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STROKE (H.C. DIENER, SECTION EDITOR)

Antiplatelet Therapy in Cerebral Small Vessel Disease

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Abstract

Purpose of Review We critically evaluate the evidence for the use of antiplatelet therapy for stroke prevention following lacunar stroke and in patients with hemorrhage-prone cerebral small vessel disease.

Recent Findings Pooled lacunar stroke subgroup analyses of all relevant randomized controlled trials to date suggest a 22% relative risk reduction in recurrent stroke by single antiplatelet therapy (RR 0.77, 95% CI 0.62–0.97) compared with placebo, no consistent suggestion of variable efficacy amongst specific antiplatelet agents, and the absence of clear benefit with dual over single antiplatelet therapy. Current data does not support withholding antiplatelet therapy where otherwise indicated in patients with cerebral microbleeds on MRI or those who have suffered intracerebral hemorrhage.

Summary Antiplatelet monotherapy appears to provide persistent secondary stroke prevention in patients with lacunar stroke. Whether phosphodiesterase inhibitors, particularly cilostazol, provide additional advantage in patients with cerebral small vessel disease is worthy of further investigation.

Keywords Lacunar stroke · Antiplatelet · Antithrombotic · Cerebral small vessel disease · Microbleed · Intracerebral hemorrhage

Introduction

Lacunar or small subcortical strokes caused by cerebral small vessel disease (CSVD) account for approximately 25% of all ischemic strokes and are a major contributor to vascular dementia [1–3]. Incident lacunar strokes tend to be less disabling and fatal than other stroke subtypes, but stroke recurrence is not uncommon despite best current management (~ 2.5%/year) [4••, 5–7].

In recent years, concern has been raised about the overall benefit of antiplatelet therapy for secondary prevention in patients with lacunar stroke, prompted by the results of the Secondary Prevention of Small Subcortical Strokes (SPS3) trial demonstrating greater mortality associated with assignment to dual antiplatelet therapy with clopidogrel plus aspirin compared with aspirin monotherapy [4••]. Further, the vascular pathology underlying lacunar stroke is shared with intracerebral hemorrhage and cerebral microbleeding that could be exacerbated by antiplatelet therapy [8•].

We summarize the pathological rationale and critically evaluate the evidence from randomized clinical trials for the use of antiplatelet therapy for secondary stroke prevention in lacunar stroke patients. Additionally, we summarize the risk/benefit of antiplatelet therapy in patients with comorbid hemorrhage-prone cerebral small vessel disease and vaso-occlusive–disease indicated antithrombotics.

Pathophysiology

C. Miller Fisher described the pathological changes underlying lacunar stroke during serial sectioning in his seminal 1969 paper [9••] as being mainly due to "segmental arterial disorganization" in arterioles 40–200 μm in diameter. However, some specimens were observed to have solely atherosclerotic plaque at the orifice of small penetrating arteries supplying the area of infarction. These early observations depicted what we currently understand to be the two main vascular pathologies underlying lacunar stroke: (i) hypertensive arteriopathy/arteriolosclerosis and (ii) branch orifice microatheromoatous disease.

This article of the Topical Collection on *Stroke*

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Arteriolosclerosis is a destructive microangioapthy resulting in collagenous thickening of the vessel wall, foamy macrophage and inflammatory cell infiltration, fibrinoid necrosis with segmental vessel wall destruction, and aneurysmal vessel wall dilatation [10]. The importance of failure of the endothelium and neuro-glio-vascular unit, with ensuing leakage of plasma into the vessel wall and perivascular space, as a trigger for arteriolosclerosis, is being increasingly recognized [10–12, 13•]. Ultimately vessel wall destruction and luminal distortion result in impaired autoregulation and vessel narrowing/occlusion. Arteriolosclerosis results in a spectrum of additional microvascular lesions that are often detectable on magnetic resonance imaging (MRI) including lacunes, leukoaraiosis, enlarged perivascular spaces [14], and cerebral microbleeds [15], as well as symptomatic intracerebral hemorrhage.

