Is routine chemical thromboprophylaxis after total hip replacement really necessary in a Japanese population?

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Prophylaxis against venous thromboembolism after elective total hip replacement is routinely recommended. Our preference has been to use mechanical prophylaxis without anticoagulant drugs. A randomised controlled trial was performed to evaluate whether the incidence of post-operative venous thromboembolism was reduced by using pharmacological anticoagulation with either fondaparinux or enoxaparin in addition to our prophylactic mechanical regimen. A total of 255 Japanese patients who underwent primary unilateral cementless total hip replacement were randomly assigned to one of three post-operative regimens, namely injection of placebo (saline), fondaparinux or enoxaparin. There were 85 patients in each group. All also received the same mechanical prophylaxis during and after the operation, regardless of their assigned group. The primary measurement of efficacy was the presence of a venous thromboembolic event by day 11, defined as deep-vein thrombosis detected by ultrasonography, documented symptomatic deep-vein thrombosis or documented symptomatic pulmonary embolism. The duration of follow-up was 12 weeks.

The rate of venous thromboembolism was 7.2% with the placebo, 7.1% with fondaparinux and 6.0% with enoxaparin (p = 0.95 for the comparison of all three groups). Our study confirmed the effectiveness and safety of mechanical thromboprophylaxis without the use of anticoagulant drugs after total hip replacement in Japanese patients.

Venous thromboembolism (VTE) is a common complication of total hip replacement (THR) for which a variety of prophylactic regimens has been recommended.1,4 Chemical and mechanical prophylaxis are often used, either in isolation or in combination. Our preference has been to use mechanical methods alone without chemical prophylaxis.

Two recent prospective studies have found that the absolute risk for VTE in Japanese patients is similar to that in European and North American patients.5,6 They showed that the prevalence of all thromboembolic events after THR ranged from 33.8% to 41.9% if no antithrombotic measures (either pharmacological or mechanical) were taken,5,6 and recommended chemical prophylaxis against VTE.

As a result, fondaparinux and enoxaparin (low-molecular-weight-heparin) have been indicated for prophylaxis for VTE in Japan since 2007 and 2008 respectively. Many Japanese surgeons now use these two drugs in combination.5,6 Although we considered that our post-operative prophylactic mechanical regimen for VTE was effective, it would be beneficial to patients if the incidence of VTE after THR could be safely reduced further by routinely using chemical prophylaxis in addition to mechanical prophylaxis. We therefore undertook a randomised, placebo-controlled trial to compare the efficacy and safety of fondaparinux or enoxaparin with a placebo in combination with mechanical methods in the prevention of VTE in patients with low risk undergoing elective THR.

Patients and Methods
The study was approved by our Institutional Review Board and written informed consent was obtained from all the patients before randomisation. Between May 2008 and March 2009, 267 consecutive patients undergoing elective primary unilateral THR at our hospital were considered for enrolment in the study. We excluded patients who had undergone bilateral and revision THR and those who were less than 20 years of age. No upper age limit was applied. Other exclusion criteria included long-term anticoagulation treatment such as unfractionated heparin, low-molecular-weight-heparin, vitamin-K antagonists, antiplatelet agents for pre-existing cardiac or cerebrovascular disease,
a history of VTE, a coagulation disorder including anti-phospholipid syndrome, the presence of a solid malignant tumour or a peptic ulcer, and major surgery in the preceding three months. We also excluded Caucasian patients. A total of 12 were excluded, leaving 255 who were evaluated with regard to the safety of the intervention and 250 who participated in an intention-to-treat trial for the determination of the efficacy of the prophylactic regime (Fig. 1).

The 255 patients were randomly assigned into three groups (each of 85) to receive post-operative subcutaneous injections of fondaparinux (Arixtra; GlaxoSmithKline, London, United Kingdom: 2.5 mg once daily), enoxaparin (Clexane; Sanofi-Aventis, Paris, France: 40 mg, 20 mg twice daily) or placebo (0.5 ml of isotonic saline) for ten consecutive days. The first post-operative injections of fondaparinux, enoxaparin and saline took place at means of 18 hours (SD 2), 17 hours (SD 2) and 18 hours (SD 2), respectively. No prophylaxis was administered before surgery.

