# Association of antihypertensive monotherapy with serum sodium and potassium levels in Chinese patients

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**Running Title:** Antihypertensive drugs and electrolytes in Chinese

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**Abstract**

**Background**

International guidelines on management of hypertension recommend any major classes of antihypertensive drugs. However the low prescribing rate of thiazides has been attributed to concerns about electrolyte disturbances and studies between antihypertensive drug classes and hyponatremia/hypokalemia among Chinese patients were scarce.

**Methods**

From clinical databases we included 2,759 patients who received their first-ever antihypertensive monotherapy from January 2004 to June 2007 in a large Territory of Hong Kong. We studied the plasma sodium and potassium levels 8 weeks after prescriptions and factors associated with hyponatremia and hypokalemia by multivariable regression analyses.

**Results**

Among major antihypertensive drug classes, thiazide users had the lowest sodium level (139.6 mEq/L, 95% C.I. 139.3, 140.0, $p<0.001$) and patients prescribed calcium channel blockers ([CCB] 3.92 mEq/L, 95% C.I. 3.89, 3.95) or thiazide diuretics (3.99 mEq/L, 95% C.I. 3.93, 4.04) had the lowest potassium levels ($p<0.001$). Multivariate analysis reported advanced age ($\geq$ 70 years, OR 7.49, 95% C.I. 2.84, 19.8, $p<0.001$), male gender (OR 2.38, 95% C.I. 1.45, 3.91, $p<0.001$) and thiazide users (OR 2.42, 95% C.I. 1.29, 4.56, $p=0.006$) were significantly associated with hyponatremia, while RAS (OR 0.31, 95% C.I.

0.13, 0.73, p=0.008) and β-blockers (OR 0.35, 95% C.I. 0.23, 0.54, p<0.001) users were less likely to present with hypokalemia. However, the proportions having normonatremic (95.1%) and normokalemic (89.4%) levels were high.

**Conclusions**

In view of the low prevalence of hyponatremia and hypokalemia associated with thiazides, physicians should not be deterred from prescribing thiazide diuretics as first-line antihypertensive agents as recommended by most international guidelines.

## Introduction

Thiazide diuretics have been recommended by international guidelines as first-line agents in the management of hypertension, including the seventh report of the Joint National Committee[1] and the National Institute of Clinical Excellence[2]. However, thiazide diuretics could induce metabolic side effects including hyponatremia and hypokalemia[3, 4], and the majority of patients admitted to hospitals due to electrolyte disturbances can be attributed to diuretic use[5]. This has recently been shown to deter physicians from prescribing thiazides to Chinese patients[6].

The majority of these reports were conducted in Caucasian countries and electrolyte profiles among Chinese hypertensive patients on thiazides have been scarce and small-scaled[7]. Ethnicity is associated with different pharmacological outcomes of antihypertensive agents and even small ethnic differences may bear substantial health resource implications[8].

The present study examined the effect of antihypertensive drug classes on hyponatremia/ hypokalemia among ethnic Chinese, and evaluated the associated factors of these electrolyte disturbances. We tested the hypothesis that the likelihood of hyponatremia and hypokalemia after antihypertensive prescriptions were similar among patients prescribed major antihypertensive classes.

## Methods

*Data source*

The Clinical Data Analysis and Reporting System (CDARS) of the Hospital Authority, Hong Kong consists of all patient records in public clinic visits since 2000. It captures patients' demographics, clinical information including diagnoses, prescription details and laboratory investigation results in every out-patient consultation. One of the major functions of CDARS is research[9]. It is the single portal of information entry in the public sector, and is a comprehensive record which allows cross-referencing when patients visit a different clinic. Also, drug prescription details are doubly checked by pharmacist professionals and any amendments were recorded in the electronic patient record. In addition to these good practices this database has been evaluated and found to have a high level of completeness with respect to demographic data (100%) and prescription details (99.98%)[10]. The present study included Hong Kong residents in the New Territory East Cluster, which has a population of around 1.3 million. It is further divided into 3 separate regions, namely Shatin, Tai-Po and the North District, from the most urbanized to the most rural regions respectively. Their median monthly household incomes in 2006 were comparable to the Hong Kong-wide figure of US$2,240. These three regions have similar median ages (38-39 years), comparable with the median age of 39 years for Hong Kong[11].

