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Impact of Introduction of Angiotensin II Antagonist on the Antihypertensive Utilization in Taiwan

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ABSTRACT

This study aimed to evaluate the long term impact of a new pharmacological class antihypertensive medicine-angiotensin II antagonist (AIIA) on the clinical utilization of existing antihypertensive medications in Taiwan. Claims data of medical service and prescriptions of antihypertensive agents during 1997 to 2002 were obtained from National Health Insurance Research Database (NHIRD). Gross growth of defined daily dose (DDD) and prescription numbers, clinical market share and prescription market share analysis, market penetration time and DDDs/prescription were used to assess AIIA's impact on the angiotensin converting enzyme inhibitors (ACEI), ß-Blockers, calcium channel blockers (CCB) and other miscellaneous antihypertensive agents. CCB had the highest gross growth of DDDs and prescription at 117.1 and 3.4 million increments, respectively. Analysis of clinical market share revealed that the introduction of AIIA had the most significant impact to the clinical utilization of miscellaneous antihypertensive agents (-5.5%) and a moderate impact on both ß-blockers (-4.5%) and ACEI (-4.1%). Whereas the greatest impact of prescription market share was observed with miscellaneous antihypertensive agents (-6.5%), a moderate impact with ACEI (-2.3%) and a very minor impact with ß-blockers (-0.9%). CCB, however, had a positive clinical market share (+3.9%) and prescription market share (+2.4%) correlated with AIIA. AIIA utilization implicated by relative growth strength for the clinical market share and prescription market share at medical center, regional hospital, district hospital and primary care clinic were 4.95:3.77:2.77:1 and 5.28:4.17:2.94:1, respectively. The introduction of AIIA did not affect the decreasing trend of clinical utilization of miscellaneous antihypertensive agents and ß-blockers since this downtrend started before AIIA introduction. On the other hand, there was increasing usage of CCB and AIIA to control hypertension in Taiwan. Medical centers were the early adaptors for AIIA and played an important role in the utilization diffusion of AIIA.

Key words: angiotensin II antagonist (AIIA), angiotensin converting enzyme inhibitor (ACEI), ß-blocker, calcium channel blocker (CCB), defined daily dose (DDD), market share, drug utilization

INTRODUCTION

Cheng and Hsieh reported that the average annual growth rate on Taiwan's total National Health Insurance drug expenditure was 6.4% from 1996 to 2002[(1)]. The drug expenditure on the cardiovascular medications between 1997 and 2002 more than doubled from 5.89 billion NTD to 11.90 billion NTD, at an annual growth rate of 19.9%[(2)]. This indicated that the rate of the cardiovascular drug expenditure in Taiwan grew at almost twice faster than that of the average drug expenditure. It also grew at a much faster rate than Canada (10.4% annual rate in 1999 to 2003), where similar national health insurance program was implemented[(3)].

Pharmacologically, antihypertensive agents are classified into the following groups: diuretics, ß-blockers, ACE inhibitors (ACEI), calcium channel blockers (CCB), angiotensin II receptor blockers (AIIA), α-blockers, central α2-agnonists, adrenergic inhibitors, and vasodilators. AIIA is a new pharmacological class of antihypertensive medication introduced into Taiwan's market in the first quarter of 1998. Before its introduction, the antihypertensive medication market could be divided into four segments by their pharmacological classes: ACEI, ß-blockers, CCB, and other miscellaneous antihypertensive agents. Based on the available evidences including the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), thiazide diuretics are recom-

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mended as the initial therapy for patients with uncomplicated hypertension. A ß-blocker without intrinsic sympathomimetic activity is suggested to be given after an acute myocardial infarction. And, a greater efficacy of the CCBs and diuretics in elderly and black hypertensive patients has also been documented. In addition, ACEI is found effective in patients who have heart failure, myocardial infarction, diabetes or proteinuric chronic renal failure. AIIAs and ACE inhibitors are likely to have similar indications and efficacy[4,5], but AIIA is particularly for patients who develop cough with ACEI[6,7]. Note that lowering blood pressure is not the sole consideration in selecting antihypertensive medication. Instead, the compelling indications, tolerability and cost effectiveness should be all taken for justification in prescribing decisions.

As more clinical data become available, AIIA gradually gains acceptance among the physicians as the first-line treatment. AIIA, with approximately 60% pricing premium over the average price of all antihypertensive drugs, would impact both total drug expenditure and drug utilization shift. It is thus worth the effort to investigate how AIIA would affect the existing drug utilization and the physicians' prescribing behaviors using the time trend analysis before and after AIIA introduction of antihypertensive prescription patterns.

