Efficacy and safety of minocycline in patients with acute ischaemic stroke (EMPHASIS): a multicentre, double-blind, randomised controlled trial

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Summary

Background Minocycline has been reported as a multi-target anti-neuroinflammatory drug with potential benefits for ischaemic stroke in preclinical models and small-scale clinical studies. The EMPHASIS trial was designed to provide robust evidence regarding its efficacy and safety in patients with acute ischaemic stroke.

Methods A multicentre, double-blind, randomised, placebo-controlled trial was conducted at 58 hospitals across China. Patients who had an ischaemic stroke in the previous 72 h with a National Institutes of Health Stroke Scale (NIHSS) score ranging from 4 to 25 and a level of consciousness score (subscale 1a of the NIHSS) of 1 or less were randomly assigned in a 1:1 ratio to receive minocycline or placebo in addition to routine treatment. Minocycline (loading dose of 200 mg, followed by 100 mg every 12 h for the subsequent 4 days) or matching placebo was administered orally. Block randomisation with a fixed block size of four stratified by study site was done with a computer-generated randomisation sequence. All patients, treating clinicians, and investigators involved in the trial were fully masked to treatment allocation. The primary outcome was an excellent functional outcome at 90 days (with a modified Rankin Scale [mRS] score of 0–1) and was analysed in all patients who were randomised and received at least one dose of the study drug, without imputation for missing data. Safety outcomes were assessed in participants who received at least one dose of the study drug and had at least one safety evaluation and included symptomatic intracranial haemorrhage at 24 h and 6 days. This trial was registered with ClinicalTrials.gov (NCT05836740) and is now completed.

Findings Between May 19, 2023, and May 20, 2024, 1724 patients were randomly assigned to minocycline (n=862) or placebo (n=862) groups. Median age was 65 years (IQR 57–71). 1151 (66·8%) patients were male and 573 (33·2%) were female. Median NIHSS score at baseline was 5 (IQR 4–7). Four patients withdrew consent (three in the minocycline group and one in the placebo group) and 19 patients were lost to follow-up (nine in the minocycline group and ten in the placebo group). At 90 days, 447 (52·6%) of 850 patients with minocycline and 403 (47·4%) of 851 with placebo had an mRS score of 0–1 (adjusted risk ratio 1·11, 95% CI 1·03–1·20; p=0·0061). Ordinal analysis across the full range of mRS scores also favoured minocycline, with an adjusted common odds ratio of 1·19 (95% CI 1·03–1·38; p=0·018). The incidence of symptomatic intracranial haemorrhage was similar between the minocycline and placebo groups at 24 h (1/860 [0·1%] *vs* 0/861 [0%]) and 6 days (3/859 [0·3%] *vs* 0/861 [0%]). No significant differences were observed in other safety outcomes, including serious adverse events (40/862 [4·6%] in the minocycline group *vs* 51/862 [5·9%] in the placebo group; p=0·24).

Interpretation Minocycline therapy initiated within 72 h of acute ischaemic stroke provided a significant functional outcome benefit compared with placebo at 90 days, without safety concerns. Future studies are needed to confirm these findings and to establish whether the benefits extend to patients with more severe or minor strokes.

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Introduction

Despite substantial advancements in ischaemic stroke treatment, including reperfusion therapy and guideline-based management, stroke remains a leading cause of long-term disability and mortality.[1] A key factor contributing to this high residual risk is the inflammatory cascade triggered during the acute phase of ischaemia. Neuroinflammation has a pivotal role in amplifying post-ischaemic injury and impairing functional recovery,[2] making it an important target for therapeutic intervention. However, the paucity of clinically effective drugs to counteract neuroinflammation in people with stroke

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†Study sites and investigators are listed in the appendix (pp 2–4)

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed from database inception to May 31, 2025, for randomised trials assessing the efficacy of minocycline in patients with acute ischaemic stroke, using the terms "minocycline" AND "stroke", with no language restrictions. This literature search identified four small-scale, single-blind randomised controlled trials (RCTs) with inconsistent findings. Three RCTs enrolled patients with acute ischaemic stroke (National Institutes of Health Stroke Scale [NIHSS] score >4 or 5) within 6–24 h of onset and reported that a 5-day oral minocycline regimen improved functional outcomes at 90 days, as measured with the modified Rankin Scale (mRS) or NIHSS. By contrast, the remaining trial recruited patients with any measurable neurological deficit within 24 h of onset, administered five doses of intravenous minocycline (over 2·5 days), and found no significant benefit on 90-day mRS scores.

A meta-analysis of three RCTs suggested that minocycline significantly improved functional independence (mRS 0–2; risk ratio 1·59, 95% CI 1·19 to 2·12; p=0·002) and reduced mRS scores (mean difference −0·67, 95% CI −1·31 to −0·03; p=0·04) at 90 days. A supplementary search of ClinicalTrials.gov identified three ongoing RCTs investigating the efficacy of minocycline in this context. Overall, minocycline could offer potential therapeutic benefits in patients with acute ischaemic stroke; however, the available clinical evidence remains scarce and inconclusive.

Added value of this study

The EMPHASIS study is the first large-scale, double-blind, randomised controlled trial to evaluate the efficacy and safety of a 4·5-day course of oral minocycline in patients with acute ischaemic stroke treated within 72 h of symptom onset. We found that patients treated with minocycline in addition to routine therapy were more likely to reach an excellent functional outcome (mRS 0–1) and a more favourable overall distribution of mRS scores than those who received placebo and routine therapy at 90 days. Moreover, minocycline did not appear to increase all safety outcomes compared with placebo. Therefore, minocycline could be implemented with routine medical therapy to reduce the risk of disability and improve neurological function in patients with acute ischaemic stroke.

