Stroke

AHA/ASA GUIDELINE

2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

A Guideline From the American Heart Association/American Stroke Association

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

Endorsed by the Society of Vascular and Interventional Neurology

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

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TOP 10 TAKE-HOME MESSAGES FOR THE SECONDARY STROKE PREVENTION GUIDELINE

1. Specific recommendations for prevention strategies often depend on the ischemic stroke/transient ischemic attack subtype. Therefore, new in this guideline is a section describing recommendations for the diagnostic workup after ischemic stroke, to define ischemic stroke etiology (when possible), and to identify targets for treatment in order to reduce the risk of recurrent ischemic stroke. Recommendations are now grouped by etiologic subtype.
2. Management of vascular risk factors remains extremely important in secondary stroke prevention, including (but not limited to) diabetes, smoking cessation, lipids, and especially hypertension. Intensive medical management, often performed by multidisciplinary teams, is usually best, with goals of therapy tailored to the individual patient.
3. Lifestyle factors, including healthy diet and physical activity, are important for preventing a second stroke. Low-salt and Mediterranean diets are recommended for stroke risk reduction. Patients with stroke are especially at risk for sedentary and prolonged sitting behaviors, and they should be encouraged to perform physical activity in a supervised and safe manner.
4. Changing patient behaviors such as diet, exercise, and medication compliance requires more than just simple advice or a brochure from their physician. Programs that use theoretical models of behavior change, proven techniques, and multidisciplinary support are needed.
5. Antithrombotic therapy, including antiplatelet or anticoagulant agents, is recommended for nearly all patients without contraindications. With very few exceptions, the combination of antiplatelets and anticoagulation is typically not indicated for secondary stroke prevention. Dual antiplatelet therapy is not recommended long term, and short term, dual

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antiplatelet therapy is recommended only in very specific patients, including those with early arriving minor stroke and high-risk transient ischemic attack or severe symptomatic intracranial stenosis.

6. Atrial fibrillation remains a common and high-risk condition for second ischemic stroke. Anticoagulation is usually recommended if the patient has no contraindications. Heart rhythm monitoring for occult atrial fibrillation is usually recommended if no other cause of stroke is discovered.
7. Extracranial carotid artery disease is an important and treatable cause of stroke. Patients with severe stenosis ipsilateral to a nondisabling stroke or transient ischemic attack who are candidates for intervention should have the stenosis fixed, likely relatively early after their ischemic stroke. The choice between carotid endarterectomy and carotid artery stenting should be driven by specific patient comorbidities and features of their vascular anatomy.
8. Patients with severe intracranial stenosis in the vascular territory of ischemic stroke or transient ischemic attack should not receive angioplasty and stenting as a first-line therapy for preventing recurrence. Aggressive medical management of risk factors and short-term dual antiplatelet therapy are preferred.
9. Several studies have evaluated secondary stroke prevention of patent foramen ovale closure since the previous guideline in 2014. It is now considered reasonable to close patent foramen ovale percutaneously in selected patients: those with younger age with nonlacunar stroke or no other cause at any age.
10. Patients with embolic stroke of uncertain source should not be treated empirically with anticoagulants or ticagrelor because it was found to be of no benefit.

PREAMBLE

Since 1990, the American Heart Association (AHA)/American Stroke Association (ASA)* have translated scientific evidence into clinical practice guidelines with recommendations to improve cerebrovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cerebrovascular care. The AHA/ASA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts.

Clinical practice guidelines for stroke provide recommendations applicable to patients with or at risk of developing cerebrovascular disease. The focus is on medical practice in the United States, but many aspects are relevant to patients throughout the world. Although it must be acknowledged that guidelines may be used to inform regulatory or payer decisions, the core intent is to improve quality of care and to align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment; furthermore, the recommendations set forth should be considered in the context of individual patient values, preferences, and associated conditions.

The AHA/ASA strive to ensure that guideline writing groups contain requisite expertise and are representative of the broader medical community by selecting experts from a broad array of backgrounds, representing different sexes, races, ethnicities, intellectual perspectives, geographic regions, and scopes of clinical practice and by inviting organizations and professional societies with related interests and expertise to participate as endorsers. The AHA/ASA have rigorous policies and methods for development of guidelines that limit bias and prevent improper influence. The complete policy on relationships with industry and other entities can be found at https://professional.heart.org/-/media/phd-files/guidelines-and-statements/policies-devolopment/aha-asa-disclosure-rwi-policy-5118.pdf?la=en.

Beginning in 2017, numerous modifications to the guidelines have been implemented to make guidelines shorter and to enhance "user friendliness." Guidelines are written and presented in a modular knowledge chunk format, in which each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text, and, when appropriate, flow diagrams or additional tables. Hyperlinked references are provided for each modular knowledge chunk to facilitate quick access and review. Other modifications to the guidelines include the addition of Knowledge Gaps and Future Research segments in some sections and a web guideline supplement (Data Supplement) for useful but noncritical tables and figures.

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1. INTRODUCTION

Each year, ≈795 000 individuals in the United States experience a stroke, of which 87% (690 000) are ischemic and 185 000 are recurrent.[1] Approximately 240 000 individuals experience a transient ischemic attack (TIA) each year.[2] The risk of recurrent stroke or TIA is high but can be mitigated with appropriate secondary stroke

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prevention. In fact, cohort studies have shown a reduction in recurrent stroke and TIA rates in recent years as secondary stroke prevention strategies have improved.[3,4] A meta-analysis of randomized controlled trials (RCTs) of secondary stroke prevention therapies published from 1960 to 2009 showed a reduction in annual stroke recurrence from 8.7% in the 1960s to 5.0% in the 2000s, with the reduction driven largely by improved blood pressure (BP) control and use of antiplatelet therapy.[5] The changes may have been influenced by changes in diagnostic criteria and differing sensitivities of diagnostic tests over the years.

The overwhelming majority of strokes can be prevented through BP control, a healthy diet, regular physical activity, and smoking cessation. In fact, 5 factors—BP, diet, physical inactivity, smoking, and abdominal obesity—accounted for 82% and 90% of the population-attributable risk (PAR) for ischemic and hemorrhagic stroke in the INTERSTROKE study (Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries).[5a] Similarly, the Global Burden of Disease Study showed that 90.5% (95% uncertainty interval, 88.5–92.2) of the global burden of stroke was attributable to modifiable risk factors.[6] A modeling study showed that targeting multiple risk factors has additive benefits for secondary prevention; specifically, aspirin, statin, and antihypertensive medications, combined with diet modification and exercise, can result in an 80% cumulative risk reduction in recurrent vascular events.[7] Although the benefits of a healthy lifestyle and vascular risk factor control are well documented,[8,9] risk factors remain poorly controlled among stroke survivors.[10–14]

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1.1. Methodology and Evidence Review

This guideline provides a comprehensive yet succinct compilation of practical guidance for the secondary prevention of ischemic stroke or TIA (ie, prevention of ischemic stroke or TIA in individuals with a history of stroke or TIA). We aim to promote optimal dissemination of information by using concise language and formatting. The recommendations listed in this guideline are, whenever possible, evidence based and supported by an extensive evidence review. A search for literature derived from research involving human subjects, published in English, and indexed in MEDLINE, PubMed, Cochrane Library, and other selected databases relevant to this guideline was conducted between July 2019 and February 2020. Additional trials published between February and June 2020 that affected the guideline recommendations were also included. For specific search terms used, please see the Data Supplement, which also contains the final evidence tables that summarize the evidence used by the guideline writing group to formulate recommendations. References selected and published in the present document are representative and not all inclusive.

An independent Evidence Review Committee was commissioned to perform a formal systematic review of a critical clinical question (Table 1) related to secondary stroke prevention, the results of which were considered by the writing group for incorporation into the present guideline. Concurrently with this process, writing group members evaluated study data relevant to the rest of the guideline. The results of these evidence reviews were evaluated by the writing group for incorporation into the present guideline.

Each topic area was assigned a primary author and a primary, and sometimes secondary, reviewer. Author assignments were based on the areas of expertise of the members of the writing group members and their lack of any relationships with industry related to the section material. All recommendations were fully reviewed and discussed among the full committee to allow diverse perspectives and considerations for this guideline. Recommendations were then voted on to reach consensus. The systematic review has been published in conjunction with this guideline and includes its respective data supplements.[15]

1.2. Organization of the Writing Group

The writing group consisted of neurologists, neurological surgeons, cardiologists, internists, and a lay/patient representative. The writing group included representatives from the AHA/ASA and the American Academy of Neurology. Appendix 1 lists writing group members' relevant relationships with industry and other entities. For the purposes of full transparency, the writing group members' comprehensive disclosure information is available online.

1.3. Document Review and Approval

This document was reviewed by the AHA's Stroke Council Scientific Statement Oversight Committee; the AHA's Science Advisory and Coordinating Committee; the AHA's Executive Committee; reviewers from the American Academy of Neurology, from the Society of Vascular and Interventional Neurology, and from the American Association of Neurological Surgeons and Congress of Neurological Surgeons; as well as by 55 individual content reviewers. The individual reviewers' relationships with industry information is available in Appendix 2.

This document was approved for publication by the governing bodies of the ASA and the AHA. It was reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons, was endorsed by the Society of Vascular and Interventional Neurology, and the American Academy of Neurology affirmed the value of the guideline.

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Table 1. Evidence Review Committee Question

Question No.	Question	Section No.
1	In patients with an ischemic stroke or TIA, what are the benefits and risks of DAPT compared to single antiplatelet therapy within 5 y for prevention of recurrent stroke?	5.19

DAPT indicates dual antiplatelet therapy; and TIA, transient ischemic attack.

1.4. Scope of the Guideline

The aim of the present guideline is to provide clinicians with evidence-based recommendations for the prevention of future stroke among survivors of ischemic stroke or TIA. It should be noted that this guideline does not cover the following topics, which have been addressed elsewhere:

- Acute management decisions (covered in the "2019 Update to the 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke"[16]),
- Intracerebral hemorrhage (ICH; covered in the "Guidelines for the Management of Spontaneous Intracerebral Hemorrhage"[17]),
- Primary prevention (covered in the "Guidelines for the Primary Prevention of Stroke"[18] and "2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease"[19]),
- Special considerations for stroke prevention in women (covered in the "Guidelines for the Prevention of Stroke in Women"[20]), and
- Cerebral venous sinus thrombosis (covered in "Diagnosis and Management of Cerebral Venous Thrombosis"[22]).

In general, with very few exceptions, the literature supports the concept that patients with TIA and those with ischemic stroke should be treated the same in terms of secondary prevention.

This guideline is divided into 4 sections:

1. Diagnostic Evaluation for Secondary Stroke Prevention
2. Vascular Risk Factor Management
3. Management by Etiology
4. Systems of Care for Secondary Ischemic Stroke Prevention.

The structure and scope of this guideline differ from those of the 2014 Guidelines for the prevention of stroke in patients with stroke and TIA[9] in several ways. First, the current guideline reflects numerous innovations and modifications that were incorporated into the AHA clinical practice guideline format. Introduced in 2017, modifications to AHA guidelines included making the text shorter and more user friendly; focusing guidelines on recommendations and patient management flow diagrams and less on extensive text and background information; formatting guidelines so that they can be easily updated with guideline focused updates; and including "chunks" of information after each recommendation.[23] Second, the Diagnostic Evaluation and Systems of Care for Secondary Prevention sections are new. The Diagnostic Evaluation for Secondary Stroke Prevention section focuses on the evidence base for laboratory and imaging studies for guiding secondary stroke prevention decisions. Often these tests are completed in the inpatient setting. The Systems of Care for Secondary Prevention section contains 3 subsections: (1) Health Systems–Based Interventions for Secondary Stroke Prevention, (2) Interventions Aimed at Changing Patient Behavior, and (3) Health Equity. The Health Equity subsection is a refocus of the 2014 guideline's section guiding management of high-risk populations. Third, this guideline does not include a separate section on metabolic syndrome because there are no unique recommendations for metabolic syndrome aside from managing each of the individual components of the syndrome. Fourth, the section on alcohol use was expanded to include the use of other substances. Finally, several additional conditions were included in the Management by Etiology section: congenital heart disease, cardiac tumors, moyamoya disease, migraine, malignancy, vasculitis, other genetic disorders, carotid web, fibromuscular dysplasia, dolichoectasia, and embolic stroke of undetermined source (ESUS).

In developing the 2021 secondary stroke prevention guideline, the writing group reviewed prior published AHA/ASA guidelines and scientific statements. Table 2 contains a list of these other guidelines and statements deemed pertinent to this writing effort and is intended for use as a reader resource, thus reducing the need to repeat existing guideline recommendations.

1.5. Class of Recommendation and Level of Evidence

Recommendations are designated both a Class of Recommendation (COR) and a Level of Evidence (LOE). The COR indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The LOE rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 3).

Numerous studies have evaluated strategies for stroke prevention in individuals without a history of stroke/TIA (ie, primary prevention studies) or included individuals with a history of stroke/TIA mixed into the pools of patients studied in smaller numbers. After carefully reviewing the literature and discussing with AHA methodologists, the writing group decided that many of these prevention strategies were important to include

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Table 2. Associated AHA/ASA Guidelines and Statements

Title	Organization	Publication year
AHA/ASA guidelines		
Guidelines for Carotid Endarterectomy[24]	AHA/ASA	1998
Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease[25]	ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS	2011
Guideline on Lifestyle Management to Reduce Cardiovascular Risk[26]	AHA/ACC	2013
Guideline for the Management of Overweight and Obesity in Adults[27]	AHA/ACC/TOS	2013
Guideline for the Management of Patients With Atrial Fibrillation[28]	AHA/ACC/HRS	2014
Guidelines for the Management of Spontaneous Intracerebral Hemorrhage[17]	AHA/ASA	2014
Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack[9]	AHA/ASA	2014
Guidelines for the Prevention of Stroke in Women[20]	AHA/ASA	2014
Guidelines for the Primary Prevention of Stroke[18]	AHA/ASA	2014
Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults[29]	ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA	2017
Guideline for the Management of Adults With Congenital Heart Disease[30]	AHA/ACC	2018
Guideline on the Management of Blood Cholesterol[31]	AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA	2018
Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke[16]	AHA/ASA	2019
Guideline on the Primary Prevention of Cardiovascular Disease[19]	ACC/AHA	2019
Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation[32]	AHA/ACC/HRS	2019
Guideline for the Management of Patients With Valvular Heart Disease[33]	ACC/AHA	2020
AHA/ASA statements		
Diagnosis and Management of Cerebral Venous Thrombosis[22]	AHA/ASA	2011
Cervical Arterial Dissections and Association With Cervical Manipulative Therapy[21]	AHA/ASA	2014
Physical Activity and Exercise Recommendations for Stroke Survivors[34]	AHA/ASA	2014
Spontaneous Coronary Artery Dissection: Current State of the Science[34a]	AHA/ASA	2018
AHA/ASA presidential advisory		
Defining Optimal Brain Health in Adults[35]	AHA/ASA	2017

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AANN, American Association of Neuroscience Nurses; AANS, American Association of Neurological Surgeons; AAPA, American Academy of Physician Assistants; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACPM, American College of Preventive Medicine; ACR, American College of Radiology; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; ASA, American Stroke Association; APhA, American Pharmacists Association; ASH, American Society of Hypertension; ASNR, American Society of Neuroradiology; ASPC, American Society for Preventive Cardiology; CNS, Congress of Neurological Surgeons; HRS, Heart Rhythm Society; NLA, National Lipid Association; NMA, National Medical Association; PCNA, Preventive Cardiovascular Nurses Association; SAIP, Society of Atherosclerosis Imaging and Prevention; SCAI, Society for Cardiovascular Angiography and Interventions; SIR, Society of Interventional Radiology; SNIS, Society of NeuroInterventional Surgery; SVM, Society for Vascular Medicine; SVS, Society for Vascular Surgery; and TOS, The Obesity Society.

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in any guideline on the prevention of recurrent stroke. There is often no reason to think that the mechanism of stroke prevention and benefits would be different in primary versus secondary prevention, although not studied within a purely secondary stroke prevention trial. Therefore, this writing group occasionally includes recommendations with evidence based in the primary prevention of atherosclerotic cardiovascular disease (ASCVD), atherosclerosis, or combined end points of cardiac disease and stroke in this guideline.

To acknowledge that some studies were not performed in a purely ischemic stroke population, the LOE was downgraded. In this way, the writing group agreed that this would provide the best and most complete recommendations to the clinician about important strategies for secondary stroke prevention. Principles guiding inclusion and extrapolation of the results of these studies were as follows:

1. The quality of the trial/trials was acceptable. (Ideally, stroke or TIA occurrence or recurrence was a prespecified end point, with clear protocols for assessing stroke end points.)
2. From a physiological perspective, the primary prevention strategy used in the study will likely be effective for secondary prevention.
3. Patients with ischemic stroke were included in the population studied when possible.

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1.6. Abbreviations

Abbreviation	Meaning/Phrase
ACC	American College of Cardiology
ACS	acute coronary syndrome
ACTIVE W	Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events
AF	atrial fibrillation
AHA	American Heart Association
AHI	apnea-hypopnea index
ARCH	Aortic Arch Related Cerebral Hazard Trial
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
ASA	American Stroke Association
ASAP	Addressing Sleep Apnea Post Stroke/TIA
ASTRO-APS	Apixaban for Secondary Prevention of Thromboembolism Among Patients With Antiphospholipid Syndrome
ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
BP	blood pressure
BUST-Stroke	Breaking Up Sitting Time After Stroke
CADISS	Cervical Artery Dissection in Stroke Study
CARDIA	Coronary Artery Risk Development in Young Adults
CAP	Continued Access Registry
CAPRIE	Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events
CAS	carotid artery stenting
CATHARSIS	Cilostazol-Aspirin Therapy Against Recurrent Stroke With Intracranial Artery Stenosis
CEA	carotid endarterectomy
CHANCE	Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events
CICAS	Chinese Intracranial Atherosclerosis
CLAIR	Clopidogrel Plus Aspirin for Infarction Reduction
CLOSE	Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence
CNS	central nervous system
COMMANDER HF	A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
COR	Class of Recommendation
COSS	Carotid Occlusion Surgery Study
CPAP	continuous positive airway pressure
CREST	Carotid Revascularization Endarterectomy versus Stenting Trial
CSPS	Cilostazol for Prevention of Secondary Stroke
CT	computed tomography
CTA	computed tomographic angiography
CVD	cardiovascular disease
DAPT	dual antiplatelet therapy
DASH	Dietary Approaches to Stop Hypertension
DCCT	Diabetes Control and Complication Trial
DESERVE	Discharge Educational Strategies for Reduction of Vascular Events
DHA	docosahexaenoic acid
DiRECT	Diabetes Remission Clinical Trial
DOAC	direct-acting oral anticoagulant
ECST	European Carotid Surgery Trial
EF	ejection fraction
ENGAGE AF-TIMI 48	Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation
EPA	eicosapentaenoic acid
EPIC-CVD	European Prospective Investigation into Cancer and Nutrition-CVD case-cohort study
ESH-CHL-SHOT	European Society of Hypertension and Chinese Hypertension League Stroke in Hypertension Optimal Treatment Trial
ESPRIT	European/Australasian Stroke Prevention in Reversible Ischaemia Trial
ESPS2	Second European Stroke Prevention Study
ESUS	embolic stroke of undetermined source
ExStroke	Physical Exercise After Acute Ischaemic Stroke
FASTEST	Efficacy and Safety of a TIA/Stroke Electronic Support Tool
FMD	fibromuscular dysplasia
FOURIER	Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk
GELIA	German Experience With Low Intensity Anticoagulation
GLP-1	glucagon-like protein 1
HbA1c	hemoglobin A_{1c}
HR	hazard ratio
ICA	internal carotid artery
ICARUSS	Integrated Care for the Reduction of Secondary Stroke
ICAS	intracranial atherosclerotic stenosis
ICH	intracerebral hemorrhage
IE	infective endocarditis
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
INR	international normalized ratio
INSPiRE-TMS	Intensified Secondary Prevention Intending a Reduction of Recurrent Events in TIA and Minor Stroke Patients
IPE	icosapent ethyl
IRIS	Insulin Resistance Intervention After Stroke
JAM	Japan Adult Moyamoya
JELIS	Japan EPA Lipid Intervention Study
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LOE	Level of Evidence
LV	left ventricular
LVAD	left ventricular assist devices
MACE	major adverse cardiovascular event
MD	mean difference
MI	myocardial infarction
MIST	Motivational Interviewing in Stroke
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NAILED Stroke	Nurse Based Age Independent Intervention to Limit Evolution of Disease After Stroke

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Abbreviation	Meaning/Phrase
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NAVIGATE ESUS	Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source
NIHSS	National Institutes of Health Stroke Scale
ODYSSEY OUTCOMES	Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab
OMEMI	Omega-3 Fatty Acids in Elderly Patients With Acute Myocardial Infarction
OR	odds ratio
OSA	obstructive sleep apnea
OXVASC	Oxford Vascular Study
PAR	population-attributable risk
PAST-BP	Prevention After Stroke–Blood Pressure
PCSK9	proprotein convertase subtilisin/kexin type 9
PFO	patent foramen ovale
PODCAST	Prevention of Decline in Cognition after Stroke Trial
POINT	Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke
PRAISE	Prevent Recurrence of All Inner-City Strokes Through Education
PREDIMED	Prevención con Dieta Mediterránea
PREVAIL	Prospective Randomised Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy
PREVENTION	Preventing Recurrent Vascular Events in Patients With Stroke or Transient Ischemic Attack
PRoFESS	Prevention Regimen for Effectively Avoiding Second Strokes
PROTECT AF	Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation
PTAS	percutaneous transluminal angioplasty and stenting
RCT	randomized controlled trial
RE-ALIGN	Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients After Heart Valve Replacement
RE-LY	Randomized Evaluation of Long-Term Anticoagulant Therapy
REDUCE-IT	Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke Study
RESPECT	Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment
RESPECT ESUS	Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source
RISE-UP	Recovery in Stroke Using PAP
ROCKET AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
RR	relative risk
SAMMPRIS	Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis
SAPPHIRE	Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy

Abbreviation	Meaning/Phrase
SAPT	single antiplatelet therapy
SAVE	Sleep Apnea Cardiovascular Endpoints
SBP	systolic blood pressure
SCD	sickle cell disease
SIT	Silent Cerebral Infarct Transfusion multi-center clinical trial
Sleep SMART	Sleep for Stroke Management and Recovery Trial
SMART	Second Manifestations of Arterial Disease
SOCRATES	Soluble Guanylate Cyclase Stimulator in Heart Failure Studies
SPAF	Stroke Prevention in Atrial Fibrillation Study
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
SPS3	Secondary Prevention of Small Subcortical Strokes
STANDFIRM	Shared Team Approach Between Nurses and Doctors for Improved Risk Factor Management for Stroke Patients
STOP	Stroke Prevention Trial in Sickle Cell Anemia
SUCCEED	Secondary Stroke Prevention by Uniting Community and Chronic Care Model Teams Early to End Disparities
SUSTAIN	Systemic Use of Stroke Averting Interventions
STRENGTH	Outcomes Study to Assess Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia
SWiTCH	Stroke With Transfusions Changing to Hydroxyurea
TARDIS	Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke
T2D	type 2 diabetes
TCAR	transcarotid artery revascularization
TCD	transcranial Doppler
TEE	transesophageal echocardiography
THALES	Acute Stroke or Transient Ischaemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death
TIA	transient ischemic attack
TOSS	Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis
TST	Treat Stroke to Target
TWiTCH	TCD With Transfusions Changing to Hydroxyurea
UKPDS	United Kingdom Prospective Diabetes Study
VAST	Vertebral Artery Stenting Trial
VHD	valvular heart disease
VISP	Vitamin Intervention for Stroke Prevention
VISSIT	Vitesse Intracranial Stent Study for Ischemic Stroke Therapy
VIST	Vertebral Artery Ischemic Stenting Trial
VISTA	Virtual International Stroke Trials Archive
VITATOPS	Vitamins to Prevent Stroke
VKA	vitamin K antagonist
VLDL	very-low-density lipoprotein
VZV	varicella zoster virus
WARCEF	Warfarin vs. Aspirin in Reduced Cardiac Ejection Fraction
WARSS	Warfarin-Aspirin Recurrent Stroke Study
WASID	Warfarin-Aspirin Symptomatic Intracranial Disease
WEAVE	Wingspan Stent System Post Market Surveillance

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Table 3. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated May 2019)*

CLASS (STRENGTH) OF RECOMMENDATION

CLASS 1 (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS 2a (MODERATE) — Benefit >> Risk

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS 2b (WEAK) — Benefit ≥ Risk

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well-established

CLASS 3: No Benefit (MODERATE) (Generally, LOE A or B use only) — Benefit = Risk

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

Class 3: Harm (STRONG) — Risk > Benefit

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)
- Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

2. GENERAL CONCEPTS

2.1. Definitions

Figure 1 illustrates the writing group's conceptual representation of ischemic stroke subtypes.

Lacunar stroke: Lacunar syndrome, with normal computed tomography (CT)/magnetic resonance imaging (MRI) or subcortical stroke measuring <1.5 cm in diameter on CT or MRI. Most, although not all, of lacunar strokes are due to small vessel disease.

Stroke attributable to small vessel disease: Subcortical stroke measuring <1.5 cm in diameter on CT or MRI without evidence of a concomitant cortical infarct.

Cardioembolic stroke: Stroke attributable to arterial occlusion from an embolus that presumably arose in the heart. Clinical and brain imaging findings are similar to those described in large artery atherosclerosis. Evidence of a previous TIA or stroke in >1 vascular territory supports a clinical diagnosis of cardioembolic stroke.

Cryptogenic stroke: An imaging-confirmed stroke with unknown source despite thorough diagnostic assessment (including, at a minimum, arterial imaging, echocardiography, extended rhythm monitoring, and key laboratory studies such as a lipid profile and hemoglobin A1c [HbA1c]).

Stroke caused by large artery atherosclerosis: Ischemic stroke in the vascular distribution of a major intracranial or extracranial artery with >50% stenosis or occlusion on vascular imaging. Clinical findings include those of

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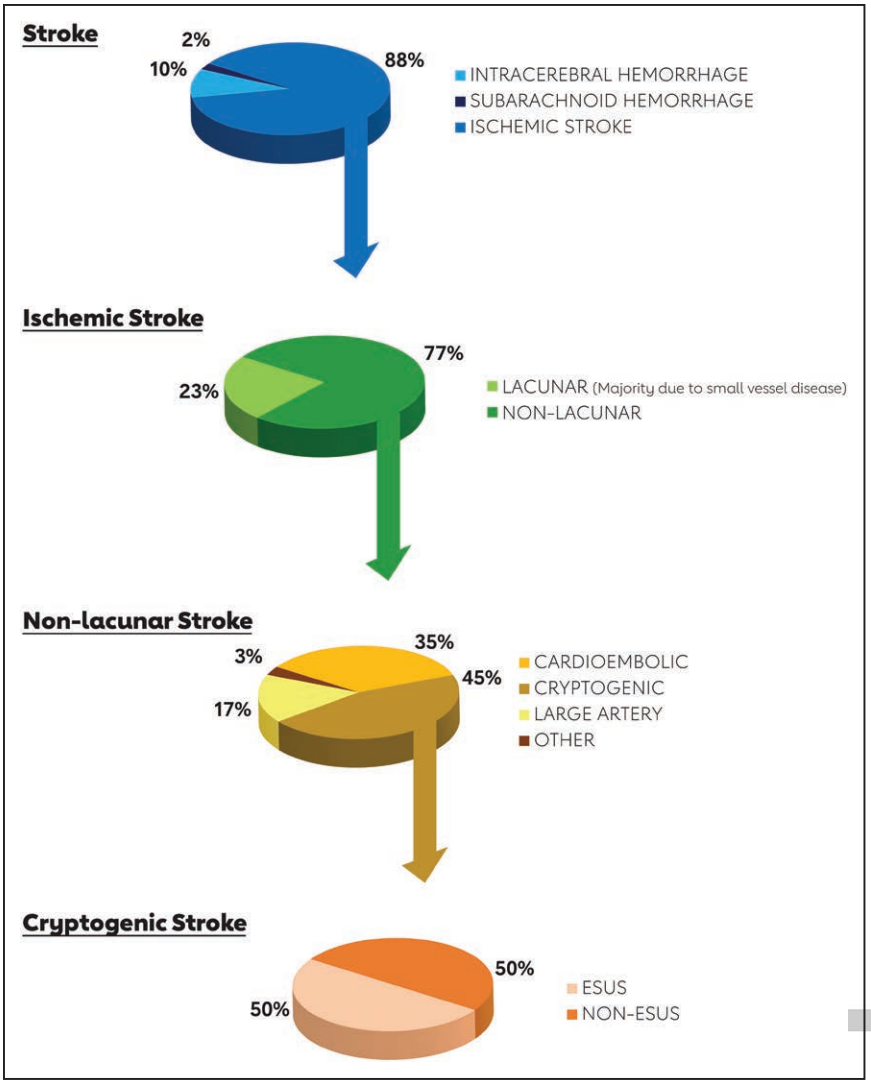

Figure 1. Conceptual representation of ischemic stroke subtypes. Percentages are approximate and are informed by Kolominsky-Rabas et al[36] and Gardener et al.[37] Precise percentages will depend on extent of testing and patient populations. Ischemic stroke subtype definitions are informed by the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification scheme[38] unless otherwise indicated. ESUS indicates embolic stroke of undetermined source.

cerebral cortical involvement or brainstem or cerebellar dysfunction. Cortical and cerebellar lesions and brainstem or subcortical lesions >1.5 cm are considered potentially caused by large artery atherosclerosis. Diagnostic studies should exclude potential sources of cardioembolic embolism.

ESUS: A stroke that appears nonlacunar on neuroimaging without an obvious source after a minimum standard evaluation (including arterial imaging, echocardiography, extended rhythm monitoring, and key laboratory studies such as a lipid profile and HbA1c) to rule out known stroke etiologies such as cardioembolic sources and atherosclerosis proximal to the stroke.[39]

A diagnosis of ESUS implies that the stroke is embolic in origin, given the nonlacunar location; however, the source of the embolus is unknown, despite a minimal standard evaluation. Although cryptogenic stroke similarly implies that the cause of the origin is unknown, the stroke is not necessarily embolic. Individuals with ESUS have cryptogenic stroke, but the converse is not always the case.

2.2. Shared Decision-Making

Shared decision-making is a key component of patient-centered care. It is a process in which clinicians describe options, provide information on risks and benefits, assist patients in evaluating those options based on their personal goals and concerns, and facilitate deliberation and decision-making. Although this document provides guidance based on a review of the literature, it is essential for clinicians to collaboratively develop care plans with patients, incorporating patients' wishes, goals, and concerns.

2.3. Contraindications

Treatment should always be tailored to patients' individual situations. Therefore, as a rule, we did not include the statement "unless contraindicated" in the recommendations. It is implicit that if a recommendation is contraindicated in a patient's circumstance, it should not be implemented.

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2.4. Adherence

A key component of secondary stroke prevention is assessing and addressing barriers to adherence to medications and a healthy lifestyle. If a patient has a recurrent stroke while on secondary stroke prevention medications, it is vital to assess whether they were taking the medications that they were prescribed and, if possible, to explore and address factors that contributed to nonadherence before assuming that the medications were ineffective.

2.5. Antithrombotic Dosing

Unless stated otherwise in the recommendations herein, the international normalized ratio (INR) goal for warfarin is 2.0 to 3.0 and the dose of aspirin is 81 to 325 mg.

2.6. Application Across Populations

Unless otherwise indicated, the recommendations in this guideline apply across race/ethnicity, sex, and age groups. Special considerations to address health equity are delineated in section 6.3, Health Equity.

3. DIAGNOSTIC EVALUATION FOR SECONDARY STROKE PREVENTION

Recommendations for Diagnostic Evaluation
Referenced studies that support recommendations are summarized in online Data Supplements 1 and 2.

COR	LOE	Recommendations
1	B-R	1. In patients suspected of having a stroke or TIA, an ECG is recommended to screen for atrial fibrillation (AF) and atrial flutter and to assess for other concomitant cardiac conditions.[40,41]
1	B-NR	2. In patients with ischemic stroke or TIA, a diagnostic evaluation is recommended for gaining insights into the etiology of and planning optimal strategies for preventing recurrent stroke, with testing completed or underway within 48 hours of onset of stroke symptoms.[42–45]
1	B-NR	3. In patients with symptomatic anterior circulation cerebral infarction or TIA who are candidates for revascularization, noninvasive cervical carotid imaging with carotid ultrasonography, CT angiography (CTA), or magnetic resonance angiography (MRA) is recommended to screen for stenosis.[46–50]
1	B-NR	4. In patients suspected of having a stroke or TIA, CT or MRI of the brain is recommended to confirm the diagnosis of symptomatic ischemic cerebral vascular disease.[51–53]
1	B-NR	5. In patients with a confirmed diagnosis of symptomatic ischemic cerebrovascular disease, blood tests, including complete blood count, prothrombin time, partial thromboplastin time, glucose, HbA1c, creatinine, and fasting or nonfasting lipid profile, are recommended to gain insight into risk factors for stroke and to inform therapeutic goals.[54,55]

Recommendations for Diagnostic Evaluation (Continued)

COR	LOE	Recommendations
2a	B-R	6. In patients with cryptogenic stroke, echocardiography with or without contrast is reasonable to evaluate for possible cardiac sources of or transcardiac pathways for cerebral embolism.[56,57]
2a	B-R	7. In patients with cryptogenic stroke who do not have a contraindication to anticoagulation, long-term rhythm monitoring with mobile cardiac outpatient telemetry, implantable loop recorder, or other approach is reasonable to detect intermittent AF.[58–60]
2a	B-NR	8. In patients suspected of having ischemic stroke, if CT or MRI does not demonstrate symptomatic cerebral infarct, follow-up CT or MRI of the brain is reasonable to confirm diagnosis.[61–65]
2a	B-NR	9. In patients suspected of having had a TIA, if the initial head imaging (CT or MRI) does not demonstrate a symptomatic cerebral infarct, follow-up MRI is reasonable to predict risk of early stroke and to support the diagnosis.[66–69]
2a	C-LD	10. In patients with cryptogenic stroke, tests for inherited or acquired hypercoagulable state, bloodstream or cerebral spinal fluid infections, infections that can cause central nervous system (CNS) vasculitis (eg, HIV and syphilis), drug use (eg, cocaine and amphetamines), and markers of systemic inflammation and genetic tests for inherited diseases associated with stroke are reasonable to perform as clinically indicated to identify contributors to or relevant risk factors for stroke.[70–72]
2a	C-LD	11. In patients with ischemic stroke or TIA, noninvasive imaging of the intracranial large arteries and imaging of the extracranial vertebrobasilar arterial system with MRA or CTA can be effective to identify atherosclerotic disease, dissection, moyamoya, or other etiologically relevant vasculopathies.[73–75]
2b	B-NR	12. In patients with ischemic stroke and a treatment plan that includes anticoagulant therapy, CT or MRI of the brain before therapy is started may be considered to assess for hemorrhagic transformation and final size of infarction.[76]
2b	C-LD	13. In patients with ESUS, transesophageal echocardiography (TEE), cardiac CT, or cardiac MRI might be reasonable to identify possible cardioaortic sources of or transcardiac pathways for cerebral embolism.[57,77–79]
2b	C-LD	14. In patients with ischemic stroke or TIA in whom patent foramen ovale (PFO) closure would be contemplated, TCD (transcranial Doppler) with embolus detection might be reasonable to screen for right-to-left shunt.[57,80]

Synopsis

Patients presenting with signs and symptoms of acute stroke will undergo an evaluation tailored to ensure that, when appropriate, they receive reperfusion therapy (Figure 2). Imaging recommendations based on acute treatment

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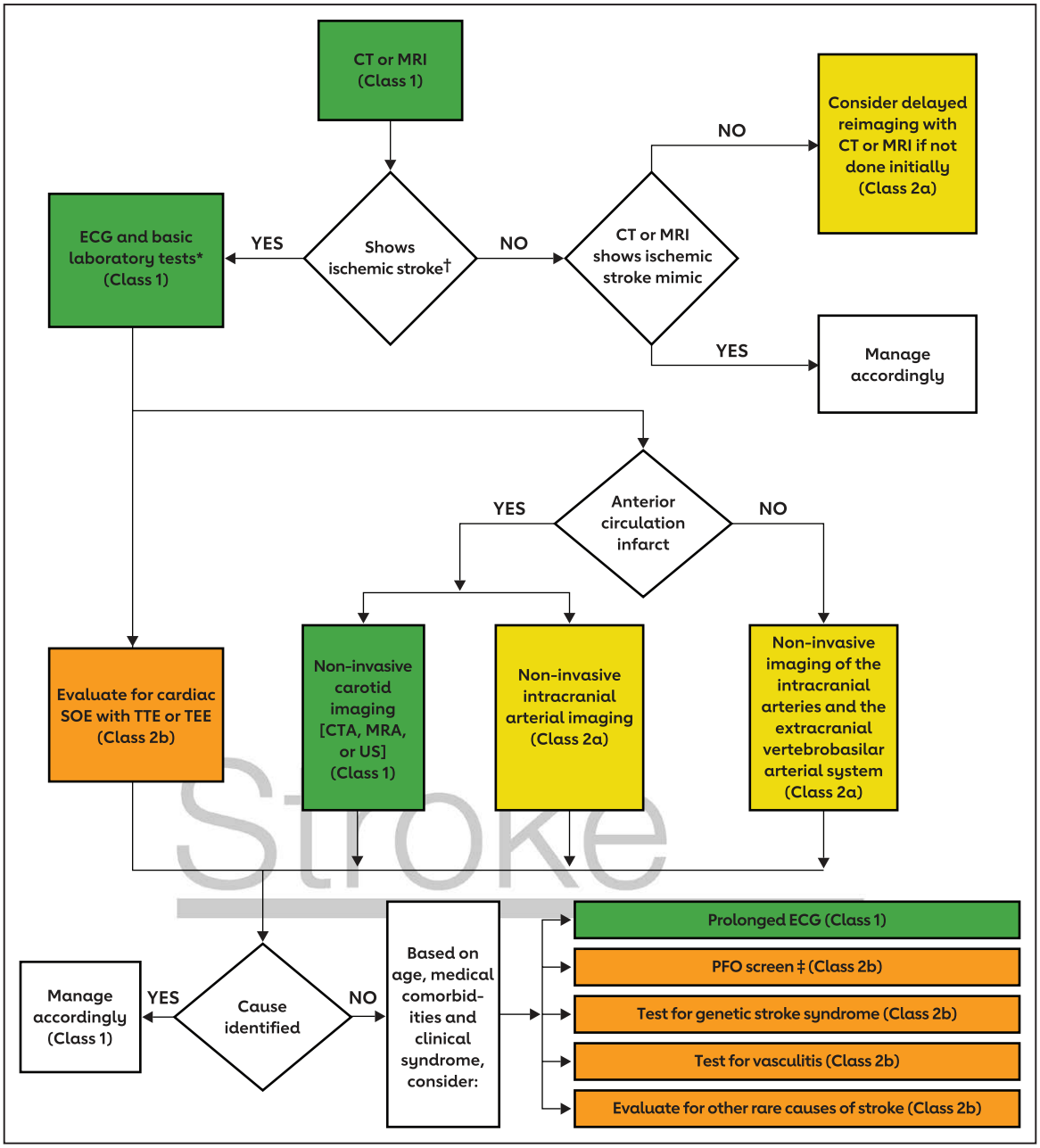

Figure 2. Algorithm for evaluating patients with a clinical diagnosis of stroke for the purposes of optimizing prevention of recurrent ischemic stroke.

Colors correspond to Class of Recommendation in Table 3. CT indicates computed tomography; CTA, computed tomography angiogram; ECG, electrocardiogram; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PFO, patent foramen ovale; SOE, source of embolism; TCD, transcranial Doppler; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; and US, ultrasound. *Basic laboratory tests include complete blood count, troponin, prothrombin time, partial thromboplastin time, glucose, hemoglobin A_{1c}, creatinine, and fasting or nonfasting lipid profile. †When a patient has a transient neurological deficit clinically characteristic of transient ischemic attack, the patient should be evaluated in the same manner as a patient who has an ischemic stroke with a corresponding cerebral infarct on imaging. ‡TTE, TEE, TCD, cardiac MRI, or cardiac CT.

considerations overlap with, but are not identical to, imaging recommendations based on secondary stroke prevention considerations. Recommendations presented in this guideline focus on evaluations done for the purposes of confirming the diagnosis of stroke and characterizing its pathomechanism by identifying potential sources of cardioembolism, thromboembolism from large artery atherosclerosis, dissection, or other disease processes such as hypercoagulability. Confirmation of stroke diagnosis may require follow-up head imaging because of poor sensitivity of noncontrast CT for small or hyperacute infarcts. Some conditions associated with stroke and with specific therapies are common (eg, AF), whereas others are relatively rare (eg, endocarditis). The variable yield of testing means that treating physicians need to exercise judgment on the likelihood that a test will alter management in a given clinical situation.

