



REVIEW ARTICLE

Small Vessel Cerebrovascular Disease and Covert Cerebral Infarcts

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Abstract

This article summarises current research findings and expert consensus about the treatment of patients in whom covert cerebral vascular disease is identified - a common incidental finding on CT head scans which can often lead to questions about clinical management and whether new medications should be started.

Research methodology: This is a review article.

Results: The evidence available suggests benefit from controlling blood pressure and cholesterol within current clinical guidelines but does not support routine use of antiplatelets. There is little specific research in this area so much guidance is extrapolated and further research is needed to guide decision making in this large patient group.

Keywords

Covert cerebral vascular disease, Small vessel disease, Covert cortical infarcts

Introduction

Many patients have CT head scans done for a variety of reasons such as head injury or confusion. The most common incidental finding in on CT head scans is small vessel disease and covert cerebral vascular disease and when these are found a decision on whether treatment should be started needs to be made.

Small vessel Cerebrovascular disease covers a range of conditions which can be picked up on brain imaging including white matter hyperintensities, lacunes, microhaemorrhages and enlarged periventricular

spaces [1]. It is caused by disease of the small vessels which perforate the brain and leads to 25% of ischaemic strokes and most haemorrhagic strokes in older patients [2]. Small vessel disease also causes vascular cognitive impairment and dementia, gait and balance problems and mood disorders. It can be seen in mixed dementia and types of dementia which are not vascular [2].

The basic pathology of small vessel disease is lipohyalinosis- in essence there is concentric hyaline thickening of the cerebral small blood vessels with loss of the elastic lamina of the vessel walls. This leads to their occlusion which in turn leads to microinfarcts as they are end arteries, it can also cause rupture causing microbleeds. The small vessels of the brain are the perforators which arise from the proximal middle cerebral arteries, posterior cerebral arteries and the brain stem perforators of the vertebral and basilar arteries. Lacunar infarcts may be caused by small vessel disease or atheromatous clots from the larger vessels they branch off from. The exact cause of lipohyalinosis is not known, as it is not atherosclerotic as in the majority of larger vessel disease different treatment approaches need to be considered [3,4].

Small vessel disease prevalence and severity increase with age. If symptoms are not evident it is described as covert, although patients and doctors may not recognise cognitive changes due to small vessel disease which is why it is no longer known as "silent" - there may be effects which have not been diagnosed and there is no



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diagnostic guideline on when effects become clinical and not covert. The same presentation could receive a different diagnosis in two different patients. Small vessel disease increases the risk of stroke, dementia and death and increased burden of disease increases the likelihood of these complications [5].

Method

Covert small vessel disease is a large and complex area covering different pathology and contributing to multiple clinical outcomes (stroke, dementia, cognitive impairment, death, mood disorders) so it is difficult to find all relevant studies and assess how interventions may affect different outcomes. The ESO (European Stroke Organisation) covert cerebral small vessel disease guidelines reviewed all available evidence up to December 2020 and gave recommendations based on this and expert opinions, I have summarised these findings below. Generally evidence was poor - many of the studies were small in size and the length of follow-up was variable and few studies were specifically done in this area.

Results

Blood pressure control

The INFINITY trial [6] is the most relevant evidence regarding blood pressure control. Patients in the intervention group had blood pressure controlled to < 130 mmHg and the control group to < 145 mmHg. This was measured over 3 years and the only difference in outcome identified was a reduction in major non-fatal cardiac events. Some reduction in white matter hyperintensity accumulation was seen but this did not lead to a noticeable clinical benefit though it is possible this may have been seen over a longer time period. There was no reduction in cognitive decline or mobility problems but there was also no increase in falls, presyncope or syncope in the intervention group. Exclusion criteria included those with dementia or a clinically impaired gait so this would exclude a significant amount of elderly frail patients.

The ACCORD trial [7] looked at controlling blood pressure to < 120 mmHg and this did show a greater rate of adverse events in the intervention group. This was not confirmed in participants of the SPRINT trial [8] aged over 75 with the same blood pressure control - serious adverse events did not reach clinical significance although there were increased rates of complications such as syncope and acute kidney injury. A previous review and meta-analysis of blood pressure and dementia showed a complex relationship with blood pressure control at different points in life having different effects on risk, but antihypertensives did seem to reduce risks [9].

