University Heart Journal
Vol. 5, No. 1, January 2009

ORIGINAL ARTICLES

Safety and tolerability of Ramipril 10 mg in high risk Bangladeshi patients following the criteria of the HOPE study: A multi center open, non comparative study

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Abstract

Renin angiotensin aldosterone system plays an important role in the pathogenesis of cardiovascular events. ACE inhibitors are known to have a beneficial effect on atherosclerosis progression affecting multiple arterial territories of the body. Several outcome trials utilizing ACE inhibitors have shown reduction of death, NH and stroke in broad range of patients. HOPE study, the landmark trial using Ramipril, has shown beneficial effects in high risk patients using Ramipril 10mg/day in the western population.

The aim of the present study was to evaluate the safety and tolerability of Ramipril 10mg/day in Bangladeshi patients. The criteria for recruitment were similar to those of the HOPE study except age (45 years or older were included in the present study). The study showed that this target dose of Ramipril would be reached in Bangladeshi patients, as in the HOPE study, in order to achieve a full therapeutic effect. Lower incidence of adverse events and less distontinuation rate of the drug was encouraging. It is concluded from the study results that Ramipril at a dose of 10mg/day can be used in Bangladeshi patients with reasonable safety and are well tolerated.

Introduction and rationale

At the beginning of the 21 century, cardiovascular disease (CVD) accounted for nearly 50% of all deaths in developed countries and 25% of those in the developing world[1,2]. This global rise in CVD may be attributed to major risk factors like diabetes, smoking, hypertension, dyslipidaemia, physical inactivity and obesity. Epidemiological and experimental data suggest that the activation of the rennin angiotensin aldosterone system (RAAS) has an important role in the pathogenesis of cardiovascular (CV) events[3]. Increased tissue angiotensin converting enzyme (ACE) activity has been demonstrated in human coronary atherosclerosis[4]. ACE inhibitors are known to have a beneficial effect on atherosclerosis progression[3]. Long-term ACE inhibition has been shown to reduce atherosclerotic lesion areas in the aorta and in the carotid and coronary arteries in normotensive animal models of atherosclerosis[5]. In the Heart Outcomes Prevention Evaluation (HOPE) study ACEI, ramipril has been assessed in patients who were at high risk for cardiovascular events but who did not have left ventricular dysfunction or heart failure[6]. In this study, a total of 9297 high-risk patients aged 55 years or older who had evidence of vascular disease or diabetes with one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure were randomly assigned to receive ramipril (10 mg once per day orally) or matching placebo for a mean of five years. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes. The trial was a two-by-two factorial study evaluating both ramipril and vitamin E. Treatment with ramipril reduced the rates of death from cardiovascular causes (6.1% as compared with 8.1% in the placebo group; relative risk 0.74; $p<0.001$), myocardial infarction (9.9% vs. 12.3%; relative risk 0.80; $p<0.001$), stroke (3.4% vs.4.9% relative risk 0.68; $p<0.001$), death from any cause (10.4% vs. 12.2%; relative risk 0.84; $p=0.005$), revascularization

procedures (16.0% vs. 18.3 %; relative risk, 0.85; p=0.002), cardiac arrest (0.8% vs.1.3%; relative risk 0.63; p=0.03), heart failure (9.0% vs. 11.5%; relative risk 0.77; p<0.001), and complications related to diabetes (6.4% vs. 7.6%; relative risk 0.84; p=0.03). It was concluded that ramipril significantly reduces the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure.

The need for safety data in Bangladeshi patients

The HOPE study was conducted in countries of North America, Western Europe and Latin America. The subgroup of patients of Asian origin was too small to be analyzed separately.

In order to evaluate the applicability of these very promising results, this study was designed to evaluate safety and tolerability of Rampiril in Bangladeshi patients with the dosage used in the HOPE study, following similar criteria of patients' selection. Age limit was amended to 45 years and above due to lower age of patients with cardiovascular disease in Bangladesh.