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Recommendation-Specific Supportive Text

1. An ECG is a simple, noninvasive means of diagnosing AF in patients with acute stroke. A meta-analysis through 2014 found that the proportion of patients diagnosed with poststroke AF in the emergency department by electrocardiography was 7.7% (95% CI, 5.0–10.8).[40] An ECG can also detect pertinent comorbidities that may have therapeutic implications. About 3% of patients presenting with acute stroke also have acute myocardial infarction (MI).[41]
2. Effective secondary prevention requires timely evaluation of stroke mechanism, with the intent of identifying modifiable risk factors. The risk of recurrent stroke in the short term and long term varies by stroke mechanism.[42–45] The risk of stroke within 90 days after a first stroke is ≈5%, but the risk can vary greatly from >10% to <1%, depending in part on mechanism.[42] Symptomatic carotid stenosis and AF are important to diagnose in a timely fashion to allow implementation of specific treatments with proven efficacy.
3. Because patients with symptomatic high-grade cervical carotid stenosis are candidates for revascularization, it is appropriate to screen for stenosis in any patient who may have such stenosis. Initial testing for carotid stenosis should be done with a noninvasive test such as CTA, MRA, or ultrasonography rather than digital subtraction angiography, with case series finding a risk of stroke ranging from 0.3% to 3.0%.[81–83] Experienced stroke centers typically have a risk of stroke attributable to digital subtraction angiography of <0.5%. For patients at high risk of carotid artery stenosis who can undergo surgery without delay, immediate CTA is the most cost-effective strategy.[84] Using consensus interpretation criteria, carotid ultrasonography has a sensitivity of 38.8%, specificity of 91.6%, and accuracy of 87.1% for ≥70% stenosis.[47] With the use of a 70% cutoff value for carotid stenosis, CTA and digital subtraction angiography were in agreement in 78 of 81 vessels (95% CI, 90–99) in a series of patients with stroke or TIA.[48] Compared with digital subtraction angiography, a meta-analysis of studies performed in 2008 found the overall sensitivity of time-of-flight MRA for the detection of 70% to 99% internal carotid artery (ICA) stenoses to be 91.2% with a specificity of 88.3%, whereas the sensitivity of contrast-enhanced MRA was 94.6% with a specificity of 91.9%.[49]
4. An accurate diagnosis of ischemic stroke or TIA is essential for justifying and optimizing stroke prevention. Many patients will have had brain imaging in the acute setting to exclude stroke mimics and to include stroke "chameleons" (stroke initially thought to be an alternative diagnosis). About 15% to 25% of patients thought to have stroke on clinical grounds will be given an alternative diagnosis with the help of brain imaging.[51] About 13% of patients with stroke or TIA thought to have a nonstroke diagnosis for their neurological symptoms will be given the diagnosis of stroke with the help of brain imaging.[52,53] A prospective, multicenter multinational study showed that, in patients with recent minor focal nonmotor, nonspeech neurological deficits, diffusion-weighted MRI detected acute infarction in 13.5% and that this finding had prognostic relevance because detection of infarction was associated with a >6-fold increase in the risk of recurrent stroke at 1 year.[85]
5. As reported in this guideline, control of hypertension (Section 4.2), blood glucose (Section 4.4), and lipids (Section 4.3) have been proven effective for reducing the risk of ischemic stroke; thus, assessment of whether the patient is at therapeutic goal for these metabolic parameters helps to optimize therapy. Fasting is not routinely required for lipid testing because the lipid profile components under fasting and nonfasting conditions differ in nonclinically significant degrees (the exception being patients with nonfasting triglycerides of >440 mg/dL, who should have fasting levels drawn).[86] HbA1c determination can detect new cases of type 2 diabetes (T2D) in ≈11.5% of patients presenting with acute ischemic stroke and prediabetes in 36.2%.[54] Abnormal blood testing can help to stratify risk so that physicians can concentrate efforts of prevention on those at highest risk. In patients with lacunar infarction, chronic kidney disease is associated with a 50% increase in risk of recurrent stroke.[55] Testing prothrombin time and activated partial thromboplastin time screens for diverse clotting and bleeding disorders that are relevant to active management of patients with acute stroke. An isolated prolonged activated partial thromboplastin time can be seen with heparin use, lupus anticoagulant, or clotting factor deficiencies.[87] All of these states or exposures are relevant to long-term management of patients with stroke. Liver failure, malnutrition, malabsorption, myeloproliferative diseases, and disseminated intravascular coagulation can cause acquired factor deficiencies and would have relevance in managing patients with stroke.[88]
6. Many diseases with specific indications for specific treatment such as patent foramen ovale (PFO), papillary fibroelastoma, myxoma, endocarditis, and intracardiac thrombi are diagnosed by echocardiography.[89] Transthoracic echocardiography is preferred over TEE for the detection of left ventricular (LV) thrombus, but TEE is superior to transthoracic echocardiogram in detecting left atrial thrombus, aortic atheroma, prosthetic valve abnormalities, native

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valve abnormalities, atrial septal abnormalities, and cardiac tumors.[89] A systematic review that included 65 studies concluded that transthoracic echocardiography in the second harmonic is cost-effective relative to TEE.[56] TEE findings will change management in ≈1 in 7 patients with ESUS.[57]

7. Randomized trials show that longer heart monitoring in patients with cryptogenic stroke results in higher detection rates for AF. A randomized study of an insertable cardiac monitor versus conventional follow-up in patients with cryptogenic stroke found that by 6 months AF had been detected in 8.9% of patients in the insertable cardiac monitor group versus 1.4% of patients in the control group (95% CI, 1.9–21.7; $P<0.001$).[58] A randomized study of patients ≥55 years of age who had had a cryptogenic ischemic stroke or TIA within the previous 6 months found AF lasting ≥30 seconds in 16.1% in the intervention group monitored with a 30-day event triggered recorder compared with 3.2% in the control group who had standard monitoring, including 24-hour electrocardiography (95% CI, 8.0–17.6; $P<0.001$).[59] Repeated Holter electrocardiographic monitoring in patients ≥60 years of age with recent stroke significantly increases the likelihood of AF detection over routine monitoring (14% versus 5%; $P=0.002$).[60] Improvement in patient outcomes with long-term rhythm monitoring has not been established.
8. A systematic review in 2012 found no evidence that multimodal MRI when used purely for diagnostic purposes improves outcomes, although there was limited evidence that it can change management.[61] The use of MRI for in-hospital stroke evaluation grew dramatically from 1999 to 2008, varying widely by state.[61] The growth was likely related to widespread appreciation of the diagnostic yield of follow-up brain imaging with MRI within 1 to 2 days. About one-quarter of acute stroke cases with an initially negative head CT will have an MRI with evidence of acute/subacute infarction.[62] An emergency department series of 252 patients presenting with atypical stroke symptoms and a negative CT found that 29 patients (11.5%) had acute ischemic stroke on MRI obtained within 24 hours.[63] For posterior circulation strokes in particular, a follow-up MRI may be appropriate to confirm a diagnosis even when the initial MRI is negative.[64] MRI with diffusion-weighted imaging is also particularly helpful in evaluating patients with low-risk TIA and mild neurological symptoms.[85] Confirming the diagnosis of acute ischemic stroke with brain imaging may help with patient education and prognostication, which in turn may promote adherence to a prescribed prevention regimen.[65]
9. About one-third of patients with stroke symptoms for <24 hours have a diffusion-weighted imaging–positive lesion.[66] A cost-effectiveness analysis of the use of MRI in patients with TIA reported in 2014 concluded that MRI was generally not cost-effective, although there might be utility to MRI in this population if the imaging is done >1 week after onset of symptoms and with a blood-sensitive sequence, if the clinical team is considering unusual causes of symptoms, or if symptoms are related to ipsilateral high-grade stenosis.[69] Predictive scores that incorporate MRI findings (eg, $ABCD^2$-I and $ABCD^3$-I) are better able to discriminate high risk of early stroke from low risk of early stroke than predictive scores that do not incorporate MRI findings (eg, $ABCD^2$) when MRI is done within 7 days of onset of symptoms.[67]
10. Stroke can be the initial manifestation of a host of systemic conditions that either are treatable by themselves or must be identified to avoid misdirected ineffective or harmful therapies. The pretest probability of finding a diagnostically meaningful abnormality for many of these tests will depend on clinical suspicion informed by demographic variables (eg, age), medical history, physical findings, and results of basic testing. For example, the yield of testing for a hypercoagulable state is low for patients >50 years of age.[90] Patients presenting with stroke will have echocardiographically confirmed infectious endocarditis in 1.7% of cases, and an initial C-reactive protein of at least 10 mg/L dramatically increased the likelihood of infectious endocarditis (odds ratio [OR], 22).[70] Use of cocaine within the prior 24 hours increases the risk of stroke in young adults by >6-fold.[71] Toxicology testing for cocaine and other drugs of abuse should be done at the time of presentation.[91,92] When diagnostic algorithms were used, monogenic causes of stroke were detected in 7% in 1 population-based study.[72]
11. Identification of symptomatic intracranial atherosclerotic disease supports treatment to aggressive antiatherosclerotic targets and is often seen as an indication for dual antiplatelet therapy (DAPT). Both MRA[73] and CTA[74] have been shown to reliably exclude high-grade intracranial atherosclerotic stenosis (ICAS) when digital subtraction catheter angiography was used as the reference test. Early identification of symptomatic extracranial vertebrobasilar stenosis identifies patients at high risk of recurrent stroke.[75]
12. Hemorrhagic transformation is often seen as a contraindication to early (<2 weeks of stroke onset) oral anticoagulation, although no randomized trial has been done that directly addresses the question. A multicenter, prospective international study of consecutive patients with acute ischemic stroke and AF that included a second CT 24 to 72 hours after stroke onset found that the presence of hemorrhagic transformation led to an average delay in anticoagulation

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of 12 days and that this delay was not associated with a significant rise in the rate of recurrent stroke.[76] Large infarcts, for example, the entire territory of either the middle, anterior, or posterior cerebral artery, had nearly twice the risk of hemorrhagic transformation as smaller infarcts in this series.[76]

13. TEE, cardiac CT, and cardiac MRI will provide actionable information in a minority of patients with acute stroke. In a prospective study of 61 patients with ESUS who underwent investigation with TEE (mean age, 44±12 years; 49% men), TEE revealed additional findings in 52% (95% CI, 40–65) of the study population, and findings changed management (initiation of anticoagulation therapy, administration of intravenous antibiotic therapy, and PFO closure) in 10 patients (16% [95% CI, 9–28]).[57] In a meta-analysis of 3562 patients with acute ischemic stroke, the pooled rate of anticoagulation therapy attributed to abnormal TEE findings was 8.7% (95% CI, 7.3–10.4).[57] In a single-center retrospective study of 1458 patients with suspected cardioembolic stroke, findings on TEE significantly changed management in 16.7%.[77] Smaller series have found that the addition of TEE to a standard stroke workup identified an indication for anticoagulation in 20% to 22.6% of cases.[93,94] Cardiac CT has a modest sensitivity (72%) and high specificity (95%) for detecting potential embolic source in patients with cryptogenic stroke in whom TEE is used as the gold standard.[78] A single-center study of consecutive patients with cryptogenic stroke who underwent both TEE and cardiac MRI found that cardiac MRI reduced the percentage of patients with cryptogenic stroke by only slightly >1%.[79]
14. TCD compares favorably with TEE for detecting right-to-left shunting, which is usually the result of PFO, now a potential target for device closure. A pooled analysis of the OXVASC (Oxford Vascular Study) data with data from 2 previous smaller studies of bubble-TCD in patients ≥50 years of age found an association between right-to-left shunting and cryptogenic TIA or nondisabling stroke (OR, 2.35 [95% CI, 1.42–3.90).[80] A pooled analysis of a systematic literature review found that TCD had a sensitivity of 96.1% (95% CI, 93.0–97.8) and specificity of 92.4% (95% CI, 85.5–96.1) compared with TEE (gold standard) for detection of right-to-left shunting.[57]

Knowledge Gaps and Future Research

Randomized trials have provided compelling evidence of specific therapies for specific subsets of patients with ischemic stroke, for example, anticoagulation in the subset of patients with AF and low risk of hemorrhage. Diagnosing these mechanistically related risk factors is an important part of the early evaluation of stroke to optimize prevention of recurrent stroke. New risk factors for stroke are being discovered through observational studies, but several knowledge gaps exist relating to the relative importance of testing to identify uncommon or rare conditions associated and potentially causally linked with recurrent stroke. The less prevalent a comorbid condition is among patients with stroke, the more challenging it is to execute successfully a well-powered clinical trial to provide high levels of evidence justifying the diagnostic testing. There are several clinical conditions associated with ischemic stroke for which trial evidence would be helpful to guide therapy:

- To better prevent cardioembolism, it would be helpful to have trials that clarify optimal duration of heart rhythm monitoring, determine the clinical significance of brief episodes of AF, and define the precise role of cardiac CT/MRI and microembolus detection with TCD.
- In terms of large artery disease, much is known about atherosclerotic stenosis, but far less is known about the importance of detecting microemboli with TCD or identifying characteristics of unstable plaque such as intraplaque hemorrhage.
- Further research is also needed to clarify the clinical significance of detecting nonatherosclerotic conditions, including carotid dissection, fibromuscular dysplasia, and carotid webs. Other uncommon causes of stroke such as CNS vasculitis and Susac syndrome suffer from a lack of well-designed clinical trials to guide therapies.

Stroke

4. VASCULAR RISK FACTOR MANAGEMENT

4.1. Lifestyle

4.1.1. Nutrition

Recommendations for Nutrition Referenced studies that support recommendations are summarized in online Data Supplements 3 and 4.		
COR	**LOE**	**Recommendations**
2a	B-R	1. In patients with stroke and TIA, it is reasonable to counsel individuals to follow a Mediterranean-type diet, typically with emphasis on monounsaturated fat, plant-based foods, and fish consumption, with either high extra virgin olive oil or nut supplementation, in preference to a low-fat diet, to reduce risk of recurrent stroke.[95,96]
2a	B-R	2. In patients with stroke or TIA and hypertension who are not currently restricting their dietary sodium intake, it is reasonable to recommend that individuals reduce their sodium intake by at least 1 g/d sodium (2.5 g/d salt) to reduce the risk of cardiovascular disease (CVD) events (including stroke).[97,98]

Synopsis

Limited evidence supports dietary interventions to reduce recurrent stroke,[96] with recommendations

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drawn from high-risk CVD and coronary heart disease populations, or dietary effects on stroke risk factors, for example, BP and cholesterol.[98] Epidemiological diet and nutrition studies identify protective effects for stroke from regular consumption of fish,[99] high consumption of fruit and vegetables[100,101] and fiber,[102] and following the Mediterranean diet[96] and the DASH (Dietary Approaches to Stop Hypertension) diet,[103] reflected in the AHA/American College of Cardiology (ACC) guideline on lifestyle management to reduce cardiovascular risk.[26] PAR for stroke for the lowest versus the highest tertile of the modified Alternative Healthy Eating Index is 18.8% (99% CI, 11.2–29.7).[5a] In the United States, the REGARDS cohort study (Reasons for Geographic and Racial Differences in Stroke Study) identified higher adherence to the Southern diet (high in added fats, fried food, eggs, processed meats, and sugar-sweetened beverages) was associated with a 39% increased risk of stroke (hazard ratio [HR], 1.39 [95% CI, 1.05–1.84]).[105] Sodium and potassium consumption, unlike many vitamins and minerals in foods, can be adjusted without altering overall dietary patterns.[26] Both high potassium consumption[106] and low salt consumption[107] are associated with lower stroke rates. No evidence supports potassium-based interventions for CVD reduction[26]; no dietary interventions of increased potassium consumption alone in stroke survivors were identified. Overnutrition is addressed in Section 4.5, Obesity.

Table 4. Dietary Details of Typical Mediterranean-Type Diets

Mediterranean diet (summarized)	DASH diet (summarized)
High monounsaturated/saturated fat ratio (use of olive oil as main cooking ingredient and/or consumption of other traditional foods high in monounsaturated fats such as tree nuts)	Limited saturated fat and cholesterol and emphasized nut consumption
High intake of plant-based foods, including fruits, vegetables, and legumes	Emphasizes fruit, vegetables, and legumes consumption
High consumption of whole grains and cereals	Emphasizes whole grains
Increased consumption of fish	
Low consumption of meat and meat products Discourages red and processed meats	Limits red and processed meats
Low to moderate red wine consumption	
Moderate consumption of milk and dairy products	Emphasizes fat-free/low-fat dairy
Discourages soda drinks, pastries, sweets, commercial bakery products, and spread fats	Limits sweets, added sugars, salt, and sugar-sweetened beverages.

DASH indicates Dietary Approaches to Stop Hypertension.
Summarized Mediterranean Diet[95,96] and summarized DASH diet.[103]

Recommendation-Specific Supportive Text

1. The interventional arms of the PREDIMED trial (Prevención con Dieta Mediterránea), comprising the Mediterranean diet with either supplemental extravirgin olive oil or tree nuts (Table 4) compared with a low-fat diet,[95] provide evidence of a reduction in stroke events in individuals with high cardiovascular risk (HR, 0.60 [95% CI, 0.45–0.80]), rated moderate-quality evidence.[96] The primary end point (MI, stroke. or cardiovascular death) identified adjusted HRs of 0.72 (95% CI, 0.54–0.95) for the Mediterranean diet with olive oil supplementation and 0.69 (95% CI, 0.53–0.91) with nut supplementation compared with the control diet. Evidence in secondary prevention is drawn from the Lyon Diet Heart trial of the Mediterranean diet with supplemental canola compared with a usual post-MI prudent diet, producing low-quality evidence of reduced CVD mortality and total mortality (adjusted HR, 0.35 [95% CI, 0.15–0.82] and 0.44 [95% CI, 0.21–0.92], respectively) in a coronary heart disease population.[96] One study in first stroke and matched control cases[108] shows each unit (1 of 55) in MedDietScore is associated with a 17% lower likelihood of ischemic stroke in participants without hypercholesterolemia (95% CI, 0.72–0.96) and 10% lower likelihood in participants with hypercholesterolemia (95% CI, 0.81–0.99).
2. A meta-analysis of 13 prospective studies and >11 000 vascular events (N=177 025 participants; follow-up, 3.5–19 years) identified that higher levels of habitual salt intake are associated with greater stroke risk (relative risk [RR], 1.23 [95% CI, 1.06–1.43]).[107] A Japanese population-based study identified that in men the highest compared with the lowest tertile of sodium intake recorded was significantly positively associated with death resulting from ischemic stroke (adjusted HR, 3.22 [95% CI, 1.22–8.53]).[109] Meta-analysis in those with established CVD identified through long-term follow-up of participants in 5 salt-reducing trials[97] reported a reduction of 1 g/d sodium (2.5 g/d salt) is associated with a 20% reduction in further cardiovascular events (RR, 0.80 [95% CI, 0.66–0.97]). The DASH-sodium trial[98] identified that for a typical US diet in the 1990s (the control diet), a reduction in sodium intake from 3.3 to 2.4 g/d reduced systolic BP (SBP) by 2.1 mm Hg ($P<0.001$), and further reducing sodium intake from 2.4 to 1.5 g/d yielded additional reductions of 4.6 mm Hg ($P<0.001$). The DASH diet was associated with a significantly lower SBP at each sodium level than the control diet.

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4.1.2. Physical Activity

Recommendations for Physical Activity
Referenced studies that support recommendations are summarized in online Data Supplements 5 and 6.

COR	LOE	Recommendations
1	C-LD	1. In patients with stroke or TIA who are capable of physical activity, engaging in at least moderate-intensity aerobic activity for a minimum of 10 minutes 4 times a week or vigorous-intensity aerobic activity for a minimum of 20 minutes twice a week is indicated to lower the risk of recurrent stroke and the composite cardiovascular end point of recurrent stroke, MI, or vascular death.[110]
2a	B-R	2. In patients with stroke or TIA who are able and willing to increase physical activity, engaging in an exercise class that includes counseling to change physical activity behavior can be beneficial for reducing cardiometabolic risk factors and increasing leisure time physical activity participation.[111–114]
2a	C-EO	3. In patients with deficits after stroke that impair their ability to exercise, supervision of an exercise program by a health care professional such as a physical therapist or cardiac rehabilitation professional, in addition to routine rehabilitation, can be beneficial for secondary stroke prevention.
2b	B-NR	4. In individuals with stroke or TIA who sit for long periods of uninterrupted time during the day, it may be reasonable to recommend breaking up sedentary time with intervals as short as 3 minutes of standing or light exercise every 30 minutes for their cardiovascular health.[115]

Synopsis

Regular physical activity reduces stroke risk[116–118]; positively affects stroke risk factors, for example, BP, cholesterol,[116] and weight[119]; and can improve endothelial function and reduce platelet aggregation, fibrinogen levels,[118,120–122] and onset stroke severity.[123] Physical inactivity (eg, sitting >4 h/d) as a cardiovascular risk behavior[124] is attenuated by increased bouts of moderate- to vigorous-intensity physical activity.[125] Low levels of physical activity are observed in acute,[126] subacute, and chronic phases of stroke, with >78% of recorded time categorized as sedentary.[127] When able, stroke survivors should aim to achieve population-based recommendations (40-minute sessions, 3 to 4 times per week of moderate- to vigorous-intensity aerobic activity),[26] and when this is not possible, their physical activity goals need to be customized to their exercise tolerance, stage of recovery, environment, available social support, physical activity preferences, and specific impairments, activity limitations, and participation restrictions as identified by the AHA/ASA guideline for physical activity and exercise.[34]

Exercise interventions positively affect disability, aerobic fitness, mobility (walking speed), and functional balance indices after stroke.[128] Efficacy of exercise interventions compared with usual care was established by a meta-analysis for risk factors after stroke, including BP, cholesterol, glucose levels, and weight.[112,113] Physical activity interventions are often delivered in multimodal, lifestyle-based programs. These are addressed in Section 6.2, Interventions Aimed at Changing Patient Behavior.

Recommendation-Specific Supportive Text

1. Planned analysis of participants in the medical management arm (n=227) of the SAMMPRIS trial (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis)[110] at the 3-year follow-up identified 49 primary end point events (stroke, MI, and vascular death), including 32 ischemic strokes. For the composite end point at 3 years, participants who were not in target for physical activity levels, defined as a Physician-Based Assessment and Counselling for Exercise score of ≥4, had a significantly higher odds of stroke, MI, and vascular death than those who did achieve this target (OR, 5.4 [95% CI, 2.4–12.1]). The Physician-Based Assessment and Counselling for Exercise score of 4 equates to 10-minute bouts of moderate physical activity (sufficient to break a sweat or to noticeably raise heart rate, eg, walking briskly, using an exercise bicycle) up to 4 times a week or 20-minute bouts of vigorous activity (eg, jogging) up to twice a week. For the end point of ischemic stroke, physical activity was the only risk factor associated with lower stroke events; those who were out of target for defined physical activity levels had an OR of 6.7 (95% CI, 2.5–18.1) for recurrent stroke compared with those who achieved the targets. Multivariable analysis controlling for low-density lipoprotein (LDL), non–high-density lipoprotein, and SBP identified that greater physical activity on the Physician-Based Assessment and Counselling for Exercise scale was independently associated with 40% lower risk of stroke, MI, or vascular death at 3 years (OR, 0.6 [95% CI, 0.4–0.8]).
2. Physical activity is a complex behavior. The ExStroke Pilot Trial (Physical Exercise After Acute Ischaemic Stroke)[129] identified no superiority for repeated encouragement and instruction to be physically active over 2 years to information provision after stroke (Physical Activity Scale for the Elderly mean difference [MD], 5.0 [95% CI, 5.8–15.9]). Similarly, wearable activity monitors and smartphone applications demonstrated no clear effect for use in conjunction with other interventions in stroke to improve step count in community settings (MD, 1930 steps [95% CI, −4410 to 550]) or inpatient rehabilitation settings (MD, 1400 steps [95% CI, 40–2840).[129a] Lifestyle-based interventions for stroke secondary prevention[111] identified a significant effect for behavioral change interventions compared with usual care to increase physical activity participation after stroke (standardized MD, 0.24 [95% CI, 0.08–0.41]). Two

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systematic reviews identified favorable effects for exercise-based interventions with counseling compared with usual care for reduction in SBP (MD, −5.3 mm Hg [95% CI, −9.0 to −1.6]; I^2=46%; N=228[112]; and MD, −5.32 [95% CI, −9.46 to −1.18]).[113] Exercise interventions initiated within 6 months of stroke/TIA have a larger effect on SBP (−8.46 mm Hg [95% CI, −12.18 to −4.75]; I^2=0%) than those initiated after 6 months (−2.33 mm Hg [95% CI, −3.94 to −0.72]; I^2=0%).[130]

3. Much of the evidence supporting exercise-based programs for stroke secondary prevention is based on participants with ambulatory stroke or TIA.[131–134] Many stroke survivors, however, encounter physical and environmental barriers to engaging in regular physical activity for health. Neurological weakness, altered perception or balance, or impaired cognition, for example, may negate their participation in conventional exercises programs. Adaptive equipment and skilled personnel can help to overcome many of these barriers to participation. A systematic review of inclusive studies of exercise-based programs in stroke identified that exercise programs are safe and feasible to implement in nonambulatory individuals, but to date, no evidence supports their impact on recurrent stroke,[135] Promising pilot studies of aerobic exercise programs inclusive of those with motor disability have shown that with adequate pre-exercise screening they are safe and feasible in both subacute and community settings and can improve cardiovascular fitness and reduce cardiovascular risk profiles.[136,137]
4. Stroke survivors were noted to be sedentary for >78% of total accelerometry time measured in a systematic review.[127] Community-dwelling, independently mobile (with/without mobility aid) individuals >6 months after stroke were identified as being sedentary for 10.9 h/d and having a low step count (mean, 2411 steps per day). These results were statistically significant compared with age- and sex-matched control subjects.[138] This prolonged sedentary time and inactivity increase future cardiovascular risk in stroke because these levels are associated with overall cardiovascular mortality (HR, 1.15 [95% CI, 1.11–1.19]) and cardiovascular incidence (HR, 1.143 [95% CI, 1.00–1.73]), with HRs more pronounced with lower physical activity levels.[124] Prespecified secondary analysis from the BUST-Stroke trial (Breaking Up Sitting Time After Stroke) identified sitting with 3-minute bouts of light-intensity activity while standing every 30 minutes decreased SBP by 3.5 mm Hg (95% CI, 1.7–5.4) compared with 8 hours of uninterrupted sitting. For participants not taking antihypertensive medications, sitting with 3-minute interruptions of either walking or light-intensity activity while standing every 30 minutes decreased SBP by 5.0 mm Hg (95% CI, −7.9 to 2.0) and 4.2 mm Hg (95% CI, −7.2 to −1.3), respectively, compared with 8 hours of uninterrupted sitting. No effect by condition for diastolic BP or plasma fibrinogen levels was observed.[115]

4.1.3. Smoking Cessation

Recommendations for Smoking Cessation
Referenced studies that support recommendations are summarized in online Data Supplements 7 and 8.

COR	LOE	Recommendations
1	A	1. In patients with stroke or TIA who smoke tobacco, counseling with or without drug therapy (nicotine replacement, bupropion, or varenicline) is recommended to assist in quitting smoking.[139–142]
1	B-NR	2. Patients with stroke or TIA who continue to smoke tobacco should be advised to stop smoking (and, if unable, to reduce their daily smoking) to lower the risk of recurrent stroke.[143–146]
1	B-NR	3. In patients with stroke or TIA. avoidance of environmental (passive) tobacco smoke is recommended to reduce risk of recurrent stroke.[147–150]

Synopsis

Cigarette smoking is an independent, potent, and dose-respondent risk factor for first ischemic stroke[147,151,152] and silent cerebral infarction,[153] approximately doubling the risk of stroke.[18] Environmental tobacco smoke (passive smoking) has been independently associated with increased risk of stroke and mortality.[147–149,155] Tobacco use is an addictive behavior, and cessation is difficult. Even after a life-threatening vascular event, roughly one-third of all smokers continue to smoke.[146,156] Persistent cigarette smoking after stroke or TIA is associated with increased longer-term mortality rates,[157–159] and evidence identifies an ≈2-fold risk of stroke recurrence in persistent smokers compared with nonsmokers[143–145] and a dose-response relationship.[143] Behavioral and pharmacological interventions for tobacco dependence are evidence based through multiple meta-analyses[139,140,160] but not in cerebrovascular disease populations.[157] No RCTs have examined smoking cessation interventions on recurrent events after stroke compared with no intervention; however, encouraging evidence of increased smoking cessation rates after stroke in multibehavioral interventions compared with usual care is emerging.[141,142]

Recommendation-Specific Supportive Text

1. A meta-analysis of smoking cessation interventions in hospitalized patients identified that intensive counseling interventions initiated in hospital with supportive contacts for at least 1 month after discharge increase smoking cessation rates compared with usual care (RR, 1.37

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[95% CI, 1.27–1.48]), with comparable findings in patients with CVD (RR, 1.42 [95% CI, 1.29–1.56]) and interventions initiated in rehabilitation hospitals (RR 1.71 [95% CI, 1.37–2.14]). Adding nicotine replacement therapy to the intervention increased cessation rates compared with intensive counseling alone (RR, 1.54 [95% CI, 1.34–1.79]).[139] High-quality evidence supports combined pharmacotherapy (nicotine replacement therapy, varenicline, or bupropion) and behavioral interventions compared with usual care, brief advice, or less intensive counseling in smoking cessation (RR, 1.83 [95% CI, 1.68–1.98]) in health care and community settings.[140] Group behavior therapy programs for smoking cessation are superior to self-help programs but are not superior to individual counseling of equal intensity.[140] In stroke trials, multibehavioral interventions have been associated with a greater likelihood of smoking cessation in the STOP trial (Stroke Prevention Trial in Sickle Cell Anemia; OR, 2.31 [95% CI, 1.99–1.33]) [141] and an increase of 17% in cessation rates compared with usual care (*P*=0.001) in the INSPiRE-TMS trial (Intensified Secondary Prevention Intending a Reduction of Recurrent Events in TIA and Minor Stroke Patients).[142]

2. Registry-based stroke studies point to an ≈2-fold increase in recurrent stroke rates for smokers. The Nanjing Stroke Registry Program (N=3069) reported 9.5% recurrence rates at 2.4 years. With nonsmokers as the reference, adjusted HRs for stroke recurrence were 1.93 (95% CI, 1.43–2.61) in persistent smokers, 1.31 (95% CI, 0.99–1.75) in quitters since stroke, and 1.16 (95% CI, 0.75–1.79) in former smokers, delineating the effects in smokers, former smokers and quitters. HRs for stroke recurrence ranged from 1.68 (95% CI, 1.14–2.48) in those who smoked 1 to 20 cigarettes daily to 2.72 (95% CI, 1.36–5.43) for those who smoked >40 cigarettes daily.[143] The Cardiovascular Health Study (N=546) similarly identifies a substantially increased risk of stroke recurrence in elderly smokers at a median 3.2-year follow-up (HR, 2.06 [95% CI, 1.39–3.56]).[144] A longitudinal study in Han Chinese individuals with ischemic stroke (N=421) identified an adjusted HR for smokers at 1 year of 2.15 (95% CI, 1.26–3.67).[145] The SMART study (Second Manifestations of Arterial Disease; N=4673) identified that smoking cessation increases life expectancy (average 5 years) and recurrent major atherosclerotic cardiovascular events occur 10 years later compared with persistent smokers.[146]

3. Primary prevention data highlight the risk of exposure to environmental tobacco smoke, also called passive smoking or secondhand smoke, on stroke rates in nonsmokers. The most recent meta-analysis identified that environmental tobacco smoke exposure compared with no exposure can increase the overall risk of stroke by 45% (OR, 1.45 [95% CI, 1.0–2.11]).[147] Other reports identify comparative rates of an OR of 1.46 (95% CI, 1.05–2.3),[148] an OR of 1.82 (95% CI, 1.34–2.49),[149] and an RR of 1.23 (95% CI, 1.16–1.31).[150] RR estimates were similar when ever exposure rather than current exposure or total rather than spousal exposure was used, and when dose-response estimates were pooled, the combined RR for the highest exposure level was 1.56 (95% CI, 1.37–1.79).[150] Data from the US National Health and Nutrition Examination Surveys identified that high exposure to environmental tobacco smoke for stroke survivors was associated with an adjusted HR for all-cause mortality of 1.72 (95% CI, 1.02–2.91), with a dose-dependent relationship observed.[148] No trials of interventions to reduce exposure to environmental tobacco smoke as a stroke secondary prevention strategy were identified.

4.1.4. Substance Use

Recommendations for Substance Use Referenced studies that support recommendations are summarized in online Data Supplements 9 and 10.		
COR	**LOE**	**Recommendations**
1	B-NR	1. Patients with ischemic stroke or TIA who drink >2 alcoholic drinks a day for men or >1 alcoholic drink a day for women should be counseled to eliminate or reduce their consumption of alcohol to reduce stroke risk.[141,161–163]
1	C-EO	2. In patients with stroke or TIA who use stimulants (eg, amphetamines, amphetamine derivatives, cocaine, or khat) and in patients with infective endocarditis (IE) in the context of intravenous drug use, it is recommended that health care providers inform them that this behavior is a health risk and counsel them to stop.
1	C-EO	3. In patients with stroke or TIA who have a substance use disorder (drugs or alcohol), specialized services are recommended to help manage this dependency.

Synopsis

The PAR for stroke associated with harmful alcohol consumption (>30 drinks per month or binge drinking >5 drinks per day at least once per month) is 3.8%, (99% CI, 0.9–14.4).[5a] In addition, binge drinking in those with known hypertension markedly increases cardiovascular mortality risk and is cumulative (HR, 4.41 [95% CI, 1.38–14.1] for ≥6 drinks; HR, 12.7 [95% CI, 3.47–46.5] for ≥12 drinks on 1 occasion).[164]

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Alcohol consumption and ischemic stroke have a J-shaped relationship, regardless of sex.[162,163] Stroke risk is associated with heavy alcohol consumption (>4 drinks in a day or >14 drinks a week in men; >3 drinks a day or >7 drinks a week in women).[18,165] The risk of harmful alcohol consumption in recurrent stroke is not well defined; >60 g/d (>4 drinks a day) has been associated with stroke recurrence at 90 days,[161] matching a meta-analysis of an RR of 1.69 (95% CI, 1.34–2.15) for ischemic stroke at that consumption level.[166] The World Drug Report (2017) relates a 23% increase in the number of estimated drug users in 11 years, reaching 255 million in 2015.[167] A sharp increase in US stroke rates attributable to IE was noted to coincide with the emergent opioid epidemic.[168] Evidence supporting an association between drug use and ischemic stroke, notably in stimulants and developing in cannabis use, is emerging[18,169–171] and must be addressed in stroke prevention strategies.

Recommendation-Specific Supportive Text

1. Although behavioral interventions, for example, the STOP (secondary stroke prevention) trial, can show decreased alcohol consumption levels,[141] their impact on recurrent stroke is not delineated. High alcohol intake (>60 g/d), however, has been identified as an independent risk factor for stroke recurrence at 90 days in minor stroke/TIA.[161] In ischemic stroke, low to moderate alcohol consumption is protective, but increased risk at higher exposure levels exists. The EPIC-CVD observational case-cohort study (European Prospective Investigation into Cancer and Nutrition-CVD) (N>32 000) identified an ischemic stroke HR of 1.04 (95% CI, 1.02–1.07) per 12–g/d increase in alcohol consumption. Compared with a reference value of 0.1 to 4.9 g/d, HRs for ischemic stroke are 1.03 (95% CI, 0.93–1.14), 1.08 (95% CI, 0.96–1.22), 1.10 (95% CI, 0.96–1.26), and 1.31 (95% CI, 1.07–1.60) for 5.0–14.9, 15.0 to 29.9, 30.0 to 59.9, and ≥60 g/d total alcohol intake, respectively.[162] In both men and women, compared with lifetime abstainers, alcohol consumption of <12 g/d (≈1 drink a day based on US conversions) is associated with the lowest risk for mortality.
2. No data confirm drug use and recurrent stroke risk. Current users of amphetamine-type stimulants have a higher ischemic stroke risk–adjusted RR (methylphenidate) of 1.6 (95% CI, 1.1–2.4)[172] and adjusted HR (any) for TIA of 3.4 (95% CI, 1.1–10.6).[169,173,174] A systematic review of cocaine use[170] identified an increased likelihood of ischemic stroke (adjusted OR, 2.03 [95% CI, 1.48–2.79])[175] and stroke (type unspecified; all-female study) for powder/paste cocaine (adjusted OR, 13.9 [95% CI, 2.8–69.0]) and crack cocaine (adjusted OR, 11.2 [95% CI, 1.1–118.8]).[176] Khat use is associated with stroke (OR, 2.7 [95% CI, 1.3–5.9).[171] Although the CARDIA study (Coronary Artery Risk Development in Young Adults) identified no significant risk for stroke/TIA as a result of cumulative lifetime cannabis use of ≥5 years or recent use,[177] increasing evidence of an association is emerging in younger-onset stroke. Acute ischemic stroke hospitalization is higher among cannabis users (OR, 1.41 [95% CI, 1.31–1.51]),[178] and the US Centers for Disease Control and Prevention[179] identified that young adults (age, 18–44 years) with recent cannabis use have higher odds of stroke compared with nonusers (adjusted OR, 1.82 [95% CI, 1.08–3.10]), which increases among frequent cannabis users (>10 d/mo; adjusted OR, 2.45 [95% CI, 1.31–4.60]).
3. An alcohol or drug use disorder is a chronic relapsing brain disease characterized by compulsive use, loss of control over intake, and a negative emotional state when not using. Therefore, specialized care is required to manage the substance dependency. In alcohol use disorders, established screening and counseling strategies such as those described in the 2004 US Preventive Services Task Force update are recommended. Long-term treatment strategies, including medication, psychological counseling, and community-based programs, are effective in the management of drug dependency.[180–182]

Lifestyle Knowledge Gaps and Future Research

Lifestyle recommendations in stroke secondary prevention draw from convincing primary prevention data and broader CVD populations. Recurrent stroke lacks robust evidence supporting interventions addressing smoking and diet/nutrition,[96,103,183] are limited to nondisabling stroke in physical activity,[110] and are absent for substance use. Optimal time windows to deliver lifestyle interventions after stroke are unknown. Future research in established stroke or TIA is required for the following:

- To identify the effects on recurrent stroke of proven dietary interventions (eg, Mediterranean or DASH diets) compared with usual care.
- To identify the effect on recurrent stroke of dietary sodium reduction or potassium increase, including the most efficacious and safe target.
- To establish whether higher recurrent stroke rates in underweight individuals[184] are attenuated with nutritional supports.
- To trial activity-based interventions (including breaking sedentary time), inclusive of individuals with mobility impairment, exploring the role of adaptive/electromechanically assisted devices when required.

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- To establish optimal physical activity prescription (frequency, intensity, time, and type [aerobic, resistance, mixed]) for secondary prevention. Potential synergistic effects of aerobic exercise combined with resistance-based strengthening exercises in stroke secondary prevention are unknown.
- To further develop stroke registries to address knowledge gaps in recurrent stroke, including the contribution of continued smoking (currently limited to Asian and older populations), heavy alcohol consumption (currently lacking), and substance use (currently lacking).
- To identify the longer-term cardiovascular consequences of newer tobacco products, for example, electronic nicotine delivery systems (electronic cigarettes/vaping), which are not currently known.
- To consider the dual use of electronic nicotine delivery systems (electronic cigarettes/vaping) with combustible cigarettes in studies relating to the longer-term cardiovascular consequences, including stroke and recurrent stroke.
- To examine the association between ischemic stroke and recurrent stroke and therapeutic cannabis use (currently unknown) and recreational cannabis use (currently limited to young adults only and using surveillance data).

4.2. Hypertension

Recommendations for Hypertension Referenced studies that support recommendations are summarized in online Data Supplements 11 and 12.		
COR	**LOE**	**Recommendations**
1	A	1. In patients with hypertension who experience a stroke or TIA, treatment with a thiazide diuretic, angiotensin-converting enzyme inhibitor, or angiotensin II receptor blockers is useful for lowering BP and reducing recurrent stroke risk.[185–189]
1	B-R	2. In patients with hypertension who experience a stroke or TIA, an office BP goal of <130/80 mm Hg is recommended for most patients to reduce the risk of recurrent stroke and vascular events.[185,190–194]
1	B-NR	3. In patients with hypertension who experience a stroke or TIA, individualized drug regimens that take into account patient comorbidities, agent pharmacological class, and patient preference are recommended to maximize drug efficacy.[188,189,195,196]
2a	B-R	4. In patients with no history of hypertension who experience a stroke or TIA and have an average office BP of ≥130/80 mm Hg, antihypertensive medication treatment can be beneficial to reduce the risk of recurrent stroke, ICH, and other vascular events.[190,191,193,197]

Synopsis

The PAR of stroke resulting from hypertension may be as high as 50% in some racial and ethnic groups.[198,199] In 2017, the AHA/ACC hypertension guideline defined hypertension as BP consistently >130/80 mm Hg.[29] Yet, for patients with prior stroke or TIA, there is concern that a possible lower BP threshold may increase the risk of stroke, or a J-curve effect. In the past, post hoc analyses of RCTs, meta-analyses, and population-based studies of patients with cerebrovascular disease have shown an inconsistent relationship between achieved SBP <120 mm Hg and poor outcomes.[200–204] New data from RCTs and large meta-analyses now provide compelling evidence that neurologically stable patients with cerebrovascular disease also benefit from a BP goal of <130/80 mm Hg and that BP targets for stroke prevention should be more aligned with targets for prevention of other cardiovascular conditions. There is insufficient evidence to recommend a lower limit of BP within the normal range for patients with prior stroke. Additional research is needed to determine the optimal timing for BP reduction after stroke[205]; therefore, these recommendations pertain to outpatient management of neurologically stable patients.

Recommendation-Specific Supportive Text

1. Diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers have demonstrated benefit in RCTs or systematic reviews of RCTs.[185–188,206] Although calcium channel blockers are recommended for the treatment of hypertension, there are limited data on their efficacy for secondary stroke prevention. However, the use of calcium channel blockers is reasonable for patients with stroke who require additional medication options.[185]
2. Data from 4 RCTs and recent meta-analyses support a benefit of treating patients with prior stroke or TIA to achieve a goal BP of <130/80 mm Hg. The RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment),[190] PAST-BP (Prevention After Stroke–Blood Pressure),[191] SPS3 (Secondary Prevention of Small Subcortical Strokes),[192] and PODCAST (Prevention of Decline in Cognition after Stroke Trial)[193] RCTs all compared intensive control of BP (SBP targets ranging from <120–<130 mm Hg) with standard BP control (SBP targets ranging from <140–<150 mm Hg) in patients with prior cerebrovascular disease. These trials all reported nonsignificant tendencies toward lower recurrent stroke rates in the intensive treatment groups. However, a meta-analysis of these 4 trials showed a significant reduction in recurrent stroke risk with an intensive versus standard target (RR, 0.78 [95% CI, 0.64–0.96]). An independent Cochrane analysis[185] of SPS3, PAST-BP, and PODCAST (done before RESPECT publication) reported a trend toward benefit of intensive BP

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targets (pooled RR for recurrent stroke, 0.80 [95% CI, 0.63–1.00]). In addition, the largest meta-analysis to date including >40 000 patients from 14 RCTs showed a significantly lower rate of recurrent stroke in patients with an achieved SBP of <130 mg Hg compared with higher SBP groups.[194] It should be noted that for patients with intracranial large artery atherosclerosis, a higher BP target may be appropriate (see Section 5.1.1).

