Venous Thromboembolism After Acute Ischemic Stroke
A Prospective Study Using Magnetic Resonance Direct Thrombus Imaging

J. Kelly, BSc, MRCP; A. Rudd, FRCP; R.R. Lewis, MD, FRCP; C. Coshall, MSC; A. Moody, FRCR, FRCP; B.J. Hunt, MD, FRCP, FRCPath

Background and Purpose—We prospectively evaluated the prevalence and clinical risk factors for venous thromboembolism (VTE) after acute ischemic stroke using magnetic resonance direct thrombus imaging, a highly accurate noninvasive technique that directly visualizes thrombus.

Method—102 unselected patients with AIS receiving standard prophylaxis with aspirin and graded compression stockings (GCS) were sequentially recruited, underwent regular clinical assessments, and were screened for VTE.

Results—The prevalence of all VTE, proximal deep vein thrombosis (PDVT), and pulmonary embolism (PE) after 21 days were 40%, 18%, and 12%, increasing to 63%, 30%, and 20% in patients with Barthel indices (BI) of ≤9 2 days after stroke (BI-2 ≤9). Clinical deep vein thrombosis and PE occurred in 3% and 5% overall; half these events were overlooked by the attending team. The true incidence of clinical events is probably higher because the natural history of subclinical PDVT was modified by screening and anticoagulation. BI-2 ≤9 or nonambulatory status 2 days after stroke were the clinical factors most strongly associated with subsequent VTE on univariate analysis. Odds ratios for any VTE and PDVT for BI-2 ≤9 versus >9 were 8.3 (95% CI, 2.7 to 25.2) and 8.1 (95% CI, 1.7 to 38.3) on multivariable analysis.

Conclusion—BI ≤9 or nonambulatory status around the time of admission identifies a subgroup of acute ischemic stroke patients at very high risk for VTE in whom the current strategy of thromboprophylaxis may be inadequate. Future thromboprophylactic studies should focus on the patients at high risk defined in this study. (Stroke. 2004;35:2320-2326.)

Key Words: magnetic resonance imaging ■ stroke, acute ■ stroke, ischemic ■ thromboembolism ■ venous thrombosis

Half of the patients with acute hemiparetic stroke not receiving venous thromboprophylaxis had predominantly subclinical deep vein thrombosis (DVT) develop within 14 days of onset in early studies, a prevalence similar to that after major orthopedic surgery.1 Low-dose heparin thromboprophylaxis has since become standard in many high-risk groups based on evidence of a reduction in clinically apparent pulmonary embolism (PE) or overall mortality or both. However, although a 14-day course of low-dose unfractionated heparin significantly reduced death and recurrent stroke at 2 weeks, it did not alter death or disability at 6 months in the International Stroke Trial (IST).2 Although guidelines differ,3-5 in the UK heparin is no longer routinely recommended after acute ischemic stroke (AIS),3 with standard thromboprophylaxis comprising aspirin and graded compression stockings (GCS).5

However, the true incidence of DVT (clinical and subclinical) in patients with AIS receiving aspirin/GCS and, hence, the effectiveness of this strategy are unknown. Recent studies suggest that clinical venous thromboembolism (VTE) after AIS now occurs in only 2% to 3% of patients receiving this regime.2,6 However, underascertainment is likely because dysphasia, hemianesthesia, and obtundation make underdiagnosis or misdiagnosis of VTE problematic, and follow-up was only 10 to 14 days, despite fatal PEs being most common 2 to 4 weeks after stroke.7

We aimed to evaluate the effectiveness of standard thromboprophylaxis with aspirin/GCS after AIS by prospectively investigating for subclinical and clinical VTE using magnetic resonance direct thrombus imaging (MRDTI). This issue is important because PE is potentially preventable, yet the absolute risk of fatal PE in the first month after stroke has been 1% to 2% in recent years,7 corresponding to hundreds of thousands of deaths annually worldwide.

