Asia-Pacific Thrombosis Advisory Board consensus paper on prevention of venous thromboembolism after major orthopaedic surgery

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Summary
The incidence of postoperative venous thromboembolism (VTE) in Asian populations is generally thought to be lower than in Western populations, and the use of thromboprophylaxis after surgery is not routine. This paper is authored by the Asia-Pacific Thrombosis Advisory Board. To provide guidance on the most effective postoperative thromboprophylaxis management, this paper reviews the available data on the incidence of VTE in Asian populations, considers current clinical guidelines for the prevention of VTE to determine whether these guidelines are applicable to Asian populations, and evaluates the potential of new thromboprophylactic agents. Based on the available evidence, it was agreed that VTE represents a genuine problem in Asian patients, although the exact incidence in local populations requires confirmation in large, well-designed clinical trials. Furthermore, there was consensus that current guideline recommendations for the routine use of postoperative thromboprophylaxis should be implemented in Asia, and that new oral agents now available represent an effective and potentially more convenient therapeutic option. In conclusion, we call for recognition that VTE is an issue in Asian patients, and that effective thromboprophylaxis is the most important strategy.

Keywords
Anticoagulation, postoperative venous thromboembolism, thromboprophylaxis

Introduction
Venous thromboembolism (VTE) comprises deep-vein thrombosis (DVT) and pulmonary embolism (PE). VTE is an important healthcare problem worldwide. It results in significant mortality, morbidity and healthcare expenditure, with PE being the most common preventable cause of hospital death (1). If undiagnosed, asymptomatic VTE can lead to chronic venous disease or recurrent VTE (2), and long-term sequelae include debilitating illnesses such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension (3, 4). In the United States, the Surgeon General recently made a ‘call to action’ to reduce the number of cases of VTE (5). At around the same time, two of the largest United States medical insurers classified hospital-acquired DVT and PE as ‘never events’, i.e. preventable medical errors that result in serious consequences for the patient, and will no longer reimburse hospital medical costs occurring as a result of these conditions (6).

Patients undergoing major orthopaedic surgery, which includes total hip replacement (THR), total knee replacement (TKR) and hip fracture surgery (HFS), are at high risk of developing VTE. In Western countries, the incidence of objectively confirmed, hospital-acquired DVT in patients who do not receive thromboprophylaxis after major orthopaedic surgery is 40% to 60% (1). An epidemiological model of the burden of VTE in the European Union estimated that approximately 30% of high-risk surgical patients who did not receive prophylaxis would develop DVT and approximately 10% would develop PE (7). There is a perception that, because of ethnic differences, the risk of VTE after major orthopaedic surgery in Asian populations is lower (8). However, this perception is gradually changing because accumulating evidence indicates an increase in the incidence of VTE in Asian populations, with some studies showing the risk of VTE to be equal to that in Caucasian populations (9–11). A growing elderly population and a Westernised lifestyle, including changing diet, could be important contributing factors to this increase (12, 13).

In clinical trials of new anticoagulants, it is necessary to use objective measures of VTE to assess efficacy. The use of mandatory venography to detect VTE was first reported by Turpie et al. in a study comparing a low-molecular-weight heparin (LMWH) with placebo for the prevention of DVT after elective hip surgery (14). Venography has since been widely adopted as a surrogate outcome.
Table 1: Rates of adjudicated symptomatic venous thromboembolism or sudden death reported in the SMART study (9). DVT, deep-vein thrombosis; PE, pulmonary embolism; SMART, Surgical Multinational Asian Registry in Thrombosis; VTE, venous thromboembolism.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Up to hospital discharge (%)</th>
<th>At one-month follow-up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic VTE or sudden death</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Symptomatic PE</td>
<td>0.2</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Venous thromboembolism in Asian populations: risk factors and pathophysiology

In Western countries, almost all patients with VTE have at least one predisposing risk factor and approximately 40% have three or more (1). Risk factors include surgery, immobility, previous VTE, increasing age, obesity, varicose veins, malignancy and inherited or acquired thrombophilia (1, 30). These factors are used to stratify patients into risk categories (low, medium or high) and help determine optimal VTE prevention strategies. There have not been any specific studies of risk factors or biological markers for VTE in hospitalised Asian patients, although they appear to be similar to those in Western populations. Risk factors that have been identified include prolonged duration of surgery, increased age, obesity, prolonged immobility, malignancy and treatment with antibiotics within one week before surgery (10, 12, 31), although not all studies have shown an association between all identified risk factors and the development of DVT (32). The risk of symptomatic VTE or sudden death at hospital discharge has been shown to be associated with chronic heart failure, varicose veins, familial or personal history of VTE and age (9).

The primary surgical indication for TKR surgery in both Western and Asian countries is osteoarthritis (33–35). Interestingly, the underlying pathophysiology leading to THR in Asian populations differs from that in Caucasians. In Western countries, the primary reason for THR surgery is also osteoarthritis (36). In Asian populations, hip osteoarthritis is less common than knee osteoarthritis (37), and one of the primary causes of THR in Asian populations appears to be avascular necrosis (37). Avascular necrosis is more likely to occur in younger patients, and studies suggest that the mean age of patients undergoing THR is lower in Asian than in Caucasian populations (37, 38).

