BRAIN. Broad Research in Artificial Intelligence and Neuroscience
e-ISSN: 2067-3957 | p-ISSN: 2068-0473
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2026, Volume 17, Issue 2, pages: 363-387
Submitted: February 19th, 2026 | *Accepted for publication:* April 21st, 2026

Microvascular Brain Pathology: Correlations Between Diabetes and Lacunar Strokes

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Abstract: *The relationship between diabetes mellitus (DM) and microvascular brain pathology is complex and not very well debated, especially when referred to lacunar strokes, a major subset of cerebral small vessel disease (CSVD). Chronic hyperglycaemia, insulin resistance, and endothelial dysfunction drive microvascular injury, often compounded by coexisting hypertension and dyslipidaemia. Imaging and cohort studies confirm that DM accelerates CSVD progression and increases the risk of lacunar strokes, while antihypertensive and lipid-lowering therapies can modulate this risk. Nonetheless, a differential diagnosis of demyelinating lesions of the brain remains complicated, especially in young patients, as DM increases the likelihood of vascular or infectious mimics, but does not fundamentally influence diagnostic or pharmacological algorithms for acquired demyelinating syndromes. The differential diagnosis for Multiple Sclerosis is also essential in young patients with an autoimmune background. There is also growing evidence that artificial intelligence (AI) and computational modelling are increasingly useful when applied to cerebrovascular disease with DM as a key risk factor, by providing: risk stratification, automated neuroimaging analysis and decision-support systems, that integrate multimodal data to predict risks, classify aetiologies and forecast outcomes (along with retinal imaging and neuroimaging AI). AI-driven cerebrovascular morphology analysis, CSVD markers and perfusion imaging analyses are advancing the ability to predict short-term and longer-term outcomes, including cognitive impairment. For all that, challenges still arise throughout data standardisation, generalisability across diabetic subgroups, integration with electronic health records or regulatory considerations that need further prospective multicenter validation. Although pharmacological management in diabetic patients with lacunar stroke may not benefit from a diabetes-specific protocol beyond standard guidelines, physiotherapy stands as both a rehabilitative and preventive tool, contributing to microvascular risk reduction through exercise, improved metabolic control, and overall lifestyle modification. While calling for larger, diabetes-stratified studies to guide future interventions and refine personalised treatment strategies, the following narrative review, with emphasis on an AI and computational modelling in diabetes-related cerebrovascular disease, offers a brief insight into the current level of knowledge and recent updates in the correlations between DM and lacunar strokes.*

Keywords: lacunar strokes; diabetes mellitus; microvascular cerebral disease; stroke.

How to cite: Reurean-Pintilei, D., Onu, I., Trofin, D., Tutu, A., & Rusu-Zota, G. (2026). Microvascular brain pathology: Correlations between diabetes and lacunar strokes. *BRAIN. Broad Research in Artificial Intelligence and Neuroscience, 17*(2), 363-387. https://doi.org/10.70594/brain/17.2/22

1. Introduction

Diabetes mellitus (DM) is a well-established vascular risk factor that intersects with cerebral small vessel disease (CSVD), especially in the form of multiple lacunar strokes. Lacunar strokes are small subcortical infarcts produced by the occlusion of penetrating arterioles and frequently occur in the setting of CSVD. DM is associated with CSVD markers such as lacunar infarcts, white matter hyperintensities (WMH), and microvascular dysfunction, within a complex process in which hyperglycaemia and insulin resistance, as well as endothelial dysfunction, mediate brain microvascular injury (Staszewski et al., 2017). The spectrum is even wider, as interactions with other risk factors (e.g., hypertension), neuroimaging biomarkers, and broader vascular health trajectories, usually influence lacunar stroke risk and CSVD burden. Within this pathophysiological background, lacunar stroke accounts for roughly a quarter of ischaemic strokes, and are typically related to other small vessel disease mechanisms, such as lipohyalinosis and microatheroma (Ferri et al., 2025).

Across multiple study designs (MRI-based imaging, cohort analyses, and systematic reviews), DM, especially type 2, consistently emerges as a contributor to CSVD severity and lacunar stroke phenotype, while antihypertensive management and cardiovascular health strategies can modulate CSVD progression in diabetes populations. Pure motor lacunar syndrome (PMLS) due to infarcts in the internal capsule posterior limb or areas supplied by lenticulostriate arteries usually correspond to small subcortical infarcts (Cheng & Dong, 2012; Norrving, 2015). Pure sensory lacunar syndrome (PSLS) can be usually found in thalamic or internal capsule thalamic regions (Norrving, 2015). Besides these particularities, sensorimotor lacunar syndrome (SMLS) represents involvement of both motor and sensory fibers within deep structures, often in the internal capsule or thalamocortical pathways (Norrving, 2015). Nonspecific manifestations, such as dysarthria-clumsy hand syndrome (DCH) is typically associated with infarcts in ventral pons or internal capsule regions supplied by perforators, while ataxic-hemiparesis (AH) typically appears due to lacunes in the basis pedunculi/basilar perforators or internal capsule connections with cerebellar pathways (Travanichakul et al., 2023). MRI scans often reveal a small (<15-20 mm) subcortical lesion in basal ganglia, thalamus, internal capsule, or brainstem consistent with a single perforating artery territory infarct. Radiologic criteria define lacunar infarcts <3-20 mm (commonly 3-15 mm in many studies) located in basal ganglia, thalamus, internal/external capsule, or brainstem (Altmann et al., 2014; Blanco-Rojas et al., 2013). When acute lacunar syndromes co-occur with multiple small subcortical lesions or white matter disease, imaging may reveal silent lacunes or more extensive CSVD. In such cases, the radiologic phenotype can shift from a single lacune to a pattern compatible with CSVD, affecting localization interpretation and prognosis (Norrving, 2015; Cheng & Dong, 2012; Bilski et al., 2023).

The frequency of lacunar strokes in DM and the related risk factor context do not provide (at least up to this moment), enough and concise differentiation between lacunar and non-lacunar strokes. This background is limited by coexisting risk factors and by diagnostic criteria (clinical plus radiologic versus purely clinical classification). This is also consistent with the contemporary discussions that emphasize precise MRI-based subtyping and risk-factor-free phenotyping to isolate stroke mechanisms (Altmann et al., 2014; Cheng & Dong, 2012).

The latest data on this topic, highlights the necessity of pharmacological compliance to guidelines, along with the utility of physiotherapy in both primary and secondary prevention, and also indicate a rapidly evolving landscape where AI and computational modelling are increasingly applied to diabetes-associated cerebrovascular disease.

2. Material and Methods

This narrative review was conducted based on a targeted literature search of major databases (PubMed, Embase, Scopus, and Web of Science) and relevant peer-reviewed articles published in English over the past 25 years. Specific eligibility criteria were considered in order to synthesise

evidence on the association between DM, CSVD, and lacunar strokes, as well as the influence of physiotherapy and pharmacological interventions in these populations.

Studies were included if they met the following criteria:

- population: adults or children diagnosed with DM (with a focus on type 2 DM);
- intervention/exposure: DM in relation to CSVD, lacunar stroke, thrombophilia, physiotherapy, or pharmacologic management;
- outcomes: incidence or markers of CSVD (e.g., lacunar infarcts, white matter hyperintensities), stroke recurrence, cognitive outcomes, and therapeutic effects;
- study types: randomised controlled trials, cohort studies, case-control studies, systematic reviews, and meta-analyses published in peer-reviewed journals.
- language: publications in English.
- exclusion criteria: case reports (except for 2 articles, included for clinical relevance), conference abstracts, animal studies, and studies without clear outcome data.

The search combined keywords such as "diabetes mellitus," "cerebral small vessel disease," "lacunar stroke," "thrombophilia," "demyelinating lesions,", "pharmacology" and "physiotherapy." Boolean operators (AND, OR) were used to refine results.

All identified records were imported into a reference manager and duplicates were removed. Two independent reviewers screened titles and abstracts for relevance. Potentially eligible articles underwent full-text review. Disagreements were resolved by consensus or by consultation with a third reviewer.

Data were extracted using a standardised form, including study design, sample size, population characteristics, exposures/interventions, outcomes, and main findings. Findings were qualitatively synthesised due to heterogeneity in study designs and outcome measures. Subgroup and sensitivity analyses were performed as data allowed.

The study selection process is illustrated in the flow chart below (Figure 1).

