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Titration of Angiotension Converting Enzyme Inhibition in Acute Anterior Infarction:

The Healing and Early Afterload Reducing Therapy (HEART) Study.

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Left ventricular (LV) remodeling post myocardial infarction (MI) has been recognized as a major mechanism for cardiovascular mortality and morbidity.[1] Treatment with an angiotensin-converting enzyme (ACE) inhibitors appears to attenuate the process of LV remodeling and dysfunction[2] and is associated with improved survival when these agents were administered within 3 to 16 days to selected post MI patients with LV dysfunction (SAVE, TRACE)[3,4] or with clinical heart failure (AIRE).[5] However, the lack of survival benefit from treatment within 24 hours of MI reported in the CONSENSUS II study[6] raised the concern that early (within 24 hours) administration of ACE inhibitors especially in elderly patients and the development of hypotension might have negative impact on survival. On the other hand, subsequent trials (GISSI-3, ISIS-4, CCS-1) which have enrolled a very large number of unselected patients have demonstrated that early treatment with ACE inhibitors is associated with improved survival.[7-9]

The Healing and Early Afterload Reducing Therapy (HEART) Study[10] was a study designed to provide mechanistic insights into the effects and potential safety associated with the administration of ACE inhibitors within 24 hours of an anterior MI.

Clinical events (death, development of heart failure, recurrent MI, unstable angina requiring non-elective cardiac catheterization) were relatively infrequent (15% overall) and were similar among the treatment groups.

The incidence of developing systolic blood pressure ≤ 90 mm Hg in the full dose (34%) and low dose (28%) were significantly higher than placebo (16%, p=0.002) and there was no difference between low and full dose. No relationship between hypotension and cardiovascular events was reported.

Data from the HEART study therefore indicate that an upward-titrated dose of ACE inhibitor can be administered to patients within 24 hours of an anterior MI with reasonable safety.

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The study was not powered to assess survival but rather to study LV topography and size. The study began in 1993 at the time when the results of the aforementioned large scale trials were not yet published. The original objective was to randomize 600 patients within 24 hours of anterior MI, a high risk patient population, to receive (1) placebo, i.e. to delay ACE inhibitor therapy for 14 days; (2) low dose ramipril (0.625 mg qd); or (3) titration within 24 hours to full dose ramipril (1.25 to 10 mg qd). However, by 1994 it became apparent that up to 50% and 70% of the lives saved in ISIS-4 and GISSI-3 respectively occurred at the first week and subsequent meta-analysis of these large scale trials suggested that a survival benefit was present as early as first 2 days after randomization.[10] The executive committee of the study therefore believed that it was no longer appropriate to withhold ACE therapy for 14 days and enrollment was therefore terminated. Accordingly, 352 patients (117 placebo, 116 low dose ramipril, and 119 full dose ramipril) were enrolled.

The demographic characteristics of the 3 study groups were quite comparable and also reflected current practice trends. Thus, 73% of the patients received thrombolytic therapy and 15% had primary angioplasty. Aspirin and ß-blockers were used in 91% and 69% respectively. Eleven percent of the placebo-treated patients had a decline of systolic blood pressure of ≥20 mm Hg. Surprisingly, over 20% of the patients who received the low dose, a dose perceived at the time of the design of the study to be hemodynamically inactive, experienced a systolic blood pressure decline of the same magnitude and this incidence was comparable to those who received the full dose. By day 3, blood pressure of the full dose group (113/69 mm Hg) was significantly lower than placebo group (108/64 mm Hg, p=0.02) and marginally lower than the low dose group (112/67 mm Hg, p=0.08).

Death at 90 days was less than 4% although the study was not powered to assess differences in these events.

Comparing the 80 patients who had systolic blood pressure of ≤90 mm Hg at any time after any dose and the 272 patients who did not, there was no difference in the incidence of death (2.5 versus 2.2%) or congestive heart failure (1.3 versus 4.0%) suggesting that adverse clinical events were not enhanced by the development of systolic hypotension of ≤90 mm Hg.

Left ventricular topography and size were assessed by echocardiography. All three study groups developed progressive ventricular enlargement. Left ventricular cavity size increased to a similar extent in the three groups although there was a trend for a lesser increase in the ramipril-treated groups. Left ventricular systolic size increased by the first day and tended to recover afterwards in the ramipril-treated groups but not in the placebo-treated group. Recovery of systolic dysfunction and wall motion abnormalities occurred in the first 14 days but more so in the ramipril-treated patients.

However, even low dose of ACE inhibitors, which are believed to be hemodynamically inactive, can lower arterial blood pressure. Hypotension as defined by a systolic blood pressure of ≤90 mm Hg occurs at any dose of the ACE inhibitor but does not appear to be accompanied by adverse clinical events although one should exert some caution in interpreting these data since the study was not powered to measure adverse events. Finally, early administration of an ACE inhibitor is associated with a trend for improvement in LV function.

Summary of ACE Inhibitor Trials Post-MI

	DRUG	NO. OF PTS.	INCLUSION CRITERIA	START AND F/U DURATION	MAIN RESULT RE: MORTALITY REDUCTION
Consensus II[6]	enalapril	6,090	MI	< 1 day to 6 mo.	not significant (stopped early)
SAVE[3]	captopril	2,231	MI, EF < 40%	3-16 days to 24-60 mo.	↓ 19% (p=0.014)
AIRE[5]	ramipril	2,006	MI, Clinical CHF	3-10 days to 6-30 mo.	↓ 27% (p=0.002)
SMILE[12]	zofenopril	1,556	Anterior MI, non-thrombolysed	6-24 hr to 12 mo.	↓ 18% (p=0.001)
TRACE[4]	trandopril	1,749	MI, wall motion index ≤ 1.2	3-7 days to 24 mo.	↓ 24% (p=0.198)
GISSI-3[7]	lisinopril	19,394	MI	under 1 day to 42 days	↓ 11% (p=0.03)
ISIS-4[8]	captopril	58,050	MI	under 1 day to 1 month	↓ 7% (p=0.02)
CCS-1[9]	captopril	13,634	MI	36 hr to 1 mo.	no significant reduction

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Data from the HEART study compliment those from the major trials such as GISSI-3, ISIS-4. The composite data from these trials indicate that treatment with ACE inhibitors in MI may be started with 24 hours after careful assessment of clinical status and consideration of contemporary therapy such as thrombolysis, aspirin and ß-blockers.

Angiotensin Converting Enzyme Inhibitors (ACE I) post-MI: