Asia Pacific Venous Thromboembolism Consensus in Hip & Knee Arthroplasty and Hip Fracture Surgery

September 2020

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Preface

Postoperative venous thromboembolism (VTE) is a significant cause of morbidity and mortality in patients undergoing hip & knee arthroplasty and hip fracture surgery, while VTE is considered potentially preventable with several modalities of prophylactic management.

The VTE prevention guidelines by the American Academy of Orthopedic Surgeons (AAOS) or the American College of Chest Physicians (AACP) have been implemented in most countries in Asia. However, there are some concerning issues and complications related to VTE prophylaxis in major joint replacement and hip fracture surgeries, according to these guidelines due to differences in the healthcare system and cultural aspect.

Among orthopedic surgeons who practice in Asia Pacific (AP) Region, some alternative options for VTE prevention in hip & knee arthroplasty and hip fracture surgery is somewhat necessary. This Asian-specific guideline/consensus statements are expected to provide better patient outcomes and compliances.

Therefore, in one-year period, we have performed AP consensus agreement on VTE prophylaxis in hip & knee arthroplasty and hip fracture surgery in Asian patients among AP orthopedic experts.

According to the results of consensus statements, some accepted methods of VTE prophylaxis are different from those published in international guidelines regarding diagnosis & risk factors and methods of prophylaxis in detail.

We hope that this AP VTE consensus will provide orthopedic surgeons who practice in Asia Pacific Region appropriate options of VTE diagnosis and prevention methods that benefit their patients with fewer complications.

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Thanainit Chotanaphuti, MD

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Satit Thiengwittayaporn, MD

Acknowledgments

The AP VTE consensus task force started in October 2019. Previously, the multi-round survey and the face-to-face meeting for final voting were expected to finish in May 2020. However, the COVID-19 pandemic situation, which detained most international traveling, became the main obstacle for this consensus. Finally, the working team decided to turn all survey rounds and the final vote to be the online system.

The working team would like to sincerely thank ***Viroj Larbpaiboonpong, MD,*** the President of the Thai Hip & Knee Society (2018-2020), who has extraordinary expertise not only in hip and knee reconstruction but also in information technology. Dr. Larbpaiboonpong's knowledge of the current IT system is the critical success of this consensus taskforce. He has worked very hard to find out a high-end online software that provides the multi-round survey according to the Delphi method and meets our consensus criteria. We can emphasize that without Dr. Larbpaiboonpong and his IT team's great help on the whole multi-round online surveys, this AP VTE consensus task force could not be possible.

The working team also would like to thank six clinical fellows in hip & knee reconstruction from Chulalongkorn University, Bangkok, Thailand, including ***Chotetawan Tanavalee, MD, Narathorn Kongsakpaisal, MD, Supparurk***

Suksumran, MD, Apisak Angsugomutkul, MD, Nikom Noree, MD, and Thanarat Reancharoen, MD. These fellows have worked very hard to search data from evidence-based medicine in orthopedics on VTE prophylaxis, reviewed articles, and revised all statements to match the AP experts' comments and satisfaction.

Finally, the working team would like to thank ***Warayapa Mingsiritham***, general secretary of AP VTE consensus, who has been working very hard on any back-office works, personal contacts, and communications. Without her determination on this formidable task force, this consensus could not result in this successful outcome.

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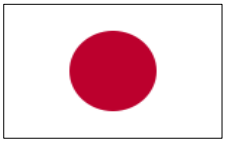

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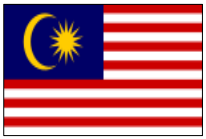

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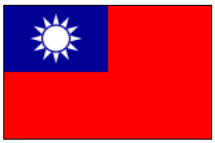

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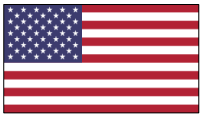
89. Pongsak Yuktanandana



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91. Christopher Scott Mow

Vietnam

92. Bui Hong Thien Khanh
93. Dang-Khoa Tran

Method & Procedures

The consensus was instructed using the Modified Delphi Method for agreement. The working team used a real-time Delphi (RTD) multi-round online software (https://calibrum.com), responding anonymously. Several world-leading institutions have used this software, such as the US Ministry of Defense, the NASA, the University of Cambridge, the University of Oxford, and the University of Melbourne.

Following receiving agreement of 93 Asia Pacific orthopedic experts to join the group, all experts were divided into three groups, including group 1: Diagnosis & Risk factors, group 2: Mechanical VTE prophylaxis, and group 3: Pharmacological VTE prophylaxis (Fig.1.)

The first-round real-time online survey was begun on 18 October 2019. There were four rounds of the survey and additional round for consensus voting. The consensus was successfully finished on 11 September 2020. In each round, experts could repeatedly view and comment on documents via the internet until the ending of survey time.

Based on evidence-based medicine and experts' opinion, a 5-round survey has optimized AP experts' agreement on debatable issues in VTE prophylaxis in hip & knee arthroplasty and hip fracture surgery before consensus voting, in terms of statements, recommendations, justifications, and references. Given approximately 1-month period of each round, all experts could have a

several times to access the survey for the online response.

All statements in the survey were accompanied by a text box allowing any comments in qualitative responses anonymously. Besides open comments, experts were requested to rate their agreement on each statement according to the Likert scale of 1-9, (1=strongly disagree, 9=strongly agree).

After closing of survey in each round, the working team and assistants went to responses of all statements, including' comments or suggestions, as well as searching out more evidence-based medicine data related commented issues.

For agreement evaluation, all statements were evaluated into three categories:

- Agreement: Likert 7, 8, and 9
- Neutral: Likert 4, 5, and 6
- Disagreement: Likert 1, 2, and 3

All passed statements must have ≥ 75% agreement from voters. Any statements having < 75% agreement were to be reviewed, revised, and resubmitted in the next round of the survey.

Again, all AP experts were asked for agreements and comments until the final round (Fig.2). After 4-round surveys, all passed statements were finally sent for online voting. The criteria of voting for consensus are as the following:

- Unanimous consensus: 100% agreement
- Strong consensus: ≥ 75% agreement

- Weak consensus: > 50%, <75% agreement

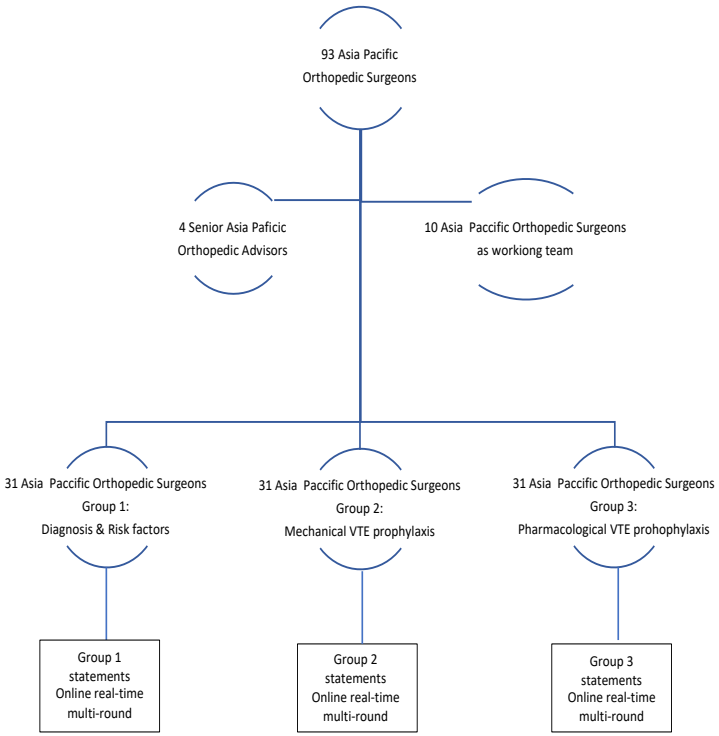

Fig. 1. *Diagram demonstrating method and procedures for AP VTE consensus*

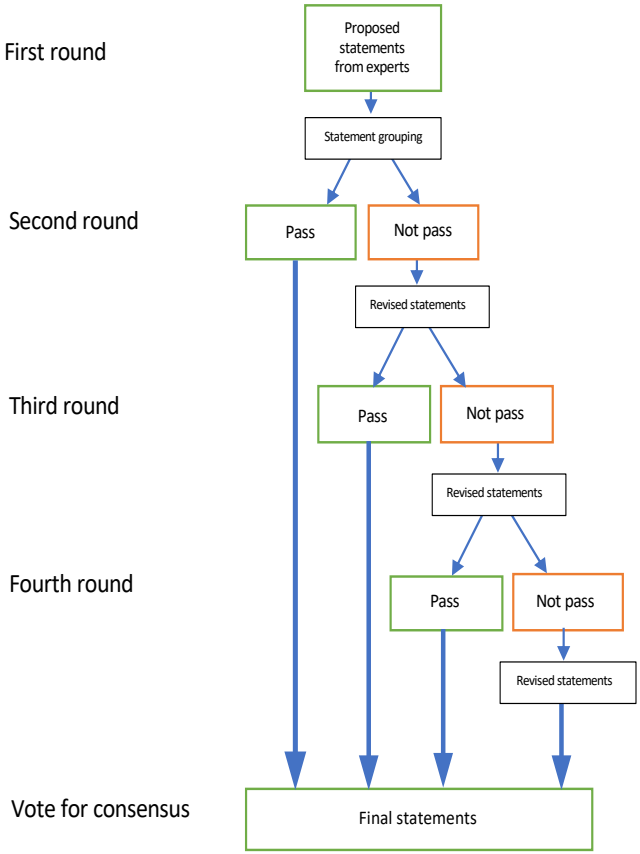

Fig. 2. *Algorithm demonstrating 4-round consensus survey using modified Delphi method and the final voting for consensus*

Group 1: Diagnosis & Risk factors

Leader:

1. Srihatach Ngarmukos

Delegates:

2. Badrul Shah Badaruddin
3. Peter Bernardo
4. Chee-Ken Chan
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26. Kriskamol Sithitool
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29. Dang-Khoa Tran
30. Siwadol Wongsak
31. Aasis Unnanuntana

Statements of Group 1:

Diagnosis & Risk factors

1. **Which surgical procedures are considered hip arthroplasty, knee arthroplasty, and hip fracture surgery?**

Recommendation:

Hip arthroplasty includes total hip arthroplasty (THA), hip hemiarthroplasty, and hip resurfacing arthroplasty. Knee arthroplasty includes total knee arthroplasty (TKA), unicompartmental knee arthroplasty (UKA), and patellofemoral arthroplasty (PFA). Hip fracture surgery includes both internal fixation and hip arthroplasty for treatment of hip fracture in adults, including femoral neck fracture, intertrochanteric fracture, and subtrochanteric fracture.

Delegate Vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification:

For Orthopedic surgery, arthroplasty means the surgical repair of a damaged joint. Prosthesis made from metal, plastic, or other materials are used to replace the damaged joint surfaces in patients with severe arthritis or other abnormal joint conditions. Arthroplasty is also use2d for the treatment of fracture around the joint, which might not be successfully treated with internal fixation.

Hip arthroplasty includes THA, hemiarthroplasty, and total resurfacing arthroplasty (1). THA involves surgical removal of damaged bone and cartilage of acetabulum and femoral head and replace them with prosthetic components. Total hip prosthesis generally consists of an acetabular component with bearing surface, the femoral component, and femoral head prosthesis (2). THA is used for the treatment of joint disease and occasionally for hip fractures. Hip hemiarthroplasty involves surgical removal of the femoral head and part of the femoral neck and replaced with a femoral prosthesis (either monobloc or modular components). No procedure is performed on the acetabulum. Hemiarthroplasty is mainly used to treat hip fractures in elderly patients, especially for displaced femoral neck fracture (3).

Total resurfacing arthroplasty involves partial removal of the femoral head (outer part) and capped with a similar-sized spherical metallic prosthesis. The acetabulum is replaced with a monobloc metal component (4).

Knee arthroplasty includes TKA and UKA. TKA involves surgical removal of damaged bone and cartilage of the distal femur and proximal tibia and replaced with a corresponding metallic femoral component, tibial component and polyethylene insert. Patella replacement "patellar resurfacing" with polyethylene component is an optional procedure during TKA, determined by the condition of patellar cartilage or surgeon's preference (5). UKA involves surgical removal of damaged bone and cartilage of only medial compartment or lateral compartment of tibiofemoral joint (distal femur and proximal tibia) and replaced with a corresponding metallic femoral

component, a tibial component, and polyethylene insert (6).

PFA involves surgical removal of damaged bone and cartilage of the patella's underside and the trochlear groove of the femur and replaced with metal and plastic components (7).

Internal fixation of hip fracture uses devices to stabilize the fracture, including multiple screws with variations of design, sliding screw-plate, cephalo-medullary nail, and other similar-function devices (8).

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2. Does UKA has a similar risk of postoperative venous thromboembolism (VTE) when compared to TKA?

Recommendation:

No, UKA has a lower risk of postoperative VTE than TKA.

Delegate Vote: Agree: 97.3%, Disagree: 2.7%, Abstain: 0% (Strong Consensus)

Justification:

Several studies demonstrated a lower incidence of postoperative VTE in UKA when compared to TKA. A recent systemic review and meta-analysis regarding the incidence of venous thromboembolism after knee arthroplasty, including 33,232 UKAs and 229,166 TKAs, was reported in 2019. This study demonstrated that UKA has a significantly lower risk of postoperative VTE than TKA (risk ratio, 0.39, $p<0.001$) using data from 12 publications from national joint registries and five publications from extensive non-national database. Remaining data analyze from randomized control trials, and extensive cohort studies show statistically non-significant trends toward lower risk of VTE in UKA (risk ratio of 0.24; $p = 0.11$ and 0.49; $p = 0.11$, respectively) (1).

Other systemic studies comparing outcomes of UKA and TKA reported a lower incidence of VTE after UKA (2/116; 1.75%) when compared to TKA (7/170; 4.1%). However, these results do not reach statistical significance (2). All three studies analyzed were also included in the meta-analysis previously mentioned (1). One of the studies was a matched-pair

prospective study from Singapore, which can represent the Asian population (3).

Another prospective study in 3,349 knee replacement patients found an incidence of postoperative deep vein thrombosis (DVT) of 0.3% in the UKA patients versus 2.2% in the TKA patients ($p<0.001$) (4).

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3. Does hemi-hip arthroplasty have a similar risk of postoperative VTE to THA in hip fracture patients?

Recommendation:

Yes, currently available evidences demonstrated that hemiarthroplasty has a similar risk of postoperative VTE to THA in hip fracture patients.

Delegate Vote: Agree: 97.3%, Disagree: 2.7%, Abstain: 0% (Strong Consensus)

Justification:

There was no significant difference between hip fracture patients who underwent a THA and those who underwent a hemiarthroplasty in VTE incidence (1, 2).

Data from The National Surgical Quality Improvement Program Database (NSQIP) show that the rate of DVT requiring therapy in hemiarthroplasty and THA in femoral neck fracture patients was similar at 0.8% (p=1.0). The rate of pulmonary embolism in hemiarthroplasty and THA in femoral neck fracture patients were 0.6% and 1.0% (p=0.154), respectively (1).

In a Propensity Score-Matched, Population-Based Study of femoral neck fracture patients, the rate of DVT was 0.9% in the hemiarthroplasty group compared to 1.1% in the THA group (p=0.553). The rate of pulmonary embolism was 1.2% in the hemiarthroplasty group compared to 0.9% in the THA group (p=0.441) (2).

Additionally, patients undergoing hip arthroplasty for fracture treatment are at significantly higher risk of

VTE than patients who underwent an elective THA (OR, 3.75; 95% CI 2.48-5.66, p<0.001) (3).

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4. Is the incidence of VTE after hip & knee arthroplasty or hip fracture surgery lower in Asian than Caucasian ethnicity?

