

AHA/ASA Scientific Statement

Scientific Statement on Prevention of Stroke in Patients with Silent Cerebrovascular Disease

A Statement for Healthcare Professionals from the AHA/ASA

*The American Academy of Neurology affirms the value of this statement
as an educational tool for neurologists.*



American Heart Association | American Stroke Association®

science is why

Writing Group Members

Eric E. Smith, MD, MPH, Chair;
Gustavo Saposnik, MD, MSc, Vice-Chair;
Geert Jan Biessels, MD, PhD;
Fergus N. Doubal, MRCP, PhD;
Myriam Fornage, PhD; Philip B. Gorelick, MD, MPH;
Steven M. Greenberg, MD, PhD;
Randall T. Higashida, MD; Scott E. Kasner, MD;
Sudha Seshadri, MD

on behalf of the American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Functional Genomics and Translational Biology; and Council on Hypertension Council,

Citation

Smith EE, Saposnik G, Biessels GJ, Doubal FN, Fornage M, Gorelick PB, Greenberg SM, Higashida RT, Kasner SE, Seshadri S; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Functional Genomics and Translational Biology; and Council on Hypertension. [Prevention of stroke in patients with silent cerebrovascular disease: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association](#) [published online ahead of print December 15, 2016]. *Stroke*. doi: 10.1161/STR.0000000000000116.

Slides Prepared by Members of the Stroke Professional Education Committee

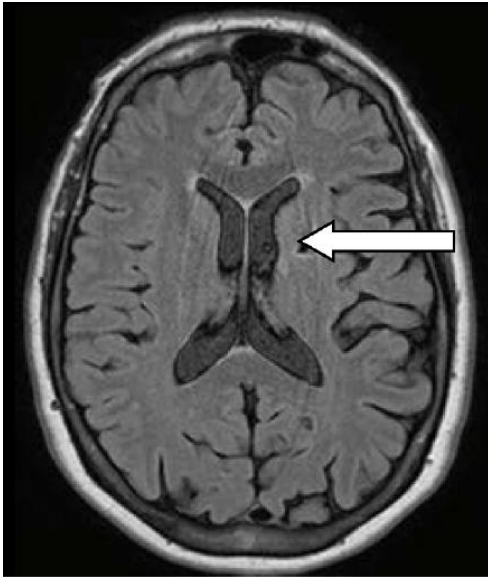
Michael T. Mullen, MD MS
Assistant Professor
Department of Neurology
Perelman School of Medicine,
University of Pennsylvania

Outline

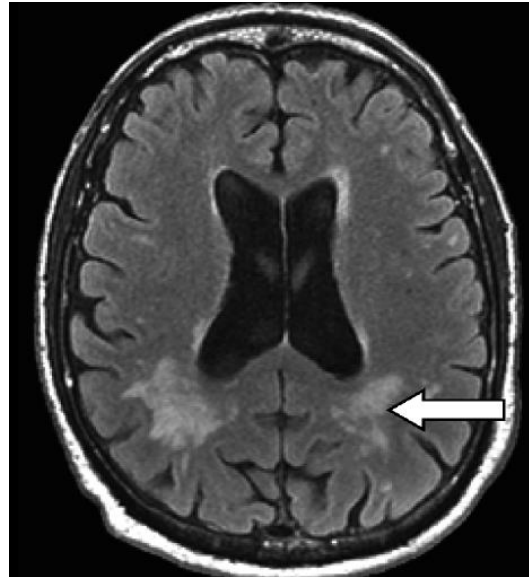
- I. Introduction
- II. Diagnosis of silent cerebrovascular disease by imaging
- III. Prevalence of silent cerebrovascular disease
- IV. Investigations for patients with silent cerebrovascular disease
- V. Prevention of symptomatic stroke in patients with silent infarcts
- VI. Prevention of symptomatic stroke in patients with white matter hyperintensities (WMH) of presumed vascular origin
- VII. Safety of anticoagulation in patients with silent cerebral microbleeds
- VIII. Safety of thrombolysis and reperfusion therapy in patients with silent cerebral microbleeds
- IX. Population screening for silent cerebrovascular disease
- X. Conclusion

