Original Article

Improvement of Blood Pressure Control in Hypertensive Patients with Renal Diseases

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For hypertensive patients with renal diseases (RD), strict blood pressure (BP) control has been recommended in recent hypertension guidelines, such as JNC VI, JNC 7, WHO/ISH 1999 and ESH-ESC 2003. We assessed the current status of BP control and the changes of BP control before and after the publication of these guidelines in 489 hypertensive patients with or without RD (age, 19–89 years, mean 59 ± 13 years) who visited the hypertension and kidney outpatient clinic at Kyushu University Hospital. The clinical characteristics of RD and non-RD patients were assessed (RD patients: age, 20–89 years, mean 60 ± 13 years, $n=311$; non-RD patients: age, 19–86 years, mean 58 ± 13 years, $n=178$). In addition, we compared the BP control status in 2003 to that in 1996. In 2003, the BP in RD patients was $134 \pm 16/78 \pm 10$ mmHg and that in non-RD patients was $138 \pm 12/83 \pm 9$ mmHg. When strict BP control was defined as $<130/80$ mmHg, the frequency of strict BP control in RD patients was 28.9% in 2003. In addition, the BP levels of RD patients in 2003 were significantly lower than those in 1996 ($134 \pm 16/78 \pm 10$ mmHg vs. $141 \pm 17/85 \pm 10$ mmHg, $p < 0.05$ for both systolic blood pressure [SBP] and diastolic blood pressure [DBP]), and the frequency of strict BP control in RD patients was higher in 2003 than in 1996 (28.9% vs. 11.8%, $p < 0.01$). The BP levels of non-RD patients in 2003 tended to be lower than those in 1996 ($138 \pm 12/83 \pm 9$ mmHg vs. $141 \pm 13/85 \pm 9$ mmHg, n.s.). In 2003, angiotensin II receptor blockers (ARBs) were more frequently prescribed to RD patients than to non-RD patients. Furthermore, the use of ARBs was markedly increased in 2003 compared with 1996. In conclusion, in our outpatient clinic, BP levels in hypertensive patients with RD have improved in recent years, and were lower than those in hypertensive patients without RD, which may in part reflect the physicians' awareness of the importance of strict BP control in RD patients, as suggested by several recent hypertension guidelines. (*Hypertens Res* 2007; 30: 295–300)

Key Words: blood pressure control, new guidelines, renal diseases, angiotensin II receptor blockers, physicians' awareness

Introduction

Hypertension is considered to be a cause as well as a complication of chronic kidney disease (1). Hypertension in chronic kidney disease increases the risk of serious adverse outcomes, including renal failure, early development and accelerated progression of cardiovascular disease, and premature death

(1–3). A number of randomized controlled trials have shown that antihypertensive treatment reduces cardiovascular mortality and morbidity and slows the progression of renal diseases (RD) (4–6). Furthermore, there is evidence that the benefit achieved is related to the extent to which blood pressure (BP) is lowered (1, 4–7). Based on the findings obtained from the large-scale clinical trials (5, 7), recent guidelines for the management of hypertension, such as JNC VI, JNC 7,

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Received February 21, 2006; Accepted in revised form December 12, 2006.

Table 1. Trends in Characteristics of Hypertensive Patients with (RD) and without Renal Diseases (Non-RD) in 1996 and 2003

