Effect of Lacidipine on Blood Pressure and Endothelial Function in Mild-to-Moderate Essential Hypertension Patients With Diabetes in Korea

Dae-Hee Kim, MD1, Il-Young Oh, MD1, Hae-Young Lee, MD1, Yong-Jin Kim, MD1, Hyo-Soo Kim, MD1, Cheol-Ho Kim, MD1, Byung-Hee Oh, MD1, Kwon-Sam Kim, MD2, Doo-II Kim, MD3, Young-Dae Kim, MD3, Kyu-Hyung Ryu, MD3, Si-Hoon Park, MD4, Sang-Hong Baek, MD5, Dong-Gu Shin, MD6, Wan Joo Shim, MD6, Tae-Hoon Ahn, MD10, Seok-Kyu Oh, MD7, Seung-Hwan Lee, MD7, Sung-Yun Lee, MD7, Myung-Ho Jeong, MD14, Wook-Sung Chung, MD7, Jun-Young Jeong, MD15, So-Yeon Choi, MD16, Si-Wan Choi, MD17 and Min-Su Hyon, MD18

1Department of Internal Medicine, College of Medicine, Seoul National University, Seoul, 2Department of Internal Medicine, Kyung Hee University College of Medicine, Seoul, 3Department of Internal Medicine, Inje University College of Medicine, Busan Paik Hospital, Busan, 4Department of Internal Medicine, Dong-A University College of Medicine, Busan, 5Department of Internal Medicine, Konkuk University College of Medicine, Seoul, 6Department of Internal Medicine, Ewha Womans University College of Medicine, Mokdong Hospital, Seoul, 7Department of Internal Medicine, The Catholic University College of Medicine, Seoul St. Mary's Hospital, Seoul, 8Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, 9Department of Internal Medicine, Korea University College of Medicine, Anam Hospital, Seoul, 10Department of Internal Medicine, Gachon University Gil Hospital, Incheon, 11Department of Internal Medicine, Wonkwang University College of Medicine, Iksan, 12Department of Internal Medicine, Yonsei University Wonju Christian Hospital, Wonju, 13Department of Internal Medicine, Inje University College of Medicine, Ilsan Paik Hospital, Goyang, 14Department of Internal Medicine, Chonnam National University College of Medicine, Gwangju, 15Department of Internal Medicine, Eulji University College of Medicine, Daejeon, 16Department of Internal Medicine, Ajou University College of Medicine, Suwon, 17Department of Internal Medicine, Chungnam National University College of Medicine, Daejeon, 18Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea

ABSTRACT

Background and Objectives: The aim of this study was to evaluate the efficacy of lacidipine in reducing blood pressure (BP) and to determine its effect on endothelial function in mild-to-moderate hypertensive patients with type 2 diabetes mellitus (DM).

Subjects and Methods: This was a prospective, multicenter, open-label, single-arm study, enrolling 290 patients with mild-to-moderate hypertension and type 2 DM. Patients were initially treated with 2 mg lacidipine orally once daily for 4 weeks, which was then increased as necessary every 4 weeks to a maximal dose of 6 mg daily. The primary endpoint was the mean change in systolic blood pressure (SBP) from baseline after 12 weeks of treatment. Secondary endpoints included mean changes in diastolic blood pressure (DBP), flow-mediated vasodilatation (FMD), and serum concentrations of biochemical markers such as high-sensitivity C-reactive protein (hs-CRP), monocyte chemo-attractant protein-1 (MCP-1), matrix metalloproteinase-9 (MMP-9), and plasminogen activator inhibitor-1 (PAI-1).

Results: Lacidipine treatment significantly reduced SBP by -13.4±13.0 mmHg (p<0.001) and DBP by -6.2±9.3 mmHg (p<0.001). Lacidipine treatment did not improve endothelial-dependent vasodilatation, despite significantly improved nitroglycerin-induced, endothelial-independent vasodilatation. MCP-1 levels significantly decreased from 283.66±110.08 pg/mL to 257.83±100.23 pg/mL (p<0.001); whereas there were no significant changes in the levels of hs-CRP MMP-9, or PAI-1.

