients with clinical suspicion of DVT. The pretest DVT probability was determined using both scores. The results show that both Wells scores perform well for proximal DVT pretest probability prediction. However, neither score was particularly useful for assessing patients who are hospitalized or patients with isolated distal DVT.

Less than one-quarter of patients with suspected deep vein thrombosis (DVT) actually exhibit the disease. Therefore, the availability of appropriate diagnostic strategies is crucial. The Wells score is considered the best prediction rule in patients with suspected DVT. It consists of nine clinical features with a potential impact on the probability of the presence of DVT and was developed in ambulatory patients presenting to tertiary care centers for a suspected first DVT episode. Recently, this score has been modified by the authors, adding a further item for previously documented DVT. In contrast to the original Wells score, the modified Wells score has only been validated in outpatients and emergency departments.

In the current study, Engelberger and colleagues prospectively enrolled 298 inpatients and outpatients with clinical suspicion of DVT. Pretest probability of DVT presence was assessed utilizing both the original and the modified Wells score. The probability was classified as low, intermediate, or high. D-dimer measurement was performed in patients without high probability of DVT based on the original Wells score.

Patients with D-dimer levels <500 μg/L did not undergo further diagnostic testing and were not treated. Complete lower limb compression ultrasound was performed in the remaining patients. Patients with diagnosed DVT were treated with anticoagulation. Objectively confirmed symptomatic venous thromboembolism within 3 months of enrollment was defined as the primary study endpoint.

Out of 298 patients with suspected DVT, 82 (27.5%) actually exhibited DVT, and 46 of them had proximal DVT. Compared with the modified score, the original Wells score regarded a higher proportion of patients as low risk (53% vs. 48%; p<0.001) and a lower proportion as high risk (17% vs. 15%; p=0.02). The prevalence of proximal DVT in each category was similar with both scores (low: 7% vs. 8%, intermediate: 16% vs. 19%, high: 36% vs. 37%).

Therefore, the authors conclude that the original and modified Wells scores perform equally well in proximal DVT pretest probability prediction. Neither score appears to be particularly useful in hospitalized patients or those with isolated distal DVT. For this reason, scores that accurately predict DVT pretest probability among inpatients with clinically suspected DVT are required.

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MRI discriminates thrombus composition and ST resolution after percutaneous coronary intervention in patients with ST-elevation myocardial infarction


In an attempt to assess thrombus age and composition, and to predict the success of primary percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction, the authors of the present work performed MRI of aspirated coronary thrombi. It was demonstrated that MRI analysis, and in particular T2 relaxation values of the aspirated material, correlated with myocardial perfusion status as measured with ST-segment resolution on electrocardiogram (ECG).

The use of magnetic resonance imaging (MRI) in evaluating patients with ischemic heart disease has been well established. MRI can provide high-resolution images of the coronary arteries, which allow the identification of the presence of intraluminal stenosis. However, other than in animal models, it has not been used for detailed analysis of coronary artery thrombus characteristics to date. In the present study, 100 consecutive ST-segment elevation acute myocardial infarction (STEMI) patients undergoing emergency percutaneous coronary intervention (PCI) were included. Material aspirated during PCI was examined firstly by MRI, then by pathological evaluation. Patient outcomes were correlated to the MRI and pathological classification results. Sufficient material was aspirated for MRI in only 59 patients. After treatment, significant ST resolution indicating adequate myocardial reperfusion was seen in 31 patients (52%), leaving 28 (48%) with inadequate myocardial reperfusion. Histological evaluation revealed three different patterns of thrombus composition, consisting predominantly of coagulated blood, fibrin, or lipids. Neither T1 nor T2 MRI values were able to differentiate between these groups. However, a tendency towards longer T2 values was observed in the patient cohort with poorer myocardial reperfusion (36.6±12.2 ms vs. 31.2±10.3 ms in patients with adequate ST resolution; p=0.09). Multivariate logistic regression analysis, including age, sex, smoking, hypertension, diabetes mellitus, and MRI variables, indicated that diabetes (odds ratio [OR] 8.1, 95% confidence interval [CI] 1.5–45.2) and T2 values (OR 1.08 per ms increase, 95% CI 1.01–1.16) were independent predictors of inadequate myocardial reperfusion. The most important study limitation was the imaging of ex vivo thrombus material with no certainty that this reliably resembled the actual intracoronary plaque or thrombus. Future studies should further investigate the potential clinical value of this MRI technique. For now, implementation of aspirated thrombus material imaging in patients with STEMI cannot be recommended.

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Adherence to guideline-directed venous thromboembolism prophylaxis among medical and surgical inpatients at 33 academic medical centers in the United States


In the present work, the authors report on a benchmark study to assess the current state of in-hospital venous thromboembolism prevention and treatment in US academic hospitals. Overall, adherence to guidelines was found to be poor, especially in surgical patients.

A benchmark method is an established quality-assessment technique that uses unblinded retrospective medical record review to describe clinical performance and compare that with best-practice standards. A total of 33 US academic hospitals participated in this study. From each center, the records of 30 patients with objectivized in-hospital venous thromboembolism, as well as the records of 30 randomly selected patients who were not diagnosed with venous thromboembolism, were examined for baseline thromboprophylaxis. The use of thromboprophylaxis was then judged against the 2004 US guidelines [1].

A total of 1555 patients were analyzed. Overall, the median correct prophylaxis rate was 47% (range 30–75%). Surgical wards significantly performed worse than medical wards (correct prophylaxis rate 41% vs. 59%; p<0.05). Several logical patient demographics were predictive of correct thromboprophylactic measures: hospital admission through an emergency department, severe illness, major surgery, and a history of venous thromboembolism.

Evidently, adherence to guidelines for correct thromboprophylaxis in medical and surgical patients in US teaching hospitals is substandard, and needs to be improved through proper education. However, owing to the lack of high-quality randomized outcome trials that provide clear assessment
Use of enoxaparin to diminish the incidence of vascular access stenosis/thrombosis in chronic hemodialysis patients


In the present study, the authors sought to investigate the effectiveness of enoxaparin in lowering the incidence of recurring vascular-access stenosis in long-term hemodialysis patients. The results indicate a trend towards a lower number of angiographic procedures in patients on enoxaparin as compared with those on unfractionated heparin, suggesting a possible role for enoxaparin as a dialysis anticoagulant.

In chronic hemodialysis patients, vascular access is frequently complicated by recurrent stenosis and/or thrombosis leading to multiple angiographic procedures to maintain patency and increasing morbidity and hospitalizations. Unfractionated heparin (UFH) is routinely used for anticoagulation during hemodialysis. However, despite the widespread use of UFH, high rates of access failure are still observed. Enoxaparin is a low-molecular-weight heparin (LMWH) that is used to prevent thrombosis during extracorporeal circulation, and nowadays is also a well-established option in hemodialysis sessions. Therefore, the aim of the present study was to compare the effects of UFH and enoxaparin on the rates of angiographic procedures and access failure in hemodialysis patients.

The present study included 28 hemodialysis patients who suffered from recurrent access stenosis and required repeated angiographic procedures to maintain access patency while treated by UFH during hemodialysis. All patients, at a non-specified endpoint, were transferred to enoxaparin treatment. The dosages of UFH and enoxaparin were based on clinical assessment of clot formation in order to achieve effective extracorporeal anticoagulation. Patients with either synthetic (50%) or native arteriovenous access (50%) were included. Patients who were on UFH for <3 months or who received enoxaparin for other causes were excluded.

Observed treatment time was 1.20±0.87 years for UFH and 3.04±2.19 years for enoxaparin. There was a trend toward a decreased procedure rate during the period of enoxaparin administration. Procedure rate (per year) was 1.76±0.92 during UFH administration and 1.30±1.01 during enoxaparin administration (p=0.078). As stated by the authors, certain limitations should be taken into account when interpreting these findings. Firstly, the retrospective design instead of a crossover, blinded, randomized design is a major limitation. Secondly, the small number of study participants and a selection bias (unspecified inclusion criteria, selection procedure, and time of treatment transfer) may have contributed to unidentified confounding factors. Moreover, the borderline significance of the difference between LMWH and UFH on access patency may be subject to a type 1 or type 2 error. Finally, since the present study included a single-arm treatment crossover, certain time-dependent variables such as advancing age, vascular calcification, and a variable clotting state may have influenced the results.

Despite the limitations, these initial results are hypothesis generating as they suggest that a trend toward a decreased number of angiographic procedures for maintaining arteriovenous access patency in patients switched from UFH to LMWH enoxaparin as anticoagulant during dialysis. However, as suggested by the authors, larger studies are required before any definite conclusions can be drawn.

A novel mechanical thrombectomy device for retrieval of intravascular thrombus


Presently available thrombectomy devices have functional limitations, such as problems with removal of organized thrombus and clot fragmentation with distal embolization. In the present work, the authors trialed a new mechanical thrombectomy device designed to remove hard and soft thrombi, without damage to blood vessels, in a pig model. This pilot study demonstrates the basic safety and efficacy of the device.

Endovascular removal of thrombus is a potentially attractive treatment option for both arterial and venous thrombotic occlusions. Currently available thrombectomy devices allow for mechanical or pharmacological removal of thrombus. However, these devices have shortcomings such as the inability to completely remove large or hard (older) blood clots. Moreover, pharmacomechanical clot removal is associated with longer procedure times and the need for patient observation in an intermediate or intensive care unit.

In this study, Monsky and colleagues evaluated a novel mechanical thrombectomy device in 26 vessels (nine superficial
femoral and eight subclavian arteries, five primary branches of the subclavian artery, which included the lateral thoracic artery and the thyrocervical trunk, as well as four external carotid arteries) from 14 pigs. For this purpose, subacut e fibrin-laden thrombus was injected into these arterial segments. The novel device consists of a microcoil element and a hollow catheter shaft attached to microcoil. The catheter is inserted over a 10-French sheath. Several eyelets are set at discrete locations along the microcoil. The device has to be advanced over a microcatheter distal to the obstruction. By retracting the core wire, loops are created inside the vessel distally and proximally to the thrombotic occlusion. By pulling back the device and microcatheter, the obstructive particle can be retrieved.

In the study, intact thrombus was retrieved from 24 of 26 vessels with a single pass of the catheter. This resulted in complete restoration of patency in 21 vessels and partial patency in a further three vessels. In five cases, embolic material fragmented during withdrawal from the sheath. In a further four cases, the catheter failed to deploy fully and the obstructive material was not entirely captured.

