Tolerability of Ramipril 10 mg Daily in High-risk Cardiovascular Patients in Taiwan: Experience from Kaohsiung Medical University Chung-Ho Memorial Hospital

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The Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that the angiotensin-converting enzyme inhibitor, ramipril, significantly reduces mortality, myocardial infarction and stroke in high-risk cardiovascular patients, beyond the benefits from blood pressure lowering. The tolerability of ramipril 10 mg/day has been an important concern when applying these results. Following the same criteria as the HOPE study, we investigated the adverse effects profile and tolerability of 10 mg ramipril in high-risk patients at our institution. In total, 92 patients with high cardiovascular risk were eligible for this study. Initially, ramipril was prescribed 2.5 mg orally once daily, and then titrated up to 5.0, 7.5, and 10.0 mg/day at 1-month intervals. The target maintenance dose was 10 mg/day. All adverse events were recorded during at least 3 months of follow-up. After 4–6 months of the titration protocol, only 18 patients (25.3%) reached and remained on ramipril 10 mg/day; 11 (15.5%), 22 (30.9%), and 20 patients (28.2%) remained on 2.5, 5.0, and 7.5 mg/day, respectively. Twenty-one patients (22.6%) had at least one adverse event. Twelve patients (13.0%) stopped treatment because of adverse effects. A total of 23 episodes of adverse events were reported, including cough (15.1%), dizziness (6.0%), and hypotension (2.4%). Ramipril was relatively well tolerated in our study population. However, only one-quarter of our patients reached the target maintenance dose of 10 mg/day. Dry cough, dizziness, and hypotension were the major side effects. About 15% of our patients discontinued ramipril treatment, which is comparable with previous reports.

Key Words: ACE inhibitor, adverse effect, tolerability
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Activation of the renin-angiotensin-aldosterone (RAA) system plays an important role in increasing the risk of cardiovascular events. In addition to aggressive management of the major risk factors for cardiovascular disease, including dyslipidemia, diabetes, hypertension, and smoking, the use of angiotensin-converting enzyme (ACE) inhibitors to block the RAA system also retards the progression of atherosclerosis and offers benefits and protection for a broad range of patients with myocardial infarction, left ventricular systolic dysfunction, diabetes, and stroke [1–7]. In the Heart Outcomes Prevention Evaluation (HOPE) study, the additional anti-atherothrombotic benefits of ramipril were observed even in patients already receiving treatment with aspirin, β-blockers, and lipid-lowering agents. Furthermore, the benefits of ramipril on mortality, myocardial infarction, stroke, cardiac arrest, heart failure, and revascularization were demonstrated beyond blood pressure lowering [8]. The vascular mechanism

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underlying ACE inhibitor use includes antagonizing vasoconstriction via angiotensin II, proliferation of vascular smooth muscle cells, rupture of plaques, improving vascular endothelial function, reducing left ventricular hypertrophy, and retarding myocyte fibrosis [9,10].

Following publication of the results of the HOPE study [8], prescriptions for ramipril increased significantly, as has concern about the safety and tolerability of the 10 mg/day dose [11–13]. The most common adverse effects of ACE inhibitor use are dry cough, angioedema, and hypotension. Severe, persistent cough limits the use of ACE inhibitors in a significant number of patients. It has been speculated that occurrence of this adverse effect is genetically predetermined; in particular, variants of the genes encoding ACE, chymase, and B2-bradykinin receptor have been implicated [14–16]. The incidence of dry cough in Asians is 15–20% higher than in Caucasians [17].

Therefore, this study investigated the tolerability and safety of ramipril 10 mg/day in high-risk cardiovascular patients in Taiwan, following similar criteria to those used for patient selection in the HOPE study.

