Review Article

Treatment Approaches to Lacunar Stroke

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Lacunar strokes are appropriately named for their ability to cavitate and form ponds or "little lakes" (Latin: *lacune -ae* meaning pond or pit is a diminutive form of *lacus* meaning lake). They account for a substantial proportion of both symptomatic and asymptomatic ischemic strokes. In recent years, there have been several advances in the management of large vessel occlusions. New therapies such as non-vitamin K antagonist oral anticoagulants and left atrial appendage closure have recently been developed to improve stroke prevention in atrial fibrillation; however, the treatment of small vessel disease-related strokes lags frustratingly behind. Since Fisher characterized the lacunar syndromes and associated infarcts in the late 1960s, there have been no therapies specifically targeting lacunar stroke. Unfortunately, many therapeutic agents used for the treatment of ischemic stroke in general offer only a modest benefit in reducing recurrent stroke while adding to the risk of intracerebral hemorrhage and systemic bleeding. Escalation of antithrombotic treatments beyond standard single antiplatelet agents has not been effective in long-term lacunar stroke prevention efforts, unequivocally increasing intracerebral hemorrhage risk without providing a significant benefit. In this review, we critically review the available treatments for lacunar stroke based on evidence from clinical trials. For several of the major drugs, we summarize the adverse effects in the context of this unique patient population. We also discuss the role of neuroprotective therapies and neural repair strategies as they may relate to recovery from lacunar stroke.

Key Words: Cerebrovascular diseases—stroke—lacunar stroke—cerebral small vessel disease

Introduction and Basic Definitions

Lacunar strokes (LS), which account for approximately 20%-30% of all ischemic strokes,[1,2] are largely due to the pathologic consequences of underlying cerebral small vessel disease (cSVD). While LS is one sequela of cSVD, cSVD is a major contributor to several neurological comorbidities, including vascular cognitive impairment, gait disorders, and intracerebral hemorrhage (ICH).[3-8] In addition to lacunar cavitations, cSVD has many neuroimaging manifestations including white matter hyperintensities (WMH), cerebral microbleeds, dilated perivascular spaces, superficial cortical siderosis, and brain atrophy. By the historical classification schema outlined in the Trial of Org 10172 in Acute Stroke Treatment (TOAST), small artery occlusions (LS) were defined as meeting the

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ACRONYM	DEFINITION
ACTIVE	Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events
ADC	apparent diffusion coefficient
aICH	asymptomatic intracerebral hemorrhage
AICLA	Accidents Ischemiques Cerebraux Lies a l'Atherosclerose
ALIAS	Albumin Treatment for Ischemic Stroke
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ASA	aspirin
ATC	Antithrombotic Trialists Collaboration
ATLANTIS	Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke
BI	Barthel index
C	controlled
CAA	cerebral amyloid angiopathy
CAPRIE	Clopidogrel versus AsPirin in patients at Risk of Ischaemic Events
CASISP	Cilostazol versus Aspirin for Secondary Ischemic Stroke Prevention
CAST	Chinese Acute Stroke Trial
CD	clopidogrel
CE	cardioembolic
CHANCE	Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events
CI	confidence interval
CS	cilostazol
CSPS	Cilostazol Stroke Prevention Study
CSPS.com	Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS.com)
cSVD	cerebral small vessel disease
CT	computed tomography
DAPT	dual antiplatelet therapy
DB	double-blind
DP	dipyridamole
DWI	diffusion-weighted imaging
ECASS	European Cooperative Acute Stroke Study
EPITHET	EchoPlanar Imaging Thrombolytic Evaluation Trial
ESPRIT	European/Australasian Stroke Prevention in Reversible Ischaemia Trial
ESPS-2	European Stroke Prevention Study-2
FLAIR	fluid-attenuated inversion recovery
FLAME	Fluoxetine for Motor Recovery after Acute Ischemic Stroke
FMS	Fugl-Meyer motor scale
FOCUS	Functional Outcomes after Acute Stroke
GABA	γ-aminobutyric acid
GI	gastrointestinal
GOS	Glasgow Outcome Scale
HbA1c	hemoglobinA1c
HR	hazard ratio
ICD	International Classification of Diseases
ICH	intracerebral hemorrhage
INR	international normalized ratio
IRIS	Insulin Resistance Intervention after Stroke
IS	ischemic stroke
IST-3	Third International Stroke Trial
IU	International Unit
IV	intravenous
JCS	Joint Committee for Stroke
LAA	large artery atherosclerosis
LAAC	left atrial appendage closure
LACI	lacunar infarction
LACI-2	LACunar Intervention-2
LS	lacunar stroke
MATCH	Management of AtheroThrombosis with Clopidogrel in High-risk patients
MC	multicenter
mg	milligram
MI	myocardial infarction
mm	millimeter
mmHg	millimeter of mercury
MRI	magnetic resonance imaging
mRS	modified Rankin scale
NE	neurological examination
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
NMDA	N-methyl-D-aspartate receptor
NOAC	non−vitamin K antagonist oral anticoagulants
NOGO	neurite outgrowth inhibitor
NR	not reported
O	other
OCSP	Oxfordshire Community Stroke Project
OHS	Oxford Handicap Scale
PACI	partial anterior circulation infarct
PE	physical exam
PI	pulsatility index
PLATO	Platelet Inhibition and Patient Outcomes
POCI	posterior circulation infarct

POINT	Platelet-Oriented Inhibition in New TIA and minor ischemic stroke
PRoFESS	Prevention Regimen for Effectively Avoiding Second Strokes
PS	prospective
R	randomized
RRR	relative risk reduction
RS	retrospective
RT	randomized
SATURN	StATins Use in IntRacerebral Hemorrhage PatieNts
SC	single-center
sICH	asymptomatic intracerebral hemorrhage
SOCRATES	Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
SPIRIT	Stroke Prevention in Reversible Ischemia Trial
SPS3	Secondary Prevention of Small Subcortical Strokes 3
SSRI	selective serotonin reuptake inhibitors
STRIVE	STandards for ReportIng Vascular changes on nEuroimaging
SWI	susceptibility-weighted imaging
TACI	total anterior cerebral infarct
TIA	transient ischemic attack
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
TP	ticlopidine
tPA	tissue plasminogen activator
UD	undetermined
UKPDS	United Kingdom Prospective Diabetes Study
WARSS	Warfarin-Aspirin Recurrent Stroke Study
WMH	white matter hyperintensities

following criteria: (1) a traditional lacunar syndrome without cortical signs, (2) supporting features such as hypertension and diabetes mellitus, (3) the lack of an infarct explaining deficits on computed tomography (CT)/magnetic resonance imaging (MRI) examination or a subcortical lesion less than 15 mm in diameter, and (4) the absence of features that suggest a high likelihood of cardioembolism or embolism from upstream arterial stenosis greater than 50%.[9]

With advances in CT and MRI technology leading to the detection of asymptomatic infarcts, more recent terminology developed by the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) consortium separates the lesion attributed to small vessel disease into several subtypes: recent small subcortical infarct and lacune of presumed vascular origin.[10] This terminology reflects a more complete understanding of the dynamic nature of cSVD such that not all subcortical infarcts form lacunar cavities but instead may form acute and chronic WMH.[11,12] Furthermore, while subcortical infarctions are often accompanied by the clinical syndromes originally described by Fisher and others,[13] subcortical infarctions can be identified incidentally by diffusion-weighted imaging (DWI) sequences on MRI scans.[14-17]

By consensus definitions set forth by the STRIVE consortium, recent small subcortical infarcts can be up to 20 mm in axial diameter on MRI and are attributed to infarcts in the territory of the arteriole perforator.[10] Lesions larger than 20 mm in the basal ganglia are excluded from this definition, because they may be caused by an infarct affecting several arteriolar penetrators. Lacunes of presumed vascular origin are the end products of small subcortical infarcts (Fig 1), although they can sometimes be difficult to distinguish from old hemorrhages or large perivascular spaces. These lacunes are frequently observed on neuroimaging scans of neurologically "healthy" individuals, although they confer an increased risk of symptomatic stroke and vascular cognitive impairment.[5,18-23] Lacunes of presumed vascular origin are subcortical, round, fluid-filled spaces between 3 mm and 15 mm (smaller than subcortical infarcts due to chronic involution of tissue). Compared to dilated perivascular spaces, lacunes have a surrounding T2 hyperintense rim and are usually larger than the 3 mm size cutoff for these lesions.[10,24,25] Lacunes are classically found in deep locations, although lobar lacunes have been recently characterized,[26] and are likely associated with cerebral amyloid angiopathy (CAA) (Fig 2). For purposes of this review, small subcortical infarcts and their accompanying clinical features will be referred to as LS.

