Patterns of antihypertensive prescribing, discontinuation and switching among a Hong Kong Chinese population from over one million prescriptions

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Abstract

Hypertension is an alarming public health problem among Chinese. The present study evaluated the prescribing patterns, discontinuation and switching profiles of antihypertensive agents and their associated factors in one Hong Kong Chinese population. Data were retrieved from computerized records for patients prescribed anti-hypertensive agents in government primary care clinics of Hong Kong from January, 2004 to June, 2007. A total of 1,069,836 antihypertensive drug visits, representing 67,028 patients, were analyzed. The most commonly prescribed drugs were Calcium Channel Blockers (CCBs) (49%), β-Blockers (BBs) (46%) and Angiotensin-Converting Enzyme Inhibitors (ACEIs) (19%). Thiazide diuretic prescribing was low (13%) and on the decline (14% in 2004 to 12% in 2007). Prescribing of ACEIs was rising (16% in 2004 to 23% in 2007). Patients' age, gender, and socio-economic status were independent predictors of class of anti-hypertensive prescribed but explained less than 3.5% of the variation observed. Drug discontinuation was highest for BBs (21%) and lowest for CCBs (12%). The high rates of discontinuation in BBs remained apparent after controlling for confounding variables. Switching was less common than discontinuation and was most likely with thiazide diuretics. To summarize, prescribing of CCBs and BBs were high and that of thiazide diuretics particularly low in this Chinese population when compared with international trends. CCBs may be a particularly favorable antihypertensive treatment in Chinese, given the high discontinuation rates of BBs and international guidelines advising

against the use of BBs as first-line therapy. The low use of thiazide diuretics warrants further clinical and cost effectiveness studies among Chinese.

Introduction

Hypertension is a global health challenge due to its high and rapidly growing prevalence in Western countries[1,2] and also in the Asia pacific region including China.[3-5] It remains generally poorly controlled[6, 7] and has been reported as the most common global risk factor for cardiovascular morbidity and mortality, thus carrying a huge public health burden.[1, 3]

Regarding the drug treatment of hypertension, the World Health Organization (1999),[8] the National Heart Foundation of Australia (1999)[9] and the European Society of Hypertension (2003)[10] recommended any major classes of antihypertensive agents as the first-line drugs subject to physicians' discretion, while the British Hypertension Society (1999)[11] and the Seventh report of the Joint National Committee (JNC-VII, 2003)[12] supported the use of thiazide diuretics as the best first-line prescription in view of accumulating trial evidence showing its efficacy, in addition to its affordability. However, these international guidelines are based largely on studies conducted among Caucasian subjects in western countries. It is unknown whether the existing literatures based on Caucasian subjects can be generalized to Chinese patients and even small ethnic differences may bear large implications for health resources.[13]

There is also a paucity of health services research in the international literature on the treatment of hypertension in China, despite the high prevalence of hypertension in China and the fact that China has a population of 1.29 billion (around 20% of the world population).[14] The prescribing patterns of anti-hypertensive agents for Chinese hypertensive patients have not been documented in large studies, and thus the implications for effectiveness and cost-effectiveness are not known. Given that persistence with antihypertensive drugs is known to reduce morbidity and mortality,[15, 16] understanding of discontinuation and switching profiles are also important in the choice of antihypertensive drug prescription.

Although studies comparing drug discontinuation rates are often based on randomized controlled trials[17-20] such studies can be limited due to selection bias[21, 22] and therefore health services-based studies are also a valuable source of evidence.[23-25] In the present study we report a recent analysis of the trends of physician prescriptions of the major antihypertensive classes among Chinese patients in primary care clinics in the public healthcare sector in Hong Kong, China. We also compare the likelihood of discontinuation and switching among various antihypertensive drug classes, and report the epidemiological and clinical factors associated with anti-hypertensive prescription for each drug class.

Materials and Methods

Data

The Hospital Authority (HA) of Hong Kong, which provides free or low cost primary and secondary care as part of the public health care sector, adopted a comprehensive computerized patient recording system in 2000 which includes patients' clinical and demographic parameters, as well as investigation results and drug prescription details. The resultant database set up by the HA has research as one of its objectives,[26] and has been evaluated in a previous study reporting high completeness in terms of patients' demographic information (100%) and prescription details (99.98%).[27] During each clinic visit, patient demographics are entered by clinic staffs according to patients' identity documents, and drug prescriptions must be entered by the attending physicians into the computer system and are double checked by the dispensing HA pharmacists. These computerized records are the sole portal of information entry by physicians at each patient visit in all primary care clinics run by the HA.

