INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Secondary Prevention of Stroke***
-April 2023-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) conducted a broad evidence-based review of pharmacologic interventions for the prevention of stroke recurrence after a first stroke or transient ischemic attack (TIA). Medication classes considered included antihypertensives, glucose lowering agents, antithrombotics, and lipid lowering agents. On the basis of this review, **the NPTC made no modifications** to the IHS National Core Formulary.

Discussion:

Americans experience over 1.2 million cerebrovascular events each year, including ischemic and hemorrhagic strokes and TIAs. Of these, approximately 183,000 are recurrent strokes. The CDC data extracted from the National Vital Statistics System suggest that stroke death is less common in American Indian/Alaska Native (AIAN) persons than in whites.[1] However, a 2019 study which included a patient cohort from the Strong Heart Study showed higher 30-day and 1-year mortality rates after stroke in AIAN patients compared to both black and white patient populations.[2]

This review examined studies which formed the basis for many of the strongest recommendations in recent guideline updates published from the American Heart Association/ American Stroke Association (AHA/ ASA) (2021) and the European Stroke Organization (ESO) (2022).[3,4]

Blood pressure reduction: The AHA/ASA strongly recommend blood pressure lowering with a target of (<130/<80) "for most patients to reduce the risk of stroke and vascular events." The ESO makes only a weak recommendation for the more intensive target. The 2001 PROGRESS Trial first demonstrated that blood pressure lowering specifically in the setting of secondary stroke prevention reduced major adverse vascular events by 26% vs placebo (ARR 4.1% vs 5.5%) using a combination ACE inhibitor and a thiazide diuretic.[5] More recent meta-analyses have added support to the value of this intervention. A 2018 Cochrane review of 8 RCTs showed a 19% risk reduction (95% CI: 0.70 to 0.93) primarily using thiazides and renin-angiotensin system inhibitors (RASi), though no conclusions could be drawn for blood pressure targets.[6] A similar risk reduction was seen in a review conducted by the ESO for its 2022 guideline, analyzing 9 RCTs comparing active treatment to placebo (OR 0.81, 95% CI: 0.71 to 0.92, *p*=0.002). In a concurrent analysis of 3 RCTs, the ESO concluded that the evidence for a treatment target of <130/80 was weak but significant (OR 0.79, 95% CI: 0.64 to 0.98, *p*=0.029). In a 2013 meta-analysis of 270,000 participants in 31 RCTs, Chen et al. showed that calcium channel blockers (CCBs) were similarly effective to ACE inhibitors and diuretics in preventing stroke, suggesting applicability for secondary prevention.[7] Subgroup analysis in the PROGRESS trial showed that patients with hemorrhagic stroke also had a significant 49% relative risk reduction for stroke of any kind, and a 2022 ESO meta-analysis of 2 trials showed a significant risk reduction for intensive vs. less intensive blood pressure targets (OR 0.25, 95% CI: 0.07 to 0.90, *p*=0.033).

Antithrombotic therapy: Long-term, single-antiplatelet therapy (SAPT) benefits most patients after non-cardioembolic ischemic stroke. Recent evidence supports use of early short-term dual-antiplatelet therapy (DAPT) recommended by both AHA/ ASA and ESO in the setting of high-risk TIA (ABCD2 score ≥ 4) and minor ischemic stroke, where the risk of early post-stroke bleeding is low (NIHSS score ≤ 3). This is anchored in the 2018 POINT Trial, in which recurrent ischemic events occurred in 5.0% of those receiving clopidogrel + ASA, compared with 6.5% of those receiving ASA + placebo (HR 0.75, 95% CI: 0.59 to 0.95; *p*=0.02), although with a higher rate of serious bleeding over the 90-day treatment period.[8] Pooled analysis of patient-level data from POINT and CHANCE (a 2013 Chinese trial evaluating the same intervention for secondary prevention) showed that 21 days of DAPT was no less beneficial than 90 days.[9] In a 2021 meta-analysis, Trifan et al. showed that risk of major bleeding with up to 30 days of DAPT was comparable to SAPT.[10] The ESO recommends 21 days of DAPT, while AHA/ASA recommend 21-90 days in this setting. Those with high-grade symptomatic intracranial artery stenosis may benefit from 90 days of DAPT based on the SAMMPRIS 2011 trial, which showed harm with intracranial stenting. All patients with atrial fibrillation should be anticoagulated with a direct oral anticoagulant except in the setting of a mechanical valve or moderate-to-severe rheumatic mitral stenosis, where warfarin is preferred. After hemorrhagic stroke, the benefit of starting or restarting antiplatelet therapy or anticoagulation must be individualized based on a balancing other vascular risk factors against the risk of re-bleeding.