Objectives

The aim of the study was to evaluate the safety and tolerability of ramipril 10mg/day in high-risk Bangladeshi patients, following the criteria of the HOPE study.

Patients and methods

1. Patients

Inclusion Criteria*:* Men and women aged 45 years or older, at high risk of developing a major cardiovascular event that had at least one of the following criteria.

(a) **Coronary artery disease (CAD) :** Previous myocardial infarction (MI), stable angina, unstable angina (UA) with documented multi-vessel coronary disease* or positive stress test (ST depression ≥ 2mm or a positive thallium), or multi-vessel percutaneous transluminal coronary angioplasty, multi-vessel coronary artery bypass graft-(CABG) , or multi-vessel coronary disease seen on angiography.

(b) **Peripheral vascular disease (PVD):** Previous limb bypass surgery or percutaneous trans-luminal angioplasty, previous limb or foot amputation, history of intermittent claudication with ankle/arm blood pressure ratio of 0.80 or lower in at least one side, significant stenosis (>50%) documented by angiography.

(c) **Previous stroke** (more than one month ago).

(d) **Diabetes** (insulin-dependent or non-insulin dependent) with one of the following cardiovascular risk factors (Diabetes +): Hypertension, (BP >160 mmHg systolic or >90 mmHg diastolic or on treatment); total cholesterol>5.2 mmol/L (>200 mg/dl); HDL cholesterol < 0.9 mmol/l (<35 mg/dl); current cigarette smoking; known microalbuminuria or any evidence of previous vascular disease.

(e) **Patients with stabilized heart failure** (at least for 4 weeks) with NYHA grade I to III were eligible.

Exclusion Criteria

(a) Exclusion criteria related primarily to absolute contra-indications for the use of ACEI, in accordance with the contra-indications, warnings and precautions of the package insert of ramipril in Bangladesh, and to the presence of other medical problems that would either interfere with participation in the trial or lead to the inability to complete the trial.

(b) **Drug use**: Inability to discontinue an on-going ACEI treatment (to switch to ramipril), or known hypersensitivity to ACEI.

(c) **Cardiovascular diseases**: Non stabilized or NYHA grade IV heart failure patients, hemodynamically significant primary valvular or outflow tract obstruction (eg. mitral valve stenosis, asymmetric septal hypertrophy, malfunctioning prosthetic valve), constrictive pericarditis, complex congenital heart disease, syncopal episodes presumed to be due to uncontrolled life-threatening arrhythmias (asymptomatic cardiac arrhythmias including ventricular tachycardia are not an exclusion criterion), planned cardiac surgery or angioplasty within 3 months (patient may be reconsidered for the trial after the procedure), cor pulmonale, heart transplant recipient.

(d) **Other conditions**: Significant renal disease defined as renal artery stenosis; creatine clearance <0.6 ml/min or serum creatinine>200 mEq/L (>2.26 mg/dl); overt nephropathy: ≥ 1 plus proteinuria on dipstick or urinary albumin excretion > 200 micrograms/minute (300 mg/24 hrs); hyperkalemia; K+ >5.5 mmol/L. Any other major non-cardiac illness expected to reduce life expectancy or interfere with study participation. Patient is simultaneously taking another experimental drug.

2. Therapeutic intervention

Under the normal practice condition patients was prescribed 2.5 mg of ramipril orally once daily for 14 days. Then (if compliance good, no side effects, no abnormal serum creatinine or potassium levels, no withdrawal of consent) the

* multivessel coronary artery disease is defined as >50% stenosis at least in two major coronary arteries. Patients at high risk of developing MI or stroke.

patient was prescribed 5 mg of ramipril orally once daily for 14 additional days, then was prescribed the maintenance therapy of 10 mg of ramipril orally once daily for 1 month (i.e., till the end of the study).

In patients with stable heart failure (NYHA grade I-III), the starting dose was 1.25mg orally once daily. After 7 days if the tolerability was good, the dosage was increased to 2.5mg once daily for 7 other days, then to 5mg once daily for 14 days, then if the tolerability was still good, to 10mg daily. This dose of 10mg was maintained for 1 month.

