Leukoaraiosis, Cerebral Hemorrhage, and Outcome After Intravenous Thrombolysis for Acute Ischemic Stroke

A Meta-Analysis

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Background and Purpose—We performed a meta-analysis to assess whether leukoaraiosis on brain computed tomographic scans of acute ischemic stroke patients treated with intravenous thrombolysis is associated with an increased risk of symptomatic intracerebral hemorrhage (sICH) or poor functional outcome at 3 to 6 months after stroke, or both.

Methods—We searched PubMed and pooled relevant data in meta-analyses using random effects models. Using odds ratios (OR), we quantified the strength of association between the presence and severity of leukoaraiosis and post-thrombolysis sICH or 3- to 6-month modified Rankin Score ≥2.

Results—Eleven eligible studies (n=7194) were pooled in meta-analysis. The risk of sICH was higher in patients with leukoaraiosis (OR, 1.55; 95% confidence interval [CI], 1.17–2.06; P=0.002) and severe leukoaraiosis (OR, 2.53; 95% CI, 1.92–3.34; P<0.0001) compared with patients without leukoaraiosis. Leukoaraiosis was an independent predictor of sICH in 6 included studies (n=4976; adjusted OR, 1.75; 95% CI, 1.58–2.27; P<0.0001). OR for leukoaraiosis and poor 3- to 6-month outcome was 2.02 (95% CI, 1.54–2.65; P<0.0001), with significant statistical heterogeneity (F, 75.7%; P=0.002). In adjusted analyses, leukoaraiosis was an independent predictor of poor outcome (n=3688; adjusted OR, 1.61; 95% CI, 1.44–1.79; P<0.0001). In post hoc analyses, including only leukoaraiosis patients in randomized controlled trials (IST-3 [third International Stroke Trial], NINDS [National Institute of Neurological Disorders and Stroke], ECASS-1–2 [European Cooperative Acute Stroke Study]; n=2234), tissue-type plasminogen activator versus control was associated with higher sICH risk (OR, 5.50; 95% CI, 2.49–12.13), but lower poor outcome risk (OR, 0.75; 95% CI, 0.60–0.95).

Conclusions—Leukoaraiosis might increase post-intravenous thrombolysis sICH risk and poor outcome poststroke. Despite increased sICH risk, intravenous tissue-type plasminogen activator treatment has net clinical benefit in patients with leukoaraiosis. Given the risk of bias/confounding, these results should be considered hypothesis-generating and do not justify withholding intravenous thrombolysis. (Stroke. 2016;47:2364-2372. DOI: 10.1161/STROKEAHA.116.014096.)

Key Words: cerebral small vessel disease • intracerebral hemorrhage • leukoaraiosis • thrombolysis • white matter hyperintensities

The effectiveness and benefit of intravenous (IV) thrombolysis using recombinant tissue-type plasminogen activator (rt-PA) within 4.5 hours for acute ischemic stroke (AIS) have been clearly demonstrated. However, early symptomatic intracranial hemorrhage (sICH) remains the most serious complication after IV thrombolysis.1 Given the increasing number of patients eligible for IV thrombolysis, especially elderly individuals with chronic comorbidities, it is crucial to understand the association between not only acute, but also preexisting signs of brain injury and the risk of early symptomatic sICH and poor outcome.

Along with clinical variables (such as age, early ischemic computed tomography [CT] changes, high blood pressure, hyperglycemia, baseline stroke severity, and large infarct volume),1 neuroimaging markers of diffuse cerebral small vessel disease might be a risk factor for thrombolysis-related sICH and poor poststroke functional outcome. Leukoaraiosis, an established cerebral microangiopathy marker, is associated with cognitive impairment, triples the risk of future stroke, and doubles the risk of death.2 Moreover, leukoaraiosis presence is independently associated with the risk of spontaneous

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sICH. Leukoaraiosis is often seen on brain CT scans of AIS patients and might increase the risk of post-thrombolysis sICH and poor outcome, as a marker of brain frailty. In this setting, previous studies have reported conflicting results.

We performed a meta-analysis to evaluate the clinical significance of leukoaraiosis in AIS patients receiving IV thrombolysis to assess (1) whether leukoaraiosis presence or severe leukoaraiosis (based on suggested visual rating scales cutoffs) is associated with increased symptomatic sICH risk and (2) whether leukoaraiosis presence in these patients is associated with poor clinical outcome at 3 to 6 months poststroke. In an exploratory subanalysis, we have also investigated the net clinical benefit of thrombolysis versus placebo in patients with leukoaraiosis included in randomized controlled trials (RCT).

**Methods**

This report was prepared with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The study was performed according to a prespecified protocol designed in house in January 2015.

