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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Scientific Update™

69TH SCIENTIFIC SESSION OF THE AMERICAN HEART ASSOCIATION, NOVEMBER 10-13, 1996, NEW ORLEANS, LOUISIANA

What Is the Optimal Dose of Angiotensin Converting Enzyme Inhibitors in Patients with Left Ventricular Dysfunction?

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Introduction

The angiotensin converting enzyme (ACE) inhibitors are established therapeutic agents for patients with heart failure[1-3] as well as patients post myocardial infarction (MI) complicated by left ventricular (LV) dysfunction[4] or clinical heart failure.[5] Most placebo-controlled trials using ACE inhibitors in the treatment of heart failure or post MI have utilized fairly large doses,[1-5] yet physicians continue to use small doses of ACE inhibitors in clinical practice without knowledge whether these small doses are therapeutically equivalent to those employed in the large trials. There are some data to suggest that high doses of ACE inhibitors are superior to low doses in producing hemodynamic improvement and increasing exercise tolerance in patients with heart failure.[6,7] However, the impact of low dose versus high dose of ACE inhibitors on the progression of disease and therefore survival in patients with heart failure or patients post MI is unclear.

The study of low dose ramipril

The question of whether low dose ACE inhibition is equally effective as a higher dose in attenuating the increase in LV volume and mass in patients post MI was addressed in a paper presented at the recent 69th Scientific Sessions of the American Heart Association in New Orleans, Louisiana.[8] In this study, 29 patients with LV ejection fraction <40% were randomized within 5 to 8 days of their first Q-wave MI to low dose (2.5 mg QD) or an upward titrated dose (5-10 mg QD) of the ACE inhibitor ramipril. Cine magnetic resonance (MR) imaging was performed 5 days and 3 months after MI.

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Left ventricular volume and mass were calculated from the serial short axis cine-MR slices using Simpson's rule. The 2 study groups were comparable in age, the proportion of anterior MI (75 versus 79%, low versus titrated dose), the use of thrombolytic agents and primary angioplasty (80 versus 71%) as well as treatment with ß-blockers, nitrates and calcium channel blockers.

Compared to baseline, systolic blood pressure at 3 months was unchanged in both the low dose (108±8 to 112±10 mm Hg) and the titrated dose group (117±21 to 112±22 mm Hg). Diastolic pressure was also unaltered in both groups. There were equal but non-significant increases in LV end diastolic volume in both groups. LV mass declined by similar magnitude in the low dose (82±18 to 70±14 gm/m^2, p=0.01) and the titrated dose group (99±28 to 85±24 gm/m^2, p=0.008). As a result, LV mass/volume ratio declined similarly in the low dose (1.25±0.21 to 1.01±0.14, p=0.0005) and the titrated dose group (1.56±0.26 to 1.17±0.19, p=0.005). LV wall thickness declined modestly but significantly in both groups. Of interest, LV ejection fraction increased significantly only in the low dose group (33±7 to 41±8%, p=0.005) and not in the titrated dose group (37±3 to 39±9%). Based on these data, the investigators concluded that low and titrated dose of ramipril produce a similar remodeling effect in patients post MI without changes in blood pressure.

Discussion of the study

These data need to be interpreted with caution for two reasons. First, although encouraging, the small sample size of the study exposes the results to the risk of type-II error. Second, the 3 month followup of the study is relatively short compared to other studies and it is possible that differences in response to ACE inhibition in the low versus titrated dose group would become discernable had the followup been extended to beyond three months. Indeed, the results of the current study contrast with those of the Healing and Early Afterload Reducing Therapy (HEART) study,[9] which was presented in the last American Heart Association meeting and discussed in a previous issue of *Scientific Update*. In HEART, patients were randomized within 24 hours of an anterior MI to receive 1) placebo, i.e. delayed ACE inhibitor for 14 days, 2) low dose ramipril (0.625 mg QD), or 3) titration within 24 hours to full dose ramipril (10 mg QD). An important observation in HEART was that lowering of arterial pressure occurred even in the low dose group and was more pronounced in the titrated group. There are many possible explanations for the differences in observations in the 2 studies and these differences underscore the importance of comparing study groups over a long period of time on hard endpoints in order to address the

question whether low dose is equally effective as high dose ACE inhibition in attenuation of progression of disease in patients with LV dysfunction. One such study is ongoing. The Assessment of Treatment with Lisinopril And Survival (ATLAS) is an international multicenter trial comparing low dose versus high dose ACE inhibitor lisinopril in patients with heart failure. To date, close to 3000 patients with LV ejection fraction <30%, New York Heart Association functional class II to IV symptoms have been randomized to receive lisinopril 2.5 to 3.0 mg + placebo QD or lisinopril 30 mg QD. The primary endpoint is total mortality. The expected date of completion of the study is September 1997 and the results of the study will be presented in the American College of Cardiology meeting in the Spring of 1998.

Conclusion

ACE inhibitors have become one of the most exciting and important additions to the medical management of left ventricular dysfunction and heart failure (Table 1). This study is an important contribution to the evolving experience with this group of drugs in our continuous attempt to generalize observations from research studies to everyday practice of medicine. Whether low dose ACE inhibition can become an accepted treatment remains uncertain although the results of this study are encouraging. Until further confirmation of these results (and a longer experience) is available, clinicians should attempt their best to administer ACE inhibitors at dose ranges comparable to those employed in the secondary prevention trials.

Table 1: 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[10]	enalapril	6,090	MI	< 1 day to 6 mo.	not significant (stopped early)
SAVE[4]	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[11]	zofenopril	1,556	Anterior MI, non-thrombolysed	6-24 hr to 12 mo.	↓ 18% (p=0.001)
TRACE[12]	trandopril	1,749	MI, wall motion index ≤ 1.2	3-7 days to 24 mo.	↓ 24% (p=0.198)
GISSI-3[13]	lisinopril	19,394	MI	under 1 day to 42 days	↓ 11% (p=0.03)
ISIS-4[14]	captopril	58,050	MI	under 1 day to 1 month	↓ 7% (p=0.02)
CCS-1[15]	captopril	13,634	MI	36 hr to 1 mo.	no significant reduction

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