CrossMark

CURRENT OPINION

# Therapeutic Potential of Transdermal Glyceryl Trinitrate in the Management of Acute Stroke

Jason P. Appleton[1] · Nikola Sprigg[1] · Philip M. Bath[1]

**Abstract** The nitric oxide donor, glyceryl trinitrate (GTN), is a candidate treatment for the management of acute stroke with haemodynamic and potential reperfusion and neuroprotective effects. When administered as a transdermal patch during the acute and subacute phases after stroke, GTN was safe, lowered blood pressure, maintained cerebral blood flow, and did not induce cerebral steal or alter functional outcome. However, when given within 6 h of stroke onset, GTN reduced death and dependency (odds ratio 0.52; 95% confidence interval 0.34–0.78), death, disability, cognitive impairment and mood disturbance, and improved quality of life (data from two trials, $n = 312$). In a pooled analysis of four studies ($n = 186$), GTN reduced between-visit systolic blood pressure variability over days 1–7 compared with no GTN (mean difference $-2.09$; 95% confidence interval $-3.83$ to $-0.35$; $p = 0.019$). The efficacy of GTN given in the ultra-acute/pre-hospital setting is currently being assessed and, if found to be beneficial, the implications for hyperacute stroke practice are significant. Here, we discuss the evidence to date, potential mechanisms of action and future possibilities, including unanswered questions, for the therapeutic potential of GTN in acute stroke.

✉ Philip M. Bath
Philip.bath@nottingham.ac.uk

1   Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, Clinical Sciences Building, City Hospital Campus, Hucknall Road, Nottingham NG5 1PB, UK

## Key Points

Transdermal glyceryl trinitrate is safe in patients with acute stroke.

Glyceryl trinitrate may improve outcome if administered within 6 h of stroke onset.

The implications for clinical practice are substantial if efficacy is confirmed. An inexpensive and effective treatment for hyperacute stroke could be adopted globally in low-, middle- and high-income countries.

## 1 Introduction

Nitric oxide (NO) is a diatomic highly reactive gas. It is an obligate molecule in health and disease with a multitude of actions. NO has vasodilatory, pro-endothelial, anti-proliferative (vascular smooth muscle cell) [1], antiplatelet [2, 3], anti-leucocyte [4], anti-inflammatory, neuroprotective, neurotransmitter and neuromodulator [5, 6] properties. It has roles in modulating blood–brain barrier integrity, cerebral blood flow (CBF), auto- and chemo-regulation [7–9], and inhibition of apoptosis [10]. NO is an endogenous inorganic soluble gas synthesised from L-arginine by three forms of NO synthase (NOS): endothelial (eNOS); inducible (iNOS); and neuronal (nNOS) [11, 12]. The second messenger cyclic guanosine monophosphate, which is broken down by phosphodiesterase, is the main mediator of downstream signalling of NO. NO is broken down via oxidation to nitrite and ultimately nitrate, and it is now apparent that NO may be made by reduction of nitrite and

nitrate. Up-regulation of the L-arginine/nitrite-NO-cyclic guanosine monophosphate pathway can be achieved by a number of means: increased substrate, administration of NO gas, induction of NO synthase activity; administration of NO donors; or inhibition of phosphodiesterase [13].

Pre-clinical experimental studies in models of ischaemia have demonstrated the role of NO in a time-dependent manner. Models of focal ischaemia have shown that NO production is increased, through nNOS activation, for up to half an hour after middle cerebral artery occlusion [14, 15]. During the first minutes following arterial occlusion, eNOS and nNOS activity increases, then falls thereafter [16]. Up regulation of iNOS occurs from 12 h after the onset of ischaemia and persists for up to 7 days [17], whilst NO within brain tissue is undetectable during this period [14]. L-arginine administered intravenously following middle cerebral artery occlusion in a rat model improved ischaemic penumbral blood flow and reduced infarct size and volume [18]. This effect was not seen in eNOS-deficient mice who developed smaller penumbral regions, larger infarcts and absent angiogenesis leading to further post-ischaemic injury [19–21]. Therefore, eNOS and eNOS-derived NO are neuroprotective in focal ischaemia, whilst nNOS- and iNOS-derived NO have deleterious effects on tissue survival with resultant poor neurological outcomes [15, 22]. Although neurotoxic in acute stroke, iNOS and nNOS are involved in neurogenesis following stroke [23, 24]. In therapeutic studies, NO donors reduced infarct size in both permanent and transient models of ischaemia, and increased cerebral blood flow in permanent models, but only if administered soon after stroke induction [25].

Blood pressure (BP) is high in 75% of people with acute stroke [26] and is associated independently with poor functional outcome and increased death (regardless of stroke type) [27, 28], stroke recurrence in ischaemic stroke (IS) [29] and haematoma expansion in intracerebral haemorrhage (ICH) [30]. High admission BP has been associated with lower rates of recanalisation in IS patients treated with thrombolysis [31], and with increased infarct volume and poor functional outcome in patients with large vessel occlusion [32]. Modulation of BP in acute stroke has long been debated; treatment of raised BP in ICH is recommended [33], and is safe in IS [34, 35].

