Cardiovascular Drugs and Therapy 1996;10:4:397–402

Editorial

1,4-Dihydropyridines versus Beta-Blockers for Hypertension: Are Either Safe for the Heart?

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Summary. **Fast-absorbed and short-acting dihydropyridines (e.g., nifedipine capsules) cause intermittent hemodynamic effects associated with sympathetic hyperactivity. In contrast, long-acting dihydropyridines, such as nifedipine GITS and amlodipine, provide, during chronic treatment, stable hemodynamic effects with little or no activation of the sympathetic nervous system. This markedly different pattern of hemodynamic changes may explain why the short-acting drugs cause little to no regression of left ventricular hypertrophy, may make angina worse, and may negatively affect cardiac outcome, whereas the long-acting drugs decrease LV mass as anticipated from the fall in blood pressure and, at least in stable coronary artery disease, produce an outcome comparable with beta-blockers. In hypertension, beta-blocker treatment appears to be associated with a short fall in positive outcome, perhaps in part related to increased rates of sudden death. Such an adverse outcome may also be due to sympathetic hyperactivity, possibly during treatment via cardiac alpha-receptors, but also during the common short periods of noncompliance due to actual increased sympathetic responses. For both drug classes, we suggest that long-acting agents be considered, providing therapeutic coverage well beyond the normal dosing interval.**

Cardiovasc Drugs Ther 1996;10:4:397–402

Key Words. **coronary artery disease, left ventricular hypertrophy, sympathetic activity, outcome**

Cardiovascular mortality still represents the leading cause of death in western societies, and in the elderly the rates increase markedly. However, because of the age distribution of the population, in absolute terms most of this mortality occurs in the middle-aged to young elderly and can be considered as "premature." This is even more obvious when one takes morbidity into account as well. For example, in the province of Ontario (Canada), in men 62% of coronary bypass surgery occurs at <65 years of age and in women 71% at <70 years of age [1]. Clearly, cardiovascular morbidity and mortality is still to a large extent premature, and interventions that could shift this premature disease to a later age would have a major positive impact. Results of the major intervention studies in hypertension indicate that the impact of antihypertensive drug treatment on coronary artery disease is thus far substantially less than expected. Most of these patients were treated with diuretics and/or beta-blockers. In contrast, diuretic-based studies in the elderly showed, across studies, an appropriate impact on both stroke and coronary artery disease (CAD) events, suggesting that at this stage in the disease process, different mechanisms lead to or trigger actual events. In one of these studies [2] beta-blocker–based treatment was ineffective in decreasing coronary events.

Thus, in younger to middle-aged hypertensives, both diuretics and beta-blockers appear to affect coronary events less than anticipated and in the elderly beta-blockers possibly may be less than optimal. These limitations may apply to antihypertensive drug therapy in general or to specific drug classes. Large-scale comparative trials are therefore needed and are currently ongoing to evaluate whether angiotensin-converting enzyme (ACE) inhibitors, calcium antagonists, and alpha$_1$-blockers are different with regard to the outcome of CAD compared with diuretics or beta-blockers. Concerns about a negative impact on the outcome of CAD in hypertensive subjects have recently been raised with regard to calcium antagonists, specifically the 1,4-dihydropyridines, and to a lesser extent beta-blockers and diuretics. In this editorial, some of the data leading to these concerns about the 1,4 dihydropyridines and beta-blockers are reviewed, and a common mechanism, that is, sympathetic hyperactivity, is proposed to cause this adverse outcome.

1,4-Dihydropyridines and Coronary Events

Rapid-acting dihydropyridines

Dihydropyridines have a number of properties that make them theoretically attractive for both the prevention and management of coronary artery disease. However, early on in their use it became apparent

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Received 16 April 1996; accepted 10 May 1996

that in a significant subgroup of patients with CAD, treatment with nifedipine capsules causes an exacerbation of angina [3]. Actual nifedipine-induced angina may occur within 20–30 minutes of ingestion of nifedipine capsules and may last for 10–15 minutes, associated with hypotension. Lowering the mean daily dose from 92 to 62 mg improved the blood pressure (BP) and the angina episodes disappeared [4]. This "paradoxical" response is not unique for dihydropyridines, and also occurs with, for example, isosorbide-induced hypotension.

