Epidemiology of post-operative venous thromboembolism in Asian patients. Results of the SMART venography study

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[1]Committees and Investigators participating in the SMART (Surgical Multinational Asian Registry in Thrombosis) Venography Study are listed in the Appendix.

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ABSTRACT

Background and Objectives

The rate of post-operative asymptomatic deep-vein thrombosis in Asian patients remains uncertain. The aim of this study was to estimate the rate of venous thromboembolism, including asymptomatic deep-vein thrombosis, in Asian patients undergoing hip or knee surgery and not receiving pharmacological thromboprophylaxis.

Design and Methods

This was a prospective observational study of a cohort of consecutive Asian patients. The primary study outcome was the composite of venographically detected asymptomatic, or confirmed symptomatic venous thromboembolism, or sudden death at hospital discharge. Bilateral venography was to be performed in all patients between days 5 and 14 after surgery. Follow-up lasted 1 month.

Results

A total of 386 patients (median age: 65 years, female: 63.7%, body-mass index ≥30 kg/m^2: 15.4%) undergoing hip (n=160) or knee (n=226) replacement surgery satisfied the study selection criteria and 326 (84.5%) had evaluable venograms. The rate of the primary outcome was 36.5% (119 patients, 99% confidence interval: 29.7 to 43.7). The rate of symptomatic venous thromboembolism was 0.9% (3 patients, 99% confidence interval: 0.1 to 3.3). During follow-up (358 patients for a median duration of 33 days after surgery), two additional episodes of symptomatic venous thromboembolism occurred. Multivariate analysis identified that knee replacement surgery, duration of surgery and treatment with antibiotics within 1 week before surgery were independent risk factors (p<0.05) for venous thromboembolism or sudden death at hospital discharge.

Interpretation and Conclusions

In Asian patients, the incidence of asymptomatic and symptomatic venous thromboembolism after major orthopedic surgery is high. These results suggest that thromboprophylaxis should be considered in these patients.

Key words: Asia, epidemiological study, orthopedic surgery, venography, venous thromboembolism.

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Several recent data have challenged the belief that postoperative venous thromboembolism is rare in Asian patients. In the recently reported prospective epidemiological study of Asian patients undergoing orthopedic surgery without receiving thromboprophylaxis (SMART), the rate of symptomatic venous thromboembolism or sudden death, as notified by the investigators, was 2.3% (99% confidence interval [CI]: 1.6-3.2), and 1.2% (28 patients, 99% CI: 0.7-1.8) after adjudication by an independent committee.[1] Chronic heart failure, varicose veins and a history of venous thromboembolism were found to be independent risk factors ($p<0.05$) for the occurrence of the primary outcome.[1] In a recent review of published studies in Asian patients undergoing surgery and not receiving thromboprophylaxis, the adjusted incidence of total (symptomatic and asymptomatic) deep-vein thrombosis was 13% (95% CI: 10-16) in general surgery, 16% (95% CI: 13-20) after total hip replacement, 50% (95% CI: 44-55) after total knee replacement, and 18% (95% CI: 12-24) after hip fracture surgery. The adjusted incidence of symptomatic pulmonary embolism was 1% (95% CI: 0-2) in general surgery and 1.4% (95% CI: 1-3) after total hip replacement.[2] Furthermore, it was shown that the incidence of fatal pulmonary embolism had increased over time.[2] Taken together, these results suggest that the risk of venous thromboembolism in Asian patients is significant and that both the risk and pattern of venous thromboembolism are comparable to those reported in Western countries.[3,4] Asymptomatic venous thromboembolism has long been recognized as a valid surrogate outcome measure for symptomatic venous thromboembolism.[5] However, the rate of post-operative asymptomatic deep-vein thrombosis in Asian patients remains uncertain.