Recommendation:

Yes, the incidence of VTE after hip & knee arthroplasty or hip fracture surgery is lower in Asian than Caucasian ethnicities.

Delegate Vote: Agree: 94.6%, Disagree: 0%, Abstain: 5.4% (Strong Consensus)

Justification:

The incidence of postoperative VTE in Asian ethnicity is likely lower than Caucasian ethnicity after hip & knee arthroplasty or hip fracture surgery.

A cohort study shows that eight of 3,070 (0.26%) Asian patients had VTE after THA, and 585 of 57,559 (1%) Caucasian patients had VTE after THA. Moreover, The Asian patients had a lower likelihood of 90-day VTE when compared with Caucasian patients (OR, 0.29; 95% CI, 0.14-0.58; $p<0.001$) (1).

Singapore cohort study of Asian patients who underwent TKA from 2006 to 2014 showed that eight of 966 patients (0.82%) had VTE after TKA. Even though seven of eight patients who had DVT recovered, one of them died due to pulmonary embolism (PE) (2).

Another cohort study of consecutive Asian patients undergoing lower-limb major orthopedic surgery showed that the patients who underwent TKA, THA, and hip fracture surgery had symptomatic VTE rate of 1.4%, 1.0%, and 0.6% respectively (3).

A prospective study of 1,608 Asian patients who underwent TKA and THA showed that the incidences of VTE after TKA and THA were 4.31% and 0.88% (4).

A large epidemiologic study from the Korean national database, which investigates the incidence of VTE after major surgery in Asia, demonstrated the rate of VTE after TKA, THA, and hip fracture surgery to be 1.08%, 0.98%, and 1.60%. Besides, the rate of DVT after TKA, THA, and hip fracture surgery was 0.71%, 0.62%, and 0.66%. Other results showed that the rate of PE after TKA, THA, and hip fracture surgery was 0.37%, 0.36%, and 0.94%. This study concluded that the rates of postoperative VTE are lower than in Caucasian populations (5).

Another prospective study of TKA in 227 Korean patients performed by a single surgeon reported that there were 3.03% proximal DVT, and 23.57% distal DVT, with no symptomatic PE, which confirmed the low VTE incidence in the Koreans undergoing TKA (6).

The 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy in 2004 documented the rate of total DVT in Caucasian patients after TKA, THA and hip fracture surgery were 41-85%, 42-57% and 46-60% and Proximal DVT in Caucasian patients after TKA, THA, and hip fracture surgery were 5-22%, 18-36% and 23-30%. This study also showed that the rate of PE in Caucasian patients after TKA, THA, and hip fracture surgery was 1.5-10%, 0.9-28%, and 3-11% (7).

Systematic review and meta-analysis study of the Asian population in 2011 showed that the rate of DVT in patients who underwent TKA was 42.5% (10.6%-62.5%) and the rate of DVT in patients who underwent THA or hip fracture surgery was 25.8% (4%-53.1%). Furthermore, the rate of PE in patients who underwent

TKA was 0.5% (0%-1.7%), and the rate of PE in patients who underwent THA or hip fracture surgery was 0.3% (0%-1.7%). The study concluded that the pooled rates of proximal and symptomatic DVT in Asians were lower than the Caucasian reports (8).

Another meta-analysis from 2013 studied Asian patients who underwent TKA, showed that the incidence of symptomatic PE was 0.01%. The incidences of overall DVT, proximal DVT, and symptomatic DVT were 40.4%, 5.8%, and 1.9% (9).

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5. Are there different degrees of VTE risk in Asian patients undergoing hip & knee arthroplasty or hip fracture surgery?

Recommendation:

Yes, Asian patients undergoing hip & knee arthroplasty or hip fracture surgery have standard and elevated VTE risks.

Delegate Vote: Agree: 94.6%, Disagree: 0%, Abstain: 5.4% (Strong Consensus)

Justification:

The incidence of postoperative VTE in Asian ethnicity is likely lower than Caucasian ethnicity after hip & knee arthroplasty or hip fracture surgery (1-3). However, there are no specific studies regarding VTE risk of Asian patients undergoing hip & knee arthroplasty or hip fracture surgery. Asian patients should be classified into standard VTE risk and elevated VTE risk.

Standard VTE risk patients have no histories or medical conditions associated with VTE before surgery (i.e., the VTE risk is solely from surgery alone).

Elevated VTE risk patients already have histories or medical conditions associated with VTE before surgery (i.e., the VTE risk is a combination of surgery and preexisting histories or medical conditions).

The exception to these statements is certain surgical factors that elevated VTE risk from usual such as bilateral procedures and prolonged surgical time

(> 2 hours) (4). These patients should be classified as an increased VTE risk group.

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6. Can a risk factor stratification based on ethnicity be used to determine proper VTE prophylaxis protocol in Asian patients?

Recommendation:

Yes, the VTE prophylaxis protocol for Asian patients can be customized by the VTE risk of each ethnicity.

Delegate Vote: Agree: 86.5%, Disagree: 8.1%, Abstain: 5.4% (Strong Consensus)

Justification:

Since the VTE risk after hip & knee arthroplasty or hip fracture surgery in the Asian population and lower than Caucasians, the experts agreed that it is justifiable that the VTE prophylaxis protocol can be adjusted from those recommended for Caucasian patients to suit Asian patient's characteristic and economic condition.

A Korean study analyzed patients undergoing major surgery between 2007 and 2011 found that the overall postoperative VTE rates for major orthopedic procedure was approximately 1.24%. The highest VTE rate was found in hip fracture surgery, approximately 1.60% (1).

A Taiwanese study analyzed 114,026 patients who underwent hip (N=61,460) or knee (N=52,556) replacement surgery from 2002 to 2006. This study found the overall incidence of postoperative VTE of 0.44%. The incidence of PE was 4/10,000 for total hip and 7/10,000 for total knee replacement (2).

A meta-analysis study showed that the incidence of symptomatic pulmonary embolism (PE) was similar in 5 Asian countries: Taiwan, Japan, Thailand, Korea, and Singapore. When compared with the incidence of DVT in Taiwan, there were no differences in the incidence of overall DVT rate in Japan, but the incidence of overall DVT rate was lower in Thailand, Korea, and Singapore. The authors identified a higher incidence of proximal DVT in Japan and Thailand, but a similar incidence in Korea and Singapore compared to Taiwan's incidence (3).

Systematic review and meta-analysis study showed that the proximal DVT rates were comparable among Asian ethnic groups: 11.8% (95% CI, 5.6-9.9) for South-East Asians, 11.0% (95% CI, 8.4-14.0) for Japanese, 7.5% (95% CI, 3.4-13.2) for Korean and 5.6% (95% CI, 2.9-9.1) for Chinese. The pooled rate was highest in South-East Asia and lowest in China. There were significant differences between Chinese and Korean patients (p=0.032), between Chinese and Japanese patients (p=0.002), and between Chinese and South-East Asian patients (p=0.007). Other comparisons were not significantly different (Korean versus Japanese, p=0.332; Korean versus South-East Asians, p=0.202; Japanese versus South-East Asians, p=0.708) (4).

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7. What is the most useful method or scoring system for stratifying the patient's risk for VTE before hip & knee arthroplasty or hip fracture surgery?

Recommendation:

Inconclusive, there is no evidence to prove which method or scoring system provides the best VTE risk stratification.

Delegate Vote: Agree: 95.9%, Disagree: 1.4%, Abstain: 2.7% (Strong Consensus)

Justification:

Ideally, VTE risk assessment and recommended prophylaxis should be specific to the population it serves. In contrast, several studies regarding the method and scoring system for stratifying the patient's risk for VTE, very few risk assessment models have been validated in the Asian population.

Caprini scoring system was a thrombosis risk assessment model which estimates the DVT probability. Depending on the total risk factor score, the patients were grouped into four categories, which included low risk, moderate risk, high risk, and highest risk (1). The Caprini score provides a consistent, accurate, and efficacious method for risk stratification and selection of prophylaxis methods. It has been validated in many versions, such as Spanish, Arabic, and Polish (2). To date, there have been a few attempts to validate the Caprini risk score of an Asian population. Chinese studies suggest that the Caprini score can effectively stratify hospitalized Chinese patients into VTE risk categories based on individual

risk factors. The classification of the highest risk level with a cumulative risk score of ≥5 provided distinct clinical information, and further stratification of this group of patients is needed (3,4). However, the patient who underwent TKA THA or hip fracture surgery was estimated at least five scores for this risk assessment model. Therefore, the benefit of this risk assessment model had been brought into question.

Wells scores identify patients as having a low, moderate, or high probability of pulmonary embolism. The reproducibility and reliability of the score have been validated. However, the original version was criticized that it might have overestimated the overall rate of pulmonary embolism in patients who were considered to have a moderate pretest probability (5). The wells score for PE was revised in 2000, to reduce the number of risk categories to two categories into the unlikely group and the likely group. The combination of a score ≤ 4.0 by this simple clinical prediction and a negative D-Dimer test can safely rule out PE in a large proportion of patients suspected of PE (6).

A study about D-dimer shows that DVT can be ruled out in a patient who is judged clinically unlikely to have DVT combined with a negative D-dimer test. Doppler ultrasound can then be safely omitted in these patients (7).

Although many methods are available, none were explicitly made for prediction of VTE after hip & knee arthroplasty or hip fracture surgery. The application of such a method should be used in combination with surgical experiences.

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8. Which patient's conditions or factors are associated with elevated VTE risk after hip & knee arthroplasty or hip fracture surgery in the Asian population?

Recommendation:

Patients' conditions or factors that were reported to significantly elevated VTE risk after hip & knee arthroplasty or hip fracture surgery include a history of previous VTE, varicose vein, congestive heart failure, and a medical history of thromboembolic stroke, and family history of VTE.

Delegate Vote: Agree: 93.2%, Disagree: 4.1%, Abstain: 2.7% (Strong Consensus)

Justification:

According to the NICE guidance in 2010, certain factors have been previously identified to increase the risk or incidence of VTE (1). These risk factors included

Active cancer and cancer treatment
Age over 60 years
Critical care admission
Dehydration
Thrombophilia
Obesity (body mass index >30 kg/m^2)
One or more significant medical comorbidities (e.g., heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
Personal history or a first-degree relative with a history of VTE

Hormone replacement therapy

Use of estrogen-containing contraceptive therapy
Varicose veins with phlebitis
Pregnant women or those who have given birth within the previous six weeks

History of VTE: A meta-analysis study showed that the fixed-effect pooled OR for patients with a history of VTE compared to those without a history of VTE was 11.87 (95 % CI, 9.93–14.18, $p<0.00001$). This finding proves that patients with a history of VTE were at a significant risk of VTE after THA or TKA (2). Besides, an observational cohort study of Asian patients undergoing lower-limb major orthopedic surgery confirmed that personal history of VTE was a significant independent risk factor ($p<0.05$) for symptomatic VTE, with odds ratios of 26.9 (3). Another observational study presented, after adjustment in the multivariate analysis, that the history of VTE was significantly associated with an increased risk of VTE at three months after hip surgery ($p<0.01$) (4).

Familial history of VTE: Multivariate analysis confirmed that the familial history of VTE was significant independent risk factors ($p<0.05$) for symptomatic VTE (3).

Congestive heart failure: The result of meta-analysis revealed that CHF was significantly associated with a higher risk for postoperative VTE with a low level of heterogeneity (OR, 2.03, 95 % CI, 1.77–2.34, $p<0.00001$) (2). Congestive heart failure was also independent risk factors ($p<0.05$) for symptomatic VTE, with odds ratios of 5.1 (3).

Varicose veins: A fixed-effect model evaluated 223,249 patients revealed that patients with varicose veins were at an elevated risk of VTE (OR, 2.60; 95 % CI, 1.74–3.88, $p<0.00001$) (2). Similarly, a multivariate

analysis of the cohort study confirmed that varicose veins were a significant independent risk factor ($p<0.05$) for symptomatic VTE, with odds ratios of 3.6 (3). Another cohort study showed that after adjustment in the multivariate analysis, varicose veins were significantly ($p<0.01$) associated with an increased risk of VTE at three months after hip surgery (4).

History of stroke: A prospective study demonstrated the result that a medical history of CVA (thromboembolic stroke) was a significant risk factor, which increased the risk of VTE by 4.8 times compared to those without VTE ($p=0.009$) (5).

Gender: A case series of Asian population showed that 30 of 977 (3.07%) female patients developed VTE, whereas only two of 631 (0.32%) male patients developed VTE after joint arthroplasty without VTE prophylaxis in the Asian population. This finding shows that female sex is a significant risk factor for VTE in the Asian population ($p=0.009$) (5). Similarly, a study that used the Korean Health Insurance Review and Assessment Service (HIRA) database showed that females had a higher relative risk for DVT than males ($p<0.001$) (6). However, for hip replacement arthroplasty, the relative risk in female patients was similar to male patients (RR, 0.97) (6).

Old age: The patients aged > 80 were at a higher risk of VTE after THA or TKA (2). A Korean study shows that when compared to patients aged < 49 years, the relative risk of DVT was five times higher in patients aged 50–69 and 10 times higher in patients aged > 70 years (6). However, A prospective study shows the average age of patients with VTE at the time of the occurrence was 79.5 years, which is 12.6 years older than the average age of the patients without VTE

(66.9 years), but the difference was not significant (p=0.992) (5).

Obesity: A prospective study of VTE after joint arthroplasty showed that patients with VTE have an average BMI of 23.03 kg/m^2, while patients without VTE had a higher average BMI of 25 kg/m^2. However, this finding was not statistically significant (p>0.05) (5). Similarly, BMI was not significantly associated with the development of DVT or PE after TKA patients in Asian Population (7). In contrast, another prospective study demonstrated that obesity is a significant risk factor of post-op VTE in the Indian population (p<0.05) was (RR = 6.909, p=0.005) (8).

Active cancer: A meta-analysis study showed that the fixed-effect pooled OR for the patients with "active" cancer compared to those without "active" cancer was 1.28 (95 % CI, 1.01–1.62, P=0.04) with a moderate-level heterogeneity (2). Similarly, malignancy was identified as a significant risk factor in Indian patients (RR = 10.214, p=0.008) (8). On the contrary, a prospective study of hip fracture patients showed that a history of malignancy was not risking factors (p>0.05) (5).

Hormonal therapy: A systematic review and meta-analysis study of the general population show that VTE risk was increased in female oral HT users compared to non-users, while non-oral HT did not significantly affect VTE risk (5, 9). However, the study included the patient after hip & knee arthroplasty or hip fracture surgery was less founded in literature. A Canadian study showed no association between postoperative VTE and hormonal therapy in patients after hip & knee arthroplasty or hip fracture surgery (10).

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9. In Asian patients, which surgical factors or perioperative patient management are associated with elevated VTE risk after hip & knee arthroplasty or hip fracture surgery?

Recommendation:

Surgical factors and perioperative patient's management that are reported to significantly elevate VTE risk after hip & knee arthroplasty or hip fracture surgery include revision surgery, bilateral surgery, prolonged surgical time, prolonged time to surgery after hip fracture, and delayed ambulation.

Surgical factors and surgical procedures, which have unclear relation to elevate VTE risk after surgery, include regional anesthesia (spinal and epidural analgesia), prolonged intraoperative pneumatic tourniquet, and perioperative blood transfusion.

Delegate Vote: Agree: 95.9%, Disagree: 1.4%, Abstain: 2.7% (Strong Consensus)

Justification:

In Asian patients, the significant factors associated with an elevated risk of VTE undergoing hip & knee arthroplasty or hip fracture surgery include revision surgery, bilateral surgery, prolonged surgical time, prolonged time to surgery after hip fracture, and delay ambulation (1, 2). Some surgical factors and surgical procedures that are unclear if they are associated with an elevated risk of VTE after hip & knee arthroplasty or hip fracture surgery are regional anesthesia (spinal and epidural analgesia), prolonged

intraoperative pneumatic tourniquet, and perioperative blood transfusion.

