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Heart Rate-Lowering and -Regulating Effects of Once-Daily Sustained-Release Diltiazem

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Summary

Background: Epidemiologic evidence suggests that an elevated heart rate (HR) is an adverse and independent prognostic factor in arterial hypertension and other cardiovascular diseases. Although diltiazem is characterized as an HR-lowering calcium antagonist, no studies have quantified the magnitude of HR changes in patients with angina or hypertension.

Hypothesis: The study was undertaken to explore the magnitude of proportional HR reduction at varying levels of resting HR with the sustained-release formulation of diltiazem (SR diltiazem) at the usual clinical doses of 200 or 300 mg once daily.

Methods: This meta-analysis was conducted on six comparative double-blind studies including 771 patients with angina or hypertension in which SR diltiazem 200–300 mg once daily was compared either with placebo or with other agents known not to influence HR (angiotensin-converting enzyme inhibitors, diuretics). Sustained-release diltiazem decreases elevated baseline HR, with an increasing effect at higher initial rates.

Results: Multiple comparisons by baseline HR category showed a significant difference between both groups for baseline HR of 74–84 beats/min and ≥ 85 beats/min ($p = 0.001$). Sustained-release diltiazem had no significant HR-decreasing effect on baseline HR ≤ 74 beats/min but appears to have a genuine regulating effect on HR: it reduces tachycardia without inducing excessive bradycardia. These findings are in contrast to those with dihydropyridine calcium antagonists, which tend to increase HR and have been associated with an adverse outcome in acute cardiovascular conditions. At the same time, there is evidence to suggest that HR-lowering calcium-channel blockers decrease cardiovascular event rates following myocardial infarction.

Conclusion: When calcium antagonists are indicated for use in patients with angina or hypertension, an HR-lowering agent, that is, diltiazem rather than dihydropyridine, should be recommended.

Key words: heart rate, heart rate-lowering calcium-channel blockers, hypertension, once-daily sustained-release diltiazem

Introduction

It is well established that pharmacologic heart rate (HR) lowering, both at rest and during exercise, has beneficial effects in patients with angina. Heart rate reduction lowers myocardial oxygen consumption, prolongs the diastolic interval during which nutritive coronary blood flow occurs, and results in an overall anti-ischemic effect.

Recent epidemiologic evidence suggests that levels of HR reduction also have long-term prognostic value. The Framingham study showed clearly that an elevated HR is an independent cardiovascular risk factor in hypertensive patients.[1] Moreover, several studies have highlighted the negative prognostic implications of elevated HR after acute myocardial infarction (MI), independent of the presence of heart failure.[2–6] Several intervention trials have shown that agents that reduce HR also improve the prognosis of patients with cardiovascular disease. For beta blockers administered following acute MI, there was a relationship between the reduction of HR and improved survival.[4] Compared with placebo, the calcium antagonist verapamil has been associated with a reduced *reinfarc-*

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tion rate in such patients.[7] Diltiazem (Mono-tildiem® 200 and 300 mg [sustained-release], Sanofi Synthélabo, Paris, France) likewise has been shown prospectively to reduce reinfarction following non-Q-wave MI, a finding confirmed by a subgroup analysis from another study and a meta-analysis.[8–10] In contrast, the short-acting dihydropyridine calcium-channel antagonists have shown no beneficial and, in some studies, even harmful effects.[11, 12] Of importance is the fact that the dihydropyridine calcium antagonists, unlike verapamil and diltiazem, induce reflex tachycardia, at least in their short acting formulations.[13, 14]

Since the dihydropyridine and non-dihydropyridine calcium antagonists appear to have contrasting effects both on HR and on clinical outcomes, we believed it was important to explore the magnitude of proportional HR reduction at varying levels of resting HR with the sustained-release formulation of diltiazem (SR diltiazem) at the usual clinical doses of 200 or 300 mg once daily. Since there are few, if any, data regarding the decremental effects of diltiazem on HR, we sought to examine the degree to which this agent affected rest and exercise HR in patients with angina or hypertension.