Owing to the myriad effects of NO described above and the low levels of endogenous NO seen in both IS and ICH [36, 37], supplementation through administration of NO donors might be beneficial. In contrast, diaspirin cross-linked haemoglobin reduces vascular NO levels [38]. In acute IS, diaspirin cross-linked haemoglobin was associated with poor neurological outcome. Hence, lowering NO can lead to worse outcomes in acute stroke, whilst increasing NO may be beneficial [39]. Here, we discuss the evidence to date, potential mechanisms of action and future

possibilities, including unanswered questions, for the therapeutic potential of the NO donor glyceryl trinitrate (GTN) in acute stroke.

## 2 Nitric Oxide Donors and Acute Stroke

NO donors can be broadly categorised into organic (e.g. GTN) and inorganic (e.g. sodium nitroprusside) nitrates, although there are many subtypes [40]. Transdermal GTN has been administered as a transdermal patch to patients with acute and subacute stroke in three phase II trials; GTN lowered BP (peripheral and central), 24-h BP, peak systolic BP (SBP), pulse pressure and pulse pressure index; increased heart rate; improved vascular compliance; and did not alter cerebral blood flow and velocity, or induce cerebral steal or increase intracranial pressure (Table 1) [41–45]. While intravenous sodium nitroprusside has antiplatelet properties [46], GTN had no such impact on platelet function and can therefore be administered in patients with ICH [41]. None of these earlier studies were powered for efficacy, and this was assessed in the large Efficacy of Nitric Oxide in Stroke (ENOS) trial [47].

ENOS enrolled 4011 participants with acute stroke (within 48 h of onset) and raised systolic BP (140–220 mmHg) and randomised these to transdermal GTN patch (5 mg) or no patch. Overall, there was no significant shift in functional outcome measured using the modified Rankin Scale at day 90 (primary outcome, adjusted common odds ratio 1.01, 95% confidence intervals [CI] 0.91–1.13) or of any secondary outcomes; further, GTN was safe with no increased reporting of serious adverse events [47]. GTN lowered BP by 7.0/3.5 mmHg as compared with control at day 1. In a pre-defined subgroup by time to randomisation (ENOS-early), those who received GTN within 6 h of stroke onset had a favourable shift in the modified Rankin Scale (adjusted common odds ratio 0.51, 95% CI 0.32–0.80), less death, less disability (Barthel Index), less mood disturbance (Zung Depression Scale), and improved cognition (telephone Mini-Mental State Examination) and quality of life (Euro-Quality of life Visual Analogue Scale and Health Utility Scale) [48]. The small ambulance-based Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT) also found that transdermal GTN 5 mg, given in the pre-hospital setting by paramedics within 4 h of ictus, improved the modified Rankin Scale at day 90 [49].

An individual patient data meta-analysis using data from the five completed GTN trials (GTN-1/2/3, ENOS, RIGHT, $n = 4197$) supported the findings that treatment with GTN within 6 h of onset ($n = 312$), but not later, improved functional outcome and secondary outcomes across a range

**Table 1** Effects of GTN in acute/subacute stroke

| | GTN-1 2001 [41] | GTN-2 2003 [42] | GTN-3 2006 [43] | RIGHT 2013 [49] | ENOS 2015 [47] | GTN 1-2 [45] | GTN 1-3 [44] |
|---|---|---|---|---|---|---|---|
| Systolic BP (mmHg) | ↓ 13 (7.8%) | | ↓ 23 (14%) | ↓ 21 | ↓ 7 | ↓ 9.4 | ↓ 9.8 |
| Diastolic BP (mmHg) | ↓ 5.2 (5.4%) | | ↓ 4 (3%) | ↓ 6 | ↓ 3.5 | ↓ 4.8 | ↓ 4.4 |
| Heart rate (bpm) | No change | No change | No change | No change | ↑ 1.7 | ↑ 4.1 | ↑ 3.9 |
| MAP (mmHg) | | ↓ 6.2% | | | | ↓ 5.0 | ↓ 6.4 |
| PP (mmHg) | | ↓ 3.9 | | ↑ 16 | | | ↓ 6.1 |
| PPI | | | | | | | ↓ 0.03 |
| RPP (mmHg.bpm) | | | | No change | | | ↓ 323 |
| Augmentation index | | Improved | | Improved | | | |
| Cerebral blood flow velocity | | No change | No change | | | | |
| Cerebral blood flow | | | No change | | | | |
| Zero flow pressure | | | No change | | | | |
| Platelet function | No change | | | | | | |
| GTN supplier (5 mg) | Schwarz Pharma | Schwarz Pharma (5 and 10 mg) | Novartis (Transiderm-Nitro) | MSD Schering-Plough (NitroDur) | UCB Pharma (Deponit-5) in 38% of sites (29%[a]) Novartis (Transiderm-Nitro) in 28% of sites (34%[a]) MSD/Schering-Plough (NitroDur) in 25% of sites (19%[a]) Meda/3M Healthcare (Minitran) in 10% of sites (3%[a]) Wuhan Jianmin in 1% of sites (2%[a]) | | |

