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REVIEW

Secondary Ischemic Stroke Prevention

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Abstract
The health burden of ischemic stroke is high and will continue to increase with an aging population. Recurrent ischemic stroke is increasingly recognized as a major public health concern with potentially debilitating sequelae. Thus, it is imperative to develop and implement effective strategies for stroke prevention. When considering secondary ischemic stroke prevention, it is important to consider the mechanism of the first stroke and the related vascular risk factors. Secondary ischemic stroke prevention typically includes multiple medical and, potentially, surgical treatments, but with the shared goal of reducing the risk of recurrent ischemic stroke. Providers, health care systems, and insurers also need to consider the availability of treatments, their cost and patient burden, methods for improving adherence, and interventions that target lifestyle risk factors such as diet or activity. In this article, we discuss aspects from the 2021 AHA Guideline on Secondary Stroke Prevention as well as highlight additional information relevant to best practices for reducing recurrent stroke risk.

Keywords Stroke · Randomized clinical trial · Secondary stroke prevention

Introduction

Stroke is the second leading cause of death worldwide, and it is characterized by high morbidity. Approximately 50% of stroke survivors are chronically disabled, and, thus, the public health burden of stroke is immense [1]. Ischemic stroke occurs when the blood flow to an area of the brain is restricted or blocked as a result of stenosis or occlusion of an artery either in the neck or brain. Hemorrhagic stroke, in contrast, is the result of rupture of a blood vessel and bleeding into the brain or on the brain's surface [2]. Because hemorrhagic stroke has distinct mechanisms of disease and prevention strategies, the focus of this article will be ischemic stroke, which is subsequently referred to as "stroke."

The risk of stroke doubles every ten years after 55 years of age. With an aging population, the prevalence of stroke will continue to increase over the next two decades [3]. One quarter of the ~ 700,000 ischemic strokes a year in the USA are recurrent strokes [4, 5]. Patients who have suffered a recurrent stroke are twice as likely to die and have worse functional outcome compared to patients with a first-ever stroke [6–9]. In addition, the hospitalization cost is twice as high for recurrent stroke compared to first ever stroke [10]. Although in this review we delineate the terms stroke and TIA separately, it is important to note that the utility of the diagnosis of TIA in this context has come under question, suggesting that the entities are equivalent when considering risk of recurrence and secondary prevention [11].

Secondary stroke prevention is distinct from primary stroke prevention because it necessitates attention to the clinical features of the initial stroke, such as the type of stroke, the mechanism, and the recognition of any contributing medical comorbidities [12]. Prevention approaches begin with identifying the most likely possible mechanism of the first stroke and optimizing the associated modifiable risk factors. The management of these risk factors is a multifaceted process and typically includes both lifestyle modifications, such as increasing aerobic activity and eating a more nutritious diet, as well as the administration of lipid lowering, blood pressure lowering, and antithrombotic medications [13]. Stroke prevention can be reasonably achieved by addressing modifiable risk factors [14]. Unfortunately, these risk factors are poorly controlled for the majority of the population and typically remain poorly controlled in many who have suffered a primary stroke [15].

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Diagnostic Evaluation

After the identification of a stroke or TIA, patients require a diagnostic evaluation to understand the mechanism of the stroke, ideally within 48 h of the suspected onset of the event [16]. The goal of this diagnostic evaluation is to tailor treatments to the patient to lower the risk of recurrent stroke. Providers should perform a CT or an MRI of the brain to ensure that the diagnosis of stroke is substantiated [17]. A laboratory workup is important, including a complete blood count, prothrombin time, partial thromboplastin time, random or fasting glucose level, HbA1c, kidney function tests, and a fasting lipid profile. These lab results can provide insights into risk factors that warrant treatment to lower the risk of recurrent stroke [18]. Additionally, providers should perform an ECG to screen for cardiac arrhythmias, primarily atrial fibrillation, and a transthoracic echocardiogram to evaluate for valvular abnormalities, intracardiac thrombus, or patent foramen ovale (indicated in individuals aged ≤ 60) [19, 20].

