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Blood pressure, Severity of Stroke and Preventive Effects of Antihypertensive Therapy in Patients with Asymptomatic Internal Carotid Artery Stenosis

Is blood pressure and antihypertensive therapy associated with outcomes of stroke?

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Master's thesis in medicine (MED-3950) [June 2021]

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Foreword

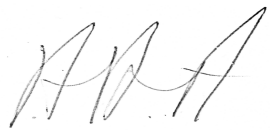
During my first years of medical school, I acquired a growing interest in preventive medicine, especially with regards to cardiovascular diseases. I took contact with Kjersti Hervik looking for a project for my master thesis and she introduced me to an exciting project she was working on. This project was aiming evaluate a number of risk factors and develop a tool for risk stratification in patients with carotid artery stenosis. She proposed that a project about hypertension, stroke risk and outcome would be a perfect fit for my thesis.

This aim of this study is to (1) strengthen the existing evidence on the correlation between hypertension and stroke, (2) Assess the relationship between systolic blood pressure level and stroke incidence and outcome and (3) assess the effects of different antihypertensive agents on the incidence and outcome of stroke.

The great majority of the work related to data collection and research approval was done by my supervisor Kjersti Hervik.

I want to give my thanks to my Kjersti Hervik for invaluable help in completing this thesis, for her guidance in every part of this project and for her constant availability whenever I was in need of assistance. In addition, I would also like to show my gratitude to my supervisor Truls Myrmel for thorough feedback and guidance on this project.

I am also grateful for my family and friends for great support. A special thanks to my friends Ashrak and Kasi for providing me with the encouragement I needed.



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Abstract

Introduction: Even though blood pressure (BP) lowering is important in the primary and secondary prevention of stroke, intensive BP lowering might be deleterious in some patients with asymptomatic carotid artery stenosis (ACAS). The optimal BP target for patients with ACAS is unknown. There are currently no studies showing the relationship between blood pressure and functional outcome of stroke in patients with ACAS. Our aim is to assess the relationship between systolic blood pressure (SBP), stroke and functional outcome of ischemic stroke (IS), in addition to possible protective effects of specific antihypertensive therapy.

Materials and methods: Patients with significant stenosis of the internal carotid artery with no prior history of cerebrovascular events were included. Electronic patient journals were individually searched, and clinical and biochemical characteristic were collected. Primary endpoints of cerebrovascular events, IS, transient ischemic attack (TIA) and favorable outcome of stroke were registered. Univariate analysis was performed using χ^2 or independent t-test for percentages and continuous variables, respectively. Potential confounders were initially inserted into the logistical regression model and subsequently removed by backward stepwise selection

Results: A total of 286 patients were included in this study. SBP was associated with increased risk of cerebrovascular events (OR, 1.013; 95% CI, 1.002 - 1.024; p, 0.017) and IS (OR, 1.018; 95% CI, 1.005 - 1.032; p, 0.009). SBP was positively associated with favorable outcome of IS (OR, 1.032; 95% CI, 1.003 - 1.061; p, 0.028). Patients using calcium channel blockers (CCB) had a significantly lower risk of TIA (p=0.016).

Conclusion: This study suggests that SBP is associated with combined cerebrovascular events and IS. In addition, SBP is proportionally associated with good functional outcome after IS. A significantly lower incidence of TIA was observed among patients using CCBs.

Abbreviations

AHT: Antihypertensive therapy

ACAS: Asymptomatic carotid artery stenosis

BP: Blood pressure

RCT: Randomized controlled trials

TIA: Transient ischemic attack

SPRINT: Systolic Blood Pressure Intervention Trial

SBP: Systolic blood pressure

PROGRESS: The Perindopril Protection Against Recurrent Stroke Study

IS: ischemic stroke

DBP: diastolic blood pressure

CBF: Cerebral blood flow

CPP: Cerebral perfusion pressure

CVR: Cerebral vascular resistance

MAP: Mean arterial pressure

$CRMO_2$: cerebral metabolic rate of O_2

OEF: Oxygen extraction fraction

CBV: Cerebral blood volume

ACEi: Angiotensin enzyme inhibitor

ARB: angiotensin II receptor antagonist

T-TLD: thiazide or thiazide-like diuretic

CCB: calcium channel blocker

DM: Diabetes mellitus

CAD: coronary artery disease

PAD: peripheral artery disease

AF: atrial fibrillation

HF: heart failure

COPD: chronic obstructive pulmonary disease (COPD),

BMI: body mass index

CKD: chronic kidney disease

mRS: modified Rankin Scale

1 Introduction

Stroke is a very common cause of mortality and morbidity, being the second leading cause of death and a leading cause of disability world-wide (1, 2). The disease burden of stroke is expected to increase due to the epidemiological shift from communicable to non-communicable diseases in addition to an ageing population (1). In Norway stroke is the 3rd and 4th leading cause of death and years of life lost, respectively (3). In addition, stroke is the 5th leading cause of disability-adjusted life years in Norway (3).

Approximately 85% of strokes are ischemic and carotid artery atherosclerosis accounts for about 23% of ischemic strokes (4). The prevalence of asymptomatic carotid artery stenosis (ACAS) is low in the general population. In the Tromsø Study, 6727 people between the ages of 25 and 84 were screened for extracranial stenosis of the internal carotid artery using Duplex ultrasound of the right carotid artery. They estimated the prevalence of carotid artery stenosis to be 5.3% and 2.7% in men and women, respectively (5).

According to the large standardized international case control study INTERSTROKE, 90% of the population attributable risk of stroke is associated with ten potentially modifiable risk factors of stroke: hypertension, smoking, diabetes mellitus, physical inactivity, diet, psychosocial factors, abdominal obesity, alcohol, cardiac cause and apolipoproteins (6). In the same study, hypertension was shown to be the most important risk factor with a population-attributable risk of 47.9%. In addition to being the most important risk factor, hypertension has been shown to be strongly correlated with stroke mortality. A meta-analysis of individual data for one million adults showed a clear relationship between hypertension and stroke mortality (7). Therefore, preventive antihypertensive treatment of patients with hypertension is important in reducing the incidence of hemmorrhagic and ischemic stroke.

There is a high prevalence of known risk factors for stroke in patients with ACAS. In a study with 864 patients, the prevalence of smoking history, hyperlipidemia and hypertension were 45%, 62% and 89%, respectively (8). This shows the importance of lifestyle intervention, antihypertensive therapy (AHT) and statins in this group of patients.

