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ARTICLES

ACE Inhibitor Use in Patients With Myocardial Infarction

Summary of Evidence From Clinical Trials

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Experimental evidence for the beneficial effects on heart failure of chronic treatment with ACE inhibitors accumulated from early 1980 in experimental models of LV dysfunction secondary to AMI. These studies demonstrated an improvement in hemodynamics, LV remodeling,[1 2 3 4] and mortality with ACE inhibitor treatment.[5 6] The effect of ACE inhibitors during the acute phase of AMI was less clear, although there was evidence of protection from ischemic damage, possibly mediated by an increase in collateral coronary blood flow.[7 8 9 10 11]

Clinical Data

The striking beneficial results of prolonged ACE inhibitor therapy in the CONSENSUS-I trial[12] on mortality of patients with advanced CHF have been followed by a series of trials in patients with less severe heart failure or asymptomatic LV dysfunction of any origin[13 14 15] or limited to AMI.[16 17 18] Consistent with the experimental data, the latter studies showed that ACE inhibition clearly produces favorable effects on mortality and LV function in selected high-risk post-AMI populations. More recent trials have addressed the role of ACE inhibition in relatively unselected patients[19 20 21 22] or in those with anterior AMI[23 24] in whom treatment was initiated during the first day of AMI. Overall, these trials indicate a small but definite benefit of about 5 lives saved for every 1000 patients treated (Table 1⇓).[21]

Table 1.

Overview of ACE Inhibitor Trials on Patients With AMI

Trial	Patients Treated With ACE Inhibitors (%)	Control Subjects, deaths/treated (%)	Agent, deaths/treated (%)
11 small trials	150/2175	153/2119	Various
	(6.9)	(7.2)	
CONSENSUS-II	219/3044	192/3046	Enalapril, IV and oral
	(7.2)	(6.3)	

Trial	Patients Treated With ACE Inhibitors (%)	Control Subjects, deaths/treated (%)	Agent, deaths/treated (%)
GISSI-3	597/9435	673/9460	Lisinopril, oral
	(6.3)	(7.1)	
ISIS-4	2088/29 028	2231/29 022	Captopril, oral
	(7.2)	(7.7)	
CCS-1	617/6814	654/6820	Captopril, oral
	(9.1)	(9.6)	
Overview	3671/50 496	3903/50 467	*P*=.006
	(7.27)	(7.73)	

4.6 lives saved per 1000 treated patients. ACE inhibitors reduced mortality in all trials, except for CONSENSUS II, in which 1-month mortality (reported in the table) was not significantly higher in enalapril-allocated patients. The plan for this trial was to recruit 9000 patients, but the study was stopped after randomization of 6090 patients. In this trial, the ACE inhibitor was administered in the first 24 hours after AMI by intravenous (IV) infusion (enalaprilat) and then orally for 6 months.

Modified from Reference 21 with permission.

Table 2⇓⇓ summarizes the evidence available from the literature (the results of the TRACE[18] and SMILE[24] studies were not available at the time of the meeting but are included for completeness, and their findings confirm previous evidence). Table 2⇓ and Fig 1⇓ summarize the background information: a decrease in the relative size of the beneficial effects is associated with a broadening of the population who might derive a clinically relevant benefit. Although the results of these trials are complementary in many ways, they also are a potential source of contradictory interpretation.[25 26 27 28 29 30] For example, are the populations randomized in CONSENSUS II,[19] GISSI-3,[20] and ISIS-4[21] concordant or discordant with respect to those of the other trials? Although ongoing trials[31] are addressing the issue of long-term secondary prevention with ACE inhibitors in patients at high risk of vascular events, no other placebo-controlled trials in the acute phase of AMI are planned. Thus, there is a need to translate the available evidence into reasonable and coherent recommendations for the use of ACE inhibitors in AMI and post-AMI patients.

