

# Prevention and Management of Cerebral Small Vessel Disease

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Lacunar infarcts/lacunes, white matter hyperintensities (WMH), and cerebral microbleeds (CMBs) are considered various manifestations of cerebral small vessel disease (SVD). Since the exact mechanisms of these manifestations differ, their associated risk factors differ. High blood pressure is the most consistent risk factor for all of these manifestations. However, a "J curve" phenomenon in terms of blood pressure probably exists for WMH. The association between cholesterol levels and lacunar infarcts/lacunes or WMH was less consistent and sometimes conflicting; a low cholesterol level probably increases the risk of CMBs. Homocysteinemia appears to be associated with WMH. It is noteworthy that the risk factors profile may also differ between different lacunar patterns and CMBs located at different parts of the brain. Thrombolysis, antihypertensives, and statins are used to treat patients with symptomatic lacunar infarction, just as in those with other stroke subtypes. However, it should be remembered that bleeding risks increase in patients with extensive WMH and CMBs after thrombolysis therapy. According to the Secondary Prevention of Small Subcortical Strokes trial results, a blood pressure reduction to < 130 mmHg is recommended in patients with symptomatic lacunar infarction. However, an excessive blood pressure decrease may induce cognitive decline in older patients with extensive WMH. Dual antiplatelet therapy (aspirin plus clopidogrel) should be avoided because of the excessive risk of intracerebral hemorrhage. Although no particular antiplatelet is recommended, drugs such as cilostazol or triflusal may have advantages for patients with SVD since they are associated with less frequent bleeding complications than aspirin.

**Keywords** Prevention; Treatment; Small vessel disease

## Introduction

Lacunar infarcts (lacunes), white matter hyperintensities (WMH), and cerebral microbleeds (CMBs) are considered various manifestations of cerebral small vessel disease (SVD). These lesions are associated with a plethora of disabilities (e.g., stroke, cognitive impairment, depression, gait disturbances, urinary symptoms).<sup>1,2</sup> Given its close association with vascular risk fac-

tors, the disabilities and mortality associated with these lesions are potentially preventable. Here we review the risk factors and management of cerebral SVD.

## Lacunar infarcts / lacunes

In this review, lacunar infarct refers to a small subcortical ischemic lesion presumably resulting from the occlusion of a perfo-

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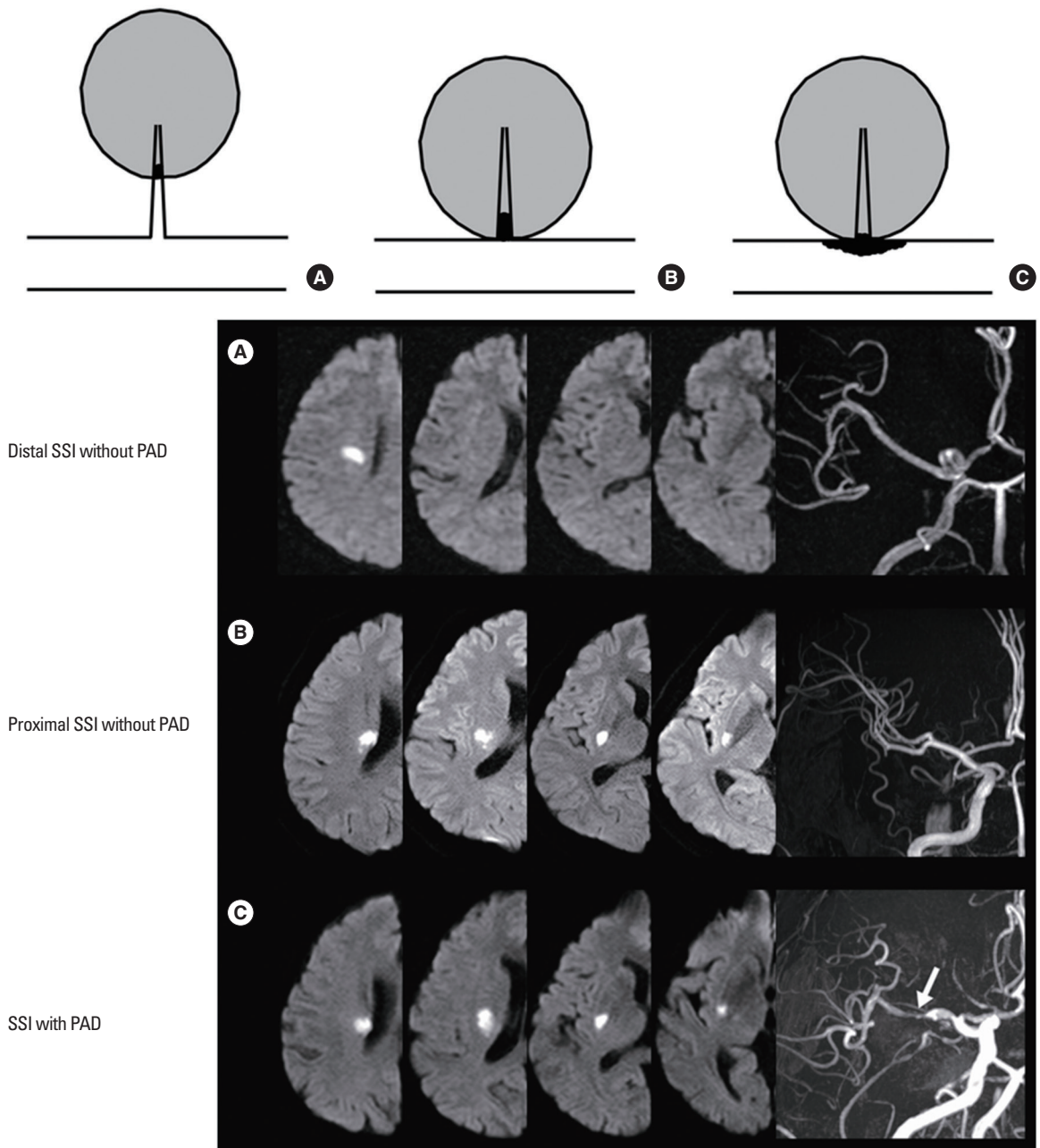
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rating arteriole that is associated with acute neurological symptoms (i.e., lacunar stroke). Lacune refers to a chronic small cavity that presumably represents the healed stage of a lacunar infarct. Note, however, that some lacunes may represent sequelae of a larger infarct or intracerebral hemorrhage (ICH).<sup>3</sup> Lacunes are often asymptomatic and are commonly found in elderly stroke-free community-dwelling subjects.

