Effects of Candesartan in the Acute Phase of Intracerebral Hemorrhage

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Background and Purpose: Uncertainty persists over the effects of blood pressure-lowering treatment in acute intracerebral hemorrhage (ICH). We assessed the effects of treatment with candesartan in acute ICH and according to different types of hematoma. *Methods:* Post-hoc analysis of the Scandinavian Candesartan Acute Stroke Trial, a randomized- and placebo-controlled, double-masked trial of candesartan in patients with any stroke within the acute phase (<30 hours) and high systolic blood pressure (≥140 mm Hg). We collected baseline computed tomography scans of participants with ICH, and characterized hematoma volume (planimetric approach), location (deep versus lobar or infratentorial), hemisphere side, and presence of intraventricular hemorrhage. The trial's 2 coprimary effect variables were the composite endpoint of vascular death, stroke or myocardial infarction, and functional outcome at 6 months according to the modified Rankin scale. We used Cox, ordinal, and binary logistic regression for analysis and adjusted for key, predefined prognostic variables. *Results:* Of 274 participants with ICH, computed tomography scans were available in 205 patients (74.8%). There were no significant differences between the candesartan and placebo groups with respect to hematoma volume (median 15.6 mL versus 13.5 mL, $P = .96$), deep location (77% versus 72%, $P = .64$), right hemisphere (49% versus 51%, $P = .46$), and presence of intraventricular hemorrhage (18% versus 11%, $P = .22$). Candesartan was associated with a significant increase in poor functional outcome in patients with deep hematoma (adjusted common odds ratio 2.27, 95% confidence interval 1.23-4.18, $P = .009$, P for interaction .015), but there was no differential effect on functional outcome or vascular events in any of the other imaging subgroups. *Conclusions:* Candesartan was not associated with any beneficial effect when initiated in the acute phase of ICH, a possible adverse effect on functional outcome in patients with deep hematomas cannot be ruled out by this study alone.

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Received January 11, 2019; revision received April 9, 2019; accepted May 12, 2019.

The trial was funded by grants from the South Eastern Norway Regional Health Authority and Oslo University Hospital. AstraZeneca supplied the study drugs, and AstraZeneca and Takeda supported the trial with limited, unrestricted grants.

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1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.05.010

Key Words: Acute stroke—intracerebral hemorrhage—blood pressure—candesartan

Introduction

Blood pressure is commonly elevated in the acute phase of intracerebral hemorrhage (ICH) and high blood pressure is an independent predictor of poor outcome,[1] in part related to hematoma expansion.[2-4] Other hematoma characteristics, such as initial volume, location, and presence of intraventricular hemorrhage are also associated with poor outcome.[5-7] Early and intensive blood pressure-lowering is recommended in international guidelines,[8,9] but many questions remain, especially regarding the timing and mode of blood pressure-lowering, and in relation to different types of ICH. The Scandinavian Candesartan Acute Stroke Trial (SCAST) of patients with acute ischemic or hemorrhagic stroke showed no effect of candesartan on outcome when commenced in the acute phase (median of 16 hours) after stroke onset and continued for 7 days.[10] The same result was also found in analyses specifically in those with hemorrhagic strokes, as diagnosed by local investigators at baseline.[11] The present analysis aimed to explore further the effects of candesartan in patients with ICH according to imaging characteristics of hematoma volume, location, and presence of intraventricular hemorrhage.

Materials and Methods

SCAST was a randomized- and placebo-controlled, double-masked trial of the angiotensin receptor blocker candesartan in 2029 patients who presented within 30 hours of either an acute ischemic or hemorrhagic stroke, and a systolic blood pressure greater than or equal to 140 mm Hg. Written, informed consent was sought from all patients. The methods and main results are outlined in detail elsewhere.[10,12] In brief, patients were randomly assigned candesartan or placebo for 7 days, with doses increasing from 4 to 16 mg once daily over the first 3 days, and with patients followed for 6 months. The 2 coprimary effect variables were the composite endpoint of vascular death, stroke or myocardial infarction, and functional outcome at 6 months according to the modified Rankin scale.

Brain Computed Tomography Scanning, Acquisition, and Adjudication

All patients underwent a diagnostic baseline cerebral computed tomography (CT) scan before the first dose of trial treatment. CT scans were reviewed according to local practice at each site. Magnetic resonance imaging scanning was used as an alternative method in some cases. CT scans were saved in uncompressed digital images in Digital Imaging and Communications in Medicine format for collection and analyses at the end of the trial. The imaging substudy was approved by the central research ethics committee.