Patients with ACAS have a higher annual risk of cardiovascular and cerebrovascular ischemic events (9). A prospective cohort of 3164 ACAS patients with over 70% stenosis showed a 1-year rate of cerebrovascular ischemic events of 5.7% compared to 3.3% in the group without ACAS (9). This gives 58% increased risk of ischemic cerebrovascular events. Other studies

have shown a risk of about 2% per year in patients with ACAS (10, 11). Optimalization of preventive medical therapy has probably reduced the incidence of stroke in this group of patients (12).

1.1 Blood pressure and stroke

There is a large body of evidence supporting the relationship between hypertension and stroke risk and mortality. As mentioned above, the INTERSTROKE-study with 26 919 participants from 32 different countries showed a population-attributable risk of 47.9% for all stroke types and 45.7% for ischemic stroke (6). Hypertension is a strong and independent risk factor for stroke and optimal medical management of hypertension is effective in the primary and secondary prevention of stroke (13).

There is overwhelming evidence on the effect of AHT on the primary prevention of cardiovascular disease and mortality. The optimal blood pressure (BP) for the prevention of cardiovascular disease is under change due to the emergence of new information that suggests beneficial effects of intensive BP lowering treatment. The American Guidelines for Management of Hypertension from 2017 recommends further lowering BP target from <140/90 mmHg in previous guidelines to <130/80 mmHg (14). The European Guidelines for the Management of Arterial Hypertension from 2018 recommends an initial BP target of <140/90mmHg and a BP target of 130/80 mmHg or lower if tolerated (15).

Both the American and European guidelines were in part influenced by the Systolic Blood Pressure Intervention Trial (SPRINT) (16). In this trial, 9361 patients with systolic blood pressure (SBP) ≥ 130, increased cardiovascular risk and without diabetes were included. Patients were randomized to an intensive treatment with a BP target of <120 mmHg or a standard treatment with BP target <140 mmHg. The primary composite outcome of myocardial infarctions, other acute coronary syndromes, stroke, heart failure or death from cardiovascular causes were lower in the intensive treatment group (HR 0.75; 95% confidence interval, 0.64 -0.89; p<0.001). However, there was no significant difference in the incidence of stroke between the intensive and standard treatment group.

A Cochrane review of randomized controlled trials (RCT) showed that blood pressure lowering drugs initiated at least 48 hours after stroke or transient ischemic attack (TIA) reduced the risk of recurrent stroke (17). Intensive BP treatment compared to standard BP

treatment did not reduce the risk of recurrent stroke, and thus supported the findings of the SPRINT trial that intensive BP treatment does not further reduce the risk of stroke.

The optimal BP target for the prevention of stroke remains uncertain, and current recommendations are in part based on the general reduction of major cardiovascular events, including stroke, seen with BP lowering (15). There has been inconsistent evidence regarding the relationship between BP and stroke incidence, mortality and outcome. Some studies have suggested a linear relationship, while others have suggested a J-curve or a U-curve relationship (18-21).

The Blood Pressure and Clinical Outcome in TIA or Ischemic Stroke (BOSS) study assessed the relationship between SBP and combined vascular events and stroke using the mean value of self-measured SBP the first 90 days after onset (18). This study showed that patients with SBP < 115 or ≥ 165 had a higher risk of stroke recurrence and combined vascular events indicating a J-curve relationship between SBP, combined vascular events and stroke recurrence. They suggested that a BP of 115-134 mmHg was the appropriate target for this group of patients.

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) suggested that BP target of 115/75 was safe and maximally protective if well tolerated in patient with previous history of cerebrovascular disease (22). They found no evidence of a J-curve relationship. This finding is supported by a meta-analysis of one million adults from 61 prospective studies with no prior history of vascular disease that showed a linear relationship between BP and stroke mortality. This study found a linear increase in stroke mortality from SBP of 115 mmHg and diastolic blood pressure 75 mmHg (7).

This shows that even though there is increasing evidence that intensive BP treatment can be effective in reducing the overall incidence of cardiovascular disease, the optimal BP target for the prevention of stroke remains uncertain.

The optimal BP for the prevention of stroke in patients with carotid artery stenosis (CAS) is unknown, and few studies have assessed this relationship. Similar to BP targets on the prevention of stroke, current guidelines on BP treatment in patients with CAS is based on the general risk-reduction of major cardiovascular events seen with BP treatment. Patient with CAS have a high risk of both cardio- and cerebrovascular events (9). There are no specific guidelines in the American or the European guidelines on the management of hypertension in

patients with CAS (14, 15). The European guidelines emphasize the increased risk of atheroembolic stroke and cardiovascular events in these patients, and recommend BP regulation complemented by lifestyle intervention. In addition, the European guidelines recommend a cautious approach to BP treatment in patients with high degree of carotid stenosis, especially when bilateral.

Patients with CAS are different from other patient groups in many ways. Firstly, CAS is predictive of, and strongly correlated with, stroke and myocardial infarction. A study with 1968 subjects with no prior history of cardiovascular disease or diabetes were examined for carotid atherosclerosis in addition to many other traditional risk factors for cardiovascular disease (23). Atherosclerotic carotid plaques were an independent and predictive risk factor for cardiovascular death (HR, 2.1; 95% CI, 1.3-3.3; p-value, 0.003). BP treatment can decrease the progression and even regress atherosclerosis and intima media thickening in this group of patients (15).

Secondly, a challenge of BP treatment in patients with a high degree of carotid stenosis, especially when bilateral, is the effect of the BP lowering on cerebral blood flow. Bilateral stenosis is not uncommon in patients with CAS and one study found that 23% of patients with CAS had bilateral stenosis (24). About 9% of patients with TIA or IS have an occluded internal carotid artery (25).

There are two main causes of TIA and IS in patients with CAS. One mechanism of stroke is the dislodging of a thrombus in the internal carotid artery and subsequent distal occlusion of a cerebral artery (26). This is the most common cause of stroke in this group of patients. Another important cause of TIA and IS in these patients is so-called hemodynamic stroke (25). As the name suggests, hemodynamic stroke is caused by cerebral hypoperfusion and not by embolism of thrombotic material. We know that patients with CAS might experience symptoms of stroke in situations with cerebral hypoperfusion, such as a change of position from sitting or lying down to a standing position (orthostatic TIA). Other situations are postprandial hypotension, loss of fluid or blood, cardiac failure or physical exercise (27).

