Mandatory contrast-enhanced venography to detect deep-vein thrombosis (DVT) in studies of DVT prophylaxis: upsides and downsides

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Summary
The introduction of venography into patient care was a major advance because it was the first accurate method for the diagnosis of DVT. Compression ultrasound has since become the preferred test for patients with suspected DVT because, unlike venography, it is simple, non-invasive and widely available. Venography has facilitated the development and approval of new anticoagulants and remains widely used as an efficacy outcome in trials of venous thromboembolism prevention. Most thrombi detected by screening venography are, however, small and unimportant for patients. In order to calculate the trade-off between an asymptomatic thrombus and a bleed we require an estimate of the number of asymptomatic thrombi that must be prevented to avoid a patient-important thrombus. A credible estimate of this ratio is not available. Therefore when used as a measure of efficacy in trials of thromboprophylaxis, venography has limitations for comparing the relative effects of alternative antithrombotic agents on outcomes important to patients.

Keywords
Deep-vein thrombosis, venous thrombosis, prophylaxis

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Venography as a diagnostic test for suspected (symptomatic) venous thrombosis

Less than 50 years ago, patients with suspected deep-vein thrombosis (DVT) were diagnosed on clinical grounds without the aid of objective diagnostic testing. Reports that many patients with fatal venous thromboembolism (VTE) were not diagnosed ante-mortem (1-3) and that only about one-half of patients with a clinical suspicion of DVT had DVT (4) challenged the accuracy of clinical diagnosis.

The uptake of venography to diagnose DVT was slow, both because its use challenged a time-honoured clinical approach, and because the test was not widely available. Clinicians accepted the presence of a persistent intraluminal filling defect on contrast venography as being diagnostic of DVT, and therefore the need to treat such patients with anticoagulants to prevent thrombus progression and reduce the risk of complications (pulmonary embolism [PE] and the post-thrombotic syndrome). Clinicians questioned, however, the validity of a normal venogram, particularly when this result contradicted their clinical judgment. They were ultimately convinced when a study demonstrated that it is safe to withhold anticoagulants in patients with suspected venous thrombosis who had a normal venogram (at 3 month follow up, 2 out of 160 patients with negative venogram suffered from a DVT [odds ratio [OR] 1.3%; 95% confidence interval [CI]: 0.15% to 4.4%]) (5). Thus, by introducing venography into routine clinical practice, many patients suspected of having DVT were spared unnecessary treatment with anticoagulants.

Venography is not without its problems. Apart from being invasive, expensive, and sometimes painful, in 10-20% of patients its interpretation is impossible for technical reasons (e.g. inability to cannulate a vein, deep veins of the leg are not filled adequately) (6). In virtually all diagnostic imaging departments, venography has been replaced by venous compression ultrasound (CUS) in patients with symptoms suspicious for DVT.

CUS does not always reliably detect distal (calf vein) DVT and some small non-occlusive proximal (popliteal and/or more proximal vein) thrombi that are routinely identified by venography (7). This limitation is not problematic because if initial CUS is normal and remains normal when repeated in about 7 days (8, 9), or if an initial whole leg CUS is negative (10), it is safe to withhold treatment. At the same time, however, these findings highlight that the vast majority of calf vein and small non-occlusive proximal vein thrombi, which comprise a large proportion of post-operative venous thrombi, are unimportant for patients (11).

Venography as an outcome measure in clinical trials for the prevention of VTE

The most important remaining role of venography, and the main subject of this review, is to improve the efficiency of clinical trials
evaluating prophylactic agents in patients at high risk of VTE. Over the years, several tests have been used to screen high risk patients for DVT, including radio-labelled fibrinogen uptake scanning (RFUS), impedance plethysmography (IPG), CUS and venography. Although venography is the most invasive and least convenient, it has prevailed as the method of choice because it proved to be more specific than RFUS (particularly after hip surgery) and more sensitive than IPG and CUS.

Most thrombi detected by screening venography are small, distal, and asymptomatic, but a small majority is large and can be complicated by major and even fatal PE. Routine screening venography to detect and treat DVT before it causes fatal PE is inappropriate because it is probably less effective than primary prophylaxis, and certainly not cost-effective.

On the other hand, screening venography has provided valuable information about the epidemiology and distribution of DVT in high-risk medical and surgical patients, and has played important roles in informing dose selection and the clinical approval process for new anticoagulants. Phase 2 dose-finding studies would be much more challenging without the use of screening venography and phase 3 studies that led to the approval of low molecular weight heparins, fondaparinux and the new oral anticoagulants (rivaroxaban, dabigatran, and apixaban) would have been prohibitively expensive without availability of screening venography to assess efficacy outcome.

Despite its importance in anticoagulant development, screening venography has major limitations when used as a surrogate for patient-important VTE (12, 13). This limitation of screening venography is illustrated by the following hypothetical example of choosing among prophylactic agents evaluated in phase 3 trials. If one antithrombotic agent “A” is more effective than another agent “B” for reducing asymptomatic venous thrombosis, but A causes more bleeding it would be inappropriate to conclude that “A” is preferred over “B”. Such a recommendation could only be made if: 1) “A” caused no more bleeding than “B” and was associated with a reduced risk of objectively diagnosed symptomatic DVT; or 2) the relative patient-importance (disutility) of an asymptomatic venographically-detected thrombosis and a bleeding episode were known.