In summary, this study demonstrates the basic efficacy and safety of endovascular mechanical clot removal. The advantage of this application is immediate retrieval of clot material without the need for intraprocedural lysis. Compared with other commercially available thrombectomy devices, however, this device has two central shortcomings. First, the obstructive lesion has to be crossed before the material can be retrieved, thereby leaving room for potential distal embolization. Second, the French size of the catheter is comparatively small. Thus, use of this device may be associated with increased bleeding rates in human application. Further studies are warranted to better define the clinical utility of this novel device.

Outpatient management of acute deep vein thrombosis: results from the OTIS-DVT registry


In the present study, the authors investigated clinical practice patterns in outpatient management of acute deep vein thrombosis (DVT) using the Outpatient Treatment of Deep Vein Thrombosis in Switzerland registry. The results suggest that use of mechanical measures...
Incidence, predictors, and outcomes of gastrointestinal bleeding in patients on dual antiplatelet therapy with aspirin and clopidogrel


This cohort study evaluated the frequency and predictors of gastrointestinal (GI) bleeding in patients on dual antiplatelet therapy. The authors concluded that the risk of bleeding is low (2.7%), although bleeding was associated with increased 30-day and 1-year mortality rate (3.7% and 19% vs. 0.0% in those without GI bleeding). In addition, history of previous bleeding and older age were predictors of bleeding events, whereas statin use appeared to have a protective effect.

The downside of the cardiovascular protective combination of aspirin and clopidogrel after percutaneous coronary intervention (PCI) is the risk of bleeding complications, mostly of gastrointestinal (GI) origin. In the present study, patients were followed for 1 year. From an overall cohort of 1852 patients who underwent PCI and were prescribed dual antiplatelet therapy for a period of ≥1 year, 50 patients with GI bleeding complications requiring hospital admission, and 202 who were not diagnosed with GI bleeding, were followed. The overall incidence of bleeding was 2.7%. Most bleeding cases presented with melena (40%) or hematemesis (22%). In 33 of these cases, bleeding was objectivized by endoscopy or colonoscopy. Univariate analysis indicated that advanced age, previous GI bleeding, and concurrent statin use were positively or negatively associated with bleeding. Upon multivariate analysis, previous bleeding (odds ratio [OR] not provided) was predictive of bleeding while statin use was protective (OR 0.24, 95% confidence interval 0.13–0.48). Additionally, patients with bleeding episodes had significantly higher 30-day and 1-year mortality rates.

Although the observation that statin use might be protective for GI bleeding is interesting, several important issues should be considered when interpreting this observation. Firstly, it is unclear how many patients were on statin therapy, and why some of them apparently were not. Nowadays, statin therapy is one of the cornerstones of coronary artery disease treatment, and all patients should be prescribed this drug. Secondly, the multivariate analysis did not include demographic variables such as nonsteroidal anti-inflammatory drug use, age, and comorbidities, which would be important factors in determining the risk of bleeding as well as survival. Finally, although previously very well established, proton-pump inhibitor use was not associated with a decreased...

(e.g. compression stockings, bandages) in symptomatic patients with proximal DVT and use of low-molecular-weight heparin for long-term therapy of cancer-associated DVT require improvements in current clinical practice to fully adhere to up-to-date guidelines.

The current treatment guidelines from the American College of Chest Physicians (ACCP) recommend therapy in patients with acute deep vein thrombosis (DVT) on an outpatient basis whenever clinically possible and on an inpatient basis if necessary. The guidelines recommend initial anticoagulation with unfractionated heparin, low-molecular-weight heparin (LMWH), or fondaparinux for at least 5 days and until the international normalized ratio (INR) target is reached for ≥24 h in patients without cancer, and administration of LMWH for 3–6 months in cancer patients, followed by administration of vitamin K antagonists (VKAs). Moreover, the ACCP guidelines recommend the use of elastic compression stockings or bandages for a minimum of 2 years to prevent post-thrombotic syndrome in patients with symptomatic proximal DVT.

Spirk and colleagues set up a prospective registry aimed at investigating clinical practice patterns in the outpatient management of individuals with acute DVT in Switzerland. A total of 534 consecutive patients with acute DVT (49% proximal, 24% recurrent, and 12% associated with cancer) were enrolled. Of these, 41% had been managed in private angiology practices, 34% in outpatient hospital departments, and 25% in private general or internal medicine practices. Compression ultrasound had been used for diagnosis in 95% of patients, whereas D-dimer testing was applied in 53%.

Subsequent to diagnosis, LMWH was prescribed for a median duration of 7 days (interquartile range [IQR] 5–12 days) in 83% of patients. VKAs were recommended for 163 days (IQR 92–183 days) in 81% of patients. Mechanical measures to prevent post-thrombotic syndrome were prescribed in 83% of patients; compression stockings or bandages for a median duration of 364 days (IQR 101–750 days) from hospital physicians, and 92 days (IQR 45–183 days) from private practice physicians (p<0.001). Among patients with symptomatic proximal DVT, mechanical measures were prescribed for at least 2 years in 24% of patients; 55% in hospital and 6% in private practice (p<0.001). Among patients with cancer-associated DVT, the median duration of LMWH therapy was 16 days (IQR 8–45 days), and 35% received LMWH for <90 days.

In summary, data from this Swiss registry indicate that the use of mechanical measures in patients with symptomatic proximal DVT and the administration of long-term therapy of cancer-associated DVT require improvement to comply with current guidelines.
risk of bleeding. This is a clear indicator of further confounding factors that were not accounted for.

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Long-term survival of patients with a history of venous thromboembolism


In the present study, the authors aimed to evaluate the long-term survival of non-cancer patients with a history of venous thromboembolism (VTE), in comparison with age- and gender-matched controls taken from the general population, by means of a retrospective survival analysis. The results suggest that, after the initial phase, VTE does not have a detrimental impact on the long-term survival of these patients.

Estimates of mortality rate after venous thromboembolism (VTE) vary considerably. Short-term mortality rate (30–90 days after VTE) varies from <3% to 5% for deep vein thrombosis (DVT) and from 6% to 23% for pulmonary embolism (PE). Less is known about long-term survival rates. Therefore, the aim of the present study was to investigate the long-term survival rate in patients with a history of DVT and/or PE, and to compare the relative survival of these patients with that of the general population.

Patients referred for thrombophilia testing between 1994 and 2007 owing to history of VTE (≥3 months after VTE), were included in the analysis. VTE was required to have been confirmed by objective methods such as phlebography, plethysmography, duplex ultrasonography, perfusion–ventilation lung scan, or computed tomography. Exclusion criteria were active cancer, asymptomatic PE, isolated visceral thrombosis, and acute VTE (<3 months). Data from 5209 VTE patients were analyzed retrospectively regarding survival. Data on the overall mortality of the general Austrian population were obtained from Statistics Austria.

Over the time-period studied, a total of 169 patients (5.3%) died. The cumulative survival in patients was 0.97 and 0.87 at 5 and 10 years, respectively. Men had a higher death rate than women (cumulative survival 0.96 vs. 0.97 at 5 years, and 0.91 vs. 0.93 at 10 years; p=0.01 for comparisons at both time-points). The lowest survival rate was observed in patients with spontaneous VTE. Of interest, duration of anticoagulation (long- vs. short-term) did not have an influence on the cumulative survival rates (p=0.96). When patients were compared with the general population, the cumulative relative survival was 1.02 (95% confidence interval 1.00–1.03). A reduced cumulative relative survival was not found in any of the analyzed subgroups (different sites of VTE, or idiopathic vs. secondary VTE).

The data from the present study show that long-term survival of patients without cancer who survive the acute phase of VTE is comparable to survival in the general population.

These findings should be interpreted with caution as far as their generalizability is concerned. The retrospective design of the study, the exclusion of cancer patients, and the selection bias of including only outpatients (thus excluding hospitalized, chronically ill, or bedridden patients) renders the application of the present findings to the general population problematic. Moreover, there is a lack of data regarding survival during the acute phase following VTE (first 3 months); therefore, the authors were unable to draw any conclusions concerning short-term survival. Nonetheless, the present study may still have clinical implications as it underscores the necessity of balancing the risk of fatal bleeding against the risk of fatal recurrent VTE in long-term anticoagulation of patients with a history of VTE.

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ORTHEPEDIC SURGERY

A systematic review of rivaroxaban versus enoxaparin in the prevention of venous thromboembolism after hip or knee replacement


The aim of the present study was to compare rivaroxaban with enoxaparin for venous thromboembolism prevention after knee joint or hip joint replacement. In all, eight randomized controlled studies (n=15246) were assessed. The results suggest that rivaroxaban is superior to enoxaparin. Therapy duration of >30 days is recommended.

Venous thromboembolism (VTE) and its two major clinical manifestations of deep vein thrombosis (DVT) and pulmonary embolism (PE) are major complications of orthopedic surgery for total hip arthroplasty (THA) or total knee arthroplasty (TKA). Rivaroxaban is a novel and reversible Factor Xa inhibitor with a promising antithrombotic effect. Its advantages over heparin and warfarin are its oral administration, short half-life, peak time, and rapid onset of antithrombotic effect.
In this systematic review, Turun and colleagues identified a total of eight studies, including 15,246 patients, comparing rivaroxaban with enoxaparin for the prevention of VTE in patients undergoing THA or TKA. Six studies compared rivaroxaban with enoxaparin 40 mg daily, two compared rivaroxaban with enoxaparin 30 mg daily, five scrutinized short-term therapy with rivaroxaban, and three investigated extended therapy with rivaroxaban. For the review, the incidence of VTE and postoperative major bleeding were considered primary efficacy and primary safety outcome measures.

Administration of rivaroxaban 10 mg daily was associated with better effectiveness compared with enoxaparin 40 mg daily (relative risk [RR] 0.58, 95% confidence interval [CI] 0.25–0.59; p<0.0001) and not inferior to enoxaparin 30 mg daily in VTE prophylaxis after joint replacement (RR 0.77, 95% CI 0.59–1.00; p=0.05). Moreover, both short-term (<15 days) and extended (>30 days) therapy with rivaroxaban 10 mg were more effective than enoxaparin 40 mg daily. Finally, no significant difference in postoperative major bleeding rates was observed when comparing rivaroxaban 10 mg daily with enoxaparin 30 mg or 40 mg daily.

Therefore, the authors conclude that rivaroxaban is superior to enoxaparin in VTE prophylaxis after THA or TKA. Based on these data, extended rivaroxaban therapy (>30 days) is recommended for VTE prophylaxis in these orthopedic patients. This manuscript constitutes the first systematic review comparing rivaroxaban with enoxaparin in patients undergoing THA or TKA. In summary, rivaroxaban 10 mg/day was found to be as safe as enoxaparin 30 mg/day and safer than enoxaparin 40 mg/day, while it was more effective than enoxaparin 30 mg/day or 40 mg/day. Further studies shedding light on cost-effectiveness issues are warranted.

