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Queen Mary Utilization of Antihypertensive Drugs Study: use of antihypertensive drug classes in the Hypertension Clinic 1996–2004

Bernard M. Y. Cheung, Yuk Lin Wong[1] & Chu Pak Lau

Department of Medicine, University of Hong Kong, Hong Kong, and [1]University of Hong Kong School of Professional and Continuing Education and University of Sunderland, Sunderland, UK

Correspondence
Dr Bernard M. Y. Cheung, University Department of Medicine, Queen Mary Hospital, Pokfulam, Hong Kong.
Tel: + 852 2855 4768
Fax: + 852 2904 9443
E-mail: mycheung@hkucc.hku.hk

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Background
Utilization of antihypertensive drugs in the hypertension outpatient clinic is surveyed periodically in the Queen Mary Utilization of Antihypertensive Drugs Study (QUADS).

Methods
Two hundred and fifty-one patients (123 men, 128 women) were interviewed in April to December 1996, 439 patients (232 men, 207 women) in January to December 99 and 228 patients (109 men, 119 women) in April to May 2004. Their case notes were reviewed.

Results
The percentages of patients receiving no drug (lifestyle modification), one, two, three and over three drugs were 7%, 48%, 36%, 7%, 3%, respectively, in 1996; 14%, 34%, 36%, 13% and 1%, respectively, in 1999; and 3%, 30%, 40%, 22% and 6%, respectively, in 2004. The number of drugs correlated with age and overweight. In 1996, 51% patients received calcium channel blockers (CCB); 46% β-blockers (BB); 32% angiotensin-converting enzyme inhibitors (ACEI); 15% thiazide diuretics; 5% α-blockers; and 0% angiotensin receptor blockers (ARB). In 1999, the respective figures were 52% CCB, 49% BB, 24% ACEI, 22% thiazide diuretics, 4% α-blockers and 2% ARB. In 2004, the respective figures were 65% CCB, 64% BB, 33% ACEI, 24% thiazide diuretics, 4% α-blockers and 7% ARB. Fewer patients on BBs reported side-effects. Only 11% were on α statin and 9% on aspirin. Blood pressure on treatment was 147 ± 21/84 ± 11 mmHg in 1999 and 144 ± 21/82 ± 11 mmHg in 2004.

Conclusions
Increasingly, multiple drugs were used for blood pressure control. Blood pressure control needs improvement, especially in diabetics. CCBs and BBs were consistently popular. Thiazide diuretics, ARBs, statins and aspirin were underused, despite favourable clinical trial evidence.

Introduction

About one billion people worldwide suffer from hypertension. There are 50 million people with hypertension in the USA and 130 million in China. Due to the 'rule of halves', only a proportion of hypertensives are treated and even fewer have good control of blood pressure [1, 2].

Hypertension is a leading risk factor for coronary heart disease and stroke. There is now strong evidence from large clinical trials that lowering blood pressure

effectively prevents these adverse outcomes [3, 4]. It is therefore important that once the diagnosis of hypertension is established, blood pressure should be adequately controlled through regular follow-up and prescription of effective antihypertensive treatment, which often entails using more than one antihypertensive drug. Accordingly, there is a need to survey the pattern of usage of antihypertensive drugs, to see if the current usage is rational, effective and tolerated. In this longitudinal study, we document the utilization of antihypertensive drugs in 1996, 1999 and 2004 as part of the Queen Mary Utilization of Antihypertensive Drugs Study (QUADS) programme [5].

Methods

Altogether, 918 patients attending the Hypertension Clinic of Queen Mary Hospital, Hong Kong, a university teaching hospital, were sampled and studied in three phases. The clinic handles referrals from family physicians, the accident and emergency department and general medical clinics. There were 251 patients interviewed in April to December 1996; 439 patients were interviewed in January to December 99 and 228 patients were interviewed in April to May 2004. In 1996 and 1999, patients were randomly selected from the clinic attendance list for interview. In 2004, every patient attending the clinic was approached. New patients attending the clinic for the first time were excluded because the diagnosis of hypertension might not have been made and any drug they were taking did not reflect the prescription practice of the clinic.