In addition, thromboembolic stroke and reduced cerebral perfusion pressures (CPP) can act synergistically in causing ischemic stroke. In the case of embolism, cerebral hypoperfusion can further exacerbate the stroke due to reduced clearance of the embolus. The location of the embolus might also be dependent on cerebral perfusion pressures (25).

Briefly, cerebral blood flow (CBF) is proportional to CPP and inversely proportional to cerebrovascular resistance (CVR). CPP is the difference between mean arterial and cerebral venous pressure. The latter is normally negligible in the absence of increased intracranial pressure or venous obstruction. CVR is determined by the blood viscosity and vessel length and radius. Only the vessel radius is available for physiological regulation. Therefore, regulation of CBF is mainly based on CVR, provided that CPP is normal (28).

The mechanism of cerebral autoregulation allows a constant CBF despite changes in mean arterial pressure (MAP) in the range between 50-150 mmHg. This is done by vasoconstriction or vasodilatation of resistance vessels. In the case of MAP below 50 mmHg the maximum vasodilatory capacity is reached, and CBF will consequently decrease. Conversely, the maximum vasoconstrictive capacity is reached in values of MAP above 150 mmHg, with subsequent increase in CBF. Increased cerebral metabolic demand is primarily regulated by cerebral metabolic rate of O_2 ($CRMO_2$). This is normally met by an increase in CBF by arteriolar vasodilatation and not by an increase in oxygen extraction fraction (OEF). When the maximum vasodilatory capacity is reached, the OEF is increased to meet the cerebral metabolic demand (28).

In patients with chronic hypertension the range of cerebral autoregulation is shifted to the right with increased lower and upper limit of autoregulation (28). Some studies suggest that the lower limit of MAP in patients with chronic hypertension is as high as 100 mmHg (29). These patients are therefore susceptible to cerebral ischemia when MAP is acutely decreased. This is demonstrated in a patient series with eight chronically hypertensive patients with focal cerebral ischemia after being treated with blood pressure lowering drugs (30).

The regional cerebral hemodynamic effects of occlusive arterial disease have been classified into three stages, depending on the effect of reduction of CPP on CBF, Cerebral blood volume (CBV) and OEF (31). In stage 0 the CPP is normal and the CBF is closely matched with cerebral metabolism. The CBV is not elevated and the CBF increases with vasodilatory stimuli. In stage I, the CPP is decreased, and subsequent vasodilatation of arterioles to maintain normal CBF, increases CBV. The OEF is not increased but the response to vasodilatory stimuli is decreased. In Stage II, the CPP is decreased below the autoregulatory cerebral capacity, and OEF is increased due to the decrease in CBF relative to $CRMO_2$.

Stage II is known as cerebral hemodynamic failure or “misery perfusion”. This occurs when the CPP goes below the vasodilatory cerebral capacity and increased OEF is necessary to meet the metabolic demand (27). In the normal resting brain, the delivery of O_2 and glucose exceeds the metabolic demand, and both OEF and the glucose extraction fraction is low. This is also known as “luxury perfusion” (32).

Patients with ACAS and low cerebrovascular reserve have a higher risk of stroke. A meta-analysis of 1061 patients with ACAS showed that patients with impaired cerebrovascular reserve, measured by response to vasodilatory stimulation with acetazolamide or increased CO_2 or by direct cerebral blood flow measurements, had a significantly higher risk of stroke (OR, 3.86; CI, 1.99-7.48) (33).

The relationship between BP and stroke recurrence in patients with symptomatic CAS is different between those with and without impaired cerebral perfusion. One study analyzed data from 130 patients with symptomatic extracranial internal carotid occlusion or intracranial stenosis or occlusion of the carotid artery or middle cerebral arteries (24) . Baseline hemodynamic measurements was performed using ^{15}O-gas positron emission tomography. In this study the authors observed an inverse relationship between SBP and risk of stroke in the territory of the diseased artery. The incidence of IS in patients with SBP <130 mmHg was significantly higher than in patients with SBP > 130 mmHg. Interestingly, higher risk of stroke was seen with lower BP in patients with impaired perfusion, while the opposite was true for patients without impaired perfusion.

1.2 Effects of different antihypertensive classes on stroke prevention

Many RCTs on antihypertensive agents and prevention of stroke has been performed. A metanalysis with 251 853 subjects assessed the effect of angiotensin enzyme inhibitors (ACEi), angiotensin II receptor antagonists (ARB), thiazide or thiazide-like diuretics (T-TLD), calcium channel blockers (CCB) and beta blockers (βB) on the primary and secondary prevention of stroke (34). The result showed a risk ratio for stroke as follows: CCB, 0.83; ARB, 0.83; T-TLD, 0.90; ACEi/ARB, 0.94; ACEi, 1.01; βB, 1.42. Only CCBs and betablockers were significantly associated with stroke showing that CCBs are most effective in prevention, and that βBs are associated with an increased risk of stroke. Another large systematic review of 29 randomized trials evaluated the effects of different antihypertensive

agents on major cardiovascular events, including stroke (35). The review showed a significant reduction in stroke risk with BP lowering regimens including ACEi, ARB and CCB.

The American College of Cardiology and American Heart Association guidelines refer to the benefit of diuretics, ACEi and ARBs in in patients with previous history of TIA or stroke seen in RCTs and systematic reviews (14). The European Society of Cardiology and the European Society of Hypertension guidelines have no description of preferred antihypertensive agents, but discourage the use of βBs as antihypertensive therapy in the secondary prevention of stroke, unless other indications are present (15).

1.3 Relationship between blood pressure and specific antihypertensive therapy on stroke risk and outcome in patients with ACAS

There are very few studies specifically assessing the relationship between blood pressure and stroke risk in patients with ACAS. A retrospective observational study with 864 patients with ACAS showed a non-significant association between suboptimal blood pressure control and stroke (8). Another study with 288 patients with asymptomatic moderate internal carotid stenosis between 50% and 75% showed that hypertension was significantly associated with increased risk of disease progression to severe stenosis and/or development of symptoms (36). The Scandinavian Candesartan Acute Stroke Trial randomized patients to candesartan or placebo in 187 patients with carotid artery stenosis in the acute phase of stroke (37). The study did not exclude patients with previous history of TIA or stroke. It showed no significant difference between the two groups but there was a non-significant association between severe stenosis, stroke progression and poor functional outcome in patients treated with candesartan.

