

Blood Pressure Lowering Treatment in Acute Stroke

S.C.A.S.T.
SCANDINAVIAN CANDESARTAN
ACUTE STROKE TRIAL

PhD thesis by

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List of Papers

- I. Sandset EC, Murray G, Boysen G, Jatuzis D, Kõrv J, Lüders S, Richter P, Roine RO, Terént A, Thijs V, Berge E. Angiotensin receptor blockade in acute stroke. The Scandinavian Candesartan Acute Stroke Trial (SCAST): Rationale, methods and design of a multicentre, randomised- and placebo-controlled clinical trial (NCT00120003). *Int J Stroke* 2010; 5: 423-7.

- II. Sandset EC, Bath PMW, Boysen G, Jatuzis D, Kõrv J, Lüders S, Murray GD, Richter PS, Roine RO, Terént A, Thijs V, Berge E. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet* 2011; 377: 741-50.

- III. Sandset EC, Murray GD, Bath PMW, Kjeldsen SE, Berge E; Relation between blood pressure in acute stroke and risk of early adverse events and poor outcome: the Scandinavian Candesartan Acute Stroke Trial. *Stroke* 2012; [E-pub ahead of print].

Selected Abbreviations

ACCESS	Acute Candesartan Cilexetil in Stroke Survivors
ACE	Angiotensin converting enzyme
A-II	Angiotensin II
AIS	Acute ischaemic stroke
ARB	Angiotensin receptor blocker
AT1R	Angiotensin type 1 receptor
AT2R	Angiotensin type 2 receptor
BI	Barthel Index
CBF	Cerebral blood flow
CPP	Cerebral perfusion pressure
CT	Computer tomography
DBP	Diastolic blood pressure
ICH	Intracerebral haemorrhage
MAP	Mean arterial pressure
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
RAS	Renin-angiotensin system
SBP	Systolic blood pressure
SCAST	Scandinavian Candesartan Acute Stroke Trial
SSS	Scandinavian Stroke Scale

1. Introduction

Stroke is a leading cause of morbidity and mortality worldwide (1;2). It is a clinical syndrome defined by the WHO as "*clinical signs of focal (or global) disturbances of cerebral function, lasting more than 24 hours, or leading to death, with no apparent cause other than of vascular origin*"(3). Substantial advances in stroke therapy have been achieved during the past 15 years, both with regards to prevention and acute treatment. Yet, blood pressure management in acute stroke remains controversial (4;5). In addition to the lack of evidence from clinical trials, data from epidemiological and pathophysiological studies are conflicting.

1.1 Cerebral haemodynamics

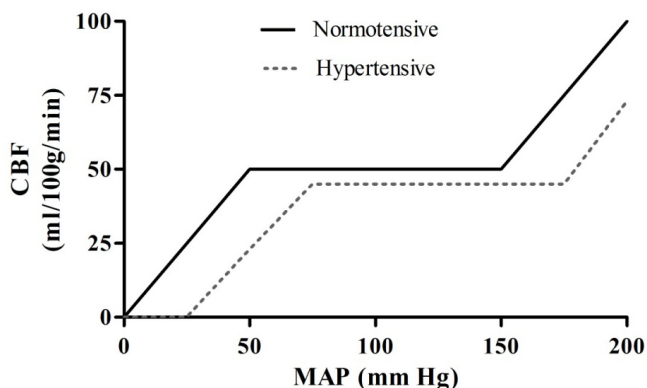
1.1.1 Haemodynamics under normal circumstances

Under normal circumstances cerebral blood flow (CBF) is maintained at a level ensuring the metabolic requirements of the brain and thereby preventing ischaemia. CBF is determined by the ratio of cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR):

$$CBF = CPP/CVR$$

where CPP is the difference between mean arterial pressure (MAP) and intracranial pressure (ICP), and CVR is determined by the size of the cerebral arterioles. Cerebral autoregulation maintains CBF relatively constant despite significant fluctuations in systemic blood pressure (resulting in changes in CPP), and it is mediated through complex myogenic and neurogenic mechanisms, which culminates in alterations in CVR; due either to vasoconstriction or vasodilation in cerebral arterioles (6-9). Figure 1 shows the cerebral autoregulatory curve. In normotensive individuals the MAP limits of autoregulation keeps CBF at 50 ml/100g brain tissue/min range from 50 to 150 mm Hg (6).

Figure 1 Cerebral autoregulation of blood flow in normotensive and hypertensive individuals. The black line indicates normal autoregulation in normotensive individuals, and the dotted line indicates the rightward shift of the curve in chronically hypertensive individuals (modified from Strandgaard et al (10) and Wityk et al (8)).



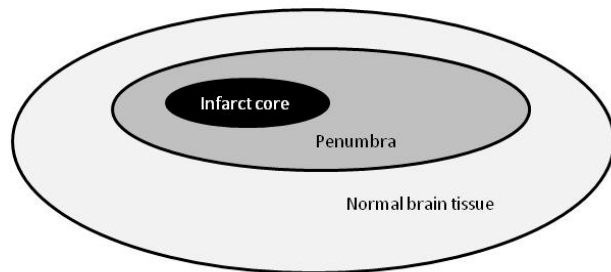
If systemic blood pressure drops below the lower limit, the vasodilatory capacity of the arterioles is exhausted and brain ischaemia will eventually follow. At the other end, if systemic pressure exceeds the upper limit, arteriolar vasoconstriction collapses, leading to endothelial damage and the resultant breakdown of the blood brain barrier. This can cause cerebral oedema and also haemorrhage. Strandgaard and colleagues demonstrated an upward shift in the autoregulatory curve in patients with chronic hypertension, resulting in a decreased capacity to maintain CBF constant at the lower MAP limits, hence a decreased tolerance to hypotension (10).

1.1.2 Cerebral haemodynamics in acute stroke

Stroke occurs as a result of a decrease in blood flow in an area of the brain below a critical threshold for a significant amount of time, ultimately causing irreversible damage and neuronal death. In a series of animal experiments, Astrup and colleagues demonstrated a critical threshold of CBF where neurons cease to function, but can still survive for a period of time (11). Figure 2 demonstrates the concept of an ischaemic penumbra. The core represents an area of irreversibly damaged tissue which is surrounded by a penumbra of hypoperfused and dysfunctional tissue. Survival time of penumbral tissue will vary among patients and depends on the localisation of cerebral vessel occlusion and the presence of collateral blood flow. Rapid reperfusion can potentially salvage the penumbra and thereby

prevent progression of the ischaemia (12;13). Aggressive blood pressure lowering may probably add an additional risk of hypoperfusion, which exceeds the penumbral threshold and thereby cause hastened progression of the infarct (10;14).

