Journal of the American College of Cardiology
© 2000 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 35, No. 7, 2000
ISSN 0735-1097/00/$20.00
PII S0735-1097(00)00638-0

Clinical Effects of Early Angiotensin-Converting Enzyme Inhibitor Treatment for Acute Myocardial Infarction Are Similar in the Presence and Absence of Aspirin

Systematic Overview of Individual Data from 96,712 Randomized Patients

Roberto Latini, MD,* Gianni Tognoni, MD,* Aldo P. Maggioni, MD,*† Colin Baigent, MB, BCH,‡ Eugene Braunwald, MD,§ Zheng-Ming Chen, PHD,‡ Rory Collins, MB, BS,‡ Marcus Flather, MD,‖ MariaGrazia Franzosi, PHD,* John Kjekshus, MD,¶ Lars Køber, MD,# Li-Sheng Liu, MD,** Richard Peto, FRS,‡ Marc Pfeffer, MD,§ Fabrizio Pizzetti, MD,†† Eugenio Santoro, MSC,* Peter Sleight, MD,‡ Karl Swedberg, MD,‡‡ Luigi Tavazzi, MD,§§ Wen Wang, MSC,** Salim Yusuf, MD,‖‖ on behalf of the Angiotensin-converting Enzyme Inhibitor Myocardial Infarction Collaborative Group[1]

Milano, Firenze, Casale Monferrato and Pavia, Italy; Oxford and London, United Kingdom; Boston, Massachusetts; Oslo, Norway; Hellerup, Denmark; Beijing, China; Göteborg, Sweden; and Hamilton, Canada

OBJECTIVES We sought to determine whether the clinical effects of early angiotensin-converting enzyme (ACE) inhibitor (ACEi) treatment for acute myocardial infarction (MI) are influenced by the concomitant use of aspirin (ASA).

BACKGROUND Aspirin and ACEi both reduce mortality when given early after MI. Aspirin inhibits the synthesis of vasodilating prostaglandins, and, in principle, this inhibition might antagonize some of the effects of ACEi. But it is uncertain whether, in practice, this influences the effects of ACEi on mortality and major morbidity after MI.

METHODS This overview sought individual patient data from all trials involving more than 1,000 patients randomly allocated to receive ACEi or control starting in the acute phase of MI (0–36 h from onset) and continuing for four to six weeks. Data on concomitant ASA use were available for 96,712 of 98,496 patients in four eligible trials (and for none of 1,556 patients in the one other eligible trial).

RESULTS Overall 30-day mortality was 7.1% among patients allocated to ACEi and 7.6% among those allocated to control, corresponding to a 7% (standard deviation [SD], 2%) proportional reduction (95% confidence interval 2% to 11%, $p = 0.004$). Angiotensin-converting enzyme inhibitor was associated with similar proportional reductions in 30-day mortality among the 86,484 patients who were taking ASA (6% [SD, 3%] reduction) and among the 10,228 patients who were not (10% [SD, 5%] reduction: chi-squared test of heterogeneity between these reductions = 0.4; $p = 0.5$). Angiotensin-converting enzyme inhibitor produced definite increases in the incidence of persistent hypotension (17.9% ACEi vs. 9.4% control) and of renal dysfunction (1.3% ACEi vs. 0.6% control), but there was no good evidence that these effects were different in the presence or absence of ASA (chi-squared for heterogeneity = 0.4 and 0.0, respectively; both not significant). Nor was there good evidence that the effects of ACEi on other clinical outcomes were changed by concomitant ASA use.

CONCLUSIONS Both ASA and ACEi are beneficial in acute MI. The present results support the early use of ACEi in acute MI, irrespective of whether or not ASA is being given. (J Am Coll Cardiol 2000;35:1801–7) © 2000 by the American College of Cardiology

From the *Istituto di Ricerche Farmacologiche "Mario Negri," Milano, Italy; the †Associazione Nazionale Medici-Cardiologi Ospedalieri, Firenze, Italy; the ‡Clinical Trial Service Unit, Radcliffe Infirmary, Oxford, United Kingdom; the §Brigham and Women's Hospital, Boston, Massachusetts; the ‖Royal Brompton Hospital, London, United Kingdom; ¶The National Hospital, University of Oslo, Oslo, Norway; the #Gentofte Hospital/University of Copenhagen, Hellerup, Denmark; the **Fu Wai Hospital, Beijing, China; the ††Santo Spirito Hospital, Casale Monferrato (AL), Italy; the ‡‡Göteborg University, Göteborg, Sweden; the §§Policlinico S. Matteo, Pavia, Italy; and the ‖‖McMaster Clinic, Hamilton General Hospital, Hamilton, Ontario, Canada. In addition to the support listed in the trial publications, the work on this project in Istituto di Ricerche Farmacologiche Mario Negri was partially funded by a Canadian Medical Research Council joint industry award with Astra, Bristol-Myers Squibb, Hoechst Marion Roussel, Merck and Zeneca; in the Clinical Trial, Service Unit was funded by the British Heart Foundation and the UK Medical Research Council.