In recent years, a type of infarct termed cerebral microinfarct has gained much attention (Fig 3).[27] These microscopic lesions (.2-3 mm) are observed during pathological studies[28] and occasionally by high field strength MRIs.[27,29-31] They occur commonly in patients with memory impairment and are independent predictors of vascular dementia.[30-32] The burden of these infarcts can be daunting, with some estimates suggesting hundreds to thousands of infarcts in a single brain.[33-35] These cerebral microinfarcts may be responsible for some of the devastating sequalae of small vessel disease. Understanding their role may provide further insight into LS pathogenesis allowing for the development of highly specific molecular targets. Because their significance is unclear, at the current time, cerebral microinfarcts should be diagnosed and treated in a similar fashion as LS, since they likely represent smaller versions of LS. With the exception of comorbid ICH,[14] when cerebral microinfarcts are encountered, a thorough evaluation for embolic sources should be performed.

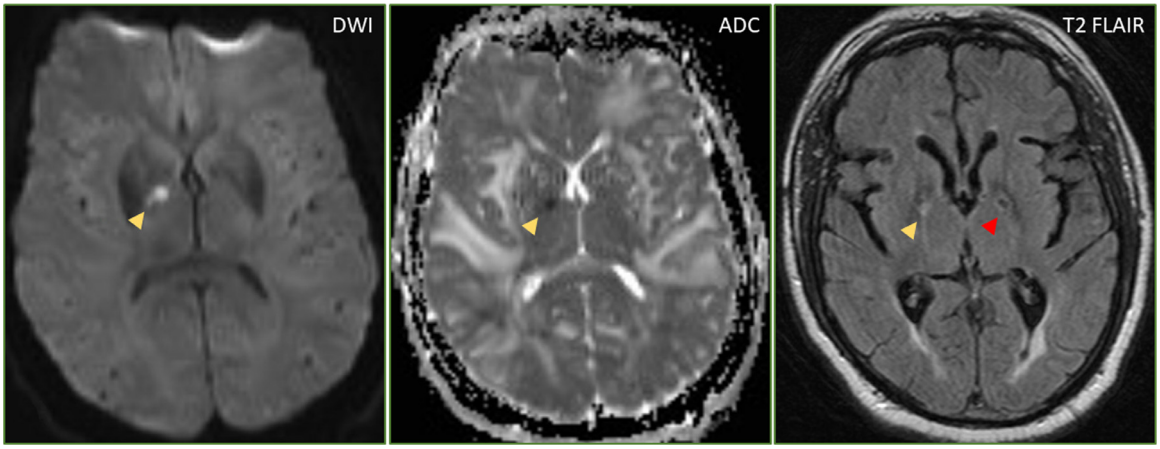

Figure 1. ***Lacunar stroke***. *Recent small subcortical infarct (yellow arrow) appears bright on the DWI sequence and dark on the ADC sequence. In the early subacute phase, there may be a corresponding WMH seen on T2 FLAIR. A small subcortical infarct may involute over time and form a fluid-filled cavity or lacune seen on the contralateral hemisphere of this patient (red arrow). Note the presence of a surrounding T2 hyperintense rim which is a useful finding to help distinguish a lacune from a dilated perivascular space. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; WMH, white matter hyperintensity.*

While there have been several recent advances in the treatment of large vessel occlusions that are impacting systems of care,[36,37] the treatment of LS has lagged in comparison. In this review, we will discuss the current therapies available for cSVD-related infarcts as well as their role in the acute and chronic settings. Our focus will be on LS due to sporadic, non-amyloid cSVD, although it is important to note that LS may also be caused by embolism, branch artery atheroma, or CAA.[26,38,39] Throughout this review, non-amyloid cSVD will be referred to simply as cSVD.[4] As determined from population-based studies, hypertension is most influential risk factor involved in cSVD formation and progression, although several additional risk factors may be involved.[40,41,264]

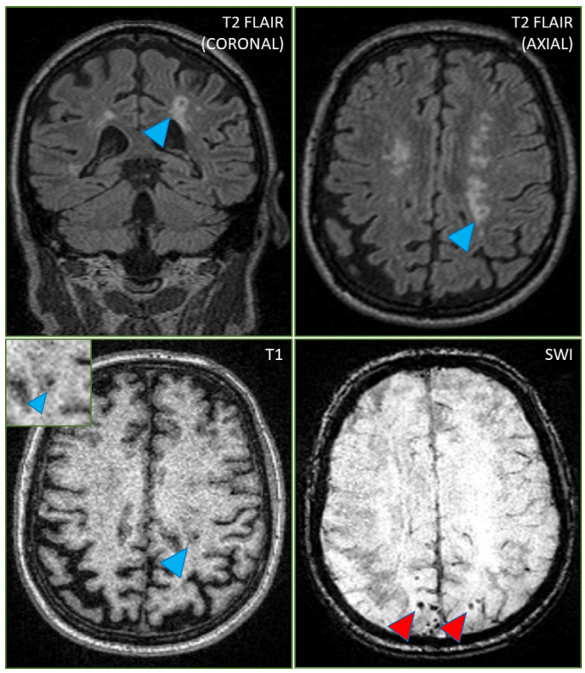

Figure 2. ***Lobar lacune***. *Lobar lacunes are a recently described entity which can be observed on T1 and T2 FLAIR sequences (blue arrows). This brain scan was taken from a patient with probable CAA. Consistent with this example, lobar lacunes are more associated with CAA than other cerebral small vessel diseases. Notably, on the SWI sequence, multiple posterior cortical microbleeds (red arrows) are seen; however, there is no microbleed corresponding to the lobar lacune. Images were graciously provided by Elif Gökçal. CAA, cerebral amyloid angiopathy; FLAIR, fluid-attenuated inversion recovery; SWI, susceptibility-weighted imaging.*

Methodology

Articles from January 1960 to December 2018 were located using the PubMed (National Center for Biotechnology Information, National Library of Medicine) database. The following search terms were employed: "lacunar stroke AND treatment" without any exclusionary terms. The search was limited to full-text articles available in English. Several additional references were

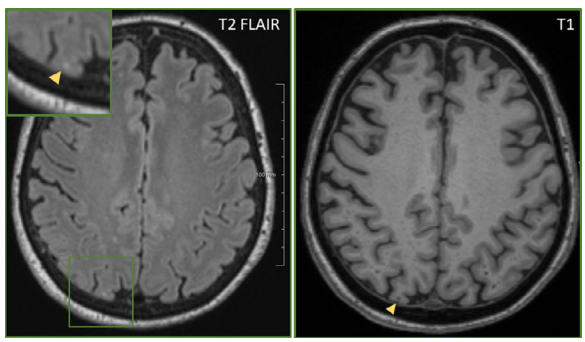

Figure 3. ***Cerebral microinfarct***. *Cerebral microinfarcts are less than 3 mm in diameter. They are hyperintense on T2 FLAIR (left, inset) and hypointense on T1 (right).*

selected by reviewing the reference lists of relevant publications. In our search, we excluded literature pertaining to other stroke subtypes including large artery atherosclerosis and cardioembolism.

Employing the above search strategy yielded a total of 1072 articles. Articles were independently screened by 2 authors (A.S.D. and R.W.R.) for their relevance to lacunar stroke therapy. After the screening process, 263 articles were ultimately selected for incorporation in this paper, generating a semi-systematic review. This review is organized by the various major categories of therapies trialed for LS: thrombolysis, anticoagulation, antiplatelet agents, and selective serotonin reuptake inhibitors (SSRIs). We then focus on risk factor modulation: blood pressure manipulation, glycemic control, and hyperlipidemia control. In these sections, we make the distinction between acute and secondary prevention efforts when they are both mentioned. Following these sections, we discuss neuroprotective and neural repair strategies. Because of the numerous trials involving thrombolytic and antiplatelet therapy, we have summarized this information in 2 tables.

General Therapeutic Considerations

In reviewing approaches for therapy and prevention of LS, there are several important considerations. A distinction should be made between prevention, acute reperfusion, neuroprotection, and chronic repair augmentation therapies. Each phase has different mechanisms and different potential therapeutic targets; many factors influence outcomes after stroke.[42]

Whether therapies are applied in the acute or chronic setting, the benefits of treatment must be carefully weighed against the risks of systemic bleeding and ICH. Both CAA-related and non-CAA-related cSVD pose an increased risk of ICH, which has a high rate of recurrence[43,44] and carries significant morbidity and mortality.[45,46] Neuroimaging findings, such as cerebral microbleeds (either the presence or absence of these lesions),[47,48] WMH,[49,50] dilated perivascular spaces,[51] and superficial cortical siderosis,[47] influence this risk and should be taken into consideration when deciding on LS therapy.[46] Since antithrombotic agents elevate ICH risk in healthy populations,[52] applying these therapies to patients with cSVD may have an even greater effect on ICH risk. Not only is there an increased risk of ICH within the stroke territory in the early phase, but there is also an increased risk of ICH in remote territories, especially with the use of thrombolytic agents or anticoagulants.[53-57] Therefore, a thorough understanding of these agents and their usage in LS is critical, even when there is a reasonable concurrent indication for their use.

