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™

Update on clinical trials: ACE inhibitors, vitamin E and cardiovascular events, moxonidine, and anti-thrombotic therapy in heart failure

A Report from the Hotline Sessions of the XXIst Congress of the European Society of Cardiology

Barcelona, Spain, August 28-September 1, 1999

Reported and discussed by:
Gordon Moe, MD

The HOPE study

The Heart Outcome Prevention Evaluation (HOPE) study is an international study designed to assess the effect of the angiotensin-converting enzyme inhibitor (ACEI) ramipril and vitamin E as an antioxidant on cardiovascular events in patients at high risk for vascular disease. The ACEIs have been shown to prolong survival in patients with heart failure.[1,2] In these patients with reduced left ventricular ejection fraction, ACEIs also reduce myocardial infarctions (MI) and unstable angina.[3] In patients with coronary artery disease, ACEI improves endothelial function.[4] In patients post-MI, ACEIs reduce the incidence of recurrent MIs and cardiac revascularizations.[5] These data therefore suggest that ACEIs may exert anti-ischemic effects and modify atherosclerosis.

Vitamin E has antioxidant and antiplatelet effects. Observational studies suggest that increased consumption of vitamin E and other antioxidants in the form of dietary supplements is associated with a lower risk of cardiovascular events.[6,7] However, definitive data from large-scaled randomized-controlled trials addressing hard clinical endpoints are still lacking. Accordingly, the principal aim of HOPE was to examine the effect of the ACEI ramipril (up to 10 mg/day) and vitamin E (400 IU/day) on cardiovascular events. The primary endpoint of HOPE was a cluster endpoint of cardiovascular (CV) death, MI, and stroke. The secondary outcomes included revascularization, unstable angina, heart failure hospitalization, diabetes complications, and cancers.

Design

A 2x2 factorial design of ramipril versus placebo and vitamin E versus placebo was used. The inclusion criteria included age >55; any evidence of vascular disease, (ie, coronary artery disease [CAD]), stroke, and peripheral vascular disease (PVD); and diabetes mellitus plus one other risk factor. The principal exclusion criteria were history of heart failure or known reduced left ventricular ejection fraction and acute ischemic event within 4 weeks. Over a period of 4.6 years, 9,541 patients were followed. The study was powered to detect a relative risk reduction (RRR) ≥12% overall and RRR ≥15-25% in the key prospectively-defined subgroups in the both the primary and secondary outcomes. Two hundred and sixty seven hospitals from 19 countries participated in the study.

The study began recruitment in January 1994. The last patient was recruited in May 1995. The study was terminated early by the Data and Safety Monitoring committee on March 23, 1999 because of clear benefit demonstrated on the ramipril arm. The investigators were notified on April 17, 1999. Closeout visits were completed by mid-August. Vital statistics were ascertained on 99.3% of the patients. The data presented in this report represent data accumulated up to August 25, 1999.

Results

The mean age of the 9541 patients was 65.9 years. Seventy-three percent were male, 81% had CAD, 52.8% had history of MI, 10.8% had stroke or transient ischemic attacks, 38.3% had diabetes, and 46.5% had hypertension. The results of the vitamin E arm of the study indicate no effect on the primary and secondary cardiovascular outcomes. The primary outcome, a composite endpoint of CV death, MI and stroke, was 16 and 15.4% for the vitamin E and placebo arms, respectively, RR =1.04, 95% CI =0.94-1.15, p=0.42. However, there was a suggestion of a significant reduction in the hospitalization and deaths from cancer, RR=0.83, 95% CI=0.78-0.99, p=0.048, and the incidence of all cancers, RR=0.84, 95% CI=0.71-0.99, p=0.034.

St. Michael's Hospital, 30 Bond St., Suite 9-004, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5330

The topics presented in *Cardiology Scientific Update* are independently determined and the content authored exclusively by physician-members of the Division of Cardiology, St. Michael's Hospital. This publication is made possible by unrestricted funding from the publisher, Snell Medical Communication Inc., which has received educational grants from the pharmaceutical industry in support of this work.