Study Cohort

The study subjects were adult patients (aged $\geq$ 18 year-old) visiting HA primary care clinics at least once during the study period January, 2004 to June, 2007 inclusive. Because of the disruption cased by the Severe Acute Respiratory Syndrome (SARS) outbreak (April to October, 2003) we have not attempted to use data accumulated between 2000 and 2003. The

inclusion criteria included General Out-Patient Clinics (GOPCs), Family Medicine Specialist Clinics (FMSCs) or Staff Clinics (SCs) in the New Territory East (NTE) cluster of Hong Kong, which provides primary healthcare services to around 1.3 million residents, representing 17.2% of the Hong Kong population.[28] This cluster is further divided into 3 separate geographical regions, namely Shatin, Tai-Po and the North district, from the most urbanized to the most rural regions respectively.

Visits at which at least one antihypertensive drug was prescribed were retrieved (thereafter termed “antihypertensive drug visits”). We excluded patients with known concomitant cardiovascular risk factors (diabetes, lipid disorders, coronary heart disease, stroke) or suffering from conditions which potentially confound antihypertensive prescription choice (benign prostatic hypertrophy, gout, chronic obstructive pulmonary diseases, asthma, heart failure). A complete list of these conditions has been published elsewhere.[27]

To maintain confidentiality, no personal identifiers had been disclosed. The study was approved by the NTE cluster, Hospital Authority and the Survey and Behavioural Research Ethics Committee (SBREC), the Chinese University of Hong Kong.

Outcomes and Associated Factors

The main outcome measure was the drug class prescribed in each antihypertensive drug visit as a proportion of patient visits where antihypertensive agents were issued, annually from January, 2004 to June, 2007. These include α-blockers, β-blockers (BBs), thiazide diuretics, Calcium Channel Blockers (CCBs), Angiotensin Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs), combination therapy (defined as prescription with single pills consisting of at least 2 active antihypertensive ingredients), polytherapy (defined as prescription of more than one antihypertensive agent in a single visit) and miscellaneous (Potassium-sparing diuretics, vasodilators and loop diuretics). In the study period Amiloride hydrochloride combined with hydrochlorothiazide represents 99.96% of the formulation of combination therapy received by our patients.

Factors which may influence choice of antihypertensive agent prescription (and for which data was available) included patients' age, gender, payment status (Fee waivers vs. payers, US$5.77 per visit inclusive of drug and investigation expenses), Service types (GOPCs, FMSCs or SCs), district of residence, visit type (new or subsequent visits) and the calendar years of prescription. In our sample, fee waivers are almost exclusively residents receiving social security allowances from the government. To qualify for fee waiving patients must be comprehensively assessed by a medical social worker who determines their inability to pay

for medical consultation fee. Accordingly payment status is regarded as a proxy measure for socioeconomic status.

The secondary outcome measure was the 180 day cumulative incidence of discontinuation and switching and the likelihood of discontinuation and switching, in terms of odds ratios, for each drug class using CCBs as a reference. Discontinuation is defined as the absence of a refill prescription on all subsequent antihypertensive drug visits without the issuance of another class of antihypertensive drugs, while switching represents absence of a refill prescription in subsequent antihypertensive drug visits but replaced with another class of antihypertensive drugs, both within the time frame of 180 days. These definitions of discontinuation and switching were similar to previous studies[24, 25] except that a longer time frame of 180 days was used instead of 90 days, taking into account the common practice of prescribing antihypertensive drugs for a period of slightly longer than 90 days in Hong Kong primary practice. In comparing discontinuation incidences among different antihypertensive drug classes, we included only newly attending patients in our study period since previous use of antihypertensive drugs could potentially affect drug tolerability and hence discontinuation rate. They had no records of any antihypertensive prescription in the clinical database and therefore were drug naïve patients as far as we can tell.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 13.0 was used for all statistical analyses. We used antihypertensive drug visit as one unit of analysis for studying prescription patterns, and individual patient as one unit of analysis for cumulative incidences of drug discontinuation and switching. We evaluated the annual trend of antihypertensive drug prescription for each drug class, in terms of proportions of all antihypertensive drug visits, from 2004 to 2007. We also compared the patterns of prescribing monotherapy, polytherapy and combination therapy. Categorical variables were analyzed by χ^2 tests. To study the association between antihypertensive drug prescription and patient characteristics, five separate binary logistic multivariate regression analyses were performed to control for all of the above associated factors. The five distinct outcomes were prescription of each of the major drug classes for all antihypertensive drug visits, respectively.

We compared the crude incidences of drug discontinuation and switching at 180 days by χ^2 tests among various drug classes, followed by multivariable logistic regression to control for all the associated factors. The odds ratios of discontinuation and switching, respectively, for each drug class were studied using CCBs as the reference group. The forward stepwise model was used as a variable selection procedure, and all p values<0.05 were regarded as statistically significant.

