Cardiac Event Rates After Acute Myocardial Infarction in Patients Treated With *Verapamil* and *Trandolapril* Versus *Trandolapril* Alone

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Angiotensin-converting enzyme (ACE) inhibitors improve survival in patients with congestive heart failure (CHF) after an acute myocardial infarction (AMI), but mortality may be as high as 10% to 15% after 1 year. Verapamil prevents cardiac events after an AMI in patients without CHF. We hypothesized that in postinfarct patients with CHF already prescribed diuretics and an ACE inhibitor, additional treatment with verapamil may reduce cardiac event rate. In this multicenter, double-blind study, patients with CHF receiving diuretic treatment were consecutively randomized to treatment with trandolapril 1 mg/day for 1 month and 2 mg/day the following 2 months (n = 49), or to trandolapril as mentioned plus verapamil 240 mg/day for 1 month and 360 mg/day for 2 months (n = 51). Trial medication started 3 to 10 days after AMI. All patients were followed for 3 months. End points in the trandolapril/trandolapril-verapamil groups were death 1/1, reinfarction 7/1, unstable angina 9/3, and readmission for CHF 6/2. The 3-month first cardiac event rate was 35% in trandolapril-treated patients and 14% in trandolapril-verapamil–treated patients (hazard ratio 0.35, 95% confidence interval 0.15 to 0.85, p = 0.015). These data suggest that verapamil reduces cardiac event rates in post-AMI patients with CHF when added to an ACE inhibitor and a diuretic.

(Am J Cardiol 1997;79:738–741)

In the Danish Verapamil Infarction Trial (DAVIT) II, the 18-month mortality rate in postacute myocardial infarction (AMI) patients without congestive heart failure (CHF) was lower in verapamil-treated than placebo-treated patients (hazard ratio 0.60, 95% confidence interval [CI] 0.39 to 0.92; p = 0.02), whereas no difference between the 2 treatments was found in patients with CHF in diuretic treatment (hazard ratio 1.01, 95% CI 0.72 to 1.43).[1,2] In the Acute Infarction Ramipril Efficacy (AIRE) study,[3] mortality rate in post-AMI patients with CHF in diuretic treatment was lower in ramipril-treated than in placebo-treated patients (hazard ratio 0.68, 95% CI 0.54 to 0.86), with no significant difference in patients not receiving diuretic treatment (hazard ratio 0.92, 95% CI 0.63 to 1.34). We hypothesized that after an AMI, patients with CHF receiving diuretic and ACE inhibitor treatment would benefit from concomitant treatment with verapamil. We conducted a double-blind, randomized study in these patients with trandolapril plus verapamil versus trandolapril alone. We used trandolapril, which in a recent Danish post-AMI trial improved survival of patients with CHF.[4]

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METHODS

The methods used in this study corresponded to those used in DAVIT II.[1]

Study population: Patients were recruited consecutively in 5 centers between March 1994 and June 1995. Patients eligible for the study were those (1) with AMI documented by typical chest discomfort and electrocardiographic changes compatible with Q or non–Q-wave infarction or bundle branch block, and elevation of lactate dehydrogenase$_{-1}$ and/or creatine kinase-MB to >25% of upper normal limit, (2) receiving diuretic treatment because of CHF during AMI (i.e., pulmonary congestion on any chest x-ray, or pulmonary crepitations/rales above the lower third of the dorsal part of the lung on auscultation, or a 3rd heart sound, or cardiogenic shock, or a combination of these), (3) able to attend the outpatient clinic, and (4) aged ≥18 years.

Exclusion criteria: Exclusion criteria were: heart failure with edemas despite diuretic treatment, Killip class IV, systolic blood pressure <90 mm Hg, second- or third-degree atrioventricular block, sinoatrial block, significant valvular or other heart disease, other severely disabling or terminal disease, serum creatinine >0.22 mmol/L, known intolerance to ACE inhibitors, already receiving treatment with β blockers or calcium antagonists, inability or unwillingness to give informed consent or cooperation, living outside the catchment area, previously randomized to the trial, and those unable to tolerate the trial medication.

Trial medication: When patients were in a stable clinical condition, they received a test dose in the

0002-9149/97/$17.00
PII S0002-9149(96)00860-0

morning between day 3 and 10 (i.e., a capsule containing trandolapril 0.5 mg and verapamil 120 mg). Patients who had no slowing of heart rate to <45 beats/min, sinoatrial or second- or third-degree atrioventricular block, orthostatic complaints, or systolic blood pressure <85 mm Hg in the following 24 hours, and agreed to continue in the trial, were randomized. Patients were consecutively randomized to treatment with identical-looking capsules containing either trandolapril 0.5 mg and verapamil 120 mg twice daily for 1 month, increased to trandolapril 1 mg and verapamil 180 mg twice daily for the following 2 months, or trandolapril 0.5 mg twice daily increased to 1 mg twice daily after 1 month. If adverse events occurred (e.g., orthostatic complaints), the treatment could be reduced to medication once daily. Compliance was checked by capsule counts. Trial medication should be withdrawn permanently with worsening CHF or angina pectoris, an increase in serum creatinine to >0.25 mmol/L, sinoatrial or second- or third-degree atrioventricular block, or if patients could not tolerate the trial medication or did not want to continue in the trial.