I. Introduction

Silent Infarct



White Matter Hyperintensity



Microbleed

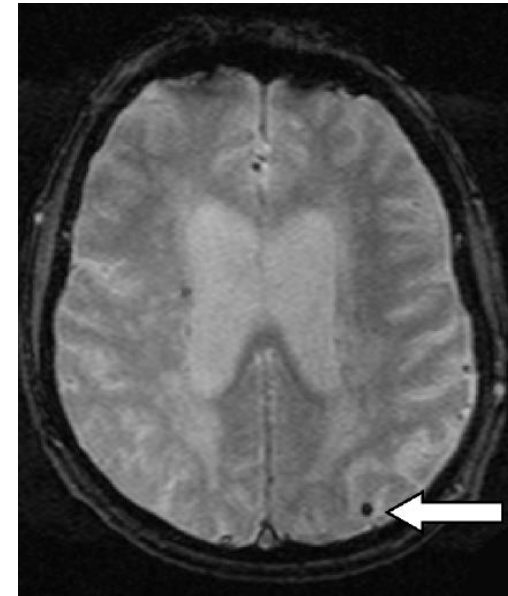


Figure 1. Left, Silent brain infarct (**arrow**) on magnetic resonance imaging (MRI) fluid-attenuated inversion recovery (FLAIR) scan. Middle, White matter hyperintensity of presumed vascular origin on MRI FLAIR. Right, Microbleed (**arrow**) on MRI T2*-weighted gradient-recalled echo sequence. See the Diagnosis of Silent Cerebrovascular Disease by Neuroimaging section for radiological terms and definitions.

I. Introduction

“**Silent**” Cerebrovascular disease is:

- Detected on neuroimaging without overt clinical symptoms
- Commonly found, particularly in older adults
- Associated with subtle cognitive and motor deficits
- Associated with increased risk of cognitive impairment and stroke

II. Diagnosis of silent cerebrovascular Disease

- MRI is more sensitive than CT for detection
- Optimal MRI examination should include:
 - DWI/ADC
 - FLAIR
 - T2
 - T1
 - SWI or GRE
 - Slice thickness $\leq 5\text{mm}$ and ideally $\leq 3\text{mm}$
 - 3T field strength preferred
 - Brain coils should be used

II. Diagnosis of silent cerebrovascular Disease

Silent Brain Infarcts

- Subcortical Lesions (80-90% of lesions)
 - CT
 - ▣ Hypodensity with similar attenuation as CSF
 - MRI
 - ▣ Focal, irregularly shaped with **tissue destruction** and **central cavitation**
 - ▣ T1 hypointense gliotic changes
 - ▣ T2 hyperintense
 - ▣ Flair: often central hypointensity with irregular rim of T2 signal

