POSITION STATEMENT ON ACE-INHIBITORS (Updated December 2002)

Well designed, large scale, randomized double-blind, placebo-controlled trials have validated the efficacy of the ACE-inhibitor enalapril in reducing hospitalizations and mortality in patients with symptomatic, chronic heart failure resulting from left ventricular systolic dysfunction (LVEF $\leq$ 35%) due to either ischemic or nonischemic causes.[1-2] Moreover, enalapril has been shown to delay the development of symptomatic heart failure and CHF hospitalization in a cohort of patients with asymptomatic left ventricular dysfunction.[4] The benefits of enalapril appear to be related to its neurohormonal antagonism as opposed to its vasodilatory properties; patients receiving enalapril are more likely to survive than those treated with combination vasodilator drugs (hydralazine, isosorbide dinitrate).[3] Whether the clinical benefits of enalapril in chronic CHF can be assumed for other ACE-inhibitors has yet to be established.

Well over 100,000 patients have been studied in randomized, placebo-controlled trials designed to evaluate the potential efficacy in prolonging life and reducing cardiovascular morbidity following acute myocardial infarction. In three such trials, high-risk patients (asymptomatic LV dysfunction or clinical heart failure) were administered an ACE-inhibitor (captopril, ramipril, or trandolapril) between 2 and 16 days after initial presentation of myocardial infarction. The ACE-inhibitor (or placebo) was continued for the duration of the trial and the patients were followed on average between 6 and 42 months. Each of the trials showed conclusively that ACE-inhibitors reduce all cause mortality and prevent progression to severe heart failure (heart failure death, CHF hospitalization, need for open label ACE-inhibitor).

Five other trials addressed the potential benefits of early-onset (within 24 hours of myocardial infarction), short-term (4 to 6 weeks) administration of an ACE-inhibitor (IV enalapril, lisinopril, zofenopril or captopril) in heterogeneous cohorts of patients after acute MI. The presence of left ventricular dysfunction or clinical heart failure was not a prerequisite for enrollment; in fact, a minority of patients would have been considered at "high risk" in these trials. With the exception of CONSENSUS II (IV enalaprilat), each of the ACE-inhibitors studied had a positive impact on survival, with approximately 5 lives saved per 1000 patients. Interestingly, with the exception of zofenopril, ACE-inhibitor therapy did not prevent the development of clinical CHF post MI at 4-6 weeks when compared to placebo. (Probably related to the short followup period.)

Based on the results of these trials, we advocate the following:

1)   All patients with left ventricular systolic dysfunction, regardless of etiology or extent of functional impairment, should be placed on an ACE-inhibitor unless contraindicated (angioedema, allergy, bilateral renal artery stenosis, intractable cough, symptomatic hypotension).

2)   Following myocardial infarction, any patient with left ventricular systolic dysfunction or clinical heart failure should be started on ACE-inhibitors.

3)   While recognizing that the benefits of ACE-inhibitor therapy on cardiovascular morbidity and mortality in the setting of left ventricular systolic dysfunction is likely related to a class effect, we advocate that such patients be placed on specific agents at doses proven to be efficacious.

> Enalapril 10 mg BID (CONSENSUS[1], SOLVD[2,4], V-HeFT II[3])
> Captopril 50 mg TID (SAVE[7], ISIS-4[13], CCS-1[14])
> Ramipril 5 mg BID (AIRE[8])
> Trandolapril 4 mg qd (TRACE[9])
> Lisinopril 10-40 mg qd (GISSI-3[11], ATLAS)
> Zofenopril 30 mg BID (SMILE[12])

ACE-INHIBITORS
I.   **Chronic Heart Failure (Ischemic and Nonischemic Cardiomyopathy)**

A.   **Effects of Enalapril on Mortality in Severe Congestive Heart Failure**
         Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)[1]

Objective: "The CONSENSUS trial was designed to study the effect on mortality of enalapril as compared with placebo, in addition to conventional therapy in severe congestive heart failure" (NYHA Class IV)

Methods: 253 patients with NYHA Class IV CHF were randomly assigned in a double – blind study to receive either placebo or enalapril (target dose 10 mg BID). Background therapy consisted of digitalis (93%), diuretics (98%), and isosorbide dinitrate (46%). Cardiomegaly had to be present on chest x-ray. Patients with acute pulmonary edema, recent MI (within past two months), unstable angina, hemodynamically significant valve disease or planned cardiac surgery were excluded. Follow-up averaged 188 days.

