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Section Editors: Marc Fisher, MD, and Kennedy Lees, MD

## The PREVAIL Trial and Low-Molecular-Weight Heparin for Prevention of Venous Thromboembolism

Keith W. Muir, MD, FRCP

Patients with stroke are at high risk for venous thromboembolism. Studies of the natural history in the era before widespread use of antiplatelet agents or physical preventive measures reported an incidence of deep vein thrombosis (DVT) of over 50% within the first days.<sup>1</sup> A lower incidence might be expected with more aggressive routine acute treatment, including early use of antiplatelet agents, early mobilization, and graduated compression stockings, but the combined control groups of randomized, controlled trials (RCTs) predominantly undertaken in the 1990s still reported an incidence of 37% when DVT was specifically sought.<sup>2</sup> Older studies found the incidence of pulmonary embolism (PE) after stroke to be 10% to 20% and to account for up to 10% of all fatalities (including cases in ambulant patients).<sup>3</sup> In contrast, symptomatic PE is consistently rarely reported in RCTs in stroke, occurring in just 0.7% of randomized subjects in the control group of trials comparing heparins with antiplatelet therapy.<sup>4</sup> However, clinical recognition of PE remains poor. Half of all PEs in one series presented as sudden death.<sup>5</sup> Clinically unrecognized PE is also common, with up to 50% of surgical patients with proximal DVT having abnormal ventilation-perfusion lung scans.<sup>6</sup> Even if PE is rare, postthrombotic syndrome resulting from venous valvular incompetence causes pain, swelling, and skin changes, including varicose eczema, and may affect over 20% of those with symptomatic DVT within 2 years.

The effectiveness of low-dose unfractionated heparin for prevention of VTE was established in the late 1970s, predominantly in surgical patients but also in stroke.<sup>7</sup> The superiority of low-molecular-weight (LMW) heparins over unfractionated heparin in other clinical settings has also been established with advantages including more predictable dose effects, easier administration, and less risk of thrombocytopenia. Two previous RCTs comparing LMW heparin with antiplatelet therapy reported reduction in symptomatic VTE events,<sup>8,9</sup> and in a systematic review of 6 previous RCTs, LMW heparins or heparinoids were associated with greater reduction in DVT or PE than unfractionated heparin (5000

U twice a day in 5 of the 6 RCTs, only one of which adjusted dose by coagulation parameters), with an OR of 0.52 (95% CI: 0.56 to 0.79).<sup>10</sup> Too few symptomatic PEs occurred in any of the RCTs to be significant as an end point in itself, but odds were reduced with heparin compared with control. The PREVAIL trial,<sup>11</sup> recently published by David Sherman and colleagues, adds considerable further data to this question, randomizing 1762 nonambulant patients with stroke.

The PREVAIL investigators chose its primary end point to be the incidence of VTE at day 14. Patients with ischemic stroke with leg weakness of at least 2 on the National Institutes of Health Stroke Scale (NIHSS) were randomized to receive either 5000 U unfractionated heparin twice a day or the 40 mg of the LMW heparin enoxaparin daily starting within 48 hours of the event and continued for 10 days. Treatment allocation was not blinded, but the end points were objectively defined by routine venography (in 82% of subjects) and/or compression ultrasound in all subjects, and results were independently reviewed blind to treatment allocation.

Not surprisingly, enoxaparin was associated with a significant relative risk reduction in VTE events compared with unfractionated heparin of 43%, representing approximately 8 fewer events per 100 patients treated (number needed to treat for benefit: 13). Those with more severe strokes, defined in the trial as NIHSS score  $\geq 14$ , were twice as likely to have VTE but were also at higher risk of bleeding complications, and the absolute risk among less severe strokes (NIHSS  $< 14$ ) in the enoxaparin group remained high at 8.3%.

The PREVAIL trial addressed a specific (and logical) end point of VTE, but has to be viewed on the background of the failure of either unfractionated or LMW heparins in a number of RCTs to reduce the end points of death or dependence, or stroke recurrence, and the main trial publication does not fully detail the results with respect to these. The failure to find a benefit for these end points has

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led many clinicians to avoid heparin in acute stroke in favor of antiplatelet therapy alone. Whether the findings of PREVAIL should influence clinical practice depends on a judgment regarding the clinical importance of VTE prevention in itself and an assessment of the safety of the interventions.

