

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

NOVEMBER 13, 2003

VOL. 349 NO. 20

Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both

Marc A. Pfeffer, M.D., Ph.D., John J.V. McMurray, M.D., Eric J. Velazquez, M.D., Jean-Lucien Rouleau, M.D., Lars Køber, M.D., Aldo P. Maggioni, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., Frans Van de Werf, M.D., Ph.D., Harvey White, D.Sc., Jeffrey D. Leimberger, Ph.D., Marc Henis, M.D., Susan Edwards, M.S., Steven Zelenkofske, D.O., Mary Ann Sellers, M.S.N., and Robert M. Califf, M.D., for the Valsartan in Acute Myocardial Infarction Trial Investigators*

ABSTRACT

BACKGROUND

Angiotensin-converting-enzyme (ACE) inhibitors such as captopril reduce mortality and cardiovascular morbidity among patients with myocardial infarction complicated by left ventricular systolic dysfunction, heart failure, or both. In a double-blind trial, we compared the effect of the angiotensin-receptor blocker valsartan, the ACE inhibitor captopril, and the combination of the two on mortality in this population of patients.

METHODS

Patients receiving conventional therapy were randomly assigned, 0.5 to 10 days after acute myocardial infarction, to additional therapy with valsartan (4909 patients), valsartan plus captopril (4885 patients), or captopril (4909 patients). The primary end point was death from any cause.

RESULTS

During a median follow-up of 24.7 months, 979 patients in the valsartan group died, as did 941 patients in the valsartan-and-captopril group and 958 patients in the captopril group (hazard ratio in the valsartan group as compared with the captopril group, 1.00; 97.5 percent confidence interval, 0.90 to 1.11; $P=0.98$; hazard ratio in the valsartan-and-captopril group as compared with the captopril group, 0.98; 97.5 percent confidence interval, 0.89 to 1.09; $P=0.73$). The upper limit of the one-sided 97.5 percent confidence interval for the comparison of the valsartan group with the captopril group was within the prespecified margin for noninferiority with regard to mortality ($P=0.004$) and with regard to the composite end point of fatal and nonfatal cardiovascular events ($P<0.001$). The valsartan-and-captopril group had the most drug-related adverse events. With monotherapy, hypotension and renal dysfunction were more common in the valsartan group, and cough, rash, and taste disturbance were more common in the captopril group.

CONCLUSIONS

Valsartan is as effective as captopril in patients who are at high risk for cardiovascular events after myocardial infarction. Combining valsartan with captopril increased the rate of adverse events without improving survival.

From the Cardiovascular Division, Brigham and Women's Hospital, Boston (M.A.P., S.D.S.); the Department of Cardiology, Western Infirmary, Glasgow, Scotland (J.J.V.M.); the Duke University Medical Center, Durham, N.C. (E.J.V., J.D.L., M.A.S., R.M.C.); the Montreal Heart Institute, Montreal (J.-L.R.); the Department of Cardiology, Rigshospitalet, Copenhagen, Denmark (L.K.); the Associazione Nazionale Medici Cardiologi Ospedalieri Research Center, Florence, Italy (A.P.M.); the Department of Medicine, Sahlgrenska University Hospital-Östra, Göteborg, Sweden (K.S.); the Leuven Coordinating Center, Leuven, Belgium (F.V.W.); the Cardiology Department, Green Lane Hospital, Auckland, New Zealand (H.W.); Medical Pharmaceutical Consultants, Randolph, N.J. (M.H.); and Novartis Pharmaceuticals, East Hanover, N.J. (S.E., S.Z.). Address reprint requests to Dr. Pfeffer at the Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at mpfeffer@rics.bwh.harvard.edu.

*The Valsartan in Acute Myocardial Infarction (VALIANT) trial investigators are listed in the Appendix.

N Engl J Med 2003;349:1893-906.
Copyright © 2003 Massachusetts Medical Society.

MULTIPLE RANDOMIZED, PLACEBO-controlled trials involving a total of more than 100,000 patients have demonstrated that angiotensin-converting-enzyme (ACE) inhibitors reduce the risk of death as well as the risk of major nonfatal cardiovascular events after myocardial infarction.¹⁻⁸ The greatest relative and absolute benefits have been obtained with long-term ACE-inhibitor therapy in high-risk patients — specifically, in those with left ventricular dysfunction, signs or symptoms of heart failure, or both.^{9,10} Angiotensin-receptor blockers offer an alternative approach to the inhibition of the renin-angiotensin system.¹¹ The identification of a functioning chymase in humans that is capable of generating angiotensin II independently of ACE provides a rationale for inhibiting the deleterious actions of angiotensin II at the AT₁ receptor more completely with an angiotensin-receptor blocker.¹² The discoveries of other angiotensin receptors with putatively favorable effects on cardiovascular function and structure support the hypothesis that angiotensin-receptor blockers, by promoting the unopposed stimulation of these receptors,¹³ may offer clinical benefits beyond those achieved with ACE inhibitors. Alternatively, since the augmentation of bradykinin levels may also contribute to the net therapeutic benefits of ACE (kininase II) inhibitors, concurrent treatment with an ACE inhibitor and an angiotensin-receptor blocker might be the most effective strategy.

We conducted the Valsartan in Acute Myocardial Infarction (VALIANT) trial to test the hypothesis that treatment with valsartan, an angiotensin-receptor blocker, alone or in combination with captopril, an ACE inhibitor, would result in better survival than treatment with a proven ACE-inhibitor regimen. Our design also specified analyses to assess noninferiority if valsartan was neither clearly superior nor clearly inferior to captopril.¹⁴

METHODS

STUDY DESIGN

We conducted a randomized, double-blind trial at 931 centers in 24 countries. Men and women 18 years of age or older who had had acute myocardial infarction (between 0.5 and 10 days previously) that was complicated by clinical or radiologic signs of heart failure, evidence of left ventricular systolic dysfunction (an ejection fraction ≤ 0.35 on echocardiography or contrast angiography and ≤ 0.40 on radio-

nuclide ventriculography), or both, as defined in the three trials we used as reference studies, were eligible.^{1,7,8} At randomization, patients were required to have a systolic blood pressure higher than 100 mm Hg and a serum creatinine concentration of less than 2.5 mg per deciliter (221 μmol per liter). Patients were permitted to have received an ACE inhibitor or angiotensin-receptor blocker up to 12 hours before randomization. The main criteria for exclusion were a previous intolerance or contraindication to an ACE inhibitor or angiotensin-receptor blocker, clinically significant valvular disease, another disease known to limit life expectancy severely, and the absence of written informed consent.¹⁴

Consenting, eligible patients were randomly assigned in a 1:1:1 ratio to receive valsartan monotherapy, valsartan plus captopril, or captopril monotherapy; an automated, interactive voice-response system was used for randomization. Therapy was begun with either 20 mg of valsartan, 20 mg of valsartan plus 6.25 mg of captopril, or 6.25 mg of captopril. Doses were gradually increased in four steps, with the goal of reaching step 3 (80 mg of valsartan twice daily, 40 mg of valsartan twice daily and 25 mg of captopril three times daily, or 25 mg of captopril three times daily) during the initial hospitalization and step 4 (160 mg of valsartan twice daily, 80 mg of valsartan twice daily and 50 mg of captopril three times daily, or 50 mg of captopril three times daily), if clinically possible, by the three-month visit. Investigators increased or decreased the doses of the study drugs at their discretion according to the patient's clinical status. Study visits took place six times during the first year and at four-month intervals thereafter; at each visit, clinical status, study outcomes, drug tolerance, quality of life, and pharmacoeconomic variables were assessed. All pre-specified end points were adjudicated by a clinical end-point committee that was unaware of the treatment-group assignments. Definitions of the end points are presented in Supplementary Appendix 1 (available with the full text of this article at www.nejm.org). A single independent data and safety monitoring board and the institutional review board or ethics committee at each participating site approved the protocol.

The Duke Clinical Research Institute and the Leuven Coordinating Center performed data processing and site management independently of the sponsor. Until the data base was locked, only the data and safety monitoring board and an independ-

ent drug-distribution group maintained the code used for treatment-group assignments. All analyses were performed at the Duke Clinical Research Institute and were verified by the sponsor. The manuscript was prepared by the academic researchers, who made the publication decisions, and was reviewed by the sponsor.

STATISTICAL ANALYSIS

There were two primary treatment comparisons: valsartan versus captopril, and valsartan plus captopril versus captopril. A two-sided significance level of 0.0253 (with Sidak's adjustment for multiple comparisons)¹⁵ was used for both comparisons. The trial was designed to enroll approximately 14,500 patients, with follow-up continuing until at least 2700 deaths had occurred, providing a power of 86 to 95 percent to detect a reduction of 15.0 to 17.5 percent in the risk of death from any cause. For the primary end point (mortality from any cause) and secondary cardiovascular outcomes, the treatment groups were compared on an intention-to-treat basis with the use of a Cox proportional-hazards model with adjustment for age and the presence or absence of previous myocardial infarction, as prespecified in the protocol. Event-rate curves were generated according to the method of Kaplan and Meier.

