Impact of Candesartan on Nonfatal Myocardial Infarction and Cardiovascular Death in Patients With Heart Failure

Catherine Demers, MD, MSc
John J. V. McMurray, MD
Karl Swedberg, MD, PhD
Marc A. Pfeffer, MD, PhD
Christopher B. Granger, MD
Bertil Olofsson, PhD
Robert S. McKelvie, MD, PhD
Jan Östergren, MD, PhD
Eric L. Michelson, MD
Peter A. Johansson, MSc
Duolao Wang, PhD
Salim Yusuf, MBBS, DPhil
for the CHARM Investigators

Context Angiotensin-converting enzyme (ACE) inhibitors reduce the risk of myocardial infarction (MI), but it is not known whether angiotensin receptor blockers have the same effect.

Objective To assess the impact of the angiotensin receptor blocker candesartan on MI and other coronary events in patients with heart failure.

Design, Setting, and Participants The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program, a randomized, placebo-controlled study enrolling patients (mean age, 66 [SD, 11] years) with New York Heart Association class II to IV symptoms who were randomly allocated to receive candesartan (target dose, 32 mg once daily) or matching placebo given in addition to optimal therapy for heart failure. Patients were enrolled from March 1999 through March 2001. Of 7599 patients allocated, 4004 (53%) had experienced a previous MI, and 1808 (24%) currently had angina. At baseline, 3125 (41%) were receiving an ACE inhibitor; 4203 (55%), a β-blocker; 3153 (42%), a lipid-lowering drug; 4246 (56%), aspirin; and 6286 (83%), a diuretic.

Main Outcome Measure The primary outcome of the present analysis was the composite of cardiovascular death or nonfatal MI in patients with heart failure receiving candesartan or placebo.

Results During the median follow-up of 37.7 months, the primary outcome of cardiovascular death or nonfatal MI was significantly reduced in the candesartan group (775 patients [20.4%]) vs the placebo group (868 [22.9%]) (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.79-0.96; $P=.004$; number needed to treat [NNT], 40). Nonfatal MI alone was also significantly reduced in the candesartan group (116 [3.1%]) vs the placebo group (148 [3.9%]) (HR, 0.77; 95% CI, 0.60-0.98; $P=.03$; NNT, 118). The secondary outcome of fatal MI, sudden death, or nonfatal MI was significantly reduced with candesartan (459 [12.1%]) vs placebo (522 [13.8%]) (HR, 0.86; 95% CI, 0.75-0.97; $P=.02$; NNT, 59). Risk reductions in cardiovascular death or nonfatal MI were similar across predetermined subgroups and the component CHARM trials. There was no impact on hospitalizations for unstable angina or coronary revascularization procedures with candesartan.

Conclusion In patients with heart failure, candesartan significantly reduces the risk of the composite outcome of cardiovascular death or nonfatal MI.

JAMA. 2005;294:1794-1798 www.jama.com

ANGIOTENSIN-CONVERTING enzyme (ACE) inhibitors reduce cardiovascular death, hospitalization for heart failure, and myocardial infarction (MI) in patients with heart failure or left ventricular systolic dysfunction and in high-risk patients with coronary artery disease or diabetes.[1-9] This effect is assumed to be due to the action of these drugs to reduce angiotensin II production, although ACE inhibitors also prevent bradykinin breakdown, which may have additional beneficial effects.[10] This raises the question of whether angiotensin II receptor blockers (ARBs) are as protective as ACE inhibitors in preventing MI. Conversely, blockade of the renin-angiotensin-aldosterone system by ACE inhibitors may be incomplete, especially during long-term treatment in patients with an activated system; in these patients, there is evidence of continued production of angiotensin II by