Table 1: Effect of ramipril on primary outcome

	Ramipril n=4645	Placebo n=4652	RR	95% CI	p
MI, stroke, CV death	13.9%	17.5%	0.78	0.70-0.86	0.000002
CV death	6.0%	8.0%	0.75	0.64-0.87	0.0002
MI	9.8%	12.0%	0.80	0.71-0.91	0.0005
Stroke	3.3%	4.8%	0.68	0.56-0.85	0.0002

The key positive finding of HOPE is the significant reduction of cardiovascular events by the ACEI ramipril. Data for the primary outcome and its components are shown in Table 1. There was a significant reduction in the primary outcome as well as individual components of this composite primary outcome. Total mortality was also significantly reduced, RR=0.83, CI=0.74-0.94, p=0.0037. Of the prespecified secondary outcomes of unstable angina, heart failure hospitalizations, revascularization, hospitalization, and deaths from cancer and all cancers, there was a significant reduction in heart failure hospitalization, RR=0.84, CI=0.64-0.97, p=0.0257 and revascularization, RR=0.85, CI=0.77-0.95, p=0.0015. Total frequency of heart failure was reduced, RR=0.78, CI=0.67-0.9, p=0.0005, as was the composite endpoint of CV death and all heart failure, RR=0.77, CI=0.69-0.86, p=0.000003, or CV death and heart failure hospitalization, RR=0.77, CI=0.68-0.88, p=0.0003. Furthermore, the significant reduction in primary endpoint was maintained in the 4676 patients (ramipril, n=2339; placebo, n=2337) with known normal left ventricular ejection fraction, RR=0.73, CI=0.63-0.84, p=0.00002, suggesting the positive finding was not due to contamination with patients with impaired heart function. Significant reduction in primary outcome and total mortality was also observed in the 3578 patients with diabetes. Furthermore, diabetes-related events such as overt nephropathy, use of laser for retinopathy, and new microalbuminuria, were significantly reduced in both diabetic, as well as nondiabetic patients. Finally, the impact of ramipril on the primary outcome was present regardless of age, gender, the presence or absence of hypertension, CAD, cerebrovascular disease, PVD, and microalbuminuria.

Treatment with ramipril was associated with only a modest (3.3 mm Hg) reduction of systolic arterial pressure. Extrapolating data from previous hypertension trials, this modest reduction of blood pressure was expected to be associated with only a 13% reduction in stroke and a 5% reduction of MIs. The 32% reduction in stroke and the 21% reduction in MIs observed in HOPE would therefore suggest that the beneficial effects of ramipril were not mediated by its blood pressure-lowering effect alone.

Summary

In summary, the HOPE study demonstrates that in patients with vascular disease or those with diabetes and one other risk factor, the ACEI ramipril reduces the incidence of a range of cardiovascular events, as well as total mortality. The data for ramipril on primary outcome essentially amounts to treating only 6 patients for 4.5 years to reduce one composite cardiovascular event. The findings of a lack of an effect of vitamin E on cardiovascular events is important and the possible impact on the development of new cancers offers some hope after the neutral results reported by trials such as the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC study)[8] and GISSI Prevention. To address these issues further, an extension of HOPE, the HOPE-TOO (Heart Outcomes Prevention Evaluation-The Ongoing Outcome) study has been proposed. The plan is to continue two-year follow up of the HOPE patients, with continued blinding for vitamin E and assessment of outcomes with ramipril unblinded. In addition, patients may be re-randomized to a combination of folic acid and vitamin B versus placebo with a proposed follow-up of 5 years.