Results

Subject Characteristics

We identified 67,113 patients who fulfilled our study inclusion criteria, representing 1,069,836 antihypertensive drug visits during the study period. Average age was 65 years and the majority were female (59 %). Among these subjects, 52,237 patients (78%) were new attendees within the study period. The detailed characteristics of this patient population have been reported previously.[27]

Annual trends of antihypertensive drug prescription

Among all antihypertensive drug visits, CCBs (49.4%) and BBs (46.2%) were the most commonly prescribed drugs, followed by ACEIs (18.9%), α-blockers (16.3%) thiazide diuretics (13.2%), and combination therapy (8.3%) (Figure 1). Among prescriptions of BBs, metoprolol (48.8%) and atenolol (46.7%) constituted the majority while for CCBs, the commonest drug was nifedipine (92.4%) followed by diltiazem (5.5%). The trends of prescribing were relatively stable for most classes of antihypertensive agents from 2004 to 2007. However, prescriptions for thiazide diuretics showed a declining trend from 14.3% in 2004 to 11.8% in year 2007 ($p<0.001$), whereas prescription of ACEIs increased significantly from 15.9% in year 2004 to 22.7% in year 2007 ($p<0.001$). The use of ARBs was exceptionally low at 0.17% and remained stable over time.

Annual trends of monotherapy, polytherapy & combination therapy

The majority of patients were on monotherapy (51.4%), followed by two class polytherapy (37.0%). The proportion of subjects prescribed at least 3 classes of antihypertensive drugs was therefore low (11.7%) (Table 1). The most common prescription for two-drug therapy consists of BB-CCB polytherapy (13.2%), followed by ACEI-CCB (3.5%). From 2004 to 2007, there was a consistent increase in the prescription of ACEI-CCB (3.0% to 4.1%, $p<0.001$) and ACEI-BB polytherapy (2.2% to 3.3%, $p<0.001$).

Factors associated with class of antihypertensive drug prescribed

In multivariate logistic regression analysis, age was independently associated with the type of anti-hypertensive prescribed (Table 2). Compared with younger patients (<50 year old) elderly patients ($\geq$ 70 years) were less likely to receive BBs (aOR 0.47). Male patients were less likely to be prescribed BBs (aOR 0.94) and thiazide diuretics (aOR 0.68). Payment status had little effect on the prescription choice. Patients attending FMSC and staff clinics were more likely to receive ACEIs (aOR 1.46 to 2.57). The district of residence also had significant effects on the prescription choices.

Regarding the fitness of the models, Nagelkerke r^2 ranged from 0.015 to 0.034 for these separate regression analyses, reflecting that these associated factors combined explained only 1.5% to 3.4% of the prescription outcome.

Factors associated with antihypertensive drug discontinuation and switching

The crude cumulative incidence of drug discontinuation at 180 days was the highest for BBs (20.8%, 95% C.I. 20.2%, 21.4%), followed by ACEIs (19.8%, 95% C.I. 18.7%, 20.9%), α-blockers (18.8%, 95% C.I. 17.6%, 20.0%) and thiazide diuretics (13.7%, 95% C.I. 12.8%, 14.6%). CCBs had the lowest discontinuation incidence of 12.0% (95% C.I. 11.5%, 12.5%; $p<0.001$). Thiazide diuretics had the highest cumulative incidence of switching at 180 days (12.2%, 95% C.I. 11.3%, 13.1%), followed by ACEIs (8.29%, 95% C.I. 7.50%, 9.08%) ($p<0.001$). The cumulative incidences of switching for α-blockers (5.66%, 95% C.I. 4.96%, 6.36%), BBs (5.72%, 95% C.I. 5.38%, 6.06%) and CCBs (6.24%, 95% C.I. 5.88%, 6.60%) were similar.

When controlled for other associated factors using CCBs as a reference (Table 3), older patients were less likely to have drugs discontinued within 180 days after the first-ever antihypertensive prescription (aOR 0.51 to 0.65, all $p<0.001$) but only the eldest group (aged $\geq$ 70 years) showed a significantly lower drug switching rate (aOR 0.79, $p<0.001$). Male patients were more likely to have drugs discontinued (aOR 1.07, $p=0.012$) but less likely to have drugs switched (aOR 0.77, $p<0.001$). When compared with CCBs, α-blockers (aOR 3.38) and BBs (aOR 2.38) were more likely to be discontinued (aOR 0.725) (both $p<0.001$). Thiazide diuretics were more likely to be switched (aOR 2.16, $p<0.001$) while BBs were less likely to be switched (aOR 0.70, $p<0.001$) compared with CCBs.

Discussion

Major findings

In this large study of over a million anti-hypertensive prescriptions issued to patients attending primary care clinics within the public healthcare system of Hong Kong from January, 2004 to June, 2007 we have found high rates of prescribing of BBs and CCBs, and low (and declining) prescribing levels of thiazide diuretics. Independent predictors of class of anti-hypertensive prescribed (including age, gender, and socioeconomic status) explained less than 3.5% of the variation observed. Drug discontinuation was high for BBs (21%) even after controlling for confounding variables. Drug switching was less common than discontinuation and was most likely with thiazide diuretics.