As mentioned above, the emergence of new data from RCTs showing the beneficial effect of intensive BP treatment compared to standard treatment have changed current American and European guidelines on BP targets in most hypertensive patients (14, 15). The optimal BP target for the prevention of stroke remains uncertain with conflicting evidence on the nature of the relationship between BP and stroke. To our knowledge, there are no studies that have assessed the optimal BP target for patients with ACAS and current guidelines are based on the general reduction of major cardiovascular events with BP treatment. Special considerations should be made regarding patients with high degree of stenosis, especially when bilateral. In patients with misery perfusion, the maximal vasodilatory capacity is reached, and cerebral perfusion pressure is mainly dependent on the MAP (27). Reduced cerebral vascular reserve

gives an increased risk of stroke, and intensive blood pressure treatment in patients with impaired cerebral perfusion might give an increased risk of stroke (24, 33). These patients have a susceptibility of hemodynamic stroke, and in the case of thromboembolic stroke reduced CPP might further worsen the stroke due to reduced clearance of the emboli (25). No studies have assessed the relationship between BP and outcomes of stroke or specific antihypertensive therapy and stroke risk and outcome in patients with ACAS.

2 Materials and Methods

This study includes 286 patients with significant stenosis of the internal carotid artery with no prior history of cerebrovascular events. Electronic patient journals were individually searched and the following clinical and biochemical characteristic were registered: Age at the time of diagnosis, gender, SBP, diabetes mellitus (DM), coronary artery disease (CAD), peripheral artery disease (PAD), atrial fibrillation (AF), heart failure (HF), chronic obstructive pulmonary disease (COPD), body mass index (BMI), chronic kidney disease (CKD), cardiovascular disease, familial history of cerebrovascular events, AHT before and after diagnosis, smoking or history of smoking, total cholesterol, date of ultrasound, degree of stenosis in the left and right internal carotid artery, IS, TIA, date of first event, modified rankin scale (mRS), death and date of death.

The asymptomatic patients in this study were primarily recruited in the Tromsø study, which is a longitudinal population-based health study, with a total of seven studies performed between 1974 and 2016 (38). Unilateral carotid examination was performed in a subgroup of patients in the fourth, fifth and sixth Tromsø study, and subsequent bilateral duplex scanning was performed in patients where carotid stenosis was identified.

The BP used in study is a one-time measurement of SBP at the time of diagnosis of ACAS. Elevated SBP is defined as SBP $\geq$ 140 mmHg. Use of specific antihypertensive agents before and after the diagnosis of ACAS was registered and grouped into CCB, ARB, ACEi, βB and alpha 1 adrenergic receptor antagonist. Primary endpoints of combined IS/TIA, IS, TIA and favorable outcome of stroke were registered. Favorable outcome was defined as mRS of 0 or 1.

Statistical analysis was performed using IBM SPSS statistics version 26 (IBM Corp, New York, USA). The demographic and clinical data are presented using descriptive statistics. Univariate analysis was performed using χ^2 or independent t-test for percentages and continuous variables, respectively. Potential confounders were initially inserted into the logistical regression model and subsequently removed by backward stepwise selection.

This study was approved by the Regional Ethical Committee, and consent was obtained from the participants. The Regional Ethical committee granted consent exemption from deceased patients. In addition, we were advised not to obtain new consent from participants recruited in the Tromsø Study, as they had previously given broad consent to participate in the population study.

3 Results

Table 1 Demographic and clinical characteristics

Variable	Value
Age	70 (8)
Gender, M/F	155/131
SBP > 140	177 (62)
SBP	153 (24)
DM	37 (13)
CAD	135 (47)
PAD	60 (21)
AF	22 (8)
HF	15 (5)
COPD	33 (12)
BMI > 35	6 (2)
CKD	40 (14)
Family history of CVD	35 (12)
Smoking or history of smoking	206 (72)
Total cholesterol > 5	171 (60)

SBP, systolic blood pressure; DM, diabetes mellitus; CAD, coronary artery disease; PAD, peripheral artery disease; AF, atrial fibrillation; HF, heart failure; COPD, chronic obstructive pulmonary disease; BMI; body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease. Values are in mean (SD) or n (%).

A total of 286 patients with significant internal carotid artery stenosis were included in this study. Baseline demographic and clinical characteristics are presented in table 1. There were more men (n=155) than women (n=131). The study population had a high mean age (mean, 70 years; SD, 8 years; range, 37-86 years). The mean SBP was elevated (mean, 153 mmHg; SD, 24 mmHg; range, 100-240 mmHg). 62% of patients had elevated SBP (n=177; median, 168 mmHg; SD 18 mmHg). 55% of men and 69% of women had elevated SBP. There was a high prevalence of risk factors for cerebrovascular disease (smoking or history of smoking, 72%; elevated total cholesterol 60%; DM, 13%). In addition, the prevalence of other comorbidities was high (CAD, 37%; PAD, 21%; AF, 8%; HF, 5%; CKD, 14%).

Univariate analysis of demographic and clinical data is presented in table 2. Significantly more women than men had elevated SBP (p: 0.015). Age was associated with elevated SBP, although this association was non-significant. Elevated SBP was not associated with age, smoking, CAD, DM, PAD, AF or BMI > 35.

Table 2 Univariate analysis of demographic and clinical data

	Elevated SBP (n = 177)	Non-elevated SBP (n = 109)	p
Age	70 (8)	69 (9)	0.065
Gender, M/F	86/91 (49/51)	69/40 (63/37)	**0.015**
DM	23 (13)	14 (13)	0.971
CAD	77 (44)	58 (53)	0.110
PAD	34 (19)	26 (24)	0.349
AF	10 (7)	12 (11)	0.099
BMI > 35	4 (2)	2 (2)	0.808
Smoking	56 (32)	46 (42)	0.070

DM, diabetes mellitus; CAD, coronary artery disease; PAD, peripheral artery disease; AF, atrial fibrillation; BMI, body mass index. Values are in mean (SD) or n (%).

The relationship between SBP, cerebrovascular events and outcomes of ischemic stroke is presented in table 3 and 4. The incidence of cerebrovascular events, IS and TIA was 31%, 16% and 16%, respectively. Among patients with cerebrovascular events, IS and TIA the prevalence of elevated SBP was 66%, 80% and 56%, respectively. 85% of patients with a favorable outcome after stroke had elevated SBP, while 65% of patients with unfavorable outcome after stroke had elevated SBP. SBP was associated with cerebrovascular events (OR, 1.013; 95% CI, 1.002 - 1.024; p, 0.017) and IS (OR, 1.018; 95% CI, 1.005 - 1.032; p, 0.009). SBP was positively associated with favorable outcome of IS (OR, 1.032; 95% CI, 1.003 - 1.061; p, 0.028).