Retrospective pharmacoeconomic analysis using claim database is commonly used to compare health costs associated with competing drugs or intervention[8]. In this study, we took the 1997-2002 ambulatory service records and prescription claim data file from the NHIRD to analyze the utilization trend of ACEI, ß-blockers, CCB and miscellaneous antihypertensive agents before and after the introduction of AIIA in Taiwan, in order to better understand how a new and innovative pharmacological class of medication may influence the utilization of the existing medications.

MATERIALS AND METHODS

I. *Data Collection*

With the launch of the National Health Insurance Program in 1995, Taiwan's healthcare system is publicly managed by the Bureau of National Health Insurance (BNHI) and covers 22 million people (98.7% of the total population) by the end of 2003. The BNHI contracted with 17,022 (93.8%) medical institutions nationwide[9]. Medical institutions are classified into four levels by their service capacity: medical center (MC), regional hospital (RH), district hospital (DH) and primary care clinic (PCC). All hospital settings provide both inpatient hospitalization service and outpatient ambulatory care service. Patients can choose between primary care clinic and outpatient service of any medical institution with tiered registration fee and co-payment. The outpatient prescription drug expenditure is covered by BNHI as part of the benefit package. The national claims data became available since 1997 which was the first time the public could access such detailed database. This claims database, called National Health Insurance Research Database (NHIRD), is managed by the National Health Research Institute (NHRI), a non-profit research organization founded and sponsored by the Department of Health. Special request to use the NHIRD data has to be reviewed and approved beforehand.

All ambulatory antihypertensive medications used in Taiwan during 1997 to 2002 were obtained from the NHIRD, which included ambulatory service records and prescription details. Both files were merged by patients' encrypted identification codes with an average matching of 99.6% and a total of 122,397,631 observed data sets for 6,228,094 patients. A total of 1021 antihypertensive products were included for analysis, which was identified from the NHI pharmaceutical reimbursement database. The data were subsequently grouped by Anatomical Therapeutic Chemical (ATC) classification system using the National Health Insurance Pharmaceutical Coding System previously developed by Yang Kao[10]. Based on this Coding System, the consumption of drugs was computed by defined daily doses (DDDs), which was the assumed average maintenance dose per day for a drug used for its main indication in adults. According to the ATC system, the antihypertensive agents were classified into the following categories: centrally acting antiadrenergic agents (C02A), peripherally acting antiadrenergic agents (C02C), antihypertensives and diuretics in combination (C02L), agents acting on arteriolar smooth muscle (C02D), combinations of antihypertensives in ATC group C02 (C02N), low-ceiling diuretics, thiazides (C03A), low-ceiling diuretics, excluding thiazides (C03B), high-ceiling diuretics (C03C), potassium-sparing agents (C03D), diuretics and potassium-sparing agents in combination (C03E), beta blocking agents (ß-blockers, C07A), beta blocking agents and thiazides (C07B), beta blocking agents and other diuretics (C07C), beta blocking agents, thiazides and other diuretics (C07D), calcium channel blockers with mainly vascular effects (CCB, C08C), calcium channel blockers with direct cardiac effects (C08D), ACE inhibitors (ACEI, C09A), angiotensin II antagonists (AIIA, C09C), and angiotensin II antagonists combinations (C09D). All antihypertensive medications except ACEI (C09A), ß-blockers (C07A), CCB (C08C) and AIIA (C09C) are classified as miscellaneous antihypertensive agents in this study. All data were presented in units or percentage per year.

II. *Method of Analysis*

Clinical market share and prescription market share are defined as the ratio of the amount of DDDs/prescriptions claimed by individual antihypertensive category to the total amount of DDDs/prescriptions claimed by all antihypertensive medication under ATC system, respectively.

Clinical market share = DDDs of individual sub C class claimed /∑ DDDs of each sub C class claimed (1)

Prescription market share = number of prescriptions claimed by individual sub C class /∑ number of prescriptions of each sub C class claimed (2)

Penetration Time ($PT_{x\%}$) is defined as the time for a specific medication or a class of medication to reach x% of the market share in a specified market, namely the medical institution.