Implications of all the available evidence

The EMPHASIS trial showed the benefit of minocycline on functional outcomes at 90 days in patients with acute ischaemic stroke. These findings add to the growing body of evidence supporting the possible role of minocycline as an effective and safe drug that can be used on top of routine medical therapy in acute ischaemic stroke. Our results invite more research into the area of assessing the neuroprotective effects of anti-neuroinflammatory agents and their possible use in ischaemic stroke.

remains a major obstacle, underscoring the urgent need for novel treatments that can attenuate this inflammatory damage and enhance recovery after stroke.

Minocycline, a widely used, well tolerated, and inexpensive tetracycline antibiotic, has emerged as a promising agent across various neurological diseases. The drug has been shown to delay progression in clinically isolated syndrome,[3] have a role in reducing intracerebral haemorrhage,[4] and, most importantly, potentially improve outcomes after stroke by targeting post-ischaemic neuroinflammation through multiple mechanisms.[5] In cerebral ischaemia models, minocycline suppressed acute microglial activation (a key initiator of the post-stroke inflammatory cascade), promoted the shift of microglia from a pro-inflammatory to an anti-inflammatory phenotype, inhibited matrix metalloproteinase pathways to preserve blood–brain barrier integrity, and reduced peripheral leucocyte infiltration into brain parenchyma.[6] These anti-inflammatory actions translate into cytoprotective effects, as evidenced by preclinical studies showing reduced infarct volumes and improved neurological outcomes.[7]

Despite encouraging preclinical findings, the MINERVA trial found no evidence that minocycline reduced microglial activation or permeability of the blood–brain barrier in people with cerebral small vessel disease,[8] and robust clinical evidence supporting the efficacy of minocycline in ischaemic stroke is currently scarce. The earliest clinical trial of minocycline in patients with acute ischaemic stroke reported potential functional benefits following a 5-day course of 200 mg daily, initiated 6–24 h after stroke onset, with effects observed up to 90 days post-stroke.[9] However, subsequent small-scale trials conducted in similar patient populations have yielded inconsistent results. These discrepancies are likely attributed to small sample sizes and heterogeneity in study design.[10–17]

Given the inconsistency in existing clinical evidence, we initiated the efficacy and safety of minocycline in patients with acute ischaemic stroke (EMPHASIS) study, which aimed to generate reliable evidence on whether, in conjunction with routine treatment, minocycline improves 90-day functional outcomes, as measured by the modified Rankin Scale (mRS), compared with placebo.

Methods

Study design

EMPHASIS was a prospective, multicentre, randomised, double-blind, placebo-controlled trial. The study was conducted across 58 hospitals in China. Ethical approval was granted by the Ethics Committees of the Beijing Tiantan Hospital (KY2023-007-04) and all the participating centres. Details of the protocol have been published[18] and

are available in the appendix (pp 54–83). This trial was registered with ClinicalTrials.gov (NCT05836740) and is now completed. This Article was prepared in accordance with the CONSORT 2025 statement.

Participants

Patients were eligible if they were aged 18–80 years and had an ischaemic stroke confirmed by brain CT or MRI within 72 h of symptom onset, with a National Institutes of Health Stroke Scale (NIHSS) score between 4 and 25, and a level of consciousness score (subscale 1a) ≤1. Additionally, only patients with either a first-ever stroke or a pre-stroke mRS score of 1 or less were included. Key exclusion criteria included allergy or resistance to tetracycline antibiotics, severe hepatic or renal insufficiency, and pregnancy or breastfeeding. A full list of the inclusion and exclusion criteria is provided in the appendix (pp 65–66). The sex of the patients was determined from their identity card, which indicated either male or female. Written informed consent was obtained from all patients or their legally designated representative when patients lacked capacity because of the severity of their condition.

Randomisation and masking

Patients were enrolled by researchers in the study site who did not have access to the randomisation and were masked during the whole process of the study. Patients were randomly assigned to receive either minocycline plus routine treatment or matching placebo plus routine treatment in a 1:1 ratio. Block randomisation with a fixed block size of four was used and stratified by study site. The random allocation sequence was generated by an independent statistical team using a centralised computer system. The minocycline and placebo capsules were identical in appearance and taste and were packaged in identical bottles labelled with a unique random number. All patients, treating clinicians, investigators, and outcome assessors were fully masked to treatment allocation.

Procedures

A loading dose of 200 mg of minocycline or placebo was administered orally as soon as possible within 30 min post-randomisation, followed by a maintenance dose of 100 mg every 12 h for the next 4 days. For patients with swallowing dysfunction, administration via a feeding tube was permitted. All patients were hospitalised and the study drugs were administered by physicians or nurses according to the protocol. Routine treatment followed national guideline recommendations (appendix p 78), with intravenous thrombolysis and endovascular thrombectomy permitted.

At baseline, demographic characteristics, medication use, medical history, physical examination, details of the presenting stroke, and NIHSS scores were obtained. Blood concentrations of high-sensitivity C-reactive protein (hs-CRP) were measured at hospitals equipped for this assay. Follow-up evaluations were undertaken at 24 (±2) h, at day 6 (±1), and at day 90 (±7) after randomisation, either via telephone or in person, by trained certified investigators. NIHSS scores were evaluated at 24 h and 6 days, and hs-CRP concentrations were reassessed at 6 days. The 90-day mRS assessments were recorded for central adjudication by an independent panel of experts who were blinded to group allocation.