Author Affiliations: McMaster University, Hamilton, Ontario (Drs Demers, McKelvie, and Yusuf); University of Glasgow, Glasgow, Scotland (Dr McMurray); Sahlgrenska University Hospital/Östra, Göteborg, Sweden (Dr Swedberg); Cardiovascular Division, Brigham and Women's Hospital, Boston, Mass (Dr Pfeffer); Duke University Medical Center, Durham, NC (Dr Granger); AstraZeneca Research and Development, Mölndal, Sweden (Dr Olofsson and Mr Johansson); Karolinska Hospital, Stockholm, Sweden (Dr Östergren); AstraZeneca LP, Wilmington, Del (Dr Michelson); and London School of Hygiene and Tropical Medicine, London, England (Dr Wang).
A list of the CHARM Investigators has been published previously.[13]
Corresponding Author: Salim Yusuf, DPhil, Population Health Research Institute, McMaster University, Room 252, McMaster Clinic, Hamilton General Hospital, 237 Barton St E, Hamilton, Ontario, Canada L8L 2X2 (yusuf@ccc.mcmaster.ca).

non–ACE-dependent pathways.[11] This raises the possibility that an ARB in combination with an ACE inhibitor may be effective in further reducing MI.

In the placebo-controlled Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program, the effect of candesartan on total mortality, cardiovascular death, and hospitalization for heart failure was examined in patients with heart failure receiving recommended therapy.[12,13] This article describes the effects of candesartan on MI and on hospitalization for unstable angina and coronary revascularization procedures in the overall CHARM program.

METHODS

The design and primary results of CHARM have been published and are summarized here.[12,13] In brief, the CHARM program consisted of 3 component trials that compared the effects of adding candesartan or placebo to optimal background therapy in consenting patients with heart failure and either preserved left ventricular ejection fraction (LVEF) (CHARM-Preserved) or reduced LVEF (CHARM-Added, enrolling patients treated with an ACE inhibitor, and CHARM-Alternative, enrolling those not receiving an ACE inhibitor because of documented intolerance). Patients were enrolled from March 1999 through March 2001.

Study Population

Patients with New York Heart Association functional class II to IV were eligible and were randomly allocated according to LVEF (≤40%, >40%) and treatment with an ACE inhibitor. All patients received candesartan or matching placebo, starting at a dosage of 4 or 8 mg once daily, which was increased as tolerated to the target of 32 mg once daily. All sites received approval from local ethics committees for the conduct of this trial, and all patients provided written informed consent.

Follow-up and Outcome Measures

After the initial dose-titration period, follow-up visits occurred every 4 months, with a minimum planned duration of 2 years. At each visit, the occurrence of study outcomes was ascertained according to the intention-to-treat principle. Causes of death and reasons for hospital admissions were classified on standard forms by the investigator, without knowledge of treatment assignment, and confirmed or refuted by a blinded central adjudication process. Death was classified as cardiovascular unless an unequivocal noncardiovascular cause of death was confirmed by the central adjudication committee. Cardiovascular death included sudden death; death due to MI, heart failure, or stroke; procedure-related death (cardiovascular investigation/procedure/operation); death due to other specified cardiovascular causes; and presumed cardiovascular deaths (ie, those for which a noncardiovascular cause had not been clearly established).

A diagnosis of MI was made if (1) levels of creatine kinase or creatine kinase-MB (or troponin I or T if these were not available) were more than twice the upper limit of normal or if levels of these same markers were 3 times the upper limit of normal within 24 hours of percutaneous coronary intervention or 5 times the upper limit of normal within 24 hours of coronary artery bypass graft surgery and if, in addition, the patient had (2) electrocardiographic changes in 2 or more contiguous leads showing new Q waves (or R waves in V_1 and V_2), left bundle-branch block, or ischemic ST–T-wave changes, or (3) typical clinical presentation with cardiac ischemic-type pain lasting more than 20 minutes, pulmonary edema, or cardiogenic shock not otherwise explained. All reported nonfatal MI events underwent blinded central adjudication. Information on hospitalization for unstable angina and coronary revascularization procedures (percutaneous coronary intervention or coronary artery bypass graft surgery) were based on the events reported by the investigator and were not centrally adjudicated.