Results:

- Study terminated prematurely because of a favorable effect of enalapril
- 73% of patients had CAD
- The overall crude mortality at 6 months was 44% in the placebo group and 26% in the enalapril group – a reduction of 40% (P = 0.002)
- At the end of one-year, mortality was 52% and 36% in the two groups respectively (P = 0.001), a relative risk reduction of 31%
- Enalapril did not affect the incidence of sudden cardiac death; however, there was a 50% reduction in mortality due to the progression of heart failure in the enalapril – treated group (P < 0.001)
- Enalapril significantly improved NYHA Class and reduced heart size
- The final mean dose level of enalapril was 18.4 mg, and of matching placebo, 27.3 mg (P < 0.001)

Conclusions: "The addition of enalapril to conventional therapy in patients with severe CHF can reduce mortality and improve symptoms. The beneficial effect on mortality is due to a reduction in death from the progression of heart failure."

A.   **Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure (SOLVD)[2]**

Objective: Assess the effect of enalapril on mortality in patients with mild – moderate CHF in the setting of left ventricular systolic dysfunction (LVEF ≤ 35%).

Methods: 2569 patients receiving conventional treatment for heart failure (90% NYHA Class II-III) were randomly assigned to receive either placebo or enalapril at doses of 2.5 to 20 mg per day in a double – blind fashion. Patients had to have an LVEF ≤ 35% (MUGA, angiography, ECHO). Exclusion criteria included unstable angina, recent MI (< one month), severe valve disease, creatinine ≥ 2.0 mg/dl. All patients eligible for the trial entered a run – in and stabilization phase with the administration of open label enalapril 2.5 mg bid for 2-7 days. A total of 4.2% of patients were excluded due to either worsening renal function, symptomatic hypotension, or noncompliance. After this phase of active dosing, the patients were placed on a regimen of matching placebo in a single – blind fashion for 14 to 17 days so that those whose clinical condition worsened when the drug was withdrawn and those who complied poorly with the regimen could be identified. Another 4.2% of patients were excluded from the study during this phase.

The followup averaged 4.14 months.

Results:

- Enalapril improved overall mortality (35.2% vs. 39.7%, reduction in risk 16%; 95% CI, 5 to 26%; P=0.0036)
  - The improvement in mortality was attributable to an 18% reduction in cardiovascular death (no difference in non-cardiovascular death was found)
  - Mortality due to progressive heart failure was reduced by 22% (95% CI 6 to 35%, P = 0.0045)
  - Enalapril did not affect death due to MI or arrhythmia

- Enalapril decreased hospitalization rates for CHF (18.2% of the placebo group and 12.2% of the enalapril group were hospitalized more than once for CHF, P < 0.001)

- The difference in mortality was observed only among the patients hospitalized at least once during the trial for CHF.

- Open-label ACE-inhibitors were used after one year in 12.4% of patients receiving placebo as compared with 6.4% of those receiving enalapril; after two years, the corresponding proportions were 20.4 and 10.1%, and after three years, 23.0 and 13.9%.

- At the final visit, 49% were receiving 10 mg of study drug twice daily (no difference between placebo, enalapril).

- By the end of the study, 32.5% of the patients in the enalapril group and 41.4% of those in the placebo group had stopped taking blinded medication.

Conclusions: "The addition of enalapril to conventional therapy significantly reduced mortality and hospitalizations for heart failure in patients with chronic congestive heart failure and low ejection fractions."

A. **A Comparison of Enalapril with Hydralazine – Isosorbide Dinitrate in the Treatment of Chronic Congestive Heart Failure (V-HeFT II)[3]**

Objective: To compare the clinical effects of enalapril with those of hydralazine and isosorbide dinitrate in patients with mild to moderate heart failure.

Methods: 804 men with evidence of cardiac dysfunction (cardiothoracic ratio $\geq$ 0.55 on chest x-ray, LVIDD > 2.7 cm/m^2, LVEF < 45% on MUGA and reduced exercise tolerance (VO$_{2max}$ < 25 ml O$_2$/kg/min) were enrolled in the trial and randomly assigned to enalapril or hydralazine – isosorbide dinitrate. Prior to receiving study drug, a baseline period of at least 4 weeks was required to establish optimal therapy with digoxin and a diuretic agent, to allow any nonstudy drugs to be discontinued, and to ensure clinical stability. Initial doses of study medication were enalapril 5 mg bid, hydralazine 37.5 mg qid, isosorbide dinitrate 20 mg qid. After 2 weeks, if the patient tolerated these initial doses, the doses were doubled; thus, the target doses consisted of either enalapril 10 mg bid or hydralazine 75 mg qid plus isosorbide dinitrate 40 mg qid. Patients with angina requiring treatment with nitrates or calcium antagonists, severe pulmonary disease, inability to perform an exercise test, and an inability to discontinue vasodilator therapy were excluded from the trial.

