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ORIGINAL ARTICLE

Assessment of reasons for not intensifying antihypertensive treatment in the Taiwanese population

Chiung-Jen Wu^{a,*}, Kwo-Chuan Lin^b, Sien-Tsong Chen^c, Wen-Ter Lai^d, Chun-Peng Liu^e, Shou-Shan Chiang^f, Yu-Yao Huang^g, Paolo Ferrari^h

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KEYWORDS

antihypertensives; guidelines; hypertension; Taiwan; therapeutic inertia Background/Purpose: Despite availability of effective antihypertensives, blood pressure (BP) control is usually inadequate. The Reasons for not Intensifying Antihypertensive Treatment (RIAT) registry evaluated the reasons behind not modifying treatment in an international, cross-sectional study in 16 countries.

Methods and results: The Taiwanese cohort of RIAT consisted of 8922 patients with untreated/ uncontrolled essential hypertension recruited from 22 centers in the country. At the first visit, physicians selected target BP and antihypertensive treatment, and at the next three visits they measured BP and modified treatment/provided justification for not modifying treatment. Mean target BP selected by physicians was $134.6/84.6 \pm 5.1/5.0$ mmHg, respectively. Patients' individual risk stratification determined the BP goals. More patients achieved targets according to the physicians' opinion than based on actual BP measurements: visit 2-50.6% vs. 48.6%; visit 3-58.4% vs. 55.2%; and visit 4-61.2% vs. 57.0%. At each visit, treatment remained unchanged for >60% patients not reaching target; the most common reason for this at visit 2 was the

E-mail address: cvcjwu@adm.cgmh.org.tw (C.-J. Wu).

^a Division of Cardiology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

^b Department of Internal Medicine, Changhua Christian Hospital, Taiwan

^c Department of Neurology, Chang Gung Memorial Hospital-Linkou, Taiwan

^d Department of Cardiology, Kaohsiung Medical University Hospital, Taiwan

^e Division of Cardiology, Kaohsiung Veterans General Hospital, Taiwan

f Department of Cardiology, Shin Kong Wu Ho-Su Memorial Hospital, Taiwan

^g Department of Cardiology, Paochien Hospital, Taiwan

^h School of Medicine and Pharmacology, University of Western Australia and Department of Nephrology, Fremantle Hospital, Perth, Australia

^{*} Corresponding author. Division of Cardiology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan.



assumption that the time was too short to assess new drug therapy and at visits 3 and 4 was the assumption that target was reached/had almost been reached.

Conclusion: About 40% Taiwanese hypertensive patients in RIAT did not reach BP targets after an average of 4 months' follow-up. The most common reason for not modifying treatment was the assumption that the target had been reached or had almost been reached.

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Introduction

Hypertension is the most common and important cardiovascular disease (CVD). It is defined as systolic blood pressure (SBP) \geq 140 mmHg and/or diastolic blood pressure (DBP) \geq 90 mmHg and/or receiving antihypertensive medication. In the past few years, Taiwan has witnessed a rapid transformation in the economy, which has led to changes in dietary patterns and lifestyles. These changes also have greatly influenced the prevalence of CVD, which is strongly determined by hypertension. It has been observed that about one-third of deaths in Taiwan are caused by hypertension-related conditions in conjunction with comorbidities.

According to a report by the World Health Organization (WHO), hypertension contributes significantly (4.5%) to the global disease burden.⁴ It is estimated that hypertension causes 7.1 million premature deaths worldwide.^{4–6} There have been many international guidelines suggesting target BP values for the management of arterial hypertension, according to the presence of risk factors or concomitant CVDs, such as maintaining BP at 130/80 mmHg or lower in diabetic and kidney disease.^{6,7}

With the objective of supporting physicians in their active management of hypertensive patients, a worldwide survey on the assessment of the Reasons for not Intensifying Antihypertensive Treatment (RIAT) trial was conducted.⁸

The previous RIAT survey identified three main reasons for not intensifying antihypertensive therapy: (i) The assumption that the time after initiating new therapy was too short to evaluate the efficacy of the treatment; (ii) either a visible improvement or an approximate achievement of target BP was observed; and (iii) the physicians were satisfied with adequate self-measured BP readings.⁹

A regional study had reported that the prescription patterns for uncomplicated hypertension in Taiwan were inconsistent with international clinical guidelines. Based on the reason of considerable differences in the health insurance system in Taiwan, and the lack of a real-world practice report regarding antihypertensive treatment from Taiwan, the RAIT study was then initiated. The present paper describes the results of this study in Taiwan, and explores our physicians' practice in teaching/community hospitals, comparing this with global practice (by primary physicians) in treating hypertensive patients.