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MEDICALLY ILL PATIENTS

Risk factor model to predict venous thromboembolism in hospitalized medical patients


In this work, the authors conducted a retrospective cohort study to assess available risk stratification tools and construct a suitable simple logistic regression model for venous thromboembolism (VTE). The findings indicate that 12 risk factors may be associated with the condition, although the risk of symptomatic VTE in general patients is low at <1%.

Among general medical patients, the incidence of venous thromboembolism (VTE) is approximately 1%; however, among patients within the highest risk group, the incidence may increase to 15%. Thromboprophylaxis with subcutaneous heparin is recommended for all medical patients at high risk for VTE. Patients with stroke, heart failure, chronic pulmonary disease, sepsis, and cancer are considered among those at high risk according to the American Association of Chest Physicians, and thromboprophylaxis is recommended in these individuals; however, there is neither validation of existing risk-stratification tools nor a specified risk-assessment procedure. Therefore, the aim of the present study was to construct a VTE risk-stratification model for hospitalized medical patients.

The study was designed as a retrospective cohort investigation of patients aged ≥18 years, admitted to 374 US hospitals during the years 2004–2005, with a primary diagnosis of pneumonia, heart failure, chronic obstructive pulmonary disease (COPD), stroke, and urinary tract infection, and a length of stay in hospital of ≥3 days. The authors recruited 242,738 patients who were randomly assigned (in a 4:1 ratio) to a derivation and a validation set. Multivariable logistic regression modeling was used to construct the risk score model, which was then applied to the validation sample. For the diagnosis of VTE, a diagnostic test and a relevant treatment were also required.

The overall incidence of VTE (during hospitalization and up to 30 days after discharge) was 0.43%. Age, length of stay in hospital, gender, primary diagnosis, cancer, inflammatory bowel disease, obesity, central venous catheter, inherited thrombophilia, steroid use, mechanical ventilation, active chemotherapy, and urinary catheter were all associated with VTE. In the validation sample, the model had a good discrimination ability of 0.75 (c statistic). Using 1% as a risk threshold, the model had a sensitivity of 28% and a specificity of 93% for predicting VTE.

The present study is of clinical value as it provides a means by which to identify medical patients at moderate-to-high risk (>1%) of developing VTE, and thus may lead to more targeted thromboprophylaxis. These findings provide an alternative prophylactic strategy to that of treating all medical patients in an effort to avoid unnecessary costs and side-effects. However, the study suffers from certain limitations. Firstly, its retrospective nature, missing VTE cases (i.e. those who had not been hospitalized or died undiagnosed), the use of thromboprophylaxis in only 30% of the study cohort, and a focus on high-risk medical patients are among the most notable. Secondly, the low sensitivity of the method, which is translated to a moderate negative likelihood ratio, suggests that the implementation of the risk score will rarely lead to important post-test probability changes.
Risk of venous thromboembolism with inflammatory bowel disease

Saleh T, Matta F, Yaekoub AY et al.

In the present work, the authors investigated the incidence of venous thromboembolism (VTE) in patients with ulcerative colitis and Crohn’s disease, using the National Hospital Discharge Survey database from the US, and covering patients from 1979–2005. The results suggest that the risk of VTE increases in hospitalized patients with ulcerative colitis, but only marginally increases in patients with Crohn’s disease.

Recent investigations have identified inflammatory bowel disease (IBD) as a risk factor for the occurrence of venous thromboembolism (VTE). However, epidemiological evidence regarding the above association is still inconclusive. Therefore, the aim of this study was to determine the incidence of VTE in patients with ulcerative colitis or Crohn’s disease.

The authors used the database of the National Hospital Discharge Survey, which consists of discharge data obtained annually from numerous hospitals within the US, thus sampling approximately 1% of total discharges. Patients discharged from hospitals from 1979 through 2005 as medical patients with a diagnosis of ulcerative colitis and Crohn’s disease according to World Health Organization International Classification of Diseases, ninth edition (ICD-9), were included in the study, whereas patients discharged without IBD were used as controls. None of the patients included had undergone a surgical procedure during the hospitalization period under consideration. Among these patients, the incidence of VTE (deep vein thrombosis and pulmonary embolism) during the index hospitalization was also determined using ICD-9 coding.

The incidence of VTE among medical patients with ulcerative colitis was 21 000 in 1 129 000 (1.85%), whereas in patients with Crohn’s disease it was 22 000 in 1 803 000 (1.22%). In comparison, among patients who had no IBD, the incidence was 10 421 000 in 918 570 000 (1.13%). These findings are translated as an increased relative risk of VTE of 1.64 (95% confidence interval [CI] 1.62–1.66) for patients with ulcerative colitis and a marginally increased risk of 1.08 (95% CI 1.06–1.09) for those with Crohn’s disease. In both diseases, the relative risk was higher for patients <40 years of age. Interestingly, in patients with Crohn’s disease, the increased risk for VTE was mainly driven by increased deep vein thrombosis episodes and not by the occurrence of pulmonary embolism.

In conclusion, this study showed that the risk of VTE is increased among hospitalized patients with ulcerative colitis and only marginally increased in patients with Crohn’s disease. Although the present study represents a large population with ethnic and geographic diversity and extensive duration of observation (27 years), it suffers from the limitations of being a retrospective analysis based on discharge notes and ICD-driven diagnoses. Furthermore, serious confounders of VTE occurrence have not been taken into account such as comorbidities, medication taken, and the possibility of patients being bedridden during hospitalization. Finally, the possibility that a proportion of the patients were hospitalized more than once cannot be excluded.

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The impact of co-morbid conditions on family history of venous thromboembolism in whites and blacks

Mili FD, Hooper WC, Lally C et al.

This case–control study was performed to evaluate the contribution of family history to the risk of venous thrombosis among blacks compared with whites, in relation to environmental risk factors such as obesity, diabetes mellitus, hypertension, and cancer. The results of this study show that the adjusted attributable fraction for venous thromboembolism was comparable between blacks and whites (16.9% vs. 18.3%). Moreover, diabetes, cancer, and obesity among blacks or among females of both races further increased the risk of venous thromboembolism by at least two- to three-fold.

Family history is a well known risk indicator for a first venous thrombosis [1]. As well as a positive family history, it has been shown that additional genetic or environmental thrombotic risk
Risk factors further increase the risk of venous thromboembolism. However, the majority of patients in these studies were white. The authors of the present work aimed to study the associations in a large population of black patients. A total of 1094 patients (537 black patients) with a deep vein thrombosis or pulmonary embolism and 1264 control patients (586 black patients) were interviewed about their family history and comorbid conditions. Overall, the impact of a positive family history was comparable between white and black patients. Using conditional logistic regression models, the authors found several specific clusters of risk factors that showed particularly increased risk for the following family members:

- First-degree relatives of black patients with venous thromboembolism who were obese or had hypertension, diabetes, or cancer.
- First-degree relatives of white patients with venous thromboembolism who were obese or had hypertension.
- First-degree relatives of black female patients with recurrent episodes of venous thromboembolism who were obese or had hypertension.

Notably, several critical study limitations complicate the correct interpretation and prohibit clinical implementation of the current findings. For instance, all risk factors, comorbid conditions, and the presence of a positive family history were self-reported and not objectivized. Further, only first-degree family members were accounted for.


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### Risk factors associated with early hepatic artery thrombosis after orthotopic liver transplantation – univariable and multivariable analysis


Early hepatic artery thrombosis constitutes a very serious complication in patients undergoing orthotopic liver transplantation, with associated high morbidity and mortality risks. The main risk factors associated with hepatic artery thrombosis are delayed arterial reperfusion and abnormal arterial graft anatomy requiring bench reconstruction. Surveillance protocols and preventive measures such as selective anticoagulation should be investigated, especially in patients with one of these risk factors.

Residual vein obstruction to predict the risk of recurrent venous thromboembolism in patients with deep vein thrombosis: a systematic review and meta-analysis


The present authors investigated whether residual vein obstruction is associated with an elevated risk of...
recurrence in deep vein thrombosis (DVT) patients. The risks and benefits of oral anticoagulation should be carefully weighed to determine the optimum duration of therapy in patients with DVT. In patients with provoked DVT, the annual recurrence risk without anticoagulation has been described as 3%, while the annual risk of major bleeding under anticoagulation is within a similar range, thereby negating any clinical benefit of longer-term anticoagulation. In contrast, the optimal duration of anticoagulation remains controversial.

Residual vein obstruction (RVO), as visualized on compression ultrasonography of a lower limb, might be an interesting predictor of the risk of recurrent venous thromboembolism (VTE) in patients with lower limb deep vein thrombosis (DVT). Carrier and coworkers performed a systematic review and meta-analysis of studies on patients with DVT who underwent assessment of RVO using duplex sonography. They identified 14 articles (nine prospective cohort studies and five randomized controlled trials) including a total of 4022 patients.

For the cohort of patients with unprovoked DVT who had stopped anticoagulation therapy at the time of sonographic RVO assessment, the presence of RVO was not associated with recurrent VTE (odds ratio [OR] 1.24, 95% confidence interval [CI] 0.9–1.7). Interestingly, RVO was associated with recurrent VTE in patients with any (unprovoked or provoked) DVT (OR 1.5, 95% CI 1.1–2.0).

Therefore, RVO was associated with a moderately elevated risk of recurrent VTE in patients with both provoked and unprovoked DVT, but not in those with unprovoked DVT following discontinuation of anticoagulation. Further prospective studies are warranted to define the role of RVO in patients with unprovoked DVT in whom the role of long-term anticoagulation is still controversial.

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Increased thrombin generation is associated with acute ischemic stroke but not with coronary heart disease in the elderly: the Three-City cohort study


The authors of the present study investigated thrombin levels in older patients with coronary heart disease (CHD) and acute ischemic stroke (AIS) to ascertain whether an association exists. No association between CHD and thrombin level was detected, but high thrombin levels were associated with AIS. This suggests a role for thrombin as a predictor of this condition, particularly in older female patients.

Thrombin is a key product of the coagulation cascade. Calibrated automated thrombography is a method of assessing thrombin generation and may provide a means of detecting hypercoagulability. The present study investigated the relationship between thrombin generation and incidence of coronary heart disease (CHD) and acute ischemic stroke (AIS).

The study was designed as a cohort–case study that involved a randomly selected sample from the initial cohort of the Three-City Cohort Study. The study population consisted of 1177 random controls and all CHD and AIS cases from the initial cohort who were followed for 4 years. Using the calibrated automated thrombography method, endogenous thrombin potential (ETP) and peak height of thrombin generation were measured on plasma samples. Subjects taking anticoagulant therapy, subjects for whom thrombin generation could not be assessed, and subjects with previous CHD or AIS were excluded from the study.

