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Bath, Philip M.W. and Wardlaw, Joanna M. (2015) Pharmacological treatment and prevention of cerebral small vessel disease: a review of potential interventions. International Journal of Stroke, 10 (4). pp. 469-478. ISSN 1747-4949

Pharmacological treatment and prevention of cerebral small vessel disease: a review of potential interventions

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Small vessel disease encompasses lacunar stroke, white matter hyperintensities, lacunes and microbleeds. It causes a quarter of all ischemic strokes, is the commonest cause of vascular dementia, and the cause is incompletely understood. Vascular prophylaxis, as appropriate for large artery disease and cardioembolism, includes antithrombotics, and blood pressure and lipid lowering; however, these strategies may not be effective for small vessel disease, or are already used routinely so precluding further detailed study. Further, intensive antiplatelet therapy is known to be hazardous in small vessel disease through enhanced bleeding. Whether acetylcholinesterase inhibitors, which delay the progression of Alzheimer's dementia, are relevant in small vessel disease remains unclear. Potential prophylactic and treatment strategies might be those that target brain microvascular endothelium and the blood brain barrier, microvascular function and neuroinflammation. Potential interventions include endothelin antagonists, neurotrophins, nitric oxide donors and phosphodiesterase 5 inhibitors, peroxisome proliferator-activated receptor-gamma agonists, and prostacyclin mimics and phosphodiesterase 3 inhibitors. Several drugs that have relevant properties are licensed for other disorders, offering the possibility of drug repurposing. Others are in development. Since influencing multiple targets may be most effective, using multiple agents and/or those that have multiple effects may be preferable. We focus on potential small vessel disease mechanistic targets, summarize drugs that have relevant actions, and review data available from randomized trials on their actions and on the available evidence for their use in lacunar stroke.

Key words: antithrombotics, blood brain barrier, blood pressure lowering, cyclic nucleotide inhibitors, nitric oxide, prostacyclin

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Introduction

Small vessel disease (SVD) causes a quarter of all ischemic strokes (lacunar stroke) (1) and is the commonest cause of vascular dementia. The cause of SVD, which also includes white matter hyperintensities (WMH), lacunes and microbleeds (2,3), is, as yet, incompletely understood. Although conventional vascular prophylaxis, such as intensive antiplatelet therapy, may not be effective for small vessel disease, there are many other therapeutic targets (4), and drugs to test in clinical trials. Here we review all available drugs with actions that are relevant to suspected mechanisms of intrinsic SVD and all available evidence on use of any of these drugs to prevent lacunar stroke and SVD.

Background

A quarter of ischemic strokes (≈30 000 per year in the UK) are lacunar or small subcortical in type (Fig. 1) (1). These usually cause mild to moderate neurological deficit with low early mortality, but can be physically disabling and have a high long-term risk of recurrence and cognitive impairment (5,6). Lacunar stroke is associated with subclinical abnormalities that contribute to the burden of brain damage causing insidious physical and cognitive deficits and vascular dementia (7), and increasing the societal impact beyond that expected from the small size of the infarct alone (3). These abnormalities are easily detected on magnetic resonance imaging (MRI) brain imaging, and include lacunar or small subcortical infarction, lacunes, white matter hyperintensities (WMH) (8) and microbleeds (9). Although they may present after a clinically-overt event, most lacunes (10), subcortical grey or white matter hyperintensities and microbleeds develop 'silently'. When numerous, all three are associated with cognitive impairment, doubling the risk of dementia and trebling the risk of stroke (11,12). Together with lacunar stroke, these features are collectively known as *cerebral small vessel disease* (SVD; Fig. 1) (2). Small haemorrhages can also present with lacunar stroke (13); and an as yet unknown proportion of large haemorrhages are also now recognized to have SVD as the major underlying pathology (Fig. 1).

Properties of pharmacological agents needed for SVD

The slow development of SVD and its chronic nature suggest that any intervention for its prevention or treatment will need to be given long-term. The high prevalence of SVD (e.g. a quarter of all
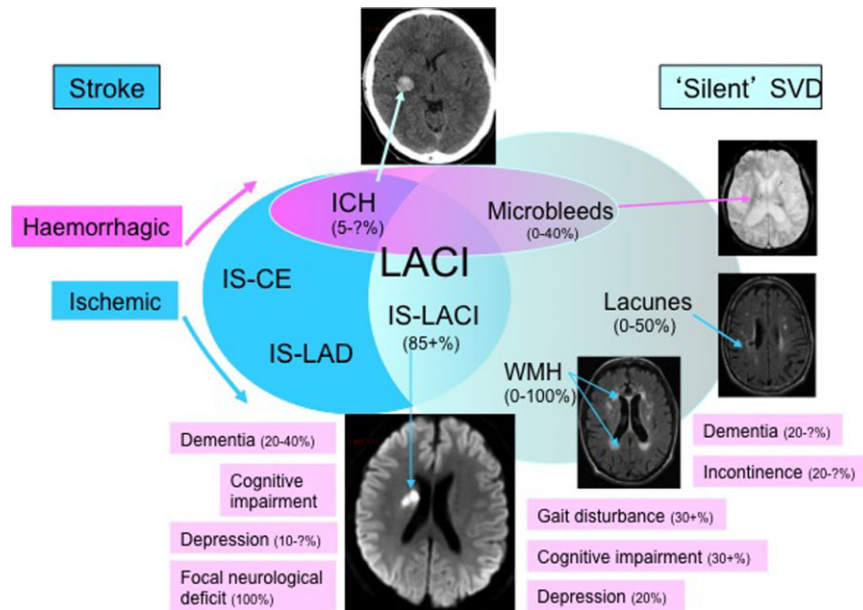
Fig. 1 Venn diagram showing relationship between small vessel disease and other forms of stroke. The embedded neuroimages show, clockwise from the top: intracerebral haemorrhage (ICH), microbleeds, lacunes ('lakes' of cerebrospinal fluid), white matter hyperintensities (WMH), and an acute lacunar infarct (LACI). Percentages relate to SVD etiologies and complications and are approximate: '?' indicates a lack of data.