Thrombolysis

In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen activator (tPA) trial revolutionized the approach to acute stroke management.[53] The European Cooperative Acute Stroke Study (ECASS)[58] was published just before the NINDS trial, and 5 additional trials followed, including ECASS II,[59] ECASS III,[60] Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) A/B,[61,62] EchoPlanar Imaging Thrombolytic Evaluation Trial (EPITHET),[63,64] and the third International Stroke Trial (IST-3).[65,66] All of these trials evaluated the efficacy of tPA in various time windows ranging from 0 to 6 hours from symptom onset. Based on the results of these trials, the standard of care is intravenous (IV) tPA for patients with acute ischemic stroke of adequate disability presenting within 4.5 hours of symptom onset. This indication includes patients with acute LS.[67]

Although there is some controversy regarding its efficacy in the LS compared to other stroke subtypes,[68] the majority of trials support the use of IV tPA in this population. In the original NINDS trial, of the total LS patients who received tPA, 63% had a favorable outcome (mRS $\leq$ 1) at 3 months compared to 40% in the control group.[53] This was the greatest risk reduction among stroke subtypes. Yet, in IST-3, which evaluated tPA administered up to 6 hours, while the overall analysis demonstrated a functional improvement at 18 months in the treatment arm, the subgroup analysis of LS patients revealed a nonsignificant trend toward worse outcomes at 3 months in the treatment arm.[66] It should be noted that both the NINDS and IST-3 trials determined stroke subtype by purely clinical examination without modern neuroimaging. In a post hoc analysis of ECASS, it was demonstrated that fewer than 20% of patients with a clinical lacunar syndrome had a corresponding lacunar infarct identified on a CT scan performed a week later.[69] This observation, which has been replicated by other groups,[70] highlights the practical problem that stroke subtype cannot be reliably determined rapidly enough to direct tPA treatment decisions.

In addition to the randomized trials of tPA, several other studies have addressed 3 major questions: (1) Is there a benefit of administering tPA to LS patients? (2) Is the benefit of tPA in LS similar to the benefit in other stroke subtypes? (3) Do LS have unique ICH risks compared to other stroke subtypes when given thrombolytic therapy? Regarding the first question, several studies have demonstrated that LS patients who receive tPA have improved functional outcomes and shorter hospital stays.[71,72] However, these positive results have not been replicated by all studies.[73,74] In nearly all the studies assessing the benefit of tPA in LS compared to other subtypes, the efficacy of thrombolysis was similar regardless of stroke type. As shown in Table 1, even the randomized trials did not always include a uniform approach to diagnosing LS. Results from observational data are highly variable with some suggesting higher ICH risk and others lower ICH risk, but an overall

Table 1. *Thrombolysis trials in lacunar stroke*

Trial	Study design	Groups	Study size	Subtyping method	Assessment of stroke	Outcome measurement	Results	ICH events
NINDS (1995)[53]	RT, MC	LAA, SVD, CE; control groups	624 (51/30)	PE	PE/CT	BI, mRS, NIHSS, GOS (3 m)	Favorable outcome (mRS < 2) in lacunar treatment group compared to placebo	No subgroup analysis, overall ICH rate was 6.4% in treatment group compared to .6% (P = .001)
Hsia et al. (2003)[254]	RS, 2-center	LAA, SVD, CE, O, UD	90 (7/0)	TOAST	PE/CT or MRI	mRS and BI (1 m and 3 m)	Nonsignificant trend toward better outcome in lacunar group	0 ICH in SVD group (not significantly different from other stroke subtypes)
Cocho et al. (2006)[68]	RS, SC	LS, non-LS	44 (11/33)	OCSP/TOAST	PE/CT or MRI	mRS (3 m)	Proportion patients with good outcome (mRS 0-1) was similar (27% LS versus 60% non-LS, P = .083)	0 sICH; aICH in 1 LS group, 3 in non-LS group (P= .99)
Hwang et al. (2008)[74]	RS, SC	LS; control group	76 (29/47) [12/26] in SVD subgroup	OCSP/ TOAST	PE/MRI	mRS (3 m)	Similar outcome between treatment and control group (31% versus 23% with favorable response (P = .463)	2 with aICH
Fluri et al. (2010)[255]	PS, MC	LS, non-LS	1048 (65/0)	TOAST	PE/CT or MRI	mRS (3 m)	Trend toward better outcome in lacunar group	ICH 12.3% (4.6% sICH) in LS group and 13.4% (5.3% sICH) in non-LS group (P > .80)
Mustanoja et al. (2011)[256]	RS, SC	LAA, SVD, CE, O, UD, mixed	957 (101/0)	TOAST	PE/CT or MRI	mRS (3 m)	SVD group with better outcomes and lower mortality	0 sICH in SVD group
Fuentes et al. (2012)[257]	PS, MC	LAA, SVD, CE, O, mixed	1479 (60/0)	ICD-10	PE/CT	mRS (3 m)	No difference among stroke subtype at 24 h, nonsignificant trend toward worse outcome in SVD group at 3 m	NR
IST-3 (2012)[66]	MC, RT	TACI, PACI, LACI, POCI, O	3035 (168/164)	PE	PE/CT or MRI	OHS (6 m)	Nonsignificant trend toward worse outcome in LACI treatment group versus control (59.5% versus 62.8%) (P = .91)	No subgroup analysis, overall ICH rate was 7% in treatment group compared to 1% in control (P < .0001)
Shobha et al. (2013)[258]	RS, MC, case-cohort	TACI, PACI, LACI, POCI; control groups	11503 (195/2001)	OCSP	PE/CT or MRI	90-d mortality, mRS (discharge)	No difference in thrombolysis benefit between LACI, PACI, or TACI	2.1% ICH rate (1.5% sICH) in LACI subtype, least among other stroke subtypes
Griebe et al. (2014)[73]	PS, SC	LS; control groups	537 (69/468)	ASCO	PE/MRI	mRS, NIHSS (3 m)	More favorable clinical improvement within 5 days, median mRS was similar in	0 sICH, aICH 11.6% in treatment group compared to 1.9% in control group (P = .001)

Table 1 (*Continued*)

Trial	Study design	Groups	Study size	Subtyping method	Assessment of stroke	Outcome measurement	Results	ICH events
							treatment versus control group (3 m)	
Lahoti et al. (2014)[71]	RS, MC	LS, non-LS; control groups	256 (102/54)	PE/MRI	PE/MRI	mRS (3 m)	Higher excellent outcomes (mRS 0-1) in non-LS treatment group ($P < .01$), higher perfect (mRS 0) outcomes in LS treatment group ($P < .01$)	2 sICH in treatment group compared to 0 sICH in control group
Pan et al. (2016)[259]	RS, SC	LAA, SVD, CE, UD	471 (82/0)	TOAST	PE	mRS (discharge)	Highest proportion of favorable outcomes in SVD group compared to stroke subtypes ($P < .01$)	1 patient with sICH and 2 with any ICH (lower than any other subtype)
Chen et al. (2016)[260]	PS, MC	LAA, SVD, CE, O, UD; control groups (NIHSS $\leq$ 5)	383 (30/56)	TOAST	PE/CT or MRI	mRS (3 m)	No difference in proportion of favorable outcomes in SVD treatment and SVD control groups (73% versus 80%, $P = .42$)	No subgroup analysis, 1 ICH overall
Zivanovic et al. (2017)[72]	RS, SC	LS; control group	81 (36/45)	OCSP	NR	mRS (discharge)	Shorter hospital stays in LS treatment group (9.5 d versus 14.3 d, $P = .004$), higher proportion of excellent functional outcomes (mRS 0-1) in LS treatment group (41.7% versus 15.6%, $P = .01$)	NR
Eggers et al. (2017)[261]	MC, non-RT	LS, non-LS, control group	10632 (496/3492)	TOAST	PE/CT or MRI	mRS (discharge, 3 m)	Better functional outcome in LS treatment group compared to placebo ($P < .001$), similar degree of improvement between LS and non-LS groups	1% in LS treatment group compared to .2% in control LS group, 2.7% in non-LS treatment group compared to 1.0% in non-LS control group ($P = .02$)

Abbreviations: aICH, asymptomatic intracerebral hemorrhage; BI, Barthel index; CE, cardioembolic; CT, computed tomography; GOS, Glasgow Outcome Scale; ICD, International Classification of Diseases; ICH, intracerebral hemorrhage; LAA, large artery atherosclerosis; LACI, lacunar infarction; LS, lacunar stroke; MC, multicenter; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale (NIHSS); NR, not reported; O, other; OCSP, Oxfordshire Community Stroke Project classification; OHS, Oxford Handicap Scale; PACI, partial anterior circulation infarct; PE, physical exam; POCI, posterior circulation infarct; PS, prospective; RS, retrospective; RT, randomized; SC, single-center; sICH, symptomatic intracerebral hemorrhage; SVD, small vessel disease; TACI, total anterior cerebral infarct; TOAST, trial of ORG 10172 in Acute Stroke Treatment classification; UD, undetermined.