Microatheromatosis is the consequence of atheroma plaque burden in the larger perforating arterioles (200–800 μm diameter) and lipid deposition into the vessel wall. Lacunar stroke can result from severely stenotic/occlusive plaques that can be complicated by acute thrombosis [11, 16]. Branch orifice microatheromatous disease is often undetectable using angiography, but may be detected using high-resolution MRI [17, 18]. Microatheromatosis is not believed to contribute to enlarged perivascular spaces or hemorrhagic lesions, hence the presence of these findings on MRI in lacunar stroke patients would favor arteriolosclerosis, while lacunes and leukoaraiosis can be manifestations of either underlying vascular pathology [19].

The distinct pathways that result in microatheromatous disease rather than arteriolosclerosis are not well understood [11], however, chronic hypertension in the main risk factor for arteriosclerosis (aka hypertensive arteriopathy), while a history of diabetes, smoking, and dyslipidemia preferentially increase the risk of atheromatous disease [20, 21].

Microthrombosis is presumed to contribute to vessel occlusion in both ateriolosclersosis and — more so — microatheromatous disease. However, as small arterioles are difficult to visualize "in vivo," and post-mortem assessments often occur several years following the symptomatic vascular event due to the largely non-fatal nature of lacunar strokes, a prominent role of microthrombosis has yet to be confirmed pathologically. The consistent benefit of intravenous thrombolysis in patients presenting with acute clinical lacunar syndromes [22], which have an 80% positive predictive value and 87–94% specificity for lacunar stroke on neuroimaging [23, 24], provides one piece of indirect supporting evidence for the role of thrombosis in lacunar stroke pathogenesis.

Antiplatelet Therapy: Insights from Randomized Controlled Trials

The SPS3 trial is the only completed phase III trial designed to investigate optimal antithrombotic therapy in lacunar stroke patients. It reported excess mortality without a significant reduction in recurrent stroke with random assignment to dual antiplatelet therapy (aspirin and clopidogrel) compared with antiplatelet monotherapy (aspirin) in patients with a recent MRI-confirmed small subcortical stroke. There has yet to be a secondary stroke prevention trial comparing the efficacy of random assignment to single antiplatelet vs. placebo in solely lacunar stroke patients [4••]. Thus, the question of whether antiplatelet agents provide any benefit at all in this patient population has been raised.

Currently, the best available evidence to guide practice in this regard comes from subgroup analyses of large randomized controlled trials designed to assess the efficacy of these agents in all ischemic stroke subtypes. A meta-analysis of 17 relevant randomized controlled trials published until December 2013 including 42234 participants with lacunar stroke reported a 22% relative risk reduction in recurrent stroke by single antiplatelet therapy (RR 0.77, 95% CI 0.62–0.97) compared with placebo, no consistent suggestion of variable efficacy amongst specific antiplatelet agents, and the absence of clear benefit with dual antiplatelet therapy over monotherapy [25••]. A major limitation of the pooled analysis is that lacunar stroke was defined in a heterogeneous manner in the included studies, lacking uniform clinical criteria, and without MRI to verify stroke subtype, in most included trials. We summarize the data for specific antiplatelet agents (Table 1) below.

Aspirin vs. Placebo

Aspirin (acetylsalicylic acid) blocks the formation of thromboxane A2, which is a potent platelet aggregant and vasoconstrictor, by irreversibly inhibiting prostaglandin H synthase (cyclooxygenase-1) in platelets and megakaryocytes.

There was no apparent reduction in the odds of death or dependency with assignment to aspirin 300 mg daily over placebo within 48 h of symptom onset in the 4616 (24% of trial cohort) patients with lacunar stroke participating in the International Stroke Trial [30]. However, a 68% relative risk reduction (RRR) in ischemic stroke was suggested amongst lacunar stroke participants taking aspirin 330 mg compared to placebo ($n = 98$; 16% of trial cohort) in the Accidents Ischémiques Cérébraux Liés à l'Athérosclérose (AICLA) trial [26] and a 17% RRR in ischemic stroke with aspirin 50 mg or dipyridamole 400 mg compared to placebo amongst 2600 (59% of cohort) patients with lacunar stroke participating in the ESPS-2 trial [39]. The effect of aspirin 160 mg was more modest for the composite outcome of stroke, myocardial infarction, or death (RRR 11%) in lacunar stroke participants ($n = 6263$, 30% of cohort) within the Chinese Acute Stroke Trial (CAST)(29). None of the aforementioned trials showed statistically significant effect modification by qualifying stroke subtype, supporting a consistent treatment effect with

