Angiotensin receptor blockade in acute stroke. The Scandinavian Candesartan Acute Stroke Trial: rationale, methods and design of a multicentre, randomised- and placebo-controlled clinical trial (NCT00120003)

Else Charlotte Sandset1,2*, Gordon Murray3, Gudrun Boysen4, Dalius Jatuzis5, Janika Kórv6, Stephan Lüders7, Przemyslaw S. Richter8, Risto O. Roine9, Andreas Terënt10, Vincent Thijs11, and Eivind Berge1, on behalf of the SCAST Study Group

Background Elevated blood pressure following acute stroke is common, and yet early antihypertensive treatment is controversial. ACCESS suggested a beneficial effect of the angiotensin receptor blocker candesartan in the acute phase of stroke, but these findings need to be confirmed in new, large trials. Aims and design The Scandinavian Candesartan Acute Stroke Trial is an international randomised, placebo-controlled, double-blind trial of candesartan in acute stroke. We plan to recruit 2500 patients presenting within 30 h of stroke (ischaemic or haemorrhagic) and with systolic blood pressure ≥ 140 mmHg. The recruited patients are randomly assigned to candesartan or placebo for 7-days (doses increasing from 4 to 16 mg once daily). Randomisation is performed centrally via a secure web interface. The follow-up period is 6-months. Patients are included from the following nine North-European countries: Norway, Sweden, Denmark, Belgium, Germany, Poland, Lithuania, Estonia and Finland. Study outcomes There are two co-primary effect variables: • Functional status at 6-months, measured by the modified Rankin Scale, and • vascular death, myocardial infarction or stroke during the first 6-months. Secondary outcome variables: • the Barthel index (functional status) • EuroQol (quality of life) and • Mini-mental state examination (cognition) at 6-months • Health economic costs during the first 6-months Funding The Scandinavian Candesartan Acute Stroke Trial receives basic funding from Norwegian health authorities. AstraZeneca supplies the trial drugs, and AstraZeneca and Takeda support the trial with limited, unrestricted grants. Summary The Scandinavian Candesartan Acute Stroke Trial is the first large trial of angiotensin receptor blockers in patients with elevated blood pressure and acute stroke, and aims to answer whether treatment with angiotensin receptor blockers is beneficial for this indication.

Key words: acute stroke, angiotensin receptors blockers, antihypertensive therapy, candesartan, randomised-controlled trial

Executive Summary

Rationale: Elevated blood pressure following acute stroke is common, and yet early antihypertensive treatment is controversial. Animal studies and one human trial suggest a beneficial effect of the angiotensin receptor blocker (ARB) candesartan in the acute phase of stroke.
Aim and Design: The Scandinavian Candesartan Acute Stroke Trial (SCAST) is an international multicentre, double-blind, randomised- and placebo-controlled trial of candesartan in acute stroke. The aim is to include 2500 patients, presenting within 30 h of stroke (ischaemic or haemorrhagic) and with systolic blood pressure ≥ 140 mmHg. Patients are randomly assigned candesartan or placebo for 7-days (doses increasing from 4 to 16 mg once daily). Randomisation is performed centrally, via a secure web interface. The follow-up period is 6-months.

Study Outcomes: There are two co-primary effect variables: (i) functional status at 6-months, as measured by the modified Rankin Scale (mRS), and (ii) the composite end-point of ‘vascular’ death, myocardial infarction or stroke during the first 6-months. Secondary effect variables include the Barthel index (functional status), EuroQol (quality of life) and Mini-mental state examination (cognition) at 6-months, in addition to health-economic costs during the first 6-months.

Summary: Scandinavian Candesartan Acute Stroke Trial is the first large trial of an ARB in patients with elevated blood pressure and acute stroke and aims to answer whether treatment with ARBs is beneficial for this indication.

Introduction and rationale
Elevated blood pressure is common in the acute phase of stroke (1, 2), and studies have shown that elevated blood pressure is associated with a poor outcome (2–6). Data from the first International Stroke Trial (IST) suggested a U-shaped relationship, with an increased risk of early death and a poor long-term outcome in patients with the highest and lowest systolic blood pressures at randomisation (2). It has long been controversial whether the elevated blood pressure should be lowered (7–11). Current clinical practice is to accept high blood pressure in the acute phase of stroke. This practice has a well-founded theoretical basis. Following a stroke, the autoregulation of cerebral blood flow is disturbed and cerebral tissue perfusion relies on systemic blood pressure. In this situation, rapid and substantial lowering of blood pressure may lead to further ischaemic damage, as shown in a trial of intravenous nimodipine including 295 patients with acute stroke (12).