As part of the SMART program, we therefore performed a prospective epidemiological study to estimate the rate of venous thromboembolism, including asymptomatic deep-vein thrombosis, in Asian patients undergoing hip or knee surgery and not receiving pharmacological thromboprophylaxis. Venous thromboembolism was assessed by venography, the reference method for detecting deep-vein thrombosis in asymptomatic patients.[5-8] A secondary objective was to determine risk factors for venous thromboembolism. The recently reported AIDA study was conducted during the same period of time as our study, in different Asian centers, and had a comparable design.[9]

Design and Methods

This was a prospective, international, multicenter, observational study of a cohort of consecutive Asian patients undergoing total hip or knee replacement. It was conducted in eight centers in three Asian countries: Bangladesh, Korea and Taiwan (*see Appendix*). None of the participating centers routinely used pharmacological thromboprophylaxis. The SMART Venography Study was conducted according to a parallel protocol of the SMART study, in different patients and centers.[1]

Patients

Asian patients aged at least 40 years old, hospitalized for a first elective total hip or knee replacement, or bilateral total hip or knee replacement if performed during the same intervention, were recruited. Patients scheduled to undergo a revision procedure or total hip or knee replacement following trauma, and those scheduled to receive thromboprophylactic drugs during their hospital stay, i.e. unfractionated heparin, low-molecular-weight heparins, heparinoids, vitamin K antagonists, hirudin, antiplatelet agents or dextran, were to be excluded. Other main exclusion criteria were the use of antiplatelet agents or vitamin K antagonists within the week preceding inclusion, and any contraindication to venography according to the investigator. The use of non-steroidal anti-inflammatory drugs, elastic bandaging, support stockings, and physiotherapy was left to the investigator's discretion.

Study design

Patients were to be systematically examined for deep-vein thrombosis by bilateral ascending contrast venography of the lower extremities[10] between days 5 and 14 after surgery. If deep-vein thrombosis was clinically suspected before the planned day of venography, ultrasonography could be performed. This was to be followed by bilateral venography in the event of any persistent doubt on ultrasonography examination. If the ultrasonography was negative, bilateral venography was to be performed on the scheduled day. Clinically suspected pulmonary embolism was to be confirmed by a high-probability lung scan, pulmonary angiography, helical computed tomography, or at autopsy. All venograms were reviewed centrally.

After hospital discharge, patients were contacted, by mail or telephone, 1 month (i.e. between 30 and 37 days) after surgery and asked to report any symptoms or signs of venous thromboembolism, bleeding and re-hospitalization. In the event of venous thromboembolism during the study, treatment was left to the investigator's discretion.

The study was conducted according to the ethical principles stated in the Declaration of Helsinki and local regulations. The protocol was approved by independent ethics committees and written informed consent was obtained before inclusion into the study.

Study outcomes

The primary study outcome was the incidence of the composite of adjudicated confirmed asymptomatic or symptomatic venous thromboembolism (defined as deep-vein thrombosis, fatal or non-fatal pulmonary embolism, or both) or sudden death at hospital discharge. Other

Table 1. Patient characteristics.

	Hip replacement (n=160)*	*Knee replacement* (n=226)*	*All patients (n=386)*
Female, no. (%)	58 (36.3)	188 (83.2)	246 (63.7)
Median age (range), yr	57 (28-77)	68 (41-85)	65 (28-85)
Age ≥ 60 yr, no. (%)	66 (41.3)	199 (88.1)	265 (68.7)
Median weight (range),† kg	63 (38-110)	64 (36-95)	63 (36-110)
Median body mass index (range),‡ kg/m^2	24 (17-45)	27 (17-42)	26 (17-45)
Body mass index ≥30 kg/m^2,‡ no. (%)	8 (5.1)	51 (22.6)	59 (15.4)
Smoking,§ no. (%)	66 (41.5)	10 (4.5)	76 (19.9)
Arterial hypertension, no. (%)	30 (18.8)	107 (47.3)	137 (35.5)
History of cancer or active cancer, no. (%)	4 (2.5)	10 (4.4)	14 (3.6)
Personal or familial history of venous thromboembolism, no. (%)	0	0	0
Known thrombophilia, no. (%)	0	0	0
Chronic heart failure, no. (%)	4 (2.5)	11 (4.9)	15 (3.9)
Chronic respiratory failure,¶ no. (%)	5 (3.1)	1 (0.4)	6 (1.6)
Varicose veins,|| no. (%)	2 (1.3)	4 (1.8)	6 (1.6)
Hormone therapy,** no. (%)	1 (0.6)	0	0