*Subjects*

Patients who newly attended the public primary care practice, coded by physicians with International Classification of Primary Care (ICPC) K86 [uncomplicated hypertension] and who were prescribed a single antihypertensive agent as the first-ever antihypertensive pharmacotherapy in the public sector during January 2004 to June 2007 were included in a retrospective manner. Only patients who had their plasma sodium and potassium levels checked 4 to 16 weeks after the prescription were included. Exclusion criteria included subjects having concomitant cardiovascular factors or clinical conditions which could confound antihypertensive prescription choice, identified by the respective ICPC codes (see Box 1). Also, patients discontinued or switched their drug prescription or received sodium or potassium supplements before electrolyte measurements were excluded. In addition, medication adherence was assessed by evidence that the patients attended for medication refill at a consultation time where their drug stocks would expire. We calculated the Medication Possession Ratio (MPR) for each patient, defined as the ratio of total days of medication supplied (not including the last prescription) to total days in a period of time[12]. Those with MPR < 0.8 were considered drug non-compliant and excluded[12]. The minimum follow-up time was 4 weeks in all the eligible cases as indicated by our database.

Each patient was classified into one drug group according to the prescription. These include β-blockers (BBs), thiazide diuretics, Calcium Channel Blockers (CCBs), drugs acting on the renin angiotensin system (RAS) and others (including α-blockers, potassium-sparing and other diuretics, vasodilators and combination therapy). We

evaluated the dosage of each prescription qualitatively as "low", "medium" or "high" according to standard drug formulary.

*Outcomes Variables, associated factors and statistical analysis*

We evaluated the mean plasma Na/K levels and proportions of patients having low (Na < 135 mEq/L; K < 3.4 mEq/L), normal (Na 136-147 mEq/L; K 3.5-5.1 mEq/L) and high (Na > 148 mEq/L; K > 5.2 mEq/L) levels among the various drug classes. We reported the glomerular filtration rate (GFR) as estimated by the Cockcroft-Gault formula[13]. We divided estimated GFR into tertiles and compared the proportion of hyponatremic vs. normonatremic patients belonging to each of the tertiles; and similarly for hypokalemic and normokalemic patients. Independent predictors and covariates include patients' age, gender, payment status (fee waivers vs. payers; each consultation costs US$5.77), district of residence, estimated GFR (in tertiles), and the antihypertensive drug classes prescribed (thiazide diuretics, BB, CCB, RAS). The "other" drug group was excluded from the multivariate analysis since it contained diuretics and combination therapy, which usually consisted of thiazide.

For descriptive analysis student's t-tests and $\chi^2$ tests were used to compare continuous and categorical variables respectively. In multivariate analyzes, we entered all the variables listed above into the regression equations with hyponatremia and hypokalemia as two separate outcome variables. Drug classes included thiazide diuretics, BB and CCB with RAS as a reference group. Since there are significant differences between districts with respect to antihypertensive prescribing, we conducted sensitivity analyzes

where district of residence was included and then excluded as an independent variable, respectively, to avoid over-controlling of covariates. All $p<0.05$ were regarded as statistically significant.