Figure 2 The ischaemic penumbra. The infarct core representing an area of irreversible damage surrounded by potentially salvageable tissue representing the penumbra (modified from Wityk RJ. Blood pressure augmentation in acute stroke. *Journal of Neurological Sciences* 2007 (15)).



Several clinical trials have suggested that cerebral ischaemia may lead to impaired autoregulation, not only in the core and surrounding penumbra, but also in the opposite hemisphere. Initial studies, performed prior to the introduction of modern imaging modalities, such as computer tomography, magnetic resonance imaging and positron emission tomography, were performed under steady state conditions using radioisotope techniques (11;12;16-20). Although these techniques gave a quantitative measure of regional CBF, demonstrating areas with dysregulation, they did not differentiate between the types of tissue (penumbra versus infarct versus normal), nor did they give information on periods of potential hypoperfusion preceding the return to stable perfusion (9;21;22). Transcranial Doppler ultrasonography, in combination with continuous blood pressure measurements, is a non-invasive technique, allowing evaluation of both steady-state and dynamic components of autoregulation. A recent systematic review of 23 studies using this technique provided further evidence that cerebral autoregulation is impaired following stroke, and that this impairment was related to neurological deterioration, the necessity for decompressive surgery, and poor outcome (21). Interestingly, a different systematic review of clinical controlled trials that administered antihypertensive agents within 7 days of

ischaemic stroke found no evidence of alteration in cerebral blood flow for any antihypertensive agent (23).

1.2 High blood pressure in the acute phase of stroke

1.2.1 Causes of high blood pressure in the acute phase of stroke

Up to 80% of patients have systolic blood pressure (SBP) ≥ 140 mm Hg at the time of hospital admission (24;25). A spontaneous fall is observed in most patients within 10-14 days (26-29). There are many potential causes of the rise in blood pressure in acute stroke. Firstly, hypertension is a major risk factor for developing stroke, and in many patients elevated blood pressure in acute stroke may reflect undetected or inadequately treated hypertension (30). Secondly, stress associated with hospital admission has been postulated as a contributing factor (31), and high levels of the stress hormone cortisol has been associated with the hypertensive response (32;33). However, when Britton et al investigated the course of blood pressure in acute stroke patients and in controls admitted acutely to hospital for other reasons, they found that both previously hypertensive and normotensive stroke patients had higher blood pressure than the matched controls (34). Finally, the hypertensive response may be caused by damage to autonomic centres in the brain causing disruption of normal blood pressure control (35), or as a result of raised intracranial pressure (the Cushing reflex) (36). Conversely, it may also represent a protective mechanism, to ensure adequate perfusion to the ischaemic area and surrounding penumbra, and thereby prevent further infarction (6;35). The latter theory is supported by the fact that in patients where recanalisation is attempted, the course of blood pressure following stroke is inversely related to the degree of recanalisation achieved (37).

1.1.2 Prognostic significance of high blood pressure and change in blood pressure in the acute phase of stroke

Several studies have examined the prognostic value of blood pressure in the acute phase of stroke on outcome, and the evidence is contradictory (38). Blood pressure has been identified as an independent predictor of poor outcome, and the relationship is U-shaped in several acute stroke populations (24;39-41). In 17398 patients included in the International Stroke Trial the risk of early death increased by 17.9% for every 10 mm Hg decrease below

the nadir of 150 mm Hg ($p < 0.0001$) and by 3.8% for every 10 mm Hg increase above the nadir. The results were similar for fatal and non-fatal stroke recurrence within 14 days, and for the risk of death and dependency at 6 months(24). Similar findings were reported from the Tinzaparin in Acute Ischaemic Stroke Trial (TAIST) (42). Rodrieguez-Yanez et al reported that new-onset high blood pressure, but not chronic hypertension, has been associated with an inflammatory response and poor neurological outcome (43). Finally, in a systematic review by Willmot et al of 32 studies, involving more than 10000 stroke patients within 7 days acute stroke, blood pressure was associated with both an increased risk of death and of death and disability in ICH, and with an increased risk of poor functional outcome in AIS (44).

On the contrary, in a Danish cohort, Jørgensen et al found that high SBP was associated with a lower frequency of stroke progression. For every 20 mm Hg SBP increase, the risk of early stroke progression (within 36 hours) decreased by 34% (95% confidence interval (CI) 55–83%). No association was found between SBP and late stroke progression (within 1 week) (45). A Chinese study, including nearly 4000 stroke patients, showed that high SBP was associated with death and disability in patients with intracerebral haemorrhage (ICH), whereas a trend towards the opposite was observed in patients with acute ischaemic stroke (AIS) (46). Data from a small Italian cohort, with AIS and SBP ranging from 140 to 220 mm Hg, suggested that high blood pressure in patients with lacunar stroke was associated with better outcome, whereas low blood pressure in patients with posterior infarcts was associated with the poorest outcome (47). The latter findings support the theory that different mechanisms may apply to the effect of blood pressure in the acute phase of the different subtypes of stroke.

Concerning changes in blood pressure in the acute phase, Olivera-Filho et al reported an increased risk of poor outcome for every 10% decrease in SBP during the first 24 hours (48). Similar findings were seen in a Spanish cohort, where a blood pressure drop of more than 20 mm Hg within the first day of AIS was the most important prognostic factor of poor outcome (40). Data from 1433 patients with ischaemic stroke included in the Glycine Antagonist in Neuroprotection (GAIN) International Trial suggested that an increase in blood pressure after stroke is associated with a higher risk of poor outcome (49).

