Is amlodipine more cardioprotective than other antihypertensive drug classes?

Chang Gyu Park

Cardiovascular disease (CVD) is the leading cause of death in industrialized countries [1,2]. Approximately half of all CVD deaths are from coronary artery disease (CAD) [3], which is the most frequent cause of mortality and morbidity. In Korea, heart disease has been the leading cause of mortality since 2012 [4]. Hypertension contributes to atherosclerotic CVD, such as stroke, heart disease, chronic kidney disease, and large-vessel disease, and it is a strong predictor of cardiovascular morbidity and mortality. Untreated hypertension is associated with ischemic and hemorrhagic stroke, myocardial infarction, and heart failure. Regimens based on each of the most commonly used antihypertensive drug classes reduced the risk of major cardiovascular events, and the reductions are roughly proportional to the blood pressure (BP) reduction achieved [5]. With the exception of heart failure, the degree of BP lowering appears to be a more important determinant of outcome than the choice of drug class [6]. Nevertheless, many large clinical studies have shown that certain antihypertensives provide relatively greater protection against organ disease, and many hypertension treatment guidelines recommended a specific class of drug for a specific disease or organ damage [6-8].

In this issue of The Korean Journal of Internal Medicine, Lee et al. [9] report the superiority of amlodipine at preventing CVD, as compared to noncalcium channel blocker (non-CCB) antihypertensive therapy. The amlodipine-based regimen produced significant reductions compared with a non-CCB-based regimen: 9% for myocardial infarction, 16% for stroke, 10% for all cardiovascular events and total mortality, and a comparable risk of heart failure compared with the overall for β-blockers and diuretics in a meta-analysis of six outcome trials.

The major differences with regard to this study are that it excluded nondihydropyridine (non-DHP) CCBs, using only an amlodipine-based regimen. Calcium antagonists, as a group, are heterogeneous and include three main classes: phenylalkylamines, benzothiazepines, and DHPs. These differ in their molecular structure, sites and modes of action, and effects on various other cardiovascular functions. Although a few clinical studies have distinguished the effects of CCB monotherapy, heart-rate lowering calcium antagonists such as verapamil and diltiazem might have an edge over DHPs in postmyocardial infarction patients.
and in diabetic nephropathy. Non-DHP CCBs can suppress the heart rate not only at rest but also during exercise. In addition, DHP CCBs are subdivided, according to the specific channel blocked, into L-channel and N-channel types, and they have different durations of action (long- or short-acting). Some studies have shown that short-acting CCBs are hazardous in ischemic heart disease, and increased mortality [10], while long-acting CCBs did not [11]. CCBs are useful in patients with left ventricular hypertrophy, asymptomatic atherosclerosis, angina pectoris, atrial fibrillation, peripheral arterial disease, isolated systolic hypertension, metabolic syndrome, and pregnancy, and in black hypertensive patients. CCBs are useful for stroke prevention, as shown in many clinical trials and meta-analyses. However, amlodipine was the comparative factor in most of these studies [12]. There are not much data for most CCBs other than amlodipine, and some of the data are anecdotal. Therefore, it is unreasonable to consider most CCBs to have the same efficacy as amlodipine.

CCBs are probably more effective at lowering BP in East Asians, who have high dietary sodium intakes according to the INTERSALT study [13]. Therefore, salt excess is considered a greater risk factor for CVD in East Asia, via a further increase in BP. In a meta-analysis of prospective studies, a high salt intake was associated with an increased risk of stroke and all CVD. CCBs, compared with other classes of antihypertensive drugs, provide more protection against stroke [12] and they seem to be more effective because the major complication of hypertension in East Asians is stroke, rather than myocardial infarction.

However, CCBs are generally not recommended for patients with, or at high risk for, heart failure due to reduced left ventricular function. Studies have shown that short-acting agents, both DHP and non-DHP CCBs, increase plasma norepinephrine levels. This is associated with adverse cardiovascular sequelae, including heart failure and mortality. By contrast, with long-acting DHP CCBs, sympathetic activation is less pronounced, and the long-acting non-DHP verapamil significantly reduced plasma norepinephrine levels. Nevertheless non-DHP CCBs are not recommended for patients with left ventricular dysfunction because of their negative inotropic effect. In a cohort of 2,466 patients in the Multicenter Diltiazem Postinfarction Trial, randomization to diltiazem or placebo did not influence the all-cause mortality of those enrolled after a myocardial infarction [4]. However, diltiazem was associated with an increased risk of death in those patients with depressed left ventricular function or acute anterior myocardial infarction with pulmonary congestion via dilatation of the pulmonary arterioles rather than by adversely affecting the heart. In comparison, amlodipine does not seem to exert unfavorable effects on the clinical course of patients with heart failure, regardless of the presence or absence of underlying CAD. In the Prospective Randomized Amlodipine Survival Evaluation 1 and 2 studies of class 3 to 4 chronic heart failure patients, amlodipine was neutral in patients with ischemic and nonischemic disease [15].

Amlodipine provided more protection against stroke and myocardial infarction than angiotensin II receptor blockers. In addition, in keeping with previous meta-analyses, amlodipine prevented more stroke than angiotensin-converting enzyme inhibitors (ACEis) and older drug classes (diuretics and β-blockers). An early BP reduction is important for cardiovascular protection in high-risk patients according to a head-to-head comparison of valsartan versus amlodipine in the Valsartan Antihypertensive Long-term Use Evaluation study [16]. Amlodipine-based therapy was significantly more effective at reducing BP, especially during the early phases of treatment. Fewer myocardial infarctions and strokes were seen in the amlodipine-based group during the first 2 years. The observed differences in the stroke rate appear to be strongly related to differences in achieved BP. This means that most of the stroke benefit was due to the benefit of lowering BP, rather than the drug used.

Another issue is the effect of amlodipine on systolic BP variability (BPV), which is a recognized marker of, and risk factor for, CVD. A meta-analysis revealed that the BPV with amlodipine was significantly lower than with atenolol or ACEis (lisinopril and enalapril) [17]. Is amlodipine better than other CCBs? Compared with other CCBs, amlodipine has greater membrane affinity, owing to its positive charge and strong lipophilicity; this prolongs the action of amlodipine. Amlodipine also has antioxidant effects, independent of calcium channel modulation, and a vasodilatory effect via the inhibition of nitric oxide release, which inhibits
platelet aggregation [18]. These pleiotropic effects of amlodipine suggest that it is more cardioprotective than other non-CCB-based treatments. Some clinical studies suggest that other long-acting CCBs, such as nifedipine and lacidipine, have antiatherosclerotic effects similar to those of amlodipine. The randomized, double-blind International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study [19] compared nifedipine GITS with the combination of amiloride plus hydrochlorothiazide (coamilozide) in hypertensive patients. It found that nifedipine GITS inhibited carotid artery thickening and slowed coronary artery calcification. The European Lacidipine Study on Atherosclerosis showed that lacidipine reduced the increase in intima-media thickness, as compared to atenolol [20]. Therefore, selective calcium antagonists work as antiatherosclerotic agents. From these data, it is evident that treatment with lipophilic third-generation long-acting CCBs improves the prognosis in patients with hypertension with atherosclerosis.

As this study showed, amlodipine itself, as opposed to other CCBs, seems to have better effects with regard to protecting against stroke, ischemic heart disease, and cardiovascular mortality. However, new randomized clinical trials need to compare the cardioprotective effect of amlodipine versus other CCBs. Until then, the evidence suggests that amlodipine is the most reasonable choice among CCBs.

Conflict of interest
No potential conflict of interest relevant to this article was reported.

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