Repurposed Drugs

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Minocycline for Acute Stroke: A Systematic Review of Clinical Efficacy, Safety, and Translational Context

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Abstract

***Background*:** Minocycline is a lipophilic, second-generation tetracycline with anti-inflammatory, anti-apoptotic, antioxidant, and matrix metalloproteinase (MMP)-modulating properties. Experimental stroke studies have suggested that these pleiotropic effects can preserve blood–brain barrier integrity, attenuate neuroinflammation, reduce infarct evolution, and potentially mitigate reperfusion-related injury. Earlier clinical studies were small and methodologically heterogeneous, leaving uncertainty about whether minocycline improves patient-important outcomes after acute stroke. The recently reported EMPHASIS trial materially changes the clinical evidence base.

***Objective*:** To systematically review clinical studies evaluating minocycline initiated during the acute phase of stroke, with emphasis on functional outcome, neurological recovery, safety, sources of heterogeneity, and implications for practice and future research.

***Methods*:** A structured evidence synthesis was undertaken using PubMed-indexed literature, major journal databases, ClinicalTrials.gov, and bibliographies of relevant reviews and trials. Eligible studies enrolled adults with acute ischemic stroke (AIS) or intracerebral hemorrhage (ICH) and evaluated systemic minocycline initiated after symptom onset against placebo, usual care, or an active control. Randomized trials, prospective dose-finding studies, and clinical trial protocols/results were included. The principal outcome was 90-day modified Rankin Scale (mRS) outcome. Risk of bias was appraised narratively using RoB 2 domains. Because early trials differed substantially in stroke phenotype, route, dose, comparator, blinding, and outcome reporting, no de novo quantitative meta-analysis was performed.

***Results*:** The evidence evolved from promising open-label studies to one negative intravenous pilot study and, most recently, a large double-blind placebo-controlled trial. Early oral studies reported unusually large benefits but were vulnerable to performance and detection bias. The 95-patient Perth intravenous pilot found no benefit on 90-day mRS 0–2, although minocycline was well tolerated. The EMPHASIS trial randomized 1724 patients with moderate-to-severe AIS within 72 hours and found a higher 90-day rate of mRS 0–1 with minocycline than placebo (52.6% vs 47.4%; adjusted risk ratio 1.11, 95% confidence interval 1.03–1.20; p=0.0061), with a favorable ordinal mRS shift and no evident excess of symptomatic intracranial hemorrhage or serious adverse events. Certainty is now moderate for a modest functional benefit in an EMPHASIS-like population, but external validity remains constrained by geographic concentration, restricted severity range, and the limited evidence in contemporary thrombectomy-treated populations and ICH.

***Conclusions*:** Minocycline is no longer supported only by mechanistic plausibility and small exploratory studies: a large blinded trial shows a modest 90-day functional benefit in AIS without a major safety signal. Nevertheless, one positive phase III trial is insufficient to establish universal routine use. Replication across diverse health systems, rigorous evaluation alongside thrombolysis and thrombectomy, mechanistic biomarker studies, and adequately powered ICH trials are needed before broad guideline adoption.

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Introduction

Acute ischemic stroke remains a leading cause of death and long-term disability worldwide. (1) Reperfusion with intravenous thrombolysis and endovascular thrombectomy has transformed treatment for selected patients, yet many patients arrive outside treatment windows, have no treatable occlusion, do not achieve successful reperfusion, or sustain residual injury despite recanalization. (2–4) A safe, scalable adjunct that reduces ischemia-reperfusion injury and improves functional recovery therefore remains a major unmet need.

The post-ischemic cascade is not confined to abrupt arterial occlusion. Injured neurons and glia release damage-associated molecular patterns that activate resident microglia, endothelial cells, and infiltrating leukocytes. This process amplifies cytokine signaling, oxidative stress, protease activity, endothelial dysfunction, blood–brain barrier (BBB) permeability, edema, and delayed cell death. (5–7) MMP-2 and MMP-9 are particularly relevant because they participate in basal lamina degradation, BBB disruption, hemorrhagic transformation, and inflammatory cell trafficking. (8–10) These observations provide a biologic rationale for multi-target therapies rather than approaches directed at a single downstream molecular event (**Figure 1**).