A typical stroke workup also includes noninvasive angiography with CT angiography or magnetic resonance angiography, although ultrasound of the arteries in the neck and brain is a potential alternative. Digital subtraction angiography is usually reserved for situations where noninvasive studies are inconclusive. Angiographic tests allow for the identification of potential arterial stenosis, thromboses, dissection, or other vasculopathies [21]. In selected patients, who lack a clear diagnosis at the end of this testing, or those designated to have an embolic stroke of undetermined source (ESUS), extended cardiac monitoring for weeks to years may be indicated, to increase the yield of atrial fibrillation diagnosis [20, 22, 23].

Major Risk Factors

The major risk factors for stroke are delineated into two subcategories, those that are modifiable and those that are not modifiable [24]. Note that when evidence from a randomized clinical trial (RCT) is provided, this is accompanied by the inclusion of an RCT identifier.

Modifiable Risk Factors

Among the modifiable risk factors are hypertension, hyperlipidemia, diabetes mellitus, smoking, physical inactivity, poor diet, and obesity. Hypertension is typically regarded as the most important of the modifiable risk factors for stroke [25]. Hypertension causes recurrent stroke through mechanisms that span every organ system and stroke etiology [26]. Hyperlipidemia, which can be both an acquired or a genetic trait, is associated with higher risk of ischemic stroke [27]. An increased level of cholesterol in the blood can lead to the buildup of atherosclerosis in arteries, which can cause stroke either through reduced blood flow, occlusive disease, or the formation of thromboemboli.

Another major risk factor for stroke is diabetes mellitus, both types 1 and 2 [28]. The morbidity of diabetes occurs through both macrovascular and microvascular disease, which respectively refers to large vessel atherosclerosis and the complications of neuropathy, nephropathy, retinopathy, and chronic microvascular disease of the brain including lacunar infarctions [29]. For the vast majority of patients, particularly those < 65 years of age, it is recommended to achieve a hemoglobin A1c (HbA1c) that is less than 7% [30]. Diabetes is associated with a twofold higher risk of stroke [31], and there is a U-shaped association of HbA1c and stroke risk, which is further pronounced for patients that are using antidiabetic, antihypertensive, or lipid-lowering medications [32]. Diabetics can reduce the risk of recurrent stroke through both medication usage and the implementation of behavioral practices that lead to better glucose control.

Active smoking causes atherosclerosis, raises blood pressure, and can trigger episodes of atrial fibrillation, all of which increase the likelihood of experiencing a stroke [33]. For patients who have experienced a stroke or TIA that continue to smoke tobacco, it is recommended that they seek counseling, which may or may not include drug therapy, to aid in quitting smoking [34]. Similarly, patients who have experienced a primary stroke or TIA that consume more than two alcoholic beverages daily for men or more than one for women should seek to reduce their consumption of alcohol to limit the risk of experiencing a second stroke [35].

Physical inactivity is also associated with an increased risk of stroke through a variety of mechanisms. In general, being sedentary leads to an overall decline in health that can indirectly contribute to experiencing a stroke [25]. Conversely, increased physical activity lowers the risk of cardiac events and other vascular issues such as stroke [36]. A study performed by the Cooper Clinic assessed the relationship between cardiovascular fitness and stroke mortality in healthy men aged 40–87 with up to a decade of follow-up. They discovered an inverse relationship such that those in the highest activity group were determined to experience a 68% lower risk of stroke and subsequent death than those in the lowest fitness group [37].