Previously published results from an open study conducted in more than 1,000 patients showed an apparent regulating effect on HR, with a more marked decrease at higher baseline HR.[15] This study lacked a control group, however, and included only patients with mild-to-moderate hypertension. Hence, there was a need to confirm these results versus placebo or active compounds not influencing HR (angiotensin-converting enzyme [ACE] inhibitors, diuretics) via a meta-analysis of controlled studies, in both angina and hypertension. In addition to this retrospective analysis, we report the results, from one of these studies, of the effects of SR diltiazem on HR during exercise stress testing in patients with angina.

Methods

Selection of Studies for the Meta-Analysis

Studies were selected in accordance with published guidelines for meta-analyses and comprised all double-blind, randomized, parallel-group studies conducted with SR diltiazem 200 and 300 mg, in both hypertension and angina, either against placebo or against active treatments with no recognized effects on HR.[16, 17] Six studies met these criteria, as well as data on file.[18–20] The design, main inclusion criteria, and varying treatment durations of these studies are summarized in Tables I and II.

Statistical Methods

Compilation of the data file for the meta-analysis: The following variables were obtained for the data pooled from the selected studies: identification of the patient (patient number), gender, age, supine systolic blood pressure, supine diastolic blood pressure, supine HR, treatment. Blood pressure and HR were recorded on inclusion into the study (before treatment) and at the last evaluation during treatment.

Statistical Analysis

Patient characteristics at baseline (Table III): The distribution of quantitative variables is shown for the population as a whole and for the individual treatment groups. The Student's *t*-test was used to compare treatment groups. Distribution by gender is also shown. The treatment groups were compared using the chi-square test.

Analysis of the change in heart rate by baseline heart rate category: Baseline HR was divided into categories according

TABLE I Description of treatments used in each clinical trial

	DILPLACOMP	DILCACOMP	DTZ 88 IV FR02	MONOMAPA	DILMOD II	DILDURANG
Placebo wash-out (weeks)	2	2	1–3	2–4	2	1
Dose adjustment (weeks)	2	4	—	—	—	—
Treatment duration (weeks)[a]	4	8	6	4	4	1
SR-diltiazem (1 capsule/day)	200 mg, then 200 mg or 300 mg	200 mg, then 200 mg or 300 mg	300 mg	200 mg	300 mg	200 mg versus 300 mg
Control group	Placebo	Captopril 25 mg/day or 50 mg/day	Enalapril 20 mg/day	Placebo	Hydrochlorothiazide/ amiloride 50 mg/ 5 mg once daily	Placebo

[a] Duration of active treatment.

Abbreviations: DILPLACOMP = DILtiazem PLAcebo COMParative trial; DILCACOMP = DILtiazem CAPtopril COMParative study, DTZ 88 IV FR 02 is a multicenter, randomized, double-blind trial to evaluate the efficacy of diltiazem 300 mg versus enalapril 20 mg administered once daily for 6 weeks in two groups of 100 patients suffering from mild to moderate hypertension, together with the effects of the combination of these products in non-normalized patients; MONOMAPA is a study comparing the 24 h antihypertensive efficacy of long-acting dilitazem 200 mg (Monotildiem LP 200 mg) to placebo by ambulatory blood pressure monitoring; DILMOD II is a multicenter study comparing the efficacy and tolerability of diltiazem 300 mg once daily to a diuretic in the moderately hypertensive elderly patient; DILDURANG = DILtiazem DURation in ANGina.