Epidemiology of postoperative VTE in Asia

The incidence of postoperative VTE in Asia has been evaluated in large epidemiological studies. The SMART (Surgical Multinational Asian Registry in Thrombosis) study assessed the incidence of symptomatic VTE or sudden death in 2,420 patients after THR, TKR or HFS without thromboprophylaxis (9). This study was conducted in 39 centres in 11 Asian countries (Bangladesh, China [Hong Kong], India, Indonesia, Korea, Malaysia, Pakistan, Philippines, Singapore, Chinese Taipei [Taiwan] and Thailand). Investigator-reported symptomatic VTE and sudden death occurred in 2.3% of patients (55 patients, 99% confidence interval [CI] 1.6–3.2) and 1.2% of patients (28 patients, 99% CI 0.7–1.8), after adjudication by an independent committee (Table 1).

The SMART venography study was a prospective observational cohort study conducted in eight centres in three Asian countries (Bangladesh, Korea and Chinese Taipei [Taiwan]) (10). The primary endpoint was the composite of venographically detected asymptomatic VTE, confirmed symptomatic VTE or sudden death at hospital discharge. A total of 326 patients undergoing TKR or
THR had evaluable venograms. The primary outcome occurred in 36.5% of patients (119 patients, 95% CI 29.7–43.7). The rate of symptomatic VTE was 0.9% (three patients, 95% CI 0.1–3.3).

The AIDA (Assessment of the Incidence of Deep-vein thrombosis in Asia) study assessed the incidence of DVT in patients undergoing THR, TKR or HFS without thromboprophylaxis (11). This study was conducted in 19 centres across various countries in Asia (China, Indonesia, Korea, Malaysia, Philippines, Chinese Taipei [Taiwan] and Thailand). The primary endpoint was the rate of DVT of the lower limbs, documented objectively with bilateral ascending venography. Of 295 evaluable patients, 41% (121 patients, 95% CI 35.4–46.7) were diagnosed with DVT; the rates varied depending on the type of surgery (Fig. 1).

The ENDORSE (Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting) study was a multinational cross-sectional survey designed, in part, to assess the prevalence of risk of VTE in the acute hospital care setting (39). Of the Asian countries included in the study (India, Thailand, Pakistan and Bangladesh), the number of surgical patients at risk of VTE ranged from 44% to 62% (Table 2).

An exhaustive literature search of published papers on the incidence of VTE in Asian populations was performed by Leizorowicz et al. (12). It showed that the adjusted incidence of DVT in patients undergoing general surgery who did not receive thromboprophylaxis was 13% (95% CI 10–16). After THR surgery the incidence was 16% (95% CI 13–20), after TKR surgery 50% (95% CI 44–55) and after HFS 18% (95% CI 12–24). Another review of papers published between 1996 and 2002 on the incidence of postoperative VTE in Asian populations reported incidences of DVT ranging from 3% to 28% based on six general and colorectal surgical papers, and 10% to 63% based on 12 orthopaedic publications (13).

Several relatively small local studies have also reported on the epidemiology of postoperative VTE in Asia. As expected, because of the size of the datasets reported and substantial differences that can exist between institutions within a country, the reported incidences were very variable. One hospital in India reported the overall incidence of VTE to be 6.12% (31). However, rates of postoperative DVT close to zero have been reported in some Indian hospitals (40, 41); whereas, in other institutions, rates as high as 28.0% to 40.3%, depending on the type of surgery, have been reported (42, 43). In Korea, reported rates of DVT after TKR ranged from 11% to 42% (44–46); after THR, rates ranged from approximately 10% to 26% (32, 47, 48). The reported incidence of DVT after TKR surgery in hospitals in Singapore ranged from 0.8% to 14.0% (33, 49–51), with rates of 7.7% reported in HFS patients (52). A study in a tertiary referral hospital in Singapore demonstrated that the prevalence of DVT in hospitalised patients has increased markedly between the periods 1996–1997 and 2002–2003, particularly after orthopaedic surgery (0.082% vs. 0.96%, respectively; p < 0.01) (53). In Chinese populations, postoperative DVT has been reported in 0.13% to 2.6% of patients (54, 55); after major orthopaedic surgery, reported rates ranged from 5.3% to 53.1% (56–59).