Bilateral procedure: A prevalence study from Korea suggested that simultaneous bilateral TKA had a significantly higher VTE rate than unilateral arthroplasty. This was due to longer operation time and excessive motion of the joints, which might increase venous stasis and endothelial injury in bilateral arthroplasty (1). Regarding THA, a meta-analysis study showed no difference in the rate of PE between simultaneous bilateral THA and staged bilateral THA patients. However, simultaneous bilateral THA patients were less likely to develop a DVT than staged bilateral THA. These may have resulted from the fact that the staged bilateral group underwent two procedures. In contrast, the simultaneous group only underwent one procedure, and additionally, staged bilateral THA patients may have limited rehabilitation ability after the first surgery because of pain in their contralateral hip (3).

Revision surgery: Revision surgery is one of the risk factors that elevated VTE risk in patients undergoing hip or knee arthroplasty. Revision surgery presents a 16.6 times higher relative risk of post-op VTE compared to primary hip & knee arthroplasty (1).

Hip fracture surgery: The symptomatic post-op VTE after occurred in 1-9% of hip fracture surgery patients (4). Prolonged surgical time and prolonged time to surgery after hip fracture are also risk factors of VTE. The operative time of longer than 105 minutes had a relative risk of 1.6 times more than the operative time of less than 105 minutes (1).

Delayed surgery: Some studies suggested that patients who had a delay of more than two days between the fracture and admission to the hospital had evidence of thrombosis. Patients having delayed hospital admission had an increased thrombotic incidence (5,6). A study in Korean patients found that the preoperative incidence of DVT in hip fractures was relatively low in the Korean geriatric population, but delayed surgery beyond 72 hours after injury increased the incidence of DVT (7).

Type of anesthesia: A Japanese study showed that spinal anesthesia was significantly associated with an increased risk of VTE in patients undergoing arthroplasty. On the other hand, VTE incidence did not differ between general anesthesia and combined epidural/general anesthesia. However, surgeons who perform hip or knee arthroplasty for patients with high VTE risk may consider avoiding spinal anesthesia, although careful consideration of risks and benefits of spinal anesthesia should be conducted (8). A meta-analysis from 5 RCTs with 487 THAs also shows no significant difference occurrence of DVT between the general anesthesia and spinal anesthesia (9).

Pneumatic tourniquet: Intraoperative pneumatic tourniquet is widely applied in knee arthroplasty. A systematic review of randomized controlled trials suggested that prolonged operation time and pneumatic tourniquet increase VTE incidence during knee arthroplasty (10). However, other studies show that prolonged operation time does not elevate VTE risk after hip and knee arthroplasty (1).

Blood transfusions: Blood transfusions can affect blood clotting cascade, leading to a hypercoagulable state. Perioperative blood transfusion is likely

associated with an increased rate of VTE. Some studies show an 8.5% higher incidence of VTE in patients who received a blood transfusion after abdominal surgery (11, 12).

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10. Which patient's factors or conditions have relation to bleeding risk following hip & knee arthroplasty or hip fracture surgery in Asian patients?

Recommendation:

There is no specific study that defined different bleeding risk between Asian and other ethnicities.

Delegate Vote: Agree: 90.5%, Disagree: 2.7%, Abstain: 6.8% (Strong Consensus)

Justification:

A multinational cross-sectional study has reported that patients' conditions that are considered as increased bleeding risks include advanced age, thrombocytopenia, hemophilia, and other hemorrhagic disorders, including intracranial hemorrhage hepatic impairment, bleeding at hospital admission, active gastroduodenal ulcer, or a known bleeding disorder (1).

ACCP Guidelines stated that numerous individual clinical factors had been linked to an increased risk of hemorrhage, including older age, anemia, and renal disease (2). Furthermore, from an evidence-based review of the literature, the risk of bleeding include Age > 65 y, previous bleeding, cancer, metastatic cancer, renal failure, liver failure, thrombocytopenia with platelets < 80,000/mm3, previous stroke, diabetes, anemia, antiplatelet therapy, poor anticoagulant control, comorbidity and reduced functional capacity, recent surgery, frequent falls, and alcohol abuse (3).

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11. Does tranexamic acid (TXA) increase the risk of VTE after hip & knee arthroplasty or hip fracture surgery in Asian patients?

Recommendation:

No, TXA does not increase VTE risk after hip & knee arthroplasty or hip fracture surgery in Asian patients.

Delegate Vote: Agree: 95.9%, Disagree: 1.4%, Abstain: 2.7% (Strong Consensus)

Justification:

TXA works by inhibiting the activation of plasminogen to prevent fibrin degradation. Due to the properties of antifibrinolytic drugs, there is concern about the increased risk of arterial thromboembolic events and venous thromboembolic events. However, many studies proved that tranexamic acid does not increase VTE risk after hip & knee arthroplasty or hip fracture surgery in Asian patients and is safe to use even in patients with increased VTE risk.

A matched outcome study showed that patients with a history of VTE had a low risk of recurrent VTE after contemporary THA and TKA, and that rate did not increase with the use of intravenous TXA (1). Several meta-analyses have shown that TXA is safe to use in patients undergoing hip & knee arthroplasty. Two meta-analysis studies suggest that tranexamic acid can reduce the volume of blood transfusion and transfusion rate. Furthermore, the application of tranexamic acid does not increase the risk of DVT or PE (2, 3). Another meta-analysis demonstrates the lack of evidence of harm from TXA in patients undergoing

TJA. Furthermore, moderate evidence supports the safety of TXA in patients undergoing TKA with an American Society of Anesthesiologists (ASA) score of 3 or higher. The benefits of TXA outweigh the potential risks of thromboembolic events, even in patients with high comorbidities (4).

Current evidences indicate that TXA efficaciously reduces total blood loss and transfusion requirements during hip fracture surgery and knee arthroplasty without significantly increasing the risk of total thromboembolic events, including DVT (5-8).

Based on available evidence, it can be concluded that the administration of TXA does not increase VTE risk after hip & knee arthroplasty or hip fracture surgery in Asian patients.

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12. Are clinical symptoms and signs of DVT (leg pain, leg swelling, distended veins, and skin discoloration) useful for a definite diagnosis of DVT after hip & knee arthroplasty or hip fracture surgery?

Recommendation:

No, clinical symptoms and signs of DVT should be used in combination with additional investigations for definite diagnosis of DVT.

Delegate Vote: Agree: 93.2%, Disagree: 2.7%, Abstain: 4.1% (Strong Consensus)

Justification:

All Patients undergoing hip & knee arthroplasty or hip fracture surgery have an inherent risk of venous thromboembolic complications. Since leg pain, leg swelling, and discoloration are common and non-specific after hip and knee surgery, they should not be solely used for diagnosis of DVT after hip & knee arthroplasty or hip fracture surgery (1, 2). These signs and symptoms, such as swelling, pain, and tenderness, can also confuse DVT and other medical conditions such as heart failure or local infection (3-5).

During the first four weeks after major surgery, a localized tenderness along the distribution of the deep venous system, entire leg swelling, calf swelling by more than 3 cm when compared with the opposite leg, pitting edema (more severe in a suspected limb), presence of collateral superficial veins (non-varicose) are highly suspicious signs of DVT. Further investigations should be performed for a definite diagnosis (6). However, the absence of clinical

symptoms and signs of DVT can help reduce the number of diagnostic tests required for patients after hip & knee arthroplasty or hip fracture surgery (6, 7).

Therefore, these clinical symptoms and signs are not reliable for the diagnosis of DVT in patients after hip & knee arthroplasty or hip fracture surgery. They should alert orthopedic surgeons to consider additional investigations for the definite diagnosis.

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13. Can pulmonary embolism (PE) occurs without clinical symptoms and signs of DVT?

Recommendation:

Yes, the PE can occur without clinical symptoms and signs of DVT.

Delegate Vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous Consensus)

Justification:

It is believed that the most common source of PE is untreated or undetected DVT, primarily from the pelvis and lower extremities. However, most patients with PE do not have detectable DVT. Only 20% of the patients with PE had an identifiable DVT (1). When PE occurs without clinical symptoms and signs of DVT, the condition has been termed "de novo pulmonary embolism" (2, 3).

Regarding PE in trauma or postoperative hip fracture surgery, it has been proposed that the clot may not originate from deep veins but may occur de novo in the lungs due to endothelial inflammatory response (4).

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14A. Is routine postoperative screening of DVT necessary in hip & knee arthroplasty?

Recommendation:

No, routine screening of DVT after hip & knee arthroplasty is not necessary.

Delegate Vote: Agree: 94.6%, Disagree: 2.7%, Abstain: 2.7% (Strong Consensus)

14B. Is routine postoperative screening of DVT necessary in hip fracture surgery?

Recommendation:

Inconclusive, there is no evidence to support routine postoperative screening of DVT.

Delegate Vote: Agree: 94.6%, Disagree: 4.1%, Abstain: 1.3% (Strong Consensus)

Justification:

VTE can occur up to 3 months after TKA and THA and is also a common cause for readmission after THA (1, 2). Routine screening after hip & knee arthroplasty cannot completely rule out postoperative DVT. In THA patients with negative venography at discharge, 20% will develop new DVT within three months without VTE prophylaxis. If VTE prophylaxis was given, the rates of symptomatic VTE would be reduced to 1.3-10% (1-3).

AAOS and ACCP clinical practice guidelines agreed and suggested against the routine use of

ultrasound for the screening of DVT in patients after knee or hip arthroplasty (4, 5).

Hip fractures surgery patients have a higher risk of DVT and PE. The reported event rate of DVT and PE in hip fractures patients range from 1.18 to 6% and 0.25 to 4.6%, respectively, despite the use of VTE prophylaxis. Regardless of these findings, ACCP guidelines do not recommend routine ultrasound screening before hospital discharge for asymptomatic patients after hip fracture surgery (5).

However, a recent study proposed routine screening for DVT before surgery due to a high incidence of VTE in femoral neck fracture (6).

References

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15. Is duplex ultrasonography a preferred initial investigation for diagnosis of DVT after hip & knee arthroplasty or hip fracture surgery?

Recommendation:

Yes, duplex ultrasonography is a useful initial investigation for the diagnosis of DVT after hip & knee arthroplasty or hip fracture surgery.

Delegate Vote: Agree: 97.2%, Disagree: 1.4%, Abstain: 1.4% (Strong Consensus)

Justification:

Duplex ultrasound is a noninvasive diagnostic tool for DVT and has now largely replaced contrast venography as the preferred test for diagnosing clinically suspected DVT (1-4).

For the diagnosis of proximal DVT, duplex ultrasonography provides a sensitivity of 94-97% and specificity of 98%. Moreover, ultrasonography has a positive predictive value of 100% and negative predictive values of 100% for symptomatic DVT. However, the positive predictive value and negative predictive values for asymptomatic DVT are 71% and 94%, respectively (1, 4-5).

The duplex ultrasound sensitivity for the diagnosis of distal DVT is relatively low at 57% and is only 48% for detecting asymptomatic calf vein thrombosis (1).

National Institute for Health and Care Excellence (NICE) has approved the recommendations for the request of proximal leg vein ultrasound scan in patients suspected of DVT with Wells score ≥ 2 ("DVT likely"). In patients with Wells score of < 1 ("DVT

unlikely"), ultrasound should be done if the D-dimer test is positive (6).

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16. In controversial cases, what is the investigation for the definitive diagnosis of deep vein thrombosis (DVT)?

Recommendation:

Lower leg venography, including conventional contrast venography, CT venography, and MRI venography, can be used for definitive diagnosis of DVT in controversial cases.

Delegate Vote: Agree: 93.2%, Disagree: 5.4%, Abstain: 1.4% (Strong Consensus)

Justification:

Leg swelling and pain can be suspicious sign of post-operative DVT. Special investigations may be required for proper evaluation. However, there is no single ideal investigation for diagnosis of deep vein thrombosis.

Conventional contrast venography has been historically quoted as a gold standard for diagnosing DVT, with a reported sensitivity of 70–100% and specificity of 60–88% (1, 2). However, conventional contrast venography is invasive, not readily available, and contraindicated in patients with renal insufficiency or allergy to contrast medium (2).

Recently, newer imaging technology such as computed tomography venography and magnetic resonance venography have been proposed as alternatives to conventional contrast venography and duplex ultrasound with comparable sensitivity and specificity (2).

Moreover, non-imaging methods such as standardized clinical probability assessment and laboratory test such as D-dimer can be safely used to rule out acute DVT (3).

Therefore, conventional contrast venography is rarely necessary for DVT diagnosis nowadays. However, it remained as a referential standard for clinical research and can be utilized when results from other methods are inconclusive. (4).

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17. What is the gold standard investigation for the diagnosis of PE?

Recommendation:

The current gold standard diagnostic investigation is pulmonary angiography. However, a computed tomographic pulmonary angiogram (CTPA) is the more preferred investigation for PE diagnosis.

Delegate Vote: Agree: 98.6%, Disagree: 1.4%, Abstain: 0% (Strong Consensus)

Justification:

PE is a potentially fatal complication following hip & knee arthroplasty and hip fracture surgery. Clinical symptoms and signs alone have limited uses for the diagnosis of PE.

Currently, pulmonary angiography is the gold standard diagnostic tool for PE. However, CTPA may be an alternative investigation for the diagnosis of PE (1-3). CTPA is the recommended imaging modality for investigation of acute PE with a diagnostic sensitivity of 57-100% and specificity of 78-100% (2). However, it should be undertaken after an assessment of the probability of PE. A recent study has shown that a combination of risk assessment, D-dimer testing, and CTPA is the most preferred diagnostic method for diagnosing PE (4, 5).

Ventilation-perfusion scanning is an alternative diagnostic tool for PE in patients who are contraindicated for intravenous contrast media such as renal failure, contrast material allergies, young females, and patients who cannot fit into the CT scanner (6).

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Group 2: Mechanical VTE prophylaxis

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Statements of Group 2:

Mechanical VTE prophylaxis

1. **Which devices have evidence supporting effective mechanical venous thromboembolism (VTE) prophylaxis in hip & knee arthroplasty and hip fracture surgery?**

Recommendation:

Mechanical devices that have evidence support as an effective mechanical VTE prophylaxis include intermittent pneumatic compression devices (IPCD), venous foot pump (VFP) devices, and graduated compression stockings (GCS).

Delegate Vote: Agree: 94.5%, Disagree: 4.1%, Abstain: 1.4% (Strong Consensus)

Justification:

According to the literature, many studies are demonstrating that mechanical devices provide effectiveness for VTE prophylaxis (1-4).

A systematic review compared using IPCD and anticoagulant for VTE event (14 RCTs and three observation studies) in patients undergoing joint arthroplasty. VTE events occurred in 163 patients (11%); however, there was no statistically significant difference between the IPCD group and the anticoagulation group in VTE events. Subgroup analyses separately evaluating IPCD alone vs. anticoagulation and IPCD plus anticoagulation vs. anticoagulation alone suggested that the combination

of IPCD plus anticoagulation may provide a substantial protective effect against VTE events (1).

A VFP is a variation of IPCD that does the intermittent pump only on foot. The proper length of IPCD to reduce the incidence of VTE is controversial. The meta-analysis comparing the effectiveness of different IPCDs to the prevention of VTE in patients after THA found that only one study had fulfilled the eligibility criteria for inclusion in this systematic review (2). This study enrolled 121 patients by assessing thrombogenesis using the D-dimer level before and after THA for VTE diagnosis. Evaluation for postoperative swelling by measuring the thigh and lower leg circumference was investigated. Fifty-eight patients were assigned to the calf-thigh pneumatic compression group, and the other 63 were assigned to the plantar compression group. At seven days postoperatively, the mean D-dimer levels of the calf-thigh compression and the plantar compression groups were not statistically different (8.86 and 9.26 μg/ml, respectively ($p=0.697$)). However, there was a significant difference in increasing of the circumference of the thigh after hip arthroplasty ($p<0.01$), with averaged 1.22% increase in the calf-thigh compression group, and 3.19% increase in the plantar compression group. Calf-thigh pneumatic compression was more effective than plantar compression for reducing thigh swelling during the early postoperative stage. At three weeks after THA, there were no patients with symptomatic DVT or PE in either calf-thigh compression or the plantar compression group at three weeks after THA (3). Also, another RCT trial from Japan reported that VFP provided a significantly lower rate of PE than the control group.