Results:

- Only 53% of randomized patients had CAD as a primary cause of heart failure.

- During an average follow-up of 2.5 years (range 6 months to 5.7 years), 32.8% of patients on enalapril and 38.2% of patients assigned to hydralazine –isosorbide dinitrate died. The mortality in the enalapril group was significantly lower than in the hydralazine-isosorbide group at 2 years (28.2% mortality reduction, P = 0.016). This trend continued throughout the study but did not quite attain statistical significance for the duration of the follow-up period (P = 0.08).

- The lower mortality in the enalapril arm was due to a lower incidence of sudden death, with or without premonitory symptoms. There was no difference in mortality from pump failure.

- No difference was seen in the incidence of acute myocardial infarction or rate of revascularization.

- Patients without CAD and with less severe symptoms of heart failure tended to benefit more from enalapril as compared to those with more advanced symptoms and presence of CAD.

- The increase in LVEF at 13 weeks was more profound in the hydralazine-isosorbide dinitrate arm than in those receiving enalapril (0.033% vs. 0.021%, $P = 0.026$).

- Oxygen consumption was increased significantly by hydralazine-isosorbide dinitrate after 13 weeks (by 0.6 ml O_2/kg/min; $P < 0.0001$) and after 6 months (by 0.8 ml O_2/kg/min; $P < 0.0001$), but not by enalapril. After 1 year, oxygen consumption began to decline progressively in both treatment arms. Peak oxygen consumption was greater in the hydralazine-isosorbide dinitrate group than the enalapril group throughout the first 2 years of followup.

- Cardiothoracic ratios were equally reduced in both treatment groups after 13 weeks and after 1 year.

- Medical adherence at final clinic visit.
  Enalapril: 22% discontinued, 8% reduced dose
  Hydralazine: 29% discontinued, 10% reduced dose
  Isosorbide dinitrate: 31% discontinued, 10% reduced dose

- Average dose of enalapril 15 mg, hydralazine 199 mg, isosorbide dinitrate 100 mg

- No difference in frequency of hospitalization for CHF or other cardiac reasons.

Conclusions: "The similar two-year mortality in the hydralazine-isosorbide dinitrate arms in our previous Vasodilator-Heart Failure Trial (26%) and in the present trial (25%), as compared with that in the placebo arm in the previous trial (34%), and the further survival benefit with enalapril in the present trial (18% mortality on enalapril) strengthen the conclusion that vasodilator therapy should be included in the standard treatment for heart failure. The different effects of the two regimens (enalapril and hydralazine-isosorbide dinitrate) on mortality and physiologic endpoints suggests that the profile of effects might be enhanced if the regimens were used in combination."

A.   The Effect of Enalapril on Mortality and the Development of Heart Failure in Asymptomatic Patients with Reduced Left Ventricular Ejection Fractions[4]

Objective: "To determine whether an angiotensin-converting-enzyme inhibitor, enalapril, could reduce mortality, the incidence of heart failure, and the rate of related hospitalizations in patients with ejection fractions of 0.35 or less who were not receiving therapy for heart failure."

Methods: A total of 4228 patients with asymptomatic left ventricular dysfunction were randomly assigned to receive enalapril or placebo in a double-blind fashion. Patients with LVEF$\leq$ 35% and who were not receiving diuretics, digoxin, or vasodilators for the treatment of heart failure were eligible. Patients were allowed to receive diuretics for hypertension, digoxin for current or past atrial fibrillation, or nitrates for angina. Eligible patients were subjected to a three-week run-in period, during which they were given enalapril for the first week and placebo for the remainder; those who had no evidence of overt heart failure at the end of this run-in period were entered into the Prevention Trial. Patients were randomly assigned to receive enalapril at an initial dose of 2.5 mg twice daily, which was gradually increased to 10 mg twice daily unless side effects developed, or a matching placebo.

Results: (average follow-up 37.4 months):

- Enalapril reduced total mortality by 8% (P = 0.30). The difference was entirely due to a reduction in deaths due to cardiovascular causes (12% reduction, P = 0.12).

- Among the deaths from cardiovascular causes, the difference in mortality between groups was observed mainly in terms of those classified as due to progressive heart failure (4% vs. 5%, P = 0.10).

- Enalapril reduced the combined endpoint of death or hospitalization for new or worsening heart failure (24.5% vs. 20.6%, risk reduction, 20%; 95% confidence interval, 9 to 30%; P < 0.001).

- The median length of time to the first hospitalization for heart failure was 13.2 months in the placebo group vs. 27.8 months in the enalapril group.

- More patients were hospitalized more than once for worsening heart failure in the placebo group (4.8% vs. 2.7%, risk reduction by enalapril 44%; 95% confidence interval 23 to 59%; P < 0.001)

- Median length of time to the development of heart failure was 8.3 months in the placebo group vs. 22.3 months in the enalapril group.