**Search Strategy and Selection Criteria**

We searched PubMed between January 1, 1995, and February 1, 2016, using a combination of search terms and Medical Subject Headings: post-thrombol}* OR thromboly* OR tPA OR rtPA OR rt-PA OR (tissue plasminogen activator) OR (thrombectomy) AND (leukoaraiosis) OR (white matter hyperintens*) OR (white matter lesion*) OR (white matter disease*) OR (white matter change*). Reference lists from all included articles, review papers on the topic, and the authors’ own files were also searched for relevant studies. Case reports were excluded and papers not published in English were translated if needed. Three authors (A. Charidimou, M. Pasi, and S. Shams) identified potentially relevant studies independently, resolving any uncertainties by discussion. The final list of included studies was decided on consensus.

Studies were eligible for inclusion if they had (1) defined and assessed symptomatic sICH risk or 3- to 6-month functional outcome in AIS patients treated with IV thrombolysis (including at least 100 cases), or both, and (2) quantified this risk in relation to the presence of leukoaraiosis on brain imaging using validated rating scales.

**Data Extraction**

Two authors (A. Charidimou and M. Pasi) independently extracted data from all potentially relevant articles. For each study, we extracted information on design, number/nature of participants (including mean age and sex), leukoaraiosis rating scale, thrombolysis treatment and dosage, follow-up duration, participants number across different leukoaraiosis severity groups, and number of participants with the outcomes of interest (sICH clearly defined according to standard criteria; poor outcome, defined as modified Rankin Score [mRS] >2 or ≥2) in each group. Where available, adjusted estimates from multivariable models of the independent association between leukoaraiosis and sICH or poor outcome were extracted from eligible studies. Disagreements were resolved by discussion and consensus. All included studies were critically appraised against an 8-item tool published by the Cochrane Methods Bias group. In included studies, severity of leukoaraiosis was measured on head CT using Van Swieten (with or without modifications), Fazekas, or ARWMC (Age-Related White Matter Changes) scale. The threshold used to define the presence of leukoaraiosis on these respective scales was any score above zero. Data on severe leukoaraiosis were extracted where available based on definitions used in each study, which were in line with standard cutoffs of visual scales.

**Statistical Analysis**

Data were pooled in a meta-analysis when at least 3 studies with relevant data were available. The cumulative prevalence (including

![Figure 1. Flow chart of literature search and study selection. IV indicates intravenous; LA, leukoaraiosis; rtPA, recombinant tissue-type plasminogen activator; and sICH, symptomatic intracerebral hemorrhage.](http://stroke.ahajournals.org/)}
95% confidence interval (CI) of leukoaraiosis presence, severe leukoaraiosis and sICH, and poor functional outcome were calculated based on the metaprob routine using exact binomial procedures. In all analyses, we used a random effects model with DerSimonian-Laird weights.11 We quantified the strength of the association between leukoaraiosis presence and severe and post-tPA sICH or 3- to 6-month mRS>2 using odds ratios (OR) and their corresponding 95% CIs, with the inverse variance method for weighting. To account for methodological variability in study design, in sensitivity analyses, we stratified observational studies or RCT. For each of the 2 outcomes, we also pooled the covariate-adjusted ORs as provided from relevant multivariable models in included studies. Similar univariable meta-analyses were performed for treatment effect (tPA versus control) in RCTs, including only patients with leukoaraiosis. When possible, we performed sensitivity analyses homogenized by mRS>2 or ≥2. We assessed statistical heterogeneity using I-squared statistics and visually through forest plot inspection. We explored publication bias with funnel plots. We used a random-effect univariable meta-regression to explore whether certain key baseline characteristics of included patient populations could have affected our results. Meta-analyses were performed using Stata 13.0 (StataCorp LP, TX).

**Results**

Eleven studies (10 unique cohorts) including a total of 7194 patients met our inclusion criteria and were pooled in meta-analysis (Figure 1).4–6,12–19 For the ECASS-1/-2 report (European Cooperative Acute Stroke Study; published only as an abstract), we contacted the lead authors to provide relevant data for the meta-analysis.18 A summary of the characteristics of included studies, methodological key issues, and quality indicators are noted in Table 1. All studies used IV tPA (1.1 mg/kg in ECASS-1 and 0.9 mg/kg in all other), rated leukoaraiosis using validated visual rating scales on CT (except

