REVIEW

Anti-Inflammatory Therapies for Atherosclerotic Stroke Prevention

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Abstract

Ischemic stroke caused by atherosclerosis is associated with the highest risk of recurrence among stroke etiologies, highlighting a residual risk that current secondary prevention strategies fail to address. Multiple lines of research implicate inflammation in the pathogenesis of atherosclerosis, including recent large cardiovascular outcome trials demonstrating that anti-inflammatory therapies can lower residual vascular risk in patients with coronary artery disease. Notably, low-dose colchicine, a long-used anti-inflammatory drug, has received approval for cardiovascular risk reduction in patients with atherosclerosis. However, translation of anti-inflammatory treatments to patients with ischemic stroke has been challenging, with the first colchicine trials showing neutral or conflicting results. In this study, we review the preclinical, genetic, and epidemiologic literature linking inflammation to atherosclerotic stroke; examine key findings of cardiovascular outcome trials for stroke prevention; and summarize completed and ongoing stroke-specific trials. We discuss the etiologic heterogeneity of ischemic stroke that may obscure anti-inflammatory treatment effects, highlighting the need for precision medicine approaches targeting patients with established atherosclerosis and vascular inflammation. Finally, we provide an overview of the emerging anti-inflammatory therapeutics that are under development for atheroprotection and outline a translational roadmap to accelerate clinical impact in stroke prevention.

Introduction

Stroke remains the second leading cause of death and a major contributor to adult disability worldwide.[e2,e3] Despite advances in prevention, the risk of recurrent vascular events after an ischemic stroke or TIA remains high.[e1] Population-based studies show a 5-year risk of recurrent stroke, acute coronary events, or vascular death of up to 40%.[e2,e3] This risk is particularly increased for stroke due to large artery atherosclerosis.[1,e4,e5] Secondary prevention strategies for these patients include low-density lipoprotein (LDL)–lowering; antiplatelet therapy; revascularization for symptomatic carotid stenosis; and control of vascular risk factors, including hypertension, diabetes, obesity, and smoking.[e6-e8] However, the substantial residual vascular risk is not fully addressed by current secondary prevention strategies.

Growing evidence highlights the role of immune mechanisms in the pathogenesis of atherosclerosis, positioning anti-inflammatory treatments as a promising prevention pillar (Figure 1).[e9,e10] Animal studies intervening with immune pathways demonstrated dramatic changes in the course of experimental atherosclerosis.[e11] More recently, phase 3 clinical trials provided proof-of-concept that anti-inflammatory treatments can reduce the risk of vascular events.[2-4] Low-dose colchicine received Food and Drug Administration (FDA) approval for lowering risk of myocardial infarction, stroke, coronary revascularization, and cardiovascular death in adult patients with atherosclerotic disease.[5,6] However, because the successful trials exclusively recruited patients with coronary artery disease, definitive evidence is lacking for risk reduction in ischemic stroke or TIA.[3,4] Consequently, colchicine has not been adopted for secondary prevention by the stroke community.

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Glossary

CCL-2 = C-C-chemokine ligand-2; **COVID-19** = coronavirus disease 2019; **CRP** = C-reactive protein; **FDA** = Food and Drug Administration; **FDG** = 18F-fluorodeoxyglucose; **HDAC9** = histone deacetylase 9; **HR** = hazard ratio; **hs** = high-sensitivity; **IL-6** = interleukin-6; **LDL** = low-density lipoprotein; **MACEs** = major adverse cardiovascular events; **NLRP3** = NLR family pyrin domain-containing 3; **RCT** = randomized controlled trial; **RR** = relative risk; **siRNA** = small-interfering RNA; **STEMI** = ST-elevation myocardial infarction.

This review outlines the preclinical, genetic, and epidemiologic literature linking inflammation to atherosclerotic stroke. We examine coronary artery disease trials and their implications for stroke prevention and zoom in on CHANCE-3 and CONVINCE, the first phase 3 studies aiming to transfer the concept of targeting inflammation to secondary stroke prevention.[7] We argue that heterogeneity in ischemic stroke etiology may dilute anti-inflammatory treatment effects, highlighting the importance of precision medicine approaches focusing on patients with atherosclerosis or vascular inflammation. We address the balance between personalization and pragmatism in trial design. Finally, we discuss proof-of-concept strategies with surrogate end points in phase 2 trials, explore anti-inflammatory interventions beyond colchicine, and propose a roadmap toward clinical translation.

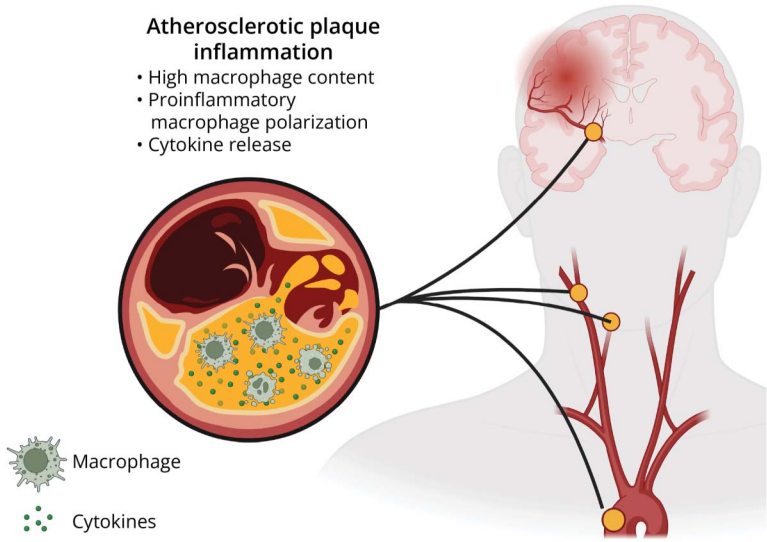
Evidence Base for Targeting Inflammation in Atherosclerosis

Studies of Atherosclerosis Specimens

Multiple lines of evidence support a role of inflammation in atherosclerosis and stroke risk (Figure 2). As early as 1913, Anitschkow described "large cells with foamy protoplasma" (now known as "foam cells") in aortas of fat-fed rabbits, which he assumed to originate from immune cells.[e12,e13] Decades later, immunohistochemistry confirmed an abundance of immune cells, primarily macrophages, in human atherosclerotic plaques.[8,e14] Modern high-throughput single-cell transcriptomic studies have uncovered a highly diverse immune cell landscape with cell types from both innate and adaptive immune systems,[9,10,e15-e19] including various macrophage and monocyte subtypes, T cells, neutrophils, B cells, dendritic cells, natural killer cells, and mast cells.[9,10,e15-e19]

