Comparing consensus guidelines on thromboprophylaxis in orthopedic surgery

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ABSTRACT

Background
Different guidelines exist regarding the prevention of venous thromboembolism (VTE) in orthopedic surgery.

Objectives
We aim to compare (inter)national guidelines and analyse their differences.

Methods
MEDLINE, the Cochrane Library and the internet were searched for guidelines on the prevention of VTE in orthopedic surgery. From these, we constructed a table comparing the different antithrombotic regimens during different orthopedic surgical and plaster cast treatments.

Results
Eleven guidelines from nine different countries and one international guideline were included. Few guidelines advise on thromboprophylaxis after plaster cast immobilization, (prolonged) arthroscopic surgery and isolated lower extremity trauma. Different opinions exist on the sole use of aspirin and mechanical prophylaxis and on the use of vitamin K antagonists after major hip and knee surgery.

Conclusion
Based on the same available literature, different guidelines recommend different thromboprophylactic regimens. Ideally, the grade of recommendation should be based on the same level of evidence world-wide. Whilst there is no agreement on the relevance of different endpoints (e.g. asymptomatic DVT), it is very difficult to reach consensus. Thromboprophylaxis guidelines should be reviewed and updated on a regular basis, because the evidence is evolving rapidly.
INTRODUCTION

Venous thromboembolism (VTE) is a serious complication of orthopedic surgery. Asymptomatic VTE is detected by means of venography in 10–40% of hospitalized patients and occurs in up to 40–60% of patients that undergo orthopedic surgery when no prophylaxis is used [1]. When thromboprophylaxis is administered, 1–10% of patients develop symptomatic VTE within the 3 months after surgery [1]. As many VTEs occur after discharge, orthopedic surgeons may have a falsely low perception of the rate of thrombosis in their practice. Understandably, orthopedic surgeons are concerned about complications such as major bleeding and wound infection associated with the use of pharmacological thromboprophylaxis. Why do surgeons have different views on the use of aspirin, heparin and vitamin K antagonists (VKA) when considering the same body of evidence? This article aims to compare both national and international guidelines on thromboprophylaxis, and to interpret their differences.

METHODS

PubMed, the Cochrane Library and the internet (using the Google search engine) were searched in February 2009 for various national and international guidelines on the prevention of VTE in orthopedic surgery. The following search terms were used: thrombosis, prophylaxis and guideline. Only guidelines considering orthopedic surgery were included. Different national medical associations’ websites were also searched. Only open access guidelines in English or German were included. It was not intended to search all countries in the world: we selected major European countries and a selection of countries from each continent, as well as the most well-known and most cited guidelines.

RESULTS

Eleven guidelines from the following associations were included: The American College of Chest Physicians (ACCP)[1], the American Academy of Orthopaedic Surgeons (AAOS) [2], the Cardiovascular Disease Educational and Research Trust (ICS) [3], the National Institute for Clinical Health and Excellence (NICE, United Kingdom) [4], the Scottish Intercollegiate Guidelines Network (SIGN) [5], Die Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF, Germany) [6], Sociedade Brasileira de Angiologia e Cirurgia Vascular (SBACV) [7], the South African Society of Thrombosis and Haemostasis [8], Medical Front International Limited (Japan) [9], the French Society
Table 1. Overview of guidelines on prevention of thrombo embolism

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<th>Intervention</th>
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VKA = vitamin K antagonist
RF= if risk factors are present
### Table 2. Comparison of grades of recommendation between guidelines

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<th>Grade</th>
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<td>RCTs: consistent results</td>
<td>RCTs: consistent results</td>
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<td>Review of RCTs</td>
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<tr>
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<td>Cohort: consistent results</td>
<td>RCTs: less consistent results</td>
<td>RCTs: low power</td>
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</table>

Australia/New Zealand, NICE, South Africa, Japan and Germany did not give grades of recommendation.
for Anaesthesiology and Intensive Care (SFAR) [10] and the Australia and New Zealand working party on the management and prevention of venous thromboembolism [11]. Table 1 summarizes the different regimens recommended by these guidelines. The grades of recommendation for the thromboprophylaxis regimens proposed are defined differently in the guidelines. The level of evidence for each grade also varies between the guidelines. An overview is provided in Table 2. Those guidelines not mentioned in Table 2 did not specify the level of evidence for their recommendations.

