Secular Trends in Prescription Patterns of Single-Pill Combinations of an Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Plus a Thiazide Diuretic for Hypertensive Patients in Taiwan

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Background: Poor adherence to recommended drug regimens is one of the fundamental issues behind suboptimal control rates of hypertension worldwide. Single-pill combinations (SPCs) improve patient adherence, decrease cost, and are increasingly prescribed in the Western societies. We conducted this study to elucidate the prescription patterns and the secular trends of SPCs in Taiwan.

Methods: We retrospectively reviewed the reimbursement database of Taiwan's National Health Insurance from 2002 to 2007. Among the one million-person random samples, information from those coded with ICD-9 401-405 and antihypertensive prescriptions was obtained.

Results: From 2002 to 2007, there had been amore than 7.5-fold increase in annual prescription frequency of SPCs of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) plus a thiazide diuretic (from 1.1% to 8.5%, $p < 0.001$) among 302,628 hypertensive patients. Likewise, among patients treated with at least ACEIs or ARBs and diuretics, the relative proportion of SPC use, in contrast to free combinations, increased markedly (from 10.8% to 54.2%, $p = 0.005$). Incorporating patient antihypertensive treatment prior to SPCs prescription,we categorized the SPC prescription patterns into 3 groups: naïve, switch, and add-on. The increase in patients taking SPCs came mostly from the naïve SPC prescription group (from 2.3% in 2002 to 28.8% in 2007 among all patients treated with ACEIs or ARBs and thiazide diuretics, $p = 0.003$). Compared to both naïve and add-on SPC users, patients in the switch group had a greater pill burden and more comorbidities, whichmight drive physicians to switch from free combinations to SPCs.

Conclusions: Single-pill combinations are well-accepted and increasingly prescribed in Taiwan, particularly in drug-naïve hypertensive patients. This finding might indicate an aggressive attitude towards early hypertension control among physicians in Taiwan.

Key Words: Angiotensin-converting enzyme inhibitor • Angiotensin receptor blocker • Diuretic • Hypertension • Single-pill combinations

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INTRODUCTION

Hypertension is the most common cardiovascular disorder in the world. It is the leading preventable cause of morbidity and mortality arising from coronary heart disease, stroke, heart failure, and renal failure.[1] In an increasing number of countries around the world, hypertension continues its upward growth trend in both pre-

valence and economic impact.[2-5] Despite the availability of a wide range of antihypertensive medications, recent analyses of National Health and Nutrition Examination Survey (NHANES) data showed that 50 to 55% of adult hypertensive patients in the United States have uncontrolled blood pressure.[6,7] In Taiwan, hypertension-related comorbidities have accounted for almost one third of the total causes of death in recent years. In 2003, the total pharmaceutical expenditure on antihypertensive medications was approximately 27% of the overall annual outpatient pharmaceutical expenditure worldwide.[8]

Only about 30% of hypertensive patients can have their conditions controlled by a single antihypertensive drug; about 40% of patients need two drugs.[9] Multiple pharmaceuticals are commonly required in hypertensive patients with diabetes, chronic kidney disease, and in elderly patients.[10] It has been shown that the nonadherence rate for patients taking a single-pill combination (SPC) is 26% lower compared to those treated with free combination regimens.[11] SPCs are thus recommended in many current guidelines for the management of hypertension.[3,4] The National Health Insurance (NHI) program, a compulsory universal health insurance implemented in Taiwan on March 1, 1995, covers more than 98% of the entire Taiwanese population.[12] The computerized reimbursement database of the NHI in Taiwan provides us with a valuable opportunity to assess the practice of antihypertensive pharmaceutical therapies in the real world. We conducted this study to look at the prescription patterns and secular trends of SPC use in Taiwan.

METHODS

Study subjects

We retrospectively reviewed the reimbursement database of Taiwan's NHI from 2002 to 2007. Among the one million-person random samples, information was obtained from those coded with ICD-9 401-405 and their antihypertensive prescriptions. Patients had to be at least 18 years in age.

