Blood Markers of Coagulation, Fibrinolysis, Endothelial Dysfunction and Inflammation in Lacunar Stroke versus Non-Lacunar Stroke and Non-Stroke: Systematic Review and Meta-Analysis

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Key Words
Biomarker · Endothelium · Inflammation · Stroke · Lacunar stroke

Abstract

Background: The cause of cerebral small vessel disease is not fully understood, yet it is important, accounting for about 25% of all strokes. It also increases the risk of having another stroke and contributes to about 40% of dementias. Various processes have been implicated, including microatheroma, endothelial dysfunction and inflammation. A previous review investigated endothelial dysfunction in lacunar stroke versus mostly non-stroke controls while another looked at markers of inflammation and endothelial damage in ischaemic stroke in general. We have focused on blood markers between clinically evident lacunar stroke and other subtypes of ischaemic stroke, thereby controlling for stroke in general. Summary: We systematically assessed the literature for studies comparing blood markers of coagulation, fibrinolysis, endothelial dysfunction and inflammation in lacunar stroke versus non-stroke controls or other ischaemic stroke subtypes. We assessed the quality of included papers and meta-analysed results. We split the analysis on time of blood draw in relation to the stroke. We identified 1,468 full papers of which 42 were eligible for inclusion, including 4,816 ischaemic strokes, of which 2,196 were lacunar and 2,500 non-stroke controls. Most studies subtyped stroke using TOAST. The definition of lacunar stroke varied between studies. Markers of coagulation/fibrinolysis (tissue plasminogen activator (tPA), plasminogen activator inhibitor (PAI), fibrinogen, D-dimer) were higher in lacunar stroke versus non-stroke although fibrinogen was no different to non-stroke in the acute phase. tPA and PAI were no different between lacunar and non-lacunar stroke. Fibrinogen and D-dimer were significantly lower in lacunar stroke compared to other ischaemic strokes, both acutely and chronically. Markers of endothelial dysfunction (homocysteine, von Willebrand Factor (vWF), E-selectin, P-selectin, intercellular adhesion molecule-1 (ICAM), vascular cellular adhesion molecule-1 (VCAM)) were higher or had insufficient or conflicting data (P-selectin, VCAM) in lacunar stroke versus non-stroke. Compared to other ischaemic stroke subtypes, homocysteine did not differ in lacunar stroke while vWF was significantly lower in lacunar stroke acutely [atherothrombotic standardized mean difference, SMD, –0.34 (–0.61, –0.08); cardioembolic SMD –0.38 (–0.62, –0.14)], with insufficient data chronically. Markers of inflammation (C-reactive protein (CRP), tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6)) were higher in lacunar stroke versus non-stroke, although there were no studies measuring TNF-α chronically and the sole study measuring IL-6 chroni-
cally showed no difference between lacunar stroke and non-stroke. Compared to other ischaemic stroke subtypes, there was no difference (CRP) or insufficient or conflicting data (TNF-α) to lacunar stroke. IL-6 was significantly lower [atherothrombotic SMD –0.37 (–0.63, –0.10); cardioembolic SMD –0.52 (–0.82, –0.22)] in lacunar stroke acutely, with insufficient data chronically. **Key Messages:** Lacunar stroke is an important stroke subtype. More studies comparing lacunar stroke to non-lacunar stroke specifically, rather than to non-stroke controls, are needed. Prospective studies with measurements taken well after the acute event are more likely to be helpful in determining pathogenesis. The available data in this review were limited and do not exclude the possibility that peripheral inflammatory processes including endothelial dysfunction are associated with lacunar stroke and cerebral small vessel disease.

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**Introduction**

Lacunar stroke is an important stroke subtype, accounting for one quarter of ischaemic strokes. Its aetiology probably differs from other stroke subtypes, usually being the symptomatic manifestation of small vessel disease rather than large vessel atheroma or cardioembolism.

A previous review [1] of symptomatic lacunar stroke versus mainly non-stroke controls suggests a pathogenic role for endothelial dysfunction but this could simply reflect having an ischaemic stroke in general [2]. Another review [3] found C-reactive protein (CRP), P-selectin and homocysteine to differ significantly between ischaemic stroke (in general) and non-stroke controls, but did not assess levels of blood markers between ischaemic stroke subtypes.

We sought to clarify if differences exist in blood markers between lacunar stroke and other ischaemic stroke subtypes by reviewing the literature for studies measuring coagulation, fibrinolysis, endothelial dysfunction and inflammation. We sought to disentangle the acute phase response by splitting the analysis on timing of the blood draw in relation to the stroke.

