Multicentre Randomised trial of Acute Stroke treatment in the Ambulance with a nitroglycerin Patch (MR ASAP)

• **Sophie A. van den Berg¹, Puck S.S. Fransen², Klaartje Caminada³, Jeannette Hofmeijer⁴, Henk Kerkhoff⁵, Nyika D. Kruijt⁶, Frank-Erik de Leeuw⁷, Arjen Siegers⁸, Paul J. Nederkoorn^{1*} and H. Bart van der Worp^{9*}, on behalf of the MR ASAP Investigators**

• From the Department of Neurology of the Academic Medical Center¹, Isala Klinieken², Rijnstate Hospital⁴, Albert Schweitzer Hospital⁵, Leiden University Medical Center⁶, Radboud University Medical Center⁷, University Medical Center Utrecht⁹ and from the Ambulance Organisations IJsselland³ and Amsterdam⁸, The Netherlands

• *Paul J. Nederkoorn and H. Bart van der Worp are co-Chief Investigators of MR ASAP

RATIONALE

Recent studies have suggested that administration of transdermal glyceryl trinitrate (GTN), or nitroglycerin, in the first hours after stroke onset increases the chance of a favourable outcome, possibly through an increase in intracranial collateral blood flow and a reduction in blood pressure.^{1,2}

AIMS

To investigate the effect of transdermal GTN, started within 3 hours of stroke onset in the prehospital setting, on functional outcome at 90 days in patients with acute ischaemic stroke or intracerebral haemorrhage.

HYPOTHESIS

Transdermal GTN administered within 3 hours of symptom onset in the prehospital setting will improve functional outcome in patients with acute stroke.

STUDY POPULATION

Inclusion criteria

- Age 18 years or older
- Probable diagnosis of acute stroke, assessed by a paramedic
- Score of 2 or 3 on the Face Arm Speech Test (FAST)
- Systolic blood pressure $\geq$ 140 mm Hg
- Possibility to start the trial treatment within 3 hours of symptom onset
- Intention to transport the patient to one of the participating hospitals

TRIAL PROGRESS

- The first patient was enrolled April 4, 2018
- By May 9, 2018: 12 patients enrolled by one ambulance service
- June 2018: enrolment by 3 ambulance services and participation of 11 hospitals

References:

1. Bath PM et al. Effect of Treatment Delay, Stroke Type, and Thrombolysis on the Effect of Glyceryl Trinitrate, a Nitric Oxide Donor, on Outcome after Acute Stroke: A Systematic Review and Meta-Analysis of Individual Patient from Randomised Trials. *Stroke Res Treat*. Hindawi Publishing Corporation; 2016;2016.
2. Appleton JP et al. Ambulance-delivered transdermal glyceryl trinitrate versus sham for ultra-acute stroke: Rationale, design and protocol for the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) trial (ISRCTN26986053). *Int J Stroke*. 2017;0(0):174749301772462.

METHODS

- Phase III multicentre prospective randomised open-label blinded endpoint (PROBE) trial.
- 1400 patients will be randomly assigned in the ambulance, in a maximum of 10 ambulance regions.
- The intervention group will receive a transdermal GTN patch 5 mg/day plus standard care. The patch will be applied in the prehospital setting and continued during hospital admission for 24 hours. The control group will receive standard stroke care.
- A deferred consent procedure is used, i.e. informed consent will be asked after enrolment in the trial.

PATIENT FLOW

OUTCOMES

Primary outcome: score on the modified Rankin Scale (mRS) at 90 days, analysed with ordinal logistic regression.

Secondary outcomes: blood pressure and collateral score at hospital admission; treatment with intravenous thrombolysis and/or intra-arterial treatment and NIHSS at 24 hours; mortality, dichotomised mRS, disability assessed with the Barthel Index (BI), quality of life assessed with the EuroQol-5D-5L, home time and patient location at 90 days.

Safety outcome: Symptomatic intracerebral haemorrhage.