Statistical Analyses

The primary composite outcome of this analysis was cardiovascular death or nonfatal MI. All randomized patients were included in the analyses except for 2 individuals for whom no data were available. Hazard ratios were estimated by finding the values of the regression coefficients in a Cox regression model (stratified for study) that maximized the partial likelihood. The Cox proportional hazards assumption was confirmed by plotting the hazards against follow-up time. The Wald statistic was used to test each coefficient separately, and 95% confidence intervals were calculated. Tests of heterogeneity of hazard ratios across studies were performed. Survival curves were estimated by the Kaplan-Meier procedure. Cox regression analyses were used to determine the uniformity of treatment effects across prespecified subgroups for the CHARM-Overall study. Analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC); $P<.05$ was used to determine statistical significance.

RESULTS

Baseline Characteristics

Baseline patient characteristics for the CHARM-Overall study were previously published.[13] Mean age was 66 (SD, 11) years. Of 7599 patients randomly allocated, 5199 (68%) were men, 4004 (53%) had experienced a previous MI, 1808 (24%) had current angina, 4681 (62%) had heart failure of ischemic etiology, 2160 (28%) had diabetes mellitus, 1228 (16%) had undergone percutaneous coronary intervention, and 1791 (24%) had undergone coronary artery bypass graft surgery. At baseline, 3125 patients (41%) were receiving an ACE inhibitor (100% in CHARM-Added, 0% in CHARM-Alternative, 19% in CHARM-Preserved); 4203 (55%), a β-blocker; 3153 (42%), a lipid-lowering drug; 4246 (56%), aspirin; and 6286 (83%), a diuretic.

MI, Fatal Coronary Events, Unstable Angina, and Coronary Revascularization

There was a significant reduction in the primary composite outcome of cardiovascular death or nonfatal MI and in

the secondary outcome of nonfatal MI alone in patients receiving candesartan compared with placebo (TABLE and FIGURE 1). There was a nonsignificant trend of fewer patients who experienced sudden death or fatal MI, but the composite outcome of fatal MI, sudden death, or nonfatal MI was significantly reduced with candesartan.

The effect of candesartan on the composite outcome of cardiovascular death or nonfatal MI was consistent across the component CHARM trials (Added, Alternative, and Preserved) (FIGURE 2). The impact of candesartan on cardiovascular death or nonfatal MI compared with placebo was also consistent across relevant subgroups (Figure 2). Candesartan had no effect on hospitalization for unstable angina or coronary revascularization procedures.

COMMENT

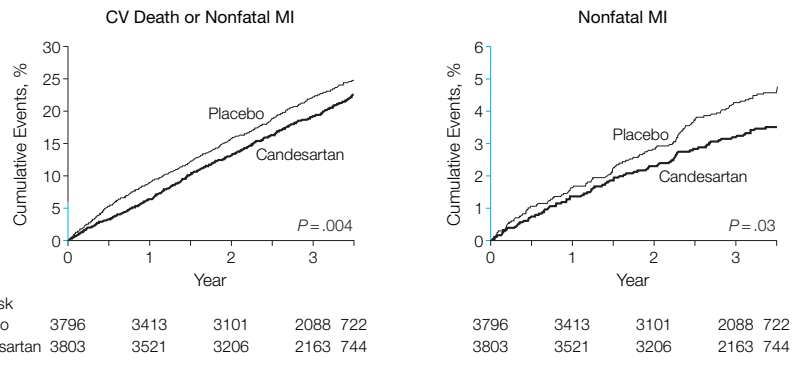
In the CHARM program, the addition of the ARB candesartan to conventional therapies for heart failure resulted in a significant reduction in the combined outcome of cardiovascular death or nonfatal MI in patients with symptomatic heart failure. These findings were consistent across all subgroups examined, including patients treated with other therapies proven to be effective in reducing the risk of MI or reinfarction. The prevention of MI broadens the potential benefit of candesartan in this patient population.

