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Pattern analysis and variations in the utilization of antihypertensive drugs in Taiwan: a six-year study

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Abstract. – BACKGROUND: In the last few years there have been changed in the pattern of consumption of antihypertensive drugs in other countries. Factors causing this variability include differences in the effectiveness of detection, guidelines for the management of hypertension, and differences in national health insurance systems among countries.

AIM: The aim of this study was to reveal patterns in the use of antihypertensive drugs in Taiwan over a six year period (2001 to 2006) and compare these results with data from other countries.

MATERIALS AND METHODS: This study performed descriptive analysis of data from the National Health Insurance Research Database (NHIRD) of Taiwan, and compared these findings with similar findings from around the world. Quantities were standardized using the defined daily dose (DDD) per 1000 inhabitants per day (DID) in accordance with WHO anatomical therapeutic classification and DDD measurement methodology.

RESULTS: The total number of DDDs prescribed in Taiwan increased from 0.66 billion in 2001 to 1.08 billion in 2006, representing 80.6 and 129.2 DID in 2001 and 2006, respectively. This indicates a significant increase in the prescription of antihypertensive drugs in Taiwan over this period. The average annual increase ranged from 10.7% for calcium channel blockers (CCBs) to 22.1% for angiotensin II receptor blockers (ARBs). All of these patterns were statistically significant ($p < 0.05$). The rapid increase in the use of ARBs resulted in its surpassing ACEIs with the second highest DID (21.9) in 2006. Though the proportional use of CCBs and ARBs has increased significantly, the use of thiazide diuretics remains low.

CONCLUSIONS: The consumption of antihypertension drugs in Taiwan increased during the period studied and the highest average annual increases were for ARBs and CCBs. Overall consumption of antihypertension drugs also increased in other countries, but differences in the relative increase for each class of drug suggest that further study may be required to clarify the origins and causes.

Key Words:
Antihypertensive drugs, Total defined daily dose, Angiotensin-II receptor blockers, Calcium channel blockers, Angiotensin-converting enzyme inhibitors.

Introduction

Considerable variability in the prevalence of hypertension (5.3 to 42.3% of different populations) has been observed in previous studies[1]. This variability may be due to differences in the measurement of blood pressure[2,3], age ranges, and the definitions used for hypertension[4]. In the last few years there have been changed in the pattern of consumption of antihypertensive drugs in other countries[1]. The factors causing this variability include differences in the effectiveness of detection[1], different guidelines for the management of hypertension[1], differences in the national health insurance systems of various countries[1], differences in the measurement of

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blood pressure[2,3], different definitions of hypertension[4] and different age ranges[1]. Few studies have specifically investigated patterns in the use of antihypertensive drugs in Taiwan. Chou et al. presented the patterns of antihypertensive medications in Taiwan according to their pharmacological classifications[5]. Their results indicated that calcium antagonists were the most frequently prescribed antihypertensive medication, appearing in 54.9% of all hypertension related prescriptions in 1998[5]. The second was beta-blockers (43.5%), followed by angiotensin-converting enzyme inhibitors (ACEIs) (31.5%), and diuretics (23.2%)[5]. The aim of this study was to describe the utilization patterns of antihypertensive drugs in Taiwan over a six-year period (2001-2006) and compare the results with data from other countries.

Materials and Methods

Data Collection

This study employed descriptive analysis of all prescriptions for antihypertensive drugs between 2001 and 2006, from the National Health Insurance Research Database (NHIRD) of Taiwan. The NHI is the Taiwanese universal health insurance program implemented in March 1995. By 2006, the NHI covered approximately 98% of the Taiwanese population, and 97% of hospitals and clinics throughout the nation[6,7]. Antihypertensive drugs were evaluated according to the Anatomical Therapeutical Chemical Classification/Defined Daily Doses (ATC/DDD) system developed by the World Health Organization[8,9]. This study categorized the antihypertensive drugs into seven major classes (ATC codes are listed in parentheses): renin-angiotensin system (ACEIs, C09A, C09B), angiotensin-II receptor blockers (ARBs, C09C, C09D); beta-blockers (C07); calcium channel blockers (CCB) (C08); thiazide-type diuretics (C03A); other diuretics (C03B, C03C, C03D, C03E); and others (C02)[8,9]. All anti-hypertensive drugs considered in this study belonged to subgroups of the seven major therapeutic groups, classified as follows[8,9]:

1. *Thiazide type Diuretics:* C03A
2. *Other Diuretics:* C03B. Low-ceiling diuretics, plain; C03C. High-ceiling diuretics, plain; C03D. Potassium-sparing agents, plain; C03E. Diuretics and potassium-sparing agents in combination.
3. *Beta blocking agents (BBs):* C07A A. Non-selective beta blocking agents, plain; C07A B. Selective beta blocking agents, plain; C07A G. Alpha and beta blocking agents; C07B, C07C and C07D. Beta blocking agents and diuretics; C07F. Beta blocking agents and other antihypertensives[8,9];
4. *Calcium channel blockers*: C08: C08C and C08D. Calcium channel blockers[8,9];
5. *ACE inhibitors (ACEIs):* C09A. ACE inhibitors, plain; C09B A. ACE inhibitors and diuretics; C09B B. ACE inhibitors and calcium channel blockers[8,9];
6. *Angiotensin II antagonists (ARBs):* C09C. Angiotensin II antagonists, plain; C09D. Angiotensin II antagonists, combinations[8,9].
7. *Other antihypertensives:* C02CA. Alpha-adrenoreceptor antagonists; C02A. Antiadrenergic agents, centrally acting; C02D. Arteriolar smooth muscle, agents acting on; C02L. Antihypertensives and diuretics in combination[8,9].

Method of Analysis

Medications were quantified in defined daily doses by assigning defined daily dose (DDD) units to each NHIRD item using the Anatomical Therapeutic Chemical (ATC) classification system[8]. All NHIRD items are classified by the ATC classification system, and can be directly linked to DDD units using the ATC Index[9].

First, the total number of DDDs dispensed in each record of the NHIRD set is calculated to determine the dose strength for each item using the following formula[9,10]:

$$\text{DDDs} = \frac{\text{N*M*Q}}{\text{DDD unit}}$$

where N is the number of prescriptions dispensed per record, M is the strength of each dose (milligrams), Q is the average quantity of doses per prescription and DDD unit is one defined daily dose for the particular NHIRD item[9]. When used for comparison, the number of DDDs prescribed is generally given per 1000 inhabitants per day[9,10]. This method of standardization adjusts for the size of the population under study, enabling meaningful comparisons of drug use across years and among different countries[9,12]. Population related data was obtained from National Statistics in Taiwan[11]. This study presents the DDDs per 1000 inhabitants per day (DID)[9,12] of each ATC category by the year and throughout the entire period of study.

Data Sources

The data in this study was derived from the entire population of Taiwan, because everyone is insured according to the law. Since March 1, 1995, when Taiwan implemented universal national health insurance (NHI) legislation, coverage has increased from 57% to 98% of the population[6,13]. As of 2007, 22.60 million of Taiwan's 22.96 million citizens were enrolled in this program[8]. This data (which includes outpatient and inpatient records) provides national estimates of exposure to antihypertensive drugs, enables the monitoring of changes in usage and allows comparison of data from Taiwan with those from other countries.

Statistical Analysis

To analyse annual trends in the use of these drugs, this study employed linear regression to calculate the mean change of DID per year, using DID as a dependent variable and regressed yearly figures as continuous variables. The least-squares method of best-fit curves was employed using analytical tools provided by Microsoft® Office Excel 2010 (Redmond, WA, USA). Trends are presented as the percentage of the average DID for each drug in the period of study. Statistical software SAS for Windows (version 9.1; SAS Institute, Cary, NC, USA) was used to conduct all data analysis.

Results

For the drugs included in the present study, the total number of DDDs prescribed in Taiwan increased from 0.66 billion in 2001 to 1.08 billion in 2006, representing 80.1 and 129.2 DID in 2001 and 2006, respectively. This indicates a significant increase in the prescription of antihypertensive drugs in Taiwan over this period. Figure 1 presents the DID and annual trends according to ATC groupings of antihypertensive drugs used from 2001 to 2006. All seven classes of drugs showed an increase in use with average yearly increases from 4.5% for ACE inhibitors to 22.1% for ARB (Figure 1). All of the trends are statistically significant ($p < 0.05$) (Figure 1). Among the classes of drugs studied the average DID of Calcium channel blockers was the highest (35.1), followed by ACEI (19.6) and beta-adrenoceptor blockers (18.9) (Figure 1). The rapid increase in the use of ARBs resulted in its surpassing ACEIs with the second highest DID (21.9) in 2006 (Table I).