Conclusion: Twelve weeks of treatment with lacidipine was effective and well tolerated in mild-to-moderate hypertensive patients with type 2 DM. In spite of inducing a significant reduction in MCP-1 levels, lacidipine did not improve endothelial function. (Korean Circ J 2010;40:632-638)

KEY WORDS: Lacidipine; Diabetes mellitus; Hypertension; Endothelium.

Received: March 3, 2010 / Accepted: May 27, 2010
Correspondence: Byung-Hee Oh, MD, Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea
Tel: 82-2-2072-3345, Fax: 82-2-2072-2577, E-mail: ohbhmed@snu.ac.kr
*Dr. Dae-Hee Kim is now affiliated with Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
Introduction

The prevalence of hypertension in patients with diabetes mellitus (DM) is extremely high (20-60%). Moreover, comorbid hypertension has been widely reported to increase the risk of cardiovascular events, which account for 86% of the deaths occurring among patients with DM; it is also known to increase the incidence of microvascular complications. However, it has been reported that only 28% of diabetic patients have adequately controlled blood pressure (BP) under 130/80 mmHg. This control rate is even lower (21.6%) among Korean patients. Although recent guidelines recommend angiotensin receptor antagonists or angiotensin-converting enzyme inhibitors as frontline antihypertensive agents in patients with DM, most patients eventually require more than 2 classes of antihypertensive agents to achieve target BP.

Lacidipine, a long-acting dihydropyridine calcium channel blocker, has been reported to reverse endothelial dysfunction, and to cause regression of atherosclerosis. The European Lacidipine Study on Atherosclerosis demonstrated that 4 years of lacidipine treatment retarded the progression of atherosclerosis more effectively than atenolol. Investigators suggested that this effect was due to restoration of endothelial function and reduction in oxidative stress.

However, the effects of lacidipine in type 2 DM patients have been only reported from small-scale, nonblinded studies. Furthermore, there is a paucity of data regarding the effects of lacidipine on endothelial dysfunction, which is observed in most patients with DM.

In this study, we evaluated the efficacy of lacidipine in reducing BP, as well as its effect on endothelial function, in mild-to-moderate hypertensive patients with type 2 DM.

Subjects and Methods

Study population

A subject was only eligible for inclusion in this study if all the following criteria applied: 1) male or female 35 to 75 years of age at screening, 2) newly diagnosed essential hypertension or essential hypertension untreated in the 2 months prior to screening, and 3) type 2 DM (ADA criteria 2004). Any subjects taking antihypertensive medications had to undergo a 2-week washout period before enrollment. The definition of hypertension was a sitting systolic blood pressure (SisBP) of ≥130 mmHg, measured with a BP cuff, because the SBP goal is less than 130 mmHg in patients with diabetes. Exclusion criteria were as follows: severe hypertension with SisBP >180 mmHg; or any serious disorder that could limit the ability of the patient to participate in the study, including severe coronary artery disease, uncontrolled DM (hemoglobin A1C >11%), or secondary hypertension.

Study design

This was a multicenter, open-label, single-arm study performed at 20 sites in the Republic of Korea. The study protocol was approved by the institutional review board at each site. Before entering the study, patients provided written, informed consent. A medical history was obtained during the screening phase, and a physical examination, 12-lead electrocardiogram, complete blood count, serum biochemistry, and routine urinalysis were performed at each center. During the 12-week treatment period, patients were initially treated with lacidipine 2 mg orally once daily for 4 weeks, and then were titrated with increasing doses every 4 weeks to a maximal dose of 6 mg daily if the SisBP did not decrease to <130 mmHg.

Blood pressure measurement

At each visit, the SisBP, sitting diastolic blood pressure (SisDBP), pulse rate, and body weight were recorded. To ensure consistency of trough values, these measurements were taken at the same time of day, before the next dose of lacidipine. At each center, a single investigator used the standard auscultatory technique for measuring BP in each patient’s arm, using a mercury sphygmomanometer produced by one company (W. A. Baum Co. Inc, Copiague, NY, USA) and an appropriately-sized BP cuff.

