SMH ST. MICHAEL'S HOSPITAL Cardiology
UNIVERSITY OF TORONTO
A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

Role of Long-term Angiotensin-converting Enzyme Inhibition Post-myocardial Infarction and the Effect on Fibrinolysis

Presented by: A.S. HALL, LEEDS, UK, AND D.E. VAUGHAN, NASHVILLE, TN, USA

Fifth World Congress on Heart Failure
May 11-14, 1997, Washington, DC

Reported by:
GORDON W MOE, MD

Angiotensin-converting-enzyme (ACE) inhibitors reduce morbidity and mortality in patients post-myocardial infarction (MI)[1-4] and have become an established mode of therapy in the secondary prevention of MI.[5] However, most studies of ACE inhibitors post-MI to date have involved relatively short-term follow-up and it is unclear how long clinicians should continue with ACE inhibitors in patients post-MI. Furthermore, several studies have suggested that ACE inhibitors reduce the incidence of angina and MI in patients with low ejection fraction. The mechanisms for the anti-ischemic effect of ACE inhibitors are unclear. Two recent presentations discussed below address these issues.

Long-Term Angiotensin-converting Enzyme Inhibition Post-myocardial Infarction

Information regarding the long-term follow-up of the use of ACE inhibitors in patients post-MI is now available. The results of the Acute Infarction Ramipril Efficacy (AIRE) study extension (AIREX) were recently presented by Dr. A.S. Hall from the University of Leeds, United Kingdom, during the Fifth World Congress on Heart Failure held in Washington, DC.

AIRE was an international, randomized, placebo-controlled study involving 2006 post-MI patients from 114 centres in 14 countries. Their post-MI course was complicated by clinical evidence of congestive heart failure. Patients were randomized between days 3 and 10 post-MI to ramipril or placebo.[2] Recruitment for AIRE began in 1989 and terminated on March 1, 1993 – six months after the 2000th patient was accepted. The minimum follow-up was 6 months; the average, 15 months. Ramipril treatment was associated with a 27% reduction of all-cause mortality.

AIREX was a three-year extension of AIRE that involved 603 patients from AIRE recruited from 30 centres in the United Kingdom. In this cohort, physicians were allowed to treat patients with ACE inhibitors as clinically indicated at the time of conclusion of AIRE but

St. Michael's Hospital
30 Bond St., Suite 701A
Toronto, Ontario M5B 1W8
Fax: (416) 864-5330

continued to be blinded as to the original randomization. The placebo (301 patients) and ramipril (302 patients) groups were comparable in all demographic characteristics. Left ventricular ejection fraction was 42.8±14.5% in 83 of placebo-treated and 44.8±17.1% in 75 of ramipril-treated patients. Thrombolysis was administered in 67.8% and 78.5% of patients, respectively.

AIREX was concluded on March 1, 1996. The minimum follow-up was 42 months. There was 100% follow-up. The primary endpoint was all-cause mortality. Intention-to-treat analysis was used. At the end of 5 years, 117 of 301 placebo-treated patients and 83 of 302 ramipril-treated patients had died. The relative risk reduction was 36% (95% CI 15-52%, p=0.002), which amounts to 11 lives saved for every 100 patients treated. Within the all-cause mortality reduction, there was a 37% reduction (95% CI 8-51%, p=0.017) of death due to recurrent MI. Table 1 compares results of AIREX to those from previous trials.

To increase the sensitivity of the analysis, exhaustion analysis of the primary treatment effects was also carried out. In this type of analysis, the data from the early period after randomization were eliminated in an attempt to ensure that an apparently long-term benefit was not accounted for by a positive effect present mainly at the early period. Accordingly, in the one month exhaustion analysis, i.e. the survival analysis began at one month post -randomization, the relative risk reduction was still 36% (95% CI 13-53%). Indeed, the 6- and 12- month exhaustion analysis revealed a persistent relative risk reduction of 37% (95% CI 11-55%, p=0.009) and 35% (95% CI 4-56%, p=0.029), respectively. Dr. Hall added that based on calculations from AIREX's 5-year follow-up, which show that 9 patients need to be treated to save one life, the cost of life saved is £2000 (based on U.K.treatment costs of £230 per patient), which compares favourably to many other treatment modalities.

The Effect of ACE Inhibition on Fibrinolysis in Post-MI Patients

Several studies have shown that ACE inhibitors reduce the incidence of recurrent MI[1] or recurrent angina[3]

Table 1: Comparative overview of six major angiotensin-converting enzyme inhibitor clinical trials: key efficacy outcomes

	Clinical trial						
	Nonacute, long term				Acute, short term		
Key efficacy outcomes	SAVE	AIRE	AIREX	ISIS-4	CCS-1	SMILE	GISSI-3
RRR for death (%) (P value)	19 (0.019)	27 (0.002)	36 (0.002)	7* (0.02)	5.6 (0.3)	25 (0.19)	11† (0.03)
Approximate time to separation of cumulative mortality/survival curves	1 year	1 month	5 year follow-up	14-35 days	–	1 month	1-2 days
Overall one-year mortality rate (%)	10††	16††	5 year follow-up	12††	–	10	–
Lives save/1000 treated	42	57	110	4.9	5.3	18	8
Lives saved/1000 treated/week	0.23	0.88	0.42	1.25	1.33	3.02	1.33
Number of patients needing to be treated to save one life	23	17	9	204	189	55	125

