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Review

Secondary stroke prevention beyond antiplatelets: The role of colchicine and GLP-1RA – an ounce of prevention is worth a pound of cure

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***Abstract*:** Stroke remains a major global health concern, ranking as the second most common cause of death and the third leading cause of disability worldwide. Despite advances in therapy and management, ischemic stroke patients continue to face high risks of recurrence, cardiovascular events, and mortality. Effective secondary stroke prevention is critical, encompassing antithrombotic therapy, management of vascular risk factors such as hypertension, dyslipidemia, and diabetes mellitus, and conducting healthy lifestyle. Approximately 80% of strokes are ischemic, with a significant proportion attributable to large-artery atherosclerosis of the extra- and intracranial arteries, particularly in the internal carotid artery. Atherothrombotic strokes, linked to plaque rupture and thrombus formation, present a notably high risk of recurrence. Inflammatory and immune mechanisms play pivotal roles in both the initiation and progression of atherosclerosis and stroke. Colchicine, an anti-inflammatory agent, has shown potential in managing cardiovascular disease, though its effects on stroke reduction and prevention have been inconsistent across studies. Its possible protective role against stroke is attributed to its anti-inflammatory actions, which include disrupting microtubule dynamics, inhibiting immune cell movement, and lowering inflammatory markers like L-Selectin and E-Selectin, while also suppressing interleukin release. Glucagon-like peptide-1 receptor agonists (GLP-1RA) agents have emerged as effective therapies for type 2 diabetes with notable cardiovascular benefits. These agents enhance glucose control while also providing protective effects against atherosclerosis and stroke. GLP-1RA drugs work by mimicking the effects of GLP-1, a peptide that regulates insulin release and glucose metabolism. They also exhibit anti-inflammatory properties, potentially reducing stroke risk through mechanisms such as improved endothelial function and reduced plaque formation. Clinical trials have indicated that GLP-1RA agents can significantly lower the incidence of nonfatal strokes and major adverse events. This narrative review underscores the importance of targeting inflammation to reduce the risk of recurrent stroke, emphasizing recent studies on colchicine and GLP-1RA. It consolidates evidence regarding the efficacy of these agents in secondary stroke prevention; however, future studies are needed to further explore their mechanisms and roles in comprehensive stroke management strategies.

Keywords: antithrombotic therapy, atherosclerosis, colchicine, GLP-1 receptor agonists, ischemic stroke

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Introduction

An ounce of prevention is worth a pound of cure.
Benjamin Franklin

Stroke is the second leading cause of death and the third cause of disability worldwide.[1] Although therapy, management, and secondary stroke prevention have been drastically improved during the last couple of years, patients with ischemic stroke still represent a group of patients at very high risk of stroke recurrence, cardiovascular adverse events, or even death.[2] Studies indicate that despite advancements in stroke management, the risk of recurrence remains significant, and approximately 11% of individuals experience a recurrent stroke within the first year following an initial event, with this rate increasing to 26% over 5 years. Also, recurrence rates vary depending on stroke subtype; for instance, large artery atherosclerosis and cardioembolic strokes exhibit higher recurrence rates, ranging from 5.7% to 51.3%.[3,4] These statistics underscore the critical need for effective secondary prevention strategies to mitigate the risk of recurrent strokes. In addition to antithrombotic, for example, antiplatelet therapy, which is crucial for secondary prevention of stroke, vascular risk factor assessment and subsequent treatment also contribute significantly to the reduction of stroke recurrence, mortality, and morbidity. Hypertension, dyslipidemia, and diabetes mellitus represent the most common and important modifiable cardiovascular risk factors among stroke patients.[5] About 80% of all stroke are ischemic, and about one-fifth of them are due to large-artery atherosclerosis. The most common site is atherosclerotic plaque in the internal carotid artery (ICA) leading to brain ischemia, known as atherothrombotic stroke that carries a threefold greater risk of recurrence compared to other types of ischemic strokes. Atherothrombotic stroke pathogenesis is mainly related to the rupture of atherosclerotic plaque, which leads to thrombus formation with the clot blocking locally the blood vessel or provoking distal emboli, which ultimately leads to ischemia and stroke.[6] Inflammation and immune mechanisms are crucially involved in the pathophysiology of the stroke development, as well as acute and chronic damage cascades following stroke, for example, immediately after stroke occurrence, a neuroinflammatory process begins in the brain, leading to systemic immunodepression primarily due to excessive activation of the autonomic nervous system. Also, atherosclerosis is characterized as an inflammatory condition, and, in addition to classical risk factors, maladaptive immune mechanisms lead to an increased risk of stroke.[7] In everyday practice, apart from a healthy lifestyle, the current pharmacological therapy for stroke prevention is based on antithrombotic, antihypertensive, lipid-lowering, and hypoglycemic therapy. Recently, an integrated ABC pathway for the therapeutic approach of ischemic stroke patients has been proposed by the European Society of Cardiology (ESC) Council on Stroke, aiming for a holistic approach to stroke patients (A—Appropriate antithrombotic therapy, B—Better functional and psychological status, and C—Comorbidities and lifestyle, patient values, and preferences).[8] In addition, especially in atherothrombotic stroke, subtype revascularization treatment may be considered in some clinical situations, such as in moderate-to-severe stenosis of carotid arteries (50%–99%).[9] However, since inflammation plays a fundamental role in the atherosclerosis development, it has been considered a strategical target for diminishing the risk of adverse cardiovascular events. The CANTOS trial—Canakinumab Antiinflammatory Thrombosis Outcome Study confirmed the "inflammation hypothesis" by demonstrating that anti-inflammatory treatment with human monoclonal antibody targeting interleukin (IL)-1β (canakinumab) led to a lower risk of cardiovascular events.[10] There is an increasing number of studies examining the effects of Colchicine, an anti-inflammatory drug that is associated with improved cardiovascular outcomes in patients with coronary artery disease. Colchicine has a broad spectrum of anti-inflammatory effects by the inhibition of neutrophil functions and alteration of multiprotein complex NLRP3 inflammasome.[11,12] Diabetes mellitus is one of the most important risk factors for stroke development, while simultaneously significantly increases the risk of future cardiovascular adverse events among ischemic stroke patients. Recent studies investigating novel antidiabetic drugs, such as glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i), were shown to reduce levels of glucose as well as to have favorable cardiovascular effects.[13] GLP-1RA are shown to have few potential protective mechanisms, which may contribute to the prevention of stroke, including stability of atherosclerotic plaque, increased nitric

oxide, reduced vascular smooth muscle proliferation, and improved function of endothelial cells.[14] Also, GLP-1RA have been shown to significantly reduce body weight and improve metabolic health, which may contribute to their protective effects against cardiovascular diseases.[15,16]

This comprehensive review consolidates the evidence regarding current pharmacological approaches and future prospects for secondary stroke prevention, extending beyond antithrombotic therapies, and primarily focused on a review of the efficacy of colchicine and GLP-1RA.

