Original Article

Effects of Candesartan on Cardiovascular Outcomes in Japanese Hypertensive Patients

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In recent years, angiotensin receptor blockers (ARBs) have begun to represent a markedly larger percentage of the antihypertensive agents used in Japan. However, it remains uncertain whether ARBs are effective for protecting against hypertension-related organ damage in the general Japanese population. In the present report, we describe the results of a single blind, randomized, prospective study conducted in 1999–2002 and employing a total of 2,048 essential hypertensive subjects (sitting blood pressure 140–180/90–110 mmHg) aged 35–79 years. Subjects were randomly assigned to receive the ARB candesartan, 2 to 12 mg daily, or conventional antihypertensive drugs other than angiotensin converting enzyme inhibitors or ARBs. We used Cox regression analysis to compare the two regimens. The primary outcome was assessed by hospitalization due to stroke, myocardial infarction, and congestive heart failure. Blood pressure was reduced from 162.1/91.1 to 140.1/78.9 mmHg in the candesartan group and from 165.9/95.9 to 138.4/81.1 mmHg in the conventional therapy group. The main outcomes were as follows: there was a 39% reduction in hospitalization for stroke (5.8 vs. 9.4 cases: relative risk [RR]: 0.61; 95% confidence interval [CI]: 0.41–0.84; $p < 0.05$) and a 57% reduction in hospitalization for myocardial infarction (RR: 0.44; CI: 0.21–0.84; $p < 0.05$) with the candesartan-based treatment compared with the conventional treatment. In spite of a significant difference in the total incidence of both stroke and myocardial infarction, there was no significant reduction in the incidence of congestive heart failure (15% reduction: 4.3 vs. 5.0; RR: 0.85; CI: 0.57–1.26). Further analysis in stratifying the subjects with or without a past history of cardiovascular diseases including stroke and myocardial infarction revealed that candesartan reduced the incidence of stroke (61% reduction; RR: 0.39; CI: 0.15–0.43; $p < 0.01$) and congestive heart failure (49% reduction; RR: 0.51; CI: 0.23–0.92; $p < 0.05$) but not myocardial infarction (RR: 0.74; CI: 0.36–1.48; $p = 0.1$) in hypertensive patients with a past history. However, conventional treatment was superior to candesartan-based treatment in reducing the incidence of stroke in the patients without a past history of cardiovascular diseases (66% reduction; RR: 0.34; CI: 0.16–0.69; $p < 0.05$). This is the first demonstration that an ARB-based antihypertensive treatment was superior to the conventional treatment for reducing the risk of stroke and myocardial infarction in Japanese hypertensive patients, especially in the patients with a past history of cardiovascular diseases. (*Hypertens Res* 2005; 28: 307–314)

Key Words: cardiovascular diseases, stroke, myocardial infarction, congestive heart failure, angiotensin receptor blocker

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A part of this study was presented at the 26th Annual Meeting of the Japanese Society of Hypertension (Fukuoka, Japan, 2003) and at the 20th Annual Meeting of International Society of Hypertension (Sao Paulo, Brazil, 2004).

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Received November 22, 2004; Accepted in revised form January 31, 2005.

Introduction

A number of large clinical trials have recently demonstrated that angiotensin II type 1 receptor blockers (ARBs) are equal to or more effective than conventional antihypertensive treatments in protecting against organ damage due to hypertension (1, 2). In Japan, ARBs are currently ranked as the second most highly prescribed antihypertensive drugs after calcium channel blockers (CCBs). Previously, Japanese physicians have been reluctant to prescribe angiotensin converting enzyme (ACE) inhibitors, mainly because of the adverse effect of dry cough (3). In addition, the leading cause of death related to hypertension has been and still remains stroke. Based on this higher incidence of stroke compared to other cardiovascular diseases, such as myocardial infarction, in Japan, primary care physicians frequently select CCBs for the treatment of subjects with hypertension (4). The finding, in a meta-analysis by Staessen *et al.*, that CCBs were effective for stroke prevention would seem to support this choice (5). Recently, however, the specific causes of hypertension-related deaths have begun to change. In 2002, the death rate due to cardiac diseases was comparable to that of stroke (6). Japanese physicians must now change their therapeutic strategy for hypertension according to this paradigm shift from stroke to myocardial infarction, angina and congestive heart failure.

