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CURRENT OPINION

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

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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.

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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

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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.

Compliance with Ethical Standards

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