Minocycline is a semisynthetic, second-generation tetracycline with high lipid solubility, good oral bioavailability, a relatively long half-life, and central nervous system penetration. (11,12) Its antimicrobial use is well established, but its potential role in neurological disease arises from non-antimicrobial actions: inhibition of microglial activation, suppression of pro-inflammatory mediators, modulation of MMP activity, attenuation of apoptosis, reduction of oxidative injury, and effects on mitochondrial pathways. (12–16) In preclinical stroke models, minocycline reduced infarct size and improved functional outcomes across a relatively broad therapeutic window. (17–20) It also showed potentially important interaction with thrombolysis: minocycline did not diminish alteplase fibrinolysis in experimental work and reduced markers associated with thrombolysis-related hemorrhagic injury. (21–23)

Translation of neuroprotection from animal models to stroke practice has repeatedly failed. Differences in species, comorbidity burden, occlusion models, anesthetic exposure, treatment timing, outcome ascertainment, and the complex clinical context of reperfusion make apparently compelling preclinical findings insufficient for clinical adoption. Early clinical minocycline studies generated enthusiasm but were small, often open-label, and heterogeneous. Two 2018 systematic reviews concluded that the drug was promising, particularly in AIS, but emphasized limited data and substantial heterogeneity. (24,25)

The publication of EMPHASIS, a large multicenter double-blind randomized trial, permits an updated assessment. This review synthesizes the clinical evidence for minocycline in acute stroke, explains why study results have differed, evaluates safety and applicability, and identifies the trials necessary to define minocycline's place in modern stroke care.

Methods

Review question and eligibility criteria

This review was structured around the following question: in adults with acute stroke, does systemic minocycline initiated after stroke onset, compared with placebo, usual care, or another control, improve functional or neurological outcome without unacceptable harm?

Eligible studies were randomized controlled trials (RCTs), controlled prospective studies, dose-finding studies, and registered/reported trials in adults with AIS or ICH. Minocycline could be administered orally, intravenously, or through a feeding tube and had to be initiated during the acute phase. Studies were eligible if they reported at least one clinical efficacy, functional, neurological, imaging, biomarker, or safety outcome. Preclinical studies were not included in the clinical evidence synthesis, but key mechanistic and translational studies were used to contextualize biological plausibility. Narrative reviews, case reports, and duplicate reports were excluded from outcome synthesis.

Information sources and search approach

A structured search was undertaken through September 12, 2026, using PubMed-indexed records, journal websites, ClinicalTrials.gov, and reference lists of relevant trials, systematic reviews, and trial protocols. Search concepts included "minocycline," "acute stroke," "ischemic stroke," "intracerebral hemorrhage," "neuroprotection," "thrombolysis," and "thrombectomy." The primary clinical reports by Lampl et al., Padma Srivastava et al., Fagan et al., Kohler et al., Amiri-Nikpour et al., and Lu et al. were specifically sought. The protocol and registry record for EMPHASIS were assessed to clarify design, population, dosing, and pre-specified outcomes. (26–31)

This is a focused systematic review rather than a prospectively registered review with a full dual-reviewer screening workflow. Consequently, it should not be interpreted as a replacement for a formal PRISMA-compliant evidence report with reproducible database line-by-line strategies and independent data extraction. Its reporting structure and critical-appraisal approach nevertheless follow PRISMA 2020 principles. (32)

Outcomes and risk of bias

The primary outcome was 90-day functional outcome measured by the mRS, preferentially excellent outcome (mRS 0–1), functional independence (mRS 0–2), or ordinal mRS shift. Secondary outcomes included NIHSS change, Barthel Index, infarct volume, hemorrhagic transformation, symptomatic intracranial hemorrhage, death, recurrent vascular events, infection, and treatment-emergent adverse events.

Risk of bias was appraised qualitatively using the domains of the revised Cochrane Risk of Bias tool (RoB 2): randomization, deviations from intended intervention, missing outcome data, outcome measurement, and selective reporting. (33,34) A pooled analysis was not recalculated because early studies had important heterogeneity in study populations, routes, dose schedules, control conditions, masking, and outcome definitions; combining their estimates with EMPHASIS without access to complete harmonized participant-level data could create misleading precision.