The following information was obtained from the patient through a structured questionnaire: age, duration of hypertension, number of years of treatment, the antihypertensive medications actually taken, other illnesses and medications, history of gestational hypertension, family history and social history. From the medical records, diagnoses of concomitant illnesses, height and weight were obtained. After 1998, use of aspirin, body fat percentage and blood pressure were also documented. In 2004, marital status, body mass index (BMI), waist circumference, hip circumference, heart rate, use of lipid-lowering drugs (statins and fibrates), potassium supplements, oral contraceptive, hormonal replacement therapy, antidiabetic medications, erectile dysfunction, tobacco and alcohol consumption, exercise habit, blood electrolytes and lipid profile were also studied. In 2004, patients were asked directly about adverse drug effects and about compliance.

BMI was calculated as the weight divided by the height squared (kg m^{-2}). Overweight was defined as BMI $\geq$ 23 kg m^{-2}; the normal range of BMI for the local population is between 18.5 and 22.9 kg m^{-2}. Blood pressure was carefully measured by a trained person in the sitting position after at least 15 min of rest. The target blood pressure was systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DBP) <90 mmHg, or SBP <130 mmHg and DBP <80 mmHg for patients with diabetes or renal disease, in whom a lower blood pressure target is beneficial [6, 7].

Antihypertensive drugs were classified into seven groups: thiazide diuretics, β-blockers (BB), calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), α-blockers and others. The latter group comprises centrally acting agents (e.g. methyldopa) and vasodilators (e.g. hydralazine).

Statistical analysis

Data were analysed using SPSS for Windows version 11.0 (SPSS Inc., Chicago, IL, USA). Patient characteristics were compared using analysis of variance or χ^2 test for continuous and categorical variables, respectively. For bivariate correlations, Spearman's rank correlation coefficients were calculated. Stepwise multiple regression was used to identify independent predictor variables. $P < 0.05$ was considered statistically significant.

Results

The characteristics of the subjects in the 1996, 1999 and 2004 surveys are shown in Table 1. Age, years since diagnosis, weight and BMI showed an increasing trend across the surveys.

Number of antihypertensive drugs

Figure 1 shows the number of antihypertensive drug classes taken by patients. The number of antihypertensive drugs taken per patient was 1.5 ± 0.06 (mean ± SE) in 1996, 1.5 ± 0.05 in 1999 and 2.0 ± 0.06 in 2004.

In 1996, the number of antihypertensive drug classes taken by a patient correlated with age, sex, weight, BMI and years since diagnosis, but not with history of gestational hypertension or family history of hypertension. It correlated with the use of any of the classes of antihypertensive drugs except methyldopa, indicating that the latter was not used as an add-on medication to control blood pressure. Multiple regression showed that age ($\beta = 0.19$, $P = 0.009$), years since diagnosis ($\beta = 0.19$, $P = 0.008$) and BMI ($\beta = 0.19$, $P = 0.006$) were independent predictors of the number of antihypertensive drug classes ($R = 0.34$, $P < 0.001$).

