THE LANCET

Vol 340 Saturday 14 November 1992 No 8829

ORIGINAL ARTICLES

Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions

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An association between raised renin levels and myocardial infarction has been reported. We studied the effects of enalapril, an angiotensin-converting enzyme (ACE) inhibitor, on the development of myocardial infarction and unstable angina in 6797 patients with ejection fractions $\leq 0{\cdot}35$ enrolled into the two Studies of Left Ventricular Dysfunction (SOLVD) trials.

Patients were randomly assigned to placebo (n=3401) or enalapril (n=3396) at doses of 2·5–20 mg per day in two concurrent double-blind trials with the same protocol. Patients with heart failure entered the treatment trial (n=2569) and those without heart failure entered the prevention trial (n=4228). Follow-up averaged 40 months. In each trial there were significant reductions in the number of patients developing myocardial infarction (treatment trial: 158 placebo *vs* 127 enalapril, $p<0{\cdot}02$; prevention trial: 204 *vs* 161 $p<0{\cdot}01$) or unstable angina (240 *vs* 187 $p<0{\cdot}001$; 355 *vs* 312, $p<0{\cdot}05$). Combined, there were 362 placebo group patients with myocardial infarction compared with 288 in the enalapril group (risk reduction 23%, 95% CI 11–34%; $p<0{\cdot}001$). 595 placebo group patients developed unstable angina compared with 499 in the enalapril group (risk reduction 20%, 95% CI 9–29%, $p<0{\cdot}001$). There was also a reduction in cardiac deaths (711 placebo, 615 enalapril; $p<0{\cdot}003$), so that the reduction in the combined endpoint of deaths, myocardial infarction, and unstable angina was highly significant (20% risk reduction, 95% CI 14–26%; $p<0{\cdot}0001$).

Enalapril treatment significantly reduced myocardial infarction, unstable angina, and cardiac mortality in patients with low ejection fractions.

Lancet 1992; **340**: 1173–78.

Introduction

Atherosclerosis and its acute clinical sequelae such as myocardial infarction are caused by multiple risk factors.[1] There is a consensus that by tackling risk factors (eg, by not smoking[2] and by lowering low-density lipoprotein cholesterol), and by using antiplatelet agents or beta-blockers the probability of myocardial infarction will be reduced. A retrospective analysis of hypertensive patients suggested that high renin levels may predict myocardial infarction or stroke[6] and a prospective study of 1717 hypertensive patients reported that a high renin profile was associated with higher rates of both myocardial infarction and death.[7] However, it is not clear whether the increases in

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plasma renin reflected the extent of underlying myocardial dysfunction secondary to advanced coronary atherosclerosis or whether stimulation of the renin-angiotensin system was directly involved in the pathogenesis of myocardial infarction. This can be best clarified by a large randomised placebo controlled study of angiotensin-converting enzyme (ACE) inhibition.

The Studies of Left Ventricular Dysfunction (SOLVD) trials provide an opportunity to assess whether use of an ACE inhibitor reduces the risk of myocardial infarction or unstable angina.[8] These two randomised trials were designed to assess the effect of enalapril versus placebo in patients with a low ejection fraction. Patients with overt heart failure requiring treatment with diuretics, digitalis, or vasodilators other than ACE inhibitors were enrolled into the treatment trial; and those without overt heart failure and not requiring therapy for this condition were entered into the prevention trial. The results from both trials, related to the main endpoints of mortality and hospital admission for heart failure, have been reported.[9,10] Data were prospectively and systematically collected on myocardial infarction (a predefined secondary endpoint) and on unstable angina and form the basis of this report.

Patients and methods

Organisation

Eligible patients were randomly assigned to treatment groups separately at 83 hospitals linked to twenty-three centres in the US, Canada, and Belgium. Data were analysed centrally at the coordinating centre (University of North Carolina). The project office was located in the Clinical Trials Branch, National Heart, Lung and Blood Institute. A steering committee, consisting of principal investigators from the centre and the project office developed and implemented the protocol. An independent data and safety monitoring board evaluated the progress of the study. The study was approved by the institutional review board of the hospitals concerned and all patients provided written informed consent.