Table. Effect of Candesartan on Development of Myocardial Infarction (MI), Cardiovascular (CV) Mortality, and Hospitalization for Unstable Angina or Coronary Revascularization Procedures

Outcome	Events, No. (%) Candesartan (n = 3803)	Placebo (n = 3796)	HR (95% CI)	*P* Value	NNT
CV death or nonfatal MI	775 (20.4)	868 (22.9)	0.87 (0.79-0.96)	.004	40
Nonfatal MI	116 (3.1)	148 (3.9)	0.77 (0.60-0.98)	.03	118
CV death	691 (18.2)	769 (20.3)	0.88 (0.79-0.97)	.01	48
Fatal MI, sudden death, or nonfatal MI	459 (12.1)	522 (13.8)	0.86 (0.75-0.97)	.02	59
Sudden death or fatal MI	360 (9.5)	394 (10.4)	0.89 (0.77-1.03)	.11	NA
Hospitalization					
Unstable angina	394 (10.4)	397 (10.5)	0.97 (0.84-1.11)	.60	NA
Coronary revascularization procedures*	236 (6.2)	241 (6.4)	0.96 (0.80-1.14)	.60	NA

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable; NNT, number needed to treat.
*Percutaneous coronary intervention or coronary artery bypass graft surgery.

Figure 1. Kaplan-Meier Analysis of Effects of Candesartan on Composite of Cardiovascular (CV) Death/Nonfatal Myocardial Infarction (MI) or on Nonfatal MI Alone



No. at Risk

Placebo	3796	3413	3101	2088	722
Candesartan	3803	3521	3206	2163	744
Placebo	3796	3413	3101	2088	722
Candesartan	3803	3521	3206	2163	744

It is of interest to compare this effect of candesartan with that of ACE inhibitors. In the Studies of Left Ventricular Dysfunction (SOLVD) treatment and prevention trials,[1] the ACE inhibitor enalapril decreased the risk of nonfatal MI by 23% (95% confidence interval, 11%-34%; $P<.001$). Although similar reductions in MI were described in the Heart Outcomes Prevention Evaluation (HOPE)[7] and the European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA)[8] studies with ACE inhibitor treatment in high- and intermediate-risk patient populations without documented heart failure or left ventricular systolic dysfunction, the Prevention of Events With Angiotensin Converting Enzyme Inhibitors (PEACE) study[9] showed no effect on nonfatal MI of adding trandolapril in low-risk patients. However, a meta-analysis of the HOPE, EUROPA, and PEACE trials indicates a reduction in total mortality.[14] Prior to CHARM, it was unknown whether ARBs would also reduce MI in patients with heart failure or other cardiovascular conditions. It is notable, therefore, that the magnitude of the reduction in cardiovascular death and nonfatal MI in CHARM was similar to that observed in SOLVD and other trials. Furthermore, the beneficial impact of candesartan was observed in patients taking β-blockers, lipid-lowering agents, or aspirin, indicating an additive and independent effect to standard therapy, as seen with ACE inhibitors. Importantly, however, candesartan also further reduced risk in patients receiving an ACE inhibitor, suggesting additional protection against cardiovascular events through increased blockade of the renin-angiotensin-aldosterone system, at least in patients with heart failure.