In the European Cooperative Acute Stroke Study (ECASS) on early thrombolytic therapy in AIS, high blood pressure at baseline and lower DBP variability in the first 72 hours was associated with better outcome at 90 days (50). Similarly, in the ECASS-II study, the dynamics of blood pressure within the first 24 hours of the patients allocated intravenous-tissue plasminogen activator (iv-tPA) was associated with haemorrhagic transformation within seven days and favourable outcome at 90 days, but only with functional outcome in patients allocated placebo (51). In The National Institute of Neurological Disorder Stroke tPA study, the likelihood of a favourable outcome was reduced with large reductions in blood pressure (52). Ntaios et al assessed the association between baseline blood pressure levels and blood pressure change and outcome in an overall stroke population, and specifically in patients with known hypertensive disease and those without. An increase in blood pressure seemed to be beneficial in patients without known hypertension and low initial blood pressure, whereas in patients with hypertensive disease, initial blood pressure levels and subsequent changes were of less importance. Patients with on-going antihypertensive therapy did not tolerate initially low blood pressure (53). Finally, a metaregression involving data from 37 trials associated large falls or increases in blood pressure with poor outcome (54).

Blood pressure >185/110 mm Hg is a relative contraindication to reperfusion therapy with intravenous thrombolysis (55), and patients with blood pressure above that level have been excluded from clinical trials. Data from 6483 patients in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) identified high SBP as significant predictor of ICH in patients treated with thrombolysis, and high DBP as a significant predictor of death and dependency at 3 months (56). Similar results were seen in a secondary analysis of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET), where the risk of parenchymal ICH following thrombolysis increased with 59% (95% CI 14-123%) for every 10 mm Hg increase in SBP (57). Data from more than 10000 patients in the Safe Implementation in Stroke – International Stroke Thrombolysis Register (SITS-ISTR) suggest a strong association of high SBP after thrombolysis with symptomatic haemorrhage and poor outcome. In addition, withholding antihypertensive treatment in known hypertensive patients was independently associated with symptomatic haemorrhage, mortality and dependency, whereas initiation of antihypertensive treatment in patients with newly recognised moderate hypertension was associated with less symptomatic haemorrhage and a trend towards more independence (58). Observational data suggest that

blood pressure lowering before intravenous tPA therapy may not be associated with a higher rate poor outcome (59). However, there is no data from randomised controlled trials to support this finding.

1.3 Effects of blood pressure lowering treatment in acute stroke

Despite conflicting evidence regarding appropriate management of blood pressure in the acute phase of stroke, there have been few trials to guide clinical practice. The lack of evidence is reflected in current clinical guidelines, which do not recommend blood pressure lowering in the acute phase of stroke (55;60;61).

The Beta-blocker Stroke Trial (BEST) randomised 302 patients with clinically diagnosed hemispheric stroke within 48 hours to atenolol, propranolol or placebo for three weeks, and showed a greater risk of mortality in the patients who received active treatment (62). The Intravenous Nimodipine West European Stroke Trial (INWEST) randomised 294 patients with either haemorrhagic or ischaemic stroke to intravenous nimodipine or placebo, and active treatment was associated with both acute neurological deterioration and poor functional outcome at 21 days (63).

More recently, the Controlling Hypertension and Hypotension Immediately Post-Stroke (CHIPPS) trial assessed the effect labetalol versus lisinopril versus placebo in patients with haemorrhagic or ischaemic stroke and with SBP >160 mm Hg. Already after 24 hours there was a significant difference in blood pressure between the combined active treatment group and the placebo group (mean SBP difference 10 mm Hg (95% CI 3–17)). There was no difference in death and dependency at 2 weeks (primary outcome), nor early neurological deterioration or the incidence of serious adverse events. These results suggest that blood pressure lowering in the acute phase of stroke may both be feasible and safe (64).

The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial is the largest secondary stroke prevention study to date, which compared, using a factorial design, telmisartan with placebo and aspirin-extended release dipyridamole with clopidogrel. Of the 20332 patients randomised 1360 were enrolled within 72 hours. A subgroup analysis showed that telmisartan significantly lowered blood pressure, but there were no differences between the groups in functional outcome or stroke recurrence (65).

Hyperacute blood pressure lowering in haemorrhagic stroke was evaluated in the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage (INTERACT) trial. This was an open trial with blinded endpoint assessment involving 404 patients with primary intracerebral haemorrhage diagnosed by CT within 6 hours of symptom onset. The patients were randomised to intensive blood pressure lowering (target <140 mm Hg) or guideline based treatment (SBP target <180 mm Hg), and the intensive treatment was associated with a near-significant smaller haematoma growth (66;67).

A Cochrane review on vasoactive drugs for acute stroke published in 2010 included 43 trials and 7649 patients, and involved 16 combinations of drug classes and routes of administration. Patients were recruited into the trials within six to 168 hours, and treatment duration was from 24 hours to six months. Calcium-channel blockers, beta-blockers, nitric oxide donors, prostacyclin and mixed antihypertensive therapy significantly lowered blood pressure during the first three days of treatment. Irrespective of drug class, there were no significant differences in outcome (68).

1.4 Effects of angiotensin receptor blockers in the acute phase of stroke

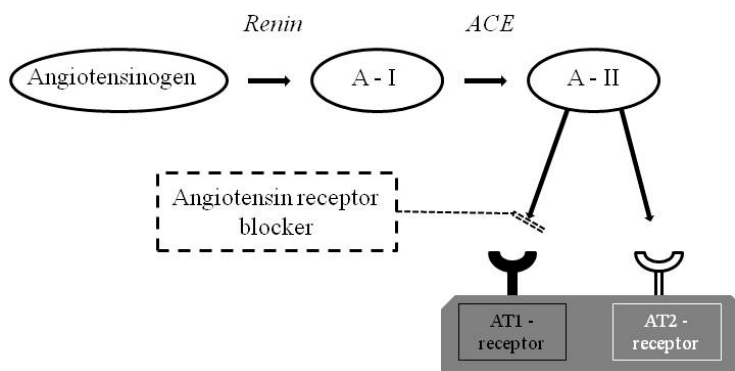
Neuroprotection can be defined as *"any strategy, or combination of strategies, that antagonises, interrupts, or slows the sequence of injurious biochemical and molecular events that, if left unchecked, would eventuate in irreversible ischaemic injury"* (69). Several neuroprotective treatment strategies have shown promising results in experimental studies. However, a successful transition to clinical practice has yet to happen (70). Still, a treatment strategy that is safe irrespective of the exact stroke diagnosis and that could be administered immediately following stroke while under pre-hospital care and improve outcome would be very welcome.