  √   Development of CHF (definition)

   1. Signs or symptoms of CHF
   2. Addition of diuretic, digoxin, vasodilator
   3. CHF hospitalization
   4. Progressive CHF causing death

Significant reductions in the incidence of heart failure were observed regardless of the definition of heart failure used.

- Risk of death increased substantially following the development of clinical CHF
  CHF: Enalapril 24.4% vs. Placebo 27.6%
  NO CHF: Enalapril 12.1% vs. Placebo 11.5%

Differences in mortality rates after development of clinical CHF may have been blunted by the fact that 40.9% of the patients in the placebo group who had heart failure subsequently received an angiotensin-converting-enzyme inhibitor.

- The relative risk of death at one year among those who were hospitalized, as compared with those who were not hospitalized, was 4.6.

- 24% of patients in the enalapril group and 27% in the placebo group had stopped taking blinded medication by the end of the study. The final mean daily dose of enalapril among all randomized patients was 12.7mg (among those taking enalapril, the mean daily dose was 16.7mg). 8% of patients in the enalapril group and 45% in the placebo group permanently discontinued the study medication because of side effects.

Conclusions: "The angiotensin – converting – enzyme inhibitor enalapril significantly reduced the incidence of heart failure and the rate of related hospitalizations, as compared with the rates in the group given placebo, among patients with asymptomatic left ventricular dysfunction. There was also a trend toward fewer deaths due to cardiovascular causes among the patients who received enalapril."

II. POST MYOCARDIAL INFARCTION

A. High risk patients (depressed LVEF, clinical signs CHF) with late onset, long-term administration of an ACE-inhibitor

i.   **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).[7]

Hypothesis: Long-term administration of Captopril to survivors of acute myocardial infarction who have baseline left ventricular dysfunction without overt heart failure requiring vasodilator therapy will reduce mortality, lessen deterioration in cardiac performance, and improve clinical outcome.

Methods: Within 3 to 16 days after myocardial infarction, 2231 patients with ejection fractions of 40% or less, but without overt heart failure or symptoms of myocardial ischemia, were randomly assigned to receive double-blind treatment with either placebo or Captopril (target dose 50 mg TID) and followed for an average of 42 months. If required, revascularization had to be performed prior to randomization. Nineteen patients were excluded due to ischemic discomfort (3 pts) or symptomatic hypotension (16 pts) following an open label test dose of 6.25 Captopril.

Results:

- Mortality from <u>all causes</u> was significantly reduced in the Captopril group (228 deaths, or 20%) as compared with the placebo group (275 deaths, or 25%); the reduction in risk was 19% (95% confidence interval, 3 to 32 %; P= 0.019).

- Regarding death from cardiovascular cause (84% of all deaths), the reduction in risk was 21% (95% confidence interval 5 to 35%; P=0.014). Noncardiac death was evenly distributed between both groups.

    - Mortality due to progressive heart failure (cardiac transplant, death during hospitalization for CHF, recent deterioration in clinical status attributed to CHF) was reduced 36% (38 vs. 58 deaths, 95% confidence interval, 4 to 58%; P=0.032)

- Patients randomly assigned to receive Captopril were less likely to develop CHF requiring open-label ACE-inhibition (11% vs. 16%, respectively; reduction in risk, 37%; 95% confidence interval, 20 to 50%; P<0.001).

- Need for open label ACE-inhibitor predicted poor outcome (37% mortality vs. 20% mortality, P<0.001).

- With Captopril therapy, the proportion of patients who required hospitalization for CHF was reduced (14% vs. 17%; risk reduction, 22%; 95% confidence interval, 4 to 37%; P=0.019).

    - Development of CHF requiring hospitalization was an indicator of poor prognosis. Among the patients with this degree of heart failure, 47% died during the trial, whereas among the patients not hospitalized for heart failure, 18% died (P<0.001).

- Captopril reduced the risk of recurrent myocardial infarction, fatal or nonfatal by 25% (95% confidence interval, 5 to 40%; P=0.015).

- 90% of those in the placebo group and 79% of those in the Captopril group reached the target dose of 150 mg/d after randomization.

Conclusions: "In patients with asymptomatic left ventricular dysfunction after myocardial infarction, long-term administration of Captopril was associated with an improvement in survival and reduced morbidity and mortality due to major cardiovascular events. These benefits were observed in patients who received thrombolytic therapy,

aspirin, or beta-blockers, as well as those who did not, suggesting that treatment with Captopril leads to additional improvement in outcome among selected survivors of myocardial infarction".

ii. **Effect of Ramipril on Mortality and Morbidity of Survivors of Acute Myocardial Infarction with Clinical Evidence of Heart Failure (AIRE)[8].**

Hypothesis: "Patients with acute myocardial infarction complicated by clinical evidence of heart failure will live longer if they receive long-term Ramipril treatment, initiated between the second and ninth days after infarction."