Materials and methods

Study design

The details of study design, sampling of medical practitioners, instruments, and measures and diagnostic conventions used

in RIAT have been published previously. ^{8,10} The RIAT program was an international, cross-sectional study of unselected patients attending primary care settings. These patients were recruited by a representative sample of medical practitioners. RIAT was carried out in three stages:

- 1. Identification of the reference guidelines for management and therapeutic targets for hypertensive patients.
- 2. Data collection to evaluate the variance between individual patient targets defined by medical practitioners and national/international guidelines.
- 3. A prospective registry to collect patient data at baseline and determine individual target BP values. Subsequent follow-up visits assessed whether or not BP targets were achieved during patient monitoring. It also included comprehensive data collection on other cardiovascular risk factors, target organ damage and associated clinical conditions related to hypertension.

The number of visits and the registry follow-up duration was decided by the investigator according to local clinical practice and was applicable to all physicians practicing in 22 community hospitals or medical centers in Taiwan. The study included four follow-up visits. The mean duration between each visit was approximately 1 month, 2 months and 3 months, respectively (see Fig. 1).

The program followed a natural approach to hypertension management, and physicians followed their usual medical practice. The physician could select an appropriate antihypertensive drug regimen at each visit.

Patients

Adult hypertensive patients (male/female) with essential hypertension that was either 'newly diagnosed and untreated' or 'previously treated and uncontrolled' were recruited. Patients with known secondary curable hypertension (i.e., pheochromocytoma, aldosterone-producing adenoma and Cushing's disease) were excluded. However, patients with renal disease were not excluded. Written informed consent was obtained from all patients.

BP targets and BP changes during the study were described and compared according to the grade of hypertension. The grades were defined according to the Joint National Committee (JNC) VII recommendations² or 2003 WHO Guidelines for hypertension management¹¹ as follows:

- grade I: SBP 140-159 mmHg or DBP 90-99 mmHg;
- grade II: SBP 160-179 mmHg or DBP 100-109 mmHg;
- grade III: SBP ≥180 mmHg or DBP ≥110 mmHg.

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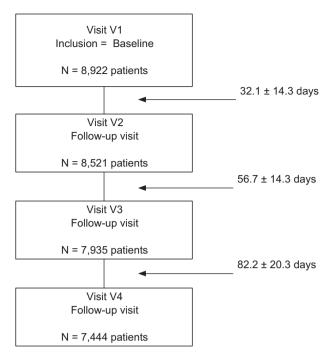


Figure 1 Study schedule.

Statistical analysis

Statistical analysis was based on all patients enrolled in the registry. Since this was a registry study, no sample size calculation was applied to it. Data were summarized using mean, median, standard deviation (SD) and range for continuous parameters; and counts and percentages for categorical parameters. Relative and absolute differences between the target value and the value at the visit were calculated. All tests performed were bilateral with a risk α equal to 5%. Analysis was performed with the SAS® software, v8.2 (SAS Institute, Cary, North Carolina, USA).

Results

From January 2004 to November 2005, a total of 8,922 (4488 men) patients were recruited in 22 centers in Taiwan. Of these, 7444 (83.4%) patients completed the study. The last follow-up visit was performed in July 2006. The baseline characteristics of this population are presented in Table 1. At baseline, average SBP was 154.3 ± 17.0 mmHg and average DBP was 86.8 ± 11.8 mmHg. The most frequently observed risk factor in this population was diabetes (n=3867; 43.4%), followed by dyslipidemia (n=3199; 36.0%) and sedentary lifestyle (n=2841; 32.0%). Hypertension was newly diagnosed in 1270 (14.3%) patients. At