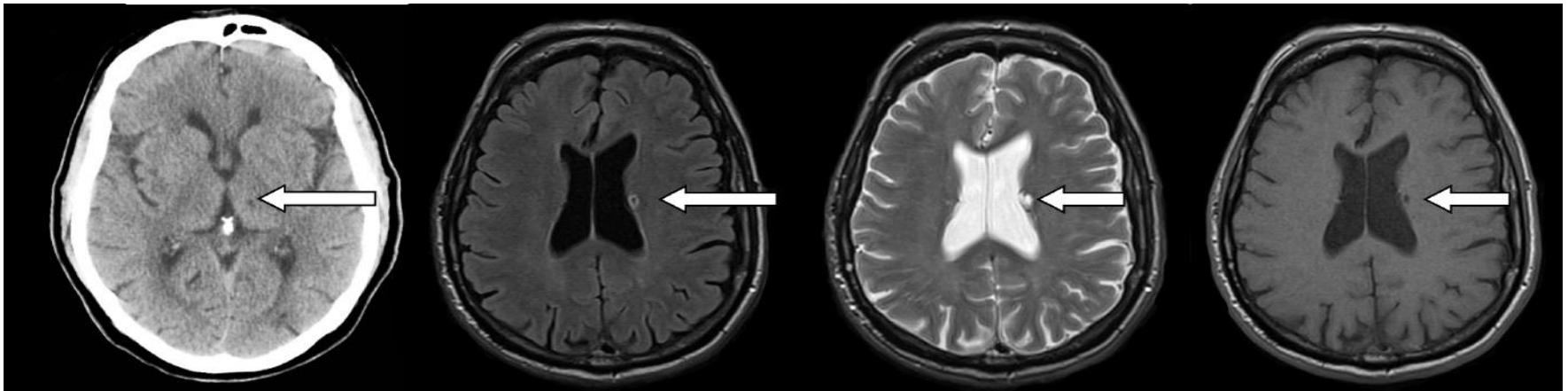


Figure 2. A small (4-mm) subcortical silent brain infarct is visible as a hypodensity in the left thalamus on computed tomography (A). On magnetic resonance imaging (different patient), a 4-mm subcortical silent brain infarct (**arrow**) is visible on fluid-attenuated inversion recovery (FLAIR; B), T2-weighted (C), and T1-weighted (D) sequences, illustrating typical imaging features of small subcortical (lacunar) infarction. On FLAIR, the lesion exhibits central hypointensity with a surround rim of hyperintensity, reflecting gliosis. (This peri-infarct hyperintensity may sometimes be absent.) The infarct exhibits hyperintensity on T2-weighted and hypointensity on T1-weighted images, similar to the signal from cerebrospinal fluid, indicating central cavitation

II. Diagnosis of silent cerebrovascular Disease

Silent Brain Infarcts

- Cortical Lesions (10-20%)
 - CT
 - ▣ Hypodensity with similar attenuation as CSF
 - MRI
 - ▣ T1 hypointense
 - ▣ T2 hyperintense
 - ▣ Atrophy may be present

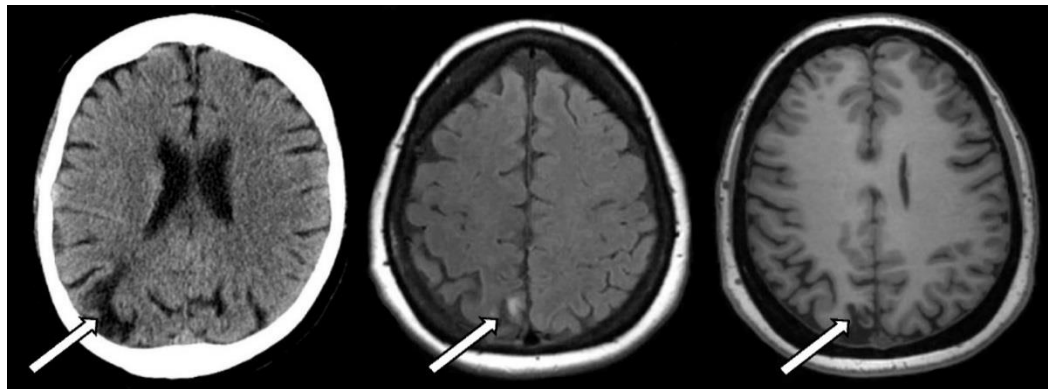


Figure 4. Cortical silent brain infarct. On computed tomography (A), a silent cortical infarct is visible in the right parietal lobe (arrow). On magnetic resonance imaging (different patient), a silent cortical infarct (arrow) is visible as a small region of T2 hyperintensity on the fluid attenuated inversion recovery image (B) in the right parietal cortex and adjacent subcortical white matter. On T1-weighted inversion-recovery spoiled gradient recalled echo imaging (C), the infarct appears hypointense, interrupting the cortical ribbon.

