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Predictors of the incidence of all-cause mortality and deaths due to diabetes and renal diseases among patients newly prescribed antihypertensive agents: A cohort study☆,☆☆

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ABSTRACT

Background: Randomized trials have shown that the major antihypertensive drug classes are similarly effective to reduce mortality, but whether these drug class difference exists in clinical practice has been scarcely explored. This study evaluated the association between antihypertensive drug class, all-cause mortality and deaths due to diabetes or renal disease in real-life clinical settings.

Methods: A clinical database in Hong Kong included all patients who were prescribed their first-ever antihypertensive agents between 2001 and 2005 from the public healthcare sector. All patients were followed up for five years, and grouped according to the initial antihypertensive prescription. The associations between antihypertensive drug class, all-cause mortality or combined diabetes and renal mortality, respectively, were evaluated by Cox proportional hazard models.

Results: From 218,047 eligible patients, 33,288 (15.3%) died within five years after their first-ever antihypertensive prescription and among which 1055 patients (0.48%) died of diabetes or renal disease. After adjusted for age, gender, socioeconomic status, service settings, district of residence, medication adherence, and the number of comorbidities, each drug class was similarly likely to be associated with mortality due to diabetes or renal disease [Adjusted Hazard Ratios (AHR) ranged from 0.92 to 1.73, $p = 0.287–0.939$] and all-cause mortality (AHR ranged from 0.83 to 1.02) except for beta-blockers (AHR = 0.815, 95% C.I. 0.68–0.87, $p = 0.024$) when ACEI was used as a reference group in propensity score-adjusted analysis.

Conclusions: These findings provide real-life evidence reinforcing that any major antihypertensive drug class is suitable as a first-line agent for management of hypertension as recommended by international guidelines.

1. Introduction

Various international guidelines have recommended the choice of first-line antihypertensive agents for the management of arterial hypertension based on high quality randomized controlled trials (RCTs). The Joint National Committee (JNC) seventh report [1] and the 2009 reappraisal of the hypertension European guidelines [2] proposed thiazide diuretics, β-blockers, calcium channel blockers (CCBs), Angiotensin converting enzyme inhibitors (AECIs) and Angiotensin receptor blockers (ARBs) as preferred first-line options. This is based on the observation in landmark RCTs that all major classes of antihypertensive drugs, except α-blockers, have been shown to reduce morbidity and mortality — and there exists few differences among them [3,4]. However, the guideline issued by the National Institute for Health and Clinical Excellence (NICE), with the assistance of the British Hypertension Society, dropped β-blockers as the first-line agent owing to its suboptimal outcomes in recent clinical trials [5].

Kaplan and Victor [6] stated that the choice of antihypertensive therapy, particularly for the first-line agent, should be made with care as more patients with less severe hypertension are being treated with medications. The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) has long recognized the limitations of event-based randomized therapeutic trials [7]. These include the need to select elderly or higher risk patients to maximize the number of events collected and achieve adequate study power. As a result, younger, uncomplicated patients with lower cardiovascular risks are under-represented, and little

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information is available on treatment benefits in a large number of hypertensive populations. Another important caveat is that therapeutic programs in RCTs usually diverge from usual clinical practice since drugs randomly allocated at trial commencement are continued irrespective of blood pressure lowering effects; but in clinical practice physicians normally do not continue the prescriptions which are ineffective. In trials the benefits conferred to patients are therefore diluted by the lack of benefits in non-responsive patients, and they are usually of short duration — which will imply that their generalizability to the general population is limited. These randomized trials should be interpreted in parallel with observational studies to achieve a balanced decision regarding the choice of the most preferred first-line antihypertensive agent.

The JNC eighth report is currently being prepared and the committee will decide whether β-blocker should remain as the first-line agent or relegated as a fourth-line agent. This task requires incorporation of observational studies in addition to the newer randomized outcome trials. Nevertheless, there is a scarcity of large scale observational studies which could inform guideline recommendations. We have previously studied the compliance profiles and 5 year incidence of cardiovascular mortality in a large Chinese population newly prescribed antihypertensive medications [8,9], in an attempt to provide real-life clinical data. It is presently unknown whether any major antihypertensive drug class is superior in terms of preventing deaths due to all causes, diabetes or renal diseases in *non-interventional* settings. The objective of this study is to test the a priori hypothesis that the incidences of all-cause mortality or deaths due to diabetes or kidney diseases, respectively, are similar among the major antihypertensive drug classes as first-line agents. The secondary objective of this study is to identify patients at higher risks for all-cause, diabetes- and renal disease-related mortality five years after antihypertensive prescriptions.