In the 1980s, a number of studies also evaluated the possible role of nifedipine capsules in preventing/delaying coronary events in patients with unstable angina pectoris or suspected myocardial infarction. None of these studies provided evidence for a positive impact on outcome. Studies such as the HINT study or SPRINT 2 were discontinued prematurely because of concern about an adverse outcome. A meta-analysis of studies published in the 1980s showed odds ratios of 1:13 and 1:14 for death or subsequent myocardial infarction (both nonsignificant) [5]. Of interest, this possible increase in coronary events appears to occur early during treatment, that is, during the first 1–2 weeks of treatment and not during the subsequent 6 months of treatment [6,7]. This finding suggests that treatment with nifedipine capsules somehow triggers coronary events without affecting left ventricular (LV) remodeling, LV function, or long-term prognosis. In patients with stable CAD, no outcome studies have been reported for short-acting dihydropyridines. However, studies performed for other reasons (e.g., to study the effects on the progression of atherosclerosis) provide evidence for concern. For example, in the INTACT study [8] in patients with stable CAD, over the 2 year follow-up period eight cardiac deaths occurred in patients taking nifedipine capsules (n = 173) compared with only two in patients on placebo (n = 175). In the study by Waters et al. [9], over the period of 2 years 14 myocardial re-infarctions occurred in patients taking nicardipine (n = 192) compared with 8 in 191 patients on placebo. Thus, whereas studies in patients with stable CAD do not prove that dihydropyridines have a negative impact on cardiac outcome, the tendency is again apparent.

One may question the validity of combining results of studies performed in different patient populations, that is, patients with stable versus unstable CAD [10]. However, in both patient populations nifedipine capsule-like dihydropyridines, may trigger coronary events through a similar mechanism(s). A meta-analysis of these combined populations showed odds ratios of 1:16 and 1:19 for mortality and (re)infarction ($p < 0.02$ for both endpoints combined) [11].

In hypertensive subjects, no outcome studies relevant for CAD have yet been reported for the short-acting dihydropyridines. MIDAS evaluated the effects of isradipine versus hydrochlorothiazide on the progression of atherosclerosis in carotid arteries. At a 1994 meeting presentation, an increased incidence of "hospitalized angina" was reported in patients on isradipine over the 3 years of follow-up [12]. However, this study has still not been published, and alternative explanations (i.e., not drug related) have been mentioned, such as differences in CAD at baseline. In the case-control study by Psaty et al. [13], the use of higher doses of short-acting calcium antagonists was associated with an increased risk of myocardial infarction compared with either diuretics or beta-blockers. In the prospective cohort study of Pahor et al. [14], in older hypertensives the use of short-acting nifedipine was associated with decreased survival, which was again more pronounced at higher doses. However, as stated by Pahor et al. [14], selective factors influencing the use of specific drugs in higher risk patients cannot be discounted in either a case-control study or a prospective cohort study. Nonetheless, because of their consistency with the findings in patients with CAD, the qualitative conclusions from these studies may be valid.

Long-acting dihydropyridines

As reviewed extensively by our group [15,16], long-acting dihydropyridines, such as amlodipine or nifedipine GITS, differ from the short-acting dihydropyridines in more than duration of action. Rapid hemodynamic responses that may cause hypotension and sympathetic hyperactivity are no longer apparent. Thus, if these mechanisms contribute to an adverse outcome [16,17], one may anticipate a more beneficial outcome during treatment with these dihydropyridines. Preliminary findings are indeed consistent with this concept. A number of double-blind, placebo-controlled studies [16] up to about ½ year of duration have evaluated the effects of nifedipine GITS and amlodipine in patients with stable chronic angina pectoris. In contrast to the high frequency of worsening of angina by nifedipine capsules [3], in all these studies only improvements in angina were noted and none reported worsening of angina. As importantly, none of these studies in about 5–600 patients reported deaths, myocardial infarctions, or development of unstable angina during active treatment. Thus, it appears that when used for symptom relief in patients with stable CAD, the antiangina responses to these long-acting dihydropyridines are predictable and are not associated with adverse outcome compared with placebo or beta-blocker treatment. For example, in a study comparing nifedipine retard tablets (n = 121) with metoprolol (n = 128), seven cardiovascular events occurred in patients on metoprolol versus "only" three in patients on nifedipine retard [18]. More importantly, results from TIBET show that atenolol (50 mg bid) and nifedipine SR (20–40 mg bid) cause similar improvements in ischemic parameters in patients with mild chronic

stable angina [19], whereas 12.8% (20.8%) of subjects on atenolol (n = 226) versus "only" 11.2% (19.8%) of those on nifedipine SR (n = 232) had a hard (hard and soft) endpoint over 2 years of follow-up [20]. Thus, the safety profile of the longer acting dihydropyridines so far is clearly not towards an adverse outcome, and an actual outcome study (even for an intermediate long-acting dihydropyridine) in patients with stable CAD is consistent with this conclusion.