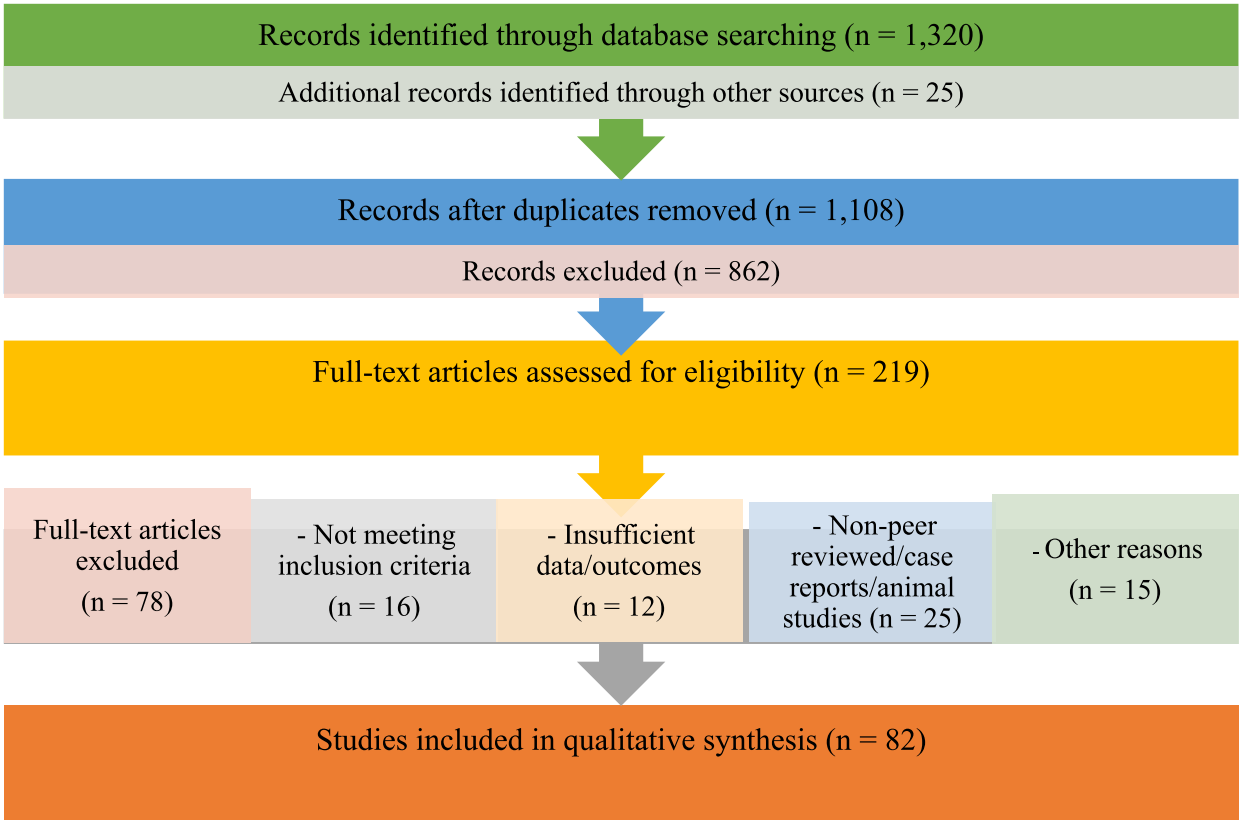

Figure 1. Flowchart of the literature research and selection algorithm

3. The Metabolic Background as a Contributor to Cerebral Small Vessel Disease

In diabetic populations, a higher prevalence and burden of CSVD markers, particularly lacunar infarcts and WMH, are repeatedly reported. DM tends to be associated with CSVD, especially lacunar stroke, according to imagistic correlations, in patients with associated hypertension and poor lipid control (Shindo et al., 2020). Various imaging/cerebrovascular reviews admit lacunar infarcts as being a central CSVD manifestation in diabetes contexts (Tang et al., 2021; Tang et al., 2020; Cui et al., 2024). DM alone is described as a risk factor for intracranial arterial disease and lacunar stroke phenotypes, suggesting patterns that align with DM's promotion of small-vessel pathology. Even cases of intracranial vessel stenosis, supporting a diabetes-small vessel disease, link to lacunar phenotypes (Zhang et al., 2022).

Also, in clinical Australian stroke populations, diabetes is reported as a significant risk factor for ischaemic stroke, with a substantial fraction of patients having DM. In spite of the fact that no stroke location mechanism shows a clear DM-specific association in that regional cohort, the broader literature still supports DM as a contributor to microvascular cerebral injury in diabetes patients presenting with stroke, based on common encountered factors, such as: endothelial dysfunction and arterial stiffness, therefore an overall negative impact upon microvascular health (Hu et al., 2022). Very often, links between DM and CSVD centre on these, with association from oxidative stress. Shan et al. (2016) (in a study based on DM type 2 patients) demonstrate that aortic arch pulse wave velocity (an index of arterial stiffness) and brachial-flow-mediated dilation (for endothelial function) correlate with lacunar infarcts and periventricular WMH, respectively, on high-resolution MRI. These data support DM-associated systemic vascular pathology as a driver of CSVD features (lacunar lesions and WMH) (Shan et al., 2016).

More than that, endothelial dysfunction is repeatedly highlighted as a key mediator of CSVD in diabetic patients, as endothelium-related mechanisms in lipohyalinosis and arteriolosclerosis are important within lacunar pathophysiology and microvascular disease severity (Norrving, 2008). Almost two decades ago, Greer et al. (2007) presented the case of a 58-year-old woman with type 1 DM, experiencing headaches, weakness, and episodes resembling a stroke, providing insight into serious diagnostic challenges and clinical considerations. The article, carrying the same relevance today, documents the physiopathological aspects of microangiopathy and inflammation, as main determinants in stroke-like recurrent events. The case raises awareness on increasing frequency of vascular events and mild residual motor deficits, within a clinical background dominated by complex microvascular and autonomic complications (Greer et al., 2007).

Hypertension is a very well-known, central, modifiable driver of CSVD. Both hypertensive control and the interaction with DM shape the lacunar risk. Meta-analytic syntheses indicate that antihypertensive therapy slows WMH progression in CSVD (with blood pressure (BP) targets around 110–129 mmHg, providing more robust WMH attenuation), but also shows fewer clear effects on brain atrophy or on lacunar incidence in some cohorts, underscoring that BP control in DM may reduce progression of certain CSVD markers rather than completely preventing lacunar events in all patients (Su et al., 2021). This combination of DM with hypertension compounds microvascular injury, and several studies note that both conditions are prevalent together in lacunar-stroke populations, supporting a synergistic impairment of small vessel health in diabetes (Shindo et al., 2020; Su et al., 2021).

DM is further associated with cognitive implications through increasing the risk for cognitive impairment. Fan et al. (2021) report that total CSVD burden correlates with medial temporal atrophy (MTA) and cognitive performance in memory-clinic patients, with WMH specifically correlating with MTA, and both CSVD burden and MTA acting as predictors of lower cognitive scores on the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). This links diabetic CSVD pathology to cognitive outcomes through imaging biomarkers (Fan et al., 2021). Systemic biomarkers linked to WMH and CSVD (endothelial integrity, angiogenesis and related pathways), while not DM-specific, are compatible with

diabetes-driven endothelial dysfunction as a driver of CSVD and later cognitive decline. The retina-brain microvascular axis literature also supports diabetes-related microvascular pathology as a fingerprint of broader CSVD burden with cognitive consequences (retinal microvascular signs correlate with CSVD MRI markers) (Kwapong et al., 2022; Cabrera DeBuc et al., 2017).

At the intersection with computational modelling in diabetes-associated CSVD, it is noteworthy to add that beyond systems biology that conceptualises the metabolic–vascular–neural axis as an integrated network, alterations in one domain (e.g., chronic hyperglycaemia) propagate through endothelial dysfunction and microvascular injury, ultimately affecting neural health. Computational models, such as agent-based simulations and network analyses, have successfully mapped these interactions and can predict the impact of interventions at various points along the evolution. Network medicine further highlights the importance of central nodes, such as endothelial health and inflammation, as both biomarkers and therapeutic targets (Barabási et al., 2011).

4. Specific Lacunar Stroke Phenotypes and Diabetes

Lacunar strokes represent a major CSVD manifestation, with a primary vascular risk profile suggesting that DM is more strongly linked with etiologies such as intracranial atherosclerosis, and in some MCA disease studies, also implying DM's predilection for small-vessel intracranial disease that yields lacunar syndromes. Nevertheless, the classic risk factor profile for lacunar stroke is also shared with other stroke subtypes, as not all lacunar patients have DM (Zhang et al., 2022; Norrving, 2008).