Outcomes

The primary efficacy outcome of the EMPHASIS trial was an excellent functional outcome at 90 days, defined as an mRS score of 0–1. The mRS scores range from 0 (no symptoms) to 5 (severe disability) and 6 (death).[19] The secondary efficacy outcomes were the distribution of 90-day mRS score assessed by ordinal shift analysis; change in NIHSS score at 24 h and 6 days compared with baseline; change in hs-CRP concentrations at 6 days compared with baseline; early neurological deterioration at 24 h and 6 days; any new stroke (ischaemic and haemorrhagic stroke) at 90 days; any new ischaemic stroke at 90 days; composite vascular events including stroke, myocardial infarction, and vascular death at 90 days, and quality-of-life assessed with EQ-5D at 90 days (which is not reported in this Article). Additional post-hoc efficacy outcomes were functional independence (mRS score ≤2) and independent ambulation (mRS score ≤3). Definitions of all outcome events are listed in the appendix (pp 5–6).

Safety outcomes included symptomatic intracranial haemorrhage at 24 h and 6 days, based on the Heidelberg Bleeding Classification;[20] antibiotic-associated diarrhoea, enteritis, and constipation at 6 days; any bleeding event classified by the Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Criteria at 90 days;[21] vascular death at 90 days; all-cause death at 90 days; and investigator-reported adverse events or serious adverse events at 90 days.

Reports of events were submitted by local trained investigators, and outcome events were reviewed by a clinical event adjudication committee composed of independent clinical experts, who were blinded to treatment allocation. A data safety monitoring board, comprising independent academic experts and statisticians not involved in the trial conduct, monitored the trial every 6 months to ensure participant safety and adherence to ethical standards.

Statistical analysis

Statistical analyses were conducted in accordance with the prespecified statistical analysis plan by the trial statistician (appendix pp 86–103). Based on data from the China National Stroke Registry III, it was estimated that 60% of patients in the placebo group would have excellent functional outcome (mRS 0–1) at 3 months after the index ischaemic stroke. The sample size calculation

assumed an absolute increase of 8% in the proportion of participants achieving an mRS score of 0–1 with minocycline, corresponding to a rate of 68%. Accounting for a 10% dropout rate, a minimum of 1672 participants (836 per group) was estimated to provide 90% power to detect the treatment effect at a two-tailed significance level of 0·05. No interim efficacy analyses were done. An independent data monitoring committee conducted regular safety assessments throughout the trial.

Efficacy outcomes were assessed in the modified intention-to-treat population, defined as all patients who were randomised and received at least one dose of the study drug. The primary outcome was analysed using complete cases without imputation for missing data.

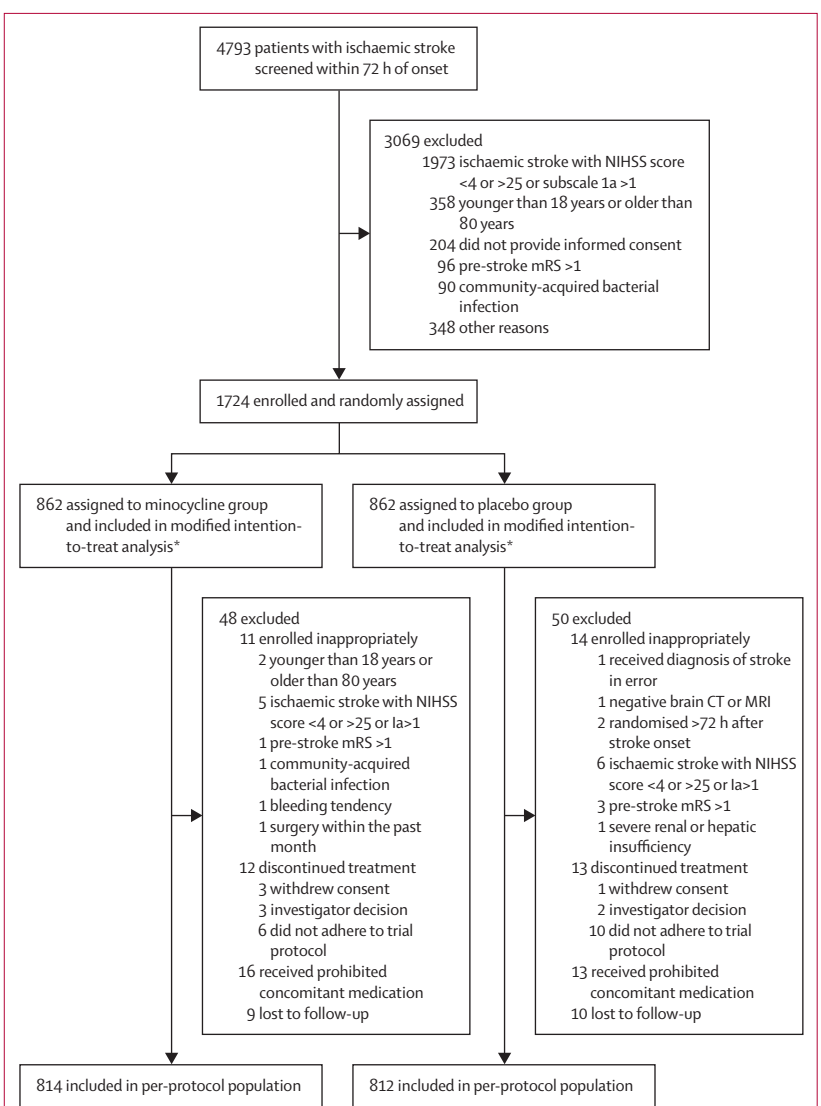

Figure 1: **Trial profile**
mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. *850 participants in the minocycline group and 851 in the placebo group had mRS scores available at 90 days and were included in the primary outcome analysis without imputation of missing data.