Interpretation of findings and relationship with published literature: prescribing patterns and trends

Similar patterns of prescribing to those found in the present study have been reported in previous smaller studies in similar settings in the public healthcare system in Hong Kong.[29-31] Practices within the private primary care system in Hong Kong are not well documented, but a recent survey of 225 private doctors' self-reported prescribing behaviour showed CCBs to be the most commonly prescribed (31%) followed by ACEIs (28.5%), diuretics (27.5%) and BBs (21.2%) with perceived drug efficacy being the top reason given for choice of drug.

However, the small size of this study (less than 5% of the private doctor population in Hong Kong) and the fact that it recorded self-reported prescribing and not actual prescribing raise questions about accuracy and representativeness.[32]

In international studies, patterns and trends in antihypertensive prescribing vary widely between countries.[33] However in many countries first-line treatment with a thiazide diuretic is common practice. In a nation-wide study by Ma et al[34] in the USA thiazide diuretics were the most commonly prescribed antihypertensive (approximately 50% of patients) with a rising trend, followed by BBs and CCBs (approximately 33% each).[23] The prescribing of ACEIs was found to be decreasing (35% in 2004). Similarly, in a large, nationally-representative study in the USA by Stafford et al 2006, high usage of CCBs and thiazide diuretics was reported.[35] A large study in patients aged over 65 years in Canada reported that diuretics were the most commonly prescribed agent in non-diabetics, followed by BBs and ACEIs with all three showing a rising trend between 1994 and 2002.[36] As shown in Table 4, the prescription patterns of various antihypertensive drug classes varied across regions.[37-41]

Low usage of diuretics has been reported in hypertensive patients of Chinese ethnicity living in the USA, when compared with other ethnic groups.[40] Suggested factors to explain inter-country variation included reimbursement policies, traditions, opinion leaders with conflicts of interests, domestic pharmaceutical production, and clinical practice guidelines.[33]

Interpretation of findings and relationship with published literature: factors associated with different prescribing patterns

Elder patients in the present study were less likely to receive BBs. This is in line with guidelines highlighting greater efficacy of thiazide diuretics and CCBs in the elderly with respect to their lower renin status.[42] Similar observations of lower usage of BBs in the elderly have also been reported in both local and international studies.[37, 38, 43] Male patients were less likely to receive thiazide diuretics and BBs than female patients. Currently there are no international authorities which recommend specific antihypertensive drugs according to gender. This finding is however consistent with some local studies,[31, 43] which suggested sexual dysfunction could be a major considering factor when prescribed to male patients[30]. Furthermore, physicians may perceive that thiazide diuretics could cause gouty attacks in male populations more frequently.[42]

The prescription of ARBs was almost twice more likely to be prescribed between 2005 and 2007 than 2004. This may be due to recent new drug marketing.[34, 44] The higher likelihood of prescribing ACEIs and ARBs in Family Medicine Specialist Clinics and staff clinics in the present study may be due to the availability of newer formularies in these clinics, referral of patients from secondary care settings (where prescription patterns may differ), and perhaps different patient expectations in these clinics. The findings that the district of residence, visit

types and calendar years were independent associated factors of antihypertensive prescription are of interest although the reasons for this cannot be determined from the present study design. However, the low weighting of all the significant predictive factors on prescription choice indicate that they are of little overall importance to the type of prescription issued. Other explanatory factors not measured in this study include physician's knowledge, views and experiences, peer influence, and the considerable marketing influence of the pharmaceutical industry within the public healthcare system.[45] A small local study reported perceived drug effectiveness and tolerability as the most crucial factors in determining first-line antihypertensive choice among trainee doctors in Hong Kong, and that more experienced trainees revealed higher awareness and adherence to evidence-based guidelines.[43]

Interpretation of findings and relationship with published literature: discontinuation and switching rates

The six-month discontinuation rate of antihypertensive drugs overall in our present study was found to be approximately 25% in each class with the exception of CCBs which was lower (18%). Study results from Burke *et al.* in 2006 using the United Kingdom General Practice Research Database (GPRD) reported a similar overall 6 month discontinuation rates of 20.3% (95% C.I. 20.0%, 20.5%)[24] among newly diagnosed hypertensive patients using similar methodology to the present study. They found that ARBs, followed by ACEIs, had the

lowest class-specific risks of discontinuation. This is different from our study result where we found CCBs to have the lowest discontinuation rate. Our study findings are also different from Hughes & McGuire's evaluation of the discontinuation percentages in 1998, from the MEDIPLUS database in UK.[46] They found the crude discontinuation rate within 6 months of drug initiation to be highest in diuretics (36%), followed by CCBs (31%), ACEIs (31%) and BBs (28%). The percentages of switching therapy in their study was highest in BBs (21%) and similar between diuretics (16%), ACEIs (16%) and CCBs (15%),[46] but in our present study the switching rate for thiazide diuretics was the highest and that for BBs the lowest. Similar studies in Italy by Mazzaglia et al. in 2005 reported ARBs had the lowest discontinuation rates, but that of ACEIs and CCBs were similar.[25] Thus the discontinuation and switching profiles of the present study are somewhat different from Caucasian studies, most notably with the low discontinuation rate of CCBs, which raises the possibility of ethnic differences.