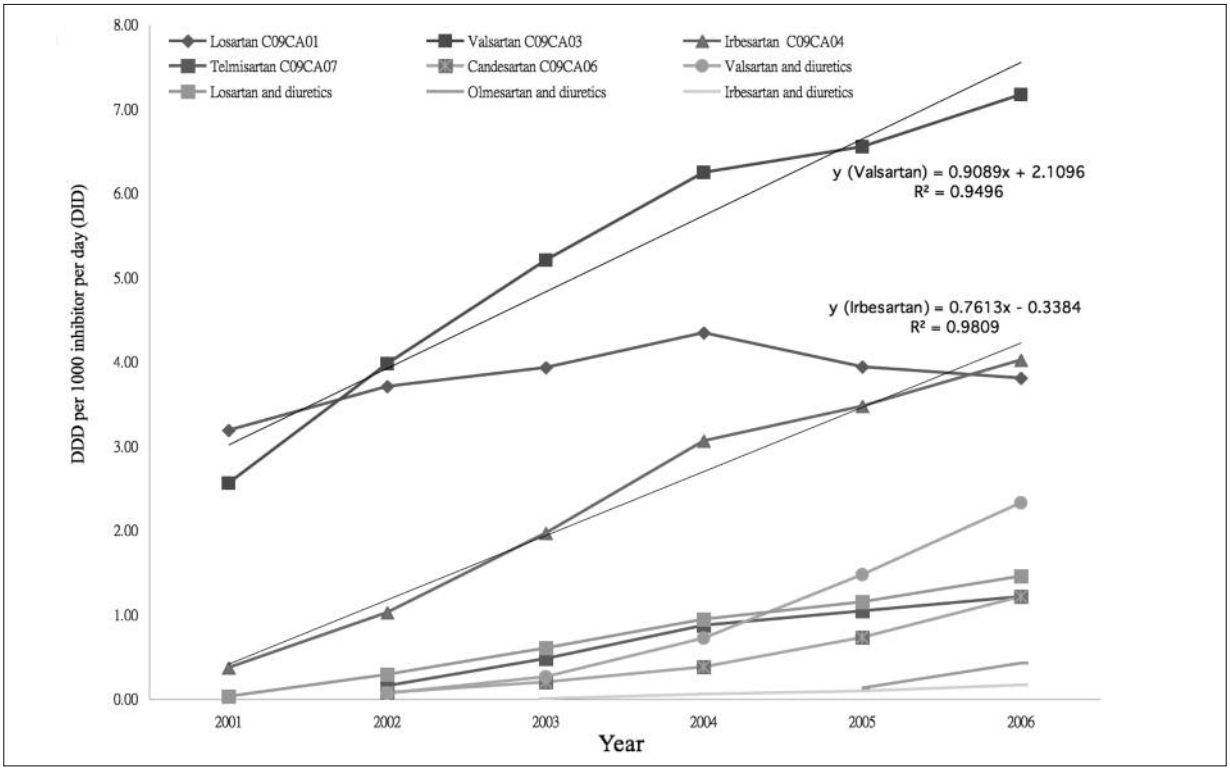

Figure 1. Consumption of anti-hypertensive drugs in Taiwan by year (Unit: DDDs per 1000 inhabitants per day, DID).

Table I. Defined Daily Doses per 1000 inhabitants per day (DID) of antihypertensive drugs from 2001 to 2006 in Taiwan.

