

Blood Pressure Control: Stroke and Stroke Prevention

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Abstract

Hypertension is the most important modifiable risk factor for primary and secondary stroke prevention.

All antihypertensive drugs are effective in primary prevention: the risk reduction for stroke is 30–42%. However, not all classes of drugs have the same effects: there is some indication that angiotensin receptor blockers may be superior to other classes of antihypertensive drugs in stroke prevention.

Seventy-five percent of patients who present to hospital with acute stroke have elevated blood pressure within the first 24–48 hours. Extremes of systolic blood pressure (SBP) increase the risk of death or dependency. The aim of treatment should be to achieve and maintain the SBP in the range 140–160 mmHg. However, fast and drastic blood pressure lowering can have adverse consequences.

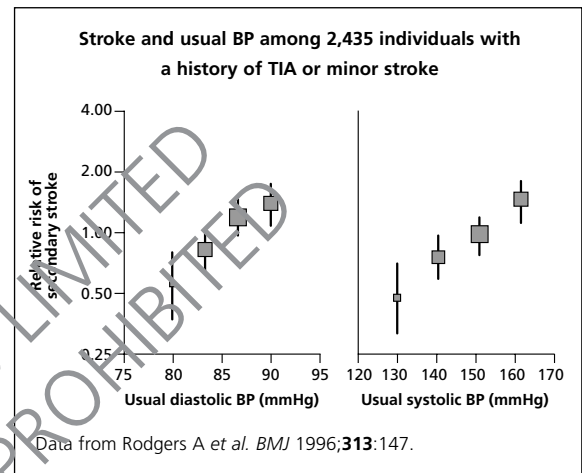
The PROGRESS trial of secondary prevention with perindopril ± indapamide versus placebo ± placebo showed a decrease in numbers of stroke recurrences in patients given both active antihypertensive agents more impressive for cerebral haemorrhage. There were also indications that active treatment might decrease the development of post-stroke dementia.

Introduction

Hypertension is the most important modifiable risk factor for stroke, and this holds true for both primary and secondary prevention. Figure 1 illustrates how the relative risk of a second stroke is related to increasing levels of both systolic and diastolic stroke in a study of 2,435 individuals with a history of transient ischaemic attack (TIA) or minor stroke. Despite this correlation, surveys show that many patients with high blood pressure (BP) are not given antihypertensive drugs and, of those who are treated, many are not well controlled.

Treatment of Hypertension in Primary Stroke Prevention

The meta-analysis by Collins and colleagues published in the *Lancet* in 1990 (335:827-39) considered the evidence from 14 prospective placebo-



Data from Rodgers A et al. *BMJ* 1996;313:147.

Figure 1

Continuous epidemiological relationship between blood pressure levels and recurrent stroke risk

controlled trials and included 37,000 patients. It showed convincingly that a relatively modest reduction in BP of 5.8 mmHg (achieved at that time by diuretics and beta-blockers) resulted in a 42% reduction in stroke probability. These results were so impressive that they spelled the end of antihypertensive trials conducted against placebo.

However, there are differences between antihypertensive drugs when it comes to reducing the risk of stroke. For example, part of the Antihypertensive and Lipid-Lowering treatment to prevent a Heart Attack Trial (ALLHAT) compared vascular events in 15,268 patients receiving diuretics versus 9,067 receiving the alpha receptor blocker doxazosin (*JAMA* 2000;283:1967-75). There was no difference in overall mortality or in mortality from vascular events and myocardial infarction but there was a significant difference in stroke risk (relative risk 1.14) in favour of diuretic treatment. For this reason, alpha blockers are not recommended as first-line antihypertensive agents.

The Blood Pressure Lowering Treatment Trialists' Collaboration examined the effects of different drug regimens on major cardiovascular events,