Table 1 Baseline demographic characteristics.						
	Taiwan data	Global data	р			
Number of patients	8922	35,302				
Gender: male, n (%)	4488 (50.3)	17,722 (50.2)				
Age (years), mean \pm SD	$\textbf{62.7}\pm\textbf{12.0}$	$\textbf{59.2}\pm\textbf{12.6}$	< 0.01			
Body mass index (kg/m 2), mean \pm SD	26.1 ± 3.9	$\textbf{25.4} \pm \textbf{3.7}$	< 0.01			
SBP (mmHg), mean \pm SD	154.3 ± 17.0	$\textbf{158.7} \pm \textbf{15.3}$	< 0.0001			
DBP (mmHg), mean \pm SD	$\textbf{86.8} \pm \textbf{11.8}$	95.2 \pm 12.0	< 0.0001			
Risk factors, n (%)						
Diabetes (%)	3867 (43.4)	9954 (28.2)	< 0.0001			
Dyslipidemia (%)	3199 (36.0)	9231 (26.2)	< 0.0001			
Physical inactivity (%)	2841 (32.0)	10637 (30.2)	< 0.005			
Family history of premature cardiovascular disease (%)	1638 (18.4)	7068 (20.1)	< 0.001			
Smoker (%)	1441 (16.2)	9328 (26.4)	< 0.0001			
Body mass index \geq 30 kg/m ² (%)	1280 (14.5)	5175 (14.7)	NS			
Other risk factors (%)	187 (2.2)	834 (2.5)	NS			
Associated or previous clinical conditions, n (%)						
Cerebrovascular disease (%)	1637 (18.4)	3639 (10.3)	< 0.0001			
Coronary heart disease (%)	1371 (15.4)	3706 (10.5)	< 0.0001			
Retinopathy (%)	780 (8.8)	1756 (5.0)	< 0.0001			
Peripheral arterial disease (%)	437 (4.9)	1320 (3.8)	< 0.0001			
Congestive heart failure (%)	384 (4.3)	2009 (5.7)	< 0.0001			
Number of antihypertensive agents, n (%)						
Any (%)	7096 (79.5)	22,887 (64.8)	< 0.0001			
1 agent (%)	2825 (39.8)	13824 (60.4)	< 0.0001			
2 agents (%)	2685 (37.8)	5768 (25.2)	< 0.0001			
3 agents (%)	1219 (17.2)	2403 (10.5)	< 0.0001			
>3 agents (%)	367 (5.2)	692 (3.0)	< 0.0001			

Abbreviations: CV, cardiovascular; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation. p by chi-squared test for categorical variables.

the time of inclusion, 4462 (55.7%), 2613 (32.6%) and 941 (11.7%) patients had grade I, II and III hypertension, respectively. The prevalence of risk factors or associated clinical conditions was generally higher in the Taiwanese cohort than in the global RIAT cohort, with the exception of smoking and family history of CVD (see Table 1). Baseline BP was lower in the Taiwanese cohort than in the global RIAT cohort, however, probably reflecting the higher proportion of patients already on treatment (proportion in Taiwan 79.5% vs. global 64.8%).

The assessment of target organ damage revealed that 711 (8.0%) patients had microalbuminuria, 926 (10.4%) patients had macroalbuminuria, 936 (10.5%) patients had increased serum creatinine and 1036 (11.7%) patients had left ventricular hypertrophy.

At the time of inclusion, 7096 (79.5%) patients were receiving at least one antihypertensive agent. Of these, 2825 (39.8%) received monotherapy, 2685 (37.8%) received two treatments, 1219 (17.2%) received three treatments and 367 (5.2%) patients received more than three treatments, see Table 1. The frequency of prescribed antihypertensive classes (alone or in combination) was: angiotensin converting enzyme (ACE) inhibitors, 14.7%; angiotensin receptor blockers, 63.0%; calcium-channel blockers, 46.0%; diuretics, 28.1%; beta-blockers, 32.8%; and others, 10.3%.

Primary endpoints

Defining the target

According to international guidelines, the mean target SBP was 134.6 \pm 5.1 mmHg, whereas the mean target DBP was 84.6 \pm 5.0 mmHg. The BP goals set by physicians at baseline were significantly lower for patients with diabetes mellitus (SBP = 130.6 \pm 2.9 mmHg and DBP = 80.7 \pm 2.6 mmHg) and were stricter than the average goal for patients with diabetes in the global RIAT cohort (SBP = 130.0 \pm 5.7 mmHg and DBP = 82.5 \pm 4.8 mmHg). 10 BP goals for patients with dyslipidemia were significantly lower (SBP = 133.4 \pm 5.0 mmHg and DBP = 83.5 \pm 4.7 mmHg) than in

patients without dyslipidemia, see Table 2. A significant difference was observed in the individual target SBP and DBP values based on the number of associated risk factors. With no risk factors, the target values were 137.3 \pm 4.5 mmHg for SBP and 87.3 \pm 4.4 mmHg for DBP; for one to two risk factors, the target values were 134.4 \pm 5.2 mmHg for SBP and 84.4 \pm 5.0 mmHg for DBP; and for three or more factors, the target values were 132.2 \pm 4.6 mmHg for SBP and 82.3 \pm 4.2 mmHg for DBP.

Identifying the reasons for not intensifying antihypertensive treatment

At visit 2, 29.4% of Taiwanese patients did not reach their BP goal, but had no change in antihypertensive treatment compared to 50.2% of patients in the global RIAT cohort for the same period, see Table 3. At visit 2, the two most frequent reasons for not modifying treatment were the time factor (51.8% of cases) and the assumption that the target was almost reached or had been achieved (17.8% of cases). At visit 4, 23.1% of the Taiwan patients still had not reached their BP goal and did not have their treatment changed, compared to 9.8% of patients in the global RIAT cohort for the same period, see Table 3. At Visit 4, the most commonly cited reason for not modifying treatment was the assumption that the target was almost reached or had been achieved (29.4%) and the time factor, i.e. the assumption that the time was too short for assessing optimum efficacy of the therapy (18.6%), see Table 3.

Secondary endpoints

Achieving the target

At baseline, the average SBP was 154.3 \pm 17.0 mmHg and the average DBP was 86.8 \pm 11.8 mmHg. At the last visit, these values averaged 135.2 \pm 14.7 mmHg and 78.7 \pm 9.6 mmHg, respectively (p <0.0001 vs. baseline). The JNC VII target values were more likely to be achieved in overall patients than in patients with diabetes (63.6% vs. 26.8%, p <0.005). Table 4 summarizes the number and

Risk factor		Target SBP		p value	Target DBP		p value
		No	Yes		No	Yes	
Diabetes	n	4734	3867		4734	3867	
	Mean \pm SD	$\textbf{137.3}\pm\textbf{4.7}$	$\textbf{130.6} \pm \textbf{2.9}$	< 0.001	$\textbf{87.3} \pm \textbf{4.4}$	$\textbf{80.7} \pm \textbf{2.6}$	< 0.001
Dyslipidemia	n	4216	3199		4216	3199	
	Mean \pm SD	$\textbf{134.6} \pm \textbf{5.2}$	$\textbf{133.4} \pm \textbf{5.0}$	< 0.001	$\textbf{84.7} \pm \textbf{5.0}$	83.5 ± 4.7	< 0.001
Physical inactivity	n	5850	2840		5850	2840	
	Mean \pm SD	$\textbf{134.4} \pm \textbf{5.2}$	134.3 ± 5.2	0.131	$\textbf{84.4} \pm \textbf{5.0}$	$\textbf{84.3}\pm\textbf{5.0}$	0.210
Family history of premature CVD	n	5453	1638		5453	1638	
	Mean \pm SD	$\textbf{134.4} \pm \textbf{5.2}$	134.9 ± 5.5	0.005	$\textbf{84.5} \pm \textbf{5.0}$	84.9 ± 5.0	0.002
Smoker	n	7288	1441		7288	1441	
	Mean \pm SD	$\textbf{134.3} \pm \textbf{5.2}$	134.8 ± 5.3	0.002	$\textbf{84.3} \pm \textbf{5.0}$	$\textbf{84.8} \pm \textbf{5.0}$	0.002
Body mass index \geq 30 kg/m ²	n	7409	1280		7409	1280	
	Mean \pm SD	$\textbf{134.3}\pm\textbf{5.2}$	$\textbf{134.4} \pm \textbf{5.1}$	0.526	$\textbf{84.4} \pm \textbf{5.0}$	$\textbf{84.5} \pm \textbf{5.0}$	0.565
Other risk factors	n	4616	187		4616	187	
	Mean \pm SD	134.0 ± 5.1	136.6 ± 5.0	< 0.001	84.0 ± 4.9	86.6 ± 4.8	< 0.001