Strengths and weaknesses of current study

As far as we are aware, our study is the largest evaluation ever conducted in the Asia Pacific region on the prescribing patterns and discontinuation profiles of antihypertensive drugs in Chinese patients treated in primary care. The major strength of our study is therefore the robust sample size generated over a 3.5 year period. The strengths and weaknesses of the

electronic data base from which this study was drawn has been discussed previously.[27] Data completeness is high for demographic and prescribing details but lower for coding of specific diseases.[27] In the present study we excluded patients with coded conditions that might influence the choice of anti-hypertensive agent prescribed (exclusion codes). We included patients coded with ICPC K86 – uncomplicated hypertension (45.7%) and those without any ICPC codes (un-coded group; 54.3%) on the assumption that most of the un-coded patients had uncomplicated hypertension. This assumption is based on our previous analysis showing that the patient characteristics with the un-coded group are very similar to the K86 group but different from exclusion group. Further sub-group analysis supports this assumption in the present study; prescribing patterns, trends, and discontinuation rates are very similar in the K86 group alone when compared with the results presented in this paper for the larger combined sample (results not shown).

Our sample is from only one territory of Hong Kong (NTEC) out of seven such clusters in the whole population and therefore is not representative of Chinese patients in other localities. However, similar patterns of prescribing to those found in the present study have been reported in previous smaller studies in other clusters of Hong Kong[29-31] and thus it is likely that our findings are generalisable in terms of primary care within the public healthcare system in Hong Kong. We cannot of course extrapolate our findings however to the private

healthcare sector. However, uncomplicated hypertension is the second commonest condition seen in primary care clinics in the public healthcare sector in Hong Kong,[47] and available data suggests that the vast majority of the population attends the public health services rather than the private sector for management of hypertension.[48] Thus our findings may well be of significance at population level in terms of hypertension management and healthcare costs.

We were unable to study the reasons of discontinuation using the existing database, although the discontinuation patterns may be a proxy measure for antihypertensive intolerability, and further work is required on this.

Implications for policy and practice

The present study suggests that CCBs are a particularly acceptable option for use in Chinese patients in the age group studied, given their high levels of prescribing and relatively low discontinuation profiles. BBs on the other hand were much more likely to be discontinued. Given recent evidence on the poorer efficacy of BBs compared with other classes, first line use of BBs should be discouraged in line with the recommendations by international authorities.[42] The rising use of ACEIs should be further explored as both its discontinuation and switching profiles were inferior to CCBs among Chinese and costs are higher than other prescription alternatives.[42]

The reasons driving the prescription patterns reported in the present study need further exploration. Recent major international guidelines - the British National Institute for Clinical Excellence (NICE),[42] the Canadian Hypertension Education Program,[49] and the World Health Organization/International Society of Hypertension (WHO/ISH)[50] unanimously recommend thiazide diuretics as the preferred drug option, whether as first-line or in polytherapy. There is no evidence in the present study that any of these international guidelines, nor the large international trials that informed them, have had any impact on the prescription patterns reported in the present study between 2004 and 2007. In the absence of any such effect from international guidelines, it is possible that locally produced Hong Kong guidelines may have more of an impact. Influencing prescribing behaviour within the primary care clinics of the Hospital Authority (the public healthcare sector) should, in theory, be easier than in the private primary care system which is currently unregulated, has no wide-spread quality assurance systems in place, and operates on a fee-for-service basis with doctors' income being directly to profit margins relating to consultation fees and drug charges.

The use of thiazide as a first-line agent has substantial support from many studies, but our findings of its higher switching rates compared with other classes of antihypertensive drugs may reflect the greater incidences of metabolic side effects such as hyponatraemia[29]. Whether such effects are more prominent in patients of Chinese race is not known. Policies to increase

the first-line use of thiazides in Hong Kong would potentially lead to considerable savings in drug costs, although fuller economic modeling is required before conclusions on cost-effectiveness can be reached.[42]

To conclude, when compared with international trends, the prescription of CCBs and BBs are high and that of thiazide diuretics particularly low in this Chinese population attending primary care in the public healthcare sector of Hong Kong. CCBs may be a particularly favorable antihypertensive treatment in this population given the high discontinuation rates of BBs, and recent international guidelines advising against the use of BB in first-line therapy. The low use of thiazide diuretics warrants further investigation including both clinical and cost effectiveness in this population. Community-wide data on prescription patterns represents a crucial information source for health authorities to plan and implement necessary guidelines and protocols in the use of antihypertensive agents.