Antihypertensive agents were categorized into six major categories, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), diuretics, and others (all other antihypertensive classes including alpha-blockers). Continuous use of the same antihypertensive medications for at least six months was needed to define a specific treatment group. In patients treated with SPCs of an ACEI or ARB plus a thiazide diuretic, they were further divided into 3 subgroups (naïve, switch, and add-on) according to their previous antihypertensive treatment immediately before prescription of SPCs. Patients were categorized as "naïve" if they did not take any antihypertensive drugs in the past 6 months prior to the index date, when SPCs were prescribed as the initial treatment for hypertension. Patients were categorized as "switch" if they took ACEI or ARB and diuretics prior to the index date, when the free combinations were switched to SPCs of the corresponding antihypertensive agents. Patients were categorized as "add-on" if they took medications other than free combinations of an ACEI or ARB and a thiazide diuretic before and had SPCs prescribed on the index date.

The demographic data of age, gender, hospitals (medical centers, regional hospitals, area hospitals or local clinics) responsible for hypertension care, numbers of other concomitant antihypertensive agents, numbers of all other concomitant medications, use of lipid-lowering therapy, use of anti-diabetic medications, and comorbidities, including diabetes mellitus, chronic kidney disease, heart disease, and cerebrovascular disease, were collected and analyzed.

Statistical analysis

All analyses were performed using the SAS statistical software package, version 9.1 (SAS. Cary, NC, USA). For univariate analysis, Pearson's chi-square test or Fisher's exact test was used for comparison of categorical variables, while Student's t-test or one-way analysis of variance (ANOVA) was used for analysis of continuous variables. All tests were two-tailed, and p values of < 0.05 were considered statistically significant.

RESULTS

Table 1 shows the prescription frequencies of various categories of antihypertensive agents among patients diagnosed as having hypertension (n = 302,628)

Table 1. Prescription frequencies among different categories of antihypertensive medications in Taiwan by year

Year	Drug Class* (%)								
	CCB	BB	D	Others	ACEI or ARB	ACEI	ACEI/D	ARB	ARB/D
2002	59.2	44.4	23.0	16.0	45.4	33.6	0.0	16.1	1.1
2003	59.9	43.4	23.9	15.2	47.1	31.4	0.0	19.5	2.4
2004	60.6	43.3	25.8	14.8	48.2	30.0	0.1	21.4	3.9
2005	61.1	42.8	26.1	14.0	47.7	28.4	0.2	21.0	5.2
2006	61.4	42.1	25.8	13.1	48.3	26.7	0.5	21.8	6.7
2007	57.7	37.9	22.3	10.8	44.5	21.8	0.8	21.4	7.6
Slope	0.11	-1.09	0.15	-0.94	0.33	-2.05	0.14	1.44	1.30
p	0.704	0.005	0.644	< 0.001	0.408	< 0.001	0.006	0.012	< 0.001

* Others including alpha-blockers; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; D, diuretic.

from 2002 to 2007. CCB was the most frequently prescribed antihypertensive agent, and its prescription rate remained stable during the study period (from 59.2% to 57.7%, p = 0.704). The frequency of prescription of ACEIs (from 33.6% to 22.6%, p < 0.001), beta-blockers (from 44.4% to 37.9%, p = 0.005), and other antihypertensive agents (from 16.0% to 10.8%, p < 0.001), decreased significantly, whereas the prescription of ARBs increased from 14.1% to 21.4% (p = 0.012) despite the fact that total prescriptions of ACEIs or ARBs remained stable (from 45.4% to 44.5%, p = 0.408). The most dramatic increase in prescription rates was for SPCs of an ACEI or ARB plus a thiazide diuretic (from 1.1% to 8.5%, p < 0.001). Likewise, among patients treated with at least ACEIs or ARBs and diuretics, the relative proportion of SPC use, in contrast to free combinations, increased markedly (from 10.8% to 54.2%, p = 0.005) (Table 2).