ischemic strokes; 45% of all age-related dementias; WMH present in 17+% at age 70 + (11,14)) suggests that any long-term intervention will need to come at modest financial cost to both individuals and society. Extrapolating from these two observations, any effective intervention will have to be administered as an oral, transdermal or nasal preparation, or possibly via a long-acting injectable. Since the target population will include many older people who may be on multiple drugs for other indications (e.g. vascular prophylaxis, arthritis, gastro-oesophageal reflux, laxatives), an intervention with limited drug interactions and once (or twice) daily administration will be preferable. The growing number of very elderly people makes it imperative that patients aged over 85 are included in future trials – few have been included in stroke prevention trials to date.

Clinical targets include reducing first or recurrent stroke, and preventing cognitive decline and physical disabilities such as impaired balance or gait, or neuropsychological symptoms (15). Imaging targets include preventing the development of new lacunes, microbleeds and brain atrophy, and delaying the worsening of WMH. It is important to use accurate lesion quantification methods and in particular to avoid confounding of imaging measurements by, for example, including a recurrent cortical or large subcortical infarct in WMH volume which would artificially inflate the apparent WMH burden. Additional targets for detecting reduced brain damage include checking if treatments reduce global brain (16) or focal regional cortical or brainstem atrophy (17,18) that occur secondary to WMH and incident lacunar ischemic strokes respectively. Importantly, the effectiveness of an agent in the acute situation does not mean that it will be effective in long-term prevention; adaptation may be a problem with some agents when given long term or expose the patient to increased risk.

Potential pharmacological interventions for preventing or treating SVD

Supplement Table S1 highlights the potential mechanisms by which multimodal drugs might work in patients with SVD, including details of potential mechanisms for which there is current evidence and relevant references. Note that many drugs have little lacunar-specific data but where available this is highlighted. A list of relevant completed trials where either patients with SVD were included, or where SVD was an outcome, is given in Supplement Table S2. Relevant systematic reviews of drugs that may be of value in SVD are listed in Supplement Table S3. Supplement Table S4 lists ongoing trials.

Acetylcholinesterase inhibitors and other anti-dementia drugs

Anti-cholinesterase inhibitors (AChEI) prevent the breakdown of acetylcholine, a neurotransmitter, by acetylcholinesterase. Four drugs are licensed for treating mild-to-moderate Alzheimer's Disease: tacrine, rivastigmine, galantamine and donepezil; a fifth licensed drug, memantine, is a non-competitive NMDA receptor antagonist. Short-term trials of these drugs in vascular cognitive impairment and vascular dementia have given mixed results but small effects have been reported for donepezil, memantine and galantamine (Supplement Table S3). Although some patients with SVD will, inevitably, have been included in these trials, the proportion is unclear. No relevant data were found for rivastigmine (Supplement Table S3).

The relevance of AChEI to the prevention or treatment of SVD is probably limited (see mechanisms listed in Supplemental Table S1): existing trials were short-term (6 months) treatment

rather than prevention studies, the observed effect on cognition assessed using the Alzheimer's Disease Assessment Scale (ADAS-Cog) was small (Supplement Table S2) and of questionable clinical relevance (ADAS-Cog ≥ 4 is considered worthwhile (19)), benefit on the ADAS-Cog is of limited relevance to VaD since it does not adequately measure executive function (the Vascular Dementia Assessment Scale, VaDAS, addresses this deficiency but relevant data for AChEI are not available), and the drugs are not disease-modifying for Alzheimer's Disease (and similarly are unlikely to be post-lacunar stroke).

Anticoagulation

Atrial fibrillation (AF) is a major risk factor for both stroke, and for cognitive decline and dementia. Although antiplatelets are ineffective for preventing stroke in patients with AF, warfarin (an antagonist of vitamin K1 recycling) reduced recurrence by two-thirds in the 'European Atrial Fibrillation Trial' (Supplement Table S2). In view of the need for regular monitoring and numerous drug and food interactions, novel fixed dose anticoagulants have been developed (apixaban, dabigatran, rivaroxaban) and these are as effective (and potentially more effective) than warfarin at preventing stroke, and recurrent stroke (subtype unspecified), in patients with AF (Supplement Table S2). Although cardioembolism is an infrequent cause of lacunar ischemic stroke (20), patients with cardioembolic sources who present with lacunar ischemic stroke should have secondary prevention treatment as any other cardioembolic stroke. Apixaban is also more effective than aspirin in AF. Unfortunately, none of these modern trials reported results for outcomes in the subgroup of patients with SVD, or on the effect of treatment on cognition or SVD as an outcome.

In view of the beneficial effect of oral anticoagulation in AF, warfarin has also been tested in patients with prior stroke (including some with a small subcortical infarct) who are in sinus rhythm. With conventional anticoagulation (INR 2–3), warfarin was not superior to aspirin (Supplement Table S2). In the SPIRIT trial, high dose warfarin (INR 3.0–4.5) was associated, as compared with aspirin, with increased intracerebral haemorrhage, particularly in patients with many WMH (Supplement Table S2).

