Prehospital transdermal glyceryl trinitrate in patients with presumed acute stroke (MR ASAP): an ambulance-based, multicentre, randomised, open-label, blinded endpoint, phase 3 trial

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Summary

Background Pooled analyses of previous randomised studies have suggested that very early treatment with glyceryl trinitrate (also known as nitroglycerin) improves functional outcome in patients with acute ischaemic stroke or intracerebral haemorrhage, but this finding was not confirmed in a more recent trial (RIGHT-2). We aimed to assess whether patients with presumed acute stroke benefit from glyceryl tr initrate started within 3 h after symptom onset.

Methods MR ASAP was a phase 3, randomised, open-label, blinded endpoint trial done at six ambulance services serving 18 hospitals in the Netherlands. Eligible participants (aged ≥18 years) had a probable diagnosis of acute stroke (as assessed by a paramedic), a face-arm-speech-time test score of 2 or 3, systolic blood pressure of at least 140 mm Hg, and could start treatment within 3 h of symptom onset. Participants were randomly assigned (1:1) by ambulance personnel, using a secure web-based electronic application with random block sizes stratified by ambulance service, to receive either transdermal glyceryl trinitrate 5 mg/day for 24 h plus standard care (glyceryl trinitrate group) or to standard care alone (control group) in the prehospital setting. Informed consent was deferred until after arrival at the hospital. The primary outcome was functional outcome assessed with the modified Rankin Scale (mRS) at 90 days. Safety outcomes included death within 7 days, death within 90 days, and serious adverse events. Analyses were based on modified intention to treat, and treatment effects were expressed as odds ratios (ORs) or common ORs, with adjustment for baseline prognostic factors. We separately analysed the total population and the target population (ie, patients with intracerebral haemorrhage, ischaemic stroke, or transient ischaemic attack). The target sample size was 1400 patients. The trial is registered as ISRCTN99503308.

Findings On June 24, 2021, the MR ASAP trial was prematurely terminated on the advice of the data and safety monitoring board, with recruitment stopped because of safety concerns in patients with intracerebral haemorrhage. Between April 4, 2018, and Feb 12, 2021, 380 patients were randomly allocated to a study group. 325 provided informed consent or died before consent could be obtained, of whom 170 were assigned to the glyceryl trinitrate group and 155 to the control group. These patients were included in the total population. 201 patients (62%) had ischaemic stroke, 34 (10%) transient ischaemic attack, 56 (17%) intracerebral haemorrhage, and 34 (10%) a stroke-mimicking condition. In the total population (n=325), the median mRS score at 90 days was 2 (IQR 1–4) in both the glyceryl trinitrate and control groups (adjusted common OR 0·97 [95% CI 0·65–1·47]). In the target population (n=291), the 90-day mRS score was 2 (2–4) in the glyceryl trinitrate group and 3 (1–4) in the control group (0·92 [0·59–1·43]). In the total population, there were no differences between the two study groups with respect to death within 90 days (adjusted OR 1·07 [0·53–2·14]) or serious adverse events (unadjusted OR 1·23 [0·76–1·99]). In patients with intracerebral haemorrhage, 12 (34%) of 35 patients allocated to glyceryl trinitrate versus two (10%) of 21 allocated to the control group died within 7 days (adjusted OR 5·91 [0·78–44·81]); death within 90 days occurred in 16 (46%) of 35 in the glyceryl trinitrate group and 11 (55%) of 20 in the control group (adjusted OR 0·87 [0·18–4·17]).

Interpretation We found no sign of benefit of transdermal glyceryl trinitrate started within 3 h of symptom onset in the prehospital setting in patients with presumed acute stroke. The signal of potential early harm of glyceryl trinitrate in patients with intracerebral haemorrhage suggests that glyceryl trinitrate should be avoided in this setting.

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Introduction

High blood pressure is common in the acute phase of ischaemic stroke or intracerebral haemorrhage, and is associated with poor outcomes.[1–4] Guidelines recommend blood pressure lowering treatment in selected patients with intracerebral haemorrhage, but the optimal management of blood pressure in patients with acute ischaemic stroke is much less clear.[5–7] Glyceryl trinitrate (also known as nitroglycerin) is a nitric oxide donor that has been proposed as a blood pressure-lowering treatment to improve outcomes in patients with acute ischaemic stroke or intracerebral haemorrhage.[8–11] In animal models of focal cerebral ischaemia, nitric oxide donors increased cerebral blood flow and reduced infarct size.[12] In two studies of patients with recent stroke, transdermal glyceryl trinitrate reduced blood pressure without reducing cerebral blood flow in the ipsilateral hemisphere or in the ischaemic penumbra.[8,13]

Subgroup analyses of the phase 3, hospital-based Efficacy of Nitric Oxide in Stroke trial (ENOS) trial,[14–16] and a pooled analysis[17] of ENOS and four earlier randomised trials in patients with ischaemic stroke or intracerebral haemorrhage, suggested that transdermal glyceryl trinitrate improved functional outcome if started within 6 h of symptom onset, with greater benefit seen in those who started the treatment earlier. In the small, ambulance-based Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT, n=41),[18] administration of transdermal glyceryl trinitrate by paramedics to patients with presumed acute stroke within 4 h of symptom onset seemed to be safe and improved functional outcome. However, the successive, large, phase 3 ambulance-based RIGHT-2 trial in the UK found no effect on functional outcome of transdermal glyceryl trinitrate in the overall study population and showed signals of a potential adverse effect on functional outcome in patients with intracerebral haemorrhage,[11] possibly due to early haematoma expansion.[19]

When RIGHT-2 was still ongoing, we started the Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch (MR ASAP) to assess the effect of transdermal glyceryl trinitrate, administered within 3 h after symptom onset in the prehospital setting, on functional outcome at 90 days in patients with acute ischaemic stroke or intracerebral haemorrhage.