2. Methods

2.1. Data source

The computerized databases, known as electronic Clinical Management System in Hong Kong, have been previously described in details [8–15]. Briefly, these databases capture patients' demographic parameters, prescription details, and clinical diagnoses in the forms of the International Classification of Diseases (ICD-9 and ICD-10) or the International Classification of Primary Care (ICPC-2). It serves as the sole portal of data entry which allows the linkage of physician-entered information at each patient visit in all public clinical settings among different districts. All drug prescriptions are inputted by the attending physicians and are cross-checked by dispensers or pharmacists using standardized procedures, and any amendments to the prescriptions after the initial consultations are also recorded in the system. This database was previously validated and it demonstrated a high level of completeness on the socio-demographic information (100%) and prescription profiles (99.8%) [10]. The sampling frame for the present study included the entire Hong Kong population, which is more than 7,000,000 as of 2012. Hong Kong is divided into three distinct regions, namely Hong Kong Island (most urbanized); Kowloon; and the New Territories (most rural). The ethics clearance of the study was obtained from the Clinical Ethics Research Committee of the Hospital Authority, and the Survey and Behavioral Research Ethics Committee of The Chinese University of Hong Kong. Informed consent was not necessary as all subjects were anonymized with unique identity numbers. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Patients

From the database, all patients who had a consultation at any public practice and who were prescribed their first-ever antihypertensive agents between the calendar years 2001 to 2003 and in 2005 (the index date) were included. The details from the calendar year 2004 were excluded due to the substantial disruption on the clinical services as a result of the outbreak of the Severe Acute Respiratory Syndrome. Patients who received any antihypertensive medications before the index date were excluded. We captured patients who died from diabetes and renal diseases, and treated the deaths due to conditions other than these two diseases within the observation period as being censored. Each patient was allocated based on the initial prescription of antihypertensive agents, namely, α-blockers, β-blockers, thiazide diuretics, CCBs and ACEIs. Patients who were prescribed ARBs and combination therapy were excluded in our data analysis because these prescriptions were relatively rare. Concomitant comorbidities include cardiovascular risk factors and medical conditions which could potentially confound the choice of antihypertensive drug class, as indicated by the respective ICPC-2 or ICD-9/ICD-10 codes. Patients were followed up until the occurrence of mortality within the study period or at the end of five years.

2.3. Outcome variables and covariates

The outcome variables were (1) all-cause mortality and (2) deaths due to diabetes mellitus (ICD-E10–E14.5) and renal diseases (ICD-9 N17–N19), respectively. The vast majority of all deaths in Hong Kong occurred in hospitals, which allows accurate case ascertainment [16]. A number of previous studies have utilized deaths in hospital as a valid proxy of patient mortality, especially for Chinese populations in which death usually occurs in hospitals [16–18]. The cause of death due to diabetes (e.g. diabetic ketoacidosis or hyperosmolar non-ketotic diabetic coma) or renal disease (e.g. uremia) was defined according to the primary cause of mortality for each patient, as determined by the physicians-in-charge when death was registered in the death certificates. The predictor variable in this study was the major class of antihypertensive drugs on its initial prescription. The interval-based proportion of days covered (PDC) was included as a covariate to take into consideration the influence of medication adherence as a potential confounder. The PDC refers to the number of days when medication is supplied in a specified period divided by the total number of days within the period. The interval-based measure of PDC is an internationally accepted metric for assessing drug adherence in large database analysis [19–21]. In this study, a five-year interval was used for the estimation of PDC. For patients who died during the five-year period, the time period between the index date and mortality was used to estimate the PDC. Similar to the approach adopted by Mazzaglia and colleagues [22], drug adherence in the present study was divided into two levels, namely: high and intermediate (PDC $\geq$ 40%) or low (PDC $<$ 40%) [23,24]. In addition, we also evaluated the rates of medication discontinuation and switching among these patients. Drug switching is defined as the absence of a refill prescription in all subsequent clinic visits combined with the prescription of another antihypertensive drug of a different class since the date of the first prescription, whereas drug discontinuation refers to repeat prescription of the same drug class lasting for $<$80% of the days in the specified period after the first-ever antihypertensive prescription date. According to international literature, we used 1 year, 2 years, 3 years, 4 years and 5 years, respectively, as the time points for measuring these two outcomes [25–27].