Colchicine

Inflammation has a significant role in the development of atherosclerosis disease. In the earliest phases, Low-Density-Lipoporitein cholesterol (LDL) is retained within the subendothelial space where it is modified by enzymatic activities and oxidative stress leading to abnormal lipid metabolism and causing endothelial injury and hemodynamic damage. Modified LDL, with its inflammatory characteristics, triggers the expression of chemokines and adhesion molecules in endothelial cells such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin, P-selectin, monocyte chemoattractant protein-1 (MCP-1), and other inflammatory factors. These inflammatory molecules facilitate the infiltration of monocytes and lymphocytes into the arterial wall, after which monocytes differentiate into macrophages, that cause a significant inflammatory response to the modified LDL by releasing additional adhesion molecules, cytokines, and other factors, such as tumor necrosis factor (TNF)-α, IL-1β, and IL-6. This inflammatory environment subsequently promotes the recruitment of vascular smooth muscle cells, which produce connective tissue, contributing to the formation of a fibrous cap within the atherosclerotic plaque. In advanced atherosclerosis, macrophages and vascular smooth muscle cells absorb modified LDL, becoming lipid-laden foam cells. Necrotic macrophages release matrix metalloproteinases and other proteolytic enzymes that degrade the extracellular matrix leading to plaque rupture, bleeding, and thrombosis, which can result in a cerebrovascular event if the carotid artery is affected.[9,17]

Colchicine is an alkaloid derived from the *Colchicum autumnale* (Autumn Crocus) plant, with the earliest report of its use as a therapy for joint inflammation dating back to 1500 B.C. Today, colchicine has been approved by the Food and Drug Administration for autoinflammatory diseases like pericarditis, Behçet's disease, Familial Mediterranean Fever, and for gout arthritis. Colchicine is an anti-inflammatory drug that is associated with improved cardiovascular outcomes. However, its effect on stroke reduction and prevention was not consistent across studies.[17]

Colchicine produces its anti-inflammatory actions in the immune cells through different pathways (Figure 1), such as disruption of the microtubule architecture and dynamics, which leads to inhibition of movement, mitotic, and phagocytic properties of the immune cells. It has also been demonstrated to reduce the expression of L-Selectin on the cytoplasmic membrane of neutrophils and E-Selectin on endothelial cells, thereby inhibiting their attachment and infiltration at the inflammation site. This prevents the subsequent release of proteolytic enzymes, cytokines, and reactive oxygen species (ROS). Additionally, colchicine indirectly suppresses ILs (IL-1β) release by disrupting the formation of the NLRP3 inflammasome, which may help explain its anti-atherosclerotic effects as observed in the CANTOS trial.[17,18]

Although the anti-inflammatory effect is unquestionable and the drug is already used for several conditions, the use of colchicine for the prevention of ischemic stroke is not yet well-established. However, there are an increasing number of studies showing a positive effect. There are also an increasing number of studies investigating the anti-inflammatory effects as a potential therapeutic option for preventing vascular complications, among which ischemic stroke is one of the most significant. Alongside its anti-inflammatory effects, colchicine is also hypothesized to potentially lower the incidence of stroke by diminishing episodes of atrial fibrillation. This theory is supported by colchicine's demonstrated effectiveness in preventing atrial fibrillation in patients undergoing cardiac surgery.[19] However, this hypothesis has not yet been fully investigated, especially since a

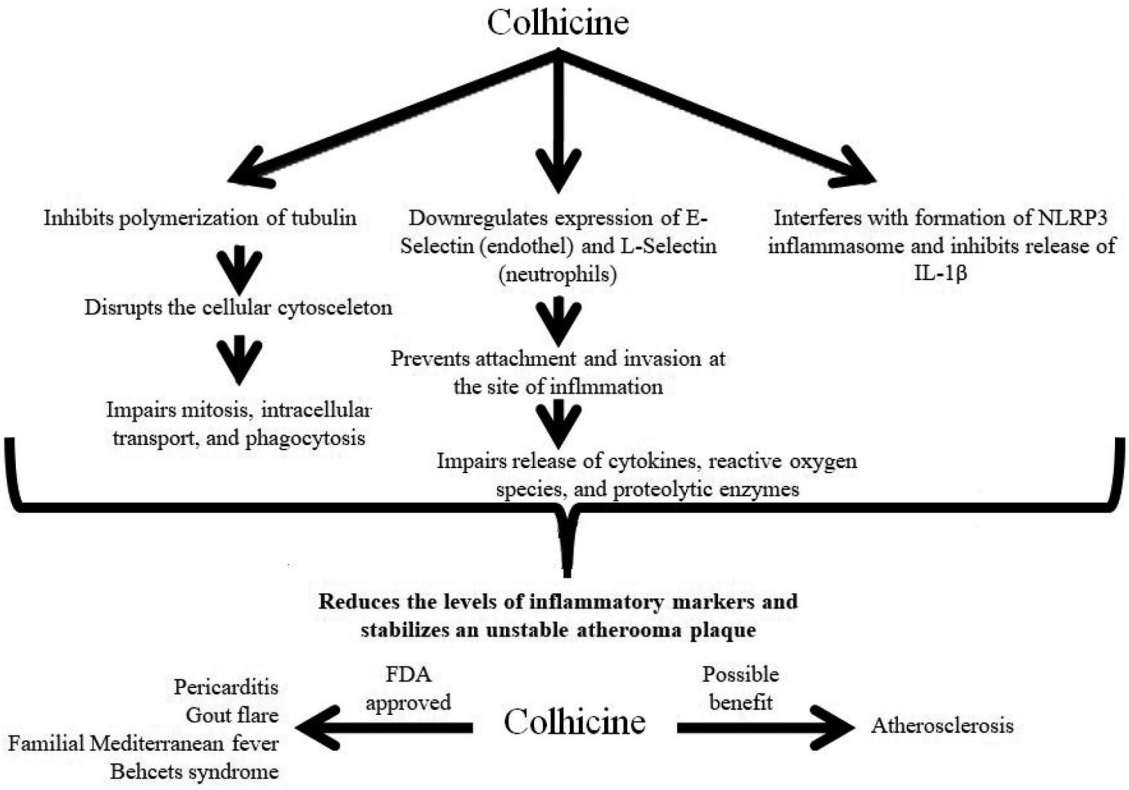

Figure 1. Anti-inflammatory mechanisms of colchicine.

meta-analysis conducted by Al-Atta et al.[20] did not support this mechanism, as colchicine did not influence the incidence of new-onset or recurrent atrial fibrillation.