Eligibility, run-in period, and randomisation

Patients with ejection fractions of 0·35 or less were eligible for either trial. Details of the measurement of ejection fraction, exclusion criteria, screening, and run-in periods have been published.[8] Patients were ineligible if they had had acute myocardial infarction during the preceding 30 days, were admitted to hospital for unstable angina, or had had a revascularisation procedure in the previous 6 months. During the run-in period all patients received 2·5 mg enalapril twice daily for 2–7 days. This was followed by 2 weeks on equivalent placebo. Patients with no need for heart failure therapy at the end of that time were entered into the prevention trial; those requiring treatment for heart failure at entry were entered into the treatment trial. Patients were randomised to enalapril (2·5 mg twice daily, titrated up to 10 mg twice daily) or matching placebo. Patients were then seen at 2 weeks, 6 weeks, at 4 months and then every 4 months until the end of the study.

Follow-up and outcome measures

At the time of this report, the vital status of 8 of 3401 patients in the enalapril group and 2 of 3396 patients in the placebo group was unknown. Causes of death and reasons for hospital admission were classified by the principal investigator on standard forms without knowledge of treatment assignment. A definite myocardial infarction was considered present if the investigator had identified this complication on a standard form or if a death certificate indicated a fatal myocardial infarction. Documentation on the criteria for this diagnosis—namely characteristic chest pain, typical electrocardiographic changes, and typical enzyme changes—was required. A myocardial infarction was considered to have been a fatal one if the patient died within 7 days of onset of symptoms. Unstable angina was defined as new onset or worsening angina pectoris requiring hospital admission, and this was based on the discharge diagnosis. Patients who had angina and were admitted for an investigation were not included in this category.

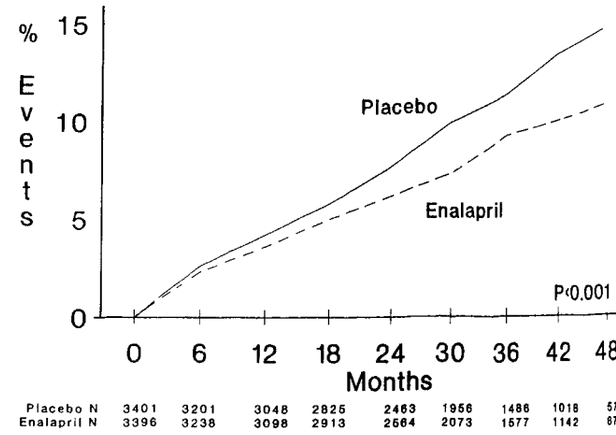

Fig 1—Cumulative incidence of myocardial infarction, combined trials.

Statistical analyses

Although there was an expectation that lowering blood pressure by an ACE inhibitor might lower coronary-heart-disease events there were also concerns that lowering blood pressure in normotensive individuals may increase the risk of cardiovascular events ("J-shaped curve"),[11] so two-sided tests have been used in statistical analyses. A stratified log-rank test was used to compare life-table curves for patients randomly assigned to the two groups.[12] The percentage reduction in events was reported as (1-RR) × 100, where RR is the estimated relative risk of an event in the enalapril group as compared with the placebo group estimated from life tables. Uniformity of treatment effects across subgroups was assessed by the likelihood-ratio test on the basis of the proportional hazards model.[13] Detailed data are provided separately for each trial and in combination in tables I and II. Given the consistency of the results in both trials, the text deals primarily with the overall data. Analysis of the impact of interim ischaemic events on prognosis was based on a time-dependent covariate analysis that adjusted for several prognostic factors (eg, ejection fraction, age, New York Heart Association functional class) and for trial and treatment allocation.