III. *Statistical Analysis*

All data analysis was performed using SAS package (Windows Release 8.02 Version TS Level 02M0) from SAS Institute Inc. (Cary, NC, USA.). Chi-square test and t-test were used to compare nominal and numerical variables, respectively, and data were considered statistically significant at $P < 0.05$. We employed linear regression to demonstrate the differences of clinical market share and prescription market share among the four levels of medical institutions. For linear regression analysis, the least-squares method of best-fit curve was done using the analytical tools provided by Microsoft® Office Excel 2003 (Redmond, WA, USA.).

RESULTS

The patient profiles are summarized in Table 1. The average age of patients taking antihypertensive medication during this period was 56.0 ± 17.2. During the 6-year period, age 60 to 70 represented the largest patient group with an average proportion of 23.32 ± 0.98% of the total patient population. Female patients were more than male ones with statistical significance (53.63 ± 0.22% vs. 45.95 ± 0.17% ; $P \leq 0.01$).

I. *Gross Growth of the Clinical Utilization of Antihypertensive Medications*

AIIA was introduced into Taiwan in the first quarter of 1998. The overall growth of the total and five sub groups of antihypertensive drugs' clinical usage in Taiwan during 1997 to 2002 in terms of drug quantity consumed (DDDs) and number of prescriptions is shown in Table 2. The results showed that total antihypertensive drug quantity consumed and prescription numbers grew by 90.9% and 47.9% in six years, respectively. The data in Table 2 demonstrated that the growth rate of prescription number for CCB and AIIA were the highest at 64.2% and 2600%, respectively. Furthermore, their increments (3.4 and 2.7 millions) in prescription number accounted for 52.6% of the total increase (11.6 millions) within six years was a major contributor to the drug quantity prescribed. On the other hand, the nearly doubled DDDs growth was more of a clinical factor depending on severity of the disease and physician's medical judgment.

II. *Market Share Analysis of the Clinical Utilization of Antihypertensive Medications*

Due to the high gross growth for almost all antihy-

Table 1. Characteristics of patients prescribed with antihypertensive medications from 1997 to 2002

	1997	1998	1999	2000	2001	2002	Total mean
Patient	2,328,204	2,650,132	2,891,479	2,892,826	3,034,745	3,118,601	
Patient Visits	16,073,491	19,194,467	21,206,820	20,296,332	22,024,726	23,063,913	
AGE (%)							
< 40	414,412 (17.80)	465,726 (17.57)	507,675 (17.56)	469,894 (16.24)	484,845 (15.98)	480,847 (15.42)	
40-49	383,671 (16.48)	452,378 (17.07)	500,516 (17.31)	498,236 (17.22)	517,125 (17.04)	517,607 (16.60)	
50-59	434,194 (18.65)	492,229 (18.57)	538,858 (18.64)	546,335 (18.89)	582,624 (19.20)	616,663 (19.77)	
60-69	578,475 (24.85)	636,694 (24.02)	672,446 (23.26)	667,904 (23.09)	684,372 (22.55)	691,651 (22.18)	
70-79	405,667 (17.42)	469,798 (17.73)	522,931 (18.09)	549,950 (19.01)	587,262 (19.35)	613,235 (19.66)	
≧80	111,785 (4.80)	133,307 (5.03)	149,053 (5.15)	160,507 (5.55)	178,517 (5.88)	198,598 (6.37)	
Mean Age (± SD)	55.36 ± 17.50	55.51 ± 17.67	55.47 ± 17.41	56.22 ± 17.00	56.44 ± 16.91	56.75 ± 16.93	56.00 ± 17.22
Gender							
Female (%)	53.79	53.80	53.79	53.68	53.48	53.26	53.63 ± 0.22*
Male (%)	45.91	45.74	45.83	45.93	46.05	46.22	45.95 ± 0.17*
Unknown (%)	0.30	0.46	0.38	0.39	0.48	0.51	

*$p < 0.01$ by Chi-square test.

Table 2. Utilizations of the antihypertensive drugs CCB, ACEI, ß-blockers (BB), AIIA and miscellaneous antihypertensive agents (MIS) in Taiwan from 1997 to 2002

Year	No. of DDDs[a] & Clinical market share (%)						No. of prescriptions[b] & Prescription market share (%)						Clinical market share/ prescription market share				
	CCB	ACEI	BB	AIIA	MIS	Total DDDs	CCB	ACEI	BB	AIIA	MIS	Total Pr	CCB	ACEI	BB	AIIA	MIS
'97	98.1	91.5	90.2	0	92.2	372.0	5.3	3.8	6.6	0	8.5	24.2					
	(26.4)	(24.6)	(24.2)	(0)	(24.8)		(21.9)	(15.7)	(27.3)	(0)	(35.1)		1.20	1.57	0.89	N/A	0.71
'98	127.2	115.8	107.1	2.9	107.3	460.3	6.6	4.7	7.8	0.1	9.7	28.9					
	(27.6)	(25.2)	(23.3)	(0.6)	(23.3)		(22.9)	(16.3)	(27.1)	(0.5)	(33.3)		1.21	1.54	0.86	1.38	0.70
'99	151.2	130.8	121.2	16.2	119.3	538.7	7.3	5	8.8	0.7	10.3	32.1					
	(28.1)	(24.3)	(22.5)	(3.0)	(22.1)		(22.7)	(15.7)	(27.3)	(2.1)	(32.2)		1.23	1.54	0.82	1.46	0.69
'00	161.2	130.8	122.4	30.7	119.1	564.2	7.1	4.7	8.5	1.2	9.6	31.1					
	(28.6)	(23.2)	(21.7)	(5.4)	(21.1)		(22.9)	(15.0)	(27.3)	(3.8)	(31.0)		1.25	1.55	0.79	1.45	0.68
'01	190.2	142.0	134.7	49.9	129.5	646.3	8	4.8	9.2	1.8	10.1	33.9					
	(29.4)	(22.0)	(20.8)	(7.7)	(20.0)		(23.5)	(14.2)	(27.1)	(5.4)	(29.7)		1.25	1.54	0.77	1.42	0.67
'02	215.2	145.9	139.5	72.2	137.3	710.1	8.7	4.8	9.4	2.7	10.2	35.8					
	(30.3)	(20.5)	(19.7)	(10.2)	(19.3)		(24.3)	(13.4)	(26.4)	(7.4)	(28.6)		1.25	1.53	0.75	1.37	0.68
$\Delta_{MS,97-02}$[c]	3.9	-4.1	-4.5	10.2	-5.5		2.4	-2.3	-0.9	7.4	-6.5		0.05	-0.04	-0.14	-0.01	-0.03
Δ_{97-02}[d]	117.1	54.4	49.3	72.2	45.1	338.1	3.4	1	2.8	2.6	1.7	11.6					
	(119.4)	(59.5)	(54.7)	(2389.7)	(48.9)	(90.9)	(64.2)	(26.3)	(42.4)	(2600.0)	(20.0)	(47.9)					

[a]DDDs represent the total antihypertensive drugs used in each year (in millions).
[b]The number of antihypertensive prescriptions claimed in each year (in millions).
[c]The figure indicates the difference of market share between 1997 and 2002 for each antihypertensive category.
[d] The figure indicates the difference of DDDs or prescription number between 1997 and 2002 except that of AIIA is based on 1998. Figure in parenthesis represents the growth rate.

pertensive medication, we transformed the absolute value into the market share, to differentiate the relative performance of the sub groups. Clinical market share and prescription market share data for each sub group of the antihypertensive medication during 1997 to 2002 are also presented in Table 2. Clinical market share was roughly equally divided into 4 segments: ACEI, ß-blockers, CCB and miscellaneous antihypertensive agents at 1997. The introduction of AIIA has clearly led to decreasing clinical utilization of ACEI, ß-blockers and miscellaneous antihypertensive agents while consumption of CCB increased. While AIIA gained 10.2% for clinical market share, ACEI lost only 4.1% market share. Miscellaneous antihypertensive agents lost the largest clinical market share of 5.5%, dropping from the second position to the fourth one, and ß-blockers lost 4.5% clinical market share, the second largest loser next to miscellaneous antihypertensive agents. CCB gained 3.9% of clinical market and 2.4% of prescription market during this period. Miscellaneous antihypertensive agents still retained the highest prescription market share at 2002 but lost more market share, from 35.1% to 28.6%, than any other group. ß-Blockers only lost a minor share of 0.9% of prescription market share and still held the second position. Segments of the prescription and clinical markets have been shifted from ß-blockers, ACEI and miscellaneous antihypertensive agents to CCB and AIIA.