TABLE II Description of main selection criteria

DILPLACOMP n = 158	DILCACOMP n = 100	DTZ 88 FR02 n = 176	MONOMAPA n = 65	DILMOD II n = 90	DILDURANG n = 182
SR-diltiazem n = 78 Placebo n = 80	SR-diltiazem n = 50 Captopril n = 50	SR-diltiazem n = 89 Enalapril n = 87	SR-diltiazem n = 30 Placebo n = 35	SR-diltiazem n = 42 Hydrochlorothiazide n = 48	200 mg SR-diltiazem n = 56 300 mg SR-diltiazem n = 66 Placebo n = 60
Uncomplicated essential hypertension 90 ≤ sDBP < 115 mmHg			90 ≤ sDBP < 110 mmHg	90 ≤ sDBP ≤ 120 mmHg	Typical stable exertional angina documented by a positive exertion test conducted on two occasions with a 7-day interval, an ischemic threshold of 3 and 12 min, and a variation in total exercise duration of < 15%.
20–70 years HR ≥ 55 beats/min	65–85 years HR ≥ 55 beats/min	16–68 years HR ≥ 55 beats/min	20–75 years HR ≥ 50 beats/min	60–85 years HR ≥ 50 beats/min	30–70 years HR ≥ 55 beats/min
Previous antihypertensive treatment discontinued					Previous anti-angina treatment discontinued

Abbreviation: SDBP = sitting diastolic blood pressure. Other abbreviations as in Table I.

to those used in the Framingham study as follows: ≤ 65 beats/min; 65–74 beats/min; 74–84 beats/min; ≥ 85 beats/min.[1] To investigate the effects of SR diltiazem and the control medications on HR, a two-way analysis of variance (ANOVA) (treatment, baseline HR category) was performed on the HR difference between inclusion and last clinical assessment. If the treatment/category interaction was significant, the treatment effect in each baseline HR category was tested, and p values were corrected using Hommel's method (correction for multiple tests).[21] Any interaction between the treatment and the baseline HR category may indicate a deviation from simple regression toward the mean; comparisons between the treatment groups (SR diltiazem and control medications) and by baseline HR category permitted identification of the specific effect of SR diltiazem on HR. The significance level was set at $p < 0.05$ (two-tailed).

TABLE III Patient characteristics at inclusion

		SR-diltiazem	Control group	Total	p Value
Gender	M: n (%)	239 (58.2)	194 (53.9)	433 (56.2)	0.23
	F: n (%)	172 (41.8)	166 (46.1)	338 (43.8)	
Age (years)	Mean (SD)	59.5 (11.6)	59.4 (11.9)	59.4 (11.7)	
	Minimum	20.0	20.0	20.0	
	Maximum	85.0	87.0	87.0	
	n	408	360	768	0.92
HR (beats/min)	Mean (SD)	75.4 (10.4)	76.7(10.0)	76.0 (10.2)	
	Minimum	47.0	48.0	47.0	
	Maximum	108.0	112.0	112.0	
	n	410	360	770	0.08
SBP (mmHg)	Mean (SD)	160.8 (19.3)	163.1(18.3)	161.9 (18.9)	
	Minimum	110.0	110.0	110.0	
	Maximum	220.0	222.0	222.0	
	n	411	360	771	0.09
DBP (mmHg)	Mean (SD)	96.0 (11.2)	98.0 (10.1)	97.3 (10.8)	
	Minimum	60.0	60.0	60.0	
	Maximum	118.0	122.5	122.5	
	n	411	360	771	0.0003

Abbreviations: M = male, F = female, DBP = diastolic blood pressure, SBP = systolic blood pressure, SD = standard deviation, HR = heart rate.

Analysis of differences in heart rate between treatments by study: To evaluate the consistency of results between studies, the differences between treatments, and differences between baseline HR category at inclusion and last assessment and their 95% confidence intervals were calculated for each study and overall; the level of the effect is the difference between the means of the two groups—those receiving either SR diltiazem or another treatment (placebo or ACE inhibitors or diuretics)—divided by the overall standard deviation (SD).

Assessment of the effect of once-daily SR diltiazem on heart rate during exercise in patients with angina: This analysis was performed as part of the Diltiazem Duration in Angina (DILDURANG) study.[18] An exercise test was conducted at baseline (Day 0) and again after a 1-week treatment (Day 7). Heart rate was measured at rest before starting the exercise test, at increasing workload increments—30, 60, 90 W—and at maximum exercise. Results were expressed as mean ± SD. Exercise HR in the three treatment groups (SR diltiazem 200 and 300 mg, and placebo) during exercise on Day 0 and Day 7 were compared using ANOVA. Two by two comparison of treatment was performed using the Student's test of comparison of least square means. The significance level was set at $p < 0.05$.