II. Diagnosis of silent cerebrovascular Disease

White Matter Lesions

- CT: hypodense
- MRI
 - ▣ T1 iso- or hypointense (but not as dark as CSF)
 - ▣ T2 hyperintense
 - ▣ **NO cavitation**
- Often called leukoaraiosis, white matter changes, small vessel ischemic disease
- Preferred terms:
 - ▣ White matter hyperintensity of vascular origin (MRI)
 - ▣ White matter hypointensity of vascular origin (CT)

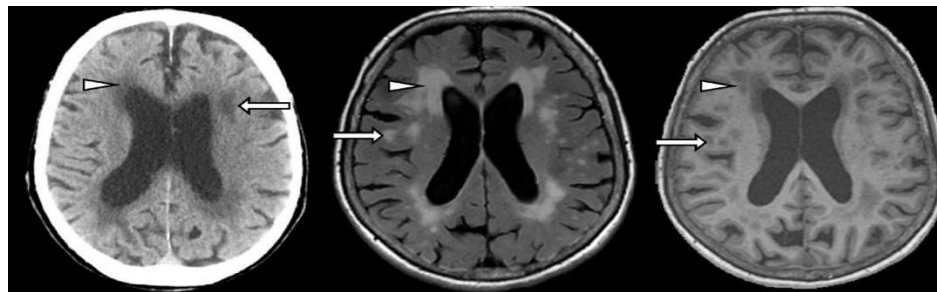


Figure 5. White matter lesions of presumed vascular origin. Extensive periventricular (**arrowhead**) and subcortical (**arrow**) white matter signal abnormalities are seen on computed tomography (CT; **A**) and magnetic resonance imaging (MRI; **B** and **C**). On CT (**A**), the abnormalities appear as white matter hypodensities. On MRI, the abnormalities appear as white matter hyperintensity (WMH) on T2-weighted sequences, including fluid-attenuated inversion recovery (**B**). On T1-weighted inversion-recovery spoiled gradient-recalled echo (**C**), some of the WMH appears mildly to moderately hypointense but without the very hypointense cerebrospinal fluid–like signal indicative of cavitation.

II. Diagnosis of silent cerebrovascular Disease

White Matter Lesions

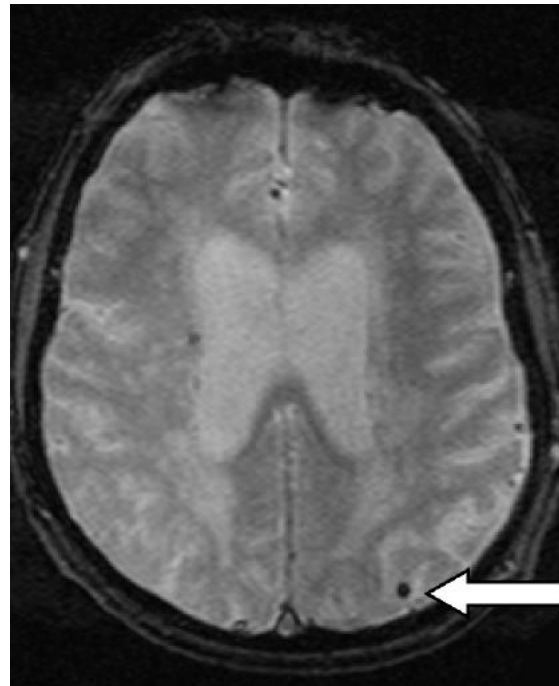
- Extent varies widely
- Fazekas Scale: a simple, visual grading system
 - ▣ Deep white matter Grading:
 - 0 = Absent
 - 1 = Punctate
 - 2 = Beginning confluent
 - 3 = Large confluent areas

[See Figure 6 in article. Fazekas visual rating scale for magnetic resonance imaging white matter hyperintensities \(WMHs\).](#) Periventricular WMH is graded as follows: 0=absence, 1=caps or pencil-thin lining, 2=smooth halo, and 3=irregular periventricular WMH extending into the deep white matter. Separately, deep (subcortical) WMH is graded as follows: 0=absence, 1=punctuate foci, 2=beginning confluence of foci, and 3=large confluent areas.