If valsartan did not prove to be superior to captopril, the noninferiority of valsartan relative to captopril was to be assessed without further adjustment of the significance level for interim analyses, since the trial was not to be concluded early because of any interim findings regarding noninferiority. In addition to the confidence interval, the P value for the test of the null hypothesis of inferiority is also provided for the assessment of noninferiority. On the basis of the reduction in mortality with the use of ACE inhibitors as compared with placebo in previous trials,^{1,7,8,10} the threshold considered to indicate noninferiority with regard to the hazard ratio for death in the valsartan group as compared with the captopril group was prespecified as 1.13. This threshold preserves at least 55 percent of the survival benefit of an ACE inhibitor. An estimate of the effectiveness of valsartan as compared with that of an imputed placebo was derived by the methods of Fisher¹⁶ and Hasselblad and Kong.¹⁷ Under the assumption of a risk reduction of 0 to 2.5 percent with valsartan as compared with captopril, 2700 events would provide the study with a power of 74 to 88 percent to demonstrate that valsartan is as effective

as captopril, given a one-sided hypothesis, with a significance level of 0.0253.

For the assessment of noninferiority, in addition to the intention-to-treat analysis, we conducted a per-protocol analysis including patients who satisfied the criteria for inclusion with regard to acute myocardial infarction and who had received at least one dose of the study medication. Assessments of safety and tolerability were based on all patients who underwent randomization and received at least one dose of the study medication. The Cox model was used to assess the effect of each treatment on the time to a reduction in the dose or permanent discontinuation of the study medication. A repeated-measures generalized linear model was used to assess trends in blood pressure and the heart rate over time. Pearson's chi-square statistic was used to compare the treatment groups with respect to the use of open-label medications, as well as for a post hoc analysis of cumulative hospital admissions for myocardial infarction or heart failure.

Preplanned biennial interim analyses (seven in total) were performed by an independent statistician and reviewed by the data and safety monitoring board. The significance level for the primary assessment of superiority was adjusted with the use of a Lan-DeMets alpha spending function (O'Brien-Fleming type).

RESULTS

STUDY PATIENTS

From December 1998 through June 2001, a total of 14,808 patients were enrolled.¹⁸ Information from 105 patients at one site was censored before unblinding, because the adequacy of the informed-consent process could not be ensured. The characteristics of the remaining 14,703 patients (4909 in the valsartan group, 4885 in the valsartan-and-captopril group, and 4909 in the captopril group) are summarized in Table 1.

Study medication was administered to all but 77 patients (0.5 percent; 24 patients in the valsartan group, 23 in the valsartan-and-captopril group, and 30 in the captopril group). The median duration of follow-up was 24.7 months, for a total of 29,226 cumulative patient-years. At the completion of the trial, the vital status was unavailable for 139 patients (0.9 percent; 53 patients in the valsartan group, 48 in the valsartan-and-captopril group, and 38 in the captopril group), 55 of whom had withdrawn consent.

Table 1. Base-Line Characteristics of the Patients.*

Characteristic	Valsartan Group (N=4909)	Valsartan-and-Captopril Group (N=4885)	Captopril Group (N=4909)
Age — yr	65.0±11.8	64.6±11.9	64.9±11.8
Race — no. (%)			
White	4604 (93.8)	4553 (93.2)	4591 (93.5)
Black	125 (2.5)	137 (2.8)	145 (3.0)
Asian	44 (0.9)	53 (1.1)	44 (0.9)
Other	136 (2.8)	142 (2.9)	129 (2.6)
Female sex — no. (%)	1544 (31.5)	1490 (30.5)	1536 (31.3)
Blood pressure — mm Hg			
Systolic	122.7±16.8	122.5±17.1	122.8±17.0
Diastolic	72.3±11.3	72.3±11.4	72.4±11.2
Heart rate — beats/min	76.2±13.0	76.2±12.7	76.2±12.8
Body-mass index†			
Median	27.34	27.24	27.14
Interquartile range	24.69–30.47	24.62–30.35	24.54–30.22
Left ventricular ejection fraction — %‡	35.3±10.4	35.3±10.3	35.3±10.4
Killip class — no. (%)			
I	1294 (26.5)	1381 (28.4)	1424 (29.1)
II	2401 (49.2)	2329 (47.9)	2346 (48.0)
III	874 (17.9)	842 (17.3)	813 (16.6)
IV	313 (6.4)	312 (6.4)	306 (6.3)
Medical history — no. (%)			
Myocardial infarction	1395 (28.4)	1376 (28.2)	1333 (27.2)
Hypertension	2732 (55.7)	2700 (55.3)	2690 (54.8)
Diabetes mellitus	1134 (23.1)	1146 (23.5)	1120 (22.8)
Heart failure	759 (15.5)	701 (14.4)	714 (14.5)
Stroke	292 (5.9)	305 (6.2)	298 (6.1)
Smoking	1556 (31.7)	1546 (31.6)	1562 (31.8)
Coronary-artery bypass grafting	355 (7.2)	327 (6.7)	344 (7.0)
Percutaneous coronary intervention	376 (7.7)	337 (6.9)	354 (7.2)

END POINTS*Mortality*

Mortality from any cause and cause-specific mortality were similar in the three treatment groups. A total of 979 patients in the valsartan group (19.9 percent) died, as did 941 in the valsartan-and-captopril group (19.3 percent) and 958 in the captopril group (19.5 percent). The hazard ratio for death in the valsartan group as compared with the captopril group was 1.00 (97.5 percent confidence interval, 0.90 to 1.11; $P=0.98$), and the hazard ratio for death in the valsartan-and-captopril group as compared with the captopril group was 0.98 (97.5 percent confidence interval, 0.89 to 1.09; $P=0.73$) (Fig. 1). The Kaplan–Meier estimates of mortality at one year were 12.5

percent in the valsartan group, 12.3 percent in the valsartan-and-captopril group, and 13.3 percent in the captopril group.

Cardiovascular Morbidity and Mortality

The rate of the secondary end point of death from cardiovascular causes, recurrent myocardial infarction, or hospitalization for heart failure was similar in the three groups (Fig. 1). The hazard ratios for death from cardiovascular causes and for a hierarchy of composite cardiovascular outcomes generated by adding important nonfatal cardiovascular events (recurrent myocardial infarction, hospitalization for heart failure, resuscitation from cardiac arrest, and stroke) to death from cardiovascular causes were all

Table 1. (Continued.)

Characteristic	Valsartan Group (N=4909)	Valsartan-and-Captopril Group (N=4885)	Captopril Group (N=4909)
Median no. of days from myocardial infarction to randomization	4.8	4.9	4.9
Site of qualifying myocardial infarction — no. (%)			
Anterior	2765 (58.7)	2831 (60.3)	2796 (59.3)
Inferior	1586 (34.1)	1601 (34.4)	1618 (34.7)
Type of qualifying myocardial infarction — no. (%)			
Q-wave	3116 (65.8)	3132 (66.4)	3195 (67.5)
Non-Q-wave	1512 (32.5)	1494 (32.2)	1452 (31.1)
Thrombolytic therapy — no. (%)			
Primary percutaneous coronary intervention — no. (%)	731 (14.9)	730 (14.9)	717 (14.6)
Other percutaneous coronary intervention after myocardial infarction but before randomization — no. (%)	1012 (20.6)	949 (19.4)	955 (19.5)
Medication — no. (%)‡			
ACE inhibitors	1936 (39.4)	1993 (40.8)	1888 (38.5)
Angiotensin-receptor blockers	54 (1.1)	53 (1.1)	67 (1.4)
Beta-blockers	3468 (70.6)	3439 (70.4)	3443 (70.1)
Aspirin	4481 (91.3)	4452 (91.1)	4485 (91.4)
Other antiplatelet agents	1232 (25.1)	1205 (24.7)	1210 (24.6)
Potassium-sparing diuretics	447 (9.1)	438 (9.0)	445 (9.1)
Other diuretics	2517 (51.3)	2459 (50.3)	2424 (49.4)
Hydroxymethylglutaryl coenzyme A reductase inhibitors	1658 (33.8)	1665 (34.1)	1691 (34.4)
Serum creatinine — mg/dl§	1.1±0.3	1.1±0.3	1.1±0.4

* Plus-minus values are means ±SD. Data on left ventricular ejection fraction were available for 3788 patients in the valsartan group, 3772 in the valsartan-and-captopril group, and 3778 in the captopril group. Data on Killip class were missing for 27 patients in the valsartan group, 21 patients in the valsartan-and-captopril group, and 20 patients in the captopril group. Data on whether there was an anterior myocardial infarction were missing for 202 patients in the valsartan group, 192 in the valsartan-and-captopril group, and 197 in the captopril group; data on inferior myocardial infarction were missing for 253 patients in the valsartan group, 231 in the valsartan-and-captopril group, and 248 in the captopril group; data on Q-wave myocardial infarction were missing for 173 patients in the valsartan group, 170 in the valsartan-and-captopril group, and 179 in the captopril group; data on non-Q-wave myocardial infarction were missing for 252 patients in the valsartan group, 244 in the valsartan-and-captopril group, and 245 in the captopril group.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Treatment with angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers was stopped before randomization.