### Table 1. Characteristics and Methodological Aspects of Included Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Country (Period)</th>
<th>Patient Number (Men)</th>
<th>Mean/ Median Age (Years)</th>
<th>Initial Stroke Severity (NIHSS)</th>
<th>Time to tPA</th>
<th>LA Prevalence (95% CI)</th>
<th>LA Visual Scale Used (Severe LA Definition if Provided)</th>
<th>FU Time (Modality)</th>
<th>Symptomatic ICH Definition</th>
<th>Functional Outcome Poststroke (Used in Our Analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Willer2</td>
<td>Retrospective single center</td>
<td>Denmark (–)</td>
<td>311</td>
<td>75.8</td>
<td>…</td>
<td>&lt;4.5 h</td>
<td>36%</td>
<td>ARWMC</td>
<td>36 h (CT)</td>
<td>ECASS-2: ICH with worsening of ≥4 points on NIHSS</td>
<td>…</td>
</tr>
<tr>
<td>Curtze6</td>
<td>Retrospective single center</td>
<td>Finland (2001–2014)</td>
<td>2451 (51%)</td>
<td>78 (72–83)</td>
<td>10 (6–16)</td>
<td>2 h (88–167 min)</td>
<td>36%</td>
<td>Van Swieten</td>
<td>…</td>
<td>…</td>
<td>mRS&gt;2 at 3 mo</td>
</tr>
<tr>
<td>Huang19</td>
<td>Retrospective single center</td>
<td>China (2009–2012)</td>
<td>101 (49%)</td>
<td>66</td>
<td>14</td>
<td>2.4 h</td>
<td>17%</td>
<td>Only LA presence assessed</td>
<td>…</td>
<td>…</td>
<td>ECASS-2</td>
</tr>
<tr>
<td>Curtze1</td>
<td>Retrospective single center</td>
<td>Finland (2001–2014)</td>
<td>2481 (62%)</td>
<td>73 (64–79)</td>
<td>14 (9–20)</td>
<td>130 min (96–167 min)</td>
<td>48%</td>
<td>Van Swieten (&gt;2)</td>
<td>24 h (CT)</td>
<td>ECASS-2</td>
<td>…</td>
</tr>
<tr>
<td>Costello13</td>
<td>Retrospective single center</td>
<td>Australia (2004–2009)</td>
<td>206 (44%)</td>
<td>81 (8)</td>
<td>12 (8.5)</td>
<td>-</td>
<td>54%</td>
<td>Van Swieten (&gt;2)</td>
<td>48 h (CT or MRI)</td>
<td>SITS–MOST: HT with worsening of ≥4 points on NIHSS</td>
<td>…</td>
</tr>
<tr>
<td>Aries14</td>
<td>Retrospective single center</td>
<td>Holland (2002–2008)</td>
<td>400 (53%)</td>
<td>68±14</td>
<td>13±8–17</td>
<td>&lt;3 h (7% pts &gt;3 h)</td>
<td>24%</td>
<td>Van Swieten (per hemisphere &gt;2)</td>
<td>24–36 h (CT)</td>
<td>Type 2 PH with worsening of ≥4 points on NIHSS</td>
<td>…</td>
</tr>
<tr>
<td>Demchuk15</td>
<td>Prospective multicentre</td>
<td>USA (1991/1994)</td>
<td>299</td>
<td>…</td>
<td>…</td>
<td>&lt;3 h</td>
<td>33%</td>
<td>Van Swieten (&gt;2)</td>
<td>24 h (CT)</td>
<td>Any neurological deterioration within 24 h associated with sICH</td>
<td>mRS&gt;2 at 3 mo</td>
</tr>
<tr>
<td>Palumbo16</td>
<td>Prospective multicentre</td>
<td>Canada (1999–2001)</td>
<td>820 (57%)</td>
<td>78.3</td>
<td>17</td>
<td>No upper limit</td>
<td>…</td>
<td>Van Swieten</td>
<td>24 h (CT)</td>
<td>sICH within 24 h from thrombolytic treatment with any neurological deterioration</td>
<td>…</td>
</tr>
<tr>
<td>Neumann-Haefeli17</td>
<td>Retrospective multicentre</td>
<td>Europe-USA (–)</td>
<td>363</td>
<td>65±14</td>
<td>13.2±6.1</td>
<td>188±64 min</td>
<td>…</td>
<td>Fazekas (MRI)</td>
<td>36 h (MRI)</td>
<td>PH</td>
<td>…</td>
</tr>
<tr>
<td>IST-313</td>
<td>RCT (r-tPA arm)</td>
<td>2000–2011</td>
<td>1507</td>
<td>…</td>
<td>11 (6–18); &gt;11 in 52%</td>
<td>&lt;3 h (71% pts &gt;3 h)</td>
<td>50%</td>
<td>Van Swieten (CT); Fazekas (if MRI)</td>
<td>7 days (CT)</td>
<td>SITS-MOST</td>
<td>Oxford Handicap scale &gt;2 at 6 mo</td>
</tr>
<tr>
<td>ECASS-1–219</td>
<td>RCT (r-tPA arm)</td>
<td>Europe, Australia, NZ (1992–1994, 1996–1998)</td>
<td>706 (60%)</td>
<td>65±11</td>
<td>13.4±5.8</td>
<td>&lt;3 h</td>
<td>34%</td>
<td>Van Swieten (&gt;2)</td>
<td>24–72 h (CT)</td>
<td>ECASS-2</td>
<td>mRS&gt;2 at 3 mo</td>
</tr>
</tbody>
</table>