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Table 1 Patterns of antihypertensive monotherapy, polytherapy and combination therapy in primary care clinics in Hong Kong

	2004 (N=238,034)	2005 (N=323,849)	2006 (N=333,824)	2007* (N=174,129)	2004-2007 (N=1,069,836)	P value
1 class	130,106 (54.66%)	155,402 (47.99%)	174,527 (52.28%)	89,465 (51.38%)	549,500 (51.36%)	<0.001
	(54.46%, 54.86%)	(47.81%, 48.16%)	(52.11%, 52.45%)	(51.14%,51.61%)	(51.27%, 51.46%)	
2 class	86,495 (36.34%)	123,231 (38.1%)	121,808 (36.49%)	63,920 (36.71%)	395,454 (36.96%)	
	(36.14%, 36.53%)	(37.88%, 38.22%)	(36.33%, 36.65%)	(36.48%,36.94%)	(36.87%, 37.06%)	
≥3 classes	21,433 (9.00%)	45,216 (13.96%)	37,489 (11.23%)	20,744 (11.91%)	124,882 (11.67%)	
	(8.89%, 9.12%)	(13.84%, 14.08%)	(11.12%, 11.34%)	(11.76%,12.07%)	(11.61%, 11.73%)	
Diuretics-BB	7,316 (3.07%)	10,277 (3.17%)	9,590 (2.87%)	4,425 (2.54%)	31,608 (2.95%)	<0.001
	(3.00%, 3.14%)	(3.11%, 3.23%)	(2.82%, 2.93%)	(2.47%, 2.62%)	(2.92%, 2.99%)	
Diuretics-ACEI	1,936 (0.81%)	2,775 (0.86%)	3,083 (0.92%)	1,878 (1.08%)	9,672 (0.90%)	<0.001
	(0.78%,0.85%)	(0.83%, 0.89%)	(0.89%, 0.96%)	(1.03%, 1.13%)	(0.89%, 0.92%)	
Diuretics-CCB	3,395 (1.43%)	4,338 (1.34%)	4,198 (1.26%)	2,067 (1.19%)	13,998 (1.31%)	<0.001
	(1.38%, 1.47%)	(1.30%, 1.38%)	(1.22%, 1.30%)	(1.14%, 1.24%)	(1.29%, 1.33%)	
BB-CCB	31,333 (13.16%)	43,310 (13.37%)	43,869 (13.14%)	22,747 (13.06%)	141,259 (13.20%)	0.006
	(13.03%, 13.30%)	(13.26%, 13.49%)	(13.03%,13.26%)	(12.91%,13.22%)	(13.14%, 13.27%)	
ACEI-CCB	7,014 (2.95%)	10,585 (3.27%)	12,119 (3.63%)	7,204 (4.14%)	36,922 (3.45%)	<0.001
	(2.88%, 3.02%)	(3.21%, 3.33%)	(3.57%, 3.69%)	(4.04%, 4.23%)	(3.42%, 3.49%)	
ACEI-BB	5,298 (2.23%)	8,161 (2.52%)	9,803 (2.94%)	5,824 (3.34%)	29,086 (2.72%)	<0.001
	(2.17%, 2.29%)	(2.47%, 2.57%)	(2.88%, 2.99%)	(3.26%, 3.43%)	(2.69%, 2.75%)	
Other combinations*	7,388 (3.10%)	10,102 (3.12%)	10,341 (3.10%)	5,484 (3.15%)	33,315 (3.11%)	0.770
	(3.03%, 3.17%)	(3.06%, 3.18%)	(3.04%, 3.16%)	(3.07%, 3.23%)	(3.08%, 3.15%)	

(CCBs: Calcium Channel Blockers; ACEIs: Angiotensin Converting Enzyme Inhibitors. N is the total numbers of prescription episodes for the corresponding year(s). Percentages by row were in parentheses, and the p values represent chi square tests of homogeneity testing prescription proportions of the respective antihypertensive drug classes among four calendar years The figures are number (% within each year) and corresponding 95% confidence intervals *Other combinations refer to prescription of ≥ 2 active antihypertensive ingredients in one-pill)

Table 2 Factors associated with antihypertensive drug class prescription in primary care clinics in Hong Kong