Anti-inflammatory agents

Steroids and non-steroidal anti-inflammatory drugs (NSAIDs) are the two archetypal classes of anti-inflammatory agents; steroids are not further discussed here since long-term use would probably cause more problems (e.g. hypertension, hyperglycemia, osteoporosis) than they might solve by attenuating SVD. NSAIDs such as aspirin, ibuprofen and naproxen inhibit the formation of inflammatory-causing prostaglandins through inhibiting the activity of cyclooxygenase-2 (COX2, Supplement Table S1), as well as inhibiting COX1 which leads to gastrointestinal bleeding. Selective COX2-inhibitors (coxibs) are not relevant here since they increase vascular events in at-risk individuals.

Many other drugs classes have anti-inflammatory effects manifest as reductions in the activity of the cellular components of inflammation (white cell activation, typically neutrophils and monocytes, and white cell-platelet conjugates), and/or soluble biomarkers (such as CRP, cytokines and interleukins). Example agents include nitric oxide (NO) donors, prostacyclin (PGI$_2$), phosphodiesterase (PDE)-inhibitors, and statins (as discussed below and in Supplement Table S1).

Antiplatelet agents

Commonly used oral antiplatelet agents after stroke include aspirin (typically 50 mg to 81 mg daily), cilostazol, clopidogrel, dipyridamole, and triflusal. Practically, aspirin and clopidogrel can be considered to have moderately potent antiplatelet effects, and cilostazol, dipyridamole and triflusal to have mild antiplatelet activity; very potent oral antiplatelet agents such as lotrafiban, a glycoprotein IIb/IIIa antagonist, are not used because of an increased risk of death and bleeding (21). Although clopidogrel is selective as an antiplatelet agent, the other drugs have extra-platelet effects, including reducing endothelial cell dysfunction, and white cell and smooth muscle cell activity (Supplement Table S1, Fig. S2). All RCT data to support their efficacy in preventing recurrence after any ischemic stroke (and TIA, for some) (Supplement Table S3). In most of the above trials, differentiation of patients with lacunar stroke from other subtypes was not done, or the results were not reported separately.

The combination of two antiplatelet drugs vs. mono antiplatelet therapy has also been studied although the data vary between acute and chronic administration after stroke. In acute stroke, short-term dual therapy is superior to mono therapy such that the reduction in early stroke recurrence exceeds any increase in major bleeding, as seen in both a meta-analysis and subsequent individual trial (Supplement Tables S2 and 3). However, the picture is mixed for chronic administration after stroke; whilst the combination of aspirin and dipyridamole is superior to either agent alone (Supplement Table S3), combined aspirin and clopidogrel are not superior to monotherapy since excess bleeding risk matches or outweighs any reduction in recurrence (Supplement Table S2) (22), particularly in patients with lacunar stroke (Bath P, European Stroke Conference, May 2012).

Across a wider and mixed group of 90 934 patients with ischemic heart disease or stroke (either receiving short- or long-term treatment), the adverse risk-benefit ratio of combined aspirin and clopidogrel vs. aspirin was confirmed in a meta-analysis of RCTs except in lacunar stroke where any reduction in MI with dual antiplatelet therapy was offset by an increase in haemorrhage and death (23). Only one completed trial has tested chronic triple antiplatelet therapy (aspirin, clopidogrel and dipyridamole) and this was stopped early because the comparator, aspirin alone, was considered unethical to give beyond 2006 (Supplement Table S2); nevertheless, in this small population of patients, mostly with lacunar stroke (71%), chronic triple antiplatelet therapy was associated with increased bleeding.

Importantly, all the above trials recruited a mixed group of patients including both lacunar and non-lacunar stroke and most did not characterize patients at baseline as one or the other. Only one RCT, the 'Secondary Prevention of Small Subcortical Stroke'

(SPS3) study (Supplement Table S2), has tested antiplatelet drugs specifically in patients with lacunar stroke. (SPS also assessed intensity of blood pressure lowering in a factorial design [Supplement Table S2].) SPS3 compared long-term therapy with combined aspirin and clopidogrel vs. aspirin alone in 3020 patients with MRI DWI-proven lacunar stroke; dual therapy caused excess haemorrhage and death and the trial was stopped prematurely. Since patients with lacunar stroke would be expected to have less atheroma (5) it is perhaps unsurprising, in retrospect, that ischemic vascular events were unchanged in the face of an increase in bleeding. A similar increase in haemorrhage was also seen in the subgroup of patients with prior stroke (47% with SVD) randomized to vorapaxar vs. placebo in the TRA-2P trial, where vorapaxar was given on top of existing antiplatelet therapy, i.e. amounting to dual therapy (24). The small subgroup in whom lacunar ischemic stroke occurs above a carotid atheromatous stenosis (20), or who have intracranial large artery or branch artery atheroma might be expected to benefit from antiplatelet drugs although such patients must have been included in SPS3 (which did not show benefit) and it is difficult to distinguish atheromatous from intrinsic small vessel lacunar ischemic stroke at present. The lack of benefit of antiplatelet agents in lacunar stroke in trials is supported by laboratory studies where particulate hemostasis, i. e. that based on platelets, is not abnormal in SVD (25,26). The effects of antiplatelets on the other types of SVD – WMH, lacunes, micro-bleeds – have not been studied in detail.