3. The magnitude of BP lowering appears to be more important for risk reduction than the class of antihypertensive agent used.[188,189,195,196] Therefore, individual patient characteristics that may affect the safety and efficacy of treatment (eg, T2D, chronic kidney disease, AF) should be taken into account in the selection of antihypertensive agents.
4. The recommended threshold BP of >130/80 mm Hg for starting antihypertensive medications is informed by the baseline BPs of patients with cerebrovascular disease studied in trials of BP treatment. Among the 4 RCTs comparing intensive and standard BP targets in patients with prior cerebrovascular disease, the RESPECT[190], PAST-BP,[191] and PODCAST[193] trials included patients with baseline SBPs as low as 125 mm Hg. In PAST-BP,[191] ≈50% of patients had baseline SBP <140 mm Hg. Similarly, in the PRoFESS trial (Prevention Regimen for Effectively Avoiding Second Strokes) of >20 000 patients with ischemic stroke,[197] ≈33% of patients had baseline SBP <135 mm Hg. The large number of subjects with prior stroke and SBP <140 mm Hg included in these trials supports the safety and efficacy of the use of antihypertensive medications in patients with SBP >130 mm Hg, which is the threshold recommended for secondary prevention of vascular events in the AHA/ACC hypertension guideline.[29]

Knowledge Gaps and Future Research

The ongoing randomized ESH-CHL-SHOT trial (European Society of Hypertension and Chinese Hypertension League Stroke in Hypertension Optimal Treatment) will provide further insight into the optimal BP target for patients with prior stroke.[207] Areas of future research on hypertension and stroke include the following:

- What is the optimal timing to begin BP lowering after acute stroke?
- What is the optimal time during the day for BP medication administration to prevent recurrent stroke?
- Do lower BP targets improve or worsen cognition in patients with prior stroke?
- What is the optimal BP target for very elderly patients with stroke?
- What is the optimal BP target for patients with diabetes with stroke?

4.3. Treatment of Hyperlipidemia for Secondary Prevention of Stroke

4.3.1. Treatment and Monitoring of Blood Lipids for Secondary Stroke Prevention

Recommendations for Treating and Monitoring Hyperlipidemia
Referenced studies that support recommendations are summarized in online Data Supplement 13.

COR	LOE	Recommendations
		Treatment
1	A	1. In patients with ischemic stroke with no known coronary heart disease, no major cardiac sources of embolism, and LDL cholesterol (LDL-C) >100 mg/dL, atorvastatin 80 mg daily is indicated to reduce risk of stroke recurrence.[208,209]
1	A	2. In patients with ischemic stroke or TIA and atherosclerotic disease (intracranial, carotid, aortic, or coronary), lipid-lowering therapy with a statin and also ezetimibe, if needed, to a goal LDL-C of <70 mg/dL is recommended to reduce the risk of major cardiovascular events.[210]
2a	B-NR	3. In patients with ischemic stroke who are very high risk (defined as stroke plus another major ASCVD or stroke plus multiple high-risk conditions), are taking maximally tolerated statin and ezetimibe therapy and still have an LDL-C >70 mg/dL, it is reasonable to treat with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor therapy to prevent ASCVD events.[211–213]
		Monitoring
1	A	4. In patients with stroke or TIA and hyperlipidemia, patients' adherence to changes in lifestyle and the effects of LDL-C–lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4 to 12 weeks after statin initiation or dose adjustment and every 3 to 12 months thereafter, based on need to assess adherence or safety.[214,215]

Synopsis

Two RCTs, SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels)[208] and TST (Treat Stroke to Target),[210] evaluated lipid-lowering therapy in patients after ischemic stroke. Both trials found significant benefit from cholesterol-lowering therapy in preventing vascular events, including stroke. SPARCL found that atorvastatin 80 mg daily reduced stroke recurrence in patients without another indication for statin therapy. TST confirmed that target LDL-C <70 mg/dL was superior to a target of 90 to 110 mg/dL for preventing major cardiovascular events. These 2 trials do not pertain to patients with cardioembolic stroke and no atherosclerotic disease. These 2 stroke-specific trials are further supported by numerous RCTs of lipid-lowering drugs that indicate that high-risk patients with ASCVD should receive high-intensity statin therapy and that if LDL-C remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin therapy, it may be reasonable to add ezetimibe and then a PCSK-9 inhibitor if necessary and if patients are deemed to be at very high risk (Table 5).

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Table 5. Very High Risk of Future ASCVD Events

Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions:
Major ASCVD events
History of ischemic stroke
Recent acute coronary syndrome (within the past 12 mo)
History of MI (other than recent ACS event listed above)
Symptomatic peripheral arterial disease (history of claudication with ankle-brachial index <0.85 or previous revascularization or amputation
High-risk conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD events
Diabetes
Hypertension
Chronic kidney disease (estimated glomerular filtration rate, 15–59 mL·min^{-1}·1.73 m^{-2})
Current smoking

The information in this table is from the 2018 AHA/ACC Guideline on the Management of Blood Cholesterol.[31] For high-intensity statin therapy, the guideline recommends atorvastatin 80 mg daily or rosuvastatin 20 mg daily. Please refer to the guideline for contraindications to high-intensity statin therapy and recommendations for moderate-intensity statin therapy. ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; and MI, myocardial infarction.

The information in this table is from the 2018 AHA/ACC guideline on the management of blood cholesterol.[31] For high-intensity statin therapy, the guideline recommends atorvastatin 80 mg daily or rosuvastatin 20 mg daily. Please refer to the guideline for contraindications to high-intensity statin therapy and recommendations for moderate-intensity statin therapy.

Recommendation-Specific Supportive Text

1. The SPARCL trial included adults who had an ischemic or hemorrhagic stroke (or TIA presumably owing to atherosclerotic causes) in the prior 1 to 6 months and an LDL-C level of 100 to 190 mg/dL. The main exclusion criteria were coronary heart disease, peripheral vascular disease, AF, a prosthetic heart valve, clinically significant mitral stenosis, or sinus node dysfunction. There was no exclusion based on ischemic stroke subtype, although practically, most patients with cardioembolic stroke would be excluded on the basis of the exclusion criteria related to cardiac disease. Eligible patients were randomized to atorvastatin 80 mg or placebo. During a median follow-up of 4.9 years, the primary end point of stroke occurred in 11.2% of patients receiving atorvastatin versus 13.1% of patients receiving placebo (adjusted HR, 0.84 [95% CI, 0.71–0.99]).[208]
2. The TST trial included adults with cerebral infarction in the prior 3 months or high-risk TIA (that included at least arm and leg motor deficit or speech disturbance lasting >10 minutes) in the prior 15 days, documented atherosclerotic disease (defined as carotid, aortic, intracranial, or coronary atherosclerotic disease), and a clear indication for statin therapy. The main exclusion criteria were a cardioembolic stroke/TIA without documented atherosclerotic disease, a baseline LDL-C <100 mg/dL while not taking a statin, inability to intensify statin therapy (already on maximum dose), or a history of symptomatic hemorrhagic stroke. Eligible patients were randomly assigned to an LDL-C target of <70 mg/dL (lower-target group) versus 90 to 110 mg/dL (higher-target group). LDL-C targets were pursued by intensification of statin therapy and the addition of ezetimibe if needed. During a median 3.5 years of follow-up, the primary composite outcome of major cardiovascular events occurred in 8.5% of those in the lower-target group versus 10.9% in the higher-target group (HR, 0.78 [95% CI, 0.61–0.98]).[210] In addition, a secondary analysis of the IMPROVE-IT trial (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) found a significantly lower risk of ischemic stroke with ezetimibe treatment (in addition to simvastatin) among patients with previous MI.[216]
3. Very high-risk patients include those with history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. In these patients, additional benefit from LDL-C lowering when LDL-C is > 70 mg/dL (1.8 mmol/L) or non–high-density lipoprotein >100 mg/dL (2.6 mmol/L) by ezetimibe and 2 PCSK9 inhibitors (evolocumab and alirocumab) was demonstrated by 3 RCTs.[211–213] This guideline strongly recommends (COR 1) that ezetimibe be added to maximally tolerated statin as a first step to further lower LDL-C. Although no RCT tested the strategy of ezetimibe first and then a PCSK9 inhibitor, ezetimibe was allowed at entry with statin therapy in both PCSK9 inhibitor trials (FOURIER [Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk] and ODYSSEY OUTCOMES [Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab]), but only 3% and 5% received ezetimibe during these trials. Ezetimibe use before PCSK9 inhibitor is recommended because ezetimibe is available as a generic drug and has proven safety.[211] This approach is supported by 2 simulation studies from large populations of very high-risk patients showing that ezetimibe plus statin therapy lowers LDL-C to <70 mg/dL (1.8 mmol/L) in most patients, leaving a minority eligible for a PCSK9 inhibitor.[217,218] In addition, the TST trial of patients with ischemic stroke used ezetimibe as second-line therapy to achieve the LDL-C

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target of <70 mg/dL (1.8 mmol/L),[210] supporting the use of ezetimibe before PCSK-9 inhibitors in patients with ischemic stroke who are not at their LDL-C targets.

4. Goals and clinical efficacy for LDL-C lowering are defined and monitored by percentage LDL-C reductions relative to baseline levels. Baseline LDL-C is estimated by pretreatment measurements, chart reviews, or measurement after drug therapy is interrupted. Without a baseline level, response to therapy is difficult to evaluate. Adherence to LDL-lowering diets reduces LDL-C levels 10% to >15%.[214] Moderate-intensity statins reduce LDL-C levels by another 30% to 49%; high-intensity statins, by ≥50%. Adding ezetimibe or bile acid sequestrants to statin therapy reduces LDL-C by an additional 15% to 25%. Adding a PCSK9 inhibitor to statin plus ezetimibe causes greater reductions. Lifestyle changes and statin therapy are commonly introduced together. The maximum percentage change occurs 4 to 12 weeks after therapy is started, at which time drug efficacy or initial adherence to therapy can be evaluated. Periodic remeasurements can confirm adherence to therapy. Because recommended intensities of drug therapies vary in adolescents, young adults, adults 40 to 75 years, those with severe hypercholesterolemia, and those treated for secondary prevention, the recommended LDL-C levels to achieve also vary. Given the modest differences in LDL-C levels associated with the postprandial state, a nonfasting sample is effective to document baseline lipid levels before initiation of statin therapy.

4.3.2. Treatment of Hypertriglyceridemia

Recommendations for Hypertriglyceridemia Referenced studies that support recommendations are summarized in online Data Supplement 13.		
COR	**LOE**	**Recommendations**
2a	**B-R**	1. In patients with ischemic stroke or TIA, with fasting triglycerides 135 to 499 mg/dL and LDL-C of 41 to 100 mg/dL, on moderate- or high-intensity statin therapy, with HbA1c <10%, and with no history of pancreatitis, AF, or severe heart failure, treatment with icosapent ethyl (IPE) 2 g twice a day is reasonable to reduce risk of recurrent stroke.[219,220]
2a	**B-NR**	2. In patients with severe hypertriglyceridemia (ie, fasting triglycerides ≥500 mg/dL [≥5.7 mmol/L]), it is reasonable to identify and address causes of hypertriglyceridemia and, if triglycerides are persistently elevated or increasing, to further reduce triglycerides in order to lower the risk of ASCVD events by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy.[221–223]

Synopsis

The categories of hypertriglyceridemia are moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175–499 mg/dL [2.0–5.6 mmol/L]) and severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.6 mmol/L]). In the former, excess triglycerides are carried in very-low-density lipoprotein (VLDL). In the latter, most patients have elevated VLDL plus chylomicrons. VLDL are atherogenic, similar to LDL. There are many causes of elevated VLDL, and it is reasonable to reduce their levels to reduce the risk of ASCVD. With severe hypertriglyceridemia, elevations of VLDL raise the risk of ASCVD, but as triglyceride levels increase, especially above 1000 mg/dL, increases in chylomicrons impart a risk of acute pancreatitis. In patients with ASCVD receiving recommended statin therapy, residual cardiovascular risk is present. Elevated triglycerides are associated with such risk. Treatment to reduce triglycerides with extended-release niacin and fibrates in addition to statin therapy has not improved cardiovascular outcomes. However, IPE has been shown to reduce major adverse cardiovascular events (MACEs; ie, cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina), including ischemic stroke, when added to moderate- or high-intensity statin therapy in patients with LDL-C of 41 to 100 mg/dL. In this study, patient enrollment criteria included T2D with multiple risk factors for ASCVD (29%) or history of ASCVD (71%).[219] Almost 60% of the entire cohort had T2D.

Recommendation-Specific Supportive Text

1. The REDUCE-IT trial (Reduction of Cardiovascular Events With Icosapent Ethyl–Insstervention Trial)[219] randomized 8179 patients with ASCVD including history of ischemic stroke or TIA (70%) or diabetes with other risk factors (30%) to IPE 2 g twice daily plus statin versus statin alone. Enrollment criteria included fasting triglycerides of 135 to 499 mg/dL and LDL-C of 41 to 100 mg/dL on statin dose for ≥4 weeks. Follow-up for a median of 4.9 years revealed a 25% reduction (17.2% IPE versus 22.0% control; HR, 0.75 [95% CI, 0.68–0.83]; $P<0.001$) in the primary end point of MACEs. Results for nonfatal stroke and TIA were the same for MACEs. No difference occurred in hemorrhagic stroke. A small, significant increase in AF occurred in those treated with IPE (5.3% versus 3.9%). Because benefits were similar across baseline triglycerides and unrelated to triglyceride levels attained, the mechanism by which IPE reduces MACEs, including secondary prevention of stroke, is unknown, possibly related to factors other than lowering triglycerides. The JELIS trial (Japan EPA Lipid Intervention Study)[220] found a 20% relative reduction of

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stroke in hypercholesterolemic patients treated with IPE, an ester derivative of eicosapentaenoic acid (EPA), and low-dose statin. Two studies, the STRENGTH trial (Outcomes Study to Assess Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia)[224] and the OMEMI trial (Omega-3 Fatty Acids in Elderly Patients With Acute Myocardial Infarction)[225] (underpowered), found no benefit from combined EPA/docosahexaenoic acid (DHA) in patients with high CVD risk, diabetes, or CVD. Treatment with EPA/DHA resulted in lower median blood EPA levels in STRENGTH than those achieved by treatment with IPE in REDUCE-IT, which had a 25% reduction in the primary end point. Because triglyceride levels were similar, higher EPA levels may account for the results seen in REDUCE-IT. In addition, the differing effects of EPA and DHA on membrane stabilization may contribute to the lack of effect with EPA/DHA compared with EPA alone or IPE.

2. Most patients with triglycerides ≥500 mg/dL (≥5.6 mmol/L) have increased VLDL and chylomicrons. Increased chylomicrons occur when triglycerides are ≥500 mg/dL (≥5.6 mmol/L). With increasing triglyceride concentrations, chylomicronemia may intensify and cause acute pancreatitis. Higher triglycerides levels convey greater risk.[222] Patients with triglycerides from 500 to 999 mg/dL are at risk of developing unrecognized marked increases in triglycerides, leading to pancreatitis. Most cases of severe hypertriglyceridemia have a genetic component, but the hallmark of hypertriglyceridemic pancreatitis is the combination of both genetic and acquired causes of elevated triglycerides.[226] To prevent acute pancreatitis, it is reasonable to reduce triglycerides whenever levels exceed 500 mg/dL. This reduction can be achieved by addressing and eliminating the underlying factors by implementing a very low-fat diet[223] and by adding fibrates or omega-3 fatty acids for patients with persistently elevated severe hypertriglyceridemia.[221] These are the most reliable therapies to reduce triglycerides to a safer level. If a fibrate is necessary in a patient being treated with a statin, fenofibrate is safer than gemfibrozil because of a lower risk of severe myopathy.[227] Severe hypertriglyceridemia during pregnancy is best managed in consultation with a lipid specialist.[228]

Knowledge Gaps and Future Research

Areas where our knowledge is limited and therefore would benefit from further research include the following:

- Combination therapy (combined EPA/DHA compared with IPE).
- The effect that placebo composition might have on lipids and outcomes (eg, mineral oil versus corn oil).

4.4. Glucose

Recommendations for Glucose
Referenced studies that support recommendations are summarized in online Data Supplements 14 and 15.

COR	LOE	Recommendations
1	A	1. In patients with an ischemic stroke or TIA who also have diabetes, the goal for glycemic control should be individualized based on the risk for adverse events, patient characteristics and preferences, and, for most patients, especially those <65 years of age and without life-limiting comorbid illness, achieving a goal of HbA1c ≤7% is recommended to reduce risk for microvascular complications.[229,230]
1	B-R	2. In patients with an ischemic stroke or TIA who also have diabetes, treatment of diabetes should include glucose-lowering agents with proven cardiovascular benefit to reduce the risk for future major adverse cardiovascular events (ie, stroke, MI, cardiovascular death).[231–236]
1	C-EO	3. In patients with an ischemic stroke or TIA who also have diabetes, multidimensional care (ie, lifestyle counseling, medical nutritional therapy, diabetes self-management education, support, and medication) is indicated to achieve glycemic goals and to improve stroke risk factors.
2a	B-R	4. In patients with prediabetes and ischemic stroke or TIA, lifestyle optimization (ie, healthy diet, regular physical activity, and smoking cessation) can be beneficial for the prevention of progression to diabetes.[237,238]
2a	C-EO	5. In patients with TIA or ischemic stroke, it is reasonable to screen for prediabetes/diabetes using HbA1c which, among available methods (HbA1c, fasting plasma glucose, oral glucose tolerance), has the advantage of convenience because it does not require fasting and is measured in a single blood sample.
2b	B-R	6. In patients with an ischemic stroke or TIA who also have diabetes, the usefulness of achieving intensive glucose control (ie, HbA1c ≤7%) beyond the acute phase of the ischemic event for prevention of recurrent stroke is unknown.[239–244]
2b	B-R	7. In patients with prediabetes and ischemic stroke or TIA, particularly those with a body mass index (BMI) ≥35 kg/mP^2, ≥35 kg/m^2 those <60 years of age, or women with a history of gestational diabetes, metformin may be beneficial to control blood sugar and to prevent progression to diabetes.[245–247]
2b	B-R	8. In patients ≤6 months after TIA or ischemic stroke with insulin resistance, HbA1c <7.0%, and without heart failure or bladder cancer, treatment with pioglitazone may be considered to prevent recurrent stroke.[248]

Synopsis

The principal disorders of glucose metabolism are type 1 diabetes, T2D, and prediabetes. Type 1 diabetes is an autoimmune disorder that results in absolute insulin deficiency and accounts for 6% of diabetes in the United States. T2D results from progressive impairment in peripheral insulin sensitivity and pancreatic insulin secretion. It accounts for 91% of diabetes in the United

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States. Prediabetes has the same pathophysiology as T2D but is associated with lower plasma glucose than in T2D. The prevalence of diagnosed diabetes among US adults is 9%.[249] Prediabetes and diabetes are associated with increased risk for first ischemic stroke (RR, 1.5%–3.7% for diabetes).[250–254] Prediabetes is present in ≈30% of patients with acute ischemic stroke[255] and is associated with increased risk for recurrence.[256] Progression of prediabetes to T2D can be prevented by maintaining a healthy weight, exercising, eating a healthy diet, and taking certain medications.[237,238,245] T2D is also present in ≈30% of patients with ischemic stroke[255] and is associated with increased risk for recurrence (RR, ≈1.6).[209,257] Remission of established T2D can be achieved by weight loss,[258–260] although no trials have established that weight loss or diabetes remission reduces risk for recurrent stroke. Recent clinical trials demonstrated that at least 1 drug in each of the 3 classes of glucose-lowering medications can reduce risk for MACEs in patients with T2D and established atherosclerotic vascular disease, including ischemic stroke or high risk: thiazolidinediones, glucagon-like protein 1 (GLP-1) receptor agonist, and sodium-glucose cotransporter 2 inhibitor. Unlike the data for the thiazolidinedione pioglitazone and some GLP-1 receptor agonists, the cardiovascular outcome trials of sodium-glucose cotransporter 2 inhibitors do not suggest a specific effect on stroke but rather on cardiovascular death, MI, and heart failure.[261]

Recommendation-Specific Supportive Text

1. Intensive control of blood sugar for patients with both type 1 diabetes and T2D has been shown to reduce risk for microvascular complications, including retinopathy, nephropathy, and peripheral neuropathy. The first evidence emerged from the DCCT (Diabetes Control and Complication Trial), which enrolled patients with type 1 diabetes between 13 and 39 years of age.[229] Participants were randomized to conventional glucose control (goal to avoid symptoms of hyperglycemia, to avoid ketonuria, and to preserve normal growth) or intensive control to achieve near-normal glucose. After a mean of 6.5 years, intensive control delayed the onset or progression of nephropathy, retinopathy, and neuropathy. The findings were confirmed for patients with T2D in the UKPDS (United Kingdom Prospective Diabetes Study).[230] As in DCCT, however, intensive control was associated with increased risk for hypoglycemia. The American Diabetes Association recommends a target HbA1c <7% for most adult patients.[262] The American Diabetes Association, however, advocates for less stringent goals (eg, 7%–8%) for patients with a limited life expectancy, history of hypoglycemia, long-standing disease, or advanced microvascular or macrovascular disease when the risk and inconvenience of intensive control outweigh the potential benefit.
2. In response to the development of new classes of glucose-lowering medications that also prevent clinical vascular disease, the American Diabetes Association, the European Association for the Study of Diabetes, and other professional organizations have revised their algorithms for the management of T2D. An evidence-based consensus report by the American Diabetes Association and European Association for the Study of Diabetes recommends metformin and comprehensive lifestyle optimization as first-line therapy.[263] In patients with established ASCVD, including ischemic stroke, when prevention of further vascular events is the priority, GLP-1 receptor agonist therapy should be added to metformin independently of baseline HbA1c. When concern for heart failure or chronic kidney disease predominates, addition of a sodium-glucose cotransporter 2 inhibitor to metformin is recommended. These developments in management have implications for the care of patients with diabetes and ischemic stroke. Clinicians should now engage patients in a discussion of the new therapies and alternatives. Through shared decision-making, clinicians should help patients decide if a GLP-1 receptor agonist or a sodium-glucose cotransporter 2 inhibitor is right for them. Risk for future vascular disease is only one consideration in selecting among available diabetes medications. Cost, side effects, desire for weight loss, aversion to injection therapy, and desire to reduce risk for hypoglycemia are also important.
3. Optimal management of T2D is achieved with a multidimensional approach that includes (1) medical nutritional therapy; (2) lifestyle counseling (for physical activity, weight loss, smoking cessation, etc); (3) diabetes self-management, education, and support; and (4) medication therapy.[263,264] For patients with overweight or obesity, it can be helpful to include intensive behavioral counseling for weight loss in medical nutritional therapy. T2D in most patients is highly responsive to weight optimization; weight loss can result in diabetes remission for some patients and reduced medication use in most.
4. Multifactorial interventions to simultaneously improve diet quality, increase physical activity, and reduce body weight reduce risk for progression to diabetes among patients with impaired glucose tolerance by 43% to 58% during 3 to 5 years of treatment.[237,238] The benefit achieved is in proportion to patients' ability to achieve lifestyle goals.
5. Approximately 20% of patients with acute ischemic stroke will be found to have undiagnosed diabetes after testing with an HbA1c or oral

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glucose tolerance test.[255] These patients are at risk for progressing to symptomatic disease and for developing complications related to their diabetes, including microvascular and macrovascular disease. With the development of drugs that both control glucose and reduce risk for major adverse cardiovascular events, it has become more important to identify all patients with diabetes after an ischemic stroke so that they can be offered appropriate therapy. Available methods to screen for diabetes include fasting blood sugar, oral glucose tolerance test, and HbA1c. Of these, HbA1c has advantages in that it is more convenient (ie, it does not require fasting), has less variability day to day, and is less likely to be perturbed by medications, stress, or illness.[265] In general, HbA1c may be more accurate than other screening tests in the immediate postevent period. It is probably the preferred method of diagnosis for patients hospitalized with an acute stroke.

6. Compared with evidence for a benefit in microvascular disease, there is less evidence for a benefit of intensive glucose control on macrovascular end points such as stroke. No macrovascular benefit was demonstrated in the main publications from DCCT, the UKPDS, or 3 other more recent trials designed to test intensive control for prevention of macrovascular disease.[239–241] However, a benefit of intensive control emerged during long-term follow-up of the DCCT[242] and the UKPDS. Two meta-analysis of 5 trials that included the UKPDS reported a benefit of intensive control for some cardiovascular outcomes but not for stroke.[243,244] No trials or meta-analyses have reported the effect of intensive control on patients with a history of stroke. Many experts conclude that the benefit of intensive control on macrovascular disease is likely restricted to younger patients with recent-onset diabetes and without established vascular disease. In this regard, however, some professional organizations recommend targeting an HbA1c of 7% to 8% or even 8% to 9% to reduce the risk for hypoglycemia in elderly individuals with limited life expectancy or significant comorbid illness.[266,267]
7. Although lifestyle change is the safest and most efficacious method to prevent progression from prediabetes to diabetes, several drugs have demonstrated benefit. In the Diabetes Prevention Program trial, patients with impaired glucose tolerance were randomized to standard lifestyle recommendations plus metformin 850 mg twice a day, standard lifestyle recommendation plus placebo, or intensive lifestyle counseling. The primary outcome, progression to diabetes, was observed in 11.0%, 7.8%, and 4.8% of patients in the placebo, metformin, and intensive counseling groups. The rate of progression was 58% lower (95% CI, 48–66) with intensive counseling and 31% (95% CI, 17–43) lower with metformin compared with standard lifestyle counseling. Metformin is well tolerated and inexpensive. Other drugs that have been shown to reduce progression to diabetes include pioglitazone,[245] acarbose,[246] liraglutide,[247] and dapagliflozin.[268] These are not as well tolerated as metformin. Liraglutide is delivered by injection.
8. Approximately 30% of patients with ischemic stroke have prediabetes as defined by HbA1c and other measures of glucose metabolism.[255] Most of these patients will have insulin resistance as a contributing cause, but insulin resistance can occur before prediabetes develops. Thus, ≈50% of patients without diabetes with ischemic stroke have insulin resistance.[269,270] Both conditions have been associated with increased risk for first ischemic stroke,[252,253,271–275] but no research has been designed to test their effect on risk for recurrent vascular events. One large clinical trial has examined the effect of a specific intervention for patients with ischemic stroke and insulin resistance. The IRIS trial (Insulin Resistance Intervention After Stroke) examined the effect of the insulin-sensitizing agent pioglitazone compared with placebo among patients without diabetes who had a recent ischemic stroke and insulin resistance. Patients with heart failure were excluded. After a mean of 3.8 years, pioglitazone reduced the risk of recurrent stroke or MI by 24% (RR, 0.76 [95% CI, 0.62–0.93]), from 11.8% among placebo recipients to 9.0% among pioglitazone recipients. Active treatment, however, was associated with weight gain and increased bone fracture risk. These adverse events have restrained clinical use of pioglitazone.

Knowledge Gaps and Future Research

Having T2D is one of the most prevalent risk factors for future stroke after an initial acute ischemic stroke or TIA. It is a promising target for secondary prevention because diabetes remission can be achieved in many patients through weight management and vascular protection can be achieved by newer glucose-lowering agents. In addition, diabetes is associated with CNS small vessel disease and vascular dementia. Potential areas of research include the following:

- It is plausible that interventions for prediabetes, established diabetes, and glucose management will reduce risk for neurocognitive outcomes and subclinical ischemic damage and discrete stroke events. The IRIS trial demonstrated that 1 glucose-lowering intervention, pioglitazone, prevented

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stroke and MI in patients with insulin resistance without diabetes. The benefit of other interventions for prediabetes, including GLP-1 receptor agonists, dietary improvement, and weight reduction, has not been investigated but would logically follow from the IRIS trial.

- The same interventions could be examined in patients with established diabetes.
- Some early investigations have explored the effectiveness of poststroke behavioral counseling and physical training, modeled on cardiac rehabilitation, for improving lifestyle after stroke.
- Because diabetes disproportionately affects Black and Hispanic communities, effective community-based research for diabetes prevention and management may yield interventions to reduce disparities in stroke risk and recovery.
- Because patients with ischemic stroke or TIA tend to be older and to have established vascular disease, the optimal goal for glycemic control remains uncertain. In this regard, however, some professional organizations recommend targeting an HbA1c of 7% to 8% or even 8% to 9% to reduce the risk for hypoglycemia in elderly individuals with limited life expectancy or significant comorbid illness.[266,267]

4.5. Obesity

Recommendations for Obesity
Referenced studies that support recommendations are summarized in online Data Supplements 16 and 17.

COR	LOE	Recommendations
1	B-R	1. In patients with ischemic stroke or TIA and who are overweight or obese, weight loss is recommended to improve the ASCVD risk factor profile.[259,276–279]
1	B-R	2. In patients with ischemic stroke or TIA who are obese, referral to an intensive, multicomponent, behavioral lifestyle-modification program is recommended to achieve sustained weight loss.[238,258,280,281]
1	C-EO	3. In patients with ischemic stroke or ASCVD, calculation of BMI is recommended at the time of their event and annually thereafter, to screen for and to classify obesity.

Synopsis

Approximately 38% of US adults have obesity.[282] By 2030, prevalence is expected to reach 50%.[283] In population studies, obesity increases risk for ischemic stroke by 50% to 100% compared with patients who have a normal weight.[284–290] The causal pathway from obesity to stroke risk is mediated by factors that track closely with weight, particularly elevated BP, AF, dyslipidemia, and hyperglycemia.[291] Obesity can be treated with intensive behavioral counseling to change eating patterns, medications that reduce appetite, and metabolic surgery. Weight loss of as little as 5% to 10% produces meaningful improvements in vascular risk factors.[279] Only 1 trial has tested the effect of an intensive lifestyle intervention for weight loss on the prevention of vascular disease, and it was stopped early for futility.[292] Inadequate average weight loss in the active treatment group and statin therapy in the control group might explain the negative findings. Observational research provides some evidence that weight loss after bariatric surgery may reduce risk for stroke.[293,294] Approximately 24% to 30% of patients with acute ischemic stroke are obese.[295] Paradoxically, they have a reduced risk for stroke recurrence,[296,297] but this is likely attributable to selection bias.[298] Weight loss after stroke is expected to improve stroke risk factors, but the effect on future brain health has not yet been directly examined.

Recommendation-Specific Supportive Text

1. Our recommendation for weight loss in patients with overweight or obesity after stroke is consistent with the 2013 AHA guideline on obesity,[27] the 2014 AHA guideline on primary prevention,[18] and other professional guidelines on management of obesity.[299] Even a modest weight loss of 5% to 10% is associated with important improvements in conventional cardiovascular risk factors.[279] In particular, weight loss can improve glucose control in patients with diabetes.[277] The DiRECT trial (Diabetes Remission Clinical Trial) compared food substitution followed by stepped food reintroduction and structured support with best practice by guideline among patients with diabetes and BMI of 27 to 45 kg/m^2. After 12 months, 24% of participants in the intervention group lost ≥15 kg compared with none in the control group. Diabetes remission was achieved in 46% of patients in the intervention group and 4% in the control group. Studies of metabolic surgery confirm that weight loss is associated with improvements in glucose control, BP, indicators of inflammation, and lipid metabolism.[259,276,278]
2. Available strategies for helping patients achieve meaningful weight loss include intensive behavioral counseling, drugs to reduce appetite, and bariatric surgery. Of these, intensive behavioral counseling is recommended as the first option in evidence-based guidelines because of its greater effectiveness and safety compared with pharmacotherapy and greater safety and lower cost compared with metabolic surgery.[27,281,299,300] Components of multicomponent behavioral programs typically include goal setting, feedback, problem solving, coaching for physical activity, and frequent individual or group meetings (at least 12 sessions in the first year).[300] Examples include the Diabetes Prevention Program,[238] Weight Watchers,[280] and

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the Counterweight Program.[258] On average, behavior-based programs achieve ≈2.4 kg greater weight loss than control intervention over up to 24 month, and participants are more likely to lose 5% of their body weight.[281] Ideally, patients with obesity, according to need, are offered care in a comprehensive bariatric program in which all strategies for weight reduction are offered.

3. In 2012, the US Preventive Services Task Force issued a Grade B recommendation to screen all adults for obesity.[301] The recommendation is consistent with the AHA guideline on obesity from 2013 and more recent guidance from other professional organizations.[27,299] Although there is no direct evidence that weight loss interventions among patients with acute ischemic stroke reduce risk for recurrent stroke or otherwise improve future brain health, there is clear evidence that intensive counseling can help patients achieve meaningful weight loss.[281] The US Preventive Services Task Force determined that the risks for intensive counseling were small to none.[300] For selected patients, pharmacotherapy and bariatric surgery also may be effective, although surgical trials typically have excluded patients with stroke. Specific benefits of weight loss among patients with ischemic stroke include improved glucose metabolism, BP, and lipid metabolism. It also has a favorable effect on obstructive sleep apnea (OSA), AF, and vascular inflammation. Screening is necessary to identify adults for referral to effective weight loss therapy.

Knowledge Gaps and Future Research

Treatment of overweight and obesity is a highly promising intervention for primary and secondary prevention of stroke. The evidence for this includes the high prevalence of overweight and obesity in the general population at risk for stroke and with completed stroke, the confirmed association between increased weight and increased risk for stroke, and the favorable effect of weight reduction on vascular risk factors, including hypertension. Weight reduction would have additional potential nonvascular benefits for patients at risk for and with established cerebrovascular disease. What holds back research on treatment of overweight and obesity for stroke prevention are the cost and complexity of available treatments. The most effective nonsurgical approaches require intensive behavioral counseling, possibly with food substitution. Research is ongoing to understand the biology of obesity and to develop more effective and convenient treatments, which may include pharmacological approaches to appetite suppression. Right now, however, trials of counseling and food substitution could be implemented safely and are urgently needed.

4.6. Obstructive Sleep Apnea

Recommendations for Obstructive Sleep Apnea
Referenced studies that support recommendations are summarized in online Data Supplements 18 and 19.

COR	LOE	Recommendations
2a	B-R	1. In patients with an ischemic stroke or TIA and OSA, treatment with positive airway pressure (eg, continuous positive airway pressure [CPAP]) can be beneficial for improved sleep apnea, BP, sleepiness, and other apnea-related outcomes.[302–314]
2b	B-R	2. In patients with an ischemic stroke or TIA, an evaluation for OSA may be considered for diagnosing sleep apnea.[302,303,315,316]

Synopsis

Sleep apnea is diagnosed by polysomnography to calculate the apnea-hypopnea index (AHI), the hourly sum of apneas (total cessation of airflow for 10 seconds) plus hypopneas (reduction in airflow by at least 30% for 10 seconds with reduced oxygen saturation). The threshold for diagnosis is AHI ≥5 with symptoms (eg, sleepiness) or ≥15 with or without symptoms.[317] The prevalence of moderate to severe sleep apnea (AHI >15) among US adults 50 to 70 years of age is estimated to be 10%.[318] Prevalence is higher in men than women and increases sharply with age and BMI. Sleep apnea is associated with increased risk for mortality,[302] stroke,[319–321] and risk factors including heart disease,[320] hypertension,[322] and AF.[302] Sleep apnea affects ≈38% to 40% (AHI >20) of patients with stroke, with >90% of cases being OSA rather than central sleep apnea.[323–326] Limited data suggest that patients with acute ischemic stroke and OSA are at increased risk for functional impairment, stroke recurrence, and death, although causation is not established.[314,327–329] Limited data from small trials show that treatment with CPAP is safe after stroke, reduces the AHI, improves sleepiness, and may improve neurological function.[304–311] Effects on vascular recurrence are uncertain, although a planned ancillary analysis in the SAVE study (Sleep Apnea Cardiovascular Endpoints) revealed that risk for stroke was lower among participants (all had a history of coronary artery disease or cerebrovascular disease) who had better adherence to CPAP therapy (HR, 0.56 [95% CI, 0.32–1.00]).

Recommendation-Specific Supportive Text

1. Our recommendation to treat patients with OSA using CPAP is consistent with a guideline from the American College of Physicians that recommends CPAP as the initial therapy.[330] In studies of various populations, treatment with CPAP effectively reduced the AHI and improved measures of sleepiness, BP control, sleep-related quality of life, and physical functioning.[302,303] As described in the above synopsis, limited data from small trials specifically among patients with stroke show that treatment with CPAP is

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safe, reduces the AHI, improves sleepiness, and may improve neurological function.[304–313] Evidence from 1 trial suggests that treatment may improve mood.[314] In a planned ancillary analysis in the SAVE trial, which enrolled patients with either coronary or cerebrovascular disease, CPAP reduced the risk for stroke in patients with better CPAP adherence.[303] The American College of Physicians recommends mandibular advancement devices as an alternative for patients who do not tolerate CPAP or who prefer mandibular advancement.[330] These devices, however, have not been specifically tested in patients with stroke.

2. OSA is common among patients with stroke, but most cases are undiagnosed.[315] The combined prevalence of known and unknown moderate to severe OSA approaches 40%. Arguing against evaluating patients for undiagnosed OSA is the absence of evidence that treatment improves stroke-related outcomes, including recurrence. Since the last version of this guideline, a trial of 2717 patients with moderate to severe OSA and coronary or cerebrovascular disease failed to show a benefit of CPAP on recurrent vascular events.[303] In favor of evaluating stroke patients is the high prevalence of undiagnosed OSA, combined with evidence that treatment improves daytime sleepiness, BP, sleep-related quality of life, and physical functioning.[302,303] If an evaluation is undertaken, options include questionnaires to identify patients at high risk for OSA who can be selectively referred for polysomnography.[332,333] However, available questionnaires show inconsistent performance in patients with stroke.[332] In addition, the prevalence of OSA after stroke is sufficiently high to justify omitting prescreening before polysomnography when detection of asymptomatic OSA is clinically warranted. Facility-based (ie, sleep laboratory–based), multichannel polysomnography is the reference standard for diagnosing OSA. Home (ie, out of sleep laboratory) monitors are appropriate in selected patients.[316,317] Although the American Academy of Sleep Medicine recommends against the use of home testing in patients with stroke,[334] recent research suggests that home testing can be effective.[315]

Knowledge Gaps and Future Research

Observational data show a high prevalence of OSA among patients with acute ischemic stroke, and small trials suggest that treatment may improve several important outcomes. Together, this considerable volume of data support the hypothesis that early detection and treatment of OSA may be helpful for selected patients. Proving this hypothesis will require adequately designed clinical trials. Such trials will need to consider the following:

- The selection of patients who might benefit from CPAP,
- Timing of testing and treatment in relation to stroke onset,
- Type of testing (in home or in facility), and
- Dose/type of CPAP.

Currently, at least 3 trials are underway that will help in this regard:

1. Sleep SMART (Sleep for Stroke Management and Recovery Trial), a randomized trial to determine whether early treatment of OSA with CPAP after ischemic stroke or TIA reduces the risk for 2 primary outcome measures: recurrent stroke, acute coronary syndrome, and all-cause mortality 6 months after the event and functional status at 3 months (ClinicalTrials.gov identifier NCT03812653).
2. The RISE-UP trial (Recovery in Stroke Using PAP) focused on optimal timing of CPAP initiation after stroke (NCT04130503).
3. ASAP (Addressing Sleep Apnea Post Stroke/TIA), which will test a quality improvement initiative in the Veterans Affairs Medical Administration and include a secondary aim of recurrent vascular disease (NCT04322162).

5. MANAGEMENT BY ETIOLOGY

5.1. Large Artery Atherosclerosis

5.1.1. Intracranial Large Artery Atherosclerosis

Recommendations for Intracranial Large Artery Atherosclerosis
Referenced studies that support recommendations are summarized in online Data Supplements 20–27.

COR	LOE	Recommendations
		Antithrombotic Therapy
1	B-R	1. In patients with a stroke or TIA caused by 50% to 99% stenosis of a major intracranial artery, aspirin 325 mg/d is recommended in preference to warfarin to reduce the risk of recurrent ischemic stroke and vascular death.[335,336]
2a	B-NR	2. In patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%–99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for up to 90 days is reasonable to further reduce recurrent stroke risk.[336–339]
2b	B-NR	3. In patients with recent (within 24 hours) minor stroke or high-risk TIA and concomitant ipsilateral >30% stenosis of a major intracranial artery, the addition of ticagrelor 90 mg twice a day to aspirin for up to 30 days might be considered to further reduce recurrent stroke risk.[340]
2b	C-LD	4. In patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the addition of cilostazol 200 mg/day to aspirin or clopidogrel might be considered to reduce recurrent stroke risk.[341–344]

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Recommendations for Intracranial Large Artery Atherosclerosis (Continued)		
COR	LOE	Recommendations
		Antithrombotic Therapy (Continued)
2b	C-EO	5. In patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the usefulness of clopidogrel alone, the combination of aspirin and dipyridamole, ticagrelor alone, or cilostazol alone for secondary stroke prevention is not well established.
		Risk Factor Management
1	B-NR	6. In patients with a stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, maintenance of SBP below 140 mm Hg, high-intensity statin therapy, and at least moderate physical activity are recommended to prevent recurrent stroke and vascular events.[110,210,337,345–349]
		Angioplasty and Stenting
2b	C-LD	7. In patients with severe stenosis (70%-99%) of a major intracranial artery and actively progressing symptoms or recurrent TIA or stroke after institution of aspirin and clopidogrel therapy, achievement of SBP <140 mm Hg, and high- intensity statin therapy (so-called medical failures), the usefulness of angioplasty alone or stent placement to prevent ischemic stroke in the territory of the stenotic artery is unknown.[350–352]
3: Harm	A	8. In patients with stroke or TIA attributable to severe stenosis (70%–99%) of a major intracranial artery, angioplasty and stenting should not be performed as an initial treatment, even for patients who were taking an antithrombotic agent at the time of the stroke or TIA.[353–359]
3: Harm	B-NR	9. In patients with a stroke or TIA attributable to moderate stenosis (50%–69%) of a major intracranial artery, angioplasty or stenting is associated with excess morbidity and mortality compared with medical management alone.[336,354,355,360]
		Other Procedures
3: No Benefit	B-R	10. In patients with stroke or TIA attributable to 50% to 99% stenosis or occlusion of a major intracranial artery, extracranial-intracranial bypass surgery is not recommended.[361]

Synopsis

ICAS is a common cause of stroke worldwide with a high rate of recurrent stroke.[362] Severity of stenosis is a strong predictor of risk of recurrent stroke in the territory of the stenotic artery, with 1-year rates as high as 18% in patients with ≥70% stenosis.[360] Therapeutic trials have demonstrated that for most patients with ICAS, antithrombotic therapy and vascular risk factor control are effective for stroke prevention. However, there may be a subset of patients (eg, those with low flow or poor collaterals) who have an even higher risk of recurrent stroke despite medical therapy.[357,363,364] Current research is focused on identifying characteristics of patients with ICAS at highest risk and studying new therapies for stroke prevention.