[1]The participants are listed in the Appendix.

Manuscript received November 16, 1998; revised manuscript received December 16, 1999, accepted February 9, 2000.

Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
ACEi	= angiotensin-converting enzyme inhibitor
ASA	= aspirin
CCS	= Chinese Cardiac Study
CONSENSUS	= Cooperative New Scandinavian Enalapril Survival Study
GISSI	= Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
ISIS	= International Study of Infarct Survival
MI	= myocardial infarction
SD	= standard deviation
SOLVD	= Studies Of Left Ventricular Dysfunction

Angiotensin-converting enzyme (ACE) inhibitors (ACEi) have been shown to improve prognosis not only when started some time after myocardial infarction (MI) in patients with evidence of left ventricular dysfunction (1–3) but also when given during the acute phase of MI in relatively unselected patients (4–8). Overall, in a recently published overview of the large-scale randomized trials, early ACEi treatment of acute MI produced a small but highly significant 7% (standard deviation [SD], 2%) proportional reduction (2 $p < 0.004$) in 30-day mortality, which corresponded to avoidance of an average of five deaths per 1,000 patients treated for one month (9). Aspirin (ASA), which is an inhibitor of platelet cyclo-oxygenase and prostaglandin synthesis, produces a much larger (27% [SD, 3%]) proportional decrease in mortality or major morbidity in this setting (10,11) and has, for some years, been used widely.

See page 1808

One of the most prominent pharmacologic actions of ACEi is to decrease arterial pressure, and this seems to be mediated not only by a reduction in angiotensin II production but also by an increase in bradykinin (12) and in the vasodilating prostaglandins I2 and E2 (13,14). The absence of a reflex increase in heart rate when blood pressure is lowered with ACEi may be partly attributable to the increased production of prostaglandins (15) and the increase in baroreflex gain resulting from lowered levels of angiotensin II in the central nervous system (16), and at least the first of these two effects might be inhibited by ASA. Moreover, ACEi treatment has been associated with depression of renal function, and it has been suggested that ASA might potentiate this unwanted action of ACEi by decreasing renal vasodilatory prostaglandin synthesis and increasing sodium and water retention (17).

It has been claimed that ASA reduces the blood pressure lowering effect of ACEi (18) and the short-term beneficial hemodynamic effects of ACEi in heart failure patients (19–21), although the latter findings were not confirmed by another study (17). A retrospective subanalysis of about 7,000 patients with left ventricular dysfunction in the Studies of Left Ventricular Dysfunction (SOLVD) trials showed a trend toward less benefit with ACEi in patients using antiplatelet agents at baseline (published only as an abstract [22]), but, again, these findings have not been confirmed by other long-term trials of ACEi.

In the context of acute MI, a preliminary analysis of 19,000 patients in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-3 trial did not indicate any impact of ASA on the clinical effects of ACEi, whereas analyses of 6,000 in the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS) II trial did indicate a nonsignificant interaction (23). More recently, a post-hoc analysis of the few (298) acute MI patients enrolled in the Captopril And Thrombolysis Study trial did not suggest that ASA attenuated the acute and long-term beneficial effects of ACEi on left ventricular function (24).

To help determine more reliably whether the effects of ACEi on mortality, or on other clinical outcomes, are materially altered by the use of concomitant ASA, we have analyzed the data on nearly 97,000 patients in the overview of the large trials of early ACEi treatment in acute MI.

METHODS

The overview was to include individual patient data from all randomized trials involving more than 1,000 patients in which ACEi treatment was started in the acute phase of MI (0 to 36 h from symptom onset) and continued for a short period of time (generally four to six weeks). Individual data were available for 98,496 patients from four such trials (Chinese Cardiac Study [CCS]-1 [4], CONSENSUS II [5], GISSI-3 [6] and International Study of Infarct Survival [ISIS]-4 [7]) but not for 1,556 patients in the one other eligible trial Survival of Myocardial Infarction Long-term Evaluation (3). The methods and main results of this overview have been presented in detail elsewhere (9). Information on ASA or other antiplatelet use (yes/no) at randomization was available for 96,712 of these patients, on which the present analyses are based: 86,484 were receiving antiplatelet therapy and 10,228 were not. The Chinese Cardiac Study-1 recorded the use of ASA alone, whereas the other three trials recorded ASA plus other antiplatelet agents, but it is reasonable to assume that the use of antiplatelets other than ASA early after MI was very low. Hence, for the purposes of these analyses, antiplatelet use is considered to be synonymous with ASA use. Information on ASA dose received by each patient was not available, although the protocol for CCS-1 recommended 160 mg daily.