Measurement of flow-mediated dilatation of the brachial artery

The examination was conducted at each center by the same examiner throughout the study, using a standard technique. Briefly, the diameter of the artery was measured using high-resolution, 2-dimensional images obtained by ultrasound with a 7.5-MHz linear-array transducer. Subjects were asked not to smoke or drink coffee or tea for at least 2 hours before the scan was performed. The right brachial artery was scanned over a longitudinal section 3 to 5 cm above the right medial elbow for the first resting image. The diameter of the brachial artery was measured from the anterior to the posterior interface between the media and adventitia (“m line”) at a fixed distance.

The mean brachial artery diameter was calculated from 4 cardiac cycles synchronized with R-wave peaks on the electrocardiography. A pneumatic tourniquet placed around the forearm distal to the target artery was then inflated to a pressure of 250 mmHg, and inflation was maintained for 5 minutes. Increased flow was then induced by sudden cuff deflation. A second scan was performed continuously for 60 seconds before, and for 120 seconds after cuff deflation. Then, 15 minutes later, another resting image was recorded. A nitroglycerin tablet (0.4 mg) was then administered sublingually, and 3 minutes later the last scan was performed. All the images were stored in DICOM format for offline analysis, and then sent to the core laboratory. Two expert sonographers an-
analyzed all the images. Interobserver coefficients of variation for measuring vessel diameters at baseline, after hyperemia, and after nitroglycerin were 3.3±0.25%, 2.9±0.28%, and 3.5±0.22%, respectively.

Blood tests
Blood samples were collected after at least 12 hours of fasting. Measurements of lipids, fasting glucose, and high-sensitivity C-reactive protein (hs-CRP) were performed in the local laboratories at each center. Other serum biochemical markers were analyzed in the central, core laboratory of GSK Korea using commercially available enzyme-linked immunosorbent assay kits from various vendors as follows: monocyte chemoattractant protein-1 (MCP-1; Bio-Rad Laboratories, Hercules, CA, USA), matrix metalloproteinase-9 (MMP-9; Amsham Biosciences, Uppala, Sweden), and plasminogen activator inhibitor-1 (PAI-1; IMUBIND, American Diagnostica, Stamford, CT, USA).

Efficacy and safety variables
The primary efficacy variable in this study was the mean change in trough SiSBP from baseline after 12 weeks of treatment. Secondary efficacy variables included mean changes in SiDBP, flow-mediated dilatation (FMD), and biochemical markers such as hs-CRP, MCP-1, MMP-9, and PAI-1 after 12 weeks of treatment.

Safety variables included the incidence of all adverse events (AEs), drug-related AEs, and the number of discontinuations. AEs were evaluated at each visit by physical examination and direct questioning. The seriousness of AEs and their relation to the study drugs were determined by the chief investigator at each center. The results of all laboratory tests were assessed by the investigators for clinical significance and for their possible relationship to the study drug.

Statistical analysis
Effectiveness was defined as >4.5 mmHg decrease in the mean SiSBP from baseline after 12 weeks of treatment. We calculated that 321 patients would be required to fulfill the following parameters: standard deviation of 20 mmHg for SiSBP, overall 1-sided significance of 0.05, 90% power, and 20% exclusion rate. In terms of absolute benefit, data from the per-protocol (PP) population were used for the main analysis and those from the intention-to-treat (ITT) population were used as a supplement. The ITT population was used primarily to evaluate tolerability.

Continuous variables were analyzed using the t-test. Changes in BPs and serum markers were analyzed using a paired t-test. All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) 12.0 (SPSS Inc, Chicago, IL, USA), and p less than 0.05 were considered statistically significant.