Specifically for the prevention of recurrent stroke, patients that remain capable of performing physical activity after their first stroke or TIA should engage in moderate intensity aerobic activity for a minimum of 10 min, four times a week, or they can choose to engage in vigorous-intensity aerobic activity for a minimum of 20 min, twice a week [38]. Furthermore, it has been

shown that performing physical activity post-stroke leads to improvements in cognitive function, including a general improvement in cognitive performance (Hedges' g [95% CI] = 0.304 [0.14–0.47]) and improvements in attention and processing speed (Hedges' g [95% CI] = 0.37 [0.10–0.63]). The greatest cognitive gains have been shown to result from exercise regimens that include both aerobic and strength training (Hedges' g [95% CI] = 0.43 [0.09, 0.77]) [39].

While performing physical activity has numerous benefits of its own, pairing this activity with a balanced and healthy diet leads to further improvements in health. Following a healthy diet is associated with the prevention of vascular events, and balanced nutritional plans such as the Mediterranean diet help in the prevention and treatment of atherosclerotic cardiovascular disease (ASCVD) [40]. A high adherence to this diet has been shown to reduce the risk of cerebrovascular events [relative risk (RR) 0.71, 95% CI 0.57–0.89] [41]. This diet emphasizes the consumption of monounsaturated fats, primarily fish, extra virgin olive oils, and plant-based foods such as nuts [42]. Increasing the consumption of fruits and vegetables has also been shown to be beneficial in preventing stroke [relative risk reduction (RRR) 0.79, 95% CI 0.71–0.84] [43]. Additionally, for hypertensive individuals who have suffered a stroke or TIA, restricting the intake of dietary sodium by approximately a gram a day has been shown to be beneficial in preventing recurrent stroke [44]. Specifically, individuals who consume ≥ 4 g of sodium per day display an increased risk of stroke (HR = 2.59; 95% CI = 1.27–5.28) than those who consume ≤ 1.5 g/day [45].

A final major modifiable risk factor for stroke is obesity or high body mass index (BMI). Obesity is a complex pathology that has both genetic and lifestyle components. By using medication and lifestyle modification to control obesity, patients can reduce their risk of stroke and ASCVD [46]. The reduction in weight helps indirectly, by improving risk factors including blood pressure and cholesterol levels [21]. More recently metabolic health in concert with BMI is being investigated in relation to stroke risk and cardiovascular disease [47]. In general, metabolically unhealthy obese individuals have an increased risk of ischemic stroke (hazard ratio, 1.30 [95% CI, 1.09–1.56]), compared to metabolically healthy participants with a normal BMI [48]. The current literature supports that for patients who have had a stroke or TIA and are obese, it is recommended that they undergo a comprehensive behavioral lifestyle modification program to achieve and sustain significant weight loss and improve fitness [49].

These modifiable risk factors, their importance, and treatments are summarized in Table 1.

Non-modifiable Risk Factors

Among the non-modifiable risk factors for stroke is age. Advanced age remains the most significant risk factor for stroke [50]. Additionally, there are racial and ethnic factors that predispose an individual to stroke. Black patients have a higher risk of stroke than White patients [51]. This increased risk is shown to be due to the influence of social determinants of health and well-being rather than inherent biology [52]. The sex of an individual also affects their risk of stroke, where for the vast majority of ages, men have a higher risk of experiencing a stroke than women [53]. However, because women live longer than men, the lifetime rate of stroke for women is higher. Family history of stroke, heart disease, and any other heritable vascular disease are also a risk factor of stroke [54]. Although stroke prevention does not particularly focus on these risk factors as they are non-modifiable, they are important considerations in the assessment of stroke risk and are potential considerations in shaping the treatment plan.

When considering secondary stroke prevention, patients who had minimal risk factor management prior to the first stroke warrant a stronger emphasis on managing risk factors and potentially more medical follow-up and exposure to healthcare. However, if an individual has few risk factors or the risk factors are well managed prior to the experience of a first stroke, then a broader approach towards considering all potential risk factors is necessitated [55].

