HYPERTENSION

Antihypertensive class matters for combination therapy

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Combination therapy is used to lower blood pressure in the majority of patients with hypertension, yet there has been little evidence as to which classes of antihypertensive agents are most effective. The publication of findings from the ACCOMPLISH trial provides an opportunity to explore the merits of various combination therapies, with a focus on renal risk reduction.

Two or more antihypertensive agents are often required to achieve satisfactory control of blood pressure (BP), particularly in patients with severe hypertension, chronic kidney disease (CKD), coronary heart disease, or diabetes mellitus. For these individuals, the recommended target BP is <130/80 mmHg.[1,2] The results of the ACCOMPLISH trial[3] and ASCOT-BPLA[4] demonstrated the cardiovascular benefits of renin–angiotensin system (RAS) blockade combined with a calcium antagonist for patients with hypertension who have cardiovascular comorbidities. Bakris *et al.* have now evaluated whether a RAS blocker combined with a calcium antagonist may also have protective advantages for renal outcomes.[5]

> “...a RAS inhibitor with a calcium antagonist appears to be an appropriate, and even superior, choice...”

The ACCOMPLISH study[3] was an international trial involving 11,506 patients with hypertension who were at high-risk of cardiovascular events (systolic BP >160 mmHg, age >55 years, and a history of vascular disease, diabetes, CKD, or left ventricular hypertrophy). The reduction in the risk of a composite end point of major cardiovascular events was so substantial in the group treated with benazepril plus amlodipine, compared with those treated with benazepril plus hydrochlorothiazide, that the trial was stopped more than 2 years early. Bakris and colleagues assessed the effects of these drug combinations on the progression to CKD among participants of the ACCOMPLISH trial.[3,5] The prespecified CKD end point was the time to the first occurrence of the composite of doubling of serum creatinine concentration, end-stage renal disease (defined as an estimated glomerular filtration rate <15 ml/min/1.73 m^2), or chronic dialysis.

As noted above, the ACCOMPLISH trial was stopped early (mean 2.9 years follow-up).[3,5] At this time point, 113 patients (2.0%) in the benazepril plus amlodipine arm met the primary renal end point compared with 215 patients (3.7%) treated with the benazepril plus hydrochlorothiazide combination. Thus, there was an absolute risk reduction of 1.7% and a 48% relative reduction in risk for renal outcomes.[5] The investigators also calculated secondary combined end points of renal and cardiovascular death, as well as renal and all-cause mortality. Both of these combined end points were reduced with benazepril plus amlodipine compared with benazepril plus the diuretic. Among patients with CKD at baseline, progression of this disease did not differ significantly between the two treatment arms (4.8% in the benazepril plus amlodipine group versus 5.5% in the benazepril plus hydrochlorothiazide group). Notably, however, there was a significant beneficial effect on CKD progression in the 7,650 patients aged over 65 years. Among these older people, the benazepril plus amlodipine combination reduced the primary renal end point by 50%, with similar reductions in the doubling of serum creatinine concentrations and a 70% reduction in the need for chronic dialysis ($P = 0.053$). Of note, only a very small proportion of patients in this study had albuminuria, making an analysis of this subgroup impossible.

There are some other limitations to this new secondary analysis of the ACCOMPLISH trial.[5] The number of renal events was compromised by the fact that the study ended 2–3 years earlier than expected. Thus, the number of patients with end-stage renal disease and those requiring dialysis were quite small. Furthermore, in both the primary report from the ACCOMPLISH study[3] and the renal outcomes analysis,[5] the end points that drove the composite were ‘soft’. For example, in the primary cardiovascular end point, a reduction in angina and coronary revascularization was more prominent for the benazepril plus amlodipine treatment group than the reductions in myocardial infarctions, strokes, or cardiovascular deaths.[3] Similarly, in the renal outcomes analysis, doubling of serum creatinine was far more common than dialysis or development of end-stage renal disease.[5] While an increase in coronary vasodilation caused by amlodipine is likely to account for the findings for the primary cardiovascular end point, the mechanism for the renal outcomes benefit is not clear. The investigators do not believe that differences in BP can explain this benefit; however, for the first year of the study, the benazepril plus amlodipine group did have a somewhat lower systolic BP than did the benazepril plus hydrochlorothiazide group.[5]