Table 2. Prescription patterns among patients treated with at least ACEIs or ARBs and thiazide diuretics by year

Year	A/D	Naïve	Switch	Add-on	A+D
2002	10.8	2.3	1.7	6.9	89.2
2003	19.8	7.7	2.4	9.7	80.2
2004	33.7	6.5	7.8	19.4	66.3
2005	43.2	9.0	11.7	22.5	56.8
2006	49.1	18.1	10.4	20.6	50.9
2007	54.2	28.8	6.2	19.2	45.8
slope	3.52	1.68	0.58	1.26	0.74
p	0.005	0.003	0.145	0.054	0.440

* A/D, single pill combinations of ACEIs or ARBs and thiazide diuretics; A+D, free combinations of ACEIs or ARBs and thiazide diuretics.

We analyzed the prescription behavior of patients treated with SPCs, and categorized the behavior into 3 patterns: naïve, switch, and add-on (Table 2). The increase in prescriptions of SPCs came mostly from drug-naïve patients (from 2.3% in 2002 to 28.8% in 2007 among all patients treated with ACEIs or ARBs and thiazide diuretics, p = 0.003). In other words, the initial use of SPCs in previously untreated hypertensive patients has steadily gained popularity in Taiwan. Compared to patients treated with free combinations of ACEIs or ARBs and thiazide diuretics, patients receiving SPCs were more often female (p = 0.026), under 55 years old (p < 0.001), taking lipid-lowering agents concomitantly, and managed at area hospitals. It is noteworthy that patients treated with SPCs had fewer comorbidities such as heart disease, chronic kidney disease and cerebrovascular disease (Table 3). This intriguing finding was primarily driven by the high percentage (38.3%) of naïve SPC users, who were generally younger and had considerably fewer comorbidities (Table 4).

As shown in Table 4, among the 3 different prescription pattern groups, patients who were switched from free combinations to SPCs had higher rates of comorbidities compared to the other 2 groups (heart disease, 16.4% vs. 35.5% vs. 20.4%; diabetes, 32.5% vs. 44.4%, 35.8%; chronic kidney disease, 3.2% vs. 7.4% vs. 3.5%; cerebrovascular disease, 11.6% vs. 18.9% vs. 14.8% for naïve, switch, and add-on groups, respectively) (Table 4). They also had higher numbers of antihypertensive agents [mean ± standard deviation (SD), 1.7 ± 2.4 vs. 2.6 ± 3.3, 1.8 ± 2.7 for naïve, switch, and add-on groups, respectively] and more frequently

Table 3. Demographics and comorbidities among patients treated with fixed or free combinations of ACEIs or ARBs plus thiazide diuretics

	A/D N (%)	A+D N (%)	p value
Gender			
Female	12330 (52.3)	20341 (51.4)	
Male	11251 (47.7)	19253 (48.6)	0.026
Age			
< 55	6594 (28.0)	9822 (24.8)	
≥ 55	16987 (72.0)	29772 (75.2)	< 0.001
Number of other concomitant antihypertensive drugs			
< 2	18050 (76.5)	30494 (77.0)	
≥ 2	5531 (23.5)	9100 (23.0)	0.173
Number of all other concomitant drugs			
< 2	13361 (56.7)	22257 (56.2)	
≥ 2	10220 (43.3)	17337 (43.8)	0.273
Type of health care institute			
Medical center	3715 (15.8)	9977 (25.2)	
Regional hospital	7863 (33.3)	12077 (30.5)	< 0.001
Area hospital	6019 (25.5)	7339 (18.5)	< 0.001
Others/clinics	5984 (25.4)	10201 (25.8)	< 0.001
Lipid-lowering agents			
No	15099 (64.0)	26629 (67.3)	
Yes	8482 (36.0)	12965 (32.7)	< 0.001
Antihyperglycemic agents			
No	16096 (68.3)	26958 (68.1)	
Yes	7485 (31.7)	12636 (31.9)	0.653
Co-morbidities			
Heart disease	5075 (21.5)	10867 (27.4)	< 0.001
Coronary heart disease	3059 (13.0)	5737 (14.5)	< 0.001
Myocardial infarction	203 (0.9)	554 (1.4)	< 0.001
Atrial fibrillation	683 (2.9)	1567 (4.0)	< 0.001
LVH	242 (1.0)	452 (1.1)	0.185
Heart failure	2007 (8.5)	5299 (13.4)	< 0.001
Diabetes			
Chronic kidney disease	960 (4.1)	2627 (6.6)	< 0.001
Cerebrovascular disease	3371 (14.3)	6000 (15.2)	0.003
Ischemic stroke	2300 (9.8)	4048 (10.2)	0.059
Cerebral hemorrhage	382 (1.6)	784 (2.0)	0.001
Transient ischemic attack	860 (3.6)	1307 (3.3)	0.021
Cognitive dysfunction and dementia	382 (1.6)	809 (2.0)	< 0.001

