The RIGHT Trial

Rapid Intervention with GTN in Hypertensive stroke Trial (RIGHT)

Determining the potential of ambulance-based randomised controlled trials in patients with hyperacute stroke; assessment of glyceryl trinitrate in lowering blood pressure.

Summary

Time from acute stroke event to treatment needs to be reduced to improve the chances of finding effective treatments. No randomised trials of ambulance-based treatment have been reported in acute stroke and the practicalities of recruiting, consenting and treating patients are unknown. High blood pressure is common in acute stroke and associated independently with a poor outcome. We will perform a randomised controlled trial of transdermal glyceryl trinitrate in 80 patients with hyperacute stroke (≤4 hours of onset) with initial consent, randomisation and treatment being performed by paramedics in the ambulance. The trial will primarily assess the feasibility and logistics of running such a trial in the NHS ambulance service thereby providing a model for use in future hyperacute stroke studies; a secondary aim is to generate novel data on the effect of GTN on BP in the hyperacute setting.

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1. BACKGROUND

Finding acute interventions which reduce early brain damage and improve outcome from acute stroke is of major importance and has proved challenging, e.g. aspirin has wide utility but modest efficacy, and alteplase the converse.[3] Anticoagulation has proved ineffective and neuroprotection approaches remain unproven.

Ambulance administration of emergency treatment is standard in acute medical emergencies, including myocardial infarction (MI: aspirin, thrombolysis) and acute asthma (bronchodilators, oxygen). Such treatments need standard diagnostic criteria thereby allowing *an accurate initial diagnosis to be made* (e.g. clinical presentation and ECG for MI); ambulance-administered treatment then needs to be tested in clinical trials. Hence, thrombolysis for MI was given 45 minutes earlier if administered in an ambulance than at hospital.[4] Treatments for acute ischaemic stroke (AIS) are not routinely administered prior to hospital since current therapies alter haemostasis (e.g. aspirin, alteplase) and need prior CT/MRI scanning to exclude primary intracerebral haemorrhage (PICH). However, *other potential treatments for acute stroke such as neuroprotection and management of physiological disequilibrium* (e.g. high blood pressure [BP], hyperglycaemia, pyrexia) do not necessarily need prior neuroimaging and could be delivered prior to hospitalisation. Any benefits of such interventions are likely to be highly time dependent so that pre-hospital administration could considerably increase treatment efficacy through reducing onset to treatment times. A recent study (FASTMag pilot) by Saver in Los Angeles of ambulance administration of intravenous magnesium (a potential neuroprotectant [5]) found that *it was possible to enrol, consent, collect basic clinical details, and administer treatment* in 20 patients with acute stroke(<12 hours of ictus).[1] The main FASTMag trial (PI: JS, http://www.fastmag.info/) is now running in 1,298 pre-hospital patients from Los Angeles and is funded by NIH/NINDS. The trial has recruited 274 patients to date: mean age 62 years, AIS 71%, TIA 2%, PICH 27%. However, no ambulance-based trials involving stroke patients have been performed in the UK, and studies are needed in pre-hospital stroke care, as highlighted at a European Commission Workshop in 2005.[6]

Recently, Ford, Jenkinson and colleagues developed a standardised and validated diagnostic tool, the 'Face Arm Speech Test' (FAST), for use by paramedical staff in the initial diagnosis of acute stroke; the Joint Royal Colleges Ambulance Liaison Committee (JRCALC) have now adopted this as the national ambulance recognition instrument.[7,8] Paramedics from the East Midlands Ambulance Service (EMAS) have used FAST since 2002 to deliver patients with probable acute CVD to the nearest acute hospital, Nottingham City Hospital (NCH) or Queen's Medical Centre (QMC), rather than always to A&E at QMC. Those patients destined for NCH are taken straight to the Acute Stroke Unit bypassing the NCH Emergency Assessment Unit, not least to aid with the rapid delivery of interventions such as thrombolysis. Hence, *FAST is already being used as a triage, diagnostic and management tool in patients with acute stroke*.

