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Medication adherence to first-line antihypertensive drug class in a large Chinese population ☆

Martin C.S. Wong [a], Wilson W.S. Tam [a,*], Clement S.K. Cheung [b], Ellen L.H. Tong [b], Antonio C.H. Sek [b], N.T. Cheung [b], Stephen Leeder [c], Sian Griffiths [a]

[a] School of Public Health and Primary Care, Faculty of Medicine, Chinese University of Hong Kong, Hong Kong
[b] Hospital Authority Information Technology Services – Health Informatics Section, Hong Kong
[c] Menzies Centre for Health Policy, University of Sydney, Australia

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ABSTRACT

Purpose: Suboptimal adherence to antihypertensive agents leads to adverse clinical outcomes. This study aims to evaluate the association between first-line antihypertensive drug class and medication adherence in a large Chinese population.
Methods: All patients prescribed ≥ one antihypertensive drug in 2001–2003 and 2005 who have paid at least two consecutive clinic visits in the public healthcare system of Hong Kong were included. We excluded patients who have followed-up in the clinics for ≤30 days. Interval-based Proportion of Days Covered (PDC) was used to assess medication adherence. All patients were followed-up for up to 5 years. Binary logistic regression analysis was used to evaluate the factors associated with optimal adherence, defined as PDC ≥ 80%.
Results: From 147,914 eligible patients, 69.2% were adherent to the antihypertensive prescriptions. When compared with angiotensin converting enzyme inhibitors (ACEIs), patients initially prescribed α-blockers (adjusted odds ratio [AOR] = 0.234, 95% C.I. 0.215–0.256), β-blockers (AOR = 0.447, 95% C.I. 0.420, 0.477), thiazide diuretics (AOR = 0.431 95% C.I. 0.399, 0.466) and calcium channel blockers (AOR = 0.451, 95% C.I. 0.423, 0.481) were significantly less likely to be drug adherers. Angiotensin receptor blockers (ARBs) and fixed-dose combination therapies were similarly likely to be medication adherent. Older age, male gender, visits in general out-patient clinics, residence in urbanized regions, and the presence of comorbidity were positively associated with optimal drug adherence.
Conclusion: Patients receiving initial prescriptions of ACEIs, ARB and combination therapy had more favorable adherence profiles than the other major antihypertensive classes in real-life clinical practice.

1. Introduction

Globally, approximately one billion people have hypertension — one of the most important causes of premature death worldwide [1]. Its prevalence is rising and it has been estimated that in 2025, it will affect up to 1.56 billion adults. In the United States, the prevalence was 31.3% [2]. Similar or even higher age- and sex-adjusted prevalence of hypertension (up to 44%) was reported in European countries, including England, Finland, Germany, Italy, Spain and Sweden [3]. In Asia-Pacific countries, its prevalence varied from 15 to 35% in urban adult populations [4]. It bears a substantial public health burden as around $37 billion is spent annually for medications, office visits, and laboratory tests related to hypertension treatment [5].

It has been demonstrated that antihypertensive medications could reduce hypertension-related complications [6], but this could only be achieved by satisfactory drug adherence. A recent study by Mazzaglia and colleagues [7] showed that patients with higher levels of antihypertensive adherence were 38% less likely to suffer from subsequent cardiovascular events, and poor medication adherence could adversely lead to unwarranted health services utilization [8].

The seventh report of the Joint National Committee recommended thiazide diuretics as a preferred first-line agent in 2003, to be prescribed alone or as part of combination therapy, for most hypertensive patients [6]. The European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) however considered all of the major antihypertensive drug classes as equivalent as first-line agents [9]. Their position statements were based on a large number of randomized controlled trials, all of which demonstrated fairly equal efficacy of the major classes of antihypertensive drugs, both in terms of blood pressure reductions and the occurrence of primary cardiovascular end-points [10–14]. Nevertheless, the ESC/ESH guideline has also mentioned some limitations of these event-based

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* Corresponding author at: 4/F, School of Public Health and Primary Care, Prince of Wales Hospital, Shatin, NT, Hong Kong. Tel.: +852 2252 8810; fax: +852 2606 3500.
E-mail address: wilsontam@cuhk.edu.hk (W.W.S. Tam).