§ To convert values for creatinine to micromoles per liter, multiply by 88.4.

similar for the valsartan group as compared with the captopril group and for the valsartan-and-captopril group as compared with the captopril group (Table 2).

Subgroup Analyses

The examination of prespecified subgroups showed no heterogeneity in the effects of treatment on the risk of death or on the secondary composite cardiovascular end point (Fig. 2). In particular, there was no excess hazard of either death or the composite

cardiovascular outcomes among patients who received valsartan plus captopril in addition to background beta-blocker therapy (Fig. 2).

Hospitalizations for Myocardial Infarction and Heart Failure

A post hoc analysis of the rate of investigator-reported hospital admissions for either myocardial infarction or heart failure showed that 919 patients in the valsartan group (18.7 percent) had a total of 1447 hospitalizations, 834 patients in the valsartan-

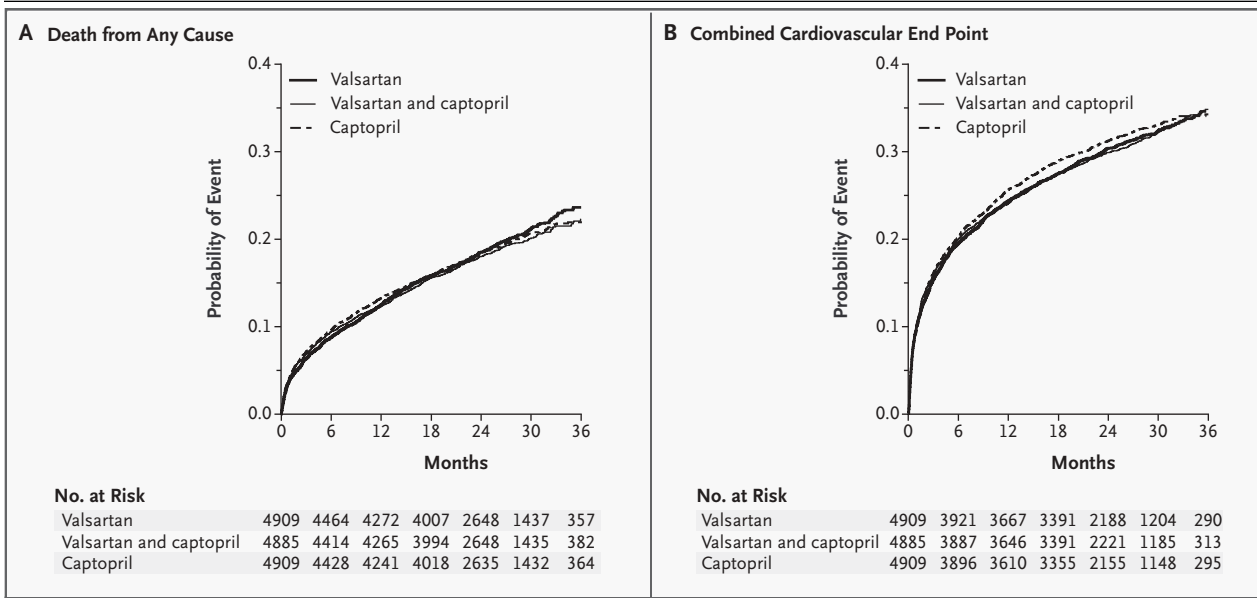


Figure 1. Kaplan–Meier Estimates of the Rate of Death from Any Cause (Panel A) and the Rate of Death from Cardiovascular Causes, Reinfarction, or Hospitalization for Heart Failure (Panel B), According to Treatment Group.

For the rate of death from any cause, $P=0.98$ for the comparison between the valsartan group and the captopril group and $P=0.73$ for the comparison between the valsartan-and-captopril group and the captopril group; for the rate of death from cardiovascular causes, reinfarction, or hospitalization for heart failure, $P=0.20$ for the comparison between the valsartan group and the captopril group and $P=0.37$ for the comparison between the valsartan-and-captopril group and the captopril group.

and-captopril group (17.1 percent) had a total of 1297 hospitalizations, and 945 patients in the captopril group (19.3 percent) had a total of 1437 hospitalizations ($P=0.50$ for the comparison of the proportion of patients and $P=0.51$ for the comparison of the number of admissions between the valsartan group and the captopril group; $P=0.005$ for the comparison of the proportion of patients and $P=0.007$ for the comparison of the number of admissions between the valsartan-and-captopril group and the captopril group).

NONINFERIORITY

Because valsartan, alone or combined with captopril, could not be considered to be superior or inferior to captopril alone, we conducted our prespecified series of analyses to test for noninferiority — comparing only the groups receiving valsartan or captopril monotherapy. With regard to mortality, valsartan was shown to be noninferior to captopril in both the intention-to-treat and per-protocol populations. In both analyses, the upper limit of the one-sided 97.5 percent confidence interval for the comparison between the valsartan group and the captopril group was within the specified margin for noninferiority ($P=0.004$ in the intention-to-treat analysis and $P=0.002$ in the per-protocol analysis). These results demonstrate that valsartan is no less effective than an ACE inhibitor in reducing the risk of death in this population, as illustrated by the analysis involving the imputed placebo that is summarized in Figure 3. We estimated that valsartan had an effect that was 99.6 percent of that of captopril (95 percent confidence interval, 60 to 139 percent). The narrow confidence intervals support the conclusion that valsartan is at least as effective as captopril in reducing the risk of major cardiovascular events (Table 2).

TOLERABILITY AND SAFETY

The proportion of patients who were no longer taking the study medication at one year was 15.3 percent in the valsartan group, 19.0 percent in the valsartan-and-captopril group, and 16.8 percent in the captopril group ($P=0.07$ for the comparison between the valsartan group and the captopril group; $P=0.007$ for the comparison between the valsartan-and-captopril group and the captopril group). Among the patients who were still taking the study medication at one year, the mean (\pm SD) doses were

Table 2. Cardiovascular Mortality and Morbidity.*

End Point	Valsartan Group (N=4909)	Valsartan-and-Captopril Group (N=4885)	Captopril Group (N=4909)	Valsartan vs. Captopril			Valsartan and Captopril vs. Captopril	
				Hazard Ratio (97.5% CI)	P Value	P Value for Non-inferiority	Hazard Ratio (97.5% CI)	P Value
	<i>number (percent)</i>							
Death from cardiovascular causes	827 (16.8)	827 (16.9)	830 (16.9)	0.98 (0.87–1.09)	0.62	0.001	1.00 (0.89–1.11)	0.95
Death from cardiovascular causes or myocardial infarction	1102 (22.4)	1096 (22.4)	1132 (23.1)	0.95 (0.87–1.05)	0.25	<0.001	0.96 (0.88–1.06)	0.40
Death from cardiovascular causes or heart failure	1326 (27.0)	1331 (27.2)	1335 (27.2)	0.97 (0.90–1.05)	0.51	<0.001	1.00 (0.92–1.09)	0.94
Death from cardiovascular causes, myocardial infarction, or heart failure	1529 (31.1)	1518 (31.1)	1567 (31.9)	0.95 (0.88–1.03)	0.20	<0.001	0.97 (0.89–1.05)	0.37
Death from cardiovascular causes, myocardial infarction, heart failure, resuscitation after cardiac arrest, or stroke	1612 (32.8)	1580 (32.3)	1641 (33.4)	0.96 (0.89–1.04)	0.25	<0.001	0.96 (0.89–1.04)	0.26

* Heart failure denotes hospitalization for the management of heart failure, and CI confidence interval.

247±105 mg of valsartan in the valsartan group, 116±53 mg of valsartan plus 107±53 mg of captopril in the valsartan-and-captopril group, and 117±49 mg of captopril in the captopril group. The proportions of patients taking the target doses were 56 percent, 47 percent, and 56 percent, respectively (P=0.97 and P<0.001 for the two comparisons with the captopril group).

At one year, open-label ACE-inhibitor treatment was being used in 7.0 percent of the patients in the valsartan group, 7.9 percent of those in the valsartan-and-captopril group, and 7.7 percent of those in the captopril group (P=0.25 and P=0.72 for the two comparisons with the captopril group). Open-label treatment with an angiotensin-receptor blocker was being used in 1.5 percent of the patients in the valsartan group, 3.0 percent of those in the valsartan-and-captopril group, and 2.9 percent of those in the captopril group (P<0.001 and P=0.82 for the two comparisons with the captopril group).