Note: parenthetical numbers in the study size column represent the size of lacunar stroke treatment group and lacunar stroke control group, respectively.

benefit is suggested by most studies. Observational data are also prone to confounding by indication, but overall the results are positive, consistent with randomized controlled trials. Unfortunately, several of these studies do not include control groups (ie, LS patients who did not receive tPA), so it is difficult to ascertain whether these patients had favorable outcomes as a result of receiving tPA (or because LS have a favorable outcome in general[75]). Although these studies used different methodologies and yielded somewhat mixed results, it is likely that tPA is beneficial and safe for LS. Acknowledging the limitations of the data, the benefit of tPA for LS appears to outweigh the risk of symptomatic ICH and should be given in the acute setting if criteria are met.[67] Indeed, this recommendation conforms to current guidelines.[67] The mechanism by which tPA is effective in cSVD-related infarcts is poorly understood. As mentioned above, embolism,[76-86] or more commonly, *in situ* formation of microthrombi in small, distal vessels is the final step that leads to ischemia in small vessel disease.[71,87] tPA may promote recanalization of these vessels thereby restoring perfusion.

Anticoagulation

Fisher postulated that anticoagulation was inappropriate for lipohyalinosis-related strokes because of the red blood cell extravasation and microhemorrhages that are associated with these lesions.[13] Several lines of evidence in the modern era support this judgment. Anticoagulation-related ICH studies indicate that leukoaraiosis, a marker of cSVD, is a risk factor for hemorrhage.[88-90] The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) demonstrated that leukoaraiosis is an independent risk factor for ICH in patients on anticoagulation (in the setting of atrial fibrillation).[91] So, there is evidence that anticoagulation should be avoided in such patients, unless there is a separate strong indication for anticoagulation without any alternative.[92]

In the acute phase of LS, few studies have examined the role of heparin and heparin-based therapies. Subcutaneous heparin was most notably studied in the first IST which enrolled nearly 20,000 patients within 48 hours of stroke symptoms.[93] In this multicenter, randomized, placebo-controlled trial (n = 19,435), patients were administered either unfractionated heparin (5,000 IU or 12,500 IU twice daily) or aspirin 300 mg daily during the 14 days after ischemic stroke. Within this 14-day time frame, the heparin group had fewer recurrent ischemic strokes than the control group (2.9% versus 3.8%); however, this benefit was counterbalanced by a commensurate increase in ICH (1.2% versus .4%). In both heparin and aspirin treatment groups, there was a trend toward fewer deaths in the first 14 days. At 6 months, heparin conferred no benefit over aspirin for the outcomes of death or functional status, and at higher doses, it increased the risk of intracranial and extracranial hemorrhage. In the IST, 24% of patients who were enrolled had LS, but there was no subgroup analysis of outcome based on stroke subtype.

Similar negative findings were reported in TOAST, a randomized, double-blind, placebo-controlled trial that administered a 7-day course of danaparoid sodium (a low-molecular weight heparinoid) to subjects (n = 1,281) within 24 hours of stroke symptom onset.[94] Although there was a trend toward a favorable response in the treatment group at 7 days, this benefit was not observed at 90 days. Similar to IST, increased intracranial bleeding was observed in the treatment group within 10 days. In this study, 24.5% of subjects in the treatment arm and 23.3% in the control arm had LS. At 3 months, this group had the highest frequency of favorable outcomes compared to other stroke types, although there was no difference in outcome between the control and treatment groups. In light of these findings, heparin is not indicated in acute LS management.

For secondary prevention of LS, data to support the avoidance of anticoagulation comes from the Warfarin-Aspirin Recurrent Stroke Study (WARSS).[95] In that study, warfarin, at INR range of 1.4-2.8, or aspirin 325 mg was administered to "non-cardioembolic" ischemic stroke patients within 30 days of stroke. The largest stroke subtype in both the warfarin and aspirin groups was LS (>55% in each group). Assessing the probability of an event at 2 years, recurrent ischemic stroke was observed in 17.8% of patients taking warfarin compared to 16% of patients taking aspirin (hazard ratio [HR] 1.13, confidence interval [CI] .92-1.38). The rate of major hemorrhage was higher in the warfarin arm (2.22 versus 1.49 per 100 patient-years, rate ratio: 1.48 [.93-2.44]), and minor hemorrhages occurred at a higher rate in warfarin arm (1.61 [1.38-1.89]). Warfarin showed no benefit over aspirin in patients with cSVD (2-year probably of event: 17.1% versus 15.2%, $P = .31$). Similar findings were reported in a 2-year prospective study (n = 386) by Evans et al examining stroke subtype in patients with atrial fibrillation.[96] Warfarin (INR goal 2.0-3.0) was superior to aspirin (70-300 mg) in patients who initially presented with cardioembolic stroke but not in patients who presented with LS in the setting of atrial fibrillation (rate of recurrent stroke was 8.8% versus 8.9%). Moreover, there was an increased risk of hemorrhage in the warfarin group compared to the aspirin group (2.5% versus .6%, $P < .05$).

For secondary prevention strategies in patients with CAA, anticoagulation is contraindicated, perhaps even for those with atrial fibrillation. The presence of CAA-related neuroimaging markers such as lobar cerebral microhemorrhages and cortical superficial siderosis suggests CAA and increases the risk of anticoagulant-associated hemorrhage.[46,92,97-99] Non-vitamin K antagonist oral anticoagulants have been shown to confer similar

risks of poor functional outcomes and morbidities[100,101] when compared to warfarin, except with perhaps decreased in-hospital mortalites.[52] This increased hemorrhagic risk raises the question of safety in patients with indications for anticoagulation, such as atrial fibrillation. The risk of hemorrhage appears to rise with increasing burden of cerebral microbleeds with relative risks up to 5-14-fold with 5 or more microbleeds.[102-104] In such cases, the decision to anticoagulate must be based on the absolute risk of hemorrhage and the competing absolute risk of ischemic stroke. In the setting of atrial fibrillation, this ischemic stroke risk rises with increasing CHA_2DS_2-VASc score.[105] Consideration of nonpharmacological methods such as left atrial appendage closure (LAAC) in nonvalvular atrial fibrillation patients with cSVD may be reasonable. Further studies are needed to fully elucidate the role of non-vitamin K antagonist oral anticoagulants versus LAAC in patients with atrial fibrillation and concurrent cSVD. Because of this uncertainty, some recent NOAC studies have been designed to exclude patients with LS given this elevated ICH risk, including a trial testing the prevention of vascular events in patients with coronary or peripheral vascular disease.[106] At the current time, NOACs and warfarin should be avoided for the sole treatment of LS.

Antiplatelet Agents

Antiplatelet agents are recommended for acute ischemic stroke when patients are not candidates for tPA or intra-arterial therapy. Among the options for antiplatelet therapy, the most robust data and safety information exist for aspirin. Aspirin inhibits cyclooxygenase, thereby reducing the production of thromboxane A2, thus inhibiting platelet aggregation irreversibly. In the general population, low-dose aspirin does not increase the risk of ICH or subdural hematoma.[107] Furthermore, in survivors of deep hemorrhages, aspirin does not seem to increase ICH recurrence risk suggesting that is safe to use in cSVD.[108,109] In addition to aspirin, dipyridamole, an adenosine deaminase and phosphodiesterase inhibitor, and clopidogrel, a thienopyridine that inhibits platelet aggregation, have also been evaluated extensively and are commonly used for secondary stroke prevention. These agents have also been studied in combination with aspirin as dual antiplatelet therapy (DAPT).

Two major trials evaluated aspirin in the acute phase of ischemic stroke: The aforementioned IST[93] and the Chinese Acute Stroke Trial (CAST).[110] In IST (discussed previously given its data on heparin), the patients treated with 300 mg aspirin experienced a reduction in recurrent stroke at 14 days (2.8% versus 3.9%; $2P < .001$), as well as nonfatal stroke or death (11.3% versus 12.4%; $2P = .02$). Importantly, the risk of hemorrhagic strokes was similar between aspirin and controls (.9% versus .8%), although aspirin increased the risk of extracranial bleeding. The CAST randomized 21,000 patients within 48 hours of stroke to a 4-week course of 160 mg of aspirin or placebo. Results of this study revealed a 14% reduction in mortality at 30 days with aspirin usage (3.3% versus 3.9%; $2P = .04$). In the same time frame, there were fewer ischemic strokes in the aspirin group compared to placebo (1.6% versus 2.1%; $P = .01$), although there was a trend towards more hemorrhagic strokes with aspirin (1.1 versus .9, $2P > .10$). In the subset of patients with LS (n = 6120, ~30% in each group), there was a 10% reduction in the relative risk of stroke recurrence or mortality at 30 days. It should be noted that in both IST and CAST, only a CT scan (and no MRI) was done in the majority of cases prior to randomization, limiting the accuracy of assigned stroke mechanisms. In light of more recent data on the risk and timing of recurrent stroke after transient ischemic attacks (TIAs) or minor ischemic strokes (discussed below), the positive findings in IST and CAST likely represent prevention of early recurrent stroke rather than effective treatment of the index stroke. Based on these data, aspirin is recommended for early treatment after acute ischemic stroke.