treated with lipid-lowering agents (30.8% vs. 45.8% vs. 36.5%) and anti-diabetic agents (28.7% vs. 39.6% vs. 31.2%), indicative of higher pill burden.

DISCUSSION

Hypertension continues to be a substantial and escalating threat to human health worldwide. According to World Health Statistics 2012, the prevalence of hypertension is 29.2% in men and 24.8% in women among adults 25 years of age or older.[13] It causes morbidities in many major organ systems, with subsequent mortalities.[1-5] However, hypertension remains a disease with a low level of awareness, and modest control rates. Many factors attributable to physicians and patients had been

Table 4. Demographics and comorbidities among patients treated with at least ACEIs or ARBs plus thiazide diuretics stratified by prescription patterns

	Naive SPC N (%)	Switch to SPC N (%)	Add-on SPC N (%)	p value
Gender				
Female	4583 (50.8)	2280 (55.2)	5467 (52.5)	< 0.001
Male	4445 (49.2)	1851 (44.8)	4955 (47.5)	
Age				
< 55	2791 (30.9)	844 (20.4)	2959 (28.4)	< 0.001
≥ 55	6237 (69.1)	3287 (79.6)	7463 (72.6)	
Number of other concomitant antihypertensive drugs				
< 2	7153 (79.2)	2674 (64.7)	8223 (78.9)	< 0.001
≥ 2	1875 (20.8)	1457 (35.3)	2199 (21.1)	
Number of all other concomitant drugs				
< 2	5409 (59.9)	1824 (44.2)	6128 (58.8)	< 0.001
≥ 2	3619 (40.1)	2307 (55.8)	4294 (41.2)	
Type of health care institute				
Medical center	1374 (15.2)	735 (17.8)	1606 (15.4)	< 0.001
Regional hospital	2946 (32.6)	1552 (37.5)	3365 (32.3)	
Area hospital	2255 (25.0)	1056 (25.6)	2708 (26.0)	
Others/clinics	2453 (27.2)	788 (19.1)	2743 (26.3)	
Lipid-lowering agents				
No	6245 (69.2)	2239 (54.2)	6615 (63.5)	< 0.001
Yes	2783 (30.8)	1892 (45.8)	3807 (36.5)	
Antihyperglycemic agents				< 0.001
No	6435 (71.3)	2495 (60.4)	7166 (68.8)	
Yes	2593 (28.7)	1636 (39.6)	3256 (31.2)	
Co-morbidities				
Heart disease	1481 (16.4)	1465 (35.5)	2129 (20.4)	< 0.001
Coronary heart disease	818 (9.1)	842 (20.4)	1399 (13.4)	< 0.001
Myocardial infarction	54 (0.6)	64 (1.5)	85 (0.8)	< 0.001
Atrial fibrillation	216 (2.4)	224 (5.4)	243 (2.3)	< 0.001
LVH	66 (0.7)	59 (1.4)	117 (1.1)	< 0.001
Heart failure	591 (6.5)	730 (17.7)	686 (6.6)	< 0.001
Diabetes	2930 (32.5)	1834 (44.4)	3731 (35.8)	< 0.001
Chronic kidney disease	286 (3.2)	307 (7.4)	367 (3.5)	< 0.001
Cerebrovascular disease	1045 (11.6)	782 (18.9)	1544 (14.8)	< 0.001
Ischemic stroke	697 (7.7)	545 (13.2)	1058 (10.2)	< 0.001
Cerebral hemorrhage	136 (1.5)	74 (1.8)	172 (1.7)	0.460
Transient ischemic attack	239 (2.6)	215 (5.2)	406 (3.9)	< 0.001
Cognitive dysfunction and dementia	119 (1.3)	90 (2.2)	173 (1.7)	0.001