**Results**

We included 2,759 eligible patient records, with a mean age of 63.6 years (95% C.I. 63.4, 64.5) (**Table 1**). The CCB group was the eldest and had the highest proportion of male patients and the BB group was the youngest and had the lowest proportion of male patients. Their electrolyte levels were measured approximately 8 weeks after prescriptions and these periods were statistically similar among antihypertensive drug classes (p=0.06). From the drug formulary we judged that > 90% of antihypertensive prescriptions were of standard dosage (i.e. medium dose), and the proportion of prescription dosage being medium when the major drug classes were compared showed no significant differences (p=0.42) (**Table 2**). Unreliable sodium and potassium levels were reported in 85 and 126 patients respectively due to lipemic or hemolytic blood samples. For all patients, the mean sodium and potassium levels were 140.0 mEq/L (95% C.I. 139.9, 140.1) and 3.99 mEq/L (95% C.I. 3.97, 4.01) respectively. Among the four major antihypertensive drug classes, thiazide users had the lowest sodium levels, whereas CCB and thiazide had the lowest potassium levels. Users of β-blockers and RAS had higher GFR than other drug classes (p<0.001) (**Table 2**). Only one patient had hypernatremia, and the proportion of patients having abnormal sodium and potassium levels were both low (3.9% and 10.6% respectively, **Table 2**).

We compared the clinical characteristics of patients having hyponatremia or hypokalemia with patients with normonatremia and normokalemia respectively. Hyponatremic patients and hypokalemic patients were significantly older than normonatremic and normokalemic patients, respectively (**Table 3**). Comparison between hyponatremic or

hypokalemic patients with normonatremic and normokalemic patients respectively according to gender, payment status, district of residence and service types of clinics were all statistically insignificant. Among all drug classes, thiazide users had higher proportions of hyponatremia than normonatremic patients, while CCB and thiazide users had higher proportions of hypokalemia than normokalemic patients (**Table 3**). When divided into tertiles, the estimated GFR among hyponatremic patients was significantly lower than normonatremic patients ($p<0.001$) whereas no difference in GFR was reported between hypokalemic and normokalemic patients ($p=0.10$) (Table 3).

Two separate, unconditional binary logistic regression analyzes were performed with hyponatremia and hypokalemia as outcome variables, respectively, to evaluate the factors related to these electrolyte disturbances. When controlled for covariates, advanced age ($\geq$ 70 years) was associated with hyponatremia when compared with patients < 50 years (**Table 4**). Male patients had significantly higher odds of hyponatremia than females. Residence in the North district (the most rural region) was negatively associated with hyponatremia or hypokalemia. Patients with the highest GFR (3$^{rd}$ tertile) were significantly less likely to have hyponatremia. Thiazide users were positively associated with hyponatremia; users of RAS and β-blockers were negatively associated with hypokalemia. When district of residence was excluded from the regression analyses, the findings remained similar.

## Discussion

*Major findings*

This study showed that thiazide diuretics had the lowest levels of plasma sodium, while CCBs and thiazide diuretics had the lowest levels of plasma potassium approximately 8 weeks after the first-ever antihypertensive prescription when compared to other drug classes, but the absolute magnitude of differences were minimal. From multivariate analyzes advanced age, male gender and thizide user were positively associated with hyponatremia, while RAS and β-blockers were less likely to present with hypokalemia when compared with CCB. However, the proportions of patients having these electrolyte disturbances were not high.

*Interpretation and relationship with literatures*

A previous study in UK general practices reported a higher proportion of hyponatremia (13.7%) and hypokalemia (8.5%) among thiazide users[14]. The same study also reported that increased age (> 70 years) was significantly associated with hyponatremia, and that hypokalemia was associated with thiazide use. In ethnic groups other than Chinese, thiazides have been shown to cause hypokalemia, and potassium levels have been shown to be linearly correlated with blood pressure levels[15]. Another study in the US has identified a positive association between thiazide use and symptomatic hyponatremia requiring hospital admission[16]. Among Chinese patients, there is one study evaluating prescriptions of diuretics in two out-patient clinics and concluded that diuretic use was associated with hypokalemia[17]. This study demonstrated that advanced age was independently related to hyponatremia. It has been recognized that elderly women could

have expanded fluid volume after increased fluid intake but decreased ability to excrete free water, which might explain the higher risks of hyponatremia among the elderly[18].