**Methods**

This review has been prepared in accordance with The PRISMA statement [4]. We extracted data and conducted the meta-analysis in accordance with MOOSE [5], which was modified for our needs using 3 reporting standards [6–8].

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**Review of Blood Markers in Lacunar Stroke**

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ranges or minimum and maximum values, as we could not assume normality of distributions. Consequently, tPA, PAI, E-selectin, P-selectin, ICAM, VCAM, CRP and TNF-α were reviewed solely by summary of individual study data. Where studies provided data at more than one acute time point, we meta-analysed only the first time point as this most often corresponded with data for non-stroke comparators. In order to see if an acute phase response affected the results we split our analysis into ‘acute’ and ‘chronic’ (bloods drawn up to and after 21 days of stroke, respectively).

Results

We identified 1,468 full papers. In all, 1,389 titles were excluded following a survey of titles and abstracts, leaving 79 for reading. Of these 10 were excluded (unable to translate) and 32 did not meet inclusion criteria (duplicates, asymptomatic subjects, non-relevant blood markers and no control group). Hand-searching identified a further 5 papers. Therefore, 42 papers were eligible, including 4,816 ischaemic strokes, of which 2,196 were lacunar and 2,500 non-stroke controls (see online suppl. fig. 1 and suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000356789). In a further 4 papers [15–18] blood was collected prior to stroke. These studies are reported separately (see online suppl. material).

Critical Appraisal of Included Studies

Over 50% of studies (22/42) used TOAST [19] to subtype ischaemic stroke. Just 4 studies [11, 20–22] (fewer than 10%) met our gold standard definition of lacunar stroke. More than half of the studies (57%) reported a ‘minimal’ definition of lacunar stroke; 1 study [23] failed to define lacunar stroke. Most studies recruited patients consecutively (31/42); 1 study recruited non-consecutively [20] and 10/42 did not report on recruitment. Two thirds of studies reported excluding cases based on co-existing disease such as concurrent infection, cancer, inflammatory disease and renal failure. One third of studies did not report on exclusion criteria. Most studies reported matching controls by age and sex to cases (24/42). Some studies matched age only (6/42) and 1 study matched sex only; 3 studies did not report on matching. Matching for co-morbidities varied from study to study. Less than 20% of studies (8/42) reported blinding of stroke assessor to blood marker values. Fewer still reported blinding of laboratory staff to stroke data (see online suppl. tables 3 and 4 for critical appraisal of included studies).

Plasma Markers

Coagulation/Fibrinolysis

Tissue Plasminogen Activator. Here, we included 5 studies [24–28] (251 lacunar strokes) of which 1 study [26] contributed 50% of the data. There were insufficient data in an appropriate format for meta-analysis. Individual studies suggest tPA was significantly higher in lacunar stroke versus non-stroke controls, both acutely and chronically. Meanwhile, tPA does not appear to differ between lacunar stroke and other stroke subtypes, either acutely or chronically.

Plasminogen Activator Inhibitor. A total of 7 studies were included [24–30] (336 lacunar strokes) but available data did not permit meta-analysis. Jood et al. [26] report levels of PAI significantly higher in lacunar stroke versus non-stroke controls acutely and chronically. They also report lower PAI in lacunar stroke versus atherothrombotic and cardioembolic stroke acutely (significance not given) but not chronically [26]; 4 other studies report no difference between lacunar and non-lacunar stroke acutely [24, 27–29].

Fibrinogen. We included 9 studies [20, 23, 25, 31–36] (622 lacunar strokes) of which 6 permitted a meta-analysis (fig. 1). Fibrinogen showed no difference in lacunar stroke versus non-stroke controls acutely but was significantly higher in lacunar stroke chronically. Fibrinogen was significantly lower in lacunar stroke versus other ischaemic stroke subtypes, both acutely [atherothrombotic SMD –0.37 (95% CI –0.51, –0.22); cardioembolic SMD –0.83 (–1.15, –0.51)] and chronically (fig. 1), although the chronic data comprised only 1 study [32]. In 2 [31, 34] of 3 [31, 33, 34] studies that could not be meta-analysed no difference was reported in levels of fibrinogen between lacunar and non-lacunar stroke in the acute phase; the third study [33] did not report on whether its findings were significant.

D-Dimer. Here, 9 studies were included [25, 30, 32, 34, 37–41] (364 lacunar strokes) of which 4 could be meta-analysed (fig. 2). D-dimer was significantly higher in lacunar stroke versus non-stroke controls, both acutely [SMD 1.42 (1.14, 1.69)] and chronically [SMD 3.22 (2.65, 3.78)]. D-dimer was significantly lower in lacunar versus other ischaemic stroke subtypes, both acutely [atherothrombotic SMD –3.59 (–4.06, –3.12)] and cardioembolic [acute SMD –5.73 (–6.38, –5.09)], acutely and chronically.