**Total hip arthroplasty (THA)**

Most guidelines agree on the use of mechanical prophylaxis as a possible additional antithrombotic measure to pharmacological thromboprophylaxis with either heparin, fondaparinux or VKA. The recommended duration of thromboprophylaxis varies from 7 to 42 days for heparin, and from 10 to 35 days for fondaparinux. Despite this, most guidelines do not advise about the optimal duration of thromboprophylaxis. The ACCP, ICS, SIGN, the French and the Brazilian guidelines, however, also support the use of mechanical devices without pharmacological prophylaxis in patients at a high risk of bleeding. The ICS states that Foot Impulse Technology (FIT) or Intermittent Pneumatic Compression (IPC) combined with Graduated Elastic Compression Stockings (GECS) represent an alternative to low-molecular-weight heparin (LMWH) (Grade A recommendation, Table 2). They can be used as long as tolerated and, thereafter, replaced by pharmacological prophylaxis for the proceeding post-operative 5 weeks. The ICS guidelines do not cite any data that compare IPC with pharmacological prophylaxis. FIT combined with GECS is probably superior to unfractionated heparin [12] and equivalent to LMWH [13,14] (Grade A). The SIGN guidelines state that foot pumps are more effective, while IPC is less effective in the prevention of proximal deep vein thrombosis (DVT) (Grade A). For this, they recommend the use of IPC in combination with GECS or foot pumps. The Japanese guidelines advise use of IPC in patients undergoing orthopedic surgery of the lower extremities without pharmacological prophylaxis. They report a lower incidence of VTE in the Japanese population due to a lower incidence of genetic abnormalities in clotting factors when compared with Western countries. Alternatively in Japan, low-dose unfractionated heparin can be used.

**Total knee arthroplasty (TKA)**

Most guidelines advise some form of pharmacological thromboprophylaxis after TKA, much like the recommendations for THA. Interestingly, the ACCP, ICS, SIGN, and the Brazilian and Japanese guidelines all recommend the sole use of mechanical prophylaxis as an alternative to pharmacological prophylaxis, whereas the other guidelines do not. This recommendation is based on five studies based on small sample sizes that show that IPC, started intra-operatively or immediately after surgery and continued until full
Comparing consensus guidelines on thromboprophylaxis in orthopedic surgery

Ambulation, is an effective means of thromboprophylaxis [1]. To date, the use of IPC alone has not been compared with combined thromboprophylaxis with IPC and either LMWH or adjusted-dose VKA in a randomized clinical trial (RCT). As the estimates of VTE protection by IPC are based on RCTs with small sample size, inconsistent results or major methodological weaknesses, mechanical prophylaxis received a lower grade of recommendation (Grade B). Furthermore, due to poor compliance, patient intolerance and the inability for treatment to be continued after hospital discharge, IPC is recommended as an alternative only to pharmacological thromboprophylaxis in patients at high risk of bleeding when pharmacological prophylaxis is not advisable. Due to the inferior efficacy, ACCP advises against the sole use of venous foot pumps (Grade A). The SIGN guidelines recommend GECS with or without IPC and foot pumps (Grade A). The ICS advises the use of IPC or FIT plus GECS as an alternative for pharmacological prophylaxis in TKA, but they state that more studies are needed (Grade B). Hip fracture surgery (HFS) HFS was not addressed in every guideline. Most of the guidelines advise the same regime as is recommended for THA. The French guideline and SIGN state that VKA should not be used as a first line prophylaxis in HFS for logistic reasons (such as monitoring), and because of a higher risk of bleeding associated with the use of VKA (Grade A). ACCP and the French guidelines prefer fondaparinux (Grade A) rather than LMWH (Grade B and C, respectively). The ACCP and the ICS advice the use of mechanical prophylaxis without pharmacological agents in the case of a high risk of bleeding (Grade A). The Australian/New Zealand guidelines, NICE and SIGN advise use of mechanical prophylaxis in addition to pharmacological prophylaxis.

Knee arthroscopy

Only five of the 11 guidelines examined actually addressed this type of surgery. Generally, thromboprophylaxis is only advised when concomitant risk factors are present [Grade A (Brazil), B (ACCP and ICS)]. Few data exist on prolonged arthroscopic procedures, such as anterior cruciate ligament reconstruction and arthroscopically assisted repair of tibia plateau fractures. Due to the longer operation time and more extensive surgery, the ACCP (Grade B) and the ICS guidelines advise use of LMWH prophylaxis, but do not provide recommendation on the duration of prophylaxis.