Table 1 Stroke prevention randomized trials that provided information on lacunar stroke as index events

Study	Total sample, *n*	Time after index event	Patients with lacunar stroke, *n* (%)	Intervention (daily dose)	Mean follow-up (months)	Outcome (events)	Effect size in lacunar stroke subgroup (95% CI)	Adverse events associated with treatment	Reference
AICLA (1983)	604	< 1 year	98 (16)	ASA vs ASA-DP vs placebo	36	Ischemic Stroke (fatal or nonfatal)[a]	ASA vs placebo RR 0.38 (0.11–1.27)	Peptic ulcer, GI bleeding, other hemorrhages	[25••, 26]
CATS (1989)	1072	1 week–4 months	275 (26)	Ticlopidine vs placebo	24	Stroke (fatal or nonfatal)[a]	RR 0.52 (0.28–0.95)	Neutropenia skin rash, diarrhea	[25••, 27]
CAPRIE (1996)	19,185	> 24 h	2543 (13, entire cohort; 40, index strokes)	Clop vs ASA	23	Stroke[a]	HR 1.01 (0.83–1.24)	Skin rash (Clop) Indegestion/ N&V and GI hemorrhage (ASA)	[28]
CAST (1997)	21,106	< 48 h	6263 (30)	ASA vs control	1	MACE[a]	RR 0.89 (0.66–1.21)	NS	[25••, 29]
IST (1997)	19,435 (ASA vs. no ASA)	< 48 h	4657 (24)	ASA vs control	6	Death or dependence	RR 1.0 (0.94–1.06)	Transfused or fatal extracranial hemorrhage	[25••, 30]
CSPS (2000)	1095	1–6 months	794 (74)	Cil vs placebo	22	Recurrent ischemic stroke	RRR 43% (3–67)	NS	[31]
AAASPS (2003)	1809	1 week–3 months	1221 (68)	Ticlopidine vs ASA	18	MACE	RR 1.19 (CI 0.82–1.72)	TTP (1 patient on Ticlopidine)	[25••, 32]
MATCH (2004)	7599	< 3 months	3148 (52)	ASA+clop vs clop	18	MACE or rehospitalization for acute ischemia	RR 0.97 (0.79–1.2)	Life threatening bleeding or major bleeding (ASA+clop)	[25••, 33]
ESPS-2 (2006)	6,602	<3 months	2600 (59)	ASA vs DP vs ASA-DP vs placebo	24	Recurrent stroke[a]	ASA-DP vs placebo: HR 0.68 (0.48–0.97)	Headache (DP), diarrhea (DP), GI bleeding or all site bleeding (ASA)	[25••, 34]
ESPRIT (2006)	2739	< 6 months	1377 (50)	ASA-DP vs ASA	42	MACE	RR 0.91 (0.7–1.17)	Headache (DP)	[25••, 35]
ECLIPse (2007)	203	< 1 week	203 (100%)	ASA+Cil vs ASA	3	Recurrent stroke[a]	RR 1.03 (0.07–16.24)	NS	[25••, 36]
PRoFESS (2008)	20,332	< 3 months	10578 (52%)	ASA-DP vs clop	30	Recurrent stroke	RR 0.96 (0.84–1.09)	Intracerebral hemorrhages (ASA-DP), headache (ASA-DP)	[25••, 37]
Uchiyama (2009)	1921	> 8 days	1341 (73%)	Ticlopidine × clop	26 w/52w	MACE	RR 0.85 (0.46–1.55)	Liver dysfunction, Neutropenia (Ticlopidine)	[25••, 38]
CSPS2 (2010)	2757	< 26 weeks	1743 (65%)	Cil vs ASA	29	Stroke	HR 0.75 (0.54–1.04)	Headache, diarrhea, palpitation, dizziness, tachycardia (Cil)	[6, 25••]
SPS3 (2012)	3020	2 weeks–6 months	3020 (100%)	ASA+clop vs ASA	40	Recurrent stroke	HR 0.92 (0.72–1.16)	Extracranial bleeding (ASA+clop)	[4••]