Drug name	ATC code(s)	2001	2002	2003	2004	2005	2006	Average	Linear regression analysis			Average annual increase %
									Coefficient*	*p*†	R^2	
Beta-adrenoceptor blockers	C07	16.6	17.1	18.0	19.3	20.9	21.4	18.9	1.04	< 0.01	97.3%	5.5%
ACE inhibitors	C09A, C09B	17.6	18.1	18.9	20.0	21.2	21.7	19.6	0.88	< 0.01	98.0%	4.5%
Angiotensin II antagonists	C09C, C09D	6.2	9.3	12.7	16.7	18.6	21.9	14.2	3.15	< 0.01	99.4%	22.1%
Other diuretics	C03B, C03C, C03D, C03E	8.1	8.7	9.5	9.6	11.0	11.5	9.7	0.69	< 0.01	97.0%	7.1%
Thiazides	C03A	2.5	2.5	2.5	3.0	3.4	3.5	2.9	0.24	< 0.01	87.1%	8.2%
Others	C02	3.3	3.3	3.5	4.0	4.3	4.6	3.8	0.29	< 0.01	93.3%	7.6%
Calcium channel blockers	C08	26.2	29.3	32.5	36.9	40.9	44.7	35.1	3.75	< 0.01	99.6%	10.7%
	Total	80.6	88.2	97.6	109.6	120.5	129.2	104.3	10.0	< 0.01	100%	9.9%

*Regression coefficients for mean change in DID per year; †*p* value of regression coefficient to test the statistical significance of mean change in DID.

Figure 2a presents the DID of various drugs in the ACEI class with a significant decreasing trend (all p values < 0.001) in the use of captopril (–11.6%), benazepril (–12.4%) and cilazapril (–25.8%). The use of quinapril also decreased; however, this change did not reach statistical significance (–4.3%, $p = 0.26$). The use of drugs with a longer acting half-life, such as enalapril (6.8%), lisinopril (7.6%) and ramipril (19.8%), also increased (all p values < 0.001). In 2006, the most frequently used (DID) ACEI was enalapril (12.4), followed by ramipril (2.0), captopril (1.9) and lisinopril (1.8) (Table II).

Most of the ARBs showed an average, annual, double-digit increase until 2006, with the exception of losartan (3.1%, $p = 0.21$), which began declining after 2004 (Figure 2b). Nonetheless, the use of losartan in combination with diuretics maintained a significant average increase of 38.3% annually ($p < 0.001$) (Figure 2b). The greatest increase among all ARBs was 106% for olmesartan, used alone or in combination with diuretics. This is likely due to its recent inclusion in NHI reimbursement in 2005 (Figure 2b). In 2006, the most frequently used (DID) ARB was valsartan (7.2) followed by irbesartan (4.0) and losartan (3.8) (Figure 2b, Table II).

Figure 3 compares the DID of antihypertensive drugs in Taiwan with those of various OECD countries[16] in 2006. The overall DID in Taiwan was lower than that of other countries; however, the DID of CCBs in Taiwan accounted for 34.6% (DID = 44.7) of all antihypertensive drugs. This proportion is different from other OECD countries. In other OECD countries, agents acting on the renin-angiotensin system (e.g. ACEIs and ARBs) had the highest DID among all classes of antihypertensive agents. Usage of these drugs was greater than double that observed in Taiwan. The DID of diuretics in Taiwan (15.0) was also lower than in other OECD countries, such as Sweden (90.2). The use of other antihypertensive drugs (ATC class C02) in Taiwan was at a level similar to that of other countries, with DID ranging from approximately 2.2 to 14.7 (Table III).

Discussion

This paper describes patterns in the consumption of antihypertension drugs. Medications were quantified by assigning each NHIRD item a DDD according to the ATC classification system. The

