Clinical Investigations

Verapamil Use in Patients with Cardiovascular Disease: An Overview of Randomized Trials

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Summary

Background: Several reports have questioned the lack of safety data on calcium antagonists as a drug class. Because this drug class is heterogeneous, unique features of certain calcium antagonists may set them apart in terms of safety and efficacy.

Hypothesis: With in excess of 7,000 person-years of observation from randomized clinical trials, verapamil was selected to evaluate whether there was evidence of harm in patients with cardiovascular disease.

Methods: MEDLINE search of English-language articles, Science Citation Index, Current Contents, manual review of cited references, pharmaceutical files, and investigator correspondence was performed. Independent review of 66 articles identified 14 randomized, parallel-group studies for inclusion. Independent, duplicate assessments were made of patient outcomes and trial characteristics (including study design, treatment dosage and schedule, duration of treatment, inclusion criteria, and sample size). Standard meta-analytic techniques were employed for analysis and interpretation of results.

Results: Based on over 4,000 person-years of observation, patients with acute myocardial infarction (MI) treated with verapamil had a decreased risk of nonfatal reinfarction compared with placebo (relative risk 0.79; 2-sided 95% confidence interval 0.65, 0.97; $p = 0.024$). Verapamil had no significant effect on overall mortality compared with placebo (rel-

ative risk ranged from 0.93; 2-sided 95% confidence interval 0.78, 1.10; $p = 0.40$ to 0.86; 2-sided 95% confidence interval 0.71, 1.04; $p = 0.13$) depending on rules used to include or exclude patients from the pooling process. For the combined outcome of death or reinfarction, verapamil use was associated with a decreased risk compared with placebo (relative risk 0.82; 2-sided 95% confidence interval 0.70, 0.97; $p = 0.016$).

In patients with angina involving a wide spectrum of disease severity, data were limited to 2,900 person-years of observation, and verapamil use did not appear to be associated with an apparent effect on mortality or MI. Data available from randomized studies of verapamil in patients with hypertension were too limited to reach conclusions (50 person-years of observation, with no deaths or MIs reported). Subgroups of hypertensive patients in two of the largest post-MI studies and the largest angina study, involving over 600 patients, yielded little useful added information.

Conclusions: In patients with MI, the risks of both nonfatal reinfarction and the combined outcome of death or nonfatal MI were reduced over intermediate-term follow-up among patients treated with verapamil compared with controls ($p = 0.024$ and $p = 0.016$, respectively). In patients with angina, no evidence for harm was noted, but in hypertension the data were too limited to draw conclusions. These findings support the need to distinguish among different calcium antagonist compounds and to emphasize the need for more data in patients with hypertension.

Key words: cardiovascular disease, calcium antagonists, meta-analysis, randomized clinical trials

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Introduction

Although calcium antagonists have established efficacy for controlling blood pressure and angina, there is a perception that they may be unsafe. Held *et al.*,^{1–3} Yusuf *et al.*,^{4,5} and Furberg⁶ provided overviews, from prospectively randomized trials in patients with acute myocardial infarction (MI), that have raised concern that calcium antagonists may increase risk of mortality and reinfarction. More recently, Psaty *et al.*⁷ in a retrospective case-control study, raised the possibil-

ity that calcium antagonists prescribed for hypertension may increase risk of MI. This study compared prior use of various antihypertensive drugs among cases with MI versus matched controls. The authors reported a 60% greater risk of MI among hypertensive patients treated with calcium antagonists compared with those treated with diuretics alone. The increased risk appeared to be dose-related. Despite substantial media attention, these results are far from definitive.⁸ Inherent limitations of the case-controlled design make it impossible to exclude potential biases that would significantly alter interpretation of results. For example, if selection of the drug used to treat hypertension is linked to factors that independently affect risk of MI, such as clinical suspicions that coronary artery disease may be present, then results are confounded. Furthermore, calcium antagonists with diverse pharmacologic profiles (e.g., lidoflazine, nifedipine, diltiazem, and verapamil) were viewed as a general class of drugs, without regard for particular mechanisms of action or delivery schedules (immediate vs. sustained release) that distinguish risk-benefit profiles of specific agents.