Statistical methods. The primary analyses were of the effects of ACEi on total mortality and were recorded up to day 30. Secondary analyses were of mortality from day 0 to day 7 and of other clinical events (persistent hypotension, renal dysfunction, stroke, reinfarction and nonfatal heart failure) up to day 30. Only the first occurrence of each

Table 1. Use of ASA Early After MI in the Four Different Trials

Study	Type of ACEi Used	Number of Patients on ASA/Total	Percentages** on ASA
CCS-1	captopril	11,134/14,884	75
CONSENSUS II	enalapril	4,787/6,090	79
GISSI-3	lisinopril	16,717/18,711	89
ISIS-4	captopril	53,846/57,027	94
Total	various	86,484/96,712	89

**Percentages are of patients with information available on antiplatelet use at study entry (see Methods section).
For acronyms see Abbreviation box.

adverse event was recorded, so the analyses are of the number of patients with at least one such event. The analyses were conducted with SAS software. Chi-squared tests were used to compare patients' baseline characteristics. For the survival analyses, the Kaplan-Meier method was used and the p value was calculated by the log-rank test. All such p values are two sided. The Mantel-Haenszel method was used to calculate stratified estimates of the proportional effects (odds ratios and percent reductions in odds) of ACEi, and comparisons of these effects in the presence and absence of ASA involved chi-squared tests for heterogeneity.

RESULTS

The prevalence of ASA use at entry was very different in the four studies (Table 1), ranging from 75% in CCS-1 to 94% in ISIS-4. Patients not receiving ASA at entry were older than those who were receiving ASA (Table 2) and also differed in terms of gender, previous history of MI, severity of MI, use of thrombolytics and use of beta-adrenergic blocking agents (Table 2).

Effects of ACEi on mortality. Overall, 30-day mortality was 7.1% among patients allocated to ACEi and 7.6% among those allocated to control, corresponding to a 7% (SD, 2%) proportional reduction (95% confidence interval 2% to 11%; 2 $p < 0.004$: Fig. 1). No significant difference was observed between the proportional effects of ACEi on mortality in the four studies. Angiotensin-converting enzyme inhibitor was associated with similar proportional reductions in 30-day mortality among the 86,484 patients who were taking ASA (6% [SD, 3%] reduction) and among the 10,228 who were not (10% [SD, 5%] reduction: chi-squared for heterogeneity on one degree of freedom = 0.4; $p = 0.5$: Fig. 1 and 2).

Likewise, the overall proportional reduction in seven-day mortality with ACEi of 9% (SD, 3%) ($p = 0.002$), the so called "early benefit" (9), was not significantly different in the presence of ASA (7% [SD, 3%] reduction) or in its absence (15% [SD, 6%] reduction: chi-squared for heterogeneity = 1.3; $p = 0.3$).

Table 2. Patient Characteristics at Randomization by ASA Utilization

	ASA (n = 86,484)	no-ASA (n = 10,228)
Age ≥ 65 yr	45%	51%
Women	25%	29%
SBP ≤ 120 mm Hg	40%	42%
HR ≥ 80 beats/min	45%	48%
Previous MI	16%	18%
Heart failure (Killip 2–3)	17%	26%
Anterior MI	37%	40%
Thrombolytic used	66%	40%
I.V. beta-blocker used	13%	7%

All 9 Comparisons ASA vs. no-ASA (chi-squared) $p < 0.0001$.
ASA = aspirin; HR = heart rate; I.V. = intravenous; MI = myocardial infarction; SBP = systolic blood pressure.

Effects of ACEi on other clinical events. Overall, ACEi doubled the incidence of persistent hypotension and renal dysfunction (Fig. 3A), but there was no suggestion that the effects of ACEi on these outcomes were different in the presence and absence of ASA: chi-squared for heterogeneity = 0.4 for persistent hypotension ($p = 0.5$) and 0.0 for renal dysfunction ($p = 0.9$).