Results
Baseline characteristics
A total of 333 patients were screened, and 290 patients (male:female=173:117) were enrolled in the study. Of them, 236 patients (81.4%) completed the study. The flow diagram of study patients is summarized in Fig. 1. Eighty subjects (33.9%) were treated with 2 mg of lacidipine throughout the study, 108 (45.8%) were titrated up to 4 mg, and 48 (20.3%) were titrated up to 6 mg.

The mean age in the study group was 56.6±9.2 (35-79) years, and 41% of the patients were over 60 years of age. The most common concomitant medications at baseline and during the study were oral hypoglycemic agents (75%), lipid-lowering agents (29%), antplatelet agents (40%), and antacids (13%). The proportions of oral hypoglycemic agents were as follows: sulfonylureas 58%, biguanides 37%, alpha-glucosidase inhibitors 13%, thiazolidinediones 14%, combination of more than two drugs 4%.

Changes in blood pressure from baseline
In the PP population (n=236), SiSBP was significantly decreased by 13.4±13.0 mmHg (from 144.0±11.4 mmHg to 130.6±12.5 mmHg, p<0.0001) after 12 weeks of treatment. In the ITT population (n=277), SiSBP also significantly decreased by 13.0±13.3 mmHg (from 144.2±12.3 mmHg to 130.9±13.1 mmHg, p<0.0001) (Fig. 2).

SiDBP decreased by 6.2±9.3 mmHg (from 88.7±8.8 mmHg to 82.5±9.0 mmHg, p<0.001) in the PP population and by 6.1±9.1 mmHg (from 88.7±8.6 mmHg to 72.0±9.4 mmHg, p<0.001) in the ITT population.

The overall response rate (SiSBP <130 mmHg) after 12 weeks of treatment was 58.5%. In the subgroup with baseline SiSBP greater than 140 mmHg (PP population, n=132), the change in

![Fig. 1. Flow diagram of study patients. ITT: intention to treat, FMD: flow-mediated dilatation, PP: per-protocol.](image-url)
SiSBP was -18.1±13.3 mmHg (from 151.6±9.7 mmHg to 133.5±13.6 mmHg, p<0.001); whereas in the subgroup with baseline SiSBP less than 140 mmHg (n=104), the change in SiSBP was -7.5±9.8 mmHg (from 134.4±3.0 mmHg to 126.9±10.0 mmHg, p=0.03).

Changes in endothelial-dependent and endothelial-independent vasodilatation

Changes in endothelial-dependent vasodilatation of the brachial artery were analyzed in the PP population. The mean baseline percentage of endothelial-dependent vasodilatation was not related to baseline body mass index, lipids, serum biomarkers, or SiSBP levels (Table 1). After 12 weeks of treatment with lacidipine, the percentage of endothelial-dependent vasodilatation changed from 5.22±4.91% to 5.52±4.92%, but this did not represent a statistically significant change (p=0.313).

In contrast, endothelial-independent vasodilatation after administration of sublingual nitroglycerin significantly increased from 13.94±7.21% to 14.97±7.42% (p=0.02). The baseline percentage of nitroglycerin-induced vasodilatation had a weak negative correlation with MCP-1 levels. All the subjects were divided into 2 subgroups. The FMD-responder group (n=130, 55.1%) included those patients who had increased endothelial-dependent vasodilatation, and the FMD-nonresponder group (n=106, 44.9%) included those patients who had no increase in endothelial-dependent vasodilatation. The FMD-responder group had significantly lower baseline triglyceride (TG) levels (150±97 mg/dL vs. 185±156 mg/dL, p=0.02) and higher baseline high density lipoprotein-cholesterol (HDL-C) levels (46±11 mg/dL vs. 49±12 mg/dL, p=0.01) (Table 2).

Changes in blood chemistry and biomarkers

HbA1C and lipid profiles, including TGs, low density lipoprotein-cholesterol, and HDL-C levels, did not change after 12 weeks of lacidipine treatment. Among the biomarkers evaluated, the plasma levels of MCP-1 significantly decreased from 283.66±110.08 pg/mL to 257.83±100.23 pg/mL (p<0.001). In contrast, hs-CRP did not show any significant change (from 0.51±1.07 mg/dL to 0.55±1.60 mg/dL, p=0.644). The results are presented in Table 2.