Methods

Study design and participants

MR ASAP was an investigator-initiated, phase 3, multicentre, ambulance-based, randomised trial with open-label treatment (glyceryl trinitrate, within 3 h of symptom onset) and blinded endpoint assessment in patients with presumed stroke. We compared prehospital treatment with transdermal glyceryl trinitrate (5 mg/day for 24 h) plus standard care versus standard care alone at six ambulance services serving 18 hospitals in the Netherlands. The full study protocol is available in the appendix (pp 27–103) and a summary has been published previously.[9]

Adult patients (aged ≥18 years) were eligible for enrolment if they had a probable diagnosis of acute stroke, as assessed by a paramedic in the prehospital setting; a face-arm-speech-time test score of 2 or 3; a systolic blood

Research in context

Evidence before this study

We searched PubMed and Embase for relevant articles published between database inception and April 28, 2022, using the terms "nitric oxide donor", "glyceryl trinitrate", "stroke" and "randomised controlled trial", and comparable terms. No language restrictions were used. Our search was restricted to the effects of glyceryl trinitrate treatment in humans within 6 h of stroke symptom onset on functional outcome and death. Meta-analysis of five randomised trials, including data from one ambulance-based feasibility trial, and a predefined subgroup analysis of a large hospital-based trial, found that glyceryl trinitrate treatment started within 6 h of stroke onset improved outcomes in patients with ischaemic stroke or intracerebral haemorrhage. In 2019, a large randomised ambulance-based trial (RIGHT-2) of glyceryl trinitrate treatment within 4 h of symptom onset found no benefit of glyceryl trinitrate in patients with stroke or transient ischaemic attack, and possible harm of glyceryl trinitrate in patients with intracerebral haemorrhage. Analysis of the combined results of the above-mentioned trials resulted in neutral effects for death or functional dependency.

Added value of this study

The findings of MR ASAP are consistent with previous findings that ambulance-delivered glyceryl trinitrate does not seem to alter functional outcome in patients with presumed acute stroke. In patients with intracerebral haemorrhage, there was evidence of a greater risk of death within 7 days in patients allocated to glyceryl trinitrate versus standard treatment alone.

Implications of all the available evidence

Transdermal glyceryl trinitrate treatment does not seem to improve outcomes if given within 3 h after stroke onset. The signal of early harm of glyceryl trinitrate in patients with intracerebral haemorrhage suggests that glyceryl trinitrate should be avoided in the prehospital setting in patients with presumed stroke.

pressure of at least 140 mm Hg; and if treatment could be started within 3 h of symptom onset. Patients with considerable pre-stroke dependency in activities of daily living, defined as staying in a chronic nursing home or rehabilitation centre, a substantially reduced consciousness level (Glasgow Coma Scale <8), or a known contraindication or hypersensitivity to glyceryl trinitrate, were excluded. A complete list of inclusion and exclusion criteria is available in the appendix (p 49).

Because of the emergency setting of our study—with the necessity for urgent transport and treatment, and the presumed incapacity of the vast majority of patients to provide informed consent at short notice—deferred consent was used in agreement with national legislation.[20] Patients or their legal representatives provided written informed consent as soon as reasonably possible after arrival to hospital but at least within 90 days of randomisation. If patients died before consent could be obtained, their data were used. If no consent was given, a restricted set of anonymised data were documented to increase the validity of the safety data. These included the following variables: study number, treatment allocation, final diagnosis, serious adverse events in the first 7 days, in-hospital death, and—only for patients with intracerebral haemorrhage—vital status at 90 days.

This study was approved by the central medical ethics committee of the Erasmus MC University Medical Center and received approval from the research board of each participating centre.

Randomisation and masking

Paramedics randomly assigned patients (1:1) to receive either open-label transdermal glyceryl trinitrate 5 mg/day for 24 h plus standard care (glyceryl trinitrate group) or standard care alone (control group). Randomisation occurred in the prehospital setting through a secure web-based electronic application using random block sizes stratified by ambulance service, which generated a unique study number for each patient. Prehospital baseline variables of participants were entered into this application before randomisation. In case of assignment to glyceryl trinitrate, randomisation was immediately followed by placement of the glyceryl trinitrate patch on the patient's shoulder, back, or chest. Patients, paramedics, local investigators, and treating nurses and clinicians were aware of treatment allocation. Outcomes at 90 days were assessed by trained research nurses, who were unaware of treatment allocation, through structured telephone interviews.

Procedures

The glyceryl trinitrate patch (Deponit-T5; Merus Labs, Luxembourg City, Luxembourg) was started immediately after randomisation in the prehospital setting and continued during hospital admission for 24 h (range 22–26). If patients allocated to treatment with glyceryl trinitrate were not diagnosed with stroke or transient ischaemic attack on hospital admission, refused participation, did not completely fulfil the eligibility criteria, or were discharged from the hospital within 24 h, the patch was removed earlier. Local investigators documented the time of removal of the patch and, if applicable, the reason for early removal. Patients in the control group received standard care, which consisted of admission to the acute stroke unit when a diagnosis of stroke was made. Participating paramedics were registered nurses specialised in ambulance care. They received study-specific training on-site or with an instruction video. Ambulance, clinical, and imaging data were entered into a secure web-based database system.

All serious adverse events within the first 7 days or until discharge, if earlier, were documented. 13 patients with ischaemic stroke due to a large vessel occlusion were subsequently enrolled in a trial of endovascular treatment.[21,22]

After 24 h (range 22–26) of treatment, local investigators collected information on haemodynamic parameters and the severity of neurological deficits. The primary outcome was assessed at 90 days after randomisation.

The trial was overseen by a steering committee that consisted of the principal investigators of all participating sites. Independent observers, who were unaware of treatment allocation, adjudicated all serious adverse events and primary outcome data with standardised interview reports. Imaging was assessed by an imaging core laboratory, consisting of trained neuroradiologists who were unaware of clinical data (except symptom side).

Outcomes

The primary outcome was functional outcome, assessed with the modified Rankin Scale (mRS) at 90 days after randomisation. The mRS is a 7-point scale, with scores as follows: 0, no symptoms; 1, no clinically relevant disability; 2, slight disability; 3, moderate disability; 4, moderate to severe disability; 5, severe disability, complete dependence of daily care; and 6, death. Scores were centrally assessed by trained research nurses (via telephone), who were unaware of treatment allocation, using a structured questionnaire (appendix pp 22–24).

Secondary outcomes were blood pressure, heart rate, body temperature, and neurological deficit, measured with the National Institutes of Health Stroke Scale (NIHSS) at hospital admission and at 24 h post-randomisation; volume of intracerebral haemorrhage on non-contrast CT at hospital admission, calculated using an automated image analysis algorithm;[23] all-cause death at 90 days; excellent (mRS score 0–1), good (mRS score 0–2), and favourable (mRS score 0–3) functional outcome at 90 days; disability, assessed with the Barthel Index at 90 days; quality of life, assessed with the EuroQoL-5 dimensions-5 levels at 90 days; and home time during the first 90 days after randomisation (the number of nights since stroke onset that are spent in the patient's own home or a relative's home). Because of