Recordings: All patients admitted to the coronary care unit with chest discomfort/pain suspected of AMI were recorded in the study database with registration of previous history, medication, and findings at physical examination. At the time of randomization physical examination, concomitant medication, clinical chemistry, blood pressure, electrocardiogram, and chest x-ray were evaluated. Patients were seen in the outpatient clinic 1, 2, and 3 months after randomization. Patients should, if at all possible, be followed in the outpatient clinic, even if they withdraw prematurely from trial medication.

End points: End points were: (1) death, 2) reinfarction with the same criteria as the index AMI, (3) unstable angina (i.e., angina with increasing frequency and intensity at rest or with a crescendo character) or, (4) readmission due to worsening CHF verified by increasing dyspnea, pulmonary congestion on chest x-ray, pulmonary edemas, or right-sided fluid retention. Any readmission during the trial period should be documented. The primary end point was the combined end point of death, reinfarction, unstable angina, and readmission due to CHF, whichever occurred first. All end points in the study period should be included in the analyses (i.e., an intention-to-treat analysis).

Ethics: The study was approved by the Danish Health Authorities and the Scientific Ethical Committees. Written informed consent was obtained before a patient received the test dose.

Data management and monitoring: Data entry was performed decentrally, as each center was equipped with a PC and a local database including screen forms with intensive logical error checking. Database and screen forms were programmed in SIR/DBMS and SIR/FORMS (Scientific Information Retrieval, Sydney, Australia), PC version 2.3. Every 2 to 3 months in the study period, all decentral databases were transferred on diskette to the database administrator (UNI-C, Aarhus, Denmark), who combined them into 1 database for preparation of study progress reports dealing with inclusion and exclusion by center and by time, and so forth. The study was monitored by regular visits to the centers of a representative from the study sponsor who was equipped with a special user-name/password that gave read-only access to the database. Thereby, the monitor could check agreement between database and patient record without being able to enter or change data. When the database containing all recorded variables and end points was finished, the randomization key was entered into the database and information about the randomized patients was transformed into a BMDP system file.

Statistical analysis: Statistical analysis was performed using the BMDP statistical package PC release 7.0, 1993. Statistical tests were 2-sided with a significance level of 0.05. Comparison of the treatment groups with respect to baseline and other variables was done with the chi-square and the Wilcoxon Mann-Whitney tests. Comparison of event curves was done using the Tarone-Ware test, a test very similar to the generalized Wilcoxon test and the log rank test, but giving equal weight to early and late differences in event rate in the treatment groups. Event curves were constructed according to the Kaplan-Meier method. hazard ratios including their 95% confidence interval were determined from a Cox regression model, with treatment group as the only independent variable.

Sample size: Because the study was planned as a feasibility study, the number of patients was based on practical considerations. Each group included at least 45 patients. With 45 patients in each group a difference in adverse cardiac events of 50% versus 25% could be detected, with a probability of 61% with a 2-sided test with a 5% level of significance.

RESULTS

Study patients: In the study period, there were 2,268 patients with suspicion of AMI admitted to the 5 coronary care units. The diagnosis of AMI was verified in 838 patients. Of these, 103 were included, received, and tolerated the test dose, but 3 did not want to continue in the trial after having received the test dose. Thus, 100 were randomized, 49 to trandolapril and 51 to trandolapril-verapamil. Reasons for not being included were: death (n = 72), no CHF or diuretic treatment (n = 406), nonconsent (n = 47), unable to cooperate (n = 26), living outside the catchment area (n = 15), known intolerance to ACE inhibitors (n = 9), treatment with calcium antagonists (n = 20) or β blockers (n = 33), sinoatrial or second- or third-degree atrioventricular block (n = 9), serum creatinine >0.22 mmol/L (n = 7), dependent edemas (n = 9), previously in the trial (n = 3), other severe diseases (n = 42), systolic blood pressure <90 mm Hg (n =4), and other reasons (n = 33).