The independent variables that were controlled for included patients' age, gender, payment status (recipients vs non-recipients of comprehensive social security assistance; each consultation in a primary care setting costs approximately US$5.77, including both investigation and prescription fees), clinic type (in- and day-patient clinics, specialist outpatient clinics [SOPCs], Accident and Emergency Departments [AEDs], general outpatient clinic [GOPC], and other clinic types), district of residence (Hong Kong Island vs Kowloon vs the New Territories; from the most urbanized to the most rural, respectively), the number of concomitant comorbidities, and the readings of systolic and diastolic blood pressure averaged over all clinic visits. The same list of comorbidities by their ICD-9 and ICPC-2 coding was used in the present study as published elsewhere [9], which were categorized under "Diabetes or impaired glucose tolerance" (23.0%), "Cardiovascular diseases" (24.3%), "Respiratory diseases" (14.6%) and "Renal diseases" (11.0%).

2.4. Statistical analysis

For descriptive analysis, Student's t tests and chi-square tests of heterogeneity were used to compare continuous and categorical variables, respectively. All the variables listed above were entered into one Cox-proportional hazard model to explore the association between initial antihypertensive drug class and mortality. All cause mortality and combined deaths due to diabetes and renal disease, respectively, were the outcome variables. To account for the confounding effects of medication change, all study participants were censored if they switched study medications, discontinued treatment (in which case they were followed for 100 days from their last prescription to identify events that may have precipitated discontinuation), commenced treatment with a different antihypertensive agent, or reached the end of the study. This is according to a methodology adopted by Dhalla et al. [25], and we followed patients for a maximum of 5 years. Also, we have conducted a sensitivity analysis where patients whose antihypertensive drug class has been switched or added on by another drug class were excluded, and a similar regression model was constructed to detect if there were any changes in the associated factors identified.

In addition, a propensity score model was developed to estimate weightings for adherence selection, namely high and intermediate vs low adherence, given the possible existence of treatment indication bias due to the observational nature of the study. Therefore, the analysis was performed with adjusted estimates weighted by the inverse estimated propensity scores in two Cox proportion hazard models according to standard statistical methodology [26,27]. To further minimize the influence of indication bias due to different baseline characteristics of patients, a high-dimensional propensity score matching to compare patients with similar observed characteristics was adopted using standardized methodology as utilized in other literature [25,28,29]. Each recipient of one antihypertensive drug class was matched with a recipient on another antihypertensive class on the basis of age at index date (within 1 year), sex, calendar year of treatment initiation, and propensity score (within 0.2 SD).

We evaluated for multicollinearity and interactions among variables to ensure the robustness of the regression model. The Statistical Package for Social Sciences version 16.0 (SPSS, Inc.) was used for all data analyses. All p values $<$ 0.05 were regarded as statistically significant.

3. Results

3.1. Participant characteristics and medication changes

A total of 218,047 eligible patients were included (Table 1). There were more female patients (54.9%) and 52.6% were aged 60 years or older. Only 15.2% received public assistance and the majority was followed up at in- or day-patient clinics and specialized out-patient clinics (59.9%). Most patients lived in the more rural regions (48.6% and 33.9% in the New Territories and Kowloon, respectively). The most commonly prescribed antihypertensive agent was beta-blockers (45.2%), CCBs (30.1%), followed by ACEIs (10.5%) and thiazide diuretics (8.0%). 6.2% of all patients were prescribed alpha-blocker as a first-line agent. Most patients (67.1%) had intermediate to good adherence, and the majority had one comorbidity or less (92.6%). Table 2 shows the cumulative incidence of medication discontinuation and switching. In both short- and long-term, users of alpha-blockers and beta-blockers had the highest discontinuation rates, whereas thiazide diuretics and ACEIs had the highest switching rates.