The largest (n = 128 lacunar strokes) of the 5 studies [39] that could not be meta-analysed found no difference in D-dimer between lacunar and atherothrombotic stroke acutely (which disagrees with the meta-analysis) and
Fig. 1. Forest plot – fibrinogen: SMD of blood markers in lacunar stroke versus non-stroke controls and versus non-lacunar stroke controls at different times after stroke. AT = Atherothrombotic; CE = cardioembolic; ON = on admission.
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lacunar mean</th>
<th>Lacunar SD</th>
<th>Lacunar total</th>
<th>Non-lacunar mean</th>
<th>Non-lacunar SD</th>
<th>Non-lacunar total</th>
<th>SMD IV, fixed (95% CI)</th>
<th>SMD IV, fixed (95% CI)</th>
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<tbody>
<tr>
<td><strong>Lacunar vs. non-stroke (acute)</strong></td>
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<tr>
<td>Takano [37], 1992 (1 day)</td>
<td>115.3</td>
<td>15.5</td>
<td>23</td>
<td>82.1</td>
<td>9.1</td>
<td>20</td>
<td>2.52 (1.70, 3.34)</td>
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<tr>
<td>Ageno [38], 2002 (1 day)</td>
<td>0.67</td>
<td>0.08</td>
<td>31</td>
<td>0.53</td>
<td>0.14</td>
<td>63</td>
<td>1.12 (0.66, 1.58)</td>
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<tr>
<td>Kataoka [32], 2000 (&lt;48 h)</td>
<td>0.7</td>
<td>0.1</td>
<td>58</td>
<td>0.6</td>
<td>0.1</td>
<td>32</td>
<td>0.99 (0.54, 1.45)</td>
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<td>Ilhan [30], 2010 (0–5 days)</td>
<td>1.36</td>
<td>0.62</td>
<td>30</td>
<td>0.35</td>
<td>0.21</td>
<td>30</td>
<td>2.15 (1.51, 2.80)</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>142</td>
<td>145</td>
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<td>1.42 (1.14, 1.69)</td>
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<td>Heterogeneity: $\chi^2 = 16.89$, d.f. = 3 ($p = 0.0007$), $I^2 = 82%$</td>
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<td><strong>Lacunar vs. non-stroke (chronic)</strong></td>
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<tr>
<td>Kataoka [32], 2000 (3 weeks)</td>
<td>1.5</td>
<td>0.2</td>
<td>58</td>
<td>0.6</td>
<td>0.1</td>
<td>32</td>
<td>5.20 (4.31, 6.09)</td>
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<tr>
<td>Takano [37], 1992 (30 days)</td>
<td>110</td>
<td>18</td>
<td>23</td>
<td>82.1</td>
<td>9.1</td>
<td>20</td>
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<td>81</td>
<td>52</td>
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<td>3.22 (2.65, 3.78)</td>
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<td><strong>Lacunar vs. AT (acute)</strong></td>
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<td>Takano [37], 1992 (1 day)</td>
<td>115.3</td>
<td>15.5</td>
<td>23</td>
<td>171.3</td>
<td>29.4</td>
<td>10</td>
<td>−2.66 (−3.67, −1.65)</td>
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<tr>
<td>Ageno [38], 2002 (1 day)</td>
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<td>0.08</td>
<td>31</td>
<td>1.34</td>
<td>0.21</td>
<td>34</td>
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<td>Kataoka [32], 2000 (&lt;48 h)</td>
<td>0.7</td>
<td>0.1</td>
<td>58</td>
<td>1.7</td>
<td>0.4</td>
<td>41</td>
<td>−3.70 (−4.36, −3.04)</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td>85</td>
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<td>−3.59 (−4.06, −3.12)</td>
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<td>Heterogeneity: $\chi^2 = 4.64$, d.f. = 2 ($p = 0.10$), $I^2 = 57%$</td>
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<td>Test for overall effect: $Z = 15.06$ ($p &lt; 0.00001$)</td>