One potential neuroprotective strategy is to modulate the renin-angiotensin system (RAS) in the brain (Figure 3). Activation of the renin-angiotensin-aldosterone system plays an important role in the pathophysiology in both hypertension and cardiovascular disease. Lately, interventions aimed at the different parts of the renin-angiotensin system have emerged as a highly effective antihypertensive treatment strategy and several studies have indicated that the beneficial effects of RAS-based treatment regimens cannot be attributed to

blood pressure reduction alone (71-75). The exact mechanism contributing to this effect is poorly understood, but a multifactorial process involving effects on cardiac and vascular remodeling, endothelial dysfunction, atrial fibrillation and thrombus formation is probable (76).

Angiotensin II (A-II) exerts most of its well defined physiological and pathophysiological actions through its angiotensin type 1-receptor (AT1R) which is found in many tissue types, including myocytes, fibroblasts, diverse cells in the kidney and the adrenal gland, and within cells of the central and peripheral nervous system. A-II acts via the AT1R to elevate blood pressure via processes, such as vasopressin release, modulation of sympathetic nerve activity, inhibition of the baroreflex activity, and stimulation of natriuresis and drinking response. Additional effects include cell growth and/or proliferation (especially of smooth muscle cells, cardiomyocytes and coronary endothelium) contributing to renal and cardiovascular end-organ damage. To the contrary, the angiotensin type 2-receptors (AT2R) are not as frequently expressed in normal tissue, but an increase has been described in pathological conditions of the nervous system, such as stroke, and it has been suggested that the actions of A-II on the AT2R include regulation of neuronal differentiation, apoptosis and axonal regeneration (77-79).

Figure 3 The renin-angiotensin system. Angiotensin receptor blockers block the effect of angiotensin II on the angiotensin type-1 receptor.



Inada et al demonstrated that AT1R blockade with candesartan was effective in preventing stroke in a strain of stroke-prone spontaneously previously hypertensive rats (80). Subsequent experimental studies have shown that administration of candesartan to spontaneously hypertensive rats may reduce both infarct size and oedema in experimentally induced ischaemia (81-83).

The Acute Candesartan Cilexetil in Stroke Survivors (ACCESS) study suggested that candesartan may be beneficial in AIS also in humans. ACCESS was a double-blind, placebo-controlled, phase II trial of candesartan in patients with AIS and elevated blood pressure. The trial was stopped following randomisation of 342 of 500 scheduled patients based on the results of an interim analysis. Patients treated with candesartan one week immediately following stroke had significantly lower risk of the composite endpoint of death and non-fatal vascular events when compared with placebo (OR 0.48; 95% CI 0.25-0.90). There was no difference in blood pressure during the intervention period between the two groups, and no significant difference in the primary endpoint (functional outcome at 3 months) (84).

1.5 Clinical guidelines for treatment of high blood pressure in the acute phase of stroke

Current clinical guidelines across the world reflect the lack of evidence from randomised controlled trials, and early management of high blood pressure in acute stroke is based on consensus of experts (55;60;61). Hence, clinical practice varies widely from country to country, and even from centre to centre. For AIS, both European and American guidelines do not recommend blood pressure lowering unless blood pressure is above the threshold of 220/120 mm Hg on repeated measurements, or there is evidence of end-organ damage. For patients eligible for treatment with intravenous tPA, blood pressure should be below \leq 185/110 mm Hg prior to administration and maintained $<$ 180/105 mm Hg thereafter. The American guidelines provide separate recommendations for patients with acute haemorrhagic stroke, and recommend aggressive blood pressure lowering if SBP is $>$ 200 mm Hg, and modest reduction to a target blood pressure of 160/90 in patients with SBP $>$ 180 mm Hg.

2. Aims

The primary aim was to assess the effect of blood pressure lowering with candesartan in patients with acute stroke and elevated blood pressure on both functional outcome, and on the risk of vascular events during a 6-months follow-up period.

The secondary aim was to assess whether a change in blood pressure in acute stroke relates to the risk of poor short- and long-term outcome.

3. Materials and methods

3.1 Study design and participants

The Scandinavian Candesartan Acute Stroke Trial (SCAST) was a multicentre, randomised and placebo-controlled, double-masked trial of candesartan in patients with acute stroke and elevated blood pressure. Patients aged 18 years or older, with a clinical diagnosis of stroke (ischaemic or haemorrhagic), presenting within 30 hours of symptom onset and with SBP ≥ 140 mm Hg, were eligible for inclusion. Exclusion criteria were contraindications to or ongoing treatment with an angiotensin receptor blocker, markedly reduced consciousness (Scandinavian Stroke Scale (SSS) consciousness score ≤ 2), clear indication, in the clinician's view, for an angiotensin receptor blocker during the treatment period (e.g. patients with chronic heart failure and intolerance to ACE inhibitors), clear indication for antihypertensive therapy during the acute phase of stroke, known pre-morbid modified Rankin Scale (mRS) score ≥ 4 , life expectancy ≤ 12 months, patient unavailability for follow-up and pregnancy or breast-feeding. Written, informed consent was sought from all patients. Non-written or waiver of consent was accepted only after approval from the applicable ethics committees. Full inclusion and exclusion criteria can be found in Paper I.

3.2 Randomisation method

The randomisation sequence was computer generated and stratified by centre with a 1:1 allocation, using blocks of six packs of candesartan or placebo. The candesartan and placebo tablets were identical in appearance and came in prepacked, consecutively numbered drug containers. Randomisation was performed centrally via a secure website. Each patient was assigned a randomisation number and received tablets from the corresponding drug container. If internet access was unavailable at the time of randomisation, investigators used the drug pack with the lowest number.

3.3 Study treatment (the acute phase)

There was a fixed dose escalation scheme: 4 mg on day 1, 8 mg on day 2 and 16 mg on days 3 to 7. Patient compliance was assessed by daily recordings of the doses that the patients received. Blood pressure was measured daily during the morning round with the patient in the supine position using a validated, automated blood pressure monitor (UA-767 Plus 30, A&D Medical, San Jose, CA, US). Dose adjustments were made if SBP was below 120 mm Hg or when clinically indicated. All patients received standard treatment in stroke units, and therapeutic agents other than angiotensin receptor blockers could be administered at the local investigators' discretion, including additional anti-hypertensive drugs in case of severe and sustained hypertension.

3.4 Treatment and visits in the follow-up period

Clinical visits took place on day 7 and at 1 and 6 months. At 3 months the Trial Coordinating Centre carried out a postal interview. All treatment in the follow-up period, including treatment with candesartan, was left to the discretion of the investigators. To avoid important differences in treatment during follow-up, candesartan was the advised antihypertensive treatment and was provided free of charge.