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randomized trials [15–17], including the need to select higher risk patients and thus uncomplicated, younger and lower risk patients were under-represented [18]. These therapeutic programs have also been criticized for not representing real clinical practice. Prolonging the observation of patients after the end of trials [19,20] might capture more "real-life" outcomes but these can only be done in an uncontrolled manner, and the problem of selection bias still exists. Thus, the expert group of the ESC/ESH advised that more "non-interventional" studies comparing the outcomes of the major antihypertensive classes, including drug adherence, should be performed.

We have previously conducted a retrospective cohort study in Hong Kong comparing the adherence profiles of different antihypertensive agents [21], and concluded that patients newly prescribed beta-blockers were significantly less likely to be adherent while those prescribed drugs acting on the renin angiotensin system (RAS) were more adherent. However, the study included only a modest number of new clinic visitors and patients were sampled from only one region of Hong Kong. Besides, there was no blood pressure levels included as potential confounders in the regression analysis. The duration of patient follow-up was very short, limited to assessment of compliance in two consecutive clinic visits only. The study has used Medication Possession Ratio (MPR) as the outcome measure for drug compliance. But recent evaluations from databases reported that MPR may overstate real adherence, and Proportion of Days Covered (PDC) should be considered instead as it is operationally defined more consistently [22,23].

Other larger-scale studies were mainly conducted among Caucasian countries and African regions [24–26]. The pharmacological actions of antihypertensive agents differed according to ethnicity, and few studies examined drug-class specific adherence profiles among Chinese individuals. Chinese people represent more than one-fifth of the world's population and reside in different parts of the world, and so far it is unknown whether the factors determining optimal antihypertensive adherence could be generalized to patients of Chinese ethnicity. The present study aimed to test the *a priori* hypothesis [21] that among first-line prescriptions of the major antihypertensive drug classes, the newer antihypertensive agents had higher while beta-blockers had lowest adherence levels. These newer medications include calcium channel blockers [CCB], ACEIs, angiotensin receptor blockers [ARBs] and fixed dose combination therapy. The older drug classes include thiazide diuretics, alpha-blockers, and beta-blockers. We also evaluated the independent factors associated with poor medication adherence.

2. Methods

2.1. Data source

The Clinical Management System (CMS) of the Hospital Authority, Hong Kong contains patient records in all public clinic visits. It consists of patients' demographics, clinical, diagnoses and prescription details in every clinic or hospital visits. It is the only route of information entry in the public healthcare system, and is comprehensive, allowing cross-referencing when patients visit a clinic in a different geographical region. Also, drug dispensations were checked by pharmacists or dispensers from standard protocols and all necessary revisions were recorded in the computerized system. Apart from these good practices, this database has previously been evaluated and possesses a high level of completeness regarding demographic (100%) and prescription information (99.98%) [27]. The present study included all regions in Hong Kong, which has a total population of more than seven million. It is further divided into 3 separate geographical regions, namely Hong Kong Island, Kowloon and the New Territories, from the most urbanized to the most rural, respectively. This study was approved by the Hospital Authority, the Clinical Ethics Research Committee, and the Surveys and Behavioral Research Ethics Committee of the Chinese University of Hong Kong.

2.2. Subjects

From the database, patients who attended any clinical practice in the public sector and newly prescribed at least one antihypertensive medication from 2001 to 2005 were included. Owing to the outbreak of the Severe Acute Respiratory Syndrome we did not include new prescriptions in the year 2004 as clinical services were disrupted. We excluded patients who had paid only one clinic visit where antihypertensive drugs were prescribed, since drug compliance could only be assessed for patients who attended at least twice for antihypertensive medications. Patients who stayed in the cohort for less than 30 days were also excluded. Each patient was classified into one drug group according to the prescription. These include α-blockers, β-blockers, thiazide diuretics, CCB, ACEIs, ARBs and combination therapy. Patient comorbidities include concomitant cardiovascular risk factors and medical conditions confounding the initial antihypertensive drug choice other than uncomplicated hypertension, as indicated by the respective International Classification of Primary Care (ICPC-2) or International Classification of Disease (ICD-9) code. Each patient was followed-up for five years, with those entering the cohort in 2005 observed up to the calendar year 2011.

2.3. Outcome variables and covariates

The outcome variable is the measure of drug compliance represented by the Proportion of Days Covered (PDC) for up to 5 years. Interval-based PDC is an internationally accepted metric for the evaluation of compliance using retrospective data [22,23]. It is defined as the number of days of medication supplied throughout the period (numerator) divided by the number of days in it (denominator). Those who have switched their medication during the follow up but covered by another antihypertensive agent were regarded as persistent in the period where the medication was replaced. PDC is a continuous variable with values ≥80% considered adherent [22,23].