In 1999, the number of antihypertensive drug classes

Table 1
Patient characteristics

	1996	1999	2004
Total number of patients	251	439	228
Men	123 (49%)	232 (53%)	109 (48%)
Women	128 (51%)	207 (47%)	119 (52%)
Age range (years)	26–82	21–89	22–90
Mean age (years)	49 ± 12	56 ± 14	53 ± 14*
Height (m)	1.62 ± 0.09	1.62 ± 0.09	1.60 ± 0.09
Weight (kg)	66.0 ± 12.0	67.2 ± 12.3	69.5 ± 14.4*
Body mass index (kg m^{-2})	25.2 ± 3.9	25.7 ± 3.9	26.9 ± 4.5*
Waist circumference (cm)	–	–	85.8 ± 10.8
Years since diagnosis	7.6 ± 7.2	9.4 ± 8.4	10.1 ± 8.9*
Taking antihypertensive drug(s)	93%	86%	97%*
Gestational hypertension in female patients	50/128 (39%)	71/187 (38%)	36/119 (30%)
Hypertension in parent(s)	72%	65%	68%
Hypertension in sibling(s)	42%	46%	
Systolic blood pressure (mmHg)	–	147.1 ± 21.3	143.9 ± 20.6*
Diastolic blood pressure (mmHg)	–	83.7 ± 11.2	81.7 ± 10.8*

*Values are shown as mean ± SD. *P < 0.05, one-way analysis of variance.*

taken by a patient correlated with age, years since diagnosis and DBP, but not with sex, weight, BMI, history of gestational hypertension or family history of hypertension. It correlated with the use of any of the classes of antihypertensive drugs except methyldopa and ARB, indicating that these were not used as add-on medications to control blood pressure. Multiple regression showed that age ($\beta = 0.36$, $P < 0.001$), years since diagnosis ($\beta = 0.20$, $P < 0.001$), BMI ($\beta = 0.10$, $P = 0.03$) and sex ($\beta = 0.09$, $P = 0.04$) were independent predictors of the number of antihypertensive drug classes ($R = 0.47$, $P < 0.001$).

In 2004, more variables were studied. The number of antihypertensive drug classes taken by a patient correlated with age, years since diagnosis, SBP, waist circumference, waist–hip ratio, diabetes, blood glucose, smoking and negatively with alcohol and drug compliance, but not with sex, weight, BMI, DBP, history of gestational hypertension or family history of hypertension. It correlated with the use of all classes of antihypertensive drugs including methyldopa and ARB, indicating that these were now used as add-on medications to control blood pressure. Multiple regression showed that age ($\beta = 0.21$, $P = 0.02$), waist circumference ($\beta = 0.23$, $P = 0.01$), SBP ($\beta = 0.27$, $P = 0.001$) and compliance ($\beta = -0.33$, $P < 0.001$) were independent predictors of the number of antihypertensive drug classes ($R = 0.58$, $P < 0.001$).

Commonly used antihypertensive drugs

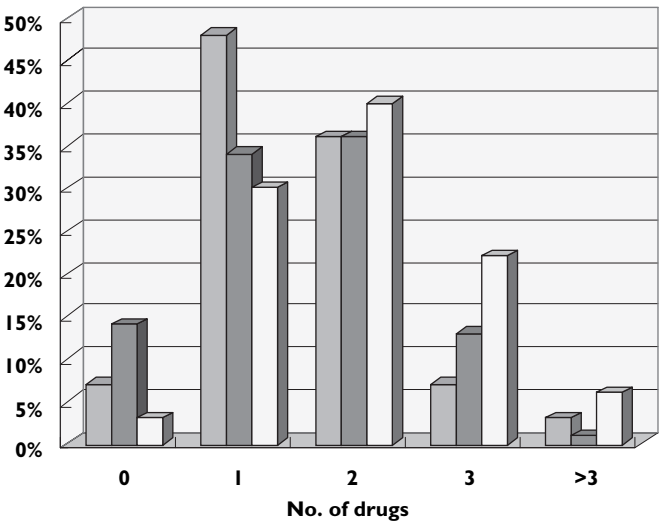
Table 2 shows the percentage of patients surveyed taking a particular class of antihypertensive drug, whereas Figure 2 shows the use of each class as a percentage of all hypertensive drugs taken by patients. Table 2 shows an increase in usage of ARB, BB, CCB and diuretics, but no increase in usage of α-blockers, ACEI, methyldopa or other drug classes. However, Figure 2 shows that the relative popularity of the different classes has remained the same since 1996, with the exception of ARBs, which started to become available in 1996. CCB and BB remained the most popular drugs, as shown in Table 3.