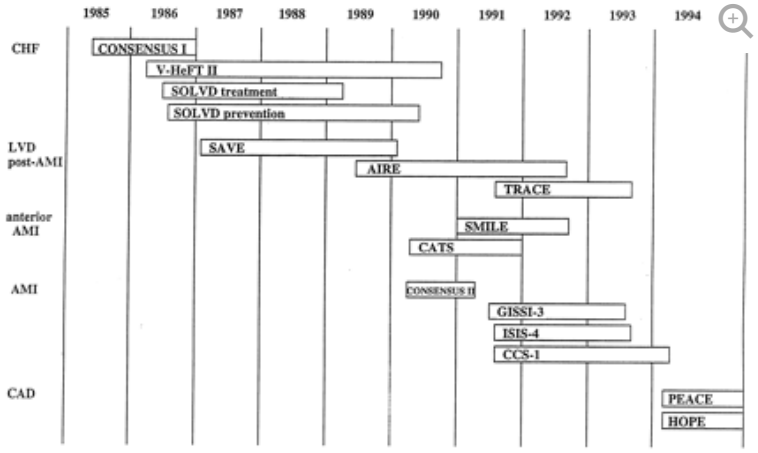

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Figure 1.

Chart showing randomized clinical trials on ACE inhibitors from CHF to coronary artery disease. Length of each bar represents the time span from the first to the last patient enrolled in each trial. LVD indicates left ventricular dysfunction; CAD, coronary artery disease.

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Table 2.

Summary of Randomized Clinical Trials

	Randomized Clinical Trials of ACE Inhibitors in Heart Failure				**Randomized Clinical Trials Inhibitors in High-Risk AMI**		
	CONSENSUS-I	SOLVD Treatment	V-HeFT II	SOLVD Prevention	SAVE	AIRE	T
Randomization, y	April 1985-December 1986	June 1986-March 1989	March 1986-September 1990	July 1986-May 1990	January 1987-January 1990	April 1991-August 1992	J A 1
Patients randomized, n	253	2569	804	4228	2231	2006	1
Patients screened[1]	…	39 924	2741	. . .	36 630	30 717	7
Randomized/screened, %					6	6.5	2

	Randomized Clinical Trials of ACE Inhibitors in Heart Failure				Randomized Clinical Trials Inhibitors in High-Risk AMI		
Population	NYHA IV (CAD, 73%; previous MI 47%)	NYHA II-III, EF ≤35% (CAD 71%; previous MI, 66%)	NYHA II-III, EF <45% (CAD, 54%; previous MI, 47%)	NYHA I-II, EF ≤35% (CAD, 83%; previous MI, 80%)	MI, EF ≤40%	MI, clinical HF	I ≤
Exclusion criteria	APE, MI<2 mo, Cr>300 µmol/L	NYHA IV, MI≤1 mo, age>80 y, Cr>177 µmol/L	MI<90 d	Clinical HF, MI≤1 mo, age>80 y, Cr>177 µmol/L	ACE inhibitor for CHF or HBP, age>80 y, Cr>221 µmol/L	NYHA IV, clinical severe RF	C t r t C µ
Drug initiation from MI	>60 d	>30 d	>90 d	>30 d	3-16 d (mean, 11 d)	3-10 d (mean, 5.4 d)	3 (c
Drug and dose, mg	Enalapril, 5 to 20 bid	Enalapril, 2.5 to 10 bid	Enalapril 5 to 20 daily	Enalapril, 2.5 to 10 bid	Captopril, 12.5 to 50 tid	Ramipril, 2.5 to 5 bid	T 1
Follow-up duration	1 d-20 mo (mean, 188 mo)	22-55 mo (mean, 41.4 mo)	6-68 mo (mean, 30 mo)	14.6-62 mo (mean, 37.4 mo)	24-60 mo (mean, 42 mo)	6-30 mo (mean, 15 mo)	2
Overall mortality, %							
Control	54	39.7	38.2[1]	15.8	24.6	23	6
Treated	39	35.2	32.8	14.8	20.4	17	3
Reduction, %	27	16	11.1	8	19	27	1
P	.003	.0036	.08	.30	.019	.002	.
Lives saved per 1000 patients per month[3]	23.6	1.1	1.7	. . .	1.0	3.5	2
Needed to be treated to save 1 life, n	7	22	19	. . .	24	17	1

CATS indicates Captopril and Thrombolysis Study; NYHA, New York Heart Association class; HF, heart failure; WMI, wall motion index; EF, ejection fraction; CAD, coronary artery disease; APE, acute pulmonary edema; Cr, serum creatinine; HBP, high blood pressure; RF, renal failure; and SBP, systolic blood pressure.

1 Figures are not comparable with post-AMI trials because of different screening procedures.

2 Hydralazine plus isosorbide dinitrate.

3 The figures should be compared with caution between studies of different durations.

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Table 2B.