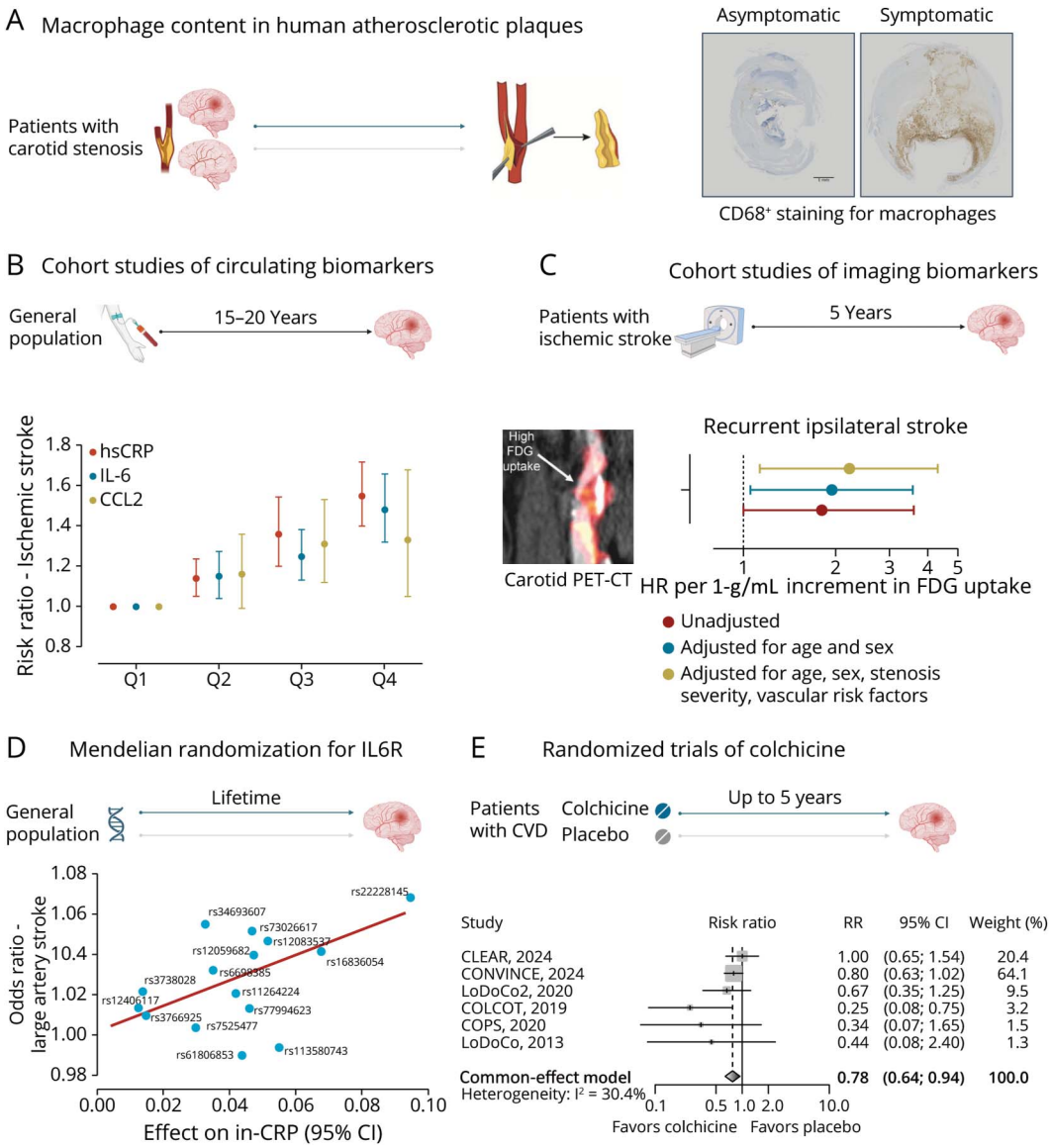
Most atherosclerosis-related strokes result from plaque rupture in brain-supplying arteries, leading to vessel occlusion or distal embolism (Figure 1).[e20] Classical immunohistochemistry studies from carotid endarterectomy specimens provide insights into the role of inflammation (Figure 2A). Plaques from patients with symptomatic carotid stenosis show greater immune cell infiltration, including monocytes, macrophages, and T cells, compared with advanced plaques from asymptomatic individuals.[11] Furthermore, plaque macrophage content is inversely associated with time from stroke symptoms to endarterectomy, suggesting higher macrophage content near rupture.[12,13] Higher intraplaque levels of proinflammatory cytokines, such as interleukin-6 (IL-6) and C-C-chemokine ligand-2 (CCL2 or MCP-1), have also been associated with symptomatic and unstable plaques.[12,22] The extent to which other immune cells detected through modern technologies are causal to plaque progression and rupture

Figure 1 Plaque Inflammation as a Contributing Mechanism to Atherosclerotic Ischemic Stroke



Immune mechanisms are involved in the local progression of established atherosclerotic lesions in brain-supplying arteries, leading to plaque destabilization and ischemic strokes.

Figure 2 Evidence Supporting the Role of Inflammation as Therapeutic Target in Atherosclerotic Stroke



(A) Carotid endarterectomy samples show higher infiltration of symptomatic carotid plaques with immune cells, including monocytes, macrophage, and T cells, when compared with advanced plaque from asymptomatic patients.[11-13] The immunohistochemistry images represent staining against CD68, a marker of macrophages in plaques removed from an asymptomatic and a symptomatic patient (examples from the AtherOMICS Biobank at the LMU University Hospital in Munich, Germany). (B) Meta-analyses of population-based prospective cohort studies support associations between midlife measurements of circulating levels of high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and CC chemokine ligand 2 (CCL2) and risk of incident ischemic stroke over follow-up periods extending up to 20 years.[14–16] (C) In vivo imaging studies of patients with ischemic stroke and carotid stenosis with 18F-fluorodeoxyglucose (FDG) PET that captures plaque inflammation show that increased FDG uptake is independently associated with a 5-year risk of stroke recurrence ipsilateral to the carotid artery stenosis.[17,18] (D) Genetic variants near the gene coding for IL-6 receptor (*IL6R*) that are associated with upregulated IL-6 signaling activity are linked to higher lifetime risk of large artery atherosclerotic stroke.[19–21] (E) A meta-analysis of colchicine clinical trials of patients with coronary artery disease or ischemic stroke shows a significant association with lower risk of ischemic stroke events.[e139]

remains largely underexplored, partly because of very small sample sizes of single-cell studies. Initial findings suggest more T cells, inflammatory macrophages, and proinflammatory smooth muscle cells, and fewer efferocytic macrophages in symptomatic plaques.[10,e21]