3.5 Effect parameters

3.5.1 Papers I and II

There were two co-primary effect variables: the composite vascular end-point of vascular death, non-fatal myocardial infarction or non-fatal stroke during the first 6 months, and functional status at 6 months, as measured by the mRS. Secondary effect variables were death from all causes, vascular death, ischaemic stroke, haemorrhagic stroke, all stroke, myocardial infarction, stroke progression, neurological status at 7 days (as measured by the SSS), and activities of daily living (as measured by the Barthel index). Safety effect variables were symptomatic hypotension and renal failure during the 7 day treatment period.

3.5.2 Paper III

The primary effect parameter was early adverse events; defined as the combined end-point of recurrent stroke, stroke progression and symptomatic hypotension during the first 7 days. Secondary effect parameters were neurological status at 7 days, difference in neurological status from baseline to day 7 and functional outcome at 6 months.

- Neurological status was measured using the Scandinavian Stroke Scale
- Difference in SSS from baseline to day 7 (Δ SSS) was defined as the change in SSS from baseline to day 7 relative to the maximal possible improvement:
 - $((\text{SSS day 7} - \text{SSS day 1}) / (\text{SSS maximum} - \text{SSS day 1})) \times 100$.
- Functional outcome was measured using the modified Rankin Scale

3.6 Definitions of clinical outcomes and events

The modified Rankin Scale is a measure of functional outcome in patients with stroke (85-87). Table 1 provides definitions for the different categories of the mRS.

Table 1 The modified Rankin Scale (mRS). Scores 0-2 are considered good outcome, whereas scores 3-6 are considered poor outcome.

Score	Clinical symptoms
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

The Scandinavian Stroke Scale is a measure of neurological outcome. It is derived from the sum of the components presented in Table 2 and has a range from 0 (maximum neurological deficits) to 58 (no deficits) (88).

Table 2 The Scandinavian Stroke Scale

Consciousness	6 = Fully conscious
	4 = Somnolent, can be awaked to full consciousness
	2 = Reacts to verbal command, but is not fully conscious
	0 = No reaction to verbal command
Eye	4 = No gaze palsy
	2 = Gaze palsy present
	0 = Conjugate eye deviation (i.e. both eyes)
Arm	6 = Raises arm with normal strength
	5 = Raises arm with reduced strength
	4 = Raises arm with flexion in elbow
	2 = Can move, but not against gravity
	0 = Paralysis
Hand	6 = Normal strength;
	4 = Reduced strength in full range;
	2 = Some movement, fingertips do not reach palm
	0 = Paralysis
Leg/foot	6 = Normal strength
	5 = Raises straight leg with reduced strength
	4 = Raises leg with flexion of knee
	2 = Can move, but not against gravity
	0 = Paralysis
Orientation	6 = Correct for time, place and person
	4 = Two of these
	2 = One of these
	0 = Completely disorientated
Speech	10 = No dysphasia
	6 = Limited vocabulary or incoherent speech
	3 = More than yes/no, but not longer sentences
	0 = Only yes/no or less
Facial palsy	2 = None/dubious
	0 = Present
Gait	12 = Walks 5 meters without aid
	9 = Walks with aids
	6 = Walks with help of another person
	3 = Sits without support
	0 = Bedridden/wheelchair

All serious adverse events reported by the investigators were adjudicated blindly by an independent Event Adjudication Committee. The definitions used for the clinical end-points are listed below:

- **Recurrent stroke:** Stroke is a clinical diagnosis, and was classified as ischaemic, haemorrhagic, or unknown type (if not documented by CT scan, MRI or autopsy). A sudden and persistent clinically significant neurological deterioration occurring after 72 hours should normally be regarded as a recurrent stroke, after exclusion of intercurrent illness, effect of medication (e.g. insomnia medication) or other reasons for deterioration. Within the first 72 hours after stroke onset it is more difficult to differentiate true recurrence from extension of the presenting lesion (“stroke progression”), unless recurrence occurs in a new arterial territory.
- **Stroke progression** is defined as a reduction of ≥ 2 points in one or more of the SSS sub-scores, after exclusion of systemic reasons for deterioration, such as drug-induced hypotension, drug-induced drowsiness, and intercurrent disease, and after exclusion of a recurrent stroke
- **Myocardial infarction:** Either one of the following criteria satisfies the diagnosis of myocardial infarction:
 1. Typical rise and gradual fall (troponin), or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following: ischaemic symptoms:
 - development of pathological Q waves on the ECG
 - ECG changes indicative of ischemia (ST segment elevation or depression)
 - coronary artery intervention (e.g. angioplasty).
 2. Pathological findings of an acute myocardial infarction
- **Symptomatic hypotension** is defined as a clinical sudden deterioration (transient or persistent) which is likely to have been caused by fall in blood pressure (normally a fall in blood pressure of $>30\%$ relative to baseline). The reasons for a fall in blood pressure should be identified (e.g. drug effect, intercurrent disease, etc.).
- **Renal failure** is defined as a rise in serum creatinine of 50% or more, measured on at least two occasions with an interval of 4 weeks or more. The cause should be sought.

- **Symptomatic deep vein thrombosis:** The clinical suspicion of DVT mandates objective confirmation by either venography or ultrasound examination.
- **Symptomatic pulmonary embolism:** The clinical suspicion of pulmonary embolism will need confirmation by ventilation-perfusion lung scintigraphy, CT pulmonary angiography or conventional pulmonary angiography, the combination of an inconclusive lung scintigraphy and diagnosed DVT, or autopsy.
- **Causes of death:** Death due to index stroke is defined as death within 4 weeks of onset of the initial/index stroke, unless an event has occurred in the interim period which was independent of/unrelated to the index stroke and serious enough to be the direct cause of death. The key discriminating features are independence and seriousness. If the patient suffered a major index stroke, death can be classified as caused by the index stroke even after 4 weeks, unless a new, serious event took place in the interim period. After 4 weeks a new, serious event should normally be considered to be the cause of death. The key discriminating feature is whether the event was serious enough to have caused the death.