If an adverse event occurred and did not allow continuing the treatment at the prescribed dose, it was advised to reduce the dosage as follows: If dosage at 2.5mg/day, decrease to 1.25 mg/day; If dosage at 5mg/day, decrease to 2.5 mg/day; If dosage at 10mg/day, decrease to 5 mg/day. If it was not possible to stay at 10mg/day after titration of dosage according to the protocol then go back down to the highest well tolerated dosage.

After completion of the study, the patient was treated according to the decision of his physician (normally, the ramipril treatment was continued, at the same dosage)

For patients being switched from other ACEIs to ramipril, the dosage regimen of ramipril was titrated in steps as described above. It was well understood that the medication of other ACEIs should be stopped, and treatment with ramipril started and titrated up to the target dose of 10 mg once daily.

3. Methodology of the study

This was a multicentre, open label non comparative study with single group open assessment involving four investigational sites in Dhaka city targeted 1000 patients to be included. Ten investigators were co-ordinated by four study site coordinators, under the supervision of the Principal Investigator.

The participants were enrolled sequentially in the four hospitals (National Institute of Cardiovascular Diseases, Dhaka Medical College & Hospital, Bangabandhu Sheikh Mujib Medical University, Sir Salimullah Medical College & Hospital) in Dhaka city during October 2003 to September 2005.

On enrollment (visit-1:Wk-0) demographic data and detailed clinical history were taken and physical examination (including BP measurement) were made. Blood urea, serum creatinine and serum potassium of the patients were measured with standard procedure. All the data were entered in the case report form (CRF). All the patients were followed up at Wk-2 (visit-2), Wk-4 (visit-3), Wk-6 (visit-4), Wk-8(visit-5) and Wk-12(visit-6). Lab investigations were done at visit-6(Wk-12) as per protocol. Scheduled study site meetings were held regarding the progress of the patients' enrollment and validity of the data in case report forms (CRF).

Several levels of data checking were organized: at monitor, study site coordinators, statistician (who did the data management). The data of CRF was entered in computer by a data entry operator and analysis was done by a statistician using SPSS software.

4. Endpoints

The endpoints were the number of patients completed the study as per protocol; number of patients reached the 10mg/day dose level and overall number of adverse events. No endpoint regarding the efficacy was collected, because the necessary observation time for cardiac events avoidance would have been several years.

5. Discontinuation Criteria

The investigator might withdraw a patient from the study at any time for any of the following reasons: protocol violation; any change in the eligibility criteria; occurrence of an event leading to treatment withdrawal; a serious event increasing the risk to the patient to an unacceptable level in the view of the investigator and/or at the patient's request.

The BMRC ethical committee approved the study protocol and all the patients gave informed consent to participate in the study.

Results

A total of 1012 patients (Table 1) were enrolled in the study. Among those 213 (21%) patients could not complete the study. Finally 799 patients were evaluated for analysis as they completed treatment as per protocol. There were 645 (80.73%) male and 154 (19.27%) female patients with age from 45~87 years (57.5±7.5), height 125~182 cm (160.6±7.9), weight 32~95 Kg (63.2±7.4), BMI 12.8~37.1 (24.6±3). Among the evaluable patients, 558 (69.8%) had attained the dosage of 10mg/d, 21 (2.6%) stayed at 7.5mg/d, 101 (12.6%) at 5mg/d and 22 (2.8%) patients at 2.5mg/d throughout the study period. 2 patients had a starting dosage of 10mg/d; and final dosage of 97 (12.1%) patients were not mentioned but they stayed at 5mg/d throughout the study period.

No adverse event (AE) was reported in 663 (83%) of those patients. The most common AE reported was mild cough in 12 (1.5%) patients but they completed the study. Other events such as dizziness, hypotension, headache, weakness

were observed in 6 (0.8%) patients. Only 3 (0.4%) of those patients discontinued the study due to hyperkalemia (2 pts) and increasing serum creatinin (1 pt). Another 3 (0.4%) patients were died suffering from multiple risk factors and who were enrolled during unstable heart failure.