The mean blood pressure at one year was 127/75 mm Hg in the valsartan group, 125/75 mm Hg in the valsartan-and-captopril group, and 127/76 mm Hg in the captopril group (P=0.17 for the comparison of systolic blood pressure and P=0.32 for the comparison of diastolic blood pressure between the valsartan group and the captopril group; P<0.001 for the comparisons of both systolic and diastolic blood pressure between the valsartan-and-captopril group

and the captopril group). Although all patients received active blood-pressure-lowering agents, the valsartan-and-captopril group had a mean systolic pressure that was 2.2 mm Hg lower than that in the captopril group after randomization (P<0.001), and the mean systolic pressure in the valsartan group was 0.9 mm Hg lower than that in the captopril group (P<0.001). The mean heart rate did not vary significantly among treatment groups.

The groups were similar in terms of the number of patients who permanently discontinued the study treatment by their own decision, the most common reason given for discontinuation (380 patients in the valsartan group, 373 in the valsartan-and-captopril group, and 355 in the captopril group; P=0.40 and P=0.44 for the two comparisons with the captopril group). The rate of adverse events related to the study treatment, the next most frequent reason for discontinuation, did differ among groups, with the highest rate occurring in the valsartan-and-captopril group and the lowest rate in the valsartan group (Table 3). Definitions of the types of adverse events that led to dose reductions or the discontinuation of study treatment are provided in Supplementary Appendix 2 (available with the full text of this article at www.nejm.org). There was a similar pattern in the rates of adverse events leading to a reduction in the dose of a study drug (Table 3). Clinical reports of hypotension were consistent with the blood-pressure

levels in that the frequency of this adverse effect leading to either a reduction in the dose of study medication or the permanent discontinuation of study treatment was highest in the valsartan-and-captopril group and lowest in the captopril group (Table 3).

Dose reductions and permanent discontinuations of study medication for renal causes were more frequent in the valsartan and the valsartan-and-captopril groups (Table 3). There were no significant differences in the number of patients with a hospitalization attributed to renal dysfunction (32 in the valsartan group, 30 in the valsartan-and-captopril group, and 21 in the captopril group; $P=0.14$ and $P=0.21$ for the two comparisons with the captopril group).

Cough, taste disturbance, and rash leading to either a dose reduction or the permanent discontinuation of study treatment were more frequent in the two groups that received captopril (Table 3). Angioedema leading to discontinuation was infrequent, occurring in 34 patients (0.23 percent), and the rate did not differ significantly among groups. No cases requiring intubation were reported.

DISCUSSION

The use of ACE inhibitors in patients with myocardial infarction has improved survival and reduced the rates of major nonfatal cardiovascular events, especially when these agents are used for long-term treatment in high-risk patients such as those with signs of heart failure, evidence of left ventricular systolic dysfunction, or both.^{9,10} Consequently, international guidelines recommend ACE inhibitors as first-line therapy for such patients.^{19,20} Clinical trials testing the efficacy of angiotensin-receptor blockers in this population of patients must therefore include a proven ACE inhibitor as an active comparison treatment or as background therapy if a placebo is used.²¹ With this approach, we found that the angiotensin-receptor blocker valsartan, at a target dose of 160 mg twice daily, is as effective as a proven regimen of captopril in improving survival and reducing cardiovascular morbidity.

To demonstrate noninferiority in this way requires a rigorous trial design with specific preplanned statistical analyses. Trials designed to show noninferiority require an appropriate reference population, a proven comparison agent and dose, a high level of adherence to treatment, and adequate statistical power.^{22,23} The criteria for inclusion in our trial

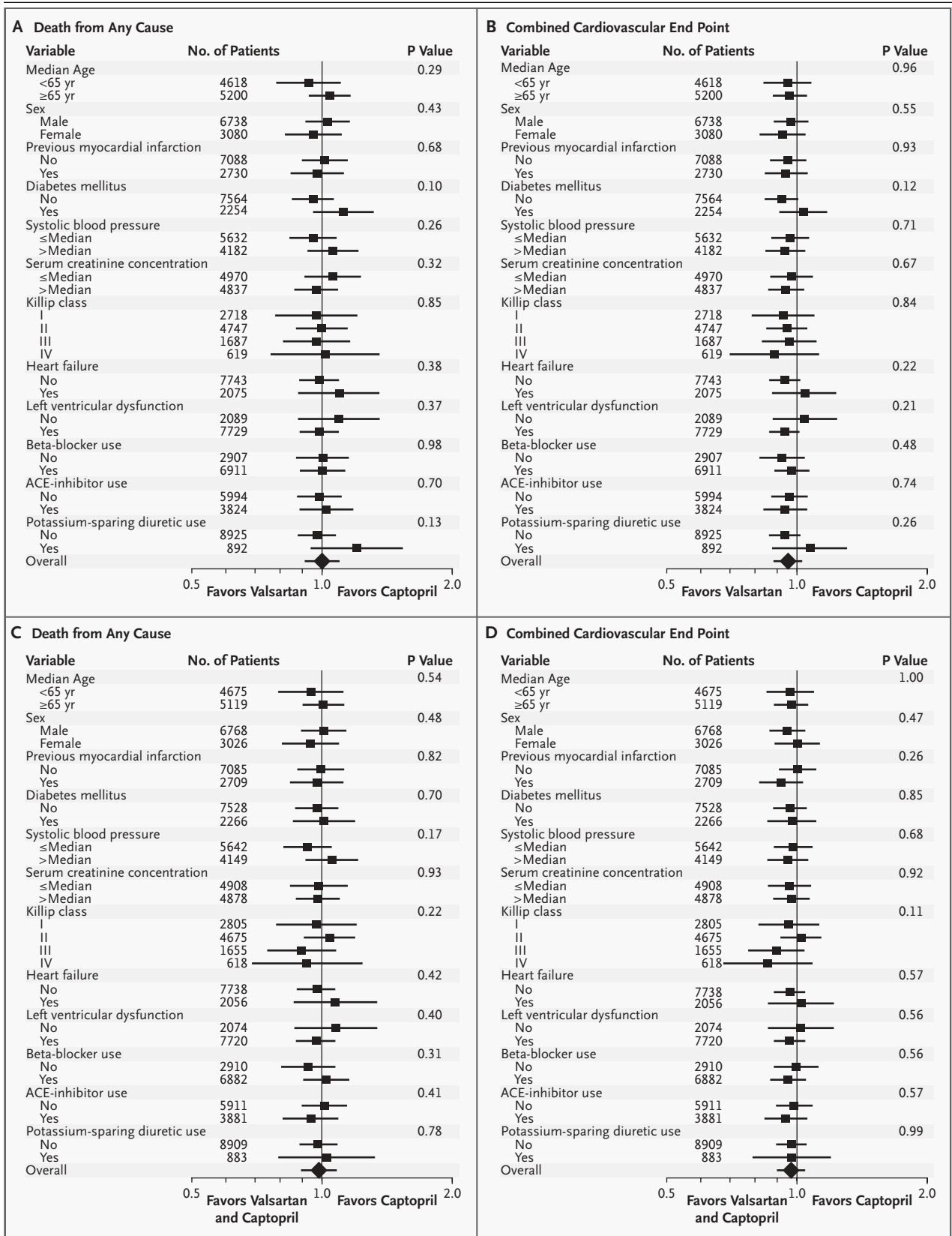
Figure 2 (facing page). Hazard Ratios and 95 Percent Confidence Intervals for Death from Any Cause (Panels A and C) and for Death from Cardiovascular Causes, Reinfarction, or Hospitalization for Heart Failure (Panels B and D).

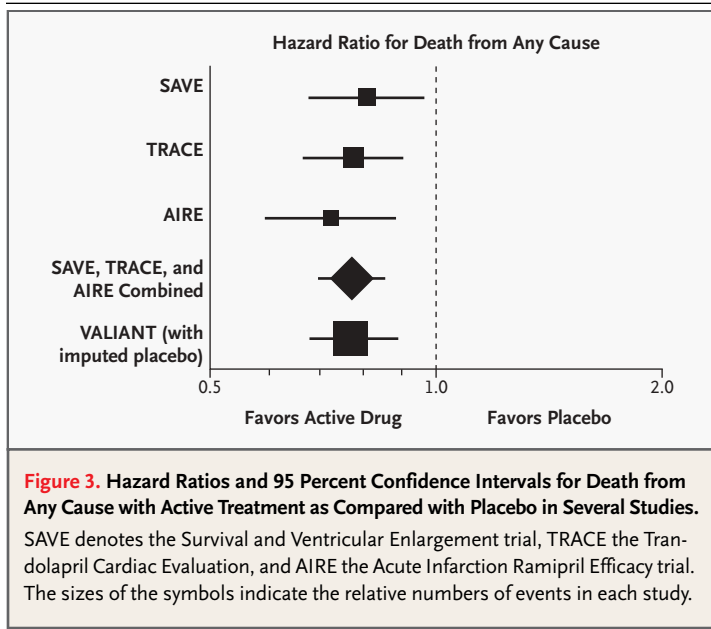
The valsartan group is compared with the captopril group in Panels A and B; the valsartan-and-captopril group is compared with the captopril group in Panels C and D.

were almost identical to those used by the three seminal studies showing the benefits of long-term ACE-inhibitor treatment after myocardial infarction.^{1,7,8} Moreover, the rates of cardiovascular events among patients who received the ACE inhibitor in our study were similar to those in the reference population.