Patients and Methods
After ethical approval, inpatients at St. Thomas’ Hospital with AIS were prospectively and consecutively recruited over 21 months...
within 7 days of onset, irrespective of the degree of neurological impairment. Exclusion criteria were primary intracerebral or subarachnoid hemorrhage, nonambulatory before admission, moribund on admission, ongoing anticoagulant treatment or prophylaxis, contraindications to MRDTI, implanted lower limb metal, and consent/assent not available. All patients underwent imaging and infarcts were subtyped according Bamfords criteria. The following stroke severity measures were recorded: age on admission, ongoing anticoagulant treatment or prophylaxis, contraindications to MRDTI, implanted lower limb metal, and consent/assent not available. All patients underwent imaging and infarcts were subtyped according Bamfords criteria.8 The following stroke severity measures were recorded: age on admission, ongoing anticoagulant treatment or prophylaxis, contraindications to MRDTI, implanted lower limb metal, and consent/assent not available. All patients underwent imaging and infarcts were subtyped according Bamfords criteria. The following stroke severity measures were recorded: age on admission, ongoing anticoagulant treatment or prophylaxis, contraindications to MRDTI, implanted lower limb metal, and consent/assent not available. All patients underwent imaging and infarcts were subtyped according Bamfords criteria.8 The following stroke severity measures were recorded: age on admission, ongoing anticoagulant treatment or prophylaxis, contraindications to MRDTI, implanted lower limb metal, and consent/assent not available. All patients underwent imaging and infarcts were subtyped according Bamfords criteria. The following stroke severity measures were recorded: age on admission, ongoing anticoagulant treatment or prophylaxis, contraindications to MRDTI, implanted lower limb metal, and consent/assent not available. All patients underwent imaging and infarcts were subtyped according Bamfords criteria.8 The following stroke severity measures were recorded: age on admission, ongoing anticoagulant treatment or prophylaxis, contraindications to MRDTI, implanted lower limb metal, and consent/assent not available. All patients underwent imaging and infarcts were subtyped according Bamfords criteria.8

The prevalence of any VTE, PDVT, and PE were 40.2%, 17.7%, and 11.8% (Table 1). Corresponding figures in patients with severe stroke (BI-2 ≤ 9) were 63% (P = 0.0001), 29.6% (P = 0.001), and 20.4% (P = 0.005). Mean ages in those with versus without VTE were 74.3 (SD, 9.2) versus 67.2 (SD, 12.7; P = 0.003). VTE was equally distributed between sexes.

All but 3 (7%) patients with VTE were identifiable on initial imaging, although distribution and extent often changed subsequently. In hemiparetic stroke, unilateral lower limb DVT affected the paretic leg in all but 1 case, although bilateral DVT occurred in 8 (22%) patients with clear bilateral images. Eighteen of 40 (45%) lower limb DTVs were proximal, with 10 extending to the popliteal vein and 8 extending to the femoral vein. Two cases of isolated pelvic DVT occurred (2% of all patients; 5% of all VTE). Observation of the natural history was limited to cases of untreated asymptomatic below-knee DVT (Figure 1). Over 2 weeks, popliteal extension occurred in 3 of 15 (20%), 7 (47%) remained unchanged, and regression or resolution occurred in 5 (33%).

### Statistical Analysis

Univariate associations between stroke severity measures as binary variables and outcomes (VTE, PDVT, and PE) were investigated using the χ² and Fisher exact tests, as appropriate. Student t test was used to examine the relationship between age as a continuous variable and VTE. Unadjusted univariate logistic regression models were used to examine associations between outcomes and binary stroke severity measures and other clinical variables. Multivariable logistic regression models investigated associations between outcomes, BI, and other significant variables on univariate analysis (except urinary incontinence and leg paresis, because these are subitems on the BI). Given the relatively small absolute number of patients with VTE, we used the heuristic that a maximum of 1 independent variable was permissible in each category over and above the reference category per 5 outcome successes per model. Hence, for models of any VTE, all clinical variables of interest were included, whereas for PDVT, binary variables BI and age were fixed in all models because of strong a priori associations with VTE with 1 additional factor serially added. For PDVT, outcomes shown for BI and age are derived from a model in which BI, age, and malignancy were entered (malignancy was chosen as the third variable in view of the strength of association with PDVT on univariate analysis).