In hypertension, the effects of amlodipine and nifedipine GITS on cardiovascular morbidity and mortality are currently being studied in large, randomized clinical trials (e.g., ALLHAT, INSIGHT). In TOMHS, all drug treatments combined (including amlodipine) tended to decrease major clinical events, but sample size was too limited to draw conclusions for individual agents [21]. A more recent case-control study from Norway [22] evaluated the association between the use of different classes of antihypertensive agents and the risk of myocardial infarction during the period 1991–1993. Compared with no treatment, treatment with diuretics and beta-blockers had only little effect on the incidence of myocardial infarction. In contrast, long-term treatment with alpha$_1$-blockers, ACE inhibitors, and calcium antagonists (73% dihydropyridines, and mainly the longer acting ones) was associated with a significant reduction (odds ratio 0.43, 0.20–0.91). Short-term exposure showed an increased risk with alpha$_1$-blockers in patients with angina, but decreases were already apparent for the calcium antagonists and ACE inhibitors. These findings clearly are in contrast to the studies by Psaty et al. [13] and Pahor et al. [14], which evaluated short-acting calcium antagonists.

In the absence of actual outcome studies, changes in surrogate endpoints can provide useful insights. For example, left ventricular hypertrophy (LVH) is recognized as a pathophysiological substrate for the development of heart failure, ventricular arrhythmias, myocardial ischemia, and sudden death. LVH is therefore an important intermediate endpoint, and persistence or progression of LVH despite effective antihypertensive therapy may reflect activation of mechanisms negatively affecting the cardiovascular system. An analysis of clinical trials assessing the effects of antihypertensive drug therapy on the regression of LVH by Cruickshank et al. [23] showed that for a given decrease in BP, rapid- and short-acting dihydropyridines are significantly less effective in decreasing LV mass than ACE inhibitors or α-methyldopa. This analysis did not include studies on long-acting dihydropyridines, such as amlodipine or nifedipine GITS. Several recent studies have shown that these dihydropyridines effectively decrease LV mass and for a given decrease in BP cause a similar regression of LVH as compared with ACE inhibitors [24,25].

Beta-Blockers and Coronary Events

Large-scale clinical trials have clearly demonstrated that both diuretics and beta-blockers can decrease cardiovascular morbidity and mortality in hypertensive patients. The positive effect of beta-blockers in patients with suspected myocardial infarction (MI) or in secondary prevention post MI has been well documented. However, this demonstrated positive effect on outcome does not necessarily imply that the extent of the effect is the optimal one that can be achieved. In young to middle-aged hypertensives, both diuretics and beta-blockers decrease coronary events less than anticipated from the fall in BP. In older hypertensives, beta-blockers are less effective in lowering BP, cause more side effects, and are possibly less effective in preventing coronary events compared with diuretics [26,27]. Thus, across all ages beta-blocker treatment appears to be associated with a short fall in positive outcome or, in other words, a relative adverse effect on outcome. Several mechanisms have been hypothesized to contribute to such an adverse effect. Recently, two studies have provided some evidence for an adverse effect of beta-blockers on rates of sudden death. Siscovick et al. [28] examined the association between treatment with thiazides and beta-blockers for hypertension and the occurrence of primary cardiac arrest in a population-based case-control study. After adjustment for potential confounders, combined therapy with low-dose thiazide (25 mg) and a potassium-sparing agent was associated with a relative risk of 0.3 (0.1–1.0) compared with beta-blocker therapy. The reverse was noted for high-dose (100 mg) thiazide (2.4, 0.7–8.0). Very similar findings were reported by Hoes et al. [29]. Diuretic-induced potassium depletion leading to cardiac arrhythmias may be the underlying mechanism for the increased risk of sudden death, as also noted in the MAPHY study [30]. However, such a mechanism cannot explain the increased risk for beta-blockers relative to combined low-dose thiazide with a K^+-sparing diuretic or other antihypertensive therapy [29]. If this effect of beta-blockers is indeed present during long-term treatment of hypertensive subjects, it would clearly diminish the potential beneficial effect of beta-blockers on survival.

"Sympathetic Hyperactivity and Coronary Risk in Hypertension" [31]

Dihydropyridines

Rapid- and short-acting versus long-acting dihydropyridines differ not just in the duration of hemodynamic effects. Since the hemodynamic responses strongly correlate with the plasma drug concentrations, rapidly absorbed formulations cause a rapid decrease in BP. Particularly at higher doses, such de-