Regarding the choice of comparison agent and dose, captopril, ramipril, and trandolapril have all been shown to be superior to placebo in long-term trials involving high-risk patients with myocardial infarction, resulting in an overall reduction in mortality of 26 percent without significant heterogeneity among agents (Fig. 3).¹⁰ Captopril offered the additional advantage of being the ACE inhibitor whose use within the first day after myocardial infarction had been studied the most; in the Fourth International Study of Infarct Survival (ISIS-4), the drug was associated with a survival advantage within the first 35 days.³ This was an important distinguishing factor, given that our protocol allowed the early initiation of the study treatment (as early as 12 hours after myocardial infarction).

In contrast to tests of superiority, analyses of noninferiority can be favorably biased because of poor adherence. The rate of adherence to captopril treatment in our study was similar to that in the Survival and Ventricular Enlargement (SAVE) trial, which showed the superiority of captopril over placebo.¹ Moreover, the prespecified per-protocol analysis included only patients who met strict inclusion criteria with regard to myocardial infarction and who had received at least one dose of study medication; the use of these criteria improves the comparison between the per-protocol analysis and previous studies of myocardial infarction and limits the influence of poor adherence. The analyses of noninferiority involving the intention-to-treat and per-protocol populations gave consistent and statistically significant results, which permits us to conclude that valsartan provides the same benefits, in terms of both survival and the risk of cardiovascular





events, that were previously achieved with ACE inhibitors in similar populations of patients.

The combination of valsartan and captopril was evaluated to determine whether incremental clinical benefits could be achieved with two inhibitors of the renin-angiotensin system. This combination regimen did not reduce mortality or the rates of key secondary outcomes in our population, despite additional lowering of blood pressure and a clear increase in the rate of intolerance to treatment. This finding is apparently discordant with those of two recent major trials involving patients with heart failure that demonstrated improvements in cardiovascular outcomes with the addition of an angiotensin-receptor blocker to conventional therapy including an ACE inhibitor.²⁴⁻²⁶ Our study, however, differed from these trials in terms of the population of patients and the regimens under study. Differences in patterns of cardiovascular risk between patients with stable heart failure and patients with acute myocardial infarction — the latter having higher risks of early death and myocardial infarction than the former — may account for some of the observed differences. In addition, in the heart-failure trials, angiotensin-receptor-blocker therapy was added to preexisting ACE-inhibitor therapy, and the two treatments were not started concurrently, nor were the doses titrated concurrently. Moreover, in our study, we titrated the dose of the ACE inhibitor to a level that has proven efficacy, whereas in the heart-failure

trials the angiotensin-receptor blocker was added to a dose of an ACE inhibitor that was chosen by the individual investigator. However, the fact that a post hoc analysis in our study showed that combination therapy resulted in an apparent reduction in the cumulative rate of admission for recurrent myocardial infarction or heart failure does at least suggest that this therapy has biologic activity that might result in the observations that have been made in patients with heart failure. The role of combination therapy with an angiotensin-receptor blocker and an ACE inhibitor is currently being studied in a major trial involving patients with vascular disease.²⁷

The inclusion of a combination-therapy group in our study also provides additional insights regarding the possible risks associated with the use of angiotensin-receptor blockers in conjunction with beta-blockers and ACE inhibitors — so-called triple therapy.²⁴ The recently published results of the Candesartan in Heart Failure — Assessment of Reduction in Mortality and Morbidity (CHARM) study have allayed somewhat the concern about potential risks in patients with chronic heart failure.^{25,26} Our study, in which approximately 70 percent of the patients were taking a beta-blocker, showed no adverse interaction with valsartan and no increased risk associated with triple therapy in patients with myocardial infarction complicated by heart failure, left ventricular dysfunction, or both.

The Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) trial compared the effects of the angiotensin-receptor blocker losartan with those of captopril on survival and other major cardiovascular outcomes in similar patients with high-risk myocardial infarction.²⁸ The findings of a trend in favor of captopril did not satisfy the trial's criteria for non-inferiority. It has been suggested that the dose of losartan used in that study and the titration schedule followed were insufficient relative to the proven captopril regimen.²⁹ Our finding that there was greater blood-pressure lowering (and more hypotension-related adverse events) associated with valsartan, which was administered in a dose that was at least as effective as the dose of captopril used, supports this view of the OPTIMAAL trial. When patients received a dose of valsartan that had the same clinical benefit as captopril, they were less likely than those receiving captopril to discontinue therapy because of a drug-related adverse event. The increased frequency of hypotension and renal problems associ-

Table 3. Adverse Events Leading to a Dose Reduction or a Discontinuation of Study Treatment.

Cause	Resulting in Dose Reduction			Resulting in Permanent Discontinuation of Study Treatment		
	Valsartan Group (N=4885)	Valsartan-and-Captopril Group (N=4862)	Captopril Group (N=4879)	Valsartan Group (N=4885)	Valsartan-and-Captopril Group (N=4862)	Captopril Group (N=4879)
	<i>number (percent)</i>					
Hypotension	739 (15.1)*	884 (18.2)*	582 (11.9)	70 (1.4)*	90 (1.9)*	41 (0.8)
Renal causes	239 (4.9)*	232 (4.8)*	148 (3.0)	53 (1.1)	61 (1.3)*	40 (0.8)
Hyperkalemia	62 (1.3)	57 (1.2)	43 (0.9)	7 (0.1)	12 (0.2)	4 (0.1)
Cough	85 (1.7)*	225 (4.6)	245 (5.0)	30 (0.6)*	101 (2.1)	122 (2.5)
Rash	32 (0.7)*	53 (1.1)	61 (1.3)	17 (0.3)*	34 (0.7)	39 (0.8)
Taste disturbance	13 (0.3)*	38 (0.8)	31 (0.6)	9 (0.2)*	16 (0.3)	21 (0.4)
Angioedema	12 (0.2)	22 (0.5)	22 (0.5)	9 (0.2)	12 (0.2)	13 (0.3)
Any of the above events†	1112 (22.8)	1404 (28.9)*	1063 (21.8)	197 (4.0)*	332 (6.8)*	280 (5.7)
Any adverse event	1437 (29.4)	1690 (34.8)*	1388 (28.4)	282 (5.8)*	438 (9.0)*	375 (7.7)
Any reason	2103 (43.1)	2342 (48.2)*	2098 (43.0)	1001 (20.5)	1139 (23.4)*	1055 (21.6)

* The difference from the captopril group is significant at $P < 0.05$.

† The totals of the numbers of patients with each type of event are greater than the numbers given for "any of the above events" because in some patients more than one type of event contributed to the decision to reduce the dose or discontinue study treatment.

ated with valsartan underscores the importance of careful monitoring when inhibitors of the renin-angiotensin-aldosterone system are used.

Given that valsartan was as effective as captopril in reducing the rates of death and other adverse cardiovascular outcomes among patients who had had a myocardial infarction, it should be considered a clinically effective alternative. The choice between these alternative treatments will depend on cumulative clinical experience, tolerability, safety, convenience, and cost.

Supported by a grant from Novartis Pharmaceuticals.

Drs. Pfeffer, McMurray, and Swedberg report having served as consultants for or having received honorariums from Novartis, AstraZeneca, Bristol-Myers Squibb, and Merck. Dr. Maggioni reports having served as a consultant for or having received honorariums from Novartis and AstraZeneca. Drs. Califf, Solomon, Velazquez, and Rouleau report having served as consultants for or having received honorariums from Novartis. Drs. Henis and Zelenkofske and Ms. Edwards are or were employees of Novartis and have stock equity in the company. Dr. Pfeffer is named as a coinventor on a patent awarded to the Brigham and Women's Hospital regarding the use of inhibitors of the renin-angiotensin system in selected survivors of myocardial infarction; there is a licensing agreement between Novartis Pharmaceuticals and the Brigham and Women's Hospital, which is not linked to sales.