The MOXCON study

It has long been known that in patients with heart failure, the degree of activation of the sympathetic nervous system correlates with mortality.[9] Recently, ß-blockade therapy has been demonstrated to reduce mortality in patients with mild to moderate heart failure.[10-12] An alternative approach to intervene the sympathetic nervous system activation is to block central sympathetic outflow by stimulating central I_1-imidazoline receptors. SR moxonidine is a relatively selective I_1-imidazoline receptor agonist.[13] Preliminary study from the pilot MOXSE study has demonstrated that 12-week therapy of SR moxonidine produces a dose-dependent reduction in plasma norepinephrine level of up to 50% in patients with moderate heart failure.

The primary aim of the SR Moxonidine for Congestive Heart Failure (MOXCON) study was therefore to evaluate the effect of SR moxonidine on all-cause mortality in patients with heart failure and New York Heart Association (NYHA) functional class II to IV symptoms. The key secondary outcomes were all-cause mortality and heart failure hospitalizations, heart failure hospitalizations, cardiovascular (CV) mortality, and the relationship between plasma norepinephrine and brain natriuretic peptide levels with the primary outcome.

Design

The study involved 425 sites from 17 countries in Europe and North America. The original plan was to recruit approximately 4540 patients with NYHA II to IV symptoms, driven by an event rate of 724 deaths from all-cause. The projected enrollment period was 1.5 years with a minimum follow-up of one year. Patients were randomized

Table 2: Baseline demographic data of patients in MOXCON	
Demographic variables	**Percent of all patients**
Age >65	52
Male	79
Caucasian	84
NYHA functional class II, III, IV	42, 53, 4

to placebo or SR moxonidine, with a forced titration from 0.25 mg bid to 1.5 mg bid orally. It should be noted that at the initiation of the study, results of the pilot MOXSE trial were not yet available and the investigators were prepared to revise the dose as MOXCON proceeded, pending the results of MOXSE.

Results

The MOXCON study was terminated abruptly on March 12, 1999 due to an excess of deaths observed in the SR moxonidine treatment group. The last study visit took place on July 21 and the data were locked on August 13,1999. At the time of termination, 2612 patients had been screened and 1938 were randomized. However, only 1933 patients had received at least one dose of the study medication. Therefore, these 1933 patients – 944 placebo and 989 SR moxonidine – constituted the intent-to-treat population for the purpose of data analysis. The demographics were evenly distributed among the two treatment groups and the composite data are therefore presented on Table 2. In addition, baseline ejection fractions, 25% for placebo versus 26% for SR moxonidine, supine plasma norepinephrine levels, 439±253 versus 458±285 pg/ml, systolic blood pressure, 128±20 versus 125±19 mm Hg, and heart rate, 75±11 versus 75±10 beats/min, were also comparable between the two groups. Over 80% of patients were on ACEIs and diuretics.

The protocol was amended in January 1999 to permit the concomitant use of ß-blockers, amounting to only 11 patients (1.2%) in the placebo group and 14 patients (1.4%) in the SR-moxonidine group. However, on March 1, 1999, it was noted 66 patients (24 in placebo and 42 in SR moxonidine group) had died. On March 8, the number of deaths increased to 71 patients (25 in placebo, 46 in SR moxonidine). The study was terminated on March 12. By August 13, the data lock date, 105 of the 1933 intent-to-treat patients had died. Ninety patients died during the trial. Eighty-two deaths occurred during the dose optimization and maintenance phase of the trial and these patients were included in the primary analysis. Primary analysis of the mortality data is shown in Table 3. There was an excess of deaths in the SR moxonidine group. Sudden death was the most frequent cause of death by treatment group in these patients. Although the numbers were relatively small, the number of deaths from all other causes was consistently higher in the SR moxonidine group. Other non-fatal CV endpoints as adjudicated by the clinical endpoints committee are shown in Table 4. There was a higher incidence for hospitalization due to worsening heart failure and acute Mis in the SR moxonidine group. Plasma norepinephrine levels were obtained on 1180 patients. Limited serial data were available due to the early termination of the study. However, a significant reduction from baseline in plasma norepinephrine levels in the SR moxonidine group relative to the placebo group was observed. The excess mortality in the SR moxonidine group could not be attributed to a failure of decline in plasma norepinephrine levels.