Tolerability

More than one AE event was reported in 40% of the patients in the ITT population (a total of 116 events in 290 patients). There were 105 events that were considered to be drug-related. The most common AEs thought to be drug-related were headache (n=16, 5.52%), palpitations (n=6, 2.07%),
This study was performed to evaluate the efficacy and tolerability of lacidipine in mild-to-moderate hypertensive patients with type 2 DM. To the best of our knowledge, this is the largest study evaluating the effect of calcium antagonists on endothelial function in hypertensive patients with DM.

Lacidipine treatment effectively reduced SBP and DBP. When the dose was titrated up to 6 mg once daily, the overall response rate after 12 weeks of treatment reached 58.5%. Although this study did not have a comparative design, the extent of lacidipine-induced SiSBP reduction in our Korean population was comparable to the effects of lacidipine seen in other races, as well as to the effects of other antihypertensive agents, such as nifedipine, amlodipine, thiazide, isradipine, and amldipine in Korean patients.

The most interesting findings in this study were related to the role of lacidipine in the improvement of endothelial dysfunction in hypertensive patients with DM. Although a few
preclinical or small-scale clinical studies have suggested the beneficial effects of lacidipine on endothelial function in nondiabetic subjects, this is the first study evaluating the effects of lacidipine on endothelial function in diabetic patients with hypertension. Twelve weeks of lacidipine therapy did not improve endothelial-dependent vasodilatation, despite the fact that endothelial-independent vasodilatation was significantly improved following administration of sublingual nitroglycerin. The lack of improvement in endothelial-dependent vasodilatation stands in contrast to previous studies which have shown an improvement in overall endothelial-dependent vasodilatation in nondiabetic patients. A number of mechanisms may be invoked in understanding the discrepancy between our results and those in the nondiabetic population. Impairment of endothelial-dependent vasodilatation is more severe in diabetic patients than it is in nondiabetic patients. Thus, 12 weeks of treatment might not be sufficient for amelioration of this impairment. Impairment of endothelial-dependent vasodilatation has been widely observed in arteries from diabetic animals, as well as from normal animals exposed to hyperglycemia. In such studies, endothelial-dependent vasodilatation had already been impaired while endothelial-independent vasodilatation remained intact. Similarly, in a few animal studies, as well as in human studies, a diminished response to nitroglycerin was also observed in diabetes, which was preceded by a disturbed response to acetylcholine. Therefore, impaired vascular response to nitroglycerin is considered to occur at a more advanced stage of vascular dysfunction in diabetes. In this study, the baseline values of nitroglycerin-induced vasodilatation were more impaired than previously reported values of normal controls, which also suggests that the population in this study might have had more advanced vascular dysfunction. Similarly, HMG-CoA reductase inhibitors (statins) have been shown to have significant beneficial effects on endothelial dysfunction in nondiabetic subjects. However, many studies have also failed to show significant statin-induced improvement in endothelial-dependent vasodilatation in subjects with type 2 DM, and only one report has demonstrated statin-induced improvement in endothelial-independent vasodilatation, as was shown in this study.

In subgroup analysis, the group with increased endothelial-dependent vasodilatation had lower TG levels and higher HDL-C levels. An elevated TG concentration may increase the levels of intracellular adhesion molecule-1 and vascular cell adhesion molecule-1, which might result in increased inflammatory responses in endothelial cells. Additionally, improvement in endothelial dysfunction seems to be independent of BP-lowering effects, because there was no difference in the baseline BP or the absolute amount of decrease in SBP between those with FMD improvement and those without improvement.