Animal studies have shown that blood pressure lowering may be beneficial following an acute cerebral infarct (13, 14). Furthermore, treatment with ARBs, like losartan and candesartan, is associated with a reduction of infarct size and improved functional outcome (15). In humans, data from the ACCESS study of 342 acute stroke patients with hypertension suggested that treatment with candesartan may reduce the risk of subsequent vascular events (16), and INTERACT showed that early intensive blood pressure reduction was well tolerated, and seemed to reduce haemataoma growth in 404 patients with acute cerebral haemorrhage (17). The PROFESS trial of the ARB, telmisartan, for long-term prevention after stroke (18) included 1360 patients within 72 h of stroke onset, but could not show any beneficial effects of telmisartan (19). However, PROFESS was designed for secondary prevention (not for intervention in the acute phase) and the subgroup of patients with acute stroke was too small for the results to be reliable.

The mechanisms by which ARBs may affect the risk of death and long-term vascular events are still unknown. Studies of angiotensin-converting enzyme inhibitors and ARBs in cardiovascular and renovascular disease indicate that the beneficial effects of these drugs are mediated partly by the inhibition of neurohumoral systems, and not only by blood pressure-lowering effects (20–23). Angiotensin converting enzyme inhibitors and ARBs given to hypertensive patients appear to be renoprotective and effective in the prevention of stroke, independent of their blood pressure-lowering effects (24–27, 28). It is therefore possible that any beneficial effect of ARBs in the acute phase of stroke is mediated by the inhibition of neurohumoral systems.

ACCESS is so far the only published study of angiotensin receptor blockade in acute stroke, and the sample size is too small for the study to be conclusive. Additional and larger studies of ARBs in the acute phase of stroke are therefore needed (9–11). SCAST is designed to provide more conclusive evidence on the effectiveness of candesartan in patients with acute stroke and elevated blood pressure. This paper presents the rationale, methods and design of the study.

Methods
Design
The Scandinavian Candesartan Acute Stroke Trial is a multicentre, randomised- and placebo-controlled, double-blind trial of candesartan in patients with acute stroke and elevated blood pressure. The study is conducted according to the Principles of the Declaration of Helsinki and Good Clinical Practice. Approvals have been obtained by regulatory agencies, and central and local ethics committees in all countries involved in the trial. Management of personal data adheres to the laws and regulations of the Data Inspectorates in the countries involved. The EudraCT number is 2004-002187-22, and the clinical trial registration number (http://www.clinicaltrials.gov) is NCT00120003.

Patient population
The aim is to recruit 2500 patients from centres in nine North-European countries: Belgium, Denmark, Estonia, Finland, Germany, Lithuania, Poland, Norway and Sweden. Patients presenting within 30 h of stroke (ischaemic or haemorrhagic) with limb affection, and systolic blood pressure ≥ 140 mmHg, are eligible for inclusion. All patients must be 18-years of age or over. Written, informed consent is sought from all patients. Nonwritten consent or waiver of consent is accepted only after consultation with, and approval from, the applicable ethics committee. The complete inclusion and exclusion criteria are listed in Table 1.
Table 1  Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Clinical stroke syndrome with limb affection, not likely to represent a transient</td>
<td>Markedly reduced consciousness (i.e. Scandinavian Stroke Scale consciousness score ≤ 2)</td>
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<tr>
<td>ischaemic attack or nonstroke pathology</td>
<td>Patient already receiving angiotensin receptor blocker</td>
</tr>
<tr>
<td>Systolic blood pressure ≥ 140 mmHg</td>
<td>Contraindications to angiotensin receptor blocker</td>
</tr>
<tr>
<td>Trial treatment possible within 30 h of symptom onset. If time of onset is not</td>
<td>Known renal failure (women: creatinine ≥ 150 μmol/l; men: ≥ 180 μmol/l)</td>
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<td>known, the time when the patient was known last to be well is used</td>
<td>Previously diagnosed bilateral renal artery stenosis</td>
</tr>
<tr>
<td>Consent (subsidiary, assent from legal acceptable representative, or waiver of</td>
<td>Previously diagnosed high-grade aortic stenosis</td>
</tr>
<tr>
<td>consent)</td>
<td>Previously diagnosed seriously impaired liver function and/or cholestasis</td>
</tr>
<tr>
<td>Age &gt; 18 years</td>
<td>Clear indication, in the clinician's view, for start of treatment with angiotensin receptor blocker during the treatment period (e.g. chronic heart failure grades III–IV, in the presence of intolerance to ACE inhibitors)</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Clear indication, in the clinician's view, for antihypertensive therapy during the acute phase of stroke (e.g. concurrent hypertensive encephalopathy or aortic dissection)</td>
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<td>Other serious or life-threatening disease before the stroke</td>
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<td>Patient severely mentally or physically disabled (e.g. Mini-mental status score &lt; 20, or modified Rankin Scale score ≥ 4)</td>
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<td>Life expectancy &lt; 12 months</td>
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<td></td>
<td>Patient unavailable for follow-up (e.g. no fixed address)</td>
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<td>Pregnant or breast-feeding women</td>
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**Randomisation**