A generalised linear model with a log link and binomial error distribution was used, incorporating a mixed effect for pooled study centre, to calculate the risk ratio (RR) with 95% CIs between the two treatment groups. A post-hoc analysis without adjustment for study centre was also done. In the sensitivity analysis, missing data were imputed using prespecified multiple imputation and a post-hoc worst-case imputation scenario, both adjusted for the mixed effect of pooled study centres, to assess their impact on the outcome and the robustness of the treatment effect estimate. A tipping point analysis using the χ^2 test without adjustment for study centre was also done.

For secondary outcomes, the main analysis was also adjusted for mixed effect of pooled study centre. A shift analysis of the mRS score at 90 days was done with an ordinal logistic regression model to calculate the common odds ratio (OR) and 95% CI. Post-hoc analyses were conducted to compare the proportions of patients achieving an mRS score of 0–2 and 0–3 between the two treatment groups. Changes in NIHSS scores and hs-CRP concentrations were analysed with a linear mixed model to estimate the effect size. Early neurological deterioration was analysed with a generalised linear model with log link and binomial error distribution to calculate the RR with 95% CI between the two treatment groups. The cumulative risks of new stroke, new ischaemic stroke, and composite vascular events were estimated with Cox proportional hazards models, and hazard ratios (HRs) and 95% CIs were reported. When multiple occurrences of the same event type were observed, the time to the first event was used in the analysis. Efficacy analyses were repeated in a per-protocol population, comprising patients who received the allocated treatment without any major protocol violations.

All safety outcome analyses were conducted based on the safety analysis set, which included participants who received at least one dose of the study drug and had at least one safety evaluation. For symptomatic intracranial haemorrhage and events of antibiotic-associated diarrhoea, enteritis, and constipation, the generalised linear model was used to compare the RR between the two groups. Poisson regression was applied, when appropriate, for the analysis of rare events. For any bleeding event, vascular death, and all-cause mortality within 90 days, the Cox proportional hazards model was used. Adverse events and serious adverse events were analysed by χ^2 or Fisher's exact tests.

Potential heterogeneity of the effect of minocycline on the primary efficacy outcome was assessed across prespecified subgroups including age, sex, hypertension, diabetes, dyslipidaemia, previous ischaemic stroke, ever smoker, alcohol use, baseline hs-CRP concentration, reperfusion therapy, time to treatment, Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification,[22] and baseline NIHSS score. More information about the

conducted analyses is presented in the statistical analysis protocol (appendix pp 86–103).

All analyses were conducted using two-sided hypothesis testing, with a significance threshold of p=0·05. Statistical analyses were performed with SAS (version 9.4).

Role of the funding source

This was an investigator-initiated trial. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 19, 2023, and May 20, 2024, a total of 4793 patients were screened for eligibility. Overall, 1724 patients were randomly assigned to minocycline (n=862) and placebo groups (n=862); all received at least one dose of the study drug and were included in both the modified intention-to-treat and safety analysis population, which were identical in this study. The last patient follow-up visit was on Aug 15, 2024, and 23 (1·3%) patients did not complete the 90-day follow-up. Among them, four patients (three [0·3%] from the minocycline group and one [0·1%] from the placebo group) withdrew consent and 19 patients (nine [1·0%] from the minocycline group and ten [1·2%] from the placebo group) were lost to follow-up. Further, 98 (5·7%) patients (48 [5·6%] from the minocycline group and 50 [5·8%] from the placebo group) with major protocol deviations were excluded from the per-protocol analysis (figure 1).

Baseline characteristics were well balanced between the two treatment groups (table 1; appendix pp 11–12). The median age was 65 years (IQR 57–71); 1151 (66·8%) of 1724 patients were male and 573 (33·2%) were female. The median baseline NIHSS score was 5 (4–7), and the median time from stroke onset to the administration of the first dose of study drugs was 41·3 h (26·2–52·4). 244 (14·2%) patients received reperfusion therapy, including 210 (12·2%) who received intravenous thrombolysis and 42 (2·4%) who underwent endovascular treatment (appendix p 12). The profile of concomitant medications administered within 1 month preceding stroke onset and during the 90-day post-randomisation period was similar across the two groups (appendix pp 11, 13).

For the primary efficacy analysis at 90 days, mRS scores were available for 850 (98·6%) participants in the minocycline group and 851 (98·7%) in the placebo group. These participants were included in the final primary outcome analysis without imputation of missing data. A total of 447 (52·6%) of 850 patients with minocycline and 403 (47·4%) of 851 with placebo had an mRS score of 0–1 at 90 days (adjusted RR 1·11, 95% CI 1·03–1·20; p=0·0061; figure 2; table 2).

Secondary outcomes are shown in table 2. At 90 days, the distribution of mRS scores significantly favoured minocycline treatment (adjusted common OR 1·19, 1·03–1·38; p=0·018; figure 2). This favourable shift was corroborated in the per-protocol analysis (adjusted common OR 1·21, 1·03–1·41; p=0·020; appendix p 17). With respect to changes in NIHSS score from baseline, minocycline significantly reduced NIHSS scores at 6 days (adjusted β –0·28, –0·50 to –0·05; p=0·015), but not at 24 h (adjusted β –0·07, –0·20 to 0·06; p=0·32).