Studies of Experimental Atherosclerosis

Since the establishment of animal models of atherosclerosis, especially *Ldlr* and *Apoe* knockout mice, genetic and pharmacologic studies have revealed several immune mechanisms as potential drug targets, including (1) blocking immune cell recruitment to plaques, for example, through targeting chemoattractant chemokines[23,24]; (2) inhibiting macrophage-produced proinflammatory cytokines such as the inflammasome–IL-1β–IL-6 axis[e22]; (3) inhibiting neutrophil extracellular traps through neutralization of resident nuclear proteins[e23]; (4) inhibiting immune checkpoint T-cell activation, for example, by disrupting CD40-CD40L signaling[e24]; and (5) stimulating inflammation resolution by activating efferocytosis.[25,e25] A concept specifically interesting in stroke

involves brain ischemia triggering a systemic inflammatory response due to release of cell-free DNA in the circulation that can promote proinflammatory activity in existing plaques, leading to early rupture and stroke recurrence.[26] Neutralizing cell-free DNA in mice led to plaque stabilization and reduced recurrence risk after experimental stroke.[26] Noteworthy, although *Ldlr* and *Apoe* knockout mice develop aortic atherosclerosis, they do not exhibit spontaneous plaque rupture, the main mechanism underlying atherosclerotic stroke or myocardial infarction in humans.[e26,e27] This may explain the translation gap between approaches achieving decelerated plaque progression in mice and therapeutics lowering vascular risk in humans.[27,e28]

Studies of Inflammatory Biomarkers

Observational studies have consistently linked inflammatory biomarkers to higher cardiovascular risk (Figure 2B). A meta-analysis of prospective studies showed a log-linear association of C-reactive protein (CRP) levels with stroke and cardiovascular events.[14] Similarly, a meta-analysis found circulating IL-6 levels to be associated in a dose-response manner with incident ischemic stroke risk, independent of conventional vascular risk factors.[15] An individual patient data meta-analysis reported that 3-fold increases in high-sensitivity (hs) CRP or IL-6 after ischemic stroke or TIA are associated with a 20%–25% increase in risk of incident major adverse cardiovascular events (MACEs).[28] In vivo imaging studies using 18F-fluorodeoxyglucose (FDG) PET to assess plaque inflammation in patients with carotid artery stenosis showed that increased FDG uptake after stroke is associated with 5-year risk of ipsilateral stroke recurrence (Figure 2C).[17,18]

Human Genetic Data

Although prospective cohort studies offer valuable insights into the etiology of cardiovascular disease, they cannot provide proof for causal involvement of specific inflammatory mechanisms. Observational studies are prone to unmeasured confounding and reverse causality,[e29] and circulating inflammatory biomarkers may not reflect inflammatory activity within atherosclerotic lesions.[e30] Eventually, causality can only be established through randomized trials. Yet, study designs that leverage genetic data offer an alternative approach for exploration of causal relationships. Because the germline genetic profile cannot be influenced by confounders or disease outcomes, genetic studies are less susceptible to biases traditionally dominating observational epidemiology.[e31] Basic scientists have long used this concept in animal models, applying genetic knockouts or knockins to study causal involvement of genes in disease processes. The recent genomic revolution facilitated a deep exploration of the genetic architecture of stroke.[29] Among 89 genomic loci associated with stroke risk, variants in the gene encoding IL-6 receptor have been linked to atherosclerotic stroke.[19,29] This finding aligns with analyses of coronary and peripheral artery diseases, highlighting the role of IL-6 signaling in atherosclerosis.[30,31,e32-e35] Collapsing multiple variants within specific genes that mimic pharmacologic inhibition of the gene product offers further insights.[20,32] These so-called drug target Mendelian randomization studies[32] confirm that genetically downregulated IL-6 signaling is associated with lower risk of ischemic stroke, particularly driven by the large artery atherosclerotic phenotype (Figure 2D).[19,e36] When analyzing a broader set of cytokines, genetically proxied CCL2 levels have been associated with risk of ischemic stroke, again primarily driven by the large artery subtype.[20,33] Individuals carrying rare loss-of-function variants in the gene encoding the receptor of CCL2 (*CCR2*) exhibit lower lifetime risk of atherosclerotic cardiovascular disease.[34] Similarly, higher genetically proxied levels of TNF-α are associated with higher risk of coronary artery disease and ischemic stroke, with concordant effects across stroke subtypes.[e37] These findings highlight the power of human genetic studies in detecting inflammatory pathways with therapeutic targeting potential for atherosclerosis.

Clinical Trials

Several clinical trials assessed anti-inflammatory strategies to reduce cardiovascular events (Table 1). In JUPITER, rosuvastatin 20 mg daily reduced LDL-cholesterol and hsCRP values by 50% and 37%, respectively, and MACE risk by 44% in healthy individuals with elevated hsCRP.[e38] In CANTOS, subcutaneous canakinumab, an anti-IL-1β antibody, given quarterly, lowered MACE risk by 17% without affecting LDL cholesterol in patients with previous myocardial infarction.[2] The COLCOT[3] and LoDoCo2 trials[4] further showed that colchicine, a long-used anti-inflammatory drug that prevents microtubule assembly thereby disrupting inflammasome activation and other proinflammatory mechanisms,[35,e39,e40] lowers the risk of recurrent vascular events in acute coronary syndromes or stable coronary artery disease, respectively. While colchicine received approval for reducing cardiovascular risk in patients with atherosclerosis,[5,6] the more recent CLEAR trial in patients with acute myocardial infarction failed to show any benefit vs placebo (hazard ratio [HR] 0.99, 95% CI 0.85–1.16).[36] The discrepancy between CLEAR and the other cardiovascular outcome trials is still not well understood. CLEAR was conducted before, during, and after the coronavirus disease 2019 (COVID-19) pandemic and had a high discontinuation rate of 26%. Analyses restricted to 1989 of 7,062 patients recruited before COVID-19 showed a HR of 0.78 (95% CI 0.60–1.02), consistent with previous trials.[e41]

Secondary Stroke Prevention Trials

CONVINCE and CHANCE-3

Against this background, the CONVINCE and CHANCE-3 trials were designed to transfer colchicine for secondary prevention in patients with ischemic stroke (Table 1). CONVINCE randomized 3,154 patients with non-cardioembolic nondisabling ischemic stroke (modified Rankin Scale score ≤3) or high-risk TIA (transient focal motor or speech symptoms with either ABCD^2 score ≥4, or diffusion-weighted imaging–positive lesion, or cranio-cervical artery stenosis ≥50%) to low-

Table 1 Completed Phase 3 Randomized Controlled Clinical Trials Evaluating Anti-Inflammatory Therapies in Cardiovascular Disease Prevention