III. *Market Share Analysis for AIIA at Different Levels of Medical Institutional Setting*

Linear regression analyses on the clinical market share and prescription market share for AIIA at four different medical settings from 1998 to 2002 are presented in Figure 1 and 2. The clinical market share slope for total, MC, RH, DH and PCC was 0.0238, 0.0349, 0.0238, 0.0208 and 0.0075 with R^2 = 0.9999, 0.9973, 0.9932, 0.9998 and 0.9797, respectively. The prescription market share slope for total, MC, RH, DH and PCC was 0.0173, 0.0280, 0.0221, 0.0156 and 0.0053 with R^2 = 0.9987, 0.9960, 0.9934, 0.9989 and 0.9741, respectively. The relative growth strength for the clinical market share and prescription market share at MC, RH, DH and PCC can be obtained by dividing the slope of each medical setting

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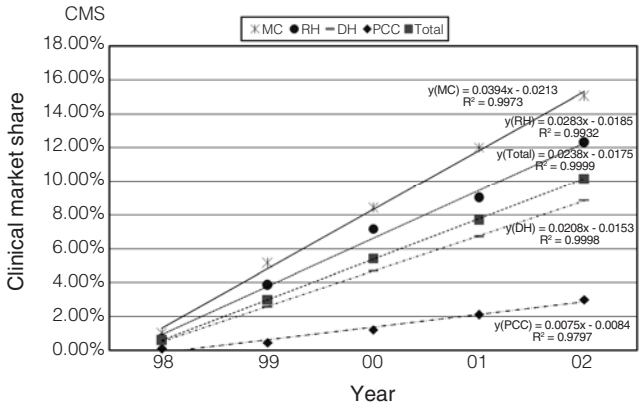

Figure 1. Linear regression analysis of the clinical market share (CMS) for total AIIA and its components at different medical settings from 1998 to 2002.

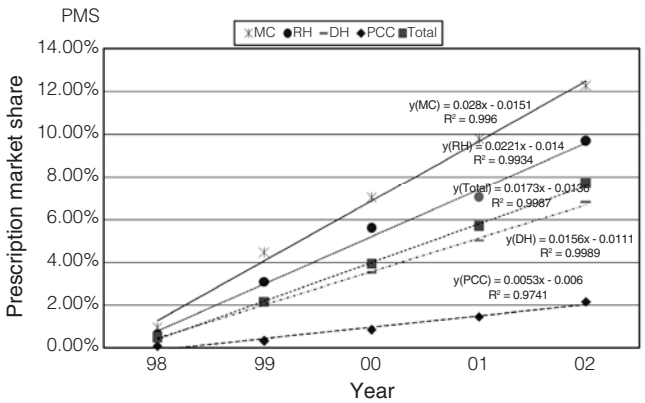

Figure 2. Linear regression analysis of the prescription market share (PMS) for total AIIA and its components at different medical settings from 1998 to 2002.

with that of PCC which yielded 4.65: 3.17: 2.77:1 and 5.28: 4.17: 2.94:1, respectively. This result clearly demonstrated that the market growth strength for AIIA is as follows: MC > RH > DH > PCC.

The 5% clinical market share penetration time ($PT_{5\%,CMS}$) for AIIA at MC, RH, DH are 1 year, 2 years and 3 years; $PT_{10\%,CMS}$ for MC and RH are 3 years and 4 years, and $PT_{15\%,\ CMS}$ for MC was 4 years. The results showed that RH had 1 to 2 years of lag behind MC to seize another 5% clinical market share. DH also took another 1 to 2 years than DH to acquire that extra 5% clinical market share.

DISCUSSION

I. *Impact of AIIA on the Gross Growth of Antihypertensive Medications*

The total drug consumption increased in a linear pattern. On the other hand, the prescription drugs had a moderate growth rate which tapered off after the first 3 years. The 47.9% prescription growth was mainly due to the intrinsic factors of patient number and patient visit increases (34% and 43%, as derived from Table 1) during the study period. The growth rate of prescription number per patient visit, a clinical factor, was found to be 4%. Both annual patient number growth and patient-visit growth might be due to easier accessibility and growing elderly population. Different means have been proposed and tested to reduce this growth, including denying or limiting reimbursement of pharmaceutics through co-payment, co-insurance or deductible and providing an incentive for patients to reduce their consumption of drugs. However, results indicated that such means had little effect on the total cardiovascular drug consumption growth[11-13].

