A 12-Month Comparison of ACE Inhibitor and Ca Antagonist Therapy in Mild to Moderate Essential Hypertension—The GLANT Study—

The GLANT Study Group*

Patients with mild to moderate essential hypertension were treated mainly with an ACE inhibitor (delapril, \(n=980\)) or a Ca antagonist (\(n=956\)) for 12 months, and the incidence of cerebrovascular and cardiovascular events as well as drug-related side effects were compared between the two groups. There were no significant differences between the clinical backgrounds of the two groups. In both groups, the blood pressure was decreased significantly from 1 month of treatment onwards, with the degree of reduction being greater in the Ca antagonist group throughout the study period (\(p<0.001\)). Cerebrovascular or cardiovascular events occurred in 11 out of 980 patients in the delapril group and 18 out of 956 patients in the Ca antagonist group (\(p=NS\)). Cerebrovascular disease developed in 5 delapril-treated patients and 11 Ca antagonist-treated patients, and heart disease developed in 5 and 7 patients, respectively (both \(p=NS\)). Discontinuation of treatment due to side effects was significantly more common in the delapril group than in the Ca antagonist group (\(p<0.001\)). There was no significant difference in the incidence of cerebrovascular and cardiovascular complications between the two groups, and the results suggested that blood pressure reduction per se did not necessarily lead to a parallel decrease in cerebrovascular and cardiovascular complications. (Hypertens Res 1995; 18: 235-244)

Key Words: GLANT study, delapril, Ca antagonists, cerebrovascular event, cardiovascular event

Among the many classes of antihypertensive agents currently available, the Ca antagonists have been most frequently used in recent years for the treatment of uncomplicated essential hypertension in Japan. The use of angiotensin converting enzyme (ACE) inhibitors has also increased recently, because these drugs may provide cardiovascular protective effects, although some side effects, such as cough, are more common with ACE inhibitors than with most other antihypertensive agents (1-3). This study was undertaken to investigate the long-term effects of ACE inhibitor and Ca antagonist therapy in a large number of patients with essential hypertension. It represents the first time that a clinical trial of long-term antihypertensive therapy has compared different classes of drugs in Japan. The preliminary results are reported here, with a comparison of side effects and cerebrovascular and cardiovascular events during the 12 months of treatment.

Patients and Methods

A study group on long-term antihypertensive therapy (the GLANT study group) was established, and a protocol was prepared by the central committee of this group (Table 1). The district coordinators (Table 2) invited local institutions to participate, and the study controller received case report forms from the coordinators for all patients who completed therapy, discontinued treatment, or dropped out.

All patients were established to have mild to moderate essential hypertension (a systolic blood pressure \(\geq 160\) mmHg and a diastolic blood pressure of 90-114 mmHg after an observation period of at least 2 weeks without antihypertensive therapy) and visited the outpatient clinics of the participating institutions between August 1990 and May 1992. The participating institutions consisted of the hospitals of the coordinators plus other institutions that were requested to participate in the study by the


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coordinators. The patients had either never previously received antihypertensive therapy or had terminated their antihypertensive therapy at least 1 month before the study. Informed consent was obtained from all patients before enrollment.

(1) Patient Selection and Enrollment
The attending physicians selected pairs of patients who matched each other as closely as possible in terms of age, blood pressure, renal function, and other background factors. One patient of each pair was given delapril and the other received a Ca antagonist. The study protocol is summarized in Fig. 1. The attending physicians filled in the patient enrollment forms within 1 week after the start of treatment and forwarded them to the controller.

(2) Antihypertensive Therapy
Delapril: Delapril treatment was commenced at the approved recommended dose of 30-60 mg/d. The maximum permitted dose was 120 mg/d. If a sufficient reduction in blood pressure was not obtained by delapril monotherapy, a β-blocker, a diuretic, or both drugs were additionally prescribed.

Ca antagonist: Any kind of commercially available Ca antagonist could be used in this study, and the approved treatment schedule for each drug was followed. If the antihypertensive effect of Ca antagonist monotherapy was inadequate, a β-blocker, a diuretic, or both drugs were additionally prescribed. However, the use of β-blockers was avoided in patients receiving diltiazem.

(3) Treatment Procedures
The goal of treatment was to reduce the blood pressure to 150/90 mmHg or less. If a sufficient reduction in blood pressure was not obtained by monotherapy, other antihypertensive agents were also used concomitantly as described above. If satisfactory blood pressure control was still not achieved, another antihypertensive agent was used in addition to the β-blocker and diuretic, and the patient was withdrawn from the study. The target duration of treatment was 12 months (Fig. 1).