High blood pressure (BP>140/90 mmHg) is common in AIS and PICH, and independently associated with a poor outcome.[9-11] These observational data imply that lowering an elevated BP could improve outcome in both AIS and PICH, providing cerebral blood flow (CBF) is not reduced in the presence of dysfunctional autoregulation. This equipoise mean that physicians caring for CVD patients remain uncertain as to whether BP should be lowered or not [12] and emphasises the need for trials of the effects of lowering BP acutely. 5 non-commercial multicentre trials are ongoing: CHHIPS (iv labetalol; po lisinopril, http://www.le.ac.uk/cv/research/CHHIPS/HomePage.html),[13] COSSACS (continue or stop prior antihypertensive therapy, http://www.le.ac.uk/cv/research/COSSACS/COSSACShome.html),[14] ENOS (transdermal glyceryl trinitrate [GTN]; continue or stop prior antihypertensive therapy, www.enos.ac.uk/),[15] INTERACT ('usual' po/iv anti-hypertensive therapy, PICH only, http://www.thegeorgeinstitute.org/research/neurological-&-mental-health/studies-&-trials/) and SCAST (po candesartan, www.scast.no/). *These trials are all hospital-based and therefore rarely recruit patients during the first 2-3 hours post ictus* so that the effect of treatment timing on safety and efficacy is difficult to assess. Additionally, *30-40% of patients with acute stroke are dysphagic* [16] so that oral treatment may be delayed or problematic (nasogastric tubes are often not tolerated; modified-release/slow-release preparations cannot be used since their pharmacokinetics are altered by crushing for insertion down the tube). *Administration of treatment prior to hospital, e.g. in the ambulance, would reduce delay providing that treatment could be given to patients with either AIS or PICH* (i.e. treatment did not alter thrombosis/haemostasis), *and those with dysphagia* (i.e. it does not require a formal swallowing assessment or oral administration of treatment).

We have developed the use of transdermal GTN (5 mg per day, a nitric oxide donor) for lowering BP in acute stroke in *three pilot/phase II randomised controlled trials*.[17-19] Nitric oxide is a candidate treatment for stroke being a key *endogenous regulator of cerebral blood flow and tissue perfusion* (CBF, probably through modulating pial vessel tone thereby potentially improving collateral blood flow*)* and has *neuroprotective* properties in experimental CVD.[20] Further, plasma NO levels (nitrate/nitrite) are *low* in acute stroke and associated with a poor outcome [21,22] so *supplementing* NO in stroke might restore its normal functions. Importantly, GTN is recommended in management guidelines for BP management, especially in the context of controlling BP during thrombolysis (e.g. NIH NINDS t-PA trial [23]), albeit without good supporting safety data.[24] *GTN lowered* 24 hour ambulatory BP (by 7%/5%),[17,18] peripheral BP (by 12%/4%) and central BP (by 13%/4%) at 1 hour;[19] reductions which are well within the <20% recommended by experts in the absence of large trial data.[25] Additionally, GTN lowered pulse pressure (HR) and rate-pressure product (RPP, non-significant trend).[26] GTN *did not alter platelet function* (aggregation, activation, and therefore *may be given to patients with PICH*,[17] in contrast to other nitric oxide donors such as sodium nitroprusside [27]), *regional CBF* (assessed using xenon CT) or middle cerebral artery blood flow velocity or pulsatility index; and did not induce cerebral steal or change cerebral perfusion pressure.[19] *GTN appeared to be safe* across the three GTN phase II trials (n=145) [17-19,28] The safety and efficacy of GTN is now being tested in the ongoing 5,000 patient *MRC-funded 'Efficacy of Nitric Oxide in Stroke (ENOS) trial* (www.enos.ac.uk/), which is also comparing the effect of continuing vs. temporarily stopping prior antihypertensive therapy.[15] ENOS has recruited 597 patients (as of 3/3/07) from 37 centres in 11 countries (Australia, Belgium, Canada, China, Hong Kong, Italy, New Zealand, Philippines, Poland, Singapore, UK) in 4 continents. The independent Data Monitoring & Ethics Committee (DMEC) found no safety concerns in the latest assessment involving 520 patients (December 2006, see www.enos.ac.uk/) and support the trial's continuation. Although ENOS allows recruitment during the hyperacute period, its hospital basis mean that few patients have been treated within a few hours of onset. Previous phase II studies have also suggested that it may be safe to administer antihypertensive therapy in acute stroke, e.g. ACCESS (n=339).[29]