Clinical assessment and computed tomography or magnetic resonance imaging is performed before entry into the trial. Functional status before the stroke (premorbid mRS), neurological status (Scandinavian Stroke Scale) and stroke subtype (Oxfordshire Community Stroke Classification), are recorded before administration of the study treatment. Blood pressure is measured twice with a validated, automated blood pressure monitor (UA-767 Plus 30, A&D Medical, San Jose, CA), in the supine position following 5 min of rest, with the cuff at the level of the heart. Measurements from the arm with the highest systolic blood pressure are used, and treatment must start within 1 h of the last measurement. A central computer performs the random allocation of treatment, via a secure web interface (http://www.scast.no). In addition, the trial uses balanced blocks of six treatments, the order of which was generated at random by a computer.

**Trial treatment and follow-up**

The trial treatment is given once daily for 7-days: 4 mg on day 1, 8 mg on day 2 and 16 mg on days 3–7, as shown in Fig. 1. There is a standard titration regardless of blood pressure levels. Dose adjustments are made if systolic blood pressure is measured below 120 mmHg, or in case of symptomatic hypotension, or other adverse events that may be caused by the trial treatment. If necessary, the trial tablets can be crushed and administered through a nasogastric tube in patients with dysphagia. Blood pressure is measured daily, during the morning round, before the administration of study drugs, with the patient lying in the supine position, after 5 min of rest, using the automated monitor provided and using the same arm that was used at randomisation.

All patients are given standard treatment in stroke units. Therapeutic agents other than ARBs can be administered during the treatment period. In case of severe and sustained hypertension, other antihypertensive medication, apart from ARBs, can be given in addition to the allocated trial treatment.

The follow-up period lasts 6-months, and clinical visits are scheduled on day 7, at 1-month and at 6-months. In addition, the Trial Coordinating Centre carries out a telephone or a postal mail interview at 3-months. To achieve identical treatment in both groups, candesartan is the advised antihypertensive therapy, unless other treatments are indicated. Candesartan is provided free of charge during the 6-month follow-up period.

Data entered over the Internet and in case report forms are monitored centrally for validity and internal consistency, to ensure high data quality and coherence with the protocol. Local monitoring is carried out whenever quality becomes an issue, and of a random sample of at least 10% of the participating centres.

**Primary outcome variables**

There are two co-primary effect variables:

(i) Functional status at 6-months, as measured by the mRS.

(ii) The composite end-point of vascular death, myocardial infarction or stroke during the first 6-months.

An independent Event Adjudication Committee will blindly evaluate all serious adverse events reported by the investigators. The mRS is graded 0–6 (where 0 means no symptoms, 3 moderate disabilities requiring some help but able to walk without assistance and 6 death). The effect of treatment on functional status will be assessed by an ordinal regression analysis taking account of the actual score on the mRS (29, 30). An analysis based on the ‘sliding dichotomy’ approach (31) will also be performed as a secondary analysis.
Secondary outcome variables

Secondary effect variables are specified in the protocol, and include the Barthel index (functional status), EuroQoL (quality of life) and Mini-mental state examination (cognition) at 6-months, and health-economic costs during the first 6-months.

Subgroup analyses are planned for stroke pathology (ischaemic vs. haemorrhagic stroke), degree of carotid artery stenosis, blood pressure at baseline, cardiac rhythm (sinus rhythm or atrial fibrillation), treatment delay, thrombolytic treatment and history of hypertension. The exact definitions of these effect variables and subgroups will be given in the final Statistical Analysis Plan, which will be written before the lock of the database and opening of treatment codes.