Some researchers hypothesized that different lacunar patterns may reflect different underlying SVD etiologies (e.g., microatheroma vs. fibrinoid necrosis) among stroke subjects and compared risk factors among different lacunar patterns.<sup>4,6</sup> Khan et

al.<sup>4</sup> found that, among SVD patients, isolated lacunar infarct with no or minimal WMH (presumably related to microatheroma) was associated with hypercholesterolemia, diabetes, and myocardial infarction, i.e., risk factors similar to large artery disease, while lacunar infarct associated with moderate to severe WMH (presumably related to fibrinoid necrosis) was associated with age and hypertension. Arauz et al.<sup>6</sup> found that diabetes, a high hematocrit, and WMH were related to multiple lacunes (presumably related to fibrinoid necrosis) but not to a single lacunar infarct (presumably related to microatheroma). Nah et al.<sup>7</sup> found that lacunar infarcts associated with parent atheroma-



**Figure 1.** Schematic drawing (upper panels) and clinical examples (lower panels) of the heterogeneous pathogenesis of single subcortical infarction. SSS, single subcortical infarction; PAD, parental artery disease. (modified from Nah et al.<sup>7</sup>).

tous disease (presumably related to a large-vessel atheromatous plaque blocking the mouth of the penetrating artery) had the highest prevalence of atheromatous indicators (i.e., coronary artery disease, asymptomatic cerebral atherosclerotic disease) and the lowest prevalence of SVD indicators (i.e., WMH, CMBs); distal lacunar infarcts without parent atheromatous disease (presumably related to fibrinoid necrosis) had the lowest prevalence of atheromatous indicators and the highest prevalence of SVD indicators; and proximal lacunar infarcts without parent atheromatous disease (presumably related to microatheroma at the proximal portion of the penetrating artery) showed intermediate features (Figure 1).

### Risk factors for lacunes

Overall, asymptomatic lacunes are much more prevalent than lacunar infarcts. In the Cardiovascular Health Study (CHS), of 3,660 community-dwelling elderly individuals, 23% had one or more lacunes (3-20 mm), most of which were subclinical (89%).<sup>8</sup> Factors associated with lacunes were age, diastolic blood pressure (BP), creatinine, pack-years of smoking, internal carotid artery stenosis, male sex, and history of diabetes. A comparison between subgroups of single, multiple, silent, and symptomatic lacunes failed to yield significant differences.

