Asymptomatic Hemorrhagic Transformation of Infarction and Its Relationship With Functional Outcome and Stroke Subtype

Assessment From the Tinzaparin in Acute Ischaemic Stroke Trial

Timothy J. England, MRCP(UK); Philip M.W. Bath, FRCPath, FRCP; Gillian M. Sare, MRCP(UK); Chamila Geeganage, MB, BS, MSc; Thierry Moulin, MD; Desmond O’Neill, FRCP; France Woimant, MD; Hanne Christensen, MD, PhD; Peter De Deyn, MD; Didier Leys, MD; E. Bernd Ringelstein, MD; on behalf of the TAIST Investigators

Background and Purpose—Asymptomatic hemorrhagic transformation of infarction (AHTI) is common, but its risk factors and relationship with functional outcome are poorly defined.

Methods—The analyses used data from the Tinzaparin in Acute Ischaemic Stroke Trial, a randomized controlled trial assessing tinzaparin (low molecular weight heparin) versus aspirin in 1484 patients with acute ischemic stroke. CT head scans (baseline, day 10) were adjudicated for the presence of hemorrhagic transformation. Stroke subtype was classified according to modified Trial of Org 10172 in Acute Stroke Treatment (small vessel, large vessel, cardioembolic) and the Oxfordshire Community Stroke Project (total anterior, partial anterior, lacunar, and posterior circulatory syndromes). Modified Rankin scale and Barthel Index were measured at 3 and 6 months. Analyses were adjusted for age, sex, severity, blood pressure, infarct volume, and treatment. Symptomatic hemorrhage was excluded.

Results—At day 10, AHTI did not differ between aspirin (300 mg; 32.8%) and medium-dose (100 IU/kg; 36.0%) and high-dose (175 IU/kg; 31.4%) tinzaparin groups (P=0.44). Relative to lacunar stroke, AHTI on follow-up CT was significantly increased in total anterior circulation syndrome (odds ratio, 11.5; 95% CI, 7.1 to 18.7) and partial anterior circulation syndrome (odds ratio, 7.2; 95% CI, 4.5 to 11.4) stroke. Similarly, relative to small vessel disease, AHTI was increased in large vessel (odds ratio, 15.1; 95% CI, 9.4 to 24.3) and cardioembolic (odds ratio, 14.1; 95% CI, 8.5 to 23.5) stroke. After adjustment for infarct volume, the presence of AHTI was not associated with outcome at 3 or 6 months as measured by the modified Rankin Scale and Barthel Index.

Conclusions—AHTI is increased in ischemic stroke with cortical syndromes and of large vessel or cardioembolic etiology. Heparin does not increase AHTI. AHTI is not associated with functional outcome.

Key Words: cerebral infarct ■ hemorrhagic transformation ■ heparin ■ aspirin ■ functional recovery

A

symptomatic hemorrhagic transformation of infarction (HTI) is a recognized complication of ischemic stroke and may be a natural evolutional change (ie, it may occur in all infarcts to some degree). However, its frequency, risk factors, and impact on prognosis are less clear. Acquisition of this baseline information is important because fibrinolytic and antithrombotic therapies are increasingly used.

A recent autopsy series of 245 consecutive acute ischemic stroke patients determined an HTI frequency of 29%.1 In a systematic review, the frequency of patients with any degree of HTI (from petechial hemorrhage to frank hematoma formation) varied from 0% to 85%.2 This variation is probably a reflection of heterogeneity between studies such as case mix, timing of scan, and scanning modality. Definition of hemorrhagic subtypes between studies also varies, making comparison difficult. HTI was radiologically defined in the National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator study as acute infarction with punctate or variable hypodensity/hyperdensity, with an indistinct border within the vascular territory.3 This was subcategorized further into HI1 and HI2 in the European Cooperative Acute Stroke Study (ECASS) I and II

Received November 13, 2009; final revision received February 22, 2010; accepted March 23, 2010.