Recommendation-Specific Supportive Text

1. In the WASID trial (Warfarin-Aspirin Symptomatic Intracranial Disease), warfarin (target INR, 2–3) compared with aspirin 650 mg twice a day was found to have a higher rate of major hemorrhages (relative difference, 5.1%) and all-cause death (relative difference, 5.4%) but did not prevent more primary end points (stroke, ICH, vascular death) (22% in both arms at a mean follow-up of 1.8 years) or ischemic strokes in the territory of the stenotic artery (2-year rate: 15% for aspirin versus 13% for warfarin).[335] The optimal dose of aspirin for secondary prevention in patients with ICAS has not been determined, but doses <1300 mg/d are probably effective given that lower doses of aspirin have been shown to be effective for secondary prevention in trials of heterogeneous causes of stroke and that patients in the medical arm of the SAMMPRIS trial were treated with 325 mg aspirin once daily alone after the first 90 days with favorable results.[336]
2. Support for the use of short-term combination aspirin and clopidogrel for secondary prevention in patients with severe ICAS comes from post hoc analyses of clinical trials and RCTs studying surrogate end points for stroke. Patients in the medical arm of SAMMPRIS with severe stenosis received aspirin and clopidogrel for 90 days followed by aspirin alone for the rest of follow-up and had a lower 1-year recurrent stroke rate (12.2%) compared with similar patients from WASID on aspirin alone (25%).[336,337] Subgroup analysis of the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events) reported that patients with ICAS who were randomized to clopidogrel and aspirin for 21 days followed by clopidogrel alone had a lower rate of stroke at 90 days (11.3%) compared with those on aspirin alone (13.6%), although the difference was not statistically significant.[338] Patients in the CLAIR trial (Clopidogrel Plus Aspirin for Infarction Reduction) randomized to aspirin and clopidogrel for 7 days had significantly decreased microemboli in the territory of the stenotic ICA or middle cerebral artery compared with those on aspirin alone and a lower rate of recurrent stroke at day 7 (0% in combination versus 3.8% in aspirin alone), but this difference was not significant.[339] In contrast to patients with heterogeneous causes of minor stroke wherein the risk of recurrent stroke plateaus within a few weeks,[365] the risk of recurrent stroke from ICAS extends well beyond 30 days.[338,353] Data from these studies also suggest that short-term combination aspirin and clopidogrel up to 90 days is safe.
3. Data from the THALES trial (Acute Stroke or Transient Ischaemic Attack Treated With

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Stroke

Ticagrelor and ASA for Prevention of Stroke and Death; discussed in more detail in Section 5.19, Use of Antithrombotic Medications in Secondary Stroke Prevention) also inform recommendations for short-term treatment with combination ticagrelor and aspirin in patients with atherosclerosis ipsilateral to the ischemic territory, including ICAS. In this prespecified subgroup analysis,[340] risk of recurrent stroke or death at 30 days among patients with ≥30% intracranial stenosis ipsilateral to the ischemic event was 9.9% in the ticagrelor 90 mg twice a day plus aspirin 100 mg once a day group versus 15.2% in the aspirin 100 mg alone group (HR, 0.66 [95% CI, 0.47–0.93]; *P*=0.016). In contrast to the THALES patients without atherosclerosis, bleeding events among the ipsilateral atherosclerosis subgroup treated with ticagrelor and aspirin were not significantly higher than in those taking aspirin alone. Of note, THALES required loading doses of both ticagrelor and aspirin. Also of note, in this analysis, ICAS was not required to be related to the index ischemic event, so some patients may not have had symptomatic ICAS. Given the lack of comparative data between various dual-antiplatelet regimens in ICAS, the choice of adding ticagrelor or clopidogrel to aspirin should be based on patient factors such as medication adherence (eg, relative cost and dose frequency), but the role of genetic studies or platelet function testing remains unclear.

4. Several RCTs have studied the efficacy of cilostazol 200 mg/d combined with other antiplatelet agents in patients with symptomatic ICAS. The TOSS-1 and TOSS-2 trials (Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis) found that cilostazol (200 mg/d) plus aspirin was as safe as aspirin alone or clopidogrel plus aspirin but was no better for stroke prevention in patients with ICAS.[341,342] The CATHARSIS trial (Cilostazol-Aspirin Therapy Against Recurrent Stroke With Intracranial Artery Stenosis) reported that the combination of cilostazol and aspirin was superior to aspirin for the prevention of the combined secondary end point of all vascular events and new silent brain infarcts (10.7% versus 25%; *P*=0.04) but had no impact on ICAS progression.[343] Subgroup analysis of the CSPS trial reported that patients with ICAS who were randomized to cilostazol plus either aspirin or clopidogrel (dual group) had a lower rate of stroke compared with those on aspirin or clopidogrel alone (4% versus 9.2%; HR, 0.47 [95% CI, 0.23–0.95]).[344] Of note, these trials were conducted in a primarily Asian population, the dose of aspirin when used in combination with cilostazol did not exceed 150 mg/d, and many were unblinded.
5. Antithrombotic agents that have been specifically studied in RCTs of patients with ICAS include warfarin, aspirin, cilostazol, and the combination of clopidogrel plus aspirin or cilostazol.
6. Post hoc analyses from WASID (N=567), the medical arm of SAMMPRIS (n=227), and the CICAS registry (Chinese Intracranial Atherosclerosis; N=2426) showed that achievement of a mean SBP <140 mm Hg during follow-up in patients with ICAS was associated with a lower risk of stroke and vascular events, even in patients with severe stenosis[110,337,345,346] or those treated early after stroke.[346] Although most patients with ICAS probably benefit from lower BP, some small studies suggest that patients with documented hemodynamic impairment[347] or those treated to SBP <120 mm Hg early after stroke[348] may not benefit, and the lower threshold associated with increased stroke risk is not known. High-intensity statin use is supported by an RCT in patients with ICAS that showed that high-intensity statins lowered the rate of cerebrovascular events[349] and by general recommendations (see Section 4.3, Treatment of Hyperlipidemia for Secondary Prevention of Stroke). An optimum target LDL for patients with ICAS has not been determined, but WASID and SAMMPRIS post hoc analyses show lower LDLs are associated with lower vascular event rates in patients with ICAS,[110,337] and a recent RCT demonstrated benefit of an LDL target <70 mg/dL in patients with stroke and atherosclerosis.[210] Moderate physical activity at least 3 to 5 times per week was the factor most strongly associated with lower risk of recurrent stroke and vascular events in a post hoc analysis of SAMMPRIS medically treated patients.[110]
7. Two uncontrolled multicenter registries reported outcomes after percutaneous transluminal angioplasty and stenting (PTAS) in patients with ICAS who have progressive symptoms or failed medical therapy (ie, had a recurrent stroke or TIA despite treatment with antithrombotic medications or risk factor control). The WEAVE prospective registry (Wingspan Stent System Post Market Surveillance) reported a periprocedural complication rate of 2.6% in 152 patients who met the specific US Food and Drug Administration Humanitarian Device Exemption criteria for Wingspan stent use, but outcomes beyond 72 hours after the procedure have not been published.[350] However, the stroke or death rate was 23.9% in the 46 patients treated off-label, many of whom had not failed medical therapy or were treated less than a week from symptom onset.[366,367] A retrospective registry of 101 patients with ICAS receiving stenting or balloon angioplasty, which included both patients who failed medical

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therapy and those with progressive stroke symptoms, reported a 90-day ischemic stroke rate of 6.7% and 90-day mortality of 11.2%.[351] Post hoc analysis of SAMMPRIS patients who had a prior stroke or TIA while on antithrombotic therapy (n=284) showed that medical therapy was superior to PTAS for the prevention of the primary end point in this subgroup (15% for aggressive medical management versus 24% for PTAS; *P*=0.043).[352] Given the lack of efficacy data, PTAS is considered investigational in this population.

8. Three RCTs have compared PTAS with medical therapy for stroke prevention in patients with recent stroke or TIA attributable to 70% to 99% stenosis. The SAMMPRIS trial (N=451) used the Wingspan stenting system; the VISSIT trial (Vitesse Intracranial Stent Study for Ischemic Stroke Therapy; N=112) used the Pharos system; and a single-center RCT in China (N=70) allowed either Wingspan or Coroflex stenting systems. Medical therapy was similar in the 3 RCTs and consisted of risk factor management and combination aspirin and clopidogrel for 90 days and then aspirin alone. All 3 RCTs showed a higher 30-day rate of cerebrovascular events or death in the PTAS group than the medical group and no benefit of PTAS beyond the periprocedural period.[353–355] Post hoc analyses of SAMMPRIS baseline characteristics failed to demonstrate any subgroup of patients who benefited from PTAS but did identify some possible high-risk features for future study.[356,357] Two other RCTs (VAST [Vertebral Artery Stenting Trial] and VIST [Vertebral Artery Ischemic Stenting Trial]) that randomized patients with intracranial and extracranial posterior circulation stenosis to PTAS or medical therapy reported no significant benefit of PTAS among the patients with ICAS.[358,359]
9. No RCTs have directly compared PTAS with medical therapy in patients with symptomatic 50% to 69% stenosis. However, the low rate of stroke on medical therapy in patients with 50% to 69% stenosis,[360] high periprocedural risk, which does not vary by degree of stenosis,[368] and lack of demonstrated benefit of PTAS in well-designed RCTs performed in a higher-risk population (70%–99% stenosis)[336,354,355] do not support the use of PTAS.
10. A large multicenter RCT comparing extracranial-intracranial arterial bypass with medical therapy in 1377 patients with recent minor stroke or TIA included patients with ≥70% intracranial middle cerebral artery (n=109) or ICA (n=149) stenosis and found higher rates of stroke in patients with ICAS treated with extracranial-intracranial arterial bypass than in those in the medical group.[361]

Knowledge Gaps and Future Research

Despite numerous advances in ICAS treatment over the past several decades, the recurrent stroke risk remains high. Further investigation into the following should be prioritized:

- Studying new therapies in well-designed clinical trials, including novel antithrombotic regimens (eg, direct thrombin inhibitors), improved endovascular treatments (eg, submaximal balloon angioplasty), indirect bypass, and ischemic preconditioning.
- Determining the interaction between hemodynamic function or collateral flow and treatments (eg, BP management and endovascular therapy).
- Developing and using surrogate markers of stroke risk (eg, plaque characteristics) or high-risk prognostic features (eg, diabetes) that may lead to new therapies or improve patient selection for future therapeutic trials.
- Genetic variants that relate to ICAS (eg, ring finger protein 213) and whether such variants affect the rate of stroke recurrence or treatment responses.

5.1.2. Extracranial Large Artery Atherosclerosis

5.1.2.1. Extracranial Carotid Stenosis

Recommendations for Extracranial Carotid Stenosis
Referenced studies that support recommendations are summarized in online Data Supplement 28.

COR	LOE	Recommendations
1	A	1. In patients with a TIA or nondisabling ischemic stroke within the past 6 months and ipsilateral severe (70%–99%) carotid artery stenosis, carotid endarterectomy (CEA) is recommended to reduce the risk of future stroke, provided that perioperative morbidity and mortality risk is estimated to be <6%.[369]
1	A	2. In patients with ischemic stroke or TIA and symptomatic extracranial carotid stenosis who are scheduled for carotid artery stenting (CAS) or CEA, procedures should be performed by operators with established periprocedural stroke and mortality rates of <6% to reduce the risk of surgical adverse events.[370]
1	A	3. In patients with carotid artery stenosis and a TIA or stroke, intensive medical therapy, with antiplatelet therapy, lipid-lowering therapy, and treatment of hypertension, is recommended to reduce stroke risk.[210]
1	B-R	4. In patients with recent TIA or ischemic stroke and ipsilateral moderate (50%–69%) carotid stenosis as documented by catheter-based imaging or noninvasive imaging, CEA is recommended to reduce the risk of future stroke, depending on patient-specific factors such as age, sex, and comorbidities, if the perioperative morbidity and mortality risk is estimated to be <6%.[369]
2a	B-R	5. In patients ≥70 years of age with stroke or TIA in whom carotid revascularization is being considered, it is reasonable to select CEA over CAS to reduce the periprocedural stroke rate.[371]
2a	B-R	6. In patients in whom revascularization is planned within 1 week of the index stroke, it is reasonable to choose CEA over CAS to reduce the periprocedural stroke rate.[372]

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Recommendations for Extracranial Carotid Stenosis (Continued)		
COR	LOE	Recommendations
2a	C-LD	7. In patients with TIA or nondisabling stroke, when revascularization is indicated, it is reasonable to perform the procedure within 2 weeks of the index event rather than delay surgery to increase the likelihood of stroke-free outcome.[373]
2a	C-LD	8. In patients with symptomatic severe stenosis (≥70%) in whom anatomic or medical conditions are present that increase the risk for surgery (such as radiation-induced stenosis or restenosis after CEA) it is reasonable to choose CAS to reduce the periprocedural complication rate.[374]
2b	A	9. In symptomatic patients at average or low risk of complications associated with endovascular intervention, when the ICA stenosis is ≥70% by noninvasive imaging or >50% by catheter-based imaging and the anticipated rate of periprocedural stroke or death is <6%, CAS may be considered as an alternative to CEA for stroke prevention, particularly in patients with significant cardiovascular comorbidities predisposing to cardiovascular complications with endarterectomy.[375]
2b	B-NR	10. In patients with a recent stroke or TIA (past 6 months), the usefulness of transcarotid artery revascularization (TCAR) for prevention of recurrent stroke and TIA is uncertain.[376]
3: No Benefit	A	11. In patients with recent TIA or ischemic stroke and when the degree of stenosis is <50%, revascularization with CEA or CAS to reduce the risk of future stroke is not recommended.[369]
3: No Benefit	A	12. In patients with a recent (within 120 days) TIA or ischemic stroke ipsilateral to atherosclerotic stenosis or occlusion of the middle cerebral or carotid artery, extracranial-intracranial bypass surgery is not recommended.[377]

Synopsis

Previous randomized clinical trials have compared CEA with best medical therapy in patients with a recent stroke or TIA. A combined analysis of these trials found the greatest benefit for CEA was in severe (70%–99%) ICA stenosis with recent symptoms. Post hoc analysis of these original trials found a greater benefit of CEA when the surgery was done in patients who were enrolled within 2 weeks of their last ischemic event. These trials were initiated >30 years ago, and current optimal medical therapy was not used in these trials. There is a paucity of data on CEA compared with current optimal medical therapy in patients with symptomatic carotid stenosis. CEA also has been compared with CAS. Across several trials, CAS was associated with a higher periprocedural stroke rate, but similar results have been seen with CEA and CAS beyond the immediate periprocedural period. Extracranial-to-intracranial bypass for internal carotid occlusion has not been demonstrated to reduce the risk of recurrent stroke.

Recommendation-Specific Supportive Text

1. A combined analysis by Rothwell et al[369] of the original CEA trials (NASCET [North American Symptomatic Carotid Endarterectomy Trial], ECST [European Carotid Surgery Trial], and VA [Veterans Affairs Trial 309]) found robust benefit for CEA in patients with severe (70%–99%) ICA stenosis (16.0% absolute benefit over 5 years). In these studies, patients were typically >40 years of age and of either sex. The NASCET method of stenosis measurement was used in the combined analysis of the 3 trials. In the original trials (NASCET and ECST), angiography was used for stenosis measurements, but more recent trials (CREST [Carotid Revascularization Endarterectomy versus Stenting Trial]) and routine clinical practice typically use noninvasive imaging, with angiography used for cases with discrepant or ambiguous results from noninvasive tests.
2. Surgical results and statistical modeling from clinical trials such as NASCET and CREST support this threshold for perioperative outcomes.[24]
3. On the basis of trials of antiplatelet therapy for patients with recent stroke or TIA, antiplatelet therapy is recommended for patients with symptomatic carotid stenosis. Similarly, antihypertensive therapy and statins are recommended for patients with symptomatic carotid stenosis. A recent trial of 2 different lipid targets for patients with a recent stroke or TIA found that an LDL target of <70 mg/dL was associated with a reduced vascular event rate compared with a target of 90 to 110 mg/dL.[377a] This trial included patients with symptomatic carotid stenosis. The use of multimodality medical therapy also has been incorporated into clinical trials.[18]
4. The analysis by Rothwell et al[369] found mild benefit in patients with 50% to 69% ICA stenosis (4.6% over 5 years). In the NASCET analysis of this stenosis range, there was no clear benefit of CEA seen in women and in patients with retinal ischemic events. In the combined analysis of symptomatic CEA trials, the number needed to treat to prevent 1 stroke was higher in women compared with men (36 versus 9). Life expectancy also should be considered when treatment decisions are made because CEA has delayed benefit.
5. Several variables have been analyzed in relation to CEA and CAS outcomes. The Carotid Stenting Trialists' Collaboration analyzed outcomes in 4754 patients from 4 clinical trials.[371] Within 120 days of study entry, HRs were calculated according to 5-year age intervals to compare CAS with CEA. In the group 65 to 69 years of age, the HR was 1.61 (95% CI, 0.90–2.88). In the group 70 to 74 years of age, the

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HR comparing CAS to CEA was 2.09 (95% CI, 1.32–3.32). This supports the recommendation for considering patient age in the selection of the procedure.

6. In addition, CEA is associated with a reduced complication rate relative to CAS in patients who undergo the procedure within 1 week of a stroke or TIA. The Carotid Stenosis Trialists' Collaboration evaluated 4138 patients randomly assigned to CEA or CAS.[372] In patients who received the procedure within 1 week of the last symptomatic event, the stroke/death rate was 8.3% with CAS versus 1.3% with CEA (RR, 6.7; P=0.002). This supports a preference for CEA in patients who undergo early revascularization.
7. Post hoc analysis of these trials found a greater benefit of CEA when the surgery was done in patients who were enrolled within 2 weeks of their last nondisabling ischemic event.[373] Therefore, if the patient is suitable for operation, early CEA is preferred.
8. In the SAPPHIRE trial (Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy), patients with high anatomic or physiologic risk for CEA were assigned to CEA or CAS.[374] The primary end point was stroke, MI, or death within 30 days or ipsilateral stroke up to 12 months. Among symptomatic patients, the primary end point occurred in 16.8% of patients undergoing CAS and 16.5% of patients undergoing CEA (P=0.95). However, the trial was not powered to evaluate only the symptomatic group of patients. This study supports the option of CAS in patients at elevated surgical risk.
9. In the CREST multicenter randomized clinical trial, CEA and CAS were directly compared in both symptomatic and asymptomatic patients. Among the 1321 symptomatic patients, over the 4-year study period, the primary end point (periprocedural stroke, death, or MI, plus later ipsilateral stroke) occurred in 8.6% of patients undergoing CAS and 8.4% of patients undergoing CEA.[375] Both surgeons and interventionalists were required to be credentialed for the study, and a periprocedural stroke/death rate of <6% (or lower) has been suggested in earlier statements.
10. TCAR is a relatively new endovascular technique that has several unique features. The interventional specialist directly accesses the common carotid artery, and flow reversal is provided to have blood drain to the femoral vein. A stent is placed at the site of ICA stenosis with no need to traverse the aortic arch. TCAR results have been analyzed in registries only thus far. A propensity score–matched analysis compared TCAR with transfemoral CAS. Among 3286 patient pairs, approximately half of the patients were symptomatic. In symptomatic patients, TCAR, relative to transfemoral CAS, was associated with a lower rate of in-hospital stroke/death (2.1% versus 4.2%), stroke (2.0% versus 3.1%), and death (0.5% versus 1.5%).[376] TCAR has not been evaluated in randomized trials thus far and has not been compared with CEA or intensive medical therapy.
11. The combined analysis by Rothwell et al[369] of CEA in patients with recent stroke or TIA found no benefit in patients with <50% ICA stenosis.
12. In COSS (Carotid Occlusion Surgery Study), 195 subjects with recently symptomatic carotid occlusion and increased oxygen extraction fraction measured by positron emission tomography were assigned to bypass surgery or medical therapy.[377] The primary end point was stroke/death within 30 days and ipsilateral stroke up to 2 years. The primary end point occurred in 21.0% of the surgery group and 22.7% of the medically treated patients (P=0.78). This supports the recommendation against bypass surgery for patients with recently symptomatic carotid occlusion.

5.1.2.2. Extracranial Vertebral Artery Stenosis

Recommendations for Extracranial Vertebral Artery Stenosis
Referenced studies that support recommendations are summarized in online Data Supplement 28.

COR	LOE	Recommendations
1	A	1. In patients with recently symptomatic extracranial vertebral artery stenosis, intensive medical therapy (antiplatelet therapy, lipid lowering, BP control) is recommended to reduce stroke risk.[378]
2b	B-R	2. In patients with ischemic stroke or TIA and extracranial vertebral artery stenosis who are having symptoms despite optimal medical treatment, the usefulness of stenting is not well established.[378]
2b	C-EO	3. In patients with ischemic stroke or TIA and extracranial vertebral artery stenosis who are having symptoms despite optimal medical treatment, the usefulness of open surgical procedures, including vertebral endarterectomy and vertebral artery transposition, is not well established.

Synopsis

Extracranial vertebral artery stenosis is thought to account for 10% of posterior circulation strokes. Revascularization procedures are not performed often for vertebral artery stenosis. Small trials (VAST, VIST) did not show a clear benefit for vertebral artery stenting, and a recent combined analysis also did not demonstrate clear benefit for vertebral artery stenting compared with medical therapy.

Recommendation-Specific Supportive Text

1. On the basis of trials of antiplatelet therapy for patients with recent stroke or TIA, antiplatelet therapy is recommended for patients with symptomatic vertebral artery stenosis. Similarly, antihypertensive therapy and statins are recommended for patients with symptomatic vertebral artery stenosis. The use of multimodality medical therapy also has been incorporated into clinical trials.[378]

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2. In a combined analysis of 3 trials (VAST, VIST, and SAMMPRIS), 244 patients were assigned to either vertebral artery stenting or optimal medical therapy.[378] The primary end point for this analysis was fatal or nonfatal strokes. Two of these trials (VAST, VIST) contributed data for patients with extracranial vertebral artery stenosis. During 1036 person-years of follow-up, the HR for stenting compared with medical therapy was 0.63 (95% CI, 0.27–1.46). Thus, no clear benefit has been shown for extracranial vertebral artery stenting.
3. No randomized trials have been performed for surgical techniques such as vertebral artery endarterectomy or transposition. Case series have been reported, but these typically lack a control group with a consistent medical treatment protocol.[379] Thus, the utility of these procedures is not well established.

Extracranial Large Artery Atherosclerosis Knowledge Gaps and Future Research

Knowledge gaps within this area include the following:

- Risk-benefit ratio of CEA to modern intensive medical therapy should be assessed.
- Previous CEA trials were initiated >30 years ago, and clinicians need comparisons of CEA with currently available intensive medical therapy options.
- As a result of the growing elderly population, more data are needed on the merits of carotid revascularization in elderly patients (>80 years of age).
- Additional information is needed on the mechanisms of sex differences in outcomes for patients with symptomatic carotid stenosis.
- Recent studies have identified that carotid plaques with <50% stenosis but high-risk features may be linked to otherwise cryptogenic ischemic strokes. More information is needed on the frequency and optimal treatment of these nonstenotic plaques with high-risk features.

5.1.3. Aortic Arch Atherosclerosis

Recommendations for Aortic Arch Atherosclerosis
Referenced studies that support recommendations are summarized in online Data Supplement 29.

COR	LOE	Recommendations
1	B-R	1. In patients with a stroke or TIA and evidence of an aortic arch atheroma, intensive lipid management to an LDL cholesterol target <70 mg/dL is recommended to prevent recurrent stroke.[210]
1	C-LD	2. In patients with a stroke or TIA and evidence of an aortic arch atheroma, antiplatelet therapy is recommended to prevent recurrent stroke.[380–385]

Synopsis

Pathological[386] and case-control[387] studies using TEE have identified complex aortic arch plaque to be independently and strongly associated with ischemic stroke. Prospective studies have found an increased stroke recurrence rate among patients with aortic plaques ≥4 mm in thickness, particularly with ulceration or mobile components[388] or without plaque calcifications.[389] There are no strong data from randomized clinical trials or even observational studies that management should be different from general secondary prevention recommendations for atherosclerotic stroke.

Recommendation-Specific Supportive Text

1. There is evidence that treating patients with ischemic stroke and evidence of atherosclerosis to an LDL target of <70 mg/dL is more effective in stroke prevention than less intensive lipid management.[210] Detailed guidance for lipid management based on age and very high-risk status is presented elsewhere in this document (see Section 4.3, Treatment of Hyperlipidemia for Secondary Prevention of Stroke). Many patients with aortic plaque and ischemic stroke will meet the criteria for very high-risk status because of concomitant atherosclerotic conditions and risk factors. In the ARCH study (Aortic Arch Related Cerebral Hazard Trial), the only randomized trial of secondary prevention of aortic plaque–associated stroke,[380] the event rate was only 20% to 30% of the >12% rate expected from observational studies.[390] This is likely attributable to the better risk factor management in the trial compared with historical studies. During the trial, mean LDL-C was reduced by ≈40 mg/dL to 83 to 84 mg/d. It is likely that event rates would be even lower with current, more intensive recommendations for hypertension and cholesterol management.
2. The only randomized trial of this condition, the ARCH study,[380] compared aspirin and clopidogrel with warfarin and was underpowered for the primary end point. Thus, the comparative benefit of these 2 treatments is unknown. However, there were 6 vascular deaths (3.4%) in the warfarin arm and none in the dual antiplatelet arm (log-rank test, P=0.013), suggesting no advantage of warfarin over dual antiplatelets. It is not known whether DAPT is preferable to single antiplatelet therapy (SAPT), but recent trials[381,382,384] have suggested that long-term DAPT generally confers increased bleeding risk without a corresponding increased antithrombotic benefit. There is strong evidence that aspirin is effective in the secondary prevention of noncardioembolic stroke or TIA.[383,385] Thus, in the absence of compelling evidence for an alternative, more effective antithrombotic treatment, long-term monotherapy with aspirin is recommended. Minor strokes that meet the inclusion criteria for the POINT study (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) also should be treated with short-term DAPT with both aspirin and clopidogrel.

Knowledge Gaps and Future Research

Knowledge gaps within this area include the following:

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- For patients with a stroke or TIA and evidence of an aortic arch atheroma, the effectiveness of long-term DAPT with aspirin and clopidogrel compared with aspirin monotherapy therapy to prevent recurrent stroke is unknown.
- For patients with a stroke or TIA and evidence of an aortic arch atheroma, the effectiveness of anticoagulation with either warfarin or a direct-acting anticoagulant compared with aspirin monotherapy to prevent recurrent stroke is unknown.
- For patients with a stroke or TIA and evidence of an aortic arch atheroma, the effectiveness of combination antiplatelet and anticoagulation therapy compared with aspirin monotherapy to prevent recurrent stroke is unknown.
- Optimal treatment strategies depending on plaque morphology and duration of treatment strategies remain unknown.

5.2. Moyamoya Disease

Recommendations for Moyamoya Disease
Referenced studies that support recommendations are summarized in online Data Supplement 30.

COR	LOE	Recommendations
2a	C-LD	1. In patients with moyamoya disease and a history of ischemic stroke or TIA, surgical revascularization with direct or indirect extracranial-intracranial bypass can be beneficial for the prevention of ischemic stroke or TIA.[391–397]
2b	C-LD	2. In patients with moyamoya disease and a history of ischemic stroke or TIA, the use of antiplatelet therapy, typically aspirin monotherapy, for the prevention of ischemic stroke or TIA may be reasonable.[393,394,397–401]

Synopsis

Moyamoya disease is an idiopathic rare steno-occlusive disease of the arteries of the circle of Willis, typically anterior circulation, with abnormal collateral development in lenticulostriate arteries, resulting in the characteristic angiographic "puff of smoke" appearance. Moyamoya disease may be more common in individuals of Asian descent, but non-Asian people can be affected.[402–404] Moyamoya disease has a bimodal distribution, with a peak in childhood (more ischemic) and adulthood (ischemic and hemorrhagic), and can be asymptomatic.[404] Although a causal relationship is not well established, similar vascular changes also may be seen in association with prior radiation exposure, Down syndrome, sickle cell disease, neurofibromatosis, and atherosclerosis. This situation is often referred to as moyamoya syndrome. Treatment focuses on preventing progression and reducing the risk of ischemic or hemorrhagic stroke. One prospective RCT (JAM trial [Japan Adult Moyamoya]) examined the efficacy of surgical revascularization for preventing hemorrhagic stroke, but there are no similar prospective RCTs for ischemic stroke prevention.[405] No prospective RCTs have studied medical management of either symptomatic or asymptomatic moyamoya disease. Although multiple case series and meta-analyses of varying sizes and quality exist, many include both patients with moyamoya disease and those with moyamoya syndrome, as well as pediatric and adult patients. Few address secondary prevention of ischemic stroke specifically or issues of ethnic/geographic variability in general. Selection bias and publication bias are significant concerns. The resulting low-quality evidence related to the secondary prevention of ischemic stroke precludes any strong recommendations.

Recommendation-Specific Supportive Text

1. Within the realm of surgery, there is considerable controversy as to what constitutes the best surgical option, direct superficial temporal artery to middle cerebral artery bypass or an indirect bypass procedure such as encephaloduroarteriosynangiosis or encephalomyosynagiosis. The differences in surgical technique even within the broad categories of direct and indirect bypass, the frequent use of combined procedures, and the heterogeneity of the patient population make it difficult to draw robust conclusions about the superiority of one procedure over another. Again, there are no prospective RCTs to inform recommendations in this area. Although several meta-analyses and case series favor direct over indirect bypass,[391–395] all but 1 of these studies combined both hemorrhagic and ischemic patients. A propensity score–matched analysis on 220 adult patients with ischemic-type moyamoya disease showed that direct bypass was superior to indirect bypass for the prevention of recurrent stroke.[391] In this series, however, the primary end point of recurrent stroke was defined as both ischemic and hemorrhagic events. In contrast, another meta-analysis[396] and a retrospective multicenter series[397] reported no difference between direct and indirect modalities.
2. Although traditionally thought to result from poor perfusion, there is some evidence that many instances of ischemia in moyamoya disease actually result from thromboembolic phenomenon.[406] In a propensity score–matched analysis, Onozuka et al[400] found that prehospital antiplatelet use was significantly associated with good functional status on hospital admission for patients with nonhemorrhagic moyamoya disease in Japan. Several meta-analyses and case series have compared antiplatelet therapy with surgical bypass or observation alone with mixed results.[393,397–399] Although some found a benefit or no difference with antiplatelet therapy,[394,397,398] others found surgery to be superior.[393,399] However, many studies include patients with both ischemic and hemorrhagic

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moyamoya disease, and conclusions are often based on subgroup analyses. Antiplatelet therapy may also be of benefit in conjunction with surgical revascularization.[401] An international survey of perceived experts in the treatment of moyamoya disease reported that the majority of non-Asian respondents recommended antiplatelet therapy, in contrast to their Asian counterparts, perhaps reflecting a difference in the typical pattern of disease seen in the 2 geographic regions.[407]

Knowledge Gaps and Future Research

Significant knowledge gaps exist in our understanding of moyamoya disease. No prospective RCT exists comparing medical management with surgical intervention for either the primary or secondary prevention of ischemic events in patients with moyamoya disease. Similarly, there are no prospective RCTs comparing the efficacy of the most common surgical revascularization procedures used for the prevention of ischemic events in this patient population. Numerous obstacles to the performance of such trials exist, including a lack of equipoise among many treating neurologists and neurosurgeons, particularly for symptomatic patients. Consideration should therefore also be given to comprehensive, adjudicated long-term registries as an alternative means of investigation. Future investigations should have the following aims:

- To better understand the natural history of moyamoya disease, including ethnic and geographic variability.
- To examine the efficacy of medical management options, including antiplatelet therapy and anticoagulation, with or without surgical intervention for ischemic moyamoya disease.
- To determine the most effective surgical intervention for moyamoya disease.
- To establish the optimal timing for surgical intervention after an acute clinical event in a patient with moyamoya disease.

5.3. Ischemic Stroke Caused by Small Vessel Disease

Recommendation for Small Vessel Stroke Referenced studies that support the recommendation are summarized in online Data Supplement 31.		
COR	**LOE**	**Recommendation**
2b	B-R	1. In patients with ischemic stroke related to small vessel disease, the usefulness of cilostazol for secondary stroke prevention is uncertain.[382,384,408–410]

Synopsis

Cerebral small vessel disease represents a common pathogenetic mechanism for ischemic stroke, accounting for 20% to 30% of cases.[36] This ischemic stroke subtype is characterized by subcortical infarcts of <15 mm in diameter or lacunes in patients often presenting with lacunar stroke syndromes.[38] Hypertension and diabetes are the most commonly recognized risk factors for small vessel disease.[38,412] Although the risk of mortality is lower after small vessel stroke compared with other stroke types, the 1-year recurrence risk is estimated at 4% per year to 11% per year.[412,413] Furthermore, small vessel disease and lacunar strokes are a leading cause of vascular dementia and vascular cognitive impairment.[414,415] Prior investigative studies have assessed the impact of BP control and antiplatelet therapy on stroke recurrence after stroke related to small vessel disease.[382,408,416,417] These studies support the general guidance for the use of antiplatelet therapy and BP recommendations referenced in relevant sections of this report. More research is needed to develop and test disease-specific treatments for secondary stroke prevention after small vessel stroke. We focus here on clinical ischemic stroke related to small vessel disease, not on silent small vessel disease, which was reviewed in a 2017 scientific statement.[418]

Recommendation-Specific Supportive Text

1. Cilostazol has been studied as an alternative to aspirin therapy for ischemic stroke related to small vessel disease. In the CSPS trial (Cilostazol for Prevention of Secondary Stroke), cilostazol was compared with placebo in 1095 Japanese patients with noncardioembolic ischemic stroke (74% small vessel stroke).[416] There was a significant reduction in the risk of recurrent stroke in the cilostazol treatment group and in participants with lacunar stroke in the subgroup analysis. Cilostazol was compared with aspirin for the prevention of ischemic stroke in the CSPS II trial, which enrolled 2575 Japanese participants, 64% of whom had small vessel stroke as the qualifying event.[417] Cilostazol was associated with a significantly reduced risk of first occurrence of ischemic or hemorrhagic stroke in the cilostazol group compared with the aspirin group. There were significantly fewer hemorrhagic events in the cilostazol group. There was a nonsignificant reduction in recurrent stroke risk in participants with small vessel stroke in the subgroup analysis. There were more reported side effects, including headache, dizziness, palpitations, diarrhea, tachycardia, and constipation, in the cilostazol group. These findings have not yet been duplicated, and the inclusion of a single ethnic group may limit generalizability.

Knowledge Gaps and Future Research

- The role of cilostazol in secondary prevention after stroke related to small vessel disease.
- Targeted strategies for secondary prevention after small vessel stroke that also reduce the risk of vascular dementia.

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5.4. Cardioembolism

5.4.1. Atrial Fibrillation

Recommendations for AF
Referenced studies that support recommendations are summarized in online Data Supplement 32.

COR	LOE	Recommendations
1	A	1. In patients with nonvalvular AF and stroke or TIA, oral anticoagulation (eg, apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin) is recommended to reduce the risk of recurrent stroke.[419–426]
1	B-R	2. In patients with AF and stroke or TIA, oral anticoagulation is indicated to reduce the risk of recurrent stroke regardless of whether the AF pattern is paroxysmal, persistent, or permanent.[427]
1	B-R	3. In patients with stroke or TIA and AF who do not have moderate to severe mitral stenosis or a mechanical heart valve, apixaban, dabigatran, edoxaban, or rivaroxaban is recommended in preference to warfarin to reduce the risk of recurrent stroke.[419–426]
1	B-NR	4. In patients with atrial flutter and stroke or TIA, anticoagulant therapy similar to that in AF is indicated to reduce the risk of recurrent stroke.[427]
1	C-EO	5. In patients with AF and stroke or TIA, without moderate to severe mitral stenosis or a mechanical heart valve, who are unable to maintain a therapeutic INR level with warfarin, use of dabigatran, rivaroxaban, apixaban, or edoxaban is recommended to reduce the risk of recurrent stroke.
2a	B-NR	6. In patients with stroke at high risk of hemorrhagic conversion in the setting of AF, it is reasonable to delay initiation of oral anticoagulation beyond 14 days to reduce the risk of ICH.[428–431]
2a	C-EO	7. In patients with TIA in the setting of nonvalvular AF, it is reasonable to initiate anticoagulation immediately after the index event to reduce the risk of recurrent stroke.
2b	B-R	8. In patients with stroke or TIA in the setting of nonvalvular AF who have contraindications for lifelong anticoagulation but can tolerate at least 45 days, it may be reasonable to consider percutaneous closure of the left atrial appendage with the Watchman device to reduce the chance of recurrent stroke and bleeding.[432–436]
2b	B-NR	9. In patients with stroke at low risk for hemorrhagic conversion in the setting of AF, it may be reasonable to initiate anticoagulation 2 to 14 days after the index event to reduce the risk of recurrent stroke.[428,429,437]
2b	B-NR	10. In patients with AF and stroke or TIA who have end-stage renal disease or are on dialysis, it may be reasonable to use warfarin or apixaban (dose adjusted if indicated) for anticoagulation to reduce the chance of recurrent stroke.[438]

Synopsis

AF is an important cause of cardioembolic stroke, and the initial clinical presentation of AF is often stroke or TIA. In patients with ischemic stroke or TIA, a diagnosis of AF allows the reduction of recurrent events by treatment with long-term oral anticoagulation. The left atrial appendage is thought to be the main source of cardioembolism in AF. In a series of patients with stroke and AF evaluated by echocardiography, 90% of identified thrombus was seen in the left atrial appendage.[432] Anticoagulation decreases thrombus formation systemically, including the left atrium, and reduces the risk of stroke or systemic embolism in AF, but at the cost of increased bleeding. Four approved direct-acting oral anticoagulants (DOACs) have been studied in large randomized trials and shown to clinically reduce the risk of thrombotic stroke with less bleeding risk compared with vitamin K antagonists (VKAs). Patients with stroke or TIA represent a higher-risk population for recurrent stroke events than the overall population studied in the largest randomized trials. Moreover, when considering use of the $CHADS_2$ or CHA_2DS_2-VASc risk calculators,[420,439,440] the presence of stroke or TIA places a patient in a category in which anticoagulation is recommended regardless of other risk factors.

Recommendation-Specific Supportive Text

1. The risk of thromboembolism from AF is reduced by anticoagulation. VKA with warfarin reduced the primary event rate in the randomized SPAF trial (Stroke Prevention in Atrial Fibrillation Study) by 67% (7.4% to 2.3%) and was superior to treatment with aspirin alone, which reduced the primary event rate by 42%.[419] Subsequent studies using risk characterization scores have further supported the effectiveness of VKAs in reducing stroke risk in AF.[420–422] Furthermore, in all scoring systems of stroke risk in AF, prior stroke or TIA alone places a patient in a risk category in which anticoagulation is recommended. Four DOACs—apixaban, dabigatran, edoxaban, and rivaroxaban—have been studied in 4 large randomized trials against VKA with consistent evidence of noninferior reduction in thromboembolic risk and reduced bleeding risk.[423–426] All trials of DOACs specifically excluded patients with valvular AF; however, up to 20% of patients in these trials had some degree of valvular heart disease (VHD). This discrepancy has led to some confusion in practice, which was clarified in the 2019 AHA/ACC/Heart Rhythm Society guideline on the management of AF.[32] DOACs should not be used in patients with moderately severe or greater mitral stenosis or a mechanical heart valve.
2. AF is the most common arrhythmia in the adult population and can be categorized by the proportion of time a given patient spends in AF as paroxysmal, persistent, or permanent. Even brief subclinical episodes of AF are associated with increased risk of stroke.[427] Anticoagulation is recommended for patients with stroke or TIA regardless of the

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amount of time spent in AF. There is no established lower limit of embolism risk from time spent in AF; furthermore, patients with AF tend to progress to greater proportions of time spent in arrhythmia over time. Moreover, up to 28% of patients are found to have AF with prolonged monitoring after stroke. Patients with a remote history of a discrete AF episode (eg, postoperative or thyrotoxicosis) represent a group at increased risk for arrhythmia recurrence,[441–444] but the objective risk of recurrence is poorly defined.