It is unknown why male patients and residents in rural districts had significantly different odds of presenting with these electrolyte disturbances from published literatures, where the underlying reasons remained to be explored.

In addition, the proportion of hyponatremic in hypokalemic patients (15.5%) was greater than normonatremic patients (9.1%) (p=0.02), highlighting this as a possible moderator of medication effect. It is consistent with the fact that potassium depletion causes a water shift from the intracellular space to the extracellular space and exchangeable potassium is hence a determinant of serum Na concentration.

Also, despite the lowest sodium level among thiazide users and lowest potassium levels among CCB users, and that multivariate regression analyzes showed that some drug classes were significantly associated with hyponatremia/hypokalemia, these absolute differences with the mean sodium and potassium values of all patients, respectively, were minimal (0.4 mEq/L and 0.07 mEq/L respectively). Since we included a large sample from the whole Territory our results may be more representative of hypertensive patients than previous studies. In addition, the inclusion of antihypertensive drug naïve patients with uncomplicated hypertension only without concomitant cardiovascular factors; drug regimen changes; or sodium and potassium supplements provides a relatively uncontaminated sample for evaluating the pharmacologic effects of antihypertensive agents. However, the lower potassium levels among CCB users remain unexplained by current published literatures, while on the contrary CCBs such as verapamil and

nifedipine, at pharmacologic doses, have been proposed to block aldosterone production causing hyperkalemia rather than hypokalemia[19].

*Limitations of the present study*

Among patients newly prescribed antihypertensive agents, we have included only those with electrolyte measured 4-16 weeks after their first-ever prescriptions. However, the basic demographic characteristics between this group and all patients were statistically similar regarding age (63.3 vs. 64.3 years, p=0.18; gender (female 55.6% vs. 56.8%, p=0.18; district of residence (residents in most urbanized areas 5.9% vs 5.6%, p=0.40) and the types of clinics attended (care under FMSC 8.0% vs. 8.7%, p=0.20).

Nevertheless, we only studied electrolyte abnormalities 8 weeks after drug prescriptions and patients had uncomplicated hypertension only, therefore the applicability of these findings to patients with multi-comorbidities should be cautious.

We have included Chinese patients in this study and it is well recognized that ethnicity is an important factor affecting the pharmacologic actions of antihypertensive drugs[8], hence these findings might not be generalizable to patients of other races. In addition, baseline electrolyte levels were not available for comparison among drug classes. Furthermore, we evaluated risk-association but not cause-and-effect relationship, which should be more appropriately addressed by a prospective study. A more comprehensive evaluation should include dietary surveys on fruit and vegetable intake which had significant bearings on plasma electrolyte levels.

*Implications to clinical practice*

Translated into clinical practice, male patients with advanced age should have their sodium levels monitored more closely. Physicians should not be deterred from prescribing thiazide. Some caution however is needed in prescribing thiazide and CCBs since the prevalence of hypokalemia (11.8% and 12.8% respectively) is still not negligible, especially when hypokalemia also causes resistant hypertension and can induce salt sensitivity. Similar studies comparing the odds of dyslipidemia and impaired fasting glucose from users of antihypertensive prescriptions reported no significant differences among antihypertensive drug classes[20-21]. The present study adds further "real-life" evidence supporting the use of the major antihypertensive drug classes as suitable first-line prescription in the initiation and maintenance of hypertension management as recommended by most international guidelines.