Consideration must be given to differences in calcium antagonists. For example, unlike increases in heart rate produced by nifedipine, heart rate-lowering effects of verapamil and diltiazem would likely cause reduction in ischemia and its consequences. Unique features of certain calcium antagonists may set them apart in terms of both efficacy and safety. Verapamil is one such widely used calcium antagonist that deserves attention. To evaluate the question of whether there exists evidence for harm with verapamil, this paper presents a systematic analysis and synthesis of published randomized, controlled trials in patients with MI, angina, or hypertension.

Materials and Methods

A protocol was first established to define the purpose of the overview, criteria for study selection, data extraction process, clinical outcomes, and methods of analysis. The goal was to integrate findings from all available, prospectively randomized clinical studies comparing verapamil with either placebo or other therapies in patients with acute MI, angina, or hypertension. Clinical outcomes defined were all-cause mortality, nonfatal reinfarction or infarction, and combination of these two events.

A MEDLINE search of the medical literature (January 1966 through April 1997) was undertaken using the key word "verapamil" alone and also coupled with the following terms: clinical trial, MI, angina, and hypertension. This was limited to English-language and human subjects studies. References listed in these publications were then reviewed to identify studies not found in the MEDLINE search, or others appearing in abstracts or papers in press. An exhaustive check of review papers, Science Citation Index, and Current Contents also were used to identify references. Finally, three investigators knowledgeable with the verapamil literature reviewed the list of publications for completeness. Based on this search, every prospectively randomized trial evaluating the comparative

efficacy and safety of verapamil was obtained to assure that the overview was comprehensive and free of selection bias.

The data extraction process was carried out by one co-author (RWM) and then cross-checked by two other co-authors (GAF, CJP) to arrive at a final set of studies and data elements for pooling. Any differences were resolved by consensus. Every published study in MI, angina, and hypertension qualified for inclusion based on adequacy of design, despite differences in outcome definitions, entry criteria, dosing regimens, and duration of follow-up. When compelling reasons existed for excluding data [e.g., failure to confirm MI after randomization in the Danish Verapamil Infarction Trial-1 (DAVIT-1)], separate analyses were performed to determine whether such exclusions would materially affect conclusions of the overview.

Standard statistical methods that completely avoid unjustifiable assumptions of comparability between different trials were used to obtain an overview of trial results.^{9, 10} This method first involves calculation of the expected number of events that occurred in the verapamil group, together with the variance (VAR). Within each study, the observed number of events in the verapamil group (denoted as O) is contrasted with number of events expected (denoted as E) under the null hypothesis of no treatment difference. Thus, the method first involves comparison of within-study effects to preserve within-study integrity. When E is subtracted from O for each study, the difference (O-E) would differ only randomly from zero if verapamil were of no benefit, whereas differences would tend to be negative if there were a benefit associated with verapamil.⁹

To evaluate the overall effect of treatment, the sum of differences between observed and expected numbers of events across all studies, $\Sigma(O-E)$, is divided by the square root of the sum of variances, $(\Sigma VAR)^{0.5}$, to yield a standard normal z statistic.^{9, 10} This value is then compared with the distribution of a standard normal N(0,1) variate to obtain a 2-sided p value. Heterogeneity tests were performed to examine whether relative risks varied significantly among different studies.

An estimate of the relative odds of an adverse outcome in the verapamil group compared with the C group is calculated using the approximate formula $\exp(z/(\Sigma VAR)^{0.5})$, with 2-sided 95% confidence interval $\exp(z/(\Sigma VAR)^{0.5} \pm 1.96/(\Sigma VAR)^{0.5})$.^{9, 10}

Results

More than 800 articles were identified in the screening process. In total, 66 reports involving verapamil for randomized, controlled trials were identified and reviewed to extract data required for this overview. Results of the same clinical trial were sometimes contained in multiple publications and were reconciled and consolidated during data extraction. A number of previous calcium antagonist overviews, as well as a recent update of the first major verapamil trial in acute MI,¹¹ DAVIT-1, were identified.¹⁻⁶ None of the previous overviews included data from a post-MI study published in 1980¹² or

two recently published trials, one regarding acute MI¹³ and the other regarding angina.¹⁴

Clinical Trial Evidence in Acute Myocardial Infarction

Seven randomized, controlled trials using verapamil in MI were identified and study design features are summarized in Table I. The studies represent more than 4,000 person-years of observation.