During the 4 years of follow-up, among all subjects included in the analysis, 186 had a CHD event (15.7%) and 87 had an AIS (7.5%). No significant association between thrombin generation and incidence of CHD was observed. In contrast, a borderline significant association of ETP and peak height with incidence of AIS (hazard ratio [HR] 1.16, 95% confidence interval [CI] 0.90–1.48, and HR 1.27, 95% CI 1.00–1.62, respectively) was found in an adjusted multivariable analysis. The results also suggested that these associations might be more important in women than in men (p values for interaction were 0.04 and 0.08, respectively).

The findings of the present study showed that elevated thrombin generation was an independent risk factor for AIS but not for CHD, suggesting a stronger association between a hypercoagulable state and the risk of AIS than CHD. Moreover, these results appeared more relevant among women, although the interaction was of borderline significance.

As stated by the authors, the main limitation of the study was the small number of incident cases, which may have resulted in a lack of statistical power. Furthermore, application of these findings to the general population should be considered with caution since study participants were restricted to community-dwelling residents with better physical and cognitive abilities than the general elderly patient population. Finally, given the study sample, the association found between thrombin generation and AIS pertains only to subjects aged >65 years.

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Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants’ data from seven trials


The aim of the present study was to ascertain how length of anticoagulation treatment and presentation of venous thromboembolism (VTE) influence recurrence risk after anticoagulation treatment is stopped, and to discover the shortest time period of anticoagulation therapy that reduces the risk of recurrence to its lowest level. This was achieved via a review of previously published randomized trial data. The results suggest that a 3-month treatment course has a similar risk of VTE recurrence compared with a longer treatment course. Unprovoked proximal deep vein thrombosis and pulmonary embolism have a high risk of recurrence regardless of when treatment is stopped.

Venous thromboembolism (VTE) is usually treated with a short course of low-molecular-weight or unfractionated heparin followed by a longer course of oral anticoagulation using vitamin K antagonists. The optimal duration of administration of oral anticoagulants is the subject of ongoing scientific discussions.

Boutitie and colleagues examined pooled data from seven randomized trials including a total of 2925 patients with a first venous thromboembolism who did not have cancer and who had received different durations of anticoagulant treatment. The primary outcome measure was a first recurrent thromboembolism after stopping anticoagulant therapy during 24 months of follow-up.

VTE recurrence rates were lower after isolated distal deep vein thrombosis (DVT) than after proximal DVT (hazard ratio [HR] 0.49, 95% confidence interval [CI] 0.34–0.71), similar after pulmonary embolism and proximal DVT (HR 1.19, 95% CI 0.87–1.63), and lower after thrombosis provoked by a temporary risk factor than after unprovoked thrombosis (HR 0.55, 95% CI 0.41–0.74). Recurrence rates were higher in patients in whom anticoagulation had been stopped at 1.0 or 1.5 months compared with at 3 months or later (HR 1.52, 95% CI 1.14–2.02) and similar if treatment had been stopped at 3 months compared with at 6 months or later. High rates of recurrence associated with shorter durations of anticoagulation were confined to the first 6 months after stopping treatment.

Risk factors for arterial and venous thrombosis in WHO-defined essential thrombocythemia: an international study of 891 patients


In the present study, the authors studied risk factors for arterial and venous thrombosis in patients with essential thrombocythemia. They report older age, a history of thrombosis, the presence of classical cardiovascular risk factors, leukocytosis, and the presence of JAK2V617F to be independent predictors of arterial thrombosis. In contrast, only male gender proved to be a predictor of venous thrombosis.

Essential thrombocythemia is a myeloproliferative neoplasm characterized by overproduction of platelets by megakaryocytes in the bone marrow in the absence of an alternative cause. The major symptoms are bleeding and both arterial and venous thrombosis. To study specific thrombotic risk factors in essential thrombocythemia, the authors performed a cohort study in 891 patients with World Health Organization (WHO)-defined essential thrombocythemia. Patients were followed for a median of 6.2 years. The incidence of non-fatal arterial events (1.2% patient-years) was higher than that of venous events (0.6% patient-years). Surprisingly, only male sex was found to be an independent predictor of venous thrombosis (hazard ratio [HR] 2.0, 95% confidence interval [CI] 1.03–3.8) in this specific cohort; older age and previous thrombosis were not. As expected, the presence of classical cardiovascular risk factors (i.e. smoking, arterial hypertension, or diabetes) was predictive of arterial thrombosis (HR 1.9, 95% CI 1.2–3.1), as was older age (HR 1.7, 95% CI 1.05–2.7), a history of thrombosis (HR 2.07, 95% CI 1.3–3.3), leukocytosis (HR 1.7, 95% CI 1.01–2.7), and presence of JAK2V617F (HR 2.6, 95% CI 1.3–5.2). Unexpectedly, the presence of extreme thrombocytosis (platelet count >1000×10⁹ cells/L) was independently associated with a lower risk of arterial thrombosis (HR 0.42, 95% CI 0.22–0.78). This latter observation might suggest that it is prudent to restrain from aggressive
platelet-lowering therapy in low-risk patients with essential thrombocythemia, especially in the absence of other risk factors.

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The metabolic syndrome and its individual components: its association with venous thromboembolism in a Mediterranean population


This case–control study aimed to establish the impact of metabolic syndrome and its components on the risk for venous thromboembolism. The results indicate that metabolic syndrome is indeed associated with an increased risk for venous thromboembolism, mainly through the effect of abdominal obesity.

Growing evidence suggests a pathophysiological link between venous thrombosis and atherothrombosis [1]. An as-yet undefined mechanism of increased thrombogenic or atherogenic factors, or both, is the likely explanation for this link. In the current study, the authors investigated the association between metabolic syndrome (a well known atherogenic risk profile including glucose intolerance, abdominal obesity, dyslipidemia, and hypertension) and venous thromboembolism (VTE). They performed a case–control study including 146 outpatients with a first objectively confirmed episode of deep venous thrombosis of the lower extremities or acute pulmonary embolism, and 150 controls without a history of VTE. Both patients (mean age 44±13 years, 46% female) and controls (mean age 43±13 years, 53% female) were subjected to blood sampling after overnight fasting for measurement of high-density lipoprotein (HDL), low-density lipoprotein (LDL), and glucose, and for thrombophilia investigation. Additionally, waist and hip circumference, height, and weight were measured. Finally, all participants completed a questionnaire on classical cardiovascular risk factors. The frequency of smoking (28% vs. 23%), hyperlipidemia (24% vs. 13%), hypertension (15% vs. 11%), diabetes (5% vs. 1%), and obesity (33% vs. 12%) was significantly higher in the cases than in the controls.

On univariate analysis, all components of metabolic syndrome as well as metabolic syndrome itself (odds ratio [OR] 2.7, 95% confidence interval [CI] 1.3–5.6) were associated with VTE. After multivariate analysis including thrombolytic defects, only abdominal obesity was found to be an independent risk factor for VTE (OR 5.7, 95% CI 3.2–10.1). Of note, major baseline demographic differences between patients and controls, although partly corrected for in the multivariate analysis, might very well be indicative of confounding of the study outcome. Nonetheless, this study supports the established hypothesis of a significant and clinically relevant pathophysiological overlap between venous thrombosis and atherothrombosis.


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CANCER AND THROMBOSIS

Long-term anticoagulation treatment for acute venous thromboembolism in patients with and without cancer. The Swiss Venous Thromboembolism Registry (SWIVTER) II


The present consensus guidelines for patients with acute cancer-associated thrombosis recommend anticoagulation therapy of indefinite duration or until resolution of the cancer. In this study of over 1000 patients with acute venous thromboembolism (VTE) enrolled in the Swiss VTE Registry II, >300 had cancer. Long-term anticoagulation treatment for >1 year duration was more regularly planned in patients with cancer than in those without, in recurrent cancer-associated VTE than in first cancer-associated VTE, and in metastatic cancer than in non-metastatic cancer. The findings suggest that long-term anticoagulation treatment (>1 year) was planned in <50% of cancer patients with acute VTE.

Venous thromboembolism (VTE) constitutes the second leading cause of death in patients with neoplasms. In comparison with patients without cancer, the risk of recurrent VTE is increased both on anticoagulation and subsequent to discontinuation of anticoagulation therapy in patients with active neoplasms. The current guidelines of the American College of Chest Physicians (ACCP) recommend anticoagulation therapy for an indefinite duration or until the neoplasm can be considered resolved.

In this study, Spirk and colleagues prospectively followed 1247 patients with acute VTE from 18 Swiss hospitals. Among these patients, 315 (25%) had cancer, of whom 179 (57%) had metastases, 159 (50%) underwent
chemotherapy, 83 (26%) had prior cancer surgery, and 63 (20%) had recurrent VTE. Long-term anticoagulation for >1 year was more often prescribed in patients with versus those without cancer (47% vs. 19%; p<0.001), with recurrent cancer-associated versus first cancer-associated VTE (70% vs. 41%; p<0.001), and with metastatic versus non-metastatic disease (59% vs. 31%; p<0.001). Moreover, recurrent VTE (odds ratio [OR] 3.46, 95% confidence interval [CI] 1.83–6.53) and the presence of metastases (OR 3.04, 95% CI 1.86–4.97) were associated with long-term anticoagulation.

In summary, these prospectively obtained data show that long-term anticoagulation therapy was maintained in less than half of cancer patients in whom an indication exists according to the ACCP guidelines. Furthermore, in cancer patients with a first episode of VTE, this rate was even lower. Physician awareness about consensus recommendations in the field of VTE needs to be improved.

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Prediction of venous thromboembolism in patients with cancer by measuring thrombin generation: results from the Vienna Cancer and Thrombosis Study
Ay C, Dunkler D, Simanek R et al.

In the present work, the authors investigated the generation of thrombin to predict cancer-associated venous thromboembolism in the Vienna Cancer and Thrombosis Study cohort of >1000 patients. It was found that patients with an elevated peak thrombin level had an increased thromboembolism risk, and consequently it is suggested that thrombin measurements may indeed be useful in identifying patients with cancer who are at greater risk of venous thromboembolism.

Cancer is thought to promote a hypercoagulable state in patients, and hence patients with cancer are considered to be at high risk for venous thromboembolism (VTE). It is hypothesized that thrombin, together with tissue factor, are the main pathophysiological substrates mediating the link between cancer and thrombosis. Therefore, the present investigators assessed whether measurement of thrombin generation could identify cancer patients at high or low risk for VTE.

The study included 1033 cancer patients with newly diagnosed cancer or disease progression after complete or partial remission, who had not recently (within the past 3 months) received chemotherapy, radiotherapy, or surgery (within the past 2 weeks). The study cohort included patients with cancer and a variety of solid and hematological tumors. Patients were observed prospectively for 2 years for the occurrence of symptomatic or fatal VTE confirmed by ultrasonography, phlebography, or computed tomography. Thrombin generation was measured by fluorogenic assay.