creases can be marked and can lead to arterial baroreflex-mediated stimulation of the sympathetic nervous system. Although during chronic treatment the arterial baroreflex may reset to an overall lower BP level, each dose will again cause a rapid fall in BP from the end of (i.e., pre-) dosing level, and again activate sympathetic tone. For example, clear increases in resting supine and particularly standing plasma norepinephrine at 1–2 hours after dosing were still observed after 6 and 12 months of treatment with a felodipine tablet twice daily [32]. Felodipine ER is longer acting, but each dose still causes a fairly rapid increase in plasma drug concentration and a decrease in BP, and significant increases in plasma norepinephrine (spillover rates) still occur during chronic treatment [33]. In contrast, consistent with a sustained antihypertensive effect over 24 hours, no dosing-related increases in plasma norepinephrine were found for nifedipine GITS, whereas amlodipine may actually decrease plasma catecholamines [34]. The latter finding is consistent with decreases in sympathetic activity noted during chronic treatment with dihydropyridines in rats, possibly related to central effects. Thus, it appears that dihydropyridines intrinsically decrease sympathetic activity in animals and possibly also in humans, but that in the case of fast-absorbed formulations this effect is counteracted by arterial baroreflex-mediated stimulation of the sympathetic nervous system.

Beta-Blockers

Treatment with beta-blockers is usually not considered to be associated with persistence of sympathetic hyperactivity. However, cardiovascular effects of the sympathetic nervous system are not just mediated through beta-receptors. For example, alpha-receptors mediate many effects, some of them clearly potentially detrimental (e.g., arrhythmogenesis). Moreover, partial compliance with drug therapy is a very common phenomenon, also in patients with hypertension or angina. In the case of short-acting beta-blockers such as propranolol, atenolol, or metoprolol (used in most outcome studies), noncompliance for a few or more days will lead to a rapid disappearance of the beta-blockade (within 1–2 days), followed by a period of enhanced beta-receptor–mediated responses [35]. The cardiovascular consequences of the beta-blocker withdrawal syndrome for outcome were reviewed by, for example, Houston and Hodge [36]. Partial compliance with beta-blocker treatment has also been found to be associated with increased risk of death post MI [37], and of coronary events in hypertensive subjects [38].

Conclusions

Both dihydropyridines and beta-blockers have a number of actions beneficial for the management of patients with hypertension or coronary artery disease. However, both classes also have the potential to negatively affect cardiovascular outcome. This negative potential may to a large extent relate to sympathetic hyperactivity either during treatment or during short periods of noncompliance. The potential for sympathetic hyperactivity to negatively affect short-term or long-term outcome has been extensively documented [31]. We previously [16] discussed several lines of evidence suggesting that intermittent increases in sympathetic activity by quickly absorbed (and usually short-acting) dihydropyridines may play a primary role in the adverse outcome noted during chronic treatment with this subclass in patients with CAD. Indeed, evidence is accumulating that long-acting dihydropyridines providing stable hemodynamic effects do not activate the sympathetic nervous system and are associated with improved outcome. For beta-blockers, no comparisons of short versus long-acting beta-blockers are available so far. Long-acting beta-blockers such as nadolol show a gradual disappearance of beta-blockade and no evidence for overshoot [35], and therefore provide more appropriate therapeutic coverage during short periods of noncompliance [39]. Considering the above-outlined consequences of partial compliance with beta-blockers for outcome, this negative aspect of beta-blocker therapy should clearly be less during treatment with long-acting beta-blockers.

In conclusion, based on our current knowledge and consistent with the guidelines from, for example, the JNC-V or the Canadian Hypertension Society, beta-blockers are still part of the first-line treatment for the management of hypertension or CAD. Long-acting dihydropyridines are promising, but more outcome data are required before they can be considered as a first-line approach and in the meantime they should remain as second or third line (i.e., after beta-blockers and/or diuretics). Considering the negative consequences of partial compliance as well, for both dihydropyridines and beta-blockers, long-acting agents should be considered, providing therapeutic coverage well beyond the normal dosing interval.

Note added in proof

Recently, Jick et al. [40] reported a case-control study from the U.K. General Practice research database on the relation between different antihypertensive drug therapies and myocardial infarction in patients with no known clinical or laboratory risk factors for MI other than hypertension during the period 1993–1994. There is little suggestion of a material difference in risk for the 2 dose levels of calcium-antagonists compared with either dose level of β-blockers or for the longer-acting and shorter-acting calcium-antagonists versus β-blockers. These authors conclude that "independent factors other than the antihypertensive drugs are likely to be the most important determinants of risk for acute MI in this population." In addition, it

is likely that in contrast to the Psaty and Pahor case-control studies, in the UK study, very few patients were taking nifedipine capsule.

Acknowledgements

Frans H.H., Leenen is supported by a career investigatorship from the Heart and Stroke Foundation of Ontario. Research from the author discussed in this editorial was supported by operating grants from the Heart and Stroke Foundation of Ontario and several pharmaceutical companies. Due to limitations imposed by the journal, only some of the relevant references have been quoted. Other references can be found in Ruzicka and Leenen [15,16].

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