APPENDIX

The following persons participated in the VALIANT trial. **Executive Committee** — M. Pfeffer (Chair), J. McMurray (Cochair), R. Califf, A. Maggioni, J.-L. Rouleau, F. Van de Werf, E. Velazquez; **Steering Committee** — P. Aylward, P. Armstrong, S. Barvik, Y. Belenkov, A. Dalby, R. Diaz, H. Drexler, G. Ertl, G. Francis, J. Hampton, A. Harsanyi, L. Køber, J. Kvasnicka, V. Mareev, J. Marin-Neto, J. Murin, M. Myers, R. Nordlander, G. Opolski, J. Soler-Soler, J. Spac, T. Stefanelli, D. Sugrue, K. Swedberg, W. Van Gilst, S. Varshavsky, D. Weaver, H. White, F. Zannad; **Clinical End-Point Committee, Brigham and Women's Hospital** — S. Solomon (Chair), D. Aguilar, A. Alvarez, M. Al-Taweel, N. Anavekar, P. Finn, F. Lopez-Jimenez, R. Mercier, M. Pfeffer, E. Lewis, S. Massom, C. Manes, A. Mirza, U. Sampson, H. Skali, N. Skali, K. Szummer, M. Tokmakova, L. Zornoff; **Clinical End-Point Committee, Duke Clinical Research Institute** — K. Mahaffey (Chair), T. Bozeman, R. Doletski, R. Lail, M. Smith, L. Taylor, B. Thomas; **Pharmacoeconomics Group** — K. Schulman, J. Radeva, S. Reed, K. Weinfurt; **Data and Safety Monitoring Board** — A. Leizorovicz (Chair), F. Boutitie (independent statistician), R. Cody, H. Dargie, C. Hennekens, S. Pocock; **Investigators: Argentina (635 patients)** — R.A. Ahuad Guerrero, J.P. Albusu, M. Amuchastegui, E.M. Avila, C.A. Bassani Arrieta, R. Bastianelli, C. Becker, J. Bono, G. Bortman, G. Bustamante Labarta, A. Caccavo, G.D. Caime, C.R. Castellanos, H. Castro, G. Covelli, C.A. Cuneo, A. Del Rio, A. Fernandez, G. Fernandez Cid, E. Ferro Queirel, J.J. Fuselli, M.A. Garcia, R. Garcia Duran, M. Garrido, A. Gentile, N.U. Gorini, H. Grancelli, E. Hasbani, M.A. Hominal, A.D. Hrabar, J.E. Leiva, R. Lopez, H.L. Lucardi, S.M. Macin, L. Mariano, A. Marinesco, R. Martingano, G.D. Martino, E.M. Marzetti, V. Mezzina, H.L. Moreno, J. Muntaner, R. Nordaby, D. Nul, A.D. Orlandini, M.A. Parra Pavich, J.C. Pomposiello, R.A. Quijano, M. Ruscullada, D. Ryba, E. Sampo, J.A. Sanchez, C.M. Serra, F. Sokn, C.H. Sosa, A. Sosa Liprandi, M. Trivi, F. Vallejos, M. Vico, N.A. Vita, D. Vogel, J.A. Volmaro; **Australia (307 patients)** — L. Arnolda, G. Aroney, P. Aylward, N. Bett, P. Carroll, D. Cross, D. Fitzpatrick, P. Garrahy, A. Hill, J. Horowitz, D. Hunt, M. Ireland, G. Lane, J. Lefkowitz, J.W. Leitch, G. Nelson, K. Rajappa, J. Rankin, D. Rees, A. Russell, B. Singh, R. Taylor, A. Thomson, J. Waites, W. Walsh; **Austria** — (27 patients): B. Eber, F.W. Krempler, P. Kuhn, M. Pichler, G. Røggla, P. Siostrzonek, T. Stefanelli,