3.7 Statistical analyses

3.7.1 Paper II:

The statistical analyses were pre-specified in a Statistical Analysis Plan which was finalised prior to the database was locked. Analysis was by intention-to-treat. Blood pressure in the treatment period was compared using the Student t-test. For the primary effect variables, Cox proportional hazards model was used for the analysis of the composite vascular endpoint, and the ordinal logistic regression was used for the analysis of functional outcome. We adjusted both analyses for the following pre-specified and known baseline predictors: age, stroke aetiology (ischaemic versus “all other”), SBP and SSS score at baseline. In addition to ordinal logistic regression, the sliding dichotomy method (89;90) and logistic regression (with conventional dichotomisation of the mRS) were performed as sensitivity analyses for functional outcome. The Hochberg method was applied to allow for the two co-primary effect variables, meaning a p-value of ≤ 0.025 had to be achieved with one of the primary effect variables, or a p-value of ≤ 0.05 had to be achieved in both primary effect variables, before a treatment effect could be claimed statistically significant (91). The secondary effect variables were analysed using the Chi-square test (or Fischer’s exact test

with low numbers). SSS score at 7 days and BI at 6 months was analysed using non-parametric tests. Pre-specified subgroup analyses were performed with the co-primary effect variables, using Cox proportional hazard model for the composite vascular end-point and the logistic regression for functional outcome. These analyses were unadjusted and the p-values represent the interaction between each subgroup and trial treatment. A per-protocol analysis was carried out on all patients treated in accordance with the protocol. We used SPSS version 18.0 for analysis (SPSS Inc., Chicago, IL, USA).

3.7.2 Paper III:

The analyses in this paper were prespecified secondary analyses. The sample comprised of the intention-to-treat population of SCAST. We assessed the possible association between the early change in systolic blood pressure (Δ SBP) and risk of early adverse events. Δ SBP was defined as the absolute difference between SBP at baseline and on day 2. Based on findings suggesting that both a significant increase in SBP or a significant decrease in SBP is associated with poor outcome (54) we classified Δ SBP into the following groups;

- Group 1: Patients with no change or an increase in SBP,

Patients with a decrease in SBP were divided into tertiles;

- Group 2, patients with a small decrease (0 – 14 mm Hg)
- Group 3, moderate decrease (14 – 28 mm Hg)
- Group 4, large decrease (\geq 28 mm Hg).

Group 2 was used as the reference group for all analyses. Baseline differences between the four groups were compared using the χ^2 method for categorical variables and one-way ANOVA with p-values for linear trend for continuous variables.

The risk of early adverse events in the four groups was analyzed using logistic regression and was reported as odds ratios (OR) with 95% confidence intervals (CI). To control for the effect of treatment we first performed stratified analyses, analysing separately patients receiving candesartan and the patients receiving placebo. We adjusted for the following known baseline predictors: age, SSS, SBP, stroke diagnosis (ischemic versus “all other”) and duration of symptoms. In the analysis of both groups combined we also adjusted for

study treatment. Neurological outcome (SSS score) at 7 days and the change in SSS score from baseline to day 7 were analyzed using the Kruskal-Wallis test, and functional outcome (mRS) using ordinal regression. Baseline hemodynamic parameters (SBP, DBP and MAP) were divided into tertiles, and the risk of early adverse events was studied using logistic regression, using the first tertile as the reference category. In order to assess the impact of a fixed change in blood pressure at any given level of SBP at trial entry, we tested the relation between Δ SBP (grouped as above) and the risk of early adverse event within each tertile of baseline SBP.

We also assessed whether the risk of early adverse events was associated with predicted/expected blood pressure reduction, and whether the effect of candesartan was dependent on the predicted/expected blood pressure reduction. We identified baseline predictors of Δ SBP (apart from allocated treatment) in the entire patient population using univariate, backward stepwise and multivariate linear regression analysis. We constructed a model to predict Δ SBP in all patients. The predicted Δ SBP was divided into tertiles (identifying patients at low, moderate or high risk of a large blood pressure decline). Within each tertile we tested whether there was an association between candesartan and the risk of early adverse events using logistic regression analysis.

3.8 Approvals, funding and monitoring

Patient enrollment in SCAST was commenced after obtaining recommendations and permissions from regulatory agencies, central and local ethics committees in all countries involved in the trial. Management of personal data adhered to the laws and regulations of the Data Inspectorates in the countries involved. The trial complied with Good Clinical Practice standards and with the Declaration of Helsinki. During the course of the trial, regional inspections were undertaken by the State Medicines Agencies in the following countries: Norway, Sweden, Germany and Lithuania. SCAST was registered internationally at ClinicalTrials.gov, unique identifier number NCT00120003, and at controlled-trials.com with unique identifier ISRCTN13643354. The EudraCT number was 2004-002187-22.

SCAST was investigator initiated and led. The sponsor of the trial was Oslo University Hospital, Ullevål. SCAST was funded by grants from the South-Eastern Norway Regional Health Authority and Oslo University Hospital, Ullevål, and by limited and unrestricted

grants from AstraZeneca and Takeda. AstraZeneca also supplied the study drugs. Both pharmaceutical companies were represented in the Trial Steering Committee, however, their representatives were non-voting. Neither company had a role in the daily running of the trial, data collection and database, or analysis and reporting of the data.

Data quality was mainly monitored centrally as data was entered into the database. In addition, a random sample of 10% of all centres was visited by the Trial Coordinating Centre for local monitoring. An independent Data Monitoring Committee reviewed the overall quality of the trial, and performed an unblinded, pre-specified interim analysis when half of the patients had been included.

4. Summary of Results

4.1 Paper I and II:

Paper I provides the rationale, design and methods of the main study. SCAST was a multicentre, randomised- and placebo-controlled, double-masked trial of candesartan in patients with acute stroke and elevated blood pressure. Patients aged 18 years, with acute stroke (ischaemic or haemorrhagic) and SBP \geq 140 mm Hg were included within 30 hours of symptom onset. They were randomly allocated to candesartan or placebo for 7 days, with doses increasing from 4 mg on day 1 to 16 mg on day 3 to 7.