Blood brain barrier (BBB) modulation

BBB function is damaged by metabolic derangement such as hyperglycemia and hypoxia, as seen experimentally in culture systems (27–29). Increased BBB permeability occurs with normal ageing (30) and is accelerated in WMH and lacunar stroke (3). However, there is little evidence on interventions that might tighten the BBB thereby reducing the transit of potentially toxic factors through the vessel wall and into parenchymal tissue. Antioxidants and VEGF antibodies strengthen the BBB in experimental studies (Supplement Table S1). Of more practical use is the observation that both cGMP (dipyridamole) and cAMP (cilostazol, pentoxifylline) modulators can improve BBB integrity, at least in experimental studies (Supplement Table S1). Other compounds of potential interest include fasudil and topiramate (Supplement Table S1).

Blood pressure (BP) lowering

Hypertension is the most important modifiable risk factor for stroke and is also the strongest known vascular risk factor for SVD. Multiple trials have shown that treating high BP reduces first stroke. Only one trial assessed the effect of BP lowering on the type of any resulting stroke; in SHEP, antihypertensive therapy (chlorthalidone, with or without atenolol or reserpine) reduced the incidence of ischemic stroke, including lacunar subtype (Supplement Table S2).

A few trials have investigated secondary prevention after stroke either testing the treatment of hypertension, or of lowering BP irrespective of starting level; these found that antihypertensive drugs reduce second stroke (Supplement Table S3). With one exception, the studies either did not phenotype the type of index stroke, or did not report these results in stroke subtypes.

The SPS3 trial compared intensive vs. guideline BP lowering and found no significant reduction in recurrent stroke (Supplement Table S2); however, there was a strong trend to reduced recurrence and meta-analysis of this and other data in SVD might well show a significant effect. In the absence of other data on lacunar stroke, data on other SVD features are relevant. Although antihypertensive therapy may be associated with less WMH progression in observational studies, little (PROGRESS, $n = 192$) or no (PRoFESS, $n = 771$) effect on WMH progression was seen in substudies of RCTs (Supplement Table S2). SPS3 found no benefit for intensive versus guideline BP lowering on long-term cognition after lacunar stroke (31).

Unlike antiplatelet therapy, where just two years of therapy can be enough to demonstrate a therapeutic effect on outcome, antihypertensive agent trials may need longer treatment and follow-up periods to detect reductions in stroke or SVD. In general, post-stroke BP trials can be criticized for starting treatment too late after ictus, not continuing treatment for long enough, and not obtaining a large enough separation in BP between treatment and control groups. Nevertheless, lowering BP too much might also be hazardous, the so-called 'J-shaped' curve, especially in older patients or in those with a prior stroke (32,33).

Blood pressure is but one hemodynamic measure altered by antihypertensive drugs and other parameters are also related to stroke, cognition and disability; these include heart rate (34), peak BP and variability (35), and rate-pressure product. Furthermore, different antihypertensive drug classes are thought to have differential effects on stroke and cardiovascular disease prevention (Supplement Table S3), but there is no information on differential effects of classes in different stroke subtypes.

Endothelin

Endothelin-1 is a potent peptide vasoconstrictor released by endothelial cells that acts as the physiological antagonist of NO (and PGI$_2$). Most research has focused on the potential treatment of systemic and pulmonary hypertension with endothelin receptor antagonists. But endothelin may contribute to vasospasm associated with subarachnoid haemorrhage (SAH), and has been used to induce experimental ischemic stroke (36,37). Although endothelin receptor antagonists (such as clazosentan and TAK-044) have been used for the treatment of SAH, their use in SVD has not been reported.

Immunosuppressive agents

The inflammatory nature of SVD suggests that immunomodulatory agents might also have a role in preventing or delaying the progression of SVD. Potent small molecules (e.g. methotrexate) and monoclonal antibodies (e.g. anti TNF-alpha) probably have no role in view of their known toxicity and carcinogenic profile, although at least one trial is soon to start testing methotrexate in

acute myocardial infarction (http://clinicaltrials.gov/show/NCT01741558); additionally, monoclonal antibodies are very expensive and usually have poor brain penetration when given systemically. But less toxic and expensive agents might be relevant such as thalidomide, a teratogen, currently used in older people in the management of myeloma. Although its mechanisms of action are incompletely elucidated, thalidomide inhibits TNF-α and is antiangiogenic. Changes in the immune response with advancing age would be a consideration if such agents were to be used in SVD.

Lipid lowering

The main therapeutic and licensed role for statins (HMG-CoA reductase inhibitors) is to lower LDL-cholesterol in patients with a high risk of developing large artery atheromatous disease (MI or stroke), or who already have it. In addition to lipid lowering, statins exhibit multiple other effects (pleiotropism) including antiplatelet, anti-inflammatory and pro-endothelial activity (Supplement Table S1). These effects are mediated, in part, by increased vascular NO production through activation of nitric oxide synthase-3 (NOS, endothelial NOS, eNOS). Statins may be categorized by:

Production method – fermentation-derived (pravastatin, simvastatin) or synthetic (atorvastatin, fluvastatin, rosuvastatin).

Potency in LDL-lowering at maximum dose – rosuvastatin > atorvastatin > simvastatin > pravastatin > fluvastatin.

Solubility – hydrophilic: fluvastatin, pravastatin, rosuvastatin; lipophilic: atorvastatin, simvastatin.

Such pharmacological differences and pleiotropic behaviour may impact on their ability to modulate the development or extension of SVD.