**Figure 1: The incidence of deep vein thrombosis (DVT) in patients undergoing total knee replacement (TKR), total hip replacement (THR) or hip fracture surgery (HFS) without thromboprophylaxis reported in the AIDA (Assessment of the Incidence of Deep-vein thrombosis in Asia) study. DVT was detected using bilateral ascending venography (11).**

**Table 2: The number of assessable surgical patients, and surgical patients at risk of venous thromboembolism reported in the ENDORSE study (39). ENDORSE, Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting study.**

<table>
<thead>
<tr>
<th>Country</th>
<th>Assessable surgical patients</th>
<th>At-risk surgical patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>2,091</td>
<td>65</td>
</tr>
<tr>
<td>USA</td>
<td>4,061</td>
<td>78</td>
</tr>
<tr>
<td>India</td>
<td>1,110</td>
<td>61</td>
</tr>
<tr>
<td>Pakistan</td>
<td>748</td>
<td>44</td>
</tr>
<tr>
<td>Thailand</td>
<td>1,001</td>
<td>62</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>962</td>
<td>48</td>
</tr>
</tbody>
</table>
In Thailand, the incidences of DVT after THR, TKR and HFS have been reported as 4%, 24% and 47.9%, respectively (60–62). Postoperative DVT has been reported in 18% of Japanese patients (63), with rates ranging from 22% to 81.3% after major orthopaedic surgery (64–67). In one Malaysian hospital, reported rates of postoperative DVT were 62.5% (68). In a small, low-risk population (n = 17) of Indonesian patients who underwent orthopaedic surgery without thromboprophylaxis, 69.2% had venographically detected VTE at hospital discharge and 23.1% had symptomatic VTE (1). The observed variation between the reported incidences of VTE in local Asian populations could be for a variety of reasons, including design of the studies, heterogeneity of the procedures performed, the methodology for assessment of DVT, and the application of different diagnostic criteria. For example, two of the Singapore studies were retrospective analyses performed in single institutions, in which suspected DVT was confirmed with duplex ultrasonography (33, 49), whereas the other two were prospective studies that used duplex ultrasonography at a specified time point post-surgery to detect DVT (50, 51). In the Korean TKR studies, VTE was detected by venography, but the timing of post-surgery venograms, and whether unilateral or bilateral venographies were performed varied between studies (44–46). These factors and many others could have an influence on VTE rates, and large, well-designed studies are necessary to confirm the incidence of VTE in Asian populations and determine whether the observed variations are real. What is clear is that Asian populations are at risk of VTE after major orthopaedic surgery and that this risk is higher than previously thought.

The incidence of PE, and deaths related to PE, may be underestimated in Asia as in Western countries. This is because of the often clinically silent nature of the disease (70). VTE can also be misdiagnosed or orthopaedic surgeons may not see the potentially fatal consequences of VTE because they are managed externally to their practice. Rates of PE (fatal and non-fatal) after major orthopaedic surgery in Caucasian populations range from 0.9% to 28% (1). The reported incidences of postoperative symptomatic PE in local Asian studies range from 0% to 1.8% (31, 49, 51, 52, 54, 61, 66, 68). The rates of symptomatic VTE or sudden death reported at one-month follow-up in both of the SMART studies were 1.5% (9, 10). In the SMART epidemiological study, symptomatic PE and sudden death both occurred in 0.2% of patients (9). In the AIDA study, PE was clinically suspected in 10 of 407 patients (2.5%) and objectively confirmed in two (0.5%) (11). In a review of the literature, the adjusted incidence of PE after general surgery was reported at 1% and, after THR, was 1.4% (12). These findings indicate that although pulmonary embolic events generally occur less frequently in Asian populations than in Western countries, they are by no means uncommon. The belief among Hong Kong Chinese that massive fatal PE is rare in Chinese populations also appears to be unwarranted. Autopsy studies have demonstrated that the incidence of fatal PE ranges from 0.2% to 6.0% and has increased consistently over a period of 30 years in Hong Kong and Japan (12). Furthermore, one study demonstrated lower but not statistically different rates of massive PE in a Hong Kong Chinese population compared with the Caucasian population, although whether this finding is applicable to a broader Asian population requires further investigation (71).

Comparisons between Asian and Western data should always be approached with caution, particularly in relation to symptomatic events. Most Western studies use asymptomatic events, assessed by mandatory venography, to determine the incidence of VTE, a process that could alter the natural history of the disease (72). In addition, knowledge of venography results could influence local investigators to overestimate the frequency of symptomatic VTE (73). Furthermore, the number of patients assessed in Asian epidemiology studies is still too small to draw definite conclusions about VTE incidence, particularly for less common symptomatic events.

### Clinical trials of thromboprophylaxis

#### Conventional agents

In early placebo-controlled studies, unfractionated heparin (UFH) was shown to significantly reduce the incidence of DVT, and importantly clinical PE and PE mortality, in patients undergoing major orthopaedic surgery (74). The development of LMWHs in the 1980s led to numerous studies that compared unfractionated heparin (UFH) with LMWHs. Meta-analyses of these studies demonstrated the superior efficacy of LMWHs compared with UFH for the prevention of VTE after orthopaedic surgery (75, 76). As a result, LMWHs became, and have remained to date, the standard of care in this indication. More recently, the indirect factor Xa inhibitor fondaparinux was developed and approved for the prevention of VTE after major orthopaedic surgery. In a meta-analysis of four phase III studies, fondaparinux demonstrated superior efficacy for the prevention of VTE compared with the LMWH enoxaparin. However, major bleeding events were more frequent in the fondaparinux group (77).