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Table 3 Reasons for not modifying blood pressure treatment if the targets had not been reached.						
Classification of reasons	Visit 2		Visit 3		Visit 4	
	Taiwan data (n = 2546, 29.9%) n (%)	Global data (n = 16769, 50.2%) n (%)	Taiwan data (n = 1978, 24.9%) n (%)	Global data (n = 12915, 38.5%) n (%)	Taiwan data (n = 1719, 23.1%) n (%)	Global data (n = 3166, 9.8%) n (%)
Time (Short timelines)	1318 (51.8)	14309 (85.3)	474 (24.0)	9870 (76.4)	320 (18.6)	1098 (34.7)
Target almost reached/achieved	452 (17.8)	526 (3.1)	632 (32.0)	1056 (8.2)	505 (29.4)	627 (19.8)
Drug discontinuation and poor compliance	118 (4.6)	327 (2)	120 (6.1)	277 (2.7)	83 (4.8)	198 (6.3)
Exceptional circumstances	377 (14.8)	416 (2.5)	448 (22.6)	474 (3.7)	482 (28.0)	506 (16.0)
Reduction of other risk factors	55 (2.2)	361 (2.2)	50 (2.5)	232 (1.8)	29 (1.7)	125 (3.9)
Side effects	55 (2.2)	107 (0.6)	49 (2.5)	87 (0.7)	55 (3.2)	75 (2.4)
Other reasons	171 (6.7)	723 (4.3)	205 (10.3)	919 (7.1)	245 (14.2)	537 (16.9)

percentage of patients not having reached the target BP at follow-up visits according to measured BP values or the physician's opinion; this percentage decreased over the course of the program. Fig. 2 displays the percentage of patients achieving target BP values and the modification of treatment at each follow-up visit.

Changing antihypertensive treatment when target BP is reached

When target BP values were reached according to the physician, a change in therapy was rarely undertaken (3.6% and 4.5% at visits 2 and 4, respectively; see Fig. 2). The most commonly cited reason was the side-effects of prescribed medication in one-quarter to one-third of cases.

Discussion

Hypertension is often poorly controlled despite increased awareness of its deleterious consequences, the availability of effective and well-tolerated antihypertensive drugs, and various international guidelines for its management. The WHO guidelines for hypertension management recommend targeting individual BP goals according to risk stratification.¹¹ Interestingly, a Swiss survey revealed that practitioners based the target BP values for hypertensive patients on their baseline BP values rather than on individual risk stratification.⁹ Therapeutic inertia, however, is another major obstacle in BP treatment that is mostly due to lack of understanding of the comparative risk-benefit profile of BP

management, and to resistance to implement the relevant guidelines. 12,13

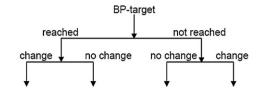
According to the Nutrition and Health Survey in Taiwan (NAHSIT) conducted during 1993–1996, only 2% of hypertensive males and 5% of hypertensive females had their hypertension under control.³ The second nationwide survey in 2002, the Taiwanese Survey on Hypertension, Hyperglycemia and Hyperlipidemia (TwSHHH) found that awareness, treatment and control of hypertension was significantly improved in the period between NAHSIT and TwSHHH.¹⁴

Although the focus of the present study is on Taiwan, we have compared the results with those of the global RIAT study in order to understand the similarities and critical differences. The percentage of newly diagnosed hypertensive patients was low, while the majority of the patients were already receiving treatment. The percentage of patients with risk factors (diabetes, dyslipidemia and physical inactivity) was significantly higher in the Taiwanese cohort than in the global cohort, but the percentage of patients with risk factors (family history of premature CVD and smoking) was significantly lower. This might reflect a selection bias among Taiwanese practitioners. The percentage of patients receiving at least one treatment at visit 1 was higher in Taiwanese patients (79.5%) when compared with global data (64.8%). However, SBP (158.7 \pm 15.3 mmHg) and DBP (95.2 \pm 12.0 mmHg) values for global patients were higher than those for Taiwanese patients.

The treatment was not modified in 29.9%, 24.9% and 23.1% of Taiwanese patients at visits 2, 3 and 4,

Table 4 Number (and percentage) of patients not reaching target blood pressure according to physicians' opinion or reported blood pressure values and change of treatment.