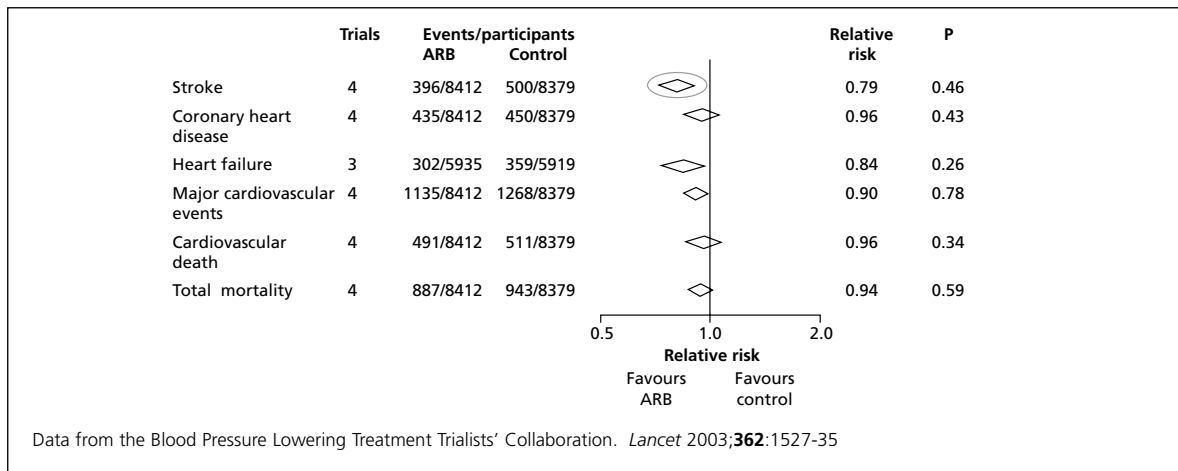


Figure 2
Some ARBs might be superior for stroke prevention

including stroke, in prospectively designed randomised trials (*Lancet* 2003;**362**:1527-35). All antihypertensive drugs are effective in primary prevention, and the relative risk reduction for stroke is 30–42%. Angiotensin-converting enzyme (ACE) inhibitors are clearly more effective than placebo in preventing stroke (relative risk [RR] 0.72), calcium channel blockers are more effective than placebo (RR 0.62) and more aggressive lowering is more effective than less aggressive lowering of BP (RR 0.77). There is a caveat, though, since too drastic lowering of the BP can worsen the patient's outcome.

There is some indication that the angiotensin receptor blockers (ARBs) may be superior to other drugs in stroke prevention. Figure 2 indicates how ARB-based regimens compare with control regimens, emphasising that there are differences between the patterns obtained with respect to cerebrovascular and cardiovascular endpoints.

Comparison of regimens using different classes of antihypertensive agents revealed that there were some differences in stroke risk but that these were only of borderline significance. Regimes based on diuretics or beta-blockers performed slightly better than those based on ACE inhibitors; and regimes based on calcium channel blockers performed slightly better than those based on diuretics or beta-blockers or ACE inhibitors.

Blood Pressure in Acute Stroke

Seventy five percent of patients who present to hospital with acute stroke have elevated BP above 140/90 mmHg within the first 24–48 hours. Of these, only half are known hypertensives; the others develop high BP *de novo* as a result of their stroke. Further, more than 80% of people who present with intracerebral haemorrhage have elevated BP.

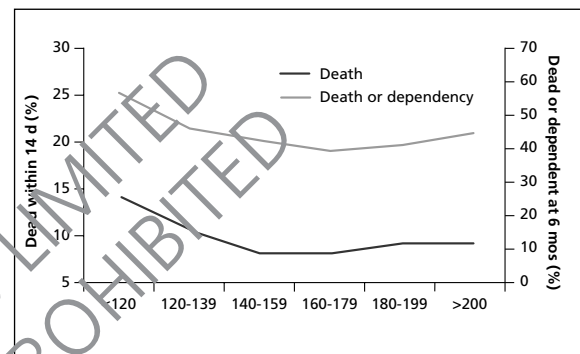


Figure 3
Influence of admission blood pressure on outcome International Stroke Trial (2002)

Results from the International Stroke Trial (Leonardi-Bee, *Stroke* 2002) – a trial whose purpose was to determine the influence of aspirin and heparin in acute stroke – are helpful in assessing how BP levels in acute stroke affect the outcome. The trial included 17,398 patients and found that systolic blood pressures (SBP) above 200 mmHg and below 120 mmHg on admission increased the chance of death and dependency (figure 3). Thus, the aim of treatment should be to achieve and maintain the SBP within the range 140–160 mmHg.

Physicians should be aware that fast and drastic BP lowering in this situation has adverse consequences. In the Intravenous Nimodipine West European Stroke Trial (INWEST) study (*Cerebrovasc Dis* 1994;**44**:204-10), patients with acute ischaemic stroke were randomised to placebo or to nimodipine either 1 mg/hour or 2 mg/hour intravenously. (This study was designed to investigate the neuroprotective properties of nimodipine.) Results are shown in figure 4. With placebo there was a slow and mild drop in BP. By contrast, nimodipine, especially in the higher dose, gave a rapid and dramatic drop in BP. This clearly affects patient outcome, for the Barthel scores were far worse in patients who received nimodipine rather than placebo.