3. All 4 randomized trials of DOACs demonstrated advantages to stroke risk reduction with the DOAC compared with a VKA with similar or improved stroke rates associated with similar or less bleeding. In the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulant Therapy), at 2 years, high-dose dabigatran was associated with lower stroke (1.11% versus 1.69%) and similar bleeding (3.11% versus 3.36%) rates compared with warfarin.[423] In ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), rivaroxaban was noninferior to warfarin with similar rates of stroke or systemic embolism (2.1 vs 2.4 per 100 patient-years) and major bleeding (5.6% versus 5.4%) in 14 264 patients followed up for 2 years.[424] The ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) of 18 201 patients demonstrated that apixaban was superior to warfarin at 1.8 years with fewer strokes or systemic embolisms (1.27% versus 1.60%) and less bleeding (2.13% versus 3.09%).[425] The ENGAGE AF-TIMI 48 trial (Global Study to Assess the Safety and Effectiveness of Edoxaban [DU-176b] vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation) showed similar rates of stroke or systemic embolism with less bleeding in 21 105 patients comparing 2 doses of edoxaban with warfarin.[426] A meta-analysis combining the data from all 4 trials found an overall 19% reduction in stroke or systemic embolism driven by a 51% reduction in hemorrhagic stroke and a 10% overall reduction in mortality.[445] The improved safety profile of DOACs in the context of noninferior thromboembolic risk leads to the recommendation to consider preferential use of a DOAC over a VKA.
4. Compared with AF, atrial flutter is a more organized macro-reentrant arrhythmia often involving the tricuspid isthmus. Atrial flutter is less common than AF overall; however, patients with atrial flutter are at increased risk for developing AF, and the risk of stroke associated with atrial flutter is similar to that associated with AF.[28] In a single-center series of 1121 patients referred for atrial flutter ablation and followed up for 2.1±2.7 years, 31.7% had AF before ablation and 23.2% of patients experienced AF after ablation for atrial flutter.[446]
5. Therapy with VKA has a narrow therapeutic window. Patients who do not maintain an INR in the therapeutic range are at increased risk for both bleeding and thrombotic events. Time in therapeutic range is an important metric indicating the overall time spent by a patient with an INR in the therapeutic range; time with subtherapeutic INRs confers greater risk of embolic events, whereas time spent with supratherapeutic INR confers risk of major bleeding. In the ACTIVE W trial (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events), patients randomized to warfarin who did not maintain >60% time in therapeutic range did not derive net benefit from anticoagulation therapy.[447] A meta-analysis of data from the 4 seminal trials of DOACs confirmed this finding, observing substantially greater benefit of DOACs compared with VKAs when the center-based time in therapeutic range was <66% (31% versus 7% improvement in major bleeding).[445] For patients who have documented suboptimal time in therapeutic range with VKA in the setting of AF and prior stroke or TIA, it is recommended to use a DOAC preferentially.
6. Patients with stroke or TIA in the setting of AF are at increased risk of recurrent ischemic stroke and at risk for ICH. Recurrent ischemic stroke risk is 0.5% per day to 1.3% per day in the first 14 days, whereas the rate of symptomatic hemorrhagic transformation after stroke ranges substantially, depending on the use of thrombolytics, with rates of 6% to 21% and 1% to 7% in the thrombolytic and placebo arms, respectively, across multiple trials of thrombolytic therapy.[428,448] Anticoagulation reduces the risk of recurrent ischemic stroke but increases the risk of cerebral hemorrhage during the acute poststroke phase.[429,449] Patients with larger cerebral infarcts are at greater risk for hemorrhagic transformation and worse bleeding with early initiation of anticoagulation[430]; thus, it is reasonable to delay initiation of oral anticoagulation for 14 days after stroke onset in that setting. Although there is no uniformly accepted definition of a large cerebral infarction, accepted definitions have included National Institutes of Health Stroke Scale (NIHSS) score >15[450] and lesions involving complete arterial territory or >1 arterial territory.[431] Moreover, patients with early signs of hemorrhage on neuroimaging are at highest risk of further intracerebral bleeding and should delay initiation of oral anticoagulation to allow healing of the blood–brain barrier.[451]

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7. Patients who have a TIA rather than stroke in the setting of AF are at relatively low risk for intracranial hemorrhage but remain at increased risk for recurrent stroke. The balance of bleeding risk versus benefit of stroke risk reduction from oral anticoagulation favors earlier initiation in the setting of TIA when no cerebral infarction is present. The relative safety of earlier anticoagulation in TIA is in contrast to the recommended delay with stroke (particularly large stroke), in which cerebral infarction can disrupt the blood–brain barrier and increases the risk of hemorrhage with initiation of anticoagulation.
8. In patients with stroke in the setting of nonvalvular AF, the left atrial appendage is the location of identified thrombus 90% of the time.[432] This observation gave rise to the concept of left atrial appendage closure to reduce the risk of stroke from AF. The Watchman device is a plug-style device placed in the ostium of the left atrial appendage to occlude it and prevent thromboembolism. It was studied in the randomized PROTECT AF trial (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) and PREVAIL trial (Prospective Randomised Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy), as well as the nonrandomized CAP (Continued Access Registry), demonstrating nonsignificant numerically greater thrombotic risk with the device but lower bleeding risk and overall net benefit.[433–436] The Watchman device is the only currently available device with US Food and Drug Administration approval for left atrial appendage closure. Other devices to close the left atrial appendage are under investigation. Current practice based on clinical trial design involves short-term (1.5 months) use of oral anticoagulation after Watchman device placement to reduce the risk of device-related thrombus followed by 4.5 months of DAPT. In patients at high bleeding risk from oral anticoagulation, left atrial appendage closure can reduce the long-term risk of bleeding with an ischemic stroke risk comparable to that of anticoagulation with VKA.
9. Cerebral infarction weakens the blood–brain barrier, increasing the risk of spontaneous hemorrhage after acute ischemic stroke, yet patients with stroke or TIA in the setting of AF are at increased risk of recurrent stroke.[428] Anticoagulation reduces the risk of recurrent embolism but increases the risk of cerebral hemorrhage during the acute post-stroke phase.[449] The optimal timing of initiating oral anticoagulation should be individualized for each patient's risk of hemorrhage versus recurrent embolism. Although the annualized risk of recurrent stroke can be significant, the daily risk of embolism from AF is generally small. For example, a patient with a 6% risk of stroke over 1 year would have a daily risk of 0.016% and a risk of 0.23% over 14 days. Nevertheless, an analysis of the VISTA cohort study (Virtual International Stroke Trials Archive) of 1644 patients found fewer recurrent strokes with initiation of VKA 2 to 3 days after stroke compared with >3 days without increased risk of symptomatic ICH.[437] In patients with larger cerebral infarcts, evidence of hemorrhage on neuroimaging, NIHSS score >9, or other features that place them at increased risk of hemorrhagic conversion after acute stroke, the balance of risk and benefit favors waiting for healing and reduced bleeding risk.[429]
10. Patients with renal failure on dialysis are at increased risk for both bleeding and thrombotic events. All DOAC medications are renally cleared, increasing the risk for drug accumulation, supratherapeutic drug levels, and bleeding events in patients with renal failure. Although overall data are limited in this population, a large retrospective study matched 2351 patients with AF on dialysis who took apixaban against 23 172 taking warfarin and found a 28% lower rate of bleeding events in those taking apixaban.[438] This finding supports the use of apixaban as an alternative choice for anticoagulation in patients with AF on dialysis.

Knowledge Gaps and Future Research

Optimal management strategies to reduce the risk of recurrent stroke in patients with AF have improved substantially with support from large trial data; however, knowledge gaps remain, including:

- The minimal duration of AF that engenders significant stroke risk and benefit of oral anticoagulation beyond the bleeding risk remains unknown. Multiple studies reflecting the increased use of monitoring technologies are ongoing.
- The safety of discontinuing oral anticoagulation after surgical appendage closure remains uncertain. Small series of surgical technologies have demonstrated technical success, but the relevance to clinical need for oral anticoagulation remains unknown.
- Multiple transcatheter approaches to left atrial appendage closure are under investigation and will provide additional options for stroke risk reduction while minimizing risk of bleeding with long-term anticoagulation.
- For patients who have had AF followed by successful ablation, the need for continued anticoagulation is uncertain and continues to be studied.
- Patients with limited postoperative AF are at increased risk of recurrence; however, further research is needed to identify which patients would benefit from long-term anticoagulation.

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- The safety of oral anticoagulation in the setting of cerebral amyloid angiopathy and in the presence of microhemorrhages remains unclear and merits further study.
- The efficacy of left atrial appendage closure compared with DOACs is unknown.
- The DOAC efficacy in morbidly obese patients is unknown.

5.4.2. Valvular Disease

Recommendations for Valvular Disease
Referenced studies that support recommendations are summarized in online Data Supplements 33 and 34.

COR	LOE	Recommendations
1	B-R	1. In patients with ischemic stroke or TIA and valvular AF (moderate to severe mitral stenosis or any mechanical heart valve), warfarin is recommended to reduce the risk of recurrent stroke or TIA.[452–457]
1	C-LD	2. In patients with a mechanical mitral valve and a history of ischemic stroke or TIA before valve replacement, aspirin (75–100 mg/d) is recommended in addition to warfarin with an INR target of 3.0 (range, 2.5–3.5) to reduce the risk of thrombosis and recurrent stroke or TIA.[458,459]
1	C-EO	3. In patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease (eg, mitral annular calcification or mitral valve prolapse) who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended to reduce the risk of recurrent stroke or TIA.
1	C-EO	4. In patients with a bioprosthetic aortic or mitral valve, a history of ischemic stroke or TIA before valve replacement, and no other indication for anticoagulation therapy beyond 3 to 6 months from the valve placement, long-term therapy with aspirin is recommended in preference to long-term anticoagulation to reduce the risk of recurrent stroke or TIA.
2a	B-NR	5. In patients with ischemic stroke or TIA and IE who present with recurrent emboli and persistent vegetations despite appropriate antibiotic therapy, early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) is reasonable to reduce the risk of recurrent embolism if there is no evidence of intracranial hemorrhage or extensive neurological damage.[460–465]
2a	C-EO	6. In patients with history of ischemic stroke or TIA and a mechanical aortic valve, anticoagulation with higher-intensity warfarin to achieve an INR of 3.0 (range, 2.5–3.5) or the addition of aspirin (75–100 mg/d) can be beneficial to reduce the risk of thromboembolic events.
2b	B-NR	7. In patients with ischemic stroke or TIA and native left-sided valve endocarditis who exhibit mobile vegetations >10 mm in length, early surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) may be considered to reduce the risk of recurrent embolism if there is no evidence of intracranial hemorrhage or extensive neurological damage.[460–465]

Recommendations for Valvular Disease Continued

COR	LOE	Recommendations
2b	B-NR	8. In patients with ischemic stroke or TIA and IE, early valve surgery (during initial hospitalization before completion of a full therapeutic course of antibiotics) may be considered in patients with an indication for surgery who have no evidence of intracranial hemorrhage or extensive neurological damage.[466,467]
2b	B-NR	9. In patients with IE and major ischemic stroke, delaying valve surgery for at least 4 weeks may be considered for patients with IE and major ischemic stroke or intracranial hemorrhage if the patient is hemodynamically stable.[460,468]
3: Harm	B-R	10. In patients with ischemic stroke or TIA and mechanical heart valves, treatment with dabigatran causes harm.*[457]

*A similar recommendation in another guideline is worded slightly differently; however, the process used to reach consensus was the same in both cases.

Synopsis

In patients with VHD (except moderate to severe mitral stenosis or a mechanical heart valve), ischemic stroke or TIA, and AF, DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin therapy.[452–457] In patients with valvular AF (ie, moderate to severe mitral stenosis or a mechanical heart valve), warfarin is recommended.[32,458,464,469–472] Antiplatelet therapy continues to be recommended over warfarin in patients with VHD other than rheumatic mitral disease and ischemic stroke or TIA.[9] For patients with prosthetic heart valves, the choice of type of antithrombotic therapy after ischemic stroke or TIA is influenced by the type of valve (bioprosthetic versus mechanical), the timing of the embolic event, prior documented compliance to antithrombotic therapy, and assessment of the function of the prosthetic valve.[9,33] Indications and timing for surgical interventions in patients with IE and stroke or TIA depend on multiple factors, including recurrent events while on antibiotic therapy, size of the vegetation, and presence of associated intracranial hemorrhage.[33,460,464–467] Figure 3 summarizes the recommended antithrombotic regimen in patients with history of ischemic stroke or TIA and different VHD conditions.

Recommendation-Specific Supportive Text

1. AF is highly prevalent in patients with VHD and represents one of the most important risk factors for ischemic stroke and TIA. In patients with prior ischemic stroke or TIA and associated AF, the distinction between valvular and nonvalvular AF is crucial because it has important implications in the selection of the optimal oral anticoagulation regimen.[452–457] Valvular AF refers to AF in the context of moderate to severe mitral stenosis or in the presence of any mechanical heart valve.[32] It is important to highlight that the term nonvalvular AF does not imply the absence of VHD but only

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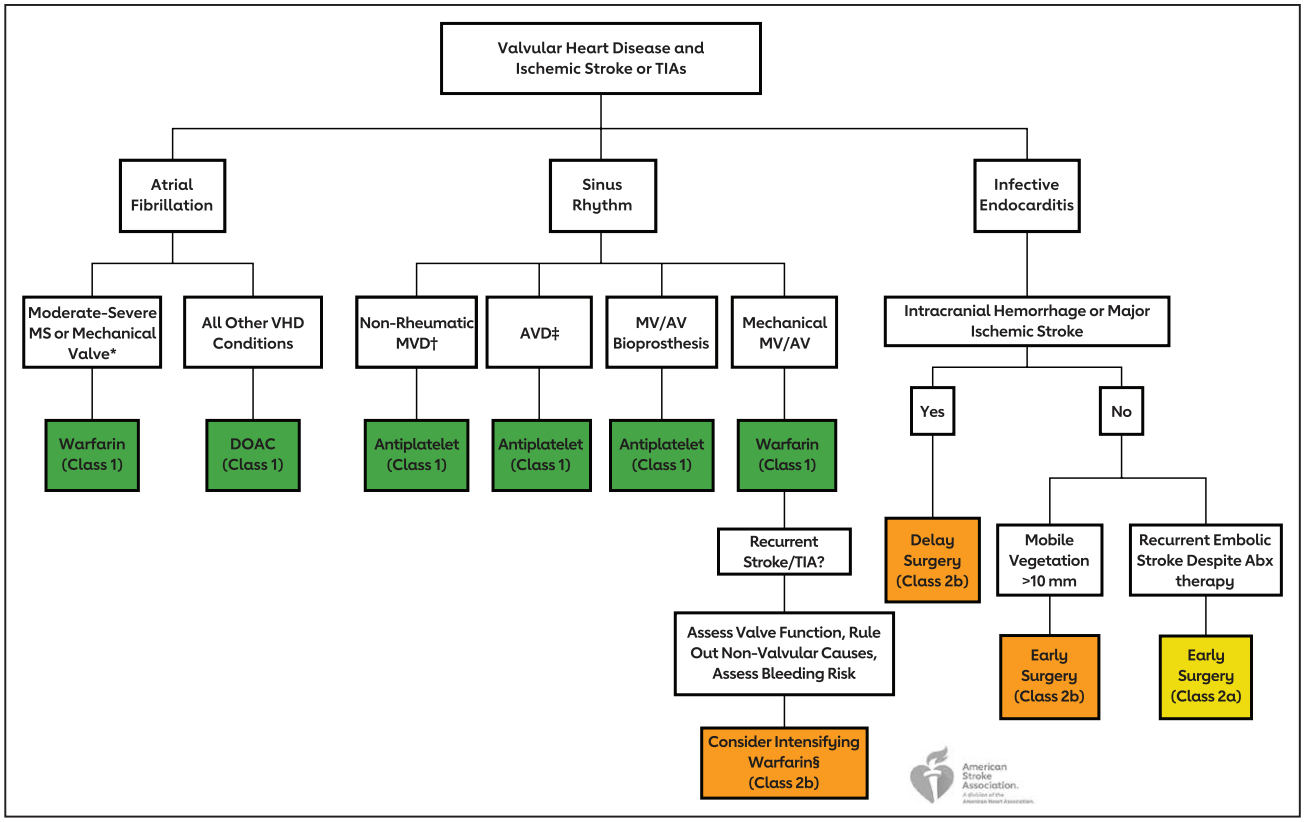

Figure 3. Recommended antithrombotic regimen in patients with history of ischemic stroke or transient ischemic attack (TIA) and different valvular heart disease conditions.

Colors correspond to Class of Recommendation in Table 3. Abx indicates antibiotics; AF, atrial fibrillation; AV, aortic valve; AVD, aortic valve disease; DOAC, direct oral anticoagulant; MAC, mitral annular calcification; MS, mitral stenosis; MV, mitral valve; MVD, mitral valve disease; MVP, mitral valve prolapse; and VHD, valvular heart disease. *Definition of valvular AF. †Includes MAC and MVP. ‡Rheumatic and nonrheumatic AVD. §Increase the target international normalized ratio by 0.5, depending on bleeding risk.

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the absence of moderate to severe mitral stenosis or mechanical heart valves (ie, AF in the setting of bioprosthetic valves, mild mitral stenosis, and any native aortic, pulmonary, or tricuspid valve disease is still considered nonvalvular).[32] According to the results of subgroup analyses of RCTs testing DOACs to prevent thromboembolic complications in patients with AF and meta-analyses of randomized trials,[452–457] in patients with VHD except moderate to severe mitral stenosis or a mechanical heart valve, ischemic stroke or TIA, and AF, DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are recommended over warfarin therapy.

2. In patients with mechanical mitral valve replacement, anticoagulation with warfarin is recommended with an INR target of 3.0 (range, 2.5–3.5).[33,473] The incidence of thromboembolism is higher in patients with mechanical prostheses in the mitral compared with the aortic position, and the rate of thromboembolism is lower in patients with a higher INR goal. In the GELIA study (German Experience With Low Intensity Anticoagulation) of patients with a mechanical mitral prosthesis, a lower INR (2.0–3.5) was associated with lower survival rates than a higher target INR range (2.5–4.5).[458] Although routine addition of aspirin to warfarin therapy in patients with mechanical valves is not recommended, patients with a history of ischemic stroke or TIA before the mechanical valve surgery represent a group with an inherently higher thromboembolic risk in whom the protection from recurrent thromboembolic events associated with the combination of aspirin and warfarin therapy may outweigh the competing bleeding risk.[459]
3. In the absence of AF, observational studies have reported conflicting results with regard to the association between nonrheumatic mitral valve disease or native aortic disease and increased risk of thromboembolic complications.[474–479] An early case-control study reported that mitral valve prolapse was associated with an increased risk for ischemic stroke.[474] More recent studies have not confirmed an association.[475–477,480] Observational studies have consistently shown that the risk for stroke in people with mitral valve prolapse is low (<1% annually).[481–483] At least 4 population-based cohort studies have evaluated the association between mitral annular calcification and stroke.[478,479,484,485]

The cumulative evidence does not support a causal association between mitral annular calcification and increased risk of thromboembolism. Similarly, there is no conclusive evidence supporting a causal association between native aortic valve disease and increased risk of stroke or TIA.[478,479] Additional distinct valvular lesions such as Libman-Sacks endocarditis,[486] age-related calcifications,[487] or bicuspid aortic valves[487] have been associated with increased risk of thromboembolism, although no properly designed trial has addressed the optimal therapeutic strategy to prevent ischemic stroke or TIA in these specific conditions. Therefore, no specific management recommendations can be made for these conditions.

4. In patients undergoing bioprosthetic mitral or aortic valve replacement surgery, oral anticoagulation with warfarin to achieve a target INR of 2.5 (range, 2.0–3.0) is reasonable for at least 3 months and for as long as 6 months after surgery in patients at low risk of bleeding.[33] This recommendation is based on the results of observational studies that have reported an increased risk of ischemic stroke early after surgery.[488–490] After 3 to 6 months after surgery, long-term therapy with only aspirin 75 to 100 mg daily is recommended.[473,491–493] Patients with a history of ischemic stroke or TIA (before the bioprosthetic valve surgery) who are already receiving antiplatelet therapy and have no indication for anticoagulation therapy should continue to be managed with antiplatelet therapy alone after the bioprosthetic valve insertion.
5. In patients with mechanical prosthetic heart valves, effective antithrombotic therapy requires continuous effective warfarin anticoagulation with an INR in the target range.[33] ACC/AHA guidance on the selection of the most appropriate antithrombotic regimen in patients with mechanical heart valves has been published in separate guidelines.[33] Anticoagulation with warfarin to achieve an INR of 2.5 is typically recommended for patients with a mechanical bileaflet or current-generation single-tilting-disk aortic valve replacement and no risk factors for thromboembolism.[458,469,472,473] However, patients with an aortic mechanical prosthesis who have a history of ischemic stroke or TIA are at higher risk of thromboembolic complications, and it is recommended to maintain the INR at a higher target of 3.0 (range, 2.5–3.5) or to add aspirin 75 to 100 mg daily.[9,33,473,494,495]
6. Neurological complications are the most frequent and severe extracardiac complications of IE, with an estimated incidence of up to 20% to 40% and a significant impact on mortality.[460–462] Ischemic cerebrovascular events represent the most common neurological complication of IE. Risk factors for ischemic stroke or TIA include vegetation size and mobility, infection with *Staphylococcus aureus*, and involvement of the mitral valve.[460] Timely and appropriate institution of antibiotic therapy is the first-line therapy for patients with IE and embolic stroke or TIA. ACC/AHA guidance on the management of patients with IE has been published in separate guidelines.[33,463] In patients with IE and recurrent embolic stroke or TIA despite antibiotic therapy, an early consideration for surgery (during the index hospitalization and before completion of a full therapeutic course of antibiotics) is reasonable if there is no evidence of intracranial hemorrhage or extensive neurological damage.[464,465]
7. Vegetation size represents an important risk factor for systemic embolization in patients with IE.[460,465] In a multicenter prospective study including 384 consecutive patients with IE who underwent TEE, embolic complications occurred in 131 cases (34.1%). Of these, 28 patients (7.3%) had an embolic event after the institution of adequate antibiotic therapy. Vegetation length was larger in patients with new embolic events (after initiation of antibiotic therapy) than in those without (median, 15.5 mm versus 9 mm, respectively; $P<0.001$). A vegetation length threshold of 10 mm was identified as having the highest predictive value for embolic events while on adequate antibiotic therapy.[465] In a small randomized trial including 76 patients with left-sided IE, severe mitral valve or aortic disease, and large vegetations (>10 mm), early surgery (within 48 hours of randomization) was associated with a significant reduction of the composite end point of in-hospital death or embolic events (HR, 0.10 [95% CI, 0.01–0.82]) compared with conventional treatment.[464]
8. Decisions on the optimal timing of surgical intervention in patients with IE after an acute stroke should balance the benefits associated with surgical correction of the IE lesion with the risk of worsening of the neurological insult attributable to ICH (typically caused by hemorrhagic conversion of ischemic lesions, mycotic aneurysms, or septic necrotic arteritis), hypotension, and further intraoperative embolization.[33] In patients with IE who have had an acute stroke without extensive neurological damage and no intracranial hemorrhage, data suggest that early surgery (with no delay) may be associated with better outcomes.[33,466,467] An early Japanese retrospective study including 181 of 244 patients with cerebral complications reported a correlation between the time delay to surgery and mortality.[466] More recently, a prospective cohort study evaluated the relationship between the timing of surgery after a stroke and in-hospital and

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1-year mortality rates.[467] A total of 198 patients with IE who underwent valve replacement surgery after a stroke were analyzed. Of these, 58 patients (29.3%) underwent early surgical treatment and 140 (70.7%) had late surgical treatment. After adjustment for other risk factors, early surgery was not associated with increased in-hospital or 1-year mortality rates.[467]

9. Hemorrhagic complications of IE are multifactorial and can result from hemorrhagic conversions of ischemic lesions, rupture of mycotic aneurysms, or septic necrotic arteritis.[460,468] Patients with hemorrhagic stroke and IE have high surgical risk for at least 4 weeks after the event. One observational study showed a substantial difference in mortality rates when patients who underwent surgery within 4 weeks of a hemorrhagic stroke were compared with those whose surgery was delayed until after 4 weeks (75% versus 40%, respectively). Notably, the rate of new hemorrhagic events after surgery was 50% in patients who underwent surgery within the first 2 weeks, 33% in patients who underwent surgery in the third week, and 20% in patients who underwent surgery at least 21 days after the neurological event.[460]
10. A phase II randomized trial comparing dabigatran and warfarin in patients with mechanical heart valves (RE-ALIGN [Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients After Heart Valve Replacement]) was stopped prematurely after enrollment of 252 patients because of an excess of thromboembolic and bleeding events in the dabigatran arm.[457] At this point, there is no published randomized study evaluating the safety and efficacy of other DOACs in patients with mechanical heart valves, and warfarin remains the only recommended oral anticoagulant in these patients.

Knowledge Gaps and Future Research

- Rheumatic mitral valve disease often results in left atrial structural changes and adverse remodeling, which predisposes to thromboembolic complications also when in sinus rhythm, a condition that has been defined as atrial cardiomyopathy.[496,497] In patients with ischemic stroke or TIA who have rheumatic mitral valve disease without AF and no other likely cause for their symptoms (eg, carotid stenosis), the role of oral anticoagulation has not been adequately investigated.
- Patients with a bioprosthetic aortic or mitral valve are typically managed with antiplatelet therapy. If an ischemic stroke or TIA occurs in these patients despite adequate antiplatelet, the benefit of switching to oral anticoagulation with warfarin or a DOAC is unknown and warrants further investigation.
- In patients with IE, small observational series suggest a role for routine neurovascular imaging studies (CT or MRA) to screen for mycotic aneurysms, which can potentially influence the treatment plan.[498,499] Further larger studies are needed to determine whether routine neurovascular imaging to screen for mycotic aneurysms in IE improves outcomes.
- Patients with transcatheter aortic valve replacement and transcatheter mitral valve replacement represent a growing population.[500,501] Antiplatelet therapy is the standard antithrombotic regimen after transcatheter aortic valve replacement,[33] whereas a combination of oral anticoagulation and antiplatelet therapy has been used with transcatheter mitral valve replacement, although with scant supporting evidence.[501] At the present time, DOACs are not routinely used in transcatheter aortic valve replacement,[502,503] and additional studies are needed to further evaluate the potential benefit of DOACs therapy to prevent ischemic stroke or TIA in this population. Furthermore, the optimal antithrombotic regimen for patients with a transcatheter aortic valve replacement who have a TIA or ischemic stroke despite adequate antiplatelet therapy is still undefined.

5.4.3. LV Thrombus

Recommendations for LV Thrombus
Referenced studies that support recommendations are summarized in online Data Supplement 35.

COR	LOE	Recommendations
1	B-NR	1. In patients with stroke or TIA and LV thrombus, anticoagulation with therapeutic warfarin for at least 3 months is recommended to reduce the risk of recurrent stroke.[504–508]
2a	C-EO	2. In patients with stroke or TIA in the setting of acute MI, it is reasonable to perform advanced cardiac imaging (eg, contrasted echocardiogram or cardiac MRI) to assess for the presence of LV thrombus.
2b	C-LD	3. In patients with stroke or TIA and new LV thrombus (<3 months), the safety of anticoagulation with a direct oral anticoagulant to reduce risk of recurrent stroke is uncertain.[509]
2b	C-EO	4. In patients with stroke or TIA in the setting of acute anterior MI with reduced ejection fraction (EF; <50%) but no evidence of LV thrombus, empirical anticoagulation for at least 3 months might be considered to reduce the risk of recurrent cardioembolic stroke.

Synopsis

Decreased contractility in the LV, particularly at the LV apex, creates the possibility of blood pooling and subsequent coagulation and thrombus formation. Thrombus in the LV is then at risk of systemic embolization. Although LV thrombus can form anytime blood stasis occurs, patients with acute MI, who have had acute vessel closure with associated loss of myocardial contractility, are at risk of forming LV thrombus. Patients with anterior MI and reduced EF are a subgroup shown to be at particular risk

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for LV thrombus formation. The associated risk of stroke or systemic embolism in the presence of LV thrombus is reduced by use of systemic anticoagulation. Over time, thrombus in the LV matures and becomes incorporated into the wall of the akinetic segment, and the risk of embolism is reduced. The exact time for each thrombus to mature to this point is unknown, but the risk of systemic embolism or stroke is reduced after 3 months. In the context of secondary stroke prevention, detection of LV thrombus is an important determinant of stroke type and appropriate therapy. Standard transthoracic echocardiography is relatively insensitive for the detection of LV thrombus. Both contrast echocardiography with the use of a microbubble contrast agent and cardiac MRI are superior imaging modalities for detecting LV thrombus compared with standard transthoracic echocardiography.

Recommendation-Specific Supportive Text

1. Patients with stroke or TIA in the context of LV thrombus should be anticoagulated until the thrombus has matured and the risk of further embolism has waned, ≈3 months. The bulk of evidence has used VKA for oral anticoagulation with a goal INR of 2.0 to 3.0. A large cohort study of 2160 patients from 1979 to 1998 noted that the risk of stroke after MI was dramatically higher in the first month after infarct and remained elevated for years afterward.[510] In the percutaneous coronary angiography era, a multicenter study of 753 patients with ST-segment elevation MI identified LV thrombus in 3.5% and 7.1% of patients after anterior ST-segment elevation MI using cardiac MRI, although mural thrombus has been noted in as many as 26% of those studied in other series.[504,505] In a meta-analysis of 8 studies encompassing 856 patients, Vaitkus and Barnathan[506] noted an increased risk of stroke or systemic embolism in the presence of LV thrombus demonstrated on echocardiogram with an OR of 5.45. Moreover, the risk of embolism was substantially reduced in the presence of oral anticoagulation with a VKA with an OR of 0.14. A smaller single-center retrospective study of 33 patients with LV thrombus on cardiac MRI compared with 66 matched controls observed a short-term risk of stroke of 9.1%; another study of LV thrombus noted stroke or systemic embolism in 7.7% of patients with documented thrombus.[505,507] Finally, a larger, more heterogeneous single-center study of 155 patients with LV thrombus found on cardiac MRI compared with 400 matched patients over 3.3 years found an annualized rate of stroke or systemic embolism of 3.7% versus 0.8% in those without LV thrombus, suggesting that an increased risk of embolism may persist.[508] It is unclear whether events in the cohort with LV thrombus were caused by the thrombus or the LV thrombus was a marker of a higher-risk population.
2. Both administration of microbubble contrast with transthoracic echocardiography and cardiac MRI have been shown to be superior to echocardiography without contrast for the detection of LV thrombus. Both modalities also increase the definition of MI size where larger areas of infarction increase the risk of thrombus formation. In a study of 210 patients with cardiac MRI and echocardiography after ST-segment elevation MI, cardiac MRI detected LV thrombus in 12.3% of patients, and echocardiography detected LV thrombus in 6.2%.[505] Another single-center study of 201 patients with ST-segment elevation MI also noted lower rates of LV thrombus detection using echocardiography (35%) and contrast echocardiography (64%) compared with cardiac MRI.[511] Overall, detection of LV thrombus is increased by administration of microbubble contrast, and cardiac MRI has the highest demonstrated sensitivity.[512] Tailoring imaging strategy on the basis of patient risk may optimize diagnostic yield.
3. In a pooled meta-analysis of studies of mural thrombus after anterior MI, use of oral anticoagulation with VKA reduced the risk of stroke by 86% and resulted in resolution of LV thrombus in 68%.[506] Anticoagulation with DOACs has been shown to be as effective as VKA for the prevention of stroke in AF and for the treatment of deep vein thrombosis and pulmonary embolism with a lower risk of bleeding and with greater convenience, driving interest in use for LV thrombus. A single-center retrospective study of anticoagulation with a DOAC in 52 patients for the treatment of LV thrombus found resolution of the thrombus in 86% of patients on follow-up echocardiography, but the study was too small to address embolic event rates.[509] A larger retrospective analysis of 514 patients with identified LV thrombi from 3 centers and a median follow-up of 351 days compared 300 patients who received warfarin with 185 patients treated with DOAC and noted a higher rate of stroke or systemic embolism in the DOAC group (HR, 2.71 versus warfarin), although this difference was noted beyond the currently recommended duration of therapy for LV thrombi.[513]
4. Patients with reduced LV systolic function (LV EF <50%) in the setting of acute anterior MI are at the greatest risk of developing LV thrombus.[514] The observed rate of LV thrombus in anterior MI was 24% in 1 series by cardiac MRI.[505] The risk of stroke among patients with defined LV thrombus has been reported to be as high as 9% to 11%.[507,515] Therefore, for patients who have stroke or TIA in the context of anterior MI with reduced EF (ie, the cardiac population at the highest risk for

Stroke

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developing thrombus), one might consider empirical anticoagulation even in the absence of demonstrated thrombus.

Knowledge Gaps and Future Research

Ventricular thrombus complicating insults to LV function can present a challenge to the care team. Our understanding is based on aging data and small case series, leaving gaps in our knowledge and opportunities for future research in diagnosis, prognosis, and therapy.

- Often, the initial manifestation of LV thrombus is stroke. Identifying patients at highest risk of developing LV thrombus before it forms may prevent stroke. Advanced imaging methods offer the promise of identifying features of ventricular remodeling or dysfunction through strain patterns, blood vector mapping, and hematologic assays that point to patients who are at highest risk and would benefit from prophylactic anticoagulation. Furthermore, the optimal timing and frequency of screening for LV thrombus remain poorly characterized and would benefit from longitudinal study.
- The optimal duration of anticoagulation in the setting of thrombus remains elusive. Natural history studies with serial advanced imaging could better determine LV thrombus embolic risk and the need for anticoagulation.

5.4.4. Cardiomyopathy

Recommendations for Cardiomyopathy
Referenced studies that support recommendations are summarized in online Data Supplements 36 and 37.

COR	LOE	Recommendations
1	C-EO	1. In patients with ischemic stroke or TIA and left atrial or left atrial appendage thrombus in the setting of ischemic, nonischemic, or restrictive cardiomyopathy and LV dysfunction, anticoagulant therapy with warfarin is recommended for at least 3 months to reduce the risk of recurrent stroke or TIA.
2a	C-LD	2. In patients with ischemic stroke or TIA in the setting of a mechanical assist device, treatment with warfarin and aspirin can be beneficial to reduce the risk of recurrent stroke or TIA.[516–523]
2a	C-EO	3. In patients with ischemic stroke or TIA in the setting of LV noncompaction, treatment with warfarin can be beneficial to reduce the risk of recurrent stroke or TIA.
2b	B-R	4. In patients with ischemic stroke or TIA in sinus rhythm with ischemic or nonischemic cardiomyopathy and reduced EF without evidence of left atrial or LV thrombus, the effectiveness of anticoagulation compared with antiplatelet therapy is uncertain, and the choice should be individualized.[524–528]
3: Harm	B-R	5. In patients with stroke or TIA and LV assist devices (LVADs), treatment with dabigatran instead of warfarin for the primary or secondary prevention of ischemic stroke or TIA causes harm.[529]

Synopsis

Compared with the general population without cardiomyopathy, patients with cardiomyopathy and impaired LV EF have a higher incidence of thromboembolism. In patients with cardiomyopathy, ischemic stroke, or TIA in sinus rhythm who have intracardiac thrombus demonstrated by echocardiography or another imaging modality,[530–532] anticoagulant therapy with a warfarin is recommended for ≥3 months (Figure 4). Patients with noncompaction cardiomyopathy represent a peculiar subgroup at higher risk of thromboembolic complications,[533–535] In patients with ischemic stroke or TIA in the setting of LV noncompaction, treatment with warfarin therapy can be beneficial. The effectiveness of oral anticoagulation compared with antiplatelet therapy in patients with cardiomyopathy and reduced EF and ischemic stroke or TIA in sinus rhythm with no evidence of left atrial or LV thrombus is uncertain, and the choice should be individualized, taking into account the bleeding risk and estimated risk of recurrent thromboembolism.[524–528] Patients with LVADs have a high prevalence of neurological complications (thromboembolic/hemorrhagic). Warfarin together with aspirin is the standard antithrombotic regimen to minimize the risk of LVAD pump thrombosis[536] and to prevent recurrent ischemic stroke or TIA. At this point, the use of DOACs in patients with LVAD should be avoided.[529]

Recommendation-Specific Supportive Text

1. The prevalence of intracardiac thrombosis in patients with cardiomyopathy has not been conclusively determined, and it varies between different underlying causes. In a retrospective database including 86 374 patients, 62 cases (0.7%) of LV thrombosis were identified. The majority of patients (81%) had ischemic cardiomyopathy, and the remaining had a nonischemic type.[537] Oral anticoagulation with warfarin has been used in patients with intracardiac thrombus, and the efficacy has been documented in several observational studies.[538,539] A duration of therapy <3 months has been associated with a higher recurrence rate.[539] The evidence for the use of DOACs in patients with intracardiac thrombus is limited largely to isolated case reports and small case series.[529,540–546] It is also important to note that DOACs have not been studied specifically to prevent thromboembolism in patients with documented LV or left atrial thrombus. In addition, uncertainty about the optimal dosing of DOACs and the long-term safety remains. Therefore, at the present time, warfarin should be preferred to DOACs in patients with ischemic, nonischemic, or restrictive cardiomyopathy; ischemic stroke or TIA in sinus rhythm; and documented left atrial or LV thrombus.

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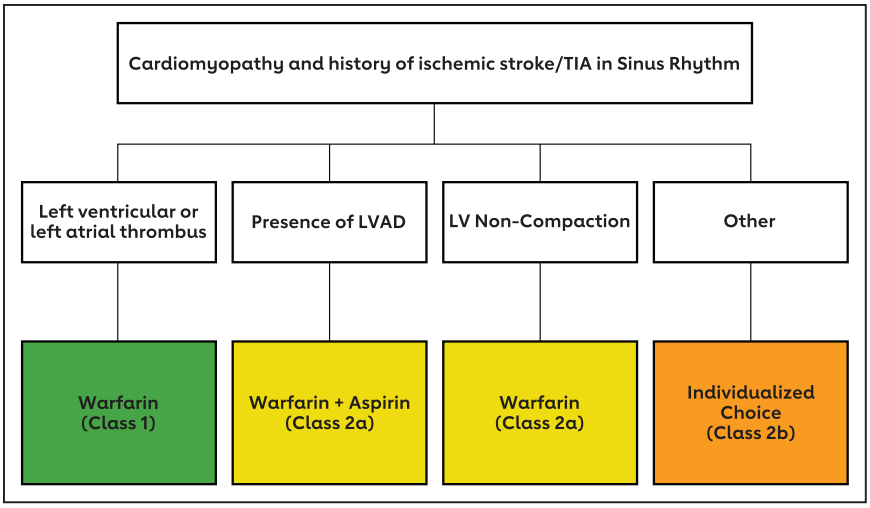

Figure 4. Anticoagulant therapy for patients with cardiomyopathy, ischemic stroke, or transient ischemic attack (TIA) in sinus rhythm. Colors correspond to Class of Recommendation in Table 3. LV indicates left ventricle; and LVAD, left ventricular assist device.

2. Thromboembolic complications represent a major therapeutic challenge in the LVAD population and can occur at any point after LVAD implantation, including the immediate postoperative period and the long-term follow-up.[516–519] The pathophysiology associated with ischemic stroke in the LVAD population is complex, and the postulated underlying mechanisms are different for early versus late strokes. In the immediate postoperative period, several surgical factors have been reported to possibly increase the risk. These factors include duration of cardiopulmonary bypass and the need for other associated surgeries (eg, coronary artery bypass surgery, valve surgery).[517,520] Pump thrombosis, reduced pump speeds, venous thromboembolism, uncontrolled hypertension, and systemic infections have been associated with late strokes.[518,519,521,522] A suboptimal anticoagulation regimen, which includes either supratherapeutic or subtherapeutic INR and no aspirin use, has also been associated with increased risk of ischemic strokes. The use of DAPT compared with acetylsalicylic acid alone in addition to warfarin does not appear to affect the rates of ischemic stroke.[523] Therefore, at the present time, the combination of warfarin and aspirin is the preferred regimen in preventing recurrent ischemic stroke.
3. LV noncompaction is a rare primary cardiomyopathy possibly caused by an arrest of normal embryogenesis of the endocardium and mesocardium that leads to the formation of prominent trabeculations and deep intertrabecular recesses within the LV wall communicating with the cavity. The inferior and lateral walls of the LV from the midcavity to the apex are most commonly involved by this process.[547] Among cohorts of patients with cardiac disease, the estimated prevalence of LV noncompaction varies from 0.9% by echocardiographic criteria to 9.8% with cardiac magnetic resonance criteria.[548] LV noncompaction has a broad spectrum of clinical manifestations, ranging from asymptomatic state to severe heart failure, ventricular arrhythmias, and thromboembolic events.[197,533,535] The risk of thromboembolism in LV noncompaction cardiomyopathy has been evaluated in several case series, which have reported an up to 24% risk of cerebral embolism at follow-up.[534,549] This increased risk has been theorized to result from blood stasis within the prominent LV trabeculations and intertrabecular recesses.[533–535] Given the shared pathophysiological basis with LV endocavitary thrombus, we make this recommendation.
4. There are 5 randomized trials evaluating the effects of antithrombotic therapy on clinical outcomes, including strokes, in patients with heart failure and reduced LV EF in sinus rhythm.[524–528] The WARCEF trial (Warfarin vs. Aspirin in Reduced Cardiac Ejection Fraction) documented no benefit of warfarin therapy compared with acetylsalicylic acid at a mean follow-up of 3.5 years for the primary outcome (death, ischemic stroke, or intracranial hemorrhage),[526] although patients on warfarin had reduced incidence of stroke, particularly patients with an EF ≥15%,[550] The more recent COMMANDER HF trial (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) randomized a total of 5022 patients with chronic heart failure, an EF of ≤40%, coronary artery disease, and elevated plasma natriuretic peptides to rivaroxaban 2.5 mg twice daily or placebo.[528] After a median follow-up of 21.1 months, the primary end point (death, MI, or stroke) occurred in 25.0% of patients assigned to rivaroxaban versus 26.2% of those receiving placebo. Patients with history of ischemic stroke and TIA were underrepresented in these trials, and the main end point always included death, which dwarfs

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the ischemic stroke outcomes. Therefore, the effectiveness of anticoagulation versus antiplatelet therapy is uncertain, and the choice should be individualized by taking into account bleeding risk and estimated risk of recurrent thromboembolism.