Results

Biological rationale and pharmacologic considerations

Minocycline is attractive as an acute stroke candidate for practical as well as biologic reasons. It is inexpensive, widely available, can be delivered orally or through a nasogastric tube, and is familiar to clinicians. Unlike narrowly targeted neuroprotectants, its proposed benefit derives from convergent effects on inflammatory and vascular injury pathways. Experimental evidence indicates suppression of microglial activation, inhibition of MMP-2/MMP-9 activity, reduction of oxidative stress and apoptosis, and preservation of BBB integrity. (13–16)

In rodent focal ischemia, minocycline reduced inflammation and protected against ischemic injury even when administration was delayed, providing a broader window than many acute neuroprotective candidates. (17,18) Low-dose intravenous regimens were neuroprotective in rat middle cerebral artery occlusion-reperfusion models. (19) Delayed treatment has also reduced activated MMP-2 and MMP-9 after experimental stroke. (20) In a relevant combination-therapy context, minocycline did not impair the fibrinolytic action of tissue plasminogen activator (tPA) in vitro and in vivo. (21) MMP inhibition has independently been associated with less thrombolysis-related hemorrhage in experimental thromboembolic stroke, and minocycline extended the experimental thrombolytic window in one model. (22,23)

However, mechanistic plausibility has two important caveats. First, inflammation is temporally dynamic: pathways that worsen hyperacute injury may also contribute to debris clearance, angiogenesis, remodeling, and repair later after stroke. (5–7) Broad anti-inflammatory treatment may therefore have timing- and phenotype-dependent effects. Second, the biological effects of minocycline cannot be assumed to be uniformly beneficial in all neurological settings. For example, suppression of chronic microglial activation after traumatic brain injury was associated with increased neurodegeneration in one study. (35) Stroke trials must therefore measure outcomes rather than infer benefit from biomarker modulation alone.

Early clinical studies

The first prominent clinical efficacy study was an open-label, evaluator-blinded trial by Lampl et al. Adults with AIS treated 6–24 hours after onset received oral minocycline 200 mg daily for 5 days or placebo/control. The trial reported a strikingly favorable 90-day functional result in the minocycline group. (26) Such a large effect was clinically provocative, but its interpretation is limited by the open-label design, relatively small cohort, and the potential for imbalances in co-interventions, rehabilitation, or clinical decision-making. Blinded assessment lessens but does not remove bias introduced by unblinded treatment allocation.

Padma Srivastava et al subsequently conducted a single-blinded controlled study in 50 patients with AIS, comparing oral minocycline 200 mg daily for 5 days with oral vitamin B. They similarly reported more favorable outcomes with minocycline. (27) The use of an active oral control rather than an indistinguishable placebo and single-blind design again creates concern about performance and assessment bias. The small sample size also makes effect

estimates unstable and vulnerable to chance baseline differences.

MINOS was a dose-finding, safety-oriented study of intravenous minocycline in acute ischemic stroke rather than a definitive efficacy trial. It supported the feasibility and tolerability of intravenous administration and helped establish an intravenous regimen for later work. (28) Pharmacodynamic analysis from an exploratory MINOS cohort suggested that minocycline was associated with reduced plasma MMP-9 levels, consistent with the proposed mechanism, although biomarker results cannot establish a clinical treatment effect. (29)

Amiri-Nikpour et al reported another open-label evaluator-blinded clinical study, suggesting neuroprotective benefit and a possible sex-dependent effect. (30) This finding is hypothesis-generating rather than practice-changing. Subgroup effects in small, unblinded or partially blinded trials are particularly susceptible to random variation and multiplicity. Nonetheless, the study highlighted the possibility that biological sex, hormonal milieu, stroke subtype, and inflammatory phenotype may modify the response to minocycline.