Patients and Methods

Patients

Men and women aged 55 years or older were eligible for this study if they had one of the following risk factors for developing major cardiovascular events: a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol level, low high-density lipoprotein (HDL) cholesterol levels, current smoking, or documented microalbuminuria). Patients with stabilized heart failure of New York Heart Association (NYHA) class I to III were also eligible. Exclusion criteria related primarily to absolute contraindications (e.g. hypersensitivity to ACE inhibitors), as well as warnings and precautions for the use of ACE inhibitors, in accordance with the package insert of Tritace (Aventis Pharma, Lance Cove, NSW, Australia) in Taiwan. Patients were also ineligible if they had other medical problems that would either interfere with participation in the trial or lead to inability to complete the trial. Exclusion criteria included: non-stabilized heart failure or clinical NYHA class IV; hemodynamically significant primary valvular or outflow tract obstruction (e.g. mitral stenosis, asymmetric septal hypertrophy or malfunctioning prosthetic valve); constrictive pericarditis; complicated congenital heart disease; syncope episode presumed to be a result of uncontrolled life-threatening arrhythmia; planned cardiac surgery or angioplasty within 3 months; cor pulmonale; significant renal disease defined as renal artery stenosis, creatinine clearance less than 0.6 mL/sec or serum creatinine greater than 2.0 mg/dL, overt nephropathy (> 1+ proteinuria on dipstick or urinary albumin excretion > 200 μg/min); hyperkalemia (potas- sium > 5.3 mEq/L); any other major non-cardiac illness expected to reduce life expectancy or interfere with study participation; and simultaneous treatment with another experimental drug or ACE inhibitor.

Study protocol

The study was designed to follow each patient for 3 months after a 10 mg daily dose, or the highest tolerable dose, of ramipril had been achieved through titration. Ramipril 2.5 mg tablets were supplied by Aventis Pharma, Taiwan. Patients without a history of heart failure were assigned to receive ramipril 2.5 mg orally once daily for 1 month, 5 mg once daily for the next month, 7.5 mg once daily for the third month, and then the maintenance dose of 10 mg once daily after the last visit. The tolerability of the study medication was assessed by reported adverse events and by monitoring blood cell count, electrolytes, serum creatinine, liver function, and fasting blood glucose.

If an adverse event occurred, the patient was advised to downgrade to half of the assigned dose and stay at that dosage for 2–3 weeks, and then increase to the previous dose. If the patient was compliant, dose titration was continued according to the protocol; if not, the patient was kept on the highest tolerable maintenance dose for 1 month.

For patients switched from other ACE inhibitors to ramipril, ramipril was titrated in the same steps as described above. It was understood that treatment with other ACE inhibitors was to be fully stopped, and treatment with ramipril started and titrated up to the target dose of 10 mg once daily.

The trial started at Kaohsiung Medical University Chung-Ho Memorial Hospital in October 2002, and ended in June 2003.

Statistical analysis

The aim of the study was to collect events when recognized by the physicians. Therefore, the evaluation variables were the number of patients who received the 10 mg/daily dose and the numbers at each highest tolerated dose, the number of treatment discontinuations (resulting from adverse events or not), the overall number of adverse events, and the number of serious adverse events. The analysis of these observations was purely descriptive. No efficacy variables

were collected because the necessary observation time would have to have been several years.

Results

Patient characteristics

A total of 92 patients, 59 males and 33 females, were enrolled in the study. The baseline characteristics of patients in the current study are compared with those of patients in the HOPE study in Table 1. The mean age in this study was 64 ± 12.2 years, similar to that in the HOPE trial, but the mean body mass index (BMI) was higher in the HOPE study (28.0 ± 4.0) than in our population (25.2 ± 4.5).

There was a significant difference in the prevalence of cardiovascular risk factors between the two studies. A larger percentage of females was recruited in our study than in the HOPE study (35.9% vs 27.5%). There were also lower percentages of patients with elevated total cholesterol (43.4% vs 65.4% in HOPE), HDL-cholesterol (26.1% vs 48.1% in HOPE), and a history of coronary artery disease (38.0% vs 51.9% in HOPE). The percentages of patients with diabetes and who smoked cigarettes were similar in the two studies. A higher percentage of patients in our study were taking concomitant β-blockers, diuretics, and lipid-lowering agents than in the HOPE study.

Overview of the protocol

Of the 92 study patients, nine dropped out at the patient's request or because of a protocol violation, 12 discontinued treatment due to adverse effects, and 71 patients completed the study (Table 2).