From the Stroke Trials Unit (T.J.E., P.M.W.B., G.M.S., C.G.), University of Nottingham, Nottingham, UK; CHU Besancon (T.M.), University of Franche-Comte, Besancon, France; Department of Age-Related Health Care (D.O.), Adelaide and Meath Hospital, Dublin, Ireland; Department of Neurology (F.W.), Lariboisière University Hospital, France; Department of Neurology (H.C.), University of Copenhagen, Bispebjerg Hospital, Denmark; Department of Neurology (P.D.), AZ Middelheim, University of Antwerp, Belgium; Clinique Neurologique (D.L.), CHRU de Lille, Lille, France; and Klinik fur Neurologie (E.B.R.), Universitat Munster, Munster, Germany.

Correspondence to Professor Philip Bath, Stroke Trials Unit, Institute of Neuroscience, University of Nottingham, Clinical Sciences Building, City Hospital Campus, Nottingham NG7 2UH, UK. E-mail philip.bath@nottingham.ac.uk

© 2010 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.109.573063

2834
A parenchymal hematoma is typically described as a homogenous hyperdense lesion with a sharp border with or without edema or mass effect\(^1\) and, again, categorized further into parenchymal hematoma 1 and parenchymal hematoma 2, depending on the size of hemorrhage.\(^3,5\)

An increase in symptomatic intracranial hemorrhage (SICH) is observed in trials assessing anticoagulation for the treatment of acute ischemic stroke,\(^6\) which negates any benefit in reducing recurrent stroke. However, the role of asymptomatic HTI (AHTI) on outcome is perhaps assumed irrelevant because, by definition, the event is asymptomatic. Nonetheless, the presence of any amount of intracranial hemorrhage could hamper long-term recovery, and the literature conveys conflicting reports regarding the influence of small amounts of blood within an infarct on outcome.\(^4,7,8\) We sought to further assess the relationship between AHTI and clinical subtype, etiology, outcome, and treatment with low molecular weight heparin (LMWH) using data from the Tinzapararin in Acute Ischaemic Stroke Trial (TAIST).\(^9\)

### Methods

#### Subjects

TAIST was a randomized, double-blind, aspirin-controlled trial comparing the safety and efficacy of treatment with tinzaparin (an LMWH) at high dose (175 anti-Xa IU/kg/d), tinzaparin at medium dose (100 anti-Xa IU/kg/d), or aspirin (300 mg od) in patients with acute ischemic stroke.\(^9\) Subjects were included within 48 hours of stroke onset, and treatment was given for 10 days. Patients were excluded with any presence of hemorrhage on prerandomization stroke onset, and treatment was given for 10 days. Patients were included from this study.

#### Follow-Up CT Scans

In addition to the baseline CT scan, a second scan was performed after the treatment period. Two radiologists, blinded to treatment and clinical findings, independently reviewed each scan, and a third radiologist adjudicated any difference of opinion with the majority decision standing. Each radiologist had \(>15\) years of experience and a full academic education. They determined the presence of HTI (and whether the amount of bleeding was present in \(<50\%\) or \(>50\%\) of the infarct) and hemorrhage, including intrainfarct hematoma, additional hematoma in another area, and blood in the ventricles and subarachnoid space. Infarct volumes were calculated using the ABC/2 rule, in which A, B, and C represent height, length, and width of the infarct.\(^10\) CT scans were performed at each center according to standard CT head scanning techniques.

A critical events committee adjudicated SICH at the end of the trial defined as CT-documented hemorrhage relating to a decline in the patient’s neurological condition.\(^9\) In the context of this analysis, any blood within an infarct that was not defined as SICH was classified as AHTI. Eleven cases of adjudicated SICH\(^9\) were excluded from this study.

#### Stroke Subtypes

The relationship with stroke classification in patients with hemorrhagic transformation of the infarct was sought. Classification was based on the Oxford Community Stroke Project\(^11\) (total anterior circulation stroke, partial anterior circulation stroke, lacunar infarct, and posterior circulation infarct) and etiology subtype based on the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification\(^12\) (cardioembolic, large artery disease, or small vessel disease).