5. The only randomized trial evaluating the benefit of DOACs (dabigatran) in stable patients after LVAD implantation was stopped prematurely because of an excess of thromboembolic events.[529] At the time of writing, there is no randomized study evaluating the safety and efficacy of other DOACs in the LVAD population, and warfarin remains the only recommended oral anticoagulant in these patients.

Knowledge Gaps and Future Research

- RCTs of stroke prevention in patients with nonvalvular AF have demonstrated that DOACs are noninferior to warfarin in preventing ischemic stroke with a lower risk of bleeding. Advantages of DOAC therapy compared with warfarin include a more predictable pharmacokinetic profile requiring no monitoring, fewer interactions with other drugs, and a rapid onset/offset of action. The extent to which data from randomized trials in nonvalvular AF can be generalized to other clinical scenarios such as prevention of thromboembolism from intracardiac thrombus in patients with congestive heart failure or prevention of recurrent stroke/TIA in patients with specific types of cardiomyopathy (eg, LV noncompaction) requires further investigation.
- Data from isolated case reports and small case series suggest that DOACs or low-molecular-weight heparin may be beneficial in these clinical scenarios, but larger-scale multicenter observational data will be necessary to clarify whether DOACs or low-molecular-weight heparin can be used safely and effectively in these patients.[551]
- The role of empirical oral anticoagulation in patients with cardiomyopathy, reduced EF, and a history of stroke/TIA should also be investigated further in future studies because these patients were largely underrepresented in RCTs of prophylactic oral anticoagulation in patients with cardiomyopathies and reduced EF.

5.4.5. Patent Foramen Ovale

Recommendations for PFO
Referenced studies that support recommendations are summarized in online Data Supplements 38 and 39.

COR	LOE	Recommendations
1	C-EO	1. In patients with a nonlacunar ischemic stroke of undetermined cause and a PFO, recommendations for PFO closure versus medical management should be made jointly by the patient, a cardiologist, and a neurologist, taking into account the probability of a causal role for the PFO.

Recommendations for PFO (Continued)

COR	LOE	Recommendations
2a	B-R	2. In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO with high-risk anatomic features,* it is reasonable to choose closure with a transcatheter device and long-term antiplatelet therapy over antiplatelet therapy alone for preventing recurrent stroke.[552–557]
2b	C-LD	3. In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO without high-risk anatomic features,* the benefit of closure with a transcatheter device and long-term antiplatelet therapy over antiplatelet therapy alone for preventing recurrent stroke is not well established.[552–557]
2b	C-LD	4. In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO, the comparative benefit of closure with a transcatheter device versus warfarin is unknown.[554]

*In the evidence, each study defines high-risk anatomic features in a different way.

Synopsis

Substantial epidemiological evidence suggesting a causal role of PFO for stroke led to randomized trials of PFO device closure in patients <60 years of age with stroke of undetermined origin. The first 3 trials[558–560] compared device closure with either antiplatelet or anticoagulant treatment, and 2 of these[558,560] showed a nonsignificant trend toward benefit of device closure. Two subsequent trials[554,556] compared device closure with antiplatelet treatment alone, and each trial showed a significant benefit of PFO closure. An additional positive trial[553] did not restrict medical treatment to antiplatelets but did limit eligibility to patients with high-risk anatomic PFO features, including larger shunt size and atrial septal aneurysm. A meta-analysis of all trials[561] found that the number needed to treat with device closure to prevent 1 recurrent stroke was 131 during 1 person-year of follow-up or 13 during 10 person-years of follow-up, which may be clinically important in this generally young population. Analysis of administrative claims data showed a 4.9% rate of serious periprocedural complication, including AF, in patients ≤60 years of age.[562] RCT data of PFO closure in patients >60 years of age are extremely limited,[553] and the rate of serious periprocedural complications in this older age group is significantly higher (10.9%).[562]

Recommendation-Specific Supportive Text

1. Recommendations for secondary stroke prevention in a patient with a PFO should be based on joint input from a neurologist with expertise in vascular neurology and a cardiologist with expertise in PFO closure (Figure 5).[563,564] Although 1 small trial with 120 patients did include some patients

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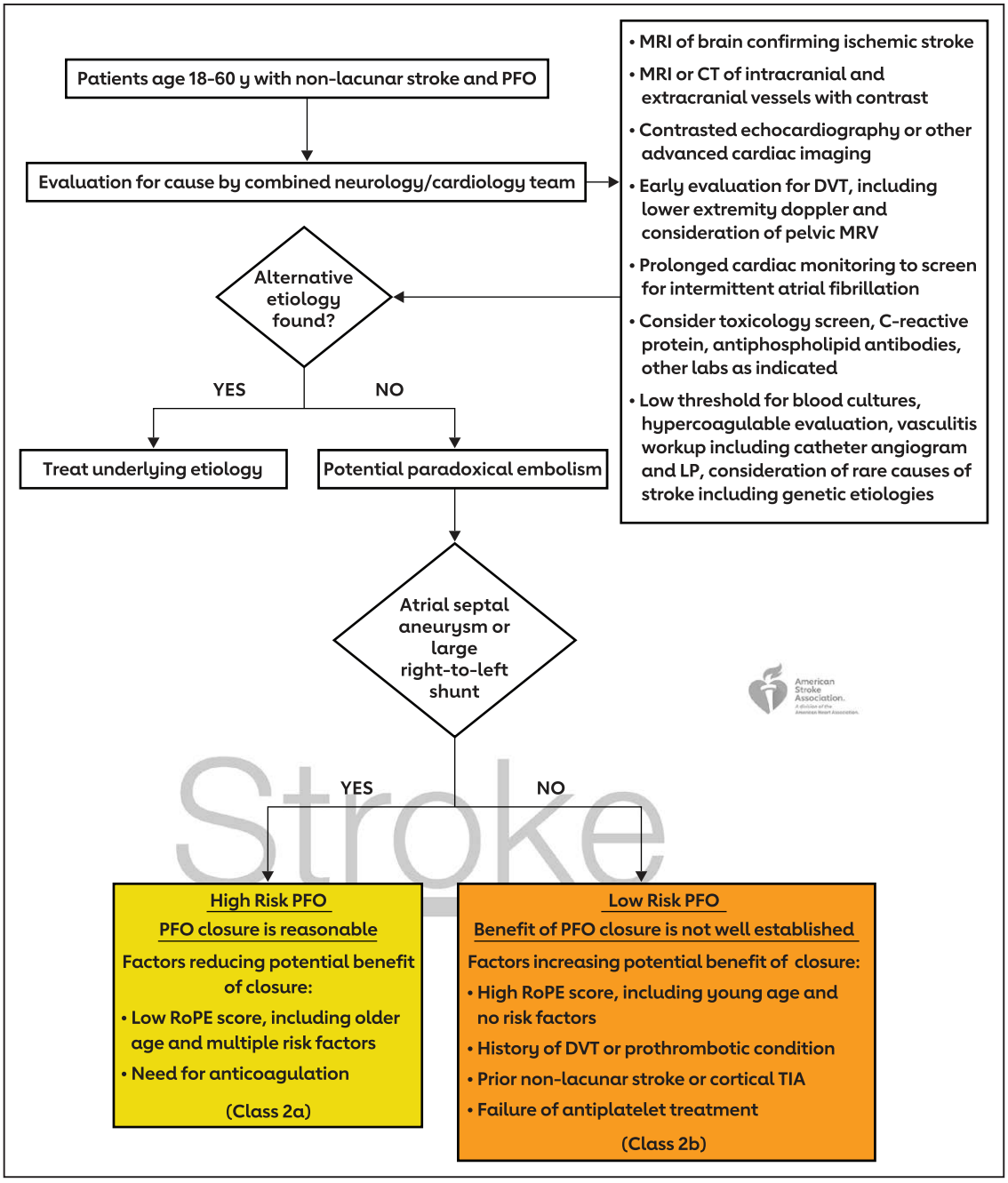

Figure 5. Patent foramen ovale (PFO) and ischemic stroke management guide.
Colors correspond to Class of Recommendation in Table 3. CT indicates computed tomography; DVT, deep vein thrombosis; LP, lumbar puncture; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; RoPE, Risk of Paradoxical Embolism; and TIA, transient ischemic attack.

>60 years of age, this should not be construed as randomized clinical trial evidence of benefit in this age group; therefore, this procedure should rarely be performed in older patients and only in very unusual clinical circumstances. It is essential that a thorough evaluation has been completed and that there is no alternative cause of the stroke. All studies[553–556] that showed benefit from PFO closure excluded lacunar strokes. Thus, the requirement that the stroke be cryptogenic is equivalent to nonlacunar stroke of undetermined source, or ESUS. Furthermore, clinical judgement is required because many strokes in the ESUS category may not have a definite cause but other lower-competing-risk conditions such as a proximal large artery disease with 40% stenosis.[565] Analysis of observational data[566] indicates that younger patients without other vascular risk factors are more likely to have PFOs that are related to their stroke. Similarly, the anatomic characteristics of the PFO need to

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be considered in decision-making (see text under Recommendations 2 and 3).

2. Two recent trials[553,554] in which the comparator was antiplatelet therapy and long-term follow-up from an earlier trial[555] in which the comparator was antiplatelet or anticoagulation therapy found a benefit of device closure. There is evidence that patients with high-risk anatomic features, including larger shunt size (defined variably), particularly an atrial septal aneurysm, are more likely to benefit from device closure.[563] The individual patient–level meta-analysis of the first 3 trials[552] found slightly greater benefit among patients with these characteristics, but the differences did not approach statistical significance. In contrast, the RESPECT trial[555] showed significant interactions between treatment and both larger shunt size (>20 microbubbles) and atrial septal aneurysm, with benefit shown only when either was present. A pooled individual patient data analysis from medically treated patients from 2 observational studies and 2 clinical trials found that atrial septal aneurysm, but not shunt size, was independently associated with recurrent stroke.[557] A meta-analysis of PFO closure trials found benefit for closure only for patients with high-risk anatomic features.[561] However, this finding may have resulted from confounding because trials that showed benefit had a higher proportion of high-risk features and limited the alternative therapy to antiplatelet therapy only, not antiplatelets or anticoagulants.[567]
3. If the PFO is considered low risk on the basis of anatomic features, it is particularly important to consider the other clinical features in deciding whether PFO is likely related to the stroke or is incidental. The Risk of Paradoxical Embolism score,[566] an index to stratify patients with cryptogenic stroke with PFO by their likelihood that the PFO is stroke related, may be helpful for patient selection. Factors in the score indicative of a higher likelihood of a PFO-dependent stroke mechanism are absence of hypertension, diabetes, prior stroke, or TIA; cortical infarct on imaging; and younger age group. Scores range from 0 to 10, with the estimated attributable fraction or probability that the PFO is stroke related ranging from 0% (95% CI, 0–4) for a Risk of Paradoxical Embolism score of 0 to 3 to 88% (95% CI 83–91) for a score of 9 to 10. The Risk of Paradoxical Embolism score attributable fraction is highly correlated with the RR reduction of device closure compared with medical therapy in randomized trials.[568]
4. The evidence suggests that PFO closure in appropriately selected patients is superior to aspirin, but it is not known whether closure is superior to warfarin. A comparison of device closure and anticoagulation was not a prespecified analysis in the CLOSE trial (Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence),[563] but a post hoc underpowered analysis of recurrent stroke found no events in the device closure group and 3 events in the warfarin group, which was not a statistically significant difference.[561] Similarly, if long-term warfarin treatment is planned, the additional benefit of closure with a transcatheter device for preventing recurrent stroke is unknown. An important consideration is that short-term trials in younger adults do not capture the long-term risk of warfarin or the long-term safety of indwelling PFO closure devices.

Knowledge Gaps and Future Research

Future research is needed within this area:

- Trials of closure versus medical management in patients ≥60 years of age with ESUS.[569]
- Further trials and individual-level meta-analysis of all randomized trial data in patients with ESUS <60 years of age addressing the benefit of PFO closure compared with aspirin in patients with a PFO without high-risk anatomic features.
- Further trials and individual-level meta-analysis of all randomized trial data addressing the benefit of PFO closure compared with long-term anticoagulation.
- Individual-level meta-analysis of all randomized trials to determine whether PFO size is independently associated with response to treatment.
- Given the evidence that residual shunts after PFO device closure are associated with increased risk of stroke recurrence,[570] studies to determine the optimal prevention strategy in this setting, including consideration of a second device closure or lifelong anticoagulant therapy.
- Large long-term prospective registries of patients with PFO closure to assess the risk of device-associated AF and the risks associated with device complications such as device erosion, fracture, and endocarditis.[571]

5.5. Congenital Heart Disease

Recommendations for Congenital Heart Disease
Referenced studies that support recommendations are summarized in online Data Supplements 40 and 41.

COR	LOE	Recommendations
1	C-LD	1. In patients with ischemic stroke or TIA and Fontan palliation, anticoagulation with warfarin is recommended to reduce the risk of recurrent stroke or TIA.[572,573]
2a	C-EO	2. In patients with cyanotic congenital heart disease and other complex lesions, ischemic stroke or TIA of presumed cardioembolic origin, therapy with warfarin is reasonable to reduce the risk of recurrent stroke or TIA.

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Synopsis

Patients with congenital heart disease represent a group at higher risk of ischemic stroke and systemic thromboembolism,[574–576] particularly in the presence of cyanotic or other complex anatomic lesions.[574–577] In these patients, it is reasonable to start oral anticoagulant therapy with a VKA (warfarin) for the secondary prevention of stroke or TIA of presumed cardioembolic origin after careful individual assessment of the competing bleeding risks associated with oral anticoagulation. Fontan repair is associated with high risk of atrial arrhythmias, intracardiac thrombosis related to atrial scarring, and right-to-left shunting from Fontan fenestration.[578–580] Patients with Fontan palliation and known or suspected thrombus, ischemic stroke or TIA, or prior atrial arrhythmia should be treated with warfarin in the absence of contraindications.[30]

Recommendation-Specific Supportive Text

1. The Fontan circulation is a palliative approach to complex single-ventricle physiology and is associated with complex hemodynamics related to an obligatory chronic elevation in central venous pressure and reduced cardiac output.[30] Consideration for antithrombotic therapy in Fontan patients should take into account the high prevalence of thrombus formation and potentially catastrophic impact of pulmonary or systemic thromboembolism. The physiology associated with the Fontan circulation may lead to stroke/TIA via different mechanisms. The associated ventricular dysfunction and abnormal ventricular morphology, the progressive atrial scarring from the Fontan surgery, and the elevated intra-atrial pressures may trigger atrial arrhythmias, increasing the risk of thromboembolic events.[581] The role of DOACs in patients with Fontan is less defined, and thus far, the published evidence is limited to small observational series.[582,583] Given the lack of conclusive evidence on the safety of DOACs in the presence of the hepatic dysfunction and altered coagulation in patients who underwent Fontan palliation, warfarin should be considered the preferred oral anticoagulant regimen.
2. Complex congenital heart disease is associated with an increased risk of stroke in adults.[574–576] Mandalenakis et al[575] conducted a large prospective registry in Sweden and documented an almost 11-fold increase in the risk of ischemic stroke in patients with congenital heart disease compared with control subjects matched by age, with the highest risk among patients with complex lesions. In a retrospective large database including >29 000 adult (age >18 years) patients with congenital heart disease, Lanz et al[574] reported an overall risk of ischemic stroke of 6.1% in women and 7.7% in men. In addition, in this study, patients with complex congenital heart disease had the highest risk (8.9% [95% CI, 6.0–11.5]). The mechanisms underlying such an increased risk of stroke are different and multifactorial and are related to the high prevalence of atrial arrhythmias, risk for paradoxical embolization (eg, cyanotic congenital heart disease), atrial mechanical dysfunction resulting from the presence of scar, and associated hyperviscosity/hypercoagulability caused by chronic hypoxemia. In patients with cyanotic and other complex congenital heart disease and ischemic stroke or TIA of presumed cardioembolic origin, treatment with warfarin is reasonable in the absence of contraindications to oral anticoagulation (eg, increased risk of bleeding).

Knowledge Gaps and Future Research

- A subset of patients with Fontan palliative surgery have a fenestration between the Fontan pathway and the pulmonary venous atrium to provide a controlled right-to-left shunt to augment ventricular preload and to partially offload systemic venous (Fontan) hypertension. Right-to-left shunt from a fenestration can be a potential source of thromboembolism and stroke.[584] Catheter closure of Fontan fenestration along with anticoagulation has been performed in some patients with a patent fenestration presenting with stroke,[585] although more data are needed to determine whether this approach is of real incremental benefit to prevent ischemic stroke or TIA compared with oral anticoagulation therapy alone.
- DOACs have been demonstrated to be noninferior or superior to dose-adjusted warfarin therapy to prevent thromboembolism and bleeding in patients with nonvalvular AF, and they have rapidly become the standard of care for these patients. Important advantages of DOAC therapy compared with warfarin include a more predictable pharmacokinetic profile requiring no monitoring, fewer interactions with other drugs, and a rapid onset/offset of action. Thus far, data on the efficacy and safety of DOACs to prevent recurrent thromboembolism in patients with congenital heart disease and history of ischemic stroke or TIA are limited to small observational series. Larger-scale multicenter observational data will be necessary to achieve adequate statistical power and to clarify whether DOACs can be used safely in patients with congenital heart disease. Multicenter registries such as that for non-VKA anticoagulants for thromboembolic prevention[585a] are currently ongoing and will provide important and needed data on the safety and efficacy of DOACs for thromboembolic prevention in patients with congenital heart disease.

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5.6. Cardiac Tumors

Recommendation for Cardiac Tumors Referenced studies that support the recommendation are summarized in online Data Supplement 42.		
COR	**LOE**	**Recommendation**
2a	C-LD	1. In patients with stroke or TIA found to have a left-sided cardiac tumor, resection of the tumor can be beneficial to reduce the risk of recurrent stroke.[586–588]

Synopsis

Primary cardiac tumors are uncommon, occurring in 0.02% of people according to a large autopsy series, and the most common primary cardiac tumors are myxoma and fibroelastoma.[589] Patients with cardiac tumors are at increased risk for stroke with an overall rate of embolism of 25% in the largest single-center study.[590] The mechanism of stroke in patients with left-sided cardiac tumors is embolic and can be either embolization of thrombus that has formed on the tumor or embolization of the tumor or piece of the tumor.[591] This finding is the basis for recommending antiplatelet or anticoagulation to conservatively managed patients. There are no prospective randomized trials of management of patients diagnosed with cardiac tumors after stroke or TIA; however, surgical excision of papillary fibroelastoma has been associated with decreased risk of stroke compared with control subjects in 1 single-center study.[592] For patients with metastatic disease to the heart or with right-sided tumors, paradoxical embolism of tumor or venous thrombus through a PFO could occur.

Recommendation-Specific Supportive Text

1. Retrospective studies have shown increased risk of stroke with left-sided cardiac myxoma and papillary fibroelastoma.[586] Atrial myxomas can occur in any cardiac chamber but are noted most frequently in the left atrium adherent to the interatrial septum. Broad morphological variation of atrial myxomas has been described, and more villous tumors are felt to have greater embolic and thromboembolic potential. Papillary fibroelastomas are fibrinous mobile tumors occurring most frequently adherent to a cardiac valve with nearly equal distribution across the cardiac valves.[587] In a single-center study of 323 patients after excision of a cardiac tumor, the OR of embolism associated with left atrial tumors was 1.95 and higher (4.17) with aortic valve tumors.[586] In another series of 725 patients with papillary fibroelastoma, tumor mobility and aortic valve location were independent predictors of embolism.[588] Less common tumors and metastatic lesions in the heart have been anecdotally associated with stroke; however, there is not enough evidence to make a consistent recommendation for those circumstances. For patients with stroke or TIA whose evaluation reveals a left-sided cardiac tumor, consideration should be given to tumor excision to reduce the risk of recurrent stroke.

Knowledge Gaps and Future Research

Cardiac tumors are rare, and systematic research has been limited to case series, leaving gaps in our understanding and opportunities for future research.

- Most cardiac tumors are found incidentally, carrying the threat of stroke or recurrent stroke, and open heart surgery is the only established treatment option. Better understanding of the risk modification from antiplatelet or anticoagulation in particular tumor subtypes or morphologies may provide alternative therapeutic options for patients. Specifically, pooled experiences including national and multi-institutional data sets may allow a better understanding of tumor subtypes, fractionation by morphology, and natural history.
- As technology advances, minimally invasive and percutaneous treatment strategies should be investigated. Similarly, advances in imaging technology will allow greater delineation of tumor subtypes and morphologies. The prognostic implications of these findings should be investigated.

5.7. Dissection

Recommendations for Dissection Referenced studies that support recommendations are summarized in online Data Supplements 43 and 44.		
COR	**LOE**	**Recommendations**
1	C-EO	1. In patients with ischemic stroke or TIA after an extracranial carotid or vertebral arterial dissection, treatment with antithrombotic therapy for at least 3 months is indicated to prevent recurrent stroke or TIA.
2a	B-R	2. In patients with ischemic stroke or TIA who are <3 months after an extracranial carotid or vertebral arterial dissection, it is reasonable to use either aspirin or warfarin to prevent recurrent stroke or TIA.[593,594]
2b	C-LD	3. In patients with stroke or TIA and extracranial carotid or vertebral artery dissection who have recurrent events despite antithrombotic therapy, endovascular therapy may be considered to prevent recurrent stroke or TIA.[595,596]

Synopsis

Extracranial carotid or vertebral dissections can be the result of trauma or spontaneous. It is a relatively uncommon mechanism of ischemic stroke that is relevant mostly to younger individuals.[597] The most common mechanism of stroke with extracranial dissection is artery-to-artery embolism[598] from an intraluminal thrombus, which is the rationale for using antithrombotic agents to decrease the rate of ischemic stroke.[599] Although most dissections heal spontaneously, a subset of patients will undergo disease progression and arterial complications such as pseudoaneurysm formation.[597]

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Recommendation-Specific Supportive Text

1. The recommendation of using antithrombotic agents is based on expert opinion. Although arterial dissection is a hemorrhagic process within the arterial wall, the most common mechanism for stroke is artery-to-artery embolism[598] from an intraluminal thrombus. This is the rationale for using antithrombotic agents to decrease the rate of ischemic stroke.[599]
2. CADISS (Cervical Artery Dissection in Stroke Study) was an open-label trial that randomized 250 patients with extracranial dissection within 7 days from symptom onset to receive either antiplatelets or anticoagulants in the following 3 months.[593] The specific agents and treatment regimens were left to the treating physician. Stroke or death occurred in 3 patients (2%) assigned to antiplatelets versus 1 patient (1%) in the anticoagulation group (OR, 0.335 [95% CI, 0.006–4.233]; P=0.63).[593] At the 1-year follow-up, there was no difference in the primary end point of stroke or death between the 2 groups: 3.2% in the antiplatelet group versus 1.6% in the anticoagulant group (OR, 0.56 [95% CI, 0.10–3.21]; P=0.51).[594] This trial supports that there is equipoise between antiplatelets and anticoagulants in the first 3 months after a cervical artery dissection.
3. Endovascular procedures are used to reconstruct cervical arterial dissections refractory to medical treatment and to treat complications such as pseudoaneurysms.[595,596] There is a lack of randomized studies to support benefit of endovascular interventions in dissections, and most of the data stem from small series. Still, reviews of the literature suggest a reasonably low rate of complications from these procedures.[595,596]

Knowledge Gaps and Future Research

Gaps in the management of cervical arterial dissection still exist and would benefit from future research:

- Early identification of patients at risk for early deterioration or complications who might benefit from endovascular therapy.
- Whether some antithrombotic agents are more efficacious if administered early in the course (eg, is anticoagulation more efficacious than antiplatelets in the acute phase?).
- The benefit of long-term antithrombotic agents.
- Management of dissections complicated with intraluminal thrombus.
- Management of intracranial dissections and risks/benefits of anticoagulation.
- The determination of what physical activities are safe and which ones need to be restricted.
- Optimal monitoring/management of pseudoaneurysms associated with dissection needs further study.

5.8. Hypercoagulable States

5.8.1. Hematologic Traits

Recommendation for Hematologic Traits
Referenced studies that support the recommendation are summarized in online Data Supplement 45.

COR	LOE	Recommendation
2a	C-LD	1. In patients with ischemic stroke or TIA of unknown source despite thorough diagnostic evaluation and no other thrombotic history who are found to have prothrombin 20210A mutation, activated protein C resistance, elevated factor VIII levels, or deficiencies of protein C, protein S, or antithrombin III, antiplatelet therapy is reasonable to reduce the risk of recurrent stroke or TIA.[600–606]

Synopsis

Hypercoagulable states refer to heterogeneous hematologic traits that predispose to venous or arterial thrombosis, which then may increase the risk of stroke, particularly in younger populations. Hypercoagulable states may increase the risk of stroke via various mechanisms. Hypercoagulable disorders may predispose to arterial or venous thrombosis. Among people with venous thrombosis, stroke may be caused by paradoxical emboli via right-to-left arterial shunt, either pulmonary or cardiac (often via a PFO). Hypercoagulable states that cause arterial thrombosis may cause stroke via distant thrombosis (eg, intracardiac) with embolization or via in situ thrombosis of the brain or cervical arteries. Suspicion for hypercoagulable states as the cause of stroke varies by clinical scenario, but they may be considered in younger populations with no identifiable cause for stroke, self- or family history of unprovoked thrombosis, prior spontaneous abortion, or coexistence of systemic signs and symptoms suggestive of hypercoagulability.

Recommendation-Specific Supportive Text

1. Thrombophilic states such as prothrombin 20210A mutation; activated protein C resistance (often caused by factor V Leiden); deficiencies of protein C, protein S, or antithrombin; and elevated factor VIII levels have been associated with higher stroke risk in selected populations without stroke,[600–602,607,608] especially among people with a PFO.[603] The risk of stroke recurrence among stroke survivors with thrombophilic traits is less well established.[604,605,608] Furthermore, although individuals who carry 1 of these disease traits may be considered hypercoagulable, the ideal treatment (antiplatelet versus anticoagulation) remains unknown. Among patients with stroke and unprovoked deep vein thrombosis with or without a positive blood test for thrombophilic states, adhering to deep vein thrombosis treatment recommendations seems reasonable if they otherwise meet eligibility criteria.[606] Therefore, in

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the absence of a diagnosis that would change the default treatment for ischemic stroke, it is uncertain whether testing for these hematologic traits is of benefit in the context of secondary stroke prevention. If in certain clinical scenarios (eg, paradoxical emboli caused by venous thrombosis or recurrent venous thrombosis) testing for thrombophilic states is considered, testing for protein C, protein S, or antithrombin levels should be deferred or repeated at least 4 to 6 weeks (or up to 6 months for factor VIII[609]) after the acute stroke given that these protein levels may be altered during the acute stroke phase.[607,608,610,611]

5.8.2. Antiphospholipid Syndrome

Recommendations for Antiphospholipid Syndrome
Referenced studies that support recommendations are summarized in online Data Supplement 46.

COR	LOE	Recommendations
1	B-NR	1. In patients with ischemic stroke or TIA who have an isolated antiphospholipid antibody but do not fulfill the criteria for antiphospholipid syndrome, antiplatelet therapy alone is recommended to reduce the risk of recurrent stroke.[612]
2a	B-R	2. In patients with ischemic stroke or TIA with confirmed antiphospholipid syndrome treated with warfarin, it is reasonable to choose a target INR between 2 and 3 over a target INR >3 to effectively balance the risk of excessive bleeding against the risk of thrombosis.[613–615]
2a	C-LD	3. In patients with ischemic stroke or TIA who meet the criteria for the antiphospholipid syndrome, it is reasonable to anticoagulate with warfarin to reduce the risk of recurrent stroke or TIA.[615]
3: Harm	B-R	4. In patients with ischemic stroke or TIA, antiphospholipid syndrome with history of thrombosis and triple-positive antiphospholipid antibodies (ie, lupus anticoagulant, anticardiolipin, and anti– β2 glycoprotein-I), rivaroxaban is not recommended because it is associated with excess thrombotic events compared with warfarin.[616–618]

Synopsis

Antiphospholipid syndrome is characterized by persistent (repeat testing 12 weeks apart) presence of lupus anticoagulant, anti-cardiolipin or anti–β2 glycoprotein-I high-titer antibodies, plus evidence of clinical criteria such as vascular thrombosis or pregnancy morbidity.[619] Serum testing for acquired antiphospholipid syndrome may be considered in the presence of a history of prior venous thromboembolism, second trimester abortion, or rheumatologic disorder. Patients with stroke and persistent seropositivity for any of the antiphospholipid antibodies may be classified as having antiphospholipid syndrome.

Recommendation-Specific Supportive Text

1. A large subgroup of WARSS (Warfarin-Aspirin Recurrent Stroke Study) was studied to evaluate whether the presence of a positive antiphospholipid antibody indicated a treatment interaction with warfarin or aspirin for secondary stroke prevention. Participants had to be 30 to 85 years of age, to be deemed safe for warfarin therapy, to have experienced an ischemic stroke within 30 days, and to have had a modified Rankin Scale score of ≤3. Investigators found no differential stroke risk reduction in people with a 1-time positive antiphospholipid antibody with warfarin (RR, 0.99 [95% CI, 0.75–1.13]) or aspirin (RR, 0.94 [95% CI, 0.70–1.28]; treatment-by-antiphospholipid interaction, P=0.91) compared with those without a positive antibody.[612] Therefore, aspirin is more preferable than warfarin because of the lower risk of bleeding with aspirin. The prevalence of antiphospholipid syndrome in the stroke population varies, but younger populations are most commonly affected.[620] Approximately 13% of patients with antiphospholipid syndrome have stroke as the initial clinical manifestation of the disease.[621] In patients with cryptogenic stroke and a history of thrombosis or rheumatological disease, it would seem reasonable to consider testing for antiphospholipid antibodies.[622,623] In older populations with increasing frequency of vascular risk factors, there is no evidence supporting the systematic testing for antiphospholipid antibodies.
2. Although no trials of antithrombotic intervention have been performed exclusively in stroke patients, the available evidence favors anticoagulation with VKA compared with aspirin to reduce recurrent arterial thromboses. An INR with a target range of 2 to 3 is preferable over an INR with a range >3 because higher-intensity anticoagulation is not superior in preventing thrombotic events and is associated with a higher risk of hemorrhagic complications.[613,614] When anticoagulation has been tested against aspirin, an INR of 2 to 3 is a typical range to be used as a comparison arm, further supporting the use of this therapeutic range as preferred.[615]
3. Limited evidence favors anticoagulation with VKA compared with aspirin to reduce recurrent arterial thromboses. In a small (N=20) RCT, patients with antiphospholipid syndrome were assigned to a single-antiplatelet arm versus triple-therapy arm (dual antiplatelets plus anticoagulation). Participants with single antiplatelets had a higher risk of recurrent stroke (log-rank test, P=0.026) with similar rates of hemorrhage during a mean follow-up of 3.9 years.[615] There are limited data to establish whether the addition of antiplatelets to anticoagulation is effective in reducing the risk of recurrent stroke in this population. The clinical consensus favors using only anticoagulation, however.[623]

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4. The role of DOACs in antiphospholipid syndrome treatment is the focus of multiple ongoing and recently completed studies. In an open-label, noninferiority RCT of patient with established antiphospholipid syndrome and triple-positive antiphospholipid antibodies, rivaroxaban was associated with higher risk of thrombotic events.[616] A similar result in favor of VKA over rivaroxaban was reported in an open-label RCT of patients with antiphospholipid syndrome. In this study, ≈60% had triple-positive antiphospholipid antibodies, but there was no statistical interaction suggestive of a differential effect among those with antiphospholipid syndrome and 1 or 2 antiphospholipid antibodies.[617] Observational data also suggest a high risk of recurrent thrombosis among patients with antiphospholipid syndrome who receive DOACs.[618] Until other ongoing trials such as ASTRO-APS (Apixaban for the Secondary Prevention of Thrombosis Among Patients With Antiphospholipid Syndrome)[624] clarify whether the increased risk of thrombosis with DOACs is a class effect versus an individual drug effect, we do not recommend the use of DOACs in general and, specifically, rivaroxaban for antiphospholipid syndrome.

Knowledge Gaps and Future Research

Although thrombophilic states have been associated with a higher risk of stroke in epidemiological studies, it is uncertain whether specific treatment should be offered to people with stroke and some of these traits. Future research on treatment for hypercoagulable states and stroke should address the following:

- It is uncertain whether, in the absence of venous thrombosis, there is an indication for anticoagulation for secondary stroke prevention in people with thrombophilic states.
- It is uncertain whether, in the absence of venous thrombosis, the presence of a PFO may modify the risk of stroke recurrence and possible preventive strategies in people with thrombophilic states suspected to have paradoxical emboli.
- Given the relatively low prevalence of thrombophilic traits in populations with stroke, larger, adequately powered multicenter studies are needed to study each trait individually.
- If a heightened risk of stroke is confirmed, clinical trials may be needed to evaluate whether anticoagulation may be useful to reduce the risk of stroke recurrence.

There is less clarity on secondary stroke preventive measures in people with antiphospholipid syndrome; consequently, the following knowledge gaps remain:

- There is an urgent need to clarify whether DOACs may be used instead of warfarin to reduce the risk of stroke in this population.
- There is a knowledge gap with respect to the role of dual antiplatelets in antiphospholipid syndrome, with reports suggesting a possible role to reduce the risk of stroke alone or in addition to anticoagulation. The absence of definitive data prevents us from providing a stronger recommendation at this point.

5.9. Hyperhomocysteinemia

Recommendation for Hyperhomocysteinemia Referenced studies that support the recommendation are summarized in online Data Supplements 46 and 47.		
COR	**LOE**	**Recommendation**
3: No Benefit	**B-R**	1. In patients with ischemic stroke or TIA with hyperhomocysteinemia, supplementation with folate, vitamin B_6, and vitamin B_{12} is not effective for preventing subsequent stroke.[625,626]

Synopsis

Although elevated serum homocysteine has consistently been associated with elevated risk of stroke and other vascular events, randomized trials of folate and B vitamin supplementation have not shown benefit in secondary prevention of stroke. Challenges in understanding the relationship between vitamin supplementation and secondary stroke prevention stem from limitations in trial design, for example, including patients with both cardiovascular and cerebrovascular events,[627,628] and enrollment from countries with varying levels of folate supplementation of foods. Although meta-analyses of patients with vascular disease, including some with cerebrovascular disease, suggest a small but significant reduction in subsequent stroke risk among those receiving supplementation, assessment of factors that may modify this relationship (including genetic variants in folate metabolism, preexisting homocysteine level, use of antiplatelet medications, renal function, and dose of B vitamin supplementation) is inconsistent among studies.[609,629–637] Although 1 primary prevention study among hypertensive patients with high homocysteine found that the addition of folic acid to enalapril was more effective in reducing first stroke among those with the methylenetetrahydrofolate reductase C677T CC/CT polymorphism,[637] it remains unknown whether folic acid or vitamin B supplementation in a specific subgroup of patients with recent stroke or TIA may be beneficial in reducing the risk of secondary stroke.

Recommendation-Specific Supportive Text

1. Results from VITATOPS (Vitamins to Prevent Stroke)[625] and VISP (Vitamin Intervention for Stroke Prevention)[626] did not show a significant reduction in risk of secondary stroke among patients with recent stroke who were randomized

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Stroke

to receive various doses of folic acid and vitamin B supplementation.

Knowledge Gaps and Future Research

Questions remain to be addressed about whether there are specific subgroups of stroke patients in whom B vitamin supplementation reduces secondary stroke risk. Randomized trials of B vitamins for secondary stroke prevention are needed in patients with stroke or TIA who do not consume folate-fortified foods. These trials may also need to consider the formulation and dose of B vitamins, the level of hyperhomocysteinemia, specific methylenetetrahydrofolate genetic polymorphisms, and the patient's renal function as possible modifiers of the relationship between B vitamins and secondary stroke reduction.[633]

5.10. Migraine

Migraine has been associated with ischemic stroke and white matter hyperintensities in numerous studies.[638,639] In patients with migraine who have had an ischemic stroke, data on the risk of recurrent stroke are limited and conflicting.[640–642] Neuroimaging studies suggest that there is brain hypoperfusion during migraine attacks, at least in severe migraine attacks with aura.[643] On the basis of these limited data, practitioners may consider implementing preventive treatments to reduce migraine frequency in patients with migraine and prior ischemic stroke. The use of oral contraceptive agents with exogenous estrogen among women with migraine, especially when combined with active smoking, has been associated with an increased risk of stroke in numerous studies, although the quality of such studies is low.[644] On the basis of these data, avoiding oral contraceptive agents with exogenous estrogen in women with migraine with aura and prior ischemic stroke may perhaps be appropriate.

Knowledge Gaps and Future Research

Observational studies provide conflicting evidence about the association between triptan therapy and stroke risk, and these studies excluded patients with prior ischemic stroke.[645] There are theoretical risks of cerebral vasoconstriction and ischemia with the use of calcitonin gene–related peptide receptor antagonists,[646] but clinical evidence to quantify such risks is lacking. Therefore, no recommendations can be made for the use of triptans and calcitonin gene–related peptide receptors in patients with migraine and prior ischemic stroke. Future studies will be required to better understand the safety of triptans and calcitonin gene–related peptide receptor antagonists in this population.

5.11. Malignancy

Recommendation for Malignancy Referenced studies that support the recommendation are summarized in online Data Supplement 48.		
COR	**LOE**	**Recommendation**
2a	B-NR	1. In patients with ischemic stroke or TIA in the setting of AF and cancer, it is reasonable to consider anticoagulation with DOACs in preference to warfarin for stroke prevention.[647–650]

Synopsis

Patients with cancer are a population at high risk for stroke.[651] The association between cancer and stroke is not surprising given the prevalence of these conditions and the commonly shared risk factors.[652] Unfortunately, secondary stroke prevention in the setting of cancer is complicated by the paucity of data in the context of multiple pathogenic mechanisms.[652] Potential mechanisms include procoagulant conditions, direct invasion or compression of blood vessels, radiation arteriopathies, infections (eg, aspergillosis), and secondary effects of chemotherapy (eg, thrombotic microangiopathy or cardiac toxicity).[652] The procoagulant mechanisms have been a main focus of the stroke prevention efforts in these patients, and antiplatelets or anticoagulants are often prescribed. However, there is uncertainty about how to best treat a potential acquired hypercoagulable state,[653] including the best choice for antithrombotic agent. Low-molecular-weight heparin agents are commonly used empirically when a hypercoagulable state is suspected, but the benefit is unclear,[654] particularly in this patient population with a high tendency for hemorrhage.[651] A specific situation in these patients that has been more adequately studied is the best anticoagulation regimen for the prevention of cardioembolism from AF,[651] which is extrapolated from subgroup analysis of the large randomized clinical trials of anticoagulation. (We also refer the reader to Section 5.13.3, Neoplastic Vasculitis.)

Recommendation-Specific Supportive Text

1. A subgroup analysis in the ROCKET AF trial comparing rivaroxaban and warfarin in patients with AF and history of cancer showed similar rates of stroke and systemic embolism 0.52 (95% CI, 0.22–1.21) and nonmajor bleeding events 1.09 (95% CI, 0.82–1.44).[647] Similarly, the efficacy (1.09 [95% CI, 0.53–2.26]) and safety (0.76 [95% CI, 0.45–1.29]) of apixaban were comparable to those of warfarin in patients with AF and history of cancer in the ARISTOTLE trial.[648] This was supported by claims data analysis looking at bleeding events of rivaroxaban (1.09 [95% CI, 0.79–1.50]), dabigatran (0.96 [95% CI, 0.72–1.27]), and apixaban (0.37 [95%

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CI, 0.17–0.79]) compared with warfarin.[649] A literature search of 31 660 patients in 5 trials in patients with AF and cancer DOACs showed a trend for more efficacy and better safety compared with warfarin.[650]

Knowledge Gaps and Future Research

- Patients who had a stroke attributable to hypercoagulability from cancer may be at a particularly high risk of bleeding with anticoagulation. In these patients, the benefit of anticoagulants for secondary stroke prevention is not well established, and further research is needed.
- The particular need of anticoagulation to prevent stroke in different type of cancers is not known and should be a matter of further research.
- In patients who had a stroke attributable to hypercoagulability from cancer who are anticoagulated, there is a paucity of data on the best treatment regimen for these patients.
- Although low-molecular-weight heparin is often used in patients with cancer and stroke to prevent thromboembolic complications, the potential benefit on stroke prevention is unknown.

5.12. Sickle Cell Disease

Recommendations for Sickle Cell Disease
Referenced studies that support recommendations are summarized in online Data Supplement 49.

COR	LOE	Recommendations
1	B-NR	1. In patients with sickle cell disease (SCD) and prior ischemic stroke or TIA, chronic blood transfusion(s) to reduce hemoglobin S to <30% of total hemoglobin is recommended for the prevention of recurrent ischemic stroke.[655–658]
2a	B-R	2. In patients with SCD with prior ischemic stroke or TIA for whom transfusion therapy is not available or practical, treatment with hydroxyurea is reasonable for the prevention of recurrent ischemic stroke.[659–665]

Synopsis

SCD is an autosomal recessive inherited hemoglobinopathy that affects people predominantly of African or Mediterranean descent.[666] The normal flexible, round red blood cell is transformed into a sickle appearance. These sickled cells have abnormal interactions with the vascular wall endothelium, other blood cells, and clotting factors.[667] This can result in thrombosis or hypoperfusion and ischemia.[666] Globally, >300 000 children are born with SCD annually, most in sub-Saharan Africa.[668] The pathophysiology of ischemic stroke in patients with SCD is large artery arteriopathy,[669] believed to be caused by intimal hyperplasia related to repeated endothelial injury and inflammation.[656,670] Progressive narrowing of arteries at the base of the brain can lead to cerebral vasculopathy or moyamoya syndrome, which can predispose a patient to both ischemic stroke and intracranial hemorrhage. There are no randomized trials for antithrombotics for secondary stroke prevention in SCD. Caution is advised when considering antithrombotics for secondary stroke prevention in patients with SCD because the stroke mechanism is less certain and patients with SCD are also at higher risk for hemorrhagic stroke. If there is evidence for other stroke mechanisms in a patient with SCD (ie, atherosclerosis), then it would be reasonable to administer antithrombotics as supported elsewhere in this guideline.