Results

Meta-Analysis on Heart Rate at Rest

Distribution by age and gender: In all, 771 patients were included in the meta-analysis, of whom 411 had received SR diltiazem. The mean ages (± SD) in the SR diltiazem and other group were 59.5 ± 11.6 and 59.4 ± 11.9 years ($p = 0.92$), respectively. Men comprised 58 and 54% of the two groups, respectively ($p = 0.23$) (Table III).

Mean blood pressure at inclusion: Mean systolic blood pressure values at inclusion did not differ significantly ($p = 0.09$) between the SR diltiazem and the control group, and were 160.8 ± 19.3 and 163.1 ± 18.3 mmHg, respectively. Mean diastolic blood pressure showed a small but significant difference of 2.8 mmHg ($p < 0.001$) between the two groups: 96.0 ± 11.2 mmHg in the diltiazem and 98.8 ± 10.1 mmHg in the control group (Table III).

Mean baseline heart rate: The mean baseline HR was 75.4 ± 10.4 beats/min in the SR diltiazem group and 76.7 ± 10.0 beats/min in the reference group ($p = 0.08$) (Table III).

Change in heart rate by category of baseline heart rate: This meta-analysis controls for differences between the two groups in any HR changes due to other aspects of management, in HR changes due to reduction in blood pressure or, in particular, in regression toward the mean; all would be as likely to occur with SR diltiazem as with the other treatments. It can be observed, therefore, that there was a significant interaction between treatment and baseline HR (Fig. 1), showing larger relative changes in HR with increasing baseline HR. In the group with baseline HR ≥ 85 beats/min, SR diltiazem reduced HR by a mean of 10.7 ± 8.3 beats/min, whereas HR in the control group decreased by a mean of 5.8 ± 10.2 beats/min ($p = 0.001$). In the group with baseline HR of 74–84, the mean reductions were 6.1 ± 7.0 on diltiazem and 2.2 ± 7.7 beats/min in the control group ($p < 0.001$). No significant HR reduction was observed in the groups with baseline HR of 65–74 or ≤ 65 beats/min. Multiple comparisons by baseline HR category showed a statistically significant difference between the two treatment groups for baseline HR of 74–84 and ≥ 85 beats/min ($p = 0.001$, corrected for multiple tests according to Hommel's method).[21] There were no significant differences between other baseline HR categories ($p > 0.65$ in both cases). The confidence intervals of the differences in HR for the different studies according to baseline HR category are shown in Figure 2.

Effect on Heart Rate at Exercise (Patients with Angina)

Heart rate at the different workloads did not differ among the three treatment groups on Day 0. The HR values on Day 7 at rest and at all three submaximal workload levels were significantly lower with SR diltiazem than with placebo. In the placebo group, the mean (± SD) HR at rest was 77.0 ± 11.7 beats/min and 100.00 ± 16.7, 116.6 ± 16.4, and 132.0 ± 16.5 beats/min at 3-minute incremental workloads of 30, 60, and 90 W, respectively. Compared with placebo, the HR changes observed at rest and during exercise with the SR diltiazem 300 mg dose were, at baseline 72.7 ± 12.2 ($p < 0.05$ vs. control); at 30 W 93.2 ± 15.4 ($p < 0.05$ vs. control); at 60 W 106.6 ± 17.9 ($p < 0.001$ vs. control); and at 90 W 120.6 ± 19.3 ($p < 0.001$ vs. control). The same comparison with the 200 mg dose shows at baseline 72.0 ± 10.2 ($p < 0.05$ vs. control); at 30 W 91.9 ± 13.4 ($p < 0.01$ vs. control); at 60 W 106.5 ± 14.6 ($p < 0.01$ vs. control); and at 90 W 120.7 ± 14.3 ($p < 0.01$ vs. control). Differences between groups in HR at maximum effort did not reach statistical significance; however, the change in maximal work output achieved was higher with SR diltiazem than with placebo, 8.9 ± 1.2 vs. 4.1 ± 1.2 KJ, respectively ($p < 0.05$), and exercise duration was longer, 71.4 ± 10.6 vs. 37.3 ± 10.2 s, respectively ($p = 0.07$).