### Outcomes

The modified Rankin Scale (TAIST primary outcome)\(^13\) and Barthel Index\(^14\) were used to assess outcome at 90 and 180 days and were recorded by face-to-face interview. A poor outcome was considered to be a modified Rankin Scale score of \(>2\), and Barthel Index of \(<60\). Stroke severity was measured using the Scandinavian Stroke Scale.\(^15\)

### Statistical Methods

Univariate analyses were performed using \(\chi^2\), Fisher exact test, and \(t\) tests where appropriate. Multivariate logistic regression models were analyzed using known baseline prognostic factors including age, sex, baseline systolic blood pressure, baseline severity, treatment group, time to treatment, cortical stroke, and etiology. An additional covariate, time–volume (time to treatment \(\times\) infarct volume) was included in the model because there is an expected interaction between these 2 baseline variables. All analyses were performed using the Mac version of SPSS (version 11.0). Significance was taken at \(P<0.05\) and 95% CIs are given.

### Results

#### Subjects and Follow-Up CT Scans

A total of 1484 patients were randomized into TAIST, of whom 1318 underwent follow-up CT scanning after treatment. Twenty-one of these scans were of poor image quality, leaving 1297 scans with analyzable data. When comparing baseline characteristics in those who developed or did not develop AHTI (Table 1), there was no difference in average age, but AHTI was more likely to occur in men, in those with a history of hyperlipidemia or atrial fibrillation, and in those with more severe stroke (low Scandinavian Stroke Scale). In contrast, those with a history of diabetes mellitus and lower systolic and diastolic blood pressure at baseline had a lower rate of AHTI.
There was no significant difference in either the presence of AHTI between aspirin, medium-dose and high-dose tinzaparin groups (aspirin 32.8%; medium-dose tinzaparin 36.0% and high-dose tinzaparin 31.4%; P = 0.44), or the average volume of infarct in which the blood was present (aspirin 10.2 cm³; medium-dose tinzaparin 10.3 cm³, and high-dose tinzaparin 11.1 cm³; P = 0.82). The infarct volume in patients with AHTI (n = 418) was significantly larger than those with pale infarcts (n = 463; Table 1). There was also no difference between groups by other types of hemorrhage, although their numbers were small (Table 2).

**Stroke Subtypes**

No differences in AHTI were observed between the treatment groups by stroke subtypes when categorized by TOAST and Oxfordshire Community Stroke Project classifications (Table 3). However, within treatment groups, stroke subtypes demonstrated a variation in the risk of AHTI. Relative to lacunar stroke, AHTI on follow-up CT was significantly increased in total anterior circulation stroke (odds ratio [OR], 11.5; 95% CI, 7.1 to 18.7) and partial anterior circulation stroke (OR, 7.2; 95% CI, 4.5 to 11.4). Posterior circulation stroke caused a nonsignificant trend toward increased AHTI (OR, 1.4; 95% CI, 0.5 to 3.6). Likewise, relative to small vessel disease, AHTI was increased in large vessel (OR, 15.1; 95% CI, 9.4 to 24.3) and cardioembolic (OR, 14.1; 95% CI, 8.5 to 23.5) stroke.

**Outcome**

After adjustment for age, sex, baseline systolic blood pressure, baseline severity, treatment group, time to treatment, cortical stroke, etiology, and infarct volume, the risk of poor outcome for all groups combined at 90 days was not significantly affected by the presence of AHTI whether measured by modified Rankin Scale score or Barthel Index (Table 4; Figure). The same held true for outcome at 180 days. If AHTI was present, the aspirin subgroup had a significantly worse outcome at 180 days for the Barthel Index only, and there were nonsignificant trends to a better outcome in the high-dose tinzaparin group. Outcome was not affected as to whether the size of AHTI within the infarct was <50% or ≥50% (Table 4).