In order to standardise treatment all the operations were undertaken or directly supervised by one surgeon (MM) using an anterolateral modified Watson-Jones approach to the hip with all patients receiving a cementless THR under general anaesthesia. We used four designs of THR: the S-ROM-A system (DePuy, Warsaw, Indiana), the Cent-Pillar system (Stryker Corp., Kalamazoo, Michigan), the Taperloc system (Biomet Inc., Warsaw, Indiana) and the Versys Hip system (Zimmer, Warsaw, Indiana). The components were selected based on the optimal implant for the shape of each patient’s femur.

Regardless of their assigned group all patients also received the same routine mechanical prophylaxis during and after operation. A thigh-high elastic compression bandage (Free-Tie; Hakujuji, Tokyo, Japan) was worn beneath a conventional pneumatic intermittent compression device which was applied to the contralateral limb in the operating theatre before the procedure and on the operated limb at the end of the procedure. The pneumatic devices were removed on the second post-operative day when the day of surgery was defined as post-operative day 1. All the patients underwent Duplex ultrasonography of the venous system of both thighs on post-operative day 1 or 2. If no proximal femoral thrombi were found they were allowed immediate full weight-bearing, with the exception of two patients, who were directed to be partial weight-bearing for two weeks. All began mobilisation exercises under the supervision of a physiotherapist within 24 hours (1 to 20) after surgery. Non-steroidal anti-inflammatory drugs were given post-operatively for control of pain according to each individual patient’s requirements.

The primary efficacy outcome was assessed by bilateral ultrasonographic studies from the external iliac vein to the proximal portions of the calf veins at post-operative day 11. All the scans were performed by experienced vascular technicians and were read by experienced radiologists who were blinded to the patient’s randomisation. Those with a negative scan were followed clinically for 12 weeks (until post-operative day 84), for signs or symptoms of deep-vein thrombosis (DVT), pulmonary emboli, or readmission to hospital because of a complication related to the chemical prophylaxis, a bleeding complication, a wound problem, or any other clinical event. Patients who were found to have a distal (calf) DVT did not receive any chemical treatment. Those with proximal DVT received anticoagulant therapy, with initial administration of

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**Figure 1** Diagram showing the details of the treatment regime with the number of patients in each group.
variables were compared by the chi-squared test and were evaluated by analysis of variance (ANOVA) or the chi-squared test. Binary percentages with the p-value calculated by one-way analysis of variance (ANOVA) were reported as the mean (SD) and 95% confidence intervals (CI) for the pre-specified pairwise comparison. Differences were considered to be statistically significant when the p-value was \( \leq 0.05 \).

### Results

Table I gives the clinical details of the patients in all three groups. There were no significant differences. The incidence of DVT detected by Duplex ultrasonography up to day 11 in the 250 patients with analysis of the primary efficacy outcome was 7.2% in the group given a placebo, 7.1% in those given fondaparinux and 6.0% in those who had enoxaparin, which was not statistically significant (chi-squared test, \( p = 0.95 \), Table II). The overall rate of DVT in the 250 patients with analysis of the primary efficacy outcome was 6.8%. The relative risk reduction of the primary efficacy outcome in the group assigned to placebo was 0.01 compared with the risk in the group assigned to fondaparinux (95% CI 0.94 to 3.94) and 0.17 when compared with the risk in the group assigned to enoxaparin (95% CI 0.74 to 3.62; Table III). Within the whole study group, 17 patients had a DVT and 16 of these had a calf thrombus alone for which no medical anticoagulant therapy was given. The latter had a further ultrasonographic examination at day 21 and/or day 28 and the thrombi had resolved completely in 13 and partially in three (Table IV). During the follow-up, one patient had a symptomatic VTE. This patient was in the fondaparinux group and had both proximal and distal DVT. A pulmonary embolism was not detected by multi-detector CT. There were no patients in any group with symptoms of pulmonary embolism. At a follow-up at 84 days, no additional episodes of VTE and no death from any cause were reported.

No major bleeding was observed in the three groups by day 11. The number of patients who had minor bleeding problems did not differ in the three groups (chi-squared test, \( p = 0.22 \), Table V).