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See **Online** for appendix

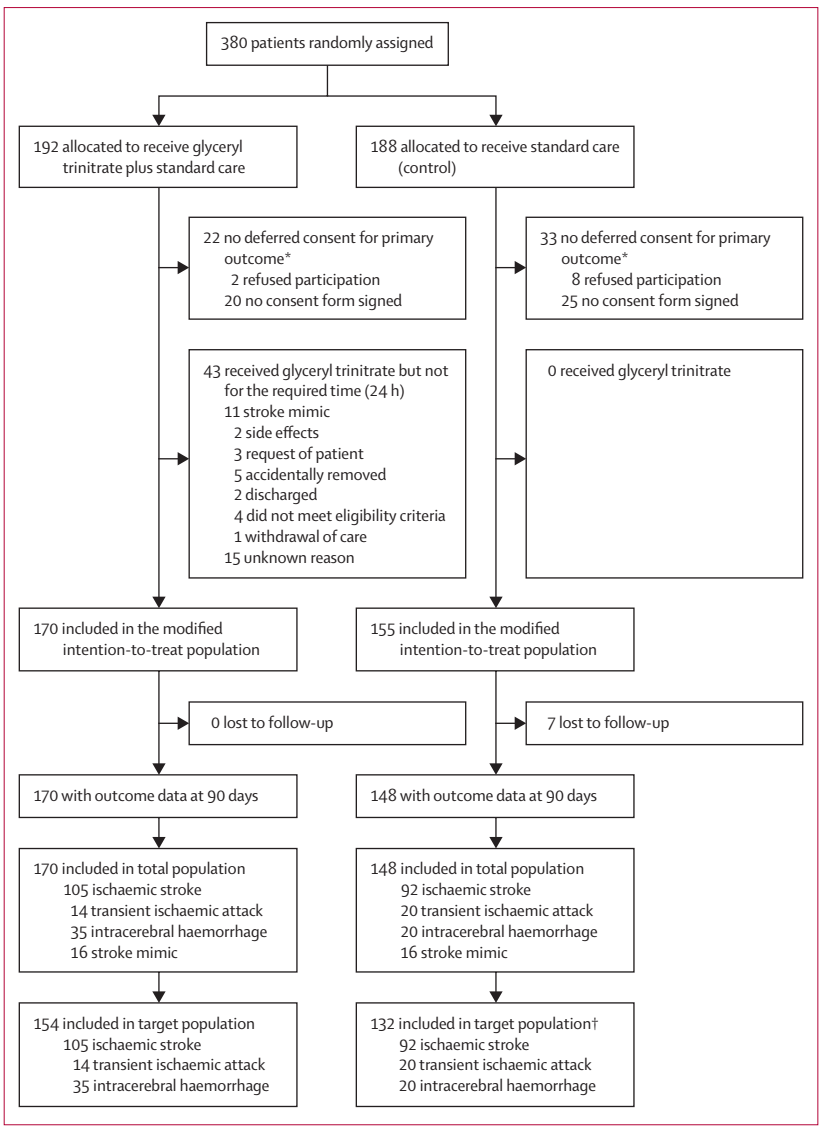

Figure 1: **Trial profile**
*Patients without deferred consent were randomly allocated to a group and received the glyceral trinitrate patch (if allocated to this group), but follow-up was not performed and these patients were not included in the intention-to-treat population. †Does not include those with missing data. 137 patients had baseline data in the target population. 155 patients had baseline data in the total population.

the safety concerns raised in RIGHT-2 in patients with intracerebral haemorrhage,[11,19] death within 7 days was added as an outcome during the course of the trial. Because some of the prespecified secondary outcomes—collateral circulation and lesion size of patients with ischaemic stroke at hospital admission and patient location during the first 90 days—were available for too few patients at database lock on Jan 5, 2022; these will be reported separately.

Safety outcomes were serious adverse events during the first 7 days or until hospital discharge, if earlier, including hypotension or hypertension requiring clinical intervention and symptomatic intracranial haemorrhage after ischaemic stroke, ascertained with the Heidelberg criteria.[24] Neurological deterioration after acute ischaemic stroke was defined as deterioration of 4 points or more on the NIHSS or 2 points or more on one NIHSS item, including death, and was assessed on clinical deterioration by the attending clinician. The cause of neurological deterioration was either uncertain (thus no follow-up imaging was performed), stroke progression, or symptomatic intracranial haemorrhage. Because of the small number of events, stroke progression and uncertain cause of neurological deterioration were combined as one category.

Statistical analyses

The statistical analysis plan was finalised before the database lock and is available in the appendix (pp 6–10). Our sample size calculations showed we required a sample of 1400 patients (n=700 in each group) to detect a shift in mRS (based on a proportional odds model), assuming an absolute risk reduction of 7% for functional dependence (mRS score 3–6), 80% power, a significance level of 5% ($p<0·05$), and 10% stroke mimics.

Missing outcome data were not imputed. We performed modified intention-to-treat analyses for all outcomes in the total population, which included all patients for whom deferred consent was obtained. We also analysed the target population, which comprised patients who provided deferred consent and were diagnosed with intracerebral haemorrhage, ischaemic stroke, or transient ischaemic attack, by modified intention to treat. The primary outcome was analysed with multivariable ordinal logistic regression to estimate an adjusted common odds ratio (OR) for a shift in the direction of a lower score, in the total population. For secondary outcomes, binary logistic regression was performed for dichotomous outcomes to estimate (adjusted) ORs. Linear regression was used for continuous outcome data to estimate (adjusted) beta coefficients. If the assumptions for linear regression were violated, we assessed for several transformations of the independent variable if they led to model improvement. Logarithmic transformation was performed for NIHSS score at baseline and at 24 h, and for intracerebral haemorrhage volumes. For NIHSS score, logarithmic transformation was done after adding 1 point to all scores so that a score of 0 would remain 0, to better approximate a normal distribution of the residuals.

Analyses for primary and secondary outcomes were adjusted for age, sex, final diagnosis (classified as ischaemic stroke, intracerebral haemorrhage, transient ischaemic attack, or a stroke-mimicking condition), score on the face-arm-speech-time test at study inclusion, systolic blood pressure at randomisation, combined Eye and Motor score of the Glasgow Coma Scale at randomisation, time from symptom onset to randomisation, pre-stroke score on the mRS, and ambulance region. Contrary to the statistical analysis plan, unadjusted ORs for safety outcomes were analysed with