In lacunar stroke cohorts, markers of endothelial dysfunction (brachial flow-mediated dilation, cerebrovascular reactivity) and higher ambulatory blood pressure values have been observed in CSVD patients, and these findings align with the DM-associated vascular phenotype that predisposes to lacunar infarcts through microvascular injury and impaired cerebral autoregulation (Knottnerus et al., 2009; Klarenbeek et al., 2013). While DM strongly associates with CSVD and lacunar infarcts, the strength and specificity of associations vary by cohort and imaging phenotype, especially since DM prevalence among stroke patients does not consistently tie DM to a particular stroke mechanism. This usually suggests heterogeneity or sample size limitations (Hu et al., 2022).

The exact causal chain from hyperglycaemia and insulin resistance to lacunar infarcts remains incompletely defined up to this day. Proposed mediators include: oxidative stress, Protein Kinase C (PKC) activation, and Receptor for Advanced Glycation Endproducts (RAGE) signalling, plus hyperglycaemia-related endothelial dysfunction. Involvement of specific proteins related to endothelial integrity and angiogenesis as mediators, are also considered, but causal inference further requires longitudinal validation. So far, trials of antihypertensive therapy in lacunar stroke show mixed effects on recurrence and progression of CSVD markers, thus, while BP lowering helps WMH progression in some contexts, it does not universally translate to lower lacunar incidence in all lacunar cohorts. This underscores the need for DM-specific CSVD trials with ideal standardised imaging endpoints, and projects implications for clinical practice and research (Su et al., 2021; Tang et al., 2020).

In people with DM, aggressive management of vascular risk factors (BP, lipids, glycaemic control) remains essential to limit CSVD progression and lacunar risk. Lowering BP to 110–129 mm Hg yields more pronounced WMH attenuation, with broader benefits on CSVD burden when combined with diabetes care (Su et al., 2021). Endothelial health assessment and vascular stiffness metrics may inform risk stratification for CSVD and lacunar risk in DM patients, particularly when imaging shows lacunar or WMH. Such noninvasive measures could be integrated into DM management pathways to identify individuals at higher lacunar risk for closer monitoring or targeted interventions (Shan et al., 2016). Imagistics plays a crucial role here, as multimodal imaging approaches that combine MRI CSVD markers with retinal microvascular imaging and plasma biomarker panels, could enhance detection of DM-related microvascular brain injury and help track therapeutic responses (Cabrera DeBuc et al., 2017).

When lacunar strokes contribute to a discrete syndrome or accompany broader CSVD manifestations, they can even present as vascular parkinsonism (VaP) or as part of the broader spectrum of parkinsonian signs in elderly or vascular-risk populations. VaP is a recognised clinical entity within the CSVD spectrum, characterised by lower-body parkinsonism, gait disturbance, pyramidal signs, urinary symptoms, and poor response to levodopa, typically in the context of evident cerebrovascular disease and MRI-detected white matter lesions or lacunes (Staszewski et al., 2017; Cannistraro et al., 2019; Hatate et al., 2016). Population- and clinic-based studies converge on VaP as an atypical parkinsonism with strong vascular associations, particularly with extensive CSVD burden (WMH, lacunes, and other markers) rather than classical nigrostriatal dopaminergic degeneration seen in idiopathic PD (Staszewski et al., 2017; Che Mohd Nassir et al., 2021; Hatate et al., 2016).

Within this background, VaP stands out as one of the most discussed overlapping clinical presentations, alongside vascular dementia and other CSVD phenotypes (Staszewski et al., 2017; Cannistraro et al., 2019; Staszewski et al., 2017; Hatate et al., 2016). For all that, the general context gets more complicated once we also relate to the DM. The aetiologic link between DM, lacunar stroke, and VaP is supported by population-based and cohort data, that indicates that individuals with DM carry elevated risk for lacunar-type events and for parkinsonian signs associated with vascular pathology in ageing populations (van Norden et al., 2011; Cannistraro et al., 2019; Staszewski et al., 2017; Hatate et al., 2016).

In studies that stratify CSVD manifestations, VaP and vascular dementia share substantial imaging burden (white matter hyperintensities, lacunes), and diabetes tends to co-occur with the CSVD phenotype that predisposes to VaP. This aligns with findings showing that the presence of WMH and lacunar lesions predicts adverse vascular outcomes and may parallel the emergence of parkinsonian signs in CSVD, particularly in older adults with DM (Staszewski et al., 2017; van Norden et al., 2011; Hatate et al., 2016).

Given the cognitive implications, DM patients with CSVD markers warrant cognitive monitoring and early interventions for vascular cognitive impairment and dementia risk, with attention to total CSVD burden rather than single markers alone (Fan et al., 2021).

Moreover, data integration in contemporary neuroscience is an ongoing phenomenon. Modern neuroscience leverages multi-modal data integration, combining genomics, proteomics, and neuroimaging, aiming to unravel the complex pathophysiology of CSVD in DM. Advanced workflows nowadays use machine learning to link multiple profiles with imaging-detectable brain changes, refining risk prediction and enabling personalised care strategies. These integrative approaches move beyond traditional descriptive studies, providing a platform for hypothesis-driven research and further model-based clinical applications (O'Connor & Price, 2018; Barabási et al., 2011).

5. Artificial Intelligence and Computational Modelling in Diabetes-Related Cerebrovascular Disease

AI and machine learning (ML) methods are increasingly being used to analyse large, multimodal datasets (clinical, laboratory, imaging, and retinal data), in order to predict stroke risk and guide management in diabetes populations (Nur et al., 2025; Medina et al., 2025; Kumar et al., 2023). This includes risk stratification models, imaging-based lesion detection and segmentation, as well as outcome prediction (e.g., functional status at the 90-day endpoint) especially by using features derived from MRI, CT and vascular imaging, often with DM as a modifier or covariate in predictive models (Medina et al., 2025; Chen et al., 2020; Chlorogiannis et al., 2023).

Computational modelling of cerebrovascular morphology, vessel geometry, and small vessel disease markers are being used to improve triage, detect occlusions, and estimate collateral status, with AI integrating convolutional neural networks (CNNs) and probabilistic atlases to automate image processing and feature extraction from angiography and CT perfusion data (Deshpande et al., 2023).

AI-assisted imaging is complemented by AI-based clinical decision support systems (AI-CDSS) designed to improve stroke care quality and outcomes. Cluster-randomised trials in large populations (e.g., in China) are assessing reductions in recurrent vascular events when AI-CDSS is used to guide imaging analysis, aetiologic assessment, and guideline-concordant treatment recommendations (Li et al., 2024).

Retinal imaging as a surrogate for cerebrovascular risk in DM proposes AI models applied to retinal fundus imaging and optical coherence tomography (OCT). These can predict stroke risk and provide prognostic information, having the advantage of being noninvasive imaging approaches, hence particularly attractive in DM due to the microvascular complications and the retinal–cerebrovascular health links. AI methods (e.g., CNNs architectures) have been reported to perform comparably to traditional stroke risk scores in correlating retinal vasculature with stroke risk and may enable scalable screening in diabetes populations (Khalafi et al., 2025). AI in stroke risk assessment uses retinal imaging and its potential to be integrated into care pathways. While focused on stroke, the retinal changes (arteriovenous ratio, tortuosity) are relevant to diabetes-related microvascular disease (Khalafi et al., 2025).

Novel neuroimaging and AI-assisted interpretation for CSVD and stroke in DM promote AI approaches for automated detection and quantification of CSVD features on MRI (e.g., white matter hyperintensities, lacunes, microbleeds). This supports risk stratification and outcome predictions. In DM cohorts, where CSVD burden is elevated, AI-enabled metrics can improve prognostication beyond conventional scales (Hu et al., 2024).

In terms of supporting evidence, Hu et al. (2024) summarise AI-based MRI applications to CSVD and discuss their potential to quantify atrophy, small vessel pathology, and related biomarkers. In this given context, AI stands out as a tool to augment radiologic assessment in CSVD (Hu et al., 2024). AI-enabled segmentation of cerebrovascular networks from baseline angiography and automatic extraction of vascular features (e.g., vessel density, branching) also improves occlusion detection, collateral grading, and prediction of 90-day outcomes. These enhance triage efficiency and prognostication in AIS, with potential applicability to diabetic patients who often present with more complex vascular anatomy or collateral status (Deshpande et al., 2023). High segmentation accuracy and improved outcome prediction when incorporating automated vascular features promote the idea that the methodology can be extended to diabetic subgroups where vascular remodelling and microvascular disease usually affect outcomes (Deshpande et al., 2023).