The Atherosclerosis Risk in Communities (ARIC) study<sup>9</sup> examined the risk factors associated with two SVD subtypes (fibrinoid necrosis and microatheroma). In this cross-sectional study of 1,827 community-dwelling participants, subcortical lesions diagnosed on magnetic resonance imaging (MRI) measuring  $\leq 20$  mm in diameter were divided into those  $\leq 7$  mm (presumably related to fibrinoid necrosis) and those measuring 8-20 mm in diameter (presumably related to microatheroma). In this study, smaller lacunes were associated with diabetes and glycated hemoglobin, whereas the larger ones were associated with low-density lipoprotein (LDL) cholesterol. These findings suggest that diabetes may be associated with fibrinoid necrosis and LDL cholesterol with microatheroma. Other factors associated with larger MRI-based lesions were hypertension and smoking.

### Risk factors for incident lacunes

Of 668 elderly community-dwelling participants, the Rotterdam Scan Study (RSS) found that incident lacunes (3-20 mm) were associated with age, female sex, and baseline carotid atherosclerosis.<sup>10</sup> The Leukoaraiosis And Disability Study (LADIS) recruited 639 elderly subjects who had at least some degree of WMH on MRI. Incident lacunes (3-10 mm) were associated with WMH load, systolic BP, and low high-density lipoprotein (HDL) cholesterol levels. There were unexpected asso-

ciations with high diastolic BP and high LDL cholesterol as factors protecting against incident lacunes.<sup>11</sup> It is important to note that the definition of lacunes in relation to size and study populations differed between the RSS and LADIS. The latter study included only small lacunes and subjects who already had at least some degree of WMH. Such differences in patients' characteristics may partially explain the disparity between the two studies.

## White matter hyperintensities

WMH of presumed ischemic origin are characterized by demyelination as well as axonal and oligodendrocyte loss with sparing of the U-fibers. Mechanisms explaining WMH may include chronic partial ischemia secondary to diffuse arteriosclerosis, hypotensive episodes (e.g., cardiac arrhythmia, diuretic uses, postural hypotension),<sup>12,13</sup> breakage of the blood-brain barrier, leakage of toxic fluids into the white matter,<sup>14</sup> venous collagenosis,<sup>15</sup> and various combinations thereof. A recent study performed serial MRI in patients with leukoaraiosis for 16 consecutive weeks and found tiny acute ischemic infarcts arising de novo in the cerebral white matter. Over time, the characteristics of these lesions approached those of pre-existing leukoaraiosis, suggesting that silent acute infarcts are also a cause of leukoaraiosis.<sup>16</sup>

Apart from age, most community-based studies have consistently shown that hypertension is associated with WMH.<sup>17-21</sup> Both the RSS and the Epidemiology of Vascular Ageing study further showed that hypertension duration was associated with WMH, while effective hypertension treatment was associated with lower risk.<sup>20,21</sup> Noteworthy is that the association between BP levels and confluent WMH may not be linear. Analysis of 10 European cohorts revealed a "J curve" phenomenon in that both increases and decreases in diastolic BP were associated with more severe WMH.<sup>22</sup> The association between low BP and WMH is probably related to impaired cerebral autoregulation, which is commonly associated with aging and/or exposure to long-standing vascular risk factors. The RSS found that impaired cerebral vasomotor reactivity was associated with WMH.<sup>23</sup> As a result of impaired cerebral vasomotor reactivity, the arteries within the brains may fail to dilate to increase cerebral blood flow in response to decreases in systemic BP, resulting in cerebral hemodynamic ischemia. In a recent subgroup analysis of the VITamins TO Prevent Stroke (VITATOPS) MRI substudy, lower baseline diastolic BP predicted cognitive decline among subjects with severe baseline WMH.<sup>24</sup> Other studies showed that postural hypotension,<sup>22</sup> increasing long-term BP fluctuations,<sup>25</sup> and various 24-hour ambulatory BP measures (e.g., greater systolic BP variability, smaller nocturnal decrease in systolic or diastolic

BP)<sup>26</sup> were associated with WMH.