	Total population		Target population	
	Glyceryl trinitrate group (n=170)	Control group (n=155)	Glyceryl trinitrate group (n=154)	Control group (n=137)
Mean age, years	72 (13)	72 (13)	72 (13)	74 (11)
Sex				
Male	98 (58%)	73 (47%)	91 (59%)	64 (47%)
Female	72 (42%)	82 (53%)	63 (41%)	73 (53%)
Prehospital FAST test score of 3*	76 (45%)	68 (44%)	74 (48%)	64 (47%)
Median prehospital systolic blood pressure, mm Hg	175 (157–191)	180 (161–195)	173 (157–190)	180 (165–196)
Median prehospital diastolic blood pressure, mm Hg	92 (81–100)	94 (84–105)	92 (81–100)	94 (84–105)
Mean prehospital heart rate, beats per min	85 (16)	84 (18)	84 (16)	84 (18)
Median duration from symptom onset to randomisation, min	71 (39–114)	53 (33–94)	69 (38–114)	55 (33–93)
Median prehospital eye and motor score of the Glasgow Coma Scale†	10 (10–10)	10 (10–10)	10 (10–10)	10 (10–10)
Premorbid modified Rankin Scale score of >2‡	21 (12%)	12 (8%)	20 (13%)	12 (9%)
Medical history				
Atrial fibrillation	28 (16%)	21 (14%)	25 (16%)	20 (15%)
Diabetes	31 (18%)	36 (23%)	28 (18%)	32 (23%)
Hypertension	89 (52%)	98 (63%)	80 (52%)	91 (66%)
Use of blood pressure-lowering drugs in the previous 3 days	88 (52%)	82 (53%)	78 (51%)	76 (56%)
Final diagnosis§				
Ischaemic stroke	105 (62%)	96 (62%)	105 (68%)	96 (70%)
Intracerebral haemorrhage	35 (21%)	21 (14%)	35 (23%)	21 (15%)
Transient ischaemic attack	14 (8%)	20 (13%)	14 (9%)	20 (17%)
Stroke-mimicking condition	16 (9%)	18 (12%)	NA	NA
Treatment with intravenous alteplase	77 (45%)	67 (43%)	75 (63%)¶	65 (56%)¶
Endovascular thrombectomy‖	31 (30%)	23 (24%)	31 (30%)	23 (24%)

Data are mean (SD), median (IQR), or n (%) in all included participants. The total population includes all patients for whom deferred consent was obtained. The target population comprises patients who provided deferred consent and were diagnosed with intracerebral haemorrhage, ischaemic stroke, or transient ischaemic attack. FAST=face-arm-speech-time. NA=not applicable. *The FAST test is a three-item prehospital stroke scale; a score of 3 indicates the combination of facial drooping, arm weakness, and speech difficulty. †Eye and motor combined sum score (maximum score of 10; a lower score indicates a greater decrease in consciousness). ‡A score of 2 or more indicates functional dependence. §Includes seven patients without primary outcome data. ¶The denominator for this percentage is the number of patients with a final diagnosis of ischaemic stroke or transient ischaemic attack. ‖The denominator for this percentage is the number of patients with a final diagnosis of ischaemic stroke.

Table 1: **Baseline characteristics for the total population and the target population**

a two-by-two contingency table because of the small number of events, instead of performing regression analyses.

Treatment effect modification was explored in prespecified subgroups of patients by adding interaction terms to the ordinal logistic regression model. Because of the potential harm of glyceryl trinitrate in patients with intracerebral haemorrhage highlighted in RIGHT-2,[11,19] the primary outcome and safety outcomes were presented in this subgroup regardless of the result of interaction tests.

We also performed a per-protocol analysis; the appendix (p 8) contains a full description of the population. Safety endpoints were additionally analysed in the safety population, which consisted of all randomised patients, irrespective of whether deferred consent was obtained.

All analyses were performed with R software (version 4.0.5). A post-hoc meta-analysis was performed for functional independence (mRS score 0–2) in patients with a final diagnosis of ischaemic stroke, intracerebral haemorrhage, or transient ischaemic attack who were enrolled within 6 h of symptom onset in three previous trials of glyceryl trinitrate treatment (ENOS, RIGHT, and RIGHT-2) and MR ASAP combined, using RevMan (version 5.4.1).

An independent data and safety monitoring board (DSMB) was appointed to conduct unblinded interim analyses on safety after 100, 200, 400, 600, and 900 patients would have completed follow-up. After publication of the RIGHT-2 results on Feb 7, 2019, which suggested the potential harm of glyceryl trinitrate in patients with intracerebral haemorrhage,[11] the frequency of these safety analyses was increased to after every 100 patients. Criteria for stopping the trial are included in the appendix (p 61) and have been published.[9] MR ASAP is registered with ISRCTN, ISRCTN99503308.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

	Total population				Target population			
	n	Glyceryl trinitrate group (n=170)	Control group (n=155)	Adjusted common OR, OR, or β (95% CI)	n	Glyceryl trinitrate group (n=154)	Control group (n=137)	Adjusted common OR, OR, or β (95% CI)
Primary outcome								
Modified Rankin Scale score at 90 days	318	2 (1 to 4)	2 (1 to 4)	0·97 (0·65 to 1·47)	286	2 (2 to 4)	3 (1 to 4)	0·92 (0·59 to 1·43)
Secondary outcomes*								
Death within 90 days	318	25/170 (15%)	20/148 (14%)	1·07 (0·53 to 2·14)	286	24/154 (16%)	20/132 (15%)	1·07 (0·53 to 2·17)
Death within 7 days	325	16/170 (9%)	4/155 (3%)	3·43 (0·96 to 12·24)	291	16/154 (10%)	4/137 (3%)	3·43 (0·96 to 12·24)
Modified Rankin Scale score at 90 days								
0–1	318	43/170 (25%)	44/148 (30%)	0·91 (0·53 to 1·59)	286	35/154 (22%)	36/132 (27%)	0·87 (0·48 to 1·61)
0–2	318	88/170 (52%)	77/148 (52%)	1·12 (0·63 to 1·99)	286	78/154 (51%)	65/132 (49%)	1·18 (0·65 to 2·14)
0–3	318	110/170 (65%)	103/148 (70%)	0·97 (0·52 to 1·82)	286	95/154 (62%)	88/132 (67%)	0·91 (0·48 to 1·73)
NIHSS score at hospital admission†	319	6 (3 to 13)	6 (2 to 11)	–0·07 (–0·22 to 0·07)	286	6 (3 to 13)	7 (2 to 12)	–0·10 (–0·25 to 0·05)
NIHSS score at 24 h†	282	3 (1 to 9)	3 (0 to 7)	–0·03 (–0·22 to 0·16)	264	3 (1 to 9)	3 (1 to 8)	–0·28 (–0·22 to 0·17)
Systolic blood pressure at hospital admission, mm Hg	322	167 (28)	172 (24)	–2·27 (–7·11 to 2·58)	290	167 (28)	174 (24)	–1·87 (–6·81 to 3·06)
Diastolic blood pressure at hospital admission, mm Hg	322	92 (19)	90 (18)	1·86 (–1·86 to 5·58)	290	92 (17)	91 (18)	1·24 (–2·54 to 5·01)
Heart rate at hospital admission, beats per min	306	84 (17)	80 (17)	3·47 (–0·41 to 7·35)	276	83 (17)	81 (17)	2·89 (–1·22 to 7·00)
EuroQoL-5D-5L score at 90 days‡	260	0·76 (0·25 to 0·88)	0·75 (0·40 to 0·88)	0·00 (–0·08 to 0·08)	245	0·63 (0 to 0·88)	0·70 (0 to 0·85)	–0·02 (–0·13 to 0·08)
Barthel Index at 90 days§	304	95 (25 to 100)	95 (50 to 100)	0·95 (–6·34 to 8·25)	275	95 (18 to 100)	90 (44 to 100)	0·34 (–7·65 to 8·34)
Home time, days¶	284	74 (0 to 90)	76 (0 to 90)	3·04 (–4·75 to 10·82)	257	70 (0 to 88)	69 (0 to 90)	3·07 (–5·48 to 11·61)
Patients with intracerebral haemorrhage								
Haematoma volume at hospital admission, mL	..	..	..	..	56	14·3 (5·2 to 36·4)	9·3 (7·0 to 32·1)	–0·13 (–0·89 to 0·64)
Death within 90 days	..	..	..	..	55‖	16/35 (46%)	11/20 (55%)	0·87 (0·18 to 4·17)
Death within 7 days	..	..	..	..	56	12/35 (34%)	2/21 (10%)	5·91 (0·78 to 44·81)