Women

In 1996, female hypertensive patients were younger (47.5 ± 10.1 *vs.* 50.7 ± 13.1, $P = 0.04$), less likely to be on drug treatment ($P = 0.007$) and likely to be on fewer drugs ($P = 0.003$). Calcium channel blockers, but not other drug classes, were less likely to be used in women [odds ratio (OR) 0.39, $P < 0.001$].

In 1999, female patients were similar to male patients in terms of age, likelihood to be on drug treatment and the number of drugs. In this sample, they were less likely to take an ACEI (OR 0.46, $P = 0.001$) but not CCB ($P = 0.57$).

In 2004, male and female patients were similar in age and the number of drugs. However, female patients were



	1996	1999	2004
N	251	439	228
0	7%	14%	3%
1	48%	34%	30%
2	36%	36%	40%
3	7%	13%	22%
4	2%	1%	5%
5	1%	0.2%	1%
6	0%	0%	0%

Figure 1
Number of antihypertensive drug classes taken by patients. 1996 (■), 1999 (■), 2004 (□)

Table 2
Percentage of patients receiving each class of antihypertensive drug

	1996	1999	2004
N	251	439	228
Alpha-blockers, %	5	4	4
ACEI, %	32	24	33
ARB, %	0	2	7
BB, %	46	49	64
CCB, %	51	52	65
Diuretics, %	15	22	24
Methyldopa, %	3	1	2
Other classes (hydralazine), %	2	0.2	1

ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker.

Table 3
The leading medication regimens

	1996	1999	2004
N	251	439	228
ACEI, %	12	6	1
BB, %	13	10	13
CCB, %	17	14	11
CCB + BB, %	16	18	17
CCB + BB + ACEI, %	11	4	10

ACEI, Angiotensin-converting enzyme inhibitor; BB, β-blocker; CCB, calcium channel blocker.

less likely to be on a CCB (OR 0.53, $P = 0.03$). Fewer women were on an ACEI, although this was not statistically significant (OR 0.69, $P = 0.18$).

The elderly

In 1996, 1999 and 2004, age was associated with drug treatment (respectively, $P = 0.004$, $P < 0.001$, $P = 0.006$), the number of drugs ($r = 0.24$, $P < 0.001$; $r = 0.39$, $P < 0.001$; $r = 0.45$, $P < 0.001$) and the use of a CCB ($P = 0.02$, $P < 0.001$, $P < 0.001$). In the 1999 and 2004 samples, achieved DBP decreased with age ($r = -0.32$, $P < 0.001$; $r = -0.24$, $P < 0.001$). Surprisingly, age did not predict the occurrence of side-effects ($P = 0.25$) nor the number of them ($P = 0.27$).

Achieved blood pressure

In 1999, the blood pressure on treatment was 147.1 ± 21.3/83.7 ± 11.2 mmHg (Table 1).

The DBP on treatment was <90 mmHg in 66% of patients (67% in men and 64% in women), but only 30% of patients (33% in men and 26% in women) had a SBP <140 mmHg as well.

In 2004, the achieved blood pressure was 143.9 ± 20.6/81.7 ± 10.8 mmHg. Ten percent of men and 7% of women achieved blood pressure in the normal range (<120/80 mmHg), whereas 36% men and 30% women achieved blood pressure in the prehypertension range (SBP 120–139 mmHg and DBP 80–89 mmHg). Blood pressure control was nonsignificantly better in men than in women (46% *vs.* 37%, $P = 0.22$). Overall, 41% had a