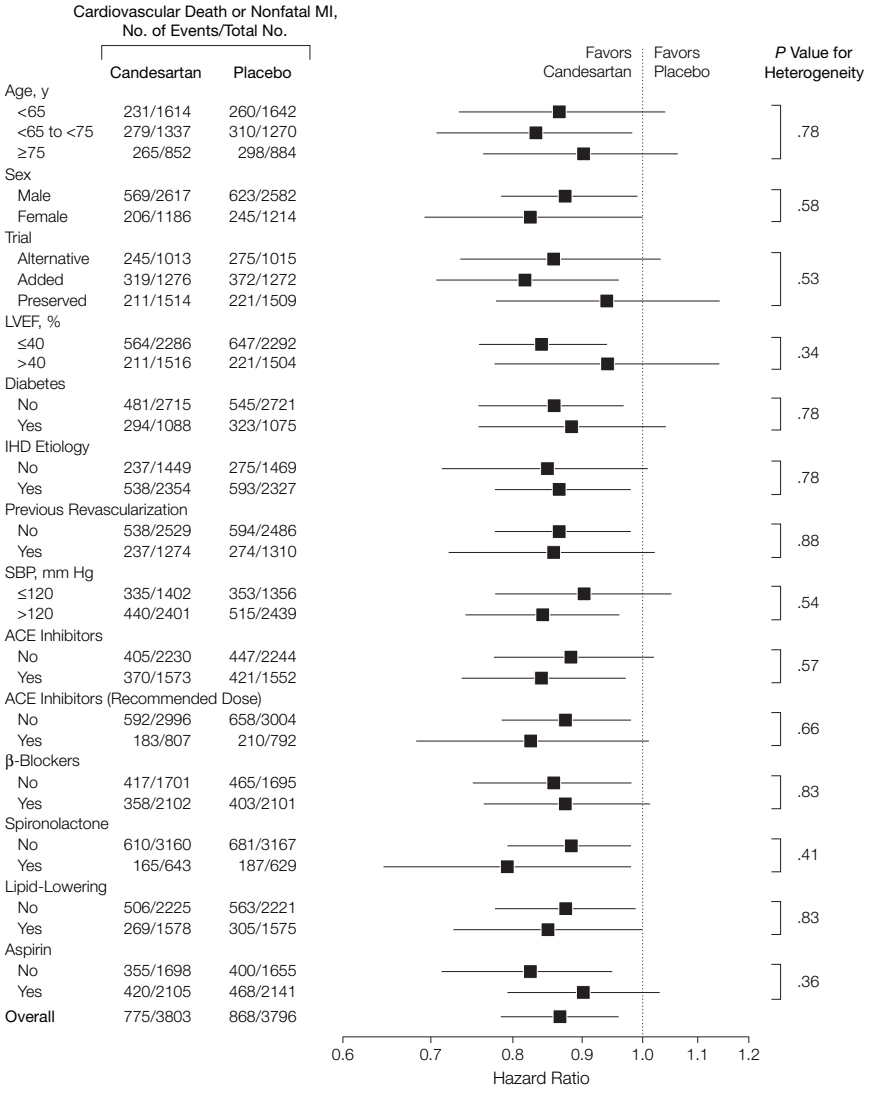
Although nonfatal MI alone and the composite outcome of cardiovascular death or nonfatal MI were significantly reduced by candesartan, there was only a nonsignificant reduction of the composite of sudden death or fatal MI. In CHARM, the number of fatal MIs was small, leading to wide confidence

intervals and statistical uncertainty about the effect of treatment. Second, although central adjudication of potential end points was used in CHARM, it is difficult to precisely classify the cause of death in patients with heart failure. While broad categories such as cardiovascular deaths vs noncardiovascular deaths are likely reliable, further subcategories may not be.[15] For example, an autopsy substudy of the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial found that a high proportion of "sudden deaths" had evidence of coronary occlusion, as did many patients thought to have died from "pump failure."[16] This underscores why the combined outcome of cardiovascular death or nonfatal MI is more reliable and better reflects the impact of candesartan on fatal or nonfatal MI in the CHARM program. In this context, our approach is consistent with that used in previous large trials.[1,7]

Candesartan did not reduce hospitalizations for unstable angina and coronary revascularization procedures. Although this differs from SOLVD, these results are similar to HOPE and EUROPA.[7,8] In the SOLVD treatment and prevention trials, hospitalizations for unstable angina were documented in 499 patients (14.7%) treated with enalapril and in 595 (17.5%) in the placebo group (risk reduction, 20%; 95% confidence interval, 9%-29%; $P=.001$).[1] The SOLVD trials were conducted from 1985-1990, when the use of β-blockers and aspirin was lower. Use of aspirin and β-blockers was 46% and 18%, respectively, in the SOLVD trials, compared with 56% and 55% in CHARM. This difference in the use of proven anti-ischemic therapy may in part explain the smaller number of events leading to hospitalization for unstable angina with wide confidence intervals in the CHARM program. In a similar fashion, the number of coronary revascularization procedures was small, with no significant effect of candesartan. Furthermore, hospital admission for unstable angina and coronary revascularization may not necessarily reflect disease progression but rather may be due to variations in physician practice styles.