identified, including the fact that multiple drugs were needed for patient treatments. Consequently, regimens that involved multiple drugs led to a low patient adherence rate, which was among the most important causes of treatment failure.[6,7,10] SPCs successfully improved drug adherence while reducing overall costs at the same time.[11] SPCs are thus recommended in many current hypertension management guidelines.[3,4] Our study intended to elucidate the prescription patterns and time trends of antihypertensive agent usage, particularly SPCs, in Taiwanese hypertensive patients, about which the NHI reimbursement database is quite representative. We found that beta-blockers were less-prescribed on a continuous basis. This trend was possibly due to evidence of the reduced effectiveness of beta-blockers in minimizing cardiovascular events,[14-18] higher with-

draw rates,[14,16] and more side effects, including new-onset diabetes and increased long-term blood pressure fluctuations.[14,15] Beta-blocker was also less cost-effective in terms of improvements in quality adjusted life years.[14] The prescription trend moved parallel with the treatment recommendations in contemporary hypertension guidelines.[3,4,14] Persistent dry cough associated with ACEI therapy is the most common adverse effect and the most frequent reason for discontinuation of ACEIs, especially in Asian populations.[19-21] ACEI prescriptions were thus steadily decreased because of its higher withdrawal rate. Recent trials showed equivalent effectiveness of ACEIs and ARBs.[22,23] Accordingly, prescriptions of ARBs increased nearly 2-fold from 2002 to 2007. However, the prescription share of ACEIs plus ARBs remained relatively stable over the study period.

Fixed-dose combinations of ACEIs or ARBs plus thiazide diuretics were the most popular SPCs during the study period. SPCs composed of an ACEI or ARB plus a CCB entered the Taiwan pharmaceutical market in 2008. From 2002 to 2007, there had been a more than 7.5-fold increase in annual prescriptions of SPCs of ACEI or ARB/diuretics. More than 90% of patients receiving SPCs of ACEIs or ARBs and diuretics were ARB-based, which might be due to the high cough rates with ACEIs in Taiwanese hypertensive patients. Among patients treated with at least ACEIs or ARBs and diuretics, our results showed that female patients, those patients less than 55 years of age, patients taking lipid-lowering agents, and patients having fewer comorbidities of heart disease, chronic kidney disease, or cerebrovascular disease were more likely to be treated with SPCs. Patients treated at area hospitals received more SPCs as well. The causes cannot be clearly identified, but pill burden, patient compliance, and financial issues related to insurance reimbursement (SPCs are generally cheaper than their free combination counterparts in Taiwan) all had substantial impacts on the physicians' willingness to prescribe SPCs.[11,24] The finding that younger hypertensive patients are more prone to be treated with SPCs may reflect the concern of the lack of flexibility with SPCs, which may cause symptomatic hypotension, particularly in the elderly. On the contrary, we noticed that older patients with greater pill burdens are more likely to have their free combined ACEIs or ARBs and diuretics switched to SPCs. Given that these patients are polypharmacy-tolerant, including ACEI or ARB with diuretics, together with high pill burden and high pharmaceutical cost, physicians can confidently switch from free combinations to SPCs.

This study, however, was limited by the lack of data regarding daily dosages of drugs, drug compliance and profiles of side effects related to prescribed medications. There was no information about the blood pressure of individual participants as well.

CONCLUSION

In conclusion, SPCs are well accepted and increasingly prescribed in Taiwan, particularly in drug-naïve hypertensive patients. This finding might indicate an aggressive attitude towards early hypertension control among physicians in Taiwan. In patients who had higher pill burden, free-combined antihypertensive medications are more likely to be switched to SPCs.

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