DAVIT-1 evaluated very early intervention using intravenous bolus at admission followed by oral treatment for 6 months.¹⁵ The second trial (DAVIT-2) evaluated oral treatment beginning 1 week post MI and continuing for 12 to 18 months.¹⁶ The Calcium Antagonist Reinfarction Italian Study (CRIS)¹⁷ evaluated oral treatment for 7 to 21 days post MI, and data were collected to 24-months follow-up. Four additional trials^{12, 13, 15, 18} contributed small numbers of patients and used early short-term treatment (initiated at admission for 2 to 10 days) and limited follow-up periods (2 days to 3 months).

For completeness, this overview incorporates DAVIT-1 results using three alternate sets of data. One corresponds to the original DAVIT-1 report¹⁵ which excluded 2,011 patients with suspected MI, randomized and receiving verapamil at study entry, who were later not confirmed to have MI. Another includes all 3,447 randomized patients, as presented in a series of overviews,^{1, 4, 5} despite the fact that patients with unconfirmed MI received no further treatment 1 week following randomization. The third includes an update of adverse outcomes reported by DAVIT investigators for patients with confirmed MI.¹¹ Given possible controversy over use of the intent-to-treat principle in this setting, it was important to examine how conclusions of the overview differed depending on study populations used for analysis.

The proportion of nonfatal reinfarctions among patients with MI for each of the six verapamil versus no active treatment control trials is presented in Table II. Because it is the only trial to have an active control group, the Hansen *et al.* trial¹³ is reported separately at the end of this MI section. With the exception of the small study ($n = 17$) by Crea *et al.*,¹⁵ results all favored verapamil-assigned patients. Results from the three largest trials (DAVIT-1,¹⁶ DAVIT-2,¹⁹ and CRIS¹⁷) that contribute essentially all of the data to the overview, are consistent in the percent reduction (range 14.1–19.8%) in nonfatal reinfarction associated with verapamil.

Relative risks and corresponding 95% 2-sided confidence limits for each of the six no active treatment control trials are presented in Figure 1, with the estimated relative risk of nonfatal reinfarction associated with verapamil. Results from each of the three largest studies (DAVIT-1, DAVIT-2, and CRIS) show consistent statistically nonsignificant trends associated with verapamil, with odds reduction in nonfatal reinfarction ranging from 15 to 22%.

There were no verapamil-group reinfarctions in either the Hansen *et al.*¹² or Bussman *et al.*¹⁸ studies so that study-specific odds ratios were unobtainable. The odds ratio was 1.25 in the Crea *et al.* study,¹⁵ favoring control ($p > 0.80$). Because these

three studies were small, their results are displayed in Figure 1 using methodology for combining data across studies.^{9, 10}

Overview analyses were based on data for each of six verapamil versus no active treatment studies separately. The three different combinations of study data, accounting for differences in reported results of DAVIT-1,^{1, 11, 16} all revealed statistically significant reductions in risk of nonfatal reinfarction associated with verapamil. A formal test for heterogeneity provided no evidence of marked between-study differences in relative risk ($p = 0.50$), thereby supporting poolability. The three combinations produced remarkably consistent odds ratios ranging from 0.79 to 0.80, corresponding to a 20 to 21% risk reduction for nonfatal reinfarction associated with verapamil. The lower 95% 2-sided confidence limits range from 0.64 to 0.65, indicating a risk reduction of 35 to 36%. The upper confidence limits indicate a 2 to 3% risk reduction. The p values range from 0.023 (using the full intent-to-treat DAVIT-1¹ population) to 0.028 (using updated DAVIT-1 results¹¹ for all patients with confirmed MI). Thus, there is an overall suggestion of benefit seen consistently among these studies, and taken together it is unlikely that harmful effects were missed.

With respect to mortality, trends indicated a statistically nonsignificant reduction in mortality associated with verapamil in several studies (Table II). The effect on mortality associated with verapamil ranged from a 5.6% increase in CRIS¹⁷ to an 18.5% reduction in DAVIT-2.¹⁹ For 1,436 patients with confirmed MI in DAVIT-1,¹⁶ the original report suggested a 7.8% reduction in mortality associated with verapamil while a similar 7.7% reduction was noted in the 1994 update. There is a slight, nonsignificant reduction in mortality associated with verapamil, ranging from 7 to 14% depending on the version of DAVIT-1^{1, 11, 16} results used (Fig. 2).