II. Diagnosis of silent cerebrovascular Disease

Microbleeds

- Only visible on MRI
 - ▣ 5-10mm, round, area of signal loss on susceptibility weighted images
 - ▣ Blooming effect: signal loss is > size of lesion
 - ▣ Important mimics to consider: calcium deposits, vessels in cross section



Microbleed (**arrow**) on MRI T2*-weighted gradient-recalled echo sequence. See the Diagnosis of Silent Cerebrovascular Disease by Neuroimaging section for radiological terms and definitions.

II. Diagnosis of silent cerebrovascular Disease

Suggestions and Considerations for Clinical Practice

MRI is preferred to CT because of greater sensitivity

Silent brain infarcts, white matter hyperintensities, and microbleeds should be reported when seen

Standard terms and definitions for clinical reporting should be used for cerebral small vessel disease (STRIVE Standards)

WMH should be reported using a standard scale, such as the Fazekas scale.

II. Diagnosis of silent cerebrovascular Disease

Areas for Further Investigation

Quantify the benefit of MRI imaging versus CT

Quantify effect of MRI field strength, resolution, scan parameters on detection

Determine sensitivity, specificity, reliability of reporting in clinical practice

Investigate advanced MRI techniques that may inform associations between silent brain infarctions and clinically relevant outcomes such as cognitive impairment, gait impairment, and mood (perfusion, vascular reactivity, white matter connectivity, atrophy, other).

III. Prevalence of silent cerebrovascular disease

Silent Infarcts

- Prevalence ranges from 8-31%
- Increases with age, prior vascular disease/risk factors, smoking

White Matter Hyperintensities

- Strongly age dependent
 - 11-21% in populations with average age 64
 - 94% in population with average age 82

Microbleeds

- 5-21% of general population, 30-40% with ischemic stroke, 60-68% of patients with primary ICH
- Strongly age dependent

III. Prevalence of silent cerebrovascular disease

Suggestions and Considerations for Clinical Practice

Silent CVD will be frequently encountered as an incidental finding on MRI and CT in older adults

Implications for clinical care are discussed later in this presentation

III. Prevalence of silent cerebrovascular disease

Areas for Further Investigation

More prevalence data are needed in younger population and from non-North American and non-European countries.

A standardized assessment method for WMH is needed, to allow for pooling data from existing cohorts

IV. Investigations for patients with silent cerebrovascular disease

- Clinical evaluation for causes of silent cerebrovascular disease seems reasonable
- There is however little evidence to support or guide this approach
- Recommendations are presented recognizing this uncertainty

IV. Investigations for patients with silent cerebrovascular disease

Silent Brain infarction

- Assess common vascular risk factors
 - Hypertension, diabetes, hyperlipidemia, smoking, physical activity, diet
- Assess for atrial fibrillation by pulse assessment followed by ECG if indicated
- Consider non-invasive carotid imaging if in correct territory
- Consider prolonged cardiac rhythm monitoring and echocardiogram if embolic pattern
 - Cortical or large subcortical (>15mm)