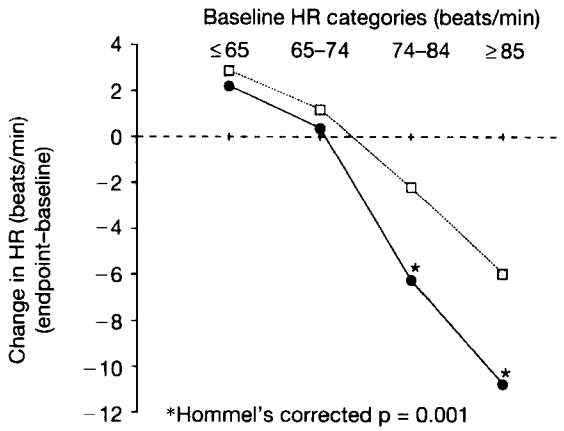

FIG. 1 Changes in heart rate for diltiazem and control groups according to baseline heart rate (HR) category. —●— SR diltiazem, - - -□- - - control group.

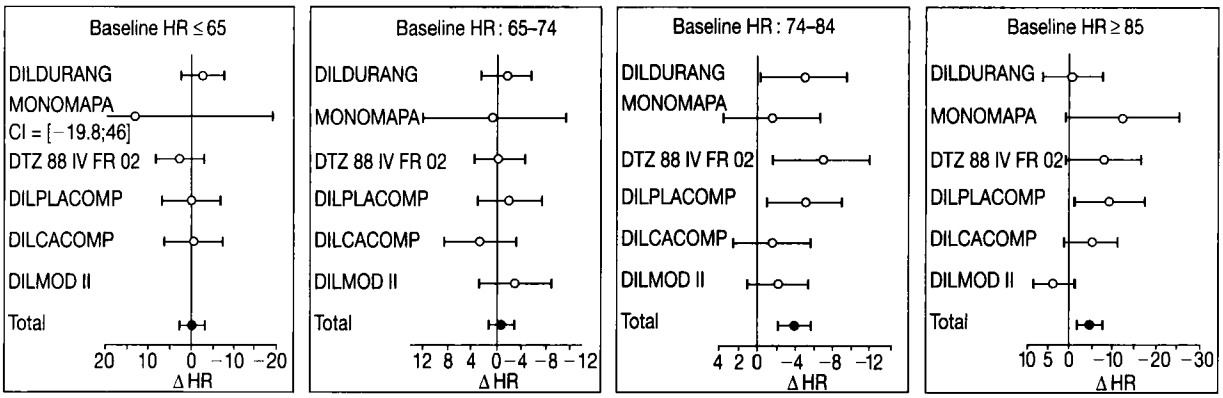

FIG. 2 Difference in heart rate (HR) (with 95% confidence interval [CI]) for different studies and overall results according to baseline heart rate category. See Table I for explanation of trial acronyms and abbreviations.

Discussion

Our findings provide evidence that in patients with angina pectoris or hypertension once-daily SR diltiazem had a discernible regulating effect on HR. This is characterized by HR slowing that was more marked at higher baseline HR, and by a lack of significant effect at lower levels of HR. These findings contrast with those obtained with the beta blocker timolol in patients following MI; in this study the percentage of patients with an HR < 60 beats/min increased from 15 to 77%, 32% of whom had an HR < 50 beats/min on treatment.[5] In patients with angina, this HR-regulating effect resulted in improved exercise performance compared with placebo and was consistent with the results of other studies showing superior exercise tolerance with diltiazem over the beta blocker metoprolol.[22,23]