Table I : General overview of the patients

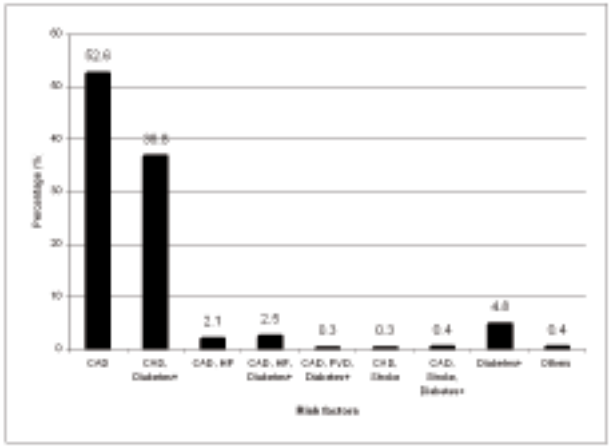
	Number	%
Number of cases in ITT*	1012	
Drop out	213/1012	21.04
Completed cases per protocol (PP)	799/1012	78.95
Reached and stayed at ramipril 10mg/day	558/799	69.84
Did not reach/stay at ramipril 10mg/day	241/799	30.16
Final dosage 7.5mg/day**	21	2.63
Final dosage 5mg/day	198	24.78
Final dosage 2.5mg/day	22	2.75
Adverse Event (AE)	21/799	2.63
Discontinued due to AE	3	0.38
Completed the study despite mild AE	18	2.25

* ITT: Intent to treat patient

**21 (2.63%) patients had final dosage of 7.5mg. After recruiting the 21 patients dosage were increased gradually and reached to 10mg/day. But due to some signs of intolerability, dosage of ramipril was reduced and titrated as per protocol to reach the highest tolerated dosage. It was found that these patients were completed the study without any adverse event further at the dosage of 7.5mg/day.

Risk factors: The details of all the risk factors: coronary artery diseases (CAD), stroke, diabetes with hypertension/ dislipidemia/ smoking/ microalbuminuria or any evidence of previous vascular disease (Diabetes +), stable heart failure (HF), peripheral vascular disease (PVD) are shown in Fig I. 420 (52.6%) patients had a history of CAD, 379 (47.4%) patients had more than one risk factors, 359 (44.9%) had Diabetes with other risk factors, 411 (51.4%) with history of MI, 43 (5.4%) with UA and 7 (0.9%) patients had CABG/PTCA. There were 5 (0.6%) patients with previous stroke, 4 (0.5%) with PVD, 710 (88.9%) with hypertension, 210 (26.3%) with hypercholesterolemia and 196 (24.5%) patients were smoker. There were 39 (4.9%) patients with HF (stage I-III). Patients with only hypertension or only diabetes were not enrolled.

Fig I. Distribution of risk factors and number of patients according to age group (n=799)



* CAD: coronary artery diseases; Diabetes +: diabetes with-ypertension/ dislipidemia/ smoking/ microalbuminuria/ any evidence of previous vascular disease; HF: heart failure; PVD: peripheral vascular diseases.

Other CV treatments: 565 (70.7%) patients were treated with CV medications other than ramipril before enrolled in the study. 238 (30.7%) of the patients were treated with ?-blockers, 201 (26%) with Calcium Channel Blockers (CCB), 95 (12.3%) with Angiotensin Receptor Blocker (ARB), 206 (26.6%) with nitrates, 101 (13%) with aspirin and other anti-coagulant agents, and 76 (9.8%) with lipid lowering agents (Table-II). After enrolment, 643 (80.5%) patients were given other CV medications than ramipril. Among those 186 (24%) were treated with ?-blockers, 116 (15%) with CCB, 3 (0.4%) with ARB, 262 (33.8%) with nitrates, 315 (40.7%) with aspirin and other anti-coagulant agents, and 212 (27.4%) with lipid lowering agents. Since the description of the concomitant treatment was mainly focused on CV medication, anti-diabetic and other treatment are only for reference.

