Primary stroke prevention and hypertension treatment: which is the first-line strategy?

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Abstract

Hypertension (HT) is considered the main classic vascular risk factor for stroke and the importance of lowering blood pressure (BP) is well established. However, not all the benefit of antihypertensive treatment is due to BP reduction *per se*, as the effect of reducing the risk of stroke differs among classes of antihypertensive agents. Extensive evidences support that angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), dihydropyridine calcium channel blockers (CCB) and thiazide diuretics each reduced risk of stroke compared with placebo or no treatment. Therefore, when combination therapy is required, a combination of these antihypertensive classes represents a logical approach. Despite the efficacy of antihypertensive therapy a large proportion of the population, still has undiagnosed or inadequately treated HT, and remain at high risk of stroke. In primary stroke prevention current guidelines recommend a systolic/diastolic BP goal of <140/<90 mmHg in the general population and <130/<80 mmHg in diabetics and in subjects with high cardiovascular risk and renal disease. The recent release in the market of the fixed-dose combination (FDC) of ACEI or ARB and CCB should provide a better control of BP. However to confirm the efficacy of the FDC in primary stroke prevention, clinical intervention trials are needed.

Introduction

Stroke is a leading cause of death and disability worldwide, exacting an enormous financial toll.[1] The total incidence of stroke is expected to increase considerably over the next two decades particularly in European Union where the estimated number of stroke events will increase to 1,500,000 by 2025.[2] Among the risk factors for stroke, epidemiological studies carried out in the past decades have definitely established that arterial hypertension (HT) is the main risk factor for stroke,[3,4] and that its disabling complications are directly associated to the severity of blood pressure (BP) increase.[5]

However, other evidences have been outlined that the risk of stroke associated with high BP values is not irreversible, as the risk of stroke incidence could be strongly reduced if BP values were controlled by and optimal antihypertensive treatment.[6] The latter is fundamental for stroke prevention as the early discontinuation of the anti-hypertensive treatment is associated with a 30% increase in risk of stroke.[7] In this respect all anti-hypertensive drugs classes may be useful in preventing stroke, but some of these may exert a cerebrovascular protection independently to their BP reduction.[6]

This paper reviews the role of HT as a risk factor for stroke, provides an update on which is the antihypertensive treatment recommended in primary stroke prevention and explores the potential efficacy of fixed-dose combination therapy in preventing stroke.

Hypertension and risk of stroke

Approximately 54% of strokes can be attributed worldwide to high BP values in both gender and in all ages.[4] As a consequence, hypertensive subjects are 3 to 4 times more likely to have a stroke than the normotensives.[8] In particular, it was established that a 2 mmHg rise in systolic BP in middle life is associated with 10% increase in risk of stroke.[9] In addition the relationship between BP and risk of first stroke is direct, continuous and independent, with the risk increasing continuously above a BP of 115/75 mmHg.[5]

Among BP components, many researchers have established a different role of systolic and diastolic on cerebrovascular risk, especially when diastolic is associated with high systolic levels. This association determines an increase of the pulsatile component of BP (pulse pressure, PP). The increase of PP is an age-related phenomenon[10] and it is commonly believed that PP is an indicator of large artery stiffness.[11] High PP is associated with higher incidence of carotid stenosis[12,13] and reduction in cerebral flow,[14,15] and is recognized as an independent predictors of stroke mortality[16,17] particularly in elderly people from general population.[18] In particular, 10 mmHg PP increases is associated with 11% increase in stroke.[19] Increase in systolic and decrease in diastolic BP results in high prevalence of isolated systolic hypertension (ISH), defined as systolic ≥140 with diastolic <90 mmHg. ISH is the most common form of HT in the elderly, and a major risk factor for stroke and cardiovascular