	All		RD		Non-RD	
	1996	2003	1996	2003	1996	2003
Number of patients	469	489	323	311	146	178
Age (years)	56±13	59±13 ^{††}	56±13	60±13 [†]	56±12	58±13
Male (%)	49.2	48.5	52.0*	50.8	41.8	44.4
Systolic blood pressure (mmHg)	141±16	135±15 ^{††}	141±17	134±16 [†]	141±13	138±12
Diastolic blood pressure (mmHg)	85±10	80±10 ^{††}	85±10	78±10 ^{†,*}	85±9	83±9
Pulse pressure (mmHg)	56±16	55±4	56±17	56±5	56±13	54±3
Pulse (/min)	71±10	73±10 [†]	72±10*	72±9	69±10	74±11 [†]
Serum urea nitrogen (mg/dl)	21±14	21±14	24±16*	25±16*	14±4	14±4
Glomerular filtration ratio (ml/min)	68±34	66±32	56±33*	53±29*	92±22	90±19
Prevalence of diabetes mellitus (%)	13.0	10.8 [†]	9.3**	10.6	21.2	11.2 [†]
Prevalence of hyperlipidemia (%)	56.9	49.9 [†]	57.3	50.5	54.8	48.9

Values are means±SD. [†] $p<0.05$, ^{††} $p<0.01$ vs. 1996 of the corresponding group, * $p<0.05$, ** $p<0.01$ vs. non-RD of the same year.

Fig. 1. The status of BP control in patients with (RD) and without renal diseases (non-RD) in 1996 and 2003.

WHO/ISH 1999, ESH-ESC 2003 and Japanese Society of Hypertension (JSH) 2004 recommend strict BP control in RD (8–11). Moreover, the development of newer classes of anti-hypertensive drugs, such as angiotensin II receptor blockers (ARBs), has had a beneficial influence on the management of hypertension with RD (2, 3, 12–25). Thus, the aim of the present study was to assess the current status of BP control in hypertensive patients with RD, and whether BP control improved during the period between 1996 and 2003, *i.e.*, before and after the introduction of recent hypertension guidelines.

Methods

We investigated 489 hypertensive patients with or without RD who had been followed at the hypertension and kidney outpatient clinic of Kyushu University Hospital in 2003, as well as 469 hypertensive patients in 1996; many patients from the 1996 group were also included in the 2003 group. The BP levels and other clinical characteristics were compared between the RD and non-RD patients. We also compared numerous clinical characteristics including sex, age, presence of diabetes mellitus (DM), presence of hyperlipidemia, and antihypertensive regimens between the patients in 1996 and

Fig. 2. The number of antihypertensive drugs used in RD and non-RD patients in 1996 and 2003.

those in 2003. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or the current use of antihypertensive drugs. In RD patients on antihypertensive treatment, we also checked the previous clinical records of each patient in order to ascertain that the patient had been hypertensive before the initiation of antihypertensive treatment. RD was considered to be present in patients with one or more of the following: a decreased glomerular filtration ratio (GFR) (<60 ml/min); chronic kidney disease as defined by National Kidney Foundation practice guidelines (26); persistent proteinuria; or diagnosis of RD based on histological examination of a renal specimen obtained by percutaneous renal biopsy. GFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula (for men, $186.3 \times [\text{serum creatinine levels}]^{-1.154} \times \text{age}^{-0.203}$; for women, $186.3 \times [\text{serum creatinine levels}]^{-1.154} \times \text{age}^{-0.203} \times 0.742$). DM was defined as fasting serum glucose ≥ 126 mg/dl, serum glucose ≥ 200 mg/dl at any time, HbA1c $\geq 6.5\%$, or the current use of hypoglycemic agents. Hyperlipidemia was defined as serum total cholesterol ≥ 220 mg/dl, serum triglyceride ≥ 300 mg/dl at any time, or the current use of antilipemic agents. Clinic BP was measured in the sitting position by physicians using a standard mercury sphygmomanometer. The average BP determined on two occasions between March and May in each year was used for the analysis. We restricted the BP measurements to the spring in order to exclude the possible influence of seasonal variation of BP on the trend of BP control during the 7-year observation period. Pulse pressure was calculated as PP = SBP – DBP. “Good control” was defined as SBP of <140 mmHg and DBP of <90 mmHg. “Strict control” was defined as SBP

of <130 mmHg and DBP of <80 mmHg.

Statistical Analysis

All values are expressed as the means $\pm$ SD. For multiple group analysis, *i.e.*, among RD patients in 1996, non-RD patients in 1996, RD patients in 2003 and non-RD patients in 2003, one-way ANOVA followed by Scheffe’s test for multiple comparisons was used. For comparisons between two groups, *i.e.*, between all hypertensives in 1996 and all hypertensives in 2003, Student’s *t*-test was performed. A χ^2 test was also utilized when appropriate. *p*-values less than 0.05 were considered to be significant. Statistical analysis was performed with the SAS program package version 8.02 (SAS Institute Inc., Cary, USA).

Results

The average BP decreased significantly from 1996 to 2003 (all hypertensive patients, from $141 \pm 16/85 \pm 10$ mmHg in 1996 to $135 \pm 15/80 \pm 10$ mmHg in 2003, $p < 0.01$ for both SBP and DBP; RD patients, from $141 \pm 17/85 \pm 10$ mmHg in 1996 to $134 \pm 16/78 \pm 10$ mmHg in 2003, $p < 0.05$ for both SBP and DBP; non-RD patients, from $141 \pm 13/85 \pm 9$ mmHg in 1996 to $138 \pm 12/83 \pm 9$ mmHg in 2003, n.s.) (Table 1). In 2003, the average BP was significantly lower in RD patients than in non-RD patients ($134 \pm 16/78 \pm 10$ mmHg vs. $138 \pm 12/83 \pm 9$ mmHg, $p < 0.05$ for DBP; Table 1). On the other hand, in 1996 the average BP was similar in RD patients and non-RD patients (Table 1).

Figure 1 shows the status of BP control in RD or non-RD

Fig. 3. The trend in the use of antihypertensive drugs in RD and non-RD patients. DIU, diuretics; α , α -blocker; β , β -blocker; CCB, Ca antagonist; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

patients in 1996 and 2003. In 2003, the frequency of strict BP control (<130/80 mmHg) in RD patients was 28.9% and that of non-RD patients was 12.9%, while in 1996 the frequency of strict BP control did not differ significantly between the two groups. In RD patients, the frequency of patients with strict BP control increased significantly from 11.8% in 1996 to 28.9% in 2003 ($p < 0.01$). In non-RD patients, this frequency tended to increase from 1996 to 2003, but the change did not reach the level of statistical significance.

The rate of patients who did not receive antihypertensive drugs decreased significantly from 11.3% in 1996 to 7.0% in 2003 in all patients, and from 12.7% to 6.4% in RD patients (Fig. 2).

Figure 3 demonstrates the trend in the prescription of different classes of antihypertensive drugs in 1996 and 2003 in each study group. Prescriptions of ARBs increased significantly in 2003 compared with 1996 in all groups (all hypertensive patients, from 0% in 1996 to 43% in 2003; RD patients, from 0% in 1996 to 50% in 2003; non-RD patients, from 0% in 1996 to 40% in 2003; $p < 0.01$, respectively). The combination therapy of angiotensin converting enzyme (ACE) inhibitors and ARBs was also used in some (primarily RD) patients in 2003 (all hypertensive patients, 5.1%; RD patients, 7.7%; non-RD patients, 0.6% in 2003).

Discussion

The present study demonstrated that the average BP was significantly lower in a group of hypertensive patients in 2003 than in a group in 1996. Furthermore, BP control was

improved to a greater extent in hypertensive patients with RD than in those without RD over the 7-year study period. These findings suggested that the BP control in RD patients has improved in recent years, probably in part reflecting physicians' awareness of the importance of strict BP control in the management of RD, as recommended by recent hypertension guidelines.

In the present study, the BP control in 2003 was better in RD patients than non-RD patients; the proportions of strict and good BP control in 2003 were 28.9% and 62.7%, respectively, in RD patients, vs. 12.9% and 46.6% in non-RD patients. On the other hand, in 1996 BP control status did not differ significantly between RD patients and non-RD patients. These findings suggest that BP control improved significantly in RD patients in recent years, but only slightly in non-RD patients. A recent survey reported that RD patients had better BP control than non-RD patients (27); however, in that study 43% of RD patients had BP measurements of 140/90 mmHg or over, suggesting that the proportion of patients with controlled BP in the present study (62.7%) may be slightly higher than that seen in the previous study (57%) (27).