Table 3: Primary analysis of the cause of death		
	Placebo (n=944)	**SR moxonidine (n=989)**
Total mortality	29 (3.1%)	53 (5.4%)
Sudden death	11 (1.2%)	26 (2.6%)
Pump failure	9 (0.9%)	15 (1.5%)
Acute MI	3 (0.1%)	5 (0.5%)
Primary arrhythmia	2 (0.2%)	4 (0.4%)

Table 4: Non-fatal cardiovascular endpoints		
	Placebo (n=944)	**SR moxonidine (n=989)**
Hospitalization for heart failure	57 (6.0%)	72 (7.3%)
Hospitalization for acute MI	6 (0.6%)	17 (1.7%)

Summary

Despite a systematic review of the available data, the reasons for the excessive mortality and non-fatal CV endpoints remain unclear. Nonetheless, the sobering results of the MOXCON study provide, for the first time, suggestive evidence that excessive suppression of the sympathetic nervous system may be detrimental in patients with severe heart failure.

The WASH study

Systemic anticoagulation plays a major role in the management of patients who have sustained a large MI and those with atrial fibrillation.[14,15] However, its role in the broader patient population with heart failure and left ventricular systolic dysfunction without MI or atrial fibrillation is unclear. Recent analyses of data from large-scale heart failure trials have suggested that there is a reduction in the risk of death in patients treated with aspirin and warfarin.[16,17] However, data from prospective randomized controlled trials are lacking.

Design

The Warfarin ASA Study in Heart Failure (WASH) study was a pilot study designed to compare the effects of ASA, warfarin, versus no antithrombotic therapy, on cardiovascular events in patients with heart failure. The study involved 17 centres from the United Kingdom and 3 centres in the United

Table 5: The WASH Study – Outcome data

	Warfarin n= 89	ASA n=91	No therapy n=99
Primary outcome: deaths, MI's, stroke	22 (24%)	29 (32%)	27 (27%)
Total mortality	22 (25%)	27 (30%)	21 (21%)
Stroke	0	2 (2%)	2 (2%)
Death and CV hospitalizations	14 (16%)	28 (31%)	23 (23%)
All-cause hospitalizations[1]	42 (47%)	58 (64%)	48 (48%)
Heart failure hospitalizations[2]	18 (20%)	22 (24%)	19 (19%)

[1] p=0.05, [2] p=0.035

States. The design was prospective open-label blinded-endpoint. Recruited patients had, in the investigator's opinion, congestive heart failure, left ventricular ejection fraction <35% (US), or left ventricular end-diastolic diameter >30 mm/m^2 BSA and fractional shortening <28% (UK). The proposed three-arm study aimed to recruit 3600 patients and to detect a 20% difference in primary outcome. No formal power calculation was conducted. The primary outcome was a composite endpoint of all-cause mortality, non-fatal MIs, and non-fatal stroke. The secondary outcome was death or CV hospitalization (for heart failure, MIs, stroke, or bleeding). The study was discontinued after 279 patients (89 in the warfarin group, 91 in the ASA group and 99 in the no antithrombotic therapy group) were recruited with 626 patient-years exposure. Seventy percent of the patients had NYHA functional class II symptoms, 60% had coronary artery disease, close to 50% had prior use of ASA. Twenty-nine patients (30%) in the control group (no antithrombotic therapy), 25 patients (28%) in the warfarin group, and 17 patients (19%), p=0.16, discontinued the study drug. The median INR for the warfarin group was 1.6.