	Minocycline (n=862)	Placebo (n=862)
Age, years	65·0 (57·0–72·0)	65·0 (57·0–71·0)
Sex		
Male	573 (66·5%)	578 (67·1%)
Female	289 (33·5%)	284 (32·9%)
BMI, kg/m²	24·8 (22·7–26·9)	24·5 (22·5–26·8)
Medical history		
Hypertension	554 (64·3%)	572 (66·4%)
Diabetes	286 (33·2%)	280 (32·5%)
Dyslipidaemia	378 (43·9%)	363 (42·1%)
Previous ischaemic stroke	238 (27·6%)	258 (29·9%)
Coronary heart disease	95 (11·0%)	114 (13·2%)
Heart failure	5 (0·6%)	6 (0·7%)
Atrial fibrillation	45 (5·2%)	39 (4·5%)
Ever smoker	325 (37·7%)	359 (41·6%)
Alcohol use	223 (25·9%)	241 (28·0%)
Medication within 1 month before stroke		
Antiplatelet agent	108 (12·5%)	122 (14·2%)
Anticoagulant agent	12 (1·4%)	13 (1·5%)
Statins	103 (11·9%)	97 (11·3%)
Antibiotics	2 (0·2%)	4 (0·5%)
Pre-stroke mRS score		
0	739 (85·7%)	744 (86·3%)
1	122 (14·2%)	115 (13·3%)
≥2	1 (0·1%)	3 (0·3%)
hs-CRP at baseline, mg/L*	2·0 (0·8–4·8)	2·0 (0·9–4·6)
NIHSS score at baseline	5·0 (4·0–7·0)	5·0 (4·0–7·0)
Stroke subtypes (TOAST classification)		
Large-artery atherosclerosis	388 (45·0%)	398 (46·2%)
Cardioembolism	49 (5·7%)	42 (4·9%)
Small vessel disease	340 (39·4%)	347 (40·3%)
Other determined aetiology	30 (3·5%)	22 (2·6%)
Undetermined aetiology	55 (6·4%)	53 (6·1%)
Time from stroke onset to treatment		
Median (IQR)	41·9 (26·1–52·8)	40·5 (26·5–52·0)
≤24 h	179 (20·8%)	175 (20·3%)
>24 to 48 h	375 (43·5%)	396 (45·9%)
>48 h	308 (35·7%)	291 (33·8%)
Reperfusion therapy	114 (13·2%)	130 (15·1%)

Data are n (%) or median (IQR). Percentages might not total 100 because of rounding. hs-CRP=high-sensitivity C-reactive protein. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. TOAST=Trial of Org 10172 in Acute Stroke Treatment. *hs-CRP data are missing for 96 patients in the minocycline group and 95 in the placebo group.

Table 1: **Baseline characteristics**

Similar results were observed in the per-protocol analysis (appendix p 17). A non-significant greater reduction in hs-CRP concentrations was seen in the minocycline group compared with the placebo group (adjusted β –2·72, –5·64 to 0·19; p=0·067), whereas the difference was statistically significant in the per-protocol analysis (adjusted β –3·06, –5·98 to –0·14; p=0·040; appendix p 17). No significant between-group differences were observed in early neurological deterioration at 24 h and 6 days.

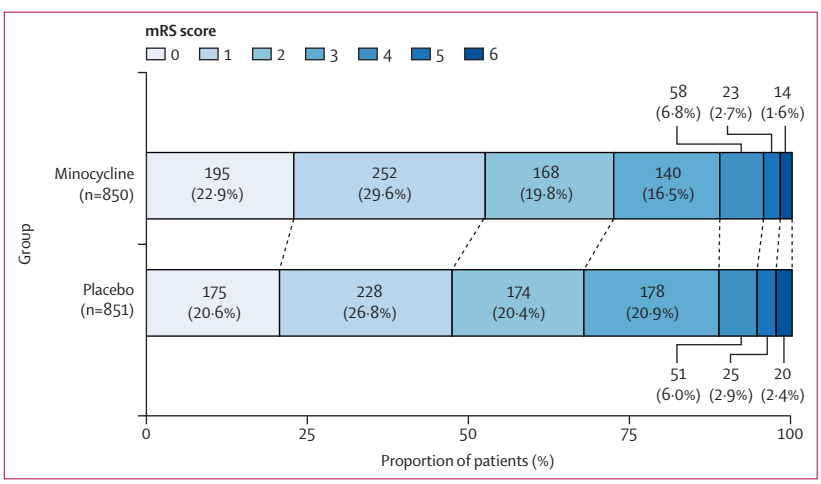

Figure 2: **Distribution of mRS scores at 90 days (modified intention-to-treat population)**
Percentages might not amount to 100% because of rounding. mRS=modified Rankin Scale.

As for the vascular events, any new stroke within 90 days occurred in 51 (5·9%) of 862 patients receiving minocycline compared with 47 (5·5%) of 862 patients in the placebo group (adjusted HR 1·09, 0·73–1·62; p=0·68). The overall risk of ischaemic stroke recurrence was 5·5% in the minocycline group and 5·0% in the placebo group (adjusted HR 1·09, 0·72–1·65; p=0·67). A composite vascular event was reported in 59 (6·8%) of 862 patients in the minocycline group and 52 (6·0%) of 862 patients in the placebo group (adjusted HR 1·14, 0·79–1·65; p=0·49).

Regarding the safety analysis, no significant differences were observed between the minocycline and placebo groups across any predefined safety outcomes (table 3). Frequencies of symptomatic intracranial haemorrhage did not differ significantly between the two treatment groups at either 24 h (1/860 [0·1%] in the minocycline group *vs* 0/861 [0%] in the placebo group) or 6 days (3/859 [0·3%] *vs* 0/861 [0%]). At 90 days, 14 (1·6%) of 862 patients had died of any cause in the minocycline group and 20 (2·3%) of 862 in the placebo group (adjusted HR 0·69, 0·35–1·36; p=0·28). A detailed summary of adverse events and serious adverse events is