Compliance

Among the 71 patients who completed the protocol, 18 reached and remained at a dose of 10 mg/day, while 53 remained at a lower dose (Table 2). Eleven, 22, and 20 patients stayed at 2.5, 5.0, and 7.5 mg/day, respectively.

Table 1. Baseline characteristics of study patients compared with those in the HOPE study

	Current study (n = 92)	HOPE study (n = 4,645)
Age (yrs)	64.0 ± 12.2	66 ± 7
BMI	25.2 ± 4.5	28 ± 4
Female	33 (35.9%)	1,279 (27.5%)
Cardiovascular risk factors		
History of stabilized heart failure	16 (17.4%)	3,691 (79.5%)
History of coronary artery disease	35 (38.0%)	2,410 (51.9%)
Myocardial infarction	17 (18.5%)	1,179 (25.4%)
CABG/PTCA	7 (7.6%)	2,045 (44.0%)
Stroke	6 (6.5%)	500 (10.8%)
Diabetes	30 (32.6%)	1,808 (38.9%)
Hypertension	59 (64.1%)	2,212 (47.6%)
Documented elevated total cholesterol level	39 (43.4%)	3,036 (65.4%)
Documented low HDL-C level	24 (26.1%)	842 (48.1%)
Current cigarette smoking	11 (12.5%)	645 (13.9%)
Medications		
β-blocker	42 (50.6%)	1,820 (39.2%)
Calcium antagonists	33 (39.7%)	2,152 (46.3%)
Nitrates	45 (54.2%)	-
Antiplatelet agents	55 (66.3%)	3,497 (75.3%)
Diuretics	20 (24.1%)	713 (15.3%)
Digoxin	4 (4.8%)	-
Lipid-lowering agents	31 (37.3%)	1,318 (28.4%)
Antiarrhythmics	6 (7.2%)	-
Anti-diabetes	23 (27.7%)	-

BMI = body mass index; CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; HDL-C = high-density lipoprotein-cholesterol.

Adverse events

Twenty-one patients (25.3%) had at least one adverse event, of whom 19 individuals had only one adverse event and two had two adverse events, giving a total of 23 reported adverse events (Table 3). Of 83 patients, 12 discontinued the study as a result of an adverse event and nine completed the study despite an adverse event. The most common adverse event was persistent dry cough. Other adverse events included dizziness, hypotension, chest discomfort, headache and numbness. No epigastric discomfort, skin rash, or elevation of serum creatine was noted. There were no significant changes in laboratory variables during the study.

Table 2. Patients completing the study and discontinuing ramipril treatment (n = 92)

	n (%)
Patients discontinuing treatment	21 (22.8%)
Patient's request	9 (9.8%)
Adverse effects	12 (13.0%)
Patients completing the entire protocol	71 (85.6%)
Reached and remained at 10 mg/day	18 (25.3%)
Failure to reach or remain at 10 mg/day	53 (74.6%)
Final dose 7.5 mg/day	20 (28.2%)
Final dose 5.0 mg/day	22 (30.9%)
Final dose 2.5 mg/day	11 (15.5%)

Discussion

ACE inhibitor-induced cough is the major problem with these drugs in high-cardiovascular-risk patients. The incidence of persistent dry cough varies in different populations [11–14]. Only 7% of patients in the HOPE study had dry cough [8]. However, in a northern Indian population, the incidence was as high as 24.3% [11]. In this study, the incidence of dry cough was 15.6%. There have been several studies with a special focus on the possible genetic polymorphism underlying tolerability, efficacy, and incidence of adverse events [14–16]. However, in these studies, ACE inhibitors were well tolerated and most patients had cardiovascular protection benefits from their ACE inhibitor. In addition, large-scale trials continue to support their widespread clinical use.

In the HOPE study, the target maintenance dose was 10 mg/day, gradually titrated from one ramipril tablet (2.5 mg) to four tablets. Compliance could be hampered if patients hesitated to take all of their tablets at the same time. Recently, ramipril has become available as a 10-mg tablet, based on the HOPE study. However, according to our study, some patients should still have titration from a lower dose with regular monitoring.