ARWMC indicates age-related white matter changes; CT, computed tomography; ECASS-2, European Cooperative Acute Stroke Study; FU, follow-up; LA, intra-arterial; ICH, intracerebral hemorrhage; IST-3, third International Stroke Trial; IV, intravenous; LA, Leukoaraiosis; MRI, magnetic resonance imaging; N/A, not assessed; NIHSS, National Institute of Health Stroke Scale; PH, parenchymal hemorrhage; RCT, randomized controlled trials; r-tPA, recombinant tissue-type plasminogen activator; sICH, symptomatic intracerebral hemorrhage; and tPA, tissue-type plasminogen activator.
Figure 2. Forest plots of leukoaraiosis and risk of post-thrombolysis symptomatic intracerebral hemorrhage. Meta-analysis of the association between symptomatic intracerebral hemorrhage (sICH) risk in patients with acute ischemic stroke treated with thrombolysis, in relation to the presence of leukoaraiosis (A) and severe leukoaraiosis (B) on computed tomography (CT) scans (**severe LA was defined with a lower cut-off; effect sizes are consistent with these 2 studies excluded16,17). C, Pooled adjusted odds ratios analysis of cohorts providing relevant data. CI indicates confidence interval; ECASS-1–2, European Cooperative Acute Stroke Study; LA, leukoaraiosis; OR, odds ratio; RCT, randomized controlled trial; rt-PA, recombinant tissue-type plasminogen activator; and sLA, severe leukoaraiosis.
for one study which used magnetic resonance imaging\(^{17}\), and assessed post-thrombolysis sICH based on clinically relevant definitions. As detailed later, not all studies provided the same range of outcome measures, resulting in different total number of patients contributing in each meta-analysis. Six studies provided data on severe leukoaraiosis (Table 1)\(^{6,13-15,17,18}\); all used the Van Swieten scale,\(^{7,8}\) and severe leukoaraiosis was defined as >2 (or >4 if each hemisphere was rated separately). There was no evidence of publication bias in the funnel plot (data not shown).

The crude prevalence of leukoaraiosis on pretreatment CT scans was 40% (95% CI, 33%–48%), whereas severe leukoaraiosis was found in 15% (95% CI, 10%–20%) of the patients (based on 7/9 studies that provided data on leukoaraiosis severity). Post-treatment sICH occurred in 4% (95% CI, 2%–6%) of patients without any leukoaraiosis versus 6% (95% CI, 4%–8%) in patients with evidence of leukoaraiosis and 9% (95% CI, 6%–12%) in those with severe leukoaraiosis (\(P<0.01\) across the groups, an absolute sICH risk increase of 2% and 5%, respectively). The risk of sICH after IV thrombolysis

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**A Leukoaraiosis and risk of poor outcome (mRS>2) after stroke**

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Events, LA (n/N)</th>
<th>Events, no LA (n/N)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curtze, 2015</td>
<td>2.20 (1.87, 2.60)</td>
<td>659/1320</td>
<td>363/1165</td>
<td>24.90</td>
</tr>
<tr>
<td>Huang, 2013(^{3})</td>
<td>5.02 (1.51, 16.73)</td>
<td>13/17</td>
<td>33/84</td>
<td>4.26</td>
</tr>
<tr>
<td>Ariës, 2010</td>
<td>3.55 (2.08, 6.05)</td>
<td>76/97</td>
<td>153/303</td>
<td>13.26</td>
</tr>
<tr>
<td><strong>Subtotal:</strong> (p&lt;0.0001) ((I^2=54.6%), (p=0.111))</td>
<td>**2.81 (1.81, 4.36))</td>
<td><strong>748/1434</strong></td>
<td><strong>549/1552</strong></td>
<td><strong>42.42</strong></td>
</tr>
<tr>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demchuk, 2008(^{35})</td>
<td>2.01 (1.21, 3.33)</td>
<td>67/99</td>
<td>102/200</td>
<td>14.03</td>
</tr>
<tr>
<td>IST-3, 2015</td>
<td>1.74 (1.41, 2.16)</td>
<td>534/765</td>
<td>423/742</td>
<td>23.46</td>
</tr>
<tr>
<td>ECASS-1, 2002</td>
<td>1.23 (0.90, 1.68)</td>
<td>128/241</td>
<td>223/465</td>
<td>20.09</td>
</tr>
<tr>
<td><strong>Subtotal:</strong> (p=0.001) ((I^2=52.0%), (p=0.124))</td>
<td>**1.59 (1.22, 2.08))</td>
<td><strong>729/1105</strong></td>
<td><strong>748/1407</strong></td>
<td><strong>57.58</strong></td>
</tr>
<tr>
<td><strong>Overall:</strong> (p&lt;0.0001) ((I^2=73.3%), (p=0.002), (X^2=18.84))</td>
<td>**2.02 (1.54, 2.65))</td>
<td><strong>1477/2539</strong></td>
<td><strong>1297/2959</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