3.2. Profiles of all-cause mortality and deaths due to diabetes and renal diseases

A total of 33,288 patients (15.3%) died within five years after their first-ever antihypertensive prescription (Table 3); and among which 1055 died due to diabetes or renal diseases. From univariate analysis, elderly patients ($p < 0.001$), male subjects ($p = <0.001$ to 0.033) and those receiving social security allowance ($p < 0.001$) were more likely to experience all-cause mortality or deaths due to diabetes or renal diseases. In addition, patients attending in-patient or day-patient clinics and specialized out-patient clinics were more likely to suffer from mortality ($p < 0.001$). The district of residence and the adherence levels to antihypertensive agents were also significant factors. The proportions of patients who died increased with the number of comorbidities in a steep dose–response manner. The proportions of all-cause mortality were the highest among users of CCBs (22.9%), ACEIs (22.4%), and alpha-blockers (19.2%), followed by thiazide diuretics (14.3%) and beta-blockers (8.2%). Regarding deaths due to diabetes or renal diseases (Table 3), patients prescribed CCBs (0.9%) and ACEIs (0.7%) had the highest rates of mortality, followed by thiazide diuretics (0.6%), alpha-blockers (0.4%) and beta-blockers (0.2%) (both $p < 0.001$).

Table 1
Baseline characteristics of patients (N = 218,047).

	N*	%	p
Gender			
Male	98,270	45.1	<0.001
Female	119,775	54.9	
Age			
<50	61,362	28.1	<0.001
50–59	42,027	19.3	
60–69	41,627	19.1	
≥70	73,011	33.5	
Public assistance			
Yes	32,827	15.2	<0.001
No	183,151	84.8	
Service type on first visit			
In-/day-patient clinic	65,860	30.2	<0.001
Special out-patient clinic	64,680	29.7	
Accident and Emergency Department	16,898	7.8	
General outpatient clinics	64,715	29.7	
Others	5885	2.7	
District of residence			
Hong Kong	38,327	17.6	<0.001
Kowloon	73,817	33.9	
New Territories	105,902	48.6	
First prescription			
ACEIs	22,985	10.5	<0.001
Alpha blocker	13,455	6.2	
Beta blocker	98,626	45.2	
CCB	65,535	30.1	
Thiazide	17,445	8.0	
Proportion of days covered (PDC)*			
<40%	71,734	32.9	<0.001
≥40%	146,312	67.1	
Co-morbidity			
0	131,088	60.1	<0.001
1	70,915	32.5	
2	14,585	6.7	
≥3	1458	0.7	

ACEI: Angiotensin converting enzyme inhibitors; CCB: Calcium channel blocker.
* PDC is defined as the number of days when medication is supplied in a specified period divided by the total number of days within the observation period.

3.3. Factors associated with all-cause mortality or deaths due to diabetes or renal diseases

From Cox Proportional Hazard analysis with all-cause mortality as the outcome measure (Table 4), it was found that *advanced age* (50–59 years; adjusted hazard ratio [AHR] = 1.924, 95% C.I. 1.639–2.259; 60–69 years; AHR = 3.401, 95% C.I. 2.803–4.126; ≥70 years; AHR = 8.844, 95% C.I. 7.348–10.645, all $p < 0.001$; referent < 50 years), *male gender* (AHR for female = 0.657, 95% C.I. 0.632–0.682, $p < 0.001$), *recipients of public assistance* (AHR = 1.375, 95% C.I. 1.320–1.433, $p < 0.001$), *attendance in in-patient or day-patient service* (AHR = 2.316, 95% C.I. 2.141–2.506, $p < 0.001$) and *the presence of at least one comorbidity* (AHR ranged from 1.266 to 1.314, $p < 0.001$) were significantly associated with all-cause deaths. Patients attending *general out-patient clinics* (AHR = 0.387, 95% C.I. 0.346–0.434, $p < 0.001$) were less likely to come across mortality. *The class of antihypertensive agents* prescribed was not significantly associated with the incidence of mortality (AHR ranged from 0.825 to 1.021, $p = 0.257$ to 0.765) except beta-blockers (AHR = 0.815, 95% C.I. 0.683–0.874, $p = 0.024$). However, when the group of beta-blockers was confined to the centrally-acting agents, its relative hazard became insignificant (AHR = 1.141, 95% C.I. 0.940–1.384, $p = 0.182$). For deaths due to diabetes or renal diseases, the associated factors were similar except gender, receipt of public assistance and medication adherence which did not report statistical significance. When compared with ACEIs, the various drug classes were similarly associated with combined diabetes and renal mortality (AHR ranged from 1.226 to 2.233, $p = 0.143$ to 0.842).

