

Is There Equipose Regarding the Optimal Medical Treatment of Patients with Asymptomatic White Matter Hyperintensities?

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Background: White matter hyperintensity (WMH) is a common manifestation of chronic ischemic microvascular disease that heralds greater risk of functional disability, stroke, and dementia. SPRINT MIND recently reported that intensive blood pressure reduction resulted in lower rates of mild cognitive impairment and WMH progression, suggesting that medical interventions could have a measurable impact on WMH. We conducted an anonymous survey of providers in the NINDS StrokeNet to better understand neurologist attitudes about asymptomatic WMH. *Methods:* We sent a 7-question survey to the 29 Regional Coordinating Centers of the StrokeNet, whose coordinators disseminated the survey to providers “involved in the care of a patient after their stroke.” *Results:* We received 136 responses. For stroke prevention therapies, including aspirin and statin therapy and blood pressure target, there was substantial equipose, with no single option receiving >50% endorsement and between 15-32% of respondents choosing the option of “not sure.” 83% of respondents indicated high or moderate enthusiasm for a trial targeting this patient population. The clinical outcomes of reduction in ischemic stroke, cognitive impairment, or dementia were high importance (>70% endorsement), while the remaining radiographic, safety, and clinical endpoints all failed to reach 50% endorsement. *Conclusions:* Our survey establishes meaningful neurologist attitudes that can inform future WMH research. There is considerable equipose regarding optimal medical treatment for patients with asymptomatic WMH and providers in StrokeNet, who would be a vital stakeholder in WMH research in the United States, enthusiastically support a clinical trial to resolve open questions on optimal medical management.

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Introduction

White matter hyperintensity (WMH) on magnetic resonance imaging, also called leukoaraiosis, is a common manifestation of chronic ischemic microvascular disease. For asymptomatic patients, WMH heralds greater risk of long-term functional disability related to cognitive impairment and dementia, stroke, gait instability, and falls.¹⁻³ The cognitive manifestations of WMH were first described by the Swiss neurologist Otto Binswanger in the late 19th century, shortly thereafter expanded upon by Alois Alzheimer's histopathological description in 1902 of diffuse loss of cerebral white matter myelin and axons accompanied by gliosis and atrophy.⁴ Alzheimer proposed the name Binswanger's Disease. The terms WMH and leukoaraiosis entered the medical lexicon in the late 1980s, when advanced neuroimaging allowed their identification

and correlation with a multitude of clinical manifestations, medical sequelae, and risk factors such as hypertension and dyslipidemia.^{5,6} The number of publications on WMH, leukoaraiosis, and Binswanger's disease has increased exponentially in the last decade as the focus transitioned from epidemiologic to interventional research. Aggressive control of hypertension, the best established WMH risk factor apart from age, was recently shown to reduce WMH progression in both the ACCORD MIND and SPRINT MIND cohorts.^{7,8} Other vascular risk factors, including dyslipidemia, smoking, diabetes, and sedentary lifestyle, have been associated with WMH.^{1,6,9,10} In patients without a history of cardiovascular disease, the guideline recommendations for these risk factors are well established (Table 1).¹¹ However, the ideal blood pressure target and other potential interventions such as statin therapy and aspirin have not been fully investigated in patients with moderate to severe WMH, a group under-represented in prior trials but highly relevant to clinical practice. Thus, we attempted to gather input from stroke clinicians on their current practice in the management of asymptomatic patients with moderate to severe WMH.

Methods

We conducted a survey of the providers in the NINDS StrokeNet to better understand current medical treatment for patients with asymptomatic WMH and enthusiasm for a clinical trial in this patient population. We sent a

Table 1. Potential risk factors for WMH and current American Heart Association recommendations for primary prevention

Risk factor	AHA goal
Blood pressure	<140/90 for all, <130/80 if higher cardiovascular risk
Cholesterol	Statin for all patients with LDL \geq 190 and all patients with diabetes regardless of LDL. More complex risk assessment for others
Diabetes	In addition to the prescription of type 2 diabetes mellitus interventions, a tailored nutrition plan focusing on a heart-healthy dietary pattern is recommended to improve glycemic control, achieve weight loss if needed, and improve other risk factors
Smoking	Abstinence
Diet	A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended
Sedentary lifestyle	Adults should engage in at least 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity

7-question survey to the 29 Regional Coordinating Centers of the StrokeNet, whose coordinators disseminated the survey to providers "involved in the care of a patient after their stroke." We do not know how many providers the survey was distributed to and, thus, cannot know the response rate. This anonymous survey was exempt from Institutional Review Board regulation given the inherently minimal risk. The survey, titled "Neurologist Attitudes About White Matter Hyperintensities," was hosted on a secure website and accessible for one month. Questions 1-4 had an associated reference case with a moderate WMH burden and were designed to gauge practice patterns for patients with asymptomatic WMH (Table 1). Questions 5-7 probed issues relevant to the approach and feasibility of conducting clinical research on this patient population. Results are presented as the number and percentage of respondents for each question response.