The main drawback of the above agents is that they are administered parenterally, making them inconvenient for use-out

### Table 3: The incidence of postoperative deep-vein thrombosis reported in local Asian studies (the types of surgery are described in the text). DVT, deep-vein thrombosis.

<table>
<thead>
<tr>
<th>Country</th>
<th>Range in incidence of postoperative DVT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>India (40–43)</td>
<td>0–40.3</td>
</tr>
<tr>
<td>Korea (32, 44–48)</td>
<td>11.0–42.0</td>
</tr>
<tr>
<td>Singapore (33, 49–53, 124)</td>
<td>0.8–14.0</td>
</tr>
<tr>
<td>China (54–59)</td>
<td>0.13–53.1</td>
</tr>
<tr>
<td>Thailand (60–62)</td>
<td>4.0–47.9</td>
</tr>
<tr>
<td>Japan (63–67)</td>
<td>22.0–81.3</td>
</tr>
<tr>
<td>Malaysia (68)</td>
<td>62.5</td>
</tr>
<tr>
<td>Indonesia (69)</td>
<td>69.2</td>
</tr>
</tbody>
</table>
side the hospital setting. UFH is also associated with heparin-induced thrombocytopenia and osteopenia, and requires monitoring when used for the treatment of VTE (78). LMWHs do not require routine coagulation monitoring and have a substantially lower risk of heparin-induced thrombocytopenia compared with UFH (79). However, in patients with significant renal impairment, drug accumulation can occur, necessitating dose adjustment in these patients (80). Drug accumulation with fondaparinux may also occur in patients with renal insufficiency (81). Elderly patients with impaired renal function may have reduced elimination and increased exposure to fondaparinux, increasing the risk of bleeding. In patients with severe renal impairment, fondaparinux is contraindicated, and, in patients with moderate renal impairment, a lower dose is recommended (82).

Vitamin K antagonists (VKAs), of which warfarin is the most commonly used, were developed in the 1940s, and until recently were the only available oral anticoagulants. A meta-analysis comparing VKAs with alternative prophylaxis demonstrated that VKAs were significantly less effective than LMWHs for the prevention of DVT (including proximal DVT), although no significant differences were seen in the incidences of PE or death (Table 4) (83). Results of a pooled analysis of the four RECORD (REgulation of Coagulation in Orthopaedic surgery to prevent Deep vein thrombosis and pulmonary embolism) trials demonstrated that rivaroxaban regimens significantly reduced the incidence of symptomatic VTE and all-cause mortality, compared with enoxaparin regimens in the three study pools analysed. No significant difference in the incidence of major bleeding was observed between the groups in any of the treatment pools; however, an increase in major plus clinically relevant non-major bleeding observed with rivaroxaban in one of the pools did reach statistical significance (89). Taking the composite of major clinical outcomes (i.e. symptomatic VTE, stroke, myocardial infarction and major bleeding) analysed during treatment and follow-up, a significant reduction in favour of rivaroxaban was demonstrated, suggesting a positive net clinical benefit.

### New oral anticoagulants

Newer anticoagulants, which target specific factors in the coagulation cascade, have recently been developed in order to address some of the limitations associated with conventional agents. These new agents include the oral, direct thrombin inhibitor dabigatran etexilate, and the oral direct factor Xa inhibitors rivaroxaban and apixaban. Dabigatran etexilate and rivaroxaban are approved in the European Union, Canada and a number of Asian countries for the prevention of VTE after elective hip or knee replacement surgery in adults. Dabigatran is administered as a 220 mg once-daily dose in healthy adults and a 150 mg once-daily dose in elderly patients and in patients with moderate renal impairment (86). Rivaroxaban is administered as a 10 mg once-daily dose (87). Apixaban is in phase III development for the prevention of VTE after TKR or THR, and is administered as a 2.5 mg twice-daily dose. The results of phase III clinical trials with these agents are summarised in Table 5.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>VKA (%)</th>
<th>LMWH (%)</th>
<th>RR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>18.0</td>
<td>13.0</td>
<td>1.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>6.0</td>
<td>4.0</td>
<td>1.51</td>
<td>0.028</td>
</tr>
<tr>
<td>PE</td>
<td>0.5</td>
<td>0.3</td>
<td>1.10</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.6</td>
<td>0.4</td>
<td>1.30</td>
<td>NS</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.0</td>
<td>3.0</td>
<td>0.78</td>
<td>NS</td>
</tr>
<tr>
<td>Wound haematoma</td>
<td>7.0</td>
<td>9.0</td>
<td>0.88</td>
<td>NS</td>
</tr>
</tbody>
</table>

In a meta-analysis of the phase III dabigatran etexilate studies (RE-MODEL, RE-MOBILIZE and RE-NOVATE), no significant differences in the safety or efficacy endpoints analysed were shown between dabigatran and standard therapy (88). Results of a pooled analysis of the four RECORD (REGulation of Coagulation in Orthopaedic surgery to prevent Deep vein thrombosis and pulmonary embolism) trials demonstrated that rivaroxaban regimens significantly reduced the incidence of symptomatic VTE and all-cause mortality, compared with enoxaparin regimens in the three study pools analysed. No significant difference in the incidence of major bleeding was observed between the groups in any of the treatment pools; however, an increase in major plus clinically relevant non-major bleeding observed with rivaroxaban in one of the pools did reach statistical significance (89). Taking the composite of major clinical outcomes (i.e. symptomatic VTE, stroke, myocardial infarction and major bleeding) analysed during treatment and follow-up, a significant reduction in favour of rivaroxaban was demonstrated, suggesting a positive net clinical benefit.