Abbreviations: *AAASPS* African American Antiplatelet Stroke Prevention Study, *AICLA* Accidents Ischémiques Cérébraux Liés à l'Athérosclérose, *ASA* aspirin, *CAPRIE* clopidogrel versus aspirin in patients at risk for ischemic events, *CAST* Chinese Acute Stroke Trial, *CATS* Canadian American Ticlopidine Study in thromboembolic stroke, *Cil* cilostazol, *Clop* clopidogrel, *CSPS* Cilostazol Stroke Prevention Study, *CSPS2* cilostazol for prevention of secondary stroke 2, *ESPS-2* European Stroke Prevention Study 2, *ESPRIT* European/Australasian Stroke Prevention in Reversible Ischaemia Trial, *GI* gastrointestinal, *HR* hazard ratio, *IST* International Stroke Trial, *ITT* intention to treat, *MACE* major adverse cardiovascular events (nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death), *MATCH* management of atherothrombosis with clopidogrel in high-risk patients, *N&V* nausea and vomiting, *NS* not significant, *PRoFESS* prevention regimen for effectively avoiding second strokes, *RR* relative risk, *RRR* relative risk reduction, *SPS3* secondary prevention of small subcortical stroke, *TTP* thrombotic thrombocytopenic purpura

[a] Secondary endpoint

aspirin monotherapy compared to placebo for secondary stroke prevention across all eligible ischemic stroke subtypes within these trials, including lacunar stroke.

Ticlopidine vs. (i. Placebo, ii. Aspirin, and iii. Clopidogrel)

As part of the thienopyridine family, the hepatic-generated active metabolites of ticlopidine block $P2Y_{12}$ adenosine phosphate (ADP) receptors on the surface of platelets, inhibiting the binding of fibrinogen and ensuing platelet aggregation.

i) The Canadian-American Ticlopidine Study (CATS, $n = 1072$, 26% lacunar strokes, follow up 3 years) in 1989 reported, in subgroup analysis of participants with lacunar stroke ($n = 275$), a HR 0.52 (95% CI 0.28–0.95) in fatal or nonfatal stroke with ticlopidine 500 mg daily compared to placebo. The treatment effect in lacunar stroke patients was consistent with that seen in all stroke patients [25••, 27].
ii) In the AAASPS trial, black participants with recent non-cardioembolic ischemic stroke within 7 and 90 days were randomized to 500 mg daily of ticlopidine vs. 650 mg daily of aspirin. Amongst patients with lacunar stroke ($n = 1121$, 68% of total cohort) recurrent stroke occurred in 6% of participants assigned to ticlopidine and 5% of those assigned to aspirin (HR 1.19, 95% CI 0.82, 1.72) during a mean follow-up of 1.54 years [25••, 32].
iii) Lacunar stroke accounted for 73% ($n = 1341$) of the qualifying events at study entry in a Japanese multicenter randomized trial comparing ticlopidine 200 mg to clopidogrel (irreversible $P2Y_{12}$ ADP receptor inhibitor) 75 mg daily [38]. Similar to the parent cohort, lacunar stroke subgroup analysis did not demonstrate any difference in the composite efficacy endpoint of cerebral infarction, myocardial infarction, and vascular death between treatment with clopidogrel and ticlopidine.

Due to the rare but serious side effects of ticlopidine, including neutropenia and thrombotic thrombocytopenic purpura, the use of alternate antiplatelet agents with more favorable safety profiles is preferred in stroke populations.

Clopidogrel vs. Aspirin

In the international clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE) trial, patients with prior atherosclerotic ischemic events (including ischemic stroke) were randomly assigned to clopidogrel 75 mg daily and aspirin 325 mg daily [28]. There were no apparent differences between both treatment arms for recurrent stroke in 2543 participants with lacunar stroke (13% of trial population; 40% of qualifying strokes) at study entry (HR 1.01, 95% CI 0.83–1.24; unpublished data).