CT images were subsequently uploaded via a secure website of the George Institute for Global Health in Sydney (Australia), using the MIStar software (Apollo Medical Imaging Technology, Melbourne, Australia), for adjudication by 2 trained reviewers, who were masked to clinical data including treatment. The analysis used methods previously described in the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) studies.[13] Hematoma volumes (mL) were calculated with computer-assisted multislice planimetric and voxel threshold techniques (MIStar software, Apollo Medical Imaging Technology, Melbourne, Australia). ICH volume was dichotomized at the median value (≤15 versus >15 mL).[14] The anatomical location within the brain parenchyma was categorized as deep (areas involving the caudate head, putamen/globus pallidus, thalamus, external capsule, internal capsule), lobar (across cortical-subcortical areas), and infratentorial (cerebellum and brainstem). Hemisphere side, presence of intraventricular hemorrhage, subarachnoid hemorrhage, remote hemorrhage, and previous hemorrhage or infarct were also recorded.

Statistical Analysis

The statistical analyses were based on patients with available baseline CT scans, in accordance with the intention-to-treat principle and the prespecified statistical analysis plan. Baseline differences between treatment groups were compared using independent *t* test, Mann-Whitney test, or χ^2 test, as appropriate. The effect of treatment on the composite vascular endpoint was analyzed by Cox regression analysis, and effect on functional outcome analyzed by ordinal logistic regression and binary logistic regression. All regression analyses were adjusted for the predefined prognostic variables: age, Scandinavian Stroke Scale score, and systolic blood pressure at baseline. We tested the effect of treatment in subgroups defined by hematoma volume (≤15 versus >15 mL), hematoma location (deep versus lobar or infratentorial), hemisphere side, and the presence of intraventricular hemorrhage. Heterogeneity of the treatment effects across hematoma subgroups was assessed by adding an interaction term to the models. All analyses were performed with the SPSS software, version 22.0 (SPSS Statistics, Chicago, IL).

Results

Of 274 ICH patients in the trial, 205 patients (74.8%) had baseline CT scans available for analyses. Table 1 shows that the clinical and imaging characteristics of the

205 patients were comparable to the total ICH patients in the trial.[11] Trial treatment was started at a median of 17 hours (interquartile range 8-23) after symptom onset in both groups. More patients in the candesartan group had atrial fibrillation, otherwise there were no significant differences in clinical characteristics between the groups. Patients with deep hematoma were younger and had more often intraventricular hemorrhage than patients with lobar or infratentorial ICH (Supplementary Table). As previously reported, blood pressure was lower in the candesartan group from day 2, and the mean systolic difference from day 4 onward was ≈5 mm Hg.[11] Figure 1 shows blood pressures in the 2 hematoma groups. In both groups, treatment with candesartan was associated with modest reduction in blood pressure. Hematoma volumes were small (median 15.5 mL, interquartile range 6.8-26.6), 149 patients (77%) had deep hemorrhage, 100 (51%) had hemorrhage in the right hemisphere, 29 (15%) had intraventricular hemorrhage, previous hemorrhage or infarct was seen in 13 (7%) of patients, and there were no differences in these imaging characteristics between the treatment groups.

Figure 2 shows the effect of candesartan on vascular events in relation to hematoma volume (≤15 versus >15 mL), hematoma location (deep versus lobar or infratentorial), hemisphere side, and the presence of intraventricular hemorrhage. There was no clear differential effect of candesartan on the risk of vascular events in any of the specified subgroups. However, candesartan was associated with a significant increase in poor functional outcome in patients with a deep hematoma (adjusted common odds ratio [OR] 2.27, 95% confidence interval [CI] 1.23-4.18, P = .009, Fig 3), and with a significant interaction between treatment allocation and hematoma location (P for interaction .015). Since atrial fibrillation was unevenly distributed between the 2 groups we performed a sensitivity analysis with atrial fibrillation included in the model, which yielded virtually identical results (adjusted common OR 2.15, 95% CI 1.14-4.06, P = .02). We also repeated the analyses using binary logistic regression (modified Rankin Scale score 0-2 versus score 3-6) and found a similar association for the deep hematoma subgroup (adjusted OR 2.67, 95% CI .95-7.44), although the difference was no longer statistically significant (P = .06). There was no differential effect of candesartan on functional outcome in any of the other imaging subgroups (P for interaction >.05).