Continued

Randomized Clinical Trials of ACE Inhibitors in High-Risk AMI Patients			**Randomized Clinical Trials of ACE Inhibitors in Relatively Unselected AMI Patients**		
SMILE	CATS	CONSENSUS-II	GISSI-3	ISIS-4	CCS-1
January 1991-December 1992	April 1990-December 1991	March 1990- March 1991	June 1991- July 1993	July 1991-August 1993	January 1990-April 1995
1556	298	6090	19 394	58 050	13 634
20 261	…	10 387	43 047	…	…
8	…	59	45	…	…
Anterior MI, nonthrombolyzed	Anterior MI, thrombolyzed	MI	MI	MI	MI
SBP<100 mm Hg, Killip 4, Cr>186 μmol/L	BP≤100/55 mm Hg, RF	BP<100/60, >105/65 mm Hg, clinical severe RF	Killip 4, SBP<100 mm Hg, Cr>177 μmol/L	SBP <90-100, Killip 4	SBP<90 mm Hg, chronic diuretic
6-24 h (mean, 15 h)	≤6 h	≤1 d	≤1 d	≤1 d	≤36 h
Zofenopril, 7.5 to 30 bid	Captopril, 6.25 to 25 bid	Enalaprilat IV, po 5 to 20 bid	Lisinopril, 2.5 to 10 once daily	Captopril, 6.25 to 50 bid	Captopril, 6.25 to 12.5 tid

Randomized Clinical Trials of ACE Inhibitors in High-Risk AMI Patients			Randomized Clinical Trials of ACE Inhibitors in Relatively Unselected AMI Patients		
12 mo	3 mo	41-180 d (mean, 6 mo; 2952 patients)	42 d	1 mo	4 weeks
6.5	4.0	9.4	7.1	7.7	9.6
4.9	6.0	10.2	6.3	7.2	9.1
24	…	…	11	7.0	6.0
.198			.03	.02	0.3
11.2	0	0	5.4	4.9	5.3
63	…	…	125	200	200

To address these issues, a meeting of investigators actively involved in the principal published ACE inhibitor trials was convened to reach a consensus on ACE inhibitor use in patients with AMI.

Methods and Participants

The GISSI group invited the coordinating groups and/or principal investigators of the CONSENSUS, AIRE, SAVE, SOLVD, ISIS-4, GISSI-3, and V-HeFT trials. A few other experts were invited, to provide a wide range of opinions, and representatives of collaborative research groups from Latin America participated, to allow discussion of the problems of transferability and relevance in different health care settings.

The meeting was held in Berlin during the XII World Congress of Cardiology and the XVI Congress of the European Society of Cardiology, September 10, 1994. The members of the panel are listed in the “Appendix.”

A summary of the existing data from the randomized clinical trials of ACE inhibitors in AMI was sent to all participants 1 month before the meeting to allow proper consideration and to avoid repetitive presentations. Confidential unpublished data from the GISSI-3, ISIS-4, and CCS-1 trials were also included.

The following questions were submitted to the panel at the same time to facilitate a productive and practice-oriented debate.

1. Is the primary indication for ACE inhibitor the treatment of the patients with AMI syndrome or with LV dysfunction that at any time complicates AMI? In the first case, should all patients or only those at higher risk be treated (ie, anterior AMI, large AMI)?

2. When should ACE inhibitor treatment be started?

3. What are the criteria of initial exclusion and subsequent withdrawal or continuation of ACE -inhibitor treatment of AMI patients?

4. Do known or suggested pathophysiological mechanisms provide a satisfactory explanation of the observed clinical effects of ACE inhibitor therapy?

Summary of Panel Discussion and Conclusions

Questions 1 and 2

Is primary indication for ACE inhibitor the treatment of the patients with AMI syndrome or with LV dysfunction that at any time complicates AMI? In the first case, should all patients or only those at higher risk be treated (ie, anterior AMI, large AMI)?

When should ACE inhibitor treatment be started?

The two questions are presented together because the answer to question 1 is integrally related to question 2. The evidence available from the trials on ACE inhibitors is documented in detail in Tables 1⇑ and 2⇑ and may be summarized as follows. Treatment with ACE inhibitors has a beneficial effect in patients selected for the presence of LV dysfunction after AMI and in relatively unselected patients presenting with AMI. The benefit increases in patients with clinical or laboratory evidence of LV dysfunction. There is still uncertainty about treating all AMI patients without contraindications to ACE inhibitors or targeting a selected higher-risk group.