Both the RSS and ARIC studies further showed that measures of arterial stiffness (e.g., brachial pulse pressure, aortic pulse wave velocity) were risk factors for WMH even after controlling for BP levels and other cardiovascular risk factors. Thus, it was proposed that arterial stiffening might expose cerebral small vessels to high pulsatile pressure and flow, hence contributing to the pathogenesis of WMH. Most studies found that smoking was associated with WMH.<sup>17,19</sup> Despite diabetes being a strong risk factor for stroke and coronary heart disease, most community-based cross-sectional studies failed to find an association between diabetes and WMH.<sup>17,18</sup> In the Helsinki Aging Brain study, WMH were associated with diabetes among relatively young (< 75 years) subjects but not among older (≥ 75 years) ones.<sup>27</sup>

The RSS found that a high homocysteine level was associated with WMH.<sup>28</sup> In a separate study evaluating the association between homocysteine and endothelial markers (ICAM1, thrombomodulin), Hassan et al.<sup>29</sup> showed that the association between homocysteine and WMH was probably mediated by endothelial activation. The RSS further showed that low vitamin B12 and folate levels, which are closely related to homocysteine metabolism, were associated with WMH independent of homocysteine level.<sup>30,31</sup> These findings suggest that low vitamin B12 and folate levels may also induce WMH through mechanisms independent of homocysteine or endothelial activation such as low vitamin B12-mediated impairment of myelin integrity. However, it must be noted that the CHS failed to find an association between WMH and homocysteine level.<sup>32</sup>

Findings on the association between cholesterol levels or statin use and WMH are less consistent and sometimes contradictory. The Cardiovascular Risk Factors and the Aging and Incidence of Dementia MRI substudy<sup>33</sup> showed that use of lipid-lowering drugs was associated with less WMH. The National Heart, Lung, and Blood Institute Twin Study found that a mid-life lower HDL cholesterol level was associated with a later-life WMH.<sup>34</sup> In contrast, the Austrian Stroke Prevention Study (ASPS) showed that a lower total cholesterol level was associated with WMH.<sup>35</sup> In another study investigating association between WMH and cholesterol level among two stroke cohorts (total of 1,135 patients), hyperlipidemia was associated with less WMH.<sup>36</sup> The authors suggested that hyperlipidemia might play a protective role in cerebral SVD. However, since statin use had high collinearity with hyperlipidemia, the authors could not rule out the possibility that the association between hyperlipidemia and WMH was related to statin use.

More recent studies evaluating the RNA expression profile in brain or blood samples showed that genes specific for WMH were associated with injury responses, oxidative stress, and in-

flammation.<sup>37,38</sup> In a large genome-wide association study of WMH burden in community-based cohorts of individuals of European descent, a novel locus on chromosome 17 was associated with WMH. Although information on the specific genes and functional variants underlying the reported associations was lacking, further characterization of this locus will provide additional insight into the mechanisms of WMH and hopefully new targets for preventive therapies.<sup>39</sup>

### Risk factors for progression of WMH

Since WMH progression is associated with clinical consequences, WMH progression may be used as a surrogate marker in preventive trials. Several longitudinal studies with serial MRI investigated the risk factors for WML progression. The majority of studies showed that baseline lesion load,<sup>10,11,40</sup> older age,<sup>10,41</sup> smoking,<sup>10,42</sup> and hypertension<sup>10,41,43</sup> predicted WMH progression. The ARIC study found that the cumulative mean systolic BP (i.e., estimated mean systolic BP over the entire period) was a much stronger predictor of WMH progression than was systolic BP obtained at individual time points.<sup>44</sup> The Three-City-Dijon MRI Study showed that not only baseline hypertension predicted WMH progression among subjects with a high baseline systolic BP ≥ 160 mmHg who were not treated with antihypertensive medication but that antihypertensive treatment started within 2 years was related to a smaller increase in WMH volume than no hypertension treatment.<sup>43</sup> However, subgroup analyses from the RSS revealed that, among those who already had severe lesions at baseline and those who were very old (≥ 80 years), higher BP did not contribute to lesion progression.<sup>10</sup> The association between BP and WMH progression was stronger in relatively young subjects and in those who did not have severe WMH at baseline.<sup>42</sup>

Most studies did not find an association between baseline diabetes and WMH progression. The association between cholesterol levels and statin use and WMH progression was again controversial. In the CHS, among those with a relatively mild initial WMH burden, increased HDL cholesterol and decreased LDL cholesterol levels were associated with an increased risk of progression; in contrast, among those with a high initial grade, statin use was associated with increased risk.<sup>42</sup> In the LADIS study, higher triglyceride levels appeared to protect against WMH progression.<sup>11</sup> In the subgroup analysis of the VITATOPS MRI-substudy, statin use was associated with less progression of WMH and less cognitive decline in subjects with severe WMH at baseline.<sup>24,45</sup>