We propose to assess the feasibility of performing an ambulance-based trial in patients with hyperacute stroke, a key question for the future testing of potential interventions aimed at neuroprotection and physiological control. We will assess the effect of GTN on BP in this setting; *GTN is an ideal treatment to assess in an ambulance-based trial since the drug is widely available and inexpensive, is easy to administer, and can be given to neuroprotect patients with either AIS or PICH (so no prior scanning is needed), and those with dysphagia*. EMAS paramedics already use GTN patches in patients with stroke who develop concurrent angina or who are peripherally shut-down and need iv access (a GTN patch is placed over a vein to induce 'local' vasodilatation).

2. AIMS OF THE STUDY

Primary Aim

To assess the feasilbility of using the ambulance service to test and deliver treatment for stroke in the hyperacute setting:

Secondary Aims:

To assess the effects of GTN on blood pressure, pulse pressure (PP) and rate pressure product (RPP) in the hyperacute setting

3. DESIGN

Ambulance-based, single city, single-blind, randomised controlled trial with blinded outcome assessment.

4. INTERVENTIONS

Transdermal GTN (5 mg) or no patch in 80 patients. Subjects will be blinded to treatment by placement of a gauze dressing over the patch or a similar area of skin; single blinding will provide value for money whilst reducing bias. [Industry is unwilling to supply active and

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placebo patches.] GTN treatment will be continued in hospital for a total of 7 days (as per ENOS [15]). Treatment will be given on top of 'best hospital care', including alteplase (if appropriate) and multimodal secondary prevention.

5. ALLOCATION OF PARTICPANTS TO TREATMENT

Each ambulance will carry two numbered opaque sealed envelope containing a dressing +/- GTN patch, according to a computer-defined sequence. Paramedics will take study medications onto the ambulance at the beginning of their shift (as they do with opiates and cardiac thrombolytics).

6. PROTECTION AGAINST BIAS

Bias will be reduced using multiple strategies: concealment of allocation; patient blinding to GTN (gauze pad over patch); measurements and follow-up blinded to treatment; assessment of patient recall of treatment;[18] exclusion of patients enrolled in other trials; analysis by intention-to-treat with adjustment for non-randomised treatment (e.g. aspirin, alteplase).

7. SUBJECTS

Inclusion criteria:

- Adult patients;
- Paramedic assessment of stroke on basis of positive 'Face & Arm weakness & Speech abnormality Test (FAST)[7,8] in the context of a call to a patient with a 'possible acute stroke';
- Event $\leq$4 hours of onset (sleep stroke - onset as bed time); high systolic BP ($\geq$140 mmHg).

Exclusion criteria

- No consent/assent is available
- GTN is indicated (e.g. concurrent angina)
- GTN is contraindicated (e.g. dehydration, hypovolaemia);
- Age <40 years;[30]
- Coma
- History of seizures[30]
- Non-ambulatory pre-morbidly (modified Rankin scale of >2)[30]
- Hypoglycaemia (if glucose tested).
- Patients from a nursing home

The limited exclusion criteria will result in a streamlined trial with generalisable results (thereby providing external validity).