The Perth intravenous pilot trial

Kohler et al conducted a multicenter prospective randomized open-label trial with blinded endpoint assessment in 95 patients with ischemic or hemorrhagic stroke. Participants were randomized within 24 hours to intravenous minocycline 100 mg every 12 hours for five doses or routine care. The 90-day primary outcome of mRS 0–2 occurred in 29/47 (65.9%) patients assigned to minocycline and 33/48 (70.2%) assigned to usual care (rate ratio 0.94, 95% confidence interval [CI] 0.71–1.25; odds ratio 0.73, 95% CI 0.31–1.71). (31)

This trial did not show efficacy. Its result is important because it tempered the large early oral-study effect sizes and demonstrated that a clinically meaningful benefit could not simply be assumed. Yet it was a pilot study and not powered to exclude modest benefit or harm. It also differed from prior studies in multiple ways: intravenous rather than oral administration, only 2.5 days of treatment rather than 5 days, a mixed AIS/ICH population, higher baseline stroke severity than one earlier study, and an open-label allocation scheme. Thus, it is evidence against a large universal effect, not conclusive evidence of no effect in every stroke population.

Safety was reassuring. Mortality and hemorrhagic transformation were similar between groups, and urinary tract infections occurred less frequently with minocycline (0% vs 14.6%; p=0.012). (31) This infection signal is biologically plausible given antimicrobial activity but should be interpreted cautiously because it was a secondary outcome in a small unblinded pilot. It does not justify using minocycline solely for infection prophylaxis after stroke.

An exploratory meta-analysis within the Perth report pooled the three then-available human trials and suggested increased odds of mRS 0–2, but heterogeneity was extreme (I^2 approximately 90%). (31) The combination of very small trials, divergent routes and controls, variable blinding, and discordant effects makes that pooled estimate unsuitable as a reliable quantitative basis for practice.

Earlier systematic reviews

Two systematic reviews published in 2018 synthesized the limited clinical literature. Malhotra et al identified seven RCTs involving 426 participants and found that minocycline showed a favorable but non-significant trend for 3-month functional independence overall (risk ratio [RR] 1.31, 95% CI 0.98–1.74). In the AIS subgroup, they reported higher mRS 0–2 rates (RR 1.59, 95% CI 1.19–2.12), higher 3-month Barthel Index scores, and lower NIHSS scores, but heterogeneity was substantial for some endpoints, including NIHSS. (24) Sheng et al. combined rodent and clinical data, finding signals of improved NIHSS and mRS outcomes in clinical studies while appropriately stressing limitations in evidence quality and clinical trial size. (25)

These reviews were useful in establishing minocycline as a plausible repurposing candidate, but their results should now be interpreted historically. They were dominated by small studies conducted before widespread current-era thrombectomy, before robust placebo-controlled phase III evidence, and before EMPHASIS. Their apparently large AIS subgroup effect estimates likely reflect a combination of genuine signal, small-study effects, and design-related bias.

EMPHASIS: pivotal contemporary evidence

EMPHASIS was a multicenter, double-blind, randomized, placebo-controlled phase III trial conducted at 58 Chinese hospitals. Eligible participants were 18–80 years old, had AIS within 72 hours, NIHSS 4–25, and pre-stroke mRS 0–1. Participants received 200 mg minocycline loading dose followed by 100 mg every 12 hours for four days, or matching placebo, in addition to guideline-based care. Oral or

nasogastric administration was permitted, which is clinically relevant in patients with dysphagia. (36)

The published trial randomized 1724 participants. At 90 days, excellent outcome (mRS 0–1) occurred in 447/850 (52.6%) in the minocycline group versus 403/851 (47.4%) in the placebo group, yielding an adjusted RR of 1.11 (95% CI 1.03–1.20; p=0.0061). (37) The absolute difference was 5.2 percentage points, corresponding approximately to one additional patient achieving mRS 0–1 for every 19 treated patients, assuming the observed effect is causal and transportable. Ordinal analysis of the full mRS distribution also favored minocycline (adjusted common odds ratio 1.19, 95% CI 1.03–1.38; p=0.018). (37)

The result is qualitatively different from early signals of extremely large benefit. EMPHASIS indicates a modest, statistically significant improvement in excellent functional outcome rather than a dramatic reversal of disability. That magnitude is clinically meaningful at a population level if replicated, particularly for a low-cost, easily administered therapy, but it requires careful interpretation. The primary analysis was performed in randomized patients who received at least one dose of study drug, without imputation for missing data; this differs from a strict all-randomized intention-to-treat approach and should be considered when interpreting effect size. (37)

