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The use of diuretics plus calcium channel blockers for hypertension may be associated with a higher risk of myocardial infarction but not stroke compared with the combination of diuretics plus β blockers

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Uncontrolled hypertension remains a problem

The primary reason for treating hypertension is to reduce the risk for cardiovascular (CV) adverse outcomes while achieving guideline recommended goal blood pressure (BP), which usually requires multiple medications from different antihypertensive classes. Yet epidemiologic data indicate that fewer than 50% of patients achieve guideline recommended goals so associated morbidity and mortality remains high. The relative contributions to lack of BP control and elevated outcome rate among inadequacies of a particular antihypertensive regimen (agent or class), physician inertia with dose titration or drug addition and patient non-adherence with a prescribed drug regimen and life style modifications, are unclear.

Observational study attempts to determine best antihypertensive drug combo

To address the first possibility, Boger-Megiddo and colleagues suggest there may be outcome differences based on antihypertensive regimen employed. The study utilised a case (n=353) control (n=952) design to assess outcomes in a low risk hypertensive population in a managed care setting. The investigators focused on antihypertensive regimens led by a diuretic (usually a thiazides diuretic) with either a β blocker, renin angiotensin system blocker or calcium antagonist (CA) as added therapy.

Disappointingly, BP control (<140/90 mm Hg) was observed in fewer than 50% overall, and cases in the diuretic plus CA group had the highest mean BP. There was a higher risk for myocardial infarction (MI) in the diuretic plus CA group (odds ratio 1.98, 95% CI 1.37 to 2.87) but not for stroke. This increased risk appeared associated with dose of CA, as the risk for MI was greater only in the very small cohort (n=23) receiving the highest dose of CA.

Was the study design adequate to address the research question?

This is not the first study using a case-control design from these authors questioning CA efficacy for hypertension associated CV risk reduction. And as with their previous research, this work has several critical limitations. First, the research question posed cannot be adequately answered with a case-control design, which requires many assumptions about

important aspects of patient care, including adherence with prescribed antihypertensive therapies, ongoing, undiagnosed medical conditions that may have influenced outcomes (eg, coronary artery disease) and interim BP control. We and others have demonstrated that duration of BP control is strongly associated with improved outcomes, yet the design did not include adjustment for any follow-up BP measure (average over years of follow-up or at a single time point). Second, they used a case population with fewer than 100 cases in two of the three comparator groups, which increases chance findings. Third, the observed <50% BP control rates are not consistent with many contemporary clinical trials and are surprising from a dedicated hypertension clinic. Lastly, and perhaps most importantly, the type of CA prescribed is not well described. These authors have previously associated increased adverse outcomes with rapid release, short acting CAs and extrapolated the risk to the CA class due to lack of evidence otherwise. As a result, use of short acting CAs has fallen out of favour for treating hypertension. Yet one third of the cases in the CA group received the short acting version of verapamil (n=35), while the specific CA used in over half the cases is not mentioned, suggesting the findings reported simply extend what we already know – short acting CAs should not be used for long term treatment of hypertension.

Prospective, randomised data refute findings

Data from several large, contemporary, randomised clinical trials in similar or higher risk hypertensive populations using long acting CAs refute the findings from this study. Long acting verapamil^{1 2} and amlodipine^{3–6} studied in over 50 000 patients collectively for outcomes including MI, stroke and mortality, (usually also including either a thiazide diuretic or an angiotensin converting enzyme (ACE) inhibitor) were either equivalent to^{1 2 4} or superior to^{3 5 6} the comparator which consisted of combination regimens primarily of a thiazide diuretic, β blocker or ACE inhibitors. In several trials^{1 2} where BP reduction and control was the same in the randomised treatment groups, outcomes were also the same. In several others^{3 5 6} BP reduction was superior in the CA group. In another trial⁴ BP reduction and control was best in the thiazide diuretic group, yet outcomes were not superior in this group. Also data with amlodipine indicates that the CA regimen reduced BP variability to a greater extent than the β blocker regimen and this reduced variability was associated with reduced risk for stroke.

Results should not influence clinical practice

Data from this study should not be used to rethink clinical practice patterns. The overwhelming strength of available evidence strongly supports continued use of long acting CAs for BP control and reduction of CV morbidity and mortality in lower risk and high risk populations, including older people, and those with diabetes.

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