**B Adjusted meta-analysis forest plot: leukoaraiosis and poor outcome (mRS>2)**

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curtze, 2015</td>
<td>2.52 (2.11, 3.02)</td>
<td>36.69</td>
</tr>
<tr>
<td>Huang, 2013</td>
<td>1.20 (1.02, 1.41)</td>
<td>45.00</td>
</tr>
<tr>
<td>Ariës, 2010</td>
<td>2.39 (1.21, 4.72)</td>
<td>2.55</td>
</tr>
<tr>
<td>ECASS-1, 2002</td>
<td>1.21 (0.92, 1.59)</td>
<td>15.76</td>
</tr>
<tr>
<td><strong>Overall:</strong> (p&lt;0.0001) ((I^2=92.9%), (p&lt;0.001))</td>
<td>**1.61 (1.44, 1.79))</td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

**Figure 3.** Forest plots of leukoaraiosis and risk of poor functional outcome. **A,** Pooled analysis of poor functional outcome 3 to 6 months poststroke according to leukoaraiosis presence, in the subset of cohorts providing relevant data. **B,** Pooled adjusted odds ratios analysis for poor outcome in cohorts providing relevant data. Poor outcome was defined as mRS>2 at 3 months in 3 studies,\(^{6,14,18}\) mRS≥2 at 3 months in 2 studies (**effect sizes are consistent with these 2 studies excluded**),\(^{15,19}\) and Oxford Handicap scale >2 at 6 months in the IST-3 trial.\(^{4}\) CI indicates confidence interval; ECASS-1–2, European Cooperative Acute Stroke Study; IST-3, third International Stroke Trial; LA, leukoaraiosis; mRS, modified Rankin scale; OR, odds ratio; and RCT, randomized controlled trials.
Leukoaraiosis in Ischemic Stroke Thrombolysis

Table 2. Univariable Random Effects Meta-Regression Analyses of the Association Between Key Characteristics of Included Cohorts and Post-Thrombolysis Symptomatic Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Potential Confounder</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (per year increase)</td>
<td>1.03</td>
<td>0.92–1.16</td>
<td>0.465</td>
</tr>
<tr>
<td>NIHSS at presentation</td>
<td>1.00</td>
<td>0.74–1.34</td>
<td>0.963</td>
</tr>
<tr>
<td>Glucose at admission, mmol/L</td>
<td>0.44</td>
<td>0.14–1.39</td>
<td>0.108</td>
</tr>
<tr>
<td>Mean systolic blood pressure, mm Hg</td>
<td>1.11</td>
<td>0.66–1.85</td>
<td>0.485</td>
</tr>
<tr>
<td>Mean diastolic blood pressure, mm Hg</td>
<td>0.74</td>
<td>0.07–7.95</td>
<td>0.350</td>
</tr>
<tr>
<td>Prevalence of hypertension</td>
<td>0.13</td>
<td>7.90e-14 to 2.21e+11</td>
<td>0.529</td>
</tr>
</tbody>
</table>

Results presented are for the meta-analysis shown in Figure 2A. CI indicates confidence interval; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

was found to be higher in patients with evidence of leukoaraiosis, when compared with patients without leukoaraiosis on CT screening (OR, 1.55; 95% CI, 1.17–2.06; P=0.002; Figure 2A). This risk was even higher in AIS patients with severe leukoaraiosis versus those without (OR, 2.53; 95% CI, 1.92–3.34; P<0.0001; Figure 2B). No evidence of substantial statistical heterogeneity was found using I-squared tests (Figure 2), whereas visual inspection of the funnel plots and the Egger’s statistical test revealed no evidence of publication bias. sICH risk was higher in observational studies and marginal for RCTs in separate sensitivity analyses (Figure 2A and 2B). Six of the included studies (n=4976 patients, 71% of the whole included patient population in the systematic review) provided adjusted effect sizes of the independent association between leukoaraiosis and sICH in multivariable analyses (adjusted for different covariates depending on each study’s results; see Table I in the online-only Data Supplement).3,14,18,19 In a pooled sensitivity analysis of these studies, leukoaraiosis remained an independent predictor of poor outcome, with an adjusted OR of 1.61 (95% CI, 1.44–1.79; P<0.0001), but high degree of statistical heterogeneity (Figure 3B). Leukoaraiosis was also a predictor or poor outcome defined as mRS≥1, in a sensitivity unvariable analysis of 4 studies which had extractable data (OR, 1.76; 95% CI, 1.23–2.51; P=0.002; F=69.2%, P=0.021; see Figure I in the online-only Data Supplement).