Cilostazol vs. (i. Placebo and ii. Aspirin)

Cilostazol is a selective cyclic adenosine monophosphate (cAMP) phosphodiesterase type 3 inhibitor. Increasing levels of cAMP and protein kinase A activity in smooth muscle cells of the vessel wall and platelets, result in vasodilation and inhibit platelet aggregation, respectively. Cilostazol additionally increases adenosine levels through inhibiting its uptake.

i) The Japanese multicenter placebo controlled Cilostazol Stroke Prevention Study (CSPS) trial assessed cilostazol 100 mg twice daily in patients with cerebral infarction between 1 and 6 months following symptom onset [31]. In the lacunar stroke subgroup, which accounted for 74% of baseline qualifying events ($n = 794$), random assigned to cilostazol compared to placebo led to a statistically significant 49% risk reduction in ischemic stroke during 2 years of follow-up [25••].
ii) Subsequently the Cilostazol Stroke Prevention 2 (CSPS 2) study demonstrated non-inferiority of cilostazol 100 mg twice daily compared to aspirin 81 mg daily for stroke prevention following non-cardioembolic cerebral infarction [6]. There was a nonsignificant trend for cilostazol to provide superior stroke prevention than aspirin in participants with lacunar stroke (HR 0.75, 95% CI 0.54–1.04; $n = 1743$ [65% of CSPS2 cohort]), and a statistically significant 54% relative risk reduction in major hemorrhagic events.

These initial favorable observations, and the potential endothelial stabilizing effects of cilostazol [40], have raised interest for their role in mitigating cerebral small vessel disease. The ongoing Lacunar Intervention 2 (LACI 2; NCT03451591) phase II trial in the United Kingdom, which is testing random assignment to cilostazol 100 mg twice daily, with or without isosorbide mononitrate in a factorial design, in patients with MRI-defined lacunar stroke is of considerable interest in this regard.

Dual Antiplatelet Therapy: i. Cilostazol/Aspirin, ii. Dypiridamole/Aspirin, and iii. Clopidogrel/Aspirin

i. In the multicenter South Korean ECLIPse trial, there was no apparent difference in recurrent stroke at 90 days in patients with their first lacunar stroke ($n = 203$; within 7 days of symptom onset) that were randomly assigned to receive aspirin 100 mg daily/cilostazol 100 mg twice daily compared to aspirin 100 mg daily/placebo [36].
ii. Sixteen percent ($n = 98$) of participants with cerebral or retinal atherothrombotic ischemic events in the French AICLA trial ($n = 98$) had qualifying lacunar stroke [26].

Randomization to aspirin 330 mg/dipyridamole (phosphodiesterase 5 inhibitor with mild phosphodiesterase 3 inhibition) 75 mg three times daily compared to aspirin 330 mg three time daily did not provide a statistically significant reduction in ischemic stroke (RR 0.59, 95% CI 0.11–3.29) [25••]. Subsequently the international ESPS-2 trial, which randomized TIA or minor ischemic stroke patients within 3 months of symptom onset to aspirin 25 mg/modified release dipyridamole 200 twice daily, demonstrated a 32% risk reduction (HR 0.68, 95% CI 0.48–0.97) in recurrent stroke with combined therapy in comparison to placebo during 1.8 years of follow-up amongst the 2600 participants (59% of trial cohort) with qualifying lacunar stroke [34]. The effect estimate in the lacunar stroke group was consistent with the 37% risk reduction seen in the entire cohort. ESPS-2 was followed by the international ESPRIT trial which compared aspirin 30–325 mg daily/dipyridamole 200 mg twice daily to aspirin monotherapy (30–325 mg daily) in minor ischemic stroke or TIA patients [35]. In ESPRIT combined therapy provided a 20% risk reduction for the composite of ischemic stroke, myocardial infarction, vascular death, and major bleeding over aspirin monotherapy in the entire cohort [1377 (50%) lacunar stroke]. In meta-analysis that included previous trials, the ESPRIT investigators reported an 18% risk reduction for the composite of stroke, myocardial infarction, and vascular death with combined therapy over aspirin monotherapy, which is similar to the 17% risk reduction with combined therapy reported in pooled subgroup analysis of participants with lacunar stroke [25••]. However, combined therapy with aspirin 25 mg/extended-release dipyridamole 200 mg twice daily subsequently did not demonstrate super stroke prevention compared to clopidogrel 75 mg daily in patients with recent ischemic stroke within 90 days participating in the international PRoFESS randomized trial [37]. These findings were consistent in the 10,578 participants (52% of study cohort) with lacunar stroke at study entry [25••]. Overall, the totality of the data from randomized controlled trials assessing combined therapy with aspirin/dypiridamole has been interpreted as providing equivalent stroke prevention to antiplatelet monotherapy. Whether patients with minor ischemic stroke or TIA, who enrolled in ESPS-2 and ESPRIT, are those who particularly benefit more from this regimen is uncertain. Compliance issues, largely due to headache, with combined aspirin/dypiridamole treatment have limited its international uptake as a first-line antithrombotic regimen of choice for stroke prevention irrespective of stroke subtype.