Data are mean (SD), median (IQR), or n (%). Given that we did not impute missing data, seven patients were removed from the primary outcome analysis. For unadjusted values, see appendix (p 15). EuroQoL-5D-5L=EuroQoL-5 dimensions-5 levels. n=number of patients with data. .. indicates no data. NA=not applicable. NIHSS=National Institutes of Health Stroke Scale. *For other secondary outcomes, see appendix (p 14). †NIHSS is a 15-item scale with a score ranging from 0 to 42; higher scores indicate a more severe neurological deficit. ‡The EuroQoL-5D-5L index value ranges from –0·33 to 1·00; a higher score indicates a better health state. §The Barthel index quantifies performance of self-care activities in daily living, ranging from 0 (severe disability) to 100 (no disability). ¶Home time is the number of nights among the first 90 days since stroke onset that are spent in the patient's own home or a relative's home. ‖Death within 90 days was missing for one patient in the control group.

Table 2: **Efficacy outcomes for the total population and the target population**

Results

The first patient was randomly allocated to a study group on April 4, 2018. On Feb 8, 2019, recruitment was temporarily halted in response to the publication of the RIGHT-2 results[11] to evaluate safety in MR ASAP, and this period was prolonged due to new mandatory implementation of national regulations regarding distribution of study medication across ambulances. After restarting the trial on Jan 12, 2020, recruitment was halted on March 20, 2020, because of the COVID-19 pandemic and was again restarted on June 15, 2020. On Feb 12, 2021, after their third safety analysis, the DSMB advised to stop recruitment of patients with intracerebral haemorrhage due to a possible safety concern in these patients. The DSMB's advice did not change after follow-up of all patients included up to Feb 12, 2021 had been completed. After unblinding and analysis of the data, the trial was definitively terminated as per the decision of the trial steering committee on June 24, 2021. The inclusion graph can be found in the appendix (p 19). This decision was made in the context of the neutral overall results of RIGHT-2; the suggestion of harm of glyceryl trinitrate in patients with intracerebral haemorrhage in RIGHT-2 and MR ASAP; and the absence of a sign of benefit of glyceryl trinitrate in MR ASAP in the first 325 patients.

Between April 4, 2018, and Feb 12, 2021, 380 patients were randomly allocated to a study group, of whom 325 were included in the modified intention-to-treat analysis. Deferred consent was obtained for 287 patients, no objection to data use was made by seven patients, and 31 patients had died before consent was sought. 170 patients were assigned to receive glyceryl trinitrate plus standard care (glyceryl trinitrate group) and 155 to receive standard care alone (control group; figure 1). Of the 55 patients who were randomly assigned to a study group but were not included in the modified intention-to-treat analysis, ten (18%) refused study participation in writing and 45 (82%) did not sign a consent form for

study participation (figure 1, appendix p 11). In the glyceryl trinitrate group, 43 (28%) patients had documented removal of the patch within the 24 h (range 22–26) treatment window (appendix p 12). No patient in the control group received glyceryl trinitrate. The main baseline variables were available for all included patients. Seven patients, all from the control group, were lost to follow-up.

Demographic and clinical characteristics of participants were mostly similar between the two treatment groups in the total population and the target population (table 1, appendix p 12). 201 patients (62%) had a final diagnosis of ischaemic stroke, 34 (10%) of transient ischaemic attack, 56 (17%) of intracerebral haemorrhage (appendix p 13), and 34 (10%) of a a stroke-mimicking condition. The median duration from symptom onset to randomisation was longer for glyceryl trinitrate (71 min [IQR 39–114]) than for control (53 min [33–94]; total population) treatment. The median prehospital systolic blood pressure was 175 mm Hg (157–191) for glyceryl trinitrate and 180 mm Hg (161–195) for control in the total population. Of 235 patients with ischaemic stroke or transient ischaemic attack, 140 (60%) were treated with intravenous thrombolysis, and of 201 patients with ischaemic stroke, 54 (27%) were treated with endovascular thrombectomy (table 1).

In the total population, there was no evidence of an effect of glyceryl trinitrate on functional outcome at 90 days compared with the control group (adjusted common OR 0·97 [95% CI 0·65–1·47]; table 2, figure 2; appendix pp 14–15).

In the prespecified subgroup analyses of treatment effect, there was weak evidence to suggest that the effect of glyceryl trinitrate on the mRS score might be modified by final diagnosis ($p_{interaction}$=0·06), with a neutral effect of glyceryl trinitrate in patients with intracerebral haemorrhage and a signal of potential harm of glyceryl trinitrate in patients with ischaemic stroke (figure 3). The effect of glyceryl trinitrate also seemed to be modified by prehospital systolic blood pressure, with a negative effect of glyceryl trinitrate in patients with a blood pressure lower than the median value of 177 mm Hg (figure 3).

In the total population, median prehospital systolic blood pressure was 175 mm Hg (IQR 157–191) for the glyceryl trinitrate group and 180 mm Hg (161–195) for the control group (table 1). History of hypertension was less common in the glyceryl trinitrate group (89 [52%] of 170 patients) than in the control group (98 [63%] of 155). Glyceryl trinitrate did not lower blood pressure at hospital admission or at 24 h (table 2; appendix pp 14–15). No differences between the two treatment groups were found for the NIHSS score at hospital admission or at 24 h, nor for excellent, good, or favourable functional outcome, Barthel Index, EuroQoL-5D-5L score, or home time at 90 days (table 2; appendix p 15).