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<td><strong>Lacunar vs. AT (chronic)</strong></td>
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<td>Kataoka [32], 2000 (3 weeks)</td>
<td>1.5</td>
<td>0.2</td>
<td>58</td>
<td>2.3</td>
<td>0.4</td>
<td>41</td>
<td>−2.65 (−3.20, −2.10)</td>
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<td>Takano [37], 1992 (30 days)</td>
<td>110</td>
<td>18</td>
<td>23</td>
<td>125</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td>51</td>
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<td>−2.02 (−2.47, −1.58)</td>
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<td>Test for overall effect: $Z = 8.86$ ($p &lt; 0.00001$)</td>
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<td><strong>Lacunar vs. CE (acute)</strong></td>
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<td>Takano [37], 1992 (1 day)</td>
<td>115.3</td>
<td>15.5</td>
<td>23</td>
<td>607</td>
<td>167.6</td>
<td>21</td>
<td>−4.16 (−5.24, −3.07)</td>
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<tr>
<td>Ageno [38], 2002 (1 day)</td>
<td>0.67</td>
<td>0.08</td>
<td>31</td>
<td>2.96</td>
<td>0.51</td>
<td>34</td>
<td>−6.06 (−7.24, −4.88)</td>
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<tr>
<td>Kataoka [32], 2000 (&lt;48 h)</td>
<td>0.7</td>
<td>0.1</td>
<td>58</td>
<td>3</td>
<td>0.5</td>
<td>38</td>
<td>−7.06 (−8.16, −5.96)</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>112</td>
<td>93</td>
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<td>−5.73 (−6.38, −5.09)</td>
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<td>Heterogeneity: $\chi^2 = 14.01$, d.f. = 2 ($p = 0.0009$), $I^2 = 86%$</td>
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<td>Test for overall effect: $Z = 17.39$ ($p &lt; 0.00001$)</td>
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<td><strong>Lacunar vs. CE (chronic)</strong></td>
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<tr>
<td>Kataoka [32], 2000 (3 weeks)</td>
<td>1.5</td>
<td>0.2</td>
<td>58</td>
<td>3.2</td>
<td>0.5</td>
<td>38</td>
<td>−4.82 (−5.62, −4.01)</td>
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<tr>
<td>Takano [37], 1992 (30 days)</td>
<td>110</td>
<td>18</td>
<td>23</td>
<td>255</td>
<td>40</td>
<td>21</td>
<td>−4.67 (−5.85, −3.48)</td>
<td>—</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>81</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
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<td>−4.77 (−5.43, −4.10)</td>
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<tr>
<td>Heterogeneity: $\chi^2 = 0.04$, d.f. = 1 ($p = 0.84$), $I^2 = 0%$</td>
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<tr>
<td>Test for overall effect: $Z = 14.03$ ($p &lt; 0.00001$)</td>
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**Fig. 2.** Forest plot – D-dimer: SMD of blood markers in lacunar stroke versus non-stroke controls and versus non-lacunar stroke controls at different times after stroke. AT = Atherothrombotic; CE = cardioembolic.
Study or subgroup                  Lacunar mean (SD) total  Non-lacunar mean (SD) total  SMD IV, fixed (95% CI)  SMD IV, fixed (95% CI)  
Lacunar vs. non-stroke (acute)     
Parnetti [42], 2004 (NS)           13.9 (5.4) 50 8.1 (2.5) 152  1.68 (1.32, 2.04)  
Jeong [44], 2011 (3 days)          11.3 (3.8) 83 11.2 (3.4) 135  0.03 (–0.25, 0.30)  
Khan [9], 2008 (2–3 days)          16.2 (11.6) 152 11.8 (5.7) 179  0.49 (0.27, 0.71)  
Eikelboom [11], 2000 (<7 days)     12.7 (5.57) 68 10.5 (3.63) 205  0.52 (0.24, 0.80)  
Subtotal (95% CI)                  353 671 0.55 (0.42, 0.69)  
Heterogeneity: $\chi^2 = 52.05$, d.f. = 3 (p < 0.00001), $I^2 = 94%$ 
Test for overall effect: Z = 8.03 (p < 0.00001)  

Lacunar vs. non-stroke (chronic)   
Hassan [12], 2004 (>2 months)      14.5 (5.21) 172 12.0 (4.05) 172  0.53 (0.32, 0.75)  
Khan [9], 2007 (>3 months)         15.14 (5.59) 47 12.49 (4.15) 38  0.53 (0.09, 0.96)  
Pavlovic [45], 2011 (1–6 months)   14.4 (5) 95 8.9 (3.9) 41  1.16 (0.77, 1.56)  
Subtotal (95% CI)                  314 251 0.66 (0.48, 0.83)  
Heterogeneity: $\chi^2 = 8.02$, d.f. = 2 (p = 0.02), $I^2 = 75%$ 
Test for overall effect: Z = 7.42 (p < 0.00001) 

Lacunar vs. AT (acute)             
Parnetti [42], 2004 (NS)           13.9 (5.4) 50 17.8 (13.5) 43  –0.39 (–0.80, 0.02)  
Beer [35], 2011 (3 days)           10.1 (3.6) 25 9.9 (4.9) 19  0.05 (–0.55, 0.64)  
Khan [9], 2008 (2–3 days)          16.2 (11.6) 152 11.6 (4.8) 40  0.43 (0.08, 0.78)  
Eikelboom [11], 2000 (<7 days)     12.7 (5.57) 68 14.1 (6.75) 63  –0.23 (–0.57, 0.12)  
Subtotal (95% CI)                  295 165 –0.02 (–0.22, 0.18)  
Heterogeneity: $\chi^2 = 10.89$, d.f. = 3 (p = 0.01), $I^2 = 72%$ 
Test for overall effect: Z = 0.21 (p = 0.83)  

Lacunar vs. CE (acute)             
Parnetti [42], 2004 (NS)           13.9 (5.4) 50 13.2 (2.5) 31  0.20 (–0.25, 0.65)  
Beer [35], 2011 (3 days)           10.1 (3.6) 25 10.2 (3.9) 43  –0.03 (–0.52, 0.47)  
Khan [9], 2008 (2–3 days)          16.2 (11.6) 152 14.3 (6.3) 72  0.19 (–0.10, 0.47)  
Eikelboom [11], 2000 (<7 days)     12.7 (5.57) 68 11.6 (4.82) 45  0.21 (–0.17, 0.58)  
Subtotal (95% CI)                  295 191 0.16 (–0.02, 0.35)  
Heterogeneity: $\chi^2 = 0.66$, d.f. = 3 (p = 0.88), $I^2 = 0%$ 
Test for overall effect: Z = 1.71 (p = 0.09)  

Fig. 3. Forest plot – homocysteine: SMD of blood markers in lacunar stroke versus non-stroke controls and versus non-lacunar stroke controls at different times after stroke. AT = Atherothrombotic; CE = cardioembolic; NS = not stated.
found D-dimer significantly lower in lacunar versus cardioembolic stroke acutely (in agreement with the meta-analysis).

**Endothelial Activation/Dysfunction**

**Homocysteine.** Overall, we included 9 studies [9, 11, 12, 29, 35, 42–45] (747 lacunar strokes) of which 8 could be meta-analysed (fig. 3). Homocysteine was significantly higher in lacunar stroke versus non-stroke controls, both acutely [SMD 0.55 (0.42, 0.69)] and chronically. Studies comparing lacunar to non-lacunar stroke drew blood acutely only and found no difference [atherothrombotic SMD −0.02 (−0.22, 0.18); cardioembolic SMD 0.16 (−0.02, 0.35)]. In 1 study [29] not included in the meta-analysis no difference was found in homocysteine between lacunar and non-lacunar stroke acutely.

**von Willebrand Factor.** We included 6 studies [13, 27, 31, 35, 46, 47] (293 lacunar strokes) of which 2 [13, 35] were meta-analysable (fig. 4). vWF was significantly higher in lacunar stroke versus non-stroke controls acutely. vWF was significantly lower in lacunar versus non-lacunar stroke [atherothrombotic SMD −0.34 (−0.61, −0.08); cardioembolic SMD −0.38 (−0.62, −0.14)] acutely. The 4 non-meta-analysable [27, 31, 46, 47] studies show conflicting results (online suppl. table 1).

**P-Selectin.** A total of 7 studies were included [27, 28, 30, 31, 46, 48, 49] (227 lacunar strokes) but available data did not permit meta-analysis. P-selectin was significantly higher in lacunar stroke versus non-stroke controls acutely but not at 1 month. Individual study reports suggest no difference between lacunar and non-lacunar stroke.

**Intercellular Adhesion Molecule-1.** We included 5 studies [21, 27, 28, 50, 51] (344 lacunar strokes) but available data did not permit meta-analysis. In 1 study [21] significantly higher ICAM was found in lacunar

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**Fig. 4.** Forest plot – vWF: SMD of blood markers in lacunar stroke versus non-lacunar stroke controls at different times after stroke. AT = Atherothrombotic; CE = cardioembolic.

---

**Study or subgroup** | **Lacunar** | **Non-lacunar** | **SMD IV, fixed (95% CI)**
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lacunar vs. AT (acute)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beer [35], 2011 (3 days)</td>
<td>164</td>
<td>56.7</td>
</tr>
<tr>
<td>Hanson [13], 2011 (&lt;10 days)</td>
<td>213</td>
<td>89.64</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>148</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: χ² = 1.75, d.f. = 1 (p = 0.19), I² = 43%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.53 (p = 0.01)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Lacunar vs. CE (acute)**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lacunar</th>
<th>Non-lacunar</th>
<th>SMD IV, fixed (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer [35], 2011 (3 days)</td>
<td>164</td>
<td>56.7</td>
<td>25</td>
</tr>
<tr>
<td>Hanson [13], 2011 (&lt;10 days)</td>
<td>213</td>
<td>89.64</td>
<td>123</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>148</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: χ² = 4.48, d.f. = 1 (p = 0.03), I² = 78%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.11 (p = 0.002)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**E-Selectin.** Here, 4 studies were included [27, 28, 35, 46] (130 lacunar strokes) but available data did not permit meta-analysis; 1 study [46] found E-selectin significantly higher in lacunar stroke versus non-stroke controls acutely but not at 1 month. Individual study reports suggest no difference between lacunar and non-lacunar stroke.

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(C) 2014. Cerebrovasc Dis 2014;37:64–75
DOI: 10.1159/000356789
Wiseman/Marlborough/Doubal/Webb/Wardlaw
another study [50] found ICAM significantly higher in lacunar versus non-stroke controls chronically. There was no difference between lacunar and other stroke subtypes acutely and no data for lacunar versus non-lacunar stroke chronically.

Vascular Cellular Adhesion Molecule-1. Here, 3 studies were included [27, 28, 51] (121 lacunar strokes) but available data did not permit meta-analysis. Results suggested no difference between lacunar stroke and non-stroke acutely and no difference between lacunar and non-lacunar stroke acutely. No studies measured VCAM chronically.

Inflammation

C-Reactive Protein. We included 8 studies [29, 34, 35, 39, 47, 49, 52, 53] (490 lacunar strokes) but available data did not permit meta-analysis; 2 studies [39, 52] provided just over 50% of the data. CRP was higher in lacunar stroke versus non-stroke acutely in 3 studies [34, 49, 52], significantly so in 2, and the other [34] did not report if the higher value was significant. CRP was significantly lower in lacunar versus atherothrombotic stroke in 1 study [34] acutely; all other studies reported no difference (or did not state significance) between lacunar and non-lacunar stroke, acutely and chronically.

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**Table 1: Blood Markers in Lacunar Stroke**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lacunar vs. non-stroke (acute)</th>
<th>Lacunar vs. AT (acute)</th>
<th>Lacunar vs. CE (acute)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lacunar mean SD total</td>
<td>Non-lacunar mean SD total</td>
<td>SMD IV, fixed (95% CI)</td>
</tr>
<tr>
<td>Domac [22], 2007 (12 h)</td>
<td>43.8, 18.5</td>
<td>19</td>
<td>15.1, 4.9</td>
</tr>
<tr>
<td>Guldiken [56], 2008 (&lt;72 h)</td>
<td>8.79, 3.73</td>
<td>16</td>
<td>4.68, 3</td>
</tr>
<tr>
<td>Beamer [23], 1995 (4 days)</td>
<td>2.8, 2.8</td>
<td>23</td>
<td>1, 0.9</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>58</td>
<td>65</td>
<td>1.30 (0.90, 1.70)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 6.79$, d.f. = 2 ($p = 0.03$), $I^2 = 71$
Test for overall effect: $Z = 6.35$ ($p < 0.00001$)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lacunar vs. AT (acute)</th>
<th>Lacunar vs. CE (acute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakase [53], 2008 (ON)</td>
<td>3, 3.7</td>
<td>42</td>
</tr>
<tr>
<td>Domac [22], 2007 (12 h)</td>
<td>43.8, 18.5</td>
<td>19</td>
</tr>
<tr>
<td>Vila [54], 2000 (&lt;24 h)</td>
<td>9.6, 9.3</td>
<td>33</td>
</tr>
<tr>
<td>Guldiken [56], 2008 (&lt;72 h)</td>
<td>8.79, 3.73</td>
<td>16</td>
</tr>
<tr>
<td>Beamer [23], 1995 (4 days)</td>
<td>2.8, 2.8</td>
<td>23</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>133</td>
<td>144</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 35.51$, d.f. = 4 ($p < 0.00001$), $I^2 = 89$
Test for overall effect: $Z = 2.73$ ($p = 0.0006$)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Lacunar vs. CE (acute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakase [53], 2008 (ON)</td>
<td>3, 3.7</td>
</tr>
<tr>
<td>Vila [54], 2000 (&lt;24 h)</td>
<td>9.6, 9.3</td>
</tr>
<tr>
<td>Beamer [23], 1995 (4 days)</td>
<td>2.8, 2.8</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>98</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 8.14$, d.f. = 2 ($p = 0.02$), $I^2 = 75$
Test for overall effect: $Z = 3.40$ ($p = 0.0007$)

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**Fig. 5.** Forest plot – IL-6: SMD of blood markers in lacunar stroke versus non-stroke controls and versus non-lacunar stroke controls at different times after stroke. AT = Atherothrombotic; CE = cardioembolic; ON = on admission.
**Tumour Necrosis Factor-alpha.** Overall, 5 studies were included [21, 22, 27, 47, 53] (252 lacunar strokes) but available data did not permit meta-analysis; 1 study [21] provides 45% of the data. In 2 studies [21, 22] levels of TNF-α were found to be significantly higher in lacunar stroke versus non-stroke controls acutely. TNF-α was significantly lower in 2 [27, 47] and no different in 2 [22, 53] studies reporting on lacunar versus non-lacunar stroke acutely. No studies measured TNF-α chronically.

**Interleukin-6.** A total of 9 studies were included [21–23, 27, 47, 53–56] (340 lacunar strokes) of which 5 could be meta-analysed (fig. 5). IL-6 was significantly higher in lacunar stroke versus non-stroke acutely [SMD 1.3 (0.9, 1.7)], and significantly lower in lacunar versus non-lacunar stroke [atherothrombotic SMD −0.37 (−0.63, −0.10); cardioembolic SMD −0.52 (−0.82, −0.22)] acutely.

In 1 non-meta-analysable study [21] IL-6 was found to be significantly higher in lacunar stroke versus non-stroke acutely, in agreement with the meta-analysed studies; 2 non-meta-analysable studies [27, 47] found IL-6 significantly lower in lacunar versus non-lacunar stroke acutely, also in agreement with the meta-analysed studies.

The only long-term study [55] found no difference between lacunar stroke and non-stroke controls from a wholly female cohort measured 3.5 years after stroke.

**Discussion**

This review assessed blood markers of coagulation, fibrinolysis, endothelial dysfunction and inflammation in lacunar stroke versus non-stroke controls and other ischaemic stroke subtypes. While many markers were higher in lacunar stroke than in non-stroke controls, they were mostly lower in lacunar versus non-lacunar stroke. A brief summary follows.

**Coagulation/Fibrinolysis**

tPA/PAI were significantly higher in lacunar stroke versus non-stroke, acutely and chronically, and did not differ between lacunar and non-lacunar stroke, acutely or chronically.

Fibrinogen did not differ between lacunar stroke and non-stroke acutely, although we only used a single time point from Kataoka et al. [32] (bloods drawn at <24 h). If we consider their second sample (at 7 days) as a further acute measurement, lacunar stroke tends towards being significantly higher than non-stroke. Fibrinogen was significantly higher in lacunar stroke versus non-stroke chronically. Fibrinogen was significantly lower in lacunar versus non-lacunar stroke, acutely and chronically. However, studies excluded from the meta-analysis tended to show no overall difference between lacunar and non-lacunar stroke and chronic data came from a single study.

D-dimer was significantly higher in lacunar stroke versus non-stroke, acutely and chronically, and significantly lower in lacunar versus non-lacunar stroke, acutely and chronically.

**Endothelial Dysfunction**

Homocysteine was significantly higher in lacunar stroke versus non-stroke, acutely and chronically, but did not differ between lacunar and non-lacunar stroke acutely (but there were no chronic phase studies).

vWF was significantly higher in lacunar stroke versus non-stroke, acutely, with conflicting evidence chronically. vWF was significantly lower in lacunar than non-lacunar stroke acutely (2 studies), with conflicting but non-meta-analysable evidence in other studies both acutely and chronically.

E-selectin was significantly higher in lacunar stroke versus non-stroke acutely (only 1 study) but not chronically and did not differ between lacunar and non-lacunar stroke, either acutely or chronically (only 1 study).

P-selectin was significantly higher in lacunar stroke versus non-stroke acutely in some but not all studies, and in the only study that reported a chronic measurement. P-selectin did not differ between lacunar and non-lacunar stroke, either acutely or chronically (only 1 study).

ICAM was significantly higher in lacunar stroke versus non-stroke, acutely and chronically (only 1 study), and did not differ between lacunar and non-lacunar stroke acutely (with no studies chronically).

VCAM did not differ between lacunar stroke and non-stroke nor between lacunar and non-lacunar stroke acutely. There were no studies chronically.

**Inflammation**

CRP was significantly higher in lacunar stroke versus non-stroke, acutely and chronically (only 1 study) and did not differ between lacunar and non-lacunar stroke acutely or chronically (only 1 study).

TNF-α was significantly higher in lacunar stroke versus non-stroke acutely with no studies chronically. There was conflicting evidence on levels of TNF-α in lacunar versus non-lacunar stroke acutely with no studies chronically.