The Valsartan in Acute Myocardial Infarction (VALIANT) trial and the Optimal Trial in Myocardial Infarction With the Angiotensin II Antagonist Losartan (OPTIMAAL) study evaluated the effects of an ARB compared with the ACE inhibitor captopril in patients with acute MI.[17,18] The VALIANT trial also compared the combination of the ARB valsartan plus captopril with captopril alone. Neither trial showed superiority of the ARB over captopril, with respect to the primary end point of all-cause mortality. In OPTIMAAL, the risk of fatal or nonfatal reinfarction was comparable in patients treated with losartan and captopril (relative risk, 1.03; 95% confidence interval, 0.89-1.18; $P=.72$).[18] In VALIANT, the number of patients who experienced an MI was similar in the groups treated with valsartan (3-year Kaplan-Meier rate,

Figure 2. Effect of Candesartan on Cardiovascular Death or Nonfatal Myocardial Infarction in Prespecified Subgroups



Values in the candesartan column may not sum to total values due to missing data for some patients. Error bars indicate 95% confidence intervals. ACE indicates angiotensin-converting enzyme; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; SBP, systolic blood pressure.

14.9%), captopril (14.2%), and the combination of valsartan plus captopril (14.1%).[19] The results of CHARM provide additional information on the effect of the ARB candesartan alone or in combination with ACE inhibitors compared with ACE inhibitors alone. The conclusion drawn from an overview of the complete data available refutes that of a recent but more selective review, which suggested that ARBs, unlike ACE inhibitors, may not reduce MI.[20]

Our observations in the CHARM-Alternative component especially suggest that the possible anti-MI effect of candesartan (and, by inference, ACE inhibitors) is angiotensin II–dependent. Furthermore, that candesartan seemed to have a beneficial effect independent of ACE inhibition suggests that non-ACE angiotensin II generation might be contributing to the continuing risk of MI in patients treated with an ACE inhibitor. Large prospective trials are needed to test these hypotheses, and at least 2 are under way (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial [ONTARGET] and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease [TRANSCEND]).[21]

In conclusion, these results from the CHARM program suggest that the use of candesartan in patients optimally treated for heart failure reduces the risk of cardiovascular death or nonfatal MI. This apparent benefit is in addition to that of other agents known to decrease MI. Further studies are required to confirm this benefit and elucidate the mechanisms responsible for the actions of candesartan on ischemic cardiovascular events in this patient population.

Author Contributions: Dr Demers had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: McMurray, Swedberg, Pfeffer, Granger, McKelvie, Michelson, Yusuf.
Acquisition of data: McMurray, Swedberg, Pfeffer, McKelvie, Östergren, Wang.
Analysis and interpretation of data: Demers, McMurray, Swedberg, Pfeffer, Olofsson, Östergren, Michelson, Johansson, Wang, Yusuf.
Drafting of the manuscript: Demers, McMurray, Swedberg, Pfeffer, Yusuf.
Critical revision of the manuscript for important intellectual content: Demers, McMurray, Swedberg, Pfeffer, Granger, Olofsson, McKelvie, Östergren, Michelson, Johansson, Wang, Yusuf.
Statistical analysis: Olofsson, Johansson, Wang.
Obtained funding: McMurray, Swedberg, Michelson.
Administrative, technical, or material support: McKelvie, Östergren, Michelson, Yusuf.
Study supervision: Demers, McMurray, Swedberg, Pfeffer, Östergren, Yusuf.
Financial Disclosures: Drs Demers, McMurray, Swedberg, Pfeffer, Granger, McKelvie, Östergren, and Yusuf have received research grants, honoraria for lectures, and/or consulting fees from a number of pharmaceutical companies manufacturing and marketing inhibitors of the renin-angiotensin-aldosterone system, including AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb/Sanofi-Aventis, Merck, Novartis, Pfizer, and Takeda. Dr Wang reported no disclosures.
Funding/Support: AstraZeneca funded the CHARM program.
Role of the Sponsor: Representatives from AstraZeneca were involved in protocol design; in collection, management, analysis, and interpretation of data; and in manuscript preparation.
Independent Statistical Review: Independent statistical review of the data included in this analysis was perfomed by Stuart Pocock, PhD (also served on the CHARM Data Safety and Monitoring Committee) and Duolao Wang, both of the London School of Hygiene and Tropical Medicine.