Angiotensin-converting enzyme inhibitor reduced the incidence of nonfatal heart failure, but, again, the proportional effect among patients receiving ASA was not significantly different from that among those who were not receiving ASA (chi-squared for heterogeneity on 1 df = 1.3: $p = 0.3$). The 30-day reinfarction rate was not affected by ACEi among those receiving ASA and among those who were not. Nor was the overall 30-day stroke rate significantly affected by ACEi (1.02% ACEi vs. 0.95% control), and, although there appeared to be a trend towards slightly more strokes with ACEi in the presence of ASA (1.0% ACEi vs. 0.8% control) and slightly fewer in the absence of ASA (1.5% ACEi vs. 2.0% control), there was no good evidence of an effect of ACEi on stroke in either circumstance. In general, the effects of ACEi on all of the clinical events examined were not shown to be influenced by ASA (global chi-squared for heterogeneity between all subgroups in Fig. 1 and 3 = 8.2: $p = 0.2$ with 6 df).

DISCUSSION

Mortality. This study indicates that, in terms of the proportional reduction in 30-day mortality after hospital ad-

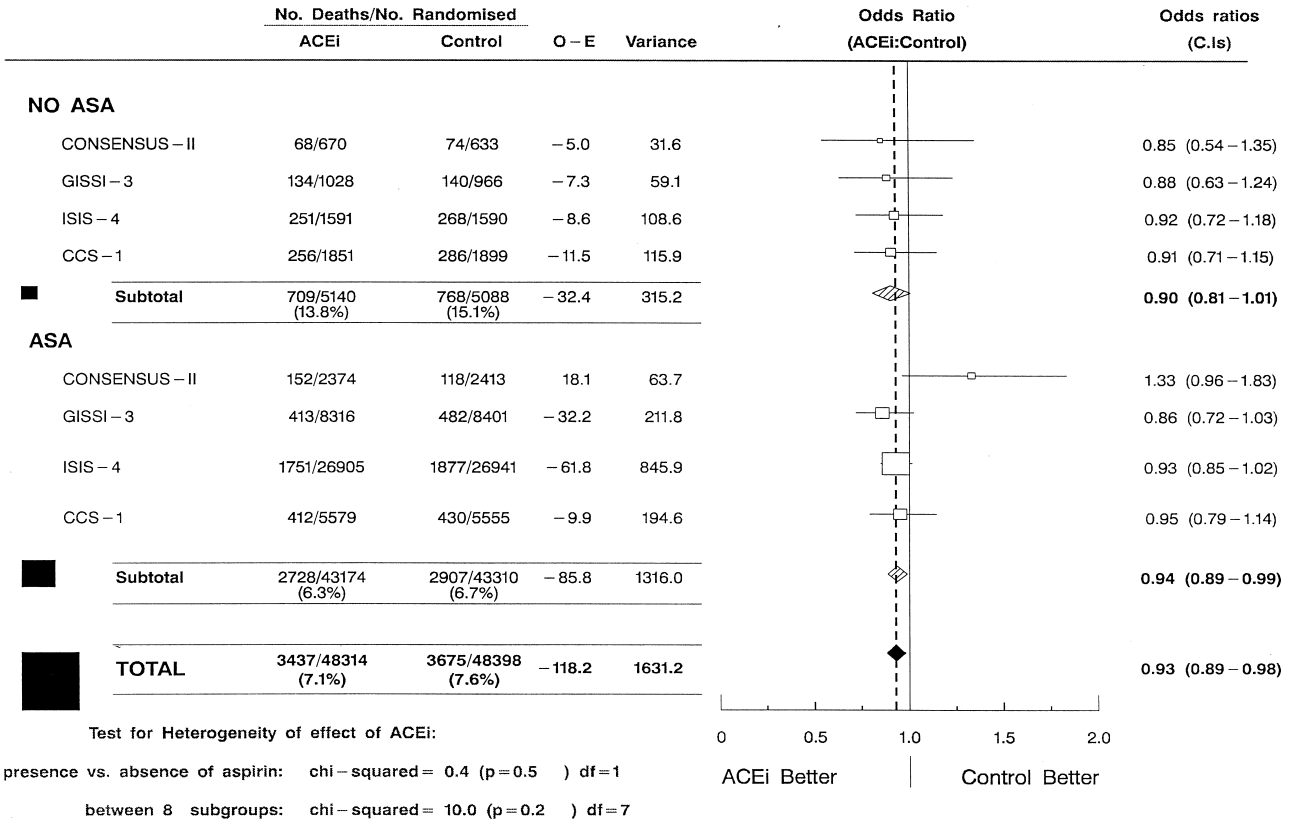

Figure 1. Proportional effect of ACEi therapy on 30-day mortality in the presence and absence of concomitant ASA. The odds ratio for each trial is represented by a **square** (area proportional to number of patients with an event), with 99% CI (**horizontal line**). The overall results for the trials and their 95% CI are represented by **diamonds**. ACEi = angiotensin-converting enzyme inhibitor; ASA = aspirin; CI = confidence intervals.