Regarding the meta-analysis study about the GCS for the prevention of DVT, 19 RCTs were identified involving 1,681 patients and 1,064 legs at a total of 2,745 analytic units. Nine studies included patients undergoing general surgery, six studies included patients undergoing orthopedic lower-limb surgery, and one study included medical patients. In the treatment group, the GCS was applied from patient admission until they were fully mobile or discharged. In the treatment group (GCS), 9% of patients developed DVT (126 of 1,391 units) in comparison with 21% in the control group (282 of 1,354 units). An overall effect of VTE prophylaxis favored treatment with GCS ($p<0.00001$) (5). However, a retrospective study on 1,259 primary TKAs in the Koreans reported that the use of IPCD alone did not reduce the DVT incidence in ethnic groups with low DVT incidence (6).

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2. Do all mechanical devices (IPCD, VFP, GCS) provide similar efficacy for VTE prophylaxis?

Recommendation:

Inconclusive. There are no enough evidences for supporting.

Delegate Vote: Agree: 95.9%, Disagree: 1.4%, Abstain: 2.7% (Strong Consensus)

Justification:

There has been a lack of strong evidence that directly compares VTE prophylaxis's effectiveness among the different mechanical devices (IPCD, VFP, and GCS). However, most experts agree that all mechanical devices for VTE prophylaxis in hip & knee arthroplasty and hip fracture surgery do not provide similar effectiveness.

Reference

No valid reference

3. Besides the mechanical device, what other non-pharmacological methods can enhance VTE prophylaxis in hip & knee arthroplasty and hip fracture surgery?

Recommendation:

Early ambulation and leg elevation can be added in the postoperative protocol of hip & knee arthroplasty and hip fracture surgery with a tendency to provide a positive effect on mechanical VTE prophylaxis.

Delegate Vote: Agree: 97.2%, Disagree: 1.4%, Abstain: 1.4% (Strong Consensus)

Justification:

A meta-analysis of 13 studies in 3,269 patients compared bed rest and early ambulation in early DVT patients who received conventional, anticoagulation, in terms of patient safety and pain. The early ambulation group did not increase the incidence of new PE, progression of DVT, or DVT related deaths ($p=0.22$) compared with bed rest group. Moreover, the benefit of early ambulation was better outcomes and remission of acute pain in the affected limb than the bed rest group ($p=0.01$) (1).

A current retrospective study on 13,384 THA and TKA patients, who did not have increased VTE risk and had mechanical VTE prophylaxis and early mobilization, showed that there were comparable VTE rates to patients who had pharmacological VTE prophylaxis (2).

The other RCT evaluated the effect of leg-elevated position in a total of 185 eligible CABG patients

randomly assigned to the supine group (n=92) or the leg-elevation group (n=93). The overall DVT was detected in 25 (13.5%) patients. There were more DVT cases in the supine position group (17 patients, 18.4%) than eight patients (8.6%) in the leg-elevation group, but it did not reach a significant difference (p=0.065) (2).

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4A. Can active foot-ankle exercise be considered mechanical VTE prophylaxis?

Recommendation:

There is no evidence that foot-ankle exercise can prevent VTE. However, it does not cause harm to patients after limb surgery.

Delegate Vote: Agree: 87.7%, Disagree: 1.3%, Abstain: 11.0% (Strong Consensus)

4B. Can active breathing exercises be considered non-pharmacological VTE prophylaxis?

Recommendation:

There is no evidence that active breathing exercises can prevent VTE.

Delegate Vote: Agree: 97.2%, Disagree: 1.4%, Abstain: 1.4% (Strong Consensus)

Justification:

There is no evidence to support that foot-ankle exercise, and active breathing exercises can prevent VTE in patients undergoing hip & knee arthroplasty and hip fracture surgery. However, we recommend that all patients practice these active exercise programs because there is no adverse effect.

A randomized controlled study showed that active ankle movement could reduce swelling of the patient's leg after lower limb surgery and improve maximum venous outflow (MVO) and maximum venous capacity

(MVC), which could prevent the formation of DVT after lower limb surgery. A total of 174 patients were randomized as the intervention group (n=96) and the control group (n=78). The intervention group received routine nursing care and active ankle movement (30 times/min for 1-7 days after surgery). The results of the study revealed that thigh circumference in the intervention group decreased compared with the control group on day 5, day 6, and day 7 after surgery (p=0.043, 0.029, 0.001, respectively), and crus circumference in the intervention group also were decreased compared with the control group on day 5, day 6, and day 7 (p=0.045, 0.032, 0.028, respectively). The MVO and MVC in the intervention group increased compared with the control group on the 7th day after surgery (p=0.024, 0.006, respectively) (1).

Deep breathing and active ankle exercise can increase blood flow velocity; however, there is no evidence that it is an effective VTE prophylaxis method. In the study of Kwon et al., 20 healthy males (mean age, 21.3 years) with no medical history of lower extremity disease were recruited. Blood flow velocity in the femoral vein was measured using a doppler ultrasound while performing four exercise protocols: quiet breathing while resting (QR), deep breathing (DB), ankle exercise with quiet breathing (AQB), and ankle exercising combined with deep breathing (ADB). There were statistically significant differences in the femoral vein's peak blood flow velocity with the four protocols ($p<0.001$). The mean (SD) peak blood flow velocity in the femoral vein was significantly different between each pair of the four protocols ($p<0.01$). The mean peak blood flow velocity in the femoral vein was highest with the ADB

protocol, which implies that the ADB protocol may be useful to prevent the blood stasis in patients at risk of deep vein thrombosis (2).

References

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5. Is an Inferior Vena Cava (IVC) filter recommended for PE prevention in hip & knee arthroplasty and hip fracture surgery patients who have a history of prior DVT?

Recommendation:

No, IVC filter placement is not recommended for preventing PE in patients who have a history of prior DVT.

Delegate Vote: Agree: 95.9%, Disagree: 1.4%, Abstain: 2.7% (Strong Consensus)

Justification:

Although a prospective study has shown that IVC filter is safe and effective for prophylaxis against PE in high-risk patients who undergo joint arthroplasty (1), IVC filter is recommended only in three clinical scenarios: 1) patients with documented VTE and classic indications, including absolute contraindication to anticoagulation, complication of anticoagulation resulting in cessation of therapy, and failure of anticoagulation; 2) patients with VTE and extended indications, including iliocaval DVT or extensive free-floating proximal DVT, difficulty establishing therapeutic anticoagulation, massive PE treated with thrombolysis or thrombectomy, chronic PE treated with thromboendarterectomy, thrombolysis for iliocaval DVT, VTE with limited cardiopulmonary reserve, recurrent PE with filter in place, poor compliance with anticoagulation, and high risk in complications of anticoagulation (e.g., risk for frequent falls); and 3) patients without VTE but risk for developing VTE and cannot receive anticoagulation or

be monitored for development of VTE, including trauma patient with high risk of VTE, surgical procedure in a patient at high risk for VTE, and medical condition with high risk of VTE (2).

References

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6. Should a mechanical device for VTE prophylaxis be routinely applied in Asian patients undergoing hip & knee arthroplasty and hip fracture surgery?

Recommendation:

Yes, a mechanical device for VTE prophylaxis should routinely apply in all Asian patients undergoing hip & knee arthroplasty and hip fracture surgery.

Delegate Vote: Agree: 84.9%, Disagree: 11.0%, Abstain: 4.1% (Strong Consensus)

Justification:

The retrospective study comparing between the patients with and without application of IPCD after primary THA in Korean patients found a significantly lower incidence of symptomatic DVT in the patients with IPCD comparing to the control group (0.1%, 1/870 cases, and 0.8%, 8/922 cases, respectively) (1). Another study evaluating symptomatic VTE after primary THA between the patients with and without application of IPCD with a low-dose aspirin for six weeks in both groups found that the incidence of symptomatic VTE was lower in IPCD group (1.3%) compared with the control group (4.1%); however, there was no statistical significance (2).

Although a retrospective study in Korean patients with no elevated VTE risk and undergoing TKA reported that the use of IPCD alone did not reduce the DVT incidence (3), the recent retrospective study on 13,384 patients undergoing THA and TKA reported that mechanical prophylaxis with early mobilization

provides comparable VTE rates to patients who had pharmacological VTE prophylaxis (4).

References

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7. Is mechanical prophylaxis alone adequate for the prevention of VTE in Asian patients after hip & knee arthroplasty and hip fracture surgery?

Recommendation:

It is inconclusive whether mechanical prophylaxis alone can be effective for VTE prevention in all Asian patients.

Delegate Vote: Agree: 95.9%, Disagree: 2.7%, Abstain: 1.4% (Strong Consensus)

Justification:

Some studies from Asian countries support using mechanical devices alone for VTE prophylaxis in Asian patients undergoing hip arthroplasty. A study on 741 patients who underwent 870 primary THAs with application of IPCD found that three patients (0.3%) developed DVT by sonography, one patient (0.1%) developed symptomatic DVT, and one patient (0.1%) developed symptomatic PE. There were no reported fatal PE. The incidence of symptomatic DVT was significantly lower compared to the historical control group (1).

Although some studies provided a lower incidence of VTE in Asian patients undergoing total joint arthroplasty compared to their Western counterparts, VTE prevention results were similar between patients who had mechanical prophylaxis alone and patients who had combined mechanical and pharmacological prophylaxis (2, 3). A retrospective comparative study enrolled 2,798 patients, who underwent TKA with mechanical VTE prophylaxis found that 102 of 2,200 patients (4.6%), with no chemoprophylaxis,

developed DVT compared to 32 of 540 patients (5.9%), with chemoprophylaxis, and the difference was not statistically significant (p=0.13). The subgroup analysis found that there were 19 (0.8%) proximal DVTs and 83 (3.8%) distal DVTs developed in the patients without chemoprophylaxis, and there were 4 (0.7%) proximal DVTs and 28 (5.2%) distal DVTs developed in the patients with chemoprophylaxis (p=0.62). The incidence of PE was equal in both groups, including 5 of 2,200 patients (0.2%) without chemoprophylaxis and 1 of 540 patients (0.2%) with chemoprophylaxis (p=0.87) (4). A cohort study from Singapore on 966 patients who underwent TKA with routine mechanical prophylaxis without chemoprophylaxis found a similarly low prevalence of clinically significant VTE (0.82%). Seven patients developed DVT, and one patient died from massive pulmonary embolism (5). A retrospective study included 2,891 consecutive TKAs in 1,933 patients, in whom GCS and IPCD were used for VTE prophylaxis after TKA. Fifty-three of the 2,891(1.83%) TKAs had suggestive symptoms or signs of VTE. Among these 53 cases, 26 (0.90%) were diagnosed as symptomatic VTE, including 10 (0.35%) symptomatic DVTs, 11 (0.38%) symptomatic PEs, and 5 (0.17%) symptomatic DVTs combined with PEs; however, there was no fatal PE (6). With appropriate patient selection and perioperative protocols, the investigators concluded that postoperative mechanical prophylaxis might be adequate for preventing VTE in Asians undergoing knee arthroplasty.

A prospective RCT by Cho et al. studied the prevalence of total DVT in 148 East Asian patients undergoing TKA and compared between fondaparinux + GCS group (n=74) and placebo + GCS

group (n=74). The prevalence of total DVT was higher in placebo + GCS group (25.7 %) than fondaparinux + GCS group (6.8 %) (p=0.002). There were no symptomatic VTE in both groups at postoperative day 90. They concluded that although combined mechanical and pharmacologic prophylaxis was more effective in preventing total DVT, the prevalence of proximal DVT and PE was still low in East Asian patients. They may routinely need combined mechanical and pharmacologic prophylaxis, except in patients with a high risk of VTE (7). Similarly, another study by Kim et al. in 1,259 primary TKAs reported that the use of IPCD alone did not reduce the DVT incidence in Korean patients with low DVT incidence (8).

Moreover, a prospective RCT by Woolson et al. compared patients who underwent THA (total N=217) among three groups; group A: IPCD alone (N=76), group B: IPCD + ASA (N=72), group C: IPCD + low dose warfarin (N = 69), then evaluated proximal DVT by venography or bilateral ultrasonography before discharge. The results showed no significant difference among the proximal DVT in all groups (group A 12%, group B 10%, and group C 9%) (9). In a systematic review from Sobieraj et al., they compared the effectiveness between combined mechanical and pharmacological VTE prophylaxis and mechanical prophylaxis alone patients who underwent TKA, THA, or hip fracture surgery. The results showed that there were no significant differences in the risk of proximal DVT (RR 0.78 [95% CI, 0.35–1.74]) and pulmonary embolism (RR 1.57 [95% CI, 0.13–19.02]) between the groups (10).

In contrast, a study from Singapore reported that mechanical prophylaxis might not adequate for reducing the rate of DVT after hip fracture surgery (11). This study was on 454 patients who underwent hip fracture surgery with mechanical prophylaxis in all cases and showed an overall DVT incidence of 6.4% (29 patients), and PE incidence of 1.3% (6 patients). Of 399 patients without chemoprophylaxis, 6.8% developed DVT (27 patients), 1% (4 patients) had a PE, and 0.25% (1 patient) had PE without DVT, while the 55 patients with chemoprophylaxis, 3.6% (2 patients) developed DVT, and 1.3% (1 patient) had a PE.

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8A. When should the mechanical VTE prophylaxis be applied in patients undergoing hip & knee arthroplasty?

Recommendation:

Mechanical VTE prophylaxis in patients undergoing hip & knee arthroplasty should be applied in the early postoperative period. The mechanical device for VTE prophylaxis can be applied intraoperatively, although there is no good evidence to support it.

Delegate Vote: Agree: 98.6%, Disagree: 1.4%, Abstain: 0% (Strong Consensus)

8B. When should the mechanical VTE prophylaxis be applied in patients undergoing hip fracture surgery?

Recommendation:

Mechanical VTE prophylaxis in patients undergoing hip fracture surgery should be applied in the preoperative period.

Delegate Vote: Agree: 93.1%, Disagree: 5.5%, Abstain: 1.4% (Strong Consensus)

Justification:

Wakabayashi et al. reported the incidence of preoperative DVT by using doppler ultrasound in the patients who underwent primary and revision TKA and found asymptomatic DVT in 17.4% (56 of 322 patients) with increased risk in patients with revision TKA, patients with rheumatoid arthritis, and patients with

connective tissue diseases. High incidence of preoperative asymptomatic DVT encourages using of mechanical prophylaxis, especially in some high-risk conditions (1).

Nam et al. reported a retrospective study of VTEs in 539 patients who underwent hip fracture surgery by comparing the patients who received preoperative mechanical prophylaxis with IPCD and GCS from time of admission to surgery (135 patients) and the patients who did not receive preoperative mechanical prophylaxis before the operation (404 patients). All the patients received postoperative mechanical and chemical prophylaxis until the day patients were discharged from the hospital. The study found an overall incidence of symptomatic DVT significantly lower in preoperative and postoperative mechanical prophylaxis than that of only postoperative mechanical prophylaxis group (2.2% vs. 7.4%). However, the incidence of symptomatic PE was no statistically different between both groups (1.5% VS 3.7%). The study showed the effectiveness of using preoperative mechanical devices to prevent symptomatic DVT after hip fracture surgery (2).