Medical Treatment

Antithrombotic Therapy

Antithrombotic therapy is the use of antiplatelet and/or anticoagulant medications to block the formation of clots. Considering the administration of these agents on a short- or long-term course is an important step in the secondary prevention of stroke [21]. For non-cardioembolic stroke, antiplatelet therapy is recommended. Although 3 weeks to 3 months of dual anti-platelet therapy (aspirin combined with clopidogrel) is beneficial in mild stroke and high-risk TIA [56] or symptomatic intracranial atherosclerosis [57], trials of longer term dual antiplatelet therapy for secondary stroke prevention have consistently shown either no benefit or harm [58–60]. For these reasons, long-term antiplatelet monotherapy is the treatment of choice for secondary stroke prevention in patients with non-cardioembolic stroke.

Aspirin, aspirin-extended release dipyridamole, or clopidogrel are all acceptable choices. In the study by Antiplatelet Trialists' Collaboration, aspirin as an agent of long-term antiplatelet monotherapy decreased the risk of subsequent

Table 1 Summary of modifiable risk factors for secondary stroke, their importance, and treatment

Risk factor	Importance	Treatment
Hypertension	Hypertension damages blood vessels and makes an individual more likely to have a stroke. The goal BP for hypertensive individuals is less than 130/80	Anti-hypertensive therapy: administration of a thiazide diuretic, angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, or calcium channel antagonist
Hyperlipidemia	An increased level of cholesterol in the blood can lead to the buildup of atherosclerosis in arteries, which can cause stroke either through reduced blood flow, occlusive disease, or the formation of thromboemboli. The goal LDL cholesterol for stroke survivors is < 70 mg/dL	If LDL cholesterol greater than 100 mg/dL, it is recommended to take a high intensity statin such as 80 mg of atorvastatin or 20–40 mg of rosuvastatin. Recheck cholesterol level 4 to 12 weeks after starting statin and every 3–12 months thereafter. If patient not at goal LDL consider ezetimibe or PCSK9 inhibitor
Type II Diabetes	Morbidity occurs through both macrovascular and microvascular disease, which respectively refers to atherosclerosis and the complications of neuropathy, nephropathy, retinopathy, and chronic microvascular disease of the brain including lacunar infarctions. For the vast majority of patients, particularly those < 65 years of age, it is recommended to achieve a HbA1c that is less than 7%	Oral or injectable hypoglycemic drugs and insulin are proven methods to achieve glycemic control. Of the many medication classes for treating T2DM, thiazolidinedione and glucagon-like-1 receptor agonists have proven benefit for stroke prevention. Recommended that patients establish care in a multimodal diabetes clinic and seek nutritional and lifestyle therapy and obtain a basic education on self-managing glucose level
Atrial fibrillation	Atrial fibrillation (AF) is an age-related condition that often exists before primary stroke and predisposes one to stroke recurrence. The condition may also develop after primary stroke and lead to a higher risk for recurrent stroke. Anticoagulation is very effective at preventing stroke recurrence	For patients that have nonvalvular AF and have had a stroke or TIA, it is recommended that they receive oral anticoagulation medications to best reduce the risk of recurrent stroke. Oral anticoagulation is recommended regardless of the pattern of AF. For patients who have had a stroke or TIA and have valvular AF, it is recommended that they be prescribed warfarin. DOACs have replaced warfarin in many non-valvular AF patients
Poor Diet	Too much dietary sodium and fat can damage arteries. Additionally, the repetitive consumption of additional calories over needed intake can lead to the accumulation of excess visceral abdominal fat, which is a risk factor for atherosclerotic disease	Develop a balanced nutritional plan emphasizing whole food, minimizing processed foods, and ensuring sufficient intake of fruits and vegetables. Depending on the condition of the patient, more regimented and restrictive diets such as the Mediterranean diet should be considered
Physical Inactivity	In general, being sedentary leads to an overall decline in health that can indirectly contribute to experiencing a stroke. Increased physical activity boosts blood flow to the brain and lowers the risk of cardiac events and other vascular issues such as stroke	Engage in moderate intensity aerobic activity for a minimum of ten minutes, four times a week, or engage in vigorous-intensity aerobic activity for a minimum of 20 min, twice a week. Moderate and vigorous are subjective terms that are dependent on the condition of the patient
Obesity	Increases in BMI directly correlate to increases in stroke risk. Additionally, excess body mass can increase the difficulty of performing exercise as well as daily activities of life post-stroke	Patients can minimize the accumulation of visceral abdominal fat by optimizing diet, activity, or taking medication shown to help combat obesity. Proven lifestyle changes include pursuing a more balanced diet and performing increased levels of physical activity
Smoking	Actively smoking can raise blood pressure, potentially leading to hypertension, as well as trigger episodes of atrial fibrillation, all of which increase the likelihood of experiencing a stroke	Counseling, nicotine replacement therapy, or oral anti-craving medications to aid in smoking cessation. Smoking cessation requires collaboration with the patient, their caregivers, and often with the primary care provider