This HR-lowering effect distinguishes once-daily SR diltiazem from the dihydropyridine subclass of calcium antagonists. In a double-blind study in hypertensive patients, there was a significant reduction in resting HR after 8 weeks of treatment with diltiazem 180–270 mg/day (84 ± 12 vs. 77 ± 14 beats/min, $p < 0.02$) while nifedipine 30–60 mg/day produced no significant change.[24] In a crossover study in stable angina, a significantly lower HR was observed with diltiazem than with placebo or nifedipine: resting HR (± SD) were 76.2 (± 15.1), 85.3 (± 14.1), and 89.1 (± 17.3) ($p < 0.01$), and peak HR during exercise were 124.1 (±13.8), 125.6 (± 14.5), and 131.4 (± 12.5), respectively ($p < 0.01$).[25] Comparable results were obtained by Bory *et al.*[26]

The overall effects of calcium antagonists on HR are the result of two opposing actions: the intrinsic negative chronotropic effect due to a decrease in slow diastolic depolarization, and the reflex-positive chronotropic effect due to sympathetic stimulation induced by peripheral arterial vasodilation. With diltiazem, the intrinsic negative chronotropic effect is predominant, leading to a moderate reduction in HR; the effect of the dihydropyridine agents, however, depends predominantly on their ability to activate the neurohumoral reflexes, resulting in a net HR increase. Furthermore, with diltiazem, the HR-lowering effect is most pronounced at the highest resting HR, with more modest reductions at lower baseline values. In an earlier study, the percentage of patients with an initial resting HR of < 60 beats/min remained unchanged at 10% during treatment.[15] It is important to note that only 1.7% of patients had an HR < 50 beats/min on 300 mg SR diltiazem.

Evidence is emerging that differences in resting HR may have important prognostic implications. Among men in the Framingham Study, the risk of cardiovascular death increased progressively with increasing HR regardless of age, and the odds of survival to the age of 75 years increased by 39% for a 1 SD decrease in HR (12 beats/min).[27] Among hypertensive patients in the Framingham Study, a raised HR was an independent risk factor for all-cause mortality, mortality from cardiovascular disease and coronary heart disease, and sudden cardiac death.[1] Several studies have also shown that an elevated HR is associated with an adverse outcome after acute MI, independent of the presence of heart failure.[2–6] In one of these studies, a mean RR cycle length (used as a surrogate measure of HR) of < 700 ms predicted cardiac death with 45% sensitivity, 85% specificity, and 20% positive predictive accuracy; moreover, when patients were stratified according to mean RR cycle length, the risk of cardiac death and sudden death increased progressively from the lowest to the highest quartile.[2] In a second study, in-hospital mortality was 5.2, 9.5, and 15.1%, respectively, for patients with HR < 70, 70–89, and ≥ 90 beats/min ($p < 0.01$); 1 year after discharge, a similar pattern of mortality was observed: 4.3, 8.7, and 11.8%, respectively.[3] A third study also reported increased in-hospital and postdischarge mortality with increasing HR on admission: total mortality was 15, 41, and 48% for patients with an admission HR of 50–60, > 90, and > 110 beats/min, respectively.[4] In a fourth study, which was a placebo-controlled comparison of timolol on mortality and reinfarction after acute MI, the lower mortality in the timolol group—7.3 vs. 12.5%, a decrease of 41.6% ($p < 0.001$)—could be attributed mainly to HR reduction.[5] A fifth study suggested that, for elderly patients with heart disease (defined as previous MI, typical angina pectoris without prior MI, hypertensive heart disease, valvular heart disease, or cardiomyopathy), the risk of developing new coro-

nary events increased by 14% for every increment of 5 beats/min after controlling for confounding variables.[28] Finally, a sixth study showed, in a multivariate analysis, that HR is of prognostic significance after MI, both for in-hospital mortality and at 6 months.[6]

Although some earlier studies (for a review, see Ref. No. 29) found no or only weakly significant associations between HR and the incidence of sudden death in patients with coronary heart disease, and death from noncardiovascular disease on multivariate analysis, this might have been attributable to correlations noted between HR and other cardiovascular risk factors, particularly blood pressure.