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9. What is the appropriate duration of mechanical VTE prophylaxis applying to patients?

Recommendation:

The mechanical VTE prophylaxis should be used during hospitalization and extended after discharge until the patient's independent ambulation is achieved.

Delegate Vote: Agree: 90.4%, Disagree: 8.2%, Abstain: 1.4% (Strong Consensus)

Justification:

According to the 2018 NICE guidelines, in elective hip surgery, the duration of mechanical VTE prophylaxis (anti-embolism stocking) should be applied until the patient is discharged in combination with pharmacological prophylaxis for 28 days. In elective knee surgery, they recommend anti-embolism stocking until discharge, combined with pharmacological prophylaxis for 14 days. If patients had a contraindication for pharmacological prophylaxis, one should consider IPCD in elective knee replacement surgery until the patient is mobile and consider anti-embolism stockings in elective hip replacement surgery until discharge (1).

In RCTs of Snyder et al. (2), they compared the duration of mechanical VTE prophylaxis (IPCD during hospitalization only or extended use at home up to 6 weeks postoperatively) with aspirin for 3 weeks postoperative TKA. The 6-week postoperative mechanical compression device therapy group experienced superior DVT prophylaxis than the group receiving mechanical compression device therapy as

an inpatient-only ($p<0.05$). The DVT rate in the post-discharge IPCD therapy group was 0% and 23.1% for the inpatient IPCD group ($p<0.001$), and there was higher satisfaction in post-discharge IPCD therapy group. So, mechanical VTE prophylaxis can be extended to after the patient is discharged from the hospital.

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10. Should mechanical VTE prophylaxis be indicated in all Asian patients who are contraindicated for pharmacological prophylaxis undergoing hip & knee arthroplasty or hip fracture surgery?

Recommendation:

Yes, a mechanical VTE prophylaxis is the most appropriate VTE prevention in Asian patients who are contraindicated for pharmacological prophylaxis. However, those patients who have acute thrombophlebitis, congestive heart failure, pulmonary edema, and limb ischemia due to peripheral vascular diseases should not receive mechanical VTE prophylaxis.

Delegate Vote: Agree: 95.9%, Disagree: 2.7%, Abstain: 1.4% (Strong Consensus)

Justification:

The VTE occurs with an incidence ranging from 14 to 57 per 100,000 person-years. However, different countries appear to have different incidences of VTE following trauma and major orthopedic surgeries. Based on Asian VTE guidelines, mechanical prophylaxis using IPCD is recommended as the primary method and additional pharmacological prophylaxis if the thrombotic risk is high, such as advanced age, immobility, cancer, surgery, and trauma (1).

From the study of Nobuhiko et al., mechanical thromboprophylaxis without anticoagulants was found to be useful in elective hip surgery in the Asian population. There were no cases of fatal PE from the

review of 3,016 patients, and only 5 cases of symptomatic VTEs were reported (2).

The 2018 NICE guidelines recommend mechanical VTE prophylaxis if pharmacological prophylaxis is contraindicated. For fragility fracture of the hip and proximal femur, one should consider IPCD at the time of admission. For elective hip surgery, one should consider anti-embolism stockings and continue until discharge from the hospital. For elective knee replacement surgery, one should consider IPCD and continue until the patient is mobile (3).

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11. What is the proper size and length of the IPCD, and GCS applied on the lower limb for VTE prophylaxis in hip & knee arthroplasty and hip fracture surgery?

Recommendation:

The proper size and length of mechanical devices should correspond to the patient's height and leg length. The length of mechanical devices should cover the lower limb, extending from the lower leg to the thigh. However, it is inconclusive whether a mechanical device covering the entire lower limb provides better VTE prevention than partial coverage.

Delegate Vote: Agree: 89.0%, Disagree: 4.2%, Abstain: 6.8% (Strong Consensus)

Justification:

A mechanical VTE prophylaxis can prevent DVT formation by two mechanisms; decreasing venous stasis and activating fibrinolysis (1). Its effect can be accomplished by compression of foot or calf alone, or by sequential compression of either foot and calf, or the calf and thigh (14 studies; mostly THA and TKA, two spinal and one trauma patients) (2). The Cochrane systematic reviews by Zhao et al. in 121 THA patients, comparing two types of IPCD (calf-thigh compression and plantar compression) found no cases of symptomatic DVT or PE either in both groups in the first three weeks after surgery, but the calf-thigh pneumatic compression was more effective reducing thigh swelling than plantar compression (3).

According to the Cochrane database on the effectiveness of length of GCS (knee-length VS thigh-

length GCS) included 3 RCTs with 496 patients from various surgical specialties, including general surgery, colorectal surgery, hepatobiliary surgery, gynecological surgery, urology, ENT and neurosurgery. There was no significant difference between different lengths of GCS in reducing the incidence of postoperative DVT (4). So, the decision on which type of IPCD and GCS should rely on patient's compliance, ease to use, and cost implication.

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12. What is the optimal IPCD protocol for VTE prevention in Asian patients?

Recommendation:

No specific IPCD protocol provides optimal VTE prevention. There are vastly different settings of pneumatic pressure, duration, and type of IPCD among different studies. However, IPCD should be applied on both operated and non-operated limbs.

Delegate Vote: Agree: 97.2%, Disagree: 1.4%, Abstain: 1.4% (Strong Consensus)

Justification:

The 2012 ACCP guidelines and a comprehensive literature review recommend using IPCDs with 18-hour application time per day (1). In the study of Delis et al. about compression pressure and range, coverage of the IPCD should include the foot and the calf at a frequency of 2–4 times per minute, and the pressure of 60–140 mmHg to lower venous pressure effectively (2). According to the study of Giddings et al., the timing for IPCD over 2 hours had a significant effect in enhancing fibrinolysis and suppressing procoagulant activation (3).

The 2018 NICE guideline for VTE prophylaxis (4) recommends the following:

For fragility fracture of the hip and proximal femur, consider intermittent pneumatic compression at the time of admission if pharmacological prophylaxis is contraindicated. Continue until the patient no longer has significantly reduced mobility relative to their routine or anticipated mobility.

For patients undergoing elective hip replacement surgery; recommends low molecular weight heparin (LMWH) for 28 days combined with anti-embolism stockings (until discharge) as one of the treatment options for VTE prophylaxis and to consider anti-embolism stockings until discharge from hospital if pharmacological interventions is contraindicated.

For patients undergoing elective knee replacement surgery, consider intermittent pneumatic compression if pharmacological prophylaxis is contraindicated. Continue until the patient is mobile.

The AAOS recommends the symptomatic PE prevention for elective hip and knee surgery (5) as the following:

Grade of Recommendation: Moderate; suggest the use of pharmacologic agents or mechanical compressive devices or both for the prevention of venous thromboembolic disease who are not at elevated risk beyond that of the surgery itself for venous thromboembolism or bleeding.

Grade of Recommendation: Consensus; patients undergoing elective hip or knee arthroplasty, and who have also had a previous venous thromboembolism, receive pharmacologic prophylaxis and mechanical compressive devices.

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13. Do combined devices for mechanical VTE prophylaxis, such as IPCD and GCS, provide better effectiveness than a single device alone?

Recommendation:

It is inconclusive whether combined devices of mechanical VTE prophylaxis will provide better effectiveness than a single device.

Delegate Vote: Agree: 94.5%, Disagree: 1.4%, Abstain: 4.1% (Strong Consensus)

Justification:

Regarding mechanical VTE prophylaxis in hip and knee arthroplasty, both IPCD and GCS reduce the incidence of VTE by increasing venous blood flow, reducing venous distention, and preventing venous stasis. A prospective study of Fordyce et al. compared A-V foot pump + GCS and GCS alone in 84 patients who had undergone THA. The incidence of postoperative DVT was significantly higher in the GCS alone (40% vs. 5%, $p<0.001$) (1). However, the retrospective study in elective primary TKA by Kim et al. compared between IPCD + GCS group (425 patients) vs. GCS alone group (420 patients). The results showed that the overall DVT was not significantly different between the two groups (14.8% in GCS alone, 11.3% in IPCD + GCS, $p>0.05$). The incidence of symptomatic DVT was 0.7% in both groups, with no fatal PE observed (2). Therefore, it remains controversial whether combined devices have better effectiveness than a single device.

In hip fracture surgery, mechanical VTE prophylactic methods can reduce the incidence of

VTE. In a study by Mehta et al., they showed that IPCD for ≥ 20 hours per day before and after surgery could reduce VTE in 434 hip fracture patients. The incidence of DVT was 11 (2.5%), and PE was 2 (0.5%) (3), compared with their previous study, which showed an incidence of DVT of 8% in 104 elderly hip fractures without mechanical thromboprophylaxis (4). However, the data of fatal PE and mortality rates are inadequate to conclude. No evidence-based study compares the effectiveness between combined devices and a single device for mechanical VTE prophylaxis (5).

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14. Do variations of IPCD (such as respiratory synchronized, mobile IPCD) available in the market provide a different efficacy on VTE prophylaxis?

Recommendation:

Inconclusive, there is no evidence whether different modes/types of IPCD provide different efficacy on VTE prophylaxis. There is only sparse evidence investigating the effects of various modes of IPCD on VTE prophylaxis.

Delegate Vote: Agree: 97.2%, Disagree: 1.4%, Abstain: 1.4% (Strong Consensus)

Justification:

In general, IPCD can be categorized into a single-chamber or multi-chamber, constant pressure or sequential pressure, slow gradual or rapid inflation devices, and portable or non-portable devices. IPCD is appropriate for VTE prophylaxis when used in the setting of current clinical guidelines. However, a systematic review by Pavon et al. showed the limitations of several evidence-based studies in comparing the effectiveness of each type of device (1). Portable IPCD has the advantage of continued use during ambulation in the early postoperative period.

A multicenter study by Colwell et al. showed non-inferior effectiveness of the use of a mobile compression device alone in preventing VTE when compared to mobile compression device and pharmacological prophylaxis (2). The study from Froimson el al. showed that the mobile IPCD proved significantly more effective than the standard IPCD

when used in conjunction with LMWH for DVT prevention in high-risk orthopedic patients. The results showed that mobile IPCD had lower rates of DVT (1.3% vs. 3.6%), lower rates of symptomatic PE (0% vs. 0.66%), better compliance (83% vs. 49%), and shorter length of hospital stay (4.2 vs. 5.0 days) (3). However, Arsoy et al., in a retrospective study, compared two types of IPCD (nonmobile + LMWH 14 days vs. mobile + ASA OD 14 days), and the results were no different in the rate of symptomatic VTEs between both groups (THA: 2.6% for the nonmobile group VS 1.9% for the mobile group; p=1.0; TKA: 1.1% versus 0%, respectively; p=0.22). This study showed the beneficial effects of both mobile and nonmobile IPCD (4).

In the mode of IPCD, an RCT from Koo et al. compared IPCD with alternate sequential compression (ASCD) VS continuous sequential compression (SSCD) of both legs in 34 patients who underwent knee and spine surgery. The outcomes found no significant difference in asymptomatic distal DVT (11.8% in ASCD vs. 29.4% in SSCD, p=0.331). There were no symptomatic DVT and proximal DVT in either group (5). Another RCT study compared two different methods of IPCD (Simultaneous compression with fixed cycling rate (SF) vs. Alternate compression with adjusted cycling rate (AA)) in 54 TKA patients. The results found that no significant difference in total DVT (55.6% in AA vs. 51.9% in SF), although the SF group showed better hemodynamic parameters (6). The meta-analysis by Elbuluk et al. compared the effectiveness of respiratory synchronized compression devices (RSCDs) and unsynchronized intermittent pneumatic compression devices (NSIPCDs) to pharmacological prophylaxis for

preventing VTE after total joint arthroplasty. The results showed that both devices had effectiveness in preventing VTE. In RSCDs group, the risk ratio of DVT and PE were 0.47 (95% CI, 0.27–0.80; I2 = 0%) and 0.62 (95% CI, 0.29–1.32; I2 = 0%), respectively. In NSIPCDs group, the risk ratio of DVT and PE were 0.51 (95% CI, 0.39–0.67; I2 5 69%) and 0.24 (95% CI, 0.04–1.47; I2 5 0%), respectively (7).

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Group 3: Pharmacological VTE prophylaxis

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28. Pariwat Taweekitikul
29. Chun Hoi Yan
30. Seng Jin Yeo
31. Pongsak Yuktanandana

Statements of Group 3:

Pharmacological VTE prophylaxis

1. Which pharmacological agents are widely accepted for VTE prophylaxis in hip & knee arthroplasty and hip fracture surgery?

Recommendation:

The widely accepted pharmacological agents for VTE prophylaxis include aspirin, unfractionated heparin (UFH), low molecular weight heparin (LMWH), adjusted dose vitamin K antagonists (VKA), synthetic pentasaccharide factor Xa inhibitor (fondaparinux), oral factor Xa inhibitor, and direct thrombin inhibitors (DTI) anticoagulants.

Delegate vote: Agree 100%, Disagree 0%, Abstain 0% (Unanimous Consensus)

Justification:

The American College of Chest Physicians (ACCP) guidelines recommend the use of LMWH, low-dose UFH, VKA, fondaparinux, apixaban, dabigatran, rivaroxaban, aspirin (all Grade 1B) for patients who undergo THA (THA) or TKA (TKA) (1). For patients who undergo hip fracture surgery, it recommends the use of LMWH, low-dose UFH, VKA, fondaparinux, aspirin (all Grade 1B) (1). Although many current guidelines have different recommendations, the variations rely on the risk of VTE, bleeding risk, and patient safety (2). Overall, the ACCP recommends LMWH as an optimal pharmacological agent for VTE

prophylaxis in patients undergoing THA, TKA, or hip fracture surgery (1).

The American Academy of Orthopaedic Surgeons (AAOS) guideline could not make absolute recommendations concerning the most effective prophylaxis agents. As a result, the guideline provides orthopedic surgeons with flexibility regarding the use of different prophylactic regimens. When choosing the medicine, orthopedic surgeons should justify VTE's risk, bleeding risk, and patient safety. Aspirin is graded as a 1A recommendation against its use in previous ACCP guidelines. However, it seems to have a better safety profile, low risk of bleeding, does not require routine blood tests, and provided comparable VTE prophylaxis, which makes it attractive to orthopedic surgeons. In contrast, fondaparinux, apixaban, dabigatran, rivaroxaban, vitamin K antagonists, and low-dose unfractionated heparin, are graded as 1B.

Aspirin is safe while it provides a low risk of bleeding with no requirement for routine blood testing (1). Several studies supported the use of aspirin for preventing VTE. The meta-analysis of using aspirin as a thromboprophylaxis agent in hip and knee arthroplasty by An et al. found that the overall rate of DVT and PE in both groups after using aspirin was 1.2% and 0.6%, respectively, and the rate of major bleeding was 0.3% (2). The pooled mortality rate was only 0.2%. A recent systematic review, including 11 relevant studies with various dosing regimens, concluded that aspirin could reduce VTE with a low risk of bleeding complication (3). According to the Prevention of Pulmonary Embolism and Deep Vein thrombosis (PEP trial) with low dose

aspirin which included 13,356 patients who underwent surgery for hip fracture and elective hip arthroplasty with the use of 160 mg aspirin comparing with placebo, it concluded that aspirin could reduce PE by 43% and symptomatic DVT by 29% without increasing death due to bleeding (4). Schousboe et al. showed that aspirin is a cost-effective choice for VTE prophylaxis following THA in patients without a history of VTE (5).

The LMWH was used instead of warfarin and unfractionated heparin (UFH) in clinical practice and VTE studies in hip & knee arthroplasty and hip fracture surgery with a particular efficacy. Several past studies over 20 years also reported in favor of LMWH than other anticoagulants (6-8). It can be administered once daily without laboratory monitoring or dose adjustment. Therefore, the use of LMWH is more convenient than UFH, including less heparin-induced thrombocytopenia (9). So, it has replaced UFH for almost any clinical indications.