**Discussion**

This secondary analysis of the TAIST trial has revealed that AHTI occurs in approximately one third of acute ischemic...
strokes, as detected by repeat CT scan after a treatment period of 10 days, and is not increased by acute treatment with LMWH (tinzaparin) when compared with aspirin. The presence of AHTI does not appear to have prognostic significance, as measured by both modified Rankin Scale and Barthel Index. In addition, AHTI is increased in ischemic stroke with cortical syndromes and of large vessel or cardioembolic etiology.

The absolute frequency of hemorrhagic change is almost certainly an underestimate of the actual value because the trial protocol excluded patients with any baseline hemorrhage, and CT scanning is relatively insensitive to determine its true extent; imaging with MRI has been shown to be more sensitive, detecting rates of HTI up to 80%. Second, CT scans at 10 days may miss some infarcts caused by fogging, whereby initially hypodense infarcts become isodense during the second and third week, causing a transient disappearance that further confounds interpretation. In addition, recent thrombolysis trials have shown considerable variation in AHTI rates using CT among placebo groups, and this appears to be related to the timing of the follow-up CT scan: 24 hours, 2.9% (NINDS); 72 hours, 18.5% (Desmoteplase in Acute Ischemic Stroke Trial); 5 days, 31% (Multicenter Acute Stroke Trial-Europe); and 7 days, 29.9% or 36.8% (ECASS I and II). The relationship between AHTI and heparin in previous trials assessing anticoagulation for acute ischemic stroke is less clear. This contrasts with SICH rates, which are increased in the treatment arms relative to control. According to TAIST, the risk of AHTI is not increased with the use of an LMWH (aspirin 32.8%, medium-dose tinzaparin 36.0%, and high-dose tinzaparin 31.4%; P = 0.44). This absent relationship between heparin treatment and hemorrhagic transformation is unexpected; evolution of blood within an infarct could be driven more by factors such as reperfusion injury and infarct size rather than by treatment with anticoagulation. The influence of lesion volume within our multivariate analysis model was highly significant, so perhaps the higher risk is simply related to infarct size. In addition, strokes resulting from cardioembolism have been shown previously to increase risk of hemorrhagic transformation. It has been suggested that cardioembolic clots are softer and lyed sooner, and therefore lead to earlier reperfusion injury and have a higher chance of hemorrhagic transformation. This notion is not supported by the TAIST data because there was no difference between large vessel or cardioembolic causes of AHTI.

![Figure](http://stroke.ahajournals.org/)

**Figure.** Outcome by modified Rankin Scale at 3 months according to presence of AHTI, comparison by Mann–Whitney U; P < 0.001.

### Table 4. Risk of a Poor Outcome at 90 and 180 Days With Presence of AHTI by Treatment Group

<table>
<thead>
<tr>
<th>Group</th>
<th>90 Days OR (95% CI)</th>
<th>180 Days OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All groups (unadjusted)</td>
<td>3.16 (2.44–4.1)</td>
<td>3.0 (2.33–3.86)</td>
</tr>
<tr>
<td>All groups (adjusted)</td>
<td>0.96 (0.62–1.49)</td>
<td>1.06 (0.70–1.61)</td>
</tr>
<tr>
<td>Aspirin (unadjusted)</td>
<td>2.81 (1.82–4.33)</td>
<td>2.69 (1.74–4.14)</td>
</tr>
<tr>
<td>Aspirin (adjusted)</td>
<td>0.87 (0.43–1.77)</td>
<td>0.68 (0.32–1.44)</td>
</tr>
<tr>
<td>Medium-dose LMWH (unadjusted)</td>
<td>3.56 (2.28–5.58)</td>
<td>3.64 (2.36–5.61)</td>
</tr>
<tr>
<td>Medium-dose LMWH (adjusted)</td>
<td>0.83 (0.37–1.85)</td>
<td>1.49 (0.70–3.16)</td>
</tr>
<tr>
<td>High-dose LMWH (unadjusted)</td>
<td>3.19 (1.99–5.1)</td>
<td>2.75 (1.75–4.31)</td>
</tr>
<tr>
<td>High-dose LMWH (adjusted)</td>
<td>0.96 (0.42–2.24)</td>
<td>0.88 (0.40–1.93)</td>
</tr>
</tbody>
</table>