### Thromboprophylaxis in Asian populations

Because the risk of VTE in Asia has been perceived to be low, there are relatively few studies assessing the efficacy of pharmacological thromboprophylaxis after major orthopaedic surgery in Asian populations. Results of the available data are summarised below in Table 6.

In an open multi-centre controlled Korean study, 100 patients undergoing elective THR received either the LMWH nadroparin calcium or no thromboprophylaxis (n = 50 in both groups) (90). Eight patients (16%) in the control group and one patient (2%) receiving thromboprophylaxis developed venographically detected DVT; PE occurred in three and one patient, respectively. In another study of nadroparin sodium, conducted in a hospital in Singapore in patients undergoing TKR, the incidence of DVT in the control group (n = 100) was 14% and in the LMWH group (n = 100) was 0% (91). In a further study that evaluated nadroparin calcium in Chinese patients undergoing hip or knee...
surgery, eight of 23 (34.8%) patients in the control group and one of 23 (4.3%) patients in the LMWH group developed DVT (92). The use of LMWH did not lead to increased bleeding complications in any of these studies.

In a Singapore hospital, 440 low-risk patients undergoing TKA were randomised to no prophylaxis, graduated compression stockings, intermittent pneumatic compression or the LMWH enoxaparin in four equal groups (93). Rates of DVT were 22%, 13%, 8% (p = 0.032 vs. control) and 6% (p = 0.001 vs. control), respectively. One patient in each of the control and graduated compression stockings groups developed a non-fatal PE. In this study, patients on enoxaparin received more blood transfusions than the control.

<table>
<thead>
<tr>
<th>Duration of therapy</th>
<th>Primary efficacy endpoint*</th>
<th>Major bleeding†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n/N)</td>
<td>P-value for difference to enoxaparin</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-NOVATE (THR), N=3,494 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran 220 mg od 28–35 days</td>
<td>6.0 (53/880)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dabigatran 150 mg od</td>
<td>8.6 (75/874)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Enoxaparin 40 mg od</td>
<td>6.7 (60/897)</td>
<td>1.6 (18/1,154)</td>
</tr>
<tr>
<td>RE-MOBILIZE (TKR), N=2,615 (125)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran 220 mg od 12–15 days</td>
<td>31.1 (188/604)</td>
<td>0.0234</td>
</tr>
<tr>
<td>Dabigatran 150 mg od</td>
<td>33.7 (219/649)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Enoxaparin 30 mg bid</td>
<td>25.3 (163/643)</td>
<td>1.4 (12/868)</td>
</tr>
<tr>
<td>RE-MODEL (TKR), N=2,101 (19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran 220 mg od 6–10 days</td>
<td>36.4 (183/503)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Dabigatran 150 mg od</td>
<td>40.5 (213/526)</td>
<td>0.017</td>
</tr>
<tr>
<td>Enoxaparin 40 mg od</td>
<td>37.7 (193/512)</td>
<td>1.3 (9/694)</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECORD1 (THR), N=4,541 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 10 mg od 31–39 days</td>
<td>1.1 (18/1,595)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Enoxaparin 40 mg od</td>
<td>3.7 (58/1,558)</td>
<td>0.1 (2/2,224)</td>
</tr>
<tr>
<td>RECORD2 (THR), N=2,509 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 10 mg od 31–39 days</td>
<td>2.0 (17/864)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Enoxaparin 40 mg od 10–14 days (with placebo for 31–39 days)</td>
<td>9.3 (81/869)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RECORD3 (TKR), N=2,531 (22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 10 mg od 10–14 days</td>
<td>9.6 (79/824)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Enoxaparin 40 mg od</td>
<td>18.9 (166/878)</td>
<td>0.5 (6/1,239)</td>
</tr>
<tr>
<td>RECORD4 (TKR), N=3,148 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 10 mg od 10–14 days</td>
<td>6.9 (67/965)</td>
<td>0.0118</td>
</tr>
<tr>
<td>Enoxaparin 30 mg bid</td>
<td>10.1 (97/959)</td>
<td>0.3 (4/1,508)</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADVANCE-1 (TKR), N=3,195 (126)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban 2.5 mg bid 10–14 days</td>
<td>9.0 (104/1,157)</td>
<td>0.06</td>
</tr>
<tr>
<td>Enoxaparin 30 mg bid</td>
<td>8.8 (100/1,130)</td>
<td>1.4 (22/1,588)</td>
</tr>
<tr>
<td>ADVANCE-2 (TKR), N=3,057 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban 2.5 mg bid 10–14 days</td>
<td>15.1 (147/976)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Enoxaparin 40 mg od</td>
<td>24.4 (243/997)</td>
<td>–</td>
</tr>
</tbody>
</table>

