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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

Early Angiotensin-converting Enzyme (ACE) Inhibitor Therapy for Myocardial Infarction

The Benefit of Lisinopril in the GISSI-III Trial

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Neurohormonal activation is a key pathophysiologic aspect of CHF. Extensive experience with ACE inhibitors, especially in the setting of significant LV dysfunction, strongly favours treatment in prolonging survival and improving symptoms. Results of GISSI-III add to that experience in patients treated early after acute MI. More recent analyses of GISSI-III demonstrate safety and efficacy of early initiation of treatment, especially when a patient's hemodynamic profile is taken into account. These observations are made stronger by very favourable cost-effectiveness analysis.

Introduction

Favourable modulation of neurohormonal activation in patients with CHF has been achieved with angiotensin-converting enzyme (ACE) inhibition. Initially, striking beneficial results of prolonged ACE inhibitor therapy on mortality were demonstrated in the CONSENSUS-1 Trial.[1] Gratifying experience in patients with advanced congestive heart failure (CHF) was followed by a series of trials in patients with less severe heart failure or asymptomatic left ventricular (LV) dysfunction of any origin[2,3,4] or secondary to acute myocardial infarction (MI).[5,6,7] Consistent with earlier experimental data, the latter studies showed that ACE inhibition clearly produces favourable effects on mortality and LV function in selected high-risk post-MI populations. More recent large-scale trials have addressed the role of ACE inhibition in relatively unselected patients[7-12] in whom treatment was initiated during the first day of MI. Overall, these trials indicate a small but definite benefit of about 5 lives saved for every 1,000 patients treated (Table 1).

ACE Inhibition Early Post-MI: GISSI-III

At the recent 46th Annual Scientific Session of the American College of Cardiology in Anaheim, California, the GISSI-III Investigators presented additional information regarding the role of lisinopril in acute myocardial infarction.[13] GISSI-III was a multicentre randomized clinical trial designed to assess the efficacy of lisinopril, transdermal nitroglycerine, and their combination in improving survival in ventricular function after acute MI.[14] Between June 1991 and July 1993, 19,394 patients were randomized from 200 coronary care units in Italy. Eligible

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Table 1: Summary of Large Trials (>1000 patients) of ACE Inhibitors in Acute Myocardial Infarction

	Study	n=	Inclusion	ACE	Timing of Randomization	Follow up (weeks)	Mortality Reduction: Absolute (Relative)	Lives saved/ 1000 pts treated
Non-acute Long-term	SAVE	2231	RNA LVEF<40%	Captopril	3-16 (11) days	168	4.2% (19%)	42
	AIRE	2006	Clinical CHF	Ramipril	2-9 (5) days	60	5.7% (27%)	57
	TRACE	1749	Echo	Trandolapril	3-7 (4) days	108	7.6% (22%)	70
Acute Short-term	CONSENSUS II	6090	All MI	IV Enalaprilat Enalapril	<24 hrs	24	-.8% (-10%)	-1
	GISSI-III	19394	All MI	Lisinopril	<24 hrs	6	0.8% (11%)	8
	ISIS-IV	58050	All MI	Captopril	<24 hrs	5	0.4% (6%)	5
	CCS-1	13634	All MI	Captopril	<36 hrs	4	0.3% (3%)	5
	SMILE	1556	Anterior MI no thrombolysis	Zofenopril	<24 hrs	6	1.8% (22%)	18

patients presented within 24 hours of symptom onset and had no clear indications for or against the use of study treatment. In a 2x2 factorial design, patients were randomly assigned to receive 6 weeks of oral lisinopril (5 mg initial dose followed by 10 mg daily) or open control as well as nitrates (intravenous for the first 24 hours, followed by transdermal nitroglycerine, 10 mg daily) or open control. Lisinopril, started within 24 hours of MI symptom onset, produced significant reductions in overall mortality (odds ratio (OR) 0.88 [95% confidence intervals (CI) 0.79-0.99]) and in the combined outcome measure of mortality and severe ventricular dysfunction (OR 0.90 [95% CI 0.84-0.98]). The systematic administration of transdermal nitroglycerine did not show any independent effect on the same outcome measures (OR 0.94 [95% CI 0.84-1.05] and 0.94 [0.87-1.02]). The favourable effect of lisinopril alone (or with nitroglycerine) was also clear in the predefined high-risk populations (elderly patients and women) for the combined endpoint. Importantly, these findings were obtained in a population intensively exposed to evidence-based medical therapy (e.g., thrombolysis, 72%; beta blockade, 31%; and aspirin, 84%).

