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Benefits and safety of transdermal glyceryl trinitrate in acute stroke: a systematic review and meta-analysis of randomised trials (Protocol)

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3 **Benefits and safety of transdermal glyceryl trinitrate in acute stroke: a systematic**
4 **review and meta-analysis of randomised trials (Protocol)**
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56 **Key words:** transdermal; glyceryl trinitrate; acute stroke
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ABSTRACT:

Introduction: High blood pressure (BP) is common in acute stroke and has adverse outcomes. Transdermal glyceryl trinitrate (GTN) has beneficial properties and can be easily administered to control BP. There is an urgent need for an updated meta-analysis as the previous review in 2016 has important limitations. We report the protocol for a systematic review and meta-analysis on the safety and benefits of transdermal GTN in acute stroke.

Methods and Analysis: We will search Medline, Pubmed, Embase, CINAHL and Cochrane Library from inception until June 2020 for randomised trials that report the efficacy and safety of transdermal GTN vs placebo/control therapy among adult patients with acute stroke. Primary outcomes include in-hospital mortality, BP lowering and late functional status. Secondary outcomes include early, late, resource utilisation and surrogate outcomes. Safety outcomes include reported adverse events. Reviewers will first screen titles and abstracts, and then full texts, to identify eligible studies. Independently and in duplicate, they will extract data, assess risk of bias (RoB) using a modified Cochrane RoB tool and quality of evidence using GRADE. Disagreement will be resolved by discussion and consultation with an external reviewer if necessary. Using a random-effects model, we will report effect sizes using relative risks and 95% confidence intervals. We will perform pre-defined subgroup analyses: intracerebral haemorrhage vs ischaemic stroke; minor (NIHSS \leq five) vs major (NIHSS $>$ five) ischaemic stroke; ischaemic stroke with vs without thrombolysis; pre-hospital vs non pre-hospital settings; time from stroke to randomisation \leq six vs $>$ six hours and high vs low overall RoB studies. We will also perform trial sequential analysis for the primary outcomes of in-hospital mortality and late functional status.

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3 **Ethics and Dissemination:** Ethics board approval is unnecessary. PROSPERO
4 registration has been obtained (CRD42020173093). The results will be disseminated
5 through publication in a peer-reviewed journal.
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10 11 12 13 **ARTICLE SUMMARY**

14 15 16 **Strengths and Limitations of Study**

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20 • This is the first update since the previous meta-analysis in 2016 on the use of
21 transdermal GTN in acute stroke which included several small trials ($n \leq 90$). This
22 meta-analysis will include the large ($n > 1000$), multi-centre RIGHT-2 trial published
23 in 2019.
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27 • This study will examine an important gap identified by the previous meta-analysis in
28 2016; i.e benefits of transdermal GTN vs placebo/control therapy in ultra-acute stroke
29 (presentation \leq six hours) in a pre-planned subgroup analysis with limited sample
30 size ($n = 312$). The data from the RIGHT-2 trial includes $>$ three times the total sample
31 size of acute stroke patients with presentation $<$ four hours used in the 2016 review.
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35 • Other strengths of this protocol include a comprehensive search strategy of published
36 and unpublished literature, an extensive predefined subgroup analysis plan and
37 inclusion of GRADE methodology to assess certainty of evidence.
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41 • This study will be the first to use trial sequential analysis on the important primary
42 outcomes of in-hospital mortality and late functional status associated with
43 transdermal GTN use in acute stroke.
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47 • Limitations to this protocol include the anticipated high clinical heterogeneity given
48 the haemorrhagic and ischaemic subtypes of acute stroke, variation in timing of
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3 randomization from onset of stroke to transdermal GTN or placebo/control therapy
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5 and reporting of outcome measures across trials.
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10 11 INTRODUCTION

12
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14 High blood pressure (BP) is present in greater than 70% of patients with acute ischaemic
15 stroke.¹ It is associated with poor outcomes including acute stroke recurrence, death within
16 a few weeks or combined death and dependency after several months.¹⁻⁴ High BP is similarly
17 common in acute intracerebral haemorrhage (ICH)⁵ and may be associated with haematoma
18 expansion and increased mortality.⁶⁻⁸

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21 It is recommended to lower BP in ICH⁹⁻¹⁰ although controversy exists regarding optimal BP
22 target in patients with ICH and there is no current literature on the role of pre-hospital BP
23 reduction. The management of high BP in acute ischaemic stroke and the decision to treat
24 or not to treat has been a constant debate since 1985. Current available guidelines
25 recommend withholding antihypertensive therapy in the early post-stroke period unless
26 there is markedly elevated BP (>220/120mmHg) or with BP >185/110mmHg for patients
27 eligible for thrombolysis or BP >180/105mmHg during the 24-hour period following
28 reperfusion.¹¹⁻¹³

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31 Nitric oxide (NO) donors are candidate agents to lower BP in acute stroke because NO is a
32 cerebral and systemic vasodilator, modulates vascular and neuronal function, is
33 neuroprotective, and inhibits apoptosis.¹⁴ In addition, vascular NO concentrations are low in
34 acute stroke which are associated with increased severity of stroke, mortality and
35 institutionalization.¹⁵ These observations support that NO supplementation might be
36 beneficial.
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3 Glyceryl trinitrate (GTN) is an example of a NO donor. Transdermal GTN administration
4 offers a constant release of the drug across the skin into the systemic circulation for 24 hours
5 which achieves sustained steady-state plasma concentrations.¹⁶ Transdermal GTN offers a
6 formulation which is easily administered in many clinical settings [pre-hospital, Emergency
7 Department (ED) and inpatient] managing acute stroke which may help to minimise
8 fluctuations in drug concentrations and hence BP.
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12 The only meta-analysis published in 2016; using data from five completed transdermal GTN
13 trials (n= 4197); reported no improvement in outcomes across a range of domains (death,
14 disability, cognition, mood, and quality of life with transdermal GTN vs placebo or control
15 therapy.¹⁷ However, in a pre-specified subgroup analysis of patients with time from stroke
16 to randomisation \leq six vs $>$ six hours (n= 312), this meta-analysis reported a favourable
17 functional outcome as measured by modified Rankin scale (mRS) at 90 days with
18 transdermal GTN. There were important limitations in this meta-analysis. Four out of five
19 selected trials had small sample sizes (n \leq 90). The remaining multi-centre ENOS trial¹⁸
20 recruited 4011 patients and it dominated the pooled analysis (95.6% of all patients and
21 86.9% of those randomised within six hours of onset). In addition, all the included trials were
22 conducted by a single research group and it is important that other research groups study
23 the role of transdermal GTN in acute stroke. Finally, a relatively small number of patients
24 (n= 312) were treated within six hours of stroke onset and these patients came from just two
25 of the five trials.
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50 The recently published multi-centre RIGHT-2 trial randomised 1149 participants with acute
51 stroke within four hours of onset to receive transdermal GTN vs sham therapy.¹⁹ The data
52 from this study more than triples that used to examine the role of transdermal GTN in ultra-
53 early stroke (onset \leq six hours). There is an urgent need to update the evidence behind the
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3 efficacy and safety of transdermal GTN in acute stroke especially among those patients with
4 ultra-early (\leq six hours) presentation.
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8 The aim of this systematic review and meta-analysis is to examine; using recent data;
9 whether transdermal GTN improves important patient centred outcomes and is safe among
10 patients with acute stroke in the pre-hospital and in-hospital settings compared to placebo
11 or control therapy by reviewing randomised controlled trials (RCTs).
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18 **METHODS**

21 **Study Registration**

22 This systematic review and meta-analysis protocol has been registered in the International
23 Prospective Register of Systematic Reviews (PROSPERO). The reference number is
24 CRD42020173093. We will adhere to the Preferred Reporting Items for Systematic Reviews
25 and Meta-Analysis (PRISMA) statement for reporting systematic review and meta-
26 analysis.²⁰
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36 **Eligibility Criteria**

37 We will include randomised trials investigating the efficacy and safety of transdermal GTN
38 vs placebo or control therapy among adult patients presenting with acute stroke.
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44 Patients aged \geq 16 years presenting with either acute ischaemic or haemorrhagic stroke in
45 the pre-hospital, ED and inpatient clinical settings will be considered. Acute stroke patients
46 are defined as those with presentation within five days of onset of symptoms. We select five
47 days since onset of symptoms as the inclusion cut-off criterion for this review because there
48 can be significant delay in presentation after an acute stroke; especially for less severe
49 ischaemic strokes.²¹ Patients with ischaemic stroke are included regardless of whether they
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3 receive thrombolysis. The comparator arms will include transdermal GTN patch, sham patch
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5 and control with existing standard therapy.
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8 Primary outcomes are important patient centred outcomes including in-hospital mortality,
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10 lowering of BP measurements and late functional status.
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13 Secondary outcomes are classified as early, late, resource utilisation and surrogate
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15 outcomes. Early secondary outcomes include development of ICH, recurrent stroke and
16
17 change in calculated National Institutes of Health Stroke Scale (NIHSS). Late secondary
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19 outcomes include reported changes in activities of daily living, cognition, quality of life and
20
21 mood. Resource utilisation secondary outcomes include length of hospital stay and
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23 discharge destination. Surrogate secondary outcomes include changes in cerebral
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25 haemodynamics and laboratory parameters like platelet aggregation.
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30 Safety outcomes include any adverse events reported by the authors.
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33 **Search Strategy**

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35 We will search Medline, Pubmed, Embase, CINAHL and Cochrane Library from inception
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37 until June 2020 without language restrictions. We will review reference lists for eligible new
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39 trials and also search ClinicalTrials.gov for ongoing or unpublished trials and for additional
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41 data from published trials. The search strategy will include the following keywords: stroke,
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43 ischaemic stroke, haemorrhagic stroke, intracerebral haemorrhage, transdermal glyceryl
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45 trinitrate, transdermal nitroglycerin, glyceryl trinitrate patch, nitroglycerin patch,
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47 trinitroglycerin, pre-hospital, mortality, blood pressure, functional outcome, humans and
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49 randomised clinical trials.
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54 **Study Selection**

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3 Reviewers (LBL, CWL, LWF and NWM) will independently and in duplicate screen the titles
4 and abstracts of all identified studies to generate a list of eligible trials from which full texts
5 will be obtained. Subsequently, the same reviewers will independently assess eligibility of
6 these full texts of published trials to decide on the final included studies. Discrepancies
7 between reviewers will be resolved through discussion and consensus or, if needed, by
8 adjudication from an external reviewer and/or contact with authors of the original trials for
9 clarification.

20 **Data Extraction**

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23 Two pairs of reviewers (LBL and CWL; LWF and NWM) will extract data from included
24 studies both independently and in duplicate. Data extracted will include the following:
25 general study information [authors, publication year and study location(s)]; study population
26 details [clinical setting- pre-hospital vs ED vs inpatient, sample size, types of strokes-
27 ischaemic vs haemorrhagic; subgroup of ischaemic strokes with thrombolysis]; details on
28 the comparator arms [different doses and duration of GTN patch; sham patch and control]
29 as well as the primary, secondary and safety outcomes as listed above.

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32 In randomized trials that included more than one arm of GTN dosing and duration, we will
33 extract data from the arm closest to a single dose regimen that is comparable to other
34 primary studies to be used for analysis.

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37 Discrepancies in data extraction will be resolved through discussion and consensus or, if
38 needed, via an external reviewer and/or contact with authors of the original trials for
39 clarification.

54 **Risk OF Bias Assessment**

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57 We will assess the risk of bias (RoB) for each outcome of the individual studies using a
58 modified Cochrane RoB instrument.²² The instrument assesses biases in the following five
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3 domains: selection bias (random sequence generation and allocation concealment);
4 performance bias (blinding of participants and researchers); detection bias (blinding of
5 outcome assessment); attrition bias (incomplete outcome data) and reporting bias (selective
6 reporting). Within each domain, we will classify the RoB as high, unclear or low. Reviewers
7 will also judge to determine whether any particular domain is impossible to achieve in any
8 of the primary studies (like blinding in trials comparing GTN patch vs existing standard
9 therapy) and likely or unlikely to affect the reported effect size of the outcome.

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12 Primary studies will be classified as having an overall high RoB when they have been rated
13 at least one domain as having high risk after exclusion of certain domain that is judged to
14 be logistically impossible to achieve for that particular trial and unlikely to affect reported
15 effect size of outcome.

16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 **Quality of Evidence**

32 We will also assess the quality of evidence for each outcome using the GRADE (Grading of
33 Recommendations, Assessment, Development and Evaluation) approach that classifies
34 evidence as high, moderate, low or very low quality based on considerations of RoB,
35 consistency, directness, precision and publication bias.²³

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38 Assessment of the individual and overall RoB categories as well as the quality of evidence
39 will be performed independently by the two pairs of reviewers (LBL and CWL; LWF and
40 NWM) with any discrepancies resolved by discussion and consensus or if necessary, via
41 consultation with an external reviewer.