Table 3 Relationship between systolic blood pressure, cerebrovascular events and outcomes of ischemic stroke

	Elevated SBP	Non-elevated SBP	Total
Cerebrovascular events	59 (66)	31 (34)	90
IS	34 (80)	11 (24)	45
TIA	25 (56)	20 (44)	45
Favorable otutcome[1]	17 (85)	3 (15)	20
Unfavorable outcome[1]	15 (65)	8 (35)	23

SBP, systolic blood pressure; IS, ischemic stroke; TIA, transient ischemic attack. Values are in n (%).

[1] Favorable outcome is defined as modified Rankin scale score 0 or 1 while unfavorable is defined as modified Rankin scale score ≥2.

Table 4 Systolic blood pressure, cerebrovascular events and outcome of ischemic stroke

	OR	p
Cerebrovascular events	1.013 (1.002 - 1.024)[2]	**0.017**
IS	1.018 (1.005 - 1.031)[3]	**0.009**
TIA	1.002 (0.988 - 1.016)[3]	0.805
Favorable outcome[1]	1.033 (1.003 – 1.063)[4]	**0.028**

BP, blood pressure; IS, ischemic stroke; TIA, transient ischemic attack. Values denoted parentheses are the 95% CI.
[1] modified Rankin scale score 0 or 1
[2] Adjusted for smoking
[3] Adjusted for family history of CVD and smoking
[4] Adjusted for age, gender and smoking

Antihypertensive treatment before and after the diagnosis of ACAS is presented in table 5. Before the diagnosis, 36% of patients used no AHT compared to 28% after the diagnosis. 49% of the patients that used no antihypertensive medications had elevated SBP. Of those who were on AHT, 40% used βB, 22% used CCBs, 19% used diuretics, 16% used ARBs, 16% used ACEis and 2% used alpha-1-adrenergic receptor antagonists. A 5-percentage point increase in the use of βBs and diuretics after the diagnosis was observed. The increase for ARB, ACEi and CCB was 3, 3 and 2 percentage points, respectively.

Table 5 Antihypertensive therapy before and after ultrasound

AHT	Before	After
No AHT	103 (36)	79 (28)
CCB	63 (22)	65 (23)
ARB	47(16)	54 (19)
ACEi	45 (16)	53 (19)
βB	113 (40)	128 (45)
Diuretics	55 (19)	69 (24)
A1B	7(2)	7 (2)
Other	25 (9)	18 (6)

AHT, antihypertensive therapy; CCB, calcium channel blocker; ARB, angiotensin II receptor antagonist; ACEi, angiotensin converting enzyme inhibitor; βB, beta blocker; A1B, alpha 1 adrenergic receptor antagonist. Values are in n (%).

The relationship between specific AHT, cerebrovascular events and TIA are shown in table 6. There was no significant correlation between specific antihypertensive therapy and combined cerebrovascular events. The incidence of cerebrovascular events in the study population was

31%, among patients using CCBs the incidence was 25%. Patients using CCBs had a significantly lower risk of TIA (p=0.016).

Table 6 Relationship between antihypertensive therapy, cerebrovascular events and TIA

	Cerebrovascular event (n = 90)	No event (n = 196)	p	TIA (n = 45)	No TIA (n = 241)	p
No AHT	24 (30)	55 (70)	0.806	15 (20)	64 (80)	0.351
CCB	16 (25)	49 (75)	0.176	4 (6)	61 (94)	**0.016**
ARB	15 (28)	39 (72)	0.517	5 (9)	49 (91)	0.147
ACEi	14 (26)	39 (74)	0.380	6 (11)	47 (89)	0.328
βB	43 (34)	85 (66)	0.486	21 (16)	107 (84)	0.779
Diuretics	23 (33)	46 (67)	0.702	8 (12)	61 (88)	0.486
other	5 (28)	13 (72)	0.728	1 (6)	17 (94)	0.221

AHT, antihypertensive therapy; CCB, calcium channel blocker; ARB, angiotensin II receptor antagonist; ACEi, angiotensin converting enzyme inhibitor; βB, beta blocker. Values are in n (%).

Table 7 shows the relationship between IS and the outcome of IS with specific AHT. Specific AHT had no significant effect on the incidence of IS or the outcome of IS.

Table 7 The relationship between specific antihypertensive therapy and ischemic stroke and outcome

	IS (n = 45)	No IS (n = 241)	p	Favorable outcome (n = 20)	Unfavorable outcome (n = 23)	p
No AHT	9 (11)	70 (89)	0.213	5 (56)	4 (44)	0.541
CCB	12 (18)	53 (82)	0.492	5 (46)	6 (54)	0.935
ARB	10 (19)	44 (81)	0.533	4 (44)	5 (56)	0.889
ACEi	8 (15)	45 (85)	0.887	4 (57)	3 (43)	0.538
βB	22 (17)	106 (83)	0.544	9 (45)	11 (55)	0.853
Diuretics	15 (22)	54 (78)	0.116	5 (39)	8 (61)	0.486
other	4 (22)	14 (78)	0.435	1 (25)	3 (75)	0.365

AHT, antihypertensive therapy; CCB, calcium channel blocker; ARB, angiotensin II receptor antagonist; ACEi, angiotensin converting enzyme inhibitor; βB, beta blocker. Values are in n (%).

4 Discussion

We observed a 1.3% and 1.8% increase in odds for every unit increase in SBP of combined cerebrovascular events and IS, respectively. These findings correspond with the a number of studies showing a proportional relationship between SBP and cardiovascular disease: A meta-analysis of 419 488 individuals described a 34% increase in the risk of cardiovascular disease for every 10mmHg increase SBP (39). Another meta-analysis of 1.3 million adults showed an 18% increase in the risk of myocardial infarction, IS and hemorrhagic stroke for evert unit increase in z score of SBP (40). Lastly, a meta-analysis including 1.25 million patients showed a 35% increase of IS for every 20 mmHg increase in SBP (41) One previous study has shown that hypertension is significantly associated with stroke, while another study showed a non-significant association between sub-optimal BP control and stroke in patients with ACAS (8, 36). In addition to hypertension, these studies found that hyperlipidemia and smoking were associated with stroke. As expected, this suggest that risk factors for stroke in the general population and in patients with ACAS are the same.