	Minocycline (n=862)	Placebo (n=862)	Adjusted treatment effect* (95% CI)	p value
mRS 0–1 at 90 days†	447/850 (52·6%)	403/851 (47·4%)	RR 1·11 (1·03–1·20)	0·0061
Ordinal mRS score at 90 days	..	..	cOR 1·19 (1·03–1·38)‡	0·018
0	195/850 (22·9%)	175/851 (20·6%)	..	..
1	252/850 (29·6%)	228/851 (26·8%)	..	..
2	168/850 (19·8%)	174/851 (20·4%)	..	..
3	140/850 (16·5%)	178/851 (20·9%)	..	..
4	58/850 (6·8%)	51/851 (6·0%)	..	..
5	23/850 (2·7%)	25/851 (2·9%)	..	..
6	14/850 (1·6%)	20/851 (2·4%)	..	..
mRS 0–2 at 90 days	615/850 (72·4%)	577/851 (67·8%)	RR 1·07 (1·02–1·12)	0·0056
mRS 0–3 at 90 days	755/850 (88·8%)	755/851 (88·7%)	RR 1·00 (0·97–1·03)	0·94
Change in NIHSS score from baseline to 24 h§	0 (0–0)	0 (0–0)	β –0·07 (–0·20 to 0·06)	0·32
Change in NIHSS score from baseline to 6 days¶	–2 (–3 to 0)	–1 (–3 to 0)	β –0·28 (–0·50 to –0·05)	0·015
Early neurological deterioration at 24 h‖	52/848 (6·1%)	54/854 (6·3%)	RR 0·97 (0·64–1·47)	0·89
Early neurological deterioration at 6 days**	56/842 (6·7%)	66/840 (7·9%)	RR 0·85 (0·59–1·21)	0·36
Change in hs-CRP from baseline to 6 days, mg/L††	0 (–1·20 to 1·97)	0·20 (–0·94 to 3·73)	β –2·72 (–5·64 to 0·19)	0·067
Stroke recurrence at 90 days	51/862 (5·9%)	47/862 (5·5%)	HR 1·09 (0·73–1·62)	0·68
Ischaemic stroke recurrence at 90 days	47/862 (5·5%)	43/862 (5·0%)	HR 1·09 (0·72–1·65)	0·67
Composite vascular events at 90 days	59/862 (6·8%)	52/862 (6·0%)	HR 1·14 (0·79–1·65)	0·49

Data are n/N (%), unless otherwise indicated. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. hs-CRP=high-sensitivity C-reactive protein. RR=risk ratio. cOR=common odds ratio. HR=hazard ratio. *Adjusted for pooled study centres using a mixed-effects model. †The mRS score is missing for 12 patients in the minocycline group versus 11 in the placebo group at 90 days. ‡A cOR >1 indicates a shift towards better mRS outcomes (ie, lower disability). §The NIHSS score is missing for 15 patients in the minocycline group versus 8 in the placebo group at 24 h. ¶The NIHSS score is missing for 21 patients in the minocycline group versus 23 in the placebo group at 6 days. ||Early neurological deterioration at 24 h is missing for 14 patients in the minocycline group versus 8 in the placebo group. **Early neurological deterioration at 6 days is missing for 20 patients in the minocycline group versus 22 in the placebo group. ††Data on hs-CRP change from baseline to 6 days are missing for 172 patients in the minocycline group versus 184 in the placebo group.

Table 2: **Efficacy outcomes (in the modified intention-to-treat population)**

provided in the appendix (pp 20–21). Serious adverse events occurred in 40 (4·6%) of 862 patients in the minocycline group and 51 (5·9%) of 862 in the placebo group (p=0·24). The incidence of adverse events of interest, including nausea, vomiting, abdominal pain, diarrhoea, tooth discolouration, dizziness, headache, and respiratory infections, also showed no significant difference between the two groups.

Subgroup analysis of the primary efficacy outcome suggested a treatment effect modification favouring minocycline in patients with a history of alcohol consumption ($p_{interaction}$=0·025), and heterogeneity in treatment effect was observed across stroke aetiology classified by the TOAST criteria ($p_{interaction}$=0·018), with apparent benefit in artery disease and small vessel disease. No evidence of differential treatment effect was noted in the remaining prespecified subgroups (appendix p 10).

Analysis of the primary outcome without adjustment for the mixed effect of study centre yielded a similar RR of 1·11 (1·01–1·22; p=0·031; appendix p 16). A consistent result was observed in the per-protocol analysis (adjusted RR 1·12, 1·03–1·22; p=0·0069; appendix p 17). Sensitivity analyses following multiple imputation for missing mRS scores showed results consistent with the primary analysis (adjusted RR 1·11, 1·03–1·20; appendix p 18). However, under the worst-case imputation scenario (ie, where all missing cases were considered unfavourable for minocycline and favourable for placebo), the treatment effect was attenuated and marginally non-significant (adjusted RR 1·08, 0·999–1·17; p=0·054; appendix p 19). The tipping point analysis indicated that 76·9% of imputation scenarios remained in favour of minocycline (appendix p 9).

In post-hoc analysis of secondary outcomes, a greater proportion of patients in the minocycline group had an mRS score of 0–2 at 90 days than that in the placebo group (615/850 [72·4%] *vs* 577/851 [67·8%]; adjusted RR 1·07, 1·02–1·12; p=0·0056). However, the proportion of patients with an mRS score of 0–3 at 90 days was similar between the two groups (755/850 [88·8%] *vs* 755/851 [88·7%]; adjusted RR 1·00, 0·97–1·03; p=0·94).

Discussion

In the EMPHASIS trial, a 4·5-day minocycline treatment regimen in combination with routine treatment significantly enhanced 90-day functional outcomes, as measured by mRS, in patients with acute ischaemic stroke (NIHSS score 4–25) presenting within 72 h of symptom onset. Regarding secondary outcomes, an improvement in NIHSS scores from baseline to 6 days and greater reduction in hs-CRP concentrations at 6 days were observed in the minocycline group compared with placebo, although the between-group difference in hs-CRP concentrations was not statistically significant. Additionally, minocycline treatment appeared to be safe, with no significant difference observed with respect to serious adverse events and other safety outcomes.

