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Scientific Update™

The PREVENT Study: Renewed Interest in the Antiatherosclerotic Effects Of CCBs

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Calcium channel blockers (CCBs) are used safely and effectively in patients with hypertension or angina. Animal data accumulated over the years, as well as limited clinical data, suggest a possible role for the antiatherosclerotic effects of CCBs. The results of the PREVENT study, while preliminary, support the possibility of a beneficial antiatherosclerotic effect. The background information and the preliminary results of this study are presented and discussed in this issue.

Development of atherosclerosis

The current hypothesis of atherosclerotic development includes an initiating toxic event whereby endothelium becomes dysfunctional. This toxic event – physical, chemical, or inflammatory in nature – leads to greater permeability of endothelium with dysfunctional consequences leading to monocyte attraction, maturation, and migration to subendothelial space. As well, there is a release of growth-promoting substances from endothelium and platelets. This cascade of events, punctuated by smooth muscle cell migration and proliferation, smooth muscle cell contraction, ongoing secretion of extracellular matrix protein, and transformation of macrophages into foam cells with endocytosis of oxidized LDL, results in the formation of an atherosclerotic plaque.

One central hypothesis in our understanding of atherosclerosis development is related to the importance of LDL cholesterol. It is not surprising, therefore, that a significant amount of work demonstrates not only a direct relationship between LDL cholesterol levels and clinical expression of atherosclerotic disease, but also a successful reduction in clinical events with strategies of aggressive LDL cholesterol reduction, (eg, most successfully with HMG-CoA reductase inhibitors). Because several important steps involved in the structural and functional changes associated with atherosclerosis are mediated by a release of calcium, the role of CCBs in preventing or limiting progression of the disease has been investigated.

CCBs and the atherosclerotic cascade

Activation of vascular smooth muscle cells is a key step in the development of atherosclerosis. CCBs may inhibit activation and proliferation of smooth muscle cells through a variety of mechanisms including reduction in proliferation in

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response to platelet-derived growth factor,[1] direct plasma membrane effects,[2] and inhibition of DNA synthesis. Thus, CCBs may interrupt the atherosclerotic cascade at a number of levels by interaction with growth factor receptors. This leads to diminished activation and proliferation of vascular smooth muscle cells.[3]

Previous studies have indicated that CCBs may reverse or diminish the extent of cholesterol deposition in the vascular wall.[4,5] These observations coupled with known physiologic effects of CCBs in preventing vasoconstriction – through endothelium dependent and independent mechanisms – paved the way towards early clinical studies.

Angiographic studies: Attempts at regression of coronary artery disease

One of the early angiographic studies compared the effect of nifedipine, propranolol, and isordil on new lesion formation in 113 patients with unstable angina.[6] Treatment was assigned in a nonrandomized fashion and was based on the results of exercise testing. Follow-up over two years demonstrated that patients treated with nifedipine had significantly less new lesion formation than those treated with either isordil or propranolol. The results of quantitative coronary angiography also demonstrated that there were significantly less patients with progression among those treated with nifedipine compared to the other two treatments.

In the INTACT study (International Nifedipine Trial on Antiatherosclerotic Therapy), 348 patients underwent repeat angiography after three years of randomized, double-blind, placebo-controlled treatment.[7] No regression was seen in patients treated with nifedipine compared to those treated with placebo; however, the number of new lesions per patient was less among those treated with nifedipine. Unfortunately, there was evidence of increased mortality in nifedipine-treated patients that was later confirmed in the meta-analysis of studies that included patients with acute coronary syndromes based on administration of short-acting nifedipine.[8]

In a Canadian study with nicardipine, David Waters and colleagues demonstrated a decrease in new lesion formation; however, multivariate analysis suggested that this benefit may have come from a blood pressure lowering effect rather than a direct antiatherosclerotic effect of nicardipine.[9]

The most striking benefit from administration of CCBs was a reduction of atherosclerosis in patients receiving heart transplantation. In this study, there was evidence of a decrease in new lesion formation and angiographically-documented prevention of disease progression in 29 patients treated with diltiazem as compared to 28 control patients who completed angiographic protocol.[10]

Most recently, the REGRESS study examined the benefit of pravastatin in hypercholesterolemic patients. Investigators demonstrated a positive interaction between pravastatin and CCBs with a reduced number of patients with new lesions among those treated with combination therapy.[11]

Potential roles for amlodipine

The relatively recent addition of amlodipine to the armamentarium of antihypertensive and antianginal therapy has resulted in its widespread use, partly because of ease of administration, apparent safety, potential benefit in patients with left ventricular dysfunction,[12] and an expanding familiarity with its use in various subsets of patients.