Study name (NCT), year	No. of participants	% of participants with history of stroke (% intervention vs % control)	Population	Intervention	Primary outcome	Follow-up	Findings	% incidence of stroke intervention vs control (HR [95% CI])
CANTOS (NCT01327846), 2017	10,061	N/A	Previous MI hs-CRP ≥2 mg/L	Canakinumab (50 mg, 150 mg, or 300 mg, SC Q 3 mo)	MACE (nonfatal MI, nonfatal stroke, or cardiovascular death)	48 mo	SC canakinumab reduced the hs-CRP in all doses SC canakinumab 150 mg Q 3 mo reduced by 25% the risk of MACEs No reduction in stroke risk observed	2.5 vs 2.8% (0.93 [0.72–1.20])
CIRT (NCT01594333), 2019	4,786	N/A	Previous MI or multivessel CAD and type 2 diabetes or metabolic syndrome	Low-dose methotrexate (target of 15–20 mg weekly)	MACE (nonfatal MI, nonfatal stroke, or cardiovascular death)	Median of 2.3 y	No reduction in IL-1β, IL-6, or CRP levels observed No reduction in MACE incidence observed No effect in nonfatal stroke risk	1.2 vs 1.3% (0.91 [0.54–1.52])
COLCOT (NCT02551094), 2019	4,745	2.6% (2.3 vs 2.8%)	MI within 30 d	Low-dose colchicine (0.5 mg daily)	MACE (cardiovascular death, resuscitated cardiac arrest, MI, stroke, urgent coronary revascularization)	Median of 22.6 mo	No reduction in hs-CRP levels (substudy) observed Low-dose colchicine reduced the risk of MACE by 23% Low-dose colchicine reduced the risk of stroke by 74%	0.2 vs 0.8% (0.26 [0.10–0.70])
LoDoCo2 (ACTRN12614000093684), 2020	5,522	N/A	Stable CAD, as evident by imaging criteria	Low-dose colchicine (0.5 mg daily)	MACEs (cardiovascular death, MI, ischemic stroke, urgent coronary revascularization)	Median of 28.6 mo	No routine measure of any biomarker Low-dose colchicine reduced the risk of MACEs by 31% No reduction in stroke risk observed	Ischemic stroke: 0.6 vs 0.9% (0.66 [0.35–1.25])
CONVINCE (NCT02898610), 2024	3,144	10.5% (10.0 vs 11.0%) Ischemic stroke as a qualifying event: 87.9% (88.0 vs 87.8%)	Non-cardioembolic ischemic stroke or high-risk TIA	Low-dose colchicine (0.5 mg daily)	MACE (fatal or nonfatal recurrent ischemic stroke, MI, cardiac arrest, or hospitalization)	Median of 33.6 mo	Colchicine reduced the hs-CRP No reduction in MACE risk observed No reduction in ischemic stroke risk observed	Ischemic stroke: 6.6 vs 8.3% (0.80 [0.62–1.03])

Continued

Table 1 Completed Phase 3 Randomized Controlled Clinical Trials Evaluating Anti-Inflammatory Therapies in Cardiovascular Disease Prevention *(continued)*

Study name (NCT), year	No. of participants	% of participants with history of stroke (% intervention vs % control)	Population	Intervention	Primary outcome	Follow-up	Findings	% incidence of stroke intervention vs control (HR [95% CI])
CHANCE-3 (NCT05439356), 2024	8,343	28.9% (28.6 vs 29.3%) Qualifying event: 88.8% (89.0 vs 88.0%)	Minor-to-moderate ischemic stroke or TIA hs-CRP ≥2 mg/L	Low-dose colchicine (0.5 mg twice daily on days 1–3, followed by 0.5 mg daily)	Any stroke	90 d	No reporting of CRP change No reduction in MACE risk observed No effect in ischemic stroke risk observed	6.3 vs 6.5% (0.98 [0.83–1.16]) Ischemic stroke: 6.2 vs 6.3% (0.98 [0.82–1.16])
CLEAR (NCT03048825), 2024	7,062	N/A	STEMI + PCI or large NSTEMI with prognostic risk factors + PCI	Colchicine (0.5 or 1 mg daily depending on body weight) and spironolactone (25 mg daily)	MACE (cardiovascular death, recurrent MI, stroke, unplanned revascularization)	Median of 3 y	Colchicine reduced CRP No reduction in MACE incidence observed No reduction in stroke risk observed	1.4 vs 1.2% (1.15 [0.72–1.84])

Abbreviations: CAD = coronary artery disease; CRP = C reactive protein; hs = high-sensitivity; MACEs = major adverse cardiovascular events; MI = myocardial infarction; NSTEMI = non-STEMI; SC = subcutaneous; STEMI = ST-elevation myocardial infarction.

dose colchicine plus guideline-based usual care vs usual care over a median follow-up of 3 years.[e42] Colchicine administration did not reduce either risk of MACE that was the primary outcome (HR 0.84, 95% CI 0.68–1.05) or recurrent ischemic stroke (HR 0.80, 95% CI 0.62–1.03).[7] Crucially, the trial suffered from low inclusion rates and protracted follow-ups during the COVID-19 pandemic, resulting in its conclusion before the planned number of outcomes could be accrued. It can be postulated that the high rates of colchicine discontinuation in CONVINCE may have had an impact toward the neutral results of the trial, as prespecified analyses indicated that there was evidence for a beneficial effect of colchicine in the subgroup of participants who were adherent to the study medication (HR 0.796, 95% CI 0.63–0.999). Consistent with previous research, patients allocated to colchicine treatment in CONVINCE had a 15% relative reduction in CRP levels at 28 days, followed by a roughly 20% reduction up to 3 years, compared with those allocated to no colchicine treatment.[37] CHANCE-3 tested the effects of short-term (90 days) low-dose colchicine treatment vs placebo in 8,343 patients with hsCRP ≥2 mg/dL, administered within 24 hours of symptom onset after a nonsevere acute ischemic stroke or TIA.[38] The study did not show any reduction in risk of subsequent stroke within 90 days for the colchicine groups, compared with placebo (HR 0.98, 95% CI 0.83–1.16).[38] CHANCE-3 assessed stroke recurrence over a very short treatment period and could not generate conclusions regarding long-term anti-inflammatory treatment with colchicine.

The most recent meta-analysis pooling colchicine randomized controlled trials (RCTs) for the prevention of vascular events reported significant risk reduction of composite myocardial infarction, cardiovascular death, or stroke in the colchicine group.[39] For ischemic stroke, no significant differences between treatment and control were found, although the effect estimate was borderline nonsignificant in the direction of favoring colchicine (relative risk [RR] 0.89, 95% CI 0.78–1.00). When excluding CHANCE-3 because of the short follow-up, there was a significant reduction in ischemic stroke (RR 0.78, 95% CI 0.64–0.94, Figure 2E). A previous meta-analysis not including CHANCE-3 and CLEAR had demonstrated a significant reduction in ischemic stroke risk under colchicine therapy.[40]

A Need for More Precise Patient Stratification?