**Bilateral surgery was performed in two and eleven patients in the hip replacement and knee replacement groups, respectively; †Data were missing for one patient in the hip replacement group; ‡Data were missing for two patients in the hip replacement group; §Current smoker or smoker within the last five years; data were missing for one patient and three patients in the hip replacement and knee replacement groups, respectively; ¶Data were missing for two patients in the knee replacement group; || Data were missing for one patient in the knee replacement group; **Including estrogen therapy, hormone replacement therapy and anti-androgen therapy.*

study outcomes were the composite of venous thromboembolism or sudden death at the 1-month follow-up, and overall mortality at 1-month follow-up.

All reported venous thromboembolic events and deaths that occurred during the course of the study were reviewed centrally by a two-member committee. Patient cases were reviewed using data from case report forms, patients' records, ultrasonography reports, venograms, angiograms, scintigrams and all other available additional documentation. Patients with no events were not reviewed. Evaluation of the main study outcomes was based on this central assessment.

Statistical analysis

The number of patients to be included in the study was set at approximately 400. It was calculated that this sample size would allow a precision of about ±4.2% at a level of 95% with an assumed event rate of 25%.

The risks of documented asymptomatic or symptomatic venous thromboembolism and sudden death at hospital discharge and at the 1-month follow-up were analyzed by multiple logistic regression. Univariate analysis was performed to screen potential variables for inclusion in the final multivariate model. The following patient-related and surgical characteristics were recorded at baseline and further tested as potential risk factors for venous thromboembolism or sudden death (primary outcome): age, gender, body-mass index, smoking (current or within the last 5 years), history of cancer or active cancer, family or personal history of venous thromboembolism, known thrombophilia, chronic heart failure, chronic respiratory failure, varicose veins, hormone therapy (i.e. estrogen, hormone replacement and anti-androgen therapy) within 1 week before surgery, time between admission and surgery, type of surgery, duration of surgery, type of anesthesia, concomitant treatment, duration of immobilization, and duration of hospital stay. Variables that were significant at the 0.10 level in the univariate analysis were included in the multivariate logistic regression analysis. Variables significant at the 0.05 level in the Wald χ^2 test in the final multivariate analysis were retained as independent predictive factors. The odds ratio and associated 95% CI for the various potential risk factors were calculated. All analyses were performed using SAS Windows V8 software (SAS Institute, Cary, NC, USA).

Results

Patients' characteristics

Between May 2002 and January 2004, 393 patients were enrolled. Seven patients were not considered in the final analysis, three because they did not undergo surgery and four because they received anticoagulant treatment within 1 week before surgery. The median age of the patients was 65 years (range: 58-85) and 63.7% of patients were female (Table 1). A body-mass index of 30 kg/m^2 or more was recorded in 15.4% of patients. Within 1 week before surgery, 307 (79.5%) patients received antibiotics, and 84 (21.8%) received non-steroidal anti-inflammatory agents.

Table 2. Surgical characteristics and treatment from surgery to discharge.

	Hip replacement (n=160)	*Knee replacement (n=226)*	*All patients (n=386)*
Median interval from admission to surgery (range), days	2 (0-8)	1 (0-23)	2 (0-23)
Median duration of surgery (range), minutes	130 (55-420)	142 (55-405)	139 (55-420)
Median duration of immobilization (range),* days	5 (1-87)	4 (1-29)	4 (1-87)
Median duration of hospital stay (range),† days	10 (3-76)	6 (3-42)	7 (3-76)
Type of anesthesia			
General anesthesia, no. (%)	139 (86.9)	159 (70.4)	298 (77.2)
Regional anesthesia, no. (%)	21 (13.1)	67 (29.6)	88 (22.8)
Graduated compression device, no. (%)	80 (50.0)	44 (19.5)	124 (32.1)
Physiotherapy, no. (%)	69 (43.1)	80 (35.4)	149 (38.6)
Aspirin, no. (%)	3 (1.9)	5 (2.2)	8 (2.1)
Non-steroidal anti-inflammatory agents, no. (%)	138 (86.3)	172 (76.1)	310 (80.3)
Anticoagulant agents,‡ no. (%)	3 (1.9)	11 (4.9)	14 (3.6)
Unfractionated heparin, no. (%)	0	2 (0.9)	2 (0.5)
Low-molecular-weight heparin, no. (%)	3 (1.9)	4 (1.8)	7 (1.8)
Vitamin K antagonists, no. (%)	2 (1.3)	7 (3.1)	9 (2.3)
Antibiotics, no. (%)	159 (99.4)	224 (99.1)	383 (99.2)