During the 2 years of observation, 77 VTE events were observed. Patients with elevated peak thrombin (defined as values ≥611 nM thrombin, representing the 75th percentile of the total study population) had an increased risk of VTE, with a hazard ratio of 2.1 (95% confidence interval 1.3–3.3; p=0.002) on multivariable analysis independent of the confounding influences of age, sex, or treatment regimen. The cumulative probability of developing VTE after 6 months was significantly higher in patients with elevated peak thrombin than in those with lower peak thrombin (11% vs. 4%; log-rank test p=0.002).

The findings of the study show that increased thrombin generation is independently associated with VTE occurrence in cancer patients. As current guidelines recommend primary thromboprophylaxis only in cancer patients during acute hospitalization or after major surgery, these findings may be of clinical relevance as they could provide a way to individualize prophylactic treatment against VTE.

Among the limitations of the study, as stated by the authors, was that serial blood measurements were not performed during follow-up. Furthermore, the inadequate standardization of the thrombin generation assays and the arbitrary selection of the thrombin generation cut-off level render the generalizability of the results problematic. In addition, there are no data regarding the sensitivity and specificity of the methods used. Finally, non-reporting of observed differences in baseline characteristics between patients with and without a VTE event raises questions about the independent association between increased thrombin generation and VTE risk. However, measurement of thrombin generation may help to identify patients with cancer at high risk of VTE. Further large, prospective studies are needed to elucidate if the assessment of thrombin generation is clinically useful for risk stratification in cancer patients.

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XXIII Congress of the International Society on Thrombosis and Haemostasis – Organizing a Successful International Congress in the Face of Natural Disaster

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The XXIII Congress of the International Society on Thrombosis and Haemostasis (ISTH) and the 57th Annual Meeting of the Scientific and Standardization Committee (SSC) of the ISTH were successfully held 24–28 July, 2011 in Kyoto, Japan. With over 4500 participants from more than 70 countries, the congress was a truly global gathering of leading scientists and clinicians specializing in disorders of blood clotting and bleeding. Exciting and late-breaking research was featured, and it provided the latest insights into translational science and state-of-the-art clinical medicine. It was this very successful congress that, 3 months earlier, was almost canceled in the wake of the terrible natural disaster occurring on 11 March 2011 in north-east Japan.

The congresses of the ISTH are the pre-eminent international events in thrombosis and hemostasis, and are held biennially in different locations around the world. The international rotation of its congresses is critical in pursuit of the Society’s mission as the leading worldwide organization dedicated to advancement in the understanding, prevention, diagnosis, and treatment of thrombotic and bleeding disorders.

Following this tradition, in 2003 the ISTH selected Kyoto as the venue for its 2011 congress. Although far in advance, the complexity and intricacies of ISTH congresses mean it is necessary to have significant lead time for the successful preparation and execution of the meeting by the Congress President and Local Organizing Committee, with the support of ISTH Headquarters.

Preparations for the 23rd ISTH congress in Kyoto progressed smoothly and at the time of the abstract deadline in early 2011 the number of submissions was on a par with the successful 2007 (Geneva) and 2009 (Boston) congresses that each attracted almost 8000 participants. The same was true for pre-registrations, which at the beginning of March 2011 were on track to reach a congress participation of an estimated 5000–6000.

Then, on 11 March 2011, the world looked on with horror as a massive earthquake struck off the north-east coast of Japan and the resulting tsunami caused unimaginable destruction and the loss of tens of thousands of lives. News networks around the world reported 24/7 on the devastation and suffering caused, and Japan was facing one of the greatest tragedies in its history.

Two days later, an additional and potentially even more threatening scenario began to unfold. It became known that the Fukushima Daiichi nuclear power plant had suffered significant damage and that some of its reactors had experienced a partial meltdown that could potentially lead to a full meltdown and widespread radioactive contamination. Reports on the levels of leaked radiation as well as the disruption to the energy supply and transportation problems started to emerge and governments around the world began to issue travel advisories and recommended curtailing non-essential travel to Japan. Large companies followed suit. Their fears were further fueled by aftershocks and the emergence of additional information about the extent of the damage caused to the nuclear facilities.

Located 500 km from the directly impacted area, Kyoto was never directly affected; however, significant uncertainty
and concerns started to emerge within the worldwide ISTH community.

Some invited speakers, abstract presenters, and also corporate partners and exhibitors began to reconsider their participation and support in the face of what was a worrisome and unpredictable situation. The ISTH was faced with a very important, urgent, and difficult decision: Should the Society proceed with holding its congress in Japan?

The ISTH Council and Headquarters were in immediate and close contact with Dr Yasuo Ikeda, the Congress President, members of his Local Organizing Committee, the selected Professional Congress Organizer, and the local authorities, to monitor and assess the situation on a daily basis. With information only slowly emerging about the extent of the aftermath of the tsunami and the nuclear threat, the ISTH Council commissioned a thorough analysis by a third-party risk assessment company. All possible scenarios were considered and the pros and cons weighed carefully. These included cancellation, relocation during the same or very similar dates to a city in Western Europe, postponement, or holding the congress as originally planned in Kyoto at the end of July.

Over a period of 4 weeks, the ISTH collected all available information and data and sought input from many influential members and partners as well as meeting and association industry experts. At the beginning of April, a month after the 11 March disaster, the ISTH Council – after careful consideration of all available information and a clear risk analysis – voted unanimously to reconfirm the original date and location of the congress. The paramount consideration at all times was the safety and well-being of the attendees, speakers, and team; however, a close second was the impact that withdrawal of the ISTH congress would have on the Japanese community and people at a time when they most needed international support.

This was at the core of the ISTH’s international communications campaign that followed the decision. The Society directly approached its members, invited speakers, those who had submitted abstracts, and pre-registered attendees, as well as corporate partners, to communicate its decision and reasoning and to issue a strong appeal to come together and support the Japanese community. The decision was met with mixed reactions as risk perceptions varied greatly among the different stakeholders and geographical constituents of the ISTH. Nevertheless, the Society and the Local Organizing Committee stood behind their decision and moved forward with the preparations. More than 2 weeks had been lost which, in the last 3 months before a congress, posed a significant set-back and organizational challenge that impacted preparations right up to the actual congress dates. Through the enormous support of all parties involved, and not least the ISTH’s members, participants, and corporate partners, the meeting took place without fault and was a resounding success.

Ultimately, some abstract presenters (mainly poster) did not attend the congress, corporate partners had significantly reduced groups of invited guests, and the number of physicians and scientists attending was lower than at previous meetings. However, despite this, the congress fulfilled its objectives in terms of scientific exchange, building community, and celebration of Japan’s recovery efforts.

Judging from communications to the ISTH after the congress, nearly all participants left Kyoto and Japan not only scientifically more enriched but also with deep admiration for the sense of community, friendship, and support of their Japanese colleagues, the country, and its people. They felt great respect for a country that is working tirelessly to rebuild itself, and attested first-hand to the success of these efforts. The ISTH could not imagine having made a better decision than to proceed with holding its 23rd congress in Japan.

The Society has learned many important lessons from this experience, which are applicable to all organizations staging congresses, be they domestic, regional, or international. International events in particular face a multitude of challenges and uncertainties, even under optimal circumstances, which make their organization particularly complex. The factors most critical to success are formal risk management plans, proper insurance coverage, and systems and an organizational setup that provides the flexibility to act and react in the face of adverse circumstances.

Fundamental to the ultimate success of the congress was the determination of the ISTH to hold the event, even if it would potentially bring a financial loss. A strong partnership between the Congress President, Local Organizing Committee, the Professional Congress Organizer, the ISTH Council, and the ISTH Headquarters, and proactive communication between the Society and its members, presenters, pre-registered attendees, and corporate partners, were key for a rational and transparent decision-making process.

The ISTH is now looking forward to its next international meetings – the 58th Annual Meeting of its SSC to be held 27–30 June 2012 in Liverpool, UK and the XXIV Congress of the ISTH to be held 29 June–4 July 2013 (together with the 59th Annual SSC Meeting) in Amsterdam, The Netherlands.
The 23rd Congress of the International Society on Thrombosis and Haemostasis (ISTH) took place on July 23–28, 2011, at the International Conference Center in Kyoto, Japan. More than 4500 people attended the meeting, which featured around 3000 oral presentations and posters from 75 countries. A wide variety of thrombosis and hemostasis topics were featured and discussed. This report focuses specifically on the results of clinical trials in the areas of venous thromboembolism (VTE) and thrombotic issues in cardiology.

Late-breaking clinical trials

Idrabiotaparinux for acute symptomatic embolism

Harry Buller (Academic Medical Center, Amsterdam, The Netherlands) presented the topic “Idrabiotaparinux for acute symptomatic embolism” on behalf of the CASSIOPEA (Clinical Study Assessing SSR126517E Injections Once-weekly in Pulmonary Embolism Therapeutic Approach) investigators. These were the results of a randomized, double-blind, non-inferiority trial of enoxaparin followed by fixed weekly doses of subcutaneous (sc) idrabiotaparinux versus enoxaparin followed by warfarin with a target international normalized ratio (INR) of 2–3 for 3 or 6 months, in patients with acute symptomatic pulmonary embolism.

Slightly more than 3200 patients were followed for the primary efficacy outcome of recurrent VTE and the primary safety outcome of clinically relevant bleeding. The trial clearly met noninferiority, with recurrent VTE occurring in 2.1% of the enoxaparin plus idrabiotaparinux group and 2.7% of the enoxaparin plus warfarin group (odds ratio 0.79, p<0.001 for non-inferiority). Enoxaparin followed by idrabiotaparinux was superior in terms of clinically relevant bleeding events. Interestingly, even after stopping treatment with idrabiotaparinux, patients continued to be protected against recurrent VTE for several months. A 50% reduction in recurrence was noted in these patients, without any additional difference in bleeding rates.

VTE prophylaxis in acutely ill medical patients

“Pharmacological prophylaxis in addition to GES did not lead to a reduction in mortality”

Professor the Lord Ajay Kakkar (Thrombosis Research Institute, London, UK) presented the results of the LIFENOX (Study to Evaluate the Mortality Reduction of Enoxaparin in Hospitalized Acutely Ill Medical Receiving Enoxaparin) in “The impact of low-molecular-weight heparin prophylaxis on mortality in acutely ill medical patients”. This double-blind, randomized, placebo-controlled trial compared enoxaparin (40 mg sc once daily) plus graduated elastic stockings (GES) with placebo plus GES in patients who were hospitalized with
an acute medical illness. Patients received treatment for 10±4 days. The primary outcome was overall mortality at 30 days, while the primary safety outcome was major bleeding during the treatment period. Of 8392 patients originally enrolled, 8307 were included in an intention-to-treat analysis that showed no significant difference between the groups in either 30-day mortality (4.9% in the enoxaparin group vs. 4.8% with placebo) or major bleeding. Thus, the use of pharmacological prophylaxis in addition to GES did not lead to a reduction in mortality rate in this patient group. However, it was noted that this study may have captured a lower-risk population, as the mortality rate in the placebo group was lower than reported in other studies on this topic.