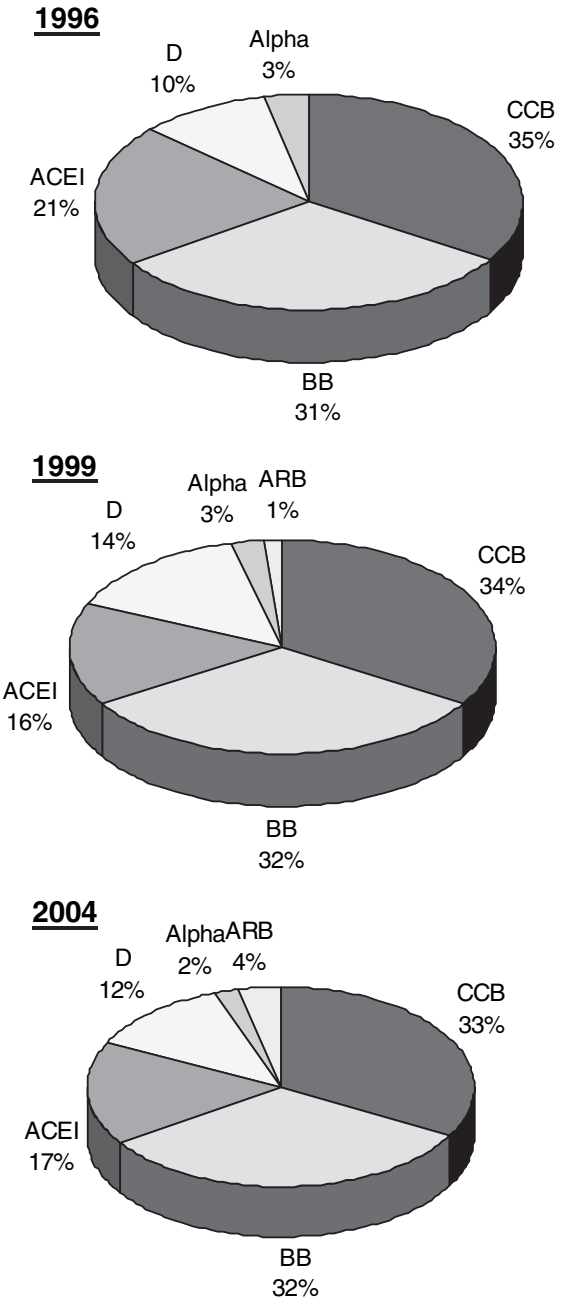


Figure 2

Use of each class of antihypertensive drug as a percentage of all antihypertensive drugs. Alpha, Alpha-blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; D, diuretic

treated blood pressure better than 140/90 mmHg. There were no significant differences between diabetic and nondiabetic patients in the achieved SBP (143.4 ± 22.8 mmHg *vs.* 143.9 ± 20.2 mmHg, $P = 0.91$) and DBP (79.9 ± 9.2 mmHg *vs.* 82.0 ± 11.1 mmHg, $P = 0.29$), respectively. Among diabetics, the blood pressure target (<130/80 mmHg) was reached in only 20% of patients. Amongst all patients including diabetics, the proportion reaching the target was only 37%.

Other medications

In 1996, 2% were taking aspirin and 5% were taking a statin. In 1999, 8% were on aspirin and 11% a statin. In 2004, 9% were on aspirin and 11% a statin.

In 1996, 5% of patients attending the hypertension clinic were diabetic and 1% were on diabetic medications. In 1999, 9% of patients attending the hypertension clinic were diabetic and 5% were on diabetic medications. In 2004, 15% were diabetic and 12% were on diabetic medications. The diabetic medications consisted of sulphonylureas and the biguanide, metformin. None of the patients was on insulin.

Adverse effects

In 2004, patients were asked if they experienced drug-related adverse effects. Among patients on antihypertensive drug therapy, 34% reported adverse effects (23% one side-effect, 8% two side-effects, 3% three side-effects). Surprisingly, the likelihood of experiencing adverse effects was unrelated to sex, age, years of treatment, number of drugs used, level of achieved blood pressure, heart rate on treatment or compliance. Fewer patients on a BB reported side-effects (OR 0.46, $P = 0.008$) and patients on BB reported fewer side-effects ($P = 0.004$).