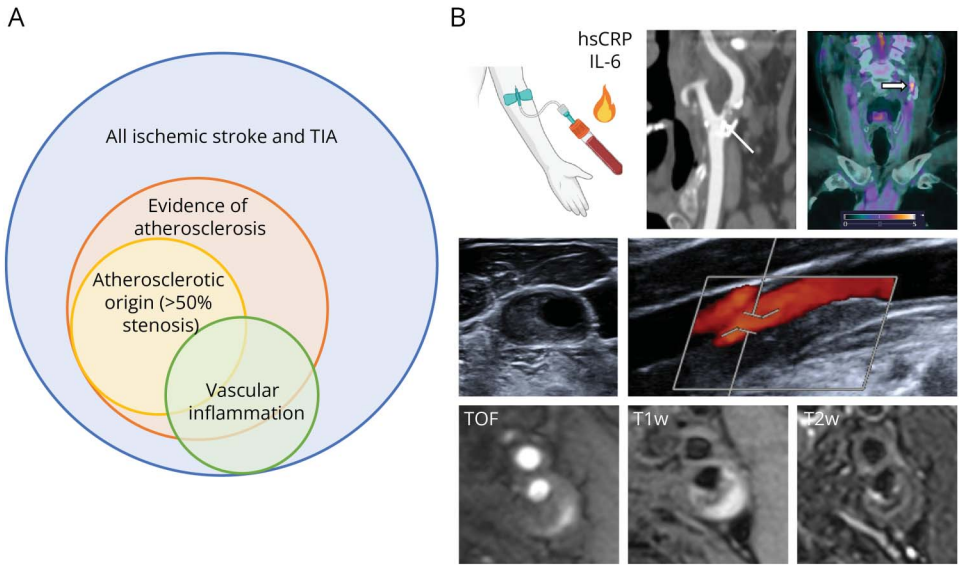
Several insights can be drawn from these trials, especially CONVINCE that tested colchicine over a longer window.[7] First, colchicine showed benefits in specific subgroups. Stroke is highly heterogeneous with multiple underlying etiologies. While CONVINCE excluded patients with a cardioembolic stroke, there were approximately 30% of patients with lacunar stroke and an unclear proportion of patients with cryptogenic stroke. Furthermore, 12% of patients had a TIA. The published study does not specify the number of participants with an incident stroke of large artery origin or with evidence of stenotic lesions in brain-supplying arteries. 22% of the study participants had a carotid stenosis >50%, and 8% had coronary artery disease. In subgroup analyses, the reduction in recurrent events was more pronounced in participants with advanced atherosclerotic disease (HR for patients with coronary artery disease 0.57, 95% CI 0.35–0.94; HR for patients with carotid stenosis >50% 0.77, 95% CI 0.51–1.15).

While lacunar strokes might be attributed to atherosclerosis of the parental artery, their primary cause is arteriolosclerosis of penetrating arterioles.[e43] The pathology of arteriolosclerosis differs from atherosclerosis, involving lipohyalinosis of the arteriolar walls.[e44,e45] While immune processes might be involved in arteriolosclerosis, their role is not as well understood as in atherosclerosis.[e46] Furthermore, lacunar strokes attributed to arteriolosclerosis are poorly defined with clinical and CT criteria alone and typically require MRI confirmation.[e47] In CONVINCE, MRI was not available for 37% of study participants, which might have influenced the accurate classification of lacunar strokes.[7] Similarly, the proportion of CONVINCE participants with cryptogenic strokes remains unknown.[7] While there is convincing evidence that some cryptogenic strokes are caused by nonstenotic atherosclerotic lesions,[41,e48-e50] other factors such as occult cardioembolism or cancer-related hypercoagulability also contribute.[e51] While inclusion of patients without atherosclerosis might have diluted the observed effect size in CONVINCE, subgroup analyses stratified by stroke etiology are still awaited.

Patient stratification could potentially help enhance treatment benefits (Figure 3). A reasonable approach could involve targeting patients with any evidence of atherosclerosis, either history of symptomatic coronary or peripheral artery disease or stenotic lesions in imaging of brain-supplying arteries, even if the latter were not causal for the qualifying event. The coexistence of competing stroke mechanisms is very common in ischemic stroke or TIA,[e52] even when atrial fibrillation–related stroke is present,[e53] making it often challenging to pinpoint a single underlying etiology. Stroke patients with atherosclerotic lesions in any artery, even if it does not supply the infarcted area or if the stroke has been classified as of underdetermined etiology, are at higher risk of stroke recurrence.[1,e54] Inflammatory markers are associated with recurrent stroke across multiple stroke etiologies, including undetermined stroke and lacunar stroke.[28] The risk of recurrence is higher even for stenoses as low as 30%.[1] Such lesions can be detected and quantified using head and neck CT angiography, which most stroke or TIA patients undergo in the acute setting, or with vascular ultrasound. Advanced techniques could further enhance risk assessment by evaluating atherosclerosis based on volumetric or morphological plaque characteristics beyond mere stenosis. For instance, specific plaque features assessed on CT angiography or MRI, such as large plaque volumes, plaque asymmetry, thin fibrous caps, large lipid cores, and intraplaque hemorrhage, are associated with higher recurrence risk.[e55-e57]

An even more interesting question is whether patient selection could be refined to include those with not only atherosclerosis but also evidence of plaque inflammation (Figure 3A). There is robust evidence linking circulating and imaging biomarkers of vascular inflammation to higher risk of incident and recurrent ischemic stroke.[42-44] Prospective cohorts of patients with ischemic stroke have demonstrated that circulating levels of hsCRP and IL-6 are associated with higher risk of recurrent vascular events.[42-44] Phase 3 trials in coronary artery disease have previously used inflammatory biomarkers, particularly hsCRP, for patient selection. For example, CANTOS specifically included patients with hsCRP levels >2 mg/L.[2] Post hoc analyses from CANTOS indicated that on-treatment levels of hsCRP <2 mg/L and IL-6 <1.65 ng/L correlated with reductions in cardiovascular risk, emphasizing the potential benefit of selecting patients with high baseline inflammatory biomarkers and room for

Figure 3 Considerations for Patient Selection for Clinical Trials Testing Anti-Inflammatory Treatments for Secondary Stroke Prevention



(A) Subgroups and overlap of patients with ischemic stroke that could be considered for secondary prevention trials of anti-inflammatory treatments. (B) Potential diagnostic modalities to be implemented for selection of patients with atherosclerosis of the brain-supplying arteries or evidence of vascular inflammation (top to bottom, left to right): circulating inflammation markers, CT angiography, 18-fluorodeoxyglucose PET (18FDG-PET-CT, kindly provided by Dr. S. Notohamiprodjo, Department of Nuclear Medicine, TUM University Hospital, Munich), carotid ultrasound, carotid magnetic resonance imaging (example images from the AtherOMICS Biobank at the LMU University Hospital in Munich, Germany). T1w = T1-weighted; T2w = T2-weighted; TOF = time-of-flight angiography.

reductions.[45,e58] By contrast, COLCOT and LoDoCo2 did not use hsCRP in their inclusion criteria, but still demonstrated risk reductions with colchicine.[3,4] Although CONVINCE did not use CRP for patient selection, it demonstrated significant and sustained reductions in CRP over 3 years after colchicine onset.[7]

A common critique of circulating CRP levels is their lack of specificity for atheroinflammation. In addition, CRP levels transiently increase during the acute phase after stroke,[e59] likely as a response to brain infarction, which may limit its utility as a marker of vascular inflammation in acute stroke settings. One potential solution is to randomize patients at a later time point after stroke, when CRP levels have stabilized. However, this approach may miss potential anti-inflammatory benefits in the acute phase, as suggested by preclinical studies.[46,e60] The temporal trajectories of CRP after stroke remain poorly characterized. Further research into the dynamic profiles of CRP, IL-6, and other emerging inflammatory biomarkers during the acute and subacute phases is urgently needed to address this knowledge gap.