vascular event by 22% [61]. Also, in a Cochrane systematic review of eight RCTs, 160–300 mg of aspirin daily initiated within 48 h of stroke onset reduced the risk of recurrent stroke without significantly increasing the risk of hemorrhagic complications. For every 1000 people treated with aspirin, seven people would avoid recurrent stroke [61, 62]. The European Stroke Prevention Study (ESPS) RCT randomly assigned patients with either stroke or TIA to aspirin/dipyridamole (325 mg/75 mg) or placebo three times a day. The aspirin/dipyridamole group showed a 33% relative risk reduction in stroke recurrence and death [63]. Because aspirin/dipyridamole causes more side effects than aspirin, most providers use aspirin monotherapy instead.

The clopidogrel vs. aspirin in patients at risk of ischemic events RCT reported that clopidogrel 75 mg daily did not differ from aspirin 325 mg in terms of relative risk reduction of vascular events for patients with prior stroke [64]. For other antiplatelet monotherapies, ticagrelor has not shown superior benefit or a better safety profile compared to aspirin in any of the available RCTs, and has a higher rate of discontinuation due to dyspnea or bleeding [65]. The CSPS RCT showed that cilostazol 100 mg two times daily vs. placebo is associated with a relative stroke risk reduction of 41.7% [66]. In the CSPS-2 RCT, at mean of 29 month follow up, cilostazol 100 mg two times daily compared to aspirin 81 mg daily had 34% relative risk reduction in stroke with a much lower frequency of hemorrhagic events (0.77% vs. 1.78%, $p=0.0004$) [67]. However, most cilostazol trials were conducted in East Asian patients, and thus, these results need further validation to be generalizable globally [68].

In the COMPASS RCT, low-dose rivaroxaban 2.5 mg twice a day plus aspirin 75 mg was compared with aspirin 75 mg daily in patients with stable atherosclerotic vascular disease without atrial fibrillation (AF). The rate of stroke recurrence was 4.1% in the combination therapy group vs. 5.4% in the aspirin alone group. However major bleeding was 3.1% vs. 1.9%, respectively [69]. For ESUS, dabigatran in the RE-SPECT ESUS trial and rivaroxaban in the NAVIGATE ESUS RCTs conferred a higher risk of bleeding, and neither medication was superior to aspirin in secondary stroke prevention [70, 71]. The AVERROES RCT did not show a higher risk of bleeding when comparing low dose apixaban (2.5 mg twice daily) to aspirin, but that trial enrolled individuals with atrial fibrillation, not ESUS, and only 14% of subjects had a prior history of stroke [72, 73]. Therefore, anti-platelet therapy remains the primary choice for ESUS.