	α-blockers	β-blockers	Thiazide	CCB	ACEI
	aOR (95% CI)	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
Patient age					
<50	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
50-59	1.56 (1.52, 1.60)	0.83 (0.82, 0.84)	1.13 (1.11, 1.15)	1.25 (1.23, 1.27)	1.03 (1.01, 1.05)*
60-69	2.66 (2.59, 2.72)	0.65 (0.64, 0.66)	1.18 (1.15, 1.20)	1.53 (1.51, 1.55)	1.04 (1.03, 1.06)
≥70	3.71 (3.63, 3.80)	0.47 (0.46, 0.48)	1.12 (1.10, 1.14)	2.00 (1.98, 2.03)	1.07 (1.05, 1.09)
Sex					
Female	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Male	1.41 (1.39, 1.42)	0.94 (0.93, 0.95)	0.68 (0.67, 0.69)	1.36 (1.35, 1.37)	1.45 (1.43, 1.46)
Payment status					
Fee waivers	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Payers	0.96 (0.95, 0.97)	1.08 (1.07, 1.09)	NS	1.09 (1.08, 1.10)	1.05 (1.04, 1.07)
Service Type					
GOPC	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
FMSC	0.40 (0.38, 0.41)	0.90 (0.89, 0.92)	0.78 (0.75, 0.80)	0.80 (0.78, 0.81)	2.57 (2.52, 2.62)
Staff clinic	0.55 (0.46, 0.65)	0.92 (0.85, 0.99)**	0.88 (0.79, 0.99)**	0.39 (0.36, 0.43)	1.46 (1.33, 1.61)
Residence district					
Shatin	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Taipo	1.75 (1.73, 1.77)	0.81 (0.80,0.81)	0.69 (0.68, 0.70)	0.96 (0.95, 0.97)	1.06 (1.04, 1.07)
Northern	1.39 (1.37, 1.41)	1.02 (1.01, 1.03)*	0.74 (0.73, 0.76)	0.91 (0.90, 0.92)	1.23 (1.22, 1.25)
Others	1.15 (1.12, 1.18)	0.97 (0.95, 0.98)	0.90 (0.88, 0.92)	0.99 (0.98, 1.01)^	1.26 (1.23, 1.28)
Visit Type					
First visit	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Subsequent visit	1.17 (1.15, 1.18)	1.09 (1.08, 1.10)	0.92 (0.91, 0.93)	1.06 (1.05, 1.07)	1.34 (1.33, 1.36)
Years on prescription					
2004	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
2005	0.90 (0.88, 0.91)	1.04 (1.03, 1.05)	0.94 (0.93, 0.96)	NS	1.16 (1.14, 1.17)
2006	0.85 (0.84, 0.86)	1.06 (1.05, 1.07)	0.87 (0.85, 0.88)	NS	1.33 (1.31, 1.35)
2007	0.80 (0.79, 0.82)	1.03 (1.02, 1.05)	0.82 (0.81, 0.84)	NS	1.50 (1.48, 1.53)

(CCBs: Calcium Channel Blockers; ACEIs: Angiotensin Converting Enzyme Inhibitors; GOPC: General Out-Patient Clinic; FMSC: Family Medicine Specialist Clinic; NS: Not Significant as parameter was excluded from initial selection procedure; aOR: adjusted Odds Ratio; The odds ratios for each variable were adjusted for all other variables.

All p values were <0.001 with the following exceptions:*p<0.005; **p<0.05; ***p=0.437)

Table 3 Factors associated with drug discontinuation and switching within 180 days

	Drug discontinuation			Drug switching		
Predictors	**Bivariate analysis Crude Odds ratios**	**Adjusted Odds Ratios[a]**	p value	**Bivariate analysis Crude Odds ratios**	**Adjusted Odds Ratios[a]**	p value
Age (years)						
<50	1.88 (1.78, 1.99)	1.00 (reference)		1.04 (0.95, 1.15)	1.00 (reference)	
50-59	0.95 (0.90, 1.01)	0.64 (0.60, 0.69)	<0.001	1.06 (0.98, 1.16)	0.96 (0.85, 1.07)	0.421
60-69	0.66 (0.62, 0.71)	0.51 (0.47, 0.56)	<0.001	1.09 (1.00, 1.20)	0.97 (0.86, 1.09)	0.590
≥ 70	0.83 (0.79, 0.88)	0.65 (0.60, 0.70)	<0.001	0.85 (0.78, 0.93)	0.80 (0.71, 0.89)	<0.001
Sex						
Female	1.00 (reference)			1.00 (reference)		
Male	1.08 (1.03, 1.14)	1.07 (1.02, 1.13)	0.012	0.78 (0.72, 0.84)	0.77 (0.71, 0.84)	<0.001
Drug class*						
CCBs	0.56 (0.52, 0.60)	1.00 (reference)		0.84 (0.77, 0.92)	1.000 (reference)	
ACEIs	1.07 (0.97, 1.19)	1.38 (1.23, 1.56)	<0.001	1.17 (1.00, 1.36)	1.22 (1.03, 1.45)	0.020
Thiazide	0.76 (0.69, 0.84)	1.29 (1.15, 1.45)	<0.001	2.14 (1.91, 2.40)	2.16 (1.89, 2.47)	<0.001
α-blockers	1.98 (1.79, 2.20)	3.38 (3.00, 3.82)	<0.001	0.71 (0.57, 0.88)	0.90 (0.72, 1.13)	0.358
β-blockers	2.02 (1.92, 2.13)	2.38 (2.21, 2.57)	<0.001	0.60 (0.54, 0.66)	0.70 (0.61, 0.79)	<0.001