First, were the events prevented by enoxaparin treatment in PREVAIL of clinical importance? The statistical difference in VTE events in PREVAIL resulted from prevention of asymptomatic DVTs. Both PE (7 of 1335 in total [0.5%]) and symptomatic DVT (5 of 1335 [3.7%]) were rare, although there were fewer of both of these events in the enoxaparin group (one PE and one symptomatic DVT versus 6 and 4, respectively, for unfractionated heparin). However, location of the clot rather than whether it causes symptoms is of greater importance, and enoxaparin was associated with significantly fewer proximal as well as distal DVTs (relative risk: 0.47, 95% CI: 0.31 to 0.72). Assumptions about the small risk of isolated distal DVT are based on the natural history after hip or knee replacement surgery, where DVTs generally start in calf veins and only approximately one in 6 progresses to involve proximal veins.<sup>6</sup> It is unknown whether the risk of extension of distal DVTs after stroke is the same, obvious differences being rapid mobilization after orthopedic procedures with accordingly reduced risk of incident DVT,<sup>6</sup> in contrast to more prolonged immobility in many patients with stroke. Measuring the final outcome at day 14 ensures better completeness of follow-up, but this early time point will not capture the full risk of VTE.

Second, was treatment safe? Major bleeding complications were rare in PREVAIL with an incidence of just over 1%. Symptomatic intracerebral hemorrhage was documented in <1% (4 of 877) of subjects in the enoxaparin group. A slight excess of major extracranial bleeds with enoxaparin was seen (7 events compared with none in the unfractionated heparin group), but there was no significant difference in events considered to represent “clinically important hemorrhage” (a post hoc definition including a composite of bleeding events). No differences in all-cause mortality were evident, and the total mortality rates (12% at day 90) were somewhat lower than previous studies would suggest should be expected given the trial population. These event rates were also on a background of more than 90% of patients receiving antiplatelet therapies.

The PREVAIL results indicate that LMW heparin in doses appropriate for VTE prophylaxis is reasonably safe even when used acutely after moderately severe ischemic stroke and on a background of modern antiplatelet therapy. Any additional hazard over unfractionated heparin is greatly outweighed by superior efficacy. Enoxaparin (or equivalent LMW heparin) should therefore replace unfractionated heparin for VTE prevention after stroke.

The more difficult issues are whether all patients require VTE prophylaxis, when it should start, and for how long treatment is necessary; PREVAIL does not answer these issues completely.

As noted, VTE is an important cause of morbidity and mortality after stroke and clinical recognition remains poor.

The high incidence of VTE in PREVAIL (11% proximal DVT or PE within 14 days in the control arm) indicates that modern stroke unit care (presumably, but not explicitly, including early mobilization and mechanical VTE preventive treatment in the trial) and antiplatelet therapy by themselves are insufficient. It is also very difficult to identify a low-risk group within the PREVAIL population. Leg weakness predominantly defines VTE risk after stroke,<sup>1,12</sup> and subgroup analyses identified no difference in benefit irrespective of age, sex, stroke severity, or obesity. It seems unlikely therefore that it will be possible to easily define a risk score that could target treatment any better than the trial entry criteria achieved. So long as there is no significant increase in hazard, prevention of VTE is a worthwhile goal and preventive treatment for all who fulfill PREVAIL entry criteria should be considered. The failure of heparins in general to reduce death or dependence, or stroke recurrence, is insufficient reason not to consider treatment; many other interventions in stroke do not affect these end points and given its low incidence, a very large trial indeed would be required for prevention of PE to be reflected in a significant reduction in all-cause mortality.

Could the bleeding risks of heparin be reduced by later introduction of preventive treatment? PREVAIL began treatment within 48 hours and on average just over 1 day after a stroke. Symptomatic intracerebral hemorrhage rates are lower when heparin is started more than 24 hours after onset compared with under 24 hours,<sup>2,8</sup> and there was no difference in observed benefit when the subgroups starting treatment within, or after, 24 hours were compared. However, most bleeding events were related to extracranial hemorrhage and whether this is also reduced by deferred treatment is not known.

PREVAIL trial treatment was mandated for only 10 days and there are no data reported on interventions thereafter. The initial difference in VTE risk appears to have been maintained up to day 90, although beyond day 14, end point events were not routinely sought by investigation. Is 10 days of treatment sufficient? Even if the majority of DVTs start in the days immediately after the stroke,<sup>13</sup> 10% of patients develop a new DVT during rehabilitation.<sup>14</sup> Incident PE continues throughout the poststroke period, at least up to 120 days.<sup>5</sup> Continued prophylaxis so long as immobility persists seems clinically logical, albeit not supported by specific evidence. Studies on the long-term safety and efficacy of LMW heparins would therefore be welcome.

The PREVAIL findings significantly advance the case for routine use of prophylactic-dose LMW heparin in immobile patients for VTE prevention after stroke. As is ever the case with heparin, further questions remain to be addressed and there is scope for further trials.

## Disclosures

None.

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