Results

From June, 1986, to April, 1990, 6797 patients were enrolled. Of these 2569 entered the treatment trial and 4228 patients the prevention trial. The clinical characteristics have been described.[9,10] Follow-up ranged from 15 to 62 months (average 40).

Myocardial infarction (fig 1)

Table I provides details on rates of fatal and non-fatal myocardial infarction separately and in combination with cardiac and total mortality. Risk reductions for myocardial infarction were similar in both trials (23% in the treatment trial, $p < 0·02$; 24% in the prevention trial, $p < 0·01$). At the end of the two trials, 362 (10·6%) patients in the placebo group had had a myocardial infarction compared with 288 (8·5%) in the enalapril group (risk reduction 23%, 95% interval [CI] 11–34%; $p < 0·001$). The reduction in non-fatal myocardial infarction appeared to be larger (29%) than the reduction in fatal myocardial infarction (14%), but the CIs of these estimates overlap substantially and provide no evidence of heterogeneity.

TABLE I—EFFECT OF ENALAPRIL ON DEVELOPMENT OF MYOCARDIAL INFARCTION, HOSPITALISATION FOR WORSENING ANGINA, AND CARDIAC AND TOTAL MORTALITY

Outcome	No of events (%)		Risk reduction (%) (95% CI)	Z score	p
	Placebo	Enalapril			
Treatment trial					
Myocardial infarction					
Fatal	91 (7·1)	69 (5·4)	27 (1, 46)	1·99	0·04
Non-fatal	83 (6·5)	66 (5·1)	23 (−6, 44)	1·58	0·11
Either	158 (12·3)	127 (9·9)	23 (2, 39)	2·17	0·02
Hospitalisation for angina*	240 (18·7)	187 (14·6)	27 (12, 40)	3·29	0·001
MI or hospitalisation for angina	350 (27·3)	282 (21·9)	25 (12, 36)	3·63	0·001
Cardiac deaths or non-fatal MI	505 (39·3)	429 (33·4)	19 (8, 29)	3·21	0·001
Cardiac death, non-fatal MI, or hospitalisation for angina	659 (51·3)	547 (42·6)	23 (14, 32)	4·63	0·0001
All deaths, non-fatal MI or hospitalisation for angina	700 (54·5)	592 (46·1)	22 (13, 30)	4·51	0·0001
Prevention trial					
Myocardial infarction					
Fatal	66 (3·1)	70 (3·3)	−4 (−45, 26)	−0·21	0·83
Non-fatal	147 (6·9)	103 (4·9)	32 (13, 47)	3·06	0·001
Either	204 (9·1)	161 (7·6)	24 (6, 38)	2·59	0·01
Hospitalisation for angina*	355 (16·8)	312 (14·8)	14 (0, 26)	1·99	0·05
MI or hospitalisation for angina	509 (24·0)	425 (20·1)	20 (9, 29)	3·35	0·001
Cardiac deaths or non-fatal MI	413 (19·5)	329 (15·6)	23 (11, 33)	3·49	0·001
Cardiac death, non-fatal MI, or hospitalisation for angina	691 (32·6)	570 (27·0)	21 (12, 29)	4·13	0·0001
All deaths, non-fatal MI or hospitalisation for angina	722 (34·1)	613 (29·0)	19 (9, 27)	3·73	0·0001
Combined trials					
Myocardial infarction					
Fatal	157 (4·6)	139 (4·1)	14 (−8, 32)	1·32	0·19
Non-fatal	230 (6·8)	169 (5·0)	29 (13, 41)	3·39	0·001
Either	362 (10·6)	288 (8·5)	23 (11, 34)	3·38	0·001
Hospitalisation for angina*	595 (17·5)	499 (14·7)	20 (9, 29)	3·61	0·001
MI or hospitalisation for angina	859 (25·3)	707 (20·8)	22 (14, 29)	4·89	0·0001
Cardiac deaths or non-fatal MI	918 (27·0)	758 (22·3)	21 (13, 28)	4·72	0·0001
Cardiac death, non-fatal MI, or hospitalization for angina	1350 (39·7)	1117 (32·9)	22 (16, 28)	6·20	0·0001
All deaths, non-fatal MI or hospitalisation for angina	1422 (41·8)	1205 (35·5)	20 (14, 26)	5·82	0·0001