The GISSI-III investigators published 6-month follow-up data and demonstrated that the beneficial effect of early lisinopril use was carried over this time frame, even after study drug discontinuation (as per protocol) at 6 weeks.[14] Among patients randomized to lisinopril, 18.1% died or developed LV dysfunction versus 19.3% of those randomized to no lisinopril (p=0.03).

Safety and Efficacy in Relation to Dose

Since concerns exist regarding the safety of early vasodilation after MI,[8] the GISSI-III investigators evaluated the impact of the study protocol-prescribed doses of lisinopril.[13] The target daily lisinopril dose by protocol was 5 mg for days one and two, then 10 mg up to 42 days. Patients with systolic blood pressure 120 mm Hg on days one through three could be given 2.5 mg. The mean lisinopril dose on day one was 4.2 ±1.6 mg; day two, 4.6 ±2.2 mg; day three, 6.3 ±3.5 mg; day four, 6.8 ±3.7 mg; discharge (up to 14 days), 7.2 ±4.2 mg.

Using a multivariate logistic model to evaluate factors most likely to influence the prescribed dose of lisinopril, Latini et al[13] found that a history of hypertension (OR 1.44 [95% CI 1.29-1.60]) was associated with 5 mg per day use on days one through four. In contrast, patients with systolic blood pressure at study entry of 100 to 120 mm Hg (OR 0.44 [95% CI 0.40-0.47]) and those age >70 years (OR 0.85 [95% CI 0.76-0.95]) received lower doses. Similarly, a history of hypertension (OR 1.73 [95% CI 1.56-1.92]) was a significant predictor of use of 10 mg of lisinopril at the time of discharge. Patients with systolic blood pressure at entry of 100-120 mm Hg (OR 0.65 [95% CI 0.61-0.70]) and women (OR 0.87 [95% CI 0.77-0.97]) received lower doses. Other factors, such as Killip class at entry, use and type of thrombolysis, use of intravenous beta blockers, diabetes mellitus, and use of beta blockers or calcium channel blockers at discharge, did not independently influence the lisinopril dose.

Latini et al[13] concluded that early lisinopril was safe and effective when used at relatively low doses, in particular, in the first several days following myocardial infarction. In addition, dose level appeared to be mainly influenced by systolic blood pressure at the time of MI presentation and a history of prior hypertension.

Compliance and Safety Profile of Early Lisinopril Use

Compliance with lisinopril treatment was reasonable, with 82.4% of patients still on treatment at 6 weeks after randomization. The highest daily dose suggested by the study protocol (10 mg) was given to 47.5% of patients with 28.3% receiving 5 mg daily and only 3.2% receiving the lowest dose (2.5 mg daily). The main reasons for lisinopril withdrawal were hypotension (9.7%) and renal function impairment (2%). It is important to note, however, that these higher rates of hypotension and renal function impairment did not result in an increase in mortality or in severe renal failure.

Cost-effectiveness of Early Lisinopril Use in Acute MI

In an earlier presentation at the American College of Cardiology, Franzosi et al presented a cost-effectiveness analysis on the early use of lisinopril in acute MI based on the GISSI-III trial.[15] Data on the use of medical resources was prospectively collected during hospitalization and charges were converted to costs. On the basis of the 6-week survival analysis of the GISSI-III study (7.5 ±3.6 lives saved per thousand patients treated with lisinopril), the comparative cost-effectiveness ratio for the use of lisinopril was US $2,300 per premature death avoided. A sensitivity analysis was conducted to examine the effects of varying the estimated absolute reduction in mortality of 7.5 lives saved per thousand patients throughout the 95% confidence intervals (0.4 -14.6 lives saved per thousand patients treated). The cost-effectiveness ratios could therefore vary from US $43,300 (0.4 lives saved) to as little as US $1,200 (14.6 lives saved) per premature death avoided. Thus, the cost-effectiveness of lisinopril treatment compares very favourably with that of other interventions for acute myocardial infarction (e.g., tPA: 8 lives saved per thousand patients treated, cost-effectiveness = US $32,000 per life saved).

Conclusions

In all patients with acute myocardial infarction who have no important contraindications (hypotension with systolic blood pressure <100 mm Hg), bilateral renal artery stenosis, renal failure, or history of cough or angioedema due to previous treatment with ACE inhibitors), ACE inhibitors such as lisinopril should be given within 24 hours after the onset of symptoms and should be continued for 6 weeks. If the patient has any evidence of left ventricular dysfunction (LVEF <40% or grade 3 on echocardiography), with or without symptoms, the therapy should be maintained for at least three years and, probably, indefinitely. Whether all patients should be treated with long-term (>6 weeks) ACE inhibitors after myocardial infarction is being tested in large-scale randomized trials.

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