Discussion

In these analyses of ICH patients, we found no beneficial effects of blood pressure-lowering treatment with candesartan in the acute phase in any of the ICH subgroups. Instead, we found that candesartan was associated with an increased risk of poor functional outcome (but not vascular events) in patients with deep ICH location. Although this may be a chance finding, it is consistent with our previous findings of a negative effect in patients with previous hypertension[10] and in patients with a lacunar stroke syndrome,[15] and support the conclusion in our previous study that there is no indication for treatment with candesartan in

Table 1. *Baseline characteristics*

	All patients (n = 205)	Candesartan (n = 106)	Placebo (n = 99)	*P* value
Age, years	68.0 (12.2)	68.0 (12.4)	68.1 (12.1)	0.97
Sex, female	61 (30)	33 (31)	28 (28)	0.66
Premorbid mRS	0	0	0	0.38
Previous hypertension	119 (62)	67 (65)	52 (58)	0.30
Previous stroke or TIA	32 (16)	20 (19)	12 (13)	0.23
Atrial fibrillation	20 (10)	17 (16)	3 (3)	0.002
Diabetes mellitus	26 (13)	18 (17)	8 (8)	0.06
Time to randomization, hours	17.0 (8.0-23.0)	18.0 (7.6-24)	17.0 (8.0-23.0)	0.95
Systolic blood pressure, mm Hg	174.7 (20.2)	173.0 (18.0)	176.4 (22.3)	0.24
Diastolic blood pressure, mm Hg	95.6 (13.6)	95.4 (12.8)	95.8 (14.6)	0.87
SSS score	39 (28-48.5)	38 (26-49)	40 (30-48)	0.93
Hematoma volume, mL	15.5 (6.8-26.6)	15.6 (7.0-25.7)	13.5 (6.8-29.3)	0.96
Deep ICH*	149 (77)	77 (78)	72 (77)	
Lobar ICH	34 (18)	18 (18)	16 (17)	0.76
Infratentorial ICH†	10 (5)	4 (4)	6 (6)	
Right hemisphere	100 (51)	49 (49)	51 (54)	0.46
Intraventricular hemorrhage	29 (15)	18 (18)	11 (12)	0.22
Subarachnoid hemorrhage	2 (1)	1 (1)	1 (1)	1.00
Remote hemorrhage	6 (3)	3 (3)	3 (3)	1.00
Previous ICH or infarct	13 (7)	6 (6)	7 (7)	0.69

Abbreviations: ICH, intracerebral hemorrhage; mRS, modified Rankin scale; SSS, Scandinavian Stroke Scale; TIA, transient ischemic attack. Data are n (%), mean ± standard deviation or median (interquartile range).
*Caudate head, putamen, globus pallidus, thalamus, external capsule, internal capsule.
†Cerebellum, brainstem.

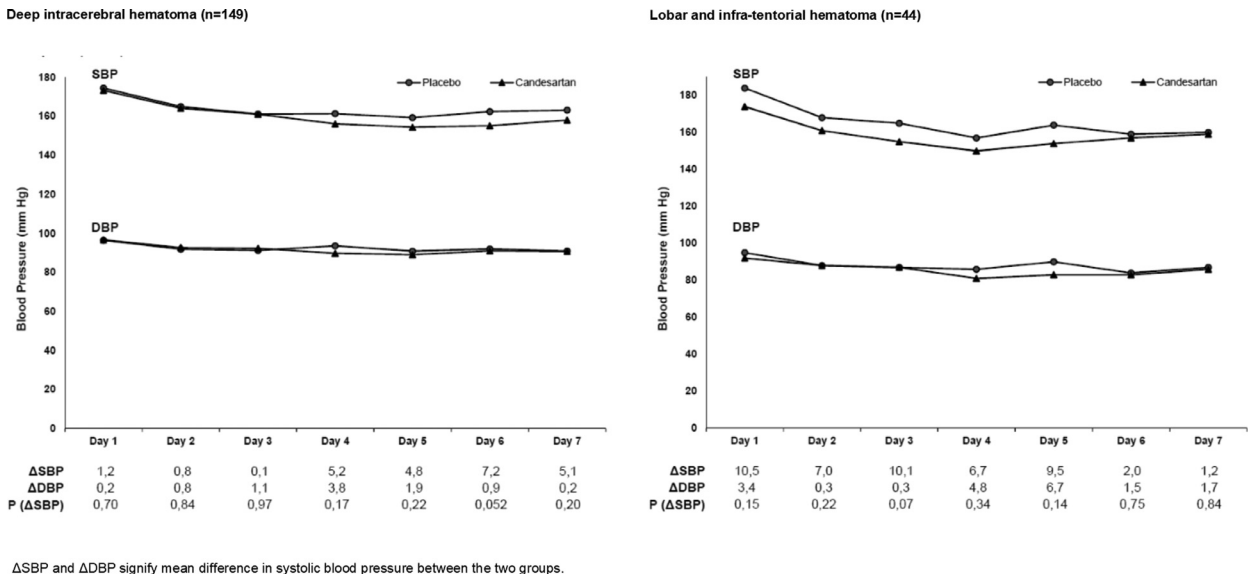

Figure 1. *Blood pressures during the treatment period, in patients with deep intracerebral hemorrhage location and lobar and infratentorial location.*

the acute phase of stroke.[10] Because patients with long-standing hypertension are disposed to damage of the small penetrating arteries, treatment with candesartan may have compromised cerebral perfusion due to a rightward shift in the cerebral autoregulatory curve,[16] and may partly explain our results.