The changes in renal function assessed by serum creatinine (rather than more precise measurements of glomerular filtration rate) have been proposed to be the result of reversible hemodynamic effects as opposed to permanent structural decline in the kidney.[6] However, the incidence of the two other end points—dialysis and end-stage renal failure—although small, also declined and approached significance for the older patient subgroup. Hence, the findings from the renal outcomes analysis of the ACCOMPLISH trial suggest that treatment with a calcium antagonist plus a RAS-inhibiting agent is more effective than a diuretic added to a

Table 1 | Hemodynamic data from the CAFE Study[7]

Parameter	Atenolol	Amlodipine	Mean difference (95% CI)	*P**
Brachial artery pressures				
Brachial SBP (mean mmHg)	133.9	133.2	0.7 (–0.4–1.7)	0.2
Brachial DBP (mean mmHg)	78.6	76.9	1.6 (0.9–2.4)	<0.0001
Brachial PP (mean mmHg)	55.3	56.2	–0.9 (–1.9–0)	0.06
Heart rate (mean bpm)	58.6	69.3	–10.7 (–11.5 to –9.8)	<0.0001
Central aortic pressures				
Central SBP (mean mmHg)	125.5	121.2	4.3 (3.3–5.4)	<0.0001
Central PP (mean mmHg)	46.4	43.4	3.0 (2.1–3.9)	<0.0001

*t-test. Abbreviations: DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

RAS inhibitor to prevent harm to the kidney as well as the heart.

To date, two major trials have demonstrated similar clinical outcome benefits for a RAS inhibitor plus dihydropyridine calcium antagonist, but the mechanism for this effect is not clear. In ASCOT-BPLA,[4] the incidence of most of the cardiovascular end points—including stroke mortality—was lower in patients who received perindopril plus amlodipine compared with those taking atenolol and a thiazide diuretic. Similarly, in the ACCOMPLISH trial,[3,5] there were fewer occurrences of the cardiovascular and renal end points with benazepril plus amlodipine than with benazepril plus hydrochlorothiazide. In both of these major studies, control of systolic BP was marginally better with the RAS inhibitor plus calcium antagonist combination therapy, but the reduction in BP was not great enough to explain the substantial benefits in the primary and secondary outcomes.

A substudy of ASCOT, known as the CAFE study,[7] demonstrated that a RAS inhibitor plus amlodipine had a larger impact over time on arterial stiffness—manifested by a greater reduction in the central, large artery pressure—than did a β-blocker plus a diuretic (Table 1). Remodeling of arterial structure with reduced large artery resistance was proposed as a mechanism for improvement in cardiovascular outcomes.[7] Whether this effect on larger arteries could translate to a benefit for the renal circulation as well has not been studied.

The highly effective antihypertensive combination of a RAS inhibitor with a dihydropyridine calcium antagonist has been recognized for 25 years.[8] However, until the completion of ASCOT[4] and the ACCOMPLISH trials,[3,5] the use of a nondiuretic-based combination therapy regimen was not widely recommended in guidelines.[1,2] On the basis of the findings from the ACCOMPLISH studies,[3,5] the combination of a RAS inhibitor with a calcium antagonist appears to be an appropriate, and even superior, choice for the treatment of high-risk patients with hypertension.

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Competing interests
The author declares associations with the following companies and organizations: Abbott, Astellas, Forest Laboratories, NicOx, the NIH, Novartis, Roche, and Takeda. See the article online for full details of the relationships.

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CEREBROVASCULAR DISEASE

Carotid endarterectomy versus stenting—long live the king?

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Carotid endarterectomy (CEA) is considered the gold standard for treatment of stenosis, but carotid artery stenting (CAS) is a less invasive procedure that offers a promising alternative. Short-term data from ICASS suggest that CEA is superior to CAS; however, features of the study design may have affected the results, and long-term data are needed before conclusions can be made.

Over the past decade, carotid artery stenting (CAS) with distal protection has become an important alternative to carotid endarterectomy (CEA), particularly in high-risk patients, such as elderly individuals (>80 years of age) or those with serious heart disease. CAS in this population—which is currently the only FDA-approved indication for this procedure—is not inferior to CEA in the short-term[1] or long-term.[2] However, evidence to support the use of CAS in a broad population is lacking. The results of the largest multicenter, randomized trial to directly compare the safety of CAS with CEA in symptomatic patients (International Carotid Stenting Study [ICSS])[3] are highly anticipated. The interim safety data from this trial have now been reported in the *Lancet*.[3]

Although the primary end point of fatal or disabling stroke in any territory at 3 years has not yet been reached, this analysis at 120 days from randomization of 1,710 patients (CAS, $n = 853$ versus CEA, $n = 857$) demonstrated an 8.5% incidence of stroke,