Finally, we observed that the levels of MCP-1, a surrogate marker for inflammation, significantly decreased after lacidipine treatment. The levels of MCP-1 in hypertensive patients have been reported to correlate with the severity of carotid intima-media thickness (IMT). In this regard, decreased MCP-1 concentrations following lacidipine treatment might be consistent with the previously reported anti-atherosclerotic effect of lacidipine. In this study by contrast, the levels of hs-CRP did not change significantly. This discrepant result was consistent with that of a previous study in which patients with coronary artery disease had significantly reduced carotid IMT without a significant change in hs-CRP levels after 6 months of lacidipine treatment. This discrepancy between hs-CRP and MCP-1 has also been demonstrated in other studies of angiotensin receptor blockers.

Levels of PAI-1, a marker of fibrinolytic balance, did not decrease after lacidipine treatment. PAI-1 levels are elevated in subjects with risk factors for atherosclerosis and insulin resistance. PAI-1 expression is known to be regulated by nitric oxide (NO) activity, and therefore NO synthase activity. In this regard, the lack of change in mean PAI-1 levels might be consistent with the insignificant endothelial-dependent vasodilatation changes observed in this study.

There are several limitations to this study. First, this is a single-arm, uncontrolled study. Owing to ethical concerns regarding not administering antihypertensive therapy to patients with confirmed hypertension, we were unable to create a control group. Second, the measurement and analysis of FMD could be observer-dependent with high variance. To reduce observer-dependent bias, two expert sonographers in the core lab analyzed all the images. Third, the measurements of lipids, fasting glucose, and hs-CRP were performed by local laboratories at each center, and the results could vary between laboratories. However, the serum biochemical markers, including MCP-1, MMP-9, and PAI-1, were all analyzed in a single central laboratory.

In summary, 12 weeks of lacidipine treatment was effective and well tolerated in diabetic patients with mild-to-moderate hypertension. Lacidipine partially improved vasorelaxation, which was associated with reduction in levels of inflammatory markers.

Acknowledgments
This study was sponsored by GlaxoSmithKline Korea.

REFERENCES
1) Arauz-Pacheco C, Parrott MA, Raskin P. Treatment of hypertension in adults with diabetes. Diabetes Care 2003;26(Suppl 1):S80-2.
2) Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560-72.
3) Kim KI, Kim Y, Kim HJ, et al. Current status and characteristics of hypertension treatment by primary physicians in Korea: data from Korean Epidemiology Study on Hypertension (KEY Study). Am J Hypertens 2008;21:884-9.
4) Sowers JR, Hafliner S. Treatment of cardiovascular and renal risk factors in the diabetic hypertensive. Hypertension 2002;40:781-8.

5) Taddeo S, Virdis A, Ghiaodoni L, Sudano I, Salvetti A. Effects of antihypertensive drugs on endothelial dysfunction: clinical implications. Drugs 2002;61:265-84.

6) Zanchetti A, Bond MG, Hennig M, et al. Absolute and relative changes in carotid intima-media thickness and atherosclerotic plaques during long-term antihypertensive treatment: further results of the European Lacidipine Study on Atherosclerosis (ELSA). J Hypertens 2004;22:1201-12.

7) Zanchetti A, Bond MG, Hennig M, et al. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. Circulation 2002;106:2422-7.

8) Fratola A, Panat G, Castiglione P, et al. Lacidipine and blood pressure variability in diabetic hypertensive patients. Hypertension 2000;36:622-8.

9) Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002;39:257-65.

10) Salako BL, Kadiiri S, Walker O, Fehintola FA. Evaluation of lacidipine (a calcium blocker) in the treatment of hypertension in black African people: a double-blind comparison with hydrochlorothiazide. Afr J Med Med Sci 1998;27:73-5.

11) Tcherdakoff P. French large-scale study evaluating the tolerability and efficacy of lacidipine. J Cardiovasc Pharmacol 1995;25(Suppl 3):S273-2.

12) Kim DH, Oh SI, Kim YK, Choi SW, Yoo WS. Efficacy and safety of nifedipine gastrointestinal therapeutic system (Adalat OROS) in patients with mild to moderate essential hypertension. Korean Circ J 1992;22:488-93.

13) Choi YJ, Lee MM, Choe SJ, et al. A randomized, double-blind clinical trial to determine the efficacy of carvedilol vs. atenolol in patients with stage 1 to 2 essential hypertension. Korean Circ J 1998;28:359-65.