Our results contrast with trials of early and intensive blood pressure-lowering in the hyperacute phase,[13,17] during which most of the hematoma expansion takes place.[18] In the INTERACT2[13] and the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-2)[17] trials, systolic blood pressure was lowered by 14 mm Hg during the first hour and 12 mm Hg during the first 2 hours, respectively. Abnormal activation of the renin-angiotensin system correlates directly with the incidence and extent of stroke, in both clinical[19] and experimental situations.[20] SCAST aimed therefore to protect against the effects of high blood pressure and activation of the

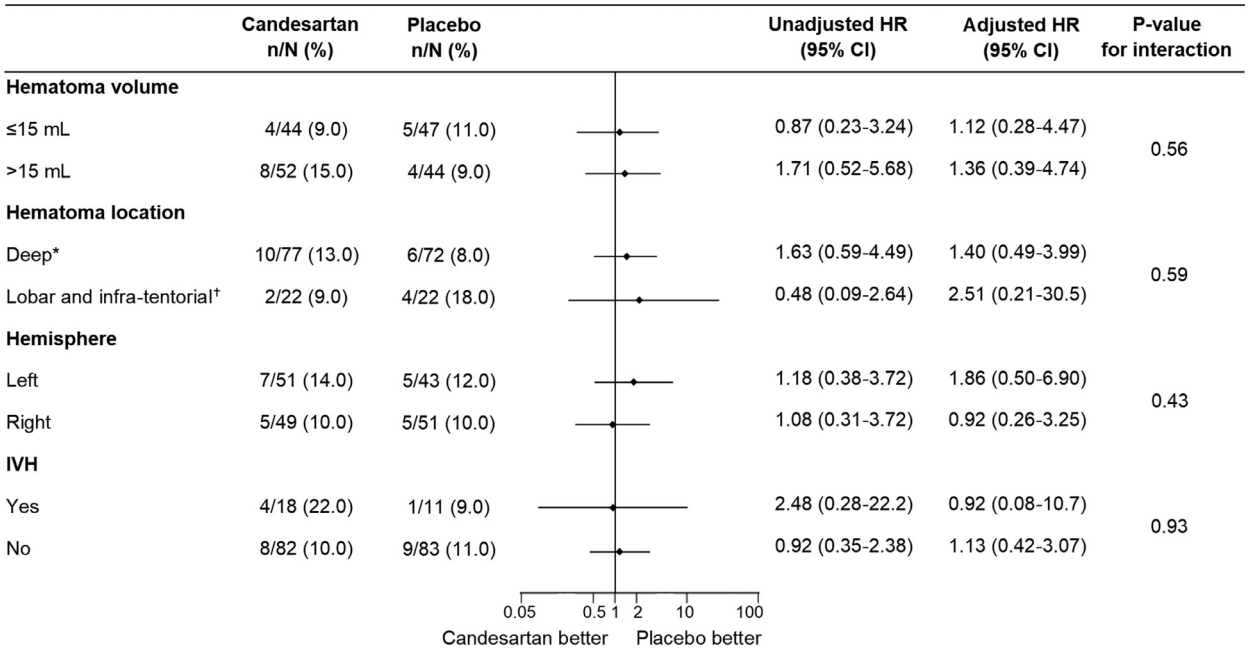

Figure 2. *Effect of candesartan on the risk of composite vascular end-point (vascular death, stroke, or myocardial infarction) in different subgroups of intracerebral hemorrhage. Abbreviations: CI, confidence interval; HR, hazard ratio; IVH, intraventricular hemorrhage. Analysis by Cox regression analysis, adjusted for age, Scandinavian Stroke Scale score, and systolic blood pressure. *Caudate head, putamen, globus pallidus, thalamus, external capsule, internal capsule. †Cerebellum, brainstem.*