iii. The MATCH trial [33] was the first large secondary stroke prevention trial to compare dual antiplatelet therapy with clopidogrel/aspirin to antiplatelet monotherapy. Participants with recent ischemic stroke/TIA within 3 months of symptom onset who had at least one additional vascular risk fator did not benefit from random assignment to clopidogrel 75 mg/aspirin 75 mg daily compared with clopidogrel 75 mg/placebo daily, but had significant increase in major bleeding, particularly beyond 90 days of treatment. These results were consistent in the 3148 (53%) of participants who had lacunar stroke at study entry (RR 0.97, 95% CI 0.79–1.20) [25••]. The SPS3 trial [4••], subsequently assessed secondary stroke prevention with aspirin 325 mg/clopidogrel 75 mg daily compared to aspirin 325 mg/placebo daily in 3020 MRI-defined recent lacunar stroke patients between 14 and 180 days of symptom onset. The antiplatelet component of the SPS3 trial was terminated prematurely after a mean follow-up of 3.4 years due to a statistically significant 52% increase in all-cause mortality with aspirin/clopidogrel, without an apparent reduction in recurrent stroke. There were non-significant trends however for a 18% relative risk (0.4% absolute risk) reduction in ischemic stroke ($p = 0.13$) and 65% relative risk (0.17% absolute risk; $p = 0.15$) increase in intracranial hemorrhage. There was more than a twofold increase in major extracranial hemorrhage with dual antiplatelet therapy.

Early Short-Term Dual Antiplatelet Therapy in Minor Lacunar Strokes

The role of short-term dual antiplatelet therapy started within 24 h of lacunar stroke remains uncertain, as the SPS3 trial excluded patients within 14 days of their stroke onset, had a median timing from stroke onset to randomization of 62 days, and continued treatment with dual antiplatelet therapy for a mean of 3.5 years.

In 2013, CHANCE investigators reported a 32% relative risk reduction in recurrent stroke amongst 5170 Chinese minor ischemic stroke/TIA patients who were randomized within 24 h of symptoms onset to dual antiplatelet therapy with aspirin 75 mg/clopidogrel 75 mg daily for 21 days followed by clopidogrel 75 mg daily for 90 days compared with open-label aspirin 75 mg daily for 90 days [41]. Similar results were replicated in an international population by the POINT investigators [42], who reported a 25% relative risk reduction in the composite of ischemic stroke, myocardial infarction, and death from ischemic vascular causes in 4881 minor ischemic stroke/TIA patients within 12 h of symptom onset who were randomly assigned to aspirin 50–325 mg/clopidogrel 75 mg daily compared to aspirin monotherapy for 90 days.

Although lacunar stroke subgroup analyses have not been presented from these trials, it is likely that lacunar stroke contributed to a considerable proportion of baseline

qualifying strokes on the basis of the high proportion of lacunar stroke in minor ischemic stroke/TIA (i.e., 50% of ESPRIT and 59% of ESPS-2) and East-Asian stroke populations (30% of CAST, 74% of CSPS, and 65% of CSPS2). Although Chinese populations are also at greater risk of intracranial atherosclerotic disease, there were no statistically significant treatment interactions observed with intracranial atherosclerotic disease within the CHANCE trial [43]. It is thus reasonable to assume, unless contradictory evidence becomes available, that consistent with the lacunar stroke subgroup analyses of prior antiplatelet stroke prevention trials outlined in our review, lacunar stroke patients enrolled within the POINT and CHANCE trials benefited similarly to the overall trial cohorts from early short-duration dual antiplatelet therapy.

Presence of Cerebral Microbleeds and/or Prior Intracerebral Hemorrhage

Sporadic age-related cerebral small vessel diseases (hypertensive arteriopathy and cerebral amyloid angiopathy) can additionally contribute to symptomatic intracerebral hemorrhages and covert cerebral microbleeds.