In the ASPS, ICAM1 levels were associated with WMH progression, further supporting the causal role of endothelial activation in the pathogenesis of WMH.<sup>41</sup> In the same study, no asso-

ciation was found between peripheral markers of coagulation activation (e.g., D-dimer, prothrombin fragments 1 and 2) and WMH progression. Although the inflammatory process has been postulated as a pathogenic mechanism for WMH, the results from longitudinal studies assessing the association between C-reactive protein levels and WMH progression were not consistent. The RSS showed a positive association,<sup>46</sup> whereas the ASPs failed to find an association.<sup>47</sup>

## Cerebral microbleeds

CMBs are small perivascular hemosiderin deposits (usually with macrophages) that presumably result from leakage through cerebral small vessels, which can be visualized as small, rounded, homogeneous, and hypointense lesions on T2\*-weighted gradient-recalled echo or susceptibility-weighted imaging MRI. More recent MRI studies suggest that the presence of CMBs is associated with an increased risk of ICH<sup>48</sup> and other neurological conditions (e.g., cognitive impairment, gait disturbance, depressive mood) and increased overall mortality.<sup>2</sup> Deep CMBs are probably associated more with fibrinoid necrosis-related deep ICH, while lobar CMBs correlated more with cerebral amyloid angiopathy (CAA)-related lobar ICH. Both SVD types may exist in the same individual. Since this review focuses on cerebral SVD predominantly associated with vascular risk factors, studies related purely to CAA-associated lobar ICH are not emphasized.

In the systematic review conducted by Cordonnier et al.<sup>49</sup> hypertension was the most consistent risk factor for CMBs in both healthy adults and those with cerebrovascular diseases. In the same review, diabetes was also associated with CMBs, but such an association was only found among healthy adults.<sup>49</sup> The RSS found that systolic BP was related to presence of deep/infratentorial CMBs, whereas diastolic BP was related to strictly lobar CMBs.<sup>50</sup> In the same study, smoking was associated with deep but not lobar CMBs.<sup>50</sup> In another study of subjects with first-ever lacunar stroke, Staals et al found that ambulatory BP measures (24-hour, day, and night systolic and diastolic BP) were more robust predictors for CMBs than the mere presence or absence of hypertension.<sup>51</sup> After distinguishing between different locations, various BP characteristics were associated with deep (or combined deep and lobar) CMBs but not with pure lobar CMBs.<sup>51</sup> In patients with lacunar infarction, Park et al.<sup>52</sup> found that, after adjustments for other factors, age (odds ratio [OR] 1.07; 95% confidence interval [CI] 1.04-1.11;  $P < 0.001$ ) and diabetes (OR, 2.17; 95% CI, 1.04-4.25;  $P = 0.036$ ) were independently associated with white microangiopathy (predominantly WMH) versus red microangiopathy (predominantly CMBs).

Similar to ICH, low total serum cholesterol levels were associ-

ated with CMBs independent of hypertension among subjects having various neurological conditions.<sup>53</sup> In the RSS, low triglyceride levels rather than HDL or LDL cholesterol levels were associated with deep/infratentorial CMBs as well as ICH.<sup>54</sup> Among subjects with previous spontaneous ICH and statin use, rather than cholesterol levels, was associated with presence and number of CMBs, especially cortico-subcortical CMBs.<sup>55</sup> However, in a study of patients with acute ischemic stroke or transient ischemic attack, previous statin use was not associated with CMB prevalence or severity.<sup>56</sup> In another study, proteinuria and homocysteinemia were associated with CMB presence and severity in patients with ischemic stroke or transient ischemic attack.<sup>57</sup> In the same study, female sex, history of atrial fibrillation, and SVD stroke subtype were also associated with CMBs.

In the RSS, carriers of the APOE  $\epsilon 4$  and  $\epsilon 2/\epsilon 2$  genotype were related to strictly lobar CMBs and not deep/infratentorial CMBs.<sup>50</sup> In the systematic review and meta-analyses, APOE  $\epsilon 4$  allele carriers are at higher risk of CMBs, particularly in strictly lobar brain locations.<sup>58</sup> Given the known associations between the APOE genotype with CAA and lobar ICH, the findings support lobar CMBs as an imaging biomarker for CAA.