There are promising results of colchicine administration for cardiovascular diseases especially for the prevention of coronary artery disease. After results of the single-center, randomized, observer-blinded LoDoCo study that included 532 patients with stable coronary artery disease comparing colchicine 0.5 mg/day versus control in the prevention of acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke, which showed effectiveness in the prevention of cardiovascular events,[11] LoDoCo2 study was conducted with more than 10 times more patients, that is, a total of 5522 participants were randomized, with 2762 allocated to the colchicine group (0.5 mg/day) and 2760 to the placebo group. The median follow-up period was 28.6 months. Primary endpoint events (composite of cardiovascular death, ischemic stroke, spontaneous myocardial infarction, or ischemia-driven coronary revascularization) were recorded in 187 patients (6.8%) in the colchicine group and 264 patients (9.6%) in the placebo group, corresponding to incidence rates of 2.5 and 3.6 events per 100 person-years, respectively (hazard ratio (HR), 0.69; 95% confidence interval (CI), 0.57–0.83; $p < 0.001$). For the key secondary endpoint (a composite of cardiovascular death, spontaneous myocardial infarction, or ischemic stroke), 115 patients (4.2%) in the colchicine group and 157 patients (5.7%) in the placebo group experienced events (incidence rates of 1.5 vs 2.1 events per 100 person-years; HR, 0.72; 95% CI, 0.57–0.92; $p = 0.007$). Thus, in this large multicenter, randomized, double-blind study, colchicine 0.5 mg/day has been proven effective for the prevention of cardiovascular events, including ischemic stroke in compression with placebo in patients with chronic coronary artery disease. However, deaths due to noncardiovascular causes occurred more frequently among patients treated with colchicine than in those receiving placebo (incidence rates of 0.7 vs 0.5 events per 100 person-years; HR, 1.51; 95% CI, 0.99–2.31).[21]

Similarly, COLCOT study showed that patients with coronary artery disease randomized within the first month after myocardial infarction treated with 0.5 mg colchicine daily had a lower incidence of myocardial reinfarction, cardiac arrest, cardiovascular death, and especially stroke. In this study, a total of 4745 patients were included, with 2366 patients assigned to the colchicine group, and 2379 to the placebo group. Patients were followed for a median of 22.6 months. The primary endpoint occurred in 5.5% of the patients in the colchicine group, as compared with 7.1% of those in the placebo group (HR, 0.77; 95% CI, 0.61–0.96; $p = 0.02$). The HR for stroke was 0.26 (95% CI, 0.10–0.70). Diarrhea occurred in 9.7% of patients receiving colchicine and in 8.9% of those on placebo ($p = 0.35$). Pneumonia, classified as a serious adverse event, was observed in 0.9% of the colchicine group compared to 0.4% in the placebo group ($p = 0.03$).[22] One year later, the COPS study with significantly fewer participants in the study compared to previous studies, specifically with 795 acute coronary syndrome and coronary artery disease patients, showed that colchicine improved clinical outcomes, including fewer ischemic noncardioembolic strokes compared to the placebo, but it is worth mentioning that about 10% of patients showed colchicine intolerance.[23] Additionally, patients from COPS and LoDoCo2 studies had a higher rate of noncardiovascular deaths in the colchicine group, although no direct correlation was found, for example, these studies demonstrated reduced adverse cardiovascular events in those treated with colchicine, but concerning signal has emerged suggesting a potential increase in noncardiovascular deaths in those receiving colchicine. Specifically, the authors of the COPS and LoDoCo2 study noted a higher incidence of noncardiovascular mortality, including deaths due to cancer, infections, and other causes unrelated to cardiovascular disease. This observation raises important concerns about the broader safety profile of colchicine. While its cardiovascular benefits are evident, the potential risks associated with noncardiovascular mortality warrant further investigation. Understanding these risks is crucial to fully assessing the overall benefit-risk profile of colchicine, especially in patient populations with comorbidities or other vulnerabilities.[9]

Overall, the mentioned independent randomized clinical studies, involving over 11,000 patients with acute and chronic cardiovascular conditions and monitored for up to 5 years, have shown that colchicine can safely slow the atherosclerosis progression and lower the risk of cardiovascular disease including stroke.[9]

In May 2024, the results of the long-awaited CONVINCE study were released at the European Stroke Organisation Conference in Basel. The CONVINCE study was a multicenter, international, randomized, open-label study aimed at evaluating whether the addition of colchicine (0.5 mg/day) to standard care could lower the incidence of recurrent stroke or cardiovascular events in patients with noncardioembolic ischemic stroke or high-risk transient ischemic attack. The primary outcome was a composite of the first recurrence of ischemic stroke, myocardial infarction, cardiac arrest, or hospitalization for unstable angina. Despite challenges posed by the COVID-19 pandemic, the study followed 3154 patients for a median duration of 34 months over nearly 6 years. In the intention-to-treat analysis, the primary outcome was observed in 153 patients assigned to colchicine (9.8%) compared to 185 patients receiving standard care (11.8%), corresponding to incidence rates of 3.32 versus 3.92 per 100 person-years. The adjusted HR was 0.84 (95% CI, 0.68–1.05; $p = 0.12$). The reduction in C-reactive protein (CRP) levels in the colchicine group indicated its anti-inflammatory effects. Additionally, the prespecified on-treatment analysis, including the subgroup of patients with a history of coronary artery disease, revealed significantly lower rates of recurrent stroke or cardiovascular events. In conclusion, although the primary endpoint was neutral, the results of the CONVINCE study support the hypothesis that colchicine therapy in long-term settings may reduce stroke recurrence and cardiovascular events specifically in patients with atherosclerotic type of stroke.[24] Also, one should take into account that the COVID pandemic reduced the planned follow-up time of CONVINCE study, which led to under-powering for the primary analysis. The findings of the three most important studies investigating efficacy of colchicine in vascular events prevention are summarized in Table 1.

