Low-Molecular-Weight Heparins or Heparinoids Versus Standard Unfractionated Heparin for Acute Ischemic Stroke (Cochrane Review)

Carl Counsell, MD; Peter Sandercock, FRCP

Objectives
A systematic review of the trials directly comparing low-molecular-weight heparins (LMWH) or heparinoids with unfractionated heparin (UFH) in people with acute confirmed or presumed ischemic stroke.

Search Strategy
We searched the Cochrane Stroke Group trials register and MedStrategy (1995). We also contacted pharmaceutical companies. Date of most recent search: May 2001.

Selection Criteria
Randomized trials comparing heparinoids or LMWH with standard UFH in people with acute ischemic stroke. We included only trials in which treatment was started within 14 days of stroke onset.

Data Collection and Analysis
The 2 reviewers independently selected studies for inclusion, assessed trial quality, and extracted the data.

Main Results
We included 5 trials involving 705 people. Four trials compared a heparinoid (danaparoid), and 1 compared an LMWH (enoxaparin) with standard UFH (Figures 1 and 2). Overall, 55/414 (13%) of the patients allocated danaparoid or enoxaparin had deep vein thrombosis (DVT) compared with 65/291 (22%) of those allocated UFH. This reduction was significant (odds ratio [OR] 0.52, 95% CI 0.56 to 0.79). However, the number of more major events (pulmonary embolism, death, intracranial or extracranial hemorrhage) was too small to provide a reliable estimate of more important benefits and risks. No data on recurrent stroke or functional outcome in survivors were available.

Implications for Practice
Clinicians who, despite the lack of evidence of overall benefit from routine anticoagulants in patients with acute ischemic stroke, still wish to use some form of anticoagulant regimen in selected patients with acute ischemic stroke should bear in mind the following: (1) The criteria to identify those few patients that might benefit from UFH, LMWH, or heparinoid have not been defined by these data. (2) Although LMWH and heparinoids appear to be more effective at preventing DVT (and possibly also pulmonary embolism) than UFH, their relative safety and cost-effectiveness compared with UFH have not been established in patients with acute stroke.

Implications for Research
Further, very large-scale trials may be worthwhile comparing (1) aspirin alone with aspirin plus low-dose LMWH (or heparinoid) in individuals at particularly high risk of DVT and PE, and (2) a more aggressive LMWH (or heparinoid) regimen with UFH and with aspirin only in certain categories of patients, eg, those with a cardiac embolic source. These trials should measure disability and recurrent stroke as well as venous thromboembolism and major hemorrhages. Given the lack of evidence for the routine use of any anticoagulant regimen in acute ischemic stroke and the evidence in favor of using aspirin, further trials comparing only heparinoids or LMWH with UFH would be hard to justify.

Reviewers’ Conclusions
LMWH or heparinoid appear to decrease the occurrence of DVT compared with standard UFH, but there are too few data to provide reliable information on their effect on other important outcomes, including death, intracranial hemorrhage, and functional independence.
The full text, data tables, results, analyses, and reference lists of this article are available in the Cochrane Library. The full text article should be cited as: Counsell C, Sandercock P. Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke. Results expressed as Peto odds ratio (OR) with a fixed-effects model. OR <1 suggests low-molecular-weight heparins or heparinoid superior to unfractionated heparin. Effects on deep vein thrombosis. (Figure 01.01.00. Counsell C, Sandercock P. Low-Molecular-Weight Heparins or Heparinoids Versus Standard Unfractionated Heparin for Acute Ischaemic Stroke [Cochrane Review]. In: The Cochrane Library, Issue 4, 2001. Oxford: Update Software. MetaView © Update Software, Oxford.)

### Table 1: Deep venous thrombosis during scheduled treatment period

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto OR (95% CI Fixed)</th>
<th>Test for heterogeneity chi-square df=3 p=0.27</th>
<th>Test for overall effect z=2.53 p=0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dumas 1994</td>
<td>13 / 89</td>
<td>17 / 90</td>
<td>0.74 (0.34, 1.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haglukken 1992</td>
<td>19 / 119</td>
<td>5 / 27</td>
<td>0.84 (0.27, 2.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinke 1988</td>
<td>5 / 156</td>
<td>6 / 26</td>
<td>0.30 (0.06, 1.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turpie 1992</td>
<td>4 / 45</td>
<td>13 / 42</td>
<td>0.29 (0.08, 0.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95%)</td>
<td>41 / 309</td>
<td>41 / 105</td>
<td>0.52 (0.31, 0.86)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2: Symptomatic intracranial haemorrhage or haemorrhagic transformation of the infarct

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto OR (95% CI Fixed)</th>
<th>Test for heterogeneity chi-square df=3 p=0.41</th>
<th>Test for overall effect z=3.19 p=0.002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dumas 1994</td>
<td>1 / 88</td>
<td>2 / 98</td>
<td>0.50 (0.05, 5.02)</td>
<td></td>
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</tr>
<tr>
<td>Haglukken 1992</td>
<td>2 / 118</td>
<td>0.27</td>
<td>0.68 (0.10, 4.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinke 1988</td>
<td>0 / 56</td>
<td>0.26</td>
<td>0.00 (0.00, 1.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turpie 1992</td>
<td>1 / 46</td>
<td>1.42</td>
<td>0.00 (0.00, 1.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95%)</td>
<td>4 / 308</td>
<td>3 / 188</td>
<td>0.90 (0.19, 4.90)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Systematic review of trials comparing heparinoids or low-molecular-weight heparins with standard unfractionated heparin in people with acute ischemic stroke. Results expressed as Peto odds ratio (OR) with a fixed-effects model. OR <1 suggests low-molecular-weight heparins or heparinoid superior to unfractionated heparin. Effects on deep vein thrombosis. (Figure 01.01.00. Counsell C, Sandercock P. Low-Molecular-Weight Heparins or Heparinoids Versus Standard Unfractionated Heparin for Acute Ischaemic Stroke [Cochrane Review]. In: The Cochrane Library, Issue 4, 2001. Oxford: Update Software. MetaView © Update Software, Oxford.)

Figure 2. Systematic review of trials comparing heparinoids or low-molecular-weight heparins with standard unfractionated heparin in people with acute ischemic stroke. Results expressed as Peto odds ratio (OR) with a fixed-effects model. OR <1 suggests low-molecular-weight heparins or heparinoid superior to unfractionated heparin. Effects on symptomatic intracranial hemorrhage or hemorrhagic transformation of the infarct. (Figure 01.06.00. Counsell C, Sandercock P. Low-Molecular-Weight Heparins or Heparinoids Versus Standard Unfractionated Heparin for Acute Ischaemic Stroke [Cochrane Review]. In: The Cochrane Library, Issue 4, 2001. Oxford: Update Software. MetaView © Update Software, Oxford.)
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