Compliance

Compliance was studied in 2004. Of 222 patients on medications for hypertension, 213 (96%) claimed good compliance with no missing medication, whereas nine (4%) reported missing one dose every 1–2 weeks. Among these nine patients, seven were men and two were women ($P = 0.19$). In this sample of clinic patients of whom relatively few were noncompliant, the only statistically significant difference in patient characteristics between the noncompliant and compliant groups was the overall number of drugs the patients took ($P = 0.02$), and in particular the number of antihypertensive drugs ($P = 0.01$). The noncompliant group was not older than the good compliance group (51.4 ± 7.5 years *vs.* 53.5 ± 13.6 years, $P = 0.08$), did not report more side-effects (11% *vs.* 35%, $P = 0.14$), and also failed to reach blood pressure target (33% *vs.* 37%, $P = 0.88$).

Discussion

It is useful to interpret the results of this study in the context of the large clinical trials and guidelines that

were published in the period 1996–2004. Since 1996, many important large clinical trials (Syst-Eur [8], HOT [9], STOP2 [10], INSIGHT [11], HOPE [12], PROGRESS [13], LIFE [14], ALLHAT [15], ANBP2 [16]) have been completed. The first outcome trial using an ARB, albeit in heart failure patients, was published [17]. Major guidelines (JNC [18–20], World Health Organization/International Society of Hypertension [21, 22], European Society of Hypertension/European Society of Cardiology [23]) have been revised.

There are many studies of antihypertensive drug usage, which usually rely on prescription records [24, 25]. However, these computerized records of drug prescription provide mainly descriptive information. We attempted to go beyond a descriptive approach and find out why drugs were being used in a particular way. We interviewed every patient and examined the medical records. In 1996 and 1999, our main objective was to profile the utilization of antihypertensive drugs. In 2004, we examined, in addition, adverse drug effects and compliance, and their relationship with antihypertensive drug usage.

In a longitudinal study, patient characteristics varied over time. In addition to ageing, there is also evidence of increases in body weight and BMI. Thus, hypertension becomes more and more a manifestation of the metabolic syndrome, so that increasingly in the hypertension clinic, patients are being treated with oral medications for Type 2 diabetes and statins for hypercholesterolaemia. This is consistent with our findings of increased prevalence of the components of the metabolic syndrome in a large study of cardiovascular risk factors in the community, the Hong Kong Cardiovascular Risk Factor Prevalence Study-2 [26].

There was a trend towards an increase in the number of antihypertensive drugs taken by patients. This might reflect a worsening of the hypertension or increased intensity of treatment, or both. In 1996, 1999 and 2004, age and indices of obesity were consistent predictors of the number of drugs used, so to an extent, the increase in the number of drugs reflected increased disease severity arising from ageing and obesity. In 2004, the number of drugs was related to SBP, suggesting increasing awareness of the importance of controlling the systolic as much as the diastolic pressure. On the other hand, there was a small but significant fall in both the systolic and diastolic blood pressure on treatment in 2004 compared with 1999, suggesting that clinicians were aiming at better blood pressure control in accordance with management guidelines [20–23], thereby using more classes of drugs to achieve it. The concept of using a combination of more than one class to achieve blood pressure targets was especially promulgated by JNC7 in 2003 and echoed in local publications [20, 27].

Despite the increase in the number of drugs, remarkably, the relative popularity of the different drug classes had not changed markedly since 1996. ARBs were introduced in the clinic in 1996, but due to cost constraints, they were only used in a minority of patients. Evidence of benefit pertained to heart failure initially [17], but later extended to the treatment of hypertension [14]. Thiazides and ACEIs were also underused, perhaps because most clinicians wanted to know the renal function and electrolytes before prescribing these drugs. The prevalence of ACEI-induced cough is high in Hong Kong [28]. As there are many drug classes available for the treatment of hypertension, patients with intolerable cough are likely to stop taking the ACEI. CCBs and BB remained the most popular drugs. The former were particularly likely to be used in men and the elderly. CCBs are popular, despite the fact that there are no guidelines recommending them over and above other drug classes and there had been concerns about their safety [29]. The efficacy of CCBs in lowering blood pressure in the Chinese is excellent [30, 31], and may explain their popularity in Asia [25]. The majority of our hypertensive patients tend to have low rather than high renin [32], so the use of CCBs is appropriate and effective [33, 34]. As renin activity decreases with age [32], CCBs effectively lower blood pressure in the elderly, perhaps explaining our observation that the elderly were more likely to be on a CCB.

We also found that the elderly were likely to take more drugs and consequently have lower diastolic pressures than younger patients. This reflects current concepts of treating hypertension in the elderly, placing the emphasis on controlling systolic and diastolic pressure, using multiple drugs if necessary [20, 27]. Although age was not a predictor of side-effects or compliance in our study, polypharmacy in the elderly can potentially cause adverse effects and noncompliance.

Current guidelines do not have separate treatment algorithms for men and women. Thus, we found very little sex difference in terms of the number of drugs and the classes used, with the exception of CCBs, which appeared to be less popular among women in 1996 and 2004, but not 1999.

In the 2004 sample, we found no relationship between drug class and the likelihood of experiencing side-effects, with the exception of BBs. Patients on BBs reported fewer side-effects, either because BBs were well tolerated or because BB side-effects necessitated withdrawal of treatment. The former is more likely, as BBs are used in nearly two-thirds of our patients.

The compliance reported in this study may be an overestimate because self-assessment of compliance is not completely reliable. Also, patients attending a hypertension clinic in a university hospital may be relatively more compliant than patients in other settings.

The mean diastolic blood pressures achieved were close to the ideal blood pressures proposed in the HOT study [9]. However, SBP needs to be controlled better. Lowering the systolic pressure further necessitates taking more drugs or at higher doses. Therefore, the right balance needs to be struck between controlling the blood pressure and compromising tolerability or compliance. Although the proportion of patients reaching blood pressure target was higher in 2004 compared with 1999, fewer than half of all patients reached blood pressure target, and the proportion was even lower among diabetics. Thus, there is an urgent need to improve blood pressure control, especially among diabetics.

In conclusion, in this study of utlization of antihypertensive drugs, we found a trend towards using multiple drugs to control blood pressure. The relative popularity of different drug classes was consistent, with CCBs and BBs being the most popular, taken by nearly two-thirds of patients. The latter were best tolerated. Diastolic but not systolic pressure was well controlled. Blood pressure control needs to be improved, especially in diabetics. Thiazide diuretics, ACEIs, ARBs, statins and aspirin were underused, despite evidence of benefit in clinical trials.

Competing interests

B.M.Y.C. and C.P.L. have, at various times in the past 5 years, been reimbursed by Astra-Zenica, Boehringer, MSD, Novartis, Pfizer, Sanofi, Schwarz and Servier for organizing, attending or speaking in scientific meetings.

B.M.Y.C. is a member of the Institute of Cardiovascular Science and Medicine, University of Hong Kong, and an investigator of the Heart, Brain, Hormone and Healthy Ageing Research Centre of the Faculty of Medicine, University of Hong Kong. Amy Cheung and Fefe Law were research nurses who performed much of the data collection and documentation. Some of the results have been presented in abstract form at the First Global Conference on Cardiovascular Clinical Trials and Pharmacotherapy, Hong Kong, 2004: Wong YL, Cheung BMY. Utilization of antihypertensive drugs in a hypertension outpatient clinic in 1998 & 2004. Cardiovasc Drugs Ther 2004; 18 (Suppl. 1): 23. Financial support: none.

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