Overall although there is no direct evidence of benefit, blood pressure control to less than < 140 mmHg

is recommended by the ESO guideline group.

Antiplatelet agents

Theoretically patients with small vessel disease would benefit from antiplatelets due to their high risk of stroke however they are also at higher risk of intracerebral bleeds and so this treatment is not without risk. The Silence study [10] was a small longitudinal study comparing aspirin with no antiplatelet treatment. Results did not reach significance but less Cerebrovascular events were seen in the treatment group and there was no increase in adverse events. Importantly in this trial microbleeds was an exclusion criteria and all participants were < 73-years-old.

The SPS3 randomised control trial looked at dual antiplatelets versus single antiplatelets in reducing risk of recurrent stroke or cognitive impairment following symptomatic lacunar stroke. They used 75 mg clopidogrel and 325 mg aspirin together in the treatment arm and there was no reduction in stroke risk but there was a significant difference in major haemorrhage and all cause mortality and the intervention arm was stopped early due to increased mortality.

The ASPREE trial [11] showed harm from aspirin in primary prevention in older patients (but did not show an increased bleeding risk - excess mortality was associated with malignancy) and no significant benefit in preventing cardiovascular events. (100 mg aspirin daily was used in patients aged over 70). Although these are larger doses of antiplatelet than typically used in the UK the lack of efficacy at higher doses is important to note.

Vascular dysfunction in small vessel disease may not be thrombotic in nature so in patients with no clear other indication for antiplatelet therapy, it should not be recommended for small vessel disease alone on current evidence. Ongoing trials are looking at this further and weaker antiplatelet agents such as cilostazol may have a role to play in future [12].

Lipid lowering therapy

Lipid lowering therapy is provided largely by statins. A study on rosuvastatin [13] looked at rosuvastatin versus placebo and found a significant reduction in both radiological small vessel disease progression and incidental stroke. Average cholesterol from this was just over 5 mmol/L at baseline and age was over 75 years in a Chinese population. The Mayo clinic aging study [14] was a cohort study which looked at the neuroimaging of those on statins for at least 5 years and those not on statins and this showed no significant difference in radiological outcomes.

There is a lack of evidence of clinical benefit with statin treatment but given their few side effects, their benefits in primary prevention of cardiovascular disease and the limited evidence of reduction of radiological small vessel disease, they should be considered in

patients with small vessel disease.

Lifestyle modification

There are few studies looking at lifestyle modifications to reduce small vessel disease. There is evidence that physical exercise can reduce dementia and slight evidence that it reduces covert small vessel disease radiologically [15]. There was no evidence of increased harm. There was no direct evidence of any other lifestyle modifications being significant but there were very few trials and promoting a healthy lifestyle should be standard advice in these patients including healthy eating, stopping smoking and exercise.

Glucose lowering therapies

Glucose lowering therapies in diabetics had no specific trial in this area and there is a mixed picture about how much diabetic control is associated with amount of covert small vessel disease. As the MIND trial [16] showed increased mortality with strict glucose control, diabetic patients should be managed as per normal guidelines.

Anti-dementia medications

It has been suggested that anti-dementia drugs could play a role in preventing small vessel disease by theoretically preventing other routes of vascular dysfunction however there are no direct studies in covert small vessel disease and studies done have shown a small effect at most in vascular cognitive impairment, so there is no role for this therapy at present [17].

Discussion

Covert infarcts can also be strokes effecting larger blood vessels rather than small vessel disease. In population studies 90% of covert strokes are lacunar infarcts (subcortical, 3-15 mm) while 10% are larger subcortical or cortical infarcts [18]. The Rotterdam scan study [19] showed that covert infarcts lead to a significantly increased risk of subsequent ischaemic stroke especially if more than one infarct was present on the scan. Given that covert cortical infarcts represent larger vessel disease (as opposed to white matter hyperintensities and other radiological findings in small vessel disease) whether or not they present clinically, they should be considered for treatment with the same secondary prevention as an overt cerebral infarct (stroke) which presents with clear neurology. However the risk to benefit ratio of antiplatelets is unclear in covert lacunar infarcts, where the pathology is not so clear.