*Data for hospitalisation for angina include both primary and secondary discharge diagnosis. Numbers of patients hospitalised with a primary diagnosis of worsening angina are: prevention trial (329 placebo, 296 enalapril, Z = 1·61), treatment trial (204 placebo, 166 enalapril, Z = 2 55) and combined trials (533 placebo, 462 enlapril, Z = 2 84)
MI = myocardial infarction

173 patients (98 placebo, 75 enalapril) died with a diagnosis of myocardial infarction without being admitted to hospital. Of the 477 patients admitted with a diagnosis of myocardial infarction, documentation of diagnostic criteria was available in 472 (98·9%) (263 placebo, 109 enalapril). 445 (94%) met two or all three diagnostic criteria (249 placebo, 196 enalapril) and 27 had only one criterion checked (14 placebo, 13 enalapril).

Unstable angina (fig 2)

Significant reductions in admissions for unstable angina were observed in the treatment trial (240 placebo, 187 enalapril; $p < 0·001$) and in the prevention trial (355 placebo, 312 enalapril; $p < 0·05$) (table I). Thus 595 (17·5%) patients in the placebo group were admitted for unstable angina compared with 499 (14·7%) in the enalapril group (risk reduction 20%, 95% CI 9–29%; $p < 0·001$).

Cardiac death, myocardial infarction, admission for angina (fig 3)

Similar reductions in both myocardial infarction and angina were observed. 859 (25·3%) patients in the placebo group and 707 (20·8%) in the enalapril group had a myocardial infarction or were admitted for angina (risk

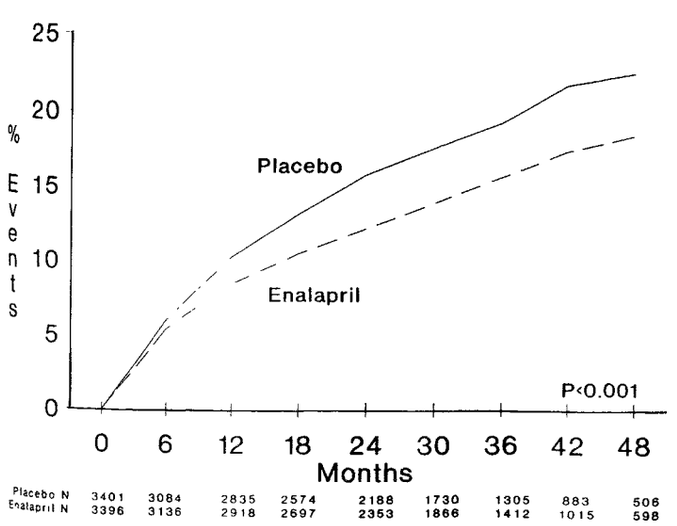

Fig 2—Cumulative incidence of unstable angina, combined trials.