Statins reduce both first and recurrent stroke (Supplement Table S3). Although there are no large trials specifically after lacunar stroke, atorvastatin reduced recurrent stroke by similar amounts in small vessel ($n = 1409$) and large artery stroke (hazard ratio 0.85, 0.70 respectively) in the SPARCL trial (Supplement Table S2). In contrast, neutral effects were seen for simvastatin on amelioration of cognitive decline in the HPS mega-trial, for pravastatin on WMH progression in 535 patients in PROSPER, for simvastatin (20 mg daily for 24 months) on WMH progression in 208 patients in ROCAS; and atorvastatin (80 mg daily for 3 months) on cerebral vasoreactivity and endothelial function in 94 patients with recent lacunar stroke (Supplement Table S2).

Neurotrophins

Cerebrolysin is a peptide product derived from pig brain with potential neurotrophic (including nerve growth factor activity) and neuroprotective activity. The drug is administered as an intravenous preparation given daily for days or weeks. Small studies have suggested that cerebrolysin might be effective in VaD (Supplement Table S3) but further trials are needed and specific effects in SVD have not been published. The relevance of cere-

brolysin to SVD prevention or treatment is unclear in view of the need for intravenous administration (although a nasal preparation is in development).

Nitric oxide/cyclic GMP system

Nitric oxide is a key autocrine and paracrine mediator in numerous physiological and pathophysiological processes. NO is synthesized from the amino acid, L-arginine, by NO synthase (including NOS-3/eNOS), and from nitrate then nitrite through reduction. It stimulates down-stream processes through the second messenger cyclic guanylate monophosphate (cGMP, Supplement Table S1, Fig. S2). cGMP is broken down by phosphodiesterase, predominantly type 5. So, the vascular L-arginine/NO/cGMP/PDE system may be up-regulated through enhancing L-arginine or nitrate levels, increasing NO synthase activity, administering NO donors, and blocking PDE activity. In respect of actions that might be relevant to the development of SVD, NO has antiplatelet, anti-leucocyte, anti-smooth muscle cell, and other anti-inflammatory activity, as well as pro-endothelial and blood-brain barrier actions (Supplement Table S1).

Increasing endogenous NO synthesis
Endogenous vascular NO synthesis may be augmented through increasing blood substrate levels of L-arginine or nitrate, e.g. through diet, detected as changes in systemic and cerebral hemodynamics in some (38–40) but not all studies (41). The activity of NOS-3 is up-regulated by statins (Supplement Table S1).

NO donors
In experimental studies, NO donors are neuroprotective (Supplement Table S3) and anti-inflammatory, e.g. through inhibiting white cell function (such as chemotaxis and adhesion, Supplement Table S1). In stroke, NO donors lower blood pressure and vasodilate cerebral vasculature (Supplement Table S2). It is important to note that NO donors vary in their antiplatelet activity – those that inhibit platelets (NO itself, and donors that spontaneously release NO such as sodium nitroprusside) and those that do not (organic nitrates such as isosorbide mononitrate and glyceryl trinitrate). The absence in platelets of the metabolic apparatus to release NO from organic nitrates explains this difference. Whether this explanation would be relevant in SVD-prevention is not clear. Circulating NO levels are low in acute, and probably chronic, stroke (42,43) although levels in lacunar stroke have not been individually reported; hence, one action of NO donors is to augment endogenous vascular NO levels.

cGMP augmentation/PDE5 inhibition
Phosphodiesterases (PDE) catalyze the hydrolysis of cyclic nucleotides (cAMP, cGMP) to inactive 5'-cyclic nucleotides (44). 11 classes of PDEs (comprising more than 60 different isoforms) exist with differential effects on cAMP and cGMP. PDE types 3 (PDE3, primarily of relevance to cAMP metabolism) and 5 (PDE5, cGMP), and their inhibitors, are of most relevance to the vasculature and management post-stroke. Relevant PDE-inhibitors are either non-selective (e.g. methylxanthines such as caffeine, pentoxifylline and theophylline) or selective, e.g.

cilostazol inhibits PDE3, dipyridamole inhibits PDE5 (Supplement Table S1). Several PDE-inhibitors also exhibit adenosine modulating effects acting either as adenosine re-uptake inhibitors (cilostazol, dipyridamole, pentoxifylline) or as adenosine receptor antagonists.

PDE5 inhibitors mimic many of the features of NO, including exhibiting mild antiplatelet activity, and endothelial protection (manifest as a reduction in von Willebrand factor) (Supplement Table S1). The main PDE5-inhibitor of clinical relevance to stroke is dipyridamole.

Dipyridamole is licensed for the secondary prevention of stroke based on trials involving monotherapy or when given with aspirin (Supplement Table S3). Although dipyridamole can cause a NO-like headache, the presence of headache (indicating the presence of cerebrovascular reactivity) is associated with a reduced rate of stroke recurrence (45).

Peroxisome proliferator-activated receptor (PPAR)-gamma agonists

Pioglitazone, a PPAR-gamma inhibitor that is licensed for diabetes management, has multiple properties that might attenuate SVD, including BP modulation, pro-endothelial activity, anti-vascular inflammation, lipid modulation, anti-smooth muscle cell proliferation, and anti- fibrinolysis (Supplement Table S1). However, treatment with pioglitazone is associated with a number of adverse events such as weight gain, heart failure, and possibly bladder cancer.

In a post hoc analysis, pioglitazone was observed to reduce recurrence and major adverse cardiovascular events (MACE) in 984 patients with type II diabetes and previous stroke in the PROactive trial; however the proportion of patients with SVD was not recorded at baseline (Supplement Table S2). Further, pioglitazone did not prevent first stroke.