(*CCBs: Calcium Channel Blockers; ACEIs: Angiotensin Converting Enzyme Inhibitors. Drug discontinuation is defined as the absence of a refill prescription 180 days after the first-ever antihypertensive drug prescribed without appearance of another class of antihypertensive agents; Drug switching is defined as the absence of a refill prescription 180 days after the first-ever antihypertensive drug prescribed but replaced with another class of antihypertensive agent. The Adjusted Odds ratios were adjusted for age, gender, payment status, service type, district of residence, visit type and calendar years on prescription)

Table 4 Comparing the prescription patterns of antihypertensive drug classes in various countries

	thiazide	β-blockers	CCB	ACEI	ARB
USA[a]	46%	33%	29%	35%	23%
UK[b]	32%*	22%	13%	13%	
Italy[c]	14%*	<3%	43%	50%	NA
Ireland[d]	15%	23%	9%	18%	3%**
Japan[e]	20%	20%	50%	15%	11%
Hong Kong[f]	13%	46%	49%	19%	0.2%

(CCB: Calcium channel blockers; ACEI: Angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers, NA: Not Available. a: Ma et al, 2006[34], b: Walley et al, 2003[37]; c: Onder et al, 2001[38]; d: Kabir et al, 2007[39]; e: Mori et al, 2006[41]; f: the present study. *including all diuretics; **Losartan and Valsartan only)

Pending verification

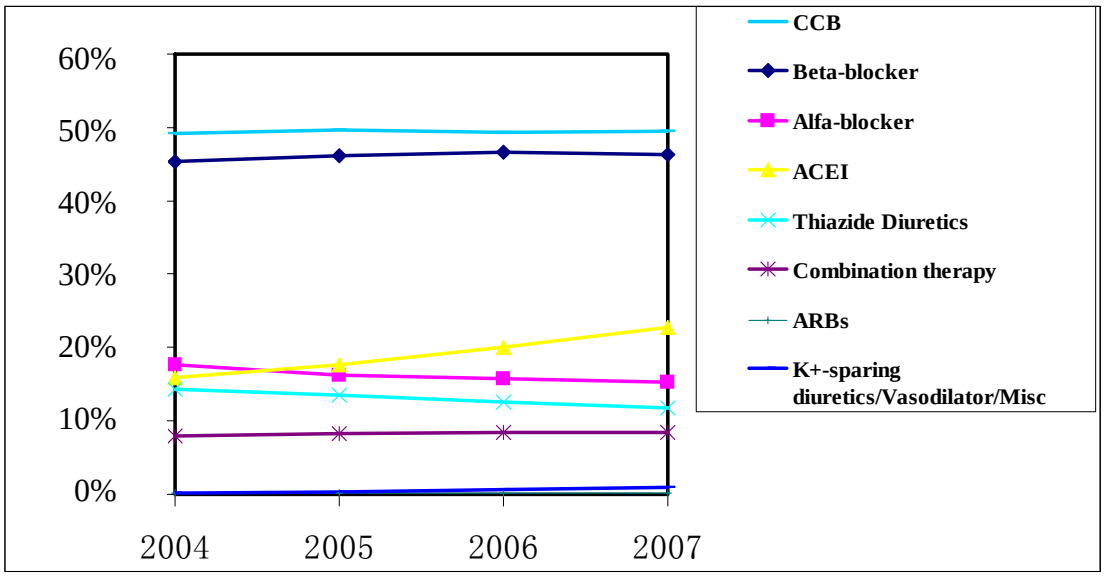
Table on "What is known about topic"

- Internationally, patterns and trends in antihypertensive prescribing have been well described but few studies addressed prescription patterns among Chinese patients
- Discontinuation and switching profiles have also been extensively studied in Caucasian populations but few among ethnic Chinese

What this study adds

- From a total of 1,069,836 antihypertensive drug visits (67,028 patients), the most commonly prescribed drugs were calcium channel blockers (CCBs) [49%], beta-blockers (46%) and Angiotensin-Converting Enzyme Inhibitors (19%), with thiazide diuretic being low (13%) and its annual prescription trend on the decline.
- Drug discontinuation was highest for BBs (21%) and lowest for CCBs (12%), while switching was less common than discontinuation and was most likely with thiazide diuretics.
- CCBs may be a particularly favorable antihypertensive treatment in Chinese and the high discontinuation rates of beta-blockers supported international guidelines advising against its use as a first-line therapy generalizable also to Chinese patients.

Figure 1 Annual trend of antihypertensive drug prescription in primary care clinics in Hong Kong



Results were shown as a percentage of patient visits where antihypertensive agents were issued