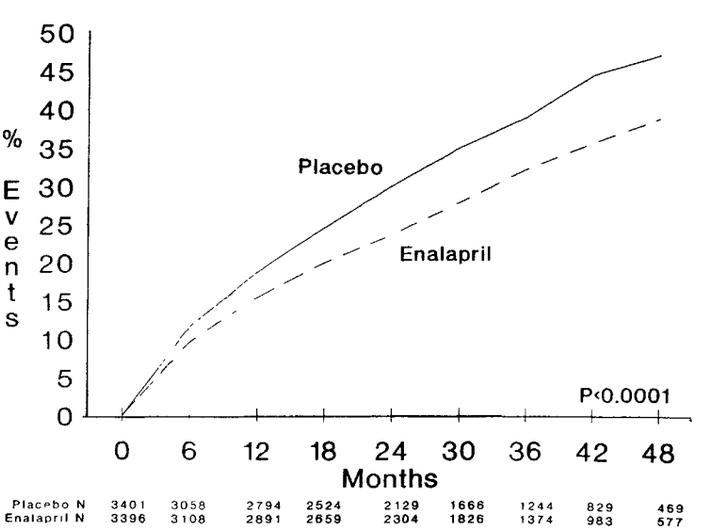

Fig 3—Cumulative incidence of cardiac death, myocardial infarction, or unstable angina, combined trials.

TABLE II—EFFECT OF ENALAPRIL OR PLACEBO ON MYOCARDIAL INFARCTION OR HOSPITALISATION FOR ANGINA BY BASELINE CHARACTERISTICS IN COMBINED TRIALS

Characteristic	Placebo		Enalapril		% reduction in risk (95% CI)	p*
	No	% events	No	% events		
Age ≤median	1692	26·1	1708	21·8	21 (9, 31)	
>median	1704	24·4	1681	19·9	22 (10, 32)	
Female	496	28·8	484	19·6	35 (16, 49)	
Male	2905	24·6	2911	21 0	19 (10, 27)	
White	2875	25·6	2843	20·8	22 (14, 30)	
Other	524	23·5	550	20·9	17 (−7, 35)	
Aetiology, ischaemic	2683	28·1	2667	24·1	18 (9, 26)	0·04
other/unknown	710	14·1	723	8·9	43 (22, 58)	
Previous MI, Yes	2517	28·2	2552	23·7	20 (11, 28)	
No	880	16·5	835	12·1	34 (14, 48)	
Angina at baseline, Yes	1216	39·1	1179	30·0	28 (17, 37)	0·01
No	2182	17·5	2214	15·9	13 (−1, 24)	
History of hypertension, Yes	1324	25·3	1328	22·0	19 (5, 30)	
No	2075	25·2	2065	20·0	25 (15, 34)	
Ejection fraction ≤median	1768	25·3	1725	20·1	27 (16, 36)	
>median	1631	25·1	1668	21·5	16 (3, 27)	
Ca channel blocker, Yes	1140	36·1	1132	29·7	21 (9, 31)	
No	2251	19·7	2255	16·4	22 (11, 32)	
Antiplatelet drugs, Yes	1553	26·3	1600	20·9	22 (10, 33)	
No	1846	24·3	1790	20·8	21 (10, 31)	
Beta-blocker, Yes	592	31·4	620	24·7	27 (10, 41)	
No	2806	23·9	2772	19·9	20 (11, 29)	
Previous CABG surgery, Yes	929	29·5	944	24·0	19 (4, 32)	
No	2472	23·7	2452	19·6	23 (13, 31)	

*For heterogeneity of effects in subgroups Ejection fraction, median = 28; Age, median = 61. CABG = coronary artery bypass graft Ca = calcium

reduction 22%, 95% CI of 14–29%; p < 0·0001). Cardiac mortality was greater in the placebo group (711 deaths, 21%) than in the enalapril group (615 deaths, 18%). The risk reduction was 17% (95% CI 7 to 25; p < 0·001). For the combined end-point of cardiac death, infarction, or hospitalisation for angina, the differences are highly significant. 1350 or 39·7% in the placebo group; 1117 or 32·9% in the enalapril group). The risk reduction for this combined end-point was 22% (95% CI 16–28%; p < 0·0001) (fig 3), and was the same in treatment (23%, 95% CI 13–32%; p < 0·001) and in the prevention (23%, 95% CI 11–33%; p < 0·001) trials.