*For captopril versus controls (no captopril); †For lisinopril versus controls (no lisinopril); ††Interpolated from mortality figures. – Data unavailable; RRR Relative risk reduction

Adapted from Huckell et al.

following MI. The mechanism of this beneficial effect is unclear. At the same meeting in Washington, DC, Dr. D.E. Vaughan of Nashville, TN, presented evidence linking the renin-angiotensin system with myocardial ischemia. He also provided evidence for a favourable effect of ACE inhibitors on fibrinolytic balance. Population studies have shown that the incidence of myocardial infarction increases with plasma renin activity, even at same levels of blood pressure. Furthermore, data from SAVE and SOLVD indicate that ACE inhibitors reduce the incidence of myocardial infarction and unstable angina in patients with depressed left ventricular function.[1,6]

The renin-angiotensin system may play a role in myocardial ischemia by promoting atherosclerosis and vasoconstriction and inducing thrombosis. In cholesterol-fed rabbits, ACE inhibitors reduce lipid staining in blood vessels. In atherosclerotic plaques, there is increased expression of plasminogen activator inhibitor-1 (PAI-1), which inhibits the generation of plasmin from plasminogen and therefore reduces the degradation of fibrin. Some evidence suggests that the ACE regulates fibrinolytic balance. For example, angiotensin II (Ang II) induces mRNA expression of PAI-I in cultured endothelial cells, and this action is possibly mediated by a product of Ang II, i.e. angiotensin IV, via a non-classical receptor subtype that is neither AT_1 nor AT_2. Treatment with ACE inhibitors reduces the vascular mRNA expression of PAI-1. Administration of Ang II increases PAI-1 antigen but has no effect on tissue-type plasminogen activator (t-PA). The stimulatory effect of Ang II on PAI-1 antigen is abolished by treatment with ACE inhibitors and Ang II blockers. On the other hand, bradykinin, which is enhanced by ACE inhibition, increases t-PA.

The effect of ACE inhibitors on fibrinolytic balance was investigated in a substudy of the Healing and Early Afterload Reducing Therapy (HEART) Study,[7] which was reported in an earlier edition of *Scientific Update*. In this study, patients were randomized within 24 hours post-MI to receive placebo or low-dose or full-dose ramipril. In the substudy, plasma levels of PAI-1 and t-PA were obtained at baseline and 14 days after randomization. Treatment with ramipril was associated with a dose-dependent decrease in plasma PAI-1 levels. The ratio of plasma PAI-1 to t-PA increased with time in the placebo group, but was unchanged in the ramipril group. These data therefore suggest that treatment with ACE inhibitors results in a favourable effect on fibrinolytic balance and that this may be one of the mechanisms responsible for the beneficial effect of these agents on angina and recurrent MI.

Conclusion

Data from AIREX suggest that patients who benefit from ACE inhibitors early after MI will benefit from long-term treatment with ACE inhibitors for at least 5 years after MI. Furthermore, a large body of experimental and clinical evidence supports an anti-ischemic role for ACE inhibitors. As concluded in closing of the meeting by Dr. C.H. Hennekens, Boston MA, the number of lives saved by ACE inhibitor therapy (57/1000 patients treated in AIRE, 110/1000 for AIREX) compares favourably with those saved by aspirin (20-30/1000), thrombolysis (30/1000), and ß-blockers (15/1000). The value of ACE inhibitors as agents for the secondary prevention of MI appears to be indisputable.

References

1. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geitman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Werthimer JH, Hawkins CM, on behalf of the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1992, 327:669-77.
2. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure *Lancet* 1993, 342:821-28.
3. Survival of Myocardial Infarction Long-Term Evaluation (SMILE) study. The effect of the angiotensin-converting enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med* 1995, 332:80-5.
4. Pedersen CT, Kober L, Carlsen J, on behalf of the TRACE Study Group. *Am Heart J* 1996, 132:235-43.
5. Huckell V, Berstein V, Crowell, Dagenais GR, Higginson LA, Isserow S, Laramee P, Liu P, McCans JL, Orchard RC, Preqitt R, Quinn BP, Samson M, Turazza F, Warnica JW, Wielgosz A. Angiotensin-converting enzyme inhibition in myocardial infarction - Part 2: clinical issues and controversies. *Can J Cardiol* 1997, 13:173-82.
6. Yusuf S, Pepine CJ, Garces C, Pouleur H, Salem D, Kostis J, Benedict C, Rousseay M, Bourassa M, Pitt B. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fraction *Lancet* 1992, 340:1173-8.
7. Pfeffer MA, LaMotte FS, Arnold JM, Rouleau JL, Goldman S, Greaves S, Klein M, Lamas GA, Lee RT, Lindpainter KC, Meapace FJ, Rapaport E, Ridker PM, Rutherford JD, Solomon SD, Timis GC, Warnica JW, Henekens CH. Titration of angiotensin-converting enzyme inhibition in acute anterior infarction: the Healing and Early Afterload Reducing Therapy (HEART) study. *Circulation* 1995, 92:I19.