As for the individual sub cardiovascular medication, CCB had the most DDDs gain followed by AIIA, ACEI, ß-blockers, and miscellaneous antihypertensive agents. CCB was also the only sub category, with the exception of AIIA due to its low base at 1998, which had more percentage growth than the whole cardiovascular medication. As for prescription growth, CCB still had the most gain followed by ß-blockers, AIIA, miscellaneous antihypertensive agents, and then ACEI. CCB, again, was the only sub category, with the exception of AIIA, that had higher percentage prescription growth than the total group. It was found that the utilization of CCB increased after the introduction of AIIA, while that of ACEI, ß-blockers and miscellaneous antihypertensive agents decreased over the study period. CCB, AIIA and ß-blockers showed a linear growth pattern for both DDDs and prescription dimension in 1997 to 2002. ACEI and miscellaneous antihypertensive agents were the two sub groups that reached plateau for prescription aspects at 1999, second year after AIIA introduction, despite their continuing DDDs growth.

II. *Normalization of the Clinical Utilization of the Antihypertensive Medication*

The gross DDDs growth was normalized with the gross prescription growth to adjust the dual growth effect. The total and individual sub group DDDs/prescription data from 1997 to 2002 are shown in Table 3. The average DDDs/prescription for the whole group in these 6 years was 17.5 ± 1.8. The average DDDs/prescription for each sub group was 14, 21 or 28. This result showed that the medication prescribed in each prescription is good for 2, 3 or 4 weeks supply. The data also showed that medication prescribed per prescription gradually increased in every sub category of antihypertensive drugs in the study period.

Among individual sub groups, ACEI had the highest absolute average DDDs/prescription followed by AIIA. However, there was no significant difference (P = 0.324) between that of ACEI and AIIA based on the

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Table 3. Quantity of antihypertensive medications claimed defined daily doses per prescription (DDDs/Rx) for total and each sub group of drugs in Taiwan from 1997 to 2002

DDDs/Rx / Year	CCB	ACEI	BB	AIIA	MIS	Total
'97	18.5	24.0	13.6	N/A	10.9	15.4
'98	19.2	24.5	13.7	21.8	11.1	15.9
'99	20.8	25.9	13.9	24.6	11.6	16.8
'00	22.7	28.1	14.5	26.3	12.4	18.2
'01	23.9	29.4	14.6	27.3	12.9	19.1
'02	24.7	30.3	14.8	27.3	13.4	19.8
Ave.±STD	21.6±2.5	27.0±2.6[a]	14.2±0.5	25.5±2.3[a,b]	12.0±1.0	17.5±1.8
$\Delta_{97\text{-}02}$	6.2	6.3	1.2	5.5[b]	2.5	4.4
$\%\uparrow_{97\text{-}02}$	33.5	26.3	8.8	25.2[b]	22.9	28.6

[a] t-test was used to compare the means of DDDs/prescriptpion of ACEI and AIIA during 1997 to 2002 ; $P = 0.324$.
[b] Figures represent the data from 1998 to 2002.

t-test, indicating that physicians in Taiwan had similar prescribing pattern in terms of the quantity of drugs prescribed per prescription for these two pharmacological classes of medication. ACEI had the highest absolute DDDs/prescription increment during these 6 years. AIIA had very close absolute and percentage increment to that of ACEI. CCB had the intermediate average DDDs/prescription but the second highest absolute increment and the highest percentage increment. ß-Blockers and miscellaneous antihypertensive agents had lower DDDs/prescription growth than the whole group average. ß-Blockers had the lowest absolute DDDs/prescription increment and percentage increment followed by miscellaneous antihypertensive agents. These data indicated that the introduction of AIIA had a negative impact on the clinical utilization pattern of ß-blockers and miscellaneous antihypertensive agents. This result thus suggested that both ß-blockers and miscellaneous antihypertensive agents were the less favorable antihypertensive medications used by the physicians.

Drug co-payment scheme was first implemented in August 1998 in Taiwan with drug co-payment ceiling of NTD 100 per physician visit. The co-payment ceiling was further raised to NTD 200 per physician visit in September 2002 to control drug consumption growth. However, this intervention had little effect on the total antihypertensive drug consumption growth due to the DDDs per prescription growth. This result is similar to that obtained by other researchers for the drug co-payment program[12,13]. It is reasonable to suspect that the physician may prescribe more medications for the patient to compensate for the co-payment increase. Under previous fee-for-service reimbursement policy in Taiwan, physicians or hospital administrators had low incentive to change the prescribing pattern or clinical guidelines since the physician or hospital would get full pharmaceutical reimbursement from BNHI.