Anticoagulation for stroke prevention is reserved for patients with proven AF, known cardiac or arterial thrombus, mechanical heart valves, or selected hypercoagulable disorders. AF sometimes exists before the first stroke and may also develop or be identified afterwards and lead to a higher risk for recurrent stroke [21]. For patients that have non-valvular or valvular AF and have had a stroke or TIA, it is recommended that they receive oral anticoagulation medications to best reduce the risk of recurrent stroke [74, 75]. For non-valvular AF, oral anticoagulation is recommended regardless of the pattern of AF [76]. For patients with a left ventricular or atrial thrombus identified during their stroke workup, it is recommended that they be anticoagulated for a duration of at least 3 months to reduce the chance of recurrent stroke [77].

The available anticoagulants for stroke prevention include warfarin and direct oral anticoagulants (DOACs). Warfarin has been a mainstay of treatment for cardioembolic stroke and hypercoagulable conditions for many years. However, DOACs have replaced warfarin in many non-valvular AF patients [78]. DOACs include rivaroxaban, apixaban, edoxaban, and dabigatran. DOACs have similar or superior efficacy in preventing strokes with reduced or similar intracranial bleeding risk compared to warfarin. The RE-LY RCT compared dabigatran with warfarin with the primary end point of stroke recurrence and systemic embolization in patients with non-valvular AF. Dabigatran was modestly superior to warfarin at 150 mg twice a day (1.11% vs. 1.69%), and non-inferior to warfarin at 110 mg twice a day (1.53% vs. 1.69%) [79]. In the AVERROES RCT, apixaban showed similar modest risk reduction compared to warfarin. Recurrence of stroke and systemic embolization was 1.27% for apixaban vs. 1.67% for warfarin [80]. However, in patients with prior history of stroke or TIA, there was no significant difference between apixaban and warfarin with regard to stroke or systemic embolization recurrence. Also, rivaroxaban was not inferior to warfarin in non-valvular AF patients in the ROCKET-AF RCT [81]. Additionally, edoxaban has shown non-inferiority in both low (30 mg once daily) and high (60 mg once daily) doses compared to warfarin in patients with non-valvular AF [82].

Antiypertensive Therapy

Hypertension is the leading modifiable risk factor for stroke with more than 50% of the global burden of stroke attributable to hypertension [83]. RCTs on antihypertensive medication have shown that there is significant decrease in first ever stroke with reduction in blood pressure [84]. Meta-analyses of RCTs have also demonstrated that lowering blood pressure would reduce the risk of stroke recurrence by 20–30% [85], but long-term blood pressure control after stroke remains poor, primarily due to undertreatment or under-adherence [86]. There is still uncertainty regarding the timing of blood pressure lowering after stroke or TIA, partly due to concerns of having a negative effect on cerebral perfusion as well as a scarcity of large RCTs on this subject [87].

A limited number of RCTs have evaluated intensive blood pressure lowering (systolic blood pressure < 130 mm Hg) vs. other less aggressive blood pressure targets. All these RCTs reported non-significant reduced risk of stroke recurrence with intensive blood pressure control [26, 88–90]. However, most clinical guidelines stipulate a BP target of 130/80 mm Hg or lower for long-term secondary stroke prevention, at least for patients with previous hypertension. The justification for this recommendation has a strong basis in the benefits of hypertension control for other organ systems including the heart and kidneys [91].

Five classes of hypertension medication have been evaluated for secondary stroke prevention, including β-adrenergic antagonists, calcium channel antagonists, diuretics, angiotensin-converting enzyme (ACE) inhibitor, and angiotensin II receptor blockers (ARBs). The majority of available RCTs have evaluated single therapy versus placebo, and therefore, no direct comparison was made between medication classes [92–95]. A recent meta-analysis of fourteen RCTs included 42,736 patients, of which two-thirds were from the PROGRESS, PRoFESS, or SPS3 trials, demonstrated that antihypertensive therapy was associated with lower stroke recurrence (RR 0.73, 95% CI 0.62–0.87) with a favorable trend that did not reach significance for incident ischemic stroke (RR 0.87; 95% CI 0.70–1.07) [85].