mission for acute MI, the benefits of ASA and the benefits of ACEi are approximately independent of each other, in which case the greater benefit will be obtained by using both treatments. In particular, Figure 1 shows that the hypothesis, generated by subgroup analyses of one particular study (23) that ACEi would be ineffective in ASA-treated patients, is refuted by the other studies in this meta-analysis, which collectively include much larger numbers of patients.

Other clinical events. Moreover, ASA does not significantly modify the safety profile of early ACEi. In particular, the results obtained on renal dysfunction, which is a serious, although infrequent, complication of ACEi treatment, show that even in that target organ no clinically relevant interaction between ACEi and ASA occurs. The large number of patients, hospitals and countries involved in these trials strongly suggests that there are no clinically important interactions between ACEi and ASA in a range of settings during the first month after acute MI. The apparently contrasting effects of ACEi on stroke in the presence and absence of ASA should not be overemphasized, and, considering the large number of comparisons done, might well be due merely to the play of chance, especially since there appears to be no clear rationale for such an interaction.

If we apply power calculations to the clinical event with the lowest incidence, renal dysfunction, an increase in odds ratio for renal dysfunction in ASA group from 1.93 (ACEi vs. control) to 3, could be arbitrarily chosen as clinically relevant. This means an increase from 1.3% (Fig. 3A) to 1.8% in the incidence of renal dysfunction in patients taking both ACEi and ASA (n = 43,174) or an absolute increase of 0.5%, corresponding to a 35% relative increase. Application of power calculations yields a value of 1-beta = 0.99 with an alpha = 0.01 (a subgroup analysis being performed). The power for other events with higher incidence will necessarily be >0.99. These considerations on statistical power should help in critically interpreting previous claims on the existence or nonexistence of an interaction between ASA and ACEi, based on analyses of smaller populations of patients (19–21,23–25).

ASA schedules. Although the available data did not allow us to determine directly various aspects of the ASA treatment (such as dose, time of initiation, duration), we can reasonably assume, based on recommendations in the protocols of at least two of the largest studies (6,7) that ASA began as soon as possible after the onset of symptoms, and its use was recorded within 36 h of onset before randomization of ACEi. More-