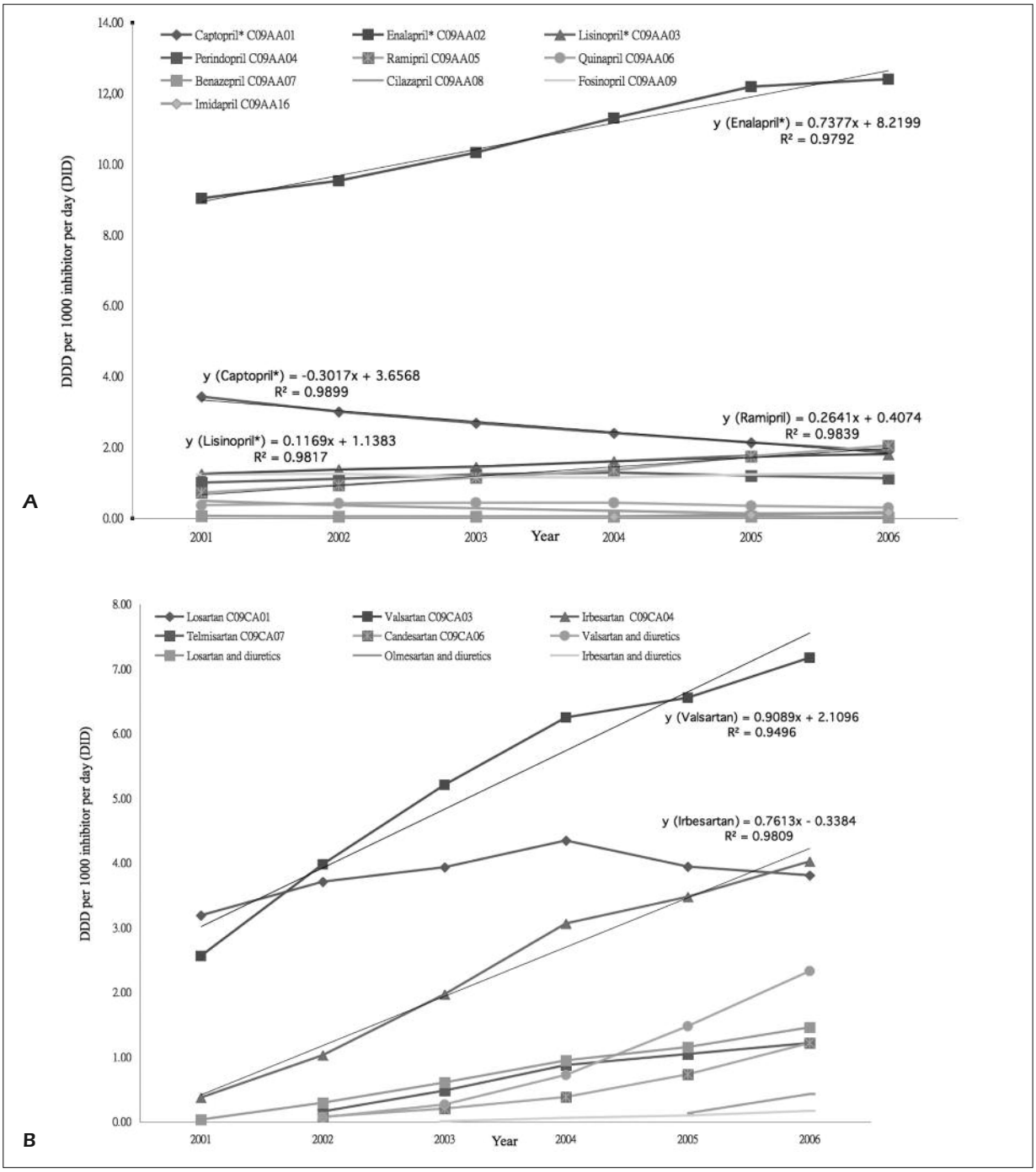

Figure 2. Consumption of ***(A)*** ACEIs ***(B)*** ARBs in Taiwan by year (Unit: DDDs per 1000 inhabitants per day, DID).

ATC/DDD system was developed by the World Health Organization as a means to measure drug consumption independent of package size and sales price. DDD represents the assumed average daily dose of a drug for its main indication in adults[8,14]. The ATC/DDD system allows comparisons within an institution, a region, a country, or internationally as well as across different time scales[8,15]. Furthermore, DDD methodology standardizes the doses of various medications into a common unit of measure, enabling the inclusion of different drugs from the same class of medication and facilitating comparisons between different classes of medications[8,14,16]. For example, the unit

Table II. Defined Daily Doses per 1000 inhabitants per day (DID) of ACEI and ARB drugs from 2001 to 2006 in Taiwan..