*Composite of any deep-vein thrombosis, pulmonary embolism and death from any cause. †For each anticoagulant drug, differing definitions of major bleeding were used for the phase III studies. The primary difference was that, in the dabigatran and apixaban studies, major bleeding included surgical-site bleeding, whereas in the rivaroxaban studies it did not. bid, twice daily; od, once daily; THR, total hip replacement; TKR, total knee replacement.
group and two had major bleeding complications. In a Japanese study that compared UFH with the low-molecular-weight heparinoid danaparoid for the prevention of VTE after hip surgery, DVT rates were 31% in the placebo group (n = 71), 9.1% in the UFH group (n = 44) and 5.5% in the danaparoid group (n = 55) (94). PE rates were 5.6%, 4.5% and 1.8%, respectively. No serious bleeding complications occurred in the UFH or danaparoid groups.

A study conducted in 150 Korean patients undergoing THR compared no prophylaxis (n = 50), ASA (n = 50) and low-molecular-weight dextran (n = 50). The incidence of DVT in each of the groups was 20%, 12% (p < 0.1 vs. control), and 6% (p < 0.05 vs. control), respectively. Both ASA and dextran were well tolerated (95). In a Chinese study, 240 patients undergoing total joint arthroplasty were randomised to receive either ASA (n = 100) or LMWH (n = 140) (96). In the ASA group, 13% had DVT compared with 7.1% in the LMWH group, although this difference was not statistically significant. No difference in bleeding events was observed between groups.

In Japanese patients undergoing THR or TKR, a placebo-controlled study to determine the optimal dose of fondaparinux was conducted (97). In TKR patients, the incidence of VTE was 65.3% in the placebo group and ranged from 9.5% to 34.2% in the fondaparinux groups (fondaparinux doses ranged from 0.75 mg to 3.00 mg). In THR patients, the rates were 33.8% vs. 14.4% to 24.2% (fondaparinux doses ranged from 0.75 mg to 3.00 mg). No significant differences in major bleeding events were found among any groups.

In Japan, edoxaban (DU-176b), an oral, direct factor Xa inhibitor in phase II development, has been evaluated for the prevention of VTE in patients undergoing TKR (98). In this randomised, placebo-controlled, dose-ranging study, the incidences of major and clinically relevant bleeding were similar across all dose groups, without significant differences between doses, compared with placebo. All edoxaban doses assessed resulted in a decrease in the incidence of VTE compared with placebo; the efficacy response was dose dependent.

Of the new oral anticoagulants, data from the subset of Chinese patients in the rivaroxaban RECORD2 and RECORD3 studies have been analysed (99). In RECORD2, the primary efficacy outcome (the composite of any DVT, non-fatal PE and all-cause mortality) occurred in one of 121 Chinese patients (0.8%) receiving extended-duration rivaroxaban and 16 of 122 Chinese patients (13.1%) receiving short-duration enoxaparin followed by placebo, with a relative risk reduction of 94%. In RECORD3, the primary

<table>
<thead>
<tr>
<th>Reference</th>
<th>Surgery</th>
<th>Drug</th>
<th>Comparator</th>
<th>Endpoint</th>
<th>Detection method</th>
<th>Incidence, n/N (%)</th>
<th>Drug Comparator</th>
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</thead>
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<tr>
<td>Yoo et al. 1997 (90)</td>
<td>THR</td>
<td>Nadroparin calcium</td>
<td>Placebo</td>
<td>DVT</td>
<td>Venography</td>
<td>1/50 (2)</td>
<td>8/50 (16)</td>
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<td>TKR</td>
<td>Nadroparin calcium</td>
<td>Placebo</td>
<td>DVT</td>
<td>Duplex ultrasonography</td>
<td>0 (0)</td>
<td>14/100 (14)</td>
</tr>
<tr>
<td>Li et al. 2001 (92)</td>
<td>THR/TKR</td>
<td>Nadroparin calcium</td>
<td>Placebo</td>
<td>DVT</td>
<td>Venography</td>
<td>1/23 (4.3)</td>
<td>8/23 (34.8)</td>
</tr>
<tr>
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<td>Placebo</td>
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<td>Duplex ultrasonography</td>
<td>6/110 (6)</td>
<td>24/110 (22)</td>
</tr>
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<td>Danaparoid</td>
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<td>DVT</td>
<td>Venography</td>
<td>3/55 (6)</td>
<td>22/71 (31)</td>
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<td>THR</td>
<td>Dextran</td>
<td>Placebo</td>
<td>DVT</td>
<td>Venography</td>
<td>3/50 (6)</td>
<td>10/50 (20)</td>
</tr>
<tr>
<td>Tian et al. 2007 (96)</td>
<td>THR/TKR</td>
<td>LMWH</td>
<td>ASA</td>
<td>DVT</td>
<td>Clinical symptoms</td>
<td>10/140 (7.1)</td>
<td>13/100 (13)</td>
</tr>
<tr>
<td>Fuji et al. 2008 (97)</td>
<td>THR/TKR</td>
<td>Fondaparinux*</td>
<td>Placebo</td>
<td>VTE</td>
<td>DVT; venography PE; lung scan, pulmonary angiography, spiral CT, autopsy</td>
<td>THR 10/70 (14.3)</td>
<td>TKR 25/74 (33.8)</td>
</tr>
<tr>
<td>Fuji et al. 2008 (98)</td>
<td>TKR</td>
<td>Edoxaban (DU-176b)*</td>
<td>Placebo</td>
<td>VTE</td>
<td>DVT; venography PE; clinical symptoms</td>
<td>8/88 (9.1)</td>
<td>33/89 (38.3)</td>
</tr>
<tr>
<td>Houshan and Wang 2008 (99)</td>
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<td>Rivaroxaban ‡</td>
<td>Enoxaparin</td>
<td>VTE</td>
<td>DVT; venography PE; lung scan, chest radiography, spiral CT, autopsy</td>
<td>1/121 (0.8)</td>
<td>16/122 (13.1)</td>
</tr>
<tr>
<td>Houshan and Wang 2008 (99)</td>
<td>TKR</td>
<td>Rivaroxaban</td>
<td>Enoxaparin</td>
<td>VTE</td>
<td>DVT; venography PE; lung scan, chest radiography, spiral CT, autopsy</td>
<td>8/63 (12.7)</td>
<td>16/66 (24.2)</td>
</tr>
</tbody>
</table>