### Results

#### Patient Characteristics

In this study, 102 AIS patients were recruited. Mean age was 70.1 (SD, 11.9); 47 (46%) were male, 86 (84%) were white, and 10 (10%) were black Caribbean. Thirty-one (30%) had total anterior circulation infarction, 27 (27%) had partial anterior circulation infarction, 11 (11%) had posterior circulation infarction, and 32 (31%) had lacunar infarction. One patient could not be classified. A history of stroke occurred in 22 (22%), VTE occurred in 2 (2%), malignancy occurred in 6 (6%), atrial fibrillation (AF) occurred in 24 (24%), diabetes occurred in 25 (25%), ischemic heart disease occurred in 16 (16%), and hypertension occurred in 57 (56%). Two died within 7 days and underwent postmortem examinations. One hundred underwent initial MRDTI, of whom 78 (78%) underwent repeat imaging. Six (3%) distal lower limb segment images on the nonparetic side were of poor quality but were included because isolated contralateral DVT after stroke is rare. Mean follow-up was 21.0 days (SD, 5.9).

#### Prevalence, Distribution, Natural History, and Symptoms of VTE

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Recognized clinical DVT and PE (Figure 2) occurred in 1% and 3% of all patients. A further 2% and 2% had unrecognized clinical DVT and PE, so that clinical DVT and PE occurred in 3% and 5%. All clinical events occurred in patients with severe stroke, in whom corresponding figures were 2% and 6%, 4% and 4%, and 6% and 9%. Two patients died of PE (overall mortality from PE: 2%; 4% in severe stroke). Hence, half of all clinical events were recognized by the attending team; half were unrecognized.

**Associations Between Binary Stroke Severity Measures, Clinical Variables, and VTE**

BI-2≤9 was the stroke severity measure most strongly associated with major VTE (PDVT and PE) on univariate analysis, with odds ratios (OR) for PDVT and PE of 9.7 (95% CI, 2.1 to 44.8; *P* = 0.004) and 12 (95% CI, 1.5 to 97.1; *P* = 0.02), compared with BI-2>9 (Table 2). Corresponding figure for nonambulatory status on day 2 were 7.3 (95% CI, 1.6 to 33.6; *P* = 0.01) and 9.2 (95% CI, 1.1 to 74.3; *P* = 0.04) compared with nonambulatory status. Hence, BI was selected as the preferred marker of stroke severity in multivariable modeling. Age older than 70, total anterior circulation infarction, leg paresis, incontinence, malignancy, and AF were also significantly associated with one or more outcomes on univariate analysis. In addition to BI-2≤9 and nonambulatory status, the following factors were significantly associated with PE on univariate analysis: malignancy (OR, 9.7; 95% CI, 1.7 to 55.1; *P* = 0.01) and atrial fibrillation (OR, 4.0; 95% CI, 1.2 to 13.9; *P* = 0.03).

On multivariable analysis (Table 3), stroke severity was strongly associated with any VTE (OR, 8.3; 95% CI, 2.7 to 25.2; *P* < 0.0001) and PDVT (OR, 8.1; 95% CI, 1.7 to 38.3; *P* = 0.008), whereas age was associated with any VTE (OR, 2.9; 95% CI, 1.1 to 7.8; *P* = 0.04).

**Discussion**

This is the first study investigating clinical *and* subclinical VTE in AIS patients receiving aspirin/GCS prophylaxis and shows a surprisingly high overall 40% incidence. We have also shown the BI or ambulatory status around the time of admission allows early stratification into subgroups at low and high VTE risk. Although aspirin/GCS prophylaxis is probably adequate if BI-2>9 or if ambulatory, it may be inadequate if BI-2≤9 or if nonambulatory. The 30% preva-
The prevalence of PDVT if BI-2 ≤ 9 is among the highest ever recorded in a high-risk group. In comparison, a recent meta-analysis showed that only 2.9% of venographically screened patients undergoing major orthopedic surgery developed PDVT, yet ongoing research further to improve orthopaedic thromboprophylactic regimes indicates the more proactive paradigm in these patients.

This is the first study to evaluate subclinical PE after AIS, but the prevalence has probably been underestimated because we altered the natural history of subclinical PDVT by screening and anticoagulation. Left untreated, clinical PE would be expected to occur in ~40% of these cases.

That most patients with VTE developing could be identified on initial imaging is concordant with data from previous studies showing that most DVTs develop in the first week. Unilateral DVT affected the paralyzed side in all but 1 case, although it was bilateral in 22%, consistent with previous findings. No previous studies have investigated for isolated pelvic DVT after stroke, which was uncommon. Observation of the natural history of DVT was restricted to patients with untreated isolated below-knee DVT, in whom proximal extension occurred in 20% over the next 2 weeks.