## Risk factors for incident CMBs

In a small series of patients ( $n = 21$ ) with ischemic stroke or transient ischemic attack, the baseline presence of CMBs and mean systolic BP predicted incident CMBs.<sup>59</sup> In the RSS, baseline CMBs, age, systolic BP, high pulse pressure, and severe hypertension were all associated with incident CMB. When stratified by location, age, systolic BP, severe hypertension, and low serum cholesterol levels predicted incident deep CMBs, whereas age and those with APOE  $\epsilon 4/\epsilon 4$  genotype predicted strictly lobar CMBs.<sup>60</sup> In another study of subjects attending memory clinics, multiple baseline CMBs, WMH severity, lacunes, and APOE  $\epsilon 2$  predicted incident CMBs, deep CMBs in particular, whereas smoking was associated with strictly lobar bleeds.<sup>61</sup>

## Treatment and secondary prevention

### Thrombolysis

Intravenous tissue plasminogen activator (t-PA) is the gold standard of treatment of acute ischemic stroke. The efficacy of t-PA is mediated through thrombolysis. However, unlike large artery disease or cardiogenic embolism, the role of the thrombus formation is not considered an important pathomechanism in lacunar infarction. Therefore, the role of t-PA in patients with lacunar infarction has been debated.

The NINDS<sup>62</sup> and subsequent studies<sup>63-66</sup> showed that t-PA was not less effective in patients with lacunar stroke than in those

with non-lacunar stroke. Although a Spanish study<sup>66</sup> showed that at day 7, patients with lacunar stroke showed the least neurological improvement in terms of absolute National Institutes of Health Stroke Scale (NIHSS) score reduction compared with other stroke subtypes ( $P=0.02$ ), a recent study using a larger number of patients with lacunar infarction ( $n=195$ ) showed that the outcomes of these patients were better than those receiving placebo (for modified Rankin scale scores 0-2; relative risk, 1.84; 95% CI, 1.59-2.13).<sup>67</sup> Therefore, current consensus and guidelines do not distinguish between ischemic stroke subtypes in terms of t-PA efficacy.<sup>68,69</sup>

Another debate comes from the possibility of an increased risk of hemorrhage in patients with WMH or CMBs. Investigators showed an increased risk of bleeding after thrombolysis in patients with a moderate to high degree of WMH.<sup>70-73</sup> However, it does not seem to exceed the benefit of t-PA therapy.<sup>69</sup> More attention has been paid to CMBs that are considered markers for hemorrhage-prone state.<sup>74</sup> In the Bleeding Risk Analysis in Stroke Imaging before thrombolysis study, investigators analyzed imaging data acquired within 6 hours after symptom onset in 570 patients with ischemic stroke treated with intravenous t-PA. Baseline T2\*-weighted MRI images were evaluated for the presence of CMBs. The primary end point was symptomatic ICH defined as clinical deterioration with an increase in the NIHSS score by  $\geq 4$  points temporally related to a parenchymal hematoma (PH) on follow-up-imaging. A total of 242 CMBs were detected in 86 of 570 patients (15.1%). The proportions of patients with symptomatic ICH were 5.8% (95% CI, 1.9-13.0) in the presence of CMBs and 2.7% (95% CI, 1.4-4.5) in patients without CMBs ( $P=0.170$ ), resulting in no significant absolute increase in the risk of ICH (3.1%; 95% CI, -2.0-8.3). The data suggested that the increased risk of symptomatic ICH attributable to CMBs is small and unlikely to exceed the benefits of thrombolytic therapy.<sup>75</sup> A meta-analysis of 790 patients revealed the same conclusion.<sup>76</sup> However, because of the rarity of patients with multiple CMBs, no reliable conclusion was made regarding risk in patients with multiple CMBs.

According to a recent study examining this issue,<sup>77</sup> among the 326 included patients, 52 (16.0%) had a single CMB, 19 (5.8%) had 2-4 CMBs, and 10 (3.1%) had  $\geq 5$  CMBs. The frequency of symptomatic ICH (sICH)/PH was 1.2%/5.7% in patients without CMBs, 3.8%/3.8% in patients with a single CMB, 10.5%/21.1% in patients with 2-4 CMBs, and 30.0%/30.0% in patients with  $\geq 5$  CMBs (for trend, each  $P<0.01$ ). The unadjusted OR per additional CMB for sICH was 1.19 (95% confidence interval, 1.07-1.33;  $P<0.01$ ) and for PH was 1.13 (95% confidence interval, 1.03-1.24;  $P=0.01$ ). Compared with patients without CMBs, both patients with 2 to 4 CMBs ( $P=0.02/P=0.02$ ) and

patients with  $\geq 5$  CMBs ( $P<0.01/P<0.01$ ) had significantly increased OR for symptomatic ICH and PH, respectively whereas in patients with a single CMB, the OR were not significantly increased ( $P=0.21/P=0.59$ ). The results indicated a higher risk of sICH and PH after intravenous thrombolysis when multiple CMBs are present with a graded relationship to increasing baseline CMB number. Therefore, the use of t-PA should be cautious in patients with multiple CMBs. Further studies are warranted to evaluate whether the risk of ICH outweighs the benefit of thrombolysis in patients with multiple CMBs.