Results

The outcome data are shown in Table 5. The three groups were comparable in most of the outcomes except for a higher incidence for hospitalizations in the ASA group, driven mostly by a higher rate for heart failure hospitalizations. There were 5 major hemorrhages, one in the ASA group and 4 in the warfarin group. There were 24 episodes of gastrointestinal serious adverse events compared to 7 episodes in the warfarin group and 3 episodes in the control group.

Summary

The investigators concluded that ASA had an adverse impact on heart failure hospitalizations and was associated with a higher incidence of gastrointestinal side effects. Warfarin appeared to reduce non-fatal CV events. However, data for this study were very difficult to interpret given its open-label design, inadequate sample size, and high withdrawal/cross-over rate. Indeed, the study was terminated because it was perceived that clinicians would no longer support being on no anti-thrombotic therapy as a viable option in patients with heart failure. These limitations notwithstanding, this study addressed an important and controversial issue. The ultimate answer to the question of the use of antithrombotic therapy in patients with heart failure will await the completion of the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) study, a Veteran Administration cooperative study that has just been initiated. Approximately 4500 patients will be randomized to double-blind aspirin 162 mg daily, double-blind clopidogrel 75 mg daily, and open-label warfarin titrated to an INR of 2.5-3.0, with a primary composite endpoint of total mortality, non-fatal stroke, and non-fatal MI.

References

1. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-1435.
2. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. *N Engl J Med* 1991;325:293-302.
3. Yusuf S, Pepine CJ, Garces C, et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992;340:1173-1178.
4. Mancini GBJ, Henry GC, Macaya C, et al. Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease. *Circulation* 1996;94:258-265.
5. Rutherford JD, Pfeffer MA, Moye LA, et al. Effects of captopril on ischemic events after myocardial infarction. Results of the survival and ventricular enlargement trial. SAVE investigators. *Circulation* 1994;4:1731-1738.
6. Hoffman RM, Garewal HS. Antioxidants and the prevention of coronary artery disease. *Arch Intern Med* 1995;155:241-246.
7. Hennekens CH, Gaziano JM. Antioxidants and heart disease: epidemiology and clinical evidence. *Clin Cardiol* 1993;4:I10-3.
8. Rautalahti MT, Virtamo JR, Taylor PR, et al. The effects of supplement with alpha-tocopherol and beta-carotene on the incidence and mortality of carcinoma of the pancreas in a randomized, controlled trial. *Cancer* 1999;86:37-42.
9. Cohn JN, Levine B, Olivari M, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;311:819-823.
10. Packer M, Bristow M, Cohen J, et al. The effect of carvedilol on survival and hospitalization for cardiovascular complications in patients with chronic heart failure. *N Engl J Med* 1996;334:1349-1355.
11. CIBIS-II Investigators and Committee. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomized trial. *Lancet* 1999;353:9-13.
12. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). *Lancet* 1999;353:2001-2007.
13. Theodor R, Weimann H-J, Weber W, Michaelis K. Absolute bioavailability of moxonidine. *Eur J Drug Metab Pharmacokinet* 1991;16:153-159.
14. Laupacis A, Albers G, Dalen J, et al. Antithrombotic therapy in atrial fibrillation. Fourth ACCP Consensus Conference on Antithrombotic Therapy. *Chest* 1995;108: 352S-9S.
15. Cairns JA, Lewis HD, Meade TW, et al. Antithrombotic agents in coronary artery disease. Fourth ACCP Consensus on Antithrombotic Therapy. *Chest* 1995;108:380S-400S.
16. Al-Khadra AS, Salem DN, Rand WM, Udelson JE, Smith JJ, Konstam MA. Warfarin anticoagulation and survival: A cohort analysis from the studies of left ventricular dysfunction. *J Am Coll Cardiol* 1998;31:749-753.
17. Dries DL, Domanski MJ, Waclawiw MA, Gersh BJ. Effect of antithrombotic therapy on risk of sudden coronary death in patients with congestive heart failure. *Am J Cardiol* 1997;79:909-913.