Safety findings were reassuring. Symptomatic intracranial hemorrhage was uncommon and similar at 24 hours (1/860 [0.1%] with minocycline vs 0/861 with placebo) and at 6 days (3/859 [0.3%] vs 0/861). Serious adverse events occurred in 40/862 (4.6%) and 51/862 (5.9%), respectively (p=0.24), with no significant differences in other reported safety outcomes. (37) The low absolute frequency of symptomatic hemorrhage means that the trial cannot prove equivalence for rare harms, especially in subgroups exposed to thrombolysis or thrombectomy; however, it provides meaningful reassurance that minocycline did not generate a major short-term safety signal in the studied population.

Ongoing and planned reperfusion-focused studies

The development landscape increasingly focuses on minocycline as adjunctive therapy during reperfusion. Clinical trials have been registered in patients undergoing endovascular treatment, including anterior-circulation thrombectomy and basilar artery occlusion, reflecting concern that recanalization alone may not address microvascular no-reflow, BBB disruption, inflammatory injury, and reperfusion-related hemorrhage. (36) The MIST-A protocol describes a multicenter prospective randomized open-label blinded-endpoint study of minocycline in anterior circulation ischemic stroke treated with intravenous thrombectomy. (38)

This approach is rational but unproven. In the contemporary stroke pathway, a neuroprotectant must not delay thrombolysis or thrombectomy and should be tested against the background of high-quality reperfusion care. Trials need prespecified analyses by reperfusion success, infarct core, collateral status, onset-to-drug time, use of intravenous thrombolysis, and hemorrhagic-risk phenotype. Imaging endpoints—final infarct volume, edema, hemorrhagic transformation, and perfusion/reperfusion quality—can help determine whether functional benefit is mediated by tissue salvage, reduced reperfusion injury, or other pathways.

Critical appraisal

Risk of bias and certainty of evidence

The evidence base contains two distinct eras (**Table 1**). The pre-EMPHASIS era consists principally of small trials with open-label or single-blind designs, limited concealment detail, non-identical controls, and often incomplete reporting of co-interventions. These studies have at least some concerns, and in several cases high risk of bias, in the RoB 2 domains of deviations from intended intervention and outcome measurement. Evaluator blinding is valuable, but it does not fully protect subjective rehabilitation-related outcomes from differences in clinical care, treatment expectations, or follow-up behavior.

The Perth trial had randomized allocation and blinded endpoint assessment but remained open-label and small; its broad confidence intervals are compatible with benefit and harm. (31) MINOS was appropriately designed for dose-finding and safety, not definitive efficacy. (28) Observed sex-specific signals require prospective validation.

EMPHASIS markedly improves certainty because it used central randomization, double blinding, matching placebo, a large sample, a prespecified functional endpoint, and a 90-day outcome horizon. Its result supports moderate certainty for a modest benefit in adults resembling its enrolled population. Residual uncertainty remains because the trial was conducted in one country, used a selected age and severity range, and has not yet been independently replicated. The certainty is lower for patients with minor stroke, very severe stroke, substantial prestroke disability, late presenters beyond 72 hours,

ICH, and those treated in reperfusion-dominant systems with high thrombectomy utilization.

Clinical heterogeneity

Clinical heterogeneity explains much of the inconsistent historical literature. Key differences include:

- **Population:** Earlier studies included different severities and, in one pilot, mixed ischemic and hemorrhagic strokes. EMPHASIS focused on moderate-to-severe AIS (NIHSS 4–25) in patients with good prestroke function.
- **Timing:** Treatment windows varied from 6–24 hours to within 72 hours. The clinically relevant therapeutic window may be determined by inflammation and BBB injury rather than the narrow time dependence of reperfusion.
- **Route and exposure:** Oral regimens commonly used 200 mg/day for five days; the Perth trial used five intravenous 100-mg doses over 2.5 days; EMPHASIS used a 200-mg load followed by 100 mg twice daily for four days. Whether route or cumulative exposure changes efficacy is not established.
- **Comparator and masking:** Controls ranged from usual care and oral vitamin B to matched placebo. The risk of bias is substantially lower in a double-blind placebo-controlled trial.
- **Background care:** Use of alteplase, thrombectomy, stroke-unit protocols, antithrombotics, and rehabilitation evolved considerably across studies and affects both event rates and generalizability.
- **Outcome definitions:** Studies reported different dichotomies of mRS, NIHSS time points, Barthel Index thresholds, biomarker measures, and imaging outcomes. Such differences make naïve pooling hazardous.