We also found a proportional relationship between SBP and favorable outcome of IS, with a 3.2% increase of favorable outcome for every unit increase in SBP. To our knowledge, this relationship has never been studied in patients with ACAS. A study with 749 patients with acute ischemic stroke showed that patients with elevated BP was associated with mild stroke, while lack of elevated BP was associated with severe stroke (42). These authors suggested an inverse relationship between elevated BP on admission and stroke severity. Another study with 264 patients with acute IS and hemorrhagic stroke, high SBP was associated with 15% increased risk of neurological deterioration in the first 48 hours, but SBP was not associated with the 90-day functional outcome in the group with IS (43). Some studies have also suggested that both high and low blood pressures increase the risk of bad outcome (21, 44).

A transitory increase in BP is very common among patients with acute stroke, and can be seen in 70-80% of patients presenting with acute stroke (45). Several mechanisms, like catecholamine secretion in response to stress, increased cardiac output and urinary retention, have been proposed as explanation to the increase in BP (28). Current guidelines from the American heart association recommend that hypotension should be corrected to maintain systemic perfusion, BP lowering to <220/120 mmHg in all patients with IS and a BP target of <185/110 mmHg in patients who are candidates for emergency reperfusion therapy (46).

The studies presented above have used admission and post-admission BP to assess the effect of BP on the functional outcome of stroke, which makes it difficult to compare them to our findings. We found that baseline SBP was significantly associated with combined cerebrovascular events, IS and favorable outcome of stroke. Importantly, SBP was not measured in the acute phase of stroke in our study.

Studies have shown that there are no alterations in autoregulatory capacity in patients with acute ischemic stroke (47). This might be different in patients with CAS. CAS is the most common reason for cerebral misery perfusion; a condition where the CPP goes below the maximal vasodilatory cerebral capacity and OEF increases to meet the metabolic demand (27). In this setting, the autoregulatory cerebral mechanisms are exhausted and CBF is a direct result of MAP. This group of patients is more sensitive to reductions in BP compared to patients without cerebral misery perfusion.

The Scandinavian Candesartan Acute Stroke Trial randomized patients to candesartan or placebo (37). 187 patients with carotid artery stenosis in the acute phase of stroke were included and no significant association between severity of stenosis, stroke progression or poor functional outcome was observed in patients treated with candesartan.

We found that the use of CCBs was significantly associated with reduced risk of TIA. Specific AHT had no significant effect on the incidence of IS or the outcome of IS. In a meta-analysis assessing the effect of specific AHT on the primary and secondary prevention of stroke, CCBs were shown to reduce the risk of stroke, while the use of βBs were associated with an increased in the risk of stroke (34). Another large systematic review on the secondary prevention of stroke showed a significant reduction of stroke risk in patients using ACEi, ARBs and CCBs (17). Patients with hemodynamic causes of stroke are especially vulnerable for variations in blood pressure. One study comparing the visit-to-visit variability of SBP between patients using CCBs and βBs showed a lower variability in the group that used CCBs (48).Therefore, Some have suggested that CCBs might be preferred in patients with hemodynamic TIAs and stroke due to reduced fluctuations in BP with CCBs (25).

To our knowledge, no previous studies have been performed on the effect of specific AHT on stroke risk and outcome in patients with ACAS. The findings in our study are supported by many other studies that show that CCBs are associated with reduced risk of stroke. CCBs

might potentially give an additional benefit because of reduced BP variability in patients with hemodynamic stroke.

This study has some limitations. Firstly, the SBP used in this study is a one-time measurement of SBP at the time of diagnosis. According to the European society of cardiology and European society of hypertension, BP can be highly variable and they recommend repeated BP measurements to confirm persistent elevation of BP (15). In addition, patients could not be followed for possible changes in AHT made by primary care physicians as these changes are not present in the hospital's patient journals. Also, the time of mRS evaluation was not standardized for all patients.

5 Conclusion

Our study suggests that elevated SBP is associated with combined cerebrovascular events and IS in patients with ACAS. Interestingly, SBP was positively associated with favorable outcome of IS. The use of CCBs was associated with lower risk of TIA. The mean age of the study population was high, and they had a high prevalence of risk factors for stroke and the prevalence of comorbidities was high. The mean SBP was elevated, and women had significantly higher SBP than men.

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Reference: A Randomized Trial of Intensive versus Standard Blood-Pressure Control. New England Journal of Medicine. 2015;373(22):2103-16.			Study design: RCT **Grade quality** ⊕⊕⊕⊕
Aim	**Material and methods**	**Results**	**Discussion/comments/checklist**
Comparing the efficacy and safety of intensive BP lowering and standard BP lowering on cardiovascular disease **Conclusion** Intensive BP lowering is superior compared to standard BP lowering in high-risk non-diabetic patients including the elderly. **Country** USA and Puerto Rico **Year of data sampling** 2010-2013	**Recruitment and participants** 9361 patients from 102 clinical sites in the United States and Puerto Rico were recruited in this study. **Inclusion/exclusion criteria** Patients with age ≥50 years, SBP 130-180 mmHg and increased risk of cardiovascular events were included. Patients with diabetes or previous stroke were excluded. **Data material** The included patients were randomized into a SBP target of <140 mmHg (n=4683) or a SBP of <120 mmHg (n=4678). Demographic data were recorded at baseline. Clinical and laboratory data were recorded at baseline and every 3 months. **Endpoints** Primary composite outcome of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure and death from cardiovascular cause. Secondary outcomes included individual outcomes of the composite outcome, all-cause mortality and composite primary outcome and all-cause mortality **Statistical analysis** Time to the first occurrence of the primary outcome between the intensive and standard treatment groups was compared using Cox proportional-hazards regression with two-sided test at 5% level of significance. Intention to treat approach was used for all randomized patients.	The primary composite outcome was significantly lower in patients receiving intensive BP lowering compared to the patients receiving standard treatment (5.2% vs. 6.8%; HR, 0.75; 95% CI, 0.64-0.89; p<0.0001). Patients receiving intensive BP lowering treatment had lower event rates of decompensated heart failure (1.3% vs 2.1%; p=0.002), cardiovascular death (0.8% vs 1.4%; p=0.0005), all-cause mortality (3.3% vs 4.5%; p=0.0003). Adverse outcomes were more frequent in the intensive group: decreased renal function (3.8% vs 1.1%; p<0.001), hypotension (2.4% vs 1.4%; p=0.001), syncope (2.3% vs 1.7%; p=0.05) and hyponatremia (3.8% vs 2.1%; p<0.0001).	• **Is the aim of the study clearly formulated?** Yes • **Who was included/excluded?** Patients with SBP 130-180 mmHg and increased risk of cardiovascular events were included. Patients with diabetes or previous stroke were excluded. • **Where the groups similar initially?** Yes. • **Procedure of randomization?** Yes. • **Were the participants/study personnel blinded?** No, but outcome adjudicator was blinded. • **Where the groups treated similarly except for the intervention?** Yes. • **Were primary outcome measures validated?** Yes, patients were followed up every 3 months. • **Were all participants accounted for at the end of the study?** Yes. Intention to treat approach was used to reduce bias. • **What are the results?** The primary outcome of significantly lower in the group receiving intensive treatment. The correlation was strong, and the CI was relatively narrow (p<0.0001; CI, 0.64-0.89) • **Can the results of the study be transferred to clinical practice?** Yes. The results from this study are valid for all patients ≥50 years, with increased risk for cardiovascular events and no history of diabetes or stroke. • **Were all relevant outcomes assesed?** Yes. • **Does the advantage outweigh the harm/cost?** Adverse events were more frequent in the group receiving intensive treatment. The advantage may outweigh the harm/cost because of significant reduction in the risk of the primary outcome. • **Are the results supported by available evidence?** Yes. **Strengths:** A RCT with a large study population and diversity. The BP targets in the two groups was achieved. . **Limitations:** A lack of generalizability to groups not included in the study. Achieving a BP goal of <120 mmHg is demanding in the over-all population Are the results plausible? Yes.