(4) Evaluation
Variables studied: The development of any new symptoms or complications was assessed at each monthly visit. The time of onset, nature, treatment, course, and relationship to the patient’s antihypertensive therapy were determined for any symptoms that developed. The blood pressure and pulse rate were measured 2 weeks before the study, at the start of the study, and every month after starting treatment. Laboratory examinations were performed before and after 12 months of treatment (or on withdrawal). Any laboratory abnormalities were followed up after the completion or withdrawal of treatment, and were regarded to be side effects. Any new symptoms that developed during treatment were also defined as side effects, unless the relationship to the patient’s antihypertensive therapy was clearly ruled out. If necessary, the dose was reduced or treatment was discontinued in the patients who developed side effects.

(5) Enrollment and Recovery of Case Report Forms
A total of 2,246 patients were enrolled, and case report forms for 2,095 patients (93.3%) were received as of January 1993.

Table 1. The GLANT Study Group

Chairman: Teruo Omae
Central committee: Kiku Arakawa, Osamu Imura, Masao Ishii, Toshio Oghara, Teruo Omae, Yoshihiro Kaneko, Morio Kuramochi, Tatsuo Kokubu, Takao Saruta, Ryooy Takeda, Kunio Hiwada, Koishiro Fukiyama, Masatoshi Fujishima, Hiroaki Matsuoka, Kazuo Yamada, and Kaoru Yoshinaga
Controller: Naokata Shimizu

![Fig. 1. Outline of the study protocol.](image-url)
Table 2.  List of Coordinators

Hokkaido

1) Sapporo Medical College  
   (Second Department of Internal Medicine)  
   Osamu Iimura
2) Hokkaido University (School of Medicine)  
   (Department of Cardiology)  
   (Formerly) Hisakazu Yasuda, Akira Kitabatake
3) Asahikawa Medical College  
   (First Department of Internal Medicine)  
   (Formerly) Sokichi Onodera, Kenjiro Kikuchi
4) Hakodate National Hospital  
   (Department of Cardiology)  
   (Formerly) Yoshiyuki Suzuki, Sadasuke Anzai

Tohoku

1) Iwate Medical University  
   (Second Department of Internal Medicine)  
   (Formerly) Masataka Kato, Katsuhiko Hiramori
2) Hirosaki University (School of Medicine)  
   (Second Department of Internal Medicine)  
   Kougou Onodera
3) Tohoku University (School of Medicine)  
   (Second Department of Internal Medicine)  
   Keishi Abe
4) Labour Welfare Corporation Tohoku Rosai Hospital  
   Kaoru Yoshinaga
5) Fukushima Medical College  
   (Third Department of Internal Medicine)  
   Soutsu Fukuchi
6) Akita University (School of Medicine)  
   (Second Department of Internal Medicine)  
   (Formerly) Tomohiro Kanazawa, Mamoru Miura
7) Yamagata University (School of Medicine)  
   (First Department of Internal Medicine)  
   (Formerly) Shoji Yasui, Hitonobu Tomoike
8) Sendai National Hospital  
   (Department of Cardiology)  
   (Formerly) Koichi Ashikawa, Shigenori Kitaoka

Kita-kanto

1) Gunma University (School of Medicine)  
   (Second Department of Internal Medicine)  
   Kazuhiko Murata
2) Dokkyo University School of Medicine  
   (Department of Internal Medicine)  
   Shigeru Yagi
3) University of Tsukuba (School of Medicine)  
   (Department of Internal Medicine)  
   Yasuo Sugishita
4) Toride Kyodo General Hospital  
   (Department of Internal Medicine)  
   Tatsuo Shigai

Koushinetsu

1) Niigata University (School of Medicine)  
   (Second Department of Internal Medicine)  
   Masaaki Arakawa
2) Shinshu University (School of Medicine)  
   (First Department of Internal Medicine)  
   Morie Sekiguchi
3) Yamanashi Medical University  
   (Second Department of Internal Medicine)  
   Kouji Tamura
4) Yamanashi Prefecture Central Hospital  
   (Department of Internal Medicine)  
   Mitsuhiro Nezu
5) Nagaoka Red Cross Hospital  
   (Department of Internal Medicine)  
   Okuhiro Arai