Safety and prescribing considerations

Short-course minocycline was generally well tolerated in the available acute-stroke trials. Nonetheless, a favorable trial safety profile does not eliminate routine prescribing precautions. Clinicians should consider tetracycline hypersensitivity, pregnancy or breastfeeding, severe hepatic dysfunction, severe renal impairment where dosing/monitoring may be relevant, prior serious tetracycline reactions, and clinically important interactions or contraindications such as concurrent systemic retinoids because of intracranial hypertension risk. Antibiotic-associated diarrhea and rare idiosyncratic hepatic, dermatologic, autoimmune, or vestibular adverse events should remain part of clinical monitoring.

Antimicrobial stewardship is also relevant. A short, targeted course might create less ecological pressure than prolonged antibiotic use, but routine off-label use in a large stroke population would expose many patients without infection to an antibiotic. The benefit–risk balance therefore depends on confirmation of clinical benefit, not simply on low drug cost or apparent short-term tolerability.

Discussion

The central conclusion of this review is that minocycline has progressed from an attractive but unproven neuroprotectant to a candidate supported by a large positive blinded trial. EMPHASIS provides the most credible estimate available: a modest absolute improvement of 5.2 percentage points in 90-day excellent functional outcome among patients with moderate-to-severe AIS treated within 72 hours. (37) The trial's favorable ordinal mRS shift and absence of an evident safety penalty strengthen the finding.

At the same time, the result should not be overstated. It does not prove that all patients with AIS should receive minocycline, nor does it establish efficacy in ICH. It does not establish that benefit is independent of reperfusion treatment, because detailed treatment-effect interactions require dedicated analyses. It does not show that a different dose, intravenous formulation, or initiation in the ultra-early ambulance setting would be better. Finally, it is one trial in a specific health system and population. The history of acute stroke pharmacotherapy argues for replication before guideline-level universal adoption.

The apparent contrast between dramatic early oral-study effects, a neutral intravenous pilot, and the modest positive EMPHASIS result is scientifically coherent. Small open-label trials tend to yield unstable and often inflated effects. The Perth pilot was too small and too heterogeneous to settle efficacy. EMPHASIS, by reducing bias and improving precision, likely offers a more realistic estimate. Rather than treating the studies as irreconcilable, the evidence can be understood as a maturation from exploratory signal to a modest but credible clinical effect.

Minocycline's potential role is as an adjunct, not a replacement for reperfusion. It should never delay diagnostic imaging, intravenous thrombolysis, transfer, or thrombectomy. Its greatest practical appeal may be that it targets inflammatory and BBB processes that persist after an occluded artery is treated and that it can be administered in settings where advanced reperfusion is unavailable. This

hypothesis requires direct testing in geographically and clinically diverse populations.

A future confirmatory program should include at least three elements. First, a multinational, placebo-controlled replication trial should test the EMPHASIS regimen or a pharmacokinetically justified alternative, with blinded centralized mRS assessment and strict all-randomized intention-to-treat analysis. Second, dedicated reperfusion trials should examine minocycline added to thrombolysis and/or thrombectomy, with imaging and hemorrhage endpoints. Third, an adequately powered ICH trial is needed because existing data are sparse and ischemic-stroke efficacy cannot be extrapolated to hemorrhagic stroke.

Biomarker-enriched designs could sharpen patient selection. Serial MMP-9, inflammatory cytokines, BBB-related markers, infarct imaging, collateral status, and reperfusion quality may identify phenotypes in which anti-inflammatory and vascular protection is most likely to matter. However, subgroup discovery must be disciplined: treatment interactions should be prespecified, biologically motivated, and replicated.

