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Calcium Channel Antagonists as Initial Hypertensive Drug Therapy A Discussion of the NORDIL Trial

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Blood pressure control has a major impact on cardiovascular disease. Treatment with either diuretic or beta-blocker-based regimens reduces the risk of stroke by approximately 38%, myocardial infarction (MI) by 16%, and heart failure by up to 40%.[1] Since the initial trials of blood pressure lowering with diuretics and beta-blockers, many new agents have been introduced. ACE inhibitors, alpha-adrenergic blockers, and calcium channel blockers are amongst the most commonly used antihypertensive agents today. Yet, until recently, there have been little data to demonstrate whether these new agents reduce adverse cardiovascular outcomes or are different from the proven and effective treatments with diuretics and beta-blockers. Does it matter how blood pressure is reduced? Is the incidence and mortality of cardiovascular disease influenced by the choice of the blood pressure lowering agent?

Pharmacological differences between antihypertensive drugs

In addition to lowering arterial blood pressure, antihypertensive agents have properties that might alter the development of cardiovascular disease. Diuretics are known to adversely impair glucose tolerance and may increase hyperlipidemia. Beta-blocking agents could act favourably by preventing cardiac arrhythmias and limiting myocardial ischemia. Angiotensin-converting enzyme (ACE) inhibitors are known to reduce the incidence of vascular complications of atherosclerosis and the onset of heart failure. The dihydropyridine calcium channel antagonists, especially when given as the short-acting preparation, can increase sympathetic activity – thereby augmenting myocardial oxygen demands – yet improve flow by limiting coronary arterial vasospasm. In contrast, calcium channel antagonists such as diltiazem reduce heart rates, prevent coronary spasm, and do not increase sympathetic stimulation. Despite potential benefits on cardiovascular outcome, the calcium channel antagonists as a class have fallen victim to adverse scrutiny, largely based on side effects observed from preparations of the first generation of the dihydropyridine class of these agents.

Efficacy of calcium channel antagonists as antihypertensive agents

When the NORDIL trial began in 1992, there were no data to show that calcium channel antagonists reduced either mortality or morbidity in patients with hypertension. At that time it was known that both diuretics and beta-adrenergic blocking agents reduced stroke, but had a lesser effect on MI. Subsequently, three trials (STONE,[2] Syst-EUR,[3] Syst-CHINA[4]) have showed the benefit of treating hypertension with calcium channel blockers in comparison with placebo.

Both Syst-Eur and Syst-China were trials of nitrendipine in patients with systolic hypertension. Stroke was reduced by almost half in both the European and Chinese populations and there was a similar trend towards a reduction of MI in both studies (Table 1). Thus, when compared with placebo, dihydropyridine calcium channel antagonists result in important reductions in cardiovascular mortality and morbidity of the same order of magnitude as that observed with earlier antihypertensive strategies with diuretics and beta-blockers. Are calcium channel blockers as effective as the early treatment strategies of diuretics and beta-blockers? To answer this question, studies such as the NORDIL[5] and INSIGHT[6] trials were conducted.

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Table 1: Placebo-controlled trials with calcium channel antagonists in hypertension				
Trial	Drug	Fatal and nonfatal event (Risk Ratio [95% CI])		
		Cardiovascular	MI	Stroke
STONE[2]	Nifedipine	0.40 (0.25-0.61)	0.94 (0.13-6.66)	0.43 (0.24-0.77)
Syst-EUR[3]	Nitrendipine	0.69 (0.55-0.86)	0.70 (0.44-1.09)	0.58 (0.40-0.83)
Syst-CHINA[4]	Nitrendipine	0.63 (0.46-0.85)	0.67 (0.39-1.15)	0.66 (0.45-0.96)

The NORDIL Trial

The NORDIL trial[5] was designed to compare outcomes (fatal or non-fatal MI or stroke) in hypertensive patients treated with either the calcium channel antagonist diltiazem or diuretics and/or beta-adrenergic blockers. The study – performed in Norway and Sweden – enrolled almost 11,000 patients who were followed for an average of 4.5 years. Patients were prospectively randomized to either open-label diltiazem or the diuretic/beta-blocker arms of the trial. The outcomes were assessed by the end-point committee who were unaware either of the allocated treatment or the blood pressure response (Prospective Randomized Open trial with Blinded Endpoint Evaluation [PROBE] design).

To qualify for the study, patients aged 50-74 years, had to have diastolic blood pressures >100 mm Hg on two occasions whilst taking no medication. Patients in the diltiazem-treated group were started on diltiazem 180-360 mg daily (from 1997, the long-acting preparation was used), and in the diuretic/beta-blocking group either a thiazide diuretic or a beta-blocker. The subsequent medication steps (Table 2) were used to achieve a target diastolic blood pressure <90 mm Hg.

The study was designed to detect a 20% difference between treatments for the primary endpoint of occurrence of fatal or non-fatal stroke or fatal or non-fatal MI.