The 1% and 3% incidence of clinically recognized DVT and PE is concordant with data from previous studies in AIS patients receiving aspirin and GCS. Although underascertainment has long been suspected, ours is the first study definitively to demonstrate it, with clinical events overlooked as often as they were recognized. Again, these figures are an underestimate for the reasons discussed.

BI-2 and day 2 ambulatory status were the severity measures most strongly associated with VTE on univariate analysis, more so than the motricity index. BI-2 was slightly superior to nonambulatory status because it was more strongly associated with major VTE, so it was selected as the representative stroke severity measure for further analysis.

### TABLE 2. Unadjusted Univariate Associations Between VTE, Stroke Severity Measures, and Other Clinical Factors Assessed 2 Days After Stroke Using Logistic Regression Models

<table>
<thead>
<tr>
<th>Variable</th>
<th>Any VTE</th>
<th>PDVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (n=47)</td>
<td>0.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Age &gt;70 (n=53)</td>
<td>3.7</td>
<td>2.1</td>
</tr>
<tr>
<td>Barthel ≤9 (n=54)</td>
<td>10</td>
<td>9.7</td>
</tr>
<tr>
<td>Nonambulatory (n=60)</td>
<td>15.3</td>
<td>7.3</td>
</tr>
<tr>
<td>Motricity index ≥33 (n=30)</td>
<td>4.9</td>
<td>4.</td>
</tr>
<tr>
<td>Total anterior circulation infarcts (n=31)</td>
<td>3.5</td>
<td>5</td>
</tr>
<tr>
<td>Partial anterior circulation infarcts (n=27)</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Posterior circulation infarcts (n=11)</td>
<td>0.3</td>
<td>—</td>
</tr>
<tr>
<td>Lacunar infarcts (n=32)</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Leg paresis (n=76)</td>
<td>5.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Incontinence* (n=36)</td>
<td>3.9</td>
<td>3.7</td>
</tr>
<tr>
<td>Malignancy (n=6)</td>
<td>3.2</td>
<td>5.4</td>
</tr>
<tr>
<td>Atrial fibrillation (n=24)</td>
<td>3.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Diabetes (n=25)</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypertension (n=57)</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>Lacunar infarcts (n=32)</td>
<td>0.4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; IE, persistent or occasional incontinence or catheterized.

*0 or 1 on the urinary continence item of the Barthel index.

### TABLE 3. Multivariable Logistic Regression Models of VTE, Stroke Severity, and Other Clinical Variables Assessed 2 Days After Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Any VTE</th>
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</thead>
<tbody>
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<td>8.3</td>
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<td>0.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Malignancy (n=6)</td>
<td>2.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Atrial fibrillation (n=24)</td>
<td>1.5</td>
<td>2.0</td>
</tr>
</tbody>
</table>

For PDVT, age >70 and Barthel ≤9 were fixed in all models with 1 additional variable serially added.
immobility. However, other studies have failed to confirm this association. The powerful association between BI 2≤9, day 2 ambulatory status, and subsequent VTE has, to our knowledge, not previously been demonstrated. We have shown that early paralysis is a less important predictor of VTE than ambulatory status and BI.

Age older than 70, malignancy, total anterior circulation infarction, AF, and urinary incontinence or leg paresis on day 2 were also associated with VTE on univariate analysis, although less so than BI and ambulatory status. Although the association between malignancy, age, and VTE in unselected patients is well-recognized, no consistent associations have emerged between various comorbidities and DVT after stroke in previous studies.

Stroke severity was the overwhelmingly important factor independently associated with VTE on multivariable analysis, with the only other significant association being between age older than 70 and any VTE (OR, 2.9; 95% CI, 1.1 to 7.8). Substitution of ambulatory status for BI in the multivariable analysis produced similar results. PE was not included because the small numbers precluded simultaneous analysis with >2 variables. However, bivariate analysis of BI/age revealed an OR for PE if BI 2≤9 of 13.9 (1.7 to 116; P=0.02), whereas bivariate analysis of BI/malignancy revealed an OR for PE if malignancy of 6.9 was present (1.1 to 43.5; P=0.04). These data should be viewed cautiously given the wide confidence intervals. No other variables associated with VTE on univariate analysis had an independent effect on multivariable analysis, although the relatively small sample size limits the certainty of this conclusion.