No significant confounding was noted in meta-regression analyses (when relevant data were provided) according to age and initial stroke severity (as measured by NIHSS) for any of the outcomes (all P values >0.1). The meta-regression results for the overall meta-analysis in Figure 1A are summarized in Table 2. All results remained consistent and of similar effect size in fixed effects models (results not shown).

Sub-Analyses of Patients With Leukoaraiosis Receiving tPA Versus Placebo in RCTs

In post hoc analyses, including only patients with leukoaraiosis in RCTs (IST-3 [third International Stroke Trial], NINDS [National Institute of Neurological Disorders and Stroke], ECASS-1–2; n=2234),4,15,18 tPA versus control was associated with higher sICH risk (7.9% versus 3.4%; Figure 4A), but these patients still benefited in terms of their 3- to 6-month outcome (OR for poor outcome: 0.75; 95% CI, 0.60–0.95 for tPA versus control; Figure 4B) without statistical heterogeneity. The effect sizes were consistent in sensitivity analyses grouped by the same mRS cutoffs (mRS≥2; n=7011518, OR, 0.62; 95% CI, 0.45–0.86; F=0% or mRS>2; n=203418, OR, 0.75; 95% CI, 0.55–1.03; F=56%).

Discussion

This meta-analysis of ≈7000 AIS patients treated with IV tPA suggests that any degree of preexisting leukoaraiosis on brain CT scans might be associated with a higher risk of early symptomatic intracerebral bleeding. In patients with severe leukoaraiosis, this risk might be more than doubled in comparison to patients without leukoaraiosis in a pooled unadjusted analysis. The presence of leukoaraiosis was also associated with nearly 2-time increase in the risk of moderate disability requiring some assistance in activities of daily living poststroke in this patient population. The results remained consistent and of similar effect size (but with a medium-to-high degree of statistical heterogeneity) in sensitivity-adjusted pooled analyses. Although tPA increased the risk of sICH by >5-fold in the patients with leukoaraiosis included in RCTs, these patients still demonstrated an overall net clinical benefit in their 3- to 6-month functional outcome, as compared with placebo.

Our meta-analysis demonstrates an association between leukoaraiosis and the risk of hemorrhagic intracranial complications and poor outcome post-IV thrombolysis, further supporting the clinical relevance of small vessel disease in this setting. Rather than causing sICH and poor outcome directly, leukoaraiosis could be considered a marker of brain frailty and a chronic microvascular disease state, likely interacting with...
other risk factors to lower the threshold for the adverse outcomes. For example, small vessel disease is associated with endothelial dysfunction,\(^20\) which in relation to matrix metalloproteinase cascade upregulation, disruption of the blood brain barrier, and hyperglycemia and hypertension in the acute stroke setting,\(^21,22\) might modify the cerebral tissue response to IV thrombolysis. This hypothesis is also supported by the findings of a similar risk of bleeding and poor outcome after thrombolysis in association with cerebral microbleeds on pretreatment magnetic resonance imaging, another marker of severely diseased small cerebral vasculature.\(^23,24\) Furthermore, evidence exists linking the microbleed count with the overall burden of leukoaraiosis.\(^25,26\) Although microbleeds, as compared with leukoaraiosis, may be a more specific marker of a bleeding-prone form of small vessel disease, they can only be detected on the blood product–sensitive magnetic resonance imaging sequences. Because magnetic resonance imaging is often not the first-line imaging modality in the AIS evaluation, including microbleed count in decision-making for IV tPA administration cannot be easily translated into clinical practice. Another potential link between leukoaraiosis and poor outcomes might be via dementia.\(^3\) Although these hypotheses are plausible, a direct link between leukoaraiosis and risk of sICH cannot be excluded.