42 43 44 45 46 47 48 49 50 51 52 53 **Data Analysis**

54 All analyses will be performed using RevMan 5.3 (Cochrane Collaboration, Oxford) software.
55 We will use DerSimonian and Laird random-effects model a priori to conduct the data
56 analysis and meta-analysis. We chose the random-effects model as it produces more

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3 conservative confidence intervals and it considers both within- and between-study
4 variability.²⁰
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8 For continuous outcomes, we will calculate the mean difference and its corresponding 95%
9 confidence intervals (CIs) whenever possible. For dichotomous outcomes, we will calculate
10 the relative risk (RR) and its corresponding 95% CIs. We will generate forest plots to
11 demonstrate the individual and pooled effect sizes for the outcome of interest if there are at
12 least two studies. We will assess for heterogeneity between studies by first visual inspection
13 of the forest plots and then using the I^2 statistic. I^2 measures the percentage of the total
14 variation in estimated effects of the outcome across studies that is due to heterogeneity
15 rather than to chance.²⁴ A I^2 value of 0% indicates no observed heterogeneity, and larger
16 values show increasing heterogeneity.
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20 Regardless of the observed statistical heterogeneity (I^2 values), we plan to conduct the
21 following a priori subgroup analyses for each outcome when each subgroup is represented
22 by at least two studies. These subgroup analyses will be: ICH vs ischaemic stroke; minor
23 (NIHSS \leq five) vs major (NIHSS $>$ five) ischaemic stroke; ischaemic stroke with vs without
24 thrombolysis; pre-hospital vs non pre-hospital (ED and inpatient) settings; time from stroke
25 to randomization \leq six vs $>$ six hours and high vs low overall RoB studies.
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29 Meta-analyses may result in Type I errors due to an increased risk of random error when
30 sparse data are collected and repeated significance testing when a cumulative meta-
31 analysis is updated with new trials.²⁵⁻²⁶ We will perform trial sequential analysis (TSA) using
32 a random-effects model for the primary outcomes of in-hospital mortality and late functional
33 status. In the TSA, we will use a statistical significance level of 5%, a power of 80% and an
34 estimated effect size difference between transdermal GTN vs placebo or control therapy as
35 reported by the included trials. TSA generates the required information size calculated as
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3 diversity-adjusted information size (DIS)²⁷ suggested by the estimated effect size difference;
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5 thereby providing important information on how many more patients need to be included in
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7 further trials. TSA also creates adjusted thresholds for statistical significance (trial sequential
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9 monitoring boundaries) with addition of each new trial.²⁵⁻²⁶ The cumulative Z curve which
10
11 includes the selected trials; if it crosses the trial sequential monitoring boundary, will signify
12
13 that a sufficient level of evidence has been reached and no further trials are needed.²⁵⁻²⁶ If
14
15 the Z curve fails to cross the trial sequential monitoring boundary, the required information
16
17 size is not reached and there is insufficient evidence to reach a conclusion.
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22 TSA will be performed using Trial Sequential Analysis v.0.9.5.10 beta (Copenhagen Trial
23
24 Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark,
25
26 www.ctu.dk/tsa).
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29 30 **PATIENT AND PUBLIC INVOLVEMENT**

31
32 We have not and will not involve new patients or the public in this protocol.
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35 36 **DISCUSSION**

37
38 Acute ischaemic and haemorrhagic strokes are frequently managed in various clinical
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40 settings; from pre-hospital, ED to inpatient. High BP is common in both types of strokes
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42 and is associated with short-term poor outcomes (acute stroke recurrence, death
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44 within a few weeks¹⁻⁴ and haematoma expansion⁶⁻⁸) and adverse effects in the longer-
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46 term (delayed death and dependency after several months¹⁻⁴). BP control is an
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48 essential part of the management of acute ischaemic and haemorrhagic strokes.
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53 NO donors are candidate agents to lower BP in acute stroke because of its various
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55 beneficial properties ranging from vasodilatation to neuroprotection and inhibition of
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57 apoptosis.¹⁴ GTN is an example of a NO donor. Transdermal GTN offers an easily
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3 administered formulation which is valuable especially in the pre-hospital and ED
4 settings to provide constant drug release.
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8 There was only a meta-analysis published in 2016¹⁷ that investigated the effects of
9 transdermal GTN in acute stroke which reported no overall benefits. However, it
10 reported a favourable functional outcome (improvement in mRS at 90 days) with
11 transdermal GTN vs placebo or control therapy in a pre-specified subgroup of patients
12 with ultra-acute stroke (time from stroke to randomization \leq six hours). The meta-
13 analysis had important limitations. Apart from the ENOS trial¹⁸, the remaining four
14 included trials had small sample sizes ($n \leq 90$) and all these trials were conducted by
15 a single research group. In addition, that subgroup analysis involving ultra-acute stroke
16 patients also suffered from a small sample size ($n = 312$).
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30 With the inclusion of the recently published multi-centre RIGHT-2 trial which recruited
31 1149 patients with acute stroke within four hours of onset¹⁹, our systematic review and
32 meta-analysis will significantly increase the sample size available for pooling of
33 studies; especially so when it will more than triple that used to examine the role of
34 transdermal GTN in ultra-acute stroke (onset \leq six hours). Our planned subgroup
35 analysis of patients with ultra-acute stroke will address a significant gap in the literature
36 that arose from the previous meta-analysis in 2016.
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46 In addition, our TSA for the important primary outcomes of in-hospital mortality and
47 late functional status will reduce Type I error. Our TSA will determine whether the DIS
48 and trial sequential monitoring boundaries for these outcomes have indeed been
49 reached in our meta-analysis; signifying that a sufficient level of evidence has been
50 attained to reach a conclusion.
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3 Other strengths of our protocol include a comprehensive search strategy of published
4 and unpublished literature, extensive subgroup analyses involving clinically important
5 patient subgroups and using GRADE methodology to assess certainty of evidence.
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10 Limitations to our protocol include the anticipated high clinical heterogeneity given the
11 haemorrhagic and ischaemic subtypes of acute stroke as well as variation in timing of
12 randomization from stroke onset to transdermal GTN or placebo/control therapy and
13 reporting of outcome measures across trials even within a subtype of acute stroke.
14
15 We will address clinical heterogeneity by evaluating for statistical heterogeneity,
16 explore pre-defined clinically important subgroup analyses and to account for
17 inconsistencies in our GRADE evaluation. In order to address for differences in
18 reporting of outcome measures across included trials, we will include a spectrum of
19 primary and secondary outcomes. We will assess reporting of these outcomes
20 independently and in duplicate and if there are discrepancies, we will resolve through
21 discussion, consensus, potentially involving an external reviewer and contact the
22 primary authors for clarification.
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39 In conclusion, this protocol describes the details and methodology of a planned
40 systematic review and meta-analysis addressing the safety and benefits of
41 transdermal GTN in acute stroke. The results of this meta-analysis are expected to fill
42 the gap in the literature on the subgroup of patients with ultra-acute stroke (onset \leq 6
43 hours), inform daily practice, clinical practice guidelines and guide areas of
44 investigation for future RCTs.
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53 **ACKNOWLEDGMENTS**

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56 We have no acknowledgments to make.
57

58 **COMPETING INTERESTS**

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1
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3 There are no competing interests to disclose.
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7
8
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11 some protected time for us to carry out this work.
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14

15 **CONTRIBUTIONS**

16
17 LBL, CWL and LWF conceived the study. LBL, CWL and LWF also wrote the study protocol
18 to be registered with PROSPERO.
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22
23 All authors contributed to protocol development. LBL, CWL and LWF drafted the study
24 protocol and this manuscript. All authors contributed to refinement of the study protocol and
25 manuscript as well as approved the final manuscript.
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32 **REFERENCES**

- 33
34
35
36 1. Leonardi-Bee J, Bath PMW, Phillips SJ, for the IST Collaborative Group. Blood
37 pressure and clinical outcomes in the International Stroke Trial. *Stroke*.
38 2002;33:1315–20.
39
40
41 2. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and
42 subsequent outcome: a systematic review. *Hypertension*. 2004;43:18–24.
43
44
45 3. Sprigg N, Gray LJ, Bath PM, et al. Relationship between outcome and baseline
46 blood pressure and other haemodynamic measures in acute ischaemic stroke:
47 data from the TAIST trial. *J Hypertens*. 2006; 24:1413–17.
48
49
50
51 4. Geeganage C, Tracy M, England T, et al. Relationship between baseline blood
52 pressure parameters (including mean pressure, pulse pressure, and variability)
53
54
55
56
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58
59
60

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2
3 and early outcome after stroke: data From the Tinzaparin in Acute Ischaemic
4 Stroke Trial (TAIST). *Stroke*. 2011;42:491–3.
5
6
7
8 5. Qureshi AI, Ezzeddine MA, Nasar A, et al. Prevalence of elevated blood
9 pressure in 563,704 adult patients with stroke presenting to the ED in the United
10 States. *Am J Emerg Med*. 2007;25:32-8.
11
12
13
14 6. Qureshi AI. The importance of acute hypertensive response in ICH. *Stroke*.
15 2013;44: Suppl 1:S67-9.
16
17
18
19 7. Dandapani BK, Suzuki S, Kelley RE, et al. Relation between blood pressure and
20 outcome in intracerebral hemorrhage. *Stroke*. 1995;26:21-4.
21
22
23
24 8. Anderson CS, Huang Y, Arima H, et al. Effects of early intensive blood pressure
25 lowering treatment on the growth of hematoma and perihematomal edema in
26 acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in
27 Acute Cerebral Haemorrhage Trial (INTERACT). *Stroke*. 2010;41:307-12.
28
29
30
31
32
33 9. Intercollegiate Stroke Working Party. National clinical guideline for stroke, 5th
34 edn. London: Royal College of Physicians, 2016.
35
36
37
38 10. Hemphill JC, Greenberg SM, Anderson CS, et al.; American Heart Association
39 Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on
40 Clinical Cardiology. Guidelines for the management of spontaneous
41 intracerebral hemorrhage: a guideline for healthcare professionals from the
42 American Heart Association/American Stroke Association.
43
44
45
46
47
48
49
50
51
52 11. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of
53 patients with acute ischemic stroke: a guideline for healthcare professionals
54 from the American Heart Association/American Stroke Association. *Stroke*.
55
56
57
58
59
60

- 1
2
3 12. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early
4 management of patients with acute ischemic stroke: a guideline for healthcare
5 professionals from the American Heart Association/American Stroke
6 Association. *Stroke*. 2018;2018:e46–e110.
7
8
9
- 10
11
12 13. Shinohara Y, Yamaguchi T. Outline of the Japanese Guidelines for the
13 Management of Stroke 2004 and subsequent revision. *Int J Stroke*. 2008;3:55–
14 62.
15
16
17
- 18
19 14. Willmot MR, Bath PMW. The potential of nitric oxide therapeutics in stroke.
20 *Expert Opin Investig Drugs*. 2003;12:455–70.
21
22
23
- 24 15. Rashid PA, Whitehurst A, Lawson N, et al. Plasma nitric oxide (nitrate/nitrite)
25 levels in acute stroke and their relationship with severity and outcome. *J Stroke*
26 *Cerebrovasc Dis*. 2003;12:82–7.
27
28
29
- 30 16. Todd PA, Goa KL, Langtry HD. Transdermal nitroglycerin (glyceryl trinitrate):
31 a review of its pharmacology and therapeutic use. *Drugs*. 1990;40:880-902.
32
33
34
- 35 17. Bath PM, Woodhouse L, Krishnan K, et al. Effect of treatment delay, stroke type,
36 and thrombolysis on the effect of glyceryl trinitrate, a nitric oxide donor, on
37 outcome after acute stroke: a systematic review and meta-analysis of individual
38 patient from randomised trials. *Stroke Res Treat*. 2016;2016:9706720.
39
40
41
42
43
- 44 18. Bath PM, Woodhouse L, Scutt P, et al. Efficacy of nitric oxide, with or without
45 continuing antihypertensive treatment, for management of high blood pressure
46 in acute stroke (ENOS): a partial-factorial randomised controlled trial. *Lancet*.
47 2015;385:617-28.
48
49
50
51
52
- 53 19. Bath PM, Scutt P, Anderson CS, et al. Prehospital transdermal glyceryl trinitrate
54 in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based,
55 randomised, sham-controlled, blinded, phase 3 trial. *Lancet*. 2019;393:1009-20.
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60
20. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *BMJ*. 2009; 339:b2700.
 21. Addo J, Ayis S, Leon J, et al. Delay in presentation after an acute stroke in a multethnic population in South London: The South London Stroke Register. *J Am Heart Assoc*. 2012;1:e001685.
 22. Higgins JPT, Altman DG, Gøtzsche PC, for Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
 23. Guyatt GH, Oxman AD, Vist GE, for GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-6.
 24. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-60.
 25. Wetterslev J, Thorlund K, Brok J, et al. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol*. 2008;61:64-75.
 26. Brok J, Thorlund K, Wetterslev J, et al. Apparently conclusive meta-analyses may be inconclusive—trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Int J Epidemiol*. 2009;38:287-98.
 27. Wetterslev J, Thorlund K, Brok J, et al. Estimating required information size by quantifying diversity in random-effects model meta-analyses. *BMC Med Res Methodol*. 2009;9:86.

Reporting checklist for protocol of a systematic review.