An alternative includes imaging biomarkers (Figure 3B). Plaque inflammation can be detected by FDG uptake on PET imaging.[e61] FDG uptake in carotid PET-CT has been associated with macrophage content in experimental and human atherosclerosis.[e62-e64] Increased FDG uptake in PET-CT carotid imaging after ischemic stroke has been associated with risk of early and late recurrence.[17,e65] FDG-PET has been used both as a screening tool and as a primary outcome in phase 2 clinical trials testing anti-inflammatory or lipid-lowering treatments.[e66-e68] However, a lack of treatment effect on FDG uptake does not necessarily indicate therapeutic inefficacy because FDG signal may not capture all relevant aspects of plaque stabilization. Future efforts may benefit from using therapy-specific biomarkers that more directly reflect the targeted mode of action.

While phase 2 studies can be tailored to precision medicine approaches, it is important to adopt pragmatic strategies when designing phase 3 trials, which require large patient populations to demonstrate efficacy. The use of advanced imaging techniques—either for patient selection or as surrogate end points—is often impractical in definitive phase 3 trials. For instance, the broader use of FDG-PET in large-scale or real-world studies is limited by factors such as radiation exposure, scanner availability, complex implementation protocols, and challenges in standardizing image acquisition and analysis.[18] Despite their limitations, circulating biomarkers—particularly hsCRP—remain the most pragmatic option because they are widely available and can help identify high-risk patients for future trials. Alternatively, CT angiography could be used to detect atherosclerotic disease because it is part of the initial diagnostic workup for most stroke patients.

Ongoing phase 3 trials use varying criteria for patient selection, reflecting different approaches to targeting atherosclerosis and inflammation (Table 2). The ZEUS trial investigates ziltivekimab, a monoclonal anti–IL-6 antibody, in patients with established atherosclerosis.[47] It enrolls patients with systemic atherosclerotic disease, including patients with a history of stroke of atherosclerotic origin or stenosis ≥50% in any brain-supplying artery. ZEUS also uses a threshold of >2 mg/L for circulating hsCRP levels, despite reducing recruitment to patients with chronic kidney disease (estimated glomerular filtration rate <60 mL/min), who typically have higher CRP levels and a higher burden of atherosclerosis than the general population. The ongoing stroke colchicine trials follow different patient selection criteria. RIISC-THETIS (planned sample size of 2,800 patients) includes patients with a recent ischemic stroke and stenosis of ≥30% in any brain-supplying artery (lower than the threshold of 50% used to define atherosclerotic origin) and does not factor in CRP levels.[e69] On the contrary, CASPER includes patients with ischemic stroke regardless of etiology, provided that

Table 2 Ongoing Phase 3 Randomized Controlled Clinical Trials Evaluating Anti-Inflammatory Therapies in Stroke Prevention

Study name (NCT)	No. of participants	Population	Intervention	Primary outcome	Follow-up	Expected date of completion
CASPER (ACTRN12621001408875)	1,500	Non-cardioembolic ischemic stroke hs-CRP ≥1 mg/L	Low-dose colchicine (0.5 mg daily)	MACEs (nonfatal stroke, acute coronary syndrome, urgent revascularisation, cardiovascular death)	Median of 3 y	December 2027
RIISC-THETIS (NCT05476991)	2,800	Atherosclerotic ischemic stroke or TIA	Low-dose colchicine (0.5 mg daily) Ticagrelor (180 mg loading dose followed by 90 mg daily)	MACEs (ischemic or undetermined stroke, MI, urgent coronary or carotid revascularization, vascular death)	Median of 3 y	September 2027
CoVasc-ICH 2 (NCT06587737)	1,125	ICH within 72 h Evidence or risk factors of atherosclerotic cardiovascular disease	Low -dose colchicine (0.5 mg daily)	MACEs (stroke, cardiovascular death, MI, arterial revascularization) and dependency (mRS scores 3–5)	Median of 3 y	April 2029

Abbreviations: CRP = C-reactive protein; hs = high-sensitivity; ICH = intracerebral hemorrhage; MACEs = major adverse cardiovascular events; MI = myocardial infarction; mRS = modified Rankin Scale; SC = subcutaneous.

they have hsCRP >2 mg/L, and aims to include 1,500 patients.[e70] Finally, CoVasc-ICH will test colchicine in a planned sample of 1,125 patients with a recent spontaneous intracerebral hemorrhage and evidence of any atherosclerotic disease—symptomatic coronary, carotid, or peripheral artery disease or imaging evidence of extracranial or intracranial atherosclerosis causing any level of stenosis—or ≥2 vascular risk factors, without applying a CRP threshold.

Integrating Novel Biomarkers Into Real-World Stroke Management

Traditionally, RCTs focus on testing an intervention in broad and inclusive patient populations.[e71] Compared with other cardiovascular indications, the etiologic heterogeneity of stroke poses challenges in selecting a target population and develop effective new therapeutics.[e72] Biomarker-based trial designs have been proposed to study treatments within heterogeneous patient subpopulations and have been successfully implemented in oncology.[e73] The introduction of biomarkers has increased success rates for new cancer therapeutics, sparkling interest for similar designs to support precision medicine therapies in other settings.[e74] However, biomarker use in clinical trials of secondary stroke prevention needs careful consideration. Biomarkers can help identify patients who are more likely to benefit or develop side effects from an intervention[e75] but need to be valid, reproducible, and readily available. Investigators and regulatory authorities need to ensure that standardized tests are available and participating centers should have laboratories that can deliver them or be able to transfer samples to a core laboratory timely and effectively. Practical problems also arise on the selection of appropriate biomarker thresholds, which can introduce uncertainty.[e76] Except for adding to trial complexity, the implementation of a biomarker during screening or follow-up needs to be included in the reimbursement schedule and may substantially increase costs[e77] if not counterbalanced by reductions in ultimate sample sizes.[e78] Finally, the implementation of biomarkers may lead to greater discrepancy between the estimated efficacy of an intervention under the ideal conditions of a trial and the effectiveness of this intervention when the treatment is used in broad clinical practice.[e79] A positive biomarker-based phase 3 trial cannot be generalized to the entire population of stroke patients, and implementation of the tested treatment would be conditional on widespread implementation of the respective biomarker.