Cerebral small vessel disease, the likely main mechanism of leukoaraiosis, is an important cause of both ischemic stroke and ICH. Of note, even in the general population, leukoaraiosis is shown to be associated with an increased risk of ICH.\(^2\)

The association between leukoaraiosis and poor functional outcome poststroke is not entirely unexpected, given that severe

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**Figure 4.** Forest plot of exploratory subanalyses of randomized controlled trials (RCTs) showing the effect of treatment (tPA vs control) in patients with LA on symptomatic intracerebral hemorrhage (sICH) (A) and poor outcome (B) risk. CI indicates confidence interval; ECASS-1–2, European Cooperative Acute Stroke Study; IST-3, third International Stroke Trial; LA, leukoaraiosis; OR, odds ratio; and tPA, tissue-type plasminogen activator.
leukoaraiosis independently predicts a more rapid decline in global functioning in older people, as demonstrated in the LADIS study (Leukoaraiosis and Disability).27 Preexisting burden of leukoaraiosis is also linked to poor cerebral tissue and clinical outcomes in AIS patients.28,29 These data, along with the abundant evidence of association between leukoaraiosis and dementia, depression, gait disturbances, and falls (all conditions that interfere with stroke recovery),2 support the role of chronic microvascular brain injury in modulation of functional outcomes after stroke. Future studies should further explore the link between leukoaraiosis and poststroke outcome, using different mRS cutoffs, for example, mRS>1 as in RCTs of thrombolysis.

Several methodological aspects of the included studies and limitations of our analyses deserve careful consideration. First, the visual rating schemes for leukoaraiosis assessment slightly varied between studies, although this is unlikely to have affected the prevalence of any or severe leukoaraiosis. A previous study indicated that despite differences, the validated visual rating scales for leukoaraiosis correlate well, especially the van Swieten and Fazekas scales.30 Second, the incidence of sICH after IV thrombolysis might vary according to the clinical, radiological, and time criteria used to define it. However, most definitions used across centers included sICH associated with clinical deterioration and, hence, are likely to be clinically relevant. An important source of heterogeneity is the inclusion of both observational (retrospective and prospective) studies and RCTs. Estimates in separate sensitivity analyses indicated that the effect size is greater in observational studies than in RCTs (but still in the same direction), raising a concern about bias and inflation of the overall results by the non-RCTs. For example, the study by Curtze et al.,3,5 the largest prospective observational study on the topic, provided similarly conservative effect estimates to RCTs,4,15,18 in contrast to retrospective small studies. Finally, the main limitation of our analysis is that it is not fully adjusted for other important variables that can potentially affect the risk for thrombolysis-related sICH and outcome, such as time from stroke onset to IV thrombolysis, baseline serum glucose, infarct volume, early ischemic CT signs, prestroke functional status, and so on. It is possible that certain variables, such as age and hypertension, might be strongly associated with sICH and both leukoaraiosis and stroke outcome. Age and hypertension might, thus, account for some portion of these relationships, despite these potential risks, patients with leukoaraiosis still seem to benefit clinically from IV tPA, as indicated in our sub-analysis of RCTs.4,31 Accordingly, our results do not justify withholding IV thrombolysis from otherwise eligible candidates solely on the basis of leukoaraiosis present on brain CT. The data presented here, however, reinforce the need for further investigation of the clinical relevance of small vessel disease markers in large multicenter studies of acute stroke and form the basis for an individual–patient data meta-analysis on the topic.

Conclusions

Although our analysis demonstrates that preexisting leukoaraiosis might increase the risk of early sICH after thrombolysis and poor outcome poststroke, it is important to note that despite these potential risks, patients with leukoaraiosis still seem to benefit clinically from IV tPA, as indicated in our sub-analysis of RCTs.4,31 Accordingly, our results do not justify withholding IV thrombolysis from otherwise eligible candidates solely on the basis of leukoaraiosis present on brain CT. The data presented here, however, reinforce the need for further investigation of the clinical relevance of small vessel disease markers in large multicenter studies of acute stroke and form the basis for an individual–patient data meta-analysis on the topic.

References

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Leukoaraiosis, Cerebral Hemorrhage, and Outcome After Intravenous Thrombolysis for Acute Ischemic Stroke: A Meta-Analysis
Andreas Charidimou, Marco Pasi, Marco Fiorelli, Sara Shams, Rüdiger von Kummer, Leonardo Pantoni and Natalia Rost

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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/47/9/2364

An erratum has been published regarding this article. Please see the attached page for:
http://stroke.ahajournals.org/content/suppl/2016/08/16/STROKEAHA.116.014096.DC1

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/08/16/STROKEAHA.116.014096.DC1
In the article by Charidimou et al, “Leukoaraiosis, Cerebral Hemorrhage, and Outcome After Intravenous Thrombolysis for Acute Ischemic Stroke: A Meta-Analysis (v1),” which published online on August 4, 2016, and appeared in the September 2016 issue of the journal (Stroke. 2016;47:2364–2372. DOI: 10.1161/STROKEAHA.116.014096), a correction is needed.

On page 2364, in title, “(v1)” is removed to read, “Leukoaraiosis, Cerebral Hemorrhage, and Outcome After Intravenous Thrombolysis for Acute Ischemic Stroke: A Meta-Analysis.”