Cerebral microbleeds are often found incidentally on MRI in about 30% of ischemic stroke/TIA patients. Their association with a heightened risk of future intracerebral hemorrhage has raised alarms about the net benefit of antithrombotic therapy in ischemic stroke/TIA patients who have CMBs on MRI, particularly in patients with a high number of CMBs (i.e., > 10) or in cases with a strictly lobar distribution suggestive of underlying cerebral amyloid angiopathy. However, CMBs also mark an increased risk of ischemic vascular events, and in ischemic stroke/TIA populations the absolute event rate of ischemic stroke far supersedes that of intracerebral hemorrhage, irrespective of the degree of CMB burden or distribution [44, 45•]. Accordingly, it is unlikely that the presence of CMBs on MRI would meaningfully modify the established net benefit of antiplatelet therapy for secondary stroke prevention. Fittingly, MRI subgroup analyses of the SPS3 trial did not demonstrate any interaction between random assignment to dual vs. mono antiplatelet therapy and the presence of CMBs on baseline MRI in lacunar stroke patients for the outcomes of recurrent stroke or death [8•]. Interestingly, patients with strictly lobar CMBs had the greatest risk of recurrent ischemic stroke during follow-up. Whether there exists a synergistic relationship between arteriolosclerosis and cerebral amyloid angiopathy, perhaps by way of impaired cerebral vascular reactivity [46] is uncertain. A direct causal relationship between cerebral amyloid angiopathy and subcortical lacunes has even recently been suggested [47].

Additionally, upwards of 30% of patients with spontaneous intracerebral hemorrhage patients are receiving antithrombotic treatment at the time of the hemorrhage for various concomitant thromboembolic diseases. The net benefit of continued antiplatelet therapy following a spontaneous ICH in such patients was recently tested in the randomized multicenter RESTART trial [48••]. In 537 participants with spontaneous ICH, randomization to antiplatelet therapy (either aspirin, clopidogrel, and/or dipyridamole) compared to no antithrombotic therapy did not seem to increase the risk of recurrent ICH, and led to a 35% ($p = 0.025$) relative risk reduction in the secondary composite outcome of non-fatal myocardial infarction, non-fatal stroke, and vascular death. Unexpectedly, there was a strong trend for a reduction in recurrent ICH with antiplatelet therapy resumption (aHR 0.51 [95% CI 0.25–1.03, $p = 0.06$). Whether these provocative findings hint at novel mechanisms in our understanding of ICH pathophysiology, or are simply due to a play of chance, remains uncertain. However, the RESTART results provide landmark data on the relative safety and net benefit of antiplatelet therapy in patients with ICH and concomitant vaso-occlusive diseases. Further reassurance is provided in the RESTART MRI subgroup analyses that did not demonstrate any treatment modification according to ICH location, or the presence and burden of MRI markers of cerebral small vessel disease, including cerebral microbleeds or cortical superficial siderosis [49•].

Conclusions

Indirect data from subgroup analyses of acute ischemic stroke thrombolysis and secondary stroke prevention trials suggest that thrombosis is actively involved in the pathophysiology of lacunar stroke. Lacunar stroke patients appear to respond the same to antiplatelet therapy as other ischemic stroke subtypes, as summarized in our review. Antiplatelet monotherapy provides persistent secondary stroke prevention in this stroke subpopulation. Whether phosphodiesterase inhibitors, particularly cilostazol, provide additional advantage in patients with cerebral small vessel disease is worthy of further investigation. Long-term stroke prevention with dual antiplatelet therapy with aspirin/clopidogrel should not be considered in lacunar stroke patients, however, until more data is forthcoming, it is reasonable to assume that lacunar stroke patients benefit similarly from this dual antiplatelet therapy regimen if initiated early (within 24 h of stroke onset) and continued for a short duration (21–90 days). Lastly, current data do not support withholding antiplatelet therapy from patients with hemorrhage-prone cerebral small vessel diseases, manifested by symptomatic ICH or incidental CMBs on MRI, who have concomitant indications for antiplatelet therapy.

Compliance with Ethical Standards

Conflict of Interest Danielle de sa Bouasquevisque, Oscar R. Benavente, and Ashkan Shoamanesh each declare no potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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