The present study was conducted as a prospective, randomized, open-labeled trial to examine the effects of candesartan, an ARB, in Japanese patients with hypertension, since there is already evidence that ARBs do exert the predicted cardioprotective effects (7–10).

Methods

Study Design and Organization

The Efficacy of Candesartan on Outcome in Saitama Trial (E-COST) was an investigator-initiated, prospective, multicenter, open-label, randomized, active-controlled, parallel-group study. The primary objective was to evaluate the long-term effects of once daily candesartan-based vs. conventional therapy in patients with hypertension. The trial protocol was approved by the ethics committees of all participating institutions, was conducted in accordance with the Declaration of Helsinki, and was overseen by an independent data and safety monitoring board. All patients gave written, informed consent.

Target Population and Treatment Schedule

This study included patients who were 35 through 79 years of age with previously treated or untreated hypertension. Patients randomized to receive candesartan- or conventional-based regimens after a 2–4 week run-in period were included

Fig. 1. The protocol of the present study. Patients randomized to receive candesartan- or conventional-based regimens after a 2–4 week run-in period were selected to be included in this analysis if their trough sitting blood pressure was between 140–180 mmHg systolic and/or their diastolic pressure was between 90–110 mmHg.

in the analysis if their trough sitting blood pressures were between 140–180 mmHg systolic and/or between 90–110 mmHg diastolic (Fig. 1). We excluded patients with a history of diabetes, or who had a fasting blood glucose level of >126 mg/dl or postprandial glucose level of >200 mg/dl.

Patients with secondary hypertension or a history of myocardial infarction or stroke within the previous 6 months were excluded. Patients with angina pectoris requiring treatment with β -blockers or CCBs, heart failure, a left ventricular ejection fraction of 40% or less, a disorder that in the treating physician's opinion required treatment with candesartan or another type of ARB, or patients receiving ACE inhibitors were also excluded. There was no stratification as part of the randomization process. From the beginning of September 1999 to the end of December 1999, a total of 2,048 patients with hypertension were randomly assigned. The randomization was performed by the envelope method. That is, the names of subjects were written on slips of paper, and the physician randomly placed the slips of paper into envelopes representing the different group assignments. All patients were followed-up until death, or for 5 years, whichever came first. Patients were followed-up for 3 years with regular visits and upward titration of medication to reach a target systolic blood pressure (SBP) of less than 140 mmHg and a diastolic blood pressure (DBP) of less than 90 mmHg.

Outcome Measures

The primary outcome was stroke, myocardial infarction and congestive heart failure, which included fatal and non-fatal incidents. These outcomes were verified by medical records at admission. Routine laboratory tests were performed in 4 central laboratories. Adverse events were monitored throughout the study. The study ran its full course and end-point follow-up was stopped on December 31, 2002.

Table 1. Demographic Data of the Patients at the Administration of the Study

	Candesartan group	Conventional group	<i>p</i>
Total	1,053	995	
Gender			
Male	468 (44.5)	515 (51.8)	<0.01
Female	585 (55.5)	480 (48.2)	
Age			
>65	528 (50.2)	527 (53.0)	
≤65	525 (49.8)	468 (47.0)	
Past history	162 (15.4)	179 (18.0)	
SBP (mean±SD)	162.1±9.2	165.9±5.8	
DBP (mean±SD)	91.1±6.1	95.9±5.6	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure.

Statistical Methods

The baseline characteristics of the two treatment groups were compared by Student's *t*-test, χ^2 testing and a nonparametric test (Wilcoxon test). Differences between treatment groups in post-randomization measures or events were evaluated by analysis of variance and with the χ^2 test.