Table 1. The findings of the most important studies investigating the efficacy of new antidiabetic agents in vascular events prevention.

Authors/year/ study	Design	Intervention	Patients	Outcome	Conclusion
Kelly et al.[24] 2024 CONVINCE	Randomized, parallel-group, open-label, blinded endpoint assessed trial	Colchicine 0.5 mg/ daily + guideline-based usual care vs usual care only	3144 (1569 (colchicine and usual care) and 1575 (usual care alone)	Composite of first fatal or nonfatal recurrent ischemic stroke, myocardial infarction, cardiac arrest, or hospitalization (at least a 24 h stay)	Although no statistically significant benefit was observed on the primary intention-to-treat analysis, the findings provide new evidence supporting the rationale for anti-inflammatory therapy in further randomized trials.
Nidorf et al.[21] 2020 LoDoCo2	Randomized, controlled, double-blind trial	Colchicine 0.5 mg/daily vs placebo	A total of 5522 patients underwent randomization; 2762 were assigned to the colchicine group and 2760 to the placebo group	Composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization	In a randomized trial involving patients with chronic coronary disease, the risk of cardiovascular events was significantly lower among those who received 0.5 mg of colchicine once daily than among those who received placebo
Tardif et al.[22] 2019 COLCOT	Randomized, double-blind trial involving patients recruited within 30 days after a myocardial infarction	Colchicine 0.5 mg/daily vs placebo	A total of 4745 patients were enrolled, 2366 patients were assigned to the colchicine group, and 2379 to the placebo group	Composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization	Among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo.

"Although the primary analysis was neutral, the signals of benefit of colchicine on secondary analyses are in line with findings from previous trials and indicate the potential of colchicine in prevention after stroke. In CONVINCE, the COVID pandemic reduced the planned follow-up time, which led to under-powering for the primary analysis by 8%. Further trials are needed in all stroke subtypes, but with particular focus on patients with objective evidence of atherosclerosis. "

Professor Peter Kelly, the principal investigator of CONVINCE

Other ongoing trials will provide further information about the use of colchicine in subsets of patients with cardiovascular disease, especially stroke. The CASPER study, which started in April 2023, targets patients with the following criteria: ischemic stroke without major disability or clinical transient ischemic attack, combined with brain imaging showing acute infarction, and high-sensitivity CRP levels exceeding 2 mg/L between 4 and 52 weeks post-event. The research aims to examine the efficacy of colchicine in preventing recurrent stroke. The study particularly emphasizes patients with elevated CRP levels to assess the anti-inflammatory effects of colchicine.[25] The results of the COLCARDIO trial are also anticipated. This study aims to determine whether administering a daily low dose of colchicine in addition to standard medical care reduces the rate of recurrent cardiac events. Additionally, as a secondary outcome, the occurrence of nonfatal stroke will be monitored. Although it is not primarily focused on stroke prevention, the study is designed to assess the anti-inflammatory protective effect of colchicine. It will include only patients with persistently high levels of inflammatory marker, for example, CRP over 2 mg/L at 4–6 weeks after the initial acute coronary syndrome event.[26] The CLEAR SYNERGY (OASIS 9) is a large multicenter, randomized, double-blind, double-dummy, 2×2 factorial design ongoing and still recruiting patients study with aim to study the effects of low-dose colchicine and spironolactone in largely unselected post-myocardial infarction patients who undergo percutaneous coronary intervention. The primary outcome for colchicine is the first occurrence of the composite of cardiovascular death, recurrent myocardial infarction, unplanned ischemia-driven revascularization, or stroke.[27] Finally, the CIAFS-1 is a pilot randomized controlled trial (RCT) investigating the feasibility of a larger study to formally evaluate the potential benefit of colchicine in reducing markers of inflammation and thrombosis in patients with atrial fibrillation who are on anticoagulation treatment for at least 3 months. It is a preparation for a phase III trial investigating the prevention of systemic embolism and stroke (ClinicalTrials.gov identifier: NCT02282098).

The results of the study "Colchicine in Patients with Acute Ischemic Stroke or Transient Ischemic Attack (CHANCE-3)" were published at the end of June 2024. The CHANCE-3 trial, a large-scale study on colchicine for acute ischemic stroke and transient ischemic attack, presents results that contrast with earlier findings suggesting potential benefits of the drug. Namely, participants were randomly allocated in a 1:1 ratio within 24 h of symptom onset to receive either colchicine (0.5 mg twice daily for the first 3 days, followed by 0.5 mg once daily) or a placebo, administered for 90 days. The primary efficacy outcome measured was the occurrence of any new stroke within 90 days post-randomization. The primary safety outcome focused on the incidence of any serious adverse events during the treatment period. All analyses for efficacy and safety outcomes were conducted using an intention-to-treat approach. A total of 4176 participants were included in the colchicine group, while 4167 received the placebo. Within 90 days, a stroke occurred in 264 patients (6.3%) from the colchicine group and 270 patients (6.5%) in the placebo group (HR, 0.98; 95% CI, 0.83–1.16; $p = 0.79$). Serious adverse events were reported in 91 participants (2.2%) from the colchicine group and 88 participants (2.1%) from the placebo group ($p = 0.83$). This trial found no significant advantage of colchicine over a placebo in reducing further ischemic events, although the authors explicitly identified several limitations of their study that could affect the interpretation and generalizability of the findings. They acknowledged that the short 90-day trial duration might not adequately capture the long-term benefits of colchicine, as seen in chronic conditions such as coronary artery disease. They also noted that high-sensitivity CRP (hs-CRP) was measured only at baseline, with no follow-up biosamples, limiting the ability to evaluate the biological effects of colchicine over time. The authors highlighted uncertainty in the primary outcome, as the CI included clinically significant values, underscoring the need for further investigation. Additionally, they pointed out the absence of detailed data on secondary prevention medications and the lack of comprehensive evaluations for cardio-embolic sources and alternative stroke etiologies, which could have influenced the results. Gender imbalance, with women being underrepresented, and seasonal recruitment variations were also noted as factors limiting the generalizability of the findings. Furthermore, the lack of data on intracranial and extracranial atherosclerosis, particularly relevant to Asian populations, was recognized as a restriction in understanding the potential role of atherosclerosis in colchicine's efficacy. Finally, the authors acknowledged that the sample size was calculated using suboptimal methods due to the scarcity of prior literature, which

may have impacted the study's statistical power.[28] To optimize future research, a longer-duration trial should be considered to capture potential long-term benefits of colchicine, which is more likely. Comprehensive follow-up biosampling and detailed data collection on secondary prevention medications, atherosclerosis, and potential cardioembolic sources are essential. Ensuring balanced gender representation and addressing seasonal recruitment variations will enhance generalizability. Future studies should also adopt robust sample size estimation methods and stratify participant groups to better evaluate colchicine's efficacy and safety across diverse populations.