## Risk factor controls

### Hypertension

Hypertension is the most important risk factor for stroke, and the benefits of lowering BP are apparent in secondary stroke prevention. Pooled analyses showed that long-term BP reduction reduces stroke recurrence by approximately 28%.<sup>78-80</sup> The Secondary Prevention of Small Subcortical Strokes (SPS3) trial is the unique study to test the target BP level as secondary prevention in patients with lacunar infarction. The investigators made two systolic BP targets of 130-149 mmHg vs.  $< 130$  mmHg in 3,020 patients with symptomatic lacunar infarction.<sup>81</sup> After the mean follow-up of 3.7 years, a 19% non-significant reduction of recurrent stroke was seen in the latter group (hazard ratio [HR], 0.81; 95% CI, 0.64-1.03). It was noteworthy that ICH was markedly reduced (63%) in patients assigned to lower BP targets (HR, 0.37; CI, 0.15-0.95,  $P=0.03$ ).<sup>82</sup> The Perindopril Protection against Recurrent Stroke Study MRI-substudy also showed that a more intensive BP-lowering regime might delay WMH progression in stroke patients.<sup>83</sup>

Therefore, it is appropriate to reduce the systolic BP to  $< 130$  mmHg in patients with lacunar infarction. There is no evidence to support the usefulness of a particular group of antihypertensives in this condition.

However, the long-term effect of BP reductions remains uncertain, especially in old patients with extensive SVD. According to a long-term cohort study, decreased diastolic BP was associated with decreased gray matter volume and cognitive impairment in older subjects who had hypertension from middle age. This is probably related to cerebral perfusion failure due to a decreased autoregulatory mechanism in patients with long-term hypertension.<sup>84</sup> Therefore, although a systolic BP reduction to  $< 130$  mmHg is currently recommended in the guidelines, and BP management may have been more cautiously made in patients with advanced age, a long history of hypertension, extensive WMH, or cognitive dysfunction.

### Dyslipidemia

Dyslipidemia, especially elevated LDL cholesterol levels, plays an important role in the development of atherosclerosis. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study is the only to examine the efficacy of high-dose statins for secondary stroke prevention in a large number of patients ( $n = 4,731$ ) with stroke or transient ischemic attack. The results showed that patients who were administered atorvastatin had a significant reduction in stroke (HR, 0.84; 95% CI, 0.71-0.99) and coronary heart disease (HR, 0.58; 95% CI, 0.46-0.73). There was a mild but significant increase in hemorrhagic stroke (HR, 5.65; 95% CI, 2.82-11.30). Because patients with SVD less often have large-artery atherosclerosis but are at an increased risk of bleeding, the efficacy of statins has been questioned in patients with lacunar infarction. However, in the SPARCL trial, 1,409 patients had lacunar infarction, and post-hoc analysis showed that the efficacy of statins was similar in this group.<sup>85</sup> Although there was an increase in outcomes of hemorrhagic stroke in patients with baseline SVD, the patients also had a reduced outcome of ischemic strokes resulting in a total benefit similar to the overall study cohort.<sup>86</sup> Therefore, it is recommended that lacunar stroke patients adhere to the current guideline.<sup>87</sup> However, previous studies did not assess WMH or CMBs in detail, so further studies are needed to examine the efficacy of statins in patients with extensive WMH or CMBs. In the Regression of Cerebral Artery Stenosis study, statin use was associated with less WMH progression among those with a severe initial WMH burden<sup>88</sup> and lower incidence of lacunes in the overall cohort.<sup>89</sup>

### Others

In the recent VITATOPS MRI-substudy, homocysteine lowering using B-vitamins was associated with a reduced WMH volume increment in those with severe baseline SVD (i.e., confluent WMH and lacunes).<sup>90</sup> In addition, vitamin E tocotrienols were recently found to attenuate the progression of WMH among healthy subjects with WMH.<sup>91</sup>