REFERENCES

1. Yusuf S, Pepine C, Garces C, et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet*. 1992;340:1173-1178.
2. 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 of left ventricular enlargement trial. *N Engl J Med*. 1992;327:669-677.
3. Torp-Pedersen C, Kober L; TRACE Study Group. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left-ventricular function after acute myocardial infarction. *Lancet*. 1999;354:9-12.
4. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandanavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;326:1429-1435.
5. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325:293-302.
6. Flather MD, Yusuf S, Kober L, et al; ACE-Inhibitor Myocardial Infarction Collaborative Group. Long term ACE-inhibitor therapy in patients with heart failure or left ventricular dysfunction: a systematic overview of data from individual patients. *Lancet*. 2000;355:1575-1581.
7. Dagenais GR, Yusuf S, Bourassa M, et al; HOPE Investigators. Effects of ramipril on coronary events in high-risk persons: results of the Heart Outcomes Prevention Evaluation study. *Circulation*. 2001;104:522-526.
8. EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362:782-788.
9. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351:2058-2068.
10. 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;37:1056-1061.
11. McKelvie RS, Yusuf S, Pericak D, et al; RESOLVD Pilot Study Investigators. Comparison of candesartan, enalapril, and their combination in congestive heart failure: Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study. *Circulation*. 1999;100:1056-1064.
12. Swedberg K, Pfeffer M, Granger C, et al; CHARM-Programme Investigators. Candesartan in Heart failure—Assessment of Reduction in Mortality and morbidity (CHARM): rationale and design. *J Card Fail*. 1999;5:276-282.
13. Pfeffer MA, Swedberg K, Granger CB, et al; CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet*. 2003;362:759-766.
14. Yusuf S, Pogue J. ACE inhibition in stable coronary artery disease. *N Engl J Med*. 2005;352:937-938.
15. Yusuf S, Negassa A. Choice of clinical outcomes in randomized trials of heart failure therapies: disease-specific or overall outcomes? *Am Heart J*. 2002;143:22-28.
16. Uretsky BF, Thygersen K, Armstrong PW, et al. Acute coronary findings at autopsy in heart failure patients with sudden death: results from the Assessment of Treatment with Lisinopril And Survival (ATLAS). *Circulation*. 2000;102:611-616.
17. Pfeffer MA, McMurray JJV, Velazquez EJ, et al; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893-1906.
18. Dickstein K, Kjekshus J; OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Lancet*. 2002;360:752-760.
19. McMurray J, Solomon S, Pieper K, et al. The effect of valsartan, captopril or both on atherosclerotic events after acute myocardial infarction: an analysis of the Valsartan in Acute Myocardial Infarction Trial (VALIANT). *J Am Coll Cardiol*. In press.
20. Verma S, Strauss M. Angiotensin receptor blockers and myocardial infarction. *BMJ*. 2004;329:1248-1249.
21. ONTARGET/TRANSCEND Investigators. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (ONTARGET/TRANSCEND) trials. *Am Heart J*. 2004;148:52-61.

