Viewpoint Article

Symptoms and clinical relevance: A dilemma for clinical trials on prevention of venous thromboembolism

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Summary
The outcomes of thromboprophylactic trials have been debated for decades. Recently, the 9th edition of the American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines based their strong recommendations only on patient-important outcomes. Practically, symptoms were considered the crucial element. Consequently, studies that primarily aimed at reducing venographic thrombi were considered less pertinent than studies that focused on symptomatic thrombosis. In the present viewpoint, we challenge the argument that “symptomatic” and “clinically relevant” are interchangeable. In particular, the case is made that asymptomatic events may be clinically relevant and that asymptomatic venographically detected thrombosis is a clinically relevant surrogate outcome for fatal pulmonary embolism.

Keywords
Prophylaxis, pulmonary embolism, thrombosis, surgery

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Received: September 4, 2012
Accepted after major revision: December 23, 2012
Prepublished online: January 24, 2013

doi:10.1160/TH12-08-0627

Introduction
Pulmonary embolism (PE) is the third most frequent cause of cardiovascular death, after myocardial infarction and stroke. The annual incidence of venous thromboembolism (VTE), which includes PE and its parent condition deep-vein thrombosis (DVT), is about one per thousand, and a previous estimation suggests that VTE is responsible for about 150,000 to 200,000 deaths every year in the United States (1). A substantial proportion of these deaths follow some kind of surgery and/or hospital stay, and many events are fatal before diagnosis can be made and therapy initiated. All these facts and the associated economic burden (2) underline the need for effective prophylactic regimens, as recently recalled by the US Surgeon General (3). Unfractionated heparin and, more recently, low-molecular-weight heparin (LMWH), fondaparinux and new oral anticoagulants have proved both efficacious and safe in reducing the number of postoperative DVT and PE and are widely used according to Consensus recommendations (4, 5). The efficacy of prophylactic regimens can be assessed by venous ultrasonography (US) (with or without pulsed doppler and color-coding), and ascending venography. Unfortunately, US turned out to be quite insensitive to postoperative, often distal (below the knee) and non-occlusive DVT (6, 7). Despite its invasive character, discomfort, and costs, venography has thus become the mandatory screening method in clinical trials to assess the efficacy of pharmacological or mechanical prophylaxis (8). In the present viewpoint, we challenge the argument that “symptomatic” and “clinically relevant” are interchangeable. In particular, the case is made that asymptomatic events may be clinically relevant and that asymptomatic venographically detected thrombosis is a clinically relevant surrogate outcome for fatal PE.

The outcome dilemma in thromboprophylactic trials
Ideally, the endpoint of trials on VTE prophylaxis should be quite frequent, reliably measurable, and clinically relevant. The ultimate aim of thrombosis prevention is to avoid death, which would make this outcome the best candidate. Fortunately enough, death is rare in this setting, which would result in very large-scale studies. Furthermore, overall postoperative mortality is influenced by factors not related to VTE. This “background noise” reduces the specificity of the study intervention and amplifies the sample size required to demonstrate efficacy of thromboprophylaxis. Similarly, the outcome “death due to VTE” has a limited diagnostic accuracy because PE is not always diagnosed before death and because autopsy rates are steadily decreasing in most countries. On the other hand, studies targeting clinically overt events carry the disadvantages of the low sensitivity and specificity of clinical signs of VTE (particularly in postoperative bedridden patients) and of the need for large numbers of patients due to the low number of events. For all these reasons, the outcome “postoperative venographic DVT” has been used. It is, however, almost invariably...
recently, the American college of chest physicians (ACCP) methodologist felt that the approach of evidence-based guidelines requires the distinction between "patient-important and surrogate outcomes". According to them, the first eight editions of the antithrombotic guidelines failed to properly recognise the implications of a surrogate widely used in thrombosis prevention trials - asymptomatic, screening detected thrombosis. The core methodologists of the 9th ACCP guidelines panel felt that the use of this surrogate generates major problems in making the trade-off between patient-important outcomes (symptomatic thrombosis and serious bleeding). For instance, if an intervention increases serious bleeding by 10 events in 1,000 patients, but reduces asymptomatic thrombosis by 100 in 1,000, what is the net benefit? Indeed, the relative importance of events such as serious bleeding, DVT and PE, is very difficult to establish. This led the 9th iteration of the ACCP guidelines to focus on symptomatic events only (10). This choice, however, implies that symptomatic is equivalent to clinically relevant (or patient-important) while asymptomatic would mean clinically irrelevant, which deserves be challenged.