In the target population, median prehospital systolic blood pressure was 173 mm Hg (IQR 157–190) for the glyceryl trinitrate group and 180 mm Hg (165–196) for the control group (table 1). mRS score at 90 days did not differ between the glyceryl trinitrate and control groups (adjusted common OR 0·92 [95% CI 0·59–1·43]), nor did secondary outcomes (table 2, figure 2; appendix pp 14–15). In patients with intracerebral haemorrhage, median haematoma volume on non-contrast CT at hospital admission was larger for those in the glyceryl trinitrate group than in the control group, but this difference was not significant (table 2, appendix p 13).

In the total population, 16 (9%) of 170 patients in the glyceryl trinitrate group and four (3%) of 155 in the control group died within 7 days of randomisation (adjusted OR 3·43 [95% CI 0·96–12·24]; table 2). Similar findings were reported in the safety population (n=380): 18 (9%) of 192 patients died within 7 days in the glyceryl trinitrate group and five (3%) of 188 in the control group (adjusted OR 3·79, 1·38–10·42; appendix p 16). Death at 90 days and safety parameters were similar across the two treatment groups (tables 2, 3; appendix p 16). In the total population, 25 (15%) of 170 patients in the glyceryl trinitrate group and 20 (14%) of 148 patients in the control group died within 90 days of randomisation (adjusted OR 1·07 [95% CI 0·53–2·14]; table 2; appendix p 15).

In the subgroup of patients with intracerebral haemorrhage, 12 (34%) of 35 patients in the glyceryl trinitrate group and two (10%) of 21 patients in the control group died within 7 days of randomisation (adjusted OR 5·91 [95% CI 0·78–44·81]; table 2). Similar findings were reported in the safety population (n=67): 14 (34%) of 41 patients died within 7 days in the glyceryl trinitrate group and three (12%) of 26 in the control group (unadjusted OR 3·98 [1·01–15·57]; appendix p 16). Death within 90 days in patients with intracerebral haemorrhage was numerically lower in the glyceryl trinitrate group than in the control group, both in the

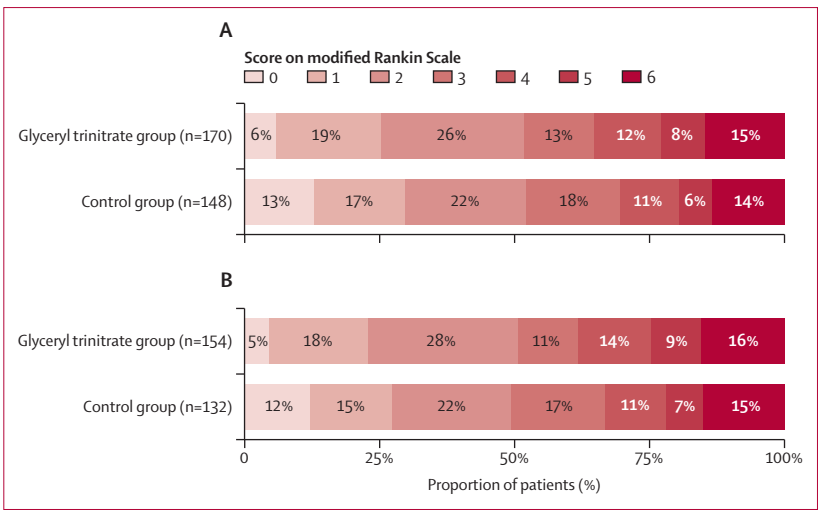

Figure 2: **Distribution of modified Rankin Scale scores at 90 days**
Data are shown according to modified intention-to-treat for the total population (A) and the target population, which consists of all patients with a final diagnosis of ischaemic stroke, intracerebral haemorrhage or transient ischaemic attack (B). Scores were not imputed for seven patients from the control group.