Large-scale trials of AI-CDSS in cerebrovascular disease also show promise for improving care quality and reducing recurrent vascular events, as diabetes often coexists with cerebrovascular disease, indicating potential additive benefits of AI-CDSS in diabetic populations by standardising imaging interpretation and guideline-based therapy decisions (Li et al., 2024). GOLDEN BRIDGE II, an AI-CDSS trial designed to improve stroke outcomes and care quality, while not diabetes-specific, is a framework directly relevant to diabetes-related cerebrovascular care (Li et al., 2024).

6. Lacunar Strokes in Relation to Thrombophilic Mutations

The context for lacunar strokes goes beyond mechanisms such as lipohyalinosis and microatheroma, when thrombophilia is added to the equation (Ferri et al., 2025). This pathophysiology is distinct from cardioembolic and large-artery atherosclerotic aetiologies. More than that, the contribution of thrombophilia to lacunar stroke risk is less well established than for venous thromboembolism or non-lacunar arterial strokes (Ferri et al., 2025; Dziedzic et al., 2023).

Protein C deficiency, protein S deficiency, and antithrombin deficiency show stronger associations with venous thromboembolism. Their associations with arterial strokes are rare and predominantly supported by case reports or small studies, while large population-level data are limited or inconclusive for stroke risk, and deficits are generally considered less impactful on arterial events than on venous thromboembolism (Middeldorp & van Hylckama Vlieg, 2008;

Arachchillage et al., 2022; Milgrom et al., 2018). Some studies in younger adults have explored associations between thrombophilic mutations and small-vessel or lacunar phenotypes, with mixed results. Some reports of associations exist in selected cohorts, but overall evidence is inconsistent and often confounded by coexisting vascular risk factors (hypertension, DM, dyslipidaemia) and small-sample designs. This leads to cautious interpretation and typically no standardised clinical recommendation to test routinely for thrombophilia in lacunar stroke without other suggestive features (Liu et al., 2024; Milgrom et al., 2018).

DM is a major driver of small-vessel cerebrovascular disease and lacunar stroke risk, often through mechanisms of microvascular damage, advanced glycation end-products, and inflammation. Several large datasets show DM as a key risk factor for lacunar strokes, sometimes with worse prognosis and higher incidence of small-vessel disease features compared with non-diabetics (Akhtar et al., 2024; Scacciatella et al., 2016). When considering thrombophilia, DM appears to interact with traditional risk factors to potentiate vascular risk, but the added predictive value of inherited thrombophilic mutations for lacunar stroke in diabetics remains uncertain. For example, in studies of *Patent Foramen Ovale* (PFO)-related stroke and other contexts, DM status can alter risk profiles, but there is enough evidence that classic thrombophilic mutations alone do not always predict lacunar outcomes in diabetics (Badea et al., 2023; Bădescu et al., 2023; Arachchillage et al., 2022; Middeldorp & van Hylckama Vlieg, 2008).

A British Society for Hematology guideline emphasises that thrombophilia testing for arterial stroke, including lacunar stroke, remains controversial and not routinely recommended, particularly given the strong influence of DM and other modifiable factors on stroke risk (Arachchillage et al., 2022). The coexistence of DM and thrombophilic mutations may, however, magnify overall vascular risk when combined with other factors, but clear, lacunar-specific associations are not yet consistently demonstrated. Where associations exist, they often reflect broader arterial disease risk or cryptogenic patterns rather than a lacunar-specific mechanism (Arachchillage et al., 2022; Middeldorp & van Hylckama Vlieg, 2008). In terms of clinical practical implications assessment and optimisation of conventional risk factors (glycaemic control, blood pressure, lipid management, smoking cessation) stand as the primary preventive strategy, aligning with guidelines that caution against routine thrombophilia testing in arterial stroke contexts (Arachchillage et al., 2022; Middeldorp & van Hylckama Vlieg, 2008).

Future studies should stratify by age, sex, diabetes duration and control, hypertension, homocysteine levels, and MTHFR variants to delineate potential additive or interactive effects. Collaborative stroke registries and genotype-phenotype analyses could help clarify whether a small subset of diabetics with particular thrombophilic profiles have an elevated lacunar risk or distinct prognosis. While some studies show enriched thrombophilia markers in subsets of cryptogenic or PFO-related stroke, many large reviews and guidelines conclude that routine thrombophilia testing does not meaningfully impact management for arterial stroke subtypes, including lacunar stroke, particularly in older adults and in the presence of DM (Arachchillage et al., 2022; Dziedzic et al., 2023; Middeldorp & van Hylckama Vlieg, 2008).

Potential subgroup effects should be taken into consideration (e.g., younger stroke patients or those with certain genetic profiles) where thrombophilia might contribute to lacunar-type events, but these findings are not universally replicated and require more targeted confirmation in diabetic populations (Esparza-García et al., 2015; Sartori et al., 2011).

In diabetic patients, besides well-known risk factor for lacunar stroke, thrombophilia testing should be performed, but in the context of cryptogenic stroke or young patients. Three categories of classification arise within this context (Figure 2).

A unanimous conclusion is that further studies based on subgroups are necessary to better understand how thrombophilia might contribute meaningfully to lacunar risk or prognosis (Ferri et al., 2025; Arachchillage et al., 2022; Dziedzic et al., 2023; Middeldorp & van Hylckama Vlieg, 2008; Akhtar et al., 2024).

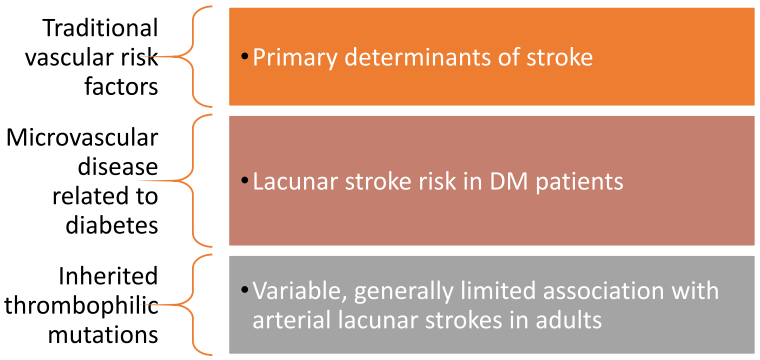

Figure 2. Major categories of determinants for lacunar stroke in DM patients

7. Differential Diagnosis of Cerebral Demyelinating Lesions in Young Patients with Diabetes

The differential diagnosis of cerebral demyelinating lesions in young patients requires distinguishing primary demyelinating diseases (multiple sclerosis (MS)-like) (e.g., paediatric-onset multiple sclerosis (POMS), myelin oligodendrocyte glycoprotein antibody-associated disease (MOG)-associated disease (MOGAD), neuromyelitis optica spectrum disorders (NMOSD) or acute disseminated encephalomyelitis (ADEM)) from mimics such as vascular, infectious, metabolic, leukodystrophic, and vasculitic processes. DM adds a vascular-comorbidity layer that can influence presentation and diagnostic considerations, but there is still limited evidence that DM alone uniquely shifts the differential toward or away from specific demyelinating aetiologies in youths (O'Mahony et al., 2013; Bigi & Banwell, 2012; Galardi et al., 2019; Gontika & Anagnostouli, 2018; Bigi et al., 2014).

The most solid contemporary guidance emphasises using comprehensive clinical assessment, MRI features, antibody testing (Aquaporin 4 (AQP4), MOG), cerebrospinal fluid (CSF) studies, and longitudinal follow-up to categorise demyelinating syndromes, with careful exclusion of non-demyelinating mimics, particularly in DM, where microvascular pathology and infection risk may confound interpretation (Galardi et al., 2019; Gontika & Anagnostouli, 2018; Paolilo et al., 2020).

ADEM and multiphasic variants, presenting with encephalopathy and polyfocal deficits, as well as MOGAD can mimic MS, often requiring antibody testing for distinction (Gontika & Anagnostouli, 2018; Paolilo et al., 2020; Bakirtzis et al., 2023; Tenembaum, 2021). POMS, an inflammatory demyelinating disease with dissemination in space and time, can be commonly diagnosed adding specific MRI criteria (McDonald-based approaches adapted for children) guide diagnosis, with disease-modifying therapies considered when MS is confirmed (Rahmlow & Kantarci, 2013; Galardi et al., 2019; Aldebasi et al., 2024; Huppke et al., 2013).