In acute ischemic stroke of mild severity, DAPT may be more effective than single-agent therapy when administered early, without significantly increasing ICH.[111] However, the efficacy and risks of DAPT have not been evaluated for LS specifically. The Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial, which administered DAPT (versus 75 mg aspirin monotherapy) within 24 hours of presentation in Chinese patients with minor stroke (NIHSS < 4) or TIA for 3 weeks after the index event, demonstrated a reduction in stroke recurrence at 90 days (8.2% versus 11.7%, $P < .001$) without a corresponding increase in hemorrhagic stroke.[112] However, a subgroup analyses of CHANCE suggest that the greatest benefit of DAPT likely occurs in patients with embolic strokes.[113,114] The Platelet-Oriented Inhibition in New TIA and minor ischemic stroke (POINT) trial tested a similar regimen of DAPT against aspirin (50-325 mg) monotherapy, but treated for 3 months rather than 3 weeks.[115] The early benefit of DAPT was again demonstrated; however, there were higher rates of major hemorrhage ($P = .02$) but not symptomatic intracranial hemorrhage in the treatment group at 3 months. The confirmatory results of the POINT trial suggests that the beneficial effect seen in CHANCE was not specific to the Chinese population. The benefits of DAPT are realized within the first few weeks, but additional DAPT confers added risk without further benefit.

Aspirin is also the mainstay of antiplatelet therapy in the chronic setting for secondary prevention of ischemic stroke in those without indications for anticoagulation. The greatest body of evidence for aspirin's benefit for secondary prevention is summarized in a meta-analysis, the 2002 Antithrombotic Trialists Collaboration (ATC).[116] The

study analyzed 195 trials comparing aspirin to placebo for the prevention of stroke, myocardial infarction, and vascular death in patients enrolled after a prior vascular event. A 22% risk reduction for ischemic stroke was observed in patients treated with antiplatelet agents (aspirin being by far the most common agent used). The 2009 ATC yielded similar results, demonstrating that aspirin reduced the risk of any serious vascular event by 19% and ischemic stroke by 22%.[117] A smaller study showed that stopping antiplatelet therapy in high-risk patients may increase the risk of stroke.[118]

Ticlopidine is a thienopyridine agent that irreversibly binds to the $P2Y_{12}$ ADP receptor subtype to inhibit platelet aggregation. As seen in Table 2, ticlopidine (administered 1 week to 4 months after stroke) was shown to reduce the risk of LS, and may be more effective than aspirin in selected populations.[119-124] However, neutropenia was a prominent side effect, which has limited its use as a first-line agent.

Clopidogrel has a mechanism of action similar to ticlopidine and does not cause neutropenia, making it an attractive candidate for secondary stroke prevention. The Clopidogrel versus AsPirin in patients at Risk of Ischaemic Events (CAPRIE) trial compared 75 mg clopidogrel with 325 mg aspirin in recent (≥1 week, but ≤6 months) stroke, myocardial infarction, or symptomatic peripheral arterial disease.[125] In this multicenter, randomized, blinded trial, there was no reduction in recurrent stroke with clopidogrel over 1.9 years (7.15% versus 7.71%, $P = .26$), although there was a reduction in the composite endpoint of ischemic stroke, myocardial infarction, or vascular death (driven mostly by a benefit seen in patients with pre-existing peripheral vascular disease). In addition, patients on clopidogrel and aspirin had similar rates of both extracranial and intracranial hemorrhage. No subgroup analysis of LS was performed in this study, however.

The Secondary Prevention of Small Subcortical Strokes 3 (SPS3) trial specifically examined the role of DAPT in secondary stroke prevention after LS.[126] This multicenter, double-blinded study enrolled patients (n = 3020) who had MRI-confirmed LS within 180 days and randomized them to aspirin 325 mg or aspirin 325 mg plus clopidogrel 75 mg (median time to randomization was over 2 months from LS). Over a 3.4-year period, the risk of stroke recurrence was similar in each group (2.5% with DAPT and 2.7% with aspirin monotherapy; $P = .48$), although there was a trend toward increased ICH with DAPT. In this study, the extracranial hemorrhage rate, mainly gastrointestinal, was almost doubled with DAPT (2.1% versus 1.1%, $P < .001$). As seen in other studies such as the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) trial,[127] ICH rates increased with DAPT, although this finding has not been replicated in all trials.[128] In SPS3, mortality was increased in the DAPT group (113 versus 77 deaths; $P = .004$).

Several other trials have included LS patients in comparisons of single- versus dual-agent antiplatelet therapy. The Management of AtheroThrombosis with Clopidogrel in High-risk patients (MATCH) trial randomized patients with recent (within 90 days) stroke or TIA (n = 3148) to either clopidogrel 75 mg or aspirin 75 mg plus clopidogrel 75 mg, and included over 50% LS in both treatment arms.[129] The median time to enrollment after stroke was 15 days.[130] At 18 months, there was no difference in the combined endpoint of ischemic stroke, myocardial infarction, or vascular death. Furthermore, major bleeding (mostly gastrointestinal) and symptomatic ICH were increased in the DAPT arm. DAPT's efficacy has also been evaluated using dipyridamole and aspirin. In the 1983 French study Accidents Ischemiques Cerebraux Lies a l'Atherosclerose (AICLA) which examined placebo versus aspirin versus aspirin/dipyridamole, in a subset of LS patients, a significant reduction in recurrent stroke risk was observed in the aspirin monotherapy and combination therapy groups compared to placebo.[131] Dipyridamole was also studied in the 1996 European Stroke Prevention Study-2 (ESPS-2),[132] and again in the 2006 European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) (Table 2), which both demonstrated a reduction in recurrent stroke without increasing ICH risk.[133] However, when the combination of twice daily dipyridamole 200 mg and aspirin 25 mg was compared to clopidogrel 75 mg in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial, there was no difference in stroke recurrence rates between groups.[134] Moreover, the DAPT group experienced more intracranial bleeding than clopidogrel alone. Collectively, these trials suggest that DAPT should be avoided in the chronic treatment of LS.[130,135,136] Not surprisingly, using more aggressive antiplatelet therapy regimens with triple antiplatelet therapy has not been shown to reduce stroke risk, but only adds to the risk of intracranial hemorrhage.[137]

In addition to aspirin, dipyridamole, and clopidogrel, several other antiplatelet agents have been developed as monotherapies for the secondary prevention of LS. Cilostazol, used most often for peripheral vascular disease, is a phosphodiesterase III inhibitor that promotes vasodilation. Evidence for its efficacy in LS comes from the Cilostazol Stroke Prevention Study (CSPS) conducted in Japan, which reported a 2.3% absolute risk reduction in the annual stroke rate compared to placebo (3.0% versus 5.2%, $P = .04$) in LS patients (mean time to randomization 83 days after stroke).[138] When compared with aspirin in CSPS II, there was a .95% absolute risk reduction in the annual incidence of stroke in the cilostazol group (2.8% versus 3.7%, $P = .04$).[139,140] Among patients with LS (randomized within 26 weeks after stroke), there was a trend toward decreased recurrent stroke with cilostazol use (6.8% versus 9.7%, $P = .09$) over a 2.4-year period. Furthermore, in LS patients, the hemorrhagic stroke risk was less