K.H. Tragl; Belgium (68 patients) — B. Bergez, D. El Allaf, W. Smolders, F. Van de Werf, A. Van Dorpe, J.-P. Vandebossche, L. Vanneste; Brazil (213 patients) — D. Albuquerque, J. Ayoub, R. Bassan, A.C. Carvalho, L.R. Castro, O. Coelho, F.A. Costa, J. Esteves, G. Feitosa, J. Filho, C. Gun, J. Kerr Saraiva, P. Leaes, L. Maia, J.A. Marin-Neto, R. Marino, E. Mesquita, L.S. Piegas, A. Rabelo, Jr., S. Rassi, A. Rassi, Jr., C. Scherr, J. Spadaro, R. Vaz; Canada (1092 patients) — M. Arnold, J. Bedard, V. Bernstein, T. Bhesania, N. Bonafede, R. Brossoit, B. Burke, R. Castan, J. Charles, M.T. Cheung, G. Chua, P. Costi, R. Davies, B. Descoings, D. Desrochers, S. Dhingra, D. Dion, L. Duchesne, J. Dupuis, R. Dupuis, F. Ervin, R. Fowlis, R. Gendreau, C. Germain, P. Giannoccaro, E. Goode, D. Gossard, G. Gosselin, G. Goulet, J. Heath, V.A. Heath, A. Hess, G. Honos, J. Howlett, T. Huynh, J. Javier, D. Kincade, W.P. Klinke, S. Kouz, K. Kwok, R. Lee, J. Lenis, S. Lepage, B. Lubelsky, R. McKelvie, J. Minkowitz, G. Moe, M. Montigny, R. Nadeau, C. Nitkin, B. O'Kelly, M. Palaic, J. Parker, T. Parker, Y. Pesant, D. Phaneuf, K. Pistawaka, G. Proulx, R. Roux, D. Rupka, D. Saulnier, M. Senaratne, F. Sestier, N. Sharma, R. St. Hilaire, J. Stone, H. Strauss, B. Sussex, P. Talbot, B. Tremblay, S. Vizek, J.W. Warnica, M. Weigel, G. Wisenberg; Czech Republic (207 patients) — J. Drazka, J. Filipovský, K. Horký, P. Janský, R. Kral, J. Kvasnicka, A. Martinek, J. Spinar, P. Svitil; Denmark (681 patients) — E. Agner, H.K. Andersen, K. Angelo-Nielsen, M. Asklund, J. Berning, M. Brøns, J. Buhl, P. Eliassen, T. Fløgstad, T. Jensen, K. Klarlund, L. Køber, K.S. Kristensen, L. Kroell, J. Larsen, S. Lind Rasmussen, H. Madsen, J. Markenvard, B. Mortensen, H. Nielsen, I. Nielsen, T. Nielsen, A. Nymann Davidson, O. Nyvad, M. Ottesen, O.L. Pedersen, H. Rickers, J. Rokkedal, M. Scheibel, H. Sejersen, E.V. Sørensen, P.J. Sørensen, S.E. Stenteberg; France (163 patients) — P. Bareiss, R. Barraine, P.D. Battistella, P. Beaufils, A. Bonneau, J.-M. Bouleuc, J.-M. Bouvier, S. Cheggour, B. Citron, D. Coisne, F. Delahaye, M. Ferriere, C. Fournier, J.-C. Kahn, A. Koenig, T. Laperche, P. Loiselet, R. Luccioni, M. Martelet, D. Matina, A. Ouakli, M. Parisot, D. Pavin, J.-C. Quiret, A. Rifai, X. Tran-Thanh; Germany (323 patients) — C.E. Angermann, G. Bauriedel, H. Bethge, M. Borst, M. Braun, H. Drexler, C. Echternach, R. Engberding, J. Epping, G. Ertl, H.-R. Figulla, P. Gaudron, R. Hambrecht, P. Hanrath, D. Hey, B. Jany, W. Karmann, H.J. Keller, B. Kohler, H.U. Kreider-Stempfle, B. Maisch, T. Matthes, T. Münzel, H.P. Nast, C. Nienaber, J. Nitsch, D. Pfeiffer, B. Pieske, U. Römmel, R. Rupp, R. Schatz, H.-P. Schultheiss, J. Senges, R. Simon, U. Solzbach, R.H. Strasser, U. Tebbe, H. Topp, T. Unger, W. Urbaszek, G.H. von Knorre, K. von Olshausen, J. Wagner, M. Wirth, M.W. Wolf; Hungary (400 patients) — M. Csanády, I. Édes, A. Erdei, B. Hanis, A. Harsanyi, A. Jánosi, E. Káló, P. Kárpati, S. Kőmives, G. Kutor, G. Moser, G. Rumi, G. Simon, F. Szabóki, J. Tarján, S. Timár, K. Tóth; Ireland (38 patients) — J.J. Barton, P. Crean, K. Daly, D. Fitzgerald, P. Kearney, D. Sugrue; Italy (753 patients) — P. Alboni, B. Aloisi, C. Antenucci, C. Bellet, D. Bernardi, A. Bini, F. Bor-tolini, A. Branzi, U. Bugatti, R. Bugiardini, V. Capuano, M. Carrone, P. Celli, F. Chiesa, V. Cicone, G. Corsini, G. De Angelis, G. Di Pasquale, R. Fanelli, G. Florizzo, P. Fioretti, A. Grieco, G. Ignone, A. Maffici, G. Maglia, R. Mangia, P. Maras, F. Masini, A. Mauric, A. Paci, G. Pettinati, R. Pirani, W. Rauhe, L. Sala, G. Sibilio, G. Slavich, G. Soravia, G. Tartarini, L. Tavazzi, P. Terrosu, G. Trevi, B. Trimarco, M. Turri, P. Tur-rini, F. Valagussa, C. Vassanelli, M. Volpe; the Netherlands (255 patients) — A.E.R. Arnold, M. Bijl, P.A.R. De Milliano, P.H.J.M. Dunselmann, Ph.W. Fels, A. Funke Küpper, A.H. Herweijer, W. Jaarsma, O. Kamp, H.J.J. Koornstra, J.A. Kragten, P.J.P. Kuijer, C.M. Leenders, A.H. Liem, G.C.M. Linssen, R.J. Lionarons, D.J.A. Lok, W.J.S. Louridtz, H.R. Michels, W.M. Muijs van de Moer, P.R. Nierop, J.L. Posma, P.H. Van der Burgh, P.M. van Kalmthout, L.H.J. van Kempen, D.J. van Veldhuisen, J.C.L. Westdorp, A.J.A.M. Withagen; New Zealand (136 patients) — N. Abdul-Ghaffar, J. French, D. Friedlander, I. Gerber, A. Hamer, C. Hammett, J. Hedley, H. Ikram, S. Mann, P. Matsis, R. Rankin, D. Scott, H. White, G. Wilkins, M. Williams, C.K. Wong; Norway (263 patients) — S. Barvik, K. Dickstein, V. Hoeg; Poland (348 patients) — W. Banasiak, M. Demczuk, A. Dyduszyński, J.H. Goch, J. Górny, M. Janion, K. Kawecka-Jaszcz, J. Kopaczewski, K. Loboż-Grudzien, M. Ogórek, G. Opolski, W. Piotrowski, P. Ruskowski, A. Rynkiewicz, R. Sciborski, M. Stopinski, M. Trusz-Gluza, T. Waszyrowski, D. Wojciechowski, K. Wrabel, J. Zambrycki; Russia (3135 patients) — V. Ananchenko, G. Arutyunov, M. Baluda, O. Barbarash, D. Belenkiy, S. Belousov, Y.B. Belousov, M. Boiarkin, I. Bokarev, R.A. Charchoglian, D.A. Chepky, G. Chumakova, V. Doschicyn, P. Dovgalevsky, L. Ermoshkina, G.S. Filonenko, I. Fomin, I. Fomina, S. Foytanov, M. Freydlina, M. Glezer, A. Golikov, B. Goloshchekin, A. Gospodarenko, N. Gratsiansky, G. Ivanov, L. Katelnitskaya, M. Khrakovskaya, O. Khrustalev, I. Klenina, V. Kostenko, M. Kozlova, O. Lapin, N. Leontieva, Y.M. Lopatin, V. Lusov, V. Markov, S. Martiushov, A. Martynov, N. Mezentseva, A. Michailov, V.R. Mkrtchyan, V. Moiseev, S. Nedogoda, A.V. Nefedov, Y. Nikitin, L. Olbinskaya, N. Perepech, A. Rebrov, K. Rogalev, M. Ruda, E. Shlyahoto, V. Shmyrova, A. Shpector, S. Shustov, Y. Shwartz, B. Sidorenko, V. Simonenko, K. Sobolev, L. Sorokin, M. Stefanenko, O. Stepura, R. Strioux, V. Sulimov, A. Sumin, A. Syrkin, B. Tankhilevitch, N. Tarasov, A. Tchutchalin, E. Troshina, A.V. Tuev, S. Vaniev, A. Vertkin, A. Vishnevsky, S. Yacushin, N. Yarokhno, V. Zadiontchenko, A. Zhorovskiy, E. Zemtsovskiy, D. Zverev; Slovakia (184 patients) — P. Brunclik, T. Duris, J. Hasilla, R. Kohn, F. Kovár, J. Murin, B. Renker, R. Rybar, M. Slanina, R. Uhliar; South Africa (58 patients) — J.M. Bennet, A.J. Dalby, D.I. Duncan, M.R. Essop, A. Kok, P. Manga, B.M.M. Posen, J.S. Roos, F.A. Snyders, L. Steingo; Spain (123 patients) — A. Bardajil Ruiz, J. Bayón Fernández, J.M. Cruz Fernández, E. Galve Basilio, M. de Miguel Díaz, E. Roig Minguell, L. Saenz Cusi, V. Valle Tudela, J.A. Velasco Rami; Sweden (490 patients) — U. Ahreemark, L. Aström, K. Boman, P. Brunmark, U. Dahlström, O. Fredholm, J.E. Frisell, P. Pann, R. Hardhammar, M. Hartford, U. Hurtig, L. Jonasson, L. Klintberg, L.-E. Larsson, P. Nicol, O. Nilsson, S.-B. Nilsson, H. Öhlin, Å. Ohlsson, J. Perk, H. Perrson, M. Peterson, G. Rasmanis, C. Ringquist, A. Stenberg, K. Swedberg, D. Tivic, I. Timberg, K. Waern Bugge, P. Wodlin; United Kingdom (840 patients) — J. Adgey, M. Al-Kholfash, R. Andrews, P. Avery, S. Ball, R. Baxter, M. Been, J. Birkhead, A. Bridges, P. Broadhurst, R. Canepa Anson, J. Cleland, P. Clifford, D. Connelly, T. Crane, J. Davies, M. Davies, J. Dhawan, F. Dunn, I. Findlay, J. Hampton, S. Hanley, P. Higham, A. Jacob, C. Jones, J. Kaski, G. Lip, R. MacFadyen, R. Mattu, H. McAlpine, J. McMurray, M. Metcalfe, A. Moriarty, C. Morley, D. Murdoch, S. Mushahwar, W. Penny, D. Pitcher, S. Puri, J. Purvis, M. Ramsey, C. Reid, G. Richardson, D. Rowlands, S. Saltissi, R. Senior, J. Shahi, L. Smith, N. Spyrou, I. Squire, J. Stephens, J. Swan, C. Travill, N. Uren, R. Vincent, N. Wheeldon; United States (3964 patients) — R. Acheate, P. Ackell, D. Adler, K. Akosah, M. Amidi, P. Amsterdam, I. Anand, J. Anderson, J. Aranda, R. Ashar, K. Ayala, R. Badger, M. Balk, P. Bannon, M. Basnight, V. Battles, C. Bayron, J. Becker, R. Belkin, B. Bellamy, R. Bellinger, J. Bengtson, S. Bennett, N. Bhalodkar, G. Bhat, R. Birkhead, J. Bittl, M. Boland, W. Book, C. Brachfeld, G. Broderick, M. Brodsky, C. Brown III, D. Bruns, J. Butler, D. Calnon, J. Calvin, A. Camacho, P. Cambier, A. Camp, P. Campbell, J.D. Cannon, Jr., S. Cansino, R. Carlson, K. Carr, P. Casale, H. Chadow, P. Chalasani, H. Chandna, D. Chapman, G. Charlton, J. Cheirif, D. Childs, J. Chin, A. Chu, D. Churchill, L. Clark, F. Cobb, H. Colfer, C. Corder, M. Croitoru, D. Cullinane, M. Cunningham, I. Dauber, T. Davis, D. Dawley, P. Deedwania, J. Delemos, A. DeLeon, G. Dennish, D.M. Denny, S. Desai, C. D'Haem, N. Dhruva, P. Dionisopoulos, E. Dixon, E. Dodin, S. Dohad, D. Dowdy, J. Drury, C. Duvernoy, A. Edin, T. Edwards, F. Eelani, M. El Shahawy, M. Ellestad, R.D. Ensley, F. Fahey, J. Farahi, J. Farnham, P. Fatal, J. Fernandez, J. Fialkow, V. Figueredo, D. Fintel, G. Fishberg, R. Fishberg, B. Fisher, P. Fitzpatrick, G. Flaker, M. Foster, W. French, M. Frey, B. Friedman, J. Furiasse, J. George, J. Ghali, J. Gilbert, P. Giles, J. Glassman, M. Gleva, R. Glynn, S. Goldman, D. Goldner, P. Goodfield, D. Gordon, J. Gottdeiner, R. Goulah, T. Grady, R. Graf, B. Graham, J. Graziano, F. Gredler, D. Greenberg, M. Greenspan, B. Gros, J. Hall, Jr., H. Hanley, B. Harris, K. Harris, C. Hartman, M.W. Hashimi, A. Hassett, W.H. Haught, D. Hill, M. Hillert, J. Hochman, J. Hodsdon, R. Hoffmann, M. Honan, D. Hsi, M. Hudson, H. Ingersoll, N. Israel, D. Jackman, B. Jackson, S. Jafri, A. Jain, A. Jain, N. Jamal, L. Jenkins, S. Jennison, M. Jones, J. Josephson, J. Kannam, A. Karamali, R. Karns, W. Katz, D. Kereiakes, E.K. Kerut, M. Kesselbrenner, J. Kieval, J. King, R. Ripperman, A. Kizilbash, K. Klancke, M. Klein, J. Kmonicek, P. Kosolcharoen, B. Kowalski, M. Kraemer, K. Kreisman, M. Kwan, W. Lafoe, P. Lai, M. Lakow, G. Lamas, L. Lancaster, J. Langager, G. Larsen, J. Lash, M. Lauer, N. Laufer, D. Laughrun, C. Lee, M. Lee-