14) Jin SB, Rhee YW, Chang SW, Kim KC, Kim SP, Song CS. Effects of dihydrochlorothiazide, propranolol, and prazosin on serum lipids in patients with hypertension. Korean Circ J 1995;15:329-36.

15) Cheong HJ, Kang HS, Choe CW, et al. Antihypertensive effects and safety of irsipadine in patients with essential hypertension. Korean Circ J 1993;23:741-9.

16) Park SW, Do YC, Kim WH, et al. Amlodipine monotherapy in patients with mild to moderate essential hypertension. Korean Circ J 1992;22:852-7.

17) Pieper GM, Gross GI. Oxygen free radicals abolish endothelium-depen
dent relaxation in diabetic rat aorta. Am J Physiol 1988;255:HR825-33.

18) Tesfamariam B, Cohen RA. Free radicals mediate endothelial cell dysfunction caused by elevated glucose. Am J Physiol 1992;263:H321-6.

19) Dai FX, Diederich A, Skopec J, Diederich D. Diabetes-induced endothelial dysfunction in streptozotocin-treated rats: role of prostaglandin endoperoxides and free radicals. J Am Soc Nephrol 1993;4:1327-36.

20) Yugar-Toledo JC, Tanus-Santos JE, Sabba M, et al. Uncontrolled hypertension, uncompensated type II diabetes, and smoking have different patterns of vascular dysfunction. Chest 2004;125:823-30.

21) Ballesloher BM, Goebbel S, Rittig K, et al. Intense cholesterol lowering therapy with a HMGC-CoA reductase inhibitor does not improve nitric oxide dependent endothelial function in type-2-diabetes: a multicenter, randomised, double-blind, three-arm placebo-controlled clinical trial. Exp Clin Endocrinol Diabetes 2005;113:324-30.

22) stroes ES, Koomans HA, de Bruin TW, Rabelink TJ. Vascular function in the forearm of hypercholesterolaemic patients off and on lipid-lowering medication. Lancet 1995;346:467-71.

23) Economides PA, Caselli A, Tiani E, Khaodhiar L, Horton ES, Veses A. The effects of atorvastatin on endothelial function in diabetic patients and subjects at risk for type 2 diabetes. J Clin Endocrinol Metab 2004;89:740-7.

24) Guerci B, Bohme P, Kearney-Schwartz A, Zannad F, Drouin P. Endothelial dysfunction and type 2 diabetes: part 2. altered endothelial function and the effects of treatments in type 2 diabetes mellitus. Diabetes Metab 2001;27:436-47.

25) Brauenerreuther V, Mach F, Steffens S. The specific role of chemokines in atherosclerosis. Thromb Haemost 2007;97:714-21.

26) Sardo MA, Campo S, Mandrafino G, et al. Tissue factor and monocyte chemoattractant protein-1 expression in hypertensive individuals with normal or increased carotid intima-media wall thickness. Clin Chem 2008;54:814-23.

27) Bae JH, Bassenje E, Lim DM, Synn YC, Kim KY, Schwemmer M. Effects of lacidipine on vascular responses in patients with coronary artery disease. Int J Cardioiol 2005;101:377-83.

28) Koh KK, Han SH, Chung WJ, et al. Comparison of effects of losartan, irbesartan, and candesartan on flow-mediated brachial artery dilation and on inflammatory and thrombolytic markers in patients with systemic hypertension. Am J Cardiol 2004;93:1432-5.

29) Juhan-Vague I, Alessi MC, Vague P. Thrombogenic and fibrinolytic factors and cardiovascular risk in non-insulin-dependent diabetes mellitus. Ann Med 1996;28:371-80.

30) Kaitt K, Fogo AR, Ma L, Schoenhband JA, Brown NJ, Vaughan DE. Plasminogen activator inhibitor-1 deficiency prevents hypertension and vascular fibrosis in response to long-term nitric oxide synthase inhibition. Circulation 2001;104:839-44.