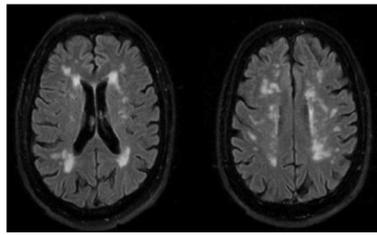
Results

We received 136 responses. A majority (64%) indicated that our reference case would meet their definition of primary stroke prevention. Regarding specific stroke prevention therapies, including aspirin and statin therapy and blood pressure target, there was substantial equipoise in regard to treatment, with no single option receiving more than 50% endorsement and between 15% and 32% of respondents choosing the option of "not sure." (Table 2) Providers reported that their current practices encounter a moderate volume of patients with at least a mild WMH burden and no history of stroke. Respondents noted significant enthusiasm for a trial targeting this patient population with 83% of respondents indicating high or moderate enthusiasm. Respondents ranked the clinical outcomes of reduction in ischemic stroke and development of cognitive impairment or dementia as high importance (>70% endorsement), while the remaining radiographic, safety, and clinical endpoints all failed to reach 50% endorsement as high importance (Table 3).

Discussion

Our survey establishes meaningful practice patterns and attitudes that can inform future WMH research. The first is that there is considerable equipoise regarding what constitutes optimal medical treatment for patients with asymptomatic WMH. The second is that providers in StrokeNet, who would be a vital stakeholder in WMH research in the United States, routinely encounter such patients in practice and enthusiastically support a clinical trial to resolve open questions on optimal medical management. However, a weakness of our study is that the respondents were limited to neurologists, who have a vested interest in trials targeting stroke or vascular dementia. Additional research focusing on primary care providers would provide a more comprehensive understanding of enthusiasm for clinical research in this patient

Table 2. Survey questions 1-4 with reference case



72-year-old female with hypertension is referred for a neurological evaluation of episodic vertigo. The patient has no history of clinical stroke, cognitive impairment, or other neurologic disease. Her PCP obtained an MRI (shown on left), which is significant for a moderate burden of chronic microvascular disease. By the time the patient is seen in neurology clinic her episodic vertigo has resolved, but she has questions about the MRI findings.

Question	Response 1	% (n)	Response 2	% (n)	Response 3	% (n)
Q1. Would you consider this a case of primary or secondary stroke prevention?	<i>Primary stroke prevention</i>	64 (87)	<i>Secondary stroke prevention</i>	25 (34)	<i>Not sure</i>	11 (15)
Q2. Does this patient have a neurologic indication for aspirin?	<i>Yes</i>	46 (62)	<i>No</i>	22 (30)	<i>Not sure</i>	32 (44)
Q3. What would your systolic blood pressure goal be for this patient?	<i><140 mm Hg</i>	27 (36)	<i><130 mm Hg</i>	46 (62)	<i><120 mm Hg</i>	27 (37)
Q4. The patient has an LDL of 95. Would you recommend statin therapy?	<i>Yes</i>	43 (57)	<i>No</i>	43 (57)	<i>Not sure</i>	15 (20)

Table 3. Survey questions 5-7

Question	Response 1	% (n)	Response 2	% (n)	Response 3	% (n)	Response 4	% (n)		
Q5. How many patients a month with at least a mild burden of white matter hyperintensity and no history of stroke do you see in your inpatient and outpatient practice?	<i>0/month</i>	7 (9)	<i>1-3/month</i>	47 (61)	<i>4-8/month</i>	27 (35)	<i>>8/month</i>	19 (25)		
Q6. Please indicate your enthusiasm for a clinical trial that enrolled patients similar to our example and evaluated the efficacy of aggressive risk factor control and/or aspirin?	<i>High enthusiasm</i>	46 (61)	<i>Moderate enthusiasm</i>	37 (49)	<i>Low Enthusiasm</i>	13 (17)	<i>No enthusiasm</i>	5 (7)		
Q7. Relying on your experience treating patients similar to our example, how important would the following outcomes be for patients with asymptomatic white matter hyperintensities in a trial of aggressive risk factor control and/or aspirin?										
Q7 sub-question			Not important	% (n)	Low importance	% (n)	Medium importance	% (n)	High importance	% (n)
Reduction of ischemic stroke risk			1 (1)		3 (4)		21 (28)		75 (101)	
Reduction of mild cognitive impairment/dementia			1 (1)		3 (4)		25 (33)		72 (96)	
Increase in intracerebral hemorrhage			1 (1)		17 (23)		34 (45)		48 (63)	
Reduction of development of gait imbalance			1 (2)		20 (27)		46 (61)		33 (44)	
Increase in cerebral microbleeds on MRI			4 (5)		32 (43)		37 (50)		27 (36)	
Reduction of white matter hyperintensity progression			8 (11)		28 (37)		44 (59)		20 (27)	

population from all shareholder perspectives. There are additional weaknesses, including that we do not know the response rate for our survey and were not able to explore the reasons for respondents' opinions.

With the recently published results of SPRINT MIND, showing that intensive blood pressure reduction resulted in lower rates of mild cognitive impairment and WMH progression,^{8,12} there is renewed interest in clinical trials with multimodal interventions that would seek to either reduce WMH progression or the risk of clinical endpoints such as dementia or stroke.¹³ Such a trial would require collaboration between stroke neurologists, cognitive neurologists, and primary care providers in neurology, internal medicine and family practice. There will be additional complexity to a trial of patients with WMH, including the different mechanisms that result in WMH, from poorly controlled hypertension to a myriad of genetic abnormalities.^{14,15} The sample size for a trial targeting the outcomes of stroke or dementia would be large, so it may be possible to a priori stratify patients by age or do genetic testing of a subset of patients, to better understand the effect of the intervention. However, despite the substantial commitment from caregivers, patients, and a funding agency that such a trial would require, the time to do so is now, given that WMH is highly prevalent in over half of adults over the age of 70.¹⁶⁻¹⁸ With widespread population ageing in the developed world, the burden of stroke and dementia requires novel risk reduction approaches, and targeting WMH progression could be one of the most important interventions.

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Disclosures

None.

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