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Synergy of antihypertensives in elderly patients with CKD

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Abstract

A recent study reports that the combination of an angiotensin-receptor blocker (ARB) and a calcium-channel blocker (versus a high-dose ARB) is associated with improved blood pressure control and reduced cardiovascular, cerebrovascular and heart failure events in an elderly chronic kidney disease population. This finding raises the possibility of using fixed-dose drug combinations to improve efficacy and compliance of antihypertensive medications.

The 2011 American College of Cardiology Foundation and American Heart Association consensus statement recommends that blood pressure is controlled to a goal of <140/90 mmHg in the elderly population if no complicating conditions are present.¹ However, blood pressure control in elderly patients is challenging, in part due to age-related alterations in drug distribution and metabolism, age-related decline in renal function and quality-of-life issues. Equally challenging is the control of blood pressure in chronic kidney disease (CKD) populations. Kim-Mitsuyama *et al.* integrated these two patient populations in the multicentre Japanese OSCAR study.² The OSCAR study was a prospective, randomized, open-label, blinded end point evaluation of 1,164 elderly (aged 65–84 years) Japanese patients with hypertension and cardiovascular disease and/or diabetes at baseline. After a run-in period where all patients received the angiotensin-receptor blocker (ARB) olmesartan at a standard dose of 20 mg per day, patients not achieving blood pressure control were randomly assigned to a doubled dose of olmesartan or to the standard dose of olmesartan in combination with a calcium-channel blocker (CCB; amlodipine or azelnidipine). Patients were followed up for 3 years.

The investigators have now published a subgroup analysis of the OSCAR study with patients categorized according to their baseline estimated glomerular filtration rate (eGFR).² Overall, a greater proportion of patients receiving the combination of an ARB plus a CCB achieved the target blood pressure of 140/90 mmHg, compared with the group receiving a high dose of a single ARB, in both CKD and non-CKD populations. In addition, patients on combination therapy had less need for additional antihypertensive medications, and when

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Competing interests

The authors declare no competing interests.

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such medications were necessary, the number of additional medications was lower. In individuals with CKD (defined as baseline eGFR <60 ml/min/1.73 m²), the incidence of primary events (a composite of cardiovascular and noncardiovascular death) was significantly greater in the high-dose ARB group than in the combination group (30 versus 16, respectively, hazard ratio 2.25). Kim-Mitsuyama *et al.* further observed that in patients with CKD, significantly more cerebrovascular and heart failure events occurred in the high-dose ARB group than in the combination group. Importantly, the presence of CKD contributed to these differences as demonstrated by treatment-by-subgroup analysis. Among patients without CKD, no differences in the incidence of primary events were seen between the two treatment groups. The authors conclude that the combination of a standard dose of an ARB plus a CCB provided better protection against cardiovascular events in patients with CKD than did a high dose of an ARB alone.

Why are these findings important? Evidence has accumulated over the years showing that good blood pressure control is important in the elderly population in terms of improving cardiovascular outcomes and slowing progression of CKD.^{1,2} Elderly patients who have CKD add an additional dimension of complexity to blood pressure control because tight control—especially in the setting of high doses of ARBs—can lead to a reduction in glomerular filtration rate, perhaps owing to efferent arteriolar dilatation. Hence, it is important to find alternative strategies to control blood pressure in the elderly CKD population.

Recent evidence from non-CKD populations shows that combination therapies may be superior to treatment with high doses of a single ARB owing to factors including—but not restricted to—improved efficacy, reduced drug-related adverse events and improved compliance.³ In this regard, several studies have shown support for the use of an ARB and an angiotensin-converting-enzyme (ACE) inhibitor in concert with a calcium antagonist, without a substantial increase in the dose and toxicity profile of these drugs (see Supplementary Table 1 online). Recent trials such as ACCOMPLISH, CARTER and EXTRA trials have gone further to show the efficacy of certain drug combinations over others in improving blood pressure and kidney parameters in select groups of patients (Supplementary Table 1 online). The reasons for CCBs being chosen as a component of the combination strategy are severalfold. Firstly, CCBs are arterial vasodilators as opposed to venous vasodilators. It is well recognized that elderly patients and those with CKD have stiff arteries that contribute to systolic hypertension and CCBs are well positioned to dilate these stiffened arteries. Secondly, CCBs may decrease arteriolar hypertrophy and decrease the amplitude of pulse wave reflections, thereby lowering blood pressure in a similar way to ARBs and ACE inhibitors but differently to diuretics and β -blockers.⁴ Furthermore, CCBs have additional effects on blood pressure via lowering pulse wave velocity and augmentation index. In addition, combination with an ARB improves the side effect of peripheral oedema associated with CCBs.⁵ From a theoretical standpoint, by blocking the L-type calcium channel, CCBs may improve calcium handling via SERCA2a in the vasculature and the heart.⁶ Improved calcium handling may, in turn, lead to improvements in diastolic and systolic function of the heart, improve vascular relaxation and may even improve proximal tubule function.^{7,8}

Besides the obvious benefits of combination therapy on blood pressure, other findings in the OSCAR study are also of interest. Firstly, the finding of a lower incidence of secondary end points such as cerebrovascular disease and heart failure in the CKD group, which might be explained by the observation in a recent report that combination therapy with CCBs improves diuresis.⁵ Secondly, although the study authors concluded that there was no difference in eGFR decline between the high-dose ARB group and the ARB plus CCB combination group, a trend towards a lower eGFR in the high-dose ARB group was seen at the end of the study; this finding would be consistent with the notion that high-dose ARBs may lower eGFR by reducing the efferent arteriolar tone. In patients without CKD, the incidence of primary events was lower in the high-dose ARB group, although this result was not significant, suggesting that high-dose ARBs could still be useful in this subset of elderly hypertensive patients. Thirdly, although high-dose olmesartan was associated with a trend towards decreasing eGFR in these elderly patients with and without CKD, no significant potassium increases were observed in the patients with CKD on high-dose olmesartan. This observation is somewhat unexpected and may be a result of the low-potassium diet of the patients and/or the fact that eGFR was still in the upper range for CKD.³

Future studies should consider not only the new observations, but also some of the shortcomings of the OSCAR study. For example, urinary albumin-to-creatinine ratio (UACR) was not measured even though it is an important prognostic indicator of morbidity and mortality in CKD and cardiovascular disease. In addition, there was no estimation of sodium intake, which can influence UACR and affect blood pressure control. The researchers also found that male gender, age and previous cardiovascular disease were associated with primary outcome events. The CKD group had greater baseline cardiovascular disease, more male patients and an older average age than the non-CKD group, and although the majority of the patients had stage 3 CKD, it is not known whether a greater number of patients with stage 4 CKD were allocated to the high-dose ARB group during randomization. The findings from Kim-Mitsuyama *et al.* cannot be extrapolated to the hypertensive African American population—another salt-sensitive group that has shown good blood pressure reductions on CCBs.⁹ In addition, it is unclear what doses of amlodipine and azelnidipine were administered in the study group and whether azelnidipine was preferentially used versus amlodipine. This point may be important as azelnidipine might have additional antioxidant and aldosterone-lowering properties over amlodipine and decrease both afferent and efferent arteriolar tone.¹⁰

In conclusion, the OSCAR study—despite its limitations—has advanced our understanding of the use of combination antihypertensives in an elderly CKD population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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