Methods: 2006 patients with clinical evidence of heart failure following acute MI were randomly allocated to receive double-blind treatment with placebo or Ramipril, target dose 5 mg BID, and followed for a minimum of 6 months (average 15 months). Heart failure post MI was defined as evidence of pulmonary venous congestion with interstitial or alveolar edema on at least 1 chest x-ray, post-tussive rales extending at least 1/3 up in the absence of chronic lung disease, or an S_3 with persistent tachycardia. Clinical evidence of heart failure could be transient. Patients with NYHA Class IV CHF, hemodynamic instability, ongoing ischemia or CHF resistant to digitalis, diuretics, and vasodilators were excluded. Objective evidence of significant LV systolic dysfunction was not required.

Results:

- Ramipril reduced <u>all cause</u> mortality by 27% (17% vs. 23%; 95% confidence interval 11% to 40%; P=0.002). Survival curves diverged as early as 30 days.

- Ramipril reduced the development of the first validated secondary event (death, progression to severe resistant heart failure, reinfarction, or stroke) by 19% (95% confidence interval, 5% to 31%; P=0.008).

  - No differences were observed with respect to the development of stroke or recurrent MI.

- Clinical benefit was consistent across subgroups (age, sex, prior MI, angina, HTN, thrombolysis, aspirin, β-blocker, digoxin, nitrates, and calcium antagonists).

- Relatively large withdrawal rate: 352 premature withdrawals from the Ramipril group and 318 from the placebo group.

Conclusions: "Oral administration of Ramipril to patients with clinical evidence of either transient or ongoing heart failure, initiated between the second and ninth day after myocardial infarction, resulted in a substantial reduction in premature death from all causes. This benefit was apparent as early as 30 days and was consistent across a range of subgroups."

iii. **A Clinical Trial of the Angiotensin-Converting-Enzyme Inhibitor Trandolapril in Patients with Left Ventricular Dysfunction after Myocardial Infarction (TRACE).[9]**

Objective: "TRACE was designed to determine whether patients who have left ventricular dysfunction soon after myocardial infarction benefit from long-term oral ACE-inhibition."

Methods: 6676 consecutive patients with 7001 myocardial infarctions confirmed by enzyme studies were screened. Of these patients, 2606 patients had echocardiographic evidence of LV systolic dysfunction (LVEF $\leq$ 35%). On days 3 to 7 after infarction, 1749 LVEF $\leq$ 35%) patients were randomly assigned to Trandolapril or placebo. (1 mg qd, titrated up to 2 mg qd on day 3 and then to 4 mg qd after 4 weeks). Evidence of clinical heart failure was not required. Patients with cardiogenic shock or absolute need for ACE-inhibitors were excluded. The duration of followup was 24-50 months.

Results:

- Trandolapril reduced <u>all cause</u> mortality (34.7% vs. 42.3%, relative risk of death 0.78; 95% confidence interval, 0.67 to 0.91, P=0.001).

- Trandolapril also reduced the risk of death from <u>cardiovascular causes</u> (relative risk 0.75; 95% confidence interval, 0.63 to 0.89; P=0.001).

- Trandolapril reduced sudden death, as defined by death within 1 hour of symptoms (relative risk, 0.76; 95% confidence interval, 0.59 to 0.98; P=0.03).

- Progression to severe heart failure (heart failure death, CHF hospitalization, need for open label ACE-inhibitor) was less frequent in the Trandolapril group (relative risk, 0.71; 95% confidence interval, 0.56 to 0.89; P=0.003).

- Unlike that observed with Captopril in SAVE, Trandolapril did not significantly reduce the risk of recurrent myocardial infarction (fatal or nonfatal).

- The favorable impact of Trandolapril on mortality was preserved in all subgroups (age, sex, AWMI, previous MI, Killip Class, diuretic, thrombolytics, aspirin, β-blockers, angina, nitrates).

- Survival curves diverged as early as 1 month.

Conclusions: "Long-term treatment with Trandolapril in patients with reduced left ventricular function soon after myocardial infarction significantly reduced the risk of overall mortality, mortality from cardiovascular causes, sudden death, and the development of severe heart failure."

B. Broad-inclusion, early-onset and short administration of an ACE-inhibitor.

i.   **Effects of the Early Administration of Enalapril on Mortality in Patients with Acute Myocardial Infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II).[10]**

Hypothesis: Intravenous Enalapril when combined with conventional therapy and initiated within 24 hours after the onset of an acute myocardial infarction will improve 6 month survival.