### Antiplatelets

Antiplatelets are generally used in non-cardioembolic stroke. Although studies focusing on lacunar infarction are rare, the benefits of various antiplatelets are considered similar between lacunar and non-lacunar infarction.<sup>92-95</sup> The SPS3 trial is the only study to focus on lacunar infarction.<sup>81</sup> Investigators enrolled 3,020 patients with lacunar infarction from North America, South America, and Spain. Patients were allocated to receive aspirin 325 mg plus clopidogrel 75 mg or aspirin 325 mg only. The trial was prematurely stopped due to increased mortality of those assigned to the combination therapy. After the mean fol-

low-up of 3.4 years, the annual recurrent stroke rate was 2.5% in patients on dual therapy versus 2.7% in those taking aspirin only. The incidence of major hemorrhage in the dual therapy group was significantly ( $P < 0.001$ ) higher (2.1% per year) than that in the aspirin monotherapy group (1.1%), while mortality was significantly increased in the former group of patients (HR, 1.52; 95% CI, 1.14-2.04;  $P = 0.004$ ). The authors concluded that, among patients with recent lacunar strokes, the addition of clopidogrel to aspirin does not significantly reduce the risk of recurrent stroke and significantly increases the risk of bleeding and death. Thus, the aspirin and clopidogrel combination should not be used in patients with lacunar infarction unless there are other specific indications. Currently, aspirin, aspirin plus dipyridamole, and clopidogrel are considered acceptable options.<sup>87</sup>

An increased risk of bleeding is the primary concern when antiplatelets are used in stroke patients, especially those with SVD. In this sense, the two drugs cilostazol and triflusal deserve attention. Results from animal<sup>96</sup> and human<sup>97,98</sup> studies showed that cilostazol causes fewer bleeding complications than aspirin. Bleeding time—which reflects *in vivo* physiological hemostasis—was prolonged by aspirin or clopidogrel but not by cilostazol. Moreover, an increase in bleeding time was not observed when cilostazol was co-administered with aspirin or clopidogrel in patients with peripheral arterial disease.<sup>99</sup> Moreover, cilostazol has an endothelial protective effect and prevents blood-brain barrier disruption in the ischemic brain.<sup>96,100</sup> In a murine stroke model, cilostazol was shown to protect microvasculature in the ischemic brain by reducing matrix metalloproteinase-9 activity.<sup>101</sup>

In the sub-group analysis of the Cilostazol for Prevention of Secondary Stroke study, a significant difference between the cilostazol and aspirin groups was observed with respect to the incidence of hemorrhagic stroke in patients with lacunar stroke.<sup>102</sup> Therefore, cilostazol seems to be safer than aspirin in terms of the risk of hemorrhagic stroke in hypertensive patients with SVD.<sup>102</sup> Moreover, as discussed before, arterial stiffening might expose cerebral small vessels to high pulsatile pressure, hence contributing to the pathogenesis of WMH. Cilostazol reportedly decreases cerebral arterial pulsatility in patients with mild WMH.<sup>103</sup> Alternatively, triflusal, a drug with an effect similar to that of aspirin but with fewer bleeding complications,<sup>104</sup> may also be used in patients with a bleeding tendency (e.g., multiple CMBs) SVD patients. Further studies are required to find the appropriate antiplatelets in patients with SVD.

### Conclusions and future direction

Despite extensive studies, many unknown factors of SVD re-

main. Thrombolysis, antihypertensives, and statins are currently used for the treatment of patients with SVD just as in those with other stroke subtypes. However, it should be remembered that bleeding risk increases in patients with extensive WMH and CMBs after thrombolysis therapy. Future studies are required to weigh the benefits and risks of thrombolysis in these patients. Based on the SPS3 trial results, a BP reduction to < 130 mmHg is recommended. However, an excessive BP decrease may induce cognitive decline in older patients with extensive WMH. Future studies are needed to examine the appropriate target BP and cholesterol levels in patients with extensive SVD.

Although the harm of dual antiplatelet therapy (aspirin plus clopidogrel) was correctly identified in patients with SVD, the appropriate antiplatelets in SVD require investigation. In particular, the efficacy of drugs such as cilostazol or triflusal, which are known to be associated with less frequent bleeding complication than aspirin, should be further investigated. Finally, as discussed above, subcortical infarction is heterogeneous. Proximal subcortical infarction, especially those associated with parental artery stenosis, has characteristics of atherosclerosis, whereas distal subcortical infarction has SVD characteristics. In this regard, treatment may have to be tailored; for example, statins and dual antiplatelets may work better in the former group of patients but may be harmful in the latter group. Previous studies disregarded the heterogeneity of small subcortical infarction, so further studies that consider this aspect should be performed.

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