NMOSD and MOGAD can be distinguished by serology (AQP4-IgG, MOG-IgG) and characteristic MRI patterns, all of which are essential in order to differentiate from MS, especially due to treatment implications (Galardi et al., 2019; Rosenthal et al., 2020). Other mimics frequently considered in the course of the differential diagnosis can be: CNS vasculitis/vascular inflammatory disorders, leukodystrophies/metabolic diseases, CNS infections, neoplasms, mitochondrial disorders, and CNS inflammatory/autoimmune encephalitides. Along this intricate background, vascular risk factors and DM may elevate suspicion for vasculitic or microvascular aetiologies in ambiguous cases (O'Mahony et al., 2013; Galardi et al., 2019; Bigi et al., 2014).

DM in youth is associated with a higher risk of vascular and inflammatory CNS phenomena via microvascular injury and metabolic dysregulation, potentially increasing the likelihood of vascular white matter changes that can confound imaging interpretation (Zhang, L. J. et al.,2023).

However, there is limited evidence that DM fundamentally redefines the core differential for demyelination. It actually heightens consideration of vascular mimics and complicates interpretation of MRI with leukoaraiosis-like patterns in some cases (Galardi et al., 2019; Paolilo et al., 2020; Bigi et al., 2014).

When DM coexists with Acquired Demyelinating Syndromes (ADS), guidelines for paediatric demyelinating disease recommend standard differential diagnostic approaches (MRI patterns, CSF analysis, antibody testing) rather than a diabetes-centred diagnostic algorithm. DM control remains a general concomitant management priority rather than a diagnostic discriminator for ADS aetiology (Paolilo et al., 2020; Bigi et al., 2014).

MRI remains the primary imaging modality, as MS tends to show dissemination in space/time with periventricular and Dawson's finger-like lesions. ADEM shows more confluent, often bilateral white-matter involvement with encephalopathy, while NMOSD/MOGAD exhibit distinct lesion topographies and optic-spinal involvement patterns that guide testing decisions (Galardi et al., 2019; Gontika & Anagnostouli, 2018; Paolilo et al., 2020; Huppke et al., 2013).

Testing for AQP4-IgG and MOG-IgG is essential to separate NMOSD and MOGAD from MS and ADEM, given treatment differences. Oligoclonal bands support MS but are less frequent in ADEM or NMOSD. CSF glucose/protein/cell counts aid in infection versus inflammatory aetiologies, with is important in diabetic patients, where infections may present atypically (Galardi et al., 2019; Gontika & Anagnostouli, 2018; Rosenthal et al., 2020; Paolilo et al., 2020).

Considering the diabetes-related vascular risk, special assessment of CNS vasculitis, small-vessel pathology, and leukodystrophies should be investigated, especially when imaging shows confluent leukoencephalopathy, and infectious/inflammatory aetiologies that may be precipitated by metabolic compromise (also to be included in the differential diagnosis). Regular re-evaluation over the first year is necessary to detect evolution towards MS, NMOSD, or MOGAD, as indicated by follow-up MRI and clinical course monitoring (Galardi et al., 2019; Paolilo et al., 2020; Turco et al., 2025; Bakirtzis et al., 2023). A synthesis of correlations between ADS and DM can be found in Table 1.

Table 1. Nuanced correlation between cerebral demyelinating lesions in young patients with Diabetes

Diagnostic Category	Key Features / Considerations	Role of Diabetes	Supportive References
Acquired Demyelinating Syndromes (ADS)	Includes ADEM, CIS, MS; diagnosed via clinical/MRI/serological criteria	Diabetes may confound imaging; does not fundamentally redefine ADS differential	Galardi et al., 2019; Paolilo et al., 2020; Bigi et al., 2014
NMOSD / MOGAD	Distinct antibody profiles (AQP4-IgG, MOG-IgG), MRI patterns	Testing is essential for distinction; diabetes can increase diagnostic ambiguity	Galardi et al., 2019; Rosenthal et al., 2020; Paolilo et al., 2020
Non-demyelinating mimics	Includes vasculitis, infections, leukodystrophies, metabolic diseases	Diabetes increases risk of vascular/infectious mimics and diagnostic complexity	O'Mahony et al., 2013; Bigi et al., 2014; Galardi et al., 2019
Diagnostic Approach	Comprehensive assessment: clinical exam, MRI, antibody and CSF testing, longitudinal follow-up	Standard differential processes recommended; optimise diabetes management in parallel	Galardi et al., 2019; Paolilo et al., 2020; Bigi et al., 2014

Abbreviations: ADEM = Acute disseminated encephalomyelitis; NMSOD = Neuromyelitis optica spectrum disorder; MOGAD = Myelin oligodendrocyte glycoprotein antibody-associated disease; CIS = Clinically Isolated Syndrome; MS = Multiple Sclerosis; MRI = Magnetic resonance imaging; ADS = Acquired Demyelinating Syndromes; AQP4-IgG = astrocyte water channel protein aquaporin 4 IgG; CSF = Cerebrospinal fluid.

Broad differential diagnosis in paediatric ADS, with potential sub-phenotype distinctions (e.g., MOGAD vs ADEM vs MS) may be overall necessary (Table 2). Some authors suggest a stronger role for MOGAD and NMOSD in younger populations than in adults, which can affect initial diagnostic weighting; others note substantial overlap and the necessity of follow-up to confirm MS in many cases.

Given the heterogeneity of ADS in children, including those with DM, there is still no consensus for a unique, diabetes-specific differential list; rather, it necessitates thorough evaluation for vascular/infectious mimics and careful interpretation of MRI/biomarkers (Rahmlow & Kantarci, 2013; Galardi et al., 2019; Gontika & Anagnostouli, 2018; Tenembaum, 2021; Paolilo et al., 2020; Huppke et al., 2013).

Table 2. Practical implications and strategies for diagnosing demyelinating lesions in young patients with Diabetes

Practical Step	Description	Diabetes-Related Considerations	References
Thorough Clinical Assessment	Assess for encephalopathy, consciousness, focal deficits	Consider vascular and infectious risk factors linked to diabetes	Galardi et al., 2019; Paolilo et al., 2020
Brain/Spinal MRI with Contrast	Evaluate lesion distribution, age, dissemination	Diabetes can cause leukoaraiosis-like changes; interpret with caution	Galardi et al., 2019; Gontika & Anagnostouli, 2018
Radiological identification of acute lacunar infarcts	Acute lacunar infarcts are small (<15-20 mm), diffusion-restricted lesions seen on DWI MRI, often in the basal ganglia, internal capsule, thalamus, or brainstem.	Diabetes increases risk for CSVD and acute lacunar infarcts due to microvascular changes; early imaging is key for prompt management in diabetic patients.	Norrving, 2015; Altmann et al., 2014; Zhang et al., 2023
Detection and monitoring of silent lacunar infarcts	Silent lacunes are often found incidentally on MRI, appearing as small hyperintense lesions without clinical symptoms; frequently coexist with other CSVD markers.	Diabetes is a risk factor for silent infarcts; regular screening and aggressive risk factor control are particularly important in diabetic populations.	Norrving, 2015; Altmann et al., 2014; Cheng & Dong, 2012; Bilski et al., 2023
Chronic lacunes follow-up	Chronic lacunes persist as CSF-filled cavities; follow-up MRI may show cavitation from recent small subcortical infarcts, with CSVD burden predicting cavitation risk.	Diabetics are more likely to have higher risk for chronic lacunes and progressive cognitive/vascular complications.	Wang et al., 2023; Bilski et al., 2023
Serum and CSF Testing	MOG-IgG, AQP4-IgG, OCBs, IgG index, infectious panels	Diabetes increases infection risk; comprehensive testing essential	Galardi et al., 2019; Rosenthal et al., 2020; Paolilo et al., 2020
Longitudinal Monitoring	Repeat imaging to assess dissemination in time and space	Diabetes may complicate progression and imaging interpretation	Galardi et al., 2019; Paolilo et al., 2020; Bakirtzis et al., 2023
Optimise Diabetes Management	Control glycaemia and vascular risk factors in parallel	Contributes to improved CNS environment for recovery	Paolilo et al., 2020; Bigi et al., 2014

Abbreviations: MRI = Magnetic resonance imaging; IgG = Immunoglobulin G; AQP4-IgG = astrocyte water channel protein aquaporin 4 IgG; MOG-IgG = Antibodies against myelin oligodendrocyte glycoprotein; OCBs = Oligoclonal Bands; CSVD = cerebral small vessel disease

The latest data on the topic support a multi-entity differential diagnosis for cerebral demyelinating lesions in young patients with DM, with primary consideration for MS, ADEM, MOGAD, and NMOSD, plus vascular/infectious/leukodystrophy mimics (Zhang, L. J. et al.,2023).

DM does not decisively redefine the differential diagnosis, but raises consideration of diabetic-related vascular/infectious processes that may resemble demyelinating pathology.