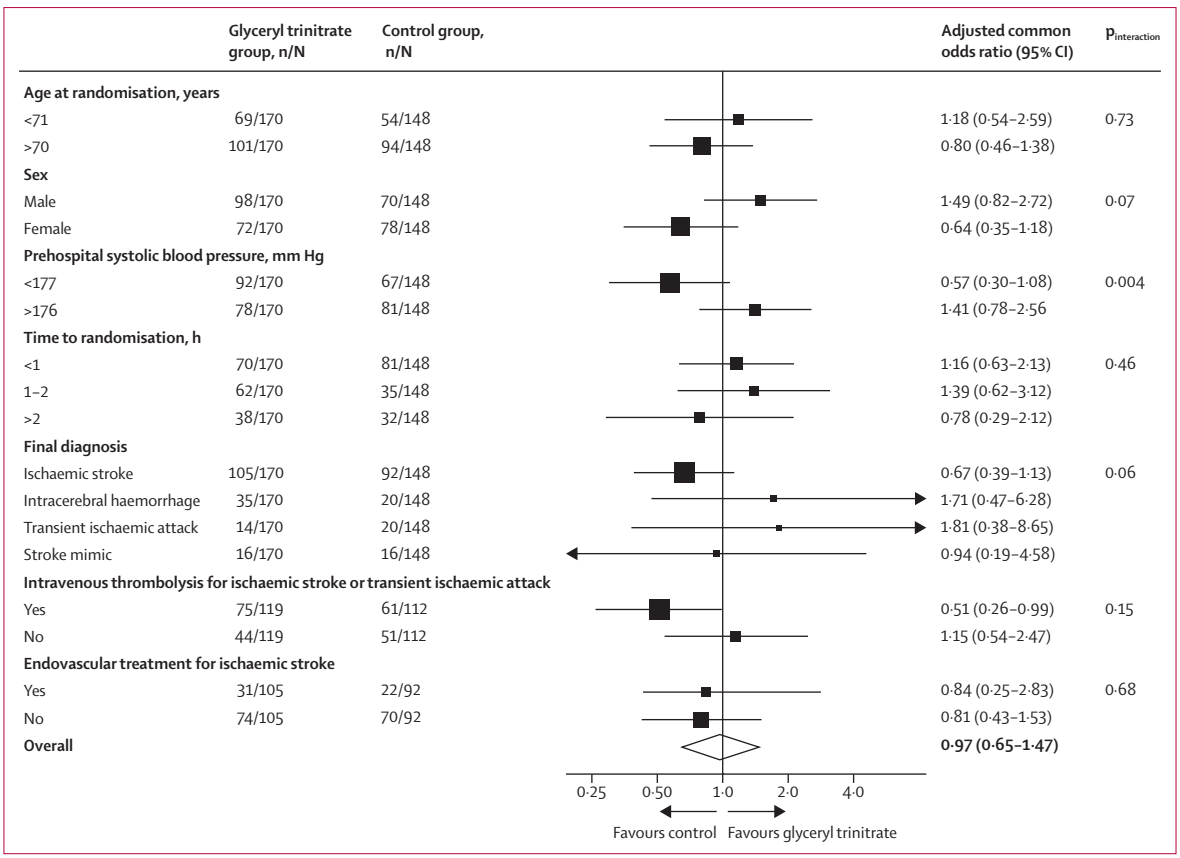

Figure 3: **Effect of glyceryl trinitrate versus control treatment on modified Rankin Scale score at 90 days in prespecified subgroups in the total population**
Data were compared by ordinal logistic regression, adjusted for age, sex, final diagnosis, score on the face-arm-speech-time test at study inclusion, systolic blood pressure at randomisation, combined Eye and Motor score of the Glasgow Coma Scale at randomisation, time of symptom onset to randomisation, pre-stroke score on the modified Rankin Scale, and ambulance region. NIHSS=National Institutes of Health Stroke Scale.

target population (16 [46%] of 35 and 11 [55%] of 20, respectively, adjusted OR 0·87 [0·18–4·17]) and in the safety population (18 [44%] of 41 and 13 [52%] of 26, respectively, unadjusted OR 0·69 [0·25–1·89]; table 2; appendix p 16).

The total number of serious adverse events was similar between the glyceryl trinitrate and control groups in the total and the target populations (table 3; appendix p 16). One patient in the control group required clinical intervention for hypotension. Clinical intervention for hypertension occurred in four patients assigned to glyceryl trinitrate and in six patients assigned to control treatment. No patients with a final diagnosis of ischaemic stroke had a symptomatic intracranial haemorrhage.

We found no evidence of an effect of glyceryl trinitrate on mRS score or other outcomes in per-protocol analyses (appendix p 17). Other safety parameters in the safety population were similar to those in the total population (appendix p 16).

An additional post-hoc analysis of stroke patients included within 6 h of symptom onset in three previous trials of glyceryl trinitrate treatment (ENOS, RIGHT, and RIGHT-2) and MR ASAP combined showed a neutral effect for functional independence (mRS 0–2; appendix p 20).

Discussion

In the 325 patients included in the total population of MR ASAP, there was no sign of improved functional outcome with glyceryl trinitrate started in the prehospital setting, within 3 h of the onset of symptoms suggestive of acute ischaemic stroke or intracerebral haemorrhage. Against the background of RIGHT-2, which found no effect of prehospital glyceryl trinitrate treatment in 1149 patients with presumed stroke, and potential harm in patients with intracerebral haemorrhage in RIGHT-2[11,19] and in MR ASAP, the steering committee decided to prematurely terminate MR ASAP on the advice of the DSMB.

The lack of evidence of benefit of very early administration of glyceryl trinitrate in RIGHT-2 and MR ASAP contrasts with the considerable benefit observed in the ambulance-based feasibility trial, RIGHT (n=41),[18] and in subgroups of patients with ischaemic stroke or intracerebral haemorrhage who received glyceryl trinitrate within 6 h of symptom onset

	Total population				Target population			
	Participants with data	Glyceryl trinitrate group (n=170)	Control group (n=155)	Unadjusted OR (95% CI)	Participants with data	Glyceryl trinitrate group (n=154)	Control group (n=137)	Unadjusted OR (95% CI)
Patients with any serious adverse event within 7 days	325	52/170 (31%)	41/155 (27%)	1·23 (0·76–1·99)	291	49/154 (32%)	39/137 (29%)	1·17 (0·71–1·94)
Hypotension*	325	0/170 (0%)	1/155 (1%)	NA	291	0/154 (0%)	1/137 (1%)	NA
Hypertension*	325	4/170 (2%)	6/155 (4%)	0·60 (0·17–2·16)	291	4/154 (3%)	6/137 (4%)	0·58 (0·16–2·11)
Pneumonia	325	13/170 (8%)	15/155 (10%)	0·77 (0·36–1·68)	291	12/154 (8%)	15/137 (11%)	0·69 (0·31–1·52)
Other infection	325	2/170 (1%)	2/155 (1%)	NA	291	2/154 (1%)	1/137 (1%)	NA
New ischaemic stroke	325	7/170 (4%)	2/155 (1%)	3·29 (0·67–16·06)	291	7/154 (5%)	2/137 (1%)	3·21 (0·66–15·74)
Extracranial haemorrhage	325	0/170 (0%)	0/155 (0%)	NA	291	0/154 (0%)	0/137 (0%)	NA
Myocardial infarction	325	0/170 (0%)	0/155 (0%)	NA	291	0/154 (0%)	0/137 (0%)	NA
Allergic reaction	325	0/170 (0%)	1/155 (1%)	NA	291	0/154 (0%)	1/137 (1%)	NA
Other	325	25/170 (15%)	16/155 (10%)	1·50 (0·77–2·92)	291	22/154 (14%)	15/137 (11%)	1·36 (0·67–2·73)
Suspected unexpected serious adverse event	325	0/170 (0%)	0/155 (0%)	NA	291	0/154 (0%)	0/137 (0%)	NA
Patients with a final diagnosis of ischaemic stroke								
Symptomatic intracranial haemorrhage	..	..	..	..	201	0/105 (0%)	0/96 (0%)	NA
Progression or neurological deterioration	..	..	..	..	201	7/105 (7%)	11/96 (12%)	0·55 (0·20–1·49)
Decompressive hemicraniectomy	..	..	..	..	201	1/105 (1%)	1/96 (1%)	NA
Patients with a final diagnosis of intracerebral haemorrhage								
Progression or neurological deterioration	..	..	..	..	56	14/35 (40%)	6/21 (29%)	1·67 (0·52–5·34)
Evacuation haematoma or surgical decompression	..	..	..	..	56	0/35 (0%)	1/21 (5%)	NA

Data are n/N (%). .. indicates no data. All adverse events are reported here. NA=not applicable. OR=odds ratio. *Requiring clinical intervention with continuous intravenous fluid or medication.