sar, L. Lefkovic, W. Leimbach, P. Leimgruber, F. Lenz, T. Lessmeier, M. Lester, M. Levitte, C. Lieberman, M. Lillestol, T. Little, F. Lopez, M. Lopez, D. Losordo, J. Lucke, G. MacDonald, H. Madyoon, R. Magorien, P. Maher, F. Maislos, R. Manda, M. Mansuri, R. McClure, D. McCord, M. J. McGreevy, F. McGrew, R. C. McKoy, P. McLaughlin, S. Mehta, F. Menapace, T. Meyer, R. Millar, G. Miller, L. Miller, A. Minisi, J. Mitchell, F. V. Mody, K. K. Mohan, S. Mohiuddin, C. Moore, R. Moore, K. Morris, M. Motta, J. B. Muhlestein, S. Murali, W. E. Musser, J. Navas, A. Niederman, E. D. Nukta, T. Nygaard, J. O'Bryan, C. O'Connor, D. O'Dea, R. Oliveros, S. Oparil, R. Orchard, E. Ostrzega, J. Owens, P. Pak, R. Palac, E. Papisafakis, C. Paraboschi, D. Pearce, D. Peizner, G. Ponce, P. Popper, C. Porter, L. M. Prisant, D. Pritzka, M. Ptacin, C. Raab, W. Radtke, P. Rahko, J. Ramirez, M. Rana, B. Reeves, Jr., C. Reimers, K. Retter, G. Revtyak, S. Rezkalla, L. Rink, E. Rivera, S. Roark, S. Rohrbeck, J. Rosenthal, P. Rossi, J. Sacco, K. Saeian, F. Saltiel, F. Samaha, C. Schechter, R. Schneider, J. Schrank, S. Schulman, G. Schuyler, R. Sequeira, Y. Shalev, K. Sheikh, S. Sheikh, M. Siddique, R. Siegel, T. Silver, C. Simek, J. Sklar, D. Small, T. Smith, R. Soucier, T. Spaedy, A. Spatz, N. Srivastava, A. Stahl, K. Stark, P. Stein, M. Stern, T. Stevens, R. Stine, S. Sundram, G. Sutliff, R. Taikowski, A. Taylor, U. Thadani, C. Thompson, M. Thompson, G. Timmis, M. Tischler, J. Torelli, S. Traub, C. Treasure, C. Tsai, V. Tschida, C. Tung, D. M. Unks, P. Urban, B. Uretsky, N. Vaganos, K. Vasudemurthy, M. Vaughan, J. Vazquez-Bauza, N. Vijay, E. Von Der Lohe, D. Vorchheimer, S. Voyce, T. Wall, M. Walsh, J. Watkins, R. Weiss, N. Wenger, J. Werner, T. Wayne, T. Whitsitt, M. Wilensky, C. Wilmer, V. Wilson, D. Wolbrette, D. Wolinsky, R. Wright, A. Yaacoub, S. Yakubov, B. Zakhary, J. Zaroff, S. Zelenkofske, M. Zolnick, D. Zwicke; *Monitoring and Site Management Organizations* — Canadian Virtual Coordinating Centre for Global Collaborative Cardiovascular Research: Lead Monitor, C. Boyd, M. Adam; Montreal Heart Institute: Lead Monitor, L. Whittom, J. Marquis; ECLA-Estudios Cardiológicos Latinoamerica: Project Leader, A. Pascual, Lead Monitor, A. Medina; Flinders Coordinating Centre: Lead Monitor, C. Astley, M. Schofield; Green Lane Coordinating Centre: Lead Monitor, M. Kelkar, O. Bucan, M. Scott; Scandinavian Clinical Research Institute: Research Manager, S. Lindbratt; Henry Ford Coordinating Center: Lead Coordinator, C. Sherlitz; Mayo Alliance for Clinical Trials: Lead Coordinator, K. Cornwell; Medicon Scandinavia: Medical Director, J. Carlsen; Brigham and Women's Hospital: Research Coordinator, R. Mercier; Parexel International: Project Director, T. Spencker, Lead Monitor, K. Pohlner; Quintiles: Project Director, A. Black, Interactive Voice Randomization Project Director, T. Steven; University of Toronto: Lead Coordinator, C. Leblanc; *Trial Operations*: Duke Clinical Research Institute — Project Leader: M. A. Sellers, Lead Coordinator: L. Rittenhouse, Lead Monitor: L. Sunas, Lead Statistician: J. Leimberger, Lead Data Manager: A. Walden; Leuven Coordinating Centre — Safety Manager, M. Moreira, Project Manager, K. Houbracken, K. Vandenberghe; Russian Clinical Helplines—Moscow: F. Ageev, A. Skvortsov, O. Narusov, G. Mareeva, J. Gurskaya; St. Petersburg: A. Shargorodskaya; Sponsor: Novartis Pharmaceuticals — Medical Directors: S. Zelenkofske, M. Henis; Project Leader: S. Edwards; Statistician: J. Gong; Programmers: X. Han, J. Shinomoto; Clinical Team: P. Barbiero, T. Jezek, J. Kaczor, N. B. Keating, R. Koempf, R. McGarry, G. Rossy, C. Salemi, A. Trapani.

REFERENCES

- Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement trial. *N Engl J Med* 1992;327:669-77.
- Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet* 1994;343:1115-22.
- ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995;345:669-85.
- Chinese Cardiac Study Collaborative Group. Oral captopril versus placebo among 13 634 patients with suspected acute myocardial infarction: interim report from the Chinese Cardiac Study (CCS-1). *Lancet* 1995; 345:686-7.
- Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med* 1995;332:80-5.
- Swedberg K, Held P, Kjeksus J, Rasmussen K, Ryden L, Wedel H. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction: results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med* 1992;327:678-84.
- The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342: 821-8.
- Køber L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995; 333:1670-6.
- Pfeffer MA. ACE inhibition in acute myocardial infarction. *N Engl J Med* 1995;332: 118-20.
- Flather MD, Yusuf S, Køber L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* 2000;355:1575-81.
- Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. *N Engl J Med* 1996;334:1649-54.
- Petrie MC, Padmanabhan N, McDonald JE, Hillier C, Connell JM, McMurray JJ. Angiotensin converting enzyme (ACE) and non-ACE dependent angiotensin II generation in resistance arteries from patients with heart failure and coronary heart disease. *J Am Coll Cardiol* 2001;37:1056-61.
- Horiuchi M, Akishita M, Dzau VJ. Recent progress in angiotensin II type 2 receptor research in the cardiovascular system. *Hypertension* 1999;33:613-21.
- Pfeffer MA, McMurray J, Leizorovicz A, et al. Valsartan in acute myocardial infarction trial (VALIANT): rationale and design. *Am Heart J* 2000;140:727-50.
- Sidak Z. Rectangular confidence regions for the means of multivariate normal distributions. *J Am Stat Assoc* 1967;62:626-33.
- Fisher LD. Active control trials: what about a placebo? A method illustrated with clopidogrel, aspirin and placebo. *J Am Coll Cardiol* 1998;31:Suppl A:49A. abstract.
- Hasselblad V, Kong DF. Statistical methods for comparison to placebo in active-control trials. *Drug Inf J* 2001;35:435-49.
- Velazquez EJ, Pfeffer MA, McMurray JJ, et al. VALsartan In Acute myocardial infarction (VALIANT) trial: baseline characteristics in context. *Eur J Heart Fail* 2003; 5:537-44.
- Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2001;38:2101-13.
- Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22:1527-60. [Erratum, *Eur Heart J* 2001;22:2217-8.]
- Skali H, Pfeffer MA. Prospects for ARB in the next five years. *J Renin Angiotensin Aldosterone Syst* 2001;2:215-8.
- Committee for Proprietary Medicinal Products. Points to consider on switching between superiority and non-inferiority. *Br J Clin Pharmacol* 2001;52:223-8.
- D'Agostino RB Sr, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts

- and issues — the encounters of academic consultants in statistics. *Stat Med* 2003;22:169-86.
24. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-75.
25. McMurray JJV, Östergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003;362:767-71.
26. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall Programme. *Lancet* 2003;362:759-66.
27. Yusuf S. From the HOPE to the ONTARGET and the TRANSCEND studies: challenges in improving prognosis. *Am J Cardiol* 2002;89:18A-25A.
28. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Lancet* 2002;360:752-60.
29. Dickstein K. What did we learn from the OPTIMAAL trial? What can we expect from VALIANT? *Am Heart J* 2003;145:754-7.

Copyright © 2003 Massachusetts Medical Society.