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1) University of Tokyo (Faculty of Medicine)  
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2) Nihon University Surugadai Hospital  
   (Department of Cardiology)  
   Nagao Kajiwara
3) Tokyo Women's Medical College  
   (Fourth Department of Internal Medicine)  
   Nobuhiko Sugino
4) The Jikei University School of Medicine  
   (Second Department of Internal Medicine)  
   Osamu Sakai
5) Kyrin University (School of Medicine)  
   (First Department of Internal Medicine)  
   Toshihiko Nagasawa
6) Keio University (School of Medicine)  
   (Department of Internal Medicine)  
   Takao Saruta
7) Kitsato University (School of Medicine)  
   (Department of Internal Medicine)  
   Kousuke Kikawada
8) Chiba University (School of Medicine)  
   (Third Department of Internal Medicine)  
   Yoshiaki Inagaki
9) Yokohama City University (School of Medicine)  
   (Second Department of Internal Medicine)  
   Masao Ishii
10) Saitama Medical School  
    (Fourth Department of Internal Medicine)  
    Jun Ishii
11) Yokohama Hypertension Research Center  
    Yoshihiro Kaneko
12) National Saitama Hospital  
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    Toshihisa Miyazaki
13) The Tokyo Metropolitan Geriatrics Hospital  
    Kizuku Kuramoto

Nagoya

1) Hamamatsu University School of Medicine  
   (Third Department of Internal Medicine)  
   Noboru Yamazaki
2) Meitetsu Hospital  
    Kazuo Yamada
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6) Gifu University (School of Medicine)  
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    Senri Hirakawa
7) National Tosei Hospital  
    (Department of Internal Medicine)  
    Morio Kuramochi, Takashi Kitamura

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1) Kanazawa University (School of Medicine)  
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   Kenichi Kobayashi
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   (Second Department of Internal Medicine)  
   Ryoyu Takeda
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   (Department of Endocrinology)  
   Shinpei Morimoto
4) Kanazawa Medical University  
   (Department of Cardiology)  
   Eiji Murakami
5) Toyama Medical and Pharmaceutical University  
    (Second Department of Internal Medicine)  
    Hiroshi Inoue
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<th>Region</th>
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<td>Minamikyushu Chuo National Hospital</td>
<td>(Department of Cardiology)</td>
<td>Kunihiko Nomoto</td>
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</table>

(As of February 1993)
The GLANT Study Group: One Year Antihypertensive Therapy with Delapril or Ca Antagonists

(6) Final Study Population
The 151 patients without case report forms were excluded from analysis, along with 53 patients who concomitantly received drugs that violated the study protocol. In addition, patients who had a history of cerebrovascular disease or myocardial infarction and those who had angina pectoris or renal impairment (serum creatinine ≥ 2.0 mg/dl) were excluded from analysis. Consequently, a total of 1,936 patients (86.2%), consisting of 980 in the delapril group and 956 in the Ca antagonist group (Fig. 2), were analyzed. The Ca antagonist group included 440 patients (46.0%) treated with manidipine, 194 patients (20.3%) with nifedipine, 83 patients (8.7%) with nisoldipine, 74 patients (7.8%) with nicardipine, 74 patients (7.8%) with nilvadipine, 57 patients (6.0%) with nitrendipine, and 34 patients (3.6%) with other Ca antagonists.

(7) Patient Profiles
Table 3 shows the clinical profiles of the two groups of patients on entry into the study. There was no difference in age, blood pressure, or pulse rate between the groups. No difference was detected between the groups with respect to cardiovascular risk factors, such as diabetes and hyperlipidemia. Monotherapy predominated in both groups, being used in 88.1% of the delapril group and 90.3% of the Ca antagonist group. Diuretics were administered to 6.1% and 2.3% of the patients in the delapril and Ca antagonist groups, respectively, while β-blockers were given to 5.2% and 7.0%. In addition, both drugs were administered to 0.6% and 0.4% of the patients, respectively.

Statistical analysis: Data were analyzed by chi-square test, U-test, or Fisher’s exact probability test as appropriate and a P value less than 0.05 was considered to indicate statistical significant.
Results

(1) Blood Pressure and Pulse Rate
Figure 3 shows the blood pressure and pulse rate profiles during the study. In both groups, the blood pressure was decreased significantly after 1 month of treatment and blood pressure reduction was maintained thereafter. The degree of reduction in blood pressure was consistently greater in the Ca antagonist group than in the delapril group ($p < 0.001$). The pretreatment blood pressure (systolic/diastolic) was 170 ± 14/99 ± 9 mmHg in the delapril group and 171 ± 14/99 ± 9 mmHg in the Ca antagonist group, and it decreased to 147 ± 17/86 ± 11 mmHg and 142 ± 15/83 ± 11 mmHg, respectively, after 12 months of treatment. The pulse rate did not change significantly in either group, as compared to the pretreatment value.