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			Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1,2,6
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	2,3,5

1	Registration		
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4		#2	
5		If registered, provide the name of the registry (such as	6
6		PROSPERO) and registration number	
7			
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9			
10	Authors		
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12			
13	Contact	#3a	
14		Provide name, institutional affiliation, e-mail address of all	1
15		protocol authors; provide physical mailing address of	
16		corresponding author	
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20	Contribution	#3b	
21		Describe contributions of protocol authors and identify the	14
22		guarantor of the review	
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26	Amendments		
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29		#4	
30		If the protocol represents an amendment of a previously	NA
31		completed or published protocol, identify as such and list	
32		changes; otherwise, state plan for documenting important	
33		protocol amendments	
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39	Support		
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42	Sources	#5a	
43		Indicate sources of financial or other support for the review	14
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45	Sponsor	#5b	
46		Provide name for the review funder and / or sponsor	14
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48	Role of sponsor or	#5c	
49	funder	Describe roles of funder(s), sponsor(s), and / or	14
50		institution(s), if any, in developing the protocol	
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1	Rationale	#6	Describe the rationale for the review in the context of what is	4,5,6
2			already known	
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6	Objectives	#7	Provide an explicit statement of the question(s) the review	6
7			will address with reference to participants, interventions,	
8			comparators, and outcomes (PICO)	
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14	Methods			
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17	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	6,7
18			design, setting, time frame) and report characteristics (such	
19			as years considered, language, publication status) to be	
20			used as criteria for eligibility for the review	
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27	Information	#9	Describe all intended information sources (such as	7
28			electronic databases, contact with study authors, trial	
29	sources		registers or other grey literature sources) with planned dates	
30			of coverage	
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37	Search strategy	#10	Present draft of search strategy to be used for at least one	7
38			electronic database, including planned limits, such that it	
39			could be repeated	
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45	Study records -	#11a	Describe the mechanism(s) that will be used to manage	7,8
46			records and data throughout the review	
47	data management			
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50	Study records -	#11b	State the process that will be used for selecting studies	8
51			(such as two independent reviewers) through each phase of	
52	selection process		the review (that is, screening, eligibility and inclusion in	
53			meta-analysis)	
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1	Study records -	#11c	Describe planned method of extracting data from reports	8
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3	data collection		(such as piloting forms, done independently, in duplicate),	
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5	process		any processes for obtaining and confirming data from	
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7			investigators	
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11	Data items	#12	List and define all variables for which data will be sought	8
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13			(such as PICO items, funding sources), any pre-planned	
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15			data assumptions and simplifications	
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19	Outcomes and	#13	List and define all outcomes for which data will be sought,	7
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21	prioritization		including prioritization of main and additional outcomes, with	
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26	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	8,9
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28	individual studies		individual studies, including whether this will be done at the	
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30			outcome or study level, or both; state how this information	
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32			will be used in data synthesis	
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36	Data synthesis	#15a	Describe criteria under which study data will be	9,10,11
37				
38			quantitatively synthesised	
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42	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe	9,10,11
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44			planned summary measures, methods of handling data and	
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46			methods of combining data from studies, including any	
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48			planned exploration of consistency (such as I ² , Kendall's τ)	
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51	Data synthesis	#15c	Describe any proposed additional analyses (such as	10
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53			sensitivity or subgroup analyses, meta-regression)	
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1	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type	NA
2			of summary planned	
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6	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	9
7			publication bias across studies, selective reporting within	
8			studies)	
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14	Confidence in	#17	Describe how the strength of the body of evidence will be	9
15	cumulative		assessed (such as GRADE)	
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BMJ Open

Benefits and safety of transdermal glyceryl trinitrate in acute stroke: a systematic review and meta-analysis of randomised trials (Protocol)

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Secondary Subject Heading:	Emergency medicine
Keywords:	ACCIDENT & EMERGENCY MEDICINE, Stroke < NEUROLOGY, NEUROSURGERY

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3 **Benefits and safety of transdermal glyceryl trinitrate in acute stroke: a systematic**
4 **review and meta-analysis of randomised trials (Protocol)**
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53 **Word count excluding title page, abstract, references, figures and tables: 3116**
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56 **Key words:** transdermal; glyceryl trinitrate; acute stroke
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ABSTRACT:

Introduction: High blood pressure (BP) in acute stroke has adverse outcomes. Transdermal glyceryl trinitrate (GTN) has beneficial properties in controlling BP. The 2016 meta-analysis and 2017 Cochrane review showed transdermal GTN was beneficial in a small patient subgroup with stroke onset \leq six hours. Larger studies focusing on this patient subgroup have since been conducted. We report the protocol for an updated systematic review and meta-analysis on the safety and benefits of transdermal GTN in acute stroke.

Methods and Analysis: We will search Medline, Pubmed, Embase, CINAHL and Cochrane Library from inception until June 2020 for randomised trials that report the efficacy and safety of transdermal GTN vs placebo/control therapy among adult patients with acute stroke. Primary outcomes include in-hospital mortality, BP lowering and late functional status. Secondary outcomes include early, late, resource utilisation and surrogate outcomes. Safety outcomes include reported adverse events. Reviewers will first screen titles and abstracts, and then full texts, to identify eligible studies. Independently and in duplicate, they will extract data, assess risk of bias (RoB) using a modified Cochrane RoB tool and quality of evidence using GRADE. Disagreement will be resolved by discussion and consultation with an external reviewer if necessary. Using a random-effects model, we will report effect sizes using relative risks and 95% confidence intervals. We will perform pre-defined subgroup analyses: intracerebral haemorrhage vs ischaemic stroke; minor (NIHSS \leq five) vs major (NIHSS $>$ five) ischaemic stroke; ischaemic stroke with vs without thrombolysis; pre-hospital vs non pre-hospital settings; time from stroke to randomisation \leq six vs $>$ six hours and high vs low overall RoB studies. We will also perform trial sequential analysis for the primary outcomes.

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3 **Ethics and Dissemination:** Ethics board approval is unnecessary. PROSPERO
4 registration has been obtained (CRD42020173093). The results will be disseminated
5 through publication in a peer-reviewed journal.
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13 **ARTICLE SUMMARY**

14 **Strengths and Limitations of Study**

- 15 • This is an updated meta-analysis which includes more recent larger trials.
- 16 • This study will examine an important gap on the benefits of transdermal GTN in ultra-
17 acute stroke (\leq six hours) identified by previous reviews.
- 18 • Other strengths include a comprehensive search strategy, an extensive predefined
19 subgroup analysis plan and inclusion of GRADE methodology to assess certainty of
20 evidence.
21 • This study will be the first to use trial sequential analysis on important primary
22 outcomes.
23 • Limitations include high clinical heterogeneity given the different subtypes of acute
24 stroke, variation in timing of randomization from onset of stroke to transdermal GTN
25 or placebo/control therapy and reporting of outcome measures across trials.
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INTRODUCTION

High blood pressure (BP) is present in greater than 70% of patients with acute ischaemic stroke.¹ It is associated with poor outcomes including acute stroke recurrence, death within a few weeks or combined death and dependency after several months.¹⁻⁴ High BP is similarly common in acute intracerebral haemorrhage (ICH)⁵ and may be associated with haematoma expansion and increased mortality.⁶⁻⁸

It is recommended to lower BP in ICH⁹⁻¹⁰ although controversy exists regarding optimal BP target in patients with ICH and there is no current literature on the role of pre-hospital BP reduction. The management of high BP in acute ischaemic stroke and the decision to treat or not to treat has been a constant debate since 1985. Current available guidelines recommend withholding antihypertensive therapy in the early post-stroke period unless there is markedly elevated BP (>220/120mmHg) or with BP >185/110mmHg for patients eligible for thrombolysis or BP >180/105mmHg during the 24-hour period following reperfusion.¹¹⁻¹³

Nitric oxide (NO) donors are candidate agents to lower BP in acute stroke because NO is a cerebral and systemic vasodilator, modulates vascular and neuronal function, is neuroprotective, and inhibits apoptosis.¹⁴ In addition, vascular NO concentrations are low in acute stroke which are associated with increased severity of stroke, mortality and institutionalization.¹⁵ These observations support that NO supplementation might be beneficial.

Glyceryl trinitrate (GTN) is an example of a NO donor. Transdermal GTN administration offers a constant release of the drug across the skin into the systemic circulation for 24 hours which achieves sustained steady-state plasma concentrations.¹⁶ Transdermal GTN offers a formulation which is easily administered in many clinical settings [pre-hospital, Emergency

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3 Department (ED) and inpatient] managing acute stroke which may help to minimise
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fluctuations in drug concentrations and hence BP.

The latest meta-analysis published in 2016¹⁷ and Cochrane review in 2017¹⁸, using data from five completed transdermal GTN trials (n= 4197), reported no improvement in outcomes across a range of domains (death, disability, cognition, mood, and quality of life with transdermal GTN vs placebo or control therapy. However, in a pre-specified subgroup analysis of patients with time from stroke to randomisation \leq six vs $>$ six hours (n= 312), these two reviews reported a favourable functional outcome as measured by modified Rankin Scale (mRS) at 90 days with transdermal GTN. There were important limitations in these reviews. Four out of five selected trials had small sample sizes (n \leq 90). The remaining multi-centre ENOS trial¹⁹ recruited 4011 patients and it dominated the pooled analysis (95.6% of all patients and 86.9% of those randomised within six hours of onset). In addition, all the included trials were conducted by a single research group and it is important that other research groups study the role of transdermal GTN in acute stroke. Finally, a relatively small number of patients (n= 312) were treated within six hours of stroke onset and these patients came from just two of the five trials.

The recently published multi-centre RIGHT-2 trial randomised 1149 participants with acute stroke within four hours of onset to receive transdermal GTN vs sham therapy.²⁰ The data from this study more than triples that used to examine the role of transdermal GTN in ultra-early stroke (onset \leq six hours). There is an urgent need to update the evidence behind the efficacy and safety of transdermal GTN in acute stroke especially among those patients with ultra-early (\leq six hours) presentation.

The aim of this systematic review and meta-analysis is to examine, using recent data, whether transdermal GTN improves important patient centred outcomes and is safe among

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3 patients with acute stroke in the pre-hospital and in-hospital settings compared to placebo
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5 or control therapy by reviewing randomised controlled trials (RCTs).
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8 **METHODS**

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10 **Study Registration**

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12 This systematic review and meta-analysis protocol has been registered in the International
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14 Prospective Register of Systematic Reviews (PROSPERO). The reference number is
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16 CRD42020173093. We will adhere to the Preferred Reporting Items for Systematic Reviews
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18 and Meta-Analysis (PRISMA) statement for reporting systematic review and meta-
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20 analysis.²¹
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26 **Eligibility Criteria**

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29 We will include randomised trials investigating the efficacy and safety of transdermal GTN
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31 vs placebo or control therapy among adult patients presenting with acute stroke.
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35 Patients aged ≥ 16 years presenting with either acute ischaemic or haemorrhagic stroke in
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37 the pre-hospital, ED and inpatient clinical settings will be considered. Acute stroke patients
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39 are defined as those with presentation within five days of onset of symptoms. We select five
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41 days since onset of symptoms as the inclusion cut-off criterion for this review because there
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43 can be significant delay in presentation after an acute stroke; especially for less severe
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45 ischaemic strokes.²² Patients with ischaemic stroke are included regardless of whether they
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47 receive thrombolysis. The comparator arms will include transdermal GTN patch, sham patch
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49 and control with existing standard therapy.
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54 Primary outcomes are important patient centred outcomes including in-hospital mortality,
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56 lowering of BP measurements and late functional status. BP parameters will include systolic
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58 BP, diastolic BP and mean arterial pressure measured at intervals stated by the authors.
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3 Late functional status will involve assessment using the mRS within three months of stroke
4 onset or later (as reported by the authors); the preferred outcome measurement for acute
5 stroke trials.²³ The hierarchical mRS scores range from 0 to 6, with a score of 0 indicating
6 no symptoms, 1 indicating some symptoms but no significant disability, 2–5 indicating
7 increasing levels of disability and dependency, and 6 indicating death.²³
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15 Secondary outcomes are classified as early, late, resource utilisation and surrogate
16 outcomes. Early secondary outcomes include development of ICH, recurrent stroke and
17 change in calculated National Institutes of Health Stroke Scale (NIHSS). Late secondary
18 outcomes include reported changes in activities of daily living, cognition, quality of life and
19 mood. Resource utilisation secondary outcomes include length of hospital stay and
20 discharge destination. Surrogate secondary outcomes include changes in cerebral
21 haemodynamics and laboratory parameters like platelet aggregation.
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32 Safety outcomes include any adverse events reported by the authors.
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35 **Search Strategy**

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38 We will search Medline, Pubmed, Embase, CINAHL and Cochrane Library from inception
39 until June 2020 without language restrictions. We will review reference lists for eligible new
40 trials and also search ClinicalTrials.gov for ongoing or unpublished trials and for additional
41 data from published trials. The search strategy will include the following keywords: stroke,
42 ischaemic stroke, haemorrhagic stroke, intracerebral haemorrhage, transdermal glyceryl
43 trinitrate, transdermal nitroglycerin, glyceryl trinitrate patch, nitroglycerin patch,
44 trinitroglycerin, pre-hospital, mortality, blood pressure, functional outcome, humans and
45 randomised clinical trials. Medical Subject Heading (MeSH) terms will include acute stroke,
46 brain infarction, brain haemorrhage, prehospital emergency care, nitroglycerin, nitric oxide
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3 donors, blood pressure, haemodynamics and cerebral haemodynamics. A proposed search
4 strategy on Medline using the Pubmed interface is attached as Appendix 1.
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8 **Study Selection**