A meta-analysis of secondary prevention stroke RCTs estimated comparative effectiveness of antihypertensive medications. The authors concluded that a diuretic-based therapy was possibly superior to other therapies [96]. Calcium channel antagonists have not been evaluated in large randomized trials of secondary stroke prevention. However, they have a similar effect on BP reduction compared to ACE inhibitors in primary stroke prevention and smaller secondary prevention studies [96, 97]. Nonetheless, diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers are considered the first line agents in preference to calcium channel blockers or beta blockers [98, 99].

Hyperlipidemia Therapy

Managing hyperlipidemia is another important aspect of secondary stroke prevention. Specifically, statin therapy is proven to lower the risk of stroke recurrence.

The heart protection study (HPS) was the first large-scale RCT of simvastatin to include patients with cerebrovascular disease. In the group of patients with previous stroke, treatment with simvastatin had no effect on stroke recurrence rate but was associated with a significant reduction of major vascular events by 20% (24.7% vs. 29.8%) irrespective of the stroke subtype [100]. Two RCTs, J-STARS and SPARCL, studied statins in non-cardioembolic stroke patients and showed significant reduction in stroke recurrence. In J-STARS, non-cardioembolic stroke patients were randomized to low dose pravastatin or placebo [101]. Patients treated with pravastatin had a significant reduction in recurrence rate of atherothrombotic stroke (0.21% for pravastatin vs. 0.64% for placebo). In the SPARCL RCT of patients with prior non-cardioembolic stroke, treatment with atorvastatin 80 mg daily had an absolute risk reduction of 2.2% for stroke but patients had a significant increase (HR 1.66, 95% CI 1.08–2.55) in the risk of ICH [102]. An exploratory analysis of SPARCL showed that high-dose atorvastatin was similarly efficacious in preventing strokes irrespective of baseline ischemic stroke subtype. Also, a recent meta-analysis on statin therapy for secondary stroke prevention showed that among 10,394 patients with prior stroke, statin treatment was associated with an absolute risk reduction of 1.6% for stroke recurrence [103].

Therefore for patients who have experienced an ischemic stroke and have an LDL cholesterol greater than 100 mg/dL, it is recommended to start a high intensity statin such as 80 mg of atorvastatin or 20–40 mg of rosuvastatin to reduce the risk of secondary stroke [104]. To ensure that hyperlipidemia is being appropriately managed, it is recommended that patients obtain measurements of their LDL-C levels 4 weeks after beginning a statin and then continue to measure levels every 3 to 6 months thereafter. Ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (evolocumab, alirocumab) have been shown to reduce the risk of cardiovascular events and can be used as an alternative in patients who cannot tolerate statins or do not have an adequate response, typically defined as an LDL-C < 70 while on therapy [51]. However, prior to considering administration of a PCSK9 inhibitor, it may be worth adding ezetimibe to the current statin treatment and assessing if LDL-C lowers to < 70 [105].

The IMPROVE-IT RCT showed that the addition of ezetimibe to standard simvastatin treatment in patients with prior stroke would result in a reduced risk of ischemic stroke. Subgroup analyses of the FOURIER and ODYSSEY OUTCOMES RCTs involving patients with a prior history of stroke confirmed a benefit of PCSK9 inhibitors in the reduction of cardiovascular events and a numerical decrease in the rate of stroke recurrence [106, 107]. Total stroke events among patients with prior stroke were non-significantly reduced with evolocumab vs. placebo (RR 0.87, 95% CI 0.65–1.16) [106].