When high-dimensional propensity score matching is used to compare patients with similar characteristics, the factors associated with both outcomes and the drug class comparison remain unchanged. In addition, sensitivity analysis by exclusion of patients whose medication was switched or added on by another drug class detected no difference in the associated factors identified. There exists no interaction or multicollinearity among the predictor variables, implying the regression analysis is robust.

4. Discussion

4.1. Major findings

The present findings showed that in general, the major classes of antihypertensive agents were similarly likely to be associated with all-cause mortality and deaths due to diabetes and renal diseases when used as first-line agents among antihypertensive-naive patients. Patients receiving beta-blockers seem to suffer from lower incidence of all-cause mortality but this is not the case with centrally-acting agents. In addition, some factors associated with mortality was identified, including old age, presence of comorbidities and the healthcare setting being in secondary care. These results, based on observations from non-interventional settings, bear significant implications for clinicians on the choice of first-line antihypertensive prescriptions.

Table 2
The cumulative incidence of antihypertensive drug discontinuation and switching at different time points.

	1 years	2 years	3 years	4 years	5 years
Discontinuation					
ACEI (22,985)	7375 (32.1%)	8639 (37.6%)	9366 (40.8%)	9739 (42.4%)	10,023(43.6%)
α-Blockers (13,455)	8403 (62.5%)	9401 (69.9%)	9868 (73.4%)	10,132 (75.3%)	10,282 (76.4%)
β-Blockers (98,626)	58,490 (59.3%)	64,032 (65.0%)	66,619 (67.6%)	68,059 (69.0%)	69,021 (70.0%)
CCB (65,535)	32,364 (49.4%)	35,061 (53.6%)	36,712 (56.1%)	37,493 (57.3%)	38,048 (58.1%)
Thiazide (17,445)	9081 (52.1%)	10,000 (57.3%)	10,516 (60.3%)	10,829 (62.1%)	11,025 (63.2%)
Switching					
ACEI (22,985)	1735 (7.6%)	2952 (12.9%)	4060 (17.7%)	5239 (22.8%)	6732 (29.3%)
α-Blockers (13,455)	459 (3.4%)	869 (6.5%)	1341 (10.0%)	1902 (14.1%)	2618 (19.5%)
β-Blockers (98,626)	4091 (4.1%)	7231 (7.3%)	10,522 (10.7%)	14,421 (14.6%)	19,259 (19.5%)
CCB (65,535)	4319 (6.6%)	7354 (11.2%)	10,466 (16.0%)	14,066 (21.5%)	18,018 (27.5%)
Thiazide (17,445)	1488 (8.5%)	2731 (15.7%)	4024 (23.1%)	5493 (31.5%)	7070 (40.5%)

ACEI: Angiotensin Converting Enzyme Inhibitors; CCB: Calcium channel blockers.
Drug switching is defined as the absence of a refill prescription in all subsequent clinic visits combined with the prescription of another antihypertensive drug of a different class since the date of the first prescription. Drug discontinuation refers to repeat prescription of the same drug class lasting for <80% of the days in the specified period after the first-ever antihypertensive prescription date.

4.2. Relationship to existing literature—all-cause mortality, renal disease and diabetes mellitus

A recent meta-analysis of RCTs comparing the incidence of all-cause mortality among the major antihypertensive drug classes [3] showed that there was no difference between patients initially prescribed beta-blockers, diuretics and renin-angiotensin system inhibitors, and the all-cause mortality rate was only marginally higher for beta-blockers compared to CCB (relative risk 1.07, 95% CI 1.00 to 1.14; I(2) = 2%). However, the authors recognized that the GRADE evidence of these findings were low and achieved mid-level evidence only, indicating that the true effect of beta-blockers may be substantially different from the review estimates [30]. Another meta-analysis involving 127 studies corresponding to 150 group comparisons with a weighted mean follow-up of 4.2 years [31] demonstrated that there exists a slightly smaller risk of end-stage renal failure among ACEI or ARB users than other antihypertensive users (relative risk 0.87, 95% C.I. 0.75–0.99, p = 0.40). The ACEI or ARB group was also associated with a statistically significant smaller serum creatinine change (−7.07 μmol/L, 95% C.I. −13.26 to −0.88) and also urine albumin excretion (−15.37 mg/day, 95% C.I. −24.72 to −6.74). However, these benefits have been attributed to lowering of blood pressure per se rather than the antihypertensive drug class used. In a post-hoc analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) among hypertensive patients aged 55 years or older with at least one cardiovascular risk factor, there were no significant differences found in the incidence of end-stage renal failure or decrement in glomerular filtration rates [32]. Furthermore, there is one significant factor which could potentially favor the effectiveness of β-blockers on reducing mortality, namely the national salt intake level. Dietary salt intake in Hong Kong was high at the time the study participants were recruited. The average sodium intake of the Hong Kong population is 203 mmol/day (4.67 g/day) [33], which is higher than western countries and also the level recommended by the WHO (<2 g/day) [34]. The findings should therefore be interpreted in the light of this potential confounder.