The example of thromboprophylaxis following major orthopaedic surgery

The risk of postoperative VTE extends beyond hospital stay while prevention is usually stopped after 7-10 days or the latest at the time of hospital discharge. Thus, the proportion of after-discharge PE was found to be at least 25% in a large survey on more than 19,000 patients who underwent general surgery (11). The effect of prolonging pharmacological prophylaxis with LMWH for up to five weeks following surgery was tested in five studies of patients undergoing total hip replacement (THR) using venography as outcome measurement (Table 1) (12-16). A statistically significant, more than 40% reduction (from 29.0% to 17.5%) of total venographic DVT was observed in the group of patients given LMWH beyond hospital discharge compared to those given placebo and in the largest one, statistical significance was also reached for the reduction of proximal DVT (7). A meta-analysis extended these findings by demonstrating that the overall risk reduction for the symptomatic events in these five trials and in one additional study that used a clinical ("symptomatic") outcome with confirmatory venography was 50% (from 3.3% with extended thromboprophylaxis to 1.6% with placebo) (Table 1) (17). These findings clearly suggest a continuum from asymptomatic DVT to fatal PE through symptomatic DVT, asymptomatic and symptomatic PE (18). By contrast, four large cohort studies and one randomised study of patients who underwent total hip replacement (THR) and were followed 4-5 weeks after discharge while prophylaxis had been stopped at discharge suggest that the risk of clinically overt VTE during follow-up is low (less than 2% symptomatic events in more than 3,700 patients) in such patients provided LMWH or warfarin was administered during the 9-15 days of hospital stay (19-21). In the latter studies, objective diagnostic confirmation was obtained only in patients with clinical symptoms or signs of DVT or PE, a policy which raises the issues of "what is symptomatic?" and "what is clinically relevant?".

More recently, the RECORD development program (22-25) of the novel oral anticoagulant rivaroxaban, a direct factor Xa inhibitor, for preventing VTE in patients undergoing major orthopaedic surgery was able to show parallel diminutions of all VTE (mainly venographic, asymptomatic DVT), major VTE, and symptomatic VTE (Table 2). In both the rivaroxaban and the comparator arm, there was a convincing continuum from symptomatic VTE and all-cause mortality to major VTE and total (mainly asymptomatic) VTE.

What is symptomatic?

Pain, swelling and cyanosis are cardinal symptoms of DVT. However, their sensitivity and specificity average only 50%. Furthermore in patients who underwent THR in the previous days or weeks, the specificity of these clinical signs and symptoms is further reduced because pain and/or swelling are likely to be present in the vast majority of such patients. Dyspnoea, chest pain and death are typical symptoms of PE. While death is undoubtedly clinically relevant and poses no diagnostic problem, dyspnoea and chest pain are highly non-specific and quite frequent symptoms in elderly patients, especially in the postoperative period.

These soft definitions of signs and symptoms of VTE raise the question of arbitrary screening, preferentially in more plaintive patients or by more anxious doctors, the so-called referral or diagnostic bias. This reduced accuracy and validity of clinically overt...
events as study outcomes primarily affect the generalizability or external validity of the study results. On the other hand, the internal validity of the comparison of different interventions would not be affected as long as the study design is methodologically sound.

What is clinically relevant?

Death represents for sure a symptomatic and clinically relevant event. Fortunately enough, it is a rare event following surgery, even following THR, to be a useful outcome in efficacy trials.

On the other hand, is a painful calf-vein thrombosis more clinically relevant than an asymptomatic iliac-vein obstruction? Or a small peripheral PE with pleuritic chest pain more relevant and dangerous than a painless, non-occlusive central embolus?

The goal of VTE prophylaxis is primarily to prevent fatal PE without inducing too many side-effects, and, secondarily, to prevent the late post-thrombotic syndrome (PTS). Nobody will seriously doubt that both fatal PE and severe PTS are very unlikely to occur in the absence of (venographic) DVT as evidenced from the event-free follow-up of patients undergoing THR and had no phlebographically-verified DVT at discharge (26).

Clinical outcomes and study sample size

Studies targeting clinical endpoints are likely to be undersized and underpowered, especially if two active drugs are being compared. Thus, to demonstrate a 40% reduction in a symptomatic event, e.g. fatal PE or symptomatic DVT following major orthopaedic surgery, from 2% to 1.2%, at least 10,000 patients are required to have 80% chance of achieving conventional statistical significance. For overall mortality, the sample size would be 20,000. In case of non-inferiority studies, these numbers would be further increased. Thus, from a patient perspective, the venographic outcome can bring an answer to the question with fewer patients included in a trial.