The independent variables which we controlled for include patients' age, gender, the receipt of public assistance (fee waivers *vs.* fee-payers; each consultation costs US$5.77 including investigation and prescription fees), clinic types visited (in- and day-patient clinics, specialist out-patient clinics [SOPCs], Accident and Emergency Departments [AEDs], general out-patient clinic [GOPC] and other clinic types), district of residence (Hong Kong Island *vs.* Kowloon *vs.* the New Territories), the number of comorbidities, the systolic blood pressure levels averaged over all clinic visits, and the antihypertensive drug class prescribed. New visitors were patients who paid their first clinic visit during the study entry period 2001 to 2005. The comorbidities included ICD-9 and ICPC-2 coding, categorized under disorders as listed below: "Diabetes or impaired glucose tolerance" (23.0%): 250, 648.8, 790.2, T90, T901; "Cardiovascular diseases" (24.3%): 410–414, 428, 430–435, 437, 438, K74–K77, K84, K90, K91, K99; "Respiratory diseases" (14.6%) 491–493, 495, 496, 500–508, 510–513, 516, 517.1, 517.2, 517.8, 518.1, 518.2, 518.3, 518.5, 518.81, 518.82, 518.89, 519.1, 519.4, 519.8, R79, R95, R96; "Renal diseases" (11.0%) 581–583, 585, 588.0, 588.1, 588.8, 588.9, 589, 590, 590.0, 590.2, 590.3, 590.8, 590.9, 591, 592, 592.0, 592.9, 593, 593.0, 593.1, 593.2, 593.5, 593.71, 593.72, 593.73, 593.81, 593.8, 593.83, 593.89, 593.9, U14, U78, U88, Y79, Y85.

2.4. Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 15.0 was used for all data analysis. For descriptive analysis Student's t-tests and χ^2 tests were used to compare continuous and categorical variables respectively. In multivariate analyzes, we entered all the variables listed above into a binary logistic regression model with good antihypertensive adherence (PDC ≥80%) as the outcome variable. We conducted sensitivity analyzes where each antihypertensive drug class was used as the reference group in the regression equations consecutively to detect any differences. As the American Heart Association has used age 20 years or older as the inclusion criteria in standard studies, we excluded those aged <20 years and re-analyzed the regression models again to identify possible change in associations. The robustness of the regression model was checked for the presence of multicollinearity. All $p<0.05$ were regarded as statistically significant.

3. Results

3.1. Participant characteristics

We included a total of 147,914 eligible patients newly prescribed at least one antihypertensive agent in the cohort. Among them, 69.2% had optimal medication adherence (Table 1). The majority were female (54.9%), and most of them were aged 60 years or older (55.6%). A significant proportion received public assistance (15.9%). Most attended SOPC (33.7%), GOPC (31.9%) and in- or day-patient clinics (26.9%). Greater proportions of patients lived in the New Territories (49.4%), followed by Kowloon (33.3%) and the Hong Kong Island (17.3%). The majority of these patients received beta-blockers (42.4%) and CCB (29.9%), followed by ACEIs (11.7%), thiazide diuretics (7.7%) and alpha-blockers (5.4%). Approximately 44% of them had concomitant comorbidities. Their average SBP and DBP were 135.8 mm Hg (SD 13.2) and 74.5 mm Hg (SD 8.5), respectively.

Table 1
Patient characteristics and medication adherence profiles.

	N[a]	%	% Compliance[b]
All	147,914	100.0	102,377 (69.2%)
Gender			
Male	66,725	45.1	47,359 (71.0%)
Female	81,189	54.9	55,018 (67.8%)
Age			
<50	36,227	24.5	22,344 (61.7%)
50–59	29,529	20.0	21,318 (72.2%)
60–69	30,988	21.0	22,504 (72.6%)
≥70	51,169	34.6	36,210 (70.8%)
Public assistance			p<0.001
Yes	23,541	15.9	16,036 (68.1%)
No	123,119	83.2	85,447 (69.4%)
Service type on first visit			p<0.001
In-/day-patient clinic	39,733	26.9	23,133 (58.2%)
Special out-patient clinic	49,895	33.7	35,691 (71.5%)
Accident and Emergency Department	6954	4.7	2305 (33.1%)
General outpatient clinics	47,124	31.9	37,999 (80.6%)
Others	4201	2.8	3245 (77.2%)
District of residence			p<0.001
Hong Kong	25,621	17.3	18,434 (71.9%)
Kowloon	49,214	33.3	33,249 (67.6%)
New Territories	73,079	49.4	50,694 (69.4%)
First prescription			p<0.001
ACEIs	17,263	11.7%	14,427 (83.6%)
Alpha blocker	8044	5.4%	5084 (63.2%)
Beta blocker	62,969	42.4%	41,149 (65.6%)
CCB	44,299	29.9%	29,810 (67.3%)
Thiazide	11,449	7.7%	8223 (71.8%)
Combined fixed dose	66	0.0%	52 (78.8%)
ARB	390	0.3%	303 (79.7%)
Combined	3717	2.5%	3329 (89.6%)
Co-morbidity			
No	82,249	55.6	54,826 (66.7%)
1	52,768	35.7	28,267 (72.5%)
2	11,668	7.9	8394 (71.9%)
≥3	1229	0.8	890 (72.4%)
SBP (mm Hg)	Mean = 135.8 (SD = 13.2)		
DBP (mm Hg)	Mean = 74.5 (SD = 8.5)		

[a] From a total of 223,287 patients excluding those visited only once or stayed ≤30 days in the cohort, a total of 147,914 eligible patients were included.
[b] Adherence is defined as a 5-year Proportion of Days Covered ≥80% (total prescription days/total days in cohort).

3.2. Factors associated with medication adherence

When optimal medication adherence (PDC ≥0.80) was used as an outcome measure in the binary logistic regression model (Table 2), female patients (AOR for male = 0.844, 95% C.I. 0.817–0.872), individuals aged 50 years or younger (AOR for patient aged >50 years ranged from 1.360 to 1.608), attendance in AEDs (AOR ranged from 0.663 to 0.762), residence in more rural regions (Kowloon and the New Territories AOR 0.855 to 0.941), and those without concomitant comorbidities (AOR = 1.091–1.145 for one or more comorbidities) were significantly less likely to be compliant. When compared with ACEIs, initial prescriptions of α-blockers (AOR = 0.234, 95% C.I. 0.215–0.256), β-blockers (AOR = 0.447, 95% C.I. 0.420–0.477), CCB (AOR 0.451, 95% C.I. 0.423–0.481) and thiazide diuretics (AOR = 0.431, 95% C.I. 0.399–0.466) were less likely to be medication adherent. The odds of adherence were however statistically similar among α-blockers, β-blockers, CCB and thiazide diuretic. Patients prescribed ARBs and fixed dose combination therapy as first-line agents were similarly likely to be medication adherent as those who received ACEIs. For each mm Hg increase in SBP, there was a 0.5% reduced odds of medication adherence. When each antihypertensive drug class was used in turn as the reference group in the regression model, or when patients aged less than 20 years were excluded, the conclusions on the association between initial antihypertensive drug class and adherence remained the same. The coefficient of determination was 0.124, suggesting that all these covariates explained around 12.4% of the variability of the adherence outcome. There was no multicollinearity of the regression analysis.

Table 2
Factors associated with optimal adherence to antihypertensive medications.