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10 Reviewers (LBL, CWL, LWF and NWM) will independently and in duplicate screen the titles
11 and abstracts of all identified studies to generate a list of eligible trials from which full texts
12 will be obtained. Subsequently, the same reviewers will independently assess eligibility of
13 these full texts of published trials to decide on the final included studies. Discrepancies
14 between reviewers will be resolved through discussion and consensus or, if needed, by
15 adjudication from an external reviewer and/or contact with authors of the original trials for
16 clarification.
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28 **Data Extraction**

29
30 Two pairs of reviewers (LBL and CWL; LWF and NWM) will extract data from included
31 studies both independently and in duplicate. Data will be extracted using a pre-designed
32 data extraction form adapted from the Cochrane Collaboration.²⁴ The data collection form is
33 attached as Appendix 2. Data extracted will include the following: general study information
34 [authors, publication year and study location(s)]; study population details [clinical setting-
35 pre-hospital vs ED vs inpatient, sample size, types of strokes- ischaemic vs haemorrhagic;
36 subgroup of ischaemic strokes with thrombolysis]; details on the comparator arms [different
37 doses and duration of GTN patch; sham patch and control] as well as the primary, secondary
38 and safety outcomes as listed above.
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52 In randomized trials that included more than one arm of GTN dosing and duration, we will
53 extract data from the arm closest to a single dose regimen that is comparable to other
54 primary studies to be used for analysis.
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3 Discrepancies in data extraction will be resolved through discussion and consensus or, if
4 needed, via an external reviewer and/or contact with authors of the original trials for
5 clarification.
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10 **Risk OF Bias Assessment**

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12
13 We will assess the risk of bias (RoB) for each outcome of the individual studies using a
14 modified Cochrane RoB instrument.²⁵ The instrument assesses biases in the following five
15 domains: selection bias (random sequence generation and allocation concealment);
16 performance bias (blinding of participants and researchers); detection bias (blinding of
17 outcome assessment); attrition bias (incomplete outcome data) and reporting bias (selective
18 reporting). Within each domain, we will classify the RoB as high, unclear or low. Reviewers
19 will also judge to determine whether any particular domain is impossible to achieve in any
20 of the primary studies (like blinding in trials comparing GTN patch vs existing standard
21 therapy) and likely or unlikely to affect the reported effect size of the outcome.
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35 Primary studies will be classified as having an overall high RoB when they have been rated
36 at least one domain as having high risk after exclusion of certain domain that is judged to
37 be logistically impossible to achieve for that particular trial and unlikely to affect reported
38 effect size of outcome. The overall RoB for each individual trial will be considered low if
39 RoB is judged to be low in all domains and unclear if RoB is judged to be unclear in any of
40 the domains.
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49 **Quality of Evidence**

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52 We will also assess the quality of evidence for each outcome using the GRADE (Grading of
53 Recommendations, Assessment, Development and Evaluation) approach that classifies
54 evidence as high, moderate, low or very low quality based on considerations of RoB,
55 consistency, directness, precision and publication bias.²⁶ We attach a summary of findings
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3 table (Appendix 3) which is adapted using the GRADEpro software to demonstrate how we
4
5 will present our GRADE assessment for the main outcomes.
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8 Assessment of the individual and overall RoB categories as well as the quality of evidence
9
10 will be performed independently by the two pairs of reviewers (LBL and CWL; LWF and
11
12 NWM) with any discrepancies resolved by discussion and consensus or if necessary, via
13
14 consultation with an external reviewer.
15
16

17 18 **Data Analysis**

19
20 All analyses will be performed using RevMan 5.3 (Cochrane Collaboration, Oxford) software.
21
22 We will use DerSimonian and Laird random-effects model a priori to conduct the data
23
24 analysis and meta-analysis. We chose the random-effects model as it produces more
25
26 conservative confidence intervals and it considers both within- and between-study
27
28 variability.²¹
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32
33 For continuous outcomes, we will calculate the mean difference and its corresponding 95%
34
35 confidence intervals (CIs) whenever possible. For dichotomous outcomes, we will calculate
36
37 the relative risk (RR) and its corresponding 95% CIs. We will generate forest plots to
38
39 demonstrate the individual and pooled effect sizes for the outcome of interest if there are at
40
41 least two studies. We will assess for heterogeneity between studies by first visual inspection
42
43 of the forest plots and then using the I^2 statistic. I^2 measures the percentage of the total
44
45 variation in estimated effects of the outcome across studies that is due to heterogeneity
46
47 rather than to chance.²⁷ A I^2 value of 0% indicates no observed heterogeneity, and larger
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49 values show increasing heterogeneity.
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54 Regardless of the observed statistical heterogeneity (I^2 values), we plan to conduct the
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56 following a priori subgroup analyses for each outcome when each subgroup is represented
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58 by at least two studies. These subgroup analyses will be: ICH vs ischaemic stroke; minor
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3 (NIHSS \leq five) vs major (NIHSS $>$ five) ischaemic stroke; ischaemic stroke with vs without
4 thrombolysis; pre-hospital vs non pre-hospital (ED and inpatient) settings; time from stroke
5 to randomization \leq six vs $>$ six hours; time from stroke to randomization \leq two vs $>$ two hours
6 and high vs low overall RoB studies.
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13 Missing data in the primary studies will be addressed in several ways. We will evaluate for
14 rates of missing data in these primary studies, reasons for missing data and to contact
15 primary authors for clarification if necessary. We will determine whether authors of these
16 primary studies attempted to address the impact of missing data by using intention-to-treat
17 analysis and performing sensitivity analyses through methods like imputation, best- and
18 worst-case scenario analyses to investigate how their reported effect size estimates had
19 changed. We will then make judgement independently, through consensus and/or
20 consultation with an external reviewer whether the reported effect size estimates (including
21 any sensitivity analyses) by the primary authors will likely or unlikely be affected by their
22 missing data. We will perform separate sensitivity analyses of our pooled results by including
23 and excluding those studies that are judged likely to be affected by missing data to
24 investigate how the pooled effect size estimates will be affected. Finally, we will also assess
25 the risk of missing data (attrition bias) of the primary studies through our RoB and GRADE
26 assessment.
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46 Meta-analyses may result in Type I errors due to an increased risk of random error when
47 sparse data are collected and repeated significance testing when a cumulative meta-
48 analysis is updated with new trials.²⁸⁻²⁹ We will perform trial sequential analysis (TSA) using
49 a random-effects model for the primary outcomes (in-hospital mortality, BP lowering and late
50 functional status). In the TSA, we will use a statistical significance level of 5%, a power of
51 80% and an estimated effect size difference (or mean difference for continuous outcomes)
52 between transdermal GTN vs placebo or control therapy as reported by the included trials.
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3 TSA generates the required information size calculated as diversity-adjusted information
4 size (DIS)³⁰ suggested by the estimated effect size difference; thereby providing important
5 information on how many more patients need to be included in further trials. TSA also
6 creates adjusted thresholds for statistical significance (trial sequential monitoring
7 boundaries) with addition of each new trial.²⁸⁻²⁹ The cumulative Z curve which includes the
8 selected trials; if it crosses the trial sequential monitoring boundary, will signify that a
9 sufficient level of evidence has been reached and no further trials are needed.²⁸⁻²⁹ If the Z
10 curve fails to cross the trial sequential monitoring boundary, the required information size is
11 not reached and there is insufficient evidence to reach a conclusion.
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24 TSA will be performed using Trial Sequential Analysis v.0.9.5.10 beta (Copenhagen Trial
25 Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark,
26 www.ctu.dk/tsa).
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32 **PATIENT AND PUBLIC INVOLVEMENT**

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35 We have not and will not involve new patients or the public in this protocol.
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38 **DISCUSSION**

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41 Acute ischaemic and haemorrhagic strokes are frequently managed in various clinical
42 settings; from pre-hospital, ED to inpatient. High BP is common in both types of strokes
43 and is associated with short-term poor outcomes (acute stroke recurrence, death
44 within a few weeks¹⁻⁴ and haematoma expansion⁶⁻⁸) and adverse effects in the longer-
45 term (delayed death and dependency after several months¹⁻⁴). BP control is an
46 essential part of the management of acute ischaemic and haemorrhagic strokes.
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55 NO donors are candidate agents to lower BP in acute stroke because of its various
56 beneficial properties ranging from vasodilatation to neuroprotection and inhibition of
57 apoptosis.¹⁴ GTN is an example of a NO donor. Transdermal GTN offers an easily
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3 administered formulation which is valuable especially in the pre-hospital and ED
4 settings to provide constant drug release.
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8 There was a meta-analysis in 2016¹⁷ and Cochrane review in 2017¹⁸ that investigated
9 the effects of transdermal GTN in acute stroke which reported no overall benefits.
10 However, they reported a favourable functional outcome (improvement in mRS at 90
11 days) with transdermal GTN vs placebo or control therapy in a pre-specified subgroup
12 of patients with ultra-acute stroke (time from stroke to randomization \leq six hours). The
13 meta-analysis and Cochrane review had important limitations. Apart from the ENOS
14 trial¹⁹, the remaining four included trials had small sample sizes ($n \leq 90$) and all these
15 trials were conducted by a single research group. In addition, that subgroup analysis
16 involving ultra-acute stroke patients also suffered from a small sample size ($n = 312$).
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30 With the inclusion of the recently published multi-centre RIGHT-2 trial which recruited
31 1149 patients with acute stroke within four hours of onset²⁰, our systematic review and
32 meta-analysis will significantly increase the sample size available for pooling of
33 studies; especially so when it will more than triple that used to examine the role of
34 transdermal GTN in ultra-acute stroke (onset \leq six hours). Our planned subgroup
35 analysis of patients with ultra-acute stroke will address a significant gap in the literature
36 that arose from these previous reviews.
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46 In addition, our TSA for the important primary outcomes will reduce Type I error. Our
47 TSA will determine whether the DIS and trial sequential monitoring boundaries for
48 these outcomes have indeed been reached in our meta-analysis; signifying that a
49 sufficient level of evidence has been attained to reach a conclusion.
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3 Other strengths of our protocol include a comprehensive search strategy of published
4 and unpublished literature, extensive subgroup analyses involving clinically important
5 patient subgroups and using GRADE methodology to assess certainty of evidence.
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10 Limitations to our protocol include the anticipated high clinical heterogeneity given the
11 haemorrhagic and ischaemic subtypes of acute stroke as well as variation in timing of
12 randomization from stroke onset to transdermal GTN or placebo/control therapy and
13 reporting of outcome measures across trials even within a subtype of acute stroke.
14
15 We will address clinical heterogeneity by evaluating for statistical heterogeneity,
16 explore pre-defined clinically important subgroup analyses and to account for
17 inconsistencies in our GRADE evaluation. In order to address for differences in
18 reporting of outcome measures across included trials, we will include a spectrum of
19 primary and secondary outcomes. We will assess reporting of these outcomes
20 independently and in duplicate and if there are discrepancies, we will resolve through
21 discussion, consensus, potentially involving an external reviewer and contacting the
22 primary authors for clarification.
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39 In conclusion, this protocol describes the details and methodology of a planned
40 systematic review and meta-analysis addressing the safety and benefits of
41 transdermal GTN in acute stroke. The results of this meta-analysis are expected to fill
42 the gap in the literature on the subgroup of patients with ultra-acute stroke (onset \leq 6
43 hours), inform daily practice, clinical practice guidelines and guide areas of
44 investigation for future RCTs.
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53 **ACKNOWLEDGMENTS**

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56 We have no acknowledgments to make.
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58

59 **COMPETING INTERESTS**

1
2
3 There are no competing interests to disclose.
4
5

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7
8
9 The authors received no financial support for this research work. However, we wish to thank
10 the research program of Ng Teng Fong Hospital Emergency Department which provided
11 some protected time for us to carry out this work.
12
13
14

15 **CONTRIBUTIONS**

16
17 LBL, CWL and LWF conceived the study. LBL, CWL and LWF also wrote the study protocol
18 to be registered with PROSPERO.
19
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22
23 All authors (LBL, CWL, LWF, NWM and TWL) contributed to protocol development. LBL,
24 CWL and LWF drafted the study protocol and this manuscript. All authors (LBL, CWL, LWF,
25 NWM and TWL) contributed to refinement of the study protocol and manuscript as well as
26 approved the final manuscript.
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34 **REFERENCES**

- 35
36
37
38 1. Leonardi-Bee J, Bath PMW, Phillips SJ, for the IST Collaborative Group. Blood
39 pressure and clinical outcomes in the International Stroke Trial. *Stroke*.
40 2002;33:1315–20.
41
42
43
44 2. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and
45 subsequent outcome: a systematic review. *Hypertension*. 2004;43:18–24.
46
47
48
49 3. Sprigg N, Gray LJ, Bath PM, et al. Relationship between outcome and baseline
50 blood pressure and other haemodynamic measures in acute ischaemic stroke:
51 data from the TAIST trial. *J Hypertens*. 2006; 24:1413–17.
52
53
54
55 4. Geeganage C, Tracy M, England T, et al. Relationship between baseline blood
56 pressure parameters (including mean pressure, pulse pressure, and variability)
57
58
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60