Plaster cast immobilization and isolated lower extremity injuries

Plaster cast immobilization is regarded as representing a moderate risk for thrombosis [1]. Thromboprophylaxis during plaster cast immobilization is only recommended by the German and the French guidelines. The German guidelines advise the use of pharmacological thromboprophylaxis in joint-immobilizing plaster casts, whereas the French guidelines advise starting prophylaxis in lower limb fractures (Grade B) and knee
injuries without fracture, irrespective of any risk factors present (grade D). With regard to isolated lower extremity injuries treated with or without operation and/or plaster cast immobilization, the ACCP guidelines advise not to give routine prophylaxis (Grade 1A). They state that it is uncertain whether thromboprophylaxis reduces clinically significant DVT or whether it is cost effective. The ICS guidelines advise LMWH if risk factors are present.

**Aspirin**

The AAOS, the SIGN and the Brazilian guidelines are the only ones to recommend aspirin as the sole measure of thromboprophylaxis (Grade B, A and A, respectively). The AAOS states that the presumed direct pathophysiologic link between DVT and pulmonary embolism (PE) has not been proven by clinical observation in joint replacement. Therefore, all studies investigating DVT rates using venography and compression ultrasonography (CUS) to assess asymptomatic thromboembolism as an endpoint are not regarded as relevant and are therefore not taken into account. To date, no RCT investigates the rate of (fatal) PE using LMWH, fondaparinux, VKA, mechanical devices or aspirin alone, because of the large number of patients needed. The 90-day non-fatal PE rate after total hip and knee surgery without prophylaxis is 0.93% and 0.41%, respectively, according to two register-based studies [15,16]. According to the AAOS, only the incidence of major bleeding under different prophylactic regimens can be retrieved from the literature, whereas the rate of PE cannot be assessed adequately. Based on two studies, aspirin is recommended because it causes less bleeding, although it does not reduce the risk of DVT [17,18]. When an elevated risk for PE is present, aspirin is not recommended. The ACCP and the French guidelines on the other hand advise clearly against the use of aspirin as the sole method of thromboprophylaxis (Grade A and B, respectively). The ACCP guideline states that aspirin is less effective than other thromboprophylactic regimens [19,20]. The efficacy of aspirin in preventing asymptomatic DVT (as detected by venography) has never been evaluated in an RCT.

**DISCUSSION**

**Agreements between guidelines**

THA, TKA and HFS All guidelines agree that heparin can be used for thromboprophylaxis in THA and TKA (Grade A). LMWH is the most intensively studied thromboprophylactic agent [1]. Pooled data from five large clinical trials [1] comparing adjusted dose warfarin thromboprophylaxis with LMWH among 2979 total hip replacement patients show that the respective rates of all DVT were 20.7% and 13.7% (P = 0.0002). Major bleedings occurred in 3.3% of the VKA recipients and 5.3% of the LMWH recipients (P = 0.002).
The pentasaccharide, fondaparinux, was approved by the American Food and Drug Association in 2001. Fondaparinux is regarded as an equal alternative to LMWH by all six guidelines developed from 2006 onward, except for the 2006 ICS guideline that gives a grade B recommendation for TKA because only one study was available at that time. The German guidelines are another exception, as they were developed in 2003. These appear to have been updated in 2008, but it is not clear whether new drugs were included. In HFS, heparin and fondaparinux are the most commonly recommended pharmacological antithrombotic agents. Major drawbacks of VKAs are logistic difficulties and the higher risk of bleeding, according to the French and SIGN guidelines (Grade A).

**Knee arthroscopy**

Thromboprophylaxis is only advised when risk factors are present [Grade A (Brazil), B (ACCP and ICS)]. Simple knee arthroscopy is associated with a low risk of thrombosis. Pooled data from prospective studies of knee arthroscopy reveal rates of 9% of asymptomatic DVT and 3% of asymptomatic proximal DVT using venography and 5% and 0.7%, respectively, when detected by CUS [1]. Two out of three RCTs on thromboprophylaxis following knee arthroscopy showed no significant difference in the incidence of VTE in patients treated with LMWH or placebo/GECS [1].

