

# Blood pressure control in older patients with carotid artery stenosis

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## Abstract

Stroke is the second largest cause of European cardiovascular and total mortality, largely due to atherosclerotic carotid artery narrowing or thromboembolism consequent to internal carotid artery stenosis. Current therapeutic indications suggest lifestyle interventions (smoking cessation, healthy diet and physical activity), adequate control of LDL-cholesterol and glycemic balance. It is nonetheless established that the most important factors in preventing stroke are antiplatelet therapy and blood pressure regulation. In fact, many physiological parameters, including age, drugs' effects and especially systemic blood pressure, can be involved in maintaining cerebral blood flow through compensation for impairment of flow within carotid arteries. Many studies demonstrate the benefits of blood pressure lowering in terms of prevention of stroke, but there are conflicting data about a specific pressure target to achieve, with some evidence in favor of "the lower the better" idea, while other identifying a too low systolic blood pressure as a cause of cerebral ischemia worsening, especially in symptomatic patients. In summary, the available data suggest the need of a tailored blood pressure treatment without inflexible targets, according to the assessment of the cardiovascular risk of each patient, the benefits of an intensive antihypertensive therapy and the comorbidities-related response to the treatment.

## Introduction

Stroke is the second largest cause of cardiovascular and total mortality in Europe, responsible for more than 1.1 million deaths each year. Cerebrovascular diseases have a deep impact not only on mortality but also on morbidity since they are the main cause of permanent neuro-

logical disability, especially in aging population. Moreover, in the past two decades the absolute incidence has globally risen while the mortality rates from stroke have decreased, thus increasing the costs of caring for stroke survivors. This high burden of stroke-related health-care costs is constantly increasing and will represent in the next years a major challenge. Thus, in a period of increasing costs of health care and aging populations it is even more important to encourage primary and secondary prevention, in order to reduce both the development of disease in healthy people and the occurrence of life-threatening events in those with established disease.

A large part of ischemic stroke is thought to be due to atherosclerotic narrowing of the carotid artery, and 10-15% of the events follow thromboembolism from a marked internal carotid artery stenosis (50-99%), which may have been suitable for carotid revascularization. The main pathophysiological mechanism underlying ischemia is in fact attributed to thromboembolism, but the hemodynamic consequences of narrowing of the vessel lumen can also result in cerebral hypoperfusion and may even potentiate the effects of distal embolization [1,2].

## Current treatment options

Early treatment of carotid stenosis, with effective medical therapies, or with careful choice of carotid endarterectomy or stenting for those with established severe disease, has the potential to prevent or delay the occurrence of many strokes. Current indications, according to the 2017 ESC guidelines on peripheral arterial disease (PAD), are in favor of lifestyle interventions, such as smoking cessation, healthy diet and physical activity, in addition to the relevant reduction of LDL-cholesterol and maintenance of glycemic control in diabetic patients. However, it is established that the most important factors in reducing the risk of stroke (first episode and recurrent events) are antiplatelet therapy and blood pressure control [3]. Hence, in patients with symptomatic carotid stenosis, long-term single anti platelet therapy (SAPT) is usually recommended, while dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is recommended for at least 1 month after Carotid Artery Stenting (CAS). In patients with asymptomatic >50% carotid artery stenosis, long-term antiplatelet therapy (commonly low-dose aspirin) should be considered when the bleeding risk is low. Regarding blood pressure control, the ESC guidelines recommendation is to keep systolic level under 140 mmHg and diastolic level under 90 mmHg, using Angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) as first-line therapy, as they have shown an efficacy in delaying plaque progression [4,2].

What kind of patients could benefit most from an early or intensive treatment? Clinical trials have shown that a higher degree of stenosis is associated with increased stroke risk, but the severity of the plaque is not the only factor to consider in early treatment decision because the presence of symptoms correlates with a higher risk, too.

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## Clinical trials

The hemodynamic effects of extracranial carotid stenosis on intracranial blood flow are in fact not well defined. Based on the results of a small trial of 44 patients, percentage stenosis and residual lumen were significantly associated with internal carotid artery flow (ICA) but not middle cerebral artery flow (MCA), suggesting that collateral pathways can provide intracranial compensation for impairment of flow within the ICA. This can be affected by physiological parameters, including age, blood pressure, and drugs' effects. Moreover, MCA flow ratio was significantly lower in symptomatic patients compared with asymptomatic ones, highlighting the potential importance of distal hemodynamics in ischemia [5].

In particular, it is well known that blood pressure has a leading importance in maintaining cerebral blood flow through the mechanism of autoregulation: the smooth muscle of arteries and arterioles constrict in response to increased pressure and dilate in response to decreased pressure (Bayliss effect), thus protecting smaller downstream vessels from damage due to changing perfusion pressures, and maintaining tissue perfusion during periods of decreased blood pressure. But, how much does systemic blood pressure influence intracranial blood flow and which is its burden on stroke risk? Is there a really safe target to be pursued?

For example, the blood pressure control through the use of ACE Inhibitors, like Perindopril, was analyzed in the Perindopril protection Against Recurrent Stroke Study (PROGRESS) trial [6]. This study demonstrated the benefits of blood pressure lowering in terms of secondary prevention of stroke.