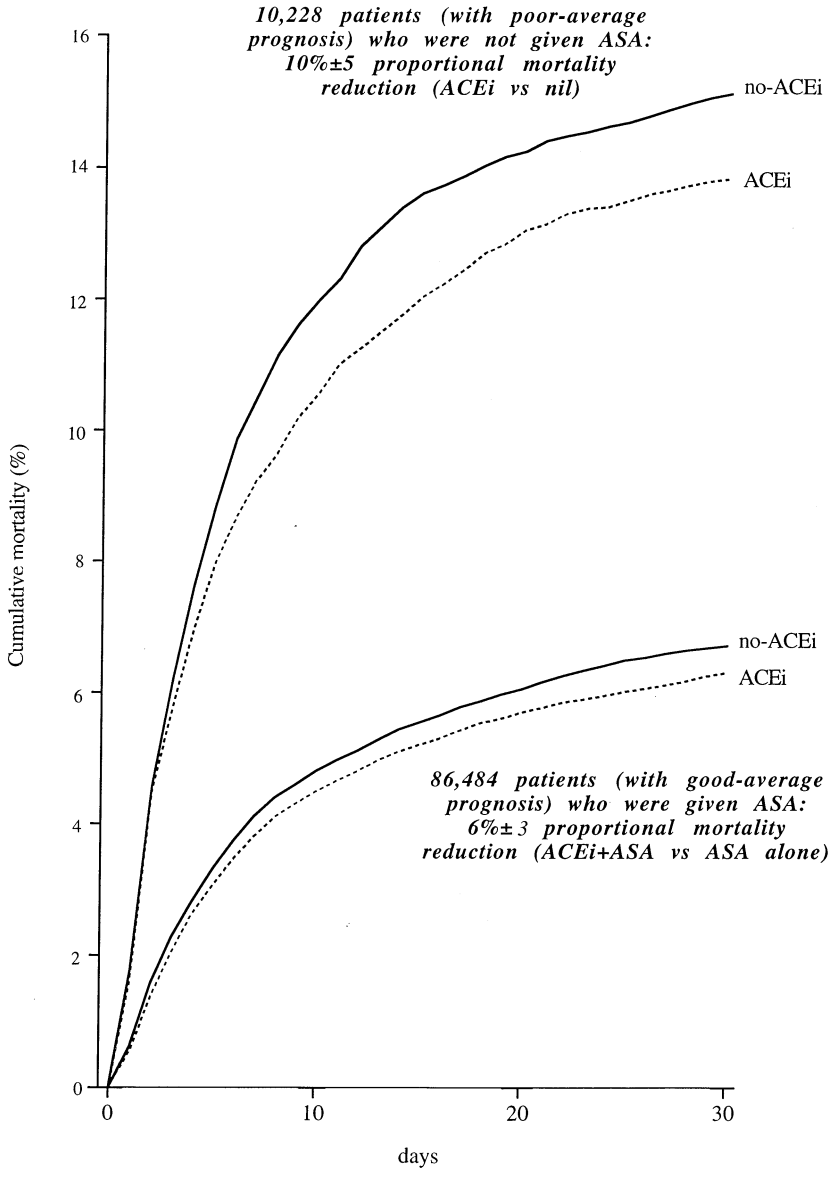

Figure 2. Randomized comparison of ACEi versus no-ACEi on 30-day mortality in (poor-average prognosis) patients who were not given ASA and in (good-average prognosis) patients who were given ASA. Note that although ASA must have been responsible for some benefit, differences in prognosis between patients may well be responsible for more than half of the difference in outcome between ASA and no-ASA in this Figure.

over, although only CCS-1 specified the ASA dose (160 mg daily), it is likely that the doses of ASA used in other studies were also generally in the range of 160 to 325 mg daily (10,11). Antiplatelet agents other than ASA were likely to have been used relatively infrequently; indeed, in GISSI-3 they were used in only 4% of patients during hospitalization, whereas 89% used ASA. Therefore, it can reasonably be assumed that the use of non-ASA antiplatelet agents is unlikely to have distorted the present analyses to any material extent. It can also be assumed that ASA was continued upon discharge in most patients; for example, in GISSI-3 78% of those on ASA at entry were still on ASA when discharged alive from the hospital.

ASA use in good and in poor prognosis patients. The lower mortality and lower rate of some other adverse events in patients receiving ASA must, to some extent, reflect the benefits of ASA (10). But it also reflects the fact that, on average, the patients not receiving ASA were older and more severely ill, and, therefore, had a worse prognosis than those who were receiving ASA (26). It is unclear why a drug like ASA, which is easy to administer, safe and of proven benefit during and after MI (10,11) should not be offered to almost all patients, especially those presenting with a poor prognosis. Perhaps this reflected previous attitudes to ASA use in older individuals (with undue concerns about adverse effects), since even at discharge ASA use appeared to be