The p values range from 0.40, using the entire intent-to-treat population,¹ to 0.13 using updated mortality data.¹¹ For the original DAVIT-1 results,¹⁶ the mortality trend favoring verapamil is not significant ($p = 0.14$). Thus, key decisions in DAVIT-1 resulting from different patient inclusion criteria have little effect on overall mortality conclusions.

The relative risk of a combined adverse outcome (death or reinfarction) in patients taking verapamil compared with controls was estimated to be 0.82 [95% 2-sided confidence interval (0.70, 0.97); $p = 0.016$], based on a combination of original 6-month DAVIT-1 results and all other studies (Fig. 3). Similar results were obtained from the meta-analysis based on 12-month DAVIT-1 data and all other studies [relative risk 0.84, 95% 2-sided confidence interval (0.72, 0.98); $p = 0.023$]. Combination of results using the Held *et al.*¹ data from DAVIT-1 was not possible since combined adverse outcome data were not reported.

The seventh MI study¹³ had an active control group in which trandolapril (T) was compared at 3 months with verapamil plus trandolapril (VT) in patients with coexisting congestive heart failure. One reinfarction occurred among 51 (2%) VT patients, compared with seven reinfarctions among 49 (14%) T patients. The odds ratio was 8.3, favoring VT ($0.05 < p < 0.10$). One death occurred in each treatment group. Combining this active control trial with the six no active treat-

TABLE 1 Summary of prospectively randomized studies of verapamil versus control in patients with acute myocardial infarction

Authors/trial (Ref. No.)	Treatment information	Time of initiation of treatment ^a	Duration of treatment	Exclusion criteria	Design	Sample size
Bussman <i>et al.</i> (19)	VER 5–10 mg/h vs. control therapy	<20 h (mean 8h)	48 h	PCWP > 15 mmHg, cardiogenic shock, left ventricular failure	Parallel group	54
Crea <i>et al.</i> (15)	VER 10 mg IV repeated × 4 within 1h post admission, followed by 80 mg 3 times daily vs. placebo	<12 h	10 Days	Age >75, SBP <90 mmHg, HR <55 beats/min, PR >0.3 s, QRS >0.1 s, 2°–3° AV block, severe HF	Parallel group, single-blind	17
Hansen <i>et al.</i> (12)	VER 0.1 mg/kg at admission; 120 mg 3 times daily for 1 week vs. no VER	Admission to CCU	1 Week (+2 week follow-up)	Age >75, use of beta blocker or CCB, cardiogenic shock, SPB <90 mmHg, HF, cardiac arrest, PQ >0.3 s, 2°–3° AV block, SA block, HR <45 beats/min, QRS >11s, CHD	Parallel group no verapamil control	61
DAVIT-I (16) and (11)	VER 0.1 mg/kg at admission; 120 mg 3 times daily for 6 months vs. placebo	Admission to CCU	6 Months	Age 75, pretreatment use of beta blocker or CCB, cardiogenic shock, SBP <90 mmHg, HF, cardiac arrest, PQ >0.3 s, 2°–3° AV block, SA block, HR <45 beats/min, QRS >11s	Parallel group, double-blind	1436 (3447) ^b
DAVIT-II (18)	VER 120 mg 3 times daily vs. placebo	7–15 Days post MI	12–18 Months	Same as DAVIT-I except req. enzymes >25% NL, HF = inability to stabilize with Lasix 160 mg daily	Parallel group, double-blind	1775
CRIS Rengo <i>et al.</i> (17)	VER 120 mg 3 times daily vs. placebo	7–21 Days post MI	24 Months	Severe HF, allergy to VER, cardiac surgery, implanted pacemaker, right ventricular failure with pulmonary hypertension, hypertension	Parallel group, double-blind	1073
Hansen <i>et al.</i> (13)	VER 120 mg plus trandolapril 0.5 mg 2 times daily for 1 month, increased to VER 180 mg plus trandolapril 1.0 mg twice daily for next 2 months vs. trandolapril 0.5 mg twice daily increased to 1.0 mg twice daily after 1 month	3–10 Days post MI	3 Months	HF with edema despite diuretic treatment, Killip class IV, SBP <90 mmHg, 2°–3° AV block, SA block, significant valvular or other heart disease, already receiving beta blockers or CCBs	Parallel group, double-blind	100

^aTime since onset of myocardial infarction (MI) symptoms.^bAll randomized: Includes patients with suspected as well as confirmed MI, as reported in Ref. No. 1.