**Disagreements between guidelines**

THA and TKA VKAs are recommended in THA and TKA in seven out of 11 guidelines. The ICS prefers LMWH and fondaparinux above VKA in THA, because two large studies showed less efficacy and higher rates of major bleeding with VKA compared with LMWH [21,22]. Moreover, warfarin was identified as a major risk factor for readmission and fatal bleeding in national registries [23,24]. When a high bleeding risk is present in THA, the sole use of mechanical devices for thromboprophylaxis is recommended by five guidelines. In TKA, mechanical devices without pharmacological prophylaxis are recommended in five guidelines, irrespective of the bleeding risk. However, the level of evidence for the sole use of mechanical devices is lower than that for pharmacological prophylaxis. Due to a lower incidence of genetic abnormalities of clotting factors compared with Western countries, Japan reports having a lower incidence of VTE, justifying their use of mechanical devices alone.

**Plaster cast immobilization and isolated lower extremity injuries**

Only four guidelines give advice on thromboprophylaxis for patients with plaster cast immobilization and isolated lower extremity injuries. Most guidelines recommend against the use of thromboprophylaxis, although some guidelines make exceptions for patients with risk factors, fractures or joint immobilizing casts. Recent evidence suggests that thromboprophylaxis is effective in reducing the rate of VTE during immobilization
of the lower extremities [25,26]. In a recent meta-analysis [25], 1456 patients from six randomized trials were included. In four studies venography was used to detect asymptomatic DVT and two studies used ultrasonography, while positive results were confirmed by venography. The mean rate of VTE reduced from 17.1% to 9.6% with the use of LMWH. The frequency of bleeding did not seem to increase with LMWH. A 2009 Cochrane review [26] reported an incidence of VTE ranging from 4.3% to 40% in patients who had a leg injury that had been immobilized in a plaster cast or a brace for at least 1 week and who received no prophylaxis or placebo. This number was significantly lower in patients who received daily subcutaneous injections of LMWH during immobilization (event rates ranging from 0% to 37%; odds ratio 0.49).

**Aspirin**

The main issue leading to conflicting recommendations on the use of aspirin is whether there is a relationship between asymptomatic DVT detected by venography or CUS and clinically important VTE (symptomatic DVT and PE). The ACCP, for instance, states that there is a strong relationship between asymptomatic DVT and symptomatic DVT and PE [27]. In contrast, the AAOS concludes that there is no convincing evidence linking asymptomatic DVT to clinically relevant symptomatic DVT and PE. The ACCP seems to put a greater emphasis on the effective reduction of VTE, and the AAOS seems more concerned with bleeding complications. Both VTE and bleeding risk are, of course, very important considerations when selecting thromboprophylaxis. The mix of hematologists and orthopedic surgeons on the specific committees seems a possible explanation for the different views. Another consideration is that a high grade of recommendation can be given against the use of aspirin as a thromboprophylactic agent when the results of high quality RCTs based on asymptomatic VTE are taken into account [20,28–31]. When the evidence from these trials is discarded, only a grade B recommendation in favour of aspirin remains.

**The future**

In order to avoid major disagreements between guidelines, several aspects need to be addressed. First, it is necessary to agree on one universal definition for grades of recommendation for different regimens. The grade of recommendation should ideally be based on the same level of evidence. Second, it will be very difficult to reach a consensus whilst there is no agreement on the relevance of different endpoints (e.g. asymptomatic DVT). Finally, guidelines should be updated continuously as new evidence becomes available. Still, local differences will exist due to differences in healthcare systems, availability of drugs or devices, and regional variations in risk factors for the development of VTE. Newer oral antithrombotic drugs such as direct thrombin and factor Xa inhibitors are not yet included in the abovementioned guidelines, although numerous studies
have been conducted since 2002. Recently, both dabigatran (an oral thrombin inhibitor) and rivaroxaban (an oral Xa inhibitor) have registered in Europe for thromboprophylaxis in orthopedic surgery patients.

In summary, based on the same available evidence, different guidelines advise different regimens of thromboprophylaxis following orthopedic procedures. Thromboprophylaxis guidelines should be reviewed and updated on a regular basis, so that all available evidence is assessed and to make sure that patients receive the highest quality and safest care possible.
REFERENCES


Comparing consensus guidelines on thromboprophylaxis in orthopedic surgery