Support for this viewpoint comes from the impact of the clinical trials comparing the then established anticoagulant enoxaparin, with the then new anticoagulant, fondaparinux, in patients undergoing major hip or knee surgery. The program comprised four randomized trials and included 7,344 patients undergoing major hip or knee surgery (14). The primary efficacy outcome was total VTE up to day 11, defined as DVT detected by mandatory venography plus symptomatic DVT and PE, and the main safety outcome was major bleeding. Meta-analysis of the four trials showed that total VTE rates were more than halved (6.5% vs 13.5%, p<0.001) in patients assigned fondaparinux with no reduction in symptomatic events (0.6% vs 0.4%, p=0.25) and at the cost of a 1.0% absolute increase in the rate of major bleeding (2.7% vs 1.7%, p=0.008) (14). Fatal PE was rare in both groups (0.06% and 0.08% for fondaparinux and enoxaparin, respectively) (Table 1). Despite the large reduction in asymptomatic venous thrombosis, guideline panels and regulatory agencies did not recommend fondaparinux over enoxaparin. Further, fondaparinux did not replace enoxaparin for elective hip or knee surgery patients in clinical practice.

Why did such a marked difference in the rate of asymptomatic thrombosis detected by venography not convince guideline panels, regulators and practicing physicians to change practice? Because the assessment of superiority of one prophylactic anticoagulant over another requires trading off of any putative benefits against increases in bleeding risk. The failure of the differences in asymptomatic events between the two groups to alter clinical practice provides tacit acknowledgment that the majority of asymptomatic events are not important for patients. Why else would a 50% relative risk reduction and a 7% absolute risk reduction in venographic events be trumped by a 1% absolute increase in major bleeding?

Table 1: Efficacy and safety outcomes of fondaparinux compared with enoxaparin thromboprophylaxis during treatment period (up to day 11) in major orthopaedic surgery. Event rates were obtained from reference 14*.

<table>
<thead>
<tr>
<th>Events</th>
<th>Fondaparinux, Events/total</th>
<th>Enoxaparin, Events/total</th>
<th>ARR†</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venographic DVT</td>
<td>174/2677 (6.5%)</td>
<td>363/2698 (13.5%)</td>
<td>7.0%</td>
<td>0.001</td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>22/3603 (0.60%)</td>
<td>15/3608 (0.40%)</td>
<td>-0.20%</td>
<td>0.25</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>2/3621 (0.06%)</td>
<td>3/3599 (0.08%)</td>
<td>0.02%</td>
<td>0.99</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>15/3616 (0.40%)</td>
<td>21/3621 (0.60%)</td>
<td>0.20%</td>
<td>0.41</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>96/3616 (2.7%)</td>
<td>63/3621 (1.7%)</td>
<td>-1.0%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

ARR, absolute risk reduction; DVT, deep-vein thrombosis; PE, pulmonary embolism. *Event rates include events occurring up to the day of venography, typically performed between day 5 and 11. †A negative sign indicates a higher event rate in the fondaparinux arm than enoxaparin arm.

The difficulty of estimating a fixed ratio between asymptomatic (venographically-detected) DVTs and symptomatic VTEs

Why, for more than 30 years, have we accepted mandatory venography as a surrogate for patient important events and are now rejecting it. Because published data and a more recent analysis fail to support the widely accepted contention that there is a fairly consistent ratio of 10:1 between asymptomatic DVT detected by mandatory screening venography and symptomatic venous thrombosis. In the analysis by Quinlan et al., estimates of the ratio of asymptomatic events that will result in a patient-important event, if left undetected, varied from 3.2:1 to 24:1 (15). As pointed out by Bounameaux and Agnelli (16), "symptomatic thrombi"
detected by venography might be incidental; but this potential bias would lead to over-reporting of symptomatic thrombosis. The second source of potential bias is that treatment of asymptomatic thrombosis detected by mandatory venography might reduce the rate of subsequent symptomatic events and so lead to under-reporting of symptomatic events. To overcome this second source of bias we performed an analysis of the 14 studies that compared the newer anticoagulants (fondaparinux, dabigatran, apixaban and rivaroxaban) with enoxaparin in major hip and knee surgery in which all of the symptomatic and fatal events were reported within the time frame of performing mandatory venography. In these analyses, the ratio of asymptomatic DVT detected by mandatory venography to symptomatic DVT ranges from 2.5:1 to over 100:1 (unpublished data). Based on these data we concluded that asymptomatic DVT detected by mandatory venography could not be used to estimate tradeoffs of improved efficacy against increase in bleeding when comparing two anticoagulants. Several factors, including the indirectness of the methods used for assessment and the lack of agreement of what constitutes a positive venogram, which are discussed elsewhere (12), are responsible for the wide variations in estimates of the probability that an asymptomatic event will lead to a patient-important event.