Extended therapy with dabigatran
Sam Schulman (Hamilton Health Sciences General Hospital, ON, Canada) presented “Dabigatran versus placebo for extended therapy of venous thromboembolism” on behalf of the RE-SONATE (Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Eteixilate in the Long Term Prevention of Recurrent Symptomatic VTE) study group. This was a double-blind trial that randomized 1343 patients with VTE who had completed 6–18 months of anticoagulant therapy to treatment with dabigatran 150 mg twice daily or placebo for an additional 6 months. This trial featured a superiority design. The primary efficacy endpoint was symptomatic recurrent VTE and related deaths, while the primary safety outcome was time to first major bleed. Extended follow-up was still ongoing at the time of the ISTH meeting, so this presentation was based on an initial set of follow-up data. The primary efficacy endpoint was reached in 0.4% of dabigatran patients and 5.6% of placebo-treated patients (hazard ratio 0.08; p<0.0001). Two patients on dabigatran had major bleeds versus no patients in the placebo group, but this difference was not significant. Therefore, extended treatment with dabigatran was associated with a 92% relative risk reduction in recurrent VTE versus placebo, with few major bleeding events.

Thrombotic disorders: clinical trials I

Intermittent pneumatic compression
“Intermittent pneumatic compression to prevent venous thromboembolism in patients hospitalized in intensive medical care units with high risk of bleeding” was presented by Karine Lacut (Hôpital de la Cavale Blanche, Brest Cedex, France). In this superiority study, 407 patients deemed to be at high bleeding risk were randomized to either intermittent pneumatic compression (IPC) plus graduated compression stockings (GCS) or GCS alone for 6 days while in an intensive care unit. The primary outcome was VTE (any symptomatic VTE, fatal PE, and asymptomatic DVT detected on ultrasound) between days 1 and 6, and was evaluated in 363 patients. Compression ultrasound was performed on day 6, with assessors blinded to treatment allocation, and study follow-up was completed at 3 months. Most patients included in the study had been admitted to the intensive care unit for intracranial hemorrhage.

The results showed a non-significant 40.2% risk reduction for VTE in the IPC plus GCS group. However, the event rate was lower than expected (5.6% in the IPC plus GCS group vs. 9.2% in the GCS-alone group), which may have been caused by a study population at lower risk for VTE; alternatively, it could be that day 6 was too early to detect DVT on ultrasound. Regardless, the study was likely underpowered to detect any superiority of IPC in addition to GCS.

Aspirin versus dalteparin following total hip arthroplasty
David Anderson (Queen Elizabeth II Health Science Centre, Halifax, NS, Canada) presented “A randomized controlled trial comparing aspirin with dalteparin for the prevention of venous thromboembolism following total hip arthroplasty,” the much-anticipated results of the EPCAT (Extended prophylaxis comparing low molecular weight heparin to aspirin in total hip arthroplasty) trial. As the title suggests, patients undergoing total hip arthroplasty (THA) were randomized to either 28 days of dalteparin 5000 units sc once daily plus oral placebo or 81 mg aspirin orally plus sc placebo, after both groups initially received 10 days of dalteparin 5000 units sc following surgery. The primary outcome was symptomatic VTE; no routine screening was performed.

The study was stopped short of its projected sample size of 2222 patients after the data and safety monitoring board advised the noninferiority criteria for aspirin had been met. There were also issues of feasibility due to the introduction of rivaroxaban for post-THA VTE prophylaxis. When the study was stopped, 766 patients had been randomized and 778 were included in an intention-to-treat analysis, which showed a 1.3% rate of VTE in the dalteparin group versus 0.3% in the aspirin group (p<0.0001 for noninferiority of aspirin, but not significant for superiority). There were no significant differences in bleeding complications, although there was a trend toward less bleeding with aspirin. Therefore, despite limitations related to premature stoppage of the trial, it appears that aspirin presents a convenient, inexpensive, and effective option for extended VTE prophylaxis after THA.

VTE prophylaxis and renal function
Amir K Jaffer (Cleveland Clinic Foundation, Cleveland, OH, USA) discussed “The impact of renal function on options for venous thromboembolism following major orthopedic surgery: insights from a randomized trial.” The analysis grouped patients from a trial of enoxaparin versus desirudin after orthopedic surgery on the basis of glomerular filtration rate (GFR). Patients were classified as “normal” if their GFR was...
over 60 mL/min, while those with a GFR of 30–60 mL/min were deemed “moderately impaired.” Of 1587 evaluable patients in the original trial, 1006 had a moderately impaired GFR. The primary efficacy outcome was major VTE and the primary safety outcome was major bleeding.

The analysis revealed that overall there were significantly fewer VTE events with desirudin, but that the VTE rate was inversely correlated with GFR in patients receiving enoxaparin. VTE was consistently reduced despite renal impairment in the desirudin group. There was no significant difference in terms of bleeding rates, which were low in all groups. These results argue against dose reductions of these agents in patients with renal dysfunction.

**Thrombotic disorders: clinical trials II**

**Apixaban versus enoxaparin**

Graham Pineo (University of Calgary, Calgary, AB, Canada) presented “Apixaban versus enoxaparin after knee or hip surgery: efficacy and safety in key clinical subgroups,” which described prespecified analyses based on age, body mass index (BMI), and renal function from the ADVANCE-2 (Apixaban Dosed Orally vs. Anticoagulation with Injectable Enoxaparin to Prevent Venous Thromboembolism-2) and -3 trials. In these studies, apixaban was shown to be superior to enoxaparin for the primary efficacy endpoint (major VTE), with no significant difference in ISTH major endpoint (the primary safety endpoint), which occurred primarily at the surgical site. In the subgroups studied, there was a significant interaction of creatinine clearance with bleeding. However, it was noted that three of the bleeds in the apixaban group occurred before the drug was given.

While there was a trend favoring enoxaparin with increased age and decreased BMI, the interaction was not significant. There was also no significant interaction between the subgroups. Therefore, the balance of benefit to risk for apixaban versus enoxaparin was maintained across age and BMI categories, but more data regarding bleeding are needed for patients with decreased creatinine clearance (<50 mL/min).

**Extended maintenance therapy**

The results of the RE-MEDY (Dabigatran in the Treatment of Venous Thromboembolism) study were presented as “Dabigatran or warfarin for extended maintenance therapy of venous thromboembolism” by Dr Schulman. In this study, patients with confirmed VTE who had received 3–12 months of anticoagulant therapy were randomized to either dabigatran 150 mg twice daily or warfarin with a target INR of 2–3 for an additional 6–36 months. This was a double-blind, double-dummy, noninferiority trial with noninferiority margins based on four previous placebo-controlled trials. Superiority testing was planned in the event that noninferiority was met. The primary efficacy outcome was symptomatic VTE and deaths related to VTE, while safety outcomes included bleeding, acute coronary syndromes (ACS), and other adverse events. The original follow-up period was extended to 36 months because of a low event rate. Modified intention-to-treat analyses were performed on 2856 patients, which included any person who received one dose of the study drug.

Noninferiority was met, with 1.8% of patients on dabigatran experiencing recurrent VTE versus 1.3% of patients on warfarin (hazard ratio 1.44; p for noninferiority=0.03). Safety analyses (based on actual treatment) were almost significant for fewer major bleeds on dabigatran, while there was a significant difference in favor of dabigatran in terms of “any bleeding.” A significantly higher number of ACS events occurred in the dabigatran group (13 patients vs. three patients on warfarin), but it is important to note that significantly more patients in the dabigatran group had a history of coronary artery disease at baseline. Therefore, dabigatran was found to be noninferior to warfarin for the extended treatment of VTE, with fewer bleeding events but more incidences of ACS.

**Recent progress in antiplatelet therapy**

One of the hottest topics of this congress was new anticoagulant and antiplatelet therapies. The symposium “Emerging antplatelet drugs” discussed recent progress in antiplatelet agents. Paul Gurbel (Sinai Hospital of Baltimore, Baltimore, MD, USA) summarized the new P2Y12 inhibitors for the treatment of coronary artery diseases; the ADP–P2Y12 interaction plays a critical role in amplifying platelet activation and is central to thrombus formation in coronary arteries. In particular, post-stenting ischemic events remain a major concern despite the clinical efficacy of clopidogrel and aspirin therapy.

Clopidogrel is characterized by high on-treatment platelet reactivity to ADP, which may affect post-stenting ischemia. The superior clinical efficacy of prasugrel over clopidogrel was demonstrated in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38) trial, prompting its recommendation in the treatment of high-risk ACS patients undergoing percutaneous coronary intervention (PCI). However, prasugrel is not recommended in patients weighing ≤60 kg or aged ≥75 years, and is contraindicated in patients with a history of stroke or transient ischemic attack since this drug increases the bleeding rate more than clopidogrel. In the PLATO trial, ticagrelor, a potent P2Y12 inhibitor, showed superior clinical efficacy compared with clopidogrel, and is thus recommended in
Europe for the treatment of patients with ACS. The reduction in mortality rate was remarkable, and prompt onset and withdrawal of antiplatelet action is of clinical benefit. Elinogrel, a new orally and parenterally effective P2Y1 receptor antagonist in development, is a more potent platelet inhibitor than clopidogrel.

“In the PLATO trial, ticagrelor showed superior clinical efficacy compared with clopidogrel”

In the same session David Morrow (Brigham and Women’s Hospital, Boston, MA, USA) discussed vorapaxar and atopaxar, new protease-activated receptor-1 inhibitors that have been tested in Phase II clinical trials. Both agents showed good efficacy in these Phase II trials, although vorapaxar was associated with a higher bleeding rate in patients with prior stroke in the TIMI 50 trial. Vorapaxar is also being studied in the TRA®CER (Trial to Assess the Effects of SCH 530548 in Preventing Heart Attack and Stroke in Patients With Acute Coronary Syndrome), which is looking at secondary prevention in patients with atherosclerotic diseases.