Paper II provides the main results of SCAST. We recruited patients from 146 centres in 9 countries from June 2005 to February 2010. In total 2029 patients were randomised; 1012 to placebo and 1017 to candesartan. Data on status at 6 months were available for 2004 patients (99%). The baseline characteristics were as expected of a stroke population. Mean blood pressure was 171/90 mm Hg and mean symptom duration before randomisation was 18 hours. 85% of the patients had a diagnosis of ischaemic stroke, whereas 14% patients had haemorrhagic stroke. There were more female patients in the placebo group (44 versus 40%), and more patients with a history of stroke or TIA in the candesartan group (25 versus 21%). Compliance with the study drugs was good and other antihypertensive treatments were given equally to both groups. During the 7 days treatment period blood pressure was significantly lower in patients allocated candesartan ($p \leq 0.001$), and the mean difference in blood pressure on day seven was 5/2 mm Hg. During the 6 months follow-up period there was no statistically significant difference between the candesartan and placebo groups in the risk of the composite endpoint of vascular death, stroke, or myocardial infarction (adjusted HR 1.09, 95% CI 0.84–1.40; $p=0.54$). Analysis of functional outcome suggested a higher risk of poor outcome in the candesartan group (adjusted common OR 1.17, 95% CI 1.00–1.38; $p=0.048$). The observed effects were similar for all pre-specified secondary end-points (including death from any cause, vascular death, ischaemic stroke, haemorrhagic stroke, myocardial infarction, stroke progression, symptomatic hypotension and renal failure) and outcomes (Scandinavian Stroke Scale score at 7 days and Barthel Index at 6 months), and there was no evidence of a differential effect in any of the pre-specified subgroups.

4.2 Paper III

Data was available from 1997 patients (98%). At baseline the mean age was 71 years, the mean blood pressure at baseline was 171/90 mm Hg and mean difference in SBP from baseline to day 2 was -12.7 ± 21.9 mm Hg. The patients with a large decrease in SBP, or an increase or no change in SBP, had a significantly increased risk of early adverse events relative to the group with a small decrease. The same trend was seen in the analysis stratified according to treatment, although the results did not reach statistical significance. An increase/no change in SBP was associated with worse neurological outcome at 7 days when compared with the other groups. These patients also had smaller improvements in SSS, but the difference did not reach statistical significance ($p=0.08$). No differences were observed in mRS at 6 months. We identified significant predictors of Δ SBP and assessed whether the risk of early adverse events was associated with predicted/expected SBP reduction. For this analysis 1947 (96%) patients had complete data and could be included in the model. Patients predicted to have a large fall in SBP were at highest risk of early adverse events. Treatment with candesartan was associated with a non-significant increased risk of early adverse events in all sub-groups, and in patients predicted to have the largest drop in SBP the risk increase was nearly significant ($p=0.07$). There was no significant heterogeneity between the three groups (p -value for the interaction =0.96).

5. General Discussion

5.1 Interpretation of the results

The overall result of SCAST was neutral, and we found no beneficial effect of blood pressure lowering treatment with the angiotensin receptor blocker candesartan in patients with acute stroke and elevated blood pressure. In the results presented in paper II, there was a non-significant trend suggesting a worse outcome in the patients who received candesartan. For functional outcome, the observed distribution of the mRS at 6 months suggested a consistent shift in disfavouring treatment with candesartan, however, the difference was not statistically significant ($p=0.048$). The same was seen for the composite vascular end-point; there was no statistically significant difference between the treatment groups. For the secondary effect variables, including recurrent stroke, myocardial infarction, stroke progression, renal failure, symptomatic hypotension and death from any cause, we observed the same non-significant trend disfavouring treatment.

The results were consistent across the pre-specified subgroups, and of particular interest, no differential effect was observed in the subgroups according to the level of blood pressure at the time of randomisation and of stroke diagnosis (ischaemic versus haemorrhagic stroke). For haemorrhagic stroke specifically, recent evidence has suggested that modest blood pressure lowering in the hyperacute phase (<6 hours) might be beneficial (66;92). In our data, the group with haemorrhagic stroke was small (274 patients) and a possible beneficial of blood pressure lowering cannot be refuted. There are currently two ongoing studies investigating this hypothesis and the first results are expected in 2013 (93;94). We saw a beneficial effect of treatment for the patients treated earlier than 6 hours of symptom onset, however, this was only seen for the composite vascular endpoint. Although, no significant heterogeneity was observed (p -value for interaction = 0.08), there was a significant trend for time (p -value base on the assumption of a linear trend = 0.02). However, only 213 patients were recruited within 6 hours and no differential treatment effect was seen between the subgroups on functional outcome. This may therefore represent a chance finding.

The results presented in paper III support the assumption that the trends disfavouring treatment with candesartan observed in paper II were caused by blood pressure lowering.

We showed that a large drop in SBP was associated with an increased risk of early adverse events, irrespective of treatment assignment. Despite the increased risk of early adverse events seen in patients with a large drop in blood pressure, there were no significant differences in neurological outcome at 7 days, the change in neurological outcome from day 1 to day 7 or functional outcome at 6 months, as seen in other studies (53;95). Not surprisingly, the patients with the highest SBP at baseline were at highest risk of early adverse events, which is similar to the U-shaped blood pressure curve found in several populations (24;39).

As discussed in the introduction, both experimental studies and the ACCESS trial suggested potential class-specific and neuroprotective effects of angiotensin receptor blockers in acute stroke, independent of their blood pressure lowering ability. In ACCESS, there was no difference in blood pressure between the groups, and treatment with candesartan did not alter the primary effect parameter which was the functional outcome. However, the trial was stopped on the basis of an interim analysis due to a significant difference in vascular events, and this may represent a false positive finding (84). A specific neuroprotective strategy primarily aims to salvage penumbra, and should therefore be administered in the hyperacute phase (within 6 hours). Hence, a beneficial effect of candesartan in acute stroke, independent of blood pressure lowering, cannot be completely ruled out. Nevertheless, the results presented in this thesis and the results of ACCESS raise doubts over this hypothesis.

Our results are compatible with the results of previous trials of blood pressure lowering drugs in acute stroke. Paper II includes a meta-analysis of randomised-controlled trials with more than 100 patients which have assessed the effect of blood pressure lowering treatment in acute stroke on death or dependency. The addition of the SCAST data did not materially alter the results of the meta-analysis and overall, there was no evidence of a beneficial treatment effect on functional outcome. These results are also in line with the results of the latest Cochrane review (68).

5.2 Strengths and limitations

A randomised and placebo controlled, double-blind trial represents the “gold standard” for clinical research. Still, several requirements need to be met to ensure valid results: i.e. selection of the study population, allocation of treatment regimens, maintenance and assessment of compliance, and achieving high and uniform rates of ascertainment of outcomes (96).