Apart from colchicine, various anti-inflammatory treatments have been investigated for ischemic stroke, including methotrexate, minocycline, vinpocetine, and melatonin, with mixed outcomes. Minocycline, known for its extensive anti-inflammatory and neuroprotective properties, has been evaluated in clinical studies.[29] Vinpocetine, an anti-inflammatory alkaloid, reduces the release of inflammatory cytokines and chemokines through the inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), showing anti-inflammatory effects in atherosclerosis and early inflammation related to ischemic stroke.[30] Melatonin, renowned for its powerful anti-inflammatory, antioxidative, and neuroprotective benefits, has demonstrated positive effects on carotid artery stenosis by reducing endothelial damage, stabilizing arterial plaques, and lessening cerebral ischemia/reperfusion injury.[31] In the Cardiovascular Inflammation Reduction Trial (CIRT) trial, a low dose of the anti-inflammatory drug methotrexate was ineffective in reducing recurrent vascular events in patients with coronary artery disease.[32]

GLP-1RA agents

Diabetes and elevated blood sugar levels are well-recognized risk factors for stroke. Recent studies have provided insight into the underlying pathogenic mechanisms and clinical conditions that could contribute to the increased susceptibility to cerebrovascular diseases in individuals with diabetes.[33,34] Metformin is the first-line medication for managing type 2 diabetes mellitus, while alternative glucose-lowering medications may be considered based on comorbid conditions or individualized treatment factors. However, the most effective glucose-lowering drug for stroke prevention remains uncertain.[35,36] The variation in the impact of glucose-lowering medications on stroke may stem from differences in how these drugs affect glucose dynamics and overall hemodynamics.[37] Diabetic patients often experience both asymptomatic and symptomatic hypoglycemia, with intensive glycemic control being a frequent cause.[38] Severe hypoglycemia can induce brain injury through neuroinflammatory pathways and has been linked to a heightened risk of stroke, even in prediabetic individuals.[39] Medications that cause greater glucose variability may also elevate stroke risk through mechanistic pathways. Evidence indicates that long-term glucose variability in individuals with type 2 diabetes mellitus is significantly associated with an increased risk of macrovascular complications, such as myocardial infarction and stroke. Evidence suggests that fluctuations in glucose levels contribute to oxidative stress, inflammation, and endothelial dysfunction, all of which accelerate atherosclerosis progression. This association is strongly supported by findings from the "Action to Control Cardiovascular Risk in Diabetes" (ACCORD) trial, a large clinical study designed to evaluate the impact of intensive glucose control on cardiovascular outcomes in type 2 diabetes. In this trial, intensive glucose control achieved an average HbA1c below 6.5%. However, data analysis revealed that higher variability in HbA1c levels over time was correlated with a greater risk of macrovascular complications. Specifically, an increase of 1% in the standard deviation of HbA1c was associated with approximately a 20% increase in cardiovascular event risk (HR, ~1.20, 95% CI, 1.10–1.30).[40,41] The findings of the most important studies investigating efficacy of new antidiabetic agents in vascular events prevention are summarized in Table 2.

SGLT2i and GLP-1RA are relatively new medications that have proven to be highly effective in managing glycemia in type 2 diabetes. As extensively documented in the literature, these drugs not only offer cardiovascular protection but also provide significant benefits to the vascular system.[47] Specifically, SGLT2i notably lower the risk of cardiovascular disease, cut the likelihood of hospitalization for heart failure by 30%, and significantly improve renal function, regardless of whether the patient has type 2 diabetes or is undergoing heart failure treatments.[47–49] Conversely, GLP-1RA works by replicating the effects of the gut-derived peptide GLP-1, which

Table 2. The findings of the most important studies investigating the efficacy of new antidiabetic agents in vascular events prevention.

Authors/year/ study	Design	Intervention	Patients	Outcome	Conclusion
Wilcox et al.[42] 2007 PROactive	Randomized, prospective, double-blind	Pioglitazone (titrated to 45 mg) vs placebo	5238 patients with type 2 diabetes and a history of macrovascular disease	The risk of stroke and other cardiovascular outcomes	In a subgroup analysis from PROactive, pioglitazone reduced the risk of recurrent stroke significantly in high-risk patients with type 2 diabetes.
Zinman et al.[37] 2015 EMPA-REG OUTCOME	Randomized, prospective, double-blind	Empagliflozin (10 or 25 mg/daily) vs placebo	7020 patients with type 2 diabetes	Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care.
Neal et al.[43] 2017 CANVAS	Integrated data from two trials	Canagliflozin vs placebo	10142 patients with type 2 diabetes and an elevated risk of cardiovascular disease	Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	Patients with type 2 diabetes and an elevated risk of cardiovascular disease who were treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal
Marso et al.[44] 2016 SUSTAIN-6	Randomized, double-blind, placebo-controlled	Once-weekly Semaglutide (0.5 or 1.0 mg) vs placebo	3297 patients with type 2 diabetes who were on a standard-care	The first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	In patients with type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, an outcome that confirmed the noninferiority of semaglutide.
Wiviott et al.[45] 2019 DECLARE-TIMI 58	Randomized, double-blind, multinational, placebo-controlled, phase III trial	10 mg of dapagliflozin daily vs placebo	17,160 patients Patients were 40 years of age or older and had type 2 diabetes, a glycated hemoglobin level of at least 6.5% but less than 12.0%, and a creatinine clearance of 60 mL or more per minute	Cardiovascular death, myocardial infarction, or ischemic stroke, e.g., MACE	In patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of cardiovascular death or hospitalization for heart failure, a finding that reflects a lower rate of hospitalization for heart failure.
Gerstein et al.[46] 2020 REWIND trial	Multicenter, randomized, double-blind, placebo-controlled trial done at 371 sites in 24 countries	1.5 mg dulaglutide/ weekly vs placebo	12 133 patients, of whom 9901 with type 2 diabetes and additional cardiovascular risk factors	Occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular or unknown causes	Long-term dulaglutide use might reduce clinically relevant ischemic stroke in people with type 2 diabetes but does not affect stroke severity.