IL-6 was significantly higher in lacunar stroke versus non-stroke acutely but did not differ chronically. IL-6 was
significantly lower in lacunar versus non-lacunar stroke acutely, but there were no chronic phase studies.

This suggests that plasma marker elevation in lacunar stroke is likely to reflect the process of having a stroke rather than that systemic inflammation or endothelial dysfunction is specific to lacunar stroke. The available data were limited and do not exclude the possibility that peripheral inflammatory or endothelial dysfunction processes are associated with lacunar stroke specifically.

There were limitations to the studies. Most were small, with varying methods and an inconsistent definition of ‘lacunar stroke’, as highlighted previously [57]. Papers reviewed used the term lacunar stroke to reflect a clinical entity, i.e. clinical presentation with a stroke, but definitions varied and we refer readers to the new neuroimaging standards [10]. We were not able to differentiate different mechanisms of lacunar stroke. Most lacunar strokes are due to recent small subcortical infarcts, and most of these relate to intrinsic small vessel disease. However, they also arise from atherothromboembolism (large artery) or cardioembolism in a small proportion of patients and it was not possible to differentiate these cases.

There was heterogeneity across several aspects of the methods. Many used TOAST [19] but as this uses risk factors to categorize patients it potentially introduces classification bias. A patient with an unclear diagnosis of lacunar stroke but concurrent hypertension or diabetes might (rightly or wrongly) be classified as ‘lacunar’ using this system, although hypertension and diabetes were equally prevalent risk factors between ischaemic stroke subtypes in 21,980 stroke patients when subtypes were classified without risk factors [58]. Several did not report on whether their findings achieved statistical significance; in the absence of an explicit statement, we report this as ‘not stated’. In some studies blood was drawn after overnight fasting, whereas in others non-fasting blood was collected. Studies used different units of measurement and assay methods. None reported on whether the patients had recent infection or neutrophilia, or if these patients were excluded. Timing of blood draw in relation to stroke varied but is important to account for each marker’s individual ‘response curve’ which changes over time. Fassbender et al. [59] found levels of IL-6 to rise rapidly following onset of ischaemic stroke, reaching a plateau at 10 h until 3 days before returning to normal by day 7. They did not subtype stroke and hence their study was not included in this review. Between-study heterogeneity on time to blood draw complicates subsequent analysis, although meta-analyses use within-study data and so will have minimized any effect of between-study variation.

Our review had limitations. We did not study markers in cerebrospinal fluid. We did not review the association of marker levels with lesion size or clinical outcome as data were sparse. Ahmad et al. [60] found markers of neuronal damage correlated with infarct size, which might explain why marker levels in non-lacunar stroke were frequently higher than in lacunar stroke in the acute phase. We were not able to analyse differences between groups reported as top versus bottom quantiles.

Our review had strengths, including assessment of differences between stroke subtypes, quality assessment of included studies, meticulous extraction of data and meta-analysis thereof, wherever suitable data were available. Previous reviews compared lacunar stroke to non-stroke controls only and therefore did not distinguish lacunar stroke specifically from stroke in general.

To determine if there is a difference in coagulation, fibrinolysis, endothelial dysfunction and inflammation in lacunar versus other stroke subtypes requires a large prospective study of blood markers in accurately phenotyped patients with lacunar versus non-lacunar stroke classified using non-risk-factor-based definitions. Future studies should clearly define and diagnose lacunar stroke, avoid subtyping stroke using risk factor-based classifications, explicitly report negative findings and significance levels, and obtain blood several weeks post-stroke to avoid confounding from an acute phase response.

Appendix

Search Strategy.

(1) brain ischemia/ or brain infarction/ or brain stem infarctions/ or cerebral infarction/ or hypoxia-ischemia, brain/ or stroke/ or (2) (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or eca or attack$)).tw.
(3) ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemi-spher$ or intracranan$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circu-lation) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
(4) 1 or 2 or 3
(5) (lacun$ or small vessels$ or small infarct$ or microinfarct$ or subcortical lesion$ or subcortical infarct$ or microvascular$ or microcirculation$)).tw.
(6) 4 and 5
(7) blood-brain barrier/ or endothel$, vascular/ or tunica intima/ or microcirculation/
(8) (endothel$ adj5 (function$ or dysfunction$ or impairment$)).tw.
(9) (endogenous tissue plasminogen activator or endogenous tPA)).tw

Review of Blood Markers in Lacunar Stroke

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References


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Disclosure Statement

None.
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and nonlacunar infarcts. Stroke 2005;36:
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