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2
3 and early outcome after stroke: data From the Tinzaparin in Acute Ischaemic
4 Stroke Trial (TAIST). *Stroke*. 2011;42:491–3.
5
6
7
8 5. Qureshi AI, Ezzeddine MA, Nasar A, et al. Prevalence of elevated blood
9 pressure in 563,704 adult patients with stroke presenting to the ED in the United
10 States. *Am J Emerg Med*. 2007;25:32-8.
11
12
13
14 6. Qureshi AI. The importance of acute hypertensive response in ICH. *Stroke*.
15 2013;44: Suppl 1:S67-9.
16
17
18
19 7. Dandapani BK, Suzuki S, Kelley RE, et al. Relation between blood pressure and
20 outcome in intracerebral hemorrhage. *Stroke*. 1995;26:21-4.
21
22
23
24 8. Anderson CS, Huang Y, Arima H, et al. Effects of early intensive blood pressure
25 lowering treatment on the growth of hematoma and perihematomal edema in
26 acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in
27 Acute Cerebral Haemorrhage Trial (INTERACT). *Stroke*. 2010;41:307-12.
28
29
30
31
32
33 9. Intercollegiate Stroke Working Party. National clinical guideline for stroke, 5th
34 edn. London: Royal College of Physicians, 2016.
35
36
37
38 10. Hemphill JC, Greenberg SM, Anderson CS, et al.; American Heart Association
39 Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on
40 Clinical Cardiology. Guidelines for the management of spontaneous
41 intracerebral hemorrhage: a guideline for healthcare professionals from the
42 American Heart Association/American Stroke Association.
43
44
45
46
47
48
49
50
51
52 11. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of
53 patients with acute ischemic stroke: a guideline for healthcare professionals
54 from the American Heart Association/American Stroke Association. *Stroke*.
55
56
57
58
59
60

- 1
2
3 12. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early
4 management of patients with acute ischemic stroke: a guideline for healthcare
5 professionals from the American Heart Association/American Stroke
6 Association. *Stroke*. 2018;2018:e46–e110.
7
8
9
- 10
11
12 13. Shinohara Y, Yamaguchi T. Outline of the Japanese Guidelines for the
13 Management of Stroke 2004 and subsequent revision. *Int J Stroke*. 2008;3:55–
14 62.
15
16
17
- 18
19 14. Willmot MR, Bath PMW. The potential of nitric oxide therapeutics in stroke.
20 *Expert Opin Investig Drugs*. 2003;12:455–70.
21
22
23
- 24 15. Rashid PA, Whitehurst A, Lawson N, et al. Plasma nitric oxide (nitrate/nitrite)
25 levels in acute stroke and their relationship with severity and outcome. *J Stroke*
26 *Cerebrovasc Dis*. 2003;12:82–7.
27
28
29
- 30 16. Todd PA, Goa KL, Langtry HD. Transdermal nitroglycerin (glyceryl trinitrate):
31 a review of its pharmacology and therapeutic use. *Drugs*. 1990;40:880-902.
32
33
34
- 35 17. Bath PM, Woodhouse L, Krishnan K, et al. Effect of treatment delay, stroke type,
36 and thrombolysis on the effect of glyceryl trinitrate, a nitric oxide donor, on
37 outcome after acute stroke: a systematic review and meta-analysis of individual
38 patient from randomised trials. *Stroke Res Treat*. 2016;2016:9706720.
39
40
41
42
43
- 44 18. Bath PMW, Krishnan K, Appleton JP. Nitric oxide donors (nitrates), L-arginine,
45 or nitric oxide synthase inhibitors for acute stroke. *Cochrane Database Syst*
46 *Rev*. 2017;4:CD000398.doi:10.1002/14651858.CD000398.pub2.
47
48
49
- 50 19. Bath PM, Woodhouse L, Scutt P, et al. Efficacy of nitric oxide, with or without
51 continuing antihypertensive treatment, for management of high blood pressure
52 in acute stroke (ENOS): a partial-factorial randomised controlled trial. *Lancet*.
53 2015;385:617-28.
54
55
56
57
58
59
60

- 1
2
3 20. Bath PM, Scutt P, Anderson CS, et al. Prehospital transdermal glyceryl trinitrate
4 in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based,
5 randomised, sham-controlled, blinded, phase 3 trial. *Lancet*. 2019;393:1009-20.
6
7
8
9
- 10
11 21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting
12 systematic reviews and meta-analyses of studies that evaluate health care
13 interventions: explanation and elaboration. *BMJ*. 2009; 339:b2700.
14
15
16
17
- 18 22. Addo J, Ayis S, Leon J, et al. Delay in presentation after an acute stroke in a
19 multethnic population in South London: The South London Stroke Register.
20 *J Am Heart Assoc*. 2012;1:e001685.
21
22
23
- 24 23. Lees KR, Bath PMW, Schellinger PD, et al. Contemporary outcome measures
25 in acute stroke research: choice of primary outcome measure. *Stroke*.
26 2012;43:1163-70.
27
28
29
30
- 31 24. Cochrane Effective Practice and Organisation of Care (EPOC). Data collection
32 form. EPOC Resources for review authors, 2017.
33 epoc.cochrane.org/resources/epoc-specific-resources-review-authors
34 (accessed 22112020).
35
36
37
38
39
- 40 25. Higgins JPT, Altman DG, Gøtzsche PC, for Cochrane Bias Methods
41 GroupCochrane Statistical Methods Group. The Cochrane Collaboration's tool
42 for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
43
44
45
46
- 47 26. Guyatt GH, Oxman AD, Vist GE, for GRADE Working Group. GRADE: an
48 emerging consensus on rating quality of evidence and strength of
49 recommendations. *BMJ*. 2008;336:924-6.
50
51
52
53
- 54 27. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-
55 analyses. *BMJ*. 2003;327:557-60.
56
57
58
59
60

- 1
2
3 28. Wetterslev J, Thorlund K, Brok J, et al. Trial sequential analysis may establish
4 when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol*.
5 2008;61:64–75.
6
7
8
9
10 29. Brok J, Thorlund K, Wetterslev J, et al. Apparently conclusive meta-analyses
11 may be inconclusive—trial sequential analysis adjustment of random error risk
12 due to repetitive testing of accumulating data in apparently conclusive neonatal
13 meta-analyses. *Int J Epidemiol*. 2009;38:287–98.
14
15
16
17
18
19 30. Wetterslev J, Thorlund K, Brok J, et al. Estimating required information size by
20 quantifying diversity in random-effects model meta-analyses. *BMC Med Res*
21 *Methodol*. 2009;9:86.
22
23
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Appendix 1. Medline Search Strategy Through Pubmed Interface

Filters:

Time period: 1st Jan 1966 to 30th June 2020

Article type: Clinical Study, Clinical Trial Phases 1 to IV, Controlled Clinical Trial, Pragmatic Clinical Trial

Species: Humans

Language restrictions: No

Age limits: 13 to 80+ years

#	Searches
1.	Acute stroke/
2.	Ischaemic stroke (tw)
3.	Haemorrhagic stroke (tw)
4.	Intracerebral haemorrhage (tw)
5.	Brain infarction/
6.	Brain haemorrhage/
7.	Prehospital emergency care/
8.	1-7 or
9.	Transdermal glyceryl trinitrate (tw)
10.	Nitroglycerin/
11.	Trinitroglycerin (tw)
12.	GTN (tw)
13.	Nitric oxide donor*/
14.	9 -13 or
15.	Mortality (tw)
16.	Death (tw)
17.	Blood pressure/
18.	Functional outcome* (tw)
19.	Haemodynamic*/
20.	Cerebral haemodynamic*/
21.	15-20 or
22.	8 and 14 and 21

Appendix 2. Data Collection Form (Adapted from Cochrane Collaboration)

General Information

Date form completed	
Name of reviewer extracting data	
Contact details of reviewer extracting data	
Title of publication	
Publication ID (first author and year of publication)	
Country in which study was conducted	
Study funding source	
Possible conflicts of interests for study authors	

Primary Study Details

1. Methods

Study Characteristics	Review Inclusion Criteria
Design (Type of randomized trial)	Blinded vs non-blinded Cross-over present
Method(s) of recruitment of participants	
Unit of allocation (individual vs cluster/group)	
Clinical setting	Pre-hospital vs Emergency Department vs Hospital
Types of intervention	Different dosing regimens of transdermal GTN

Types of comparator	Standard therapy vs placebo
Types of outcome measures	Primary: Secondary: Safety:

2. Study Population and Setting

Study population description	Stroke subtypes: haemorrhagic vs ischaemic Stroke onset to randomization Other stroke subgroups (like IV thrombolytics, etc)
Inclusion criteria	
Exclusion criteria	
Start date	
End date	
Duration of participation (recruitment to last follow-up)	

3. Participants (in intervention vs control/placebo groups)

Total number of individuals randomized	Intervention group: Control/ placebo group:
Total number of clusters randomized (if applicable)	Intervention group: Control/ placebo group:
Number of withdrawals/exclusions	Intervention group: Control/ placebo group:
Number of cross-overs	Intervention group:

	Control/ placebo group:
Baseline imbalances	
Other treatments (apart from intervention vs control/placebo)	Intervention group: Control/ placebo group:
Subgroups measured	
Subgroups reported	

4. Outcomes (create a separate section for each outcome)

Outcome name	
Outcome type (Primary vs secondary vs safety)	
Time points when outcome was measured (from start or at end of intervention or control/placebo)	
Time points reported	
Outcome definition	
Method(s) of outcome assessment (using any tool/scale, etc)	
Is the outcome assessment tool validated?	
Persons measuring and /or reporting outcome	
Imputation of missing data	
Analysis via intention-to-treat or per-protocol or both	

5. Results (create a separate section for each outcome)

Outcome	
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Dichotomous or continuous	
Subgroup	
Time point	
Results (may have more than two arms)	Intervention group: Control/placebo group
Number of missing participants	Intervention group: Control/placebo group:
Number of cross-over	Intervention group: Control/placebo group:
Statistical methods used and appropriateness of these methods	

Risk of Bias Assessment (create a separate section for each outcome)

Domain	Risk of bias (High/Low/Unclear)	Support for Judgement
Random sequence generation (selection bias)		
Allocation concealment (selection bias)		
Blinding of participants and personnel (performance bias)		
Blinding of outcome assessment (detection bias)		
Incomplete outcome data (attrition bias)		

Selective outcome reporting (reporting bias)		
Other bias		

For peer review only

Appendix 3. Summary of findings table

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transdermal GTN	Control/placebo therapy	Relative (95% CIs)	Absolute (95% CIs)		
In-hospital mortality (follow up: range 1 day to 3 months) [Primary Outcome]												
Mean arterial pressure (follow up: range 1 day to 10 days) [Primary Outcome]												
Modified Rankin Scale (follow up: range 3 months to 12 months) [Primary Outcome]												
Development of intracerebral haemorrhage (follow up: range 1 day to 10 days) [Secondary Outcome]												
Deterioration of NIHSS scores by at least 4 points during hospitalization (follow up: range 1 day to 10 days) [Secondary Outcome]												
Length of hospital stay (follow up: range 1 day to 3 months) [Secondary Outcome]												
Number of hypotensive episodes requiring intervention* (follow up: range 1 day to 10 days) [Safety Outcome]												

GTN: Glyceryl trinitrate; CIs: Confidence intervals; NIHSS: National Institutes of Health Stroke Scale
 *Interventions include discontinuing transdermal GTN, administration of intravenous fluids and/or inotropic drugs

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1,2,6
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	2,3,5