### Discussion

Our data showed that a regimen of both mechanical prophylaxis and the administration of anticoagulant drugs such as fondaparinux or enoxaparin did not produce a significantly

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<th>Table I. Details (mean, so) of the patients in the three groups</th>
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<td><strong>Placebo</strong> (n = 83)</td>
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* chi-squared test
lower incidence of post-operative VTE than a regimen of mechanical prophylaxis alone, and every treatment group had a low prevalence of VTE. This suggests that routine post-operative chemical thromboprophylaxis may not be necessary to achieve efficacy if patients have mechanical prophylaxis and mobilise early. Our opinion has been supported elsewhere.2,7,8 Buehler et al7 reported that the prevalence of proximal DVT was significantly lower in patients who had progressive weight-bearing immediately after primary cementless THR (0.0%) than in those who had delayed weight-bearing (19%). Sugano et al8 reported no cases of fatal pulmonary embolism, one of symptomatic pulmonary embolus and four of symptomatic DVT in 3016 patients who had post-operative mechanical thromboprophylaxis alone and mobilised early. We believe that if the natural mechanism for venous return in the lower limb is enhanced mechanically, combined with early weight-bearing, the incidence of post-operative VTE can be reduced. Since it has been estimated that 90% of cases of symptomatic pulmonary embolism originate from DVT in the lower limb,9 prevention of the formation of these thrombi has become the standard goal after THR. Fondaparinux and enoxaparin have been recommended as agents for routine thromboprophylaxis after THR.10,11 However, with
better management of pain, the rapid mobilisation of patients and improvement in mechanical prophylactic devices, some authors have questioned the need for routine chemoprophylaxis.\textsuperscript{1,3,12} Our findings have supported this. Pitto et al\textsuperscript{11} and Colwell et al\textsuperscript{12} reported that mechanical prevention of VTE after THR was as effective as chemical prevention. Dorr et al\textsuperscript{2} recommended a multimodal thromboprophylactic regimen based on an individualised risk assessment for VTE. Parvizi, Azzam and Rothman\textsuperscript{13} reported that routine chemoprophylaxis after THR with low-molecular-weight-heparin and warfarin, as advised by the seventh American College of Chest Physician guidelines,\textsuperscript{10} did not reduce the mortality rate and could even induce haemorrhagic complications.

Although VTE is a major issue in Western countries, it has traditionally been thought to be rare in Asian populations.\textsuperscript{14} There is some evidence to suggest that genetic differences partially explain the lower risk of VTE in Asian patients. Of the genetic traits, activated protein C resistance known as Factor V Leiden prevails, and is found in approximately 30\% to 50\% of patients with VTE in Western countries.\textsuperscript{15} It has been reported that the thrombophilia due to Factor V Leiden increased the risk of VTE by about seven times in heterozygotes and by about 80 times in homozygotes.\textsuperscript{16,17} It has been found in about 5\% of Caucasians,\textsuperscript{18,19} but not in the Japanese population.\textsuperscript{20,21} Another genetic trait which predisposes to VTE is the prothrombin G20210A mutation, which is found in 4\% to 6\% of Caucasians,\textsuperscript{20} but again is absent in Japanese.\textsuperscript{22} With regard to those genetic differences which may contribute to the different risk for VTE between Japanese and Caucasians, we think that post-operative pharmacological thromboprophylaxis according to the guidelines of Western countries should not be routinely recommended in a Japanese population.

Our study had several limitations. First, the sample size was small. Since we had no reliable data on the rate of post-operative VTE in Japanese patients using mechanical prophylaxis alone, we based the sample size on the assumption of a frequency of VTE of 20\% in such patients. However, if the incidence of VTE after THR in patients with mechanical prophylaxis alone is really as low as that shown in our study, a much larger sample size would be required to demonstrate equivalence, non-inferiority or superiority in efficacy. Secondly, our study was from a single centre. Thirdly, our conclusion may be valid only for an Asian demographic. Fourthly, there was no control group with a different rehabilitation programme for comparison. There would clearly be ethical problems with recruiting such a group. Finally, the use of Duplex ultrasonography may also have limited our findings since positive venographic findings have been used as an endpoint in large randomised, prospective studies in Japan and in Western countries.\textsuperscript{5,6,23-26} Contrast venography is more sensitive than ultrasonography,\textsuperscript{27} but since it is invasive and uncomfortable, repeated investigation using this technique is impractical. However, Duplex ultrasonography is non-invasive, safe and repeatable. Therefore, a reduction in detected DVT by Duplex ultrasonography can be assumed to be a reasonable goal for post-operative thromboprophylaxis and this has become the diagnostic standard in most Japanese hospitals.

In our Japanese population the incidence of VTE after THR was low in those patients who received prophylaxis by conventional mechanical methods alone without chemical prophylaxis, and was not decreased by the addition of pharmacological anticoagulation. Our data support the findings of others\textsuperscript{1,3,12,13} in that routine chemical thromboprophylaxis after THR should not be advised and that a risk-stratified approach should be followed.

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\textbf{References}