*BP* blood pressure, *bpm* beats per minute, *ENOS* Efficacy of Nitric Oxide in Stroke trial, *GTN* glyceryl trinitrate, *MAP* mean arterial pressure, *PP* pulse pressure, *PPI* pulse pressure index, *RIGHT* Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial, *RPP* rate pressure product, ↓ indicates a decrease, ↑ indicates an increase

[a] Percentage of sites for ENOS-early (within 6 h)

of domains: cognition; death; disability; mood; and quality of life (Table 2) [50]. The time-dependent effect on functional outcome was seen in both IS and ICH; a finding supported by a subgroup analysis of participants with ICH from the ENOS trial [51]. Those with ICH who received GTN within 6 h of onset had significant improvements in functional outcome, cognition, disability, mood and quality of life at 90 days compared with those who did not receive GTN [51]. In the aforementioned meta-analysis, those with IS who received thrombolysis, given either before or after randomisation, had a significant shift to less death or dependency in the presence of GTN. A tendency to improved outcome was also seen in those with IS who did not receive intravenous alteplase [50].

Further trials are needed to confirm whether GTN is efficacious when given early in patients with acute stroke; one study, the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2), is assessing transdermal 5-mg GTN patch vs. sham in 850 patients with presumed stroke within 4 h of onset, SBP >120 mmHg and FAST score 2 or 3; paramedics perform consent, recruitment and treatment in the pre-hospital setting.

**Table 2** Clinical outcomes with GTN in acute stroke [50]

|  | All GTN | Randomisation ≤6 h |
|---|---|---|
| Patients (%) | 4197 | 312 (7.4) |
| End of treatment | | |
| Death | 1.15 (0.79, 1.68) | 0.94 (0.23, 3.81) |
| Neurological deterioration | 1.29 (1.00, 1.66) | 0.58 (0.28, 1.23) |
| Stroke recurrence | 1.39 (0.88, 2.18) | 0.46 (0.14, 1.54) |
| SSS (/58) | 0.33 (−0.26, 0.91) | 2.33 (−0.42, 5.09) |
| NIHSS[a] | −0.28 (−0.70, 0.14) | **−2.07 (−3.81, −0.34)** |
| Day 7 | | |
| Non-oral feeding[a] | 0.97 (0.82, 1.15) | 0.59 (0.32, 1.08) |
| Hospital | | |
| Length of stay (days) | 0.07 (−1.30, 1.44) | 0.02 (−4.59, 4.63) |
| Physiotherapy[a] | 0.94 (0.79, 1.12) | 0.90 (0.40, 2.05) |
| Occupational therapy[a] | 1.01 (0.72, 1.41) | 1.15 (0.36, 3.68) |
| Speech therapy[a] | 0.95 (0.84, 1.08) | 1.01 (0.44, 2.29) |
| Day 90 | | |
| Modified Rankin Scale | 0.99 (0.89, 1.10) | **0.52 (0.34, 0.78)** |
| Death | 0.87 (0.71, 1.07) | **0.32 (0.14, 0.78)** |
| Barthel Index | 1.73 (−0.08, 3.55) | **9.64 (3.19, 16.09)** |
| Quality of life (HUS) | 0 (−0.02, 0.02) | 0.05 (−0.02, 0.13) |
| Quality of life (EQ-VAS) | 0.69 (−1.06, 2.43) | 5.97 (−0.30, 12.24) |
| Mood (ZDS) | −0.38 (−1.80, 1.04) | **−8.34 (−13.32, −3.36)** |
| Cognition (t-MMSE) | 0.34 (−0.16, 0.84) | **2.09 (0.65, 3.54)** |
| Cognition (TICS-M) | 0.16 (−0.55, 0.88) | **3.56 (1.20, 5.91)** |
| Cognition (animal naming) | −0.06 (−0.60, 0.47) | 1.63 (−0.13, 3.39) |

Data are number (%), mean difference, or odds ratio with 95% confidence intervals. Comparisons by binary logistic regression, ordinal logistic regression or multiple linear regression, with adjustment for trial. Significant ($p < 0.05$) results are in bold

*BI* Barthel Index, *EQ-VAS* Euro-Quality of life Visual Analogue Scale, *GTN* glyceryl trinitrate, *HUS* Health Utility Scale (derived from Euro-Quality of life 5-dimensions (EQ5D)), *NIHSS* National Institutes of Health Stroke Scale, *SSS* Scandinavian Stroke Scale, *TICS-M* Telephone Interview Cognition Scale, *t-MMSE* Telephone Mini-Mental State Examination, *ZDS* Zung Depression Scale