The extension of the indication of early treatment to an unselected AMI population is supported by the consideration of the following. In the absence of absolute predictive criteria, short-term treatment is likely to offer protection from LV dysfunction to many patients before they develop it. There is evidence in the GISSI-3 and ISIS-4 trials of a very early benefit (Fig 2⇓) when reliable, objective measurement of LV dysfunction may be impractical. A beneficial effect of ACE inhibitor treatment in GISSI-3 and ISIS-4 is observed across a wide range of patients, although as expected the benefit was less in patients at lower risk. For example, the GISSI-3 results show that 33 patients with an impaired hemodynamic state at entry (Killip class >1) had to be treated for 1 life to be saved; 333 patients without complications (Killip class 1) had to be treated for 1 life to be saved. Nevertheless, the number of lives saved in the group of lower-risk patients is important in absolute terms because of the greater prevalence of this group of patients (ie, 24 lives saved in Killip class 1 versus 39 in Killip class >1 in GISSI-3). The potential risk of an ACE inhibitor therapy started early after AMI is small and does not obscure its net benefit, as shown by GISSI-3 results: persistent hypotension and renal dysfunction were significantly more common among lisinopril-treated patients than among control subjects (Fig 3⇓), and most of the cases of persistent hypotension (>80%) and more than half of those of renal dysfunction occurred within 7 days of randomization. However, a subsidiary analysis of GISSI-3 and ISIS-4 showed that in the same period (days 0 through 7) mortality was lower in the ACE inhibitor–allocated patients (Fig 2⇓).

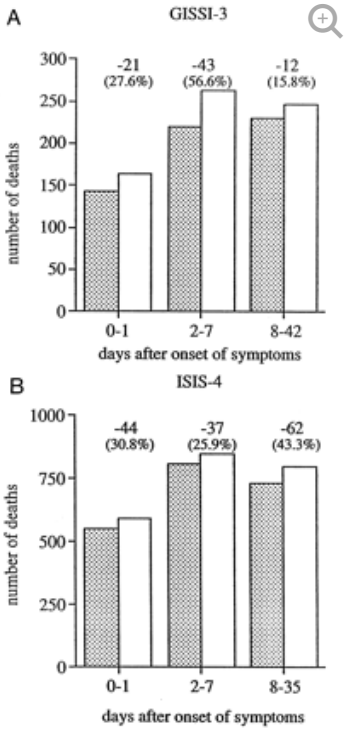

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Figure 2.

Bar graphs showing that in GISSI-3 and ISIS-4 ACE inhibitors saved lives during the very early phases. A, In the GISSI-3 lisinopril-allocated patients (cross-hatched bar), there were 76 fewer deaths than in the control-allocated group (open bar): 21 fewer for days 0 through 1, 43 fewer for days 2 through 7, and 12 fewer for the following days of treatment. B, In the ISIS-4 captopril-allocated patients (cross-hatched bar), there were 143 fewer deaths than in the control-allocated group (open bar): 44 fewer for days 0 through 1, 37 fewer for days 2 through 7; and 62 fewer for the following days of treatment. Absolute reductions and percent contribution to total benefit are shown for each time interval.

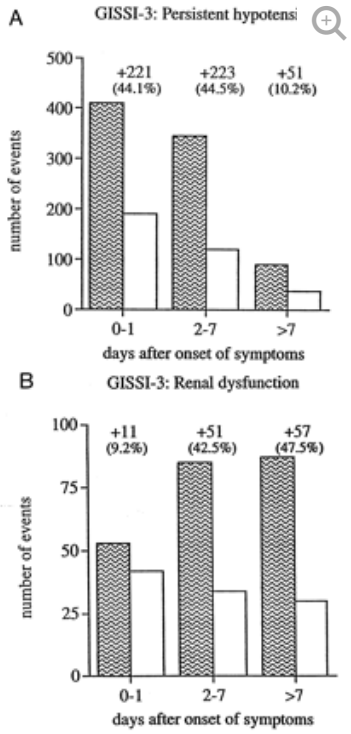

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Figure 3.