Recommendation-Specific Supportive Text

1. The recommendations for treatment of patients with SCD are based on stroke primary prevention studies in a pediatric population and a secondary stroke prevention study in a population of pediatric patients with SCD with silent cerebral infarctions (SIT [Silent Cerebral Infarct Transfusion] multi-center clinical trial).[671] The STOP trial was a randomized, placebo-controlled trial that showed that a long-term prophylactic transfusion strategy was effective for the primary prevention of stroke in children with SCD and high TCD velocities.[655] Blood transfusion was used because it was demonstrated effective in reducing recurrent clinical ischemic stroke and progression of arterial stenosis in a series of children with SCD.[656] This was associated with a reduction in the rate of recurrent stroke during a mean follow-up of 3 years compared with historical control subjects.[657] Most of the patients in the series were children, and it is unclear whether adults have the same untreated risk or benefit from treatment.[658] Regular transfusions are associated with long-term complications, especially iron overload, typically requiring iron chelation therapy. The SIT trial showed reduced recurrent stroke in children with SCD and silent cerebral infarct who underwent transfusion compared with observation.[671]
2. SWiTCH (Stroke With Transfusions Changing to Hydroxyurea) was a randomized secondary stroke prevention trial in a pediatric SCD population that found no recurrent strokes with long-term transfusion but 10% with hydroxyurea.[659] In situations in which transfusion is not available, a nonrandomized study of patients with an initial stroke suggested that patients who do not receive hydroxyurea have a higher recurrent stroke risk (HR, 9.4 [95% CI,1.5–70.6]).[660] TWiTCH (TCD With Transfusions Changing to Hydroxyurea) was a primary stroke prevention randomized trial of children with SCD and abnormal TCD velocities (>200 cm/s) but no severe vasculopathy on MRA[661] who had received 1 year of transfusions. Children were subsequently randomized

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to transfusion or hydroxyurea. Noninferiority was shown: 3 TIAs in each group and no new MRI stroke in either group. Hematopoietic cell transplantation can be curative for SCD[662] but is usually undertaken in children refractory to other treatment; it results in survival without SCD in 80% to 90% of patients. Clinical and subclinical infarctions have been reported to be arrested by this procedure.[663] Surgical bypass has been reported with improved outcomes in patients with SCD with moyamoya, but no randomized data are available.[664,665] Given the lack of experience with antithrombotics, antihypertensive agents, and statins for secondary stroke prevention in SCD, specific recommendations cannot be stated outside of general treatment recommendations.

Knowledge Gaps and Future Research

Most studies for primary or secondary stroke prevention in SCD were conducted in the pediatric population. Therefore, there is a gap in understanding whether transfusion or hydroxyurea recommendations in the pediatric population hold true in the adult patient with SCD with symptomatic or asymptomatic stroke, elevated TCD velocities, or vessel imaging notable for vasculopathy.

5.13. Vasculitis

5.13.1. Autoimmune Vasculitis

Recommendations for Autoimmune Vasculitis
Referenced studies that support recommendations are summarized in online Data Supplement 50.

COR	LOE	Recommendations
1	B-NR	1. In patients with ischemic stroke or TIA and symptoms attributed to giant cell arteritis, immediate initiation of oral high-dose glucocorticoids is recommended to reduce recurrent stroke risk.[672–681]
2a	B-NR	2. In patients with ischemic stroke or TIA and diagnosis of giant cell arteritis, methotrexate or tocilizumab therapy adjunctive to steroids is reasonable to lower the risk of recurrent stroke.[682–690]
2a	B-NR	3. In patients with ischemic stroke or TIA and diagnosis of primary CNS angiitis, induction therapy with glucocorticoids and/or immunosuppressants followed by long-term maintenance therapy with steroid-sparing immunosuppressants is reasonable to lower the risk of stroke recurrence.[691–696]
3: Harm	B-R	4. In patients with ischemic stroke or TIA and confirmed diagnosis of giant cell arteritis, infliximab is associated with recurrent ocular symptoms and markers of disease activity and should not be administered.[697–704]

Synopsis

Autoimmune vasculitis is a subset of disease that may cause stroke. The overall prevalence of autoimmune vasculitis in stroke population is very low but age dependent. In cohorts of younger patients (eg, age <45 years), vasculitis may account for 0% to 20% of stroke cases, depending on the depth of workup.[705] In older population, the proportion of strokes caused by vasculitis is smaller because of the increasing burden of aging-related risk factors. Vasculitis may cause stroke by directly causing brain arterial inflammation, which subsequently results in endothelial damage and promotes thrombosis.[706] Alternatively, extracranial vasculitis may cause stroke by promoting artery-to-artery embolism, flow obstruction attributable to endothelial thickening, or aneurysmatic wall damage.[707] The overall approach to treat vasculitis causing stroke is with immunosuppressants and antiplatelets, but the choice of immunosuppressant and regimens is specific to the type of vasculitis.

Recommendation-Specific Supportive Text

1. Giant cell arteritis is a rare vasculitis (incidence rate, 9–16 per 100 000 per year in individuals ≥50 years of age) that can cause stroke in ≈7% of confirmed cases.[672–674] Patients with symptoms of giant cell arteritis should be treated urgently, and high-dose steroids should be initiated quickly within the first 24 hours after symptoms onset to reduce the risk of permanent blindness and to increase the chance of visual recovery.[675–678] Practitioners should keep a high index of clinical suspicion to consider giant cell arteritis in the differential. Laboratory testing such as elevated sedimentation rate or C-reactive protein and a compatible semiology may be the only available elements to make a decision to initiate treatment.[679] If available, ultrasound finding of a halo sign surrounding a temporal artery may be helpful in diagnosis giant cell arteries.[680,681] Biopsy confirmation should not be imperative to initiate treatment in cases in which giant cell arteritis seems to be the most likely diagnosis.
2. In addition to steroids, it is reasonable to consider adjunctive, steroid-sparing therapy in the treatment of patients with stroke thought to be caused by giant cell arteritis. In a patient-level meta-analysis of 3 randomized clinical trials, methotrexate use was associated with lower risk of diseases relapses.[682] Similarly, 1 phase I clinical trial and 1 phase II clinical trial support the use of tocilizumab to increase the rate of sustained glucocorticoid-free remission.[683,684] Takayasu arteritis is more common in Asian countries compared with Europe or the United States, and it tends to occur in younger people compared with those with giant cell arteritis.[685,708] Takayasu arteritis may cause stroke directly by causing cerebral vasculitis or extracranial stenosis, most often of the common carotid arteries.[686] Observational studies support the use

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of steroids plus adjunctive therapy that may include methotrexate,[687] azathioprine,[688] or leflunamide.[689] There are no data to support 1 agent over the other in terms of efficacy in stroke risk reduction among patients with Takayasu arteritis. In adults with ischemic stroke or TIA and diagnosis of giant cell arteritis or Takayasu arteritis, a slow taper of oral steroids to a target of ≤5 mg/d after 1 year is reasonable in light of reports of exacerbation after rapid steroid withdrawal.[690,709]

3. Primary CNS angiitis or vasculitis is a rare cause of stroke (2.4 cases per 1 million patient-years),[691] and it affects predominantly younger populations (mean age at presentation, 45 years) and is slightly more prevalent in men.[692] In cases with confirmed primary CNS angiitis, administration of high-dose steroids is supported by observational data.[693,694] In most cases, slow tapering of steroids followed by the addition of a steroid-sparing agent seems preferred over long-term monotherapy with steroids because of a higher rate of relapse and poorer outcomes with steroid monotherapy.[694,695] Some commonly used maintenance steroid-sparing agents include cyclophosphamide,[693,694,696] azathioprine,[692–694] mycofenolate mofetil,[692,693] methotrexate,[692] or rituximab.[696] There are no robust data related to efficacy between these agents. Therefore, we recommend an interdisciplinary follow-up for patient with primary CNS angiitis and that the choice of steroid-sparing agent be made considering the profile of each agent and associated comorbidities.
4. Infliximab should not be used to treat patients with stroke and giant cell arteritis. This recommendation is based on a phase II clinical trial that randomized patients with giant cell arteritis to infliximab (5 mg/kg body weight) versus placebo after steroid-induced remission. During follow-up, patients who received infliximab had a higher risk of disease activity at 12 weeks (eg, lower chances of remission) than those who received placebo.[697]

5.13.2. Infectious Vasculitis

Recommendations for Infectious Vasculitis
Referenced studies that support recommendations are summarized in online Data Supplement 51.

COR	LOE	Recommendations
1	B-NR	1. In patients with ischemic stroke or TIA and infectious vasculitis such as varicella zoster virus (VZV) cerebral vasculitis, neurosyphilis, or bacterial meningitis, treating the underlying infectious etiology is indicated to reduce the risk of stroke.[710–716]
2a	C-LD	2. In patients with ischemic stroke or TIA in the context of HIV vasculopathy, daily aspirin plus HIV viral control with combined antiretroviral therapy is reasonable to reduce the risk of recurrent stroke.[717–723]

Synopsis

Infectious diseases may cause stroke through various mechanisms. Direct infection of cerebral arteries by VZV may cause inflammation, endothelial activation, and thrombosis.[724] Infectious cardiomyopathies may cause stroke by increasing the risk of cardioembolic stroke, as in the case of Chagas disease.[725–728] Infection with HIV may cause stroke by multiple mechanisms, including increased risk of cerebral infection or opportunistic neoplasias, as well as accelerated atherosclerosis in the setting of certain antiretroviral agents.[729,730] Basilar meningitis caused by *Mycobacterium tuberculosis*, *Treponema pallidum*, or Cryptococcus may cause stroke by contiguous spreading of the inflammation in the cerebrospinal fluid to the brain arteries at the base of the skull.[731–734]

Recommendation-Specific Supportive Text

1. Stroke associated with CNS infection should be considered a life-threatening emergency and should be triaged accordingly. The risk of stroke recurrence depends on the underlying infection, and the treatment should be target as indicated. It may be helpful to consult with an infectious disease expert as needed. VZV vasculitis may present with large and small artery strokes in the context of arterial luminal irregularities, beading, or stenosis.[710,711] Patients in whom VZV vasculitis is suspected should undergo a lumbar puncture for anti-VZV immunoglobulin G, immunoglobulin M, and polymerase chain reaction. Anti-VZV immunoglobulin G has the highest sensitivity of the 3 tests. A negative VZV polymerase chain reaction does not rule out VZV vasculitis.[712,713] If suspicion of VZV vasculitis is high, it may be reasonable to treat empirically while awaiting the results of confirmatory tests. Acyclovir is the drug of choice for the treatment of VZV infection.[714] Among patients with stroke and diagnosed neurosyphilis, intense treatment with penicillin G is mandated.[735] In some instances, there may be coexisting comorbidities that may also predispose to stroke such as large artery atherosclerosis or AF. In such cases, treating neurosyphilis is still indicated in addition to the confounding competing risk of stroke. Testing for HIV is indicated in patients with stroke and diagnosis of neurosyphilis. This recommendation is supported by a relatively high coexistence (5%–16%) of both sexually transmitted diseases.[715,716]
2. Secondary stroke prevention among patients with HIV vasculopathy is focused on daily antiplatelets and treatment aimed at restoring the CD4 counts and immune system. There are no randomized data to support these claims. Restoring the immune system as captured by the CD4 count is indicated in all patients with HIV regardless of whether they have stroke.[717]

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The presence of stroke may be seen as an even greater indication to treat the most devastating consequences of HIV infection and associated immunosuppression. Observational data support this approach in patients with HIV vasculopathy.[718–721] Some authors have noted a possible link between the initiation of combined antiretroviral therapy and stroke risk, suggesting an immune reconstitution-like syndrome in these cases.[722,723] It is uncertain whether steroids may play a role in stroke risk reduction in this clinical setting.

5.13.3. Neoplastic Vasculitis

Synopsis

Neoplastic vasculitis refers to inflammation of the brain arteries resulting from direct invasion of neoplastic cells, as opposed to paraneoplastic vasculitis in which the inflammation of the brain arteries is not attributable to direct tumor invasion or compression. Conditions in this category are rare and include lymphomatoid granulomatosis and angiotropic or intravascular lymphoma (also known as angioendotheliomatosis)[736] among other even less common disorders.[737,738] Treating the underlying malignancy also reduces the risk of recurrent stroke. The relatively rare occurrence of neoplastic vasculitis is a challenge for the systematic study of the disease. Even less homogeneous information exists on what strategy may be the most effective to reduce the risk of stroke recurrence thought to be attributable to a neoplastic vasculitis. Angiotropic lymphoma is perhaps the most commonly reported neoplastic vasculitis in the literature. In a large meta-analysis of cases of angiotropic lymphoma reported between 1957 and 2012, only 8% presented with stroke-like symptoms.[736] Given the observational nature of the report, limited information is available on how to reduce the risk of stroke recurrence. Therefore, we advise treating the underlying malignancy. A multidisciplinary team is recommended for the management of these complex patients.

Vasculitis Knowledge Gaps and Future Research

CNS autoimmune vasculitides are a broad spectrum of disorders that may present with stroke. Although studies focused on people with stroke and CNS vasculitis are not common, we inferred that treating the underlying vasculitis may help reduce the risk of stroke. The treatment of choice varies, depending on each condition. We have identified areas in which further research is needed to better diagnose or treat these heterogeneous conditions:

- A growing area of interest and future research includes the use of biological drugs that may target more specifically the disputed pathways in some of these disorders. It is highly encouraged that stroke be incorporated as an independent outcome in future trials.
- Steroids are often used to treat autoimmune vasculitis. This may be problematic in people with coexisting vascular risk such as hypertension and diabetes. Further research is needed on the safety profile of long-term steroids and steroid-sparing agents in stroke populations. Similarly, the timing of steroid initiation and poststeroid biopsy yield should be further delineated.
- In adults with ischemic stroke or TIA and symptoms of giant cell arteritis, the benefit of an initial high-dose intravenous pulse of steroids versus oral steroids in stroke prevention is uncertain.
- For the treatment of VZV vasculitis, the role of steroids as adjunctive therapy to acyclovir is not well established.
- Chronic inflammation is often found in people living with well-controlled HIV infection. It is uncertain whether, in addition to comprehensive vascular risk factor control, there may be a role for additional immunomodulation in this population.

5.14. Other Genetic Disorders

Recommendations for Other Genetic Disorders
Referenced studies that support recommendations are summarized in online Data Supplements 51 and 52.

COR	LOE	Recommendations
1	C-LD	1. In patients with ischemic stroke or TIA and cystathionine β-synthase deficiency, pyridoxine (in responsive patients) and a low-methionine, cysteine-enhanced diet supplemented with pyridoxine, vitamin B_{12}, and folate are recommended to reduce plasma homocysteine to population normal levels and thereby reduce the risk of recurrent ischemic stroke.[739,740]
2b	B-NR	2. In patients with ischemic stroke or TIA and Anderson-Fabry disease, agalsidase alfa or agalsidase beta is of uncertain value in preventing recurrent stroke or TIA.[741]

Synopsis

Beyond SCD, other rare diseases cause stroke or stroke-like syndromes for which there are specific therapies. Recently, there have been randomized trials of enzyme replacement therapy in Anderson-Fabry disease, but such methodology is rare. Even in Anderson-Fabry disease, it has been difficult to adequately power studies to assess efficacy for stroke prevention.[742] Although in 1 German population the prevalence of Fabry disease in young men with first-time cryptogenic ischemic stroke was reported to be as high as 2.17%,[743] it appears that, for most populations of young men with first-time cryptogenic stroke, the rate is <1%.[744] The prevalence rate appears to be higher in young patients with recurrent cryptogenic ischemic stroke relative to young patients with first-time cryptogenic stroke.[743]

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Recommendation-Specific Supportive Text

1. An ecological study of a newborn screening program in Ireland supports the effectiveness of interventions to drive free homocysteine to ≤11 mmol/L to prevent thromboembolic events.[739] A study of treatment of severe hyperhomocysteine performed in Australia, the Netherlands, and Ireland on patients who had cystathionine β-synthase deficiency (mean age, 27.8 years; range, 2.5–70 years) supported a dramatic reduction of risk of vascular events relative to a historical cohort study (RR, 0.091 [95% CI, 0.043–0.190]; $P<0.001$).[740]
2. A systematic review of RCTs of agalsidase alfa or beta in patients with Anderson-Fabry disease found that the enzyme replacement therapy improved pain-related quality of life but that their effects on morbidity or mortality required further study.[741]

Knowledge Gaps and Future Research

- Specific treatments are needed for several single-gene disorders associated with high risk of stroke, including mitochondrial myopathy, encephalopathy, lactic acidosis, stroke-like episodes, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy, cathepsin-A–related arteriopathy with strokes and leukoencephalopathy, retinal vasculopathy with cerebral leukodystrophy, and cases of pathogenic mutations in the *COL4A1/COL4A2* genes.[745] Because of the low prevalence of these conditions, generating high-quality evidence for therapies for single-gene disorders that cause stroke will be challenging but not impossible.
- For patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes, prospective multicenter single-arm studies suggest that oral L-arginine may extend the interictal phase of stroke-like spells and intravenous L-arginine may improve headache, nausea/vomiting, impaired consciousness, and visual disturbances. However, the intravenous treatment may result in fevers and lower hemoglobin.[746] L-Arginine may work by acting as a nitric oxide precursor.[747] Although L-citrulline raises nitric oxide production more than L-arginine, it has not been systematically studied in humans.[747] Future RCTs are needed to clarify dosage, timing of initiation relative to onset of an attack, duration of therapy, and safety for nitric oxide precursors for treating patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes before treatment recommendations can be made.

5.15. Carotid Web

Recommendations for Carotid Web
Referenced studies that support recommendations are summarized in online Data Supplement 53.

COR	LOE	Recommendations
1	B-NR	1. In patients with carotid web in the distribution of ischemic stroke and TIA, without other attributable causes of stroke, antiplatelet therapy is recommended to prevent recurrent ischemic stroke or TIA.[748,749]
2b	C-LD	2. In patients with carotid web in the distribution of ischemic stroke refractory to medical management, with no other attributable cause of stroke despite comprehensive workup, carotid stenting or CEA may be considered to prevent recurrent ischemic stroke.[748–750]

Synopsis

Carotid web is a thin, circumferential shelf-like filling defect that arises from the posterior wall of the ICA bulb visualized on CTA or carotid angiography. Pathologically, carotid web is a variant of fibromuscular dysplasia and can be classified as focal or multifocal. Platelet deposition can occur in the corrugations of carotid web, forming a nidus for potential blood flow stagnation and thromboembolism. Carotid web is a known cause of ischemic stroke in young patients <65 years of age; it is detected in up to 9.5% of patients <65 years of age with anterior circulation stroke of unknown cause.[751]

Recommendation-Specific Supportive Text

1. The optimal management of symptomatic carotid web is unknown. Medical management with antithrombotic therapy is first-line treatment; however, it is not known whether SAPT, short-term DAPT, or anticoagulant therapy is superior. In the absence of such data, it is recommended to treat patients with antiplatelet therapy first line or to follow antithrombotic recommendations in this guideline.
2. There is a high risk of recurrent stroke or TIA in patients with symptomatic carotid web on medical management, estimated in 29% to 56% of patients.[749,750] Carotid stenting or CEA is a good alternative treatment for patients with symptomatic carotid web, with published series revealing no recurrent stroke risk.[748,749]

Knowledge Gaps and Future Research

The optimal medical or interventional management of symptomatic carotid web is unknown. Future prospective research evaluating the natural history of symptomatic carotid web on medical management compared with interventional management would be of interest and evolve to multicenter randomized trials comparing medical management (ie, antiplatelet versus anticoagulant, then best medical therapy versus carotid stenting or CEA) if enough patients can be identified.

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Stroke

5.16. Fibromuscular Dysplasia

Recommendations for Fibromuscular Dysplasia
Referenced studies that support recommendations are summarized in online Data Supplement 54.

COR	LOE	Recommendations
1	C-LD	1. In patients with fibromuscular dysplasia (FMD) and a history of ischemic stroke or TIA without other attributable causes, antiplatelet therapy, BP control, and lifestyle modification are recommended for the prevention of future ischemic events.[752,753]
2a	C-EO	2. In patients with a history of ischemic stroke or TIA attributable to dissection, with FMD, and no evidence of intraluminal thrombus, it is reasonable to administer antiplatelet therapy for the prevention of future ischemic events.
2b	C-LD	3. In patients with cervical carotid artery FMD and recurrent ischemic stroke without other attributable causes despite optimal medical management, carotid angioplasty with or without stenting may be reasonable to prevent ischemic stroke.[754]

Synopsis

FMD is a nonatherosclerotic segmental disease of small or medium-sized arteries that can result in arterial stenosis, occlusion, intraluminal thrombus, aneurysm, or dissection.[752] It can involve the extracranial carotid, vertebral. and renal arteries. On a histological level, FMD affects the musculature or media layer of the vessel wall, leading to medial fibroplasia and the appearance of a "string of beads" on angiography imaging. Multiple fibrous webs can serve as a nidus for platelet deposition[755] or obstruct flow, resulting in thromboembolic TIA or ischemic stroke. Women are more commonly affected than men. The frequency of neurological events in the US FMD registry was noted: 13.4% had TIA; 5% had experienced amaurosis fugax; 12% had experienced cervical artery dissection; and 9.8% had had a stroke.[756]

Recommendation-Specific Supportive Text

1. High BP is common in patients with FMD, from either essential hypertension or renovascular hypertension related to FMD.[752] The optimal BP target for patients with FMD is unknown. In the US FMD registry, most patients were on antihypertensive medicine.[753] Smoking cessation should be encouraged for all patients with FMD who smoke because of its health benefits in the general population. The recommendation of using antiplatelet therapy for secondary stroke prevention is based on current practice and expert opinion.[752,753,755] In the US FMD registry, 73% of patients were prescribed antiplatelet therapy; aspirin was the most common agent.[753] There are no placebo-controlled randomized trials of patients with symptomatic or asymptomatic FMD comparing aspirin with placebo. Statins are not routinely prescribed for isolated FMD in the absence of another indication.
2. Dissection is a common manifestation associated with FMD, present in 11% to 15% of patients with spontaneous carotid or vertebral artery dissection.[757,758] In the US FMD registry, ischemic stroke was present in 19% of patients presenting with cervical artery dissections.[759] The CADISS study demonstrated equivalent efficacy for recurrent stroke risk in patients with spontaneous, symptomatic cervical carotid dissection randomized to antiplatelet versus anticoagulant for 3 months (3% versus 1%; P=0.66) (see Section 5.7, Dissection).
3. This recommendation has been adapted from a prior guideline by Brott et al[25] on carotid angioplasty with or without stenting in symptomatic patients with patients to COR 2b. There are no comparative data evaluating medical management versus angioplasty or stenting for patients with FMD and recurrent ischemic stroke. A case series of 7 patients with symptomatic FMD revealed no complications with balloon angioplasty.[754]

Knowledge Gaps and Future Research

The optimal medical or interventional management of symptomatic FMD is unknown. Future prospective research evaluating the natural history of symptomatic FMD on medical management compared with interventional management would be of interest and evolve to multicenter randomized trials comparing medical management (ie, antiplatelet versus anticoagulant, then best medical therapy versus carotid angioplasty or carotid stenting) if enough patients can be identified.

5.17. Dolichoectasia

Recommendation for Dolichoectasia
Referenced studies that support the recommendation are summarized in online Data Supplement 55.

COR	LOE	Recommendation
2a	C-LD	1. In patients with vertebrobasilar dolichoectasia and a history of ischemic stroke or TIA without other attributable causes, the use of antiplatelet or anticoagulant therapy is reasonable for the prevention of recurrent ischemic events.[760–764]

Synopsis

Vertebrobasilar dolichoectasia is characterized by the fusiform dilatation and elongation and tortuosity of the vertebral and basilar arteries. Vertebrobasilar dolichoectasia is associated with traditional ischemic stroke risk factors such as increasing age, hypertension, and male sex. However, its relationship to atherosclerotic disease is less clear.[765–767] Although many patients may be asymptomatic, others may present with a variety of

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clinical syndromes, including cranial nerve or brainstem compression, obstructive hydrocephalus, subarachnoid hemorrhage, and ischemia.[760,764,768] Ischemic events may be related to thromboembolic phenomenon but may also result from the disruption of small perforating vessels.[764,769] Asymptomatic patients have the most favorable prognosis,[764] whereas those presenting with compressive symptoms or demonstrating progressive enlargement have a worse prognosis.[760,768,770] The rate of recurrent ischemic stroke may be quite high,[761,771,772] with 1 study reporting a rate of 19% at just under 2 years.[761] Increasing basilar artery diameter, diffuse intracranial dolichoectasia, and associated ischemic heart disease increased the risk of recurrent events.[761] Many patients with vertebrobasilar dolichoectasia are treated medically with antithrombotic medication, but high-quality evidence on the management strategies for patients with vertebrobasilar dolichoectasia, particularly in the setting of a prior ischemic stroke or TIA, is lacking. Several case series describe endovascular techniques[773–775] and various surgical interventions[114,775–778]; however, there is little evidence that such treatments reduce the risk of additional ischemic events in patients who present with an ischemic stroke or TIA. The literature on dolichoectasia of the anterior circulation in patients with prior ischemic stroke or TIA is even more sparse; therefore, this topic is not addressed in this guideline.

Recommendation-Specific Supportive Text

1. There are no prospective RCTs comparing antithrombotic therapies with observation alone. However, case series tend to suggest that antithrombotic therapy lowers the risk of recurrent ischemic events compared with the natural history.[761,762] There are also no prospective RCTs comparing antiplatelet strategies (either aspirin or second-generation antiplatelet drugs) with anticoagulation. The case series reviewed demonstrated no clear or consistent benefit for 1 form of antithrombotic therapy over another.[760–763] Although 1 small case series favored anticoagulation, not all of the patients in that series presented with ischemic symptoms, and the series consisted of patients with fusiform aneurysms rather than true vertebrobasilar dolichoectasia.[762] Although the risks of hemorrhage appear to be low in patients presenting with ischemic symptoms,[764] there are insufficient data to provide a recommendation for anticoagulation over antiplatelet therapy.

Knowledge Gaps and Future Research

Many important issues about the management of patients with vertebrobasilar dolichoectasia remain unclear. Some of these include the following:

- Development of an agreed-on definition for vertebrobasilar dolichoectasia that is distinguishable from the definition of a fusiform aneurysm.
- Accumulation of more robust natural history data with detailed clinical outcomes.
- Clarification of the type, dosing regimens, and efficacy of antiplatelet therapy versus anticoagulation for primary and secondary ischemic stroke prevention.
- Improved understanding of the role of reconstructive procedures, whether endovascular or open surgical, in the management of patients with vertebrobasilar dolichoectasia.

5.18. Embolic Stroke of Undetermined Source

Recommendations for ESUS
Referenced studies that support recommendations are summarized in online Data Supplement 56.

COR	LOE	Recommendations
3: No Benefit	B-R	1. In patients with ESUS, treatment with direct oral anticoagulants is not recommended to reduce risk of secondary stroke.[779,780]
3: No Benefit	B-NR	2. In patients with ESUS, treatment with ticagrelor is not recommended to reduce the risk of secondary stroke.[781]

Synopsis

ESUS is an evolving stroke subtype commonly defined as a nonlacunar cryptogenic ischemic stroke. Lack of a standard definition has complicated studies of ESUS, with 1 review finding that many studies use variable diagnostic criteria, including type and duration of cardiac rhythm monitoring.[782] This complexity in defining ESUS is one of the reasons proposed for the negative clinical trials of anticoagulation compared with antiplatelet medication for stroke prevention[779,780] and fuels much of the ongoing research to further define the association between markers of atrial cardiopathy and methods of assessing cardiac rhythm disorders and risk of recurrent stroke. Subgroup analyses of the NAVIGATE ESUS study (Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source) suggest that patients with left atrial diameter >4.6 cm may benefit from anticoagulation[783] but those with PFO did not.[784] A post hoc analysis of patients with ESUS enrolled in the SOCRATES trial (Soluble Guanylate Cyclase Stimulator in Heart Failure Studies) did not find an association between ticagrelor treatment and reduced vascular event risk.[781] Ongoing randomized trials that may provide additional information about the efficacy of treatments to prevent recurrent stroke among patients with ESUS include studies using prolonged rhythm monitoring to identify patients, studies that select patients with various markers of atrial dysfunction,[785] and trials that include MRI-defined

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new ischemic events (silent strokes) as clinical trial outcomes.[786–788]

Recommendation-Specific Supportive Text

1. The NAVIGATE ESUS and RESPECT ESUS (Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source) randomized trials found no reduction in secondary stroke risk among patients with ischemic stroke or TIA who were treated with a direct oral anticoagulant.[779,780]
2. A post hoc subgroup analysis of subjects with ESUS enrolled in the SOCRATES trial (4329 subjects, 32.8%) found no treatment effect by ESUS category of ticagrelor on recurrent vascular event risk.[781]

Knowledge Gaps and Future Research

Although ongoing trials may help address some of the questions about ESUS, knowledge gaps persist related to the definition of ESUS and optimal treatment for secondary stroke prevention:

- What markers of atrial dysfunction are most strongly associated with recurrent stroke risk?
- Are there clinical factors that help identify patients with ESUS who may benefit from anticoagulation rather than antiplatelet treatment for secondary prevention?

One of the primary challenges in identifying treatments to reduce the risk of second stroke in patients with ESUS is the difficulty of clearly defining criteria for ESUS diagnosis. Future trials should address these topics:

- The use of different strategies for long-term arrhythmia detection and their impact on ESUS diagnosis criteria.
- The use of additional cardiac markers of atrial pathology, including atrial size, and their impact on ESUS diagnosis criteria, secondary stroke risk, and response to anticoagulation.

5.19. Use of Antithrombotic Medications in Secondary Stroke Prevention

As described in prior sections of this guideline, recommendations for secondary stroke prevention have been constructed on the basis of the best evidence among patients with a specific cause of their initial ischemic stroke. For patients with noncardioembolic ischemic stroke who do not have a specific identified cause, questions about optimal antithrombotic medication use for secondary prevention may thus arise. In general, when those specific antithrombotic recommendations vary slightly from the general recommendations that follow in this section, the most specific recommendation should be prioritized.

Recommendations for Antithrombotic Medications
Referenced studies that support recommendations are summarized in online Data Supplements 57–59.

COR	LOE	Recommendations
1	A	1. In patients with noncardioembolic ischemic stroke or TIA, antiplatelet therapy is indicated in preference to oral anticoagulation to reduce the risk of recurrent ischemic stroke and other cardiovascular events while minimizing the risk of bleeding.[789,790]
1	A	2. For patients with noncardioembolic ischemic stroke or TIA, aspirin 50 to 325 mg daily, clopidogrel 75 mg, or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily is indicated for secondary prevention of ischemic stroke.*[791–794]
1	A[SR]	3. For patients with recent minor (NIHSS score ≤3) noncardioembolic ischemic stroke or high-risk TIA (ABCD^2 score ≥4), DAPT (aspirin plus clopidogrel) should be initiated early (ideally within 12–24 hours of symptom onset and at least within 7 days of onset) and continued for 21 to 90 days, followed by SAPT, to reduce the risk of recurrent ischemic stroke.[382,384,410,795,796]
2b	B-R[SR]	4. For patients with recent (< 24 hours) minor to moderate stroke (NIHSS score ≤5), high-risk TIA (ABCD^2 score ≥6), or symptomatic intracranial or extracranial ≥30% stenosis of an artery that could account for the event, DAPT with ticagrelor plus aspirin for 30 days may be considered to reduce the risk of 30-day recurrent stroke but may also increase the risk of serious bleeding events, including ICH.[797]
2b	B-NR	5. For patients already taking aspirin at the time of noncardioembolic ischemic stroke or TIA, the effectiveness of increasing the dose of aspirin or changing to another antiplatelet medication is not well established.[410,798–800]
3: Harm	A[SR]	6. For patients with noncardioembolic ischemic stroke or TIA, the continuous use of DAPT (aspirin plus clopidogrel) for >90 days or the use of triple antiplatelet therapy is associated with excess risk of hemorrhage.[381,382,801]

SR indicates systematic review.

*The subgroup of patients with noncardioembolic stroke who meet clinical criteria for DAPT have a more specific recommendation for antiplatelet therapy as described in Recommendation 3.

Synopsis

Patients with stroke/TIA not attributable to other stroke causes related to specific antithrombotic recommendations (eg, AF, intracranial stenosis) should receive antithrombotic therapy for the prevention of recurrent stroke. If patients with mild stroke or high-risk TIA are evaluated early after the onset of their stroke, starting short-term DAPT followed by long-term SAPT is preferred compared with SAPT according to the reduction of risk of early recurrent stroke.[384,410] Beyond 90 days after stroke, DAPT is associated with increased risk of bleeding and no benefit in long-term reduction of recurrent stroke risk.[381,382] For patients not treated until later after their stroke event, use of any SAPT is indicated to reduce long-term recurrent

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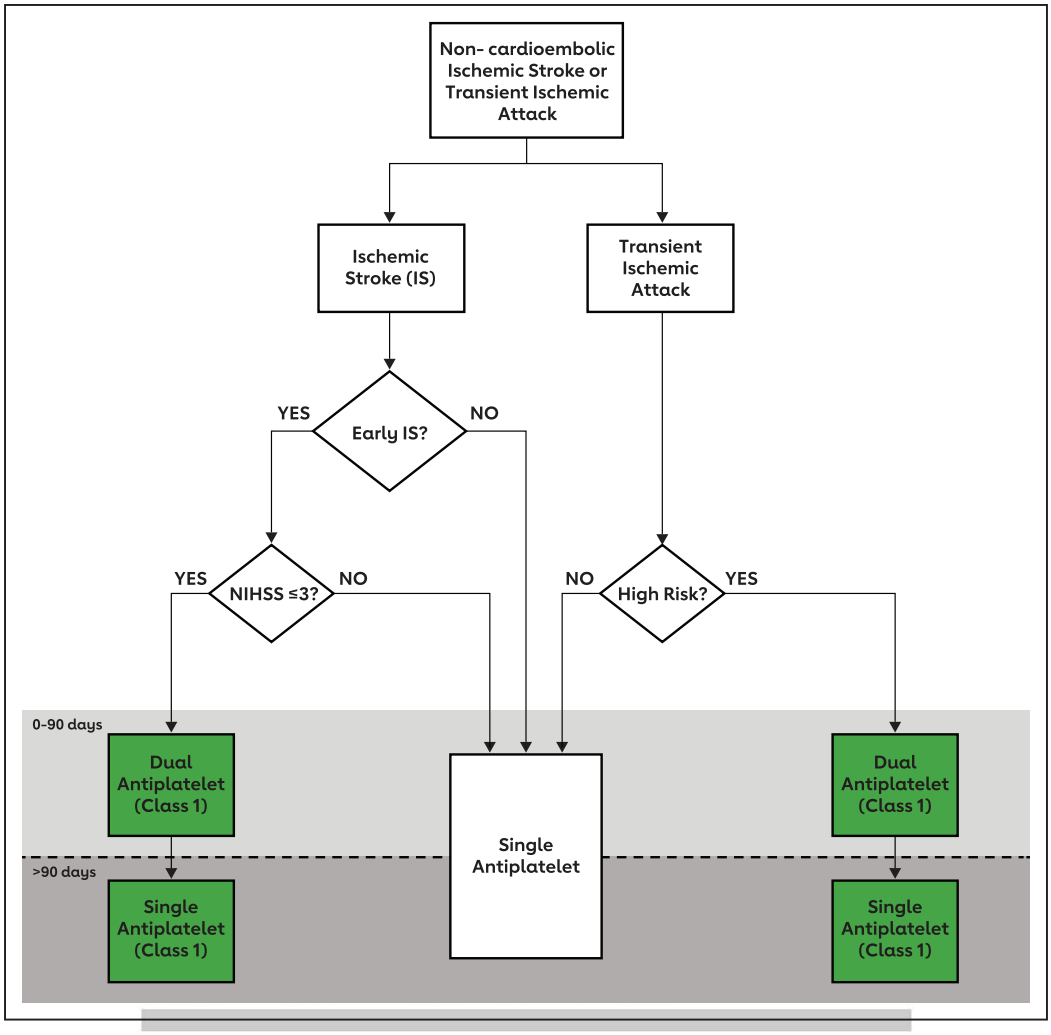

Figure 6. Antiplatelet therapy for noncardioembolic stroke and transient ischemic attack (TIA).
Note: Algorithm does not apply to patients who receive acute thrombolysis. Note: Please see Section 5.1.1 for recommendations related to severe symptomatic intracranial large vessel stenosis. Early ischemic stroke (IS), <24 hours from onset; high-risk TIA, ABCD^2 score ≥4; low-risk TIA, ABCD^2 score <4; dual antiplatelet, acetylsalicylic acid (ASA)+clopidogrel. Colors correspond to Class of Recommendation in Table 3. NIHSS indicates National Institutes of Health Stroke Scale. Data from Brown et al,[15] Pan et al,[409] and Wang et al.[410]

stroke risk. Although the optimal time to switch from DAPT to SAPT to maximize benefit and reduce risk is not entirely clear, benefit in stroke reduction with DAPT may be maximized as early as the first 21 days after the event.[802] This treatment approach is summarized in Figure 6, with consideration of clinical event criteria, DAPT versus SAPT, and length of therapy. Triple therapy with aspirin, clopidogrel, and dipyridamole and use of anticoagulation in this population are not recommended on the basis of increased bleeding risk and no benefit in stroke reduction.[790,801]

Recommendation-Specific Supportive Text

1. The WARSS study randomized 2206 patients with stroke not attributable to cardioembolism or high-grade carotid stenosis to adjusted-dose warfarin (INR, 1.4–2.8) versus aspirin 325 mg.[790] The primary end point of 2-year recurrent ischemic stroke or death was no different between the 2 groups (17.8% warfarin versus 16% acetylsalicylic acid; HR, 1.13 [95% CI, 0.92–1.38]). Similarly, a subsequent meta-analysis of 8 other trials of VKA among 5762 patients with TIA or nondisabling noncardioembolic stroke found no benefit in secondary stroke prevention with the use of oral anticoagulation of various intensities compared with antiplatelet agents (medium-intensity anticoagulation: RR, 0.80 [95% CI, 0.56–1.14]; high-intensity anticoagulation: RR, 1.02 [95% CI, 0.49–2.13]); both medium-intensity anticoagulation and high-intensity anticoagulation were associated with a significantly increased risk of bleeding.[789]
2. A series of single antiplatelet trials conducted in patients with noncardioembolic stroke did not use clinical eligibility criteria in the same manner as the more recent DAPT trials. Thus, some patients in the general noncardioembolic stroke pathogenesis group may qualify for the more

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specific recommendation for early DAPT. For those who do not meet DAPT clinical criteria, SAPT is recommended. The PRoFESS trial found no difference in secondary stroke prevention after noncardioembolic stroke for aspirin-dipyridamole versus clopidogrel.[794] The ESPRIT trial (European/Australasian Stroke Prevention in Reversible Ischaemia Trial)[792] suggested that aspirin-dipyridamole may be slightly more effective than aspirin alone for vascular event prevention, as did the ESPS2 trial (Second European Stroke Prevention Study).[791] ESPS2 also showed that aspirin alone is more effective than placebo in reducing recurrent stroke. The CAPRIE trial (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events) was not focused strictly on secondary prevention but found fewer events among patients treated with clopidogrel compared with those treated with aspirin, although no benefit was seen in stroke reduction among the stroke subgroup. A pooled analysis of trials in patients with lacunar stroke suggested that any of the evaluated antiplatelet agents were similarly effective compared with placebo.[793] Aspirin dosing may be guided by a recent patient-level pooled analysis of data from primary prevention RCTs that showed weight-based dosing (eg, aspirin 75–100 mg for patients weighing <70 kg and higher doses for those >70 kg) is more effective for the prevention of vascular events.[803] However, similar studies have not been performed for secondary stroke prevention.