[a] Unadjusted using the Mantel–Haenszel random-effects model

# 3 Mechanisms of Action of Glyceryl Trinitrate in Acute Stroke

If transdermal GTN is found to be beneficial in the management of acute stroke, there are several potential mechanisms through which its actions may be mediated (Table 3). First, BP lowering may reduce early recurrent events in IS [29] and haematoma expansion in ICH [30]. The ability of GTN to lower BP without reducing CBF or cerebral perfusion pressure, or increasing intracranial pressure, may be due to its vasodilatory effect thus increasing blood flow exiting the cranium [43]. Second, in addition to high SBP being associated with poor clinical outcomes in acute stroke, other haemodynamic variables including higher peak SBP, mean arterial pressure, pulse pressure, pulse pressure index and increased SBP variability are independently associated with worse functional outcome, death, recurrent stroke and early neurological

deterioration [52–54]. The published effects of GTN on haemodynamic measures in acute stroke are detailed in Table 1. New data on SBP variability from the four pilot studies (GTN 1-3 and RIGHT) are included in Table 4. Between-visit systolic BP variability was calculated as standard deviation (SD) and coefficient of variation (CoV = SD/mean) of SBP over days 1–7 across each trial individually and across all four trials as a whole. The mean difference between GTN and no GTN was calculated using analysis of covariance with adjustment for baseline SBP and trial as appropriate. GTN reduced SBP variability (SD and CoV) over days 1–7 when given within 4 h in the RIGHT pre-hospital trial in both adjusted and unadjusted analyses. When pooled together, there was significant heterogeneity seen across the trials for both SD ($I^2 = 75\%$) and CoV ($I^2 = 79\%$). This heterogeneity likely represents the small sample sizes of each of the trials and the varying time from stroke onset to randomisation. Therefore,

**Table 3** GTN in acute stroke: mechanisms of action and unanswered questions

| Issue | Prior observations | Comment |
|---|---|---|
| Time | Reperfusion therapies exhibit time dependency: thrombolysis [56] and thrombectomy [57] | Apparent time-dependent effect mirrors thrombolysis and thrombectomy |
| Stroke type | | |
|   Ischaemic stroke | BP lowering may reduce recurrent events | Apparent benefit: vasodilatory effects may improve blood flow in large arteries ('front door') [43] and pial arteries/collaterals ('back door') [58]; new data awaited |
|   Intracerebral haemorrhage | BP lowering may reduce haematoma expansion [65] | Apparent benefit; new data awaited |
| Stroke syndrome | | |
|   Lacunar | | Unclear effect; further analyses and new data awaited |
|   Total anterior circulation | | Apparent benefit: tendency for improved functional outcome in total anterior circulation in ENOS [47]; further analyses and new data awaited |
| Stroke severity | | |
|   Severity | | Apparent benefit: tendency for improved functional outcome in severe stroke in ENOS [47]; further analyses and new data awaited |
| Safety | | |
|   Carotid stenosis | BP lowering might reduce perfusion | Initial safety seen in all levels of ipsilateral carotid stenosis in ENOS [47]; further analyses and new data awaited |
|   Large vessel occlusion | | Unknown; further analyses and new data awaited |
|   Dehydration and stroke | Large drops in BP may occur in dehydrated patients given antihypertensive medication | Relevance to GTN unknown; further analyses and new data awaited |
|   Stroke mimics | | No adverse effect seen in RIGHT [49]; new data awaited |
| Duration of therapy | | Tachyphylaxis seen in GTN-1/2 and ENOS [41, 42, 47]. RIGHT-2 is assessing 4 days of treatment whilst planned trials will assess 1 or 2 days of treatment |
| Route of administration | Transdermal drugs allow easy application and removal without need for swallowing assessment or intravenous access | GTN given by transdermal patch |
| Pre-stroke BP-lowering therapy | Antihypertensive medication is regularly taken prior to stroke [47] | No interaction between this and GTN seen in ENOS [47] |
| Haemodynamics | | |
|   BP derivatives | Increased MAP, PP, PPI, peak SBP and SBP variability are associated with poor outcomes | GTN reduces MAP, PP, PPI, peak SBP and variability [44, 55] |
|   Heart rate | High heart rate [54] and impaired heart rate variability [66] are associated with worse outcome | GTN increases heart rate by 2–4 beats per minute. Tendencies to reduced rate pressure product (RPP = SBP × HR) suggest that the effect of GTN on HR is more than offset by BP reduction [44]; further analyses and new data awaited. Effect on heart rate variability to be ascertained |

*BP* blood pressure, *ENOS* Efficacy of Nitric Oxide in Stroke trial, *GTN* glyceryl trinitrate, *MAP* mean arterial pressure, *PP* pulse pressure, *PPI* pulse pressure index, *RIGHT2* Rapid Intervention with Glyceryl trinitrate in Hypertensive Stroke Trial-2, *SBP* systolic BP

adjustment was made for baseline SBP and trial, after which GTN significantly reduced SBP variability (SD) compared with no GTN. Pre-specified secondary analysis of haemodynamic parameters in ENOS is awaited [55].