8. CONSENT/ASSENT

Local Research Ethics Committee approval is required from the Nottingham Research and ethics committee before recruitment can commence. Informed written consent will be obtained from each patient; if the patient is unable to write (e.g. in the presence of dominant hand weakness, ataxia or dyspraxia), witnessed verbal consent may be recorded on the consent form. Alternatively, assent may be obtained from relatives or carers if the patient is unable to give meaningful consent (e.g. in cases of dysphasia, confusion, or reduced conscious level). These approaches are standard practice in acute stroke trials. Third party assent by an experienced, independent clinician would also be accepted in the event that no relatives were available.

9. CO-ENROLMENT IN OTHER TRIALS

Concurrent uncoordinated co-enrollment of patients into two or more trials has the potential for introducing bias, e.g. when the treatments have a similar mechanism of action or when adverse events could interact. Patients should not be enrolled into RIGHT if they are already in another drug trial. Patients subsequently be co-enrolled into non-drug trials.

10. BASELINE DATA:

Paramedics will collect clinical information using their standard proforma, including baseline Glasgow Coma Scale and BP, and BP 15 minutes following placement of the gauze/patch. In-ambulance management (monitoring, oxygen, fluids) will also be recorded. This information will be transcribed from paramedic form to the trial CRF in hospital. Further information will be collected in hospital: pre-morbid dependency (modified Rankin Scale, mRS); prior hypertension and medication(s); ischaemic heart disease; heart rate/rhythm (ECG); temperature; impairment (Scandinavian Stroke Scale, SSS); glucose; and blood urea/haematocrit (measures of dehydration).

11. FOLLOW UP

At the end of treatment (day 7 or earlier if discharged), hospital discharge/death (information on: CT scan, carotid duplex; acute treatment and secondary prevention); and day 90.

12. OUTCOME MEASURES

Primary:

- Time from ictus to randomisation.

Secondary:

Analyses will be performed in all patients and those with confirmed AIS/PICH.

In ambulance:

- Proportions of patients (i) randomised : approached about joining; (ii) randomised : carried in ambulance; and (iii) treated according to protocol : all randomised (= diagnostic accuracy); (iv) reasons for not enrolling (presence of exclusion criteria, refusal of consent); (v) effect of GTN on BP prior to ED arrival.

At presentation to hospital:

- Times from ictus to ED arrival, and treatment to ED arrival; effect of GTN on BP at 2 hours in patients with confirmed acute stroke (per protocol analysis); impairment (FAST; SSS); BP (BHS validated Omron 705CPII), HR and derivatives (PP, MAP, RPP) at 2 and 12 hours post administration of GTN.

In hospital:

- Daily BP/HR/PP/RPP over 7 days; rates of headache, hypotension/hypertension needing intervention.

Day 7:

- Death (cause); SSS; death/deterioration (day 7–0 SSS >5 points);[32] recurrence-progression;[32] symptomatic intracranial events (haemorrhage, mass effect); major extracranial haemorrhage; final diagnosis (15-20% of patients with stroke mimics may be FAST positive [8]).

At discharge/death:

- Length of stay in hospital; discharge disposition (death, institution, home).

Three months:

- Death; death or dependency (mRS>2); disability (Barthel Index, BI<60);[33] quality of life (EuroQoL); cognition (MMSE [33]); mood (Zung [34]); by face-to-face follow-up by blinded adjudicator.

Paramedics:

- Interview on experience and views of consent and treatment; audit of routine care.

13. COMPLICANCE

Transdermal GTN is easy to administer, including to dysphagic or semiconscious patients; compliance can be checked visually. GTN can cause headaches leading to patient withdrawal; the incidence of headache was low in our pilot studies and averages 9.3% over the ENOS trial start-up phase (but has led to few discontinuations). 85% of patients in ENOS have received $\geq$4 days of GTN/control.

14. TABULATION ANALYSIS

Primary outcome will be evaluated using tabulation of ambulance parameters and haemodynamic parameters. Secondary outcome will be evaluated by comparison by intention-to-treat of GTN versus no GTN, with adjustment for baseline value (by ANCOVA).