Hazard ratios (relative risks [RR]) and 95% confidence intervals (CIs) were obtained from the Cox proportional hazards regression model (11). The risk reduction for candesartan vs. the conventional treatment was calculated as $100 \times (1 - \text{RR})$. Results of the primary end-point analysis were independently validated by experts from the statistics laboratories (Fields Works Co., Ltd., Hyogo, Japan). All data are reported as the means±SEM. The final analysis of the primary end-point variable was tested at a two-sided 5% significance level. All other tests were done using two-sided 5% significance levels. Statistical significance was set at $p < 0.05$. SPSS software, version 11.0.1 (SPSS Inc., Chicago, USA) was used for statistical analysis.

Results

Follow-Up and Blood Pressure Control

Patients assigned to receive either candesartan- or conventional-based treatment had similar characteristics except with respect to two items: SBP/DBP and the proportion of males (Table 1). The mean follow-up time (from randomization to death, loss to follow-up, or the end of the study) was 3.1 ± 0.4 years. Seventy-seven point three percent and 81.9% of patients continued their medication until the end of the study in the candesartan and the conventional groups, respectively (Fig. 2).

The mean sitting blood pressures at the end of follow-up and at the last visit preceding a primary end point were reduced from $162.1 \pm 9.2/91.1 \pm 6.1$ to $140.1 \pm 7.6/78.9 \pm 5.4$

Fig. 2. Results of the patients who completed the protocol. By the end of the study, 238 subjects in the candesartan group and 180 in the conventional therapy group had dropped out of the E-COST for various reasons that were not directly related to medically adverse effects.

Fig. 3. Serial changes in blood pressure in both groups. The mean sitting blood pressures was reduced from $162.1/91.1$ to $140.1/78.9$ mmHg in the candesartan group and from $165.9/95.9$ to $138.4/81.1$ mmHg in the conventional therapy group. The basal levels of both SBP and DBP of the candesartan group were significantly lower than those of the conventional therapy group ($p < 0.001$).

mmHg in the candesartan group and from $165.9 \pm 5.8/95.9 \pm 5.6$ to $138.4 \pm 7.9/81.1 \pm 7.5$ mmHg in the conventional therapy group, respectively. The basal levels of both SBP and DBP of the candesartan group were significantly lower than those of the conventional therapy group ($p < 0.001$) (Fig. 3). However, at the end of the study, there were no significant differences in DBP and a significant difference was again found in SBP. A blood pressure of less than $140/90$ mmHg was achieved for 75% of those taking candesartan and 76% of those taking conventional antihypertensive drugs. The serial changes in SBP and DBP control in the patients with or without a past history of cardiovascular event are shown in Table 2. The percentage of patients who were taking statins or aspi-

Table 2. Changes in Blood Pressure (mmHg)

	Years			
	0	1	2	3
Systolic blood pressure				
Candesartan treated				
With past history	163.3±5.5	144.3±4.2	139.9±5.6	141.1±5.1
Without past history	161.1±6.3	141.6±4.9	139.0±6.3	139.8±4.3
Conventional treated				
With past history	166.4±6.2	139.1±4.8	137.6±5.0	138.4±5.8
Without past history	165.2±5.3	138.3±5.3	137.1±5.1	137.6±5.4
Diastolic blood pressure				
Candesartan treated				
With past history	92.1±3.4	82.6±4.1	81.0±3.3	79.3±4.0
Without past history	90.7±4.4	80.2±3.6	80.6±4.2	78.1±4.8
Conventional treated				
With past history	96.2±4.1	81.2±5.2	79.0±5.5	80.9±4.2
Without past history	95.3±4.4	80.3±4.8	79.8±4.8	81.3±4.3

rin at the beginning of the study was higher among patients with a past history of cardiovascular events than among those without such a history (185/295 [68%] vs. 165/1,412 [12%]).

Occurrence of End Points

The main outcomes of this study were that there was a 39% reduction in the incidence of stroke (5.8 vs. 9.4 cases; RR: 0.61; 95% CI: 0.41–0.84; $p<0.05$) and a 57% reduction in the incidence of myocardial infarction (1.2 vs. 2.8 cases; RR: 0.44; CI: 0.21–0.84; $p<0.05$) with the candesartan-based treatment compared with the conventional treatment. In spite of the significant difference in the total incidence of both stroke and myocardial infarction, there was no significant reduction in the incidence of congestive heart failure (15% reduction: 4.3 vs. 5.0 cases; RR: 0.85; CI: 0.57–1.26). Further analysis in stratifying the subjects with or without a past history of cardiovascular diseases including stroke and myocardial infarction revealed that candesartan reduced the incidence of stroke (61% reduction; RR: 0.39; CI: 0.15–0.43; $p<0.01$) and congestive heart failure (49% reduction; RR: 0.51; CI: 0.23–0.92; $p<0.05$) but not myocardial infarction (RR: 0.74; CI: 0.36–1.48; $p=0.1$) in hypertensive patients with a past history (Table 3). Four persons died in each group: two deaths in each group were due to malignant neoplasm, one death in the candesartan group and two in the conventional group were due to traffic accidents, and one patient in the candesartan group died while taking a bath. No particular cause of death was predominant.

Adverse Events and Safety Profile

Candesartan was better tolerated with fewer overall and drug-related discontinuations. No other unexpected or clinically important changes in laboratory values were seen.

Dosage of Drugs

The initial dose of study medication was 4 mg in 263 (25%) and 8 mg in 726 (69%) patients. At the end of the study, the dose of candesartan was 4 mg in 195 (24%) and 8 mg in 579 (71%) patients due to discontinuation in 238 patients (22%) of the candesartan group and 180 patients (18%) of the conventional-therapy group. The mean daily doses were 6.85 ± 1.75 mg at the start and 6.99 ± 1.73 mg at the end of the study. Only 21.5% of the patients who received the candesartan-based treatment were taking more than two additional drugs. In contrast, 71.5% of the patients who received the conventional-based treatment were taking more than two additional drugs. As a CCB, the following drugs were used: amlodipine (2.5–10 mg/day) (75% in the candesartan group; 82% in the conventional group), benidipine (2–8 mg/day) (11% in the candesartan group; 8% in the conventional group), cilnidipine (10 mg/day) (8% in candesartan group; 6% in conventional group), and long-acting nifedipine (20–80 mg/day) (6% in the candesartan group; 4% in the conventional group). The lists of antihypertensive drugs used in combination are shown in Table 4.

Discontinuation of Study Therapy

By the end of the study, 238 patients (23%) in the candesartan group and 180 patients (18%) in the conventional therapy group had discontinued from the E-COST for various reasons that did not directly relate to medically adverse effects in the 2 groups.

Discussion

Our results show that an antihypertensive treatment based on an ARB, candesartan, was better than conventional-based

Table 3. Incidence of Cardiovascular Events

Event		Candesartan	Conventional	Relative risk	95% CI
Heart failure	Total	35 (4.3%)	41 (5.0%)	0.85	0.57–1.26
	With past history	11 (8.7%)	25 (17.0%)	0.51	0.23–0.92
	Without past history	24 (3.5%)	16 (2.4%)	1.45	0.70–3.08
Myocardial infarction	Total	10 (1.2%)	23 (2.8%)	0.44	0.21–0.84
	With past history	7 (5.6%)	11 (7.5%)	0.74	0.36–1.48
	Without past history	3 (0.4%)	12 (1.8%)	0.24	0.08–0.69
Stroke	Total	47 (5.8%)	77 (9.4%)	0.61	0.41–0.84
	With past history	23 (18.3%)	69 (46.9%)	0.39	0.15–0.43
	Without past history	24 (3.5%)	8 (1.2%)	2.91	1.31–6.79

Incidences in each group were expressed in number of patients (%).

treatment in reducing the frequency of stroke, myocardial infarction, and congestive heart failure. The main outcome was that the candesartan-based treatment reduced the incidence of stroke by 39% and that of myocardial infarction by 57% compared with the conventional treatment. Patients receiving candesartan also showed a reduction in the incidence of congestive heart failure, but this trend did not reach the level of statistical significance. Moreover, analysis of the presence or absence of cardiovascular diseases including stroke and myocardial infarction at enrollment revealed that candesartan was significantly more effective in secondary prevention of stroke and congestive heart failure but not myocardial infarction compared to the conventional antihypertensive treatment.