Abbreviations: VER = verapamil, IV = intravenous, SBP = systolic blood pressure, HR = heart rate, AV = atrioventricular, CCU = coronary care unit, PCWP = pulmonary capillary wedge pressure, CCB = calcium-channel blocker, HF = heart failure, CHD = coronary heart disease, MI = myocardial infarction, NL = normal, SA = sinoatrial. ▲

TABLE II Randomized clinical trials of verapamil versus control in patients with myocardial infarction

Authors/ (Ref. No.)	Verapamil			Control		
	Number of nonfatal reinfarctions (%)	Number of deaths (%)	Total number of patients randomized	Number of nonfatal reinfarctions (%)	Number of deaths (%)	Total number of patients randomized
Bussman <i>et al.</i> (18)	0 (0)	0 (0)	29	0 (0)	0 (0)	25
Crea <i>et al.</i> (15)	4 (50)	0 (0)	8	4 (44.4)	2 (22.2)	9
Hansen <i>et al.</i> (12)	0 (0)	3 (10.7)	28	4 (12.1)	4 (12.1)	33
DAVIT-1 (16)	50 (7.0)	92 (12.8)	717	60 (8.3)	100 (13.9)	719
DAVIT-1 (1)	50 (2.9)	149 (8.6)	1729	60 (3.5)	145 (8.4)	1718
DAVIT-1 (11)	54 (7.5)	92 (12.8)	717	63 (8.8)	101 (14.1)	719
DAVIT-2 (19)	84 (9.6)	95 (10.8)	878	107 (11.9)	119 (13.3)	897
CRIS (17)	39 (7.3)	30 (5.7)	531	49 (9.0)	29 (5.4)	542

ment trials caused a slight improvement in the positive overview results for reinfarction and no effect for death.

Clinical Trial Evidence in Angina

Of 43 prospectively randomized trials in patients with angina, 40 were short-term crossover trials, with treatment duration of ≤ 4 weeks. Because of this short treatment duration and difficulty in assigning outcomes to treatment in a crossover trials, these studies were not found acceptable for this overview. Further, they would contribute very few events as there were only two deaths and four nonfatal MIs. Table III summarizes the three remaining parallel-group, double-blind trials selected for the angina overview.

The Angina Prognosis Study in Stockholm (APSIS)¹⁴ trial included 809 patients with chronic stable angina, randomized

to verapamil or metoprolol for a duration of 6 to 75 months. The trial by Mehta *et al.*²⁰ was a 3-month, placebo-controlled study in 15 patients with severe angina. The trial by Hoberg *et al.*,²¹ was a 7-month placebo-controlled study in 196 patients with angina severe enough to warrant angioplasty. These studies span a broad spectrum of patients with angina. The total person-years of observation is estimated in excess of 2,900 person-years (using 2,887 person-years from APSIS¹⁴ and estimating for the other studies^{20, 21}). Thus, the body of evidence in angina is markedly less in terms of both person-years of observation and number of events compared with post-MI patients.

Given the paucity of data in the angina population, a formal pooled analysis offered little insight into the risk of adverse outcome associated with verapamil use in the angina population. Taken individually, the studies raise no clear cause for

^a Combined for display only. No verapamil-group reinfarctions in either Hansen *et al.* (Ref. 12) or Bussman *et al.* (Ref. 18) make the study-specific odds ratios uninterpretable, while the odds ratio is 1.25 for Crea *et al.* (Ref. 15) favoring control. Hansen *et al.* (Ref. 13) with active comparison group not included.

FIG. 1 Randomized clinical trials of verapamil versus no active treatment in patients with myocardial infarction. Ref. Nos. in parentheses.

FIG. 2 Randomized clinical trials of verapamil versus no active treatment in patients with myocardial infarction. Ref. Nos. in parentheses.

concern. With respect to nonfatal infarction in the study by Mehta *et al.*,²⁰ there was one event among nine patients treated with verapamil versus none of six patients on placebo. There were no events reported among the 196 patients evenly divided between verapamil and placebo in the Hoberg *et al.*²¹ study. The APSIS trial also showed no marked differences between treatment groups: nonfatal MI occurred in 14 of 403 verapamil patients (3.5%) versus 17 of 406 patients (4.2%) treated with the active control agent metoprolol ($p = 0.60$).