Hyperglycemia Therapy

For patients who have had an ischemic stroke or TIA and have type 2 diabetes (T2DM), the goal HgbA1c is < 7. Oral or injectable hypoglycemic drugs and insulin are proven methods to achieve glycemic control. Of the many medication classes for treating T2DM, thiazolidinedione (TZD) and glucagon-like-1 (GLP1) receptor agonists have shown

some benefit for secondary stroke prevention. A Cochrane review comparing TZDs and placebo for secondary stroke prevention identified four RCTs with 1163 participants and reported that TZDs are associated with reduced stroke recurrence (RR 0.52, 95% CI 0.34 to 0.80) [108].

A meta-analysis of RCTs, including 56,004 participants, on the effects of GLP1s on major adverse cardiovascular events, demonstrated a significant reduction in cardiovascular events and stroke. GLP-1 s were also associated with a significant reduction in fatal and non-fatal stroke (HR: 0.84; 95% CI 0.76–0.94) [109]. If patients have difficulty managing their glucose levels, it is recommended that they establish care in a multimodal diabetes clinic and seek nutritional and lifestyle therapy and obtain a basic education on self-managing glucose level.

Carotid Stenosis Therapy

If extracranial carotid artery stenosis is identified, it can be treated by carotid endarterectomy or carotid artery stenting [8]. For patients who have had a TIA or a nondisabling ischemic stroke within the past 6 months that have severe ($\geq$ 70% stenosis) ipsilateral carotid artery stenosis, carotid revascularization decreases the risk of future stroke by 16%. However, when the stenosis severity is 50–69% the recommendation to revascularize is strongest when it is determined that the risk of perioperative morbidity and mortality is less than 6% [110]. Equally important are patient-specific factors in the decision making, as the decision to undergo an invasive procedure is complex and personal. For patients who elect to undergo carotid revascularization, the procedure should be performed by surgeons with expertise in placing a stent or performing endarterectomy to meet the risk assessment of less than 6% [111]. Additionally, patients should be receiving intensive medical therapy coupled with antiplatelet and lipid-lowering therapy combined with an aggressive antihypertensive regimen to offer the best chance at preventing recurrent stroke [104].

Investigational Therapies

There are a variety of drugs under investigation for secondary stroke prevention, primarily in the antithrombotic class. For example cilostazol, which is a phosphodiesterase 3 inhibitor, remains under investigation for potential use in preventing secondary stroke [112, 113]. Two pharmaceutical companies are conducting large multinational RCTs of oral factor XIa inhibitors as add-on to antithrombotic therapy in patients with non-cardioembolic stroke and high-risk TIA. However, the recently published phase 2b study of Bayer's factor XIa inhibitor for stroke prevention (PACIFIC-Stroke, $n = 1808$) failed to show a benefit for secondary stroke prevention, but may have been underpowered [81]. Additionally, there are emerging lipid-lowering agents for stroke prevention that include oral small molecules (bempedoic acid, oral inhibitor of ATP citrate lyase), monoclonal antibodies (evinacumab targeting angiopoietin like protein 3), and various ribonucleic acid (RNA) knockdown strategies (inclisiran, siRNA-targeting PCSK9; AROANG3, siRNA-targeting angiopoietin like protein 3; olpasiran, siRNA-targeting LPA). While these agents may be proven to have benefit for secondary stroke prevention, considerations of cost, side effects, and effectiveness will need to be evaluated prior to widespread adoption.

Conclusion

The management of both vascular and lifestyle risk factors remains central to the prevention of secondary stroke. Ischemic stroke etiology is important in developing patient-specific recommendations for prevention of recurrent stroke, and as such performing a proper diagnostic workup of the primary stroke is essential. Approaching management of risk factors from a multidisciplinary perspective that includes medical, surgical, behavioral, and self-management education offers the best chance of success.

Many of the changes an individual must make after experiencing a stroke or TIA are behavioral. As such, it is necessary that patients be provided with opportunities to improve knowledge of their medical conditions and personalized methods to ensure maximal treatment adherence. Only through these methods can providers ensure that patients are well apprised of their condition, risk factors, and what they can do to prevent recurrent stroke.

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