Outcomes and regulatory agencies

Clinical research in the prevention of VTE is mainly driven by the clinical development of new pharmacological compounds aimed at improving the results of the currently used regimens. Regulatory agencies have issued methodological requirements for drug registration. The recent guidelines of the European Agency for Medicinal Products (EMEA) set the stage for future research in the prevention of VTE. For superiority studies it is required that the new compound shows its superiority for proximal DVT and/or any (proximal plus distal) DVT, symptomatic objectively confirmed PE and death from all causes including PE. For non-inferiority studies more sensitive outcomes are required, such as a composite end point consisting of proximal DVT, symptomatic objectively confirmed non-fatal PE and VTE-related deaths.

Table 2: Results of the RECORD development program of rivaroxaban for thromboprophylaxis after major orthopaedic surgery.

<table>
<thead>
<tr>
<th>Study</th>
<th>Total VTE* n/n (%)</th>
<th>Major VTE† n/n (%)</th>
<th>Symptomatic VTE and all-cause mortality n/n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban arm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECORD 1</td>
<td>18/1595 (1.1)</td>
<td>4/1668 (0.2)</td>
<td>10/2209 (0.5)</td>
</tr>
<tr>
<td>RECORD 2</td>
<td>17/854 (2.0)</td>
<td>6/961 (0.6)</td>
<td>5/1228 (0.4)</td>
</tr>
<tr>
<td>RECORD 3</td>
<td>79/824 (9.6)</td>
<td>9/908 (1.0)</td>
<td>8/1220 (0.7)</td>
</tr>
<tr>
<td>RECORD 4</td>
<td>67/965 (6.9)</td>
<td>11/1122 (1.2)</td>
<td>12/1256 (0.8)</td>
</tr>
<tr>
<td>Total</td>
<td>181/4238 (4.3)</td>
<td>40/4677 (0.9)</td>
<td>35/6183 (0.6)</td>
</tr>
<tr>
<td>Comparator arm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECORD 1</td>
<td>58/1558 (3.7)</td>
<td>33/1678 (2.0)</td>
<td>15/2224 (0.7)</td>
</tr>
<tr>
<td>RECORD 2</td>
<td>81/859 (9.3)</td>
<td>49/962 (5.1)</td>
<td>20/1229 (1.6)</td>
</tr>
<tr>
<td>RECORD 3</td>
<td>166/878 (18.9)</td>
<td>24/925 (2.6)</td>
<td>26/1239 (2.1)</td>
</tr>
<tr>
<td>RECORD 4</td>
<td>97/959 (10.1)</td>
<td>15/1020 (1.5)</td>
<td>21/1508 (1.4)</td>
</tr>
<tr>
<td>Total</td>
<td>402/4254 (9.4)</td>
<td>121/4585 (2.6)</td>
<td>82/6200 (1.3)</td>
</tr>
</tbody>
</table>

* Total VTE (venous thromboembolism) refers to all thromboembolic events but mainly consists of asymptomatic venographically-detected DVT (screening). † Major VTE consists of proximal DVT, non-fatal PE and VTE-related death. All numbers refer to the treatment duration pool analysis. For details refer to the original publications.

Conclusions

- **Symptomatic does not necessarily mean clinically relevant:** a symptomatic outcome may be without clinical relevance whilst an asymptomatic outcome may be clinically highly pertinent.
- In thromboprophylactic trials, venographic DVT correlates with symptomatic events and can be assessed more reliably. US might probably be used as an alternative to venography in situations in which proximal DVT is more frequent, such as in THR, but a consensus remains to be reached between specialists and regulatory agencies and recent data casts doubt about the accuracy of this method for screening purposes (27).
- Finally, haemorrhage should also be considered for evaluating the net effect of thrombosis prophylaxis but efficacy and safety outcomes should be comparable, e.g. in terms of mortality and/or morbidity. In other words, mortality-adjusted thromboembolic and bleeding outcomes should be developed for useful comparisons of thromboprophylactic regimens.
- The patient perspective, the requirements of the regulatory agencies and the guidelines are clearly different. These three perspectives need be reconciled before new large thromboprophylactic trials are initiated.

Conflicts of interests

Henri Bounameaux reports receiving consulting fees and lecture fees from Bayer Healthcare, Daichi Sankyo, Pfizer, Boehringer-Ingelheim and Sanofi-Aventis. Giancarlo Agnelli reports receiving...
consulting fees from Bayer Healthcare, Boehringer-Ingelheim, and Daichi Sankyo and lecture fees from Bayer Healthcare, Bristol-Myers Squibb, and Sanofi-Aventis.

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References