Methods: 6090 patients presenting within 24 hours of the onset of chest pain and pathologic ECG (ST segment elevation in 2 or more contiguous leads or new Q waves) and/or cardiac enzyme elevation and blood pressure above 100/60 mmHg were randomly assigned to treatment with either Enalapril or placebo, in addition to conventional therapy. Patients with hemodynamic compromise requiring vasopressor agents for support, untreated third-degree AV block, severe valvular stenosis or a clear indication for treatment with ACE-inhibitors were excluded. Any treatment with thrombolytic agents or IV beta-blockers was to be completed before administration of Enalapril or placebo. Treatment was started with an IV infusion of 1 mg Enalapril diluted in 100 ml of 0.9% saline or an infusion of placebo to run over a 2 hour period. The infusion was stopped if the systolic blood pressure fell below 90 mmHg or the diastolic pressure fell below 60 mmHg, but it could be restarted after stabilization of hemodynamics. Six hours after the infusion was completed, therapy was continued with oral enalapril or placebo (2.5 mg BID on day 2, 5 mg BID on day 3, 10 mg qd on day 4, then 20 mg qd thereafter).

A nonsignificant trend indicating an increase in mortality among patients with early hypotensive reactions prompted the Safety Committee to recommend that the minimal blood-pressure limit for enrollment be increased to 105/65 mmHg and that the duration of infusion be increased to 3 hours. If the systolic pressure fell by more than 30 mmHg or if the BP decreased below 100/60 mmHg, the infusion could not be restarted.

If heart failure developed, patients were treated with digitalis, diuretics and nitrates. If ACE inhibition was considered necessary, the patient was withdrawn from the study.

Results:

- The trial was stopped early based on a very high probability that the null hypothesis would apply, and on concern about a possible adverse effect among elderly patients with early hypotensive reactions.

- Heart failure had occurred before the index infarction in 6% and heart failure was associated with the index infarction in 18%.

- All cause mortality: Placebo 9.4% vs. Enalapril 10.2%, P=0.26. Relative risk of Enalapril treatment 1.10 with a 95% confidence interval of 0.93 to 1.29.

- Enalapril did not impact on the rate of subsequent reinfarction or hospitalization for heart failure.

- Mortality essentially the same among patients with previous infarction, anterior infarction, history of CHF, acute pulmonary edema or heart failure after admission. Mortality somewhat higher in elderly patients (≥ 70 yrs) given Enalapril (placebo vs. Enalapril, 15% vs. 17%; P=0.07).

- Treatment was changed because of worsened heart failure in 30% of the placebo group and 27% of the Enalapril group (P>0.006).

- Long-term mortality was higher among patients given Enalapril who had hypotension after the first dose (17%) than among the other patients given this agent (9.3%) or among patients given placebo who had hypotension (12%).

Conclusions: "Enalapril therapy started within 24 hours of the onset of acute myocardial infarction does not improve survival during the 180 days after infarction."

ii.   **GISSI-3: Effects of Lisinopril and Transdermal Glyceryl Trinitrate Singly and Together on 6-Week Mortality and Ventricular Function after Acute Myocardial Infarction.[11]**

Objective: "To assess the efficacy of Lisinopril, transdermal glyceryl trinitrate (GTN), and their combination in improving survival and ventricular function after acute myocardial infarction."

Methods: Patients were eligible if they had chest pain, onset < 24 hours prior to admission, accompanied by elevation or depression of the ST segment of at least 1mm in one or more peripheral leads of the ECG or of at least 2 mm in one or more precordial leads. The diagnosis of definite acute MI required two of the following criteria to be satisfied: typical ischemic chest pain; new appearance of abnormal Q waves with evolutionary ST and T wave changes on serial ECG tracings; or a rise in total CPK to at least twice the upper limit of normal. 19,394 patients were randomly assigned 6 weeks of oral lisinopril (5 mg initial dose and then 10 mg daily after 48 hours) or open control as well as nitrates. (intravenous GTN x 24 hours, 5 μg/min with an increase 5-20 μg/min every 5 minutes for the first 30 minutes until the systolic BP fell by at least 10%, as long as BP systolic > 90 mmHg. After 24 hours, patients were treated with GTN 10 mg/d patch) or open control. 2D ECHO was done at the 6-week clinic visit to assess segmental left ventricular systolic function. Patients with severe heart failure, Killip Class 4, systolic blood pressure $\leq$ 100 mmHg were excluded.