(2) Cerebrovascular or Cardiovascular Events and Mortality
Cerebrovascular or cardiovascular events occurred in 11 patients in the delapril group and 18 patients in the Ca antagonist group ($p = NS$; Table 4). Cerebrovascular disease was newly diagnosed in 5 delapril-treated patients and 11 Ca antagonist-treated patients ($p = NS$), while cardiac disease was newly diagnosed in 5 and 7 patients, respectively ($p = NS$). Three patients in the delapril group and 4 patients in the Ca antagonist group died during the study ($p = NS$). In the delapril group, there was 1 death due to myocardial infarction, 1 sudden death, and 1 death due to cancer. In the Ca antagonist group, the cause of death was cerebrovascular disease in 3 patients and cancer in 1 patient (Table 5).

(3) Side Effects
A total of 226 symptoms were identified as side effects in 195 (19.9%) of the 980 patients in the

Table 4. Cerebrovascular and Cardiovascular Complications

<table>
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<tr>
<th></th>
<th>Delapril group ($n=980$)</th>
<th>Ca antagonist group ($n=956$)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients (%)</td>
<td>No. of deaths (%)</td>
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<td>Cerebrovascular</td>
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<td>Cerebral hemorrhage</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
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<tr>
<td>Cerebral infarction/thrombosis</td>
<td>3 (0.3)</td>
<td>8 (0.8)</td>
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<td>TIAs</td>
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<tr>
<td>Cardiovascular</td>
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<td>2 (0.2)</td>
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<tr>
<td>Myocardial infarction</td>
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<td>Sudden death</td>
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<td>Angina pectoris</td>
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<td>Heart failure</td>
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<td>Arrhythmia</td>
<td>2 (0.2)</td>
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<tr>
<td>Retinal hemorrhage</td>
<td>1 (0.1)</td>
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</tr>
</tbody>
</table>

TIA = Transient ischemic attacks.
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delapril group and 168 symptoms were identified as side effects in 126 (13.2%) of the 956 patients in the Ca antagonist group (p < 0.02 and p < 0.001, respectively; Table 6). Cough was the major symptom in the delapril group, and was reported in 138 patients (14.1%). The major symptoms in the Ca antagonist group included facial flushing in 42 patients (4.4%), palpitations/tachycardia in 27 patients (2.8%), and dizziness in 20 patients (2.1%). Treatment was withdrawn due to side effects in 95 patients (9.7%) in the delapril group and 28 patients (2.9%) in the Ca antagonist group (p < 0.001). In addition, there were 198 abnormal laboratory findings that were probably attributed to treatment in 149 patients of the delapril group and 181 such abnormalities in 130 patients of the Ca antagonist group (p = NS; Table 7). One hundred seventy-one patients in the delapril group and 157 patients in the Ca antagonist group dropped out due to personal reasons of the patients.

### Discussion

Antihypertensive drugs with various modes of action, such as ACE inhibitors, Ca antagonists, and \( \alpha_1 \)-blockers, are widely used in clinical practice. Unlike diuretics, these drugs have been reported to have minimal adverse metabolic effects (in fact, favorable effects have actually been reported (4, 5)), and they are expected to be more useful in the prevention of cardiovascular complications. In Europe, the effect of antihypertensive therapy on the development of cardiovascular complications is currently being evaluated in a double-blind study in which patients are randomly assigned to receive Ca antagonists, ACE inhibitors, diuretics, and placebo (Syst-Eur Study) (6); however, the final results have not yet been reported. The final results of the treatment of mild hypertension study (7) have recently been reported in the United States. In this study,
patients with mild hypertension were divided into six groups and placed on nutritional-hygienic regimens. Each group was randomly assigned to receive a Ca antagonist, β-blocker, diuretic, α₁-blocker, ACE inhibitor, or placebo under double-blind conditions. The results indicate a lower incidence of major cardiovascular and other clinical events in the drug-treated groups, but there was no significant difference in these events among the different antihypertensive agents owing to the small number of patients studied. In the present study, we performed a preliminary, 12-month comparison between delapril and Ca antagonists (mainly dihydropyridine derivatives such as manidipine and nifedipine) in about 2,000 patients with mild to moderate essential hypertension. We compared the antihypertensive effect, the incidence of side effects, and the cerebrovascular and cardiovascular morbidity and mortality rates between these two classes of drugs. Both in the delapril group and the Ca antagonist group, nearly 90% of the patients were treated by monotherapy. A significant and persistent reduction in blood pressure was obtained in both groups, and the degree of this reduction was greater in the Ca antagonist group. Although this suggested that the antihypertensive effect of Ca antagonist therapy was more potent than that of delapril, the use of an inadequate dose of delapril may have contributed to these results (Fig. 4). In addition, the incidence of side effects was significantly lower in the Ca antagonist group than in the delapril group. However, the incidence of cerebrovascular events was slightly higher in the Ca antagonist group, although the difference with the delapril group was not statistically significant.