**Data were missing for 7 and 11 patients in the hip replacement and knee replacement groups, respectively; †Data were missing for 6 and 10 patients in the hip replacement and knee replacement groups, respectively; ‡A patient could have received more than one anticoagulant agent.*

Surgical characteristics and concomitant treatments after surgery

The majority (58.5%) of patients underwent surgery for knee replacement (Tables 1 and 2). The median interval from admission to surgery was 2 (range: 0-23) days and the median duration of hospital stay was 7 (range: 3-76) days. Operations were conducted mainly under general anesthesia (77.2% of patients).

From surgery to hospital discharge, graduated compression devices were applied to 32.1% of patients and physiotherapy was provided to 38.6%. Aspirin and non-steroidal anti-inflammatory drugs were administered to 2.1% and 80.3% of patients, respectively. Unfractionated heparin, low-molecular-weight heparin and/or vitamin K antagonists were given to 3.6% of patients. Most patients (99.2%) received antibiotics.

Venous thromboembolic events until hospital discharge

Venography was performed in 348 (90.2%) patients from 3 to 22 days after surgery (median: 7 days). The main reasons for not performing venography were patient withdrawal from the study (n=12) and patient refusal (n=12). All venograms were reviewed centrally, and 326 (84.5%) were considered to be evaluable. Among these, 272 (83.4%) were performed between days 5 and 14 after surgery (as planned), 47 were performed before day 5 (44 on day 4 and 3 on day 3), and 7 after day 14 (6 on day 15 and one on day 22).

The rate of the composite of adjudicated asymptomatic or symptomatic venous thromboembolism or sudden death up to hospital discharge was 36.5% (119 patients, 99% CI: 29.7-43.7; Table 3). The rate of symptomatic venous thromboembolism, all events corresponding to episodes of deep-vein thrombosis, was 0.9% (three patients, 99% CI: 0.1-3.3). Both distal deep-vein thrombosis and proximal deep-vein thrombosis occurred more frequently in patients undergoing total knee replacement than in those undergoing total hip replacement.

Clinical events up to one month

Overall, 92.7% of patients (n=358) were followed up for a median of 33 (range: 5–102) days after surgery; 14 patients were lost to follow-up, 13 patients withdrew consent and one patient died.

From discharge to the end of follow-up, two additional episodes of adjudicated symptomatic venous thromboembolism occurred. One patient, who underwent a knee replacement, presented with asymptomatic distal deep-vein thrombosis at day 4, experienced a symptomatic deep-vein thrombosis during follow-up. In addition, one patient who had a hip replacement experienced a pulmonary embolism. The rate of the composite of adjudicated symptomatic venous thromboembolism or sudden death at the 1-month follow-up was 1.5% (5/323 patients; 99% CI: 0.3-4.3). Overall, 1.9% (6/322) of patients were re-admitted to hospital during the follow-up.

Risk factors for symptomatic venous thromboembolism or sudden death

Among baseline and surgical characteristics of patients, and risk factors previously identified in Western patients,[3,4] age, gender, smoking habit, obesity (a body mass index of more than 30 kg/m^2), knee replacement surgery, duration of surgery, treatment with antibiotics within 1 week before surgery, and duration of hospital

Table 3. Adjudicated rate of events up to hospital discharge.