Drug name	ATC code(s)	2001	2002	2003	2004	2005	2006	Average	Linear regression analysis			Average annual increase %
									Coefficient*	p^+	R^2	
ACEI												
Captopril	C09AA01	3.44	3.02	2.69	2.42	2.14	1.90	2.60	-0.30	< 0.01	99.0%	-11.6%
Enalapril	C09AA02	9.04	9.54	10.33	11.30	12.20	12.41	10.80	0.74	< 0.01	97.9%	6.8%
Lisinopril	C09AA03	1.26	1.37	1.45	1.62	1.77	1.81	1.55	0.12	< 0.01	98.2%	7.6%
Perindopril	C09AA04	1.00	1.12	1.24	1.29	1.20	1.14	1.17	0.03	0.29	26.6%	2.4%
Ramipril	C09AA05	0.73	0.94	1.15	1.36	1.76	2.05	1.33	0.26	< 0.01	98.4%	19.8%
Quinapril	C09AA06	0.38	0.43	0.45	0.45	0.36	0.30	0.39	-0.02	0.26	29.7%	-4.3%
Benazepril	C09AA07	0.07	0.06	0.06	0.05	0.05	0.04	0.05	-0.01	< 0.01	94.1%	-12.4%
Cilazapril	C09AA08	0.49	0.38	0.28	0.22	0.14	0.14	0.28	-0.07	< 0.01	94.1%	-25.8%
Fosinopril	C09AA09	1.24	1.25	1.18	1.15	1.24	1.27	1.22	0.00	0.83	1.3%	0.2%
Imidapril	C09AA16				0.05	0.11	0.18	0.11	0.07	< 0.01	99.8%	58.6%
ARB												
Losartan	C09CA01	3.19	3.71	3.94	4.35	3.95	3.81	3.82	0.12	0.214	35.3%	3.1%
Valsartan	C09CA03	2.57	3.98	5.21	6.25	6.56	7.17	5.29	0.91	< 0.01	95.0%	17.2%
Irbesartan	C09CA04	0.38	1.03	1.98	3.07	3.48	4.02	2.33	0.76	< 0.01	98.1%	32.7%
Telmisartan	C09CA07		0.16	0.48	0.88	1.05	1.22	0.76	0.27	< 0.01	96.7%	35.4%
Candesartan	C09CA06		0.09	0.21	0.39	0.73	1.22	0.53	0.28	< 0.01	93.0%	53.2%
Valsartan and diuretics	C09DA03		0.07	0.27	0.72	1.48	2.34	0.98	0.57	< 0.01	94.5%	58.8%
Losartan and diuretics	C09DA01	0.04	0.29	0.61	0.95	1.16	1.46	0.75	0.29	< 0.01	99.6%	38.3%
Olmesartan and diuretics	C09DA08					0.13	0.43	0.28	0.30	< 0.01	100.0%	106.0%
Irbesartan and diuretics	C09DA04			0.01	0.06	0.10	0.17	0.08	0.05	< 0.01	98.1%	59.7%

*Regression coefficients for mean change in DID per year; ^+p value for regression coefficient to test the statistical significance of mean change in DID.

Table III. Defined Daily Doses per 1000 inhabitants per day (DID) of antihypertensive drugs in Taiwan and other OECD countries[16] in 2006.

Drugs	ATC	Taiwan	Australia	Belgium	Sweden	United Kingdom	Germany
Beta-adrenoceptor blockers	C07	21.4	25.8	69.5	55.4	36	77.3
ACE inhibitors and angiotensin II antagonists	C09	43.6	117.7	106	106.6	135.7	187.7
Diuretics	C03	15.0	29.5	44.5	90.2	73.1	70.6
Calcium channel blockers	C08	44.7	48.4	44.4	47.7	62.4	59.4
Others	C02	4.6	4.9	6.2	2.2	14.7	12.5
Total		129.2	226.3	270.5	302.1	321.9	407.5

of DDDs per 1000 inhabitants per day (DID) has previously been used to demonstrate differences (nationally and internationally) in the utilization of antidiabetics[17-19], antibiotics[20], and cardiovascular[21-24] and psychotropic drugs[25,26].