Although there has been a gradual decline in the incidence of stroke due to hypertension in Japan, a reduction in the incidence of stroke remains an important target in the treatment of hypertension (6).

In this study, the candesartan-based antihypertensive treatment resulted in a marked reduction of stroke compared to the conventional antihypertensive treatment without ARBs. These results are encouraging, since they suggest that candesartan may have significant effects on stroke and myocardial infarction over and above its effects on blood pressure, which in turn suggests that factors other than blood pressure-lowering effects might be important for the reduction of stroke. Similar findings were observed in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study (12), in which the incidence of stroke was 5% in the losartan-treated group and 7% in the atenolol-treated group; both drugs thus achieved an approximately 28% reduction in stroke incidence, although there were small differences in blood pressure reduction between the two groups. In the present study, there was a substantial blood-pressure reduction with both antihypertensive treatments (*i.e.*, the candesartan and the conventional treatment) and a small but significant difference in the levels of SBP at the end of the study. The levels of DBP in the candesartan-based treatment group were lower than those in the conventional-based treatment group, but these differences did not reach the level of

statistical significance. In the present study, the conventional treatment was superior to candesartan-based treatment in reducing stroke in the patients without a past history of cardiovascular diseases, as reflected by the small differences in SBP (5, 13).

In the present study, a past history of vascular disease significantly influenced the incidence of stroke. The risk for stroke in the patients with a past history of cardiovascular disease was approximately 5 times higher than that of patients without a past history of such disease. The overall reduction in recurrent stroke risk seen in the present study was of comparable size to the reduction in the Perindopril Protection against Recurrent Stroke Study (PROGRESS) (14) and the overall reduction in initial stroke risk was of comparable size to the reduction in the Heart Outcomes Prevention Evaluation (HOPE) Study (32%) (15). In the present study, a more marked reduction in the risk of recurrent stroke was found, probably due to the differences in incidence of stroke between the Western countries and Japan. In the Western countries, the incidence of stroke is lower than in Japan. However, the incidence of cardiovascular diseases in the Western countries is higher than that in Japan. In the present study, the incidence of stroke was 5 to 7%. On the other hand, that of myocardial infarction was 2%. In addition, we cannot exclude the possibility that the small but not significant difference in the number of patients with past cardiovascular history between the candesartan group (162) and conventional group (179) affected the present outcome.

A recent large-scale clinical trial showed no significant difference in the incidence of myocardial infarction between a group receiving ARBs and a group receiving more conventional therapy (12). Moreover, in the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) Trial (16), myocardial infarction was significantly more frequent in the group receiving valsartan, an ARB. Unlike ACE inhibitors, which have been proven effective for reducing mortality and morbidity from myocardial infarction (17), ARBs have not been clearly shown to prevent the progression of ischemic events. In the present study, treatment with candesartan reduced the incidence of myocardial infarction in the patients

Table 4. Combined Antihypertensive Drugs

	Candesartan (<i>n</i> =815)	Conventional (<i>n</i> =815)
Diuretics	5.4%	3.9%
β-Blockers (including α-β blockers)	15.5%	34.0%
CCBs	48.1%	90.5%
Others	7.8%	16.8%

CCBs, calcium channel blockers; amlodipine (2.5–10 mg/day: 75% in candesartan group; 82% in conventional group), benidipine (2–8 mg/day: 11% in candesartan group; 8% in conventional group); cilnidipine (10 mg/day: 8% in candesartan group; 6% in conventional group); long-acting nifedipine (20–80 mg/day: 6% in candesartan group; 4% in conventional group).