At the time of randomization (mean [± SD] 8 ± 2 days after admission to the hospital), no statistically significant differences were present when com-

TABLE I Allocated Treatment, Patient Characteristics, and Clinical Findings at Randomization

	Trandolapril (n = 49)	Trandolapril/Verapamil (n = 51)
Men	35	40
Previous history		
Myocardial infarction	12	13
Stable angina pectoris	20	22
Congestive heart failure	8	4
Systemic hypertension	9	13
Diabetes	8	6
Stroke	1	3
Previous smoker	9	16
Smoker	21	20
Findings in the CCU		
Thrombolysis	24	27
Ventricular tachycardia	4	4
Q-wave infarction	19	19
Cardiogenic shock	1	1
Findings at randomization		
QRS ≥0.12	7	4
Congestion on chest x-ray	11	9
Atrial fibrillation	2	2
Non-trial medication		
Thiazides	2	4
Loop diuretics	49	49
Spironolactone	5	5
Aspirin	45	46
Digoxin	13	9
Nitrates, long-lasting	21	19
Age (yr)	69.5 ± 10	68.4 ± 9
Systolic blood pressure (mm Hg)	122 ± 16	125 ± 17
Diastolic blood pressure (mm Hg)	72 ± 9	75 ± 10
Heart rate (beats/min)	74 ± 12	76 ± 12
Serum creatinine (mmol/L)	0.10 ± 0.03	0.11 ± 0.02
Serum potassium (mmol/L)	4.1 ± 0.4	4.0 ± 0.3
Serum sodium (mmol/L)	139 ± 3	139 ± 3

Values are expressed as number of patients or mean ± SD.
CCU = coronary care unit.

TABLE II Allocated Treatment, Cardiac Events and Three-Month Event Rate

	Trandolapril Events	Trandolapril/Verapamil Events
Patient	49 —	51 —
Death	1 (2)	1 (2)
RI	7 (14)	1 (2)
UAP	9 (18)	3 (6)
Readmission due to CHF	6 (12)	2 (4)
Readmission, other reasons	9 (18)	7 (14)
Death, RI, or UAP*	14 (29)	5 (10)
Death, RI, UAP or CHF*	17 (35)	7 (14)

*Whichever occurred first.
Values are expressed as number (%).
CHF = congestive heart failure; RI = reinfarction; UAP = unstable angina pectoris.

paring the 2 groups of patients with respect to history and baseline variables (Table I).

Duration of the trial and compliance: The observation period was 92 ± 8 days in the trandolapril group and 92 ± 10 days in the trandolapril-verapamil group. No patients were lost to follow-up. At the end of the 3-month treatment period, 38 patients in each group were still taking trial medication. Reasons for premature permanent termination of trial medication in the trandolapril group (n = 11) were: did not wish to continue treatment (n = 2), worsening CHF (n = 3), angina pectoris (n = 3), arrhythmias (n = 2), and other reasons (n = 1). Reasons for termination of medication in the trandolapril-verapamil group (n = 13) were: death (n = 1), did not wish to continue (n = 3), noncompliance (n = 1), angina pectoris (n = 2), hypotension (n = 3), coughing (n = 1), and other reasons (n = 2). Compliance with trial medication was good. Based on capsule counts, 97% of the prescribed medication was taken by patients in each group while receiving treatment.

End points: At end of follow-up, 2 deaths were reported, 1 due to reinfarction in the trandolapril group and 1 due to CHF in the trandolapril-verapamil group. A first reinfarction was recorded in 7 patients allocated to trandolapril and in 1 patient allocated to trandolapril-verapamil. Unstable angina pectoris was recorded in 9 trandolapril-treated and in 3 trandolapril-verapamil–treated patients, and readmission was due to worsening CHF in 6 and 2 patients, respectively (Table II).

The primary end point in this study was the combination of death, reinfarction, unstable angina, and readmission due to worsening CHF. Three-month first event rates were 35% in the trandolapril group and 14% in the trandolapril-verapamil group (hazard ratio 0.35, 95% CI 0.15 to 0.85, p = 0.015) (Figure 1). Three-month first event rates based on a combined end point of death, reinfarction, or unstable angina were 29% and 10% respectively, (hazard ratio 0.31, 95% CI 0.11 to 0.86, p = 0.018).

DISCUSSION

Calcium antagonists are often considered contraindicated in patients with CHF,[5,6] but calcium antagonists are prescribed to a large number of post-AMI patients with reduced ejection fraction or CHF as evaluated from the Survival And Ventricular Enlargement (SAVE),[7] AIRE,[3] TRAndolapril Cardiac Evaluation (TRACE),[4] and Survival of Myocardial Infarction: Long-term Evaluation (SMILE)[8] studies in which 42%, 16%, 28%, and 10% of patients, respectively, were treated with calcium antagonists at randomization. Limited information is available about the events in patients treated versus those not treated with calcium antagonists. No information is available about the type of calcium antagonist used, nor is there any indication for the use of a calcium antagonist in patients included in these 4 studies. In the SAVE study, the mortality