15. TIMELINES

Phase	0-2	3-19	20-24
Train ambulance/research staff	+		
Recruit patients		+	
Follow-up final patients			+

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Present/write-up results			+

16. APPROVALS
We will seek Local Research Ethics Committee and R&D approval, and obtain an ISRCTN. A DMEC (comprising Professor Peter Sandercock - Edinburgh, Dr Henning Mast – Associate Professor in Nottingham) will assess BP and safety data (death, impairment, dependency) when 20 and 40 patients have been recruited and had 7 days of follow-up. Ms Laura Gray (Medical Statistician) will prepare data for the DMEC.

17. DATA SHARING AND PRESERVATION STATEGY
Anonymised data will be documented and shared (agreements already exist) with: the prospective 'Acute Blood Pressure Management Consortium' (CHHIPS, COSSACS, ENOS, INTERACT, SCAST); Cochrane 'Blood pressure in Stroke Collaboration' (BASC);[35,36] and other researchers (assessed case-by-case). Since GTN patches are sourced from the NUH pharmacy, we have no commercial agreements or partnerships with pharma and no intellectual property is likely to result from the trial.

18. DESIGN PARADIGM
Since the primary aim of the study is to test the consent and enrolment of patients into a clinical study within the pre-hospital phase of acute stroke, it might be argued that patients should not be randomised to an experimental treatment. Use of existing/standard treatments (such as fluids or oxygen) does not need consent. An experimental treatment could be given without randomised control therapy but this would not allow safety to be assessed adequately and it would miss the opportunity for gathering additional comparative information on GTN, e.g. safety and effect on BP. Further, ENOS has recruited few patients with hyperacute stroke so the proposed trial offers the chance to help address this limitation. Postponing enrolment until hospital admission will not address the primary question of exploring the feasibility of performing randomised controlled trials in ambulances. Additionally, it is not practical for assessing hyperacute effects of GTN on BP since although 25% patients reach hospital within 3 hours (and a further 25% over the next 3 hours),[2] enrolment into trials immediately after admission is fraught with delays related to the structure of A&E/EDs and acute stroke services. We believe the proposed plan allows two separate and important questions to be addressed within one trial.

19. SERVICE USER INVOLVMENT
NHS Paramedics from East Midlands Ambulance Service will initiate consent and treatment. In hospital trial procedures will be performed by the research staff funded by this grant. *The Nottingham Stroke Patients forum discussed and supported the trial on 11/1/2006 and would be willing to take part if affected with a further* stroke*. The trial has been presented to, and is supported by, the EMAS board*.

20. POWER CALCULATION
Since the primary aim of the study is qualitative by assess the feasibility of performing clinical trials in patients with acute stroke whilst being transported by ambulance to hospital, and no such previous trials have been performed in the UK, we have not performed a sample size calculation on this outcome. We aim to enrol/randomise 80 patients over 18 months ($\geq$1 patients/week), a feasible recruitment rate given the annual number of patients admitted to NUH. [Of note, the FASTMag pilot study recruited 20 patients.[1]] Based on our previous clinical trials,[17-19] the sample size of 80 will provide >90% power for detecting a 14 (SD 14) mmHg reduction in BP with GTN (assuming significance of 5% and randomisation 1 : 1 GTN : control). We believe this sample size is sufficient to provide convincing evidence on the utility and issues related to performing ambulance-based trials, and of assessing the effect of GTN on BP in the hyperacute setting.

21. EXPECTED VALUE OF RESULTS
The issue of performing trials in the pre-hospital phase of stroke is critical if ictus-to-treatment times are to be reduced. Although pro- and anti-haemostatic agents (alteplase, anticoagulation, aspirin for AIS) could not be tested without prior neuroimaging, many other potential treatments could, including those assessing neuroprotectants (as in FASTMag) and the management of physiological disequilibrium (e.g. BP [as here], glucose, oxygen, coma).