Diagnostic strategy should still prioritise MRI-based dissemination assessment and targeted antibody testing (AQP4, MOG) where necessary, as well as CSF studies, and altogether a longitudinal follow-up, in line with paediatric ADS guidelines and updated reviews (Rahmlow & Kantarci, 2013; Galardi et al., 2019; Gontika & Anagnostouli, 2018; Tenembaum, 2021; Paolilo et al., 2020; Bigi et al., 2014; Huppke et al., 2013; Bakirtzis et al., 2023).

8. Contextual Pharmacology for Patients with Diabetes and Lacunar Strokes

The pharmacological management of lacunar stroke in people with DM aims towards a standard secondary-prevention strategy for small vessel disease, with DM acting as a major comorbidity that amplifies vascular risk. Across studies, antiplatelet therapy, blood pressure and lipid lowering, as well as glycaemic control, remain essential, while evidence specifically addressing diabetes-unique pharmacology for lacunar stroke is often only extrapolated from the broader topic of CSVD and lacunar stroke specific literature (van Sloten et al., 2020; Simon, 2002; Bath & Wardlaw, 2015; Arboix et al., 2017).

Key pharmacological themes still considered nowadays include well-defined protocols that can be synthesised as in Figure 3, especially: antiplatelet use (single antiplatelet therapy preferred over routine dual therapy in lacunar stroke), statin therapy with meaningful LDL-C lowering, strict BP targets to reduce recurrent lacunar events, consideration of cilostazol (or similar drugs) as a potentially favourable option for lacunar stroke in some cohorts, and overall attention to diabetes-specific vascular risk modifiers, such as microvascular complications and glycaemic control, which is primordial and influences both recurrence and outcomes (van Sloten et al., 2020; Nishiyama et al., 2023; Bath & Wardlaw, 2015; Arboix et al., 2017).

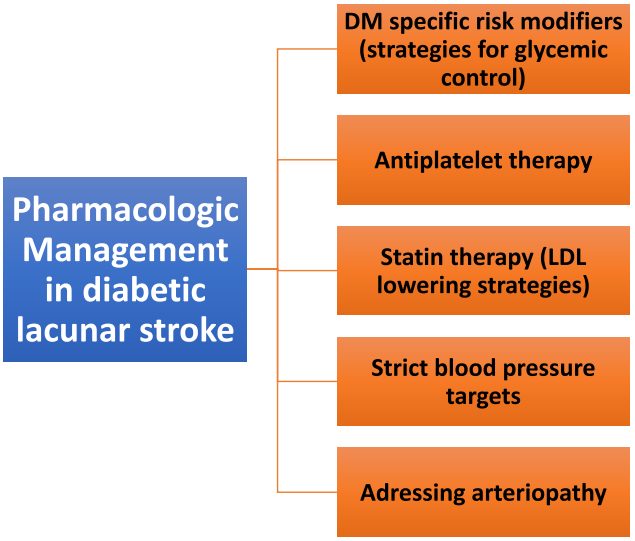

Figure 3. Main classes of pharmacological interventions in DM with associated cerebral lacunar lesions

DM amplifies lacunar stroke risk and can modify vascular risk factor interactions; however, evidence supporting diabetes-specific pharmacological modifications for lacunar stroke beyond standard CSVD prevention remains inconclusive. Genotype–phenotype and imagistic studies increasingly agree upon the interplay between DM risk, lipid biology, BP, and lacunar stroke, but do not necessarily establish a diabetes-centric pharmacological protocol for lacunar stroke up to this point (van Sloten et al., 2020; Zhang et al., 2023).

The SPS3 trial (secondary prevention of small subcortical strokes) established that dual antiplatelet therapy (aspirin plus clopidogrel) did not reduce recurrent ischaemic stroke compared with single antiplatelet therapy, and increased bleeding, prompting guideline recommendations

favouring Single Antiplatelet Therapy (SAPT) in typical lacunar stroke contexts, including in patients with diabetes (Bath & Wardlaw, 2015; Nishiyama et al., 2023).

Adding cilostazol to single-agent therapy may reduce recurrent ischaemic stroke in lacunar patients without a significant rise in major bleeding, suggesting a potential role for cilostazol as part of a tailored antithrombotic approach in certain populations, including older patients where vascular risk is high. While specific diabetes-specific subgroup data are limited, the overall signal supports exploring cilostazol in select lacunar patients after careful risk stratification (Nishiyama et al., 2023).

Statin therapy reduces recurrent stroke risk as part of comprehensive vascular risk reduction. Trials like SPARCL demonstrated general stroke risk reduction with statins across subtypes, though lacunar-specific data are often pooled with other ischaemic strokes. Given the DM association with dyslipidaemia and CSVD, statins remain a cornerstone of secondary prevention in diabetics with lacunar stroke, aligning with broader stroke guidelines (van Sloten et al., 2020; Bath & Wardlaw, 2015). Practical implications concentrate on aiming for guideline-recommended LDL targets with statin therapy unless contraindicated, and periodically monitoring for statin-associated adverse effects. Adherence to the treatment is mandatory in order to optimise microvascular and macrovascular risk reduction, especially since furthermore, cerebral small vessel disease and lacunar stroke are strongly linked to hypertension. The SPS3 trial reported that targeting SBP <130 mmHg reduces recurrent lacunar events and lowers intracerebral haemorrhage risk, supporting strict BP control as a central preventive strategy in diabetic patients with lacunar stroke, who frequently have comorbid hypertension (Bath & Wardlaw, 2015; van Sloten et al., 2020).

It is worth mentioning that the direct impact of glycaemic management on lacunar stroke recurrence is twofold: good glycaemic control reduces microvascular complications that contribute to small vessel disease, while hypoglycaemia risk and drug interactions must be considered. Genome-informed studies and MR analyses increasingly link type 2 DM risk to lacunar stroke, underscoring the importance of comprehensive diabetes management as part of primary and secondary prevention strategies. However, there is no universally accepted diabetes-specific pharmacological regimen uniquely tailored to lacunar stroke beyond standard diabetes care and vascular risk factor modification (van Sloten et al., 2020; Zhang et al., 2023; Knottnerus et al., 2009). Even so, drug repurposing and MR-guided targets point to potential future directions in lacunar stroke pharmacology, including agents influencing cerebral microvascular function, lipid pathways, and glycaemic control. Current data suggest that calcium-channel blocker-mimetic effects and LDL-lowering strategies may confer protective signals against lacunar stroke, but these findings are largely from MR analyses and drug-target MR studies, not yet translated into routine practice for lacunar stroke in diabetics (Zhang et al., 2023; Wardlaw et al., 2009).

Some limitations and nuances arise, since many pharmacological data come from mixed lacunar and non-lacunar stroke populations, or from small vessel disease cohorts rather than diabetes-only lacunar subgroups; thus, extrapolation to diabetics should be considered nuanced in clinical practice, according to every single patient and their particularities. Larger, diabetes-stratified, lacunar-specific trials are needed to define whether diabetics derive differential benefit or risk from specific agents or regimens (van Sloten et al., 2020; Bath & Wardlaw, 2015; Nishiyama et al., 2023). There is data though, on the fact that DM can alter vascular risk factor interactions (e.g., dyslipidaemia impact, BP response), which may influence individual treatment choices and targets, reinforcing personalised medicine approaches (van Sloten et al., 2020; Simon, 2002).

Good perspectives emerge from novel available therapies. In people with DM, Inclisiran's LDL-C lowering effect has been consistently demonstrated, and cardiovascular outcomes trials (e.g., ORION program, VICTORION programs) orientate towards efficiant lipid lowering impact, that translates into reductions in major adverse cardiovascular events (MACEs), including ischaemic stroke (Ray et al., 2023; Alradwan et al., 2024; Huang et al., 2025). Early patient-level analyses suggest an early trend toward reduced MACEs with Inclisiran (Ray et al., 2023).

Zilebesiran is an RNA interference therapeutic agent with a prolonged duration of action, that inhibits hepatic angiotensinogen synthesis, and targets hepatic angiotensinogen (AGT). So far, it has been showing very good and durable blood pressure reduction in phase I/II studies (KARDIA-1/2) and has the potential to reduce hypertensive and end-organ risk. Given hypertension is a major driver of stroke in DM, Zilebesiran could contribute to primary and secondary stroke prevention indirectly through BP lowering and vascular protection (Addison et al., 2023; Ye et al., 2023; Morosan et al., 2025; Kanbay et al., 2025).