1	Registration		
2			
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4		#2	6
5		If registered, provide the name of the registry (such as	
6		PROSPERO) and registration number	
7			
8			
9			
10	Authors		
11			
12			
13	Contact	#3a	1
14		Provide name, institutional affiliation, e-mail address of all	
15		protocol authors; provide physical mailing address of	
16		corresponding author	
17			
18			
19			
20	Contribution	#3b	14
21		Describe contributions of protocol authors and identify the	
22		guarantor of the review	
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24			
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26	Amendments		
27			
28			
29		#4	NA
30		If the protocol represents an amendment of a previously	
31		completed or published protocol, identify as such and list	
32		changes; otherwise, state plan for documenting important	
33		protocol amendments	
34			
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39	Support		
40			
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42	Sources	#5a	14
43		Indicate sources of financial or other support for the review	
44			
45	Sponsor	#5b	14
46		Provide name for the review funder and / or sponsor	
47			
48	Role of sponsor or	#5c	14
49	funder	Describe roles of funder(s), sponsor(s), and / or	
50		institution(s), if any, in developing the protocol	
51			
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53	Introduction		
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1	Rationale	#6	Describe the rationale for the review in the context of what is	4,5,6
2			already known	
3				
4				
5				
6	Objectives	#7	Provide an explicit statement of the question(s) the review	6
7			will address with reference to participants, interventions,	
8			comparators, and outcomes (PICO)	
9				
10				
11				
12				
13				
14	Methods			
15				
16				
17	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	6,7
18			design, setting, time frame) and report characteristics (such	
19			as years considered, language, publication status) to be	
20			used as criteria for eligibility for the review	
21				
22				
23				
24				
25				
26				
27	Information	#9	Describe all intended information sources (such as	7
28			electronic databases, contact with study authors, trial	
29	sources		registers or other grey literature sources) with planned dates	
30			of coverage	
31				
32				
33				
34				
35				
36				
37	Search strategy	#10	Present draft of search strategy to be used for at least one	7
38			electronic database, including planned limits, such that it	
39			could be repeated	
40				
41				
42				
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44				
45	Study records -	#11a	Describe the mechanism(s) that will be used to manage	7,8
46			records and data throughout the review	
47	data management			
48				
49				
50	Study records -	#11b	State the process that will be used for selecting studies	8
51			(such as two independent reviewers) through each phase of	
52	selection process		the review (that is, screening, eligibility and inclusion in	
53			meta-analysis)	
54				
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1	Study records -	#11c	Describe planned method of extracting data from reports	8
2				
3	data collection		(such as piloting forms, done independently, in duplicate),	
4				
5	process		any processes for obtaining and confirming data from	
6				
7			investigators	
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11	Data items	#12	List and define all variables for which data will be sought	8
12				
13			(such as PICO items, funding sources), any pre-planned	
14				
15			data assumptions and simplifications	
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17				
18	Outcomes and	#13	List and define all outcomes for which data will be sought,	7
19				
20	prioritization		including prioritization of main and additional outcomes, with	
21				
22			rationale	
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25				
26	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	8,9
27				
28	individual studies		individual studies, including whether this will be done at the	
29				
30			outcome or study level, or both; state how this information	
31				
32			will be used in data synthesis	
33				
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35				
36	Data synthesis	#15a	Describe criteria under which study data will be	9,10,11
37				
38			quantitatively synthesised	
39				
40				
41	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe	9,10,11
42				
43			planned summary measures, methods of handling data and	
44				
45			methods of combining data from studies, including any	
46				
47			planned exploration of consistency (such as I ² , Kendall's τ)	
48				
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51	Data synthesis	#15c	Describe any proposed additional analyses (such as	10
52				
53			sensitivity or subgroup analyses, meta-regression)	
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1	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type	NA
2			of summary planned	
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5				
6	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	9
7			publication bias across studies, selective reporting within	
8			studies)	
9				
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14	Confidence in	#17	Describe how the strength of the body of evidence will be	9
15	cumulative		assessed (such as GRADE)	
16	evidence			
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22 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution
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24 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

Benefits and safety of transdermal glyceryl trinitrate in acute stroke: a systematic review and meta-analysis of randomised trials (Protocol)

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3 **Benefits and safety of transdermal glyceryl trinitrate in acute stroke: a systematic**
4 **review and meta-analysis of randomised trials (Protocol)**
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54
55

56 **Key words:** transdermal; glyceryl trinitrate; acute stroke
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ABSTRACT:

Introduction: High blood pressure (BP) in acute stroke has adverse outcomes. Transdermal glyceryl trinitrate (GTN) has beneficial properties in controlling BP. The 2016 meta-analysis and 2017 Cochrane review showed transdermal GTN was beneficial in a small patient subgroup with stroke onset \leq six hours. Larger studies focusing on this patient subgroup have since been conducted. We report the protocol for an updated systematic review and meta-analysis on the safety and benefits of transdermal GTN in acute stroke.

Methods and Analysis: We will search Medline, Pubmed, Embase, CINAHL and Cochrane Library from inception until June 2020 for randomised trials that report the efficacy and safety of transdermal GTN vs placebo/control therapy among adult patients with acute stroke. Primary outcomes include in-hospital mortality, BP lowering and late functional status. Secondary outcomes include early, late, resource utilisation and surrogate outcomes. Safety outcomes include reported adverse events. Reviewers will first screen titles and abstracts, and then full texts, to identify eligible studies. Independently and in duplicate, they will extract data, assess risk of bias (RoB) using a modified Cochrane RoB tool and quality of evidence using GRADE. Disagreement will be resolved by discussion and consultation with an external reviewer if necessary. Using a random-effects model, we will report effect sizes using relative risks and 95% confidence intervals. We will perform pre-defined subgroup analyses: intracerebral haemorrhage vs ischaemic stroke; minor (NIHSS \leq five) vs major (NIHSS $>$ five) ischaemic stroke; ischaemic stroke with vs without thrombolysis; pre-hospital vs non pre-hospital settings; time from stroke to randomisation \leq six vs $>$ six hours and high vs low overall RoB studies. We will also perform trial sequential analysis for the primary outcomes.

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3 **Ethics and Dissemination:** Ethics board approval is unnecessary. PROSPERO
4 registration has been obtained (CRD42020173093). The results will be disseminated
5 through publication in a peer-reviewed journal.
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11 12 13 **ARTICLE SUMMARY**

14 15 16 **Strengths and Limitations of Study**

- 17 • This is an updated meta-analysis which includes more recent larger trials.
- 18 • This study will examine an important gap on the benefits of transdermal GTN in ultra-
19 acute stroke (\leq six hours) identified by previous reviews.
- 20 • Other strengths include a comprehensive search strategy, an extensive predefined
21 subgroup analysis plan and inclusion of GRADE methodology to assess certainty of
22 evidence.
23
- 24 • This study will be the first to use trial sequential analysis on important primary
25 outcomes.
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- 27 • Limitations include high clinical heterogeneity given the different subtypes of acute
28 stroke, variation in timing of randomization from onset of stroke to transdermal GTN
29 or placebo/control therapy and reporting of outcome measures across trials.
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INTRODUCTION

High blood pressure (BP) is present in greater than 70% of patients with acute ischaemic stroke.¹ It is associated with poor outcomes including acute stroke recurrence, death within a few weeks or combined death and dependency after several months.¹⁻⁴ High BP is similarly common in acute intracerebral haemorrhage (ICH)⁵ and may be associated with haematoma expansion and increased mortality.⁶⁻⁸

It is recommended to lower BP in ICH⁹⁻¹⁰ although controversy exists regarding optimal BP target in patients with ICH and there is no current literature on the role of pre-hospital BP reduction. The management of high BP in acute ischaemic stroke and the decision to treat or not to treat has been a constant debate since 1985. Current available guidelines recommend withholding antihypertensive therapy in the early post-stroke period unless there is markedly elevated BP (>220/120mmHg) or with BP >185/110mmHg for patients eligible for thrombolysis or BP >180/105mmHg during the 24-hour period following reperfusion.¹¹⁻¹³

Nitric oxide (NO) donors are candidate agents to lower BP in acute stroke because NO is a cerebral and systemic vasodilator, modulates vascular and neuronal function, is neuroprotective, and inhibits apoptosis.¹⁴ In addition, vascular NO concentrations are low in acute stroke which are associated with increased severity of stroke, mortality and institutionalization.¹⁵ These observations support that NO supplementation might be beneficial.

Glyceryl trinitrate (GTN) is an example of a NO donor. Transdermal GTN administration offers a constant release of the drug across the skin into the systemic circulation for 24 hours which achieves sustained steady-state plasma concentrations.¹⁶ Transdermal GTN offers a formulation which is easily administered in many clinical settings [pre-hospital, Emergency

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3 Department (ED) and inpatient] managing acute stroke which may help to minimise
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fluctuations in drug concentrations and hence BP.

The latest meta-analysis published in 2016¹⁷ and Cochrane review in 2017¹⁸, using data from five completed transdermal GTN trials (n= 4197), reported no improvement in outcomes across a range of domains (death, disability, cognition, mood, and quality of life with transdermal GTN vs placebo or control therapy. However, in a pre-specified subgroup analysis of patients with time from stroke to randomisation \leq six vs $>$ six hours (n= 312), these two reviews reported a favourable functional outcome as measured by modified Rankin Scale (mRS) at 90 days with transdermal GTN. There were important limitations in these reviews. Four out of five selected trials had small sample sizes (n \leq 90). The remaining multi-centre ENOS trial¹⁹ recruited 4011 patients and it dominated the pooled analysis (95.6% of all patients and 86.9% of those randomised within six hours of onset). In addition, all the included trials were conducted by a single research group and it is important that other research groups study the role of transdermal GTN in acute stroke. Finally, a relatively small number of patients (n= 312) were treated within six hours of stroke onset and these patients came from just two of the five trials.

The recently published multi-centre RIGHT-2 trial randomised 1149 participants with acute stroke within four hours of onset to receive transdermal GTN vs sham therapy.²⁰ The data from this study more than triples that used to examine the role of transdermal GTN in ultra-early stroke (onset \leq six hours). There is an urgent need to update the evidence behind the efficacy and safety of transdermal GTN in acute stroke especially among those patients with ultra-early (\leq six hours) presentation.

The aim of this systematic review and meta-analysis is to examine, using recent data, whether transdermal GTN improves important patient centred outcomes and is safe among

1
2
3 patients with acute stroke in the pre-hospital and in-hospital settings compared to placebo
4
5 or control therapy by reviewing randomised controlled trials (RCTs).
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8 **METHODS**

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10 **Study Registration**

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12 This systematic review and meta-analysis protocol has been registered in the International
13
14 Prospective Register of Systematic Reviews (PROSPERO). The reference number is
15
16 CRD42020173093. We will adhere to the Preferred Reporting Items for Systematic Reviews
17
18 and Meta-Analysis (PRISMA) statement for reporting systematic review and meta-
19
20 analysis.²¹
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26 **Eligibility Criteria**

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28
29 We will include randomised trials investigating the efficacy and safety of transdermal GTN
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31 vs placebo or control therapy among adult patients presenting with acute stroke.
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35 Patients aged ≥ 16 years presenting with either acute ischaemic or haemorrhagic stroke in
36
37 the pre-hospital, ED and inpatient clinical settings will be considered. Acute stroke patients
38
39 are defined as those with presentation within five days of onset of symptoms. We select five
40
41 days since onset of symptoms as the inclusion cut-off criterion for this review because there
42
43 can be significant delay in presentation after an acute stroke; especially for less severe
44
45 ischaemic strokes.²² Patients with ischaemic stroke are included regardless of whether they
46
47 receive thrombolysis. The comparator arms will include transdermal GTN patch, sham patch
48
49 and control with existing standard therapy.
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53
54 Primary outcomes are important patient centred outcomes including in-hospital mortality,
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56 lowering of BP measurements and late functional status. BP parameters will include systolic
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58 BP, diastolic BP and mean arterial pressure measured at intervals stated by the authors.
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3 Late functional status will involve assessment using the mRS within three months of stroke
4 onset or later (as reported by the authors); the preferred outcome measurement for acute
5 stroke trials.²³ The hierarchical mRS scores range from 0 to 6, with a score of 0 indicating
6 no symptoms, 1 indicating some symptoms but no significant disability, 2–5 indicating
7 increasing levels of disability and dependency, and 6 indicating death.²³
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15 Secondary outcomes are classified as early, late, resource utilisation and surrogate
16 outcomes. Early secondary outcomes include development of ICH, recurrent stroke and
17 change in calculated National Institutes of Health Stroke Scale (NIHSS). Late secondary
18 outcomes include reported changes in activities of daily living, cognition, quality of life and
19 mood. Resource utilisation secondary outcomes include length of hospital stay and
20 discharge destination. Surrogate secondary outcomes include changes in cerebral
21 haemodynamics and laboratory parameters like platelet aggregation.
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32 Safety outcomes include any adverse events reported by the authors.
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35 **Search Strategy**

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38 We will search Medline, Pubmed, Embase, CINAHL and Cochrane Library from inception
39 until June 2020 without language restrictions. We will review reference lists for eligible new
40 trials and also search ClinicalTrials.gov for ongoing or unpublished trials and for additional
41 data from published trials. The search strategy will include the following keywords: stroke,
42 ischaemic stroke, haemorrhagic stroke, intracerebral haemorrhage, transdermal glyceryl
43 trinitrate, transdermal nitroglycerin, glyceryl trinitrate patch, nitroglycerin patch,
44 trinitroglycerin, pre-hospital, mortality, blood pressure, functional outcome, humans and
45 randomised clinical trials. Medical Subject Heading (MeSH) terms will include acute stroke,
46 brain infarction, brain haemorrhage, prehospital emergency care, nitroglycerin, nitric oxide
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3 donors, blood pressure, haemodynamics and cerebral haemodynamics. A proposed search
4 strategy on Medline using the Pubmed interface is attached as Appendix 1.
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8 **Study Selection**

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10 Reviewers (LBL, CWL, LWF and NWM) will independently and in duplicate screen the titles
11 and abstracts of all identified studies to generate a list of eligible trials from which full texts
12 will be obtained. Subsequently, the same reviewers will independently assess eligibility of
13 these full texts of published trials to decide on the final included studies. Discrepancies
14 between reviewers will be resolved through discussion and consensus or, if needed, by
15 adjudication from an external reviewer and/or contact with authors of the original trials for
16 clarification.
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28 **Data Extraction**

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30 Two pairs of reviewers (LBL and CWL; LWF and NWM) will extract data from included
31 studies both independently and in duplicate. Data will be extracted using a pre-designed
32 data extraction form adapted from the Cochrane Collaboration.²⁴ The data collection form is
33 attached as Appendix 2. Data extracted will include the following: general study information
34 [authors, publication year and study location(s)]; study population details [clinical setting-
35 pre-hospital vs ED vs inpatient, sample size, types of strokes- ischaemic vs haemorrhagic;
36 subgroup of ischaemic strokes with thrombolysis]; details on the comparator arms [different
37 doses and duration of GTN patch; sham patch and control] as well as the primary, secondary
38 and safety outcomes as listed above.
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52 In randomized trials that included more than one arm of GTN dosing and duration, we will
53 extract data from the arm closest to a single dose regimen that is comparable to other
54 primary studies to be used for analysis.
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3 Discrepancies in data extraction will be resolved through discussion and consensus or, if
4 needed, via an external reviewer and/or contact with authors of the original trials for
5 clarification.
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10 **Risk OF Bias Assessment**