MACE, major adverse cardiovascular events; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes.

enhances glucose-stimulated insulin release from the pancreas.[50] For individuals with type 2 diabetes, GLP-1RA has been demonstrated to decrease the incidence of major adverse cardiovascular events, such as nonfatal myocardial infarction and nonfatal stroke.[47]

Incretins are a class of metabolic peptide hormones that are synthesized in the gastrointestinal tract. They were first identified in 1929 by La Barre, who termed them "incretins," meaning "intestine secretion of insulin." These hormones are released in response to food intake to align metabolic reactions with blood glucose levels. They regulate insulin secretion from pancreatic β-cells and simultaneously control glucagon release from α-cells. Key members of this group include GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), alongside glucagon and peptides derived from proglucagon.[51] GLP-1, a peptide consisting of 31 amino acids, is a product of post-translational processing of preproglucagon in enteroendocrine cells located in the intestinal epithelium, specifically from the L cells in the distal colon and ileum. It is also synthesized in the neurons of caudal medulla spinalis. It has a brief biological half-life of about 1–2 min, due to its rapid degradation by dipeptidyl-peptidase-4 (DPP-4) when glucose levels drop, helping to prevent hypoglycemia.[52] GLP-1 receptors are members of the G-protein coupled receptor family. When GLP-1 binds related receptors, they activate adenylate cyclase, leading to increased levels of intracellular cyclic adenosine monophosphate (cAMP). Elevated cAMP levels subsequently activate the protein kinase A signaling pathway, which is crucial for regulating insulin release from pancreatic β-cells.[47]

As previously noted, GLP-1 has a very brief duration of action. To enhance glycemic control, researchers have developed GLP-1 analogs that mimic incretin effects and have longer-lasting impacts. Available GLP-1RA include Exenatide (Byetta®), Dulaglutide (Trulicity™), Semaglutide (Ozempic®, Rybelsus, and Wegovy), Liraglutide (Victoza and Saxenda), and Lixisenatide (Lyxumia and Adlyxin). Most of these medications are administered via subcutaneous injection, with the exception of Rybelsus, which is taken orally. GLP-1RA agents enhance glucose-dependent insulin production and secretion while reducing glucagon levels. This leads to decreased stress on the liver and pancreatic β-cells, improving insulin sensitivity in tissues. In adipose tissue, these drugs boost glucose uptake, encourage lipolysis, and increase the synthesis of free fatty acids, whereas in muscle tissue, they support glucose oxidation and glycogen formation. GLP-1 influences gastric emptying, motility, and acid secretion, thereby aiding digestion. Additionally, these agents reduce appetite by modulating nutrient intake through brain interactions, offer cardioprotective benefits, and promote natriuresis in the kidneys.[47,53] Clinical studies have shown significant reductions in body weight and HbA1c levels with GLP-1RAs.[54]

GLP-1RA agents have demonstrated cardiovascular benefits across various studies.[55] However, the mechanism behind these effects is still unclear. One aspect of atherosclerosis involves the proliferation and migration of vascular smooth muscle cells in which GLP-1 receptors are present within the neointima and that Exendin-4 (Ex-4), a GLP-1RA, could inhibit pathological vascular smooth muscle cells proliferation.[47] Also, a recent study showed that liraglutide treatment prevent vascular smooth muscle cells proliferation and migration induced by hyperglycemia through pathways involving ERK1/2 and PI3K/Akt.[44,55] In Figure 2, possible mechanisms by which GLP-1RA agents exert cardiovascular benefits are shown.

Another key feature of atherosclerosis is the recruitment of monocytes and their migration into the subendothelial space, where they transform into foam cells by taking up modified lipoproteins. GLP-1RA drugs have been shown to positively affect macrophages by lowering their inflammatory cytokine expression.[56] In animal studies, several protective effects of GLP-1RA agents were shown: reduced macrophage infiltration and apoptosis in atherosclerotic plaques, reduced monocytic adhesion in aortic wall tissue, diminished development of atherosclerotic plaques, normalization of blood pressure, reduced cardiac hypertrophy and vascular fibrosis, decreased inflammation and endothelial dysfunction, and oxidative stress.[57–59] Atherosclerosis onset is linked to the chronic exposure of endothelial cells to high blood glucose and hyperlipidemic conditions, which, combined with oxidative stress, activate inflammatory responses leading to monocyte and neutrophil adhesion to the endothelium. Preserving endothelial function is, therefore, crucial for protection against atherosclerosis. Studies indicate that GLP-1RAs exhibit anti-inflammatory properties in endothelial cells

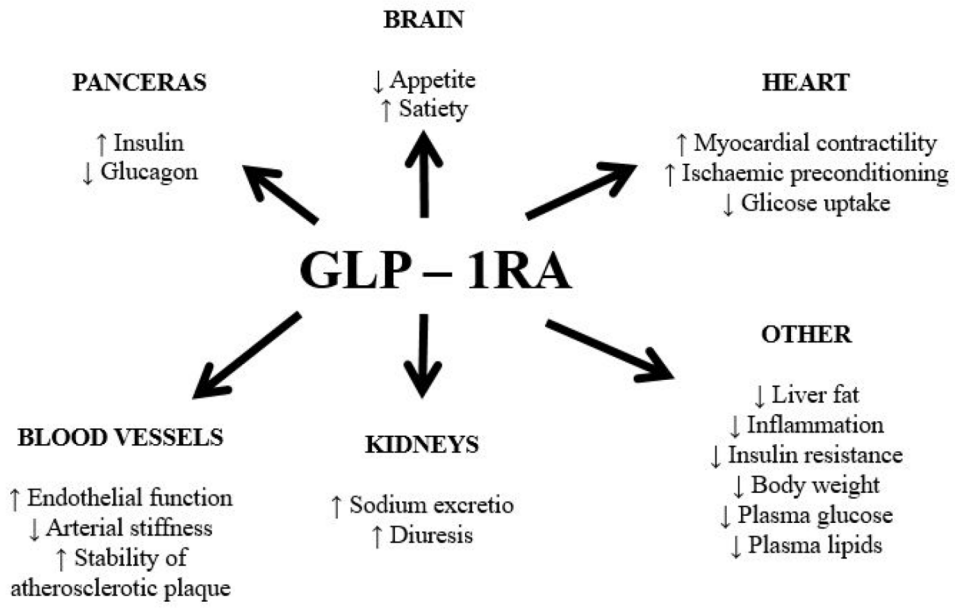

Figure 2. Possible mechanisms by which GLP-1RA agents exert beneficial effects on the cardiovascular system.
GLP-1RA, glucagon-like peptide-1 receptor agonists.