Results:

- Lisinopril, started within 24 hours from AMI symptoms, decreased <u>all cause</u> mortality by 11% (6.3% vs. 7.1%, odds ratio 0.88 [95% CI 0.79 – 0.99]) at 6 weeks. The survival curves separated early (day 0-1) and continued to diverge throughout the next 6 weeks.

- Lisinopril treatment led to a reduction in the 6-week combined outcome measure of mortality and severe ventricular dysfunction (LVEF < 35% or 45% or more myocardial segments with evidence of injury on ECHO), odds ratio 0.90 [95% CI 0.84 – 0.98]; P=0.009.

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- Lisinopril did not reduce the 6-week incidence of clinical CHF.

- The main reasons for Lisinopril withdrawal were hypotension (9.7%) and renal function impairment (2.0%).

- 13.3% took non-study ACE-inhibitors for hypertension or heart failure.

- Six-weeks treatment with transdermal GTN did not produce a significant benefit in terms of total mortality or the combined endpoint of mortality/severe LV dysfunction.

- 57.1% of controls received some form of nitrate therapy during the 6-week followup period, most often to treat angina.

- No significant differences between GTN-allocated and control patients were noted in terms of reinfarction, revascularization procedures, persistent hypotension, or renal dysfunction.

- The combination of lisinopril and transdermal GTN produced a 17% total mortality reduction versus control (6.0% vs. 7.2%) odds ratio 0.83 [95% CI 0.70-0.97], P = 0.021) and a favorable impact on the combined endpoint of mortality/severe LV dysfunction (14.8% vs. 17.0%, odds ratio 085 [95% CI 0.76 – 0.94], P = 0.0028).

Conclusions: Lisinopril, either alone or in combination with GTN, improves 6-week survival and ventricular function when administered within 24 hours of the onset of acute myocardial infarction.

iii. The Effect of the Angiotensin-Converting-Enzyme Inhibitor Zofenopril on Mortality and Morbidity after Anterior Myocardial Infarction (SMILE).[12]

Hypothesis: Six-week administration of Zofenopril, administered within 24 hours after the onset of acute anterior MI, in patients not undergoing thrombolysis will reduce the short-term and long-term incidence of death or severe heart failure.

Methods: A total of 1556 patients were enrolled within 24 hours after the onset of symptoms of acute anterior myocardial infarction (progressive changes in the ST segments or T waves in at least 2 contiguous precordial leads with or without new abnormal Q waves), ineligible for thrombolysis because of late admission or contraindications to systemic fibrinolysis. Eligible patients received either placebo or Zofenopril (target dose 30 mg BID) for 6-weeks. Patients were excluded from the study if they were in cardiogenic shock, had a systolic blood pressure below 100 mmHg, had a history of CHF, or a serum creatinine > 2.5.

Results:

- The incidence of death or severe CHF (any 3 of the following: S_3, bilateral pulmonary rales, radiographic evidence of pulmonary edema or peripheral edema, despite the concomitant administration of digoxin, diuretics, and vasodilators and necessitating open-label treatment with an ACE-inhibitor) was significantly reduced in the Zofenopril group (7.1% vs. 10.6%, risk reduction 34% [95% CI, 8 to 54%; P = 0.018]) at 6 weeks.

    - The reduction in risk was 46% (95% CI, 11 to 71%; P=0.018) for severe CHF and 25% (95% CI, -11 to 60%; P=0.19) for death.

- After one year of observation, the mortality rate was significantly lower in the Zofenopril group (10% vs14.1%, RR 29% [95% CI 6-51%; P=0.011]).

- Target daily dose of 60 mg was achieved in 86.1% of patients in the placebo group and 78% of those in the Zofenopril group.

Conclusions: Treatment with Zofenopril significantly improved both short-term and long-term outcome when this drug was started within 24 hours after the onset of acute myocardial infarction and continued for 6 weeks.

iv. 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.[13]

Objective: To evaluate the effects of 1 month of Captopril, 1 month of isosorbide mononitrate, and 24 hours of intravenous magnesium on mortality and major morbidity in a wide range of patients, low-risk as well as high-risk, with definite or suspected acute myocardial infarction.