*3 mg dose. †60 mg dose. ‡Extended-duration prophylaxis with rivaroxaban versus short-duration prophylaxis with enoxaparin. ASA, acetylsalicylic acid; CT, computed tomography; DVT, deep-vein thrombosis; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism.

Table 6: Prophylaxis after major orthopaedic surgery in Asian populations.

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efficacy outcome occurred in eight of 63 (12.7%) Chinese patients receiving rivaroxaban and 16 of 66 (24.2%) of Chinese patients receiving enoxaparin, with a relative risk reduction of 48% (p = 0.175). No major bleeding events occurred in either arm of both studies. The findings in the Chinese population were consistent with the results in the total study population (Fig. 2).

The results of these studies in Asian populations support those in Caucasian populations, and demonstrate that the use of thromboprophylaxis after major orthopaedic surgery reduces the risk of VTE. In addition, the benefits associated with thromboprophylaxis are not generally associated with a clinically significant increase in the risk of bleeding complications.

Guidelines for the prevention of VTE

The American College of Chest Physicians (ACCP) and the American Association of Orthopaedic Surgeons (AAOS) have developed guidelines for the prevention of postoperative VTE. The ACCP guidelines strongly recommend that patients undergoing elective THR, TKR or HFS, who are at high risk of VTE, should use a LMWH, fondaparinux or a VKA. After surgery, prophylaxis is recommended for a minimum of 10 days and up to 35 days after hip replacement surgery or HFS, and an extension to 35 days is suggested in some patients after knee replacement (1). For the prevention of PE after THR or TKR surgery, the AAOS guidelines recommend a LMWH, synthetic pentasaccharide, warfarin or ASA (100). The ACCP guidelines, in contrast, do not recommend the use of ASA as a sole method of thromboprophylaxis. The observed disparity between the two guidelines is a result of the AAOS guidelines not taking into account the need to prevent DVT, or the full weight of clinical trials evidence for the link between DVT and PE (101).

There is some debate within the Asian thrombosis community as to whether international guidelines, predominantly derived from studies in Caucasian populations, are appropriate for the management of Asian patients, particularly given the variability in the incidence of VTE observed in ‘local’ Asian populations. The development of specific local or national guidelines may be the ultimate goal, and Japan (102), Korea (103) and China (104) have recently developed and published their own guidelines on the prevention of VTE, largely based on the ACCP guidelines. In the absence of local guidelines, the consensus of the Asia-Pacific Thrombosis Advisory Board is that the evidence-based ACCP guidelines should be adopted. However, it is acknowledged that guidelines need to be flexible and their implementation practical at all levels of care. Furthermore, an accurate knowledge of evidence-based risk factors will help predict and prevent postoperative VTE, and can be incorporated into a decision support system for appropriate thromboprophylaxis use.

Figure 2: The incidence of the composite of total venous thromboembolism (VTE) and all-cause mortality in the total study population and in the subset of Chinese patients in RECORD2 (A), which compared extended-duration rivaroxaban prophylaxis (31–39 days) with short-duration enoxaparin prophylaxis (10–14 days), and RECORD3 (B), which compared rivaroxaban with enoxaparin prophylaxis for 10–14 days. ARD, absolute risk difference; RRR, relative risk reduction.
The ultimate objective of guidelines is to ensure the best clinical outcome for patients. Non-adherence to guidelines and sub-optimal use of thromboprophylaxis for the prevention of post-operative VTE is a problem worldwide (25, 105). Currently, in the majority of Asian hospitals, pharmacological VTE prophylaxis after surgery is not the standard of care, even in high-risk patients (39, 106, 107).