by downregulating NF-κB activation and reducing levels of ICAMs and VCAMs (VCAM-1) in human coronary and aortic endothelial cells in vitro.[60]

Several studies have highlighted the anti-inflammatory effects of GLP-1RA agents. For instance, dulaglutide reduces proinflammatory cytokines and chemokines via the JNK/NF-κB signaling pathway, while liraglutide lowers serum MCP-1 and NF-κB levels in type 2 diabetes patients when combined with insulin. Additionally, liraglutide has been shown to protect against nonalcoholic fatty liver disease by decreasing inflammasome components in mouse models, and it improves inflammatory and oxidative states, hemostasis, and endothelial function in sepsis or endotoxemia models, primarily through AMPKα1 and cAMP/PKA signaling pathways.[47,61]

Based on the above, particularly regarding the protective effect of GLP-1RA medications on the development of atherosclerosis, their role in diabetes control, and their impact on reducing inflammation, it is reasonable to suggest that these drugs could play a significant role in the prevention of stroke, particularly among diabetic patients.

Some trials have indicated a notable 9% reduction ($p = 0.012$) in the risk of nonfatal stroke associated with newer glucose-lowering medications in comparison with placebo, mainly attributed to a 16% reduction associated with GLP-1RA treatment. Additionally, significant benefits of GLP-1RA in preventing nonfatal stroke were demonstrated in the SUSTAIN-6 and Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND) trials. In summary, these studies showed that the link between reduced glycated hemoglobin levels and the risk of nonfatal stroke was strongly significant (beta = −0.531, $p = 0.008$, variance explained = 100%). Specifically, a 1% (10.93 mmol/mol) greater reduction in glycated hemoglobin was associated with a 41% lower risk of nonfatal stroke.[62] These findings suggest that GLP-1RA agents, especially those with longer half-lives, might be particularly effective in preventing major adverse cardiovascular events and possibly reducing stroke risk.[63] In 2021, a network meta-analysis of randomized clinical trials, which included a total of 21 trials with 170,930 participants, compared the efficacy and safety of GLP-1RA, SGLT2i, and DPP-4 inhibitors. The analysis revealed that only GLP-1RA was associated with a reduced risk of stroke compared to placebo.[64]

Recent meta-analysis study performed by Wei et al. in 2022 aimed to evaluate the risk of stroke, including both ischemic and hemorrhagic types, in patients with type 2 diabetes mellitus receiving GLP-1RA therapy. Researchers conducted a comprehensive search of RCTs on GLP-1RA therapy and cardiovascular outcomes from various databases including Medline (via PubMed), Cochrane Library, Embase, and the ClinicalTrials.gov. The analysis included data from 60,081 randomized participants across 8 trials and revealed that GLP-1RA treatment was associated with a statistically significant reduction in the risk of total stroke (~17%; Relative Risk (RR) = 0.83, 95% CI, 0.73–0.95, $p = 0.005$) and ischemic stroke (~17%; RR = 0.83, 95% CI, 0.73–0.95, $p = 0.008$) compared to placebo. However, there was no significant effect on the risk of hemorrhagic stroke (RR = 0.83, 95% CI, 0.57–1.20, $p = 0.31$). The authors concluded that GLP-1RA therapy significantly lowers the risk of ischemic stroke in individuals with type 2 diabetes and cardiovascular risk factors. It is crucial to highlight that the use of GLP-1RA agents did not significantly lower the risk of hemorrhagic stroke, even though the relative risk for hemorrhagic stroke was comparable to that for ischemic stroke. This lack of statistical significance may be attributed to the limited number of events and the study's power. Despite the meta-analysis indicating no significant reduction in the relative risk for hemorrhagic stroke, the overall absolute risk increase is concerning, with 50 events occurring among 29,069 patients treated with GLP-1RA agents.[65] Similarly, in a recent meta-analysis of Adamou et al., investigating the impact of GLP1-RA therapy on stroke risk, the authors reviewed 1369 studies, of which 11 were suitable, involving a total of 82,140 participants with a combined follow-up of 247,596 person-years. The group treated with GLP-1RA experienced a significantly reduced stroke rate compared to the placebo group, with consistent results regardless of the frequency of drug administration (daily or weekly). Furthermore, this group also showed a lower incidence of nonfatal strokes, with no variation based on administration frequency, method (subcutaneous vs oral), or the presence of diabetes. They concluded that this meta-analysis of 11 cardiovascular outcome trials indicates that GLP-1RA therapy leads to a 16% relative decrease in stroke risk compared to placebo.[66]

The retrospective cohort study performed by Yang et al. evaluated the impact of GLP-1RA agents on preventing ischemic stroke in Asian patients with type 2 diabetes without existing cardiovascular disease. The study followed 6534 GLP-1RA users and 6534 nonusers over a median period of 3 years. Results indicated that overall, GLP-1RA use did not significantly reduce the risk of ischemic stroke hospitalization compared to nonuse (adjusted HR, 0.69), but those with a GLP-1RA supply of over 251 days had a decreased risk of hospitalization for ischemic stroke (adjusted HR, 0.28).[67] This study is significant because it did not spread the outcome across various cardiovascular events but focused specifically on stroke. Similarly, in exploratory analyses of the REWIND trial, it was found that patients randomized to receive dulaglutide experienced a significant reduction in their risk of ischemic stroke. There were no notable differences in the risk of hemorrhagic stroke during follow-up, and similar trends were observed in the subgroup of participants with a history of stroke.[68]