Turning to the incidence of diabetes-from the ALLHAT trial, patients without diabetes at baseline have higher incidence of diabetes at 4 years in the thiazide diuretic group (11.0%) than the CCB (9.3%) and ACEI group (7.8%) [35]. Nevertheless, these and other metabolic differences did not translate into any overall disadvantages for the thiazide diuretic group after the average follow-up of 4.9 years. Furthermore, additional epidemiological analysis examining the association of 2 year fasting glucose changes with cardiovascular disease and renal events reported no significance overall and separately in the diuretic group [36]. Also, among those who developed incident diabetes by 2 years compared with those who did not, there was no subsequent increase in risks for any major disease outcomes and mortality, with an exception of congestive heart failure [37]. Thus far, we are not aware of any large-scale observational studies comparing these major antihypertensive drug classes on mortality rates.

Table 3
Number and percentages of all-cause mortality and deaths due to diabetes or renal diseases within 5 years after the initial antihypertensive prescription.

	All-caused mortality (n = 33,288)		Mortality due to diabetes or renal disease (n = 1055)	
	N (%)	p	N (%)	p
Gender		<0.001		
Male	18,864 (19.2%)		510 (0.52%)	0.033
Female	14,424 (12.0%)		545 (0.46%)	
Age (years)		<0.001		<0.001
<50	1663 (2.7%)		29 (0.0%)	
50–59	2263 (5.4%)		41 (0.1%)	
60–69	4646 (11.2%)		126 (0.3%)	
≥70	24,713 (33.9%)		859 (1.2%)	
Public assistance		<0.001		<0.001
Yes	10,110 (30.8%)		322 (1.0%)	
No	22,640 (12.4%)		720 (0.4%)	
Service type on first visit		<0.001		<0.001
In-/day-patient clinic	22,776 (34.7%)		707 (1.1%)	
Special out-patient clinic	5056 (7.6%)		216 (0.3%)	
Accident and Emergency Department	945 (5.6%)		25 (0.1%)	
General outpatient clinics	3669 (5.7%)		80 (0.1%)	
Others	839 (14.3%)		27 (0.5%)	
District of residence		<0.001		0.001
Hong Kong	6112 (12.0%)		191 (0.5%)	
Kowloon	12,967 (17.6%)		407 (0.6%)	
New Territories	14,209 (13.4%)		457 (0.4%)	
First prescription		<0.001		<0.001
ACEIs	5144 (22.4%)		157 (0.7%)	
Alpha blocker	2579 (19.2%)		59 (0.4%)	
Beta blocker	8091 (8.2%)		173 (0.2%)	
CCB	14,974 (22.9%)		566 (0.9%)	
Thiazide	2500 (14.3%)		100 (0.6%)	
Proportion of days covered		<0.001		<0.001
<40%	10,290 (14.4%)		285 (0.4%)	
≥40%	22,998 (15.7%)		770 (0.5%)	
Co-morbidity		<0.001		<0.001
0	13,651 (10.4%)		122 (0.1%)	
1	14,915 (21.0%)		462 (0.7%)	
2	4198 (28.8%)		379 (2.6%)	
≥3	524 (35.9%)		92 (6.3%)	

ACEI: Angiotensin converting enzyme inhibitors; CCB: Calcium channel blocker.

Table 4
Association between initial antihypertensive medications and mortality due to diabetes or renal disease 5 years within cohort entry by Cox Proportional Hazard Analysis.