Time course of effects (figs 1 and 2)

During the first 3 months after randomisation there was little difference in the incidence of either myocardial infarction or hospital admission for angina. Non-significant trends towards fewer such events in the enalapril group were apparent at 6 months for both events. Thereafter the differences between the enalapril and placebo groups continued to widen.

Effects in subgroups (table II)

Before examination of the effects of treatment in subgroups, baseline characteristics that might influence the results were identified. These were the aetiology of underlying cardiac disease (ischaemic, hypertension, other causes), concomitant drug use (nitrates, antiplatelet drugs, beta-blockers, calcium blockers), prior coronary artery bypass graft surgery, entry blood pressure, and presence or absence of angina. Analyses were also done on the basis of ejection fraction and functional status, although there was no prior expectation of the treatment effect varying in these subgroups.

There appeared to be no heterogeneity of effect of enalapril on myocardial infarction among most of the various subgroups examined. However, the reduction in myocardial infarction and unstable angina was significantly greater among those with angina at entry into the study. There also appeared to be greater benefit among those without prior ischaemic heart disease. However, these subgroup analyses should be cautiously interpreted and need independent confirmation.

Blood pressure (table III)

Systolic and diastolic BP were significantly lower in the patients randomly assigned to enalapril than in the placebo group, by 6 and 4 mm Hg respectively. A significantly lower BP was seen as early as the first post-randomisation visit, 2 weeks after starting therapy (125/77 mm Hg placebo, 119/74 mm Hg enalapril); and this difference persisted. There were no differences in heart rate between the two groups at baseline or follow-up. To evaluate the results by degree of BP reduction while preserving the randomised comparisons, the BP decline at the end of 7 days of therapy with enalapril before randomisation was compared with BP reduction 6 weeks and 4 months after randomisation in the enalapril group. This demonstrated a modest correlation

TABLE III—EFFECT OF BASELINE BP OR BP REDUCTION (RESPONSE TO 2·5 MG ENALAPRIL BEFORE RANDOMISATION) ON REDUCTION IN ISCHAEMIC EVENTS IN COMBINED TRIALS

Baseline (mmHg)	% reduction in		
	MI	Angina	MI + Angina
SBP ≤124	29	20	22
SBP >124	17	17	19
DBP <80	22	23	22
DBP ≥80	25	15	22
SBP reduction <6	12	19	18
SBP reduction ≥6	34	20	26
DBP reduction <4	12	19	18
DBP reduction ≥4	32	19	25

SBP = systolic, DBP = diastolic BP, MI = myocardial infarction Angina = hospital admission for worsening angina