Future Perspectives

Next-Generation Immunotherapies

Several emerging therapies targeting immune mechanisms are in clinical development for atherosclerosis and may hold potential for stroke prevention (Figure 4 and eTable 1). Beyond ziltivekimab,[47,48] 2 other IL-6–targeting antibodies are progressing through phase 2 trials: the intravenously administered clazakizumab is advancing to a phase 3 trial in dialysis patients[49] while the subcutaneously administered pacibekitug is being tested for quarterly/monthly dosing in 120 patients with chronic kidney disease, elevated hsCRP, and atherosclerosis.[e80] IL-6 receptor–targeting monoclonal antibodies such as tocilizumab and sarilumab are already approved for autoimmune diseases.[e81] Tocilizumab has shown promise in phase 2 trials, reducing hsCRP levels in the acute ST-elevation myocardial infarction (STEMI) and non-STEMI,[50,e82] while increasing myocardial salvage in STEMI.[50]

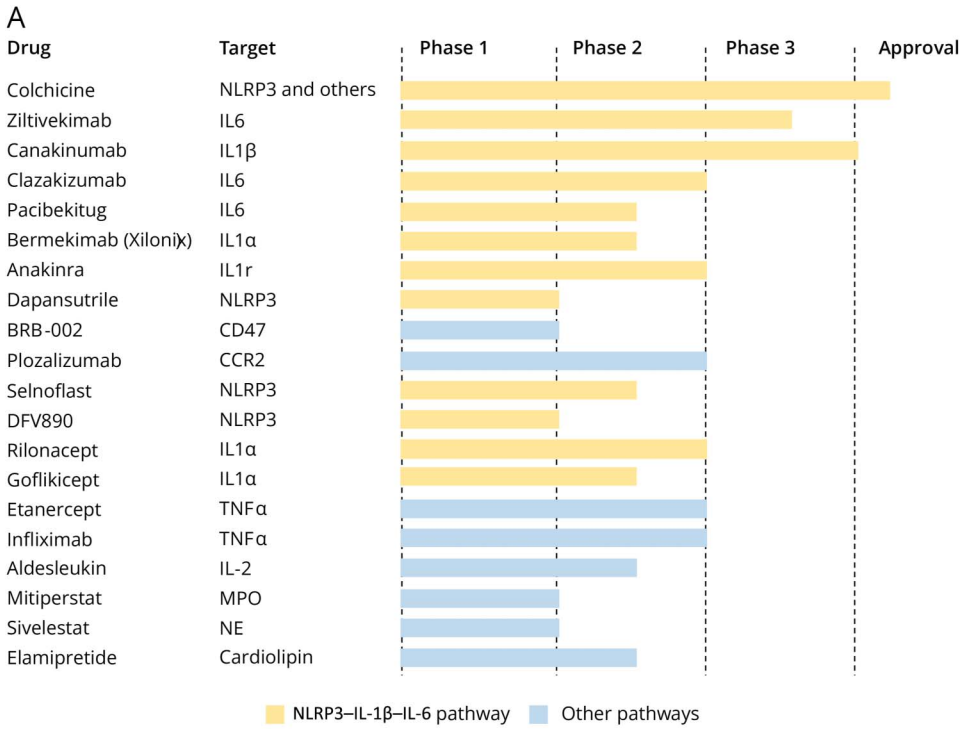
Upstream of IL-6, several drugs in development target IL-1 or the NLR family pyrin domain-containing 3 (NLRP3) inflammasome.[e83] IL-1 has 2 isoforms, IL-1α and IL-1β, each contributing differently atherosclerosis.[e84] Canakinumab, which specifically targets IL-1β, was the first anti-inflammatory therapy to demonstrate atheroprotective effects in a phase 3 study.[2] Anakinra, an IL-1 receptor antagonist, which nonselectively inhibits IL-1 signaling, significantly reduced hsCRP in 2 phase 2 studies of patients with acute coronary syndromes.[51,e85] Bermekimab (Xilonix), targeting IL-1α, showed a nonsignificant trend toward reduced restenosis and MACE rates in patients undergoing percutaneous femoral artery revascularization.[e86] Targeting the NLRP3 inflammasome is also under investigation. Dapansutrile, an oral selective NLRP3 inhibitor, completed a phase 1b trial in patients with stable systolic heart failure, demonstrating acceptable safety and tolerability.[e87] Further upstream, histone deacetylase 9 (HDAC9) is a potential upstream regulator of NLRP3, which emerged from human genetic studies as causally linked to atherosclerotic stroke and has support from cellular and animal studies.[e88] While specific HDAC9 inhibitors are lacking, valproate is a nonspecific HDAC inhibitor, reduces atherosclerosis burden in animal models, and is epidemiologically associated with lower stroke risk in human studies.[e89]

Beyond the NLRP3–IL-1β–IL-6 axis, emerging therapeutic approaches target mechanisms such as immune cell recruitment to plaques,[23] or impaired efferocytosis.[e90] The CCL2/CCR2 pathway is central to monocyte mobilization from the bone marrow and chemoattraction to atherosclerotic lesions.[33] Its causal involvement in both atherosclerotic stroke and coronary artery disease is supported by experimental,[e91-e94] genetic,[34,e95] and epidemiologic[16,e96,e97] data. A phase 2 trial of MLN1202, an anti-CCR2 antibody, in patients with vascular risk factors showed significant CRP reductions.[52] Efferocytosis, the clearance of dead cells to resolve inflammation, is disrupted in atherosclerosis, leading to accumulation of apoptotic and necrotic tissue within the plaque, resulting in local inflammation. CD47 upregulation in the surface of apoptotic cells transmits antiphagocytic signals, which impair inflammation resolution. Anti-CD47 antibodies have shown benefit in mouse models,[e98] and a first-in-human phase 1 trial testing the molecule BRB-002 is completed. Additional molecules are being evaluated in early-phase trials (Figure 4).

Novel Biomarkers of Vascular Inflammation

More specific biomarkers for vascular inflammation would be necessary for patient selection for personalized strategies or as

Figure 4 Therapies Approved and Under Development Targeting Immune Mechanisms for Lowering Vascular Risk in Patients With Atherosclerotic Cardiovascular Disease



(A) Drugs across the clinical development landscape. Yellow indicates drugs targeting the NLRP3–IL-1β–IL-6 pathway, and blue indicates drugs targeting other pathways. (B) Mechanisms targeted by the specified drugs. Bold indicates drugs targeting the NLRP3–IL-1β–IL-6 pathway. CCR2 = receptor of CCL2; IL-6 = interleukin-6; NLRP3 = NLR family pyrin domain-containing 3; TNF = tumor necrosis factor.

efficacy readouts in phase 2 studies. Imaging biomarkers offer spatial resolution for detecting inflammation in specific arterial beds. Beyond FDG, several novel PET tracers have been approved for human research to capture specific features of plaque biology.[e99-e103] Recent studies revealed the potential to assess inflammation in coronary CT angiography by analyzing pericoronary adipose tissue.[e104,e105] This model suggests that inflammation induces paracrine degeneration of perivascular adipocytes, observable as fat attenuation in CT imaging,[e106] but it remains largely unexplored in brain-supplying arteries.[e107-e109] MRI and ultrasound can identify plaque features suggestive of inflammation such as non-calcified, lipid-rich necrotic cores but lack specificity for inflammation itself.[e110,e111] Experimental approaches, such as ultrasmall superparamagnetic iron oxide–enhanced MRI,[e112,e113] dynamic contrast-enhanced MRI,[e114] and contrast-enhanced ultrasound,[e115] have shown promise for directly visualizing inflammatory activity.