3. Recommendations for the short-term (21–90 days) use of DAPT with aspirin and clopidogrel are informed by 2 major RCTs,[384,410] 4 meta-analyses,[802,804–806] and a systematic review by an AHA Evidence Review Committee.[15] Both the CHANCE and POINT trials compared DAPT with SAPT with aspirin initiated early after onset (<24 and <12 hours, respectively) of minor stroke (NIHSS score ≤3) or high-risk TIA (ABCD^2 score ≥4) but varied in duration of DAPT treatment (21 and 90 days, respectively). DAPT dosing was also slightly different in the 2 trials: POINT used a 600-mg clopidogrel load (then 75 mg daily) and an aspirin regimen of 50 to 325 mg daily, whereas CHANCE used a 300-mg clopidogrel load (then 75 mg daily) and an aspirin load of 75 to 300 mg followed by 75 mg daily. Both trials demonstrated a reduction in recurrent ischemic stroke at 90 days. Further analyses of POINT revealed that the benefit of DAPT was seen primarily in the first 21 days.[365] Meta-analyses that included other DAPT trials also have shown a reduction in recurrent stroke from DAPT compared with aspirin monotherapy, but the benefit is limited if not started early (<7 days) after the index event. Although most studies showed some increase in bleeding risk with DAPT, this was offset by the stroke prevention benefit if limited to short-term use.[795,796,806]
4. The use of ticagrelor (180-mg loading dose, then 90 mg twice daily) plus aspirin (300- to 325-mg loading does, then 75–100 mg daily) for 30 days was shown in the THALES trial to be slightly superior to aspirin alone in preventing recurrent stroke (recurrent stroke rate, 5% versus 6.3%; P=0.004) but was also associated with significantly increased risk of severe bleeding (0.5% versus 0.1%; P=0.001).[797] ICH was also significantly increased among the DAPT group (0.4% versus 0.1%; P=0.01), and significantly more patients in the DAPT group discontinued treatment because of bleeding (2.8% versus 0.6%; P<0.001); the number needed to treat to prevent 1 primary outcome event was 92, and the number needed to harm was 263 for severe bleeding. Further study of this DAPT combination is needed to fully evaluate benefit and risk and to determine whether there is a specific subgroup most likely to benefit. The use of ticagrelor alone compared with aspirin was not associated with any reduction in cardiovascular events.[807] The use of ticagrelor plus aspirin for the subgroup of patients with ipsilateral carotid artery stenosis and intracranial stenosis is discussed in Section 5.1.1, Intracranial Large Artery Atherosclerosis.[808]
5. No randomized trials have focused on the question of changing long-term antiplatelet therapy for the prevention of recurrent stroke. A meta-analysis suggested that, among the 4 studies that examined stroke outcomes, there was a reduced risk of recurrent stroke (HR, 0.70 [95% CI, 0.54–0.92]) among patients who switched from 1 antiplatelet agent to another or to DAPT.[800] However, both of the RCTs that specifically examined recurrent stroke used DAPT rather than switching antiplatelets. In a subgroup analysis of the SPS3 trial, there was no benefit from the addition of clopidogrel to aspirin among patients with ischemic stroke who were already taking aspirin (risk of recurrent stroke, 3.1% versus 3.3%; HR, 0.91 [95% CI, 0.61–1.37]).[798] In a subgroup of patients already on aspirin in the CHANCE trial, there was a reduction in recurrent stroke among patients with clopidogrel added to aspirin versus aspirin alone (12.3%–9.0%; HR, 0.66 [95% CI, 0.47–0.92]).[410] A prospective registry study found that maintaining aspirin therapy was associated with higher recurrent stroke rates (8.0%) compared with switching to another antiplatelet (6.9%) or adding another antiplatelet (6.6%).[799]
6. Long-term use of DAPT with aspirin and clopidogrel has been shown in 2 secondary stroke

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prevention RCTs[381,382] to have no benefit over SAPT for recurrent stroke prevention and to have a significantly increased risk of ICH and major bleeding. The exact duration of DAPT at which the risk of hemorrhage begins to outweigh the benefit of stroke prevention is unknown, but meta-analyses report as early as 21,[802] 30,[805] or 90 days.[806] Older patients[804] and those with more severe stroke[806] appear to be at higher risk of ICH with DAPT. Triple antiplatelet therapy with aspirin, clopidogrel, and dipyridamole was compared with standard antiplatelet therapy in the TARDIS trial (Triple Antiplatelets for Reducing Dependency after Ischaemic Stroke), which found no difference in stroke outcomes and a significantly increased risk of bleeding with triple antiplatelet therapy.[801] There may be other non–stroke-related indications for DAPT beyond 90 days after stroke (eg, recent drug-eluting cardiac stent placement), but these indications should be clarified to ensure that DAPT is not continued indefinitely beyond the clinically recommended time frame.

Knowledge Gaps and Future Research

To date, most DAPT trials have used aspirin and clopidogrel in combination for 21 to 90 days, but whether the duration of treatment should be 21 days, 90 days, or some other amount of time is not fully established. Similarly, whether other combinations of medications are equally or more beneficial is not known. The risk of DAPT among patients with stroke who may be more likely to experience hemorrhagic transformation of the ischemic stroke or other bleeding complication such as those with large stroke or microhemorrhages remains uncertain.

Pharmacological responsiveness to antiplatelet therapy has been studied most extensively in patients with acute CVD, but the utility of such tests for guiding adjustment of antiplatelet medications for long-term prevention remains unclear. Relatively few head-to-head comparisons of antiplatelet medications have been evaluated for the prevention of recurrent stroke, and in the existing trials, the benefit of 1 medication over another is small.

Despite the common practice of changing antiplatelet medications in patients already taking 1 medication at the time of stroke, there is relatively little evidence from RCTs to support the benefit of this practice. Finally, although DOACs may be beneficial in vascular event reduction in patients with stable CVD (COMPASS [Cardiovascular Outcomes for People Using Anticoagulation Strategies]),[809] whether they have any role in secondary stroke prevention for patients with recent noncardioembolic stroke remains an unanswered question. In summary, further research is needed in the following areas:

- Optimal combination of medications, timing of initiation, and duration of DAPT.
- Effectiveness and potential harm of DAPT among specific subgroups of patients according to stroke characteristics, laboratory or genetic tests, or other factors.
- Effectiveness/selection of a given antiplatelet agent over another in specific subgroups of patients with noncardioembolic stroke.
- Benefit of switching antiplatelet agent for patients already taking 1 antiplatelet medication at the time of stroke.
- Effectiveness of DOACs compared with or in combination with antiplatelet therapy for secondary stroke prevention among patients with noncardioembolic ischemic stroke.

6. SYSTEMS OF CARE FOR SECONDARY PREVENTION

6.1. Health Systems–Based Interventions for Secondary Stroke Prevention

Recommendations for Health Systems–Based Interventions
Referenced studies that support recommendations are summarized in online Data Supplements 60–62.

COR	LOE	Recommendations
1	C-EO	1. In patients with ischemic stroke or TIA, voluntary hospital-based or outpatient-focused quality monitoring and improvement programs are recommended to improve short-term and long-term adherence to nationally accepted, evidence-based guidelines for secondary stroke prevention.
2a	B-R	2. In patients with ischemic stroke or TIA, a multidisciplinary outpatient team-based approach (ie, care provision with active medication adjustment from advanced practice providers, nurses, or pharmacists) can be effective to control BP, lipids, and other vascular risk factors.[810–817]
2a	B-R	3. In patients presenting to their primary care provider as the first contact after TIA or minor stroke, it is reasonable to use a decision support tool that improves diagnostic accuracy, stratifies patients in risk categories to support appropriate triage, and prompts the initiation of medications and counseling for lifestyle modification for secondary stroke prevention to reduce the 90-day risk of recurrent stroke or TIA.[818]

Synopsis

Optimal treatment recommendations exist for many stroke risk factors. However, treatment targets are often unmet after ischemic stroke and TIA, thereby increasing the risk of recurrent events.[819–825] Health system approaches to acute stroke management have transformed care delivery and have led to improved access to stroke treatment and improved stroke outcomes.[826–828] Similar approaches to poststroke care and secondary prevention hold promise for improving risk factor control after stroke.[829] Risk factor control is affected by patient, provider, and system-level factors. We define health systems-based interventions

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for secondary stroke prevention as those that influence vascular risk factor treatment and control by influencing provider or patient behaviors. These are often multicomponent interventions that fit into categories defined by Wensing et al[829] and referenced in a Cochrane review of interventions for secondary stroke prevention.[830] Categories include interventions that involve revision of professional roles, collaboration between multidisciplinary teams, integrated care services, knowledge management systems, and quality management systems. We review best available data here but consider that the generalizability of findings may be affected by the study setting, patient access to care after an acute stroke, and other patient demographic characteristics.

Recommendation-Specific Supportive Text

1. Adherence to evidence-based guidelines for secondary stroke prevention is affect by health system–level, hospital-level, provider-level, and patient- and community-specific factors. Regular hospital and outpatient-based programs for adherence and risk factor monitoring provide the opportunity to identify areas of need and to optimize strategies to improve care quality, improve risk factor control, and ultimately reduce the risk of recurrent stroke and TIA. The Get With The Guidelines registry is an example of an inpatient registry used for quality monitoring and improvement.[831]
2. Interventions that include a multidisciplinary team–based approach to care may be beneficial for risk factor control and secondary prevention after ischemic stroke and TIA. In the ICARUSS study (Integrated Care for the Reduction of Secondary Stroke) conducted in Australia, an integrated shared-care model intervention was associated with a significant decrease in SBP at 12 months compared with usual care.[810,811] Several additional studies, including NAILED Stroke (Nurse Based Age Independent Intervention to Limit Evolution of Disease After Stroke; Sweden) and PREVENTION (Preventing Recurrent Vascular Events in Patients With Stroke or Transient Ischemic Attack; Canada), showed significant benefit for BP lowering when nurses or pharmacists were involved in BP management.[812–814] In the SUSTAIN study (Systemic Use of Stroke Averting Interventions), investigators tested an intervention that included a nurse practitioner/physician assistant care manager, group clinics, self-management support, and care coordination to enhance risk factor control. There was no between-group difference in the primary outcome of mean SBP; however, the intervention group was more likely to achieve LDL goals compared with the usual care group.[815] Additional evidence for the benefit of team-based interventions for secondary prevention of stroke is derived from nonrandomized data. In Ontario, Canada, Stroke Prevention Clinics evolved as an interdisciplinary approach to stroke assessment, prevention, and risk factor management.[832] Patients are referred to these clinics from their primary doctors after TIA or after emergency department visit for TIA or stroke. Care in these clinics has been associated with increased use of evidence-based strategies for stroke prevention and decreased risk of mortality at 1 year compared with patients who are not referred to such clinics.[816] In the COMPASS pragmatic trial (United States), there was no benefit of a stroke transitional care model on secondary behavioral outcomes for risk factor control; however, implementation of the model into real-world practice was a major barrier. Additional ongoing and recently completed randomized trials are evaluating the impact of team-based interventions on risk factor control and secondary prevention after ischemic stroke and TIA.[833–838]
3. In the FASTEST study (Efficacy and Safety of a Transient Ischaemic Attack [TIA] Electronic Support Tool) conducted in New Zealand, use of an electronic decision support tool for TIA and stroke management by general practitioners was compared with usual care for patients presenting to their general practitioner as first care contact after stroke or TIA.[818] The tool was designed to improve diagnostic accuracy, to support appropriate triage, and to guide providers in appropriate medication and nonpharmacological (lifestyle counseling) management. TIA and stroke recurrence at 90 days was significantly lower in the intervention group compared with the usual care group, and patients receiving the intervention were more likely to receive guideline-adherent care. This study provides evidence for the use of an electronic decision support tool to guide primary care providers in the management of TIA or minor stroke.

Knowledge Gaps and Future Research

More research is needed to determine the most effective models of postacute care to address risk factor control and secondary stroke prevention in stroke survivors. The following knowledge gaps are highlighted:

- Effective transitions of care from the acute setting to the community affect access to postacute care for secondary prevention. Research on the most effective transitions of care strategies for secondary stroke prevention is needed.
- Many patients have multiple risk factors for recurrent stroke. Health systems–based interventions that address simultaneous control of multiple risk factors for secondary stroke prevention are needed.
- Patients who are uninsured and underinsured may have limited access to poststroke care. Interventions to improve care access and to mitigate the impact

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of lack of insurance on poststroke risk factor control and secondary stroke prevention are needed.

- Additional studies are needed to evaluate the impact of decision support tools on risk factor control and secondary stroke prevention after stroke hospitalization.
- The impact of telemedicine on acute stroke care is well established.[839] Although telemedicine offers many potential benefits over in-person care, patients with stroke may face multiple barriers to engaging in telemedicine, including cognitive impairment and physical disability. Research is needed to evaluate the impact of telemedicine on poststroke risk factor control and secondary stroke prevention.
- Once proven effective, interventions must be implemented across hospital and health systems in order to achieve desired outcomes. Research that examines the implementation of interventions across health systems is needed.

6.2. Interventions Aimed at Changing Patient Behavior

Recommendations for Behavior Change Interventions
Referenced studies that support recommendations are summarized in online Data Supplements 63 and 64.

COR	LOE	Recommendations
1	B-R	1. In patients with ischemic stroke or TIA, behavior change interventions targeting stroke literacy, lifestyle factors, and medication adherence are recommended to reduce cardiovascular events.[131,134,840]
2a	B-R	2. In patients with ischemic stroke or TIA, teaching self-management skills or using behavior change theory (eg, motivational interviewing) can be beneficial in improving medication adherence.[840–843]
2a	B-R	3. In patients with stroke or TIA, combined exercise-based and behavior change interventions are probably indicated in preference to behavior interventions alone, exercise interventions alone, or usual care to reduce physiological stroke risk factors such as SBP.[111–113,829]
2a	B-R	4. In patients with TIA or nondisabling stroke, engagement in targeted secondary prevention programs (eg, cardiac rehabilitation programs or exercise and lifestyle counseling programs) can be beneficial to reduce risk factors and recurrent ischemic events.[133,134]
2a	B-NR	5. For patients with disabling stroke who are discharged from acute services, engaging in targeted secondary prevention programs (eg, an adapted cardiac rehabilitation program or structured exercise including aerobic activity and healthy lifestyle counseling) can be beneficial to reduce vascular risk factors and mortality.[111,844]
3: No Benefit	B-R	6. In patients with stroke or TIA, provision of health information or advice about stroke prevention is essential; however, information or advice alone, in the absence of a behavioral intervention, is not an effective means to change modifiable, lifestyle-related risk factors in order to reduce future ischemic events.[129,829,845]

Synopsis

Hypertension, smoking, T2D, physical activity, diet, psychosocial factors, abdominal obesity, alcohol, cardiac causes, and apolipoproteins account for 91.5% of the PAR for ischemic stroke, similar across world regions, sexes, and ages.[5a,846] One in 3 US citizens has at least 1 of these risk factors,[847] which can be modulated by health behaviors, indicating a focus for stroke secondary prevention and self-care.[848] Changing entrenched behavior is difficult, and sustaining change over time is challenging. Several systematic reviews examine lifestyle interventions after stroke; optimal approaches to reduce recurrent stroke remain unknown.[112,840,841,849] Guidance on changing behaviors associated with chronic disease at an individual level is available[850]; however, a Delphi consensus identified that interventions to self-manage lifestyle risk factors after stroke need to be contextualized to the capacities, needs, and personal priorities of the individual and their families.[851] Lifestyle change after stroke is more attainable when the lifestyle counseling is interactive, the advantages of behavior change are perceived as beneficial, and the counselor has sufficient resources (eg, availability of healthcare professionals' time; appropriate counseling materials; knowledge and skills), highlighting a training need for healthcare staff to ensure good-quality counseling and patients' adherence to healthier behavior.[852]

Recommendation-Specific Supportive Text

1. Longer-term follow-up in behavioral interventions after stroke addressing recurrent events is lacking.[111,112,840] However, meta-analysis (from 4 identified studies; N=4053; I^2=0) demonstrates that multimodal interventions addressing active education about risk factors, medications, and medication compliance and interventions to modify ≥1 lifestyle risk factors decrease the odds of recurrent cardiac events (OR, 0.38 [95% CI, 0.16–0.88]), although no significant difference in the odds of recurrent TIA/stroke was reported in this review.[840] Two small multimodal RCTs show promise for reducing cardiovascular end points. However, the small trial numbers dictate that results must be interpreted with caution pending larger, more definitive trials. A 24-week Japanese RCT (N=70)[134] comprising exercise, salt restriction, and nutrition advice compared with usual care terminated at a median follow-up of 2.9 years when the prespecified efficacy point for the intervention was reached for the primary end point (composite stroke death, cardiac death, and hospitalization for stroke recurrence, MI, angina pectoris, or peripheral artery disease; (adjusted HR, 0.194 [95% CI, 0.121–0.737]). Long-term effects (3.5 years) of an exercise and education program, compared with usual care in TIA or minor stroke patients (N=60), found that

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within the intervention group, recurrent stroke, minor stroke, or TIA events were reduced compared with the usual care group (RR, 0.23 [95% CI, 0.07–0.72]; number needed to treat, 3) and a reduction in mortality associated with the intervention (RR, 0.11 [95% CI, 0.01–1.98]; number needed to treat, 8).[131]

2. Adhering to pharmacological secondary prevention strategies is an important self-care behavior in stroke secondary prevention. However, nonadherence to medication regimens is reported in up to 40% of individuals with stroke.[853] Multimodal interventions have been shown in a meta-analysis to improve compliance with antithrombotic medications (OR, 1.45 [95% CI, 1.21–1.75]; I^2=0%; N=2792) and statins (OR, 2.53 [95% CI, 2.15–2.97]; I^2=0%; N=2636).[840] Self-management interventions have similarly shown a moderate effect size in adherence to prescribed secondary prevention medications after stroke (standardized MD, 0.31 [95% CI, 0.07–0.56]; I^2=0%; N=802).[841] In the MIST phase III RCT (Motivational Interviewing in Stroke; N=386), improving adherence to secondary stroke prevention strategies through motivational interviewing demonstrated positive effects on self-reported medication adherence 9 months after stroke (RR, 4.295 [95% CI, 1.56–11.84]; P=0.0049) but no associated reduction in recurrent stroke (RR, 0.67 [95% CI, 0.19–2.33]).[842] Assistive technology may play an emerging role. The SMS4Stroke (Short Messaging Service for Stroke) trial (N=200) showed an adjusted MD of 0.54 (95% CI, 0.22–0.85) in the Morisky Medication Adherence Scale score after 2 months of receiving short messaging service reminders for each dose of medication.[843]
3. Systematic reviews of lifestyle interventions compared with usual care after stroke identify favorable effects on reducing BP.[111,112] A mean SBP reduction of −3.6 mm Hg (95% CI, −5.6 to −1.6; I^2=33%, N=650) has been noted.[112] Subgroup analysis identified nonsignificant effects for behavior interventions alone, significant effects for cardiovascular exercise interventions (MD, −3.9 mm Hg [95% CI, −6.5 to −1.3]; I^2=19; N=70), and larger effects for combined exercise and lifestyle interventions (MD, −5.3 mm Hg [95% CI, −9.0 to −1.6]; I^2=46%; N=228). A systematic review of exercise-based interventions on cardiovascular risk factors after stroke[113] reported similar reductions in SBP in addition to other physiological outcomes (fasting insulin and glucose and high-density lipoprotein cholesterol). Mean SBP reductions in exercise interventions with or without other interventions (MD, −5.32 [95% CI, −9.46 to −1.18]) were greater than those observed with exercise interventions alone (MD, −2.51 [95% CI, −4.72 to −0.30]).[113] A review of educational/behavioral interventions (excluding exercise) showed no effect on SBP.[829]
4. Cardiac rehabilitation reduces cardiovascular mortality in coronary heart disease.[854] Emerging evidence supports its broad application in TIA/nondisabling stroke populations. One small RCT (N=22) demonstrated superiority to usual care in risk profiles, perceived physical functioning, and mental health when patients with TIA/nondisabling stroke access existing programs.[133] A cohort study (N=80) of participants with TIA attending a 6-month cardiac rehabilitation program demonstrated a significant (26%) increase in the lowest mortality risk category of the Duke treadmill score and significant improvements in fitness, total cholesterol/high density lipoprotein ratios, waist circumference, and BMI.[132] Two RCTs demonstrated promising longer-term reductions in cardiovascular events. A mixed exercise program combined with education and lifestyle counseling (N=60) demonstrated reduced recurrent stroke or TIA events in the intervention group compared with the usual care control group (RR, 0.23 [95% CI, 0.07–0.72]) and a reduction in mortality (RR, 0.11 [95% CI, 0.01–1.98]) at 3.5 years.[131] A tailored intervention of exercise, salt restriction, and nutrition advice for 24 weeks compared with usual care (N=70) was also associated with a reduction in the primary composite endpoint of cardiovascular outcome (HR, 0.194 [95% CI, 0.121–0.737]) at 2.9 years.[134]
5. The Cochrane nonpharmacological interventions (based on cardiac rehabilitation) review for preventing vascular events after stroke/TIA[855] identified 1 pilot RCT of cardiac rehabilitation compared with usual stroke care (N=48), demonstrating promising and statistically significant gains in vascular risk profiles and cardiovascular fitness. A systematic review of lifestyle interventions in stroke identified this study and 2 others broadly matching cardiac rehabilitation in their format and concluded that, although meta-analysis was not possible, all studies were associated with significant improvements in health profiles and management of risk,[111] with this approach endorsed in the AHA/ASA physical activity and exercise recommendations for stroke survivors.[34] A recent prospective cohort study with a matched subgroup comparison (N=609) evaluated a Stroke Recovery Programme with 3 components: physician visits, outpatient therapy, and modified cardiac rehabilitation consisting of group therapy of 4 to 5 patients with stroke directed by a specially trained physical therapist and physical therapy assistant compared with usual rehabilitation. Nonrandomized subgroup

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analysis comparing Stroke Recovery Programme participants (n=76) and matched pairs of nonparticipants (n=66), in addition to functional gains, identified an age-adjusted HR of 0.11 (SE, 1.07 [95% CI, 0.01–0.90]; *P*=0.039) for the effect of participant group, suggesting that nonparticipants had a 9 times higher hazard of mortality.[844]

6. Although acknowledging that educating patients with stroke or TIA about their condition and the causes of their stroke is an important aspect of stroke care, evidence does not support its role in modifying health risk behaviors. The Cochrane review of interventions for improving modifiable risk factor control in the secondary prevention of stroke identified that patient education alone does not lead to improvements in modifiable risk factor control or the prevention of recurrent cardiovascular events.[829] The recent STANDFIRM trial (Shared Team Approach Between Nurses and Doctors for Improved Risk Factor Management for Stroke Patients; N=563) of specialist review and nurse education found no effect on attainment of cardiometabolic targets for secondary prevention.[845] Similarly, the ExStroke trial (N=314 ambulatory participants with stroke) identified that repeated encouragement with verbal instruction on being physically active over a 2-year period after stroke was not an effective means of increasing physical activity participation.[129]

Knowledge Gaps and Future Research

Current knowledge gaps in this area include the following:

- The optimal behavior change intervention to reduce recurrent stroke is unknown at present, as is the optimal window to deliver interventions of this nature.
- Multiple systematic reviews of lifestyle-based behavioral interventions identify an existing knowledge gap relating to the potential of the interventions reported to date to affect outcomes of recurrent stroke and other cardiovascular end points in the longer term, beyond the intervention period.[111,112,840]
- Many behavioral interventions in published trials after stroke fail to identify whether a behavior change theory underpinned the intervention delivered, making it difficult to ascertain successful and unsuccessful components of complex behavior change interventions.[849]
- A significant knowledge gap exists with respect to the specific or allied role of family caregivers and dyads in stroke secondary prevention in both the promotion and maintenance of health behaviors after stroke.

To address these shortfalls, future prospective, multicentered randomized controlled trials are required that consider and report the following:

- A clearly identified behavior change theory as a basis for intervention
- A documented time point after stroke for targeted intervention delivery
- A detailed intervention description that identifies the frequency and duration of the intervention, the personnel required to deliver the intervention, the intervention setting (eg, subacute care, community care, mixed), and the skill level and training in behavioral counseling of the interventionist
- Data collection that permits disaggregation by sex and other relevant characteristics to identify responders/nonresponders to intervention.

6.3. Health Equity

Recommendations for Health Equity
Referenced studies that support recommendations are summarized in online Data Supplement 65.

COR	LOE	Recommendations
1	C-EO	1. In patients with stroke or TIA, evaluating and addressing social determinants of health (eg, literacy level, language proficiency, medication affordability, food insecurity, housing, and transportation barriers) when managing stroke risk factors is recommended to reduce healthcare disparities.
1	C-EO	2. In patients with stroke or TIA, monitoring the achievement of nationally accepted, evidence-based performance measures is recommended to allow inequities to be identified and addressed.
1	C-EO	3. In patients with stroke or TIA, systematic adoption of the Agency for Healthcare Research and Quality Universal Precautions Toolkit for Health Literacy is recommended to integrate health literacy into the secondary prevention of stroke.
2b	B-R	4. In patients from urban, predominantly minority, or low-socioeconomic-status groups with stroke or TIA, the optimal intervention model for improving stroke risk factor control and reducing disparities is unknown.[815,856–859]

Synopsis

Certain populations have documented inequities in recurrent stroke risk and vascular risk factor control after stroke. Many of these inequities are caused and perpetuated by structural racism, defined as "the normalization and legitimization of an array of dynamics (historical, cultural, institutional and interpersonal) that routinely advantage White people while producing cumulative and chronic adverse outcomes for people of color."[860,861] Non-White populations have higher recurrent stroke risk,[862,863] are less likely to receive guideline-recommended secondary stroke prevention interventions,[864] and have poorer risk factor control after stroke.[10,13,819,865,866] Other populations at risk for inequities in risk factor control after stroke include women, rural dwellers, the elderly, immigrants, individuals with low socioeconomic status, and lesbian, gay, bisexual, transgender, and queer or questioning individuals.[20,867–873] Although standardizing

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care and increasing the consistency of care have been shown to reduce race/ethnic inequities in care,[874] special approaches may be required to actively reduce recurrent stroke risk in populations at risk for inequities and to address the underlying structural determinants of inequities. Several RCTs have tested secondary stroke prevention interventions in predominantly Black, Hispanic, and low-socioeconomic-status populations.[815,856–859] The optimal approaches for reducing recurrent stroke risk in high-risk populations are unclear; however, key strategies include evaluating and addressing social determinants of health, implementing evidence-based protocols, monitoring adherence to evidence-based guidelines on a population level, enhancing health and stroke literacy and self-management skills, and using the Agency for Healthcare Research and Quality Universal Precautions Toolkit of Health Literacy.

Recommendation-Specific Supportive Text

1. Socioeconomic inequalities are strong predictors of cardiovascular risk.[873] Interventions should be tailored to patients' socioeconomic and educational status, as well as cultural, work, and home environments.[19,875] Examples of upstream social determinants of health that affect treatment adherence and ASCVD health outcomes include comorbid mental illness, lack of health literacy, exposure to adversity (eg, home/community violence, trauma exposures, safety concerns), financial strain, inadequate housing conditions, lack of food security (ie, access to affordable and nutritious food), structural and individual discrimination, and inadequate social support.[876] The Centers for Medicare & Medicaid Services has developed a screening tool to assess 5 domains of non–health-related measures that affect health outcomes: housing instability, food insecurity, transportation difficulties, utility assistance needs, and interpersonal safety.[877]
2. In 2010, the National Institute of Neurological Disease and Stroke convened an expert panel to provide recommendations on key priorities for health disparities research in stroke. One recommendation was to use population-based surveillance to assess achievement of evidence-based guidelines.[878] Alliances with the federal government through the National Institute of Neurological Disease and Stroke, Centers for Disease Control and Prevention, nonprofit organizations such as the AHA/ASA, and medical specialty groups such as the American Academy of Neurology and the Brain Attack Coalition are needed to coordinate, develop, and optimize implementation of evidence-based stroke prevention recommendations.[9]
3. The AHRQ Universal Precautions Toolkit for Health Literacy[879] is a publicly available document that includes a 21-step approach to ensuring that written and oral instructions to patients are clear, understandable, and sensitive to health literacy. Healthcare providers who listen, speak slowly, use nonmedical language, encourage questions, apply teach-back methods, address language differences, are culturally competent, and incorporate graphics in their teaching promote a culture sensitive to health literacy.[880]
4. Several RCTs have tested secondary stroke prevention interventions in predominantly Black, Hispanic, and/or low-socioeconomic-status populations.[815,856–859] In all trials, primary outcomes improved in the intervention and control groups without significant differences between the 2 arms. A few of the trials showed improvement in secondary outcomes or subpopulations. The SUSTAIN trial (Systemic Use of Stroke Averting Interventions) of a culturally tailored Chronic Care Model–based intervention (incorporating advance practice provider delivery of evidence-based care, protocols, real-time decision support, self-management support, and education) in a multiracial/multiethnic population in a safety-net setting showed better LDL control (secondary outcome) in the intervention arm; intervention participants were more likely to lower LDL <100 md/dL compared with control subjects (OR, 2.0 [95% CI, 1.1–3.5]).[815] In the PRAISE trial (Prevent Recurrence of All Inner-City Strokes Through Education) of peer-led community-based poststroke self-management workshops in the inner city, the primary composite outcome of BP, LDL, and antithrombotic use at 6 months was not different in the intervention and control arms, but a higher proportion of those randomized to the intervention had controlled BP at 6 months (76% versus 67%; P=0.02).[858] Finally, a subgroup analysis of Hispanic individuals enrolled in the DESERVE trial (Discharge Educational Strategies for Reduction of Vascular Events), evaluating the efficacy of a culturally tailored skills-based intervention, revealed a 9.9–mm Hg greater reduction in SBP compared with control.[857]

Knowledge Gaps and Future Research

Numerous RCTs of culturally tailored complex secondary stroke prevention interventions in populations at high risk for inequities have failed to show a clear improvement in primary outcomes compared with usual care. Further research is needed to determine optimal strategies for reducing inequities in risk factor control after stroke. Key populations at risk for inequities include those from Black, Hispanic, and indigenous backgrounds; women; the elderly; immigrants; lesbian, gay, bisexual, transgender, and queer or questioning individuals; and those with low income, low educational attainment, limited English proficiency, unstable housing, inadequate social support, concurrent substance abuse, comorbid psychiatric illness, or history of incarceration. Although epidemiological studies have elucidated race/ethnicity–, age-, and sex-specific disparities in risk factor control after stroke, less is known about risk factor control among other

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vulnerable populations at risk for inequities. Specific gaps and areas for future research include the following:

- A more thorough understanding of which populations have inequities in risk factor control after stroke.
- A more nuanced understanding of the drivers of inequities in risk factor control after stroke, including social determinants of health and structural racism.
- Strategies for improving risk factor control among groups at risk for inequities.
- Strategies for addressing social determinants of health among stroke survivors.

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ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Disclosures

Appendix 1. Writing Group Relationships With Industry and Other Entities (Relevant): 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Dawn O. Kleindorfer	University of Michigan	NIH (epidemiology of stroke)†	None	None	None	None	None	None
Amytis Towfighi	University of Southern California	NIH/NINDS (secondary stroke prevention trial)†	None	None	None	None	None	None
Seemant Chaturvedi	School of Medicine, University of Maryland	Boehringer-Ingelheim (grant support)*	None	None	None	None	None	NINDS (executive committee CREST 2)*
Kevin M. Cockroft (AANS/CNS WG Representative)	Penn State Hershey Medical Center	Medtronic (PI for multi-institution study)†; Nico Corp (PI for multi-institution study)†	Intersocietal Accreditation Commission (Board of Directors)*	None	None	Actuated Medical*	Medtronic†; Minnetronix*	None
Jose Gutierrez	Columbia University Medical Center	NIH (PI in research grant)†	None	None	Hanna, Campbell & Powell, LLP*; Heidell, Pittoni, Murphy & Bach, LLP*; Aaronson Rappaport*; Johnson, Graffe, Keay, Moniz & Wick*; Luca Law, PLLC*	None	None	None
Hooman Kamel	Weill Cornell Medical College	BMS (BMS provides in-kind study drug [apixaban/aspirin/placebo] for ARCADIA trial, of which he is co-PI)†; Boehringer Ingelheim (Endpoint Adjudication Committee for a trial of empagliflozin)†; Medtronic (unpaid Steering Committee member of STROKE AF Trial)*; NIH/NINDS (co-PI of ARCADIA trial, PI of LANTERN observational study of atrial cardiopathy and racial disparities in stroke, coinvestigator of a stroke policy simulation model project)†; Roche Diagnostics (Roche Diagnostics provides in-kind study assay kits [NT-proBNP] for ARCADIA trial, of which he is co-PI)†; Clinical Endpoint Adjudication Committee for an RCT related to empagliflozin, a diabetes drug. The trial sponsor is Boehringer-Ingelheim. I am contracted to do this through Quintiles†	None	None	None	None	None	None
Walter N. Kernan	Yale School of Medicine	None	None	None	None	None	None	None
Steven J. Kittner	Veterans Affairs Maryland Health Care System; University of Maryland School of Medicine	R01NS100178 (analysis grant of SiGN, an established ischemic stroke genetics consortium)†; R01NS105150 (establishes a new consortium for the study of the genetics of early-onset ischemic stroke)†; 2U01NS036695-15A1 (genetic and environmental risk factors for hemorrhagic stroke)†; R01 NS086905-01 (established automated pipeline for extracting MRI brain imaging phenotypes and mapping genes associated with variation in these traits)*; Regeneron (no personal research support at present but discussing joint research involving exome sequencing of ischemic strokes in young adults internationally)*	None	None	None	None	None	None

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Appendix 1. Continued

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Enrique C. Leira	University of Iowa, Hospitals and Clinics	NIH/NINDS salary support through U24 and R21 grant mechanisms)†; Keystone Heart (performed local neurological assessments as a local co-PI in a cardiology trial)*; Edwards Lifesciences (performed local neurological assessments as a local co-PI in a cardiology trial)*; Bayer AG and Jansen LLC (was the local PI for the NAVIGATE-ESUS trial)*; ZZ Biotech (consulting in the RHAPSODY acute trial proposal that will be submitted to NIH)*; NIH-Fred Hutchinson Research Center (adjudicate stroke events for the WHI NIH Study)*	None	None	None	None	None	None
Olive Lennon	University College Dublin, School of Public Health, Physiotherapy and Sports Science, Health Sciences Centre (Ireland)	EU MSCA (research exchange programme grant)*; UCD (seed funding dissemination grant)*	None	None	None	Cft Recruitment Ltd registration No. 642571*; Cft Recruitment Ltd registration No. 642571 (immediate family members)†	None	None
Debbie Lombardi-Hill (patient representative)	Self-employed	Vanderbilt University Medical Center (consultant to a PCORI-funded Comparative Effectiveness Trial for Stroke Post-Acute Care)*	None	None	None	Lombardi Hill Consulting Group, LLP†; Stroke Challenges, LLC*	None	Lombardi Hill Consulting Group, LLP (owner/ principal)†; Stroke Challenges, LLC (cofounder/ co-owner)*
James F. Meschia	Mayo Clinic	NINDS (Crest-2 Trial; he is one of 3 co-PIs for this trial that compares revascularization with and without intensive medical management. The trial is funded by NINDS. His support is funding for salary substitution to devote ≈30% of his effort to the trial)†	None	None	None	None	None	None
Thanh N. Nguyen	Boston Medical Center	Medtronic (PI Clear Study)*	None	None	None	None	None	None
Peter M. Pollak	Mayo Clinic	None	None	None	None	None	None	None
Pasquale Santangeli	Hospital of the University of Pennsylvania	None	None	Abbott Medical*; Biosense Webster*; Biotronik*; Medtronic*	None	None	Abbott Medical*; Baylis Medical*; Biosense Webster*	None
Anjail Z. Sharrief	University of Texas Medical School at Houston	None	Omron (donation of blood pressure machines for clinical care and research)*	None	None	None	None	None
Sidney C. Smith Jr	University of North Carolina	None	None	None	None	None	None	None
Tanya N. Turan (AAN WG Representative)	Medical University of South Carolina	Sanofi-Regeneron (alirocumab is donated to the CREST2, for which she is the director of medical management)†	None	None	None	None	Boehringer Ingelheim*; Gore*; Pfizer†	None
Linda S. Williams	Roudebush VA Medical Center	VHA (VA HSR&D PI)†	None	None	None	None	None	None

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*Modest.

†Significant.

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Appendix 2. Peer Reviewer Relationships With Industry and Other Entities (Comprehensive): 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

Peer reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Mary Amatangelo	Massachusetts General	None	None	None	None	None	None	None
Hugo Aparicio	Boston University School of Medicine	American Academy of Neurology Career Development Award†	Alzheimer's Association Research grant†	None	None	None	None	None
Negar Asdaghi	University of Miami	None	None	None	None	None	None	None
Devin Brown	University of Michigan	NIH†	None	Grand Rounds Honorarium–The Ohio State University*	None	None	None	AHA*
Askiel Bruno	Medical College of Georgia at Augusta University	NINDS†; Georgia Rehabilitation Foundation†	None	Abbott Pharma*	None	None	None	None
Cheryl Bushnell	Wake Forest Baptist Health	None	None	None	None	Care Directions, LLC*	ZZ Biotech, Clinical Advisory Committee for RHAPSODY II trial*	None
Dominique Cadilhac	Monash University	Amgen (paid to Institution)†	None	None	None	None	None	Medtronic (donation paid to Institution)*
Clay Cauthen	University of Texas	None	None	Novartis*	None	None	None	None
Tiffany Chen	University of Pennsylvania	None	None	None	None	None	None	None
Ephraim Church	Penn State Health	None	None	None	None	None	None	None
John Cole	University of Maryland	NIH/NINDS R01*	None	None	None	None	None	None
Gioacchino Curiale	Boston University Neurology Associates	None	None	None	National Medical Consultants PC*	None	None	None
Mary Cushman	None	None	None	None	None	None	None	None
Alexandra Czap	McGoven Medical School, University of Texas	NIH†	None	None	None	None	None	None
Colin Derdeyn	University of Iowa	None	None	None	None	None	None	None
Marco R. Di Tullio	Columbia University	NIH/NINDS†	None	None	None	None	None	None
Kenneth Gaines	Vanderbilt University Medical Center	PCORI: C3FIT National PI†; USDA Distance Learning and Telemedicine Grant†	None	None	Expert witness for medical malpractice*	Stroke Link Health†	None	None

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Peer reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/advisory board	Other
Philip B. Gorelick	Michigan State	Local Site PI for C3FIT recurrent stroke prevention trial funded by PCORI†	None	None	None	None	None	Bayer*; Novartis*
Virginia Howard	University of Alabama at Birmingham	NIH†	None	None	None	None	None	None
Judy Huang	Johns Hopkins University	None	None	None	Weber Gallagher*	Longeviti*	None	None
Silvio Inzuccchi	Yale School of Medicine	None	None	None	None	None	Boehringer Ingelheim*; AstraZeneca†; Novo Nordisk†; Merck*	None
Ashutosh Jadhav	Barrow Brain and Spine Institute	None	None	None	None	None	None	None
Salomeh Keyhani	University of California, San Francisco	None	None	None	None	None	None	None
Anthony Kim	University of California San Francisco	SanBio†	None	None	Consultant*	None	None	None
Christopher Kramer	University of Virginia	Regeneron†	None	None	None	None	None	None
Sandeep Kumar	Beth Israel Deaconess Medical Center; Harvard Medical School	NIH/NINDS†	None	None	None	None	None	None
Lester Y. Leung	Tufts Medical Center	NIH†	None	None	None	None	None	None
Helmi Lutsep	Oregon Health & Science University	None	None	None	None	None	BMS*; Axiomatic–SSP trial*; Coherex Medical–Physician Advisory Board for Wavecrest*; NINDS/Mayo–Stroke Adjudication Committee for CREST2*; Medscape Neurology*	Modest*
Alice Ma	Royal North Shore Hospital	None	None	None	None	None	None	None
Prachi Mehndiratta	University of Maryland	None	None	None	None	None	None	None
J. Mocco	Mount Sinai Health System	Microvention†; Penumbra†; Stryker†	None	None	None	BlinkTBI†; Cerebrotech†; Corindus†; Echovate†; Endostream†; Imperative Care†; Medtronic†; NTI†; Rebound Therapeutics†; RIST†; Serenity†; Spinaker†; Synchron†; Truvic†; Vastrax†	Cerebrotech†; Corindus†; Endostream†; Imperative Care†; Rebound Therapeutics†; Synchron†; Vastrax†; Viseon†	DePuy Synthes (F&B)*
Sara Partington	University of Pennsylvania	None	None	None	None	None	None	None
Aman Patel	Massachusetts General Hospital	Siemens†	None	None	None	None	Microvention†; Medtronic*; Penumbra*	None
Sabrina Phillips	Mayo Clinic	None	None	None	None	None	None	None
Aleksandra Pikula	University of Toronto	Canadian Institute of Health Research*	Canadian Stroke Consortium*	None	None	None	None	None

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Raymond Reichwein	Penn State Health	Athersys†	None	None	None	None	None	None
Gustavo Rodriguez	Texas Tech School of Medicine	None	None	None	None	None	None	None
Christianne Roumie	VA Tennessee Valley Healthcare System; Vanderbilt University	VA†; CSRD†; NIH/NHLBI†; AHRQ†; PCORI†	None	None	None	None	None	None
Julie Shulman	Boston University Medical Center	NIH†	None	None	None	None	None	None
Jason Sico	Yale University	VA†	None	None	None	None	None	None
James Siegler	Cooper University Hospital	None	None	None	None	None	Ceribell†	None
Brian Silver	University of Massachusetts Medical School	None	None	None	Law firms for expert review†	None	Women's Health Initiative review and committee work*; Best Doctors, Inc. case reviews*	Honoraria for reviews for Ebix, MedLink, Medscape*
Eric Smith	University of Calgary†	Canadian Institutes of Health Research†; Brain Canada†	University of Ottawa Heart Institute†; McMaster University†	None	None	None	Bayer*; Biogen*; Cyclerion*; Javelin*	UpToDate*
Farzaneh Sorond	Feinberg School of Medicine Northwestern University	None	None	None	None	None	None	None
Barney Stern	Johns Hopkins University	None	None	None	None	None	None	None
Jeffrey Switzer	Augusta University	None	None	None	None	None	None	None
Stavropoula Tjoumakaris	Thomas Jefferson University	None	None	None	None	None	None	None
Stanley Tuhrim	Mount Sinai Hospital	None	None	None	None	None	None	None
David Wang	Barrow Neurological Institute	None	None	Boehringer Ingelheim*	None	None	None	None
Babu Welch	University of Texas Southwestern Medical Center	None	None	Stryker Neurovascular*	None	None	Medtronic; Microvention*; Stryker Neurovascular*	Peter Lazic*
Deborah J. Wexler	Massachusetts Hospital and Harvard Medical School	NIDDK†	None	None	None	None	None	Novo Nordisk*
Daniel Woo	University of Cincinnati	NIH†	None	None	None	None	None	None
Bradford Worrall	American Academy of Neurology	NIH†	None	None	None	None	None	None
Henry Klar Yaggi	Yale School of Medicine	None	None	None	None	None	None	None
Richard Zweifler	Tulane University	None	None	None	None	None	None	None

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*Modest.

†Significant.

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the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery [published corrections appear in *Circulation*. 2011;124:e146 and *Circulation*. 2012;126:e26]. *Circulation*. 2011;124:e54–e130. doi: 10.1161/CIR.0b013e31820d8c98

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