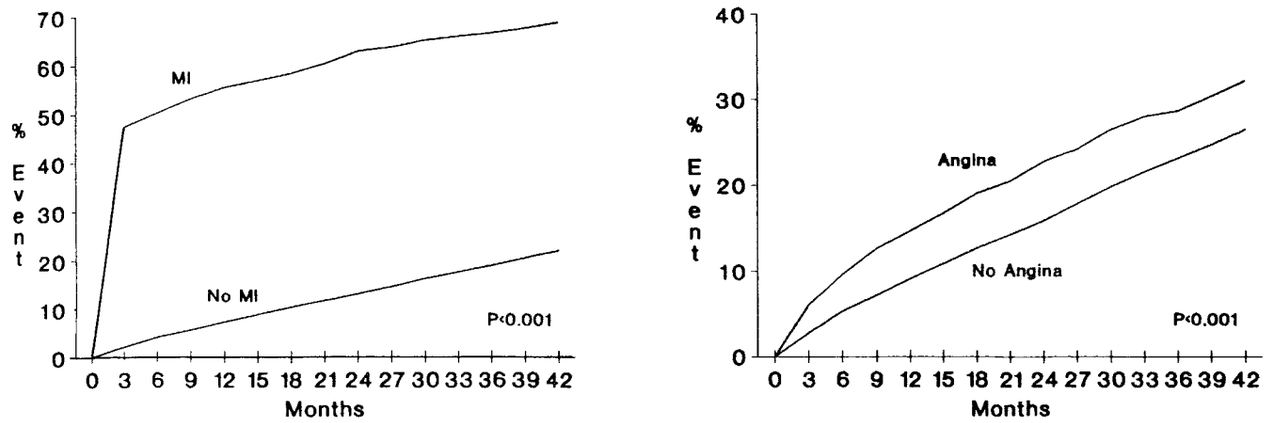

Fig 4—Risk of death in patients who develop myocardial infarction (MI) (left hand panel) or unstable angina (right hand panel) compared with patients in whom those events did not develop.

(r = 0·52 systolic, r = 0·54 diastolic) at 6 weeks, with almost identical correlations at 4 months. Patients were then divided into two groups (above and below the median) based upon the degree of BP pressure reduction after the run-in period. There was a trend towards larger reductions in myocardial infarction and unstable angina among those with a greater reduction in systolic and diastolic BP pressures, although the test for interaction was not significant (table II). Risk reductions in myocardial infartion and unstable angina were similar in patients with baseline BP above and below 124 mmHg systolic or 80 mm Hg diastolic.

Prognostic impact of interim myocardial infarction or unstable angina

Among 650 patients with a myocardial infarction during the study the 1-year mortality rate was 55·4% compared with 7·3% among the 6147 patients without myocrdial infarction (adjusted relative risk (RR) 7·8, 95% CI 6·9–8·8) (fig 4). 25% of all deaths in the study were preceded by an interim myocardial infarction. Even after exclusion of deaths during the first 7 days after an infarction, mortality was higher in those who had an interim infarction (RR 3·5, 95% CI 2·9–4·2). The 12–month rates of hospital admission for heart failure were 20·5% and 8·6% respectively (RR 2·1, 95% CI 1·6–2·6). For the 1094 patients with unstable angina, the 1-year mortality rate was 14·6% compared to 9·0% among the 5703 patients without unstable angina (RR 1·4, 95% CI 1·2–1·6) (fig 4). The 1-year rates of hospital admission were 15·3% and 8·4%, (RR 1·6, CI 1·4–1·9). 34% of all deaths in the study were preceded by an interim myocardial infarction or hospital admission for unstable angina.

Discussion

This study demonstrated, in both trials, significant reductions in myocardial infarction, unstable angina, and cardiac mortality in patients with low ejection fractions treated with the ACE inhibitor enalapril plus conventional therapy. Enalapril reduced the risk of major ischaemic events by about 22%. Previous reports from SOLVD[9,10] and the Cooperative North Scandinavian Enalapril Survival Study[14] demonstrated reductions in deaths from and hospital admissions for heart failure with ACE inhibitor therapy. Development of myocardial infarction and unstable angina greatly increased the risk of death and hospital admission for heart failure. Our latest data show that prevention of major ischaemic events should be an integral part of the management of patients with heart failure or left-ventricular dysfunction.

Myocardial infarction was a secondary endpoint specified in the protocol; hospital admission for angina was not and there are no objective criteria for the diagnosis of unstable angina, so data on this endpoint should be cautiously interpreted. However, the differences observed in unstable angina are likely to be unbiased because the diagnosis was made blind and the data were collected prospectively on standard forms. The reduction in unstable angina was significant in each trial and the combined data from both trials are highly significant. The reduction in unstable angina is supported by a reduction in myocardial infarction as both of these outcomes are likely to have some similarities in their pathogenesis. Previous small trials reported conflicting results on the effect of ACE inhibitors on the severity of stable angina pectoris.[15,16] In some previous studies there was benefit, whereas in others there was either no effect or an exacerbation of angina. However, all previous studies have been small and lasted only 6 weeks to 3 months, and none evaluated impact on unstable angina or infarction. In our study, reductions in unstable angina and myocardial infarction were not apparent until at least 6 months. Thereafter, the rates of these events were significantly reduced. This contrasts with the reduction in hospital admission for worsening heart failure with enalapril which was observed shortly after randomisation and was much reduced by 6 months. This suggests that the beneficial effects of enalapril on ischaemic events were unlikely to be due to an immediate effect such as reduction in myocardial oxygen demand by an effect on preload and afterload (as seen with beta-blockers)[5] or an effect on coagulation factors (as seen with antiplatelet agents[4] or anticoagulants.[17] The delay in the reduction of ischaemic events resembles the pattern observed in trials of cholesterol lowering.[18]