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13 We will assess the risk of bias (RoB) for each outcome of the individual studies using a
14 modified Cochrane RoB instrument.²⁵ The instrument assesses biases in the following five
15 domains: selection bias (random sequence generation and allocation concealment);
16 performance bias (blinding of participants and researchers); detection bias (blinding of
17 outcome assessment); attrition bias (incomplete outcome data) and reporting bias (selective
18 reporting). Within each domain, we will classify the RoB as high, unclear or low. Reviewers
19 will also judge to determine whether any particular domain is impossible to achieve in any
20 of the primary studies (like blinding in trials comparing GTN patch vs existing standard
21 therapy) and likely or unlikely to affect the reported effect size of the outcome.
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35 Primary studies will be classified as having an overall high RoB when they have been rated
36 at least one domain as having high risk after exclusion of certain domain that is judged to
37 be logistically impossible to achieve for that particular trial and unlikely to affect reported
38 effect size of outcome. The overall RoB for each individual trial will be considered low if
39 RoB is judged to be low in all domains and unclear if RoB is judged to be unclear in any of
40 the domains.
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49 **Quality of Evidence**

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52 We will also assess the quality of evidence for each outcome using the GRADE (Grading of
53 Recommendations, Assessment, Development and Evaluation) approach that classifies
54 evidence as high, moderate, low or very low quality based on considerations of RoB,
55 consistency, directness, precision and publication bias.²⁶ We attach a summary of findings
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2
3 table (Appendix 3) which is adapted using the GRADEpro software to demonstrate how we
4
5 will present our GRADE assessment for the main outcomes.
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8 Assessment of the individual and overall RoB categories as well as the quality of evidence
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10 will be performed independently by the two pairs of reviewers (LBL and CWL; LWF and
11
12 NWM) with any discrepancies resolved by discussion and consensus or if necessary, via
13
14 consultation with an external reviewer.
15
16

17 18 **Data Analysis**

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20 All analyses will be performed using RevMan 5.3 (Cochrane Collaboration, Oxford) software.
21
22 We will use DerSimonian and Laird random-effects model a priori to conduct the data
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24 analysis and meta-analysis. We chose the random-effects model as it produces more
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26 conservative confidence intervals and it considers both within- and between-study
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28 variability.²¹
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33 For continuous outcomes, we will calculate the mean difference and its corresponding 95%
34
35 confidence intervals (CIs) whenever possible. For dichotomous outcomes, we will calculate
36
37 the relative risk (RR) and its corresponding 95% CIs. We will generate forest plots to
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39 demonstrate the individual and pooled effect sizes for the outcome of interest if there are at
40
41 least two studies. We will assess for heterogeneity between studies by first visual inspection
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43 of the forest plots and then using the I^2 statistic. I^2 measures the percentage of the total
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45 variation in estimated effects of the outcome across studies that is due to heterogeneity
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47 rather than to chance.²⁷ A I^2 value of 0% indicates no observed heterogeneity, and larger
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49 values show increasing heterogeneity.
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54 Regardless of the observed statistical heterogeneity (I^2 values), we plan to conduct the
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56 following a priori subgroup analyses for each outcome when each subgroup is represented
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58 by at least two studies. These subgroup analyses will be: ICH vs ischaemic stroke; minor
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3 (NIHSS \leq five) vs major (NIHSS $>$ five) ischaemic stroke; ischaemic stroke with vs without
4 thrombolysis; pre-hospital vs non pre-hospital (ED and inpatient) settings; time from stroke
5 to randomization \leq six vs $>$ six hours; time from stroke to randomization \leq two vs $>$ two hours
6 and high vs low overall RoB studies.
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13 Missing data in the primary studies will be addressed in several ways. We will evaluate for
14 rates of missing data in these primary studies, reasons for missing data and to contact
15 primary authors for clarification if necessary. We will determine whether authors of these
16 primary studies attempted to address the impact of missing data by using intention-to-treat
17 analysis and performing sensitivity analyses through methods like imputation, best- and
18 worst-case scenario analyses to investigate how their reported effect size estimates had
19 changed. We will then make judgement independently, through consensus and/or
20 consultation with an external reviewer whether the reported effect size estimates (including
21 any sensitivity analyses) by the primary authors will likely or unlikely be affected by their
22 missing data. We will perform separate sensitivity analyses of our pooled results by including
23 and excluding those studies that are judged likely to be affected by missing data to
24 investigate how the pooled effect size estimates will be affected. Finally, we will also assess
25 the risk of missing data (attrition bias) of the primary studies through our RoB and GRADE
26 assessment.
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46 Meta-analyses may result in Type I errors due to an increased risk of random error when
47 sparse data are collected and repeated significance testing when a cumulative meta-
48 analysis is updated with new trials.²⁸⁻²⁹ We will perform trial sequential analysis (TSA) using
49 a random-effects model for the primary outcomes (in-hospital mortality, BP lowering and late
50 functional status). In the TSA, we will use a statistical significance level of 5%, a power of
51 80% and an estimated effect size difference (or mean difference for continuous outcomes)
52 between transdermal GTN vs placebo or control therapy as reported by the included trials.
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3 TSA generates the required information size calculated as diversity-adjusted information
4 size (DIS)³⁰ suggested by the estimated effect size difference; thereby providing important
5 information on how many more patients need to be included in further trials. TSA also
6 creates adjusted thresholds for statistical significance (trial sequential monitoring
7 boundaries) with addition of each new trial.²⁸⁻²⁹ The cumulative Z curve which includes the
8 selected trials; if it crosses the trial sequential monitoring boundary, will signify that a
9 sufficient level of evidence has been reached and no further trials are needed.²⁸⁻²⁹ If the Z
10 curve fails to cross the trial sequential monitoring boundary, the required information size is
11 not reached and there is insufficient evidence to reach a conclusion.
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24 TSA will be performed using Trial Sequential Analysis v.0.9.5.10 beta (Copenhagen Trial
25 Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark,
26 www.ctu.dk/tsa).
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32 **PATIENT AND PUBLIC INVOLVEMENT**

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35 We have not and will not involve new patients or the public in this protocol.
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38 **DISCUSSION**

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41 Acute ischaemic and haemorrhagic strokes are frequently managed in various clinical
42 settings; from pre-hospital, ED to inpatient. High BP is common in both types of strokes
43 and is associated with short-term poor outcomes (acute stroke recurrence, death
44 within a few weeks¹⁻⁴ and haematoma expansion⁶⁻⁸) and adverse effects in the longer-
45 term (delayed death and dependency after several months¹⁻⁴). BP control is an
46 essential part of the management of acute ischaemic and haemorrhagic strokes.
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55 NO donors are candidate agents to lower BP in acute stroke because of its various
56 beneficial properties ranging from vasodilatation to neuroprotection and inhibition of
57 apoptosis.¹⁴ GTN is an example of a NO donor. Transdermal GTN offers an easily
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3 administered formulation which is valuable especially in the pre-hospital and ED
4 settings to provide constant drug release.
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8 There was a meta-analysis in 2016¹⁷ and Cochrane review in 2017¹⁸ that investigated
9 the effects of transdermal GTN in acute stroke which reported no overall benefits.
10 However, they reported a favourable functional outcome (improvement in mRS at 90
11 days) with transdermal GTN vs placebo or control therapy in a pre-specified subgroup
12 of patients with ultra-acute stroke (time from stroke to randomization \leq six hours). The
13 meta-analysis and Cochrane review had important limitations. Apart from the ENOS
14 trial¹⁹, the remaining four included trials had small sample sizes ($n \leq 90$) and all these
15 trials were conducted by a single research group. In addition, that subgroup analysis
16 involving ultra-acute stroke patients also suffered from a small sample size ($n = 312$).
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30 With the inclusion of the recently published multi-centre RIGHT-2 trial which recruited
31 1149 patients with acute stroke within four hours of onset²⁰, our systematic review and
32 meta-analysis will significantly increase the sample size available for pooling of
33 studies; especially so when it will more than triple that used to examine the role of
34 transdermal GTN in ultra-acute stroke (onset \leq six hours). Our planned subgroup
35 analysis of patients with ultra-acute stroke will address a significant gap in the literature
36 that arose from these previous reviews.
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46 In addition, our TSA for the important primary outcomes will reduce Type I error. Our
47 TSA will determine whether the DIS and trial sequential monitoring boundaries for
48 these outcomes have indeed been reached in our meta-analysis; signifying that a
49 sufficient level of evidence has been attained to reach a conclusion.
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3 Other strengths of our protocol include a comprehensive search strategy of published
4 and unpublished literature, extensive subgroup analyses involving clinically important
5 patient subgroups and using GRADE methodology to assess certainty of evidence.
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10 Limitations to our protocol include the anticipated high clinical heterogeneity given the
11 haemorrhagic and ischaemic subtypes of acute stroke as well as variation in timing of
12 randomization from stroke onset to transdermal GTN or placebo/control therapy and
13 reporting of outcome measures across trials even within a subtype of acute stroke.
14
15 We will address clinical heterogeneity by evaluating for statistical heterogeneity,
16 explore pre-defined clinically important subgroup analyses and to account for
17 inconsistencies in our GRADE evaluation. In order to address for differences in
18 reporting of outcome measures across included trials, we will include a spectrum of
19 primary and secondary outcomes. We will assess reporting of these outcomes
20 independently and in duplicate and if there are discrepancies, we will resolve through
21 discussion, consensus, potentially involving an external reviewer and contacting the
22 primary authors for clarification.
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39 In conclusion, this protocol describes the details and methodology of a planned
40 systematic review and meta-analysis addressing the safety and benefits of
41 transdermal GTN in acute stroke. The results of this meta-analysis are expected to fill
42 the gap in the literature on the subgroup of patients with ultra-acute stroke (onset \leq 6
43 hours), inform daily practice, clinical practice guidelines and guide areas of
44 investigation for future RCTs.
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53 **ETHICS AND DISSEMINATION**

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3 Ethics board approval is unnecessary. PROSPERO registration has been obtained
4
5 (CRD42020173093). The results will be disseminated through publication in a peer-
6
7 reviewed journal.
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10 **ACKNOWLEDGMENTS**

11
12
13 We have no acknowledgments to make.
14
15

16 **COMPETING INTERESTS**

17
18
19 There are no competing interests to disclose.
20
21

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23
24
25 The authors received no financial support for this research work. However, we wish to thank
26
27 the research program of Ng Teng Fong Hospital Emergency Department which provided
28
29 some protected time for us to carry out this work.
30
31

32 **CONTRIBUTIONS**

33
34
35 LBL, CWL and LWF conceived the study. LBL, CWL and LWF also wrote the study protocol
36
37 to be registered with PROSPERO.
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41 All authors (LBL, CWL, LWF, NWM and TWL) contributed to protocol development. LBL,
42
43 CWL and LWF drafted the study protocol and this manuscript. All authors (LBL, CWL, LWF,
44
45 NWM and TWL) contributed to refinement of the study protocol and manuscript as well as
46
47 approved the final manuscript.
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50 **REFERENCES**

- 51
52
53
54 1. Leonardi-Bee J, Bath PMW, Phillips SJ, for the IST Collaborative Group. Blood
55
56 pressure and clinical outcomes in the International Stroke Trial. *Stroke*.
57
58 2002;33:1315–20.
59
60

- 1
2
3 2. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and
4 subsequent outcome: a systematic review. *Hypertension*. 2004;43:18–24.
5
6
7
- 8 3. Sprigg N, Gray LJ, Bath PM, et al. Relationship between outcome and baseline
9 blood pressure and other haemodynamic measures in acute ischaemic stroke:
10 data from the TAIST trial. *J Hypertens*. 2006; 24:1413–17.
11
12
13
- 14 4. Geeganage C, Tracy M, England T, et al. Relationship between baseline blood
15 pressure parameters (including mean pressure, pulse pressure, and variability)
16 and early outcome after stroke: data From the Tinzaparin in Acute Ischaemic
17 Stroke Trial (TAIST). *Stroke*. 2011;42:491–3.
18
19
20
21
22
- 23 5. Qureshi AI, Ezzeddine MA, Nasar A, et al. Prevalence of elevated blood
24 pressure in 563,704 adult patients with stroke presenting to the ED in the United
25 States. *Am J Emerg Med*. 2007;25:32-8.
26
27
28
29
- 30 6. Qureshi AI. The importance of acute hypertensive response in ICH. *Stroke*.
31 2013;44: Suppl 1:S67-9.
32
33
34
- 35 7. Dandapani BK, Suzuki S, Kelley RE, et al. Relation between blood pressure and
36 outcome in intracerebral hemorrhage. *Stroke*. 1995;26:21-4.
37
38
39
- 40 8. Anderson CS, Huang Y, Arima H, et al. Effects of early intensive blood pressure
41 lowering treatment on the growth of hematoma and perihematoma edema in
42 acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in
43 Acute Cerebral Haemorrhage Trial (INTERACT). *Stroke*. 2010;41:307-12.
44
45
46
47
48
- 49 9. Intercollegiate Stroke Working Party. National clinical guideline for stroke, 5th
50 edn. London: Royal College of Physicians, 2016.
51
52
- 53 10. Hemphill JC, Greenberg SM, Anderson CS, et al.; American Heart Association
54 Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on
55 Clinical Cardiology. Guidelines for the management of spontaneous
56
57
58
59
60