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**Box 1 Exclusion criteria for patients coded with the following International Classification of Primary Care (ICPC) code**

| | |
|---|---|
| K87 | Complicated hypertension |
| T90 | Diabetes mellitus |
| T901 | Impaired glucose tolerance |
| T92 | Gout |
| T93 | Lipid disorder |
| K90, K91 | Stroke and cerebrovascular accident |
| K74, K76 | Ischemic heart diseases |
| K75 | Acute myocardial infarction |
| K77, K84, K99 | Heart failure and heart diseases |
| R79, R95, R96 | Chronic obstructive pulmonary diseases, asthma |
| D97 | Cirrhosis/other liver disease |
| D11 | Diarrhea |
| D10 | Vomiting |
| U14, U88, Y85, U78, Y79 | Urological conditions |

## Table 1: Patient characteristics (N=2,759)

| | β-blockers (n=633) | Thiazide (n=311) | CCBs (n=828) | RAS (n=140) | Others** (n=847) | p value |
|---|---|---|---|---|---|---|
| | % | % | % | % | % | |
| **Age** (years) | | | | | | |
| <50 | 24.8 | 16.4 | 15.2 | 19.3 | 11.6 | <0.001 |
| 50-59 | 32.1 | 25.1 | 20.7 | 28.6 | 20.0 | |
| 60-69 | 19.7 | 23.2 | 22.7 | 20.7 | 21.4 | |
| ≥70 | 23.4 | 35.4 | 41.4 | 31.4 | 47.1 | |
| **Mean Age** | 59.2 | 63.2 | 65.4 | 62.4 | 66.6 | |
| (SD) | (12.8) | (12.6) | (13.7) | (13.8) | (13.4) | <0.001 |
| (95% CI) | (58.3-60.3) | (61.8-64.6) | (66.4-64.3) | (60.1-64.4) | (65.7-67.5) | |
| **Gender** | | | | | | |
| Male（%） | 36.7 | 40.5 | 48.8 | 42.9 | 47.7 | <0.001 |
| **Payment status** | | | | | | |
| Fee-waivers | 35.9 | 37.0 | 36.7 | 30.0 | 32.7 | 0.26 |
| Fee-payers | 64.1 | 67.0 | 63.3 | 70.0 | 62.3 | |
| **District of residence** | | | | | | |
| Shatin | 39.5 | 32.5 | 41.1 | 36.4 | 49.0 | <0.001 |
| Taipo | 18.8 | 14.5 | 22.0 | 24.3 | 20.1 | |
| North | 35.4 | 47.3 | 32.1 | 33.6 | 24.1 | |
| Others | 6.3 | 5.8 | 4.8 | 5.7 | 6.8 | |
| **Service type** | | | | | | |
| General | 89.6 | 90.4 | 92.5 | 87.1 | 88.0 | <0.001 |
| FMSC | 7.6 | 6.1 | 5.8 | 10.0 | 11.0 | |
| Staff clinic | 2.8 | 3.5 | 1.7 | 2.9 | 1.1 | |
| **Period form prescription to electrolyte measurement (weeks)** | 8.41 (8.16-8.67) | 7.90 (7.57-8.23) | 8.45 (8.24-8.67) | 8.24 (7.67-8.81) | 8.91 (8.68-9.14) | 0.06* |

(CCB: Calcium Channel Blockers; RAS: drugs acting on the renin angiotensin system; FMSC: Family Medicine Specialist Clinic. The p values represent chi square tests among the different antihypertensive drug classes across variables in that row. *these p values involve comparison of the first four drug groups only. ** including α-blockers (65%), single pill with at least two antihypertensive drug component (33.8%), and miscellaneous (1.2%; potassium-sparing diuretics and vasodilators)