Masakatsu Nishikawa (Mie University Graduate School of Medicine, Mie Japan) followed on with a review of recent progress in phosphodiesterase III inhibitors. Cilostazol has a multipotent action, inhibiting platelet aggregation and inducing vasodilation. Restenosis of coronary arteries after PCI is attenuated with cilostazol, and the agent shows superior efficacy compared with aspirin in preventing stroke recurrence. K-134, a more potent antiplatelet agent, is under investigation in a Phase II clinical trial. K-134 has been shown to bind with CD36, a collagen receptor found on platelets.

In an oral communication, Eva Katona (University of Debrecen, Debrecen, Hungary) presented on the development of reference methods for evaluating the efficacy of aspirin using a monoclonal antibody against acetylated cyclooxygenase (COX)-1; acetylated COX-1 is increased by aspirin administration and decreased following withdrawal. This technique may prove to be useful in monitoring patient adherence to aspirin.

**New anticoagulant therapy**

In the Sol Sherry Memorial Lecture, Kenneth A Bauer (Harvard Medical School, Boston, MA, USA) summarized the recent progress in anticoagulant therapy with oral direct inhibitors of thrombin and Factor Xa. Until recently, vitamin K antagonists such as warfarin have been the only oral anticoagulants. When compared with warfarin, novel anticoagulants share several advantages such as a rapid onset of action, no need for monitoring or dose adjustments, and few interactions with food or other drugs. In addition, based on the clinical evidence so far, it has been suggested that novel anticoagulants are more efficacious than warfarin.

The direct thrombin inhibitor dabigatran and the three Factor Xa inhibitors rivaroxaban, apixaban, and edoxaban differ...
in terms of bioavailability, dosage, and renal excretion rate; these differences could provide some clues for anticoagulant selection. For example, it has been suggested that Factor Xa inhibitors may be more effective than dabigatran following orthopedic surgery. In addition, Prof Bauer discussed a health economics study that has investigated the economic impact of using novel anticoagulants in patients with non-valvular atrial fibrillation (AF). This study suggested that novel anticoagulants are potentially more cost-effective than existing agents.

Late-breaking clinical trials: new anticoagulants

APPRAISE-2: apixaban for acute coronary syndromes

Patients with ACS frequently experience recurrent ischemic events, despite the use of currently recommended antiplatelet therapy. The results of the APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events – 2) study therefore drew attention. John H Alexander (Duke University Medical Center, Durham, NC, USA) presented the results in a late-breaking clinical trials session entitled “Apixaban for prevention of acute ischemic events in patients with acute coronary syndromes.”

APPRAISE-2 was conducted at 858 sites in 39 countries. Patients with ACS within 7 days and at least two additional risk factors for recurrent ischemic events were eligible for the study, and a total of 7392 patients underwent randomization. All patients received standard antiplatelet therapy, including aspirin and thienopyridine. Patients were randomly assigned in a blinded fashion to receive apixaban, an orally active direct Factor Xa inhibitor, at dose of 5 mg twice daily or matching placebo. The trial was terminated prematurely on the recommendation of the data and safety monitoring committee because of an increase in major bleeding events with apixaban in the absence of counterbalancing reduction in recurrent ischemic events.

J-ROCKET AF: rivaroxaban for atrial fibrillation

Warfarin is effective for stroke prevention in patients with AF but has several major limitations. Rivaroxaban, an oral direct Factor Xa inhibitor, is therefore being developed as a potential alternative to warfarin. The J-ROCKET AF (Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) was designed to evaluate the safety and efficacy of rivaroxaban for the prevention of stroke and systemic embolism in Japanese patients with AF. The results were presented by Masatsugu Hori (Osaka Medical Center for Cancer and Cardiovascular Diseases Osaka, Japan) in a late-breaking clinical trials session.

In the global ROCKET AF trial, rivaroxaban 20 mg once daily demonstrated noninferiority to warfarin for the primary efficacy outcome of stroke and systemic embolism in patients with AF. In the J-ROCKET AF study, rivaroxaban 15 mg once daily (10 mg once daily in patients with creatinine clearance 30–50 mL/min) was chosen to address Japanese clinical practice. The target INR was 1.6–2.6 for patients aged 70 years and older.

“In J-ROCKET AF, rivaroxaban was noninferior to warfarin with respect to safety”

Event rates for the principal safety endpoint (composite of major and non-major clinically relevant bleeding) were 18.04% per year for rivaroxaban and 16.42% per year for warfarin, demonstrating the noninferiority of rivaroxaban to warfarin with respect to the principal safety outcome. For efficacy, a strong trend toward a reduction in stroke and non-central nervous system embolism was observed in patients treated with rivaroxaban. These data are consistent with the global ROCKET AF trial results.

Recombinant thrombomodulin for treatment of DIC

High-mobility group protein B1 (HMGB1) is an abundant protein in the nucleus that acts as a signal of tissue damage when released into the extracellular milieu. When HMGB1 is disseminated throughout the systemic circulation, it promotes the development of systemic inflammatory response syndrome and disseminated intravascular coagulation (DIC), and acts as a lethal mediator. In a session on coagulation and inflammation, the results of recombinant human soluble thrombomodulin (rTM) treatment for patients with DIC were presented and the implications of HMGB1 were discussed.

Ikuro Maruyama (Kagoshima University School of Medicine, Kagoshima, Japan) presented the results of a multicenter, double-blind, randomized trial, and reported on the efficacy and safety of rTM in DIC with heparin as a control. In 227 DIC patients with infection, DIC resolution rate in the rTM group was higher than in the heparin group (67.5% vs. 55.6%, respectively) and 28-day mortality rate was lower, suggesting that rTM may be valuable in the treatment of DIC with infection [1]. In a poster presentation, Noritaka Yada (Nara Medical University, Nara, Japan) reported on an investigation into the therapeutic effect of rTM in patients with septic DIC. They found that tumor necrosis factor-α, interleukin-6, and HMGB1 were decreased significantly at day 3 in the group treated with rTM, and concluded that rTM may be beneficial in patients with septic DIC via its antithrombogenic and anti-inflammatory properties.
In a separate poster presentation, Shinya Fujita (Kansai Medical University, Osaka, Japan) reported data on the correlation between platelet activation markers and HMGB1 in patients with DIC associated with hematological malignancy. DIC patients exhibited a significant decrease in HMGB1 levels after rTM therapy.

Recent topics on heparin-induced thrombocytopenia

Heparin is widely used as a parenteral anticoagulant for preventing VTE and treating DIC, and in hemodialysis, catheter intervention, and extracorporeal bypass circulation. Heparin-induced thrombocytopenia (HIT) is a relatively rare but serious adverse event induced by the immune response to heparin. It has recently attracted attention, as the pathophysiology of HIT has been substantially clarified and preventing serious thromboembolism is clinically important in HIT patients. A total of 40 papers were presented on HIT topics at this congress, providing new insights into the pathogenesis, diagnosis, and treatment of HIT.

Theodore E Warkentin (McMaster University, Hamilton, ON, Canada) reviewed recent advances in the diagnosis and treatment of HIT in a state-of-the-art lecture entitled “HIT paradigms and paradoxes.” He emphasized that HIT is caused by only a minority of antibodies against platelet factor 4 (PF4)/heparin complexes that have strong platelet-activating properties. The wider application of PF4-dependent immunoassay (ELISA), which has much greater sensitivity for the larger subset of non-platelet-activating antibodies, has resulted in HIT overdiagnosis in many centers.

Several paradoxes of HIT were highlighted: (1) HIT is a platelet-activating disorder with venous thrombosis as its predominant clinical manifestation; (2) “delayed-onset” HIT can lead to a dramatic worsening of HIT-associated thrombosis, despite cessation of heparin; (3) partial thromboplastin time (PTT) monitoring of direct thrombin inhibitor treatment, and confounding of PTT monitoring by HIT-associated consumptive coagulopathy, infers that this therapeutic approach may fail in the subset of patients with the most severe HIT; (4) the highly sulfated pentasaccharide anticoagulant fondaparinux may cause HIT, yet also appears to be an effective treatment for this disorder; and (5) the transience of the HIT immune response indicates that many patients with previous HIT can safely receive heparin in the future.

The “Platelet immunology” session of the 57th Annual Meeting of the Scientific and Standardization Committee (SSC) focused on assessments of newly developed assay systems for the appropriate and prompt diagnosis of HIT. A new whole-blood impedance aggregometry assay with rapid turn-around time may prove to be a feasible method of detecting clinically relevant HIT antibodies. It was proposed that the Platelet Immunology SSC could organize an international workshop comparing the new whole-blood impedance aggregometry assay with other established functional assays.

Conclusion

The 23rd meeting of the ISTH brought together delegates from around the world to share their research and experiences, and featured many new and exciting clinical trial results. As stated by ISTH Chairman Henri Bounameaux, the goal of the congress was to “create educational experiences where bench meets bed for the best of our patients.” It certainly appears that this goal was achieved.

Disclosures

The authors have no competing financial interests to disclose.

Reference

For the first time, the annual congress of the European Society of Cardiology (ESC) was held in Paris, France. The overall number of participants remains on the increase, with approximately 33 000 people attending this year. Indeed, over those 5 days it became difficult not to meet the participants dans le métro, dans les cafés ou au Louvre. The number of abstracts submitted for presentation also rose again this year to >10 800, of which almost 4300 were accepted for presentation. At 25 000 square metres, the industry exhibition has grown to the verge of breathtaking. As in previous years, the “Hot Line” sessions were extremely popular with the audience. The topics covered a broad field, ranging from novel anticoagulants that have the potential to revolutionize current therapeutic concepts to even covering the effects of laughter on the vasculature. A number of landmark studies that are likely to impact on clinical practice are summarized here.

Reduction of events in patients with AF by inhibition of Factor Xa: ARISTOTLE and ROCKET AF

The presentation of the results of the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation) trial by Christopher Granger (Duke University, Durham, NC, USA) coincided with their publication in the New England Journal of Medicine [1].

Apixaban stands a chance of changing prescribing practice in daily care. Over the last 60 years, warfarin has been the only available oral anticoagulant. Research efforts have recently identified Factor Xa and thrombin as favorable targets for the action of novel anticoagulants, and animal data suggest that targeting Factor Xa may be preferable to thrombin because of fewer bleeding complications [2]. The first substance in this class, antistasin (a naturally occurring Factor Xa inhibitor in salivary glands of the Mexican leech Haementeria officinalis) was isolated in 1987 [3].

Apixaban is a potent, selective, reversible, oral Factor Xa inhibitor. In the ARISTOTLE trial, apixaban was found to be superior to warfarin in preventing stroke or systolic embolism in patients with atrial fibrillation (AF). In addition, the drug was associated with lower rates of bleeding and mortality than warfarin. Apixaban was given at a dose of 5 mg twice daily and compared with warfarin in 18 201 patients with AF and at least one risk factor for the development of stroke. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism, and the ARISTOTLE trial was designed to test for noninferiority of apixaban versus warfarin. ARISTOTLE was also designed to test for superiority compared with warfarin if the noninferiority criteria were met.