Our trial focused on patients with acute ischaemic stroke (NIHSS score 4–25), a subgroup with a heightened inflammatory response and potentially greater therapeutic benefit. Moreover, recognising that the biphasic role of microglia—the primary immune-cell

	Minocycline (n=862)	Placebo (n=862)	Adjusted treatment effect (95% CI)*	p value
Symptomatic intracranial haemorrhage at 24 h†	1/860 (0·1%)	0/861 (0%)	..	..
Symptomatic intracranial haemorrhage at 6 days‡	3/859 (0·3%)	0/861 (0%)	..	..
Antibiotic-associated diarrhoea, enteritis, and constipation at 6 days‡	0/859 (0%)	2/861 (0·2%)	..	..
Any bleeding event at 90 days	63/862 (7·3%)	69/862 (8·0%)	HR 0·90 (0·64–1·27)	0·56
Minor bleeding§	56/862 (6·5%)	63/862 (7·3%)	HR 0·88 (0·61–1·26)	0·49
Moderate bleeding§	1/862 (0·1%)	2/862 (0·2%)	HR 0·50 (0·05–5·52)	0·57
Severe bleeding§	8/862 (0·9%)	6/862 (0·7%)	HR 1·34 (0·46–3·85)	0·59
Any bleeding event at 90 days¶	..	..	cOR 0·91 (0·64–1·30)‖	0·60
None	799/862 (92·7%)	793/862 (92·0%)	..	..
Minor	54/862 (6·3%)	61/862 (7·1%)	..	..
Moderate	1/862 (0·1%)	2/862 (0·2%)	..	..
Severe	8/862 (0·9%)	6/862 (0·7%)	..	..
Vascular death at 90 days	10/862 (1·2%)	16/862 (1·9%)	HR 0·62 (0·28–1·36)	0·23
All-cause death at 90 days	14/862 (1·6%)	20/862 (2·3%)	HR 0·69 (0·35–1·36)	0·28

Data are n/N (%), unless otherwise indicated. HR=hazard ratio. cOR=common odds ratio. *Adjusted for pooled study centres using a mixed-effects model. †Data on symptomatic intracranial haemorrhage at 24 h are missing for two patients in the minocycline group and one in the placebo group. ‡Data on symptomatic intracranial haemorrhage and antibiotic-associated diarrhoea, enteritis, and constipation at 6 days are missing for three patients in the minocycline group and one in the placebo group. §In patients with multiple bleeding events of differing severity, the earliest event for each severity category (ie, minor, moderate, and severe) was included in the analysis. ¶In patients with multiple bleeding events, the highest severity was used for analysis. ‖A cOR >1 indicates a shift towards more bleeding and bleeding of greater severity.

Table 3: **Safety outcomes (in the safety population)**

target of minocycline—could initially exacerbate ischaemia-induced injury and later support neural repair,[2] a short-course minocycline regimen was adopted in our trial to target acute-phase, post-stroke inflammation, thereby contributing to the growing body of evidence supporting its potential functional benefits.

Our results are consistent with previous interventional studies: three open-label randomised trials in patients with acute ischaemic stroke (NIHSS >4 or 5) have shown that a 5-day course of oral minocycline (200 mg/day), initiated within 6–24 h of onset, improved 90-day functional outcomes, as assessed by the mRS or NIHSS.[9,12,14] A meta-analysis of three randomised trials including 242 patients with ischaemic stroke showed a significant improvement in 3-month functional outcomes with minocycline.[23] However, in the MINOS study, which enrolled patients with any measurable neurological deficit and administered intravenous minocycline (3–10 mg/kg per day for 3 days) within 6 h of onset, a clinical benefit was observed at 7 days, but was not sustained at 90 days.[10,11] Moreover, four additional trials reported no significant functional improvement at 90 days.[13,15–17] Multiple factors could account for the inconsistency between these results, including random variation from the small sample size, difference in minocycline administration and dosage, and patient heterogeneity.

Regarding patient selection, drawing from previous trials, the EMPHASIS study enrolled patients irrespective of reperfusion therapy to enhance the generalisability of the findings. In subgroup analysis, functional outcomes did not differ significantly between patients who received reperfusion and those who did not. However, the interpretation of this finding could be constrained by the small number of patients receiving reperfusion therapy. Preclinical evidence suggests that minocycline could extend the therapeutic window for tissue plasminogen activator (tPA), and the STAIR X consortium has recommended adjunctive brain cytoprotectants in the context of thrombectomy.[24–25] We hypothesise that combining minocycline with reperfusion therapy could further improve clinical outcomes, and future studies are required to validate this theory. Additionally, our trial extended the enrolment window to 72 h after stroke onset, which is the most substantial deviation from previous studies. This modification was guided by imaging-based evidence indicating minimal microglial activation within the first 72 h, followed by a marked increase thereafter.[26] We proposed that administering minocycline within this timeframe could still provide benefit and enhance feasibility in routine clinical practice. The prespecified subgroup analyses did not reveal a significant improvement in primary outcomes in patients with shorter onset-to-treatment intervals. However, administration within 24 h post-stroke remains a promising approach to further clarify the optimal time-dependent effects of minocycline.