Events	*Hip replacement (n=134) no. (%)*	*Knee replacement (n=192) no. (%)*	*All patients (n=326) no. (%)*
Venous thromboembolism or sudden death (primary outcome)	23 (17.2)	96 (50.0)	119 (36.5)
Asymptomatic deep-vein thrombosis	22 (16.4)	94 (49.0)	116 (35.6)
Vena caval thrombosis	2 (1.5)	0	2 (0.6)
Proximal deep-vein thrombosis only	0	1 (0.5)	1 (0.3)
Proximal and distal deep-vein thrombosis	3 (2.2)	26 (13.5)	29 (8.9)
Distal deep-vein thrombosis only	17 (12.7)	67 (34.8)	84 (25.8)
Symptomatic venous thromboembolism	1 (0.7)	2 (1.0)	3 (0.9)
Symptomatic deep-vein thrombosis	1*	2†	3
Symptomatic pulmonary embolism	0	0	0
Sudden death	0	0	0

**Distal deep-vein thrombosis; †One proximal and one distal deep-vein thrombosis.*

stay after surgery were associated with venous thromboembolism (asymptomatic or symptomatic) or sudden death at hospital discharge in the univariate analysis. Multivariate analysis confirmed that knee replacement surgery, duration of surgery and treatment with antibiotics within 1 week before surgery were significant independent risk factors ($p<0.05$) for venous thromboembolism or sudden death at hospital discharge, with odds ratios of 5.81, 1.47 and 3.08, respectively (Table 4). The same analyses performed in the subgroup of patients undergoing knee replacement surgery gave similar results.

Discussion

This study is one of the largest epidemiological studies conducted in Asian patients to evaluate the rate of venous thromboembolism after hip or knee replacement surgery, including asymptomatic deep-vein thrombosis. We used bilateral venography, the gold standard for detecting deep-vein thrombosis in asymptomatic patients.[5-7] In addition, as in modern large Western studies, all venograms were reviewed centrally. The proportion of evaluable patients (84.5%) was high compared with the percentages of patients evaluable for primary efficacy (69.0 to 82.0%) recently reported in large multicenter studies using venography in orthopedic surgery,[11–16] and the vast majority of patients (92.7%) underwent clinical follow-up. We found a rate of asymptomatic or symptomatic venous thromboembolism or sudden death (primary outcome) of 36.5% (99% CI: 29.7-43.7) and a rate of proximal deep-vein thrombosis of

Table 4. Multivariate analyses of significant risk factors for venous thromboembolism or sudden death at hospital discharge (primary outcome).

Potential predictive factors	*Odds Ratio*	*95% confidence interval*	*p*
Increasing age (years)			0.8281
Gender (male *vs.* female)			0.9214
Smoking habit (present *vs.* ex- or non-smoker)			0.7940
Body mass index (≥30 kg/m^2 *vs.* < 30 kg/m^2)			0.2714
Type of surgery (knee *vs.* hip replacement)	5.81	3.29 to 10.27	<0.0001
Duration of surgery (hours)	1.47	1.08 to 2.01	0.0155
Antibiotics before surgery (yes *vs.* no)	3.08	1.50 to 6.33	0.0022
Hospitalization during surgery (days)			0.0598

9.8% at hospital discharge. Both the primary outcome and proximal deep-vein thrombosis occurred more frequently in patients undergoing knee replacement surgery (50.0% and 14.1%, respectively) than in those undergoing hip replacement surgery (17.2% and 3.7%, respectively). Besides knee replacement surgery, duration of surgery was identified as an independent risk factor for venous thromboembolism at hospital discharge, as was treatment with antibiotics within 1 week before surgery. The latter finding was unexpected and may be related to chance as we could not conceive any obvious relationship between the prevention of infection and post-operative venous thromboembolism. It is worth noting that these high rates of events were observed in a study population with a low risk profile for venous thromboembolism. First, patients scheduled to receive thromboprophylaxis were excluded from our study. In addition, only 15.4% of patients were obese and none reported a previous history of venous thromboembolism compared with approximately 26% and 4.5%, respectively, in recent studies performed in Western patients undergoing orthopedic surgery.[17] Thus, it is likely that the venous thromboembolism rates observed in our study represent a conservative estimate of the true rates in Asian patients undergoing hip or knee replacement without receiving thromboprophylaxis.

