Title	Calcium channel blockers revisited
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Citation	Hong Kong Medical Journal, 2002, v. 8 n. 4, p. 300-301
Issued Date	2002
URL	http://hdl.handle.net/10722/45135
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Calcium channel blockers revisited

Calcium channel blockers (CCBs) are a major class of drugs used in the treatment of hypertension, angina, and cardiac arrhythmias. Among the CCBs, there is much heterogeneity in terms of their effect on heart rate, cardiac contractility, peripheral vascular tone, and with respect to half-life. The CCBs can be broadly divided into the dihydropyridines (eg nifedipine) and the non-dihydropyridines (eg verapamil). Short-acting dihydropyridines, such as immediate-release nifedipine, cause a rapid decrease in blood pressure and a reflex tachycardia as they do not suppress heart rate. Long-acting formulations and CCBs with longer half-lives were thus developed to overcome large fluctuations in blood pressure.

Although CCBs are undoubtedly effective in lowering blood pressure, until the last few years, there have not been substantial clinical outcome data demonstrating their impact on cardiovascular events. Indeed, earlier case-control studies from Furberg et al[1] and others raised doubts about the safety of this class of drugs,[1-4] which were approved and marketed on the basis of their effect on blood pressure as a surrogate end-point. These studies suggested that CCBs were associated with increased risk of myocardial infarction,[1] cancer,[2] and gastrointestinal haemorrhage.[3] The lack of prospective data from large clinical trials meant that these doubts were hard to dismiss.

Fortunately, in the last few years, several important clinical trials—STONE (Shanghai Trial of Nifedipine in the Elderly),[5] Syst-Eur (The Systolic Hypertension in Europe),[6] and Syst-China (Systolic Hypertension in China)[7]—involving CCBs, have been completed and published. On the whole, these have been reassuring with regard to the safety of CCBs. The incidence of strokes was reduced in these trials. The major question is, however, not whether CCBs are better than placebo, since diuretics and beta-blockers are already proven therapy for hypertension, but whether or not CCBs are equivalent to diuretics and beta-blockers. The STOP-2 (Swedish Trial in Old Patients with Hypertension-2 study),[8] NORDIL (Nordic Diltiazem study),[9] and INSIGHT (Intervention as a Goal in Hypertension Treatment[10]) trials addressed this question with head-to-head comparisons of drug classes. In essence, CCBs were not shown to be significantly better or worse than older treatments. Whilst CCBs have been vindicated to a large extent, the fact is that they tend to be more expensive than diuretics and beta-blockers. From a public health perspective therefore, one must question whether it is justifiable to prescribe CCBs rather than cheaper, older treatments.

The WHO-ISH (World Health Organization-International Society of Hypertension) guidelines on the management of hypertension published in 1999 endorsed the use of any of six classes of antihypertensive drugs, including CCBs, as first-line agents.[11] This differs from the American Joint National Committee-VI guidelines which continue to recommend diuretics and beta-blockers as first-line treatment because of their demonstrated efficacy in numerous trials.[12] Pooling recent clinical trials involving comparisons of CCBs with other classes have shown a disturbing pattern.[13,14] Whereas CCBs appeared slightly superior to angiotensin-converting enzyme inhibitors (ACEIs) in the prevention of strokes, and no difference in overall mortality between the two classes was seen, CCBs appeared notably inferior to ACEIs in the prevention of coronary events.[13] These findings are consistent with the demonstrated beneficial effect of beta-blockers and ACEIs after myocardial infarction and in heart failure, and the failure to demonstrate such benefits of CCBs. This has led to the suggestion that CCBs should not be the first choice in patients at cardiovascular risk unless multiple drugs are needed to control their blood pressure.[15]

In this new decade, things have turned full circle. Although CCBs regained favour when the placebo-controlled trials were completed, with more clinical trial data comparing different antihypertensive drug classes, they have been found wanting. Interestingly, alpha-blockers have also emerged as inferior agents to diuretics in the ALLHAT (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study.[16]

Though there was 'more heat than light' in the debate over CCBs a few years ago, we now have hard clinical evidence on which to base our judgements. From the clinician's point of view, CCBs will continue to be useful for those patients primarily at risk of stroke rather than coronary heart disease, and for those with severe hypertension requiring combination therapy. For those with mild hypertension requiring monotherapy, diuretics and beta-blockers are proven and very cost-effective treatments; they should be used unless contraindicated or not tolerated by the patient. Angiotensin-converting enzyme inhibitors should be considered, especially in the light of the HOPE (Heart Outcomes Prevention Evaluation) study,[17] for patients who have coronary artery disease, cerebrovascular disease, peripheral vascular disease, or diabetes mellitus with at least one other risk factor.

In the Far East where strokes are common and coronary heart disease is less prevalent than in Caucasian populations, the benefits of CCBs may be more pronounced. In terms of lowering of blood pressure, CCBs are very effective for Chinese patients.[18-20] There has been a trend towards lower blood pressure treatment targets, especially in patients with diabetes or nephropathy.[11,12] The best way of optimising blood pressure control is to use a combination

of antihypertensive drugs. In this clinical scenario, CCBs are useful and safe agents.

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