Methods: "Patients were eligible if they were thought to be within 24 hours of the onset of symptoms of suspected acute MI with no clear indications for, or contraindications to, any one of the study treatments – Captopril, isosorbide mononitrate, or magnesium." Patients who were given intravenous or other non-study nitrate for just a few days could still be entered (use of non-study nitrates was recorded at randomization). The protocol did not mandate any exclusion criteria but left it to the physician's discretion. The presence of cardiogenic shock, RV infarction, or persistent hypotension were suggested exclusions. Antiplatelet and fibrinolytic therapy was recommended. Study treatment was generally to be started immediately after the early lytic phase. Magnesium was begun within 2 hours of the start of the fibrinolytic in about 50% of all randomized patients and in about 75% of those randomized within 0-6 hours of the onset of their symptoms. Half of all patients were allocated randomly to receive 1 month of oral Captopril (6.25 mg initial dose, 12.5 mg 2 hours later, 25 mg 10-12 hours later and then 50 mg twice daily for 28 days) and half received placebo. Half of all patients were allocated randomly to receive 1 month of oral controlled-release isosorbide mononitrate (Imdur: 30 mg initial dose, 30 mg 10-12 hours later, and then 60 mg each morning for 28 days) and half received placebo. Half of all patients were allocated randomly to receive 24 hours of IV magnesium sulfate (8 mmol initial bolus injection over about 15 min followed by 72 mmol in about 50 ml infused over 24 hours) and half to open control.

Results:

- Infarction was confirmed in 92% of all randomized patients and 4% suffered a subsequent reinfarction during their hospital stay.

- 4% of patients had cardiogenic shock and 17% were reported to have heart failure.

- Captopril reduced 5 week mortality post MI (7.19% vs. 7.69%, RR 7% [95% CI 13% to 1% reduction, P=0.02]). The benefits of early Captopril treatment persisted for at least 1 year with a small non-significant benefit after the first month.

- The proportional reductions in 5-week mortality with Captopril was fairly similar in the presence and in the absence of the other study treatments (i.e., mononitrate or magnesium) suggesting there were no strong interactions between the effects of the different study treatments.

- Patients with an entry systolic blood pressure < 100 mmHg tended to fare worse with Captopril (14.2% mortality on Captopril vs. 12.4% on placebo, P=NS).

- Captopril did not influence reinfarction rates.

- Captopril did not reduce in-hospital heart failure.

- A small excess of cardiogenic shock was reported with Captopril (5 excess per 1000; P< 0.01), predominantly on days 0-1, but there was no significant difference in deaths attributed to cardiogenic shock.

- Study treatment was terminated due to hypotension more frequently in patients receiving Captopril (10.0% vs. 4.8%; 52 excess per 1000, P < 0.0001), about half of which was observed on days 0-1. This was observed more frequently in patients who presented with entry systolic pressure < 100 mmHg.

- Isosorbide mononitrate did not affect 5 week or 1 year mortality, even after controlling for open-label nitrate use. No particular subgroup appeared to benefit either.

- Isosorbide mononitrate did not influence reinfarction rates.

- IV magnesium led to a 6% proportional increase in 5-week mortality which was not statistically significant. Followup to 1 year did not indicate any further divergence or convergence of the survival curves. Whether or not the patient received thrombolytic therapy did not influence the neutral effects of magnesium on survival.

- IV magnesium was associated with small but significant increases in heart failure, cardiogenic shock, deaths attributed to cardiogenic shock, bradycardia, and hypotension severe enough to require termination of study treatment.

Conclusions: Captopril therapy started early in acute MI prevents about 5 deaths per 1000 in the first month, with somewhat greater benefits in higher risk patients (previous MI, heart failure, anterior MI, tachycardia). The benefit achieved at 1 month persists for at least the first year. Intravenous magnesium was ineffective. Oral nitrate therapy was found to be safe but did not produce a clear reduction in 1 month mortality.

v. **Oral Captopril Versus Placebo among 13,634 Patients with Suspected Acute Myocardial Infarction: Interim Report From the Chinese Cardiac Study (CCS-1).[14]**

Objective: To evaluate the effect of Captopril on 4 week mortality when given within 36 hours after the onset of suspected myocardial infarction.

Methods: Eligible patients presented within 36 hours of the onset of symptoms of suspected acute MI (with or without ST elevation on initial ECG). Patients were excluded if they had a clear indication or contraindication to ACE-inhibition or if they had persistent hypotension. Half of all patients were randomized to 4 weeks of oral Captopril (6.25 mg initial dose, 12.5 mg 2 hours later if blood pressure did not fall profoundly, and then to 12.5 mg TID) and half to matching placebo.

Results:

- Captopril reduced 4-week mortality (9.05% vs. 9.59%, absolute reduction of 5.3 fewer deaths per 1000 patients, P = NS).

- Captopril was associated with a significant excess of persistent hypotension (16.3% Captopril vs. 10.8% placebo; 55 excess per 1000; P < 0.0001), mostly early after the start of treatment, with a trend towards an increased mortality in patients with entry systolic blood pressure < 100 mmHg. A non-significant excess of cardiogenic shock was reported with Captopril without an increase in inotrope use or death.

Conclusions: Though not statistically significant, Captopril therapy started within 36 hours of MI prevents about 5 deaths per 1000 in the first month following MI.

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