Table II. Cardiovascular medications other than Ramipril used before and after enrollment (n=779)

Concomitant medication	Before enrollment		After enrollment		Change (%)
	N	%	N	%	
β-blockers	238	30.7	186	24	↓7%
CCB	201	26	116	15	↓11%
ARB	95	12.3	3	0.4	↓12%
Nitrates	206	26.6	262	33.8	7%
Aspirin or other platelet inhibitors	101	13	315	40.7	28%
Diuretics	35	4.5	24	3.1	↓1.5%
Digoxin	21	2.7	18	2.3	↓0.4%
Lipid-lowering agents	76	9.8	212	27.4	17%
Antiarrhythmics	14	1.8	9	1.2	↓0.6%
Anti-diabetic drugs	53	6.8	139	18	11%
Others medication	301	38.9	162	20.9	↓18%

*Cumulative number of each medication.

* CCB: calcium channel blockers; ARB: angiotensin receptor blockers;

Adverse events (AE): 21 (2.63%) individual reported at least one AE, in which 12 (1.5%) patients had mild cough and 6 (0.8%) had other AEs like dizziness, hypotension, headache, weakness but all this 18 patients completed the study despite the AEs. Only 3 (0.4%) patients discontinued the study due to hyperkalemia (2 pts) and increasing of serum creatinine (1 pt). The most common AE was mild cough, which was probably related to study medication. 3 (0.4%) patients were died suffering from multiple risk factors and who were enrolled during unstable heart failure.

Cross analysis was done to find the relationship of final dosage of Ramipril with occurrence of adverse event. However, 8/9 was able to continue on ramipril 10 mg/d, and 10/12 continued on either 5 or 2.5 mg/d. As shown in the Table III, frequency of AEs among the final dosage groups does not seem that occurrence of this event to be dose-dependent.

Table III: Relation of final dosage of Ramipril and adverse events

	Adverse Event						
Dosage of Ramipril (mg)	Mild cough	K+ & Cr.	Others	Total	No. of pts on the final dosage	%	RR
2.5	1	0	0	1	22	4.5	1.85
5	6	2	3	11	198	5.5	3.48
7.5	0	0	0	0	21	0	
10	5	1	3	9	558	1.6	0.33
Total	12	3	6	21	799		

*RR: relative risk ratio

Changes in BP, PR and Lab Values: At first visit (V1; Wk-0) and final visit (V6; Wk-12) after three month, mean serum creatinine was 1.09 mg/dl and 1.14 mg/dl, blood urea was 29.1 mg % and 28.2 mg %, serum K+ was 4.1 mmol/l and 4.2 mmol/l, pulse rate was 79/min and 76/min, systolic BP was 130 mmHg and 119 mmHg and diastolic BP was 83 mmHg and 76 mmHg.

Table IV: Changes in BP, PR and Lab value (n=799)

Mean	Cr. (mg/ dl)	Urea (mg %)	K+ (mmol /l)	PR/ min	SBP mm of Hg	DBP mm of Hg
Visit 1 (Wk-0)	1.09	29.1	4.1	79	130	83
Visit 6 (Wk-12)	1.14	28.2	4.2	76	119	76

Cr: serum creatinine; Urea: blood urea; K+: serum potassium; PR: pulse rate; SBP: systolic blood pressure; DBP: diastolic blood pressure

Discussion

The purpose of the present study was to evaluate the safety and tolerability of ramipril among the Bangladeshi patients. The criteria for recruitment were similar to those of the HOPE Study except age (45 years or older) and patients with heart failure were enrolled in this study.