IV. Investigations for patients with silent cerebrovascular disease

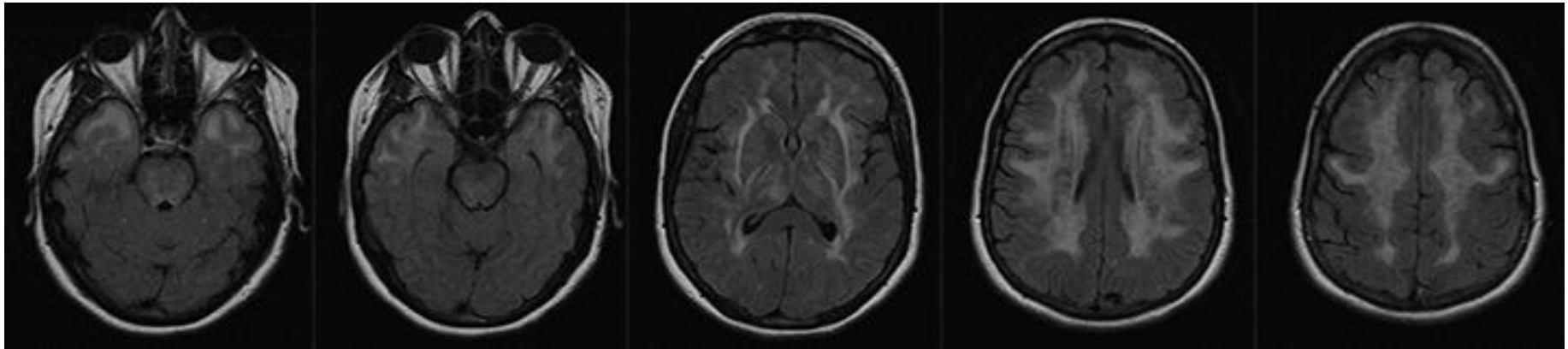
White Matter Hyperintensities

- Consider evaluation if WMH excessive for age
 - Typically Fazekas 2 or 3
- Assess common vascular risk factors
 - Hypertension, diabetes, hyperlipidemia, smoking, physical activity, diet
- Assess for atrial fibrillation by pulse assessment followed by ECG if indicated
- Carotid ultrasound, echocardiography, extended telemetry are probably **NOT** necessary

IV. Investigations for patients with silent cerebrovascular disease

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

- Rare, genetic cause of extensive WMH
- Typically symptomatic but may be detected prior to onset
- Autosomal dominant, so usually strong family history
- Clinical triad: migraines, early onset stroke and dementia
- MRI: extensive WMH with involvement of the **anterior temporal lobe** and **external capsule**.
- Consider specialist referral and/or genetic testing only in patients with appropriate phenotype



Images courtesy Michael Mullen MD, personal collection

IV. Investigations for patients with silent cerebrovascular disease

Microbleeds

- Two patterns:
 - Deep: most likely from hypertension
 - Lobar: consider Cerebral Amyloid Angiopathy (CAA)
- Assess common risk factors for ICH: **HYPERTENSION**
- Consider further imaging for vascular malformation, tumor, etc. when silent hemorrhages **>10mm** identified

IV. Investigations for patients with silent cerebrovascular disease

Microbleeds & CAA

- Lobar >> Deep microbleeds may be suggestive of CAA
- Boston Criteria validated for diagnosis of CAA in patients with **symptomatic** lobar ICH
- Utility of Boston Criteria in patients with microbleeds but no prior symptomatic ICH is uncertain.

Boston Criteria for CAA

| Definite CAA |
|---|
| Full postmortem with: Lobar, cortical, or corticosubcortical hemorrhage Severe CAA with vasculopathy No other cause |
| Probable CAA w/pathology |
| Clinical data and pathologic tissue (evacuated hematoma or biopsy) with: Lobar, cortical, or corticosubcortical hemorrhage Some degree of CAA in specimen No other cause |
| Probable CAA |
| Clinical data and MRI or CT with: Multiple hemorrhages (lobar, cortical, or corticosubcortical) Age ≥ 55 No other cause |
| Possible CAA |
| Clinical data and MRI or CT with: Single lobar, cortical, or corticosubcortical hemorrhage Age ≥ 55 No other cause |

IV. Investigations for patients with silent cerebrovascular disease

Areas for Further Investigation

Causes and pathophysiology of silent CVD, particularly for WMH

Diagnostic yield & cost effectiveness of investigations for causes of silent cerebrovascular disease

Benefit of aggressive risk factors modification in this population

V. Prevention of symptomatic stroke in patients with silent infarcts

Silent Brain Infarcts

- Increased risk of subsequent stroke
 - Hazard ratio 1.5 to 3.3
 - Risks is independent of vascular risk factors
 - More silent infarcts = higher risk
- If there is ipsilateral carotid stenosis
 - Non-lacunar silent infarct associated with higher risk
 - ▣ Risk is intermediate between asymptomatic and symptomatic stenosis
- If there is atrial fibrillation
 - Uncertain whether silent infarction is associated with higher risk