There were no deaths reported in studies by Hoberg *et al.*²¹ and Mehta *et al.*,²⁰ and mortality was comparable in the vera-

pamil and metoprolol groups of APSIS¹⁴ (6.2 vs. 5.4%, respectively) ($p = 0.64$). The combined outcome analysis also showed no difference between the active comparator and verapamil in APSIS,¹⁴ with a total of 39 events occurring in each of the two treatment groups.

Clinical Trial Evidence in Hypertension

Studies evaluating verapamil in hypertension also were examined. Of 17 prospectively randomized trials, 12 were short-term cross-over trials, and no deaths or nonfatal infarctions

FIG. 3 Randomized trials of verapamil versus no active treatment in patients with myocardial infarction. Ref. Nos. in parentheses.

TABLE III Summary of prospectively randomized studies of verapamil versus control in patients with angina

Authors/ (Ref. No.)	Treatment information	Duration of treatment	Exclusion criteria	Design	Sample size
Mehta <i>et al.</i> (20)	VER 320 mg/day increased to 480 mg/day for nonresponders vs. placebo	3 Months	HF, severe hypertension, hypotension, left bundle-branch block, bradycardia, AV block, valvular or congenital cardiac lesions, atrial flutter or fibrillation	Double-blind, parallel group	15
Hoberg <i>et al.</i> (21)	VER-SR 240 mg 2 times daily vs. placebo	7 Months	Acute MI, age > 70 years, previous revascularization procedure, HF, bradycardia	Double-blind, parallel group	196
Rehnqvist <i>et al.</i> (14)	VER-SR 240 mg 2 times daily vs. metoprolol 200 mg o.d.	6–75 Months	MI within last 3 years, unstable angina, anticipated need for revascularization within 1 month, noncompensated HF, contraindications to study drugs, significant valvular disease	Double-blind, parallel group	809

Abbreviations as in Table I.

were observed in any of the studies. The remaining five parallel, randomized, double-blind studies^{22–26} compared verapamil with either propranolol or nifedipine and contributed less than 50 person-years of observation with small sample sizes (12–142 patients) and/or relatively short treatment periods (2–24 weeks). Despite the fact that no deaths or nonfatal infarctions were observed in these trials, these studies were uninformative in reaching conclusions about the safety of verapamil because they were limited in both treatment duration and size.

Discussion

Methods

Recent publications have raised questions concerning the lack of safety data on calcium antagonists. For patients with MI, angina, or hypertension, this led us to the systematic assembly and combination of results from all published randomized, controlled trials evaluating verapamil, the first calcium antagonist available for clinical use. An analysis of verapamil data is important because of the large number of individuals who are taking this drug and the wide public attention directed at reports questioning the safety of this class of drugs. Past overviews have not focused on important differences among calcium antagonists and the need to take these differences into account when examining the role of these agents in long-term therapy of patients with cardiovascular disease. Unlike prior overviews, we focused only on verapamil, used all of the data available from randomized trials, and critically examined the “robustness” of conclusions based on intent-to-treat rules for patient inclusion. To eliminate the possibility of selection biases, a systematic search for all relevant trials was performed to identify studies for inclusion in the overview, regardless of size or duration.⁹ Methods were used to pool data that preserve within-study comparisons and combine treatment effects in a

weighted fashion to give greater weight to the larger and longer studies.^{9, 10}

Post-Myocardial Infarction Evidence

The largest source of data on verapamil exposure in a controlled setting comes from studies examining its use in prevention of reinfarction and death following MI. Our findings are based on controlled trials comprising in excess of 4,000 person-years of observation following MI.

The combined analysis in patients with MI indicates that verapamil use is associated with statistically significant reductions in risk of nonfatal reinfarction and the combined outcome of nonfatal reinfarction or death. Verapamil use was associated with a trend toward a somewhat lower risk of death, although risk reductions did not achieve statistical significance. These results are based on overall study populations and therefore are likely to represent the “average” verapamil effect. Some have suggested that left ventricular systolic dysfunction (LVSD) may represent a distinct subgroup of patients in whom verapamil is harmful.²⁷ This warning is useful for clinical practice, since extrapolation of our MI results to those with MI and LVSD may not be appropriate. Verapamil data for our overview did not allow a formal examination of this (and other) subgroup hypotheses. However, recent reports suggest that this subgroup requires additional evaluation. For example, in DAVIT-2, verapamil treatment was associated with a significant reduction in diuretic use at 18 months compared with placebo.^{19, 28} Because verapamil use is known to be associated with peripheral edema, which may prompt more diuretic use, this finding could be due to improved left ventricular function. Such a suggestion is supported by a recent report indicating that verapamil, when given with trandolapril to patients with coronary artery disease and reduced systolic function, is associated with improvement in left ventricular systolic wall motion.²⁹ As described earlier in