## Table 2: Electrolyte and renal function by antihypertensive drug groups

| | β-blocker (n=606) | Thiazide (n=306) | CCBs (n=801) | RAS (n=136) | Others* (n=826) | p values |
|---|---|---|---|---|---|---|
| | % | % | % | % | % | |
| **Dosage** | | | | | | |
| High | 0.0 | 0.0 | 0.0 | 0.0 | 0.1 | 0.42 |
| Medium | 74.3 | 71.2 | 72.2 | 67.6 | 85.3 | |
| Low | 25.7 | 28.8 | 27.8 | 32.4 | 14.5 | |
| **Sodium (mEq/l)** | | | | | | |
| low (≤ 135) | 3.8 | 5.9 | 3.7 | 5.1 | 6.3 | 0.53 |
| normal (136-147) | 96.0 | 94.1 | 96.3 | 94.9 | 93.7 | |
| high (≥ 148) | 0.2 | 0.0 | 0.0 | 0.0 | 0.0 | |
| **Potassium (mEq/l)** | | | | | | |
| Low (≤ 3.4) | 5.0 | 11.8 | 12.8 | 4.4 | 9.5 | <0.001 |
| Normal (3.5-5.1) | 93.4 | 86.6 | 86.6 | 95.6 | 89.2 | |
| High (≥ 5.2) | 1.7 | 1.6 | 0.6 | 0.0 | 1.3 | |
| **Plasma Levels (Mean ± 95% C.I)** | | | | | | |
| **Sodium (mEq/l)** | 140.3 (140.0-140.5) | 139.6 (139.3-140.0) | 140.2 (140.0-140.4) | 139.8 (139.3-140.3) | 139.7 (139.5-139.9) | <0.001 |
| **Potassium (mEq/l)** | 4.07 (4.03-4.10) | 3.99 (3.93-4.04) | 3.92 (3.89-3.95) | 4.04 (3.97-4.11) | 4.00 (3.96, 4.03) | <0.001 |
| **Serum Creatinine** (mg/dl) (95 % C.I.) | 0.90 (0.88-0.97) | 0.98 (0.95-1.02) | 0.99 (0.97-1.02) | 0.93 (0.88-0.97) | 1.04 (1.02-1.07) | <0.001 |
| **Estimated GFR**** (ml/min) (95% C.I.) | 84.87 (82.21-86.63) | 72.26 (71.61-76.91) | 73.37 (71.61-75.14) | 78.68 (75.14-83.10) | 68.95 (67.19-70.72) | <0.001 |

(CCB: Calcium Channel Blockers; RAS: drugs acting on the renin angiotensin system. We excluded 85 and 126 patients with sodium and potassium readings, respectively, regarded as unreliable due to lipemic or hemolyzed samples. The p values represent chi square tests among the first four antihypertensive drug classes across variables in that row
*including α-blockers (65%), single pill with at least two antihypertensive drug component (33.8%), and miscellaneous (1.2%; potassium-sparing diuretics and vasodilators)
**The estimated Glomerular Filtration Rate was derived from the Cockcroft-Gault formula

**Table 3 Characteristics of hypertensive patients presented with hyponatremia and hypokalemia compared to all patients**

| | Patients with Na ≤ 135mEq/L (n=130) | Patients with Na 136-147mEq/L (n=2543) | p | Patients with K ≤ 3.4 (n=252) | Patients with K 3.5-5.1mEq/L (n=2386) | p |
|---|---|---|---|---|---|---|
| **Mean Age (95% C.I.)** | 73.2 (71.0-75.4) | 64.0 (63.5-64.5) | <0.001 | 65.9 (64.1-67.7) | 64.0 (63.5-64.5) | 0.03 |
| | % | % | | % | % | |
| **Gender** | | | | | | |
| Male | 51.5 | 44.5 | 0.14 | 40.5 | 45.2 | 0.17 |
| **Payment** | | | | | | |
| Fee-waiver | 39.2 | 34.9 | 0.36 | 34.9 | 35.1 | 0.95 |
| Payers | 60.8 | 65.1 | | 65.1 | 64.9 | |
| **District of residence** | | | | | | |
| Urban areas | | | | | | |
| Rural areas | 93.1 | 94.0 | 0.66 | 96.0 | 94.1 | 0.20 |
| | 6.9 | 6.0 | | 4.0 | 5.9 | |
| **Service types** | | | | | | |
| General | 93.1 | 90.0 | 0.43 | 92.9 | 89.8 | 0.21 |
| FMSC | 6.2 | 8.0 | | 6.3 | 8.1 | |
| Staff clinics | 0.8 | 2.0 | | 0.8 | 2.1 | |
| **Drug classes** | | | | | | |
| β-blockers | 29.5 | 32.9 | <0.001 | 17.2 | 34.2 | <0.001 |
| Thiazide | 23.1 | 16.3 | | 20.7 | 16.0 | |
| CCB | 38.5 | 43.6 | | 58.6 | 41.9 | |
| RAS | 9.0 | 7.3 | | 3.4 | 7.8 | |
| **Estimated GFR*** | | | | | | |
| First tertile (≤63.30 ml/min) | 51.5 | 32.4 | <0.001 | 32.9 | 33.2 | 0.99 |
| Second tertile (63.31-84.54 ml/min) | 29.2 | 33.5 | | 33.7 | 33.4 | |
| Third tertile (≥84.64 ml/min) | 19.2 | 34.1 | | 33.3 | 33.4 | |