- 1
2
3 intracerebral hemorrhage: a guideline for healthcare professionals from the
4 American Heart Association/American Stroke Association.
5
6 *Stroke*. 2015;46:2032–60.
7
8
9
- 10 11. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of
11 patients with acute ischemic stroke: a guideline for healthcare professionals
12 from the American Heart Association/American Stroke Association. *Stroke*.
13 2013;44:870–947.
14
15
16
17
18 12. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early
19 management of patients with acute ischemic stroke: a guideline for healthcare
20 professionals from the American Heart Association/American Stroke
21 Association. *Stroke*. 2018;2018:e46–e110.
22
23
24
25
26
27
28 13. Shinohara Y, Yamaguchi T. Outline of the Japanese Guidelines for the
29 Management of Stroke 2004 and subsequent revision. *Int J Stroke*. 2008;3:55–
30 62.
31
32
33
34
35 14. Willmot MR, Bath PMW. The potential of nitric oxide therapeutics in stroke.
36 *Expert Opin Investig Drugs*. 2003;12:455–70.
37
38
39
40 15. Rashid PA, Whitehurst A, Lawson N, et al. Plasma nitric oxide (nitrate/nitrite)
41 levels in acute stroke and their relationship with severity and outcome. *J Stroke*
42 *Cerebrovasc Dis*. 2003;12:82–7.
43
44
45
46 16. Todd PA, Goa KL, Langtry HD. Transdermal nitroglycerin (glyceryl trinitrate):
47 a review of its pharmacology and therapeutic use. *Drugs*. 1990;40:880-902.
48
49
50
51 17. Bath PM, Woodhouse L, Krishnan K, et al. Effect of treatment delay, stroke type,
52 and thrombolysis on the effect of glyceryl trinitrate, a nitric oxide donor, on
53 outcome after acute stroke: a systematic review and meta-analysis of individual
54 patient from randomised trials. *Stroke Res Treat*. 2016;2016:9706720.
55
56
57
58
59
60

18. Bath PMW, Krishnan K, Appleton JP. Nitric oxide donors (nitrates), L-arginine, or nitric oxide synthase inhibitors for acute stroke. *Cochrane Database Syst Rev.* 2017;4:CD000398.doi:10.1002/14651858.CD000398.pub2.
19. Bath PM, 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;385:617-28.
20. Bath PM, Scutt P, Anderson CS, et al. Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. *Lancet.* 2019;393:1009-20.
21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *BMJ.* 2009; 339:b2700.
22. Addo J, Ayis S, Leon J, et al. Delay in presentation after an acute stroke in a multethnic population in South London: The South London Stroke Register. *J Am Heart Assoc.* 2012;1:e001685.
23. Lees KR, Bath PMW, Schellinger PD, et al. Contemporary outcome measures in acute stroke research: choice of primary outcome measure. *Stroke.* 2012;43:1163-70.
24. Cochrane Effective Practice and Organisation of Care (EPOC). Data collection form. EPOC Resources for review authors, 2017. epoc.cochrane.org/resources/epoc-specific-resources-review-authors (accessed 22/11/2020).

- 1
2
3 25. Higgins JPT, Altman DG, Gøtzsche PC, for Cochrane Bias Methods
4
5
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7
8
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11
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15
16
17
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42
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45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
26. Guyatt GH, Oxman AD, Vist GE, for GRADE Working Group. GRADE: an
emerging consensus on rating quality of evidence and strength of
recommendations. *BMJ*. 2008;336:924-6.
27. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-
analyses. *BMJ*. 2003;327:557–60.
28. Wetterslev J, Thorlund K, Brok J, et al. Trial sequential analysis may establish
when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol*.
2008;61:64–75.
29. Brok J, Thorlund K, Wetterslev J, et al. Apparently conclusive meta-analyses
may be inconclusive—trial sequential analysis adjustment of random error risk
due to repetitive testing of accumulating data in apparently conclusive neonatal
meta-analyses. *Int J Epidemiol*. 2009;38:287–98.
30. Wetterslev J, Thorlund K, Brok J, et al. Estimating required information size by
quantifying diversity in random-effects model meta-analyses. *BMC Med Res
Methodol*. 2009;9:86.

Appendix 1. Medline Search Strategy Through Pubmed Interface

Filters:

Time period: 1st Jan 1966 to 30th June 2020

Article type: Clinical Study, Clinical Trial Phases 1 to IV, Controlled Clinical Trial, Pragmatic Clinical Trial

Species: Humans

Language restrictions: No

Age limits: 13 to 80+ years

#	Searches
1.	Acute stroke/
2.	Ischaemic stroke (tw)
3.	Haemorrhagic stroke (tw)
4.	Intracerebral haemorrhage (tw)
5.	Brain infarction/
6.	Brain haemorrhage/
7.	Prehospital emergency care/
8.	1-7 or
9.	Transdermal glyceryl trinitrate (tw)
10.	Nitroglycerin/
11.	Trinitroglycerin (tw)
12.	GTN (tw)
13.	Nitric oxide donor*/
14.	9 -13 or
15.	Mortality (tw)
16.	Death (tw)
17.	Blood pressure/
18.	Functional outcome* (tw)
19.	Haemodynamic*/
20.	Cerebral haemodynamic*/
21.	15-20 or
22.	8 and 14 and 21

Appendix 2. Data Collection Form (Adapted from Cochrane Collaboration)

General Information

Date form completed	
Name of reviewer extracting data	
Contact details of reviewer extracting data	
Title of publication	
Publication ID (first author and year of publication)	
Country in which study was conducted	
Study funding source	
Possible conflicts of interests for study authors	

Primary Study Details

1. Methods

Study Characteristics	Review Inclusion Criteria
Design (Type of randomized trial)	Blinded vs non-blinded Cross-over present
Method(s) of recruitment of participants	
Unit of allocation (individual vs cluster/group)	
Clinical setting	Pre-hospital vs Emergency Department vs Hospital
Types of intervention	Different dosing regimens of transdermal GTN

Types of comparator	Standard therapy vs placebo
Types of outcome measures	Primary: Secondary: Safety:

2. Study Population and Setting

Study population description	Stroke subtypes: haemorrhagic vs ischaemic Stroke onset to randomization Other stroke subgroups (like IV thrombolytics, etc)
Inclusion criteria	
Exclusion criteria	
Start date	
End date	
Duration of participation (recruitment to last follow-up)	

3. Participants (in intervention vs control/placebo groups)

Total number of individuals randomized	Intervention group: Control/ placebo group:
Total number of clusters randomized (if applicable)	Intervention group: Control/ placebo group:
Number of withdrawals/exclusions	Intervention group: Control/ placebo group:
Number of cross-overs	Intervention group:

	Control/ placebo group:
Baseline imbalances	
Other treatments (apart from intervention vs control/placebo)	Intervention group: Control/ placebo group:
Subgroups measured	
Subgroups reported	

4. Outcomes (create a separate section for each outcome)

Outcome name	
Outcome type (Primary vs secondary vs safety)	
Time points when outcome was measured (from start or at end of intervention or control/placebo)	
Time points reported	
Outcome definition	
Method(s) of outcome assessment (using any tool/scale, etc)	
Is the outcome assessment tool validated?	
Persons measuring and /or reporting outcome	
Imputation of missing data	
Analysis via intention-to-treat or per-protocol or both	

5. Results (create a separate section for each outcome)

Outcome	
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Dichotomous or continuous	
Subgroup	
Time point	
Results (may have more than two arms)	Intervention group: Control/placebo group
Number of missing participants	Intervention group: Control/placebo group:
Number of cross-over	Intervention group: Control/placebo group:
Statistical methods used and appropriateness of these methods	

Risk of Bias Assessment (create a separate section for each outcome)

Domain	Risk of bias (High/Low/Unclear)	Support for Judgement
Random sequence generation (selection bias)		
Allocation concealment (selection bias)		
Blinding of participants and personnel (performance bias)		
Blinding of outcome assessment (detection bias)		
Incomplete outcome data (attrition bias)		

Selective outcome reporting (reporting bias)		
Other bias		

For peer review only

Appendix 3. Summary of findings table

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Transdermal GTN	Control/placebo therapy	Relative (95% CIs)	Absolute (95% CIs)		
In-hospital mortality (follow up: range 1 day to 3 months) [Primary Outcome]												
Mean arterial pressure (follow up: range 1 day to 10 days) [Primary Outcome]												
Modified Rankin Scale (follow up: range 3 months to 12 months) [Primary Outcome]												
Development of intracerebral haemorrhage (follow up: range 1 day to 10 days) [Secondary Outcome]												
Deterioration of NIHSS scores by at least 4 points during hospitalization (follow up: range 1 day to 10 days) [Secondary Outcome]												
Length of hospital stay (follow up: range 1 day to 3 months) [Secondary Outcome]												
Number of hypotensive episodes requiring intervention* (follow up: range 1 day to 10 days) [Safety Outcome]												

GTN: Glyceryl trinitrate; CIs: Confidence intervals; NIHSS: National Institutes of Health Stroke Scale
 *Interventions include discontinuing transdermal GTN, administration of intravenous fluids and/or inotropic drugs

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1,2,6
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	2,3,5

1	Registration		
2			
3			
4		#2	6
5		If registered, provide the name of the registry (such as	
6		PROSPERO) and registration number	
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10	Authors		
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12			
13	Contact	#3a	1
14		Provide name, institutional affiliation, e-mail address of all	
15		protocol authors; provide physical mailing address of	
16		corresponding author	
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18			
19			
20	Contribution	#3b	14
21		Describe contributions of protocol authors and identify the	
22		guarantor of the review	
23			
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26	Amendments		
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29		#4	NA
30		If the protocol represents an amendment of a previously	
31		completed or published protocol, identify as such and list	
32		changes; otherwise, state plan for documenting important	
33		protocol amendments	
34			
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39	Support		
40			
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42	Sources	#5a	14
43		Indicate sources of financial or other support for the review	
44			
45	Sponsor	#5b	14
46		Provide name for the review funder and / or sponsor	
47			
48	Role of sponsor or	#5c	14
49	funder	Describe roles of funder(s), sponsor(s), and / or	
50		institution(s), if any, in developing the protocol	
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53	Introduction		
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1	Rationale	#6	Describe the rationale for the review in the context of what is	4,5,6
2			already known	
3				
4				
5				
6	Objectives	#7	Provide an explicit statement of the question(s) the review	6
7			will address with reference to participants, interventions,	
8			comparators, and outcomes (PICO)	
9				
10				
11				
12				
13				
14	Methods			
15				
16				
17	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	6,7
18			design, setting, time frame) and report characteristics (such	
19			as years considered, language, publication status) to be	
20			used as criteria for eligibility for the review	
21				
22				
23				
24				
25				
26				
27	Information	#9	Describe all intended information sources (such as	7
28			electronic databases, contact with study authors, trial	
29	sources		registers or other grey literature sources) with planned dates	
30			of coverage	
31				
32				
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36				
37	Search strategy	#10	Present draft of search strategy to be used for at least one	7
38			electronic database, including planned limits, such that it	
39			could be repeated	
40				
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44				
45	Study records -	#11a	Describe the mechanism(s) that will be used to manage	7,8
46			records and data throughout the review	
47	data management			
48				
49				
50	Study records -	#11b	State the process that will be used for selecting studies	8
51			(such as two independent reviewers) through each phase of	
52	selection process		the review (that is, screening, eligibility and inclusion in	
53			meta-analysis)	
54				
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1	Study records -	#11c	Describe planned method of extracting data from reports	8
2				
3	data collection		(such as piloting forms, done independently, in duplicate),	
4				
5	process		any processes for obtaining and confirming data from	
6				
7			investigators	
8				
9				
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11	Data items	#12	List and define all variables for which data will be sought	8
12				
13			(such as PICO items, funding sources), any pre-planned	
14				
15			data assumptions and simplifications	
16				
17				
18				
19	Outcomes and	#13	List and define all outcomes for which data will be sought,	7
20				
21	prioritization		including prioritization of main and additional outcomes, with	
22				
23			rationale	
24				
25				
26	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	8,9
27				
28	individual studies		individual studies, including whether this will be done at the	
29				
30			outcome or study level, or both; state how this information	
31				
32			will be used in data synthesis	
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36	Data synthesis	#15a	Describe criteria under which study data will be	9,10,11
37				
38			quantitatively synthesised	
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42	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe	9,10,11
43				
44			planned summary measures, methods of handling data and	
45				
46			methods of combining data from studies, including any	
47				
48			planned exploration of consistency (such as I ² , Kendall's τ)	
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51	Data synthesis	#15c	Describe any proposed additional analyses (such as	10
52				
53			sensitivity or subgroup analyses, meta-regression)	
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1	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type	NA
2			of summary planned	
3				
4				
5				
6	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	9
7			publication bias across studies, selective reporting within	
8			studies)	
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14	Confidence in	#17	Describe how the strength of the body of evidence will be	9
15	cumulative		assessed (such as GRADE)	
16	evidence			
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22 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution
23 License CC-BY 4.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool
24 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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