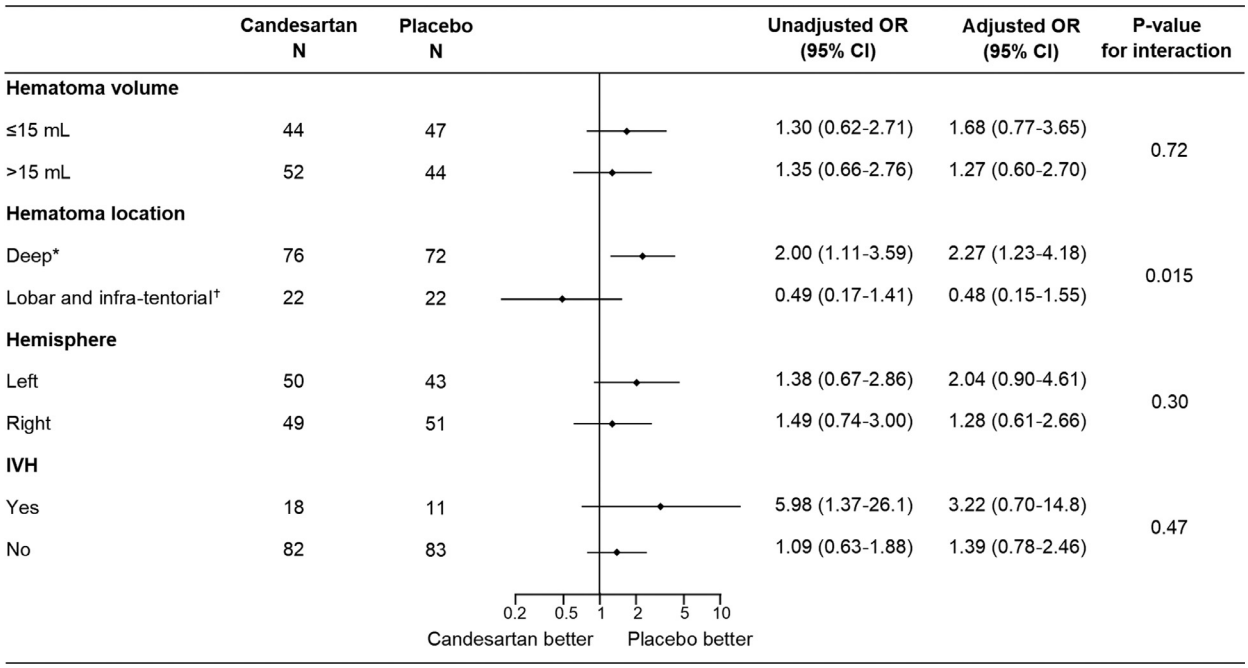

Figure 3. *Effect of candesartan on poor functional outcome in different subgroups of intracerebral hemorrhage. Abbreviations: CI, confidence interval; IVH, intraventricular hemorrhage; OR, odds ratio. Analysis by ordinal logistic regression analysis, adjusted for age, Scandinavian Stroke Scale score, and systolic blood pressure. *Caudate head, putamen, globus pallidus, thalamus, external capsule, internal capsule. †Cerebellum, brainstem.*

renin-angiotensin system in the acute phase of stroke, and the mean difference between the candesartan and placebo groups was of ≈5 mm Hg from day 4 onwards.

Strengths of this study include the use of data from a randomized-controlled trial of blood pressure-lowering treatment in the acute phase of stroke, the central, blinded expert adjudication of hematoma parameters, the blinded clinical outcome assessments, and the completeness of follow-up. Limitations include the post-hoc analyses of a trial subgroup, with potential for chance finding, random error and residual confounding related to low numbers and multiple testing, the unavailability of imaging data from one fourth of the patients, and the unavailability of serial CT studies and CT perfusion imaging, which precluded an assessment of hematoma expansion and cerebral blood flow. Also, we did not have data on anticoagulant therapy, which may have influenced hematoma size in the acute phase. Our findings are therefore considered exploratory, and require confirmation in larger datasets.

In summary, we found no beneficial effects of blood pressure-lowering treatment with candesartan in the acute phase of ICH. A possible adverse effect on functional outcome in patients with deep hematomas cannot be ruled out by this study alone.

Conflicts of Interest

P.M.B. received travel support from AstraZeneca to attend meetings in the trial steering committee. C.A. received travel support and honoraria from Takeda and advisory board fees from Amgen. E.B. received payment for lectures given at meetings arranged by AstraZeneca. The other authors report no conflicts.

Author Contributions

M.J. performed the statistical analysis and wrote the first version of the manuscript. R.G. and S.Y. adjudicated the CT scans. T.E.B., C.D., C.A., P.M.B., and B.W.K. commented on the manuscript. E.B. supervised the study and commented on the manuscript. E.C.S. supervised the analysis and commented on the manuscript.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.05.010.

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