For individuals with lacunar strokes, these new available therapies may provide complementary pathways: Inclisiran lowers atherogenic lipoproteins and potentially reduces large-vessel stroke risk, while Zilebesiran lowers BP and may prevent microvascular injury, though evidence for lacunar stroke-specific prevention remains to be established in dedicated trials (Ray et al., 2023; Huang et al., 2025; Morosan et al., 2025). Strictly related to diabetes patients, Inclisiran and Zilebesiran address the two major modifiable stroke risk factors: dyslipidaemia and hypertension, with high plausibility that these effects will translate into reduced small vessel stroke risk (Ren & Danser, 2025; Huang et al., 2025; Morosan et al., 2025). Combination strategies targeting both LDL-C and BP hold the greatest theoretical promise, contingent on the demonstration of net clinical benefit in future trials (Ren & Danser, 2025; Morosan et al., 2025).

9. The Role of Physiotherapy in Managing Microvascular Risk Factors

Physiotherapy (PT) is not only a rehabilitation modality in cerebrovascular disease, but also a component of a broader strategy to control microvascular risk factors through physical activity, lifestyle modification, and cardiovascular risk management (Sheik et al., 2023; O'Sullivan, 2008; Ungvári et al., 2021; van Sloten et al., 2020).

PT contributes to microvascular risk reduction by improving blood glucose control, promoting favourable lipid and BP profiles through activity, reducing obesity, and enhancing endothelial function and cerebral perfusion. These effects are supported by data on diabetes-associated microvascular disease and cognitive/vascular outcomes, which underscore the centrality of vascular risk factor control in reducing lacunar-related morbidity (van Sloten et al., 2020; Novak & Hajjar, 2010; Kalaria, 2010; Chui, 2007).

Practical PT strategies often include structured aerobic and resistance training programmes, balance and gait rehabilitation, dual-task and cognitive-motor training, and education for self-management. Integration with medical therapy and multidisciplinary care is also essential to optimise microvascular outcomes in DM patients (Wong & Chang, 2022; Novak & Hajjar, 2010; Chui, 2007).

The high prevalence of lacunes, WMHs, and microinfarcts, which underpin lacunar strokes, is a compelling reason to consider PT as a lifestyle choice, not to mention the need in geriatric population with associated arthritis, which alongside neuropathy, increases the risk of falls and hence, further comorbidities (Umemura et al., 2017; Scott & Rosenberg, 2022; Novak & Hajjar, 2010; Mekala & Qiu, 2025; Kalaria, 2010).

Hypertension and DM are among the strongest vascular risk factors driving microvascular pathology, including blood-brain barrier disruption and endothelial dysfunction, which mediate lacunar stroke risk and related cognitive impairment (Ungvári et al., 2021; Kalaria, 2010; Chui, 2007).

The interactions between DM, microvascular disease, and neurodegeneration are bidirectional and complex: DM accelerates microvascular ageing and cerebral small vessel pathology, which in turn can exacerbate vascular contributions to cognitive impairment and dementia, including VaD and mixed dementia with Alzheimer's disease pathology (Ungvári et al., 2021; van Sloten et al., 2020; Kalaria, 2010; Iadecola et al., 2019).

PT can be used as a tool for microvascular risk modulation through aerobic and resistance exercise, which improves insulin sensitivity, glycaemic control, lipid profiles, and BP, thereby addressing major microvascular risks (Kalaria, 2010; Chui, 2007; Alfaro et al., 2018). PT can also

enhance cerebral perfusion and endothelial function indirectly via exercise-induced improvements in vascular health, which may slow down the progression of cerebral small vessel pathology and reduce future lacunar events (Novak & Hajjar, 2010; Kalaria, 2010; Chui, 2007).

Motor rehabilitation after lacunar stroke, including gait and balance training, can reduce sedentary behaviour, improve physical activity levels, and contribute to better metabolic and vascular risk profiles, potentially lowering recurrence risk of both macro and microvascular brain injury (Table 3) Ungvári et al., 2021; van Sloten et al., 2020; Novak & Hajjar, 2010).

Table 3. Specific physiotherapy strategies aligned with contextual outcomes

Intervention Type	Description	Outcomes/Benefits	Supporting References
Structured aerobic conditioning	Moderate-intensity walking, cycling, or treadmill training tailored to the patient's capacity.	Improves HbA1c, fasting glucose, and blood pressure; reduces microvascular risk.	Kalaria, 2010; Chui, 2007; Alfaro et al., 2018
Resistance and strength training	Progressive resistance training to enhance muscle mass.	Improves glycaemic control, lipid metabolism, insulin sensitivity, and cardiovascular risk; especially relevant for older adults with diabetes.	Kalaria, 2010; Alfaro et al., 2018
Balance and gait rehabilitation	PT focusing on balance, proprioception, and safe gait post-lacunar stroke.	Reduces fall risk, supports activity participation, sustains vascular benefits, and improves metabolic control.	Sheik et al., 2023; O'Sullivan, 2008; van Sloten et al., 2020
Cognitive-motor training	Incorporates dual-task or cognitive-motor training.	Helps preserve cognitive function and gait, addresses VCID-relevant outcomes alongside motor recovery.	Kalaria, 2010; Iadecola et al., 2019
Education and self-management	Provides education on exercise, pacing, weight/nutrition management, and adherence to cardiovascular risk modification.	Reinforces behaviours that attenuate microvascular risk in diabetes and after lacunar stroke.	Novak & Hajjar, 2010; Chui, 2007; Alfaro et al., 2018

Abbreviations: HbA1c = haemoglobin A1c; VCID = Vascular Contributions to Cognitive Impairment and Dementia.

Optimal PT outcomes require multidisciplinary coordination in controlling vascular risk factors as a central purpose to prevent additional lacunar strokes and reduce VCID risk (Ungvári et al., 2021; van Sloten et al., 2020; Kalaria, 2010; Iadecola et al., 2019). PT should adapt to stroke subtype and cognitive status, especially in lacunar stroke patients with DM, by the use of individualised plans considering autonomic status, comorbidities, and cognitive function, as essential to maximize safety, adherence, and vascular benefits (Sheik et al., 2023; O'Sullivan, 2008; van Sloten et al., 2020).

PT-led interventions to lacunar stroke recurrence or microvascular outcomes in diabetic populations are limited, relating more to overall improvements through lifestyle changes. Nonetheless, the purpose remains that of an improved endothelial function that sustains a better metabolic control (van Sloten et al., 2020; Novak & Hajjar, 2010; Kalaria, 2010; Chui, 2007; Alfaro et al., 2018).

PT's cognitive benefits may also be mediated through vascular mechanisms, but high-quality trials clarifying these causal pathways are warranted (Novak & Hajjar, 2010; Iadecola et al., 2019; Alfaro et al., 2018). Practical clinical implications can be further synthesised as in Figure 4.

Integration with pharmacological management (antihypertensives, antidiabetic agents, statins, where appropriate) is essential to optimise microvascular health while achieving functional rehabilitation goals (Ungvári et al., 2021; Kalaria, 2010; Chui, 2007).