The enrolled patients had moderately severe hypertension (173/105 pre-treatment), were obese (body mass index = 27.8 kg/m^2), had moderate hypercholesterolemia (6.4 mMol/L), and only 6.9% were diabetic. Just over half of the patients had never had antihypertensive treatment before. Patients in the diuretic/beta-blocker arm of the study had a greater fall in systolic blood pressure than those in the diltiazem group (BP change: diltiazem group 20.3/18.7 mm Hg; diuretic/beta-blocker group 23.3/18.7 mm Hg; difference in systolic pressure p<0.001). At the end of the treatment period, 50% of patients were taking diltiazem alone, and 45% were on either a diuretic or a beta-adrenergic blocker. Whereas 93% of patients were still on either a beta-blocker or diuretic, only 77% were taking diltiazem at the end of the study. This difference probably is due to the choice of two entry drugs in the diuretic/beta-blocker arm of the study.

Almost the same number of patients in both groups had fatal/nonfatal vascular events (diltiazem group (403), diuretic/beta-blocker group (400)). Diltiazem was significantly more effective in reducing the rate of stroke (fatal and non-fatal) (Figure 1). Although there were more MIs in the diltiazem group, yet the difference between groups did not achieve statistical significance. There was no significant difference between the two treatment groups in diabetic patients, and neither treatment changed the onset of atrial fibrillation or heart failure.

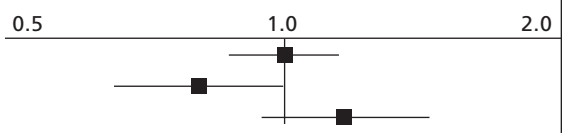
Withdrawals from randomized treatment (23% on diltiazem, and 7% in the beta-blocker/diuretic group) probably reduced the power of the study to show a difference between treatments. A similar problem was encountered in the INSIGHT study,[6] where 40% patients were withdrawn from calcium channel antagonist treatment and 30% from the diuretic group.

Other studies comparing calcium channel blocking agents to a treatment strategy using diuretics or a beta-blocking agent have also shown no difference in either mortality or the occurrence of the combined endpoint of fatal or nonfatal stroke or MI. Cause-specific effects were not as clearly defined, with no reduction in the incidence of stroke by the calcium channel antagonist in either the INSIGHT[6] or STOP-2[7] trials (Table 3). MI also occurred at rates not significantly different from those in either

Table 2: Treatment stages in the Nordil Trial		
	Diltiazem	Diuretic/Beta-blocker
Stage 1	Diltiazem 180-360 mg daily	Thiazide or beta-blocker
2	ACE inhibitor added	Thiazide and beta-blocker
3	Diuretic and/or beta-blocker added	ACE inhibitor or alpha blocker added
4	Any other antihypertensive treatment	Any other antihypertensive treatment except calcium channel blocker

Figure 1: Relative risk of cardiovascular events in the NORDIL Trial

	Relative risk* (95% CI)	p
Primary endpoint	1.00 (0.87-1.15)	0.97
Stroke, fatal and non-fatal	0.80 (0.65-0.99)	0.04
MI, fatal and non-fatal	1.16 (0.94-1.44)	0.17



treatment strategy. When the results are combined in a meta-analysis, there is no difference in the occurrence of major cardiovascular events (fatal or non-fatal MI or stroke) between the two treatments. However, stroke is reduced by calcium channel blockers (RR 0.87, 95% CI, 0.77-0.98), whereas MI (RR 1.12, 95% CI, 1.00-1.26) and heart failure (RR 1.12, 95% CI, 0.95-1.33) are less frequent in the group managed with diuretics or beta-adrenergic blockers.

The Furberg Meta-Analysis

Curt Furberg has recently published the results of a meta-analysis comparing cardiovascular outcomes in patients treated with calcium channel antagonists to outcomes with other hypertensive treatments. This analysis examines nine randomized comparative clinical trials and reports that antihypertensive treatment with calcium channel blockers is associated with a 26% higher risk of MI, and a 27% risk of heart failure. Eight trials with calcium channel blockers (6 dihydropyridines and 2 nondihydropyridines) were included: INSIGHT (nifedipine),[6] NORDIL (diltiazem),[5] STOP-2 (felodipine or isradipine),[7] FACET (flosequinan-ACE inhibitor trial), MIDAS (isradipine),[8] ABCD (nisoldipine),[9] and CASTEL (nifedipine).[10]

Critics of the meta-analysis have commented that it is inappropriate to lump together studies as if the calcium channel blockers have similar pharmacokinetic and pharmacodynamic properties. The meta-analysis used data from the FACET and and interim results from the ABCD trials that investigated treatment in patients with diabetic nephropathy. The ABCD study showed increased incidence of MI in patients treated with calcium channel antagonists compared to those receiving ACE inhibitors; yet there was no significant difference in either cardiovascular or overall mortality between the groups. Furthermore, the MI rate in the calcium channel group was similar to that reported in historical controls. Any difference is likely due to the vasculo-protective effect of ACE-inhibitors so clearly demonstrated in the HOPE trial,[11] rather than a harmful effect of calcium channel blockers. ACE inhibitors have been shown to have special benefit in diabetic nephropathy and are clearly the first choice of treatment in this group of high risk patients. Furthermore, the analysis included studies (eg, MIDAS[8] and CASTEL[10]) using short-acting preparations of calcium channel antagonists that were taken only once daily, rather than the recommended twice daily dosing.