In previous Asian epidemiological studies, the rate of systematically detected deep-vein thrombosis varied considerably, ranging from 0 to 64.3% after hip replacement surgery and from 11.3% to 76.5% after knee replacement surgery.[1] However, the majority of these studies were small in size and some used unilateral venography of the operated leg or ultrasonography, creating uncertainty as to the actual rate of asymptomatic deep-vein thrombosis in these settings. The more recent AIDA study was conducted in 407 Asian patients undergoing orthopedic surgery in six Asian countries and used bilateral venography to screen for asymptomatic deep-vein thrombosis 6-10 days after surgery, with central adjudication of venograms.[9] Its results were very similar to ours, with a

rate of total deep-vein thrombosis of 41.0% (95% CI: 35.4-46.7) and a rate of proximal deep-vein thrombosis of 10.2%. As in our study, the rates of adjudicated deep-vein thrombosis and proximal deep-vein thrombosis were higher in patients undergoing knee replacement surgery (58.1% and 17.1%, respectively) than in those undergoing hip replacement surgery (25.6% and 5.8%, respectively). In a recent study in Taiwan conducted on three groups of patients receiving either nadroparin, indomethacin or no treatment, and undergoing bilateral venography up to 7 days after total knee arthroplasty, the rates of total and proximal deep-vein thrombosis in the control group were 71% and 5.9%, respectively.[18] In another study conducted in Singapore on 149 patients undergoing total knee arthroplasty, the rate of proximal deep-vein thrombosis detected by ultrasonography performed on post-operative day 5 or 6 was 4.7%.[19] Our results are remarkably consistent with those obtained in the above-mentioned studies, conducted during the same period of time in different centers and countries, and unequivocally indicate that asymptomatic venous thromboembolism occurs frequently after orthopedic surgery in Asian patients, at rates similar to those reported in Western patients (42-57% and 41-85% for hip and knee replacement surgery, respectively),[3,4] at least with respect to knee replacement surgery.

In our study, the rate of symptomatic venous thromboembolism or sudden death was 0.9% at hospital discharge and 1.5% at 1 month follow-up. Again, previous small epidemiological studies performed in Asian patients undergoing major orthopedic surgery, and using different designs and confirmatory diagnostic tools, gave disparate results with rates of symptomatic events ranging from 0.0% to 47.1%.[20-25] However, in the recently reported large epidemiological study in 2420 Asian patients (11 Asian countries) undergoing major orthopedic surgery (SMART), the rates of the composite of adjudicated confirmed symptomatic venous thromboembolism or sudden death were 1.2% (99% CI: 0.7-1.8) up to hospital discharge and 1.5% (99% CI: 1.0-2.3) at 1 month,[2] which are similar to those found in our study. Recent data regarding the rate of symptomatic events in Western patients undergoing orthopedic surgery without receiving thromboprophylaxis are limited. In one study, however, symptomatic events were reported in 1.2% of such patients, 10 days after surgery,[26] a rate close to those reported in Asian patients in the SMART study and in the present study. As in AIDA and SMART, very few symptomatic events occurred after hospital discharge, in contrast to rates ranging from 2.7 to 4.3% in Western patients during the month following 1 week of thromboprophylaxis.[27-30] Treatment of asymptomatic deep-vein thrombosis based on the local site assessment of venography may have modified the natural history of the disease, preventing the occurrence of symptomatic events after discharge.[9] Lack of awareness of clinical symptoms in Asian patients may also contribute to this discrepancy.[2]

In conclusion, without pharmacological thromboprophylaxis, the incidence of asymptomatic and symptomatic venous thromboembolism after major orthopedic surgery in Asian patients is high. These results suggest that thromboprophylaxis should be considered in this context. To our knowledge, only five small open studies have evaluated a prophylactic method in Asian patients.[18,31-34] These studies were small in size and the beneficial effect of treatment was in general not statistically significant, but all showed that prophylaxis could reduce the rate of venous thromboembolism to some extent. Although these data should be confirmed in larger well-conducted multicenter studies, we believe that there is no reason why the benefit of thromboprophylaxis, well documented in the West,[4] should not also be achieved in Asian patients.