Prostacyclin/cyclic AMP system

Prostacyclin I_2 (PGI$_2$), related prostaglandins (e.g. PGE$_2$), and their mimics, exert many of the effects seen with NO and cGMP modifying agents (Supplement Table S1). This includes antiplatelet, anti-smooth muscle and anti-inflammatory activity, and pro-endothelial effects. PGI$_2$ is synthesized from prostaglandin H$_2$ by prostacyclin synthase. Since PGH$_2$ is synthesized by COX1/2 (PGH$_2$ synthase), PGI$_2$ production is attenuated by aspirin. Many of the effects of PGI$_2$ are mediated by the second messenger, cyclic adenosine monophosphate (cAMP, Fig. 2), which is broken down by PDE3 (among other PDEs).

Prostacyclin and mimetics

Intravenous PGI$_2$ has been assessed in several small trials in acute stroke (Supplement Table S3). In the context of SVD prevention/treatment, PGI$_2$ and its prostaglandin derivatives and mimetics (e.g. beraprost, treprostinil), are probably not suitable agents since they have to be given intravenously or very frequently by inhalation, and no suitable oral preparations are available.
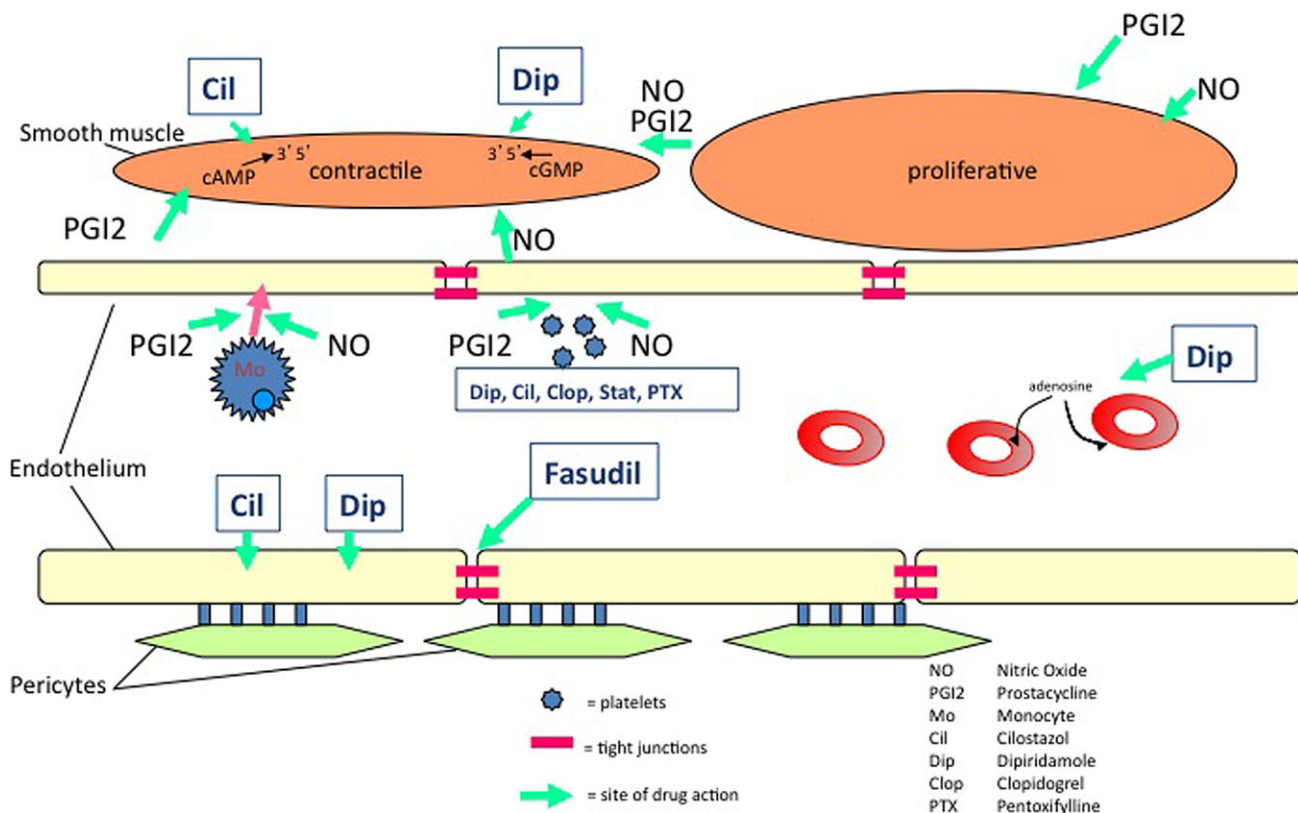

Fig. 2 Targets and potential pharmacological interventions for preventing and/or treating small vessel disease. The green arrows indicate the site of some actions of a drug. The diagram indicates drugs acting on red blood cells, platelets, endothelial cells, smooth muscle cells (and potentially on pericytes).

cAMP augmentation/PDE3 inhibition

The PGI$_2$/cAMP system may best be stimulated chronically by reducing the metabolism of cAMP with an oral PDE3 inhibitor such as cilostazol, pentoxifylline or triflusal. PDE-inhibitors have the added advantage that they may increase NO production by modulating dimethylarginine dimethylaminohydrolases (Supplement Table S1).