III. *Comparison of Antihypertensive Utilization Using Market Share Methodology*

Market share analysis removes the intrinsic growth factor that we faced in the gross growth analysis by focusing only on the relative product strength within its own group. Pharmaceutical industry is a regulated field with a very high entry barrier. Larger market share generally means stronger market power and higher profit[14,15]. Pharmaceutical companies use various means to influence the prescribing decisions. Of these, detailing is probably the most important way of communicating with and informing physicians about a drug's performance. Other promotion activities include advertising in medical journals, annual conference at medical association, direct mail, post-marketing research (PMR) programs, and continuing medical education (CME) events[16]. The main market share determinants in these highly regulated industries are government regulation, competitors' pricing, advertisement, and promotion[17,18]. Therefore, using the market share analysis as an indicator to reflect both the clinical performance and promotion campaigns allows us to compare the utilization trend among the different pharmacological classes of the antihypertensive medications.

AIIA, with remarkable increase in market share, shows no sign of slowing growth. In the US, AIIA use among hypertensive adults had reached 9.0% during 1999 to 2002[19]. AIIA shares similar pharmacologic effect with ACEI with less cough side effect. It was expected that AIIA would gradually replace ACEI. However, the 10.2% clinical market share or 7.4% prescription market share growth of AIIA could not totally account for the

substitution of ACEI (4.1% and 2.3% loss, respectively). Actually, the combined market share of ACEI and AIIA increased over this 6-year period. It is quite clear that the growing clinical and prescription market share of AIIA is mainly from the loss of ß-blockers and miscellaneous antihypertensive agents. Furthermore, CCB utilization was raised concurrently with AIIA, and both the clinical market share and prescription market share were increased by 3.9% and 2.4%, respectively. This finding indicated that the antihypertensive regimen adopted by physicians in Taiwan had gradually changed.

Clinical market share, reflecting the physicians' preference, is a quantity indicator for the clinical utilization of a specific product or a sub group for the treatment of a disease or symptom[14,15]. By tracking the clinical market share trend for each sub class, we observed that ACEI continued to gain physicians' support at the first year of AIIA's introduction until 1999, 2nd year after AIIA's introduction. The rate of ACEI switching to other medication was gradually accelerating over the next 4 years, dropping from 25.2% at 1998 to 20.5% at 2002. ß-Blockers and miscellaneous antihypertensive agents lost 4.5% and 5.5% of clinical market share over the study period at a fluctuating but decreasing rate. Both categories lost clinical market share even before the introduction of AIIA, indicating that utilization of both groups were at downtrend before AIIA's introduction. AIIA and CCB gained physicians' preference for the antihypertensive treatment with a 10.2% and 3.9% clinical market share growth at the expense of ACEI, ß-blockers and miscellaneous antihypertensive agents.

However, clinical market share suffers from various medical factors such as severity of the disease and social factors such as duration of prescription period paid by the insurance company. Because specific drugs must get into the prescribing physician's mind first, prescription market share is more of a clinical preference indicator and provides another aspect for drug utilization analysis. Namely, prescription market share is more dependent upon the physicians' prescribing favorites than clinical market share, while clinical market share deals with the quantity of medication prescribed. The latter would be dependent on the severity of the disease and the physicians' prescribing pattern. By comparing the clinical market share and prescription market share for AIIA, it is understandable why longer time is needed to penetrate the prescription market than the clinical market. For example, 5% of clinical market share and prescription market share of AIIA was reached at 2000 and 2001, respectively. 10% of clinical market share of AIIA was reached at 2002 while only 7.4% of prescription market share was reached at the same year.