V. Prevention of symptomatic stroke in patients with silent infarcts

- No high level evidence to guide clinical practice
- Screen patients for clinically overt TIA/Stroke
 - If prior TIA/Stroke → Secondary prevention targets
 - If no prior TIA/Stroke → Primary prevention targets
- Although benefit not proven, may consider that these patients are at increased risk when making antithrombotic, statin, or carotid revascularization decisions

V. Prevention of symptomatic stroke in patients with silent infarcts

Suggestions and Considerations for Clinical Practice

Reasonable to follow primary prevention guidelines to prevent stroke in patient with silent infarcts who have NOT had a TIA or symptomatic stroke

Obtain a careful history of prior symptoms of TIA or stroke. When present secondary prevention guidelines should be followed

Silent brain infarction predicts increased risk of subsequent symptomatic stroke, independent of known vascular risk factors

Reasonable to consider increased risk of stroke when making treatment decisions, but unproven if this improves risk prediction compared to existing tools.

No clinical trial data to show whether the benefit of asymptomatic carotid revascularization differs in patients with or without silent brain infarction.

V. Prevention of symptomatic stroke in patients with silent infarcts

Areas for Further Investigation

Clinical trials of antithrombotic and other stroke prevention strategies in patients with silent brain infarction but no prior symptomatic stroke

Added value of silent brain infarcts for predicting risk of cardiovascular events in the general population.

VI. Prevention of symptomatic stroke in patients with vascular WMH

High burden of WMH associated with increased risk of symptomatic stroke

- Meta-analysis found Hazard Ratio 3.1 (95% CI 2.3-4.1)
- “High burden” not uniformly defined
 - No specific threshold
- Difficult to quantify risk for individual patients
- Insufficient evidence to regard WMH as equivalent to prior symptomatic stroke

VI. Prevention of symptomatic stroke in patients with vascular WMH

Evidence for vascular risk factor control is limited

- Blood pressure control may reduce WMH progression
- Conflicting data on utility of statins
- Aggressive glucose lowering associated with worsening WMH
- Antithrombotic therapy may increase risk intracerebral hemorrhage

VI. Prevention of symptomatic stroke in patients with vascular WMH

Suggestions and Considerations for Clinical Practice

Reasonable to follow primary prevention guidelines to prevent stroke in patient with vascular WMH

WMH alone, in the absence of other vascular risk factors is probably not sufficient to start antithrombotic therapy

Blood pressure lowering appears most promising for preventing progression of WMH, although clinical relevance is uncertain

VI. Prevention of symptomatic stroke in patients with vascular WMH

Areas for Further Investigation

Whether WMH confers added predictive utility compared to existing risk prediction rules.

The relationship between baseline WMH and incident stroke risk

RCTs of vascular risk reduction in patients with WMH

Clinical impact of reduced WMH progression on risk of stroke and cognitive impairment

VII. Safety of anticoagulation in patients with silent microbleeds

- Anticoagulation dramatically reduces the risk of stroke in atrial fibrillation
- Major risk of anticoagulation is intracranial hemorrhage
 - Annualized rate 0.47% with warfarin in population based studies
 - NOACs (dabigatran, apixaban, rivaroxaban, edoxaban) have lower risk (RR 0.48)
- **Key Clinical Questions:**
 - Do silent microbleeds confer an elevated risk of ICH?
 - Is this risk great enough to offset benefit of anticoagulation in a fib?

VII. Safety of anticoagulation in patients with silent microbleeds

- No direct evidence of effect of microbleeds on risks/benefits of anticoagulation
- Microbleeds associated with increased risk of both ICH and ischemic stroke in general population
- Risk likely varies based on number/etiology of microbleeds
 - Arteriosclerosis vs. CAA
- Decision analysis using Markov models **favor anticoagulation** under most circumstances.