Data Monitoring Committee (DMC)

When half of the patients have been included in the trial, an interim analysis will be performed. The unblinded results of this analysis will be reviewed by an independent DMC.

Sample size

In recent trials in general acute stroke (mainly ischaemic stroke), the risk of ‘death or dependency’ at the end of follow-up (3–6-months) in the control group (mainly placebo) ranged from 55% to 70% (32–35). Based on these trials, it seems realistic to expect that, overall, 60% of placebo-treated general acute stroke patients. Assuming that the relative risk reduction will be 25% (instead of 40%, as in ACCESS), 2200 patients in total will have to be included in the trial (assumptions: 2\(\alpha > 5\%\), 1\(−\beta \geq 80\%\)). The use of two co-primary effect variables will reduce statistical power. To account for this, for losses due to noncompliance and losses due to incomplete follow-up, a study of 2500 patients in total is planned.

Statistical considerations

The use of ordinal regression to analyse the mRS scores will be expected to increase the statistical power of this analysis substantially (30). The Hochberg method (37) will be applied to allow for the fact that there are two co-primary efficacy parameters. A P-value of 0.025 will need to be achieved with one of the primary efficacy parameters, or a P-value of 0.05 will need to be achieved with both primary efficacy parameters, before a treatment effect can be claimed at the 5% significance level. Ninety-five per cent confidence intervals will be calculated for the estimated treatment effects; however, these will be interpreted cautiously because of the more stringent significance level required with the two co-primary efficacy parameters.

Trial organisation and funding

The trial is investigator-initiated and investigator-led, and is conducted principally independent of the pharmaceutical industry (AstraZeneca, Malmö, Sweden, and Takeda, Osaka, Japan). The Sponsor of the trial is the Oslo University Hospital, Ullevaal, and the Trial Coordinating Centre is based at that hospital. The Trial Steering Committee is composed of investigators from all the participating countries. AstraZeneca’s representatives in the Committee are nonvoting.

The trial is financially supported by the South-Eastern Norway Regional Health Authority and Oslo University Hospital, Ullevaal. AstraZeneca supplies the study drugs, and AstraZeneca and Takeda support the trial with limited, unrestricted grants.

Summary and conclusions

SCAST aims to answer whether ARBs are beneficial in patients with acute stroke and elevated blood pressure. It is the largest trial to date of blood pressure lowering treatment in the acute phase of stroke, and the first large trial using an ARB for this indication.
SCAST Committees

SCAST Steering Committee: Professor P. M. Sandset (Chairman, Norway), Professor A. Terent (Sweden), Dr B. Carlberg (Sweden), Dr A. Lindgren (Sweden), Professor N. G. Wahlgren (Sweden), Professor G. Boysen (Denmark), Dr G. Andersen (Denmark), Dr H. Iversen (Denmark), Professor D. Russell (Norway), Professor S. E. Kjeldsen (Norway), Dr L. Thomasen (Norway), Professor T. Bruun Wyller (Norway), Dr B. Indredavik (Norway), Professor P. Bath (UK), Professor G. Murray (UK), Professor V. Thijs (Belgium), Dr G. Vanhooren (Belgium), Dr P. Desfontaines (Belgium), Professor R. O. Roine (Belgium), Dr J. Körv (Estonia), Dr D. Jatuzis (Lithuania), Dr P. Richter (Poland), Dr S. Lüders (Germany), Professor J. Schrader (Germany), Dr E. C. Sandset (Norway), Dr E. Berge (Norway). Non-voting members: Dr B. Karlson (AstraZeneca, Sweden), A. Fransson (AstraZeneca, Sweden), P. Hasvold (AstraZeneca, Norway), B. Springer (AstraZeneca, Denmark).

SCAST Event Adjudication Committee: Professor S. Strandgaard (Chairman, Denmark), Professor R. Salvesen (Norway), Professor N. G. Wahlgren (Sweden), Professor G. Boysen (Denmark), Dr G. Andersen (Sweden), Dr A. Lindgren (Sweden), Professor B. Indredavik (Sweden), Professor G. Murray (Norway), Professor T. Bruun Wyller (Norway), Dr B. Springer (AstraZeneca, Denmark).

References