FMSC: Family Medicine Specialist Clinic; CCB: Calcium Channel Blockers; RAS: drugs acting on the renin angiotensin system; GFR: Glomerular filtration rate. The percentages were across rows for drug classes and across columns for other variables. The p values represent student's t tests (for mean age) and chi square tests (for other variables) between the two groups of patients

*The estimated Glomerular Filtration Rate was derived from the Cockcroft-Gault formula. GFR is divided into tertiles and the figures in the respective row represent the percentages of patients in the column belonging to the respective tertile.

**Table 4 Factors associated with hyponatremia and hypokalemia among Chinese patients on antihypertensive monotherapy**

| | Hyponatremia (Na ≤ 135 mEq/l) (n=130) | | | | | | Hypokalemia (K ≤ 3.4 mEq/l) (n=252) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **n** | **%** | **cOR (95% C.I.)** | **p** | **aOR (95% C.I.)** | **p** | **n** | **%** | **cOR (95% C.I.)** | **p** | **aOR (95% C.I.)** | **p** |
| **Age (years)** | | | | | | | | | | | | |
| < 50 | 12 | 2.7 | 1.0 (ref.) | | 1.0 (ref.) | | 41 | 9.3 | 1.0 (ref.) | | 1.0 (ref.) | |
| 50-59 | 9 | 1.4 | 0.52 (0.22-.24) | 0.13 | 0.46 (0.15-1.40) | 0.17 | 54 | 8.5 | 0.92 (0.60-1.41) | 0.70 | 0.87 (0.52-1.46) | 0.60 |
| 60-69 | 14 | 2.4 | 0.90 (0.41-1.95) | 0.78 | 1.43 (0.51-3.97) | 0.50 | 42 | 7.3 | 0.78 (0.50-1.23) | 0.28 | 0.81 (0.44-1.47) | 0.48 |
| ≥ 70 | 95 | 9.3 | 3.69 (2.00-6.80) | **<0.001** | **7.49 (2.84-19.8)** | **<0.001** | 115 | 11.3 | 1.26 (0.86-1.83) | 0.24 | 1.30 (0.70-2.39) | 0.41 |
| **Gender** | | | | | | | | | | | | |
| Female | 63 | 4.3 | 1.0 (ref.) | | 1.0 (ref.) | | 150 | 10.2 | 1.0 (ref.) | | 1.0 (ref.) | |
| Male | 67 | 5.6 | 1.33 (0.93-1.89) | 0.12 | **2.38 (1.45-3.91)** | **0.001** | 102 | 8.5 | 0.82 (0.63-1.07) | 0.15 | 0.89 (0.63-1.25) | 0.50 |
| **Payment** | | | | | | | | | | | | |
| Fee-waivers | 51 | 5.4 | 1.0 (ref.) | | 1.0 (ref.) | | 88 | 9.4 | 1.0 (ref.) | | 1.0 (ref.) | |
| Fee-payers | 79 | 4.6 | 0.83 (0.58-1.19) | 0.31 | 1.09 (0.67-1.78) | 0.73 | 164 | 9.5 | 1.01 (0.77-1.33) | 0.95 | 1.16 (0.83-1.63) | 0.39 |