IV. *Variations of the Utilization Trends among Antihypertensive Agents*

Higher clinical market share/prescription market share value usually means more favorable choices among physicians because they tend to prescribe more DDDs per prescription while lower clinical market share/prescription market share value means un-favorable choices for the physicians. Clinical market share/prescription market shares for ß-blockers and miscellaneous antihypertensive agents were less than 1 even before the introduction of AIIA while that of ACEI, AIIA and CCB were more than 1 (Table 2). ACEI had the highest and relatively stable but declining clinical market share/prescription market share ratio during the study period. AIIA had the second highest but fluctuating clinical market share/prescription market share ratio. CCB also had a relative stable but rising clinical market share/prescription market share ratio. ß-Blockers, on the other hand, lost the highest clinical market share/prescription market share ratio. It is interesting to note that, even though ACEI, ß-blockers and miscellaneous antihypertensive agents all lost market shares with the decreased clinical market share/prescription market share ratio; none of them had similar patterns. ß-Blockers lost very small prescription market share but larger clinical market share and thus had the most clinical market share/prescription market share loss. This means that even though ß-blockers still remains in the treatment regimen but has the lowest absolute and percentage DDDs/prescription growth (at 1.2; 8.8%, respectively, see Table 3). Physicians may simply add additional medications such as CCB or AIIA to the treatment regimen to control the hypertension. It seems that ß-blockers will probably stay in the physicians' prescription list based on the high prescription market share value at the end of the study period. As for the miscellaneous antihypertensive agents, it lost similar significant portion on clinical market share and prescription market share and thus had very little clinical market share/prescription market share change. This indicated that the physicians switched from this category to other pharmacological class of antihypertensive medication. As for ACEI, due to its high leverage clinical market share/prescription market share ratio, it had a moderate prescription market share loss and a high clinical market share loss. ACEI actually had the highest absolute and the second highest percentage DDDs/prescription growth among all sub groups (Table 3). These mixed signals indicated that while some physicians may switch ACEI to other categories, some physicians still rely more on ACEI to treat their patients. AIIA, even though with higher prescription market share and clinical market share gains than CCB, had fluctuating pattern and a minute loss on clinical market share/prescription market share ratio. This may be due to the fact that AIIA is still at the high growth phase. CCB is another prominent winner with triple positive gains on clinical market share, prescription market share and clinical market share/prescription market share ratio. This may be due to the fact that CCB is in the slow growth phase.

It has been demonstrated that MC was the early adaptor for AIIA and played an important role in the utilization diffusion of AIIA. The $PT_{5\%,PMS}$ for AIIA at MC,

RH, DH are 2 years, 2 years and 3 years and $PT_{10\%,PMS}$ for MC is 4 years. Prescription market required longer penetration time than clinical market in all 4 different medical sectors. Judging from both market growth momentum and penetration time parameters, it is apparent that size of the medical institution plays an important role in the introduction phase of a new class of medication: the larger the institution, the stronger the market momentum and the faster penetration would be.

V. *Comparison of Prescribing Antihypertensive Agents in Taiwan with International Guidelines*

In the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (7^{th} US JNC), one of the key messages was "thiazide-type diuretics should be used in drug treatment for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes"[20]. Similarly, the latest WHO guideline states that "for the majority of patients without a compelling indication for another class of drug, a low dose of a diuretic should be considered as the first choice of therapy on the basis of comparative trial data, availability and cost"[21]. However, our study indicated that current practice in Taiwan was not in line with the international guidelines. The data of prescription number in Table 2 implied that ß-blockers were the predominant prescribed medication for antihypertensive management during 1997 to 2002 in Taiwan. A study conducted by Cheng *et al.* at a MC in 2001 also confirmed our observation that diuretics were not the drug of choice for antihypertensive management. Instead calcium-channel blockers were most commonly used alone and in general practices, despite the fact that they should be used in second-line treatments[22].

VI. *Limitation*

This study was conducted based on the most recent available claim data from the NHIRD. In general, health resource allocation is better measured or evaluated by financial amount rather than by volume serviced[9]. However, we tried to analyze the clinical unitization of antihypertensive pharmaceutics through the volume serviced via different point of view in this study. Pharmaceutical utilization pattern is influenced by multiple variables. Patients' accessibility, patient population profile, physician profile, hospital scale, introduction of new innovative chemical compound or generic products, pharmaceutical marketing effort toward physician or patient, drug approval process, drug pricing and reimbursement policy, pattern of persistence in using medications, number of prescribed medication classes, specific medication at enrollment etc. are just a few variables that interwoven together[23]. Information regarding some of the above factors is generally lacking or unable to be quantified. Other limitations for database studies include: data quality, sources of bias, population characteristics, insufficient generalizability, cohort characteristics, and clinical outcomes[24]. Some may also question our focus on a process of care intervention (antihypertensive prescribing) rather than clinical outcomes[3]. It is important to note that the claims database in this case merely represents the final result of the time trend of the pharmaceutical quantity consumed and the number of prescriptions prescribed in the "real world" environment. We could only try to analyze these data through macroscopic point of view. We did not attempt to disseminate all the factors that affect the prescribing behavior. Only with this in mind will we be able to gain more knowledge in this field.

CONCLUSIONS

The market share methodology allows us to differentiate the physicians' prescribing pattern shift. The results suggest that the introduction of AIIA did not consistently affect the utilization of various antihypertensive drugs. The clinical market shares of ß-blockers and miscellaneous antihypertensive agents decreased from 1997 to 2002, while the use of CCB and AIIA to control hypertension increased. MC was the early adaptor for AIIA and played an important role in the utilization diffusion of AIIA.

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