Unfortunately, no data are available on the practicality, logistics (patient recruitment, paramedic involvement), diagnostic accuracy, and consent issues of performing trials in the UK ambulance environment in patients with hyperacute stroke*; our study will provide vital information relevant to these questions*. The data relating to GTN will provide further safety data for our programme of developing transdermal GTN as a treatment modality in acute stroke.

22. REFERENCES

1. Saver JL, Kidwell C, Eckstein M, Starkman S, for the FAST-MAG Pilot Trial Investigators. Prehospital neuroprotective therapy for acute stroke. Results of the field administration of stroke therapy-magnesium (FAST-~MAG) pilot trial. *Stroke* 2004;**35:**106-108.
2. Harraf F, Sharma AK, Brown MM, et al. A multicentre observational study of presentation and early assessment of acute stroke. *BMJ* 2002;**325**(17).
3. Bath PMW, Lees KR. ABC of arterial and venous disease - Acute Stroke. *British Medical Journal* 2000;**320:**920-923.
4. Schofer J, Buttner J, Gen G, et al. Prehopsital thrombolysis in acute myocardial infarction. *The American Journal of Cardiology* 1990;**66:**1429-1433.
5. Intravenous Magnesium Efficacy in Stroke (IMAGES) Study Investigators. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. *Lancet* 2004;**363:**439.
6. Meairs S, Wahlgren N. Summary of stroke research priorities. The European Commission Stroke Workshop. Brussels, 2005.
7. Harbison J, Massey A, Barnett L, Hodge D, Ford GA, 1414. Rapid ambulance protocol for acute stroke. *Lancet* 1999;**353:**1935.
8. Mohd Nor A, McAllister C, Louw SJ, et al. Agreement between ambulance paramedic and physician recorded neurological sings with face arm sppech test (FAST) in acute stroke patients. *Stroke* 2004;**35:**1355-1359.
9. Leonardi-Bee J, Bath PMW, Phillips SJ, Sandercock PAG, for the IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke* 2002;**33:**1315-1320.
10. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension* 2004;**43**(1)**:**18-24.
11. Sprigg N, Gray LJ, Bath PMW, et al. Relationship between outcome and baseline blood pressure and other haemodynamic mreasures in acute ischaemic stroke: data from the TAIST trial. *J Hypertension* 2006;**24**(7)**:**1413-1417.
12. Bath PMW, Weaver C, Iddenden R, Bath FJ. A trial of blood pressure reduction in acute stroke. *Age Ageing* 2000;**29:**554-555.
13. The CHHIPS Trial Group. CHHIPS (Controlling Hypertension and Hypotension Immediately Post Stroke) pilot trial: rationale and design. *Journal of Hypertension* 2005;**23**(3)**:**649-655.
14. COSSACS Trial group. COSSACS (Continue or Stop post-Stroke Antihypertensives Collaborative Study): rationale and design. *J Hypertension* 2005;**23:**455-8.
15. The ENOS Trial Investigators. Glyceryl trinitrave vs. control, and continuing vs. stopping temporarily prior antihypertensive therapy, in acute stroke: rationale and design of the Efficacy of Nitric Oxide in Stroke (ENOS) trial (ISRCTN99414122). *International Journal of Stroke* 2006;**1:**245-249.
16. Bath PMW, Bath-Hexall FJ, Smithard DG. Interventions for dysphagia in acute stroke. *The Cochrane Database of Systematic Reviews 2004* 2000;**4**.
17. Bath PMW, Pathansali R, Iddenden R, Bath FJ. The effect of transdermal glyceryl trinitrate, a nitric oxide donor, on blood pressure and platelet function in acute stroke. *Cerebrovasc Dis* 2001;**11:**265-272.
18. Rashid P, Weaver C, Leonardi-Bee JA, Fletcher S, Bath FJ, Bath PMW. The effects of transdermal glyceryl trinitrate, a nitric oxide donor on blood pressure, cerebral and cardiac haemodynamics and plasma nitric oxide levels in acute stroke. *J Stroke Cerebrovasc Dis* 2003;**13:**143-151.