Third, the time dependency of early treatment with GTN is akin to that seen in both thrombolysis and endovascular therapy, so-called reperfusion treatments [56, 57]. As described, GTN is a potent vasodilator, which may have effects in different parts of the vascular tree: large cerebral arteries, increasing 'front door' and peri-lesional perfusion without inducing cerebral steal [43]; and surface pial arteries, increasing collateral ('back door') perfusion [58]. Fourth, in the context of thrombolysis, GTN may be synergistic through vasodilatation of the occluded or partially occluded artery, which may allow exogenous and endogenous thrombolytic compounds better access to clot.

**Table 4** Effect of GTN on blood pressure variability in acute/subacute stroke

| Trial | Patients (n) | OTR (h) | SD SBP days 1–7 | | | | CoV SBP days 1–7 (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Unadjusted | p value | Adjusted | p value | Unadjusted | p value | Adjusted | p value |
| GTN-1 [41] | 37 | <120 | −2.0 (−6.4, 2.4) | 0.36 | −2.7 (−6.8, 1.4) | 0.19 | −1.2 (−3.7, 1.3) | 0.32 | −1.5 (−4.0, 1.0) | 0.23 |
| GTN-2 [42] | 90 | <72 | 0.1 (−2.2, 2.3) | 0.96 | 0.1 (−2.0, 2.3) | 0.92 | 0.2 (−1.4, 1.7) | 0.83 | 0.2 (−1.3, 1.7) | 0.81 |
| GTN-3 [43] | 18 | <120 | 1.2 (−3.7, 6.0) | 0.62 | 1.4 (−3.4, 6.3) | 0.54 | 2.4 (−0.5, 5.2) | 0.10 | 2.5 (−0.5, 5.4) | 0.10 |
| RIGHT [49] | 41 | <4 | **−7.7 (−12.1, −3.3)** | **0.001** | **−7.2 (−11.5, −2.8)** | **0.002** | **−4.9 (−8.0, −1.8)** | **0.003** | **−4.9 (−8.1, −1.7)** | **0.003** |
| Combined | 186 | | −1.6 (−3.8, 0.6) | 0.14 | **−2.1 (−3.8, −0.4)** | **0.019** | −0.7 (−2.2, 0.7) | 0.31 | −1.2 (−2.4, 0.0) | 0.058 |

Data are mean difference (95% confidence intervals) with adjustment for baseline SBP ± trial. Significant ($p < 0.05$) results are in bold

*CoV* coefficient of variation, *GTN* glyceryl trinitrate, *OTR* onset to randomization, *RIGHT* Rapid Intervention with Glyceryl trinitrate in Hypertensive Stroke Trial, *SBP* systolic blood pressure, *SD* standard deviation

GTN also appears to prepare patients for thrombolysis by lowering systolic BP below the licensed threshold of 185 mmHg. A non-significant increase in both rates of thrombolysis and earlier treatment was seen in RIGHT [49]. Last, the neuroprotective effects of GTN mediated via NO may prevent cell death from ischaemia [10, 18].

## 4 Unanswered Questions

Although ENOS confirmed the overall safety of GTN in acute stroke [47], several distinct scenarios warrant further discussion (Table 3). First, patients with carotid stenosis as the cause of their stroke often have high BP at presentation and whether to lower their BP is subject to debate. Owing to dysfunctional cerebral autoregulation, higher BP leads to higher cerebral perfusion pressure, increasing the risk of cerebral oedema and haemorrhagic transformation of infarction, whilst BP reduction may compromise CBF extending infarction [30]. Across all levels of ipsilateral carotid artery stenosis within ENOS (2038 participants with carotid imaging data), GTN was safe with no evidence of harm [47]. However, data for patients with severe bilateral carotid stenosis are sparse, given its rarity, although a meta-analysis of three trials found that lower BP was associated with increased stroke recurrence [59]. In this group, BP lowering should be avoided pending further data. A post-hoc analysis of the ENOS dataset is planned for further clarification of this important patient subgroup. Second, and similarly, the advent of endovascular therapy for proximal anterior circulation vessel occlusions in acute IS poses several challenges including how to manage BP without potentially compromising CBF; the ongoing RIGHT-2 trial will include a subgroup of patients who have thrombectomy following GTN-sham treatment. Third, dehydration is a common finding in patients with acute stroke and was associated with poor outcomes in a stroke registry study [60]. BP lowering in the setting of dehydration may lead to precipitous drops in BP, which could be harmful; the effect of GTN in this scenario is unclear and a subgroup analysis of ENOS may prove illuminating. Last, the administration of an agent that may improve outcome when given as early as possible will inevitably mean that patients with conditions mimicking stroke will receive treatment. Therefore, it is imperative that GTN is safe in this group; a question for ongoing and future trials.