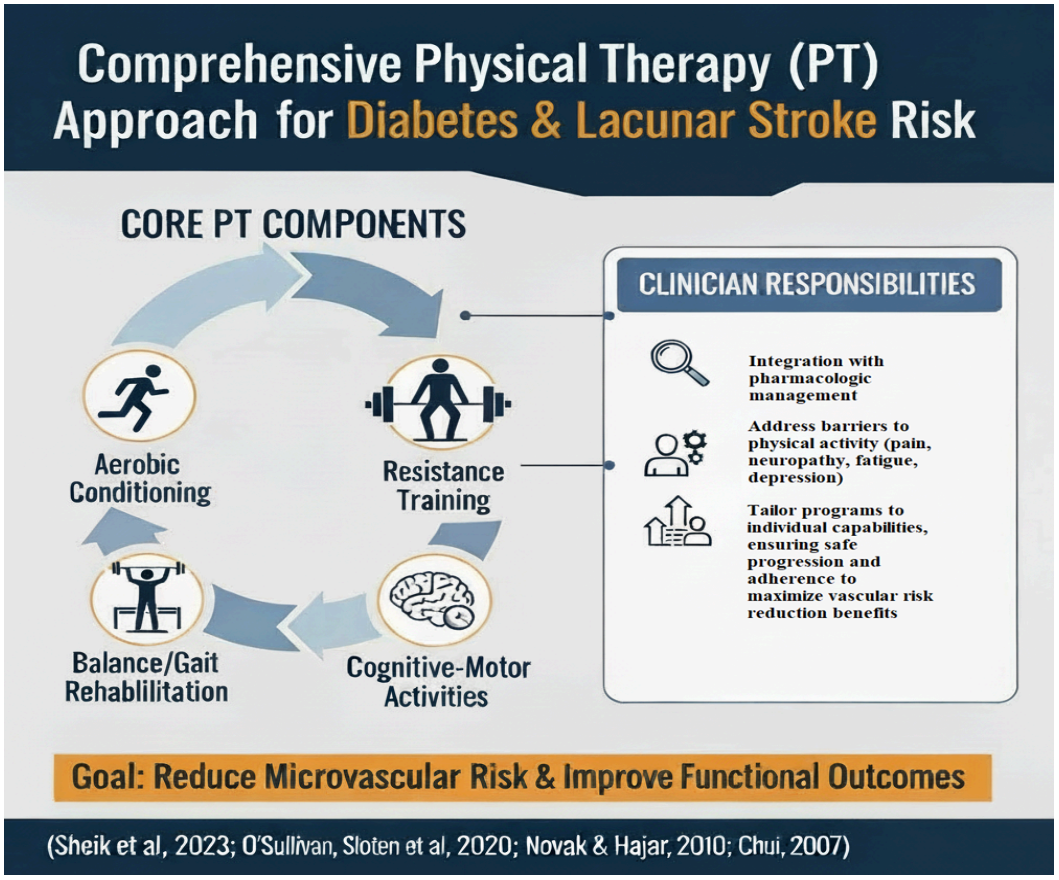

Figure 4. Practical clinical implications of Physical Therapy

10. Brief Synthesis on Clinical Prediction Across Domains Based on AI Integration

The discussion regarding biomarkers and the role of AI in multimodal data integration for VCID, includes: imaging, plasma biomarkers, and cognitive assessments (Swartz et al., 2025). AI-driven brain age estimation and brain age gap (BAG) analyses link DM, stroke, and vascular burden to accelerated brain ageing. DM and stroke seem to correlate with greater BAG and with MRI-visible CSVD markers, supporting AI-based brain health metrics as potential predictors of cognitive outcomes in diabetes-associated cerebrovascular disease. BAG associates with stroke and DM, and also correlates with CSVD burden in a broader context in which these AI-derived biomarkers may refine risk stratification for diabetic patients at cerebrovascular risk (Marseglia et al., 2024).

Outcome prediction after minor or major cerebrovascular events in DM proposes AI models that integrate imaging markers of CSVD with clinical data to predict short-term outcomes (e.g., 90-day mRS) and overall prognosis in AIS/TIA cohorts. Diabetes-specific subgroup data are still limited; however, these AI approaches are directly translatable to DM populations given higher a priori risk. CSVD markers also predict short-term outcomes after minor cerebrovascular events, therefore the same approach can be adapted to diabetic cohorts where CSVD burden is higher (Chen et al., 2020).

Biomarkers also act as guided risk stratification, especially blood-based biomarkers (e.g., albumin-to-globulin ratio, adipokines), which have been explored as modulators of stroke risk and vascular pathology. Furthermore, AI-enabled integration with imaging and clinical data could enhance risk stratification in DM but still requires prospective validation (Fu et al., 2025; Chlorogiannis, D. D. et al., 2021). More supporting evidence comes in the form of Apparent Glycation Ratio (AGR) and stenosis associations, as well as adipokines, which indicate vascular inflammation and atherosclerosis relevance. Combining these biomarkers with AI models seems to

improve diabetes-related risk characterization in the long run (Fu et al., 2025; Chlorogiannis, D. D. et al., 2021).

AI may also show a promising prospective in carotid plaque and lesion characterisation, as carotid plaque imaging with AI-based analysis improves risk prediction for cerebrovascular events, an important consideration in DM, where atherosclerosis is prevalent. AI-aided plaque assessment (volume, inflammation, rupture indicators) complements luminal stenosis assessment, with potential diabetes-specific implications given higher metabolic risk (Saba et al., 2019; Chlorogiannis, D. D. et al., 2021). AI-enabled carotid plaque characterisation links adipokines to carotid stenosis severity, and together suggest that AI-augmented plaque phenotyping could refine stroke risk as we understand it in DM (Saba et al., 2019; Chlorogiannis, D. D. et al., 2021).

In spite of all that, although many AI models show strong performance in training datasets, they face generalisability concerns across populations with different DM prevalence, glycaemic control, and comorbidities. External validation in diverse diabetic cohorts is needed to ensure performance in real-world diabetes care settings (Nur et al., 2025; Hu et al., 2024; Chen et al., 2020). Effective AI-CDSS require seamless integration with electronic health records, imaging repositories, and ophthalmic data (retina/OCT). Standardising data formats and imaging protocols across centers is also essential for reliable model deployment in diabetes populations (Li et al., 2024; Medina et al., 2025; Chlorogiannis et al., 2023). More consideration should address regulatory clearance, clinician trust, interpretability, and ethical considerations, particularly when AI-based tools influence treatment decisions for stroke prevention in DM (Khalafi et al., 2025; Li et al., 2024; Chlorogiannis et al., 2023).

While many AI tools are capable of leveraging DM as a risk factor, granular diabetes-related vascular pathophysiology (e.g., microvascular retinal- or neurovascular coupling alterations, glycaemic variability impacts on CSVD) requires targeted modelling that explicitly accounts for glycaemic metrics and DM duration/severity in predictive features (Khalafi et al., 2025; Marseglia et al., 2024; Chen, 2025).

Practical implications for research and clinical practice altogether include multimodal AI models with DM as a covariate or cohort stratifier. This involves combining retinal imaging, MRI/CT vascular imaging, CSVD markers, and laboratory data (AGR, adipokines, inflammatory markers), in order to build robust risk prediction and prognostic models tailored to diabetes populations. Retinal imaging itself, as a scalable screening tool, is to be considered here. Given DM the high microvascular burden, AI-enhanced retinal imaging could serve as a noninvasive screen to identify individuals at elevated cerebrovascular risk, enabling targeted neuroimaging and preventive strategies (Khalafi et al., 2025).

AI-driven triage and decision support in stroke management would definitely be useful for stroke triage, collateral assessment, and outcome prediction, especially in diabetic patients who may present with complex vascular phenotypes. Large pragmatic trials of AI-CDSS in stroke care will inform adoption in diabetes contexts (Deshpande et al., 2023; Li et al., 2024).

Future investments in AI methods should aim to quantify CSVD burden and brain ageing markers in diabetic cohorts, with outcome validation on cognition and functional status to address VCID risk (Hu et al., 2024; Swartz et al., 2025; Marseglia et al., 2024).

11. Conclusions

DM significantly amplifies the risk and burden of microvascular cerebral pathology, with lacunar strokes serving as a prominent clinical manifestation of small vessel disease in this population. The interplay between chronic hyperglycaemia, insulin resistance, endothelial dysfunction, and traditional vascular risk factors (particularly hypertension and dyslipidaemia) drives the progression of cerebral small vessel disease and the development of lacunar infarcts. While classical inherited thrombophilia mutations appear to have a limited and inconsistent association with lacunar stroke risk in diabetic adults, their role in specific subgroups remains an area for future research.

Diagnostic approaches for young diabetic patients with cerebral white matter lesions should remain broad, utilising comprehensive clinical, imaging, and laboratory assessments to distinguish between primary demyelinating syndromes and vascular or infectious mimics. DM does not fundamentally influence the differential diagnosis, but necessitates heightened vigilance for overlapping pathologies. This is particularly important because therapeutic management in patients with diabetes and lacunar stroke centres on effective vascular and metabolic risk factor modification, with beneficial effects from new classes of medication. This provides the context for physiotherapy and structured lifestyle interventions, which continue to play an important role in both rehabilitation and reduction of microvascular risk.

Ongoing research is still needed to refine risk stratification, and especially to elucidate the contribution of thrombophilia in diabetic lacunar stroke, since the differential diagnosis is often difficult and misleading in this category of young patients. This will facilitate the optimisation of both pharmacological and non-pharmacological specific interventions, since multi- and interdisciplinary, individualised care remains essential to improve outcomes in this complex patient population.

The latest data indicate a rapidly evolving landscape where AI and computational modelling are increasingly applied to diabetes-associated cerebrovascular disease through three converging streams:

- imaging-based AI (neuroimaging and ophthalmic imaging) for risk stratification and outcome prediction;
- stroke triage and management, leading to standardising care;
- biomarker-integrated, multimodal AI frameworks. This concept combines imaging with serum markers and clinical data to refine risk assessment and prognostication.

While promising, all these advancements require diabetes-specific validation across diverse populations, robust integration with electronic health records, and careful consideration of regulatory and ethical issues before widespread clinical deployment.

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