The systematic review and meta-analysis of Kumar et al. in 2019 suggest that fondaparinux is significantly superior in reducing VTE (composite of DVT and PE) to LMWH for perioperative arthroplasty surgery. However, they suggest that clinicians be aware of the higher risk of major bleeding, especially surgical site bleeding with fondaparinux (10). Previous studies of fondaparinux also showed similar results. The 2002 meta-analysis of 4 RCTs compared fondaparinux with enoxaparin in major orthopedic surgery. Fondaparinux significantly reduced the VTE incidence (182 [6.8%] of 2682 patients) compared with enoxaparin (371 [13.7%] of 2703 patients), with a current odds reduction of 55.2% (95% CI, 45.8%-

63.1%; P<0.001). The effect was consistent across all types of surgery and all subgroups. Major bleeding occurred more frequently in the fondaparinux group (P=0.008). However, the incident of clinically relevant bleeding (leading to death or reoperation) did not differ between groups (11). Another RCT of Kenneth A. compared fondaparinux with enoxaparin in TKA. The fondaparinux group had a significantly lower incidence of venous thromboembolism (12.5 %[45 of 361 patients]) than the enoxaparin group (27.8 percent [101 of 363 patients]; reduction in risk, 55.2 %; 95 % CI, 36.2 to 70.2; P<0.001). Major bleeding occurred more frequently in the fondaparinux group (P=0.006), but there were no significant differences between the two groups in the incidence of bleeding leading to death or reoperation or occurring in a critical organ (12).

Direct factor Xa inhibitors work by binding to the active site of factor Xa blocking the interaction with its substrate. Examples of oral direct factor Xa inhibitors are rivaroxaban, apixaban, edoxaban, and betrixaban. The ACCP recommends rivaroxaban and apixaban in the same manner as fondaparinux (1). Rivaroxaban is an FDA approved oral direct factor Xa inhibitor that requires no monitoring. A meta-analysis investigated the efficacy of 2.5 mg of apixaban or 10 mg of rivaroxaban against enoxaparin as prophylaxis after total hip and knee arthroplasty that oral factor Xa inhibitors were superior to enoxaparin in preventing DVT. However, there was no difference in the rate of PE, mortality, or postoperative wound infection (13). Another meta-analysis by Guofeng Ma et al. included 6 RCTs with 13,790 patients. They showed that the incidence of DVT significantly decreased with the use of direct Xa inhibitors (both twice daily and once daily

regimes) comparing with the enoxaparin treatment ($p<0.01$) (14).

Rivaroxaban has numerous studies about the effectiveness of preventing DVT (15-18). When comparing extended rivaroxaban (10mg daily 31-39 days) with short-term enoxaparin (40mg once daily 10-14 days) in THA, the result showed that the DVT, nonfatal PE and all-cause mortality up to day 30–42 occurred in 17 (2.0%) patients in the rivaroxaban group, compared with 81 (9.3%) in the enoxaparin group (16). When comparing rivaroxaban (10mg once daily) with enoxaparin (30 mg twice daily) in TKA, the result showed that the DVT, nonfatal PE and all-cause mortality up to day 17 occurred in 67 (6.9%) of patients in the rivaroxaban group, compared with 97 (10.1%) in the enoxaparin group (absolute risk reduction 3.19%, 95% CI, 0.71-5.67; p=0.0118).

An RCT using apixaban (2.5 mg twice daily for 10–14 days) comparing with enoxaparin (30 mg twice daily for 10–14 days) in TKA reported lower rates of clinically relevant bleeding (16). Two randomized controlled trials, using apixaban (2.5 mg twice daily), showed superior efficacy compared to enoxaparin (40 mg daily) (20, 21). Overall, there were no significant differences in the rates of major bleeding between apixaban and enoxaparin.

Direct thrombin inhibitor (dabigatran) works by binding specifically to the active center of thrombin and inactivating free and fibrin-bound thrombin. This process is reversible, leaving a small amount of free and active thrombin to control hemostasis. In the United States, dabigatran etexilate is an FDA approved oral direct thrombin inhibitor for the prevention of atrial fibrillation and stroke, but not for

VTE prophylaxis after THA and TKA. A study of dabigatran indicated that over 12–15 days of treatment, dabigatran etexilate (150 mg or 220 mg once daily) was not as effective as enoxaparin (30 mg twice daily) in preventing total VTE and mortality in patients undergoing TKA (22). However, an RCT study by Eriksson et al. demonstrated that over 6–10 days of treatment, dabigatran etexilate (220 mg or 150 mg once daily) was non-inferior to enoxaparin (40 mg once daily) for the prevention of VTE in patients undergoing TKA (23). There was no significant difference in the frequency of major bleeding or the overall rate of adverse events between either dose of dabigatran etexilate and enoxaparin. Similarly, another trial in patients undergoing THA with extended VTE prophylaxis (for 28–35 days) reported the same outcomes (24). Another trial of Eriksson et al. demonstrated that extended prophylaxis with oral dabigatran etexilate (220 mg once daily) was effective as subcutaneous enoxaparin (40 mg once daily) in reducing the risk of VTE after THA, and superior to enoxaparin in reducing the risk of major VTE, with similar safety profiles (25).

Warfarin was the first oral anticoagulant widely used in the United States and has been in use since 1954. It is a vitamin K antagonist that inhibits the synthesis of active vitamin-K-dependent coagulation factors (factors II, VII, IX, and X as well as protein C). Therapeutic anticoagulation is reached 24 to 72 hours after the initial dose. Usually, 5 or 10 mg of warfarin is given the night before or the night of surgery, and then dosing is adjusted to maintain an International Normalized Ratio (INR) of 2.0. The rate of DVT using low-dose warfarin ranges from 35% to 59% (26). When comparing warfarin to LMWH, LMWH was more

effective in preventing DVT formation ($p<0.05$) but no difference to warfarin in preventing symptomatic events, including PE (27, 28). The risks of warfarin include bleeding and multiple drug interactions. The use of warfarin also requires regular monitoring of the INR. Enoxaparin 40 mg subcutaneously once daily or 30 mg subcutaneously twice daily for 7-14 days postoperatively can reduce the incidence of VTE significantly (29, 30). however, a meta-analysis showed that 15-30% of patients had venographic evidence of DVT on the discharge date despite patients receiving enoxaparin for 7-14 days (31).

Mismetti et al. conducted a meta-analysis of vitamin K antagonists (VKA) (32). They reported that VKA was more effective than a placebo or no treatment in reducing DVT [567 patients, RR, 0.56; 95% CI, 0.37-0.84, $p<0.01$] and clinical PE (651 patients, RR, 0.23; 95% CI, 0.09-0.59, $p<0.01$). However, there was a higher rate of wound hematoma (162 patients, RR, 2.91; 95% CI, 1.09-7.75, $p=0.03$) compared to the placebo. In contrast, VKAs were less effective than LMWH in preventing total DVT and proximal DVT (9,822 patients, RR, 1.51; 95% CI, 1.27-1.79, $p<0.001$; and 6,131 patients, RR,1.51; 95% CI, 1.04- 2.17, $p=0.028$, respectively). The differences between VKA and LMWH in major hemorrhage and wound hematoma were not significant.

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2. Is the protocol for pharmacological VTE prophylaxis similar among knee arthroplasty, hip arthroplasty, and hip fracture surgery?

Recommendation:

No, although a general protocol for pharmacological VTE prophylaxis can apply to all patients who undergo knee arthroplasty or hip arthroplasty or hip fracture surgery, different prophylaxis protocols should be considered based on the risk stratification of patients.

Delegate vote: Agree: 97.2%, Disagree: 1.4%, Abstain: 1.4% (Strong Consensus)

Justification:

According to the American College of Chest Physicians (ACCP), hip fracture patients are at high risk for deep vein thrombosis (DVT) and pulmonary embolism (PE). In this patient group, the ACCP recommends using of LMWH, low-dose UFH, VKA, fondaparinux, aspirin (all Grade 1B) or an IPCD (Grade 1C) for VTE prophylaxis, whereas it does not recommend using apixaban, rivaroxaban, or dabigatran (1). The duration of pharmacological VTE prophylaxis should continue for 28 to 35 days postoperatively. Also, some guidelines do not recommend aspirin, apixaban, rivaroxaban, dabigatran, and direct oral anticoagulants (DOACs) for VTE prophylaxis in hip fracture surgery (2, 3). However, a personalized protocol for pharmacological VTE prophylaxis may be used based on the surgical plan, underlying condition, and risk of thrombosis in each patient.

Recently, the American Academy of Orthopaedic Surgeons (AAOS) and the ACCP developed new evidence-based guidelines for venous thromboembolic prophylaxis after total joint arthroplasty. Based on a review of the available literature, the AAOS guideline panel was unable to recommend a specific prophylaxis regimen or duration of prophylaxis following routine total joint arthroplasty. The optimal duration of thromboprophylaxis after total knee replacement remains controversial. It is a common practice to administer prophylaxis using low molecular-weight heparin (LMWH) or unfractionated heparin (UFH) until discharge from hospital, usually 7 to 14 days after surgery (4). International guidelines recommend extending thromboprophylaxis for up to 35 days following major orthopedic surgery, but the recommendation is weak due to moderate-quality evidence (5). Extended (4-week) prophylaxis with fondaparinux can produce a 96% reduction in risk of DVT and an 89% reduction in risk of symptomatic VTE events relative to perioperative (1-week) prophylaxis. As the only anticoagulant approved in the United States for thromboprophylaxis in hip fracture patients, fondaparinux offers more effective prophylaxis against VTE without compromising safety (6).

Jeong et al. compared the clinical efficacy and side-effect profiles of aspirin, dextran 40, and low-molecular-weight heparin (enoxaparin) in preventing thromboembolic phenomena after hip fracture surgery. Among the three pharmacologic agents, they found a low incidence of thromboembolic phenomena, pulmonary embolism, fatal pulmonary embolism, with no difference in thromboembolic prophylaxis efficacy (7).

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3. Should pharmacological prophylaxis be administered in all Asian patients who undergo hip & knee arthroplasty and hip fracture surgery?

Recommendation:

In Asian patients with elevated VTE risk and undergoing hip & knee arthroplasty and hip fracture surgery, a pharmacological prophylaxis should be administered, except patients with increased bleeding risk or contraindications for pharmacological prophylaxis.

Delegate vote: Agree 89.0%, Disagree 5.5%, Abstain 5.5% (Strong Consensus)

Justification:

There are several studies to show that Asian ethnicity is associated with a lower DVT and VTE incidence than the Caucasians (1-5). However, in all patients, regardless of ethnicity with elevated VTE risk, the pharmacological prophylaxis is recommended (6-8).

Although there is no validated risk assessment model applied for Asians, there are no studies to show that Asians have a higher bleeding risk than Caucasians after surgery in the presence of anticoagulants such as UFH, LMWH, Fondaparinux, and the new oral anticoagulants. Ngoh et al. have proposed using the Caprini risk score for VTE prevention in Asians (9). A mechanical VTE prophylaxis is suitable in patients with a high risk of bleeding.

According to the current guidelines, the type of pharmacological prophylaxis should be considered

following risk stratification. The pharmacological prophylaxis is contraindicated in active bleeding, and untreated congenital coagulopathies (6,7), and only IPCD is recommended for this group of patients. Contraindication for IPCD include acute thrombophlebitis, suspected DVT, congestive heart failure, pulmonary edema, and leg ischemia due to peripheral vascular disease (6-8).

In conclusion, a combination of pharmacological and mechanical VTE prophylaxis is recommended for Asian patients who have elevated VTE risk, based on risk stratification. A mechanical prophylaxis could be considered to use alone in patients who had increased bleeding risk.

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4. Considering VTE risk and bleeding risk, which method of VTE prophylaxis should apply for Asian patients undergoing hip & knee arthroplasty or hip fracture surgery?

4A. Standard VTE risk without bleeding risk

Recommendation:

Mechanical prophylaxis alone or pharmacological prophylaxis combined with mechanical prophylaxis

Delegate vote: Agree 97.2%, Disagree 1.4%, Abstain 1.4% (Strong Consensus)

4B. Elevated VTE risk without bleeding risk

Recommendation:

Pharmacological prophylaxis combined with mechanical prophylaxis

Delegate vote: Agree 98.6%, Disagree 0%, Abstain 1.4% (Strong Consensus)

4C. Standard VTE risk with bleeding risk

Recommendation:

Mechanical prophylaxis alone

Delegate vote: Agree 97.2%, Disagree 1.4%, Abstain 1.4% (Strong Consensus)

4D. Elevated VTE risk with bleeding risk

Recommendation:

Mechanical prophylaxis alone or combined with aspirin

Delegate vote: Agree 86.3%, Disagree 8.2%, Abstain 5.5% (Strong Consensus)

Justification:

The 2008 AAOS guidelines recommended that mechanical prophylaxis have no bleeding risk. Therefore, they should remain in place regardless of VTE risk or bleeding risk (1).

The 2018 European guidelines on perioperative venous thromboembolism prophylaxis suggest the use of aspirin for VTE prevention after THA, TKA, and hip fracture surgery in patients with an increased bleeding risk (Grade 2C) (2).

According to the 2012 ACCP guidelines, it recommended using dual prophylaxis with an antithrombotic agent and an IPCD during the hospital stay in patients undergoing major orthopedic surgery (Grade 2C) (3).

The 2018 NICE guideline recommended using anti-embolism stockings until discharge, combined with LMWH as an option in patients undergoing elective THA and TKA. For hip fracture, it is recommended to consider intermittent pneumatic compression (IPCD) at the time of admission if pharmacological prophylaxis is contraindicated. Continue until the patients no longer have significantly reduced mobility (4).

According to the ASH 2019 guideline, depending on the risk of VTE and bleeding based on the individual patient and the type of surgical procedure,

it recommended using combined prophylaxis or mechanical prophylaxis alone. For patients considered at high risk of bleeding, the balance of effects may favor mechanical methods over pharmacological prophylaxis. For patients considered at high risk of VTE, combined prophylaxis is favored over mechanical or pharmacological prophylaxis alone (5).

The SIGN guideline suggested that patients with increased risk of bleeding should be given mechanical prophylaxis alone. Pneumatic foot pumps can be considered for prophylaxis as an alternative to IPC in orthopedic surgery patients. However, it did not recommend combined mechanical with pharmacological prophylaxis (6).

The study of Bin Abd Razak et al. in Singapore showed the low prevalence of VTE using mechanical prophylaxis alone without chemoprophylaxis in patients who underwent TKA. The prevalence of significant VTE is only 0.82% (8/966 patients). With proper patient selection, risk stratification, and stringent perioperative protocols, mechanical prophylaxis alone without routine chemoprophylaxis may be enough in Asians undergoing TKA (7).

The systematic review and meta-analysis of Kakkos SK, including 1399 patients from 6 RCTs, concluded that the addition of IPCD with pharmacological prophylaxis had benefits in DVT prevention in patients undergoing both knee and hip replacement. In TKA, the rate of DVT was reduced from 18.7% with anticoagulation alone to 3.7% with combined modalities. (risk ratio (RR) 0.27, p=0.03; NNT : 7) In THA, the rate of DVT was reduced from 9.7% with anticoagulation alone to 0.9% with

additional mechanical compression (RR 0.17, p<0.001; NNT: 12) and the rate of DVT was reduced from 8.7% with mechanical compression alone to 7.2% with additional pharmacological prophylaxis (RR 0.84) but not significant. In contrast, the incidence of PE could not be interpreted (8).