The mechanisms that may have led to the observed differences in myocardial infarction and major ischaemic events are not clear. Several studies have demonstrated a continuous association between raised BP and increased risk of myocardial infarction even among people with diastolic BP below 90 mm Hg.[19] An overview indicates that a 5 mm Hg or so difference in diastolic BP is associated with a 21% difference in incidence of coronary heart disease events. In previous trials of antihypertensive therapy, a 5–6 mm Hg reduction in diastolic BP was associated with a 14% reduction in coronary heart disease events.[20] In our trial the difference in diastolic BP was 4 mm Hg, yet we observed a 23% reduction in myocardial infarction. Therefore, the

benefits we observed may only be partly explained by the reductions in BP.

However, there are important differences in patient selection between our trial (normotensive high-risk individuals with pre-existing cardiac damage) and the trials of antihypertensive therapy (patients with higher BP but few with obvious cardiac damage). In SOLVD the entry BP was 125/77 mm Hg which is considered to be in the normal range; and a 4 mm Hg reduction was associated with fewer ischaemic events. Furthermore, these benefits were observed even among those with initial BP below 124/80 mm Hg and among those with the greatest reductions in BP. Extrapolation of these data suggest that lowering diastolic BP below 90 mm Hg in high-risk individuals may not be harmful and likely to be even beneficial.

Another intriguing possibility is that ACE inhibitors may block some of the direct adverse effects of angiotensin-II on the coronary circulation and myocardium. Gavras et al have reported that infusion of large doses of angiotensin-II resulted in myocardial infarction in 6 out of 7 rabbits.[21] Alderman et al have reported that hypertensive patients with high-renin profiles have a higher risk of myocardial infarction.[7] Our data support the possibility that enalapril had a favourable effect in reducing cardiac ischaemia and infarction by reducing angiotensin-II levels. Angiotensin-II can adversely affect the balance between increased cardiac oxygen demand and supply by either a direct coronary vasoconstrictor effect[22] or by increased inotropy by its ability to raise cytosolic Ca^{2+} concentration in the myocardium.[23] In addition, angiotensin-II regulates proto-oncogenes that control cell growth and differentiation involved in both the vascular wall and myocardium.[23,24] Prolonged use of ACE inhibitors restores normal endothelial function and vascular dilatation in animal models of heart failure and prevents the proliferative response to vascular injury.[23,26] It is therefore likely that reduction in ischaemic events observed may be due to multiple beneficial effects of an ACE inhibitor that include BP lowering, coronary vasodilatation, an antiproliferative effect on vascular smooth muscle, prevention of atherosclerosis progression and myocardial hypertrophy, and favourable effects on endothelial function.

Although our data are based on patients with low ejection fraction, the observation of benefit in subgroups defined by level of ejection fraction, aetiology, and against a background of different drugs raises the possibility of a wider role for ACE inhibitors in preventing major ischaemic events in other populations. This hypothesis should be tested in trials of patients with hypertension or other risk factors that predispose to infarction and among patients with ischaemic heart disease and preserved ventricular function.

A list of SOLVD investigators and centres has been published.[9] The study was largely funded by the US National Heart, Lung and Blood Institute with additional contributions from Merck, Sharpe and Dohme, which had no involvement in the design, conduct, analysis, or interpretation of the data.

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