### Modified Rankin Scale Score >2

<table>
<thead>
<tr>
<th>Group</th>
<th>90 Days OR (95% CI)</th>
<th>180 Days OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All groups (unadjusted)</td>
<td>2.71 (2.02–3.66)</td>
<td>2.53 (1.89–3.36)</td>
</tr>
<tr>
<td>All groups (adjusted)</td>
<td>0.73 (0.44–1.22)</td>
<td>0.92 (0.57–1.50)</td>
</tr>
<tr>
<td>All groups (unadjusted)</td>
<td>2.84 (1.87–4.28)</td>
<td>2.56 (1.73–3.79)</td>
</tr>
<tr>
<td>All groups (adjusted)</td>
<td>0.80 (0.52–1.24)</td>
<td>0.70 (0.48–1.04)</td>
</tr>
</tbody>
</table>

### Barthel Index <60

<table>
<thead>
<tr>
<th>Group</th>
<th>90 Days OR (95% CI)</th>
<th>180 Days OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All groups (unadjusted)</td>
<td>3.38 (2.97–4.94)</td>
<td>3.35 (2.58–4.34)</td>
</tr>
<tr>
<td>All groups (adjusted)</td>
<td>0.96 (0.62–1.48)</td>
<td>1.31 (0.86–2.0)</td>
</tr>
<tr>
<td>Medium-dose LMWH (unadjusted)</td>
<td>4.0 (2.57–6.21)</td>
<td>3.59 (2.28–5.63)</td>
</tr>
<tr>
<td>Medium-dose LMWH (adjusted)</td>
<td>0.87 (0.46–1.27)</td>
<td>0.76 (0.46–1.27)</td>
</tr>
<tr>
<td>High-dose LMWH (unadjusted)</td>
<td>3.64 (2.32–5.70)</td>
<td>2.62 (1.67–4.13)</td>
</tr>
<tr>
<td>High-dose LMWH (adjusted)</td>
<td>0.59 (0.26–1.37)</td>
<td>0.57 (0.25–1.31)</td>
</tr>
</tbody>
</table>

All values adjusted for age, sex, blood pressure, baseline Scandinavian Stroke Scale, treatment group, time to treatment, infarct volume and time-volume (time to treatment x infarct volume).

*Significant after adjustment.
The variation in HTI definition between studies makes comparison difficult, and a range of classification systems were suggested previously.\textsuperscript{3,5,26} Nonetheless, the presence of AHTI in this study (which encompasses H11 and H12) is not associated with poor outcome. This is in agreement with previous reports from smaller studies; only parenchymal hematoma 2 was associated with poor outcome in ECASS I and II,\textsuperscript{4,5} and asymptomatic intracerebral hemorrhage did not influence long-term outcome in the NINDS recombinant tissue plasminogen activator trial.\textsuperscript{27} Of note, analysis of the NINDS data did not correct for infarct volume and included only 21 patients with asymptomatic intracerebral hemorrhage (13 in the tissue plasminogen activator group and 8 in placebo group). However, ECASS I and II did adjust for infarct size, but it was categorized (therefore decreasing statistical power) into none, \(\leq 33\%\) of middle cerebral artery territory, and \(>33\%\) of middle cerebral artery territory. In contrast, other thrombolysis studies have indicated that lesser degrees of hemorrhagic infarction may be harmful.\textsuperscript{7,8} One these trials included just 51 patients,\textsuperscript{7} and the other\textsuperscript{8} used data from a registry and also did not correct for lesion volume, therefore potentially overestimating the effects of HTI on outcome. The strength of the TAIST data lies in its large sample size (418 CT scans with AHTI and 463 pale infarcts) and a more precise calculation of infarct volume using ABC/2.\textsuperscript{10}