In patients with mild to moderate essential hypertension, the stepped-care approach using diuretics

Table 7. Abnormal Laboratory Findings

<table>
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<th>Item</th>
<th>Delapril group (n=980)</th>
<th>Ca antagonist group (n=956)</th>
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<td>RBC</td>
<td>8 incidents (0.8%)</td>
<td>3 incidents (0.3%)</td>
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<td>WBC</td>
<td>14 (1.4%)</td>
<td>17 (1.8%)</td>
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<td>Hemoglobin</td>
<td>12 (1.2%)</td>
<td>13 (1.5%)</td>
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<td>GOT</td>
<td>15 (1.5%)</td>
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<tr>
<td>GPT</td>
<td>21 (2.1%)</td>
<td>25 (2.6%)</td>
</tr>
<tr>
<td>BUN</td>
<td>20 (2.0%)</td>
<td>16 (1.7%)</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>4 (0.4%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>16 (1.6%)</td>
<td>14 (1.5%)</td>
</tr>
<tr>
<td>Na</td>
<td>3 (0.3%)</td>
<td>5 (0.5%)</td>
</tr>
<tr>
<td>K</td>
<td>11 (1.1%)</td>
<td>6 (0.6%)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>20 (2.0%)</td>
<td>5 (0.5%)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>27 (2.8%)</td>
<td>37 (3.9%)</td>
</tr>
<tr>
<td>Urinary protein</td>
<td>18 (1.8%)</td>
<td>22 (2.3%)</td>
</tr>
<tr>
<td>Urinary glucose</td>
<td>9 (0.9%)</td>
<td>9 (0.9%)</td>
</tr>
<tr>
<td>Total number of anomalies</td>
<td>198</td>
<td>181</td>
</tr>
<tr>
<td>No. of subjects with abnormalities</td>
<td>149 (15.2%)</td>
<td>130 (13.6%)</td>
</tr>
</tbody>
</table>

![Fig. 4. Daily doses of the main drugs. Figures in parentheses indicate percentages.](image)
vascular and cardiovascular complications. Howev-
er particular marked (8-15). Large-scale studies of
antihypertensive agents have generally compared
prophylactic effect on cerebrovascular disease being
reportedly in the VA, ANBPS, OSLO, MRC, and MAPHY studies. Thus, after
taking into account the influence of age, the car-
diovascular disease morbidity, especially that due to
coronary artery disease, appears to be lower in treat-
ed Japanese hypertensive patients than in Western
patients. This may suggest that Western patients
have more risk factors for cardiovascular disease
than Japanese. It also appears necessary to assess
cardiovascular and cerebrovascular morbidity in re-
lated to the type of antihypertensive therapy em-
ployed, since diuretics and beta blockers were pri-
arily used in the Western studies, whereas an
ACE inhibitor and Ca antagonists were used in the
present study.

In this study, the incidence of cerebrovascular
disease tended to be lower in the group treated with
delapril, despite the fact that its antihypertensive
effect was lower than that in the Ca antagonist
group. These findings suggest that the hypotensive
effects of antihypertensive agents may not neces-
sarily parallel with their organoprotective effects. The
effect of delapril on cerebrovascular disease needs
to be investigated more extensively in the future.

In conclusion, the present study suggests that the
incidence of side effects was significantly lower and
the blood pressure reduction was significantly great-
er in the Ca antagonist group than in the delapril
group, however, the greater blood pressure reduc-
tion per se was not necessarily associated with a re-
duction of cerebrovascular and cardiovascular
events. Since the present 12-month trial was con-
ducted as a preliminary study, we plan to extend
the duration of treatment and investigate the effects
of these two classes of drugs on the long-term out-
come in our two groups of patients.

Acknowledgement

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