without a past history of cardiovascular events. In the patients with a past history of cardiovascular events, there were no significant differences in the incidence of myocardial infarction. This might be explained by the fact that the patients with a past history of cardiovascular events were being treated with a statin or antiplatelet drug such as aspirin. This may have contributed to the failure of treatment with candesartan to reduce the rate of cardiovascular events in these patients. Similar findings were reported by a recent clinical trial (the Prevention of Events with Angiotensin Converting Enzyme Inhibition Trial; PEACE)—*i.e.*, the addition of an ACE inhibitor did not provide further benefit in terms of protecting against death from cardiovascular causes, myocardial infarction, or coronary revascularization (18). Interestingly, 70% of patients in the PEACE Trial were receiving lipid-lowering therapy and had an average left ventricular ejection fraction of 58%. In the present study, 68% of the patients with a past history of cardiovascular events received statins, antiplatelet drugs, or both, and the patients who had a lower left ventricular ejection fraction of less than 40% were excluded. In consideration of these findings and those of the PEACE Trial, we conclude that the inhibition with ACE inhibitors or ARBs has no beneficial effect on cardiovascular events in patients with a past history of cardiovascular events who are being intensively treated with statins and/or antiplatelet drugs.

Recently the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Study (10, 19, 20) demonstrated that candesartan use causes a 21% reduction in the risk of congestive heart failure among patients who have heart failure and left ventricular ejection fraction higher than 40%. Furthermore, in the CHARM Study, there were no significant differences in the total number of patients with myocardial infarction and stroke between the candesartan and the placebo groups. In our study, we excluded the patients with heart failure or left ventricular ejection fraction of 40% or less and found a 15% reduction of congestive heart failure in the candesartan group compared to the conventional group. Although this result did not achieve

statistical significance, further analysis revealed that in the patients with a past history of cardiovascular events, treatment with candesartan reduced the incidence of congestive heart failure by 45%, and this result was significant. This indicates that in patients with a high risk of cardiovascular events, treatment with ARBs would be beneficial for prevention of congestive heart failure.

Some limitations to this study need to be mentioned. First, E-COST was not financially supported by any pharmaceutical company or by the Japanese government, and thus neither the physicians nor the subjects were compensated financially. This may have influenced the fact that a greater number of patients discontinued the study in spite of well-tolerance for both candesartan and conventional antihypertensive therapy. Second, the study was not carried out in a double-blind manner but rather as an open-label study. These kinds of defaults in methodology might have induced some preference bias in the two groups; however, no significant differences between the two groups were noted, except the higher SBP of patients in the conventional groups compared to the candesartan group at the beginning of the study. In addition, the small difference between the two groups with respect to the number of patients with a past history of cardiovascular diseases did not reach the level of statistical significance. It therefore appears that the use of an open-label, randomized design to evaluate the effects of candesartan on cardiovascular mortality and morbidity in the present study was valid. Third, this study was discontinued at 3 years of follow-up for two major reasons: the rapid appearance of ARBs in the Japanese market led to a relatively large number of patient withdrawals, and the difference in the composite end point (stroke, myocardial infarction and congestive heart failure) between the candesartan and the conventional groups became statistically significant. This shorter period compared to the other large clinical trials, which were usually conducted for at least for 5 years in hypertensive patients, might have been partly responsible for the present finding that there was no significant difference in the incidence of all cardiovascular events between candesartan and the conventional groups, especially in hypertensive patients without a past history of cardiovascular disease.

Candesartan has already been established as an effective once-daily blood-pressure-lowering drug with excellent tolerability, an effective agent for blocking angiotensin II type I-receptor, and an effective agent for conferring protection against further cardiovascular events in patients with a history of congestive heart failure (8–10) and non-fatal stroke (21).