Lipid lowering: The AHA/ASA recommends treatment with high-dose atorvastatin based in part on the 2006 SPARCL trial, in which 4731 patients without known cardiovascular disease were randomized to receive 80 mg atorvastatin or placebo following non-cardioembolic ischemic stroke or TIA. After 4.9 years of follow-up, 11.2% receiving atorvastatin and 13.1% receiving placebo had a fatal or nonfatal stroke (5-year ARR: 2.2%, HR 0.84, 95% CI: 0.71 to 0.99, *p*=0.03;

unadjusted p=0.05).[11] The results of the 2020 Treat Stroke to Target trial and post-hoc analysis of other trials, including SPARCL, form the basis for AHA/ASA and ESO guideline recommendations to target an LDL-c of <70 mg/dL. ESO meta-analyses, which included subgroup analysis of cardiovascular prevention trials, showed that use of statin therapy may cause six hemorrhagic strokes per 1000 people treated but prevent 40 major cardiovascular events.[4] Statin use must be individualized after hemorrhagic stroke.[12]

Glucose lowering: Both the ESO and AHA/ASA recommend an A1c treatment target of <7% for most diabetic patients after stroke while acknowledging the lack of evidence for prevention of macrovascular outcomes, including stroke, and the need to individualize targets in frail or older patients. Both guidelines weakly recommend the use of pioglitazone for stroke prevention in insulin resistant or diabetic patients based on the 2016 IRIS trial[13], with AHA/ASA strongly recommending use of medicines with "proven cardiovascular benefit." The 2016 SUSTAIN-6 trial of semaglutide versus placebo showed a 2.3% ARR reduction in MACE (HR 0.74, 95% CI: 0.58 to 0.95; p<0.001 for non-inferiority), including a 1.1% reduction in nonfatal stroke (HR 0.61, 95% CI: 0.38 to 0.99; p=0.04).[14]

Findings:

Modifiable risk factors are implicated in as high as 90% of strokes. AIAN patients have higher rates of early mortality after stroke than black and Caucasian populations. Evidence supports high-level, guideline-directed recommendations for secondary prevention of stroke and TIA. Long-term blood pressure reduction to a target of <130/80 prevents ischemic and hemorrhagic stroke recurrence, if it can be safely achieved. Thiazide diuretics, RAS-inhibitors, and CCBs are the initial preferred agents. Long-term antiplatelet therapy is recommended for patients with non-embolic ischemic stroke, and 21-90 days of DAPT (clopidogrel and low-dose ASA after initial early loading) is standard-of-care after low-risk stroke or high-risk TIA. Anticoagulation is recommended after most embolic strokes, provided there is an identifiable source. Lipid lowering is recommended after an initial non-embolic ischemic stroke or TIA using statin therapy to target an LDL-c of <70 mg/dL. Though high-quality evidence for intensive glucose lowering to prevent stroke does not exist, evidence suggests benefit for pioglitazone or glucagon-like peptide-1 receptor agonists, and an A1c target to prevent microvascular disease remains safe in many patients after stroke. The IHS National Core Formulary currently includes the principal agents needed for guideline-directed secondary prevention of stroke in primary care, therefore no changes were recommended.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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