Cilostazol: Cilostazol is licensed for peripheral vascular disease (PVD) (46) but has also been shown to reduce recurrent ischemic stroke, with fewer haemorrhagic complications than aspirin (Supplement Tables S2–S4). Cilostazol was also assessed in chronic lacunar stroke for effects on forearm vascular reactivity (47), and acute lenticulostriate stroke for neurological deterioration (48). Experimentally, cilostazol may enhance white matter regeneration after ischemia (Supplement Table S2) (49); in SHRSP, it both improved motor and cognitive function and reduced infarct size as compared with aspirin (50). Further trials of cilostazol beyond those listed in Supplementary Table S4 are thought to be ongoing.

Pentoxifylline: Pentoxifylline, propentofylline and pentifyline are related methylxanthines that have been studied in several trials in acute ischemic stroke and dementia prevention (Supplement Table S3); although some results were promising, the RCTs were small and of suboptimal design. Pentoxifylline is licensed for the treatment of PVD and improves the healing of venous leg ulcers. Theophylline, another methylxanthine (and commonly found in tea), has similar effects.

Triflusal has multiple modes of action including acting as an inhibitor of COX1 (in platelets but not endothelium) and PDE3, protecting PGI$_2$ from metabolism, and promoting the release of NO (through stimulating NOS-3) from white cells. Triflusal is licensed for the prevention of recurrent vascular events in high-risk individuals.

None of the larger stroke trials of PDE-inhibitors have focused on patients with SVD; indeed stroke subtype was usually not phenotyped so the beneficial results might be more or less relevant for patients with SVD as compared with other types of stroke.

Rho-kinase (ROCK)-antagonists

Fasudil, a selective rho-kinase inhibitor, increases the integrity of the blood brain barrier and reduces small muscle cell proliferation (Supplement Table S1) in acute experimental models of stroke. It improved early neurological deficit vs. placebo in 160 patients with acute ischemic stroke; the subtype of stroke was not specified in this study (51) and there are no specific data for SVD. The effects on chronic BBB dysfunction, which might have a different mechanism to that seen after acute ischemic stroke, are not known.

Stimulants

Stimulant agents include sympathomimetics (e.g. amphetamine) and eugeroics (which increase catecholaminergic and histaminergic activity in the brain). Modafinil, an eugeroic that inhibits dopamine transport, is licensed for the treatment of narcolepsy, and potentially enhances cognition and reduces fatigue. However, its role in stroke and SVD remains untested. Although amphetamine has been assessed for promoting recovery after stroke, it increased BP and was associated with increased deaths (Supplement Table S3).

Vitamins

Amongst multiple classes of vitamins, the ones potentially of most interest to stroke are those that modulate homocysteine metabolism, namely B6, B12 and folate. Although trials of these failed to prevent stroke recurrence (Supplement Table S3), a small neuroimaging substudy (using MRI) from the large VITATOPS trial suggested that B vitamins might be associated with less WMH change in patients with severe WMH at baseline (Supplement Table S2).

Xanthine oxidase inhibitors

Allopurinol and febuxostat, xanthine oxidase inhibitors, lower plasma uric acid levels and are licensed for the prevention of gout (Supplement Table S3). Allopurinol also increases NO availability, has anti-inflammatory effects, reduces augmentation index (reducing stiffness in large compliance arteries), reduces left ventricular hypertrophy, and modulates BP. However, the type, magnitude and direction of the relationship between urate and vascular disease is unclear, and might be explained by co-association with body mass index (52). The effects of allopurinol in clinical trials are mixed, and allopurinol is associated with adverse events at high dose. In a small study in 50 patients with subcortical stroke, allopurinol did not alter cerebral vasoreactivity, augmentation index or soluble markers of inflammation (Supplement Table S2).

Other potential therapeutic strategies

Multiple other interventions may have properties that are relevant to SVD-prevention:

Information from experimental stroke models: Several other interventions have been proposed as treatment or prevention strategies for SVD, including nicotiflorin (a flavonoid), minocycline and relaxin (Supplement Table S3). However many of the experimental models were not relevant to human intrinsic SVD and the evidence for any of these drugs is limited by small numbers and suboptimal methods.

Lifestyle modifications (53): These include smoking cessation, salt reduction, increased dietary nitrates, dietary flavonones (54), a healthy diet (55), and exercise (56). However, whether any of these have differential effects on lacunar stroke/SVD or are simply good for general health is unclear. Clearly smoking cessation is a major public health target worldwide and should be encouraged. Decreasing salt intake reduces blood pressure, platelet adhesion and oxidative stress and improves vascular function in salt-replete and sensitive individuals (57,58) so probably benefits both large artery disease and SVD. Short-term dietary nitrates increase frontal white matter perfusion (40) and increase cerebrovascular

reactivity in young people (59). L-arginine supplements (e.g. in the form of 'Heart bars') reduce eclampsia (60). Some trials are testing multiple risk factor interventions, i.e. two or more of the above (61). A recent systematic review identified 25 non-pharmacological and eight multiple risk factor intervention trials; of these, 16 were published and 17 ongoing (Supplement Tables S3 and S4); these trials are not discussed further here. It is worth noting that lifestyle modifications can be difficult to implement, and are very difficult to sustain chronically in a trial environment.

Cognitive interventions: Several ongoing trials are assessing a variety of cognitive interventions, including coaching, strategy training, and reading skills. Such trials are not discussed further here.