In summary covert infarcts and small vessel disease have a high prevalence in the population and increase risk of stroke, lead to cognitive impairment, gait and mood problems. There is little direct evidence in this area as much of the evidence is taken from subgroups of larger studies and so the recommendations are largely

based on known risk of harm and extrapolation from less direct evidence. Overall controlling blood pressure and cholesterol within suggested clinical guidelines and encouraging healthy lifestyles are suggested, but given the lack of evidence of benefit in primary prevention and the risk of harm, antiplatelets are not recommended purely for small vessel disease. In larger covert cortical or subcortical cerebral infarcts, the decision is less clear and should be made in conjunction with the patient as a shared decision.

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References

1. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, et al. (2013) Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 12: 822-838.
2. Pasi M, Cordonnier C (2020) Clinical relevance of cerebral small vessel diseases. *Stroke* 51: 47-53.
3. Brainin M, Heiss W (2019) Textbook of stroke medicine. (3rd edn), Cambridge: Cambridge University Press, UK.
4. Pendlebury S, Giles M, Rothwell P (2009) Transient ischemic attack and stroke: Diagnosis, investigation and management. Cambridge: Cambridge University Press, UK.
5. Dettle S, Schilling S, Duperron MG, Larsson SC, Markus HS, et al. (2019) Clinical significance of magnetic resonance imaging markers of vascular brain injury: A systematic review and meta-analysis. *JAMA Neurol* 76: 81-94.
6. White WB, Wakefield DB, Moscufo N, Guttmann CRG, Kaplan RF, et al. (2019) Effects of intensive versus standard ambulatory blood pressure control on cerebrovascular outcomes in older people (INFINITY). *Circulation* 140: 1626-1635.
7. Cushman WC, Evans GW, Byington RP, Goff Jr DC, Grimm Jr RH, et al. (2010) Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 362: 1575-1585.
8. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, et al. (2016) Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥ 75 years: A randomized clinical trial. *JAMA* 315: 2673-2682.
9. Ou YN, Tan CC, Shen XN, Xu W, Hou XH, et al. (2020) Blood pressure and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 209 prospective studies. *Hypertension* 76: 217-225.
10. Maestrini I, Altieri M, Di Clemente L, Vicenzini E, Pantano P, et al. (2018) Longitudinal study on low-dose aspirin versus placebo administration in silent brain infarcts: The

- silence study. *Stroke Res Treat* 2018: 7532403.
11. McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, et al. (2018) Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med* 379: 1509-1518.
 12. McHutchison C, Blair GW, Appleton JP, Chappell FM, Doubal F, et al. (2020) Cilostazol for secondary prevention of stroke and cognitive decline: Systematic review and meta-analysis. *Stroke* 51: 2374-2385.
 13. Guo Y, Li Y, Liu X, Cui Y, Zhao Y, et al. (2020) Assessing the effectiveness of statin therapy for alleviating cerebral small vessel disease progression in people \geq 75 years of age. *BMC Geriatr* 20: 292.
 14. Ramanan VK, Przybelski SA, Graff-Radford J, Castillo AM, Lowe VJ, et al. (2018) Statins and brain health: Alzheimer's disease and Cerebrovascular disease biomarkers in older adults. *J Alzheimer's Dis* 65: 1345-1352.
 15. Landman TR, Thijssen DH, Tuladhar AM, Leeuw FE de, et al. (2021) Relation between physical activity and cerebral small vessel disease: A nine-year prospective cohort study. *Int J Stroke* 16: 962-971.
 16. Launer LJ, Miller ME, Williamson JD, Lazar RM, Gerstein HC, et al. (2011) Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): A randomised open-label substudy. *Lancet Neurol* 10: 969-977.
 17. Battle CE, Abdul-Rahim AH, Shenkin SD, Hewitt J, Quinn TJ, et al. (2019) Cholinesterase inhibitors for vascular dementia and other vascular cognitive impairments: A network meta-analysis. *Cochrane Datab Syst Rev* 2: CD013306.
 18. Smith EE, Saposnik G, Biessels GJ, Doubal FN, Fornage M, et al. (2017) Prevention of stroke in patients with silent cerebrovascular disease: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 48: e44-e71.
 19. Vermeer SE, van Dijk EJ, Koudstaal PJ, Oudkerk M, Hofman A, et al. (2002) Homocysteine, silent brain infarcts, and white matter lesions: The rotterdam scan study. *Ann Neurol* 51: 285-289.