For the Asian studies, the study of Sang et al. in Chinese patients using prospective RCT design, patients were randomized into four groups to receive graduated compression stockings (GCS) alone (group A, n=159), GCS +low molecular weight heparin (LMWH) (group B, n=157), GCS +intermittent pneumatic compression (IPC) (group C, n=153), and GCS +IPC +LMWH (group D, n=156). The overall incidence of DVT was 5.1%. Group A had the highest incidence of DVT (8.8%), followed by group C (5.2%), group B (3.8%), and group D (2.6%). There was a significant difference in the incidence of DVT between groups A and D. The incidence of DVT was significantly lower in LMWH-treated patients (group B and group D) than in non-LMWH-treated patients (group A and group C). The authors concluded that combine mechanical and pharmacological VTE prophylaxis had shown better effectiveness of VTE prevention than mechanical or pharmacological prophylaxis alone (9).

A systematic review of major orthopedic surgeries showed that LMWH + mechanical device had a significantly decreased risk of total DVT (odds ratio 22.7, 95%CI, 1.27-407) compared to LMWH alone in THA patients. In TKA patients, the antiplatelet + mechanical device group had a lower incidence of total DVT than the group where antiplatelet alone was used (10).

In a case series, Takahashi et al. studied 38 patients who underwent lower extremities orthopedic surgery with the highest risk of both venous thrombosis and bleeding. A portable pneumatic compression device was used to prevent VTE. The results showed that the incidence of asymptomatic DVT was 5.3%, and symptomatic DVT was 2.6%. No major bleeding or adverse events were observed (5). Also, a retrospective study from Peng et al., reviewed all patients with hemophilia A or B (total N=98) who underwent primary THA (N=39) and TKA (N = 67) using a mechanical prophylaxis without chemoprophylaxis. They found that there was only one hemophilia B patient with clinically significant VTE, with the incidence of 1.02% (6). Perez et al. reported similar results in a review of patients with hemophilia A or B who underwent 71 THA or TKA. Compression stocking was applied to all patients, of whom 10.5% had IPCDs, and 2.5% had LMWH. Only one patient who received LMWH had asymptomatic DVT. The incidence of symptomatic VTE was 0.5%. They concluded that hemophilia patients who had a high risk of bleeding were safe for using mechanical prophylaxis of DVT alone without chemoprophylaxis (11).

Patients with bleeding risk, such as acute liver failure, concurrent use of anticoagulants, lumbar puncture/epidural/spinal anesthesia expected within the next 12 hours, lumbar puncture/epidural/spinal anesthesia within the previous 4 hours, acute stroke, thrombocytopenia (platelets < 75 x 109/l), uncontrolled systolic hypertension (≥ 230/120 mmHg), untreated inherited bleeding disorders are a contraindication for anticoagulants (12-14). Previous major bleeding, severe renal failure, concomitant

antiplatelet agent, extensive surgical dissection, and revision surgery are general risk factors for bleeding (12-14). In patients with bleeding risk, an IPCD is indicated (12-14).

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5. Does the dosage and the duration of perioperative tranexamic acid affect the pharmacological VTE prophylaxis in patients undergoing hip & knee arthroplasty and hip fractures surgery?

Recommendation:

No, tranexamic acid administration, at the dosage and the duration administered in hip & knee arthroplasty and hip fracture surgery, is not associated with elevated VTE risk for patients without a known history of VTE.

Delegate vote: Agree 95.9%, Disagree 0%, Abstain 4.1% (Strong Consensus)

Justification:

There is still no conclusive evidence that tranexamic acid increases the risk of VTE. Administration of oral, topical, or intravenous TXA in patients without a known history of VTE does not increase the risk of developing VTE compared to placebo during the perioperative episode of a primary TJA. A meta-analysis investigating the impact of TXA administration on VTE's risk included 77 high and one moderate quality randomized clinical trials (1). Almost all studies (92%) excluded patients with a history of a thromboembolic event. In hip arthroplasty, there were 22 RCTs using IV TXA, and the result showed that the rate of VTE using IV TXA was 2.8%, whereas the rate of VTE in placebo was 2.1% (RR 1.20; 95% CI 0.62-2.33; I2 = 0%). The rate of VTE using topical TXA was 1.2%, while the rate of VTE in placebo was 1.5% (RR 1.0; 95% CI, 0.21-4.89; I2 =

0%). These results demonstrated no difference in the VTE rate in the TXA group than in the placebo group. In knee arthroplasty, there were 35 RCTs included using IV TXA, and the result showed that the rate of VTE using IV TXA was 2.8%, whereas the rate of VTE in placebo was 3.1% (RR 0.87; 95% CI, 0.58-1.32; I2 = 0%). The rate of VTE using topical TXA in 25 RCTs was 2.6%, whereas the rate of VTE in placebo was 2.9% (RR 0.89; 95% CI, 0.54-1.48; I2 = 0%). The rate of VTE using oral TXA in five RCTs was 3.3%, whereas the rate of VTE in placebo was 3.6% (RR 0.87; 95%CI, 0.38-2.04; I2 = 0%).

When combining TKA and THA, there were 58 RCTs included for IV TXA; the number of patients in each group was 2,131 and 2,137, respectively. The rates of VTE were equivalent at 2.8% for both IV TXA and placebo (RR 0.98; 95% CI, 0.69-1.39; I2 = 0%). For topical TXA, 31 RCTs comparing topical TXA and placebo had 1,509 and 1,502 patients per group. Topical TXA had a similar rate of VTE compared to placebo at 2.2% and 2.5%, respectively (RR 0.89; 95% CI, 0.56-1.41; I2 = 0%). Moreover, the clinical practice guideline of the American Association of Hip and Knee Surgeons (AAHKS) gives a "strong" recommendation that the administration of TXA does not increase risk in VTE (2).

For hip fracture, the meta-analysis of 11 RCTs in 892 patients found that DVT occurred in 16 of 423 patients (3.8%) in the TXA group compared with 8 of 431 patients (1.9%) in the control group (p=0.66, I2 = 0). When using fixed-effect meta-analysis model, the result showed that the risk of DVT was similar in both groups (RR,0.02; 95%CI, 0.01-0.04, p=0.13) (3), which

means that the use of TXA in hip fracture is safe and does not increase the risk for VTE.

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6. Does pharmacological VTE prophylaxis increase the incidence of wound drainage and/or infection in patients undergoing hip & knee arthroplasty and hip fractures surgery?

Recommendation:

Yes, pharmacological VTE prophylaxis may increase wound drainage. Prolonged wound drainage was reported as a significant predictor of wound infection after THA. However, there is no evidence that anticoagulant for VTE prophylaxis increases the risk of infection in TKA and hip fractures surgery.

Delegate vote: Agree 98.6%, Disagree 1.4%, Abstain 0% (Strong Consensus)

Justification:

Pharmacological VTE prophylaxis may increase bleeding, leading to increased wound drainage from a suction catheter, and can also lead to increased subcutaneous wound bleeding and an increase in surgical wound drainage from a surgical wound (1). Patel et al. conducted a retrospective study of 1,211 THA patients and 1,226 TKA patients. They found that prophylaxis against VTE with low-molecular-weight heparin was associated with a significant increase in wound drainage after THA ($p=0.027$) but not after TKA. Also, there was prolonged wound drainage in the group treated with low-molecular-weight heparin compared to the groups treated with coumadin or aspirin and mechanical compression. On the fifth day after the operation, the low-molecular-weight heparin group had more wound drainage than the aspirin group ($p=0.003$). Moreover, there was a strong

positive correlation between the length of hospital stay and the number of days until the surgical wound was dry ($r=0.29$, $p<0.001$). The correlation was stronger in the THA group ($r=0.34$, $p<0.001$) compared to the TKA group ($r=0.26$, $p<0.001$). Prolonged wound drainage was a significant predictor of wound infection after THA (OR 1.42; 95% CI, 1.18-1.71, $p<0.001$), and each day of prolonged drainage was associated with a 42% increase in the risk of wound infection. However, prolonged wound drainage did not increase the risk of infection in TKA (1).

Agaba et al. conducted a cohort study of VTE prophylaxis in THA. They found that warfarin was associated with the highest number of postoperative complications at 30 days following surgery. The complications of warfarin consisted of I&D (OR 2.04; 95% CI, 1.67–2.50), hematoma (OR 1.95; 95% CI, 1.63–2.33), transfusion (OR 2.29; 95% CI, 2.11–2.49), PE (OR 1.72; 95% CI, 1.49–1.98), DVT (OR 1.53; 95% CI, 1.39–1.67), PJI (OR 1.44; 95% CI, 1.26–1.64), hemorrhage (OR 1.92; 95% CI, 1.51–2.44). The apixaban complications were hematoma (OR 4.0; 95% CI, 2.10–7.63) and hemorrhage (OR 3.59; 95% CI, 1.46–8.79) during the 30 days following surgery. There were no statistically significant complications associated with enoxaparin, rivaroxaban, or fondaparinux during the 30-day postoperative period (2).

The above paragraph is not clear. What were the treatment groups? Was warfarin compared against all the drugs described?

Runner et al. studied databases from 2014 to 2016 in a total of 22,072 primary joint arthroplasty cases. The study showed that patients receiving prophylaxis

with aspirin or sequential compression device was associated with patients having no increased complications (95.5% vs. 93.0%, p<0.001). The use of prophylaxis with heparin, enoxaparin, warfarin, rivaroxaban, fondaparinux and all other prophylactic strategies was associated with a higher likelihood of mild thrombosis (0.9% vs. 0.2%, p<0.001), mild bleeding (1.3% vs. 0.4%, p<0.001), moderate thrombosis (1.2% vs. 0.4%, p<0.001), moderate bleeding (2.7% vs 2.1%, p=0.002), severe bleeding events (1.2% vs. 0.9%, p=0.010), infection (1.9% vs, 1.3%, p=0.001), and death within 90 days (0.7% vs. 0.3%, p<0.001) (3).

Prolonged wound drainage associated with anticoagulation following THA or TKA has been associated with infection and increased length of hospital stay. Previous studies have investigated the risk of bleeding, prolonged wound drainage, and length of hospital stay between current medications, such as aspirin, LMWH, warfarin, rivaroxaban, and fondaparinux, not find significant differences in these complications. However, a retrospective study from Runner et al. has shown that except for aspirin, all other chemoprophylaxis agents increase the risk of bleeding (3).

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7A. Among all available pharmacological agents for VTE prophylaxis, which is the most appropriate for the Asians undergoing elective hip and knee arthroplasty?

Recommendation:

Aspirin is the most appropriate agent for patients with standard VTE risk. Direct oral anticoagulants (DOACs) or LMWH are the most appropriate agents for patients with elevated VTE risk.

Delegate vote: Agree 82.2%, Disagree 8.2%, Abstain 9.6% (Strong Consensus)

7B. Among all available pharmacological agents for VTE prophylaxis, which is the most appropriate for the Asians undergoing hip fracture surgery?

Recommendation:

Inconclusive, there is not enough evidence to support the most appropriate agents.

Delegate vote: Agree 93.2%, Disagree 4.1%, Abstain 2.7% (Strong Consensus)

Justification:

According to the ACCP guideline released in 2012, for patients undergoing THA or TKA, it recommended using one of the following: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, UFH, VKA, aspirin (all grade 1B), or an IPCD (grade 1C). It is recommended for patients undergoing hip fracture surgery using one of the following: LMWH,

fondaparinux, UFH, VKA, aspirin (all grade 1B), or an IPCD (grade 1C). It also recommended using LMWH in preference to the other agents for patients undergoing TKA & THA and hip fracture surgery (Grade 2B) (1).

The NICE guidelines were released in 2018 and recommended aspirin or LMWH or rivaroxaban for patients undergoing elective knee replacement. For patients undergoing elective hip replacement, it recommended LMWH or rivaroxaban. For patients undergoing hip fracture surgery, it recommended LMWH or fondaparinux (2).

The ASH guidelines, released in 2019, recommended using aspirin or anticoagulants for patients undergoing THA or TKA. If the anticoagulants are selected, it is recommended DOACs over LMWH. If DOAC is not selected, it is recommended LMWH rather than warfarin. For patients undergoing hip fracture repair, use LMWH or UFH (3).

Although a study from Singapore showed a low prevalence of VTE in patients undergoing TKA without chemoprophylaxis (4), aspirin could be an option for pharmacological prophylaxis in elective hip and knee arthroplasty, which was recommended by the ACCP guideline, the NICE guideline, and the ASH guideline. Several meta-analyses suggested that aspirin is safe and good efficacy following total joint arthroplasty and demonstrated non-inferiority to other anticoagulants (5-9). The RR of VTE after THA and TKA was 1.12 (95% CI, 0.78-1.62) for aspirin compared with other anticoagulants. Comparable findings were observed for DVT (RR, 1.04; 95% CI, 0.72-1.51) and PE (RR, 1.01; 95% CI, 0.68-1.48). The risk of adverse events, including major bleeding, wound hematoma, and

wound infection, was not statistically significantly different in patients receiving aspirin vs. other anticoagulants. When analyzing THAs and TKAs separately, there was no statistically significant difference in the risk of VTE, DVT, and PE between aspirin and other anticoagulants. Aspirin had a VTE risk not statistically significantly different from LMWH (RR, 0.76; 95% CI, 0.37-1.56) or rivaroxaban (RR, 1.52; 95% CI, 0.56-4.12) (9). Aspirin is an inexpensive, widely available, and well-tolerated agent that does not require routine blood tests and provides less adverse events, such as hematoma. Due to the lower prevalence of VTE in Asians with several studies supporting the use of aspirin, it is reasonable to use aspirin as the pharmacological VTE prophylaxis in those who are considered having a standard VTE risk.

For Asian patients who have elevated VTE risk and undergo elective hip and knee arthroplasty, there were some studies favored using aspirin in these patients. According to the retrospective study of Tan et al. (8) on 60,467 joint arthroplasties, patients were considered high risk by score > 70 points using the venous thromboembolism calculator described by Huang et al. (10). They concluded that the use of warfarin, LMWH in higher-risk patients did not necessarily result in a reduction in symptomatic VTE. In contrast, aspirin administered to higher-risk patients seemed to be as effective as potent anticoagulation and more effective than warfarin (8). A study from Huang et al. in 30,270 patients concluded that aspirin is as effective as and safer than warfarin for VTE prophylaxis after total joint arthroplasty, even in patients at higher risk of venous thromboembolism. However, due to limited evidence of using aspirin for VTE prophylaxis in TKA and THA, it is reasonable that

more potent anticoagulants should be considered to use for elevated VTE risk patients rather than aspirin.

In patients with hip fractures, immobility has been reported to increase risks for VTE. The risk of venous thromboembolism calculator by Parvizi et al. (11) defines fractures as one of the risks of venous thromboembolism. Therefore, patients with hip fractures should be classified as elevated risk patients. Although aspirin was only recommended in hip fracture surgery by the ACCP guideline, other guidelines favored other anticoagulant drugs. A systematic review study by Drescher FS in 2014 concluded that aspirin, when compared with anticoagulation, may be associated with a higher risk of DVT following hip fracture repair but was similarly effective after lower extremity arthroplasty (12). However, a study in China by Huang et al. in 390 patients concluded that aspirin was equivalent to the direct oral anticoagulant rivaroxaban after hip fracture surgery (13). The LMWH was recommended by the ACCP guideline, the NICE guideline, and the ASH guideline, and the SIGN guideline. The ACCP recommended DOACs in elective hip and knee arthroplasty, but not included hip fracture surgery; however, the NICE guideline, the ASH guideline, and the SIGN guideline preferred DOACs over LMWH.

As most guidelines and systematic review supported using anticoagulants rather than aspirin in patients who undergo hip fracture surgery, it is reasonable that more potent anticoagulants than aspirin should be used for this group of patients.

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8. Which pharmacological agents for VTE prophylaxis are the most cost-effective for Asian patients undergoing hip and knee arthroplasty?

Recommendation:

In patients without elevated risk for VTE, aspirin is a more cost-effective prophylactic agent than other agents.