Increases in the consumption of pharmaceutical appear to be the result of an increase in the prevalence of hypertension. The prevalence of hypertension reached 972 million cases (26.4% of the global population) in 2000 and is expected to reach 1.56 billion (29.2% of the global population) by 2025. This represents an increase of 60% in 25 years[27,28]. The prevalence of hypertension in Taiwan is only slightly lower than that of other countries[29]; however, the use of drugs to treat this disorder is considerably lower (Figure 3). According to a previous study, the Nutrition and Health Survey in Taiwan (NAHSIT) conducted during 1993 to1996, only 2% of hypertensive males and 5% of hypertensive females had their hypertension under control[30]. The second nationwide survey, the Taiwanese Survey on Hypertension (2002), Hyperglycemia and Hyperlipidemia (TwSHHH) found that the awareness, treatment and control of hypertension had improved significantly in the ensuing period[31]. Wu et al[30] investigated 8922 patients in a Taiwanese cohort of RIAT (The Reasons for not Intensifying Antihypertensive Treatment) with untreated/uncontrolled hypertension[30]. The authors found that the num-

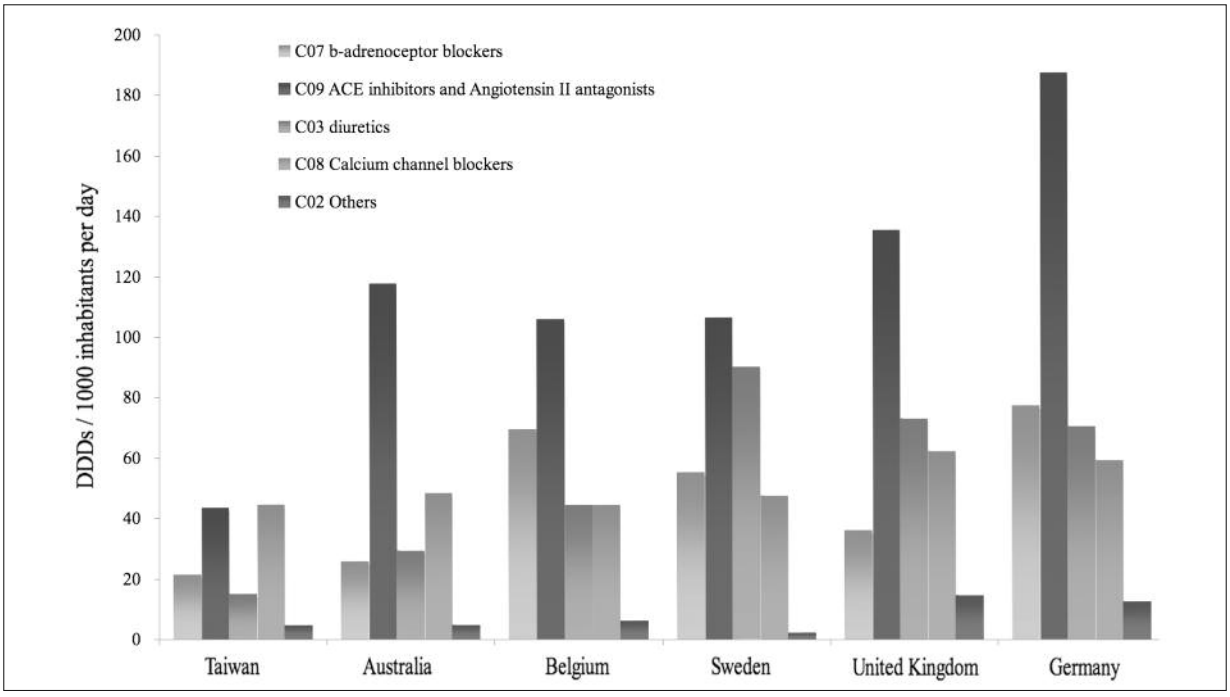

Figure 3. Consumption of antihypertensive agents in Taiwan and other OECD countries[16] in 2006 (unit: DDDs per 1000 inhabitants per day, DID).

ber of newly diagnosed hypertensive patients in Taiwan was lower and the therapeutic inertia was higher than the global RIAT average, resulting in a greater number of patients not being treated to target[30]. These findings indicate a potential undertreatment or delay in treatment of hypertension in Taiwan[30]. This study also determined that the use of drugs to treat hypertension is considerably lower in Taiwan than in OECD countries (Figure 3).