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19. Willmot M, Ghadami A, Whysall B, Weaver C, Bath P. Glyceryl trinitrate, a nitric oxide donor, lowers blood pressure but not cerebral blood flow in patients with acute/subacute stroke. *Cerebrovasc.Dis.* 2005;**19**(suppl 2)**:**31 (abstract).
20. Willmot M, Gray L, Gibson C, Murphy S, Bath PMW. Systematic review of nitric oxide donors and L-arginine in experimental stroke; effects on infarct size and cerebral blood flow. *Nitric Oxide* 2005;**12:**141-9.
21. Ferlito S, Gallina M, Pitari GM, Bianchi A. Nitric oxide plasma levels in patients with chronic and acute cerebrovascular disorders. *Panminerva Medicine* 1998;**40:**51-54.
22. Rashid PA, Whitehurst A, Lawson N, Bath PMW. Plasma nitric oxide (nitrate/nitrite) levels in acute stroke and their relationship with severity and outcome. *J.Stroke Cerebrovasc.Dis.* 2003;**12**(2)**:**82-87.
23. Brott T, Lu M, Kothari R, et al. Hypertension and its treatment in the NINDS rt-PA stroke trial. *Stroke* 1998;**29:**1504-1509.
24. Slyter H. Ethical challenges in stroke research. *Stroke* 1998;**29:**1725-1729.
25. Lavin P. Management of hypertension in patients with acute stroke. *Arch.Int.Med.* 1986;**146:**66-68.
26. Gray LJ, Sprigg N, Rashid PA, Willmot M, Bath PMW. Effect of nitric oxide donors on blood pressure and pulse pressure in acute and subactue stroke. *Journal of Stroke and Cerebrovascular Diseases* 2006;**15**(6)**:**245-249.
27. Butterworth RJ, Cluckie A, Jackson SHD, Buxton-Thomas M, Bath PMW. Pathophysiological assessment of nitric oxide (given as sodium nitroprusside) in acute ischaemic stroke. *Cerebrovasc Dis* 1998;**8:**158-165.
28. Bath PMW, Willmot M, Bath FJL-B, J. Nitric oxide donors (nitrates), L-arginine, or nitric oxide synthase inhibitors in acute ischaemic stroke. *The Cochrane Database of Systematic Reviews 2004* 2002(4).
29. Schrader J, Luders S, Kulchewski A, et al. The ACCESS Study. Evaluation of acute candesartan therapy in stroke survivors. *Stroke* 2003;**34:**1699-1703.
30. Kidwell CS, Starkman S, Eckstein M, Weems K, Saver JL. Identifying stroke in the field. Prospective validation of the Los Angeles prehospital stroke screen (LAPSS). *Stroke* 2000;**31:**71-6.
31. Bath PMW. Acute Stroke. In: Day S, ed. Clinical Trials, 2005.
32. Bath P, Lindenstrom E, Boysen G, et al. Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial. *Lancet* 2001;**358:**702-710.
33. Wade DT. Measurement in neurological rehabilitation. Oxford: Oxford University Press, 1992.
34. Zung WWK. A self-rating depression scale. *Archives of general psychiatry* 1965;**12:**63-70.
35. Blood pressure in Acute Stroke Collaboration (BASC). Interventions for deliberately altering blood pressure in acute stroke (Cochrane Review). The Cochrane Library. 4 ed. Oxford: Update Software, 2001.
36. Blood pressure in Acute Stroke Collaboration (BASC). Vasoactive drugs for acute stroke (Cochrane Review). The Cochrane Library. 4 ed. Oxford: Update Software, 2001.