Reference: Jusufovic M, Sandset EC, Bath PM, Karlson BW, Berge E. Effects of blood pressure lowering in patients with acute ischemic stroke and carotid artery stenosis. Int J Stroke. 2015;10(3):354-9.			Study design: RCT **Grade quality** ⊕⊕⊕
Aim	**Material and methods**	**Results**	**Discussion/comments/checklist**
Assess the effect of BP lowering using candesartan in the acute phase of stroke in patients with carotid artery stenosis. **Conclusion** BP lowering with candesartan. **Country** Multi-center study from in nine European countries. **Year of data sampling** 2010	**Recruitment and participants** 2029 participants were recruited from 146 centers in nine European countries. A separate analysis was performed for patients with carotid artery stenosis and ischemic stroke. **Inclusion/exclusion criteria** Patients ≥ 18 years with ischemic stroke presenting within 30h after onset of symptoms and BP > 140/90mmHg were included in the study. Patients were randomized into placebo or candesartan treatment for 7 days after stroke onset. **Data material** Out of the 1733 with ischemic stroke 806 had no or insignificant stenosis, 97 had moderate stenosis, 90 had severe stenosis and 740 had no carotid artery data. Blood pressure was measured daily in all patients **Endpoints** This study had two co-primary endpoints: the composite outcome of vascular death, myocardial infarction, or stroke in the first 6 months and functional outcome after 6 months using modified Rankin Scale. In this sub study, early stroke progression was included as a secondary endpoint. **Statistical analysis** One-way ANOVA, χ^2 test or the mann-whithney U test was used for baseline comparison of patients. Independent t-test was used to compare BP values during the treatment. Cox proportional hazard models and logistic regression was used to analyze the primary outcomes. Intention to treat approach was used for all randomized patients.	Progressive stroke occurred more in patients with carotid artery stenosis that were treated with candesartan (p=0.04) with a trend towards increasing risk with the severity of stenosis. There was no significant difference in the vascular endpoint or functional outcome.	• **Is the aim of the study clearly formulated?** Yes. • **Who was included/excluded?** Patients with hemorrhagic stroke, patients with >30 hours since onset of stroke, and patients with BP > 140mmHg were excluded. Patients ≥ 18 years with ischemic stroke presenting within 30h after onset of symptoms and BP > 140/90mmHg were included • **Where the groups similar initially?** Yes • **Procedure of randomization?** Yes. • **Were the participants/study personnel blinded?** This study was double blinded • **Where the groups treated similarly except for the intervention?** Yes. • **Were primary outcome measures validated?** Yes, the participants had clinical visits at day 7, and after 1 and 6 months. At 3 months the coordinating center did a telephone or postal interview. • **Were all participants accounted for at the end of the study?** Yes. Intention to treat approach was used for all randomized patients. • **What are the results?** Progressive stroke occurred more in the group treated with candesartan and showed a trend towards increased risk the severity of stenosis. • **Can the results of the study be transferred to clinical practice?** Yes. • **Were all relevant outcomes assesed?** Yes. • **Does the advantage outweigh the harm/cost?** Yes. • **Are the results supported by available evidence?** Yes. **Strengths:** A double blind randomize placebo-controlled trial. **Limitations:** Only angiotensin receptor blocker was used, and there might be a difference between different classes of antihypertensive agents. Only 187 patients had significant stenosis.

Reference: Shah Z, Masoomi R, Thapa R, Wani M, Chen J, Dawn B, et al. Optimal Medical Management Reduces Risk of Disease Progression and Ischemic Events in Asymptomatic Carotid Stenosis Patients: A Long-Term Follow-Up Study. Cerebrovasc Dis. 2017;44(3-4):150-9.			Study design: Retrospective observational study **Grade quality** ⊕⊕
Aim	**Material and methods**	**Results**	**Discussion/comments/checklist**
To assess the effect of optimal medical management in patients with asymptomatic carotid artery stenosis. **Conclusion** Intensive medical therapy results in lower incidence of ischemic stroke (IS), transient ischemic attack (TIA), carotid revascularization (CRV and progression of severity of carotid stenosis (PSCS) **Country** USA **Year of data sampling** 2017	**Population** Patients who underwent carotid duplex ultrasound (DUS) from January 2001 to December 2014 with at least moderate carotid artery stenosis, asymptomatic at the time of diagnosis, at least three DUS during the study period. Patients with history of CRV were excluded. Data was collected through detailed manual chart review of patients' electronic patient journals. **Main endpoint** Primary endpoints were IS/TIA, CRV and PSCS. **Statistical analysis** The study cohort was divided into sub-groups based on the number of risk factors controlled and the annual incidence of IS/TIA and CRV in addition to PSCS was compared. Student t test, chi-square, or Fisher exact test was used as appropriate. Multivariate analysis was performed and variables with p<20 in the univariate analysis was included.	A total of 864 patients were included. In the univariate analysis LDL > 100mg/dL and low potency statins were significantly associated with higher risk of IS/TIA/CRV. LDL > 100mg/dL, no or low potency statin use and history of smoking was associated with PSCS. A progressive decrease in risk of IS/TIA/CRV and PSCS was seen with the number of factors controlled.	• **Is the aim of the study clearly formulated?** Yes. • **Were the exposed individuals representative for a defined population?** Yes • **Were the exposure and end points measured similarly and in a reliable way?** Yes • **Were the study personnel blinded?** No • **Was the study prospective?** No • **Were all participants accounted for at the end of the study?** Yes. The study was retrospective. • **Was time of follow-up sufficient to detect positive and/or negative outcomes?** Yes. • **Are important confounding factors accounted for?** Yes. • **Can the results of the study be transferred to the general population?** Yes. • **Were all relevant outcomes assessed?** Yes. • **Are the results supported by available evidence?** Yes. • **What do the results mean for clinical practice?** This study showed that optimal medical treatment is important in patients with asymptomatic carotid artery stenosis. **Strengths:** No strengths mentioned. **Limitations:** Retrospective study with inherent limitations. Not able to establish the current smoking status on all patients. Diabetic control status was not available for all patients.