Delegate vote: Agree 90.4%, Disagree 1.4%, Abstain 8.2% (Strong Consensus)

Justification:

A study by Mostafavi et al. compared the cost and health benefits of anticoagulation using warfarin or aspirin following TJA and demonstrated that the cost per quality-adjusted life-year (QALY) gained by aspirin was $24,506.20 at the age of 55 and $47,148.10 at the age of 85 following THA and $15,117.20 and $24,458.10 after TKA, which were higher than those of warfarin. They concluded that, in patients who did not have elevated PE risk, the use of aspirin provided higher QALYs and lower cost than warfarin in all ages in both THA and TKA (1).

A study from Schousboe et al. compared the cost-effectiveness of LMWH or 160 mg aspirin for VTE prophylaxis after total joint arthroplasty. For patients undergoing THA at the ages of 55 and 70, the costs per QALY gained for LMWH compared with aspirin were $315,000 and $1.4 million. At the age of 80 or 85 years, aspirin cost less and saved more QALYs than LMWH. For patients undergoing TKA at ages 55, 70, and 85, the costs per QALY gained with LMWH were $36,000, $112,000, and $448,000. They concluded that aspirin is

a cost-effective choice for VTE prophylaxis following THA for patients with no history of VTE. The preferred choice following TKA depends on age and is uncertain for those younger than 80 years old. (level II evidence) (2).

A study by Dawoud et al. compared 15 VTE prophylaxis strategies in elective THA with 12 VTE prophylaxis strategies in elective TKA. They concluded that a strategy consisting of LMWH for ten days, followed by aspirin for 28 days, was the most cost-effective for elective THA. A foot pump strategy followed closely by aspirin (low dose) was the most cost-effective for elective TKA (3).

Based on these three studies, it seems that aspirin is a cost-effective VTE prophylaxis agent and can be used safely in patients without a history of VTE who are at low risk for the development of VTE following hip or knee arthroplasty. Although these three studies did not investigate Asian patients, the Asia Pacific VTE consensus experts agreed that a similar recommendation could apply to Asian patients.

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9. In Asian patients, how long should the pharmacological prophylaxis be given for hip & knee arthroplasty and hip fracture surgery?

Recommendation:

Although the optimal duration of pharmacological prophylaxis remains inconclusive, the recommended minimum duration should be 10-14 days.

Delegate vote: Agree 83.6%, Disagree 9.6%, Abstain 6.8% (Strong Consensus)

Justification:

The NICE guideline, released in 2018, recommended pharmacologic prophylaxis for 28 days in THA, 14 days in TKA, and one month in hip fracture surgery (2).

The American Society of Hematology (ASH) guideline released in 2019 recommended extended antithrombotic prophylaxis over short-term antithrombotic prophylaxis for patients undergoing major surgery (not specific only to orthopedic surgery). Extended prophylaxis was considered as beyond three weeks (range: 19-42 days), and short-term prophylaxis was considered as up to 2 weeks (range: 4-14 days) (3).

The Scottish Intercollegiate Guidelines Network (SIGN) guideline released in 2010 recommended extended pharmacologic prophylaxis for orthopedic surgery (recommendation grade A). However, the optimal duration of extended prophylaxis is unclear. The benefit of post-discharge extended prophylaxis with low molecular weight heparin (LMWH) is higher in THA than TKA patients (4).

According to a systematic review (8 RCTs in THA, 1 RCT in TKA, and 1 RCT in hip fracture surgery) comparing prolonged-duration (21 days) with standard-duration (7 to 1- days) thromboprophylaxis, it demonstrated that, in THA, there were fewer symptomatic VTE, PE, nonfatal PE, DVT, asymptomatic DVT, and proximal DVT events than with standard-duration prophylaxis. In hip fracture surgery, patients who received prolonged prophylaxis had fewer symptomatic objectively confirmed VTE, DVT, proximal DVT, and distal DVT events than those who received standard-duration prophylaxis. However, in TKA, there were no statistically significant differences in any reported outcomes between prolonged-duration prophylaxis and standard-duration prophylaxis (5).

A prospective study by Nair et al. in 197 patients undergoing elective THA and TKA and having extended thromboprophylaxis for four weeks compared with a historical group of 795 patients with short-term thromboprophylaxis for only 7-11 days. Both groups had a 40-mg daily dose of LMWH (enoxaparin), and mechanical thromboprophylaxis with confirmed VTE as the primary efficacy endpoint. They concluded that extended thromboprophylaxis (4 weeks) was more effective than short-term prophylaxis (7-10 days) (6).

A study by Parvizi et al. showed that the highest prevalence of symptomatic VTE occurs one week after total joint arthroplasty. In detail, 81% occurred within three postoperative days, 89% within one postoperative week, and 94% within two postoperative weeks. They recommended to continue prophylaxis until the end of these periods (7).

In contrast, two recent two studies, Pedersen et al., demonstrated different outcomes. The first study in 2015, a retrospective review of all primary THA from the National Joint Registry of Denmark, n = 16,865, demonstrated that the 90-day risks of VTE were 1.1% (short), 1.4% (standard), and 1.0% (extended), yielding adjusted hazard ratios (aHRs) of 0.83 (95% CI, 0.52-1.31) and 0.82 (95% CI, 0.50-1.33) for short and standard versus extended treatment. The risk of major bleeding was 1.1% (short), 1.0% (standard), and 0.7% (extended), resulting in aHRs of 1.64 (95% CI, 0.83-3.21) and 1.24 (95%CI, 0.61-2.51) for short and standard versus extended thromboprophylaxis. They concluded that no difference in the risks of symptomatic VTE, VTE/death, or bleeding concerning thromboprophylaxis duration (8).

The second study in 2019, a retrospective study of all primary THA from the Nordic Arthroplasty Register Association (NARA) grouped all patients operated in Denmark and Norway, n = 55,540, divided into three groups: short (1–5 days), standard (6–14 days), and extended (≥15 days) duration of thromboprophylaxis. They demonstrated that the 90-day cumulative incidence of VTE was 1.0% for patients with standard treatment (9), 1.1% for those with short-term treatment (adjusted hazard ratio [aHR] of 1.1, 95% CI, 0.8–1.5) and 1.0% for those with extended treatment (aHR of 0.9, 95% CI, 0.8–1.2). The aHRs for major bleeding were 1.1 (95% CI, 0.8–1.6) for short and 0.8 (95% CI, 0.6–1.1) for extended vs. standard treatment. Patients with short and extended treatment had aHRs for death of 1.2 (95% CI, 0.8–1.8) and 0.8 (95% CI, 0.5–1.1) vs. standard treatment, respectively. Patients who started short treatment postoperatively had an aHR for the death of 1.8 (95% CI, 1.1–3.1) and absolute risk

difference of 0.2%, whereas patients who started short treatment preoperatively had an aHR for the death of 0.5 (95% CI, 0.2–1.2) and absolute risk difference of 0.3% compared with patients who had standard treatment with post- and preoperative start, respectively (9).

In conclusion, from these two studies, short duration prophylaxis had comparable effectiveness to extended duration prophylaxis in THA. However, these evidences were weak due to observational study designs from the National Joint Registry.

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10. What is the optimal dose, starting time, and duration of aspirin usage for VTE prophylaxis in Asian patients who undergo hip & knee arthroplasty?

Recommendation:

Low dose aspirin ranging from 81-162 mg/day is sufficient for VTE prophylaxis. However, the starting time of administration and duration of usage of aspirin remains inconclusive.

Delegate vote: Agree 97.3%, Disagree 0%, Abstain 2.7% (Strong Consensus)

Justification:

Several studies supported the use of low dose aspirin for VTE prophylaxis. The systematic review of Azboy et al. in 45 studies in three categories: <162 mg of aspirin as low dose, >162 mg of aspirin daily as high dose, and warfarin. The duration of aspirin prophylaxis we also defined three categories: <4 weeks, four weeks, and >4 weeks). In the low dose group, dosages of aspirin ranged from 75 mg daily to 160 mg daily. In the low dose group, two studies looked at Asian patients. These two studies were done in China, using aspirin 100 mg daily. Both studies demonstrated that aspirin 100 mg daily had a comparable effect for VTE prophylaxis as low molecular weight heparin (LMWH) (1, 2).

There were no significant differences in symptomatic pulmonary embolism, symptomatic deep vein thrombosis, 90-day mortality, or major bleeding between patients receiving low-dose or high-dose aspirin for the entire systematic review. Compared

with warfarin, there was also a higher risk of symptomatic deep vein thrombosis (DVT) with warfarin (1.68%, 95% CI, 1.1-2.8) compared to low-dose aspirin (0.52%, 95% CI, 0.2-1.5) (p=0.035). The studies included in this systematic review reported various durations of aspirin prophylaxis ranging from 14 days to 6 weeks. They found no significant difference between incidences of PE or DVT and the different durations of aspirin treatment examined (<4 weeks, four weeks, and >4 weeks) (3).

Three studies compared low dose aspirin with high dose aspirin directly in the same population. From both studies the study for the complication of VTE prophylaxis by Faour et al. in 2018, and 2019 (4, 5), the first study was done in TKA (TKA), retrospective design, including 5666 patients, low dose group received aspirin 81 mg twice a day (n=1,327), high dose group received aspirin 325 mg twice a day (n=4,339). Also, all patients received pneumatic compression stockings, the duration of treatment was 4-6 weeks. The incidence of VTE was 1.5% in the 325-mg group and 0.7% in the 81-mg group (p=0.02). Symptomatic DVT was 1.4% in the 325-mg aspirin compared with 0.3% for the 81-mg aspirin (p=0.0009). Regression model showed no correlation between aspirin dose and VTE incidence (OR, 1.03; 95% CI, 0.45-2.36; p=0.94) or DVT (OR, 0.50; 95% CI, 0.16-1.55; p=0.20). The incidence of PE was 0.2% in the high-dose aspirin group compared with 0.4% in the low-dose aspirin group (p=0.13). Bleeding was 0.2% in the 325-mg aspirin group and 0.2% in the 81-mg aspirin group (p=0.62), and 90-day mortality was similar (0.1%) between the groups (p=0.56) (4). The second retrospective study included 3,936 THA patients with low-dose aspirin 81 mg twice

a day (n=1,033), high-dose aspirin 325 mg twice a day (n=2,903) and 4- to 6-week duration of treatment. The 90-day incidence of symptomatic VTE was 1.0% in the 325 mg group and 0.6% in the 81-mg group (p=0.35). Symptomatic DVT incidence was 0.8% in the 325 mg group and 0.5% in the 81 mg group (p=0.49), and the incidence of symptomatic PE was 0.3% in the 325 mg group and 0.2% in the 81 mg group (p=0.45). Furthermore, bleeding occurred in 0.8% of the 325 mg group and 0.5% of the 81 mg group (p=0.75), and 90-day mortality was not different (0.1%) between the groups (p=0.75). After accounting for confounders, regression analyses showed no difference between aspirin doses and the 90-day incidence of symptomatic VTE (odds ratio [OR], 0.90; 95% CI, 0.29-2.85; p=0.85) or symptomatic DVT (OR, 0.96; 95% CI, 0.26-3.59; p=0.95) (5). In conclusion of these two studies, low-dose aspirin was not inferior to high-dose aspirin for the prevention of VTE after TKA and THA

From the study of Parvizi et al. in 2018, this prospective crossover study included 4,651 patients, a low dose group received aspirin 81 mg twice a day (n=1,459), high dose group received aspirin 325 mg twice a day (n=3,192), duration of treatment was four weeks. The incidence of venous thromboembolism of 0.1% (95% CI, 0% to 0.3%) in the 81 mg aspirin group (1 with deep venous thrombosis and 1 with pulmonary embolism) was not significantly different (p=0.345) from 0.3% (95% CI, 0.1-0.6) in the 325 mg aspirin group (7 with deep venous thrombosis and 5 with pulmonary embolism). The incidence of gastrointestinal bleeding or ulceration of 0.3% (95% CI, 0-0.5) in the 81 mg aspirin group was slightly, but not significantly (p=0.66), lower than the 0.4% (95% CI, 0.2%-0.6) in the 325 mg aspirin group. The

incidence of acute periprosthetic joint infection was 0.2% (95% CI, 0-0.4) in the 81 mg aspirin group compared with 0.5% (95% CI, 0.2-0.7) in the 325 mg aspirin group (p=0.28). The 90-day mortality rate was similar in both groups at 0.1% (95% CI, 0-0.2) in the 81 mg aspirin group and 0.1% (95% CI, 0-0.2) in the 325 mg aspirin group (p=0.78) (6).

In conclusion, low dose aspirin ranging from 81-162 mg/d is not inferior to high dose aspirin of 325-650 mg/d for VTE prophylaxis. The duration of aspirin usage has wide variation from 14 days to 6 weeks. However, the evidence available on the optimal time of administration and the optimal duration of aspirin usage for VTE prophylaxis is of limited quality and remains inconclusive.

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11A. Should the dose and duration of pharmacological VTE prophylaxis in Asian patients with standard VTE risk be adjusted from the recommended dose and duration by the American or European guidelines?

Recommendation:

There is evidence that a lower dose of the pharmacologic agent is effective, but there is limited evidence for the administration's timing. Therefore, a lower dose with delayed pharmacologic administration can apply in Asian patients with standard VTE risk.

Delegate vote: Agree 87.7%, Disagree 4.1%, Abstain 8.2% (Strong Consensus)

11B. Should the dose and duration of pharmacological VTE prophylaxis in Asian patients with elevated VTE risk be adjusted from the recommended dose and duration by the American or European guidelines?

Recommendation:

There is limited evidence that a lower dose and/or delayed administration of the pharmacologic agent is effective in Asian patients with elevated VTE risk. Therefore, the recommended dose and duration should apply in Asian patients with elevated VTE risk.

Delegate vote: Agree 89.0%, Disagree 5.5%, Abstain 5.5% (Strong Consensus)

Justification:

There is evidence which demonstrated that Asian patients have lower DVT prevalence than Caucasians. Bin Abd Razak et al. showed the prevalence of VTE without chemoprophylaxis in Singaporean patients who underwent TKA and mechanical prophylaxis alone. The prevalence of significant VTE is 0.82% (8/966 patients), which is significantly lower than Caucasians (1). Also, the mean body weight of Asian patients is lower than Caucasian. Fuji et al. found that the mean body weight of Japanese THA and TKA patients who participated in their study was approximately two-thirds of their Caucasian counterparts (2). They adjusted their DVT prophylaxis regimen by decreasing enoxaparin dose to 20 mg bid and confirmed that it is the proper regimen in Japanese patients.

Mihara et al. performed a retrospective study of DVT prophylaxis using low dose aspirin in 3,295 Japanese patients who underwent THA (3). The patients were divided into low-risk VTE group (n=3,077) and high-risk VTE group (n=218), Low-risk patients received aspirin (100 mg/day) for 28 days postoperatively. High-risk patients, such as those diagnosed with obesity and/or with a history of VTE, received anticoagulants (enoxaparin or edoxaban) for five days postoperatively, followed by 100 mg/day of aspirin for 28 days. They demonstrated that no VTE-related mortality. There was a low incidence of symptomatic DVT and PE (0.03%). There was no postoperative fatal bleeding or bleeding from any organ, such as gastrointestinal and cerebral hemorrhage. This study concluded that the hospital's risk-stratified protocol using low-dose aspirin or anticoagulants effectively prevented symptomatic

VTE. These results were better than those reported from Western countries (4).

There are two studies from China by Yi et al. and Zou et al. using aspirin 100 mg daily. Both studies demonstrated that aspirin 100 mg daily had a comparable effect for VTE prophylaxis as LMWH (4, 5).

Therefore, the usual dose and duration in hip or knee arthroplasty may not be necessary in standard risk VTE Asians due to the lower rate of VTE and lower body weight compared to Caucasians.

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