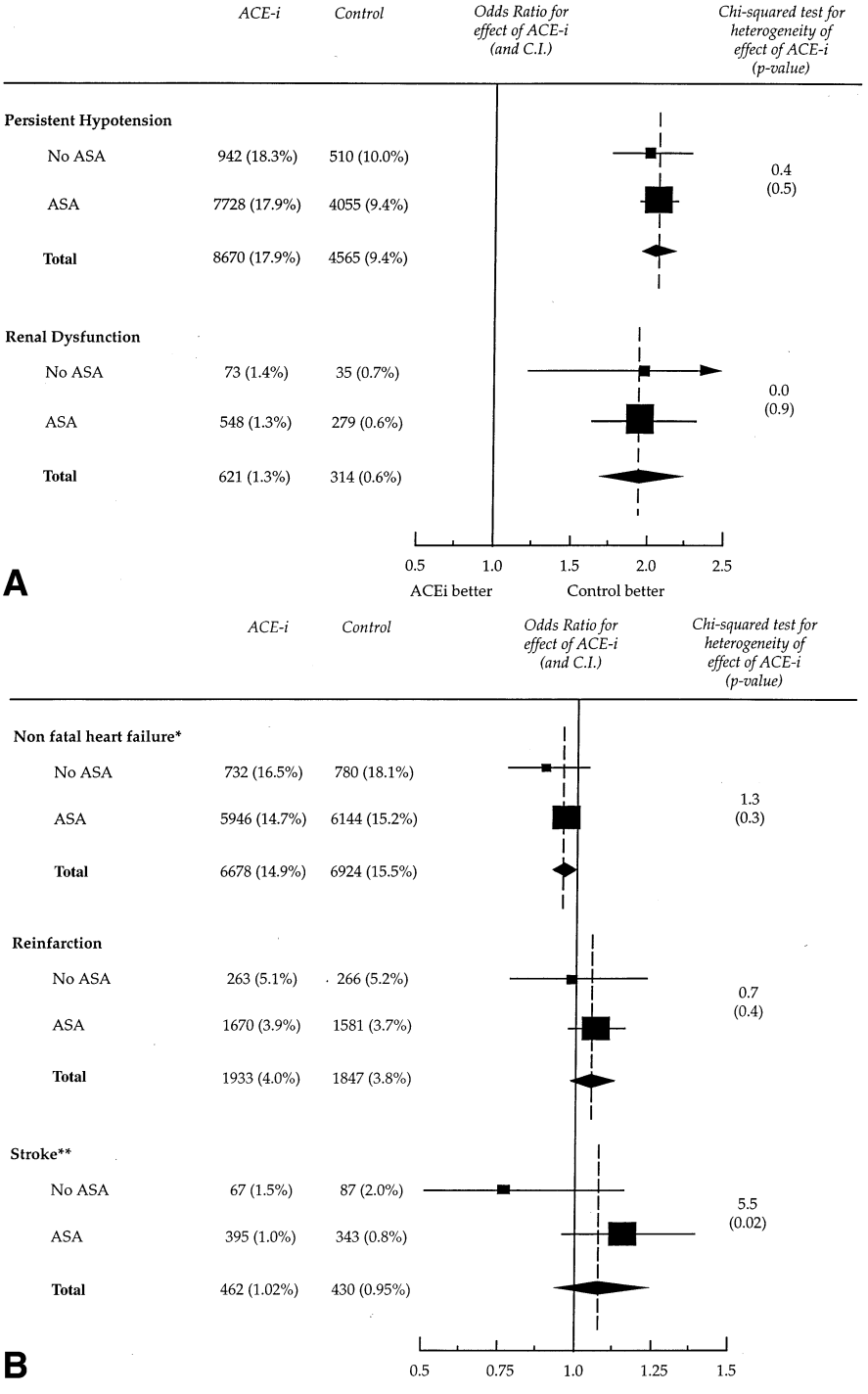

Figure 3. **(A)** Effects of ACEi therapy on 30-day incidence of persistent hypotension and renal dysfunction in the presence and absence of concomitant ASA. **(B)** Effects of ACEi therapy on 30-day incidence of heart failure, reinfarction and stroke in the presence and absence of concomitant ASA. *Percentages for heart failure are of patients surviving at day 30; **CONSENSUS-II patients are excluded from this analysis because data on stroke were not available.

slightly less in older patients (for example, in GISSI-3 it was given to 88% of those aged ≥65 years compared with 91% of those aged <65 years).

Conclusions. The present analyses of clinical outcomes among nearly 97,000 MI patients show that ACEi are safe and moderately effective when given early after MI, irrespective of whether (as will normally be the case nowadays) ASA is also being given. Likewise, despite the suggestion of an interaction with ASA in SOLVD (22), consideration together of all large trials of long-term ACEi in MI patients with signs or symptoms of left ventricular dysfunction (1–3)

shows that ACEi is of additional value even in patients who are being given ASA.

Guidelines suggesting a possible negative interaction between ASA and ACEi in the setting of MI now need to be reconsidered.

APPENDIX

THE ACE INHIBITOR MYOCARDIAL INFARCTION COLLABORATIVE GROUP:

Steering Committee (early and late trials): GISSI-3: L. Tavazzi, G. Tognoni. ISIS-4: R. Collins, C. Baigent, M. Flather, R. Peto, P. Sleight. CCS-1: Z-M. Chen, L-S. Liu, W. Wang. CONSENSUS II: J. Kjekshus, K. Swedberg. AIRE: S. Ball. TRACE: L. Køber, C. Torp-Pedersen. SAVE: E. Braunwald, L. Moyé, M. Pfeffer. SOLVD: S. Yusuf.

Coordinating Centers: Early trials: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI): M.G. Franzosi, R. Latini, A.P. Maggioni, E. Santoro, L. Santoro, G. Zuanetti. Late trials: Canadian Cardiovascular Collaboration (CCC), McMaster Clinic: M. Flather, J. Pogue, Y. Wang, S. Yusuf.

Acknowledgments

We thank Luisa Galbiati for the invaluable secretarial support in communications within the Collaborative Group and in manuscript preparation.