As previously alluded to, GTN positively influenced several clinical outcomes when given early in both IS and ICH [50]. Whether GTN has the same effects in patients with lacunar syndromes, lacunar strokes or small vessel disease is unclear and further analysis is required. In addition to answering these and other questions, current and future trials will need to record data on other outcomes including

thrombolysis, thrombectomy, neurosurgical procedures (e.g. hemicraniectomy), feeding status, therapy usage and length of stay (overall, intensive care unit), as these may be influenced by the efficacy of GTN. Indeed, early GTN was associated with less nasogastric and more oral feeding in ENOS-early (unpublished). Importantly, all the trial data for GTN in acute stroke are from one group of authors; others need to replicate and confirm these findings in differing countries, healthcare settings and stroke populations.

## 5 Glyceryl Trinitrate in Acute Stroke: What Does the Future Hold?

There are few evidence-based treatments for the management of acute stroke. In acute IS, intravenous thrombolysis [56], thrombectomy [61] and decompressive hemicraniectomy [62] each have high efficacy but low utility, whilst aspirin has high utility but low efficacy [63]. Managing patients with all stroke types in stroke units has very high utility with medium-level efficacy [64]. In comparison, GTN has high utility, low cost (£5/$7 per patient), is easily administered and should be easy to implement if efficacy is confirmed. Importantly, the source of the patch does not influence efficacy; participants within ENOS (including those randomised within 6 h) received patches from different manufacturers, whilst the other GTN trials used one manufacturer to supply each trial (Table 1).

In the future, GTN could be used on a global scale in developing and developed countries, rural and urban areas, before and in hospital, and in a variety of healthcare settings. The possibility of an inexpensive and effective intervention for the management of acute stroke is a welcome prospect in the current economic climate.

## References

1. Murad F, Waldman S, Monlina C, et al. Regulation and role of guanylate cyclase-cyclic GMP in vascular relaxation. Prog Clin Biol Res. 1987;249:65–76.
2. Radomski MW, Palmer RMJ, Moncada S. Endogenous nitric oxide inhibits human platelet adhesion to vascular endothelium. Lancet. 1987;ii:1057–8.
3. Radomski MW, Palmer RMJ, Moncada S. The anti-aggregating properties of vascular endothelium: interactions between prostacyclin and nitric oxide. Br J Pharmacol. 1987;92:639–46.
4. Bath PM, Hassall DG, Gladwin AM, et al. Nitric oxide and prostacyclin: divergence of inhibitory effects on monocyte chemotaxis and adhesion to endothelium in vitro. Arterioscler Thromb. 1991;11:254–60.
5. Garthwaite J, Charles SL, Chess-Williams R. Endothelium derived relaxing factor on activation of NMDA receptors suggests role as intercellular messenger in the brain. Nature. 1988;336:385–8.
6. Dawson TM, Snyder SH. Gases as biological messengers: nitric oxide and carbon monoxide in the brain. J Neurosci. 1994;14:5147–59.
7. Tanaka K. Is nitric oxide really important for regulation of the cerebral circulation? Yes or no? Keio J Med. 1996;45:14–27.
8. White RP, Vallance P, Markus HS. Effect of inhibition of nitric oxide synthase on dynamic cerebral autoregulation in humans. Clin Sci. 2000;99:555–60.
9. Lavi S, Egbarya R, Lavi R, Jacob G. Role of nitirc oxide in the regulation of cerebral blood flow in humans: chemoregulation versus mechanoregulation. Circulation. 2003;107(14):1901–5.
10. Kim YM, Talanian RV, Billiar TR. Nitric oxide inhibits apoptosis by preventing increases in caspase-3-like activity via two distinct mechanisms. J Biol Chem. 1997;272(49):31138–48.
11. Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature. 1987;327(6122):524–6.
12. Palmer RMJ, Ashton DS, Moncada S. Vascular endothelial cells synthesise nitric oxide from L-arginine. Nature. 1988;333:664–6.
13. Bath PMW. The effect of nitric oxide-donating vasodilators on monocyte chemotaxis and intracellular cGMP concentrations in vitro. Eur J Clin Pharmacol. 1993;45:53–8.
14. Malinski T, Bailey F, Zhang ZG, Chopp M. Nitric oxide measured by a porphyrinic microsensor in rat brain after transient middle cerebral artery occlusion. J Cereb Blood Flow Metab. 1993;13:355–8.
15. Huang Z, Huang PL, Panahian N, et al. Effects of cerebral ischemia in mice deficient in neuronal nitric oxide synthase. Science. 1994;265:1883–5.
16. Kader A, Frazzini VI, Solomon RA, Trifiletti RR. Nitric oxide production during focal cerebral ischemia in rats. Stroke. 1993;24:1709–16.
17. Niwa M, Inao S, Takayasu M, et al. Time course of expression of three nitric oxide synthase isoforms after transient middle cerebral artery occlusion in rats. Neurol Med Chir (Tokyo). 2001;41:63–72.
18. Morikawa E, Huang Z, Moskowitz MA. L-arginine decreases infarct size caused by middle cerebral arterial occlusion in SHR. Am J Physiol. 1992;263:H1632–5.
19. Huang Z, Huang PL, Ma J, et al. Enlarged infarcts in endothelial nitric oxide synthase knockout mice are attenuated by nitro-L-arginine. J Cereb Blood Flow Metab. 1996;16:981–7.
20. Lo EH, Hara H, Rogowska J, et al. Temporal correlation mapping analysis of the hemodynamic penumbra in mutant mice deficient in endothelial nitric oxide synthase gene expression. Stroke. 1996;27:1381–5.