Table 3: **Safety outcomes for the total population and the target population**

in ENOS and pilot trials.[15,17] This disparity might be explained by differences in trial design, patient population, or by chance. In MR ASAP and RIGHT-2, the times to start of treatment (median 63 min and 70 min, respectively) were shorter than in the preceding trials (mean 4·6 h for patients included in the 6-h time window in ENOS), with the exception of RIGHT, which included just 41 patients. In MR ASAP and RIGHT-2, patients were treated with glyceryl trinitrate for 1 or 3 days, respectively, whereas treatment duration in ENOS was 7 days. ENOS-2 is currently investigating the feasibility of in-hospital glyceryl trinitrate treatment in the 3–5 h window after symptom onset in patients with acute ischaemic stroke or intracerebral haemorrhage (EUCTR2020-001304-42-GB). In MR ASAP, there was no blood pressure lowering effect of glyceryl trinitrate at hospital admission, which could be explained by the short transport times to the hospital of less than 15 min.

Although the overall effect of glyceryl trinitrate in RIGHT-2 and MR ASAP was similar, there are differences between the studies with regard to subgroup analyses. By contrast with RIGHT-2, in the prespecified subgroup analysis by final diagnosis we found no sign of harm of glyceryl trinitrate at 90 days in MR ASAP patients with intracerebral haemorrhage. In RIGHT-2, there was a strong trend towards worse functional outcome with glyceryl trinitrate,[11,19] and glyceryl trinitrate was associated with increased haematoma on hospital admission (assessed as maximum length) and increased mass effect on neuroimaging.[19] The increased risk of early death after intracerebral haemorrhage in RIGHT-2 is consistent with the evidence in MR ASAP indicating the potential for more deaths at 7 days with glyceryl trinitrate compared with control. Glyceryl trinitrate might have a negative effect on early haemostasis by counteracting vasoconstriction and inhibiting platelet aggregation, leading to an increase in haematoma volume, although this outcome was not found in a previous study in patients with acute stroke.[19,25,26] In RIGHT-2, haematoma volume was larger in patients assigned to glyceryl trinitrate than in patients assigned to control treatment. In the 56 patients with intracerebral haemorrhage in MR ASAP, we found larger haematoma volumes in those assigned to glyceryl trinitrate than in those assigned control treatment, but this difference was not statistically significant. Haematoma volumes were substantially smaller in MR ASAP (median 14·3 mL [glyceryl trinitrate] and 9·3 mL [control]) than in RIGHT-2 (mean 38·4 mL [glyceryl trinitrate] and 32·3 mL [control]),[19] which could partly explain the difference between the two trials in the effect of glyceryl trinitrate on outcomes at 90 days in patients with intracerebral haemorrhage.

Subgroup analyses of MR ASAP suggest that patients with a prehospital systolic blood pressure lower than the median value of 177 mm Hg might have poorer outcomes with glyceryl trinitrate than with standard care alone, and that those with higher systolic blood pressure might benefit. Although such a difference in the effect of

glyceryl trinitrate is biologically plausible, this finding should be interpreted with caution since all subgroup analyses in this neutral trial were exploratory (albeit prespecified) and underpowered. This warning applies to an even greater extent to the interaction between glyceryl trinitrate and stroke type, as supported by our finding of potential benefit for patients with intracerebral haemorrhage contrasting sharply with that of potential harm in RIGHT-2.[19]

MR ASAP has several strengths. Main baseline data were 100% complete and we attained near-complete (98%) follow-up of the primary outcome in the modified intention-to-treat population. Independent observers adjudicated the mRS scores and the serious adverse event reports and evaluated all neuroimaging, all whilst unaware of treatment allocation, thereby avoiding biased assessments. Of the 201 patients with a final diagnosis of ischaemic stroke, 70% were treated with intravenous thrombolysis and 27% with endovascular thrombectomy, reflecting current acute stroke practice. One in ten patients we enrolled had not had a stroke or transient ischaemic attack, a proportion which is higher than that of stroke-mimicking conditions in the prehospital FAST-MAG trial in the USA[27] but is considerably lower than in RIGHT-2.[11] We determined safety endpoints for the entire randomised population by documenting a restricted set of anonymised data from non-consenting patients, thereby increasing the reliability of our safety results.

Our study had some limitations, of which the most important are the early termination of the trial and the considerable proportion (14%) of patients for whom no consent was obtained. Withdrawal of patients might have introduced selection bias, particularly because absence of consent was more frequent in the control group than in the glyceryl trinitrate group. In previous stroke trials with deferred consent, refusal rates were 1–6%, but patients were not allocated in the prehospital setting in those trials.[21,22,28] In MR ASAP, no consent form was signed in 45 (82%) of 55 refusals to participate in the study. Obtaining written deferred consent proved to be difficult, which might have been caused by poor communication in the emergency setting if the patient had undergone prehospital randomisation, or by fast patient turnover. Therefore, deferred consent in prehospital stroke trials requires dedicated research personnel at all participating study sites. Nevertheless, we believe this trial of prehospital administration of glyceryl trinitrate would not have been feasible if informed consent had been required before randomisation, given that this patient population often lacks decision-making capacity within the narrow therapeutic time windows. Moreover, the trial faced logistical challenges leading to a slower than expected inclusion rate, as was also reported in a previous trial of prehospital blood pressure lowering therapy.[29] Another limitation is that not all baseline characteristics were well balanced between the treatment groups, particularly prehospital systolic blood pressure and time from symptom onset to randomisation. The difference in prehospital systolic blood pressure could have been caused, in part, by the greater proportion of control participants with a history of hypertension (*vs* the glyceryl trinitrate group). Since the baseline variables were recorded before randomisation, the imbalances cannot be explained by selection bias so are probably due to chance.

In summary, we found no sign of benefit of ambulance-delivered glyceryl trinitrate started within 3 h of symptom onset in patients with presumed acute stroke. The signal of potential early harm of glyceryl trinitrate in patients with intracerebral haemorrhage suggests that there is no role for glyceryl trinitrate treatment in presumed stroke in the prehospital setting.

For the **CONTRAST consortium website** see https://www.contrast-consortium.nl

Contributors

SAvdB, PJN, and HBvdW designed the trial. SMUV and SAvdB did the statistical analyses, with input from PJN, HBvdW, HFL and DN. SAvdB wrote the first draft of the manuscript, with input from SMUV, PJN and HBvdW. All authors contributed to the collection of data and to the writing of the manuscript, had full access to all the data in the study, and had final responsibility for the decision to submit for publication. SAvdB and SMUV have accessed and verified the data.

Declaration of interests

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Data sharing

With publication, de-identified data collected for the study, including individual participant data and a data dictionary defining each field in the set, can be made available to interested parties on reasonable request, and if in line with privacy regulations. Data can be requested at least 18 months after publication of this manuscript, with a proposal at the website of the Collaboration for New Treatments of Acute Stroke (CONTRAST) consortium, or by sending an e-mail to the corresponding author.

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