disease.[20] Large-scale placebo-controlled clinical trials have demonstrated the efficacy on stroke prevention of treating elderly with ISH.[21,22] However the studies of Langer *et al.*[23] and of Benetos *et al.*[24] showed higher stroke mortality in treated hypertensives having a prevalent decrease in diastolic. Low diastolic levels have been associated with increased coronary events, a phenomenon known as *the J-curve effect*.[25] Interestingly, this relationship was not observed for stroke and was not present among patients who had undergone coronary revascularization.[26] In contrast to the heart, the brain is very infrequently subjected to J-curve effect as the brain's blood flow autoregulation depends mostly on systolic BP.[27] This was confirmed by the results of the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study (ONTARGET), where no J-curve pattern did appear for stroke.[28] For the latter the assumption *the lower the systolic BP, the lower the risk* was correct, and it was confirmed in a meta-analysis by Staessen *et al.*[29] who found in treated and untreated elderly patients with ISH low systolic levels be associated with a strong benefit for stroke prevention.

Blood pressure targets to achieve in primary stroke prevention

Despite the overwhelming evidence that HT represents the first risk factor for stroke and that the cerebrovascular benefits the most from BP lowering, no randomized clinical trials provided a BP target for effective primary prevention of stroke.[30] Current international guidelines recommend a systolic/diastolic goal of <140/<90 mmHg in the general population and <130/<80 mmHg in diabetic subjects and in those with renal disease.[31,32] Whether a lower target has further benefits in primary

stroke prevention is uncertain. Although in a meta-analysis comparing trials with more-intensive than those with less-intensive targets of BP found a 23% reduced risk of stroke in the former than in the latter, the target <140/<90 mmHg was not achieved.[33] In the HOT study there was no difference in rates of stroke among groups of hypertensive patients who achieved mean diastolic values of 85.2, 83.2 or 81.1 mmHg.[34] For ISH, no trial has been performed. Finally, the investigators of the HYVET trial[35] provided evidence that antihypertensive treatment is beneficial also in the elderly and in very-elderly subjects (>80 years of age); the latter a group excluded from most other trials of antihypertensive therapy. The primary end point of HYVET was fatal or nonfatal stroke. At two years of follow-up, active treatment was associated with a 30% reduction in the rate of all strokes and a 39% reduction in the rate of death from fatal stroke. The greater reduction of risk was observed for a BP target of <150/<80 mmHg in treated patients over age 80, but the efficacy of further reductions in BP needs to be established.

What are the available evidences with renin angiotensin system blockade?

In the hypertensives, the renin angiotensin system (RAS) has been linked to the risk of stroke.[36,37] Therefore, it has been suggested that RAS blockade would provide a neuroprotective effect. In the literature studies with ACEI have produced different results in primary stroke prevention. In the Heart Outcomes Prevention Evaluation (HOPE) study, ramipril reduced all stroke by 32% and fatal stroke by 61% compared with placebo.[38] On the contrary, in the Captopril Prevention Project, fatal and nonfatal strokes were found to be more frequent in patients randomized to captopril than to conventional therapy.[39] In the ALLHAT, lisinopril was less effective in preventing stroke than diuretic therapy.[40] As a consequence, the common belief in that in clinical practice ACEI in primary stroke prevention it has yet to be fully confirmed. On the other hand, it has been well established that the inhibition of the negative effects of angiotensin in the cerebral circulation by ARB, determines a neuroprotective effect through the over activation of the AT2 receptors (*see below*). This observation comes from large clinical trials. In the LIFE study, that enrolled hypertensive patients with left ventricular hypertrophy, losartan significantly reduced the rate of fatal and nonfatal stroke by 25%.[41] In the SCOPE, candesartan-based treatment reduced non-fatal stroke by 30% and all stroke by 24% compared with placebo in elderly subjects.[42] In the JIKEI Heart study, the HTs receiving valsartan had a significant reduction

of stroke risk when compared with those not taking ARB.[43] Valsartan and other ARB appear to reduce the risk of stroke more than placebo in primary stroke prevention. This result was also confirmed in a meta-analysis of about 50,000 patients, where treatment with ARB were associated with a significant reduction of stroke risk (~8%) compared with ACEI.[44]

In conclusion the cerebrovascular benefits of ARB seem to be class-related rather than drug-related and in general all ARB might be used in primary stroke prevention.