Preventing and treating SVD

Existing data

Ultimately, new large scale RCTs will be needed to assess whether specific interventions can prevent the development of SVD and/or treat its progression. But information is required now on whether current guideline-based treatments (e.g. antihypertensives, antiplatelets and statins) have any benefit for preventing first or recurrent lacunar stroke; much might be learnt from existing trials of these interventions, especially where patients with identified SVD were randomized (e.g. with lacunar stroke as in SPS3 (22,62)), or where SVD outcomes were recorded (such as WMH, as assessed in a PRoFESS substudy, Supplement Table S2).

To this end, the authors are coordinating a data-pooling project with the aim of collecting individual patient data on clinical and neuroimaging measures from appropriate RCTs. The aim is to assess whether existing pharmacological interventions already have evidence for preventing SVD development and progression. Nevertheless, this approach will be limited since most trials did not accurately-phenotype the diagnosis or outcome of SVD; further, even where subtyping was attempted, the imperfect distinction of lacunar from non-lacunar stroke based on clinical syndrome plus CT scanning (as used in most previous trials) will have misclassified about 20% of lacunar as non-lacunar strokes and *vice versa* (63), thus adding 'noise' to any retrospective analysis.

Ongoing and planned RCTs

A number of ongoing trials are assessing patients with SVD, as described in Supplement Table S4. These may be categorized according to their design:

Aim: Prevention of new events, or treatment of existing disease.

Patients: SVD absent or present, pre- or post-stroke, cognition normal or impaired.

Intervention: Drug, device, or management strategy (intensity of treatment).

Comparator: Placebo, or open-label.

Outcome: Prevention of SVD or stroke, functional outcome, cognition or neuroimaging measure.

Design: Double-blind placebo-controlled, single-blind blinded-outcome, or open-label blinded-outcome.

Which interventions should be tested for SVD?

This review has highlighted potential mechanisms that might modulate SVD and several drugs with one or more of these relevant mechanisms of action. However, as yet none of these interventions have been shown definitely to prevent or treat SVD. Nevertheless, some provisional conclusions can be drawn:

1. Both BP and lipid lowering are standard secondary prevention interventions after an ischemic stroke or TIA. Similarly, both have biologically plausible mechanisms by which they might prevent SVD. But their routine use means that further testing would necessitate a comparison either of intensive vs. standard (guideline) lowering, or a comparison of drug classes (as discussed above).

2. Potent antiplatelet agents (aspirin, clopidogrel) do not appear to have a role since they are already used routinely, either individually or together, after ischemic stroke whilst long-term intensive treatment based on their combination is associated with increased major intra- and extra-cranial bleeding (Supplement Tables S2 and 3).

3. Agents that increase cAMP or cGMP appear promising with theoretical protective effects on endothelium and the blood-brain barrier, and attenuating effects on inflammation, platelets, smooth muscle cell and white cells. Hence drugs that induce cAMP or reduce its degradation (PDE3 inhibitors such as aminophylline, cilostazol, pentoxifylline or triflusal), or induce cGMP (NO donors) or reduce its degradation (PDE5 inhibitors such as dipyridamole) are candidates for testing, especially since all are already licensed for clinical use. One concern is that the mild anti-platelet effects of PDE inhibitors (e.g. cilostazol, dipyridamole) and their chronic co-administration with a potent antiplatelet agent (such as clopidogrel) might increase bleeding, although this was not seen when aspirin and dipyridamole were used together in ESPS-2 and ESPRIT (Supplement Table S2).

4. To maximize modulation of the multiple systems that contribute to the development and extension of SVD, it may be necessary to use either drugs that have multiple mechanisms of action (such as NO donors, PDE-inhibitors and statins, Supplement Table S1), or combinations of drugs, or a mix of both.

5. Potential combinations of drugs are either:
   a. Those that have unrelated but potentially synergistic effects. Useful combinations might include assessing two or more of the various types of interventions described above, e.g. intensive BP lowering and statins, PPAR-gamma antagonist and xanthine oxidase inhibitor, or intensive BP lowering and raising NO.
   b. Combining agents that have related effects, e.g. by raising cAMP and cGMP. Potential combinations include dipyridamole and pentoxifylline (64), dipyridamole and cilostazol (65), and isosorbide mononitrate and cilostazol. Alternatively, hybrid drugs that comprise a NO donor and cAMP modulator might be relevant, e.g. cilostazol dinitrate (66).

6. It is conceivable that some treatment strategies might have differential effects on the various types of SVD; whilst BP lowering might be beneficial on all, statins and antiplatelets might be beneficial in reducing lacunar stroke but increase symptomatic bleed-

ing from micro-bleeds due to their antithrombotic activity. This emphasizes the need to monitor all features of SVD in future trials.

Conclusions

There are no established therapeutic strategies for either preventing or treating SVD although more information about *strategies to avoid* and that *show promise* are emerging (4). A number of routine vascular prophylaxis strategies, especially lowering BP, might reduce SVD but their current guideline use means any future trials would have to test intensity of treatment. Other potential interventions are not in routine use post stroke and have multiple activities with the potential for targeting mechanisms of SVD formation. It is clear that further trials dedicated to preventing the development or worsening of SVD are now required.

Acknowledgements

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Effects of drug classes and individual drugs on general categories of mechanisms that might be relevant for preventing or treating small vessel disease.

Table S2. Completed randomized controlled trials that either included patients with small vessel disease (SVD), or where SVD was an outcome.

Table S3. Published systematic reviews of drugs and drug classes in stroke that may be worth testing for the prevention or treatment of small vessel disease.

Table S4. Ongoing randomized clinical trials where either (i) patients with small vessel disease (SVD) are included, or (ii) SVD is an outcome.