It is interesting to note that Furberg is a principal investigator in the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT).[12] This trial is currently evaluating the cardiovascular effectiveness of different antihypertensive drug regimens and has enrolled more than 42,000 high risk hypertensive patients (including 15,000 diabetics). This study continued to enroll patients taking calcium channel antagonists without any concern expressed by the data safety monitoring committee, yet did discontinue alpha blocker treatment with doxazosin when this treatment was shown to be associated with an increased incidence of heart failure.[13]

Are there differences between "conventional" and the newer antihypertensive agents?

The controversy surrounding the use of calcium channel antagonists as primary treatment of hypertension continues despite the recent trials. However, it is likely that we still do not have a true answer to the question: Are calcium channel antagonists different from conventional management with beta-blockers and/or diuretics? The NORDIL, INSIGHT, and the STOP-2 studies were designed as superiority trials to show a 20-25% dif-

Table 3: Comparison of calcium channel antagonist-based treatment of hypertension with diuretic and/or beta-adrenergic blockers

Trial	Drug	Fatal and nonfatal event (Risk Ratio [95% CI])		
		Cardiovascular	MI	Stroke
INSIGHT[6]	Nifedipine	1.07 (0.89-1.29)	1.10 (0.83-1.46)	0.94 (0.70-1.28)
NORDIL[5]	Diltiazem	1.04 (0.92-1.18)	1.14 (0.95-1.37)	0.80 (0.65-0.99)
STOP-2[7]	Isradipine or Felodipine	1.00 (0.90-1.10)	1.12 (0.93-1.34)	0.88 (0.74-1.05)

ference in primary outcome between the medication arms. Although no statistical difference was demonstrable for the primary endpoints, the three trials failed to detect a relative risk difference of 20-25% between the treatment groups.

Is a <20-25% difference between treatments important? In a condition as common as hypertension, a 15-20% reduction (or increase) of events especially in a higher risk population, could translate into a very large absolute difference in outcomes. Conclusions have been drawn from these trials that reduction in blood pressure is the most important factor and that the choice of medication is unimportant. None of these trials was designed to show equivalence between the treatment groups and due to the relatively small number of endpoints, future trials would need to capture at least 1000 events to detect a 15% difference in treatments. As such massive trials are unlikely, we shall depend upon combined analyses such as the WHO-ISH Blood Pressure Lowering Treatment Trialists Collaboration.

It would be wrong to deny patients effective treatment for blood pressure management. Calcium channel antagonists have been shown to be extremely effective in improving cardiovascular outcome especially in the high risk diabetic population as in the HOT[14] and Syst-Eur[15] trials. Calcium channel antagonists such as diltiazem are an effective and extremely well tolerated treatment with proven reduction of cardiovascular mortality and morbidity. When compared with placebo, long-acting calcium channel blockers reduce cardiovascular mortality and morbidity in high risk patients, especially stroke. They are particularly effective in the elderly and in the management of hypertension in the African-American population: groups with a high risk of stroke.

Until more definitive information is available from trials such as ALLHAT and the WHO-ISH Collaboration, consideration must be given to a risk structured management of hypertension. It remains possible that antihypertensive treatment given to patients with a risk below a certain threshold will have no effect on outcome, or even increase mortality from all causes and coronary heart disease. At higher levels of risk, any possible adverse effect of the treatment is reduced by the much greater benefits of blood pressure control.

Conclusion

The NORDIL trial[5] has shown in a large clinical trial designed to reflect real-life clinical practice that a treatment strategy using diltiazem as the initial antihypertensive medication, results in similar overall cardiovascular outcomes as in patients started on the more traditional diuretic or beta-blocker. Yet stroke occurred less frequently in the patients receiving diltiazem.

Compared to placebo, calcium channel antagonists used to manage hypertension result in a marked reduction in stroke and a lesser reduction in MI. In the three large comparative trials of calcium channel antagonists and the diuretic/beta-blocker strategy, there was uniformly no difference in the combined cardiovascular outcome (death, stroke and MI). However, a meta-analysis of these comparative studies has suggested that calcium channel blockers, although reducing the incidence of stroke, might increase MI compared to the beta-blocker/diuretics. These differences between treatments are of borderline significance. Furthermore, it is possible that this outcome is not due to any harmful effect of calcium channel antagonists, but results from the well known cardio-protective benefit of beta-blockers in patients with prior cardiac damage. Patients with previous MI should preferentially receive a beta-blocker: treatment that is associated with improved survival. Patients with a high risk of stroke, such as the elderly and Afro-Americans, may benefit from the enhanced reduction of stroke associated with treatment with diltiazem.

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