Are there evidences with CCB?

Different studies have compared the effects of CCB vs. placebo or an active treatment for preventing stroke events.[45-47] In particular, nitrendipine-based treatment reduced the incidence of fatal and nonfatal stroke by 38%.[48] In the ACTION study, nifedipine GITS reduced the risk of any stroke or TIA by 30% compared with placebo in hypertensive patients whit high cardiovascular risk.[49] CCB have also been shown to provide better protection against fatal and nonfatal stroke than older drugs, such as β-blockers, diuretics and ACEI.[50,51] This has particularly been observed in a meta-analysis involving 4 trials, where CCB have been shown to provide benefit compared to ACEI.[52] In the ASCOT study, amlodipine reduced fatal and nonfatal stroke better than atenolol (+23%).[53,54] Moreover, the risk of stroke with amlodipine was statistically less when compared with non-ARB antihypertensive drugs and with ARB therapies separately.

What are the available evidences with diuretics?

In the literature, it is well known that diuretic therapy, particularly thiazide diuretics, reduced the risk of stroke compared to placebo or to no antihypertensive treatment.[55] This has particularly been observed in the elderly with ISH. In the Systolic Hypertension in the Elderly Program (SHEP) chlorthalidone caused a 36% reduction in the incidence of stroke.[56] The SHEP documented that the benefit of BP lowering therapy is maintained also in very elderly hypertensives aged ≥80 years.[57] Another meta-analysis found that diuretic therapy was superior to ACEI therapy,[58] particularly in blacks.[40] However, because of their lower tolerance and efficacy on regression of target organ damage compared with ARB, ACEI and CCB, in clinical practice diuretics are rarely used alone as first-line treatment for primary stroke prevention.

What is the mechanism of modulation of the pathophysiology of stroke by renin angiotensin system blockade and CCB?

Lowering BP is *per se* the most important determinant of stroke risk reduction.[59] This

has particularly been observed with CCB.[35] However this benefit appears in part independent of BP lowering.[54,60] The same result were been found with ARB, suggesting that these agents also have some BP-independent benefits. In experimental animal models, pre-treatment with an ARB at a sub-antihypertensive dose was more effective than an ACEI for reducing infarct size and neurological deficits following transient focal ischemia.[61]

The mechanisms by which CCB and ARB prevent stroke beyond BP reductions is unknown, although it is common belief that these antihypertensive drugs promote their protective action on stroke by reducing the progression towards the vascular and cardiac organ damage associated with hypertension.[62]

The increase of carotid intima-media thickness (IMT) is an independent risk factor of stroke[63] and it is well established that - despite comparable reductions in BP - CCB reduce IMT more than ACEI do.[64] This has particularly been observed in the INSIGHT study, where the hypertensives receiving nifedipine gastrointestinal-transport-system (GITS) had greater regression of IMT than those taking diuretic.[65]

In the same manner, ARB reduce IMT more than atenolol despite a similar effect on BP, an effect that seems to be mediated by improvements in nitric oxide production and decreases in oxidative stress.[66,67] Changes in central aortic pressure but not in peripheral BP could explain some differences between CCB and other antihypertensive drugs. In the CAFE study, despite comparable brachial pressures, amlodipine-based treatment reduced central systolic BP more than atenolol.[68] It has been suggested that heart rate is a major determinant of the difference between central and brachial BP, and might account for the less effective lowering of central BP with atenolol. As a consequence, in the CAFE study the effect on central BP and heart rate could explain some of the differences in stroke incidence between atenolol and amlodipine.