The independent association observed between AHTI and baseline blood pressure is unexpected because it might be anticipated that higher pressures would be associated with a higher risk of bleeding; however, the opposite was seen. In a separate analysis of the TAIST trial,\textsuperscript{28} no significant correlation between baseline blood pressure and HTI was observed once adjustments for baseline values had been made. Although high baseline blood pressure is independently associated with a poor outcome after stroke, this was not shown to be through an association with increased hemorrhagic transformation, cerebral edema, or mass effect.\textsuperscript{38} Moreover, patients with blood pressure in excess of 220/120 were excluded from TAIST, confounding these results further. Ongoing trials of blood pressure management and involving serial imaging (eg, Efficacy of Nitric Oxide in Stroke\textsuperscript{29} and Scandinavian Candesartan Acute Stroke Trial) will help determine the relationship between blood pressure and HTI. A second unexpected result was the apparent protective effect of diabetes from AHTI in univariate analysis. This conflicts with current evidence, suggesting that diabetes and hyperglycemia lead to higher rates of hemorrhagic transformation\textsuperscript{30} and SICH.\textsuperscript{31} However, this association becomes insignificant once confounders (age, sex, blood pressure, and baseline severity) are accounted for (data not shown). The mechanisms underlying the effect of diabetes and hyperglycemia on hemorrhagic infarcts and the management of blood sugar after stroke remain unclear and subject to further clinical trials.\textsuperscript{32}

This study has several limitations. First, establishing whether a patient is genuinely asymptomatic from the presence of intracranial blood is subject to the sensitivity of the Scandinavian Stroke Scale and the opinion of the original investigators and TAIST Critical Events Committee. To allow for this, all patients with adjudicated SICH were excluded from the study. A second caveat is the presence of selection bias; randomization into a controlled trial can lead to underrepresentation of certain groups. In the context of the present trial, TAIST excluded patients with very mild stroke, those with severe hypertension, and those with preexisting hemorrhage on baseline CT scan. As a result, AHTI rates may be underestimated. Finally, increasing interest is focusing on the role of frailty in the outcome of age-related illnesses such as stroke, with negative impacts on treatment and outcome.\textsuperscript{33} Although frailty was not measured, it is possible that future studies should focus on assessing this important attribute in stroke because it differs from age, and, unlike aging, it is potentially amenable to intervention.\textsuperscript{34}

Despite the above limitations, TAIST was a robust, high-fidelity, randomized controlled trial with no treatment effect observed in a large number of patients allowing hypothesis-generating analyses. Overall, this analysis has provided an insight into AHTI, its relationship with stroke subtypes, and its negligible effect on clinical outcome.

**Acknowledgments**

We thank Leo Pharma A/S for sharing the TAIST database, members of the trial advisory committee (P.D., Gudrun Boyesen, D.L., Jan-Ewint Olsson, D.O., B.R., and Jan-Jacob van der Sande) and the critical events committee (H. Buller).

**Sources of Funding**

The analyses and their interpretation were performed independently of Leo Pharma A/S. T.E. and G.S. were supported by the Medical Research Council and British Heart Foundation, respectively. P.M.W.B. is Stroke Association professor of stroke medicine.

**Disclosures**

P.M.W.B. was chief investigator for the TAIST Trial. P.M.W.B., T.M., D.O., F.W., P.D.D., D.L., and E.B.R. were members of the TAIST Trial Steering Committee.

**References**

Asymptomatic Hemorrhagic Transformation of Infarction and Its Relationship With Functional Outcome and Stroke Subtype: Assessment From the Tinzaparin in Acute Ischaemic Stroke Trial

Timothy J. England, Philip M.W. Bath, Gillian M. Sare, Chamila Geeganage, Thierry Moulin, Desmond O’Neill, France Womant, Hanne Christensen, Peter De Deyn, Didier Leys and E. Bernd Ringelstein

on behalf of the TAIST Investigators

*Stroke*. 2010;41:2834-2839; originally published online October 28, 2010;
doi: 10.1161/STROKEAHA.109.573063

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/12/2834

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/