There are several mechanisms by which an elevated HR might be involved, either directly or indirectly, in the pathogenesis of coronary heart disease. In monkeys fed an atherogenic diet, a high HR correlated with the extent of coronary artery atherosclerosis and with enhanced plaque formation.[30,31] Also, tachycardia is itself a sign of sympathetic activation which, in turn, not only raises levels of blood pressure, but also has deleterious effects on other cardiovascular risk factors, including total cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, and insulin. Sympathetic stimulation also induces left ventricular hypertrophy.[32] Thus, tachycardia itself may be either an independent risk factor or indirectly a prognostic marker for other pathogenetic mechanisms.

By contrast, HR-lowering pharmacologic agents may have a beneficial effect on prognosis. Several trials of the use of beta blockers following acute MI have shown a relationship between the reduction of HR and improved survival (for a review, see Ref. No. 4). In a meta-analysis of the Multicenter Diltiazem Postinfarction Trial (MDPIT) and the Danish Verapamil Infarction Trial II (DAVIT-II), a reduction was noted in the mortality rate and rate of reinfarction in patients recovering from a non-Q-wave MI treated either with diltiazem or with verapamil, another rate-limiting calcium antagonist.[10] A similar meta-analysis of 5,677 patients post myocardial infarction (Q-wave or non-Q-wave) from DAVIT-I, DAVIT-II and MDPIT showed an overall 10% cumulative reduction in the composite trial endpoint of cardiac death or nonfatal MI during a mean follow-up of 550 days among patients randomized to an HR-lowering calcium antagonist, compared with placebo ($p = 0.035$).[33,34] By contrast, the Secondary Prevention Reinfarction Israel Nifedipine Trial (SPRINT II) and the Holland Interuniversity Nifedipine-Metoprolol Trial (HINT) revealed an inferior survival in patients with coronary disease treated with short-acting nifedipine.[11,12] This effect has been linked to nifedipine's positive chronotropic action.

Limitations

The retrospective nature of our analysis limits its interpretation. It remains to be shown in a prospective manner that calcium-channel blockers that lower HR correspondingly reduce the incidence of cardiovascular events in patients with hypertension or angina. A large prospective trial, the Nordic Diltiazem study (NORDIL) with diltiazem is now under way to address this issue.[35] Another prospective study, Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post-Thrombolysis (INTERCEPT) has recently been published showing that diltiazem reduced non-fatal cardiac events.[36,37]

Also, while it seems clear that increasing levels of HR is deleterious, it is currently premature to conclude that the decrease in HR alone is prognostically beneficial. Indeed, HR-lowering drugs with proven beneficial effects (beta blockers, nondihydropyridine calcium antagonists) also have other mechanisms of action. Moreover, drugs which do not alter HR (ACE inhibitors, aspirin, statins) have been demonstrated convincingly to decrease cardiovascular event rates.

Conclusions

This meta-analysis clearly demonstrates that, in patients with hypertension or angina, particularly in those whose initial HR was > 74 beats/min, SR diltiazem, at a doses of 200–300 mg once daily, slows HR, suggesting a more marked effect at higher initial rates. Sustained-release diltiazem at these doses does not appear to alter HR significantly when the baseline rate is ≤ 74 beats/min.

These findings indicate that once-daily SR diltiazem has a downregulating effect on HR, reducing tachycardia without inducing excessive bradycardia. These observations are in contrast to those obtained with dihydropyridine calcium antagonists, which tend to increase HR and have been associated with an adverse outcome in acute cardiovascular conditions. Prespecified post hoc analyses in patients recovering from MI indicate that HR-lowering calcium antagonists such as diltiazem or verapamil decrease subsequent cardiovascular events, particularly recurrent infarction. Thus, when calcium-channel blockade is indicated clinically, HR-lowering agents—especially once-daily, sustained-release preparations with HR-lowering effects—should be preferred to the dihydropyridine subclass of drugs, which are known to raise HR and increase cardiac events.

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