Target not reached Visit 2		it 2	Vis	sit 3	Visit 4	
	Taiwan data n (%)	Global data <i>n</i> (%)	Taiwan data <i>n</i> (%)	Global data <i>n</i> (%)	Taiwan data <i>n</i> (%)	Global data <i>n</i> (%)
According to the physicians' opinion	4190 (49.4)	21162 (63.0)	3294 (41.6)	15880 (47.0)	2881 (38.8)	5152 (16.0)
According to reported blood pressure values	4356 (51.4)	21811 (65.0)	3547 (44.8)	16723 (50.0)	3194 (43.0)	6200 (19.0)
Treatment not changed	2572 (61.4)	16904 (79.9)	2009 (61.0)	13034 (82.1)	1744 (60.6)	3240 (62.9)
Treatment changed	1615 (38.6)	4247 (20.1)	1283 (39.0)	2838 (17.9)	1135 (39.4)	1910 (37.1)



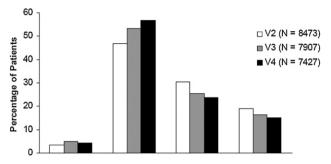


Figure 2 Percentage of patients achieving the target BP values and modification of treatment.

respectively, despite not having reached the target BP values. These results differ from the global results. The most commonly cited reason at all visits for global patients not reaching their BP targets and not having treatment modification was physicians' assumption that the time was too short to assess the efficacy of treatment. In Taiwanese patients, however, although the time factor was the most commonly cited reason at visit 1, the most common reason at the last two visits was the physicians' assumption that the target BP values were reached or had almost been reached.

At the end of this study, about 61% of Taiwanese patients achieved BP targets in physicians' opinions and 57% achieved their targets according to the BP values that were measured. In the global study, however, a significantly higher percentage of patients reached their BP targets in physicians' opinions (84%) and according to the BP values measured (81%). Thus, despite the higher percentage of patients having at least one cardiovascular risk in the Taiwanese cohort, therapeutic inertia was higher among Taiwanese practitioners than in the global data, resulting in a higher number of patients not treated to target at visit 4 in Taiwan. This is noteworthy because at baseline the Taiwanese practitioners defined stricter BP targets than those reported in the global analysis for certain subgroups of hypertensive patients (e.g. those with diabetes), and had less therapeutic inertia at visit 2 (target not reached/ no change in treatment: Taiwanese practitioners 52% vs. global practitoiners 85%). According to global data, the percentage of patients achieving BP targets was higher in previously untreated patients (92%) than in treated patients (80%). When the target value was reached for the first time, 30.7% of patients were taking a single drug, 36.8% were receiving two drugs and 22.3% were receiving three treatments. A more accurate treatment adaptation taking into consideration hypertension management guidelines and other risk factors (e.g. diabetes, dyslipidemia and physical inactivity) could provide better results.

Over and above achieving BP targets, proper treatment modification for keeping the BP values below their targets is crucial. Earlier studies have identified core actions for practitioners to instigate in order to achieve abovementioned objectives¹⁵ and have discussed a number of innovative approaches, such as decision support systems, patient-centered counseling or revisiting patient profiles.² There is also the need for additional clinical trials to validate different therapeutic goals for high-risk patients instead of the current agreed SBP goal of 130 mmHg.¹⁶

There are some limitations to our study. As this was not a population-based survey, the findings do not represent the general population. Secondly, four visits within 4 months to specifically manage hypertension may not be realistic in practice. Additionally, no pre-specified approach was recommended to intensify antihypertensive treatment. Thus, the results, particularly those related to the high BP control rate, may be difficult to reconcile at a larger scale. The participating physicians were practicing in community hospitals or large medical centers so the results may not reflect real-world practice for primary care physicians in Taiwan.

Conclusion

Individual target BP values were aligned with international guidelines in the majority of Taiwanese hypertensive patients, a high percentage of whom were receiving antihypertensive treatment. Nonetheless, achievement of the target BP value was better in global patients than in Taiwanese patients, probably on account of the higher therapeutic inertia among Taiwanese practitioners at visit 4. The most commonly cited reason for not modifying treatment despite not achieving target BP values was the assumption that the patients had reached or almost achieved target BP.

Hypertension control in Taiwan may improve if awareness and adherence to BP management guidelines is increased among Taiwanese practitioners, and steps should be taken to counter therapeutic inertia in the long-term management of hypertension.

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