Bar graphs showing that in GISSI-3 persistent hypotension (A) occurred chiefly during the acute phase of AMI, with >80% of the cases occurring within day 2 from randomization, while excessive renal dysfunction (B; clinically defined by attending cardiologists) occurred throughout the hospitalization. These two events were consistently more frequent in patients treated with lisinopril (patterned bar) than in control subjects (open bar). Absolute increase of events and percent contribution to total increase are shown for each time interval. Data on timing of the event are missing for 12 patients with persistent hypotension and 1 with renal dysfunction.

In conclusion, evidence of an early benefit in unselected AMI patients was considered complementary to the favorable effects in patients with LV dysfunction by some members of the panel but disputed by others. All agreed that patients with a clinically large AMI and/or current or previous LV failure should certainly be considered for early treatment with an ACE inhibitor in the absence of contraindications (eg, hypotension).

Question 3

What are the criteria for initial exclusion and subsequent withdrawal or continuation of ACE inhibitor treatment of AMI patients?

Exclusion Criteria

The safety profile of patients treated within 24 hours from the onset of symptoms appears acceptable if the following exclusion criteria are applied: high risk of further serious hemodynamic deterioration (systolic blood pressure ≤100 mm Hg) and specific contraindications (history of clinically relevant renal failure, history of bilateral stenosis of the renal arteries, or documented allergy to ACE inhibitors).

Patients with low systolic blood pressure (100 to 110 mm Hg) in the first 24 hours after the onset of symptoms should be monitored carefully.

No specific additional risk was shown in GISSI-3 or ISIS-4 for elderly patients or women, so ACE inhibitors are not contraindicated in these populations.

Withdrawal or Continuation

The consistency of data on the role of ACE inhibitors from trials in patients with LV dysfunction or heart failure complicating AMI (as in the AIRE, SAVE, and TRACE studies) strongly indicates that ACE inhibitors should be given to these patients. For this reason, if at any time after AMI clinical signs and/or symptoms of LV dysfunction occur or are diagnosed instrumentally, treatment should be continued over a long period of time. In other words, as soon as a patient becomes an “AIRE- or SAVE-like patient,” he or she should be treated according to the indications of these studies (this recommendation was applied in the GISSI-3 and ISIS-4 trials).

On the other hand, if a patient does not show signs or symptoms of LV dysfunction, it is likely that treatment can be stopped safely after 4 to 6 weeks (based on existing evidence from GISSI-3 and ISIS-4). In this case, the patients should ideally be reevaluated after a reasonable period (ie, 4 to 6 months) to check for evidence of LV function. The appearance of persistent hypotension or clinically relevant renal dysfunction should be considered an indication for ACE inhibitor dose reduction or withdrawal (at least temporarily).

Question 4

Do the suggested pathophysiological mechanisms provide a satisfactory explanation of ACE inhibitor clinical effects?

Even if randomized clinical trials alone cannot provide answers on specific pathophysiological mechanisms, the results of ACE inhibitor trials in patients with LV dysfunction do appear to fit the remodeling hypothesis based on experimental studies and represent a good example of the consistency of a mechanistic hypothesis with the clinical data. The exploratory analysis of echo data from GISSI-3[32] supports this hypothesis in a large, relatively unselected population of patients treated very early after AMI. Although the changes observed in LV volumes are small, they are statistically and clinically significant, as already shown in a subgroup of patients from the SAVE trial.[33] A small decrease in LV volume in the whole population is consistent with a reduction in the incidence of LV dysfunction.[20]

Post hoc analyses of randomized clinical trials suggest that additional mechanisms (vasodilator and neurohormonal effects), in addition to the effect on long-term remodeling, might contribute substantially to the favorable effect of ACE inhibitors. This is suggested by the early beneficial effects (days 0 through 7, Fig 2⇑) documented in GISSI-3 and ISIS-4 and the reduced number of ischemic events reported by the SOLVD and SAVE trials after long-term ACE inhibition (although as expected no evidence of such an effect has been found with the short-term treatments in GISSI-3 and ISIS-4).

In particular, activation of the renin-angiotensin system in the first few days after AMI[34] may increase heart rate and systemic vascular resistance and decrease coronary artery perfusion,[35] which may lead to infarct expansion. The early benefit observed in GISSI-3, ISIS-4, and CSI-1 could be explained in this way.

Summary Statements

1. Patients with signs or symptoms of LV dysfunction at any time after AMI warrant prompt initiation of long-term (lifelong?) ACE inhibitor treatment unless contraindications exist.