Technological advances over the past decade have expanded the scope of biomarker research. First, high-throughput omics enable the simultaneous measurement of thousands of

circulating molecules, which could capture more specific signatures of vascular inflammation than traditional markers.[e116] Key challenges include variations between platforms (e.g., aptamer-based, antibody-based, and mass spectrometry proteomics) and the need for rigorous validation and standardization.[e117] Second, deep learning is transforming medical imaging, allowing the detection of biological patterns beyond human perception. These advances hold promise for vascular imaging–based personalized risk stratification. Developments in coronary CT angiography already allow reproducible assessment of plaque characteristics, including plaque burden, calcification, vulnerability, and inflammation, across the coronary vasculature.[e118,e119]

Assessing Efficacy Through Surrogate End Points

In the cardiovascular field, phase 3 outcome trials require very large sample sizes,[e120] with phase 2 studies focusing on causal intermediate biomarkers such as blood pressure, hemoglobin A1c, and LDL cholesterol, all accepted as surrogates by the FDA.[e121] However, anti-inflammatory treatments target a new mechanism, for which no accepted surrogate exists that could serve as proof-of-concept efficacy readout in phase 2. For example, most phase 2 trials testing anti-inflammatory treatments used CRP as the primary end point,[48,49,52] a broad inflammatory marker that is not a causal mediator of cardiovascular disease.[e122] Consequently, therapies, such as IL-6 inhibitors, may progress to phase 3 trials without concrete evidence of their impact on cardiovascular inflammation, as opposed to more general effects on systemic inflammation. To accelerate development, phase 2 studies could incorporate advanced vascular imaging (e.g., PET, CT, and MRI) to detect early signs of efficacy. In coronary artery disease, research has established strong correlations between imaging-based measures of plaque burden and vulnerability with clinical outcomes.[e123] Stroke trials could adopt a similar approach with imaging-based end points in proof-of-concept studies that could provide early signals of efficacy while also informing phase 3 trial design. These trials can identify responsive patient subgroups, uncover biomarkers predictive of outcomes, and guide dosing and follow-up durations. This strategy could help prioritize the most promising treatments and streamline progression to phase 3.

Balancing Immunosuppression With Host Response

Targeting inflammatory pathways faces key safety challenges, particularly the risk of impairing host response. In CANTOS, canakinumab was associated with a small, albeit significant, increase in fatal infections.[2] Stroke patients are particularly vulnerable to infections, especially in the acute phase or if the stroke causes dysphagia, which can lead to poor hospital outcomes and mortality. Beyond infections, other side effects also limit tolerability. Although colchicine did not increase infection risk or mortality, >10% of discontinued treatment because of gastrointestinal symptoms.[e124] This highlights the need to target immune pathways involved in plaque inflammation, while sparing host defense mechanisms. A promising approach, albeit still in early development, involves the targeted delivery of therapies to plaques, for example, small-interfering RNA (siRNA) encapsulated in nanoparticles.[e125-e127] For example, siRNA nanoparticles against *Ccl2* have been directed to bone-marrow endothelial cells to inhibit monocyte release and improve healing in mouse models of myocardial infarction.[e128] Other studies have achieved nanoparticle delivery to the fibrous cap, lesional macrophages, and endothelial cells in preclinical atherosclerosis models.[53,54,e129,e130] Stroke-specific issues also bear important considerations. Inflammatory processes contribute to infarct remodeling after stroke, and disrupting this process in the acute or subacute phase might influence recovery.[e131] Reassuringly, the colchicine stroke trials did not raise safety signals related to worse functional outcomes.[7,38] Stroke patients are also at higher bleeding risk in the acute phase due to impaired blood barrier in the infarcted area. Early post-stroke anti-inflammatory treatments could interfere with immune mechanisms involved in the repair process, thus increasing bleeding risk.[e132] However, this is less relevant for long-term secondary prevention trials that extend beyond the acute phase.

Targeting Inflammation for Stroke Prevention Beyond Atherosclerosis

While anti-inflammatory therapies are in translational development for atherosclerosis, growing evidence implicates inflammation in other stroke etiologies as well. Mouse studies show that stroke triggers a systemic immune response, which can worsen comorbidities,[e133] including post-stroke cardiac dysfunction and fibrosis driven by IL-1β–mediated inflammation.[46] NLRP3 activity is elevated in cardiomyocytes from patients with atrial fibrillation while NLRP3 overexpression in mouse cardiomyocytes induces an atrial fibrillation phenotype.[e134] *Il6* deletion in hypertensive mice prevents cardiac dysfunction, inflammation, and fibrosis.[e135] Human studies also support IL-6's role in cardioembolic stroke: the RELY study found elevated IL-6 levels to be associated with stroke risk in atrial fibrillation.[e136] Although Mendelian randomization studies have not conclusively linked IL-6 signaling to cardioembolic stroke, they do support a causal role in atrial fibrillation.[19] Genetically proxied IL-18—another NLRP3-regulated cytokine—has been strongly associated with cardiac remodeling, atrial fibrillation, and cardioembolic stroke.[55] Clonal hematopoiesis, a driver of age-related chronic inflammation, has also emerged as a driver of atrial fibrillation and heart failure in both experimental and epidemiologic settings.[56,e194] In cerebral small vessel disease, elevated CRP levels have been associated with higher burden of white matter hyperintensities in the Atherosclerosis Risk in Communities study,[e138] and preclinical data link hypertension to a neuroinflammatory response involving microglial activation, IL-1β production, and white matter loss.[57] Post hoc analyses of anti-inflammatory stroke trials stratified by underlying etiology may clarify whether targeting inflammation could benefit patients with cardioembolic or small vessel stroke.

Conclusions

Inflammation is a key contributor to stroke pathogenesis and a promising emerging therapeutic target. The CHANCE-3 and CONVINCE trials, despite not meeting their primary end points, provided key insights that reinforce the importance of precision medicine in stroke prevention. Future studies should refine patient selection, prioritizing those most likely to benefit. While colchicine's potential in stroke prevention remains to be fully realized, subgroup analyses suggest benefits in patients with atherosclerosis, supporting further investigation. Next-generation targeted immunotherapies, such as IL-6 or CCL2/CCR2 inhibitors, represent exciting possibilities. Moving forward, the challenge lies in designing pragmatic yet personalized trials that navigate stroke heterogeneity while identifying patient populations most likely to benefit from anti-inflammatory strategies.

Author Contributions

M.K. Georgakis: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. P. Melton: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. L. Živković: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A. Kopczak: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. A.H. Katsanos: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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