Appendix

The members of the SMART (Surgical Multinational Asian Registry in Thrombosis) Study Group were: Steering Committee: TK Chang, MKI Choudhury, CD Han, CH Hu, SY Kim, YH Kim, A Leizorovicz, CJ Wang, MC Yoo; Central Venography Reading: F Becker, Besançon, France; Central Review of Clinical Events: F Becker, Besançon, France; A Leizorovicz, Lyons, France; data monitoring and statistical analysis: A Leizorovicz, Lyons, France; participating centers: Bangladesh (1 center): MKI Choudhury, Dhaka; South Korea (4 centers): CD Han, Seoul, SY Kim, Taegu, YH Kim, Kyunggi-do, MC Yoo, Seoul; Taiwan (3 centers): TK Chang, Taipei, CH Hu, Changhua, CJ Wang, Kaoshiung.

Author's Contributions

AL is a member of the Steering Committee: he contributed to the conception and design of the study and to the analysis and interpretation of the results. Moreover, he is the main writer of the manuscript and I fully approves the submitted version.

Conflict of Interest

Presented in part at the 18th International Congress on Thrombosis, June 20-24, 2004, Ljubljana, Slovenia. The authors reported no potential conflicts of interest.

References

1. Leizorovicz A, Turpie AGG, Cohen AT, Wong L, Yoo MC, Dans A for the SMART Study Group. Epidemiology of venous thromboembolism in Asian patients undergoing major orthopedic surgery without thromboprophylaxis. The SMART Study. J Thromb Haemost 2005;3:28-34.
2. Leizorovicz A, Turpie AGG, Cohen AT, Dhillon KS, Angchaisuksiri P, Wang CJ. Epidemiology of post-operative venous thromboembolism in Asian countries. Int Angiol 2004; 13:101-8.
3. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126:338S-400S.
4. Nicolaides AN. Prevention and treatment of venous thromboembolism. International Consensus Statement. Guidelines according to scientific evidence. Int Angiol 2006;25:101-61.
5. Segers AEM, Prins MH, Lensing AWA, Buller HR. Is contrast venography a valid surrogate outcome measure in venous thromboembolism prevention studies? J Thromb Haemost 2005;3:1099-2002.
6. Kearon C, Julian JA, Newman TE,