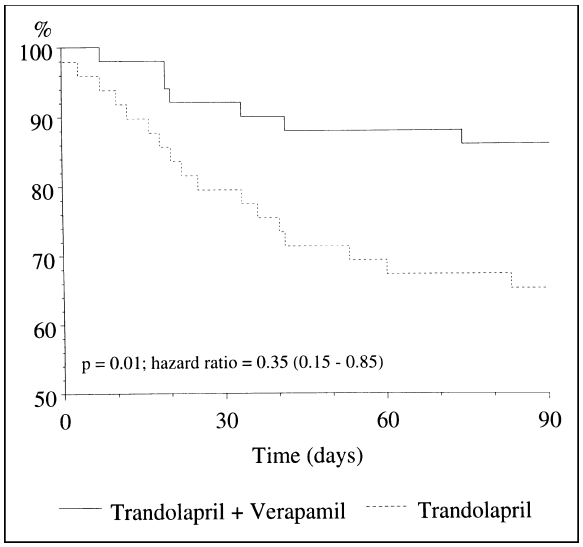

FIGURE 1. Cardiac event-free curves according to Kaplan-Meier and allocated treatment, intention-to-treat analysis. Cardiac event is defined as death, reinfarction, unstable angina, and readmission due to worsening congestive heart failure whichever occurred first.

rate in patients prescribed a calcium antagonist was 24.8% in the placebo and 20.6% in the captopril group (risk reduction 19%, 95% CI −7 to 38); in patients not treated with calcium antagonists the corresponding figures were placebo 24.6%, captopril 20.4% (risk reduction 19%, 95% CI −2 to 36).[9] In the AIRE study, the relative hazard of death of ramipril- versus placebo-treated patients was 0.59 (95% CI 0.36 to 0.97) in patients prescribed a calcium antagonist; in patients not prescribed a calcium antagonist the relative hazard was 0.76 (95% CI 0.61 to 0.95). No information is available about the absolute mortality rates. In the SMILE study, the calcium antagonist–treated patients had an event rate of 15.8% in those treated with placebo and 2.7% in those given zofenopril ($p = 0.005$, risk ratio 14%, 95% CI 3 to 66). The corresponding figures in patients not taking calcium antagonists were 10.0% and 7.6% ($p = 0.12$, risk ratio 74%, 95% CI 51 to 107).

The present study is the first to evaluate the feasibility of using verapamil in post-AMI patients with CHF treated with a diuretic and an ACE inhibitor, trandolapril. Verapamil was well tolerated, was safe, and significantly reduced cardiac events. Thus, no patients in the trandolapril-verapamil group versus 3 patients in the trandolapril group stopped trial medication and 2 versus 6 were readmitted due to worsening CHF. One trandolapril-verapamil–treated patient versus 7 trandolapril-treated patients had reinfarction. Prevention of reinfarction is important because it has been demonstrated that the mortality rate is increased up to 5 times in post-AMI patients with reinfarction compared with patients without reinfarction.[10,11] In the DAVIT II trial, reinfarction was also prevented by verapamil in patients without CHF.[1]

The verapamil dose of 240 to 360 mg/day corresponds to the dose used in the DAVIT II trial.[1] The dose of trandolapril 1 mg/day increasing to 2 mg/day is half the maximal dose in the TRACE study.[4] The dose of 2 mg was chosen because we considered it risky to induce severe orthostatic hypotension by adding a high dose of verapamil to the maximal dose of trandolapril. In fact, 3 patients treated with trandolapril-verapamil stopped the trial medication due to hypotension.

This study verifies the findings from DAVIT II and the AIRE study, that based on relatively simple clinical evaluations, it is possible to define a post-AMI population with a high risk of a subsequent serious cardiac event.

A limitation of the present study is the short observation period. A larger study with a longer observation period is necessary to evaluate effects on later mortality and cardiovascular events.

APPENDIX

DAVIT centers and investigators: This study was conducted by the Steering Committee of the DAVIT study. The following were involved in screening and follow-up of patients in the study: *Hillerød:* Johnny K. Madsen, Margit Borring; *Hvidovre:* Lisbeth Tingsted, Christian Jespersen, Merete Vaage-Nilsen, Charlotte Sørum, Nete Skov, Kirsten Meier; *Nykøbing F:* Bente Petersen, Pernille Bille-Hansen; *Nyborg:* Ole Pedersen-Bjergaard; *Holstebro:* Dorte Kimer; *Independent observer:* Erik Kjøller, Sct. Elisabeth Hospital, Copenhagen; *Observer at the meetings of the Steering Committee:* Otto Jensen, MEDA AS. Monitor: Günther Ruf, Knoll AG; *Data management and statistical analyses:* Leif S. Mortensen; *Steering Committee:* K. Mellemgaard, B. Sigurd, L. Hagerup, F. Pedersen, O. Pedersen-Bjergaard, J. Fischer Hansen (chairman).

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