	Crude odds ratios	Adjusted odds ratios $R^2 = 0.124$
Gender		
Male	1.000	1.000
Female	0.860 (0.841, 0.879)*	0.844 (0.817, 0.872)*
Age (years)		
<50	1.000	1.000
<60	1.613 (1.561, 1.667)*	1.360 (1.298, 1.425)*
<70	1.648 (1.595, 1.703)*	1.476 (1.407, 1.548)*
≥70	1.504 (1.462, 1.547)*	1.608 (1.534, 1.686)*
Public assistance		
Yes	0.942 (0.914, 0.971)*	0.965 (0.924, 1.008)
No	1.000	
Service type on first visit		
In-/day-patient clinic	1.000	1.000
Specialist out-patient	1.803 (1.754, 1.854)*	2.613 (2.502, 2.728)*
Accident and Emergency Department	0.356 (0.337, 0.375)*	0.711 (0.663, 0.762)*
General outpatient clinics	2.988 (2.899, 3.080)*	5.690 (5.464, 5.926)*
Others	2.436 (2.260, 2.625)*	3.911 (3.571, 4.284)*
District		
Hong Kong	1.000	1.000
Kowloon	0.812 (0.785, 0.839)*	0.855 (0.817, 0.895)*
New Territories	0.883 (0.856, 0.911)*	0.941 (0.902, 0.983)*
Number of co-morbidities		
0	1.000	1.000
1	1.320 (1.289, 1.352)*	1.145 (1.107, 1.184)*
2	1.282 (1.229, 1.339)	1.114 (1.050, 1.183)*
≥3	1.313 (1.158, 1.489)*	1.091 (0.915, 1.300)
First prescription		
ACEIs	1.000	1.000
Alpha blocker	0.338 (0.318, 0.359)*	0.234 (0.215, 0.256)*
Beta blocker	0.375 (0.359, 0.392)*	0.447 (0.420, 0.477)*
CCB	0.404 (0.387, 0.423)*	0.451 (0.423, 0.481)*
Thiazide	0.501 (0.473, 0.531)*	0.431 (0.399, 0.466)*
Combined fixed dose	0.730 (0.404, 1.319)	0.810 (0.266, 2.463)
ARB	0.774 (0.600, 0.997)*	1.322 (0.745, 2.344)
SBP (mm Hg)	1.001 (1.000, 1.002)	0.995 (0.994, 0.996)*
DBP (mm Hg)	1.000 (0.998, 1.002)	

Optimal adherence is defined as Proportion of Days Covered ≥0.80.
* p<0.05.

4. Discussions

4.1. Main findings

This study found a low level of adherence of 69.2% among patients newly prescribed antihypertensive medications. Better adherence was associated with initial antihypertensive prescriptions of combination therapies (89.6%), ACEIs (83.6%) and ARBs (79.7%). Adherence rates of β-blockers were non-inferior to thiazide diuretics and CCBs. Risk factors predicting poor medication adherence included young age, female gender, clinical setting of AEDs, residence in more underprivileged regions, and the absence of comorbidities.

4.2. Relationship to existing literature

Our previous study in one region of Hong Kong [21] reported an overall short-term adherence rate of 85.5% assessed by MPR over two consecutive clinic visits, and found that older age, female gender, fee-payers (no public assistance), attendance in family medicine specialist clinics, and follow-up visits were positively associated with better medication adherence. The overall adherence rate among patients newly prescribed an antihypertensive agent was 79.1%. ACEIs had the highest adherence rates (88.0%) while beta-blockers had

significantly lower adherence rates (81.3%) when compared with thiazide diuretics (84.5%). The present study reported much lower adherence levels across all drug classes as compared to the previous study [21], and we showed that β-blockers were not inferior to other older antihypertensive agents.

A recent retrospective cohort study linking four clinical databases in Ontario [26] studied the adherence profiles of newly treated hypertensive patients. The overall cohort had a high 1- and 2-year MPRs of 94.4% and 96.9%, respectively, and adherence was significantly better with ACEIs (AOR 1.17, 95% C.I. 1.10–1.25) and worse with beta-blockers (AOR 0.79, 95% C.I. 0.73–0.86) when compared with diuretics. The study also identified factors of poor adherence, including male gender, old age, urban residence, and the presence of at least one comorbidity. On the contrary, the majority of other studies in Western countries had similar findings with the current study. For instance from a real practice analysis in Italy [28], poorer adherence was associated with younger age and female gender among both incident and prevalent hypertensive patients. The absence of comorbid cardiac diseases was associated with poorer medication adherence among incident elderly hypertensives [29]. In two other studies using the Department Veterans Affairs' Pharmacy database [30,31], younger age and the absence of comorbidities were positively associated with lower adherence. A retrospective medical and pharmacy claims data for Maryland Medicaid patients found that younger age and higher Charlson Comorbidity Index (CCI) were associated with lower adherence, yet the prescription of combination therapies favored medication adherence [24]. Most other similar studies reported higher levels of adherence among patients prescribed ACEIs, CCBs or angiotensin receptor blockers [30,32–34] than those prescribed diuretics and beta-blockers. In summary, the risk factors for poor medication adherence evaluated in this study were compatible with those from the majority of international literature, but the non-inferiority of beta-blockers, as well as the superiority of combination therapy, ARBs and ACEIs as first-line antihypertensive agents were novel findings among ethnic Chinese individuals.