| **District of residence** | | | | | | | | | | | | |
| Shatin | 72 | 6.5 | 1.0 (ref.) | | 1.0 (ref.) | | 139 | 12.7 | 1.0 (ref.) | | 1.0 (ref.) | |
| Taipo | 31 | 3.7 | 0.91 (0.59-1.40) | 0.66 | 1.28 (0.74-2.23) | 0.38 | 51 | 7.2 | 0.75 (0.53-1.05) | 0.10 | 0.67 (0.44-1.02) | 0.06 |
| North | 18 | 2.0 | 0.30 (0.18-0.51) | **<0.001** | 0.39 (0.20-0.75) | 0.005 | 52 | 6.0 | 0.44 (0.32-0.61) | **<0.001** | 0.37 (0.24-0.55) | **<0.001** |
| Others | 9 | 5.6 | 0.86 (0.42-1.75) | 0.68 | 0.75 (0.22-2.54) | 0.64 | 10 | 6.5 | 0.48 (0.24-0.92) | **0.025** | 0.40 (0.17-0.94) | 0.04 |
| **Estimated GFR* (**ml/min) | | | | | | | | | | | | |
| 1st tertile (≤63.30) | 67 | 3.8 | 1.0 (ref.) | | 1.0 (ref.) | | 83 | 4.7 | 1.0 (ref.) | | 1.0 (ref.) | |
| 2nd tertile (63.31-84.54) | 38 | 2.1 | 0.55 (0.36-0.82) | **0.003** | 0.71 (0.40-1.27) | 0.24 | 85 | 4.8 | 1.02 (0.74-1.41) | 0.89 | 0.72 (1.12-0.46) | 0.14 |
| 3rd tertile (≥84.64) | 25 | 1.4 | 0.36 (0.22-0.57) | **<0.001** | **0.35 (0.15-0.80)** | **0.013** | 84 | 4.7 | 1.02 (0.74-1.40) | 0.93 | 0.60 (1.08-0.34) | 0.08 |
| **Drug classes** | | | | | | | | | | | | |
| CCB | 30 | 3.7 | 1.0 (ref.) | | 1.0 (ref.) | | 102 | 12.8 | 1.0 (ref.) | | 1.0 (ref.) | |
| RAS | 7 | 5.1 | 1.40 (0.60-3.24) | 0.44 | 1.77 (0.74-4.25) | 0.20 | 6 | 4.4 | 0.32 (0.14-0.74) | **0.005** | **0.31 (0.13-0.73)** | **0.008** |
| β-blockers | 23 | 3.8 | 1.01 (0.58-1.76) | 0.96 | 1.62 (0.90-2.90) | 0.11 | 30 | 5.0 | 0.36 (0.23-0.54) | **<0.001** | **0.35 (0.23-0.54)** | **<0.001** |
| Thiazide | 18 | 5.9 | 1.61 (0.88-2.93) | 0.12 | **2.42 (1.29-4.56)** | **0.006** | 36 | 11.8 | 0.91 (0.61-1.37) | 0.67 | 1.05 (0.69-1.60) | 0.81 |

(cOR: crude odds ratios; aOR: adjusted odds ratios; GFR Glomerular Filtration Rate; FMSC: Family Medicine Specialist Clinic; RAS: drugs acting on the renin angiotensin system; CCB: Calcium Channel Blockers. All the adjusted odds ratios were adjusted for Glomerular filtration rate and the variables listed in this table with hyponatremia and hypokalemia as outcome variables respectively. All the percentages were across rows.

*The estimated Glomerular Filtration Rate was derived from the Cockcroft-Gault formula)