In other prespecified subgroups, we unexpectedly observed potential beneficial effects of minocycline in patients with a history of alcohol consumption. In ischaemic stroke models, minocycline has attenuated alcohol-induced exacerbation of neurological deficits by modulating neuroinflammation; however, no previous clinical trial has reported an interaction similar to that observed in our study.[27] Whether this finding is merely incidental or reflects a true effect of minocycline on alcohol-related neuroimmune interactions remains uncertain. Furthermore, we observed a possible treatment effect favouring minocycline in patients with undetermined stroke aetiology, but the underlying mechanism is unknown, and the small sample size suggests this could be a chance finding. Nevertheless, apparent benefit was seen in participants with large-artery disease or small vessel disease. Finally, with regard to sex-specific effects of minocycline-mediated neuroprotection reported by previous studies,[14] no such differential effect was observed in our study.

As for vascular events, there was no evidence that a 4·5-day course of minocycline reduced the risk of recurrent stroke, ischaemic stroke, or composite vascular events, which aligns with its proposed mechanism of targeting neuroinflammation rather than the atherothrombosis process. The short duration of treatment restricted to the acute phase and the small number of events could also account for the absence of sustained vascular benefit over 90 days. Whether prolonged administration of minocycline to suppress ongoing inflammation might confer greater protection against recurrent vascular events remains uncertain. Nevertheless, given the biphasic role of microglia, long-term minocycline use should be approached with caution. In neurodegenerative diseases, including Alzheimer's disease, long-term administration of minocycline has not shown clinical benefit, whereas in people with amyotrophic lateral sclerosis, it has even been associated with accelerated disease progression.[28–29] These findings suggest that optimal timing, dosage, and duration of minocycline treatment can differ across diseases, potentially depending on the dynamic roles of microglia and neuroinflammation.

From a safety perspective, symptomatic intracranial haemorrhage is a major safety concern in acute ischaemic stroke, particularly in people receiving reperfusion therapy. Data from preclinical stroke models have indicated that minocycline does not interfere with tPA fibrinolysis, and could reduce haemorrhage, improve neurological outcomes, and reduce mortality.[4] In our trial, bleeding did not differ between the groups. Other adverse reactions more commonly associated with minocycline, such as gastrointestinal symptoms and dizziness,[28–29] occurred at similar rates in both groups. Overall, short-term use of minocycline during the acute phase of ischaemic stroke appears to be safe and well tolerated.

To the best of our knowledge, EMPHASIS is the largest randomised, double-blind trial showing a 90-day benefit

of minocycline in patients with acute ischaemic stroke, with potential implications for clinical practice and future research of anti-neuroinflammatory strategies in stroke management. Our trial has several strengths, supporting a more robust assessment of minocycline's efficacy and safety compared with previous trials. The risk of random error was minimised through a large sample size with high follow-up rates, and bias was reduced through centralised randomisation and strict blinding of treatment assignments. Additionally, the minimal difference in the number of adverse effects suggests a low likelihood of unmasking influencing the outcomes.

Nevertheless, several limitations apply. First, the EMPHASIS trial was conducted exclusively in China, with all participants being Chinese, whereas previous studies have reported ethnic and regional differences in stroke characteristics and potentially in treatment response.[30] Furthermore, the study set an upper age limit of 80 years for enrolment owing to concerns that older patients are at higher risk of complications and disability. As such, the results might not be applicable to non-Asian populations or to individuals older than 80 years. Second, although patients with a baseline NIHSS score of less than 4 were excluded in our study, the final median baseline NIHSS score was 5. This score is probably because the trial was primarily conducted in primary or secondary care hospitals, where patients with milder strokes are more commonly managed. Consequently, our findings primarily reflect outcomes in patients with non-minor ischaemic stroke, and those without the most severe stroke; as a result, generalisability to people with more severe or minor stroke remains uncertain. Third, the observed proportion of patients with excellent functional outcome and the treatment effect were lower than expected, potentially reducing the statistical power of the study, particularly for secondary outcomes. Additionally, the borderline statistical significance of our findings and their potential sensitivity to the direction of outcomes in the missing data represent important limitations. These limitations should be carefully considered when interpreting the results. Fourth, hs-CRP concentrations in our trial were not centrally analysed, and variability in test results could have arisen between research sites due to differences in reagents and instruments. However, the centre-stratified block randomisation design might have mitigated some of these site-specific differences. Fifth, block randomisation with a fixed block size of four could have posed a minimal risk of allocation predictability, although blinding and identical study drugs likely mitigated this. Finally, potential discrepancies between preclinical models and clinical patients highlights the need for further investigation into the mechanisms by which minocycline exerts its effects in people with stroke.

In conclusion, administration of minocycline within 72 h of symptom onset in patients with acute ischaemic stroke (NIHSS score 4–25) was associated with improved functional outcomes at 90 days, as measured by the mRS, compared with placebo. No significant safety concerns were identified. These findings suggest that minocycline could be a safe, cost-effective, and accessible therapeutic option for patients with acute ischaemic stroke. However, further studies are warranted to confirm these results and to establish whether the benefits extend to patients with more severe or minor strokes.

Contributors

YilW and LG proposed the study conception and study design. SCJ, PA, PMB, LL, XiZ, and YoW supervised the study design. YL, LG, and JW prepared the first draft of the report. PMB, SCJ, GT, and F-DS provided essential revisions, and all coauthors reviewed and revised the Article. YL, LG, JW, QY, MZ, HY, BQ, CL, YicW, YY, XuZ, HQ, and XL were involved in trial conduct, patient management, and data collection. DZ supports data management. YP and LW prepared the statistical analysis plan and conducted statistical analyses. YilW, YL, LG, YP, and LW accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Data from the EMPHASIS study are not currently publicly available. Criteria for access and the data repository location will be established after completion of the primary analyses and publication of the main trial results. Upon submission of a formal written request (including protocol and analysis plan) to the corresponding author, and subsequent approval by the steering committee, the statistical code and output will be made available to facilitate result reproduction.

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