The median length of follow-up in the ARISTOTLE trial was 1.8 years. The primary outcome occurred in 1.27% of patients per year in the apixaban group compared with 1.60% in the warfarin group (hazard ratio [HR] for noninferiority of apixaban 0.79, 95% confidence interval [CI] 0.66–0.95; p<0.001). This finding remained true even when tested for superiority of apixaban (p=0.01). Importantly, the rate of major bleeding was lower in the apixaban group than in the warfarin group (2.13% vs. 3.09% per year; p<0.001), as was the rate of death from any cause (3.52% vs. 3.94% per year; p=0.047). Although the risk of hemorrhagic stroke was lower with apixaban than with warfarin (0.24% vs. 0.47% per year; p<0.001), no difference was detected with regard to the occurrence of ischemic stroke (0.97% vs. 1.05% per year; p=0.42). According to the investigators, for every 1000 patients treated for the duration of the trial, apixaban prevented a stroke in six patients, a major bleed in 15 patients, and death in eight patients compared with warfarin [1].

Another intriguing study into the effects of a direct Factor Xa inhibitor was the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation). The results from this trial were initially presented at the American Heart Association Annual Meeting 2010 (14–17 November, Chicago, IL, USA), and the results were published earlier this year in the New England Journal of Medicine [4]. The trial originally randomized 14 264 patients to the novel Factor Xa inhibitor rivaroxaban at a dose of 20 mg/day (or 15 mg/day if creatinine clearance was 30–49 mL/min) or warfarin, dosed to maintain international normalized ratio between 2–3. Keith Fox (University of Edinburgh,
Edinburgh, UK) presented results from a sub-study of 2950 patients (20.7%) who received the lower dose of rivaroxaban because their glomerular filtration rate was significantly reduced. This sub-study found that the results of the main trial were maintained in patients with impaired kidney function. The primary endpoint of stroke or systemic embolism occurred in 2.52 per 100 patient-years with rivaroxaban 15 mg/day versus 2.77 per 100 patient-years with warfarin (HR 0.84, 95% CI 0.57–1.23) in the per-protocol population. Similar results were obtained in the intention-to-treat analysis (HR 0.86, 95% CI 0.63–1.17). Thus, the authors concluded that dose adjustment in ROCKET AF yielded results consistent with the main trial in comparison with dose-adjusted warfarin.

Safety of dabigatran in combination with antiplatelet drugs: new data from RE-LY

Another study into the effects of a novel agent that could replace warfarin in the prevention of stroke in patients with AF is the RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial of dabigatran. This trial was originally published in 2009 [5], and included 18,113 patients with AF who were randomized to one of two doses of dabigatran, or to warfarin. In contrast to apixaban or rivaroxaban, dabigatran is a direct inhibitor of thrombin. The original results showed that the 150 mg twice-daily dose of dabigatran was superior, and the 110 mg twice-daily dose noninferior, to warfarin in preventing stroke and systemic embolism (primary endpoint). Antonio Dans (University of the Philippines, Manila, The Philippines) presented data from 6,952 patients (38.4%) who received concomitant therapy with aspirin or clopidogrel while participating in the trial. Similar to in the main study, dabigatran 110 mg twice daily was noninferior to warfarin in terms of preventing stroke and systemic embolism. This finding was true whether patients were being treated with concomitant antiplatelet agents (HR 0.93, 95% CI 0.70–1.25) or not (HR 0.87, 95% CI 0.66–1.15; p for interaction=0.7). The safety of dabigatran at a dose of 110 mg twice-daily was superior to that of warfarin in terms of major bleeding. However, Dr Dans noted that the rates of major bleeding increased when antiplatelet agents were given with anticoagulants (adjusted HR 1.60, 95% CI 1.41–1.81). Dabigatran at a dose of 110 mg twice-daily had the lowest risk of major bleeding compared with at higher 150 mg twice-daily dose or with warfarin. Unfortunately, no head-to-head comparison of a thrombin inhibitor and a Factor Xa inhibitor is currently available in patients with AF.

Therapeutic increase of HDL cholesterol: some hope after dal-VEssel and dal-Plaque

Attention was also paid to the presentation of the results of the dal-VEssel (Vascular Effects and Safety of Dalcetrapib in Patients with or at Risk of Coronary Heart Disease) and dal-Plaque (Safety and Efficacy of Dalcetrapib on Atherosclerotic Disease using Novel Non-Invasive Multimodality Imaging) trials, both of which used dalcetrapib, a novel cholesteryl ester transfer protein (CETP) inhibitor that is intended to raise serum levels of high density lipoprotein (HDL) cholesterol. Thomas Lüscher (University of Zurich, Zurich, Switzerland) reported the results of the randomized, double-blind, placebo-controlled, Phase IIb dal-VEssel trial that included 476 subjects with HDL levels <50 mg/dL who had or were at risk of developing coronary artery disease. Patients were randomized to receive 600 mg/day of dalcetrapib or placebo in addition to pre-existing medication. Brachial flow-mediated dilation was assessed as a proxy marker of endothelial function. The design of the trial has been published previously [6].

Treatment with dalcetrapib reduced CETP activity by approximately 50% and increased HDL-cholesterol levels by 31% (from 39 mg/dL to 48 mg/dL). No change in the levels of low density lipoprotein (LDL) cholesterol was noted. Importantly, no increase in blood pressure was observed, as is found during treatment with other CETP inhibitors. However, there was also no change in brachial flow-mediated dilation after 12 weeks (primary endpoint) or 36 weeks. Dr Lüscher said that dalcetrapib “was a bit less potent than torcetrapib, which increased HDL cholesterol in the range of 60–70%.” However, he suggested that this fact may also turn out to be an advantage. Dr Lüscher added that he was also disappointed with the results, because “flow-mediated dilation was not improved. It wasn’t worsened, but it wasn’t improved either.” He concluded that these results should set the stage for “the safety of the drug to be tested in a large outcome trial.”

Data from the dal-Plaque trial were also presented. The results of this placebo-controlled, multicenter study into the effects of dalcetrapib on imaging measures of plaque inflammation and burden were presented by Zahi Fayad (Mount Sinai Medical Center, New York, NY, USA). After 6 months, there was no evidence of a pro-inflammatory effect with dalcetrapib, and less atherosclerotic disease was found in those treated with the drug compared with placebo after 24 months. Again, the study’s rationale and design had been published previously [7]. The hypothesis that dalcetrapib may prevent future cardiovascular events is currently under evaluation in the dal-HEART (Dalcetrapib HDL Evaluation Atherosclerosis and Reverse cholesterol Transport) study that is scheduled to enrol >17,000 patients [8].
Vessel function and the effects of a good belly laugh

Michael Miller and colleagues (University of Maryland School of Medicine, Baltimore, MD, USA) studied the effects of laughter on the vasculature. The investigators asked volunteers to watch segments of a funny movie such as “There’s Something About Mary” on one day and a stressful movie such as the opening segment of “Saving Private Ryan” on another. Each volunteer served as his or her own control. The results were surprising: although the stressful movie yielded vasoconstriction in the brachial artery, watching a funny movie led to vasodilation. Overall, more than 300 measurements were performed and revealed a 30–50% difference in blood vessel diameter between laughing (vasodilation) and mental stress (vasoconstriction). Dr Miller explained that “the magnitude of change we saw in the endothelium after laughing was consistent and similar to the benefit we might see with aerobic exercise or statin use.” He concluded with the suggestion to “eat your veggies, to exercise, and to get a good belly laugh every day.”

K Dimitriadi et al. (University of Athens, Athens, Greece) studied the inter-relationship between smoking, serum levels of biomarkers such as high-sensitivity C-reactive protein (hs-CRP), osteoprotegerin (OPG), and fibrinogen, and plasminogen-activator inhibitor type-1 (PAI-1) in 245 patients with newly diagnosed essential hypertension stage I or II. In total, 115 patients were classified as current smokers and the remaining 130 as non-smokers. Diastolic blood pressure values obtained during an office visit were higher in smokers than in non-smokers (97±8 mmHg vs. 93±7 mmHg; p<0.05). This was also true for 24-h diastolic blood pressure (85±10 mmHg vs. 80±8 mmHg; p=0.001). Compared with non-smokers, smokers were found to have higher levels of hs-CRP (p<0.005), OPG (p<0.005), fibrinogen (p=0.02), and PAI-1 (p=0.004), and these findings were independent of several confounding factors. Dr Dimitriadi concluded that “smoking in essential hypertension is accompanied by increased inflammatory processes, atherosclerosis progression, and impairment of the thrombosis/fibrinolysis system.”

Rule-out of DVT in secondary care

Geert-Jan Geersing (University Medical Center Utrecht, Utrecht, The Netherlands) presented data regarding the accuracy of the Wells rule [9] that is used to rule-out deep venous thrombosis (DVT). The Wells rule implements a scoring system that includes nine factors such as the presence of cancer and swelling of the entire leg or the calf. The Wells rule has recently been challenged and the Oudega rule suggested [10]; the Wells rule may be particularly useful in secondary care (i.e. in patients referred with suspected DVT), whereas the Oudega rule may be preferable in the setting of primary care (i.e. for the initial evaluation in ruling in or ruling out DVT).

Individual patient data from 11 different studies was analyzed to assess the accuracy of the Wells rule when combined with D-dimer testing. A total of 10 014 patients (3114 from primary care, 6900 from secondary care) were evaluated. At a cut-off ≤1 combined with a negative D-dimer test, the failure rate of the Wells rule was 1.0% (95% CI 0.3–1.7) in primary care compared with 1.4% (95% CI 0.8–2.0) in secondary care. Corresponding values for efficiency were 26% and 36%, respectively. Similarly, at a cut-off ≤0 combined with a negative D-dimer test, the failure rates were 0.8% (95% CI 0.1–1.5) versus 0.9% (95% CI 0.4–1.4) and the corresponding efficiencies were 21% versus 26% in primary and secondary care, respectively. The authors concluded that low Wells scores combined with negative D-dimer testing are safe and efficient in detecting DVT in both primary and secondary care.

Summary

A large number of important studies investigating novel therapeutic avenues were presented at this year’s ESC annual congress and, in particular, the presentation of the direct Factor Xa inhibitors apixaban and rivaroxaban and the direct thrombin inhibitor dabigatran will impact on daily prescribing practice. Indeed, these drugs are likely to soon be implemented into guidelines for AF and will simplify treatment of this disease. It is hoped that our patients will benefit from this practice in terms of reductions in morbidity and mortality.

Disclosures

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References

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