The recommendation that anticoagulant prophylaxis should be used in most high-risk patients is derived from clinical trials with low-dose heparin, which showed that these anticoagulants reduce the relative risk of fatal PE and non-fatal symptomatic VTE by about 70% compared with no prophylaxis (17). Since these earlier publications, surgical techniques have improved and the baseline risk of post-operative fatal PE has decreased. Despite differences in the incidence of asymptomatic venographic thrombosis in contemporary clinical trials in elective major orthopaedic surgery comparing newer anticoagulants with enoxaparin (18-28), the post-operative mortality, assessed at the time of venography is very low and similar among groups (Table 2). Thus, in comparisons between two anticoagulants, the absolute difference in symptomatic events is less than 1 in 100 and in total mortality is in the order of 1 or 2 per 1,000. In such comparisons, although reductions in asymptomatic event rates that trend in the same direction as reductions in symptomatic events are reassuring, the uncertain and (probably) negligible importance of asymptomatic thrombosis makes it inappropriate to combine asymptomatic and symptomatic events when trading off a putative increase in efficacy with an increase in bleeding.

Trading-off thrombosis prevention against causing bleeding

Even if we were to establish a consistent ratio of asymptomatic events prevented to symptomatic events prevented – or if we were to directly measure symptomatic events – making a trade-off with symptomatic bleeding would be challenging because of lack of reliable information regarding the importance to the patient and health care system of a post-operative VTE and a post-operative bleed. Post-operative symptomatic VTE can be complicated by the post thrombotic syndrome or chronic thromboembolic pulmonary hypertension whereas post-operative wound bleeding may require surgical drainage, can delay hospital discharge, and has the potential to prolong convalescence and to lead to wound infection and long-term joint dysfunction (29). Unfortunately reliable quantitative information on these post-operative complications is not available.

Conclusions

The use of screening venography to detect asymptomatic thrombosis in high-risk medical and surgical patients has made phase 2 clinical dose-finding studies with new anticoagulants possible. Screening venography has also increased the feasibility of performing phase 3 trials designed to compare new anticoagulants with low-molecular-weight heparin and has been critical for the

Table 2: Pooled estimates of efficacy and safety of newer anticoagulants, rivaroxaban, dabigatran and apixaban compared with enoxaparin thromboprophylaxis during treatment period in major orthopedic surgery trials. Event rates were obtained from references 17–27*.

<table>
<thead>
<tr>
<th>Events</th>
<th>Rivaroxaban, events/total</th>
<th>Enoxaparin, events/total</th>
<th>ARR*</th>
<th>Rivaroxaban, events/total</th>
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<th>Enoxaparin, events/total</th>
<th>ARR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venographic DVT</td>
<td>159/4248 (3.74%)</td>
<td>356/4264 (8.35%)</td>
<td>4.61%</td>
<td>951/4806 (19.79%)</td>
<td>462/2828 (16.33%)</td>
<td>-3.45%</td>
<td>253/4057 (6.24%)</td>
<td>403/4030 (10.0%)</td>
<td>3.76%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic VTE</td>
<td>28/6132 (0.46%)</td>
<td>68/6138 (1.11%)</td>
<td>0.65%</td>
<td>45/6403 (0.70%)</td>
<td>29/3687 (0.79%)</td>
<td>0.08%</td>
<td>22/5835 (0.38%)</td>
<td>26/5824 (0.45%)</td>
<td>0.069%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td>8/4809 (0.17%)</td>
<td>15/4813 (0.31%)</td>
<td>0.15%</td>
<td>10/6403 (0.16%)</td>
<td>1/4144 (0.024%)</td>
<td>-0.13%</td>
<td>8/5835 (0.14%)</td>
<td>4/5824 (0.07%)</td>
<td>-0.068%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>24/6183 (0.39%)</td>
<td>13/6200 (0.21%)</td>
<td>-0.18%</td>
<td>81/6429 (1.26%)</td>
<td>48/3719 (1.29%)</td>
<td>0.03%</td>
<td>42/5770 (0.73%)</td>
<td>54/5755 (0.94%)</td>
<td>0.21%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ARR, absolute risk reduction; DVT, deep-vein thrombosis; PE, pulmonary embolism. *Event rates include events occurring up to the day of venography, typically performed on days 5-15 in patients undergoing total knee replacement, and between days 32 and 40 in those undergoing total hip replacement. †A negative sign indicates that event rate in new anticoagulant arm was higher than the enoxaparin comparator arm.
success of the development and approval of new anticoagulants. Differences in venographic rates are reassuring when they trend in the same direction as the symptomatic events, but as evidenced by the fondaparinux comparisons with enoxaparin, they are discounted by even modest, but statistically significant increases in bleeding. Screening venography may continue to have a role in the future if new anticoagulants are introduced to compete with the current impressive array because phase 2 dose-finding studies not only inform dosing for VTE prevention but also for other indications (e.g. atrial fibrillation). On the other hand, the decisions to choose one antithrombotic agent over another for VTE prevention should rely on adequately powered (very large) studies using patient-important outcomes - the alternative, modeling studies, will always leave appreciable uncertainty.

Conflicts of interest
None declared.

References