The primary cardiovascular protective mechanisms of GLP-1RA agents are currently being studied and include their anti-inflammatory, anti-atherosclerotic, and antioxidant properties, as well as their role in reducing thrombotic events. Ex-4 has been shown to prevent macrophage foam cell formation by decreasing inflammatory and adhesion molecules in macrophages and monocytes, thereby reducing their buildup in arterial walls. Preclinical research indicates that liraglutide can inhibit oxidative stress and inflammation in endothelial cells through calcium and AMP-activated protein kinase (AMPK) pathways and can slow early-stage atherosclerotic plaque formation while stabilizing existing plaques.[69] GLP-1RA agents also lower inflammatory cytokines like IL-6, IL-1b, and TNF-a, and are suggested to have antioxidant and neuroprotective effects by enhancing vascular endothelial growth factor production and reducing proinflammatory cytokines. They also reduce ROS by inducing antioxidant gene expression and protect against glucotoxic damage by inhibiting key signaling pathways. Additionally, Ex-4 has been shown to inhibit thrombus growth in both normoglycemic and hyperglycemic mice. Real-world evidence suggests that liraglutide significantly decreases carotid intima-media thickness in patients with metabolic syndrome, and its direct effects include reducing cerebral infarct volume in ischemia-reperfusion injury models. These findings support the notion that may primarily exert their beneficial effects on

stroke prevention through their anti-atherosclerotic and vascular protective properties.[64,67]

Findings from previous meta-analyses, including the latest meta-analysis by Stefanou et al., conducted in 2024, show that treatment with GLP-1RA drugs significantly reduces major adverse cardiovascular events, overall mortality, and cardiovascular-related deaths in patients with type 2 diabetes. Additionally, GLP-1RAs significantly decrease the incidence of all-cause and nonfatal strokes in the same patients. Similar results have been shown for dual GIP and GLP-1RA tirzepatide. GIP/GLP-1RA tirzepatide.[70] Same group of authors in another meta-analysis showed that GLP-1RA drugs, as well as tirzepatide, lower cardiovascular risk and overall mortality in overweight or obese adults without diabetes. Moreover, these treatments help reduce the likelihood of myocardial infarction. However, data on stroke remain limited, and further RCTs are needed to assess the neuroprotective effects of these emerging anti-obesity medications.[71]

SGLT2i have been found to significantly lower the risk of death or hospitalization due to heart failure. Consequently, these medications have been incorporated into the latest ESC guidelines for managing both acute and chronic heart failure, being highlighted as a key component of the recommended treatment approach.[72] On the other hand, GLP-1RA agents are effective in reducing stroke occurrences in patients with type 2 diabetes and existing atherosclerotic cardiovascular disease. As a result, they have been included in stroke prevention guidelines by several organizations, including the American Stroke Association.[73] Also, it is important to highlight that the 2020 Canadian Best Stroke Practices recommend GLP-1RA agents for patients with type 2 diabetes who have previously had a stroke and have not yet met their HbA1C goals.[74] Additionally, the Diabetes, Cardiorenal, and Metabolism Task Force supports the use of GLP-1RA drugs, recognizing their effectiveness in both primary and secondary stroke prevention for individuals with type 2 diabetes.[75]

According to current guidelines and research, the use of GLP-1RA agents for stroke prevention is not specifically indicated for patients without type 2 diabetes. Further studies are needed to evaluate their effectiveness and safety in this population.

Additionally, it is worth mentioning that the treatment of diabetes, particularly with GLP-1RA agents, plays a significant role in managing comorbidities commonly associated with the condition, such as atherosclerotic cardiovascular disease, atrial fibrillation, heart failure, and chronic kidney disease. GLP-1RA drugs have shown considerable benefits in reducing the risk of major cardiovascular events in patients with diabetes, especially those with atherosclerotic cardiovascular disease, including reductions in stroke, myocardial infarction, and cardiovascular death. In fact, studies indicate that these drugs lower the occurrence of stroke by 19% compared to placebo, alongside significant improvements in hospitalization rates and reductions in major cardiovascular events. Though the impact of GLP-1RAs on atrial fibrillation remains somewhat controversial, they have been shown to significantly reduce the likelihood of atrial fibrillation development in diabetic patients, even if this did not lead to a corresponding decrease in stroke rates. In heart failure, GLP-1RAs offer notable advantages in improving overall cardiovascular outcomes compared to other therapies. However, their effects are less pronounced in preventing hospitalization for heart failure than those observed with SGLT2i. Regarding chronic kidney disease, GLP-1RAs agents contribute to favorable outcomes, but SGLT2i remain the primary choice for kidney protection. Overall, GLP-1RAs play a crucial role not only in controlling glucose levels but also in protecting against the progression of cardiovascular and renal diseases, making them a vital part of diabetes management in patients with these comorbid conditions.[76]

Conclusion and future perspectives

The future of stroke prevention holds exciting possibilities with emerging therapies that target both metabolic and inflammatory pathways. Recent advancements suggest that modern antidiabetic drugs, such as GLP-1RA agents and SGLT2i, offer significant benefits in controlling glucose levels and reducing the risk of cardiovascular events, including stroke.[44,45] These drugs improve overall cardiovascular health, potentially lowering stroke risk through mechanisms beyond glycemic control. In parallel, colchicine, traditionally used for gout treatment, has shown promise in reducing inflammation and preventing cardiovascular events.[11,12] Its ability to target inflammatory pathways associated with atherosclerosis suggests a role in preventing stroke by mitigating systemic inflammation.[18]

Future research should explore large-scale, long-term trials that evaluate the combined effects of these antidiabetic agents and colchicine on stroke prevention. These studies should also integrate other preventive modalities, such as lifestyle modifications and blood pressure management, to assess their collective impact on reducing stroke incidence. By combining pharmacological interventions with lifestyle changes and other preventive measures, we can develop more effective strategies to mitigate stroke risk and improve outcomes for patients globally.

Declarations

Ethics approval and consent to participate

Our study did not require ethical board approval because it did not involve working with patients; rather, it is a review of the current literature on cutting-edge issues related to stroke prevention.

Consent for publication

None.

Author contributions

Milija D. Mijajlović: Conceptualization; Formal analysis; Supervision; Writing – original draft; Writing – review & editing.

Natan M. Bornstein: Conceptualization; Methodology; Supervision; Writing – review & editing.

Vuk Aleksić: Formal analysis; Supervision; Validation; Visualization; Writing – review & editing.

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