	All cause mortality		Mortality due to diabetes or renal disease	
	Hazard ratio (95% C.I.)	p	Hazard ratio (95% C.I.)	p
Gender				
Male	1.000		1.000	
Female	0.657 (0.632, 0.682)	<0.001	1.146 (0.905, 1.452)	0.259
Age (years)				
<50	1.000		1.000	
50–59	1.924 (1.638, 2.259)	<0.001	1.235 (0.422, 3.613)	0.700
60–69	3.401 (2.803, 4.126)	<0.001	2.687 (0.756, 9.546)	0.127
≥70	8.844 (7.348, 10.645)	<0.001	7.253 (2.230, 25.38)	0.001
Public assistance				
No	1.000		1.000	
Yes	1.375 (1.320, 1.433)	<0.001	1.004 (0.778, 1.297)	0.973
Service type				
In-/day-patient clinic	2.316 (2.141, 2.506)	<0.001	2.440 (1.544, 3.855)	<0.001
Special out-patient clinic	0.753 (0.685, 0.829)	<0.001	1.175 (0.667, 2.065)	0.579
Accident and Emergency	0.615 (0.398, 0.953)	0.029	1.368 (0.073, 25.53)	0.834
General outpatient clinics	0.387 (0.346, 0.434)	<0.001	0.271 (0.133, 0.551)	<0.001
Others	1.000		1.000	
District of residence				
Hong Kong	1.000		1.000	
Kowloon	1.029 (0.995, 1.063)	0.099	1.049 (0.865, 1.273)	0.624
New Territories	0.963 (0.921, 1.006)	0.093	0.918 (0.699, 1.205)	0.537
First prescription				
ACEIs	1.000		1.000	
Alpha blocker	0.825 (0.591, 1.151)	0.257	1.251 (0.139, 11.28)	0.842
Beta blocker	0.815 (0.683, 0.874)	0.024	1.226 (0.382, 3.932)	0.732
CCB	1.020 (0.895, 1.163)	0.765	1.901 (0.805, 4.490)	0.143
Thiazide	0.970 (0.815, 1.156)	0.735	2.233 (0.717, 6.953)	0.166
Proportion of days covered (PDC) at 6 months				
<40%	1.000		1.000	
≥40	0.908 (0.887, 0.930)	<0.001	0.993 (0.863, 1.144)	0.927
Co-morbidity				
0	1.000		1.000	
1	1.266 (1.142, 1.405)	<0.001	4.119 (1.984, 8.551)	<0.001
2	1.271 (1.143, 1.414)	<0.001	12.60 (6.060, 26.18)	<0.001
3	1.314 (1.150, 1.500)	<0.001	26.38 (12.44, 55.93)	<0.001

ACEI: Angiotensin converting enzyme inhibitors; CCB: Calcium channel blocker.

4.3. Study limitations

This is the first and the largest observational study evaluating the factors associated with all-cause and non-cardiovascular mortality in a large Chinese population. The completeness of the database and the good dispensing practice make the study findings more robust. In addition, the accuracy of the independent variable (antihypertensive drug class) and the outcome measures (mortality) further strengthen the results. However, some of the limitations should be addressed. Firstly, we assume that patients were taking the medications prescribed as they were documented in the database which is an inherent assumption for database studies. Furthermore, the dataset does not consist of all potential confounders which could be controlled, such as the severity of comorbidity, the blood pressure levels, and some covariates including lifestyle factors which were not routinely captured in clinical databases. Moreover, indication bias for treatment according to medication classes exists despite the use of propensity scores. One might also argue that regression analysis could not completely control confounders because of the presence of residual confounding. Lastly, critics might comment that the duration of observing mortality for only 5 years after initial antihypertensive prescriptions might not be long enough to capture clinically meaningful outcomes, and prolonging the observational period is warranted in future studies.

5. Conclusions: implications to clinical practice

The present findings showed that all major drug classes were similar in terms of all-cause as well as combined diabetes and renal mortality, respectively. These observational data further strengthened the findings from RCTs which were conducted in interventional settings. Our findings are therefore compatible with the international guidelines. Physicians should not be deterred to prescribe beta-blockers as the first-line antihypertensive drug for management of arterial hypertension. The study added evidence to the existing findings from event-based randomized therapeutic trials, that any major antihypertensive drug class is suitable as a first-line agent for managing hypertension.

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