Many earlier studies have demonstrated the efficacy of ramipril 10mg in the reduction of CV risk. The HOPE trial showed that ramipril10 mg/day significantly reduced the risk of CV mortality (-16%), acute MI (-20%) and stroke (-32%) in patients with evidence of vascular disease or diabetes plus one CV risk factor. In the AIRE trial, ramipril up to 10 mg/day reduced significantly all-cause mortality by 27% in survivors of acute MI with clinical evidence of heart failure. The HOPE TIPS[7] study showed that a majority of patients with high CV risk in a wide range of clinical practice settings can be treated with ramipril titrated to 10 mg daily with good tolerability. The predominance of Asian patients in this study helps all to start believe about the relevance of findings derived mainly from Western countries and indicates the practicality and likely effectiveness of this proven treatment in different regions.

However, although long-term use of a daily dose of ramipril 10 mg has been shown to provide adequate CV protection, there are fears regarding the tolerability of this dose in the Bangladeshi population with smaller average body mass index (BMI). It is a common practice to prescribe lower doses of ramipril (5mg) in Bangladesh.

The CV benefits of a daily higher dose (10 mg) ramipril observed earlier are not found with an lower daily dose (1.25 mg) in patients with type 2 diabetes and albuminuria[8]. In the SECURE study[3], 732 high-risk patients were randomised to receive ramipril 2.5 mg/day, ramipril 10 mg/day or a placebo, and the progression of atherosclerosis was monitored. The study, although not powered to compare the two ramipril doses, showed a trend suggesting a dose-dependent effect with the highest benefit for those receiving ramipril 10 mg/day. Thus, the evidence currently available suggests that higher doses of ramipril are better than lower ones in patients with high CV risk and that high doses, when titrated appropriately, are generally well tolerated in the majority of patients with atherosclerotic disease.

ACE inhibitors have benefits beyond their BP lowering effects on CV outcomes. The results of the HOPE MICRO

study in people with diabetes showed that the cardiovascular benefit of ramipril (10 mg/day) was greater than that attributable to the decrease in blood pressure.

In the present study, despite soliciting reports on adverse events, there was no significant adverse event. While one of the limitations of this study conducted in the real-world practice setting is the poor reporting of adverse events by doctors, it is of value to note that the no adverse event in this study was 97.37% (778 out of 799 patients who were prescribed ramipril 10 mg completed the study).

In terms of the severity of the adverse events, 18 mild cases were reported. Cough was the most common adverse event. Other adverse events were dizziness, hypotension, headache and weakness. Relatively, the rates of adverse events and discontinuation of treatment were lower than those reported in HOPE Study[6] but the observation period was much shorter in our study.

According to the study the severity of the main adverse events and the treatment discontinuation with the relationship to the dosage of ramipril and no definite relationships could be found. Moreover, the relationship with the dosage of ramipril in 799 cases was analyzed. However, the adverse events and necessity for discontinuation were not found to be related with the dosage increasing. And during the follow-up, about 70% patients with cardiovascular high risk factors were able to adhere to the target dosage for 2 months (the duration of the study was chosen in order to consider most of the adverse events, which usually occur at the beginning of ACEI treatment).

Lower incidence of adverse events and less discontinuation rate of ramipril in this study was encouraging. It showed that the target dose of ramipril would be reached in Bangladeshi patients as in the high risk patients of the HOPE study, in order to achieve a full therapeutic effect.

It can be concluded that ramipril 10mg (as used in the HOPE study) can be used in Bangladeshi patients with reasonable safety and are well tolerated. The results are encouraging for treating high-risk patients with the dose of ramipril, as in HOPE study, to achieve the desired outcomes.

NB: Ramipril (Tritace®) manufactured by sanofi-aventis Bangladesh Limited was used in the study.

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Acknowledgement

1. S M Ahsan Habib, Assistant Professor, Department of Cardiology, Bangabandhu Sheikh Mujib Medical University, Dhaka.
2. Md. Idris Ali, Assistant Professor, Department of Cardiolog, National Institute of Cardiovascular Disease, Dhaka
3. Md. Ashraf Uddin Sultan, Research Assistant, Department of Cardiology, Bangabandhu Sheikh Mujib Medical University, Dhaka.