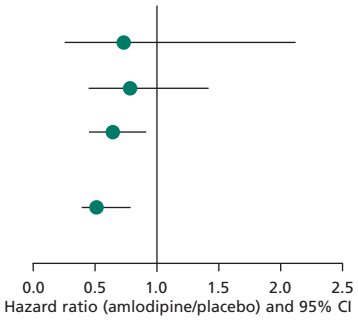
PREVENT

Experience with amlodipine, together with previous information on potential antiatherosclerotic effects of CCBs, led to the Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) study,[13] a multicentre, randomized, placebo-controlled, double-blind, angiographic trial in which 825 patients with coronary artery disease were treated with standard medical care plus amlodipine (5 mg daily for two weeks) with a subsequent increase (10 mg daily), or standard medical care alone. The primary hypothesis of the study was that administration of amlodipine over three years would

Table 1: PREVENT: Summary of the effects of amlodipine besylate on cardiovascular morbidity and mortality

	Relative risks			
	Hazard ratio	95% CI	% reduction	p-value
All-cause mortality	0.74	0.26-2.12	—	0.57
Major vascular events*	0.82	0.47-1.42	—	0.47
Other nonfatal vascular events**	0.65	0.47-0.91	35%	0.01
Major vascular procedures***	0.54	0.39-0.77	46%	0.001

* Major vascular events: Fatal/non-fatal MI or stroke, any other fatal vascular event
** Hospitalization for angina, CHF
*** Percutaneous transluminal coronary angioplasty, coronary artery bypass graft



reduce progression of early atherosclerotic segments (<30%) based on mean minimal diameter of these segments. Secondary endpoints included not only measures of coronary artery disease progression, but also measures of carotid atherosclerosis progression. Primary and secondary angiographic analysis were based on quantitative coronary angiographic measures performed at the Core Laboratory at Vancouver Hospital and Health Sciences Centre under the direction of Dr. John Mancini.

The results of the PREVENT study (Table 1) were presented at the ACC meeting and revealed interesting data. In terms of progression of lesions — as defined by primary analysis — no difference was demonstrated in reduction of minimal luminal diameter among patients treated with amlodipine compared to those treated with placebo (-0.095 vs -0.092 mm, p=NS). However, secondary analysis of carotid atherosclerosis progression, based on measures of intimal medial thickness (IMT), revealed regression in patients treated with amlodipine (-0.0072 mm) compared to progression in placebo-treated patients (+0.0363 mm, p=0.01). Thus, potential antiatherosclerotic effect from amlodipine was seen more readily in relation to carotid artery, than to coronary artery analysis. Given the potential difference in the imaging modality, the sub-study (NORMALISE) of the upcoming CAMELOT study will use intravascular ultrasound (IVUS) to increase the sensitivity of atherosclerotic detection.

Clinical outcomes were designated as secondary endpoints in the PREVENT study. There were no differences observed with respect to mortality, infarction, or stroke. However, there was a significant reduction in both the frequency of hospitalizations for angina and in the need for revascularization when amlodipine was added to usual care (background therapy).

Since hypertension is a much more significant risk factor for cerebrovascular disease as compared to hypercholesterolemia for coronary artery disease, the blood pressure-lowering effects of amlodipine may have been responsible for some of these observations. While interesting, these preliminary observations are consistent with previous experience summarized above and do not support the use of CCBs for regression or prevention of progression of coronary atherosclerosis. However, the *post-hoc* analysis indicating potential clinical benefit may deserve further studies. Other studies in hypertensive patients have already demonstrated the beneficial effect of CCBs in reducing stroke and related morbidity and mortality.[14]

Conclusion

Calcium channel blockers continue to be a safe and effective therapy in patients with hypertension or stable coronary artery disease. Unlike other CCBs, amlodipine appears to be safe in patients with left ventricular dysfunction based on the results of the PRAISE study, and its potential benefit in patients with non-ischemic cardiomyopathy is now being formally addressed in PRAISE II.

The antiatherosclerotic effects of CCBs have been investigated previously and in general, have not supported anticipated benefit in preventing progression of coronary artery disease. Certainly, results with lipid-lowering therapy, in particular with HMG-CoA reductase inhibitors aimed at LDL cholesterol reduction, have been much more rewarding. Recent experience with amlodipine in the PREVENT study supports these observations and further studies such as CAMELOT and NORMALISE should help to clarify its role in the treatment of patients with cardiovascular disease and atherosclerosis.

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