Conclusions

Minocycline has a credible mechanistic rationale and a favorable practical profile as an adjunctive acute stroke therapy. Early small trials were encouraging but methodologically fragile, and a small intravenous pilot was neutral. The large double-blind EMPHASIS trial now demonstrates a modest improvement in 90-day functional outcome in moderate-to-severe AIS treated within 72 hours, without an apparent increase in serious adverse events or symptomatic intracranial hemorrhage. (37)

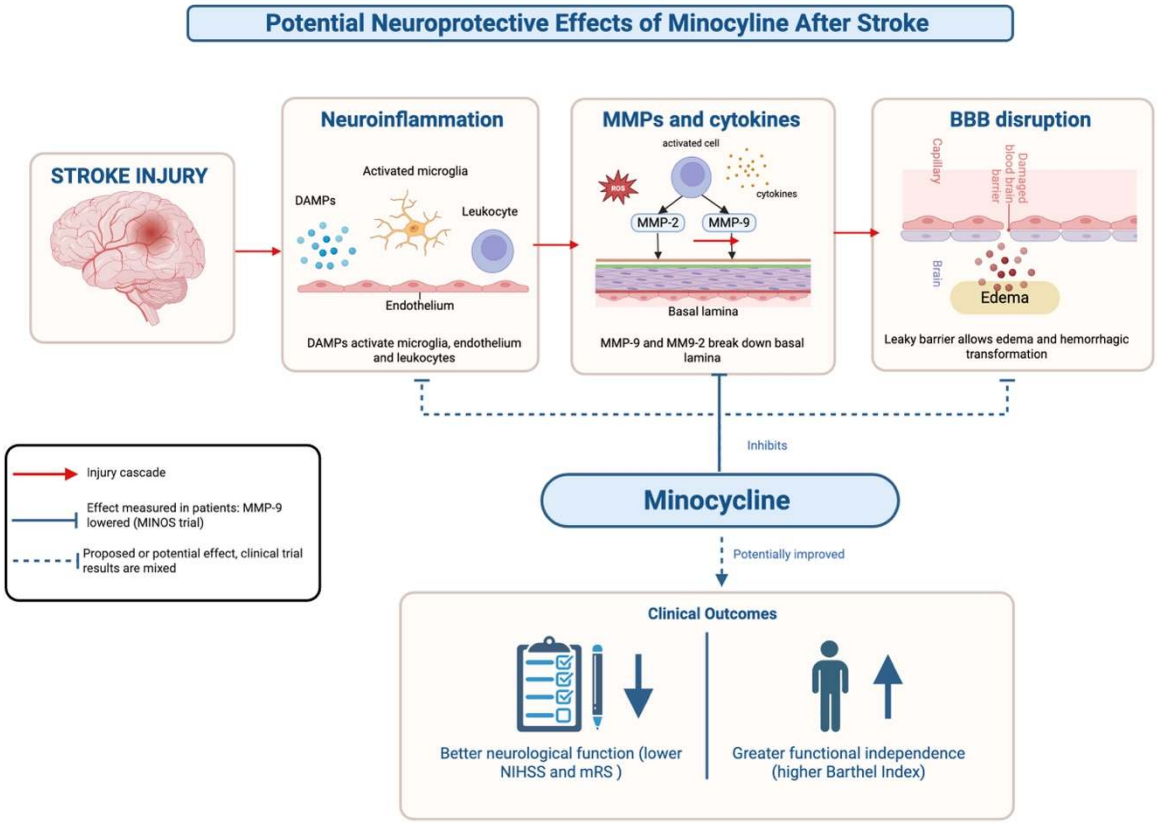
For current practice, minocycline should be considered investigational or selectively protocol-based rather than a universal standard of care pending independent confirmation and guideline review. The evidence most strongly supports further replication in AIS, particularly in contemporary reperfusion-treated populations. Efficacy in ICH, optimal route and duration, biological responders, and long-term safety remain unresolved.