VII. Safety of anticoagulation in patients with silent microbleeds

Suggestions and Considerations for Clinical Practice

It is reasonable to proceed with oral anticoagulation despite detection of microbleeds when anticoagulation is otherwise indicated for non-valvular atrial fibrillation (NVAF) according to existing primary or secondary prevention guidelines.

It is reasonable not to perform routine MRI screening for microbleeds in NVAF patients.

For NVAF patients in whom anticoagulation is indicated but who are considered at particularly high risk of future ICH based on microbleed number and location, it may be reasonable to administer dabigatran, rivaroxaban, apixaban, or edoxaban in preference to warfarin.

It may be reasonable to follow AHA/ASA primary stroke prevention guidelines in patients with microbleeds, although microbleeds alone are likely not sufficient for starting antiplatelet or statin medications.

VII. Safety of anticoagulation in patients with silent microbleeds

Areas for Further Investigation

Direct measurement of ICH risk among microbleed positive individuals treated with warfarin or NOACs.

Consider MRI sub-studies in current and future trials of oral anticoagulants to investigate whether microbleed positive subgroups, such as those with strictly lobar microbleeds, are at higher ICH risk.

VIII. Safety of thrombolysis & reperfusion in patients with silent microbleeds

- Intravenous thrombolysis and endovascular thrombectomy have proven benefit for acute ischemic stroke
- IV tPA:
 - Data are conflicting
 - May be an increased risk, but absolute difference is low
 - May not outweigh the known, strong benefit of tPA.
- Endovascular thrombectomy:
 - Insufficient data to assess association between microbleeds and ICH or outcome

VIII. Safety of thrombolysis & reperfusion in patients with silent microbleeds

Suggestions and Considerations for Clinical Practice

It is reasonable to administer systemic intravenous tPA in patients with one or more microbleeds

Clinicians should not withhold endovascular thrombectomy based on the presence of microbleeds in an otherwise eligible patient.

For patients with microbleeds and a large vessel occlusion who are eligible for tPA, withholding tPA and proceeding directly to thrombectomy is unproven.

VIII. Safety of thrombolysis & reperfusion in patients with silent microbleeds

Areas for Further Investigation

Determine whether clinical disability and mortality are different in patients with vs. without microbleeds treated with tPA and/or endovascular thrombectomy using observational studies and/or registries.

Further stratification of risk based on number and location of microbleeds.

IX. Population screening for silent cerebrovascular disease

- No prior studies addressing the utility of screening
- Progression of silent cerebrovascular disease is associated cognitive decline, but:
 - No established treatment to prevent progression
 - Absolute risk of subsequent stroke/dementia is low
 - Screening costs would be high
- For all the above reasons, screening is not recommended

IX. Population screening for silent cerebrovascular disease

Suggestions and Considerations for Clinical Practice

Screening for silent cerebrovascular disease is not warranted in asymptomatic persons.

Neuroimaging should be reserved for patients with clinical signs such as focal neurological symptoms or cognitive decline.

Areas for Further Investigation

Randomized clinical trials showing that silent cerebrovascular disease progression can be reduced and that this decreases the incidence of clinically meaningful outcomes, such as symptomatic stroke or cognitive decline.

X. Conclusion

- Silent cerebrovascular disease is a common problem of aging
- Silent infarcts and white matter hyperintensities are associated with increased risk of ischemic stroke
- Cerebral microbleeds are associated with an increased risk of both ischemic stroke and intracerebral hemorrhage
- Evidence for how to investigate or manage patients with silent cerebrovascular disease is lacking

X. Conclusion

Acknowledging current limitations in knowledge:

- Silent infarcts and WMH
 - Assess for traditional vascular risk factors
 - Treat according to primary prevention guidelines
- Microbleeds
 - Blood pressure control
 - ICH risk is NOT sufficient to outweigh benefits of anticoagulation in non-valvular atrial fibrillation
 - Treatment with IV tPA and endovascular thrombectomy should not be withheld in patients who are otherwise eligible



life is why™

es por la vida™

全為生命™