Reprint requests and correspondence: Dr. Roberto Latini, Department of Cardiovascular Research, Istituto Mario Negri, Via Eritrea, 62, 20157 Milano, Italy. E-mail: latini@irfmn.mnegri.it.

REFERENCES

1. Pfeffer MA, Braunwald E, Moyé LA, et al., for the SAVE Investigators.. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial (SAVE). N Engl J Med 1992;327:669–77.
2. 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.
3. Kober L, Torp-Pedersen C, Carlsen JE, et al., for the TRAndolapril Cardiac Evaluation (TRACE) Study Group. 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.
4. 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.
5. Swedberg K, Held P, Kjekshus J, Rasmussen K, Rydén L, Wedel H, for the CONSENSUS II Study Group. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. N Engl J Med 1992;327:678–84.
6. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on six-week mortality and ventricular function after acute myocardial infarction. Lancet 1994;343:1115–22.
7. ISIS-4 Collaborative Group. ISIS-4: a randomized 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.
8. Ambrosioni E, Borghi C, Magnani B, for the Survival of Myocardial Infarction Long-term Evaluation (SMILE) Study Investigators. 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.
9. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in early treatment of acute myocardial infarction. Systematic overview of individual data from 100,000 patients in randomized trials. Circulation 1998;97:2202–12.
10. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;ii:349–60.
11. Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy. I: Prevention of death, myocardial infarction and stroke by prolonged antiplatelet therapy in various categories of patients. Br Med J 1994;308:81–106.
12. Blais C, Drapeau G, Raymond P, et al. Contribution of angiotensin-converting enzyme to the cardiac metabolism of bradykinin: an interspecies study. Am J Physiol 1997;273:H2263–71.
13. Swartz SL, Williams GH, Hollenberg NK, Levine L, Dluhy RG, Moore TJ. Captopril-induced changes in prostaglandin production. Relationship to vascular responses in normal man. J Clin Invest 1980;65:1257–64.
14. Packer M. Interaction of prostaglandins and angiotensin II in the modulation of renal function in congestive heart failure. Circulation 1988;77 Suppl I:I64–73.
15. Zucker IH, Chen J-S, Wang W. Renal sympathetic nerve and hemodynamic responses to captopril in conscious dogs: role of prostaglandins. Am J Physiol 1991;260:H260–66.
16. Heesch CM, Crandall E, Turbek JA. Converting enzyme inhibitors cause pressure-independent resetting of baroreflex control of sympathetic outflow. Am J Physiol 1996;270:R728–37.
17. Sturrock NDC, Struthers AD. Nonsteroidal anti-inflammatory drugs and angiotensin converting enzyme inhibitors: a commonly prescribed combination with variable effects on renal function. Br J Clin Pharmac 1993;35:343–8.
18. Brooks PM, Day RO. Nonsteroidal antiinflammatory drugs—differences and similarities. N Engl J Med 1991;324:1716–25.
19. Hall D, Zeitler H, Rudolph W. Counteraction of the vasodilator effects of enalapril by aspirin in severe heart failure. J Am Coll Cardiol 1992;20:1549–55.
20. Spaulding C, Charbonnier B, Cohen-Solal A, et al. Acute hemodynamic interaction of aspirin and ticlopidine with enalapril. Circulation 1998;98:757–65.
21. Baur LHB, Schipperheyn JJ, van der Laarse A, et al. Combining salicylate and enalapril in patients with coronary artery disease and heart failure. Br Heart J 1995;73:227–36.
22. Pitt B, Yusuf S, for the SOLVD Investigators. Studies of left ventricular dysfunction (SOLVD): subgroup results. J Am Coll Cardiol 1992;19:215A.
23. Nguyen KN, Aursnes I, Kjekshus J. Interaction between enalapril and aspirin on mortality after acute myocardial infarction: subgroup analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). Am J Cardiol 1997;79:115–9.
24. Oosterga M, Anthonio RL, de Kam P-J, Kingma JH, Crijns HJGM, van Gilst WH. Effects of aspirin on angiotensin-converting enzyme inhibition and left ventricular dilation one year after acute myocardial infarction. Am J Cardiol 1998;81:1178–81.
25. Leor J, Riecher-Reiss H, Goldbrourt U, et al. Aspirin and mortality in patients treated with angiotensin-converting enzyme inhibitors. A cohort study of 11,575 patients with coronary artery disease. J Am Coll Cardiol 1999;33:1920–5.
26. Krumholz HM, Radford MJ, Ellerbeck EF, et al. Aspirin in the treatment of acute myocardial infarction in elderly Medicare beneficiaries: patterns of use and outcomes. Circulation 1995;92:2841–7.