21. Cui X, Chopp M, Zacharek A, et al. Role of endothelial nitric oxide synthase in arteriogenesis after stroke in mice. Neuroscience. 2009;159:744–50.

22. Zhao X, Ross ME, Iadecola C. L-arginine increases ischemic injury in wild-type mice but not in iNOS-deficient mice. Brain Res. 2003;966:308–11.

23. Sehara Y, Hayashi T, Deguchi K, et al. Distribution of inducible nitric oxide synthase and cell proliferation in rat brain after transient middle cerebral artery occlusion. Brain Res. 2006;1093:190–7.

24. Sun Y, Jin K, Childs JT, et al. Neuronal nitric oxide synthase and ischemia-induced neurogenesis. J Cereb Blood Flow Metab. 2005;25(4):485–92.

25. Willmot M, Gray L, Gibson C, et al. A systematic review of nitric oxide donors and L-arginine in experimental stroke; effects on infarct size and cerebral blood flow. Nitric Oxide. 2005;12(3):141–9.

26. Oppenheimer S, Hachinski V. Complications of acute stroke. Lancet. 1992;339(8795):721–4.

27. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA. Blood pressure and clinical outcomes in the International Stroke Trial. Stroke. 2002;33(5):1315–20.

28. Vemmos KN, Tsivgoulis G, Spengos K, et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. J Intern Med. 2004;255(2):257–65.

29. Sprigg N, Gray LJ, Bath PM, et al. Relationship between outcome and baseline blood pressure and other haemodynamic measures in acute ischaemic stroke: data from the TAIST trial. J Hypertens. 2006;24(7):1413–7.

30. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. Hypertension. 2004;43(1):18–24.

31. Tsivgoulis G, Saqqur M, Sharma VK, et al. Association of pretreatment blood pressure with tissue plasminogen activator-induced arterial recanalization in acute ischemic stroke. Stroke. 2007;38(3):961–6.

32. Goyal N, Tsivgoulis G, Iftikhar S, et al. Admission systolic blood pressure and outcomes in large vessel occlusion strokes treated with endovascular treatment. J Neurointerv Surg. 2016. doi:10.1136/neurintsurg-2016-012386.

33. Hemphill J, Greenberg S, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage. Stroke. 2015;46:2032–60.

34. Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database Syst Rev. 2014;10:CD000039.

35. Appleton JP, Sprigg N, Bath PM. Blood pressure management in acute stroke. Stroke Vascular Neurol. 2016;00:e000020.

36. Ferlito S, Gallina M, Pitari GM, Bianchi A. Nitric oxide plasma levels in patients with chronic and acute cerebrovascular disorders. Panminerva Med. 1998;40:51–4.

37. Rashid PA, Whitehurst A, Lawson N, Bath PMW. Plasma nitric oxide (nitrate/nitrite) levels in acute stroke and their relationship with severity and outcome. J Stroke Cerebrovasc Dis. 2003;12(2):82–7.

38. Schultz S, Grady B, Cole F, et al. A role for endothelin and nitric oxide in the pressor response to diaspirin cross-linked hemoglobin. J Lab Clin Med. 1993;122:301–8.

39. Saxena R, Wijnhoud AD, Carton H, et al. Controlled safety study of a hemoglobin-based oxygen carrier, DCLHb, in acute ischemic stroke. Stroke. 1999;30:993–6.

40. Wang P, Xian M, Tang X, et al. Nitric oxide donors: chemical activities and biological applications. Chem Rev. 2002;102(4):1091–134.

41. Bath PMW, Pathansali R, Iddenden R, Bath FJ. The effect of transdermal glyceryl trinitrate, a nitric oxide donor, on blood pressure and platelet function in acute stroke. Cerebrovasc Dis. 2001;11:265–72.

42. Rashid P, Weaver C, Leonardi-Bee J, et al. The effects of transdermal glyceryl trinitrate, a nitric oxide donor, on blood pressure, cerebral and cardiac hemodynamics, and plasma nitric oxide levels in acute stroke. J Stroke Cerebrovasc Dis. 2003;12(3):143–51.