We have extensively discussed the plausible explanation of the demographic and clinical risk factors for poor adherence in previous studies [21,35–39]. Younger patients were less likely to be adherent, where we postulate that this might be due to their busy working schedule, or they were in general less health conscious than older patients. It is however unknown why female patients were less adherent than male subjects, and as we previously mentioned [21] current literature is rather mixed on the association between gender and medication adherence [40]. In addition, it is not surprising to find that higher blood pressure was associated with poorer compliance, as the effect of suboptimal compliance on poorer blood pressure control has been widely recognized [6–8]. For the drug class differences, there existed few comparative data on the major antihypertensive drug classes in Chinese patients. As highlighted by Friedman and colleagues [26], the reasons for differences in medication adherence across drug classes were likely multifactorial — ranging from drug tolerability, dosing frequency, and patient perceived adverse effects as potential contributors.

From the clinical guideline of the ESC/ESH [15], it was highlighted that the main benefits of antihypertensive agents were due to lowering of blood pressure *per se*, and that the major classes were equally suitable for initiation and maintenance of antihypertensive therapy. However, it also stated as one of its important position statements that the choice of first-line agents should depend on many factors, including anticipated compliance profiles. The guideline also contains extensive descriptions of the advantages of combination therapy. These include better blood pressure and complication control; lower dosage of either drugs used in the combination therapy and thus fewer incidences of side effects; and the feasibility in some regions that two agents can be administered in a single tablet. Therefore, in conjunction with our findings, we would recommend combination therapy, ARBs, and ACEIs as potentially more favorable first-line options in the management of arterial hypertension among antihypertensive-naive patients.

4.3. Strengths and limitations

This is the first-ever evaluation among Chinese patients of this scale studying the predictors of antihypertensive adherence. It involved a large number of patients newly prescribed different antihypertensive drug classes, observed for longer periods of 5–10 years. Its inclusion of all regions of Hong Kong enhances its representativeness and generalizability. We captured data from real-life clinical practice which could better reflect the reality than interventional trials. Also, the robustness of the clinical database, its completeness and the good dispensing practices further increased the reliability of the findings. However, some limitations should be mentioned. Firstly, we used PDC as the metric to assess medication adherence, although this has been internationally recognized as a measure in retrospective database analysis [22,23]. Critics might argue that patients were not actually taking the drugs that were dispensed. In addition, the reasons why adherence was poorer in some specific patient groups could not be further evaluated from the current dataset. Also, there might exist other confounders for medication adherence, such as educational attainment [25], depressive symptoms [41], the presence of stressful life events [41] and patient beliefs and behavior [42].

5. Perspectives

It follows that patients with risk factors for poor adherence should be given more attention with regard to their medication taking behavior — including adherence-enhancing initiatives offered by physicians, clinics and the community. Recent initiatives for designing and implementing community-based, adherence-promoting programs should be more focused. It is anticipated that their target towards younger patients, female subjects, residents in more rural regions, and those without concomitant comorbidities could lead to better cost-effectiveness. The relatively low, although not too inferior, adherence level of beta-blockers is compatible with guideline recommendations [6] on their conservative views of beta-blockers as first-line agents. Combination therapy, ARBs and ACEIs might be more favorable among Chinese patients based on adherence profiles, and this conclusion could be further strengthened by further evaluations between drug class and clinical outcomes in non-interventional settings. Future research should also explore whether better medication adherence as assessed by PDC is related to lower health service utilization and reduced rates of morbidity and mortality, as well as the unexplained difference in compliance profiles according to age and gender [40].

Novelty and significance

1) What is new?

From 147,914 patients newly prescribed at least one antihypertensive medication, 69.2% were adherent. Combination therapy and calcium channel blockers were significantly more adherent as compared to other major antihypertensive drug classes. Beta-blockers were the least medication adherent. Older age, male gender, visits in general out-patient clinics, residence in urbanized regions, and the presence of comorbidity were positively associated with optimal drug adherence.

2) What is relevant?

Given the equal efficacy of the major antihypertensive drug classes to prevent cardiovascular events and mortality, the superior adherence profiles of combination therapy and calcium channel blockers point towards them as more favorable first-line antihypertensive agents for

management of arterial hypertension in clinical practice. Patients identified as at higher risks for poor adherence are priority targets for intervention, and should receive more focused medication compliance-enhancing programs.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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