Table 1. Minocycline in acute stroke: study characteristics and results

Study	Country	Study Design	N (IG/PG)	Mean age	Time to treatment (mean IG/PG)	Minocycline regimen	Outcome measured	Results
Lampl et al. (2007)	Israel	open-label, evaluator-blinded study	74 / 77	66.7 ± 11.11	6–24 h	minocycline 200 mg/day/5 days vs placebo	Changes from baseline to day 90 in NIHSS in the minocycline group vs placebo; also mRS and BI	NIHSS and mRS were significantly lower and BI scores were significantly higher in minocycline-treated patients (day 90 NIHSS 1.6 vs 6.5; mRS 0.9 vs 2.1; BI 94.9 vs 77.6 , p<0.0001). Deaths, MI, recurrent strokes, and hemorrhagic transformations during follow-up did not differ.
Padma Srivastava et al (2012)	India	randomized single-blinded open-label study	23 / 27	52.7 ± 15.3	6–24 h (13.5 vs 11.99)	minocycline 200 mg/day 5 days vs vitamin B capsules.	mRS, mBI, NIHSS, MRI brain at 1, 7 and 30 days. Primary outcome: changes at 90 days.	NIHSS was significantly better in patients minocycline group had at day 30 and 90 (p=0.05 and p=0.043) mRS scores and BI in minocycline group at 90 day follow up (p=0.04).
Amiri-Nikpour et al (2014)	Iran	open-label evaluator-blinded clinical study	26 / 27	65.89 ± 8.35	6-24 h	minocycline 200 mg oral mg/day/5 vs no minocycline**	NIHSS score at baseline 30, 60 and 90 days. Sex based analysis.	NIHSS score was significantly lower in the minocycline-treated compared with control on day 90 (median 4 IQR 4-7 vs 7 IQR 5-8 ; p=0.031). NIHSS score on day 30 and 60 was not significantly different. In males NIHSS was lower at days 30, 60 and 90 (p<0.05). No death, MI, recurrent stroke was observed in either group at 90 days.
Kohler et al (2013)	Australia	Randomized, open label, blinded endpoint, pilot (ischemic and hemorrhagic)	47 / 48	67.7 (IG) vs 67.9	Within 24h (10.7)	Minocycline 100 mg IV every 12 h x 5 doses vs no minocycline	Survival free of handicap mRS ≤ 2 at 90 days. Secondary NIHSS, BI, death, hemorrhagic transformation, infection, adverse events.	No significant difference in primary and secondary outcomes between the two groups, mRS 0-2 in 65.0% vs 70.2% ; 4.2% deaths in both groups. Fewer urinary tract infections with minocycline (p=0.012)
Lu et al., EMPAHSIS (2026)	Multicenter China	Randomized, double blind, placebo controlled	862 / 862	65.0	Within 72 h (41.3 h)	Minocycline 200 mg loading dose followed by 100 mg every 12 h for 4 days vs placebo	Excellent functional outcome at 90 days mRS 0-1. Secondary: mRS shift, NIHSS at 24 h and 6 days, change in hs-CRP at 6 days, early neurological deterioration, new stroke at 90 days, vascular events and death. Safety outcomes.	mRS 0-1 at 90 day was seen in 52.6% in the minocycline group vs 47.4% in the placebo group (adjusted RR 1.11, 95% CI 1.03-1.20; p=0.0061). At 90 days the shift of mRS score significantly favored the minocycline group. NIHSS scores were significantly lower in the minocycline group at 6 days but not at 24 hours.

IG = intervention group; PG = control group; MI= myocardial infarction **All patients in this study also received aspirin 100 mg daily

Figure 1. Proposed neuroprotective mechanisms of minocycline after acute stroke



Stroke injury releases damage-associated molecular patterns (DAMPs), which activate microglia, endothelial cells, and infiltrating leukocytes (neuroinflammation). Activated cells release cytokines, reactive oxygen species (ROS), and matrix metalloproteinases (MMP-9 and MMP-2), which degrade the basal lamina and tight junctions. The result is disruption of the blood-brain barrier (BBB), with edema and hemorrhagic transformation. Minocycline is proposed to inhibit these steps and so reduce secondary brain injury, which would be reflected in better neurological function (lower NIHSS and mRS scores) and greater functional independence (higher Barthel Index).

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