Practical management of new anticoagulants

The new oral anticoagulants have the potential to simplify thromboprophylactic management (108). Some considerations regarding the practical management of the approved oral agents, rivaroxaban and dabigatran, are outlined below.

Antidote

Neither rivaroxaban nor dabigatran has a specific antidote. However, in the event of an overdose or in a bleeding emergency, a number of steps can be taken. For rivaroxaban, the use of activated charcoal to reduce absorption can be considered. If bleeding occurs, rivaroxaban should be discontinued or the next dose delayed and the source of bleeding investigated. If bleeding continues, appropriate symptomatic treatment (e.g. blood product or component transfusion) should be considered. Factor VIIa may also be considered if life-threatening bleeding cannot be stopped (87). For dabigatran, treatment should be discontinued and the source of bleeding investigated. As dabigatran is excreted predominantly by the renal route, adequate diuresis must be maintained. The initiation of appropriate treatment (e.g. surgical haemostasis or the transfusion of fresh frozen plasma) should be considered. Dabigatran can be dialysed, although there is no clinical evidence to demonstrate the utility of this approach (86).

Coagulation monitoring

The predictable pharmacokinetics and pharmacodynamics of rivaroxaban and dabigatran have been established in clinical trials (109–117). For rivaroxaban, these findings were confirmed in healthy Chinese subjects (118). Because of their predictability, neither of these agents requires coagulation monitoring. Current techniques refined for monitoring VKAs, such as prothrombin time measurement, are not appropriate for monitoring the safety and efficacy of these new oral anticoagulants. However, there is some evidence that prothrombin time assays calibrated to rivaroxaban concentrations may be used in the future to assess the pharmacodynamic effects of rivaroxaban if required (119).

Development of guidelines on the prevention of venous thromboembolism: key needs

- Identify levels of risk
- Localise guidelines
  - Base on local data where possible and match guideline recommendations with supporting data
  - Develop with a multidisciplinary group
  - Ensure guidelines are practical and usable at all levels of care
  - Audit guidelines to make sure they achieve clinical goals
- Allow flexibility within the guidelines regarding:
  - Need for preoperative anticoagulation
  - Postoperative management with mechanical devices in addition to anticoagulation
  - Duration of thromboprophylaxis
- Consider best practice for the management of new oral anticoagulants

Use with epidural catheters

With rivaroxaban, an epidural catheter should not be removed earlier than 18 hours (h) after the last administration of rivaroxaban. The next rivaroxaban dose should be administered no earlier than 6 h after the removal of the catheter and if traumatic puncture occurs rivaroxaban administration should be delayed for 24 h (87). The use of dabigatran is not recommended in anaesthetised patients with postoperative indwelling epidural catheters. The first dose of dabigatran should be administered at least 2 h after the catheter is removed and these patients will require frequent observation for neurological signs and symptoms (86).

Concomitant use of non-steroidal anti inflammatory drugs

Neither rivaroxaban nor dabigatran etexilate has been shown to have a pharmacokinetic interaction with non-steroidal anti-inflammatory drugs (NSAIDs). Studies in healthy male subjects demonstrated no clinically relevant interaction between rivaroxaban and ASA or rivaroxaban and naproxen (120, 121). In patients undergoing THR or TKR, bleeding risk was not significantly increased relative to enoxaparin by concomitant use of NSAIDs or ASA (122). When dabigatran etexilate was co-administered with diclofenac, the plasma exposure of both medicinal products remained unchanged (111). In patients undergoing THR or TKR, patients co-administered dabigatran with NSAIDs or ASA had a similar bleeding risk to those taking dabigatran alone (123). However, because of the risk of haemorrhage with NSAIDs, patients should be observed closely for signs of bleeding.
Appendix

The following are co-authors and members of the Asia-Pacific Thrombosis Advisory Board: A. Cohen (Chair, United Kingdom), R.C. Geng (China), B. Yang (China), K. Tambunan (Indonesia), S.H. Lee (South Korea), S.K. Hian (Malaysia), P. Iqbal (Pakistan), E. Pasion (Philippines), J. Fletcher (Australia), H. Salem (Australia), Y.L. Kwong (Hong Kong), J.S. Bhanusanwrian (India), D. Oh (Korea), L.L. Heng (Singapore), P. Angchaisukiri (Thailand).

Conclusion

The risk of postoperative VTE in Asian patients is real and clinically significant. The consensus view of the Asia-Pacific Thrombosis Advisory Board is that anticoagulant therapy is the most important preventative strategy for VTE after major orthopaedic surgery. We recommend its use in a wide range of patient populations to reduce morbidity, mortality and healthcare expenditure associated with VTE. We also encourage adherence to clinical guidelines to optimise the benefits of thromboprophylaxis. Furthermore, we believe that the introduction of new oral anticoagulants is likely to simplify patient management and facilitate adherence to guidelines, and advocate the sharing of best practice as clinical experience with these agents grows.

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