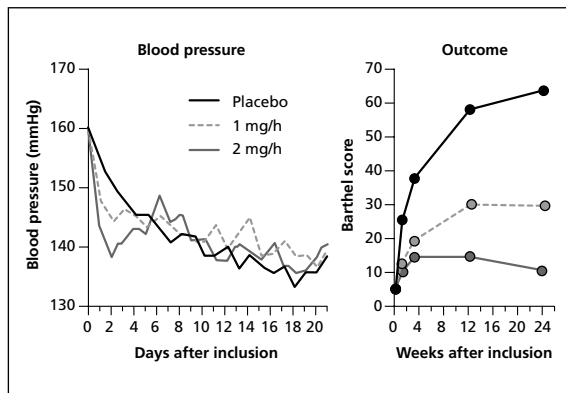


Figure 4
Blood pressure in the acute phase of stroke and outcome (INWEST-study)

Further information comes from the Acute Candesartan Cilexetil therapy in Stroke Survivors (ACCESS) trial, which was a safety trial to establish whether it was safe to give candesartan cilexetil in the acute phase of stroke to people with elevated BP. Patients were randomised to placebo or candesartan for the first seven days and then people in the placebo group were re-randomised if their BP was still high (*Stroke* 2003;**34**:1699-703).

There was a gradual fall in systolic and diastolic pressures in patients in the placebo group over the first seven days (figure 5), and exactly the same pattern was observed in patients who took candesartan. This pattern contrasts with the rapid drop in BP seen with nimodipine in INWEST. Interestingly, patients in the candesartan group had significantly fewer vascular events over three months than the people who initially received placebo. Thus, candesartan (and perhaps other ARBs) must have some biological activity that is nothing to do with lowering the BP.

The ACCESS trial was not powered to detect any effect on long term outcome but that is a critical question. Others include:

- Should existing antihypertensive medication be continued or discontinued in patients with acute stroke?
- What would be the effect of giving ARBs to acute stroke patients with a normal BP?
- What are the thresholds and targets for lowering and raising BP in acute stroke?

Treating Hypertension in Secondary Stroke Prevention

Until recently, there have been few data on secondary stroke prevention. The Individual Data Analysis of Antihypertensive intervention (INDANA) Project Collaborators Meta-analysis evaluated nine placebo-controlled trials that included a total of 6,752 patients (*Stroke* 1997; **28**:2557-62). Antihypertensive treatment was found to be effective in secondary prevention of stroke, with a relative risk reduction of 28%,

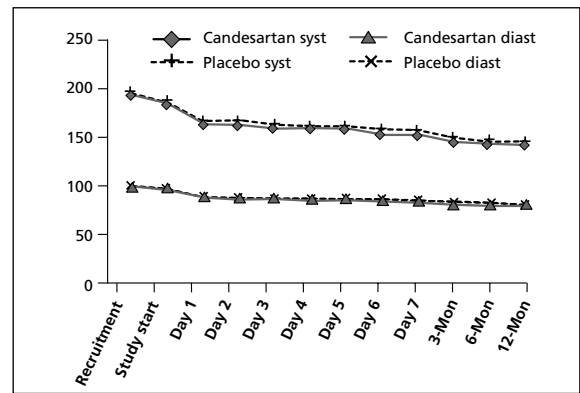


Figure 5
Blood pressure reductions in the ACCESS study

Table 1
Types of stroke observed in the PROGRESS trial, and relative risk reductions (RRR)

Type	RRR
Fatal or disabling	33%
Not fatal or disabling	24%
Ischaemic	24%
Cerebral haemorrhage	50%
Total	28%

$p=0.01$. This is a smaller risk reduction than that seen in primary stroke prevention (42%) but the figures are similar to those for primary prevention in that antihypertensive treatment has a greater effect on stroke than on MI (-12%, ns) and mortality rates (-14%, ns). This is related to the fact that the highest risk for an event following a stroke is for a second stroke, not an MI.

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a secondary prevention trial performed in patients who had already had a stroke (*Lancet* 2001;**358**:1033-41). They were given a perindopril run-in and then randomised to perindopril \pm indapamide or to placebo \pm placebo. Only those patients randomised to both active antihypertensive agents had a reduction in number of stroke recurrences. A subgroup analysis of the types of stroke observed in the trial was performed, and the results are shown in table 1.

Thus, cerebral haemorrhage was the type of stroke most effectively reduced by this dual ACE inhibitor and diuretic treatment regimen in the PROGRESS trial. This is an important finding since the prognosis of cerebral haemorrhage is much worse than that for cerebral thrombosis, with double the mortality rate.