<table>
<tr><td colspan="3">Reference: Dua A, Patel B, Kuy S, Seabrook GR, Tondravi N, Brown KR, et al. Asymptomatic 50% to 75% internal carotid artery stenosis in 288 patients: risk factors for disease progression and ipsilateral neurological symptoms. Perspect Vasc Surg Endovasc Ther. 2012;24(4):165-70.</td><td colspan="2">Study design: Retrospective observational study
Grade quality ⊕⊕</td></tr>
<tr><td>Aim</td><td>Material and methods</td><td>Results</td><td colspan="2">Discussion/comments/checklist</td></tr>
<tr><td>To assess risk factors for disease progression and ipsilateral neurological symptoms among patients with asymptomatic moderate carotid artery stenosis.
Conclusion
Male gender, coronary artery disease, hyperlipidemia and hypertension are risk factors for disease progression and ipsilateral neurological symptoms.
Country
USA
Year of data sampling
2008</td><td>Population
All patients evaluated from 1. January 2008 to 31. December 2008 with 50-75% carotid artery stenosis on duplex ultrasound and no prior history of neurovascular symptoms were included. Patients were evaluated at 6- or 12-months interval. The data was analyzed retrospectively.

Main endpoint
Disease progression to severe stenosis, ipsilateral event such as TIA, amaurosis fugax or stroke.

Statistical analysis
Descriptive statistics and fisher’s exact test to determine significance in the univariate analysis.</td><td>A total of 288 patients were included. Coronary artery disease, hyperlipidemia and hypertension was associated with increased incidence of disease progression and ipsilateral neurological events ($p<0.05$). Specific p-values are not provided.</td><td colspan="2">• Is the aim of the study clearly formulated? Yes.
• Were the exposed individuals representative for a defined population? Yes.
• Were the study personnel blinded? No
• Was the study prospective? No.
• Were all participants accounted for at the end of the study? Yes. The study was retrospective.
• Was time of follow-up sufficient to detect positive and/or negative outcomes? Yes.
• Are important confounding factors accounted for? No.
• Can the results of the study be transferred to the general population? Yes.
• Were all relevant outcomes assessed? Yes.
• Are the results supported by available evidence? Yes.
• What do the results mean for clinical practice? The results show the importance of controlling for modifiable risk factors in this group of patients.
Strengths: No strengths mentioned.
Limitations: Retrospective design, lack of cohort comparison and small number of patients with disease progression.</td></tr>
</table>

<table>
<tr><td colspan="3">Reference: Kvistad CE, Logallo N, Oygarden H, Thomassen L, Waje-Andreassen U, Naess H. Elevated admission blood pressure and stroke severity in acute ischemic stroke: the Bergen NORSTROKE Study. Cerebrovasc Dis. 2013;36(5-6):351-4.</td><td>Study design: Retrospective observational study
Grade quality ⊕⊕</td></tr>
<tr><td>Purpose</td><td>Material and methods</td><td>Results</td><td>Discussion and comments</td></tr>
<tr><td>Assess the relationship between admission blood pressure and severity of stroke in the acute phase of ischemic stroke.
Conclusion
Inverse relationship between elevated blood pressure and stroke severity.
Country
Norway
Year of data sampling
2013</td><td>Population
A total of 749 patients with ischemic stroke admitted to hospital <6 after onset of stroke were included in this study.
Main endpoint
A single blood pressure measurement was done immediately after admission. Elevated blood pressure was defined as systolic pressure > 140 mmHg or diastolic pressure > 90 mmHg. The severity of stroke on admission was assessed using National Institute of Health Stroke Scale (NIHSS). Mild, moderate and severe stroke was defined as NIHSS score <8, 8-14 and ≥ 15, respectively. Favorable short-term outcome was defined as modified Rankin Scale of 0 or 1 at day 7 or at discharge if discharged earlier.
Statistical analysis
Logistical regression was used to assess the relationship between severity of stroke and favorable outcome of stroke with blood pressure. Potential confounders from the univariate analysis were entered in the initial analysis and removed by backwards stepwise selection.</td><td>Patients with elevated blood pressure had a lower median NIHSS score on admission (p = 0.003), more frequently presented with mild stroke (p = 0.001) and less frequently with severe stroke (p = 0.001). No association was seen between elevated blood pressure and favorable short-term outcome (p=0.906).</td><td>• Is the aim of the study clearly formulated? Yes.
• Were the exposed individuals representative for a defined population? Yes.
• Were the study personnel blinded? No
• Was the study prospective? No.
• Were all participants accounted for at the end of the study? Yes. The study was retrospective.
• Was time of follow-up sufficient to detect positive and/or negative outcomes? Yes.
• Are important confounding factors accounted for? The results were adjusted for possible confounding factors.
• Can the results of the study be transferred to the general population? Yes.
• Were all relevant outcomes assessed? Yes.
• Are the results supported by available evidence? Yes.
• What do the results mean for clinical practice? This study suggests an inverse relationship between elevated blood pressure and stroke severity on admission.
Strengths: No strengths mentioned.
Limitations: BP was only measured one time in each patient, continuous variables were dichotomized, only short term outcome was obtained.</td></tr>
</table>