The increase of left ventricular mass is an independent risk factor for stroke.[6] In a meta-analysis, CCB and ARB were reported to reduce left ventricular mass index by 11% and 13%, respectively.[69]

There is evidence that antihypertensive treatment with ARB and ACEI prevents new-onset of non-valvular atrial fibrillation, a condition that is common in the hypertensives and associated with 5-fold increased risk of embolic stroke.[70] RAS blockade appears to reduce the incidence of stroke by 51% in patients with new-onset atrial fibrillation.[71] Although results obtained from the few clinical studies were mostly post-hoc analysis, the benefits in terms of stroke prevention seem to be superior in subjects with cardiac damage secondary to HT and with heart failure.[71-75]

Potential benefit of fixed-dose combination therapy

Despite the availability of a wide range of antihypertensive agents, almost two-thirds of the hypertensives fail to achieve the BP goals recommended by current ESH/ESC hypertension guidelines and have poorly controlled BP.[62] As a consequence, they remain at a high risk of morbid and fatal stroke and require effective treatment options. Sub-optimal BP control is often due to poor patient compliance and results in a significant health and economic burden. Numerous clinical trials have shown that most patients require at least two antihypertensive agents to achieve adequate BP control and associated significant reductions in stroke morbidity and mortality. Combination therapy using two drugs with different mechanisms of action achieves better efficacy and tolerability outcomes than treatment with either component drug alone. Furthermore, when this combination is administered as a fixed-dose combination, other benefits are achieved, such as an improved compliance and potentially lower costs of treatment. The good efficacy and tolerability of the fixed-dose of a CCB with an ACEI or an ARB is well established, and this combination is recommended in the reappraisal of the ESH/ESC guidelines as a first choice in high-risk hypertensive patients.[31] In clinical trials the fixed-dose combination improves BP to a greater extent than either drug as monotherapy and, when compared with antihypertensive mono-therapies, it may also offer equivalent or better efficacy and the same or improved tolerability. Therefore, fixed-dose combination has the potential to reduce both the risk of stroke and the non-drug healthcare costs associated with HT.

Direct neuroprotective benefit of the antihypertensive agents

As mentioned above, RAS blockade seems to determine a direct neuroprotective effect. This is particularly true for ARB, as it has been observed that angiotensin II induces cerebrovascular hypertrophy and remodelling, inhibits endothelium-dependent relaxation and disrupts the blood-brain barrier.[36] Two types of angiotensin II receptors have been implicated to explain this benefit.[76,77] Type 1 receptors, expressed in different tissues, induce vasoconstriction, sodium and water retention, smooth-muscle proliferation, and vascular endothelial damage, while type 2 receptors, expressed in fetal tissues and up-regulated in ischemic brain tissue, modulate the type 1 receptor activity reducing inflammation and neuronal apoptosis and inducing vasodilation, thereby mediating neuroprotective effect.

There is some evidence that ARB may provide greater reduction in the risk of stroke than diuretics, long-acting dihydropyridine CCB, ACEI and β-blockers despite similar reduction in BP.[78] This evidence has particularly been demonstrated with losartan vs. atenolol,[41] candesartan vs. hydroclothiazide [42] and eprosartan vs. nitrendipine[79] in clinical studies where the risk of stroke was low. However, the ONTARGET study was unable to show a significant reduction in stroke with telmisartan than ramipril.[28] In addition, CCB and ARB seem to have BP-independent effects on stroke in animal models, probably via a reduction of inflammation in cerebral microvessels,[80] protection of cerebral circulation (improving of cerebral blood flow auto-regulation) and reduction of superoxide production.[81,82] However, these data should be cautiously translated to humans, where these mechanisms have not been readily observed.

Conclusions

Hypertension remains the most important established and modifiable classic vascular risk factor for stroke, and antihypertensive treatment the most effective strategy for preventing stroke as well as other BP-related target organ damage. Reduction in BP is generally more important than the choice of specific agents, but some classes of antihypertensives offer direct neuroprotective benefit: those acting on RAS blockade, CCB and thiazide diuretics represent the three classes with the strongest effect in primary stroke prevention. The use of fixed-dose combination of these drugs may increase patient compliance and persistence to antihypertensive treatment. However further studies are required to evaluate the neuroprotective effect of FDC therapy in primary stroke prevention.[83]

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