SCAST was a large, randomised-controlled trial with blinded assessments of outcomes, independent and blinded adjudication of events and near complete follow-up. This is the main strength of our study. All analyses presented were planned in advance of trial execution and for the secondary analyses presented in paper III, we have serial, standardized blood pressure measurements with a validated automated blood pressure monitor.

For both co-primary effect variables, in all subgroups, and in all the secondary effect variables, including the analyses presented in Paper III, the results are highly consistent pointing towards high internal validity of the results. We also believe that the results have high external validity and that the results can be generalised to the general stroke population. Firstly, the trial was performed across multiple centres in nine countries, and the patients included were similar to those admitted to normal stroke services. Secondly, the inclusion criteria were broad, encompassing both patients with haemorrhagic or ischaemic stroke and with SBP more than 140 mmHg. Selection bias will always be an issue in clinical trials. Screening logs were kept at 14 high-recruiting centres and indicated that the reasons for exclusion were those commonly seen in clinical practice. The most frequent reason for exclusion was symptom duration longer than 30 hours (34%). This, together with the mean time to inclusion being 17.6 hours (SD 8.1), indicate that the patients were not recruited in the hyperacute setting (<6 hours) and we cannot dismiss a possible effect in this subgroup.

Although SCAST provides robust estimates for the main outcomes, the statistical power is limited for subgroup analyses. Moreover, the comparisons presented in paper III are non-randomised, with the inherent possibility of confounding effects from variables that were not included in the analyses. In particular, there is a risk of confounding when combining the patients in the two treatment groups. However, the results of the analyses stratified by

treatment groups were nearly identical to the result of the analysis of both treatment groups combined, albeit not statistically significant.

The recruitment rates were lower than planned throughout the period and ultimately, the trial was closed earlier than planned and without reaching the original target of 2500 patients. The decision to stop recruitment was made purely on administrative grounds (expiration of both trial funding and of the study drugs), without knowledge of the data. Initial sample size calculation for functional outcome were based on analysis using a conventional statistical methods, dichotomising the mRS. By adopting an ordinal approach to the analysis of functional outcome the achieved statistical power for this effect variable exceeded its original target, even though recruitment was stopped prematurely (97;98). This gain in statistical efficiency is apparent when comparing the results of the conventional dichotomous analysis presented as a sensitivity analysis in paper II with the main results of the ordinal regression analysis.

5.3 Considerations on the statistical analysis of the primary effect variables

5.3.1 Analysis of two co-primary effect variables

In SCAST, we had two co-primary effect variables. Traditionally in stroke trials, the main outcome is functional status, and this is most commonly measured by the mRS (Table 1) whereas the effect variable commonly used in hypertension trials is the composite endpoint of death, stroke or myocardial infarction. The results which lead to the premature closure of ACCESS, was not functional outcome, but the difference between the groups in vascular events and there was a need to replicate the ACCESS results in a larger trial. It was therefore necessary to include both effect variables equally. When assessing multiple effect variables, one has to bear in mind the increased chance of a false positive finding and a more stringent approach to statistical significance levels is required. Moreover, in our study, death was included in both our co-primary effect variables, i.e. they were not independent. We therefore applied the conservative approach of the Hochberg method, meaning a p-value of 0.025 had to be achieved with one of the primary effect variables, or a p-value of 0.05 or less had to be achieved with both primary effect variables, before a treatment effect could be claimed statistically significant (91).

5.3.2 Ordinal methods for analysis of functional outcome

Traditionally, stroke trials have dichotomised ordinal outcome scales such as the mRS (mRS 0-2 = good outcome, mRS 3-6 = poor outcome), creating a binary outcome variable which can be easily analysed using the Chi² test or by logistic regression for adjusted analysis. Lately, more efficient approaches to utilise all categories of the mRS has been widely discussed within the stroke community. The sample size calculation for SCAST was based on a conventional fixed dichotomy of the functional outcome, however, the original Statistical Analysis Plan specified that an ordinal method should be used for analysis. During the course of the trial, statistical research showed that ordinal methods could increase statistical power substantially, equivalent to allowing a reduction of the order of 30% in the sample size without loss of statistical power (90;97;98).

Ordinal regression assumes that treatment effect is consistent across all categories of the mRS, meaning that the OR is the same for mRS = 1 as for mRS = 5. This assumption can be tested using a “goodness-to-fit” test. When applied to our data, there was no evidence that the assumption was violated ($p=0.85$). A report from “the Optimising Analysis of Stroke Trials (OAST) Collaboration” examined data from individual trials, and found that 85% of data sets did not significantly violate this assumption (98). Although ordinal regression increases statistical sensitivity, the main drawback with the analysis is the lack of an intuitive interpretation of the common OR. A recent report from the European Stroke Organisation Outcomes Working Group strongly encourage future stroke trials to adopt ordinal methods both with regards to sample size calculations and results (99).

6. Conclusions and future perspectives

From this work, we conclude that there is no evidence of a beneficial effect of blood pressure lowering treatment with an angiotensin receptor blocker in patients with acute stroke and elevated blood pressure. For most of the effect variables, treatment with candesartan was associated with a non-significant increased risk for worse outcome. There are currently several on-going trials that will help to clarify whether this is a generalisable finding, and whether there are subgroups of patients or different approaches to blood pressure management where a treatment benefit can be obtained.

- **INTERACT-2 (93) and ATACH-II (94)** will provide evidence of blood pressure lowering within 6 hours of haemorrhagic stroke specifically.
- **ENOS (100)** is ongoing and recruits patients with either haemorrhagic or ischaemic stroke within 30 hours of symptom onset. To date more than 3000 patients have been randomised to treatment with nitric oxide or placebo. ENOS will provide evidence of a different approach to blood pressure lowering in acute stroke. The trial is also testing the hypothesis of continuing or stopping antihypertensive treatment in previously known hypertensive patients, a highly relevant question in clinical practice.
- **ENCHANTED** is currently ongoing and randomises patients to intensive (target SBP < 140 mm Hg) versus guideline based (target SBP < 180 mm Hg) reduction in blood pressure, and to low-dose (0.6 mg/kg) versus standard-dose (0.9 mg/kg) intravenous tPA. The trial aims to provide evidence as to whether intensive blood pressure lowering in the setting of intravenous tPA improves outcome and reduces the risk symptomatic intracerebral haemorrhage.

7. References

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8. Papers I - III