43. Willmot M, Ghadami A, Whysall B, et al. Transdermal glyceryl trinitrate lowers blood pressure and maintains cerebral blood flow in recent stroke. Hypertension. 2006;47:1209–15.

44. Gray LJ, Sprigg N, Rashid PA, et al. Effect of nitric oxide donors on blood pressure and pulse pressure in acute and sub-actue stroke. J Stroke Cerebrovasc Dis. 2006;15(6):245–9.

45. Geeganage CM, Bath AJ, Bath PM. The effect of transdermal glyceryl trinitrate on 24 h ambulatory blood pressure in acute/subacute stroke. Int J Stroke. 2011;6(4):290–4.

46. Butterworth RJ, Cluckie A, Jackson SH, et al. Pathophysiological assessment of nitric oxide (given as sodium nitroprusside) in acute ischaemic stroke. Cerebrovasc Dis. 1998;8(3):158–65.

47. Bath P, Woodhouse L, Scutt P, et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. Lancet. 2015;385(9968):617–28.

48. Woodhouse L, Scutt P, Krishnan K, et al. Effect of hyperacute administration (within 6 hours) of transdermal glyceryl trinitrate, a nitric oxide donor, on outcome after stroke: subgroup analysis of the Efficacy of Nitric Oxide in Stroke (ENOS) trial. Stroke. 2015;46:3194–201.

49. Ankolekar S, Fuller M, Cross I, et al. Feasibility of an ambulance-based stroke trial, and safety of glyceryl trinitrate in ultra-acute stroke: the rapid intervention with glyceryl trinitrate in Hypertensive Stroke Trial (RIGHT, ISRCTN66434824). Stroke. 2013;44(11):3120–8.

50. Bath PM, Woodhouse L, Krishnan K, 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. 2016;2016:9706720.

51. Krishnan K, Scutt P, Woodhouse L, et al. Glyceryl trinitrate for acute intracerebral haemorrhage: results from the Efficacy of Nitric Oxide in Stroke (ENOS) trial, a subgroup analysis. Stroke. 2016;47(1):44–52.

52. Manning L, Hirakawa Y, Arima H, et al. Blood pressure variability and outcome after acute intracerebral haemorrhage: a post-hoc analysis of INTERACT2, a randomised controlled trial. Lancet Neurol. 2014;13:364–73.

53. Sare GM, Ali M, Shuaib A, Bath PMW, for the VISTA Collaboration. Relationship between hyperacute blood pressure and outcome after ischemic stroke: data from the VISTA Collaboration. Stroke. 2009;40:2098–103.

54. Geeganage C, Tracy M, England T, et al. Relationship between baseline blood pressure parameters (including mean pressure, pulse pressure, and variability) and early outcome after stroke: data from the Tinzaparin in Acute Ischaemic Stroke Trial (TAIST). Stroke. 2011;42:491–3.

55. Bath PM, Houlton A, Woodhouse L, et al. Statistical analysis plan for the 'Efficacy of Nitric Oxide in Stroke' (ENOS) trial. Int J Stroke. 2014;9(3):372–4.

56. Emberson J, Lees K, Lyden P, et al. Effect of treatment delay, age and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014;384(9958):1929–35.

57. Fransen PS, Berkhemer OA, Lingsma HF, et al. Time to reperfusion and treatment effect for acute ischemic stroke: a randomized clinical trial. JAMA Neurol. 2015;73(2):190–6.

58. Morikawa E, Rosenblatt S, Moskowitz MA. L-arginine dilates rat pial arterioles by nitric oxide-dependent mechanisms and increases blood flow during focal cerebral ischaemia. Br J Pharmacol. 1992;107(4):905–7.

59. Rothwell PM, Howard SC, Spence JD. Relationahsip between blood pressure and stroke risk in patients with symptomatic carotid occlusive disease. Stroke. 2003;34:2583–90.

60. Liu CH, Lin SC, Lin JR, et al. Dehydration is an independent predictor of discharge outcome and admission cost in acute ischaemic stroke. Eur J Neurol. 2014;21:1184–91.

61. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;397(10029):1723–31.

62. Vahedi K, Hofmeijer J, Vacaut E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol. 2007;6:215–22.

63. Sandercock PAG, Counsell C, Gubitz GJ, Tseng MC. Antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev. 2008;3:CD000029.

64. Stroke Unit Trialists Collaboration. Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev. 2007;(4):CD000197.

65. Tsivgoulis G, Katsanos AH, Butcher KS, et al. Intensive blood pressure reduction in acute intracerebral hemorrhage: a meta-analysis. Neurology. 2014;83:1523–9.

66. Tang S-C, Jen H-I, Lin Y-H, et al. Complexity of heart rate variability predicts outcome in intensive care unit admitted patients with acute stroke. J Neurol Neurosurg Psychiatry. 2015;86:95–100.