2. Treatment of AMI patients with ACE inhibitors may be started the first day after timely and careful observation of their hemodynamic and clinical status and after administration of routinely recommended treatments (thrombolysis, aspirin, and β-blockers). No absolute “efficacy” criteria currently are available to recommend selection of preferential subgroups in the early phase of AMI.

3. Within the time frame of 24 hours after AMI, there is no evidence that in relatively unselected AMI patients early treatment with ACE inhibitors provides more efficacy. However, because mortality is highest in the acute phase of AMI, treatment should not be delayed unnecessarily.

4. Discontinuing ACE inhibitor treatment that was begun in the early phase of AMI should be considered in patients without asymptomatic LV dysfunction after 4 to 6 weeks. Further reassessment of LV function might be considered 4 to 6 months after AMI.

5. The dose of an ACE inhibitor can be individualized on the basis of safety criteria (eg, hemodynamic response) because simple criteria of efficacy, especially in the early phase, are not available. However, the target dose should be that used in the clinical trials.

6. A planned meta-analysis of existing trials should allow more reliable focusing on predefined subgroups of patients at higher risk of side effects or with better-defined profiles of potential benefit.

Appendix

International Panel

Stephen Ball, University of Leeds (AIRE); Jay N. Cohn, University of Minnesota (V-HeFT); Rory Collins, Radcliffe Infirmary (ISIS); Henry J. Dargie, University of Glasgow; Rafael Diaz, Instituto Cardiovascular de Rosario (ECLA); Alistair Hall, University of Leeds (AIRE); Peter Held, Astra Hässle (CONSENSUS); Bodh I. Jugdutt, University of Alberta; John Kjekshus, University of Oslo (CONSENSUS); Marc A. Pfeffer, Harvard Medical School (SAVE); Philip A. Poole-Wilson, National Heart & Lung Institute; Thomas Ryan, Boston University; Edgardo Sandoya, Sociedad Uruguaya de Cardiologia (ECLA); Rolf Schroeder, Berlin University (ISIS); Maarten Simoons, Erasmus Universiteit; Peter Sleight, cochair, University of Oxford (ISIS); Leopoldo Soares Piegas, Instituto Dante Pazzanese (ECLA); Carlos Tajer, Instituto Medico Antartida (ECLA); and Salim Yusuf, McMaster University (SOLVD, ISIS, and HOPE). Drs Ball and Hall actively participated in the meeting but did not share all the views expressed in the Summary Statements, particularly statement 2.

GISSI Group, Italy

Ernesto Correale, Maria Grazia Franzosi, Enrico Geraci, Stefano Ghio, Paolo Marino, Francesco Mauri, Gian Luigi Nicolosi, Fausto Rovelli, Eugenio Santoro, Luigi Tavazzi, Alberto Volpi, and Giulio Zuanetti.

Rapporteurs

Marcus Flather, McMaster University (ISIS); Roberto Latini, Istituto Mario Negri (GISSI); and Aldo P. Maggioni, Istituto Mario Negri and ANMCO (GISSI).

Selected Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
AIRE	=	Acute Infarction Ramipril Efficacy Study
AMI	=	acute myocardial infarction
CCS	=	Chinese Cardiac Study
CHF	=	congestive heart failure

CONSENSUS	=	Cooperative New Scandinavian Enalapril Survival Study
ECLA	=	Estudios Cardiologicos LatinoAmerica
GISSI-3	=	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico 3
HOPE	=	Heart Outcomes Prevention Evaluation
ISIS-4	=	International Study of Infarct Survival–4
LV	=	left ventricular
SAVE	=	Survival and Ventricular Enlargement Trial
SMILE	=	Survival of Myocardial Infarction: Long-term Evaluation
SOLVD	=	Studies of Left Ventricular Dysfunction
TRACE	=	Trandolapril Cardiac Evaluation Study
V-HeFT	=	Veterans Administration Cooperative Vasodilator–Heart Failure Trial

Acknowledgments

All the participants listed in the Appendix contributed to the present paper by attending the meeting in Berlin and/or carefully revising two versions of the manuscript. We thank Luisa Galbiati for the secretarial help in organizing the meeting and preparing the manuscript.

Footnotes

Participants in the meeting, held September 10, 1994, in Berlin, Germany, are listed in the "Appendix."

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