In particular, in the population of patients with a history of cerebrovascular events, the reduction of ischemic risk with active blood pressure lowering treatment was statistically significant precisely in the large artery-related ischemic stroke, in contrast with cardio-embolic or lacunar ischemic stroke [7].

Conflicting data are available over the preferable blood pressure targets in patients with carotid artery atherosclerotic disease. The SPRINT trial has indicated a new possible threshold for the treatment of hypertension in patients with increased cardiovascular risk. This population included patients with: a 10-year risk of cardiovascular disease of 15% or greater based on Framingham risk score; an age of 75 years or older; chronic kidney disease; clinical or subclinical cardiovascular disease other than stroke, such as those with carotid stenosis [8].

Patients with diabetes mellitus and cerebrovascular disease were excluded. Wright *et al.* demonstrated a prognostic benefit of a target systolic blood pressure of less than 120 mmHg as compared to 140 mmHg in terms of cardiovascular events and death from any cause across all prespecified subgroups of the population. Obviously, higher rates of some adverse events, such as hypotension, syncope, electrolyte abnormalities and acute renal failure, occurred in the intensive treatment group than in the standard-one.

The findings of SPRINT trial were in contrast with the results of some previous trials. In particular, the ACCORD trial [9] did not provide evidence of cardiovascular and mortality benefits for lower systolic blood pressure target in patients with high cardiovascular risk, which included also those with anatomical evidence of a substantial amount of atherosclerosis.

However, these two studies differed in regard of the type of enrolled patients (exclusively participants with diabetes in the ACCORD trial), the sample size and the study design (the ACCORD trial considered comparison of standard and intensive glycemic and lipid treatment targets in the same analysis).

## Future perspectives

Recently a new concept of a proportional relative risk reduction according to the magnitude of the obtained blood pressure decrease has been introduced. The systematic review and meta-analysis of Ettehad *et al.* [10] suggested that every 10 mmHg reduction in systolic blood pressure resulted in a reduction of the risk of major cardiovascular disease by 20%, coronary heart disease by 17%, stroke by 27%, heart failure by 28% and death from any cause by 13%, regardless of baseline systolic blood pressure values. In fact, there was no evidence of a disappearance of the proportional effects in patients with lower baseline systolic blood pressure (<130 mmHg). Furthermore, these findings resulted to be powerful in various population of patients with or without history of cardiovascular disease at the baseline. The benefits of blood pressure lowering were similar regardless the baseline disease history. Subgroups of patients with diabetes or chronic kidney disease had a smaller, but significant, risk reduction in major cardiovascular disease events. Finally, also the choice of the antihypertensive drug seemed to influence the outcomes. For example,  $\beta$ -blockers were less effective in the prevention of major cardiovascular disease events, stroke and renal failure than the other medication, meanwhile calcium-channels blockers were superior to other drug classes for the prevention of stroke but inferior for the prevention of heart failure.

In summary, the available data suggest the need of a more individualized blood pressure treatment without inflexible blood pressure targets, according to the assessment of the cardiovascular risk of each patient, the benefits of an intensive antihypertensive therapy and the comorbidities-related adverse event or response to the treatment.

Finally, although carotid endarterectomy (CEA) seemed to be superior to medical therapy for the reduction in 5 to 10 years of the stroke risk [11,12], medical treatment is considered by the Society of Vascular Surgery (SVS) the preferred option for "high-risk for CEA" in asymptomatic carotid artery stenosis group [1]. In this population antihypertensive treatment resulted to be independent predictors of reduced risk of ipsilateral stroke and transient ischemic attack and of any stroke or cardiovascular death [3]. The correlation between anti-hypertensive drugs and ipsilateral stroke or TIA was mediated by blood pressure control.

Thus, how much should the pressure be lowered? Is the lower blood pressure the better? In a Japanese clinical study has been shown that in patients with impaired cerebral perfusion as demonstrated by PET-TC, the risk of recurrent stroke was higher with lower blood pressure (SBP<130 mmHg) [13]. In patients with impaired cerebral perfusion low systolic blood pressure may aggravate cerebral ischemia, while in patients with sufficient cerebral perfusion the risk may be lower with low blood pressure level. Other studies found that in the rare case of symptomatic bilateral significant carotid stenosis (>70%) the risk of cerebrovascular disease is significantly increased when SBP is lower than 140 mmHg; no increase in this risk was found in the case of unilateral significant carotid artery stenosis.

In the chronic phase of a cerebral infarction (1 month after the onset), the Japanese Society of Hypertension guidelines recommend to aim at a BP target of less than 140/90 mmHg avoiding excessive lowering in patients with marked stenosis of bilateral carotid stenosis or occlusion of a main trunk of cerebral arteries [14]. Especially, if the patient complains of symptoms of cerebral circulatory insufficiency during treatment (dizziness, light-headedness, weakness, exacerbation of neurological symptoms) a reduction in the dose or change in the type of antihypertensive drug is recommended.

This approach is consistent with the 2011 AHA guidelines, in which it is currently recommended to treat with antihypertensive drugs patients with extracranial carotid stenosis in order to obtain a blood pres-

sure below 140/90 mmHg. The benefit of antihypertensive drugs in the settings of symptomatic extracranial carotid stenosis is less demonstrated, thus a less stringent target blood pressure is recommended in these patients [15].

Finally, it is reasonable to affirm that lower blood pressure is better in every patients but those who have symptoms of exacerbating cerebral ischemia.

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