This is one of the first studies using MRDTI as the diagnostic standard. This novel technique detects methemoglobin in clot, providing a positive image of thrombus without the need for intravenous contrast, unlike other imaging modalities that have identified thrombus either as a filling defect or in terms of surrogates. MRDTI is noninvasive, allows simultaneous imaging of the legs and chest, and is highly accurate, with a 98% sensitivity and 96% specificity for DVT demonstrated in a recent study when compared with a composite standard of venography and ultrasound. Because venography is invasive and ultrasound only moderately sensitive for asymptomatic DVT, we felt MRDTI to be an optimal imaging technique for use in this study, although clinical use might be limited by availability.

Our management policy for subclinical DVT was based on the following premises: nonextending below-knee DVT is associated with an incidence of clinically important PE of ≤1% if cardiorespiratory reserve is adequate; untreated subclinical PDVT is associated with a ≥10% risk of fatal PE; the 3-month risk of fatal PE in treated PDVT is 0.4%; 10 days of full-dose low-molecular-weight heparin (LMWH) after AIS causes an excess risk of intracranial hemorrhage (ICH) and extracranial hemorrhage (ECH) of 1.2% and 0.4%; and the excess risk of major bleeding caused by 3 months of warfarin in patients with previous AIS is 1%. These data suggesting subclinical PDVT after AIS should usually be treated, but that observation might be preferable for asymptomatic isolated below-knee DVT if cardiopulmonary reserve is adequate. We followed existing guidelines recommending serial imaging over 2 weeks to exclude proximal propagation if below-knee DVT was left untreated.

Our definition of “unrecognized clinical” VTE is arbitrary. It was felt necessary to impose such a definition because severely impaired stroke patients with VTE are less likely to report symptoms than nonstroke patients, and if not systematically sought, clinical VTE will often only be diagnosed at postmortem examination. We attempted to strike a balance between this scenario, and one of labeling VTE as “unrecognized clinical” on the basis of very minor signs.

A limitation of the study is that 22% of patients underwent initial but not follow-up MRDTI. This is unlikely to have altered the overall VTE incidence because most of these patients were ambulant and VTE-negative on initial imaging, thus being a subgroup with a very low likelihood of having VTE subsequently develop. A further limitation is the relatively small sample size. However, the highly significant associations between stroke severity and VTE suggest our conclusions are robust.

The main implication of this study is that it identifies a subgroup after AIS in which there is an urgent need to reduce VTE-related morbidity and mortality. Although a temperate approach may be appropriate in some severely disabled patients, it is notable that in earlier series one-third to two-thirds of stroke patients dying from PE were improving at the time of death. A thromboprophylactic trial of low-dose LMWH plus aspirin targeted to high-risk patients as identified in this study, titrated to ambulatory status, and with careful ascertainment for clinical VTE would be justified. Our data indicate that almost 300 per 1000 such patients receiving aspirin/GCS only would be expected to have PDVT develop, with fatal PE likely in at least 30, and nonfatal clinical PE in perhaps twice this number. In the IST, low-dose unfractionated heparin caused 3 of 1000 additional ICHs and 3 of 1000 additional ECHs when added to aspirin, together with 11 of 1000 fewer recurrent ischemic strokes. Assuming similar risks and benefits with low-dose LMWH, that it was only 50% effective in preventing PE, and that all major bleeding episodes occurred in ∼50% of patients with severe stroke versus none in nonsevere stroke, then for every 1000 patients treated, 15 fatal PEs, 30 nonfatal clinical PEs, and 1 recurrent ischemic strokes might be prevented, at a cost of 6 ICHs and 6 ECHs. In the absence of further information, judicious addition of low-dose LMWH to aspirin in patients with severe stroke thought to have a reasonable prognosis, no evidence of ICH, and judged to be at low risk for bleeding could be considered based on these data. Patients with severe AIS should also be regularly examined for subtle clinical evidence of VTE, with a low threshold for diagnostic testing using the preferred local modality.

In summary, our data show that VTE remains common after AIS and that clinically apparent VTE is often overlooked. Most events occurred in patients with BI 2=9 or who were nonambulatory around the time of admission, a subgroup in whom aspirin/GCS prophylaxis may be inadequate. This study should raise awareness of the important contribution of VTE to morbidity and mortality after stroke and catalyze research into improved thromboprophylaxis.
Acknowledgments
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References
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