Results, a randomized, double-blind study in patients with acute MI and congestive heart failure, comparing verapamil and trandolapril to trandolapril alone, suggested that addition of verapamil reduces adverse outcomes.¹³ Clearly, more research is warranted in the area of differential effects of treatment among subgroups of patients with coronary artery disease, particularly now that angiotensin-converting enzyme (ACE) inhibitors are considered standard therapy for patients with LVSD. Randomized trials using other calcium antagonists in such patients receiving an ACE inhibitor (e.g., PRAISE, V-HeFT III, DIDI, and DEFIANT II) have shown no evidence for harm.³⁰⁻³²

Angina Evidence

Evidence based on the angina population is not as complete. The largest study (APSYS) involved over 800 patients followed for 6 to 75 months, with approximately 2,800 person-years of observation. There were no differences between verapamil and metoprolol (a known cardioprotective agent in this setting) in either nonfatal infarction or death rates. The other small placebo-controlled trials contributed negligible numbers of events.

Hypertension Evidence

Effects of verapamil in hypertensive subgroups of post-MI or angina populations also have been reported (DAVIT-1 Hypertension, 1996, private communication, Knoll Pharmaceutical)^{33,34} and appeared consistent with those in the respective full randomized studies. In DAVIT-1, 7 of 71 (9.9%) patients on verapamil versus 9 of 62 (14.5%) patients on placebo had a nonfatal reinfarction. Eight of 149 (5.4%) patients on verapamil in DAVIT-2 had a nonfatal reinfarction versus 13 of 152 (8.6%) patients on placebo. There was a 12.7% (13.4%) verapamil death rate versus 12.9% (16.5%) placebo death rate in DAVIT-1 (DAVIT-2). In APSIS, the number of cardiovascular deaths was 6 among 104 patients on verapamil (5.8%) versus 12 among 115 patients on metoprolol (10.4%). These hypothesis-generating subgroup analyses are subject to well-known problems in their analysis and interpretation, however.³⁵ More important, these subgroup analyses address the safety question in patients who have coexisting hypertension, not hypertension alone. Recently, the Verapamil in Hypertension and Atherosclerosis Study (VHAS) randomized 1,414 hypertensive patients to either verapamil or chlorthalidone.³⁶ After 2 years of treatment, the occurrence of cardiovascular events was similar for both treatment groups. These findings provide the background for the ongoing 27,000-patient International Verapamil/trandolapril Study (INVEST).

Conclusion

For patients with MI, the aggregate of existing data presented here does not support the hypothesis that verapamil use is associated with harm. Using the overall number of roughly

1,660 subjects with confirmed MI as the basis for statistical power considerations, we calculated statistical power to be >80% to detect a relative risk of $\geq 15\%$ (2-sided $\alpha = 0.05$ level). Thus, because our relative risk estimates favored verapamil, it is very unlikely that important deleterious effects of verapamil went undetected among post-MI patients. The limited data for patients with angina preclude similar confidence in excluding potential deleterious effects in these patient populations. In the hypertensive population, the paucity of data provides no evidence for either benefit or harm relative to prevention of major cardiovascular events.

A recent review of adjunctive drug therapy for acute MI by Hennekens *et al.*³⁷ included selected summary data for only three of the controlled clinical MI trials with verapamil. They concluded that there were neither harmful nor beneficial effects associated with use of nondihydropyridines in general. Their review focused mainly on mortality and reached no conclusion about any individual calcium antagonist. In contrast, our study includes all seven published verapamil randomized controlled trials in MI, and we showed that there was a statistically significant 16-17% overall reduction in death or nonfatal reinfarction associated with verapamil in patients with MI. Thus, combining all calcium antagonists together as a broad drug class with similar safety profiles is not supported. In addition, the consistency of our overall findings was evaluated through presentation of per study data, evaluation of three alternative sets of DAVIT-1 data, including the most recent and presumably more correct DAVIT-1 data,²⁷ and analysis of other adverse outcomes of considerable economic importance (e.g., nonfatal reinfarction and death).

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