Most patients in our study had at least two cardiovascular risk factors and concomitant use of other cardiovascular medication. The definition of adverse events was decided

Table 3. Incidence of adverse events and influence of ramipril use (n = 83)

	n (%)	Discontinued	Continued
Cough	13 (15.6%)	10*	3
Dizziness	5 (6.0%)	2*	3
Hypotension	2 (2.4%)	2	0
Chest discomfort	1	0	1
Epigastralgia	0	0	0
Rash	0	0	0
Elevated serum creatine	0	0	0
Headache	1	0	1
Thirst	0	0	0
Numbness	1	0	1
Edema	0	0	0
Nausea	0	0	0
Elevated serum potassium	0	0	0
Shock	0	0	0
Liver function impairment	0	0	0
Oral ulcer	0	0	0
Epistaxis	0	0	0
Total events	23	14	9

*Two patients suffered from both cough and dizziness.

by the individual physician's observation and judgment. Notably, most laboratory values were kept within stable levels throughout the study period.

Although efficacy parameters were not included in this study, there were two major cardiovascular events in two separate patients. Both patients had an episode of non-ST elevation myocardial infarction, and were admitted to the coronary care unit for intensive care. Most other patients were able to tolerate their maintenance dose.

Study limitations

Several limitations of this study should be mentioned. First, it was conducted at one institution. However, the number of patients was sufficient to reflect real practice and the real adverse event rate in our daily clinical practice. Second, unlike the HOPE study, most patients in our study did not have symptoms or signs of significant heart failure, and all patients were given 2.5 mg/day as the initial dose. Third, most patients were taking a combination of anti-hypertensive agents concomitantly with ramipril. It is possible that blood pressure would be relatively reduced, which makes titrating ramipril difficult. However, the dose of ramipril was titrated as tolerated if patients were stable and asymptomatic.

Conclusion

The ACE inhibitor ramipril was relatively well tolerated in our study population. However, only one-quarter of our patients could reach the target maintenance dose of 10 mg/day. Persistent dry cough, dizziness, and hypotension were the major concerns when prescribing ACE inhibitors to these patients. About 15% of our patients discontinued ramipril treatment because of these adverse events, which is compatible with previous reports.

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Ramipril 每日 10 毫克劑量對於高心血管危險因子病患耐受性研究 — 高醫的臨床經驗

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在大規模 HOPE 研究已證實每日 10 mg 的 ramipril 用藥可以降低高心血管危險因子病患將來發生腦血管與心血管疾病機會與死亡率，並且遠超過血壓下降程度所能帶來的好處。然而使用每日 10 mg 的 ramipril 用藥時，病人的耐受性一直是臨床上重視的課題。本觀察性臨床研究，遵循 HOPE 臨床研究模式，評估本院高危險群病人使用每日 10 mg ramipril 之耐受性與副作用情況。總共有 92 位病人接受本臨床試驗。依據病人耐受性，將 ramipril 劑量從每日 2.5 毫克(每錠劑 2.5 毫克)，慢慢每月調高到每日 5 毫克、每日 7.5 毫克直到每日 10 毫克。維持劑量目標保持在每日 10 毫克。所有病人至少追蹤三個月以上並記錄其副作用報告。結果顯示只有 18 位病人達到每日 10 mg 的 ramipril 的治療劑量。其餘分別有 11 位 (15.5%)、22 位 (30.9)、以及 20 位 (28.2%) 病人達到每日 5 毫克、每日 7.5 毫克及每日 10 毫克 ramipril 治療劑量。有 21 位 (22.6%) 病人至少報告過一種副作用。有 12 位病人 (13.0%) 因為副作用而必須停止試驗。總共有 23 起副作用事件報告，其中乾咳佔 15.1%，暈眩佔 6.0%，低血壓則佔 2.4%。我們的結論是，雖然大多數的病人對於 ramipril 的耐受性還不錯，但是能順利達到每日 10 mg 的 ramipril 的治療劑量的病人數只有大約四分之一。乾咳、暈眩及低血壓等副作用仍是醫師在開立此類處方時最常見的問題。本試驗因為上述副作用而必須停藥的病人比例大約在 15%，與過去文獻報告的數據接近。

關鍵詞：血管加壓素轉換脢抑制劑 ramipril、副作用、耐受性

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