Table 2. *Antiplatelet therapy in lacunar stroke*

Study	Design	Treatment Groups	Enrollment; Duration	LS Size[136]	Stroke Classification	Outcome	Adverse events
AICLA (1983)[131]	DB, MC, R	330 mg ASA/330 mg ASA + 75 mg DP/ placebo	IS within 1 y; 3 y	98 (16%)	JCS (NE and CT)	Fatal/nonfatal stroke lower in ASA versus placebo ($P < .05$) and ASA + DP group ($P < .06$)	2 deaths from ICH overall; similar systemic bleeding in DP + ASA and ASA
CATS (1989)[120]	DB, MC, R, C	500 mg TP/placebo	1 w-4 m after IS; 2 y	274 (26%)	NE	30% RRR for combined IS, MI, or death in TP versus placebo ($P = .006$)	Increased neutropenia in TP
ESPS-2 (1996)[132]	DB, MC, R, C	50 mg ASA/400 mg DP/ 50 mg ASA + 400 mg DP/placebo	IS within 3 m; 2 y	2600 (59%)	NE	IS risk reduced by 18% in ASA ($P = .013$), 16% in DP ($P = .039$), 37% in ASA + DP group ($P < .001$)	Highest all-site and GI bleeding in ASA group
IST (1997)[93]	Open R, MC	300 mg ASA/control	within 48 h after IS; 6 m	4616 (24%)	OCSP (CT scan)	IS recurrence and death within 14 days reduced (2.8% versus 3.9%; $2P < .001$)	No increase in hemorrhagic stroke
CAST (1997)[110]	MC, R, C	160 mg ASA/placebo	within 48 h after IS; 4 w	6,263 (30%)	OCSP	Reduction in mortality and recurrent IS (1.6% versus 2.1%; $2P = .01$)	Increase in hemorrhagic stroke (1.1% versus .9%; $2P > .10$)
CSPS (2000)[138]	DB, R, C	100 mg CS BID/placebo	IS within 1-6 m; 2 y	794 (74%)	NE and CT/ MRI	Stroke reduction by 43.3% with CS in LS group ($P = .0373$)	Similar ICH in CS versus placebo, no increase in GI bleeding
AAASPS (2003)[123]	DB, MC, R	500 mg TP/650 mg ASA	7-90 d after IS; 2 y	1221 (68%)	TOAST and CT/MRI	Stroke, MI, or vascular death similar between TP and ASA	Similar rate of GI bleeding
MATCH (2004)[129]	DB, MC, R, C	75 mg CD + 75 mg ASA/ 75 mg CD	IS/TIA within 3 m; 18 m	3148 (53%)	TOAST	No difference among IS, MI, or vascular death between groups	Increased ICH and GI bleeding with CD + ASA ($P < .0001$)
ESPRIT (2006)[133]	MC, R, C	30-325 mg ASA + 200 mg DP BID/30-325 mg ASA	IS within 6 m; 3.5 y	1377 (50%)	NE and CT/ MRI	Death from all causes, nonfatal IS/MI lower with combination therapy	Similar fatal ICH and major bleeding
FASTER (2007)[262,*]	MC, R, C	75 mg CD + 325 mg ASA/ 325 mg ASA	IS within 24 h; 90 d	113 (29%)	TOAST (CT or MRI)	Similar IS rate in CD and ASA (7.1% versus 10.8%; $P = .19$)	2 ICH in CD versus 0 in placebo ($P = .50$)
PRoFESS (2008)[134]	DB, MC, R, C	25 mg ASA + 200 mg DP BID/75 mg CD	IS within 90 d; 2.5 y	10,578 (52%)	NE and CT/ MRI	No difference in recurrent IS between groups	Increased intracranial bleeding in ASA + DP versus CD

(*Continued*)

Table 2 (*Continued*)

Study	Design	Treatment Groups	Enrollment; Duration	LS Size[136]	Stroke Classification	Outcome	Adverse events
Uchiyama et al. (2009)[263]	DB, MC, R	75 mg CD/200 mg TP	IS within 8 d; 26 or 52 w	1341 (73%)	NE and CT/MRI	No difference in IS, MI, or vascular death between CD and TP	Similar rate of major hemorrhage
CSPS2 (2010)[139]	DB, MC, R	100 mg CS BID/81 mg ASA	IS within 26 w; 2.4 y	1743 (65%)	NINDS-III and CT/MRI	IS recurrence lower in CS versus ASA (2.76% versus 3.71%; $P = .0357$)	In LS group, fewer hemorrhagic strokes in CS versus ASA (.36% versus 1.20%, $P = .003$)
SPS3 (2012)[126]	DB, MC, R	325 mg ASA + 75 mg CD/ 325 mg ASA	IS within 180 d; 3.4 y	3020 (100%)	NE and MRI	Similar IS recurrence in DAPT and ASA; increased mortality in DAPT (.04% versus .03%; $P = .004$)	Higher major hemorrhage in DAPT versus ASA (2.1%/y versus 1.1%/y, $P < .001$); similar ICH rate
SOCRATES (2016)[153]	DB, MC, R	90 mg ticagrelor BID/ 100 mg ASA	IS within 24 h; 90 d	3839 (29%)	NE and CT/MRI	Similar IS, MI, or death between ticagrelor and ASA (7.3% versus 8.0%, $P = .40$)	Similar ICH rate between ticagrelor and ASA (.2% versus .3%, $P = .30$)

Abbreviations: ASA, aspirin; C, controlled; CD, clopidogrel; CS, cilostazol; CT, computed tomography; DAPT, dual antiplatelet therapy; DB, double-blind; DP, dipyridamole; GI, gastrointestinal; ICH, intracerebral hemorrhage; IS, ischemic stroke; JCS, Joint Committee for Stroke; LS, lacunar stroke; MC, multicenter; MI, myocardial infarction; MRI, magnetic resonance imaging; NE, neurological examination; NINDS, National Institute of Neurological Disorders and Stroke; OCSP, Oxfordshire Community Stroke Project; R, randomized; RRR, relative risk reduction; TIA, transient ischemic attack; TOAST, Trial of ORG 10172 in Acute Stroke Treatment classification; TP, ticlopidine.

Note: parenthetical numbers in the study size column represent the percentage of LS.

*Trial terminated early.

in patients taking cilostazol versus aspirin,[141] a finding that was replicated in the Cilostazol versus Aspirin for Secondary Ischemic Stroke Prevention (CASISP) study.[142] The authors postulated that since LS may be related to endothelial dysfunction and failed autoregulation, treatment with cilostazol may be an appropriate therapy given its vasodilatory properties. Furthermore, cilostazol has been shown to decrease the pulsatility index (PI), a marker of cSVD, in transcranial Doppler studies at 90 days in acute LS.[143] In small studies, other combinations of cilostazol such as cilostazol-probucol or cilostazol-edaravone have also demonstrated improved functional outcomes in patients with silent LS.[144,145] Interestingly, cilostazol is being studied as a long-term DAPT option in conjunction with aspirin or clopidrogrel in the Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS.com) study (ClinicalTrials.gov identifier: NCT01995370).[146] Although chronic DAPT with aspirin and clopidogrel have failed because of their increased hemorrhage risks, cilostazol in combination with other agents may be safe due to cilostazol's reduced risk of hemorrhage compared to aspirin (based on CSPS II and CASISP mentioned above).[139,140,142] A subgroup analysis of LS was performed in CSPS.com, although the findings of this trial remain unpublished.

While the studies of cilostazol seem promising, it is not used as a first-line agent in many countries for 2 major reasons: (1) headache is a common side effect with cilostazol use that affects 10% of cilostazol users[147,148] and (2) the majority of studies using cilostazol (including CSPS.com) were performed in Asian populations; therefore, its efficacy in non-Asian populations remains unclear.[149] However, the ongoing study, LACunar Intervention (LACI-2) Trial-2 (ClinicalTrials.gov identifier: NCT03451591) will address whether cilostazol will be beneficial in preventing LS and slowing the progression of cSVD in non-Asian populations. At the current time, it can be concluded that cilostazol is an acceptable alternative as a secondary prevention strategy in LS. Moreover, it may be useful in patients with aspirin resistance who are able to tolerate its side effects.[150]

Another antiplatelet agent used for secondary prevention in LS is ticagrelor, which has been adopted as a staple for use in acute coronary syndrome.[151] Ticagrelor is a direct-acting agent which reversibly binds to the P2Y12 receptor on platelets.[152] In the Platelet Inhibition and Patient Outcomes (PLATO) trial for acute coronary syndrome,[151] there was an increase in hemorrhagic stroke rates with ticagrelor compared to clopidogrel (23 [.2%] versus 13 [.1%], P= .10) while ischemic stroke rates were similar. Recently, the Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial (n = 13,199) compared twice daily ticagrelor 90 mg with aspirin 100 mg for 90 days in patients with small strokes (NIHSS $\leq$ 5) within 24 hours of symptom onset.[153] In a subgroup analysis of LS, there was no significant difference among stroke, myocardial infarction, or death within 90 days.[154] ICH was rare in this study, but did not differ significantly between ticagrelor and aspirin.

Serotonin Reuptake Inhibition

There is some literature that suggests that the use of SSRIs may be efficacious after- stroke.[155,156] Much of this evidence derives from the Fluoxetine for Motor Recovery after Acute Ischemic Stroke (FLAME) trial[157] and other smaller randomized controlled trials.[158-161] FLAME was a double-blind, placebo-controlled trial conducted at 9 centers in France that randomized patients (n = 118) with recent (within 5-10 days) ischemic stroke and hemiplegia/hemiparesis to receive fluoxetine 20 mg or placebo for 3 months. At 90 days, patients in the treatment arm had a significant improvement in motor symptoms, as measured by the Fugl-Meyer motor scale (FMS), and disability, as measured by the modified Rankin Scale (mRS). In the FLAME trial, only 3% of patients in the fluoxetine group and 10% of patients in the control group had LS. By contrast, in the recent double-blind, placebo-controlled Fluoxetine on Functional Outcomes after Acute Stroke (FOCUS) trial, fluoxetine 20 mg or placebo was administered to patients (n = 3127) for 6 months. This study, which included 15% LS, showed that fluoxetine administration did not improve disability as measured by mRS at 90 days; however, it did not assess FMS as a surrogate for motor function.[162]

Although SSRIs may be beneficial after stroke, there are also conflicting data suggesting that SSRIs cause an increased risk of ICH.[163-168] In one population-based cohort, it was shown that this risk was the greatest in the first 30 days of SSRI use and when used in combination with oral anticoagulants.[168] In a meta-analysis of several SSRI trials, there was a slight increase in ICH risk with SSRI use, but the absolute rate of ICH with SSRI use was low.[169] Although the use of fluoxetine in LS is probably safe, given that patients with cSVD are already at an increased risk of ICH, it should be judiciously used in high-risk LS patients, such as those with previous ICH, extensive WMH, cerebral microbleeds, and concurrent anticoagulation use. Further studies specifically evaluating ICH risk in LS patients taking SSRIs are needed.