Our finding that candesartan was effective for treating patients with essential hypertension may suggest that this agent would also be useful for treating numerous cardiovascular diseases complicated by hypertension.

Acknowledgements

The authors wish to thank Professor T. Saruta for his excellent and careful review of our manuscript.

Appendix

Members of the E-COST Group

Akihiko Kanai (Kanai Clinic), Akiko Iino (Iino Clinic), Atsushi Yoshikawa (Yoshikawa Surgery and Gastrointestinal Clinic), Hakuko Kojima (Kojima Clinic), Hiromichi Suzuki (Musashi Ranzan Hospital, Chichibu Hospital, Saitama Medical School, Ikebukuro Hospital), Hiroshi Nakamura (Tokorozawa Ishikawa Clinic), Hiroshi Suga (Suga Clinic), Hiroshi Takei (Takei Clinic), Hiroyuki Yamamoto (Yamamoto Clinic), Hisao Saitou (Saitou Clinic), Hitoshi Okuaki (Okuaki Medical), Ikurou Osuga (Tsurugashima Ikenodai Hospital), Isao Toyoda (Toyoda Geka Iin), Junichi Shibuya (Shibuya Clinic), Junji Shimizu (Shimizu Medical Clinic), Kazuhisa Mori (Kakuei Clinic), Kazumine Lin (Kahinata Clinic), Kazunobu Egawa (Egawa Clinic), Kazunori Ogino (Ogino Hospital), Kazuo Yoshida (Akiya Hospital), Kazuya Hayashida (Hayashida Clinic), Kenji Kaneko (Kaneko Clinic), Kento Mashiko (Kodama Central Hospital), Kimihiko Yukisada (Yukisada Hospital), Kouya Sakamoto (Sakamoto Clinic), Kuninori Komahashi (Komahashi Clinic), Manabu Yamada (Fujikura Hospital), Masaharu Kaneko (Irumadai Clinic), Masahiko Matsumoto (Matsumoto Clinic), Masahiko Tanaka (Kan-etsu Hospital), Masahiko Tanaka (Tanaka Clinic), Masami Yamada (Yamada Clinic), Masao Toyoda (Toyoda Clinic), Masashi Ichiyama (Sakura Ganka Naika), Masataka Nishizawa (Seto Hospital), Masaya Minato (Minato Clinic), Michiko Horinaka (Horinaka Hospital), Naofumi Isogai (Isogai Clinic), Noriyo Sekine (Sekine Clinic), Shigeru Kawaguchi (Wakaba Hospital), Shinichi Yoshida (Yoshida Clinic), Sou Yuzawa (Mihashi Yuzawa Geka Iin), Susumu Hanzawa (Mitsuwachou Clinic), Susumu Hirano (Hirano Clinic), Shoji Usuda (Usuda Clinic), Tadaomi Suzuki (Kitamoto Central Clinic), Takamasa Haruta (Haruta Iin), Takashi Imamura (Yono House Clinic), Tatsuya Sekiyama (Sekiyama-Iin), Tatsuyuki Iijima (Iijima Clinic), Tohru Kon (Akiya Hospital), Toshiaki Ishii (Tsurugashima Ikenodai Hospital), Toshiaki Yokota (Yokota Clinic), Toshio Ito (Imai Medical Hospital), Toshio Komazaki (Saino Clinic), Tsukasa Nakamura (Misato Junshin General Hospital), Yasuhiro Imai (Tsurugashima Ikenodai Hospital), Yoneo Arai (Arai Clinic), Yoshiaki Okubo (Okubo Clinic), Yoshie Takazawa (Takazawa Clinic), Yoshiharu Uchida (Uchida Medical Clinic), Yoshihiro Hatano (Hatano Clinic), Yoshimasa Nakamura (Nakamura Surgical Clinic), Yoshio Kojima (Kojima Clinic), Youjiro Ono (Ono Seikeigeka Hihuka Iin), Yukio Shimizu (Shimizu Clinic), Yumeko Ota (Kanri Center Clinic).

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