As shown in Figure 1, from 2001 to 2006, the average annual use of CCBs increased and was the most common treatment in Taiwan (Figure 3). This situation is very different from that observed in other OECD countries. This is perhaps because previous studies have demonstrated that CCBs[32-34] are both safe and effective in the control of blood pressure[32-34]. Definitive evidence that long-acting dihydropyridine CCBs are not associated with an increase in cardiovascular events was most recently provided by the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT)[35]. Furthermore, Liou YS et al[36] found that the use of CCBs and ARBs was not associated with new-onset diabetes (NOD) among elderly Taiwanese. Both diuretics and beta-blockers have been reported to accelerate NOD in patients with hypertension[36]. Under special conditions, for example among patients with diabetes or patients with chronic kidney disease, the latest guidelines recommend that CCBs be used in combination with ACEIs or ARBs to enhance BP control[37]. Another consideration may be the comparatively lower cost of CCBs[38,39]. However, the available data does not extend beyond 2006, indicating that further studies may be required to confirm this point.

The National Health Insurance (NHI) of Taiwan has not yet established definitive guidelines for antihypertensive drug therapy; therefore, physicians are free to prescribe any drugs as initial treatment. Liu et al. previously reported that CCBs and beta-blockers were the most frequently prescribed antihypertensive drugs for newly diagnosed hypertension patients without complications in Taiwan[19]. In this study however, though the DID in 2006 was highest for CCBs (34.6%), the second greatest DID was ARBs (16.9%). The average annual increase in the use of ARBs (22.1%) and ACEIs (4.5%) can be attributed to specific factors. First, the prevalence of cardiovascular disease and diabetes has been rising in Taiwan. Second, the mortality rate for cardiovascular disease has decreased over time; hence, individuals are being prescribed ACE inhibitors and ARBs for longer periods. Third, observational studies have reported a higher adherence rate with ACE inhibitors than with conventional therapy, implying that ACE inhibitors provide better tolerance[40]. Finally, clinical guidelines and the results of clinical trials have promoted the prescription of ARBs and ACE inhibitors[41-44]. Several guidelines suggest that the efficacies of ACE inhibitors and ARBs are equivalent. Both these drug classes are recommended for patients with macroalbuminuria or diabetic nephropathy[41-44], due to a significant reduction in all-cause mortality, cardiovascular events, and the progression of chronic kidney disease[41-44]. However, there is still no consensus as to the comparative efficacy of ACE inhibitors or ARBs[45]. ARBs are also prescribed for patients who are unable to tolerate ACE inhibitor-induced coughing[42]. As shown in Figure 1, the average annual increase in the use of ARBs is far greater than that of ACEIs and the average annual increase in the use of all ARB drugs has increased (Figure 2). In the UK, Ross et al[46] assessed the cost implications of changing prescription patterns for antihypertensive drugs in the Grampian region over a one-year period. The number of prescriptions for newer agents such as ARBs increased by a greater extent than for established drugs such as beta-adrenoceptor blockers and thiazides (246.27% vs. 33.98% and 60.00%, respectively)[46]. Our study noted a similar increase in the number of prescriptions for newer agents such as ARBs (Figure 1).

This study has a number of limitations. First, adherence to medication has always been a problem in the management of hypertension[47]; therefore, this study cannot account for the actual use of antihypertensive medications. This means that there may be differences in the adherence rate, depending on the class of medication prescribed. Second, we were unable to link the pharmacy database to patient diagnoses. This prevented us from determining the number of patients with coexisting illnesses that may have influenced drug choice and also whether patients without hypertension used these drugs for other purposes. However, we do not believe that these factors greatly influenced our results, considering that the prevalence of hypertension far exceeds that of other disorders for which these drugs may be used. Furthermore, over the time span of this study, it is unlikely that any major shift occurred in the treatment patterns that would result in a higher proportion of patients receiving these medications for illnesses other than hypertension.

Conclusions

The consumption of antihypertension drugs in Taiwan increased during the period studied and the highest average annual increases were for ARBs and CCBs. Overall consumption of antihypertension drugs also increased in other countries, but differences in the relative increase for each class of drug suggest that further study may be required to clarify the origins and causes.

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Competing Interests

The Authors declare that they have no competing interests.

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