Blood Pressure Manipulation and Flow Augmentation

The current guidelines for acute ischemic stroke regardless of stroke subtype are to allow patients to autoregulate blood pressure to maintain perfusion for 24 hours, up to a systolic blood pressure of 220 mm Hg for patients who did not receive tPA and 180 mm Hg for those who received tPA.[67,170] However, the role for permissive hypertension in LS has not been fully examined, and the

role for therapeutic hypertension induced with vasopressors is controversial.[171] While therapeutic hypertension is thought to primarily benefit patients with large vessel occlusion,[172] there may be some role for permissive or induced hypertension in the treatment of stuttering lacunes.[173] Alternative therapies to augment cerebral blood flow such as expanding the circulation with albumin infusions have been used with varying efficacy.[174-177] However, in a randomized, double-blinded trial examining high-dose albumin treatment for ischemic stroke (ALIAS) (of which about one-fifth were LS), administration of albumin within 5 hours of stroke did not improve mRS or NIHSS at 90 days and was associated with more pulmonary edema.[178] After the acute phase of autoregulation (generally 24 hours post-symptom onset), blood pressure should be gradually reduced to normotension as rapid overcorrection may worsen stroke symptoms.

For primary and secondary prevention of LS, there is a large body of evidence for aggressive blood pressure control. At a population level, it has been suggested that the incidence of LS has been declining due to improved management of hypertension in the modern era.[40,179] Specifically for LS, hypertension doubles the risk of recurrent stroke while diabetes increases it by 1.5-fold.[180] Furthermore, while blood pressure control is accepted as essential in all strokes,[181] there is a paucity of evidence regarding specific blood pressure targets for each stroke subtype. In one small study, however, hypertension was more commonly seen with acute LS, independent of pre-stroke hypertension.[182] Although the PRoFESS study did not perform a subgroup analysis of stroke subtypes, 52% of the study population (n = 20,332) included LS.[183] In that study, patients treated with telmisartan approximately 15 days after stroke achieved an average blood pressure reduction of 3.8/2.0 mm Hg. However, after a 2.5-year follow-up, there was no difference in recurrent stroke or ICH with telmisartan therapy. What remained unclear however was whether greater reductions of above 3.8/2.0 mm Hg would result in improved outcomes. The SPS3 study provided additional insight into this question.

SPS3 investigated more aggressive blood pressure targets specifically in LS.[184] A total of 3020 patients with recent (180 days) MRI-confirmed LS were randomized to a systolic blood pressure goal of 130-149 mm Hg versus a goal of <130 mm Hg. Although there was no significant reduction in stroke rate (2.77% versus 2.25%, P= .08), the risk of ICH was reduced with lower blood pressure targets (.11% versus .29%, P= .03). The mean systolic blood pressure achieved in the higher blood pressure target arm was 138 mm Hg compared to 127 mm Hg in the lower target arm. Given that cSVD itself poses a greater risk of ICH, a systolic blood pressure goal of <130 mm Hg for recent LS is reasonable and is concordant with recent recommendations set forth by the American College of Cardiology.[185] Importantly, in the SPS3 study, there were few adverse events reported in patients randomized to a lower blood pressure target suggesting that aggressive blood pressure control is safe and may be efficacious.[186]

Glycemic Control and Diabetes Management

In acute ischemic stroke, current guidelines recommend treatment of hyperglycemia.[67,170] Hyperglycemia is due in part to cortisol and norepinephrine release during acute ischemic stroke and may have deleterious effects due to free radical production.[187] Although there is ample evidence to suggest that hyperglycemia at presentation is associated with worse outcomes,[188] there are limited data suggesting that treating hyperglycemia improves outcomes.[189,190] Not only is diabetes a risk factor for all stroke subtypes,[191] but it is an independent risk factor for first-time LS[192-194] and portends worse outcomes.[195] For primary prevention, the United Kingdom Prospective Diabetes Study (UKPDS) compared Type 2 diabetic patients who were given intensive treatment (average HbA1c 7.0%) to traditional treatment (average HbA1c 7.9%) and showed no significant reduction in stroke incidence (P = .52). However, this study may not have been sufficiently powered to detect a stroke-specific relationship and/or the intensive control may not have been "intensive enough" to substantially impact stroke incidence.[196] Regarding secondary prevention, in the SPS3 study, about 37% of all patients were noted to have diabetes mellitus.[197] These patients were found to have increased intracranial atherosclerosis, a predilection to develop posterior circulation strokes, and more white matter disease burden.[198] Mortality, recurrent stroke, and myocardial infarction risks were doubled in this patient cohort.[197]

Pioglitazone, a thiazolidinedione, may be helpful for reducing vascular events after ischemic stroke. In the Insulin Resistance Intervention after Stroke Trial (IRIS), insulin-resistant individuals (n = 3876) with recent stroke were randomized to 45 mg pioglitazone daily versus placebo.[199] At 4.8 years, patients randomized to the treatment arm had decreased rates of stroke and myocardial infarction compared to placebo (9.0% versus 11.8%, P= .007). Furthermore, the incidence of diabetes within that time frame was reduced in patients who received pioglitazone (3.8% versus 7.7%, P< .001), although there was an increased incidence of fractures in this group. Roughly 30% of patients in both the treatment and placebo groups were composed of patients with LS.[200] Recently, pioglitazone's benefit has been extended to patients with prediabetes, suggesting that it may be more widely adopted as a secondary prevention strategy in the future.[201]

Controlling Hyperlipidemia and Statins

While it is well- established that hypercholesterolemia is a risk factor for large vessel atherosclerosis, there are

conflicting data pertaining to hyperlipidemia as a risk factor for cSVD and LS.[202-207] Regarding treatment of hypercholesteremia, one meta-analysis revealed that statins reduced the incidence of all strokes through a reduction in LDL.[208] In one early study of patients with cerebrovascular or other occlusive artery disease, there was a 28% reduction in ischemic stroke when patients were given simvastatin 40 mg daily.[209] The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial proved that high-intensity statin treatment results in a reduction in subsequent fatal stroke and cardiovascular events in patients without coronary artery disease.[210] A subsequent subgroup analysis showed that there was no difference in treatment outcome regardless of stroke subtype, suggesting that atorvastatin may be beneficial for LS. However, this study was limited in that it was not powered to assess such differences.[211] In a post hoc analysis of SPARCL, there was an increased risk of hemorrhage among patients with baseline cSVD-related LS who received statins (2.8% versus .57% in placebo arm, HR 4.99) although this was counterbalanced by a reduction in ischemic stroke recurrence (11.2% versus 14.6%, HR .76).[212,213] Therefore, in most cases, statins should be used for the treatment of LS unless the pre-existing risk of hemorrhage is unacceptably high (recurrent ICH, multiple microbleeds, etc.).[214] The StATins Use in IntRacerebral Hemorrhage PatieNts (SATURN) study (National Institutes of Health/National Institute of Neurological Disorders and Stroke) examining the safety of statin continuation after spontaneous lobar ICH will provide additional insight as to their safety in lacunar stroke.