Ginsberg JS. Noninvasive diagnosis of deep venous thrombosis. Ann Intern Med 1998;128:663-77.
7. Davidson BL. What are the most reliable detection methods for deep vein thrombosis and pulmonary embolism to be used as endpoints in trials of venous thromboprophylaxis. Haemostasis 1998;28 Suppl 3:113-9.
8. Committee for Proprietary Medicinal Products. Points to consider on clinical investigation of medicinal products for prophylaxis of intra- and post-operative venous thromboembolic risk. The European Agency for the Evaluation of Medicinal Products. London, 29 June 2000; CPMP/EWP/707/98.
9. Piovella F, Wang C-J, Lu H, Lee K, Lee LH, Lee WC et al. Deep-vein thrombosis rates after major orthopedic surgery in Asia. An epidemiological study based on postoperative screening with centrally adjudicated bilateral venography. J Thromb Haemost 2005;3:2664-70.
10. Rabinov K, Paulin S. Roentgen diagnosis of venous thrombosis in the leg. Arch Surg 1972;104:134-44.
11. Bauer KA, Eriksson BI, Lassen MR, Turpie AGG for the Steering Committee of the Pentasaccharide in Major Knee Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001;345:1305-10.
12. Eriksson BI, Bauer KA, Lassen MR, Turpie AGG for the Steering Committee of the Pentasaccharide in Hip-Fracture Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med 2001;345:1298-304.
13. Lassen MR, Bauer KA, Eriksson BI, Turpie AGG, for the European Pentasaccharide Hip Elective Surgery Study (EPHESUS) Steering Committee. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. Lancet 2002; 359:1715-20.
14. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR, for the PENTATHLON 2000 Study Steering Committee. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. Lancet 2002;359:1721-6.
15. Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Mouret P, Rosencher N, et al. Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement. The METHRO III Study. Thromb Haemost 2003; 89:288-96.
16. Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Lassen MR, Mouret P, et al. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: the EXPRESS study. J Thromb Haemost 2003; 1:2490-6.
17. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR, for the Steering Committees of the Pentasaccharide Orthopedic Prophylaxis Studies. Fondaparinux versus enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery. A meta-analysis of 4 randomized double-blind studies. Arch Intern Med 2002;162:1833-40.
18. Wang CJ, Wang JW, Weng LH, Hsu CC, Huang CC, Yu PC. Prevention of deep-vein thrombosis after total knee arthroplasty in Asian patients. J Bone Joint Surg 2004;86:136-40.
19. Nathan S, Aleem MdA, Thiagarajan P, Das De S. The incidence of proximal deep vein thrombosis following total knee arthroplasty in an Asian population: a Doppler Ultrasound study. J Orthop Surg 2003;11:184-9.
20. Atichartakarn V, Pathepchotiwong K, Eurvilaichit C. Deep vein thrombosis after hip surgery among Thai. Arch Intern Med 1988;148:1349-53.
21. Yoo MC, Kang YH, Kim YH, Kim SH. A prospective study on the use of nadroparin calcium in the prophylaxis of thromboembolism in Korean patients undergoing total hip replacement. Intern Orthop 1997;21:399-402.
22. Wang CJ, Wang JW, Chen LM, Chen HS, Yang BY, Cheng SM. Deep vein thrombosis after total knee arthroplasty. J Formos Assoc 2000;99:848-53.
23. Fong YK, Ruban P, Yeo SJ, Lee BP, Lo NN, Seow KH, et al. Use of low molecular weight heparin for prevention of deep vein thrombosis in total knee arthroplasty. A study of its efficacy in an Asian population. Ann Acad Singapore 2000;29:439-41.
24. Kim YH, Suh JS. Low incidence of deep vein thrombosis after cementless total hip replacement. J Bone Joint Surg 1988;70:878-81.
25. Mok CK, Hoaglund FT, Rogoff SM, Chow SP, Ma A, Yau ACMC. The incidence of deep vein thrombosis in Hong Kong Chinese after hip surgery or fracture of the proximal femur. Br J Surg 1979;66:640-2.
26. Samama CM, Clergue F, Barre J, Montefiore A, Ill P, Samii K. Low molecular weight heparin associated with spinal anesthesia and gradual compression stockings in total hip replacement surgery. Br J Anaesth 1997;78:660-5.
27. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomized trials. Lancet 2001;358:9-15.
28. Cohen AT, Bailey CS, Alikhan R, Cooper DJ. Extended thromboprophylaxis with low molecular weight heparin reduces symptomatic venous thromboembolism following lower limb arthroplasty. A meta-analysis. Thromb Haemost 2001;85:940-1.
29. Hull RD, Pineo GF, Stein PD, Mah AF, MacIsaac SM, Dahl OE, et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. Ann Intern Med 2001;135:858-69.
30. O'Donnell M, Linkins LA, Kearon C, Julian J, Hirsh J. Reduction of out-of-hospital symptomatic venous thromboembolism by extended thromboprophylaxis with low-molecular-weight heparin following elective hip arthroplasty: a systematic review. Arch Intern Med 2003;163:1362-6.
31. Inada K, Shirai N, Hayashi M, Matsumoto K, Hirose M. Post-operative deep venous thrombosis in Japan. Incidence and prophylaxis. Am J Surg 1983;145:775-9.
32. Yoo MC, Kang YH, Kim YH, Kim SH. A prospective study on the use of nadroparin calcium in the prophylaxis of thromboembolism in Korean patients undergoing total hip replacement. Intern Orthop 1999;21:399-402.
33. Ho YH, Seow-Choen F, Leong-A, Eu KW, Nyamn D, Teoh MK. Randomized, controlled trial of low molecular weight heparin versus no deep vein thrombosis prophylaxis for major colon and rectal surgery in Asian patients. Dis Colon Rectum 1999;42: 196-203.
34. Kim YH, Choi IY, Park MR, Park TS, Cho JL. Deep vein thrombosis after uncemented total hip replacement. Bull Hosp Jt Dis 1997;56:133-9.