



Lowering blood pressure with candesartan in the first 7 days after stroke did not improve outcome at 6 months.

Clinical Problem: A 71-year-old female is admitted to you with a left MCA ischemic stroke 20 hours ago. Her current blood pressure is 160/93 mmHg. You wonder if she would benefit from having her blood pressure lowered in the acute phase (after the first 24 hours) of her stroke.

Clinical Question: In patients with stroke, does lowering blood pressure in the acute phase improve morbidity or mortality?

Search Strategy:

Pubmed was searched using the search terms “hypertension” AND “acute stroke” and limited to meta-analysis, humans and English. This yielded 3 articles; however, none of these articles found sufficient evidence to conclude whether lowering blood pressure was beneficial in acute stroke.

Pubmed was then searched using the same search terms with limits of randomized-controlled trial, humans and English. This search yielded 24 articles. The SCAST study was chosen because it was the most recent and had the largest number of patients.

Clinical Bottom Lines:

1. Starting candesartan to lower blood pressure within 30 hours of stroke symptom onset and treating for 7 days was not associated with reduced vascular events or improved functional outcome at 6 months.
2. There was a small but significant increased risk of stroke progression in the candesartan group (p=0.04).

The Evidence:

Multicentre, randomized, double-blind, placebo-controlled trial. Patients were randomized to receive candesartan 4 mg on day 1, 8 mg on day 2 and 16 mg on days 3-7 or placebo. A total of 2029 patients from 9 North-European Countries were followed for 6 months. The aim of the study was to determine if blood pressure lowering with candesartan is useful in patients with hypertension and acute stroke.

Inclusion Criteria: Patients were 18 years or older with a clinical diagnosis of ischemic or hemorrhagic stroke within 30 hours of symptom onset and a systolic blood pressure higher than 140 mmHg.

Patients were excluded if there were contraindications to or current treatment with an angiotensin-receptor blocker (ARB), clear indication for antihypertensive treatment (with or without an ARB) during the acute phase of stroke, Scandinavian Stroke scale (SSS) score ≤ 2 , known pre-morbid modified Rankin score (mRS) of 4 or more, life expectancy ≤ 12 months, pregnant or breastfeeding, or patient unavailable for follow-up.

Outcomes: Primary outcomes were: 1) composite endpoint of vascular death, non-fatal myocardial infarction, or non-fatal stroke in the first 6 months 2) functional status at 6 months, measured by the mRS. Secondary outcomes included death from all causes, vascular death,

ischemic stroke, myocardial infarction, stroke progression, neurological status at 7 days and activities of daily living measured by the Barthel Index. Safety outcomes were symptomatic hypotension and renal failure.

Data:

Primary Outcomes:

	Candesartan (n=1017)	Placebo (n=1012)	Hazard Ratio/ Odds Ratio	P value
Composite vascular endpoint	120 (12%)	111 (11%)	HR: 1.09 (0.84-1.41)	0.52
Unfavourable functional status at 6 months (mRS 3-6)	348 (35%)	331 (33%)	OR: 1.12 (0.90-1.41)	0.32

Secondary Outcomes:

	Candesartan (n=1017)	Placebo (n=1012)	Risk Ratio (95% CI)	P value
All cause death	84 (8%)	78 (8%)	1.07 (0.80-1.44)	0.65
Vascular death	63 (6%)	60 (6%)	1.05 (0.74-1.47)	0.80
Ischemic stroke	58 (6%)	50 (5%)	1.15 (0.80-1.67)	0.44
Myocardial infarction	16 (1%)	11 (1%)	1.45 (0.68-3.10)	0.34
Stroke progression	65 (6%)	44 (4%)	1.47 (1.01-2.13)	0.04
Neurological status at 7 days (SSS score)	51 (38-56)	51 (41-56)		0.13
Activities of daily living at 6 months (Barthel index)	100 (80-100)	100 (85-100)		0.47

Comments:

1. The study did not meet its predefined requirement for sample size of 2500 patients secondary to slow enrollment and expiry of the research grant. The decision to stop the trial was purely administrative and without any knowledge of the results, but this may have affected the power to detect a true superiority of candesartan to placebo.
2. The study was well designed and had a low rate of dropouts and patients lost to follow-up.
3. There was a non-significant trend towards placebo being superior to treatment with candesartan for functional outcome at 6 months, death, myocardial infarction, neurological status at 7 days and Barthel Index at 6 months.
4. It would have been beneficial to include a separate analysis to indicate results of treatment initiation within 24 hours and after 24 hours as this has important clinical implications.
5. The reduction in blood pressure in the treatment group was modest (mean difference 5 mmHg systolic and 2 mmHg diastolic), and may not have been large enough to demonstrate a beneficial effect.
6. The guidelines for treating blood pressure with other agents were at the discretion of the

treating physician and thus inconsistent. The guidelines used were not reported; e.g. threshold for initiating additional antihypertensives was stated as “severe and sustained hypertension”.

7. The study did not differentiate between stroke subtypes, and although subgroup analyses did not show significant differences between groups, small effect sizes cannot be excluded, especially among the hemorrhagic stroke subgroup (n=274).
8. The number of patients who received thrombolytic therapy was similar in each group (candesartan: 69, placebo: 82); therefore, differences between groups cannot be explained by an unbalanced use of thrombolytics.

References:

1. Sandset EC et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): A randomized, placebo-controlled, double-blind trial. *Lancet*. 2011;377:741-50.
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Key Words: blood pressure, hypertension, acute stroke, morbidity, mortality

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