This correction has been made to the current online version of the article, which is available at http://stroke.ahajournals.org/content/47/9/2364.
Supplemental Tables

Supplemental Table 1. Extracted data from multivariable analyses of included studies on the independent effect of different variables on the main outcomes of the meta-analyses: A. Symptomatic intracerebral haemorrhage (ICH) and B. poor functional outcome at 3-6 months.

### A. sICH

<table>
<thead>
<tr>
<th></th>
<th>Age (year)</th>
<th>NIHSS</th>
<th>Early CT sign</th>
<th>Leukoaraiosis</th>
<th>HTN</th>
<th>diabetes</th>
<th>statin</th>
<th>Onset to treatment</th>
<th>Blood glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curtze 2015¹</td>
<td>1.24 (0.82–1.89)</td>
<td>2.37 (1.50–3.76)</td>
<td>2.33 (1.53–3.55)</td>
<td>2.62 (1.71–4.02)</td>
<td>1.07 (0.69–1.65)</td>
<td>1.02 (0.59–1.75)</td>
<td>1.61 (1.06–2.45)</td>
<td>1.77 (1.08–2.90)</td>
<td>1.61 (1.13–2.29)</td>
</tr>
<tr>
<td>Palumbo, 2007²</td>
<td>X</td>
<td>X</td>
<td>N/A</td>
<td>√</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>√</td>
</tr>
<tr>
<td>Costello, 2012³</td>
<td>X</td>
<td>1.00 0.96–1.05</td>
<td>√ 1.13 1.01–1.27</td>
<td>X 0.47 0.05–4.23</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Willer, 2015⁴</td>
<td>√</td>
<td>X</td>
<td>dense artery sign X</td>
<td>X</td>
<td>Systolic BP X</td>
<td>N/A</td>
<td>N/A</td>
<td>X</td>
<td>¹</td>
</tr>
<tr>
<td>Aries, 2010⁵</td>
<td>X</td>
<td>√ 1.09 1.02–1.17</td>
<td>X 1.90 0.78–4.68</td>
<td>Systolic BP X</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A N/A</td>
<td>1.19 0.99–1.44</td>
</tr>
<tr>
<td>Neumann-Haefelin, 2009⁶</td>
<td>X</td>
<td>√</td>
<td>N/A</td>
<td>√ 2.9</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>ECASS-1-2⁷</td>
<td>√</td>
<td>-</td>
<td>N/A</td>
<td>X</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
<td>X X</td>
<td></td>
</tr>
</tbody>
</table>

### B. mRS>2, 3-6 months

<table>
<thead>
<tr>
<th></th>
<th>Age (year)</th>
<th>NIHSS</th>
<th>Early CT sign</th>
<th>Leukoaraiosis</th>
<th>HTN</th>
<th>diabetes</th>
<th>statin</th>
<th>Onset to treatment</th>
<th>Blood glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curtze, 2015⁸</td>
<td>1.53 (1.37–1.70)</td>
<td>2.27 (2.10–2.47)</td>
<td>2.27 (2.10–2.47)</td>
<td>1.82 (1.50–2.20)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1.51 (1.28–1.78)²</td>
<td>1.68 (1.41–2.01)</td>
</tr>
</tbody>
</table>

X: no association in multivariable analyses  
n/a: variable not included in multivariable analyses  
√: variable independently associated in multivariable analyses  
OR and CI are provided only when reported

sICH:

Curtze 2015¹ - Multivariable Model: age, onset to treatment, early infarct sign, Whalund scale > 1, blood glucose at admission, hyperdensity artery sign, diabetes mellitus, atrial fibrillation, hypertension, statin use, NIHSS at admission

Costello, 2012³ - Multivariable Model: age, NIHSS, Leukoaraiosis

Aries, 2010⁵ - Multivariable Model: antiplatelet therapy, age, NIHSS score, early ischaemic changes, serum glucose level, hypertension, smoking, hyperlipidaemia, gender, atrial fibrillation, previous stroke/TIA

Neumann-Haefelin, 2009⁶ - Multivariable Model: Age, NIHSS, IA or IV thrombolysis were included in the multivariable model, LA

mRS 2-3

Curtze, 2015⁸ - Multivariable Model: age, onset to treatment, early infarct sign, Blennow scale > 3 (LA), blood glucose at admission, hyperdensity artery sign, NIHSS at admission
Supplemental Figure

Supplementary Figure 1. Forest plots of leukoaraiosis and risk of poor outcome (defined as mRS>1) after stroke. Pooled analysis of poor functional outcome 3-6 months post-stroke according to leukoaraiosis presence, in the subset of cohorts providing relevant data.
Supplemental References


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