Several studies have demonstrated the relationship between the degree of BP lowering and reduction of cardiovascular events. In the MDRD study, more aggressive BP lowering slowed the progression of RD, and thus the importance of strict BP control was proposed for patients with proteinuria (5). In the United Kingdom Prospective Diabetes Study (UKPDS 38), tight BP control in patients with hypertension and type 2 DM achieved a clinically important reduction in the risk of deaths and complications related to DM (7). In

addition, in the HOT trial, intensive lowering of BP (target DBP ≤ 80 mmHg) was associated with a lower rate of cardiovascular events and death in patients with hypertension and DM (4). Based on these observations, the recent hypertension management guidelines recommended strict BP control, particularly in patients with proteinuria or RD (8–11).

In the present study, the frequency of RD patients receiving antihypertensive treatment increased significantly from 1996 to 2003. In addition, the number of antihypertensive agents prescribed increased significantly in RD patients in 2003 compared with that in 1996 (1.6 ± 1.0 in 1996 vs. 1.9 ± 1.0 in 2003; $p < 0.01$), implying that physicians have adopted an increasingly aggressive attitude toward achieving BP control. We therefore consider that the improvement of BP control in the present study might be partially attributable to physicians' increasing awareness of the importance of strict BP control in RD patients, as proposed by several recent hypertension guidelines.

Several studies have suggested that the combined treatment with ACE inhibitors and ARBs may be more renoprotective than treatment with either agent alone (12, 20–22, 24), and, indeed, in some RD patients, the combination of ACE inhibitors and ARBs was also prescribed in the present study. The improvement of BP control by using antihypertensive agents, such as ACE inhibitors or ARBs, has also been reported in previous studies (2, 3, 12–25). A significant increase in the prescription of ARBs was observed in 2003 compared with 1996 in RD patients. Although this was also the case for non-RD patients, prescription rate of ARBs was higher in RD patients than non-RD patients. We, therefore, consider that the improved BP control in RD patients may also be partly attributable to a more frequent use of ARBs and/or ACE inhibitors.

There are several limitations in this study. First, this was basically a cross-sectional study; because the study populations of 1996 and 2003 were slightly different, direct comparison between the groups was difficult. However, because of the progressive nature of RD, it is also difficult to compare the clinical characteristics of the same study subjects after a long-term follow-up period. Second, because of the guideline recommendation of strict BP control in RD patients, it is possible to speculate that the antihypertensive treatment might have been initiated even in patients with relatively lower BP levels in 2003. However, in RD patients we did confirm the presence of hypertension before the initiation of antihypertensive treatment by assessing previous clinical records. Third, it is now recognized that lifestyle modifications, such as salt restriction and body weight reduction, lower BP to some extent. It is therefore possible that lifestyle modification might have partly contributed to the improvement in BP control in the study groups. Fourth, the study subjects consisted of patients seen by specialist physicians, and thus their characteristics may not be representative of patients seen by general practitioners.

In conclusion, the average BP level was significantly lower

in RD patients compared with non-RD patients in 2003, and the BP level in RD patients was also lower in 2003 than in 1996, resulting in the higher proportion of RD patients with strict BP control in 2003. This improvement of BP control might be attributable in part to the higher recognition by physicians of the importance of strict BP control as well as the more frequent use of inhibitors of the renin-angiotensin system, e.g., ARBs. The present study suggests that the recommendations of the recent guidelines for the management of hypertension with RD have indeed had a substantial influence on the treatment of hypertension in RD patients. It still remains to be fully elucidated whether such an improvement in BP control contributes to the preservation of renal function.

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