Experimental Agents for Neuroprotection and Neural Repair

A final category of potential therapeutics consists of agents that may offer neuroprotection or augment neural repair. Neuroprotective agents are intended to act acutely to protect the ischemic brain before it is irreversibly infarcted, while agents designed to augment repair aim to replace lost elements and promote plasticity. The former is most likely to be effective in the first few hours following stroke, while the latter is most likely to be effective within the first few weeks to months after stroke.[215]

When developing agents that target brain parenchyma, the elements of the neurovascular unit should be considered. Although it has been applied more readily to large vessel occlusions,[216-218] the neurovascular unit as a concept relates to the interactions among neurons, astrocytes, microglia, endothelial cells, and smooth muscle cells. Collectively, the unit is involved in maintaining synapses, regulating neurotransmitters, energy metabolism, the blood-brain barrier, and blood flow. Many agents targeting the health of the neurovascular unit have been tested in cell culture and animal models of stroke; however, none have translated into effective therapies for human patients.[219,220] Major pathways that have been targeted include neuronal death mechanisms, excitotoxicity, and inflammation.[216,217,221] NMDA receptor antagonists are among the most commonly evaluated neuroprotective therapies given their propensity for reducing excitotoxicity in acute stroke. Agents such as NA-1, thought to reduce NMDA-mediated injury, as well as magnesium, which has other pleiotropic effects,[222,223] have shown some promise in preliminary trials.[223-226] In addition, modulation of the ACE2-Ang-(1-7)-Mas axis in stroke patients has gained attention in recent years[227] given its demonstrated efficacy in models of small and large vessel stroke.[228-231]

Among the possible reasons for the failure of neuroprotective agents to translate clinically is the underestimation of white matter injury in human stroke. While a human brain is composed of nearly 50% white matter, most rodent brains are composed of only 15%[232] illustrating that many standard rodent models fail to mimic human white matter injury in acute stroke. This highlights the need for an improved understanding of both white matter ischemia and the need to develop preclinical models that specifically target white matter. An important distinction between white matter and gray matter is that white matter blood flow is lower than that of gray matter and contains fewer collateral networks.[219] In addition, unique modulation of intracellular calcium between gray and white matter leads to differences in cell death mechanisms.[233-237] Because of these distinctions, the concept of the oligovascular unit has been applied to strokes that preferentially affect the white matter.[238]

In addition to neuroprotective strategies, several targets for augmenting neural repair have been proposed including axonal sprouting, neurogenesis, gliogenesis, and neuronal excitability.[215] Neural repair specifically affecting the white matter (which is more relevant to LS) has only been studied in recent years. These agents are intended to work by stabilizing the blood-brain barrier, repairing the oligovascular unit, modulating glial scarring, augmenting remyelination, and preventing axonal degeneration.[238-240] When white matter undergoes ischemia, endogenous repair mechanisms are initiated involving oligodendrocyte progenitor cells,[241] which proliferate, migrate, and differentiate into myelinating oligodendrocytes.[242,243] In the process of glial scar formation, several cell surface and extracellular matrix proteins have been shown to inhibit axonal growth and impair the ability of oligodendrocytes to myelinate new axons. These detrimental molecules include neurite outgrowth inhibitor (NOGO), ephrin ligands, and chondroitin proteoglycans.[244] In mice, NOGO receptor 1 blockade was shown to overcome

remyelination failure after LS and stimulate functional recovery.[245]

In recent years, agents that augment neural repair, such as cerebrolysin, have shown promise in human studies.[246] With these neural repair augmentation strategies, it is important to note that the timing of administration is crucial. Many agents that augment repair can have deleterious effects in the acute setting.[215] For example, drugs that inhibit tonic inhibitory GABA signaling or augment excitatory AMPA glutamatergic signaling increase infarct size when given 3-5 days after stroke in mice. However, when given after this period, they instead enhance motor recovery.[247,248]

Key Points

- Lacunes are subcortical, round, fluid-filled spaces between 3 mm and 15 mm.
- Cerebral microinfarcts are microscopic lesions (.2-3 mm) that are observed by high-resolution T1, FLAIR, and double inversion recovery MRI sequences.
- Cerebral microinfarcts should be managed similarly to lacunar strokes.
- Cerebral small vessel disease confers an increased risk of intracranial hemorrhage even without the use of antithrombotics.
- Tissue plasminogen activator should be administered to lacunar stroke patients.
- Anticoagulation including non-vitamin K antagonist oral anticoagulants should be avoided in lacunar stroke patients unless there is a separate indication for anticoagulation without any alternative.
- Left atrial appendage closure should be considered in patients with lacunar stroke and atrial fibrillation.
- Aspirin is the mainstay of therapy for lacunar stroke in both acute and chronic settings.
- Dual antiplatelet therapy as a long-term secondary prevention strategy should be avoided.
- Clopidogrel and cilostazol monotherapy are acceptable alternatives for secondary lacunar stroke prevention.
- Selective serotonin reuptake inhibitors appear to be safe in lacunar stroke, although their efficacy is unclear.
- A systolic blood pressure goal of less than 130 mm Hg is reasonable in the outpatient setting.
- Pioglitazone may be reasonable in lacunar stroke patients with insulin resistance.
- Statin therapy should be used in most cases of lacunar stroke.
- In the unique case of the "stuttering lacune," no therapy beyond antiplatelet regimens can be recommended.
- Neuroprotection and neural repair strategies are promising and may play major roles in the future of lacunar stroke therapy.

"Stuttering" Lacunes

LS are occasionally preceded by repetitive TIAs, described as "capsular warning syndrome" given the propensity for the resultant stroke to be found in the internal capsule.[249,250] This acute "stuttering lacune" is of particular interest as viable tissue at risk might be eventually lost. While the exact pathophysiology of the stuttering lacune is unclear, it may be a result of hemodynamic compromise of a small penetrating vessel.[249] Various therapies for this type of stroke have been tested, although none have proven efficacious in a large, randomized trial. In one case series of 7 patients, administration of 300 mg of clopidogrel resulted in a resolution of symptoms in 4 patients and stabilization of symptoms in the other 3.[251] Intracranial hemorrhage was not observed in this small series, although the mean age of the participants was less than 65. Others have speculated that anticoagulation may have a role for the acutely stuttering lacune, especially the non-vitamin K antagonist oral anticoagulants which appear to have an improved safety profile.[252] In one early series of 4 patients with progressive weakness, heparin did not prevent worsening of neurological symptoms.[253] Nonpharmacological strategies for the stuttering lacune have included therapeutic hypertension as well as volume expansion without any clear benefit.[173,249] Given the small nature of these studies, no clear recommendation can be given for the treatment of this unique subtype of LS. However, as with LS in general, anticoagulation should be avoided.

Conclusion

Currently, there are limited therapies available for the treatment of LS (Fig 4). In the acute setting, thrombolysis with IV tPA in LS is the standard of care and its efficacy is well supported by several trials. In the chronic setting, antiplatelet agents are the mainstay of therapy, although their effect on reducing stroke recurrence is modest. Oral anticoagulants and combination antithrombotics are not indicated for prevention of LS recurrence, and they are known to increase ICH risk in this setting. Modulating risk factors such as diabetes, hypercholesterolemia, and hypertension continue to play key roles in reducing stroke recurrence. Neuroprotection and neural repair augmentation are promising, as the development of agents that specifically promote the health of the oligovascular unit could aid in reducing stroke morbidity and mortality. Further research into these areas may allow for the generation of targeted therapeutics capable of minimizing parenchymal damage acutely, while aiding in repair thereafter.

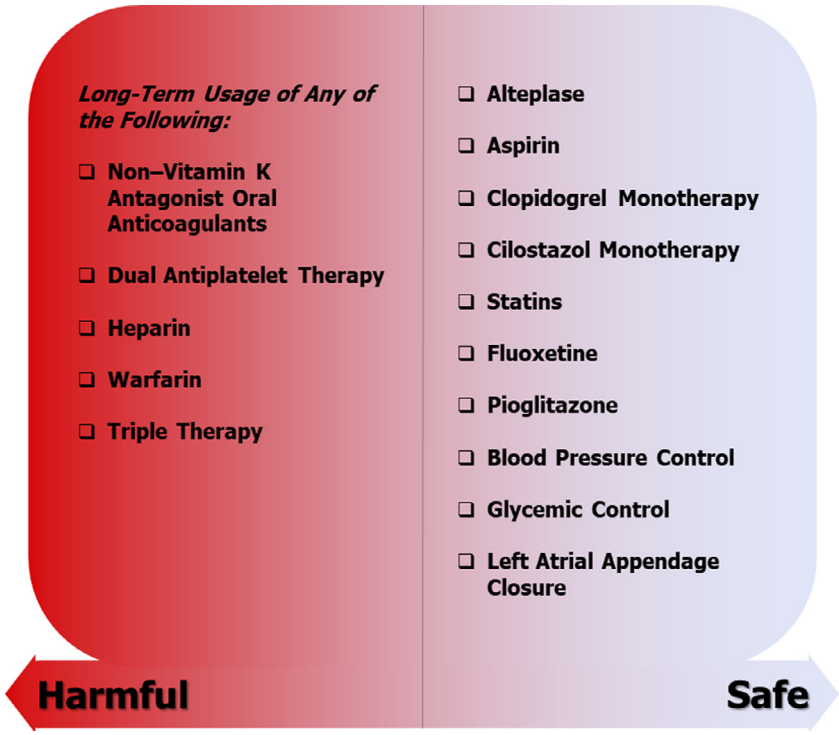

Figure 4. ***Safety of therapies for lacunar stroke.*** *This schematic highlights the major therapies that have been trialed in lacunar stroke. The harmful therapies (left side) should be avoided in most lacunar stroke patients. The safe therapies are listed on the right side.*

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Conflicts of Interest/Disclosures

The authors report no conflicts of interest or disclosures.

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