The incidence of all-cause, cardiovascular and respiratory disease admission among 20,252 users of lisinopril vs. perindopril: a cohort study

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Running Title: Admission among lisinopril and perindopril users

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Abstract

Background: Major international guidelines do not offer explicit recommendations on any specific angiotensin-converting enzyme inhibitor (ACEI) agent over another within the same drug group. This study compared the effectiveness of lisinopril vs. perindopril in reducing the incidence of hospital admission due to all-cause, cardiovascular disease and respiratory disease.

Methods: Adult patients who received new prescriptions of lisinopril or perindopril from 2001 to 2005 in all public hospitals and clinics in Hong Kong were included, and followed up for ≥2 years. The incidence of admissions due to all-cause, cardiovascular disease and respiratory disease was evaluated, respectively, by using Cox proportional hazard regression models. The regression models were constructed with propensity score matching to minimize indication biases.

Results: A total of 20,252 eligible patients with an average age of 64.5 years (standard deviation 15.0) were included. The admission rate at 24 months within the date of index prescription due to any cause, cardiovascular disease and respiratory disease among lisinopril vs. perindopril users was 24.8% vs. 24.8%, 13.7% vs. 14.0% and 6.9% vs. 6.3%, respectively. Lisinopril users were significantly more likely to be admitted due to respiratory diseases (adjusted hazard ratios [AHR]=1.25, 95% C.I. 1.08 to 1.43, p=0.002 at 12 months; AHR=1.17, 95% C.I. 1.04 to 1.31, p=0.009 at 24 months) and all cause (AHR=1.12, 95% C.I. 1.05 to 1.19, p<0.001 at 24 months) than perindopril users.

Conclusions: These findings support intra-class differences in the effectiveness of ACEIs, which could be considered by clinical guidelines when the preferred first-line antihypertensive drugs are recommended. (250 words)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; PDC, proportion of days covered; CI, confidence interval; AHR, adjusted hazard ratios

Introduction

Globally, hypertension is one of the most significant risk factors for cardiovascular disease and all-cause mortality. [1] The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) have recommended the prescription of angiotensin-converting enzyme inhibitors (ACEIs) for the treatment of hypertension, heart failure and myocardial infarction. [2] The ESH/ESC guideline [3], the National Institute for Health and Care Excellence [4] and 8th Joint National Committee (JNC 8) [5] consistently recommend ACEIs as one of the first line drug classes for management of arterial hypertension. In certain situations including diabetic nephropathy, post-myocardial infarction, heart failure, and left ventricular dysfunction [6, 7], ACEIs are particularly preferred owing to the ability to provide the greatest end-organ protection. [4] The enthusiasm to prescribe ACEIs extends beyond their effectiveness to reduce blood pressure (BP), since as a monotherapy they are as effective as most other major antihypertensive drug classes. [8]

Multiple studies have reported comparable antihypertensive efficacy between the multiple ACEIs and angiotensin II receptor blockers (ARBs) with no consistent differences in clinical outcomes, including death, cardiovascular events, quality of life, rate of single antihypertensive agent use, lipid levels, progression to diabetes, left ventricular mass or function, and kidney disease. [9] In addition, evidence from the Blood Pressure Lowering Treatment Trialists' Collaboration showed the existence of similar BP-dependent effects of ACEIs and ARBs for the risk of cardiovascular and stroke events; yet the ACEI alone had an added BP-independent benefit in reducing risk of coronary heart disease. [10] A more recent meta-analysis documented that ACEIs and ARBs were equally protective against myocardial infarction and mortality. [11]

Nevertheless, there is an important knowledge gap to be addressed. Evidence from face-to-face trials that directly compared the effectiveness of different entities of ACEIs were rare, and meanwhile the major international guidelines [3-5] do not offer explicit recommendations on any specific ACEI agent over another within the same drug group. The perindopril and lisinopril are the two most commonly prescribed ACEIs. A meta-analysis of randomized controlled trials showed that perindopril resulted in significantly fewer patients reaching primary end-points, including stroke, mortality, and myocardial infarction. [12] When these three endpoints were used as a composite outcome, the effect size of perindopril alone was larger than that of the combined ACEI analysis. Perindopril showed a significant risk reduction of the composite endpoints by 18% when compared with the overall ACEI effect. [12] Furthermore, in our recent analysis of a population-based study from 15,622 hypertensive patients, perindopril users were found to have lower all-cause and cardiovascular mortality than lisinopril users. [13]

The objective of this study was to compare the effectiveness of perindopril and lisinopril, which were the two most commonly prescribed ACEIs, on reducing hospital admission due to any cause, cardiovascular disease and respiratory disease. We tested the *a priori* hypothesis that there was no difference in the incidence of admission between the two drug classes.

Methods

Data Source

Patient information was extracted from an electronic clinical database, covering the entire Hong Kong population with more than 7 million people during the study period in the public health care sector. Patients' medication history, sociodemographic characteristics, and clinical diagnoses coded in the form of International Classification of Diseases (ICD-9) or International Classification of Primary Care (ICPC-2) in each consultation at different clinic locations were documented by the clinical management system. This computerized system is the only portal of information entry in all public health care settings across all geographical regions of Hong Kong (i.e. the New Territories, Kowloon, and Hong Kong Island). In all clinical consultations, medical doctors entered the prescription details as part of their routine practice. The details were subsequently sent to pharmacy professionals for drug dispensing. This electronic patient record system captured all amendments of prescriptions following the attending physicians' consultations. The database has been validated previously, and we found a high level of completeness of patients' demographic profiles (100%) and prescription details (99.8%). [14] We declared that this database has also been employed for analysis in previous studies. [13, 15-22] The present study was performed in accordance with the ethical guidelines of the Declaration of Helsinki. The study was approved by the Clinical Ethics Research Committee of the Hospital Authority and the Survey and Behavioral Research Ethics Committee of The Chinese University of Hong Kong.

Patients

Patients were eligible if they: (1). visited any public inpatient and outpatient settings in the period 2001-2005; (2). were newly prescribed perindopril or lisinopril as their initial antihypertensive agent; (3). did not receive antihypertensive drugs other than ACEIs before the index date, which was defined as the date of the first prescription record. We excluded subjects whose ACEI prescriptions lasted for less than 1 month; and whose antihypertensive agent was switched to

another medication for 2 years within the index date. Concomitant comorbidities of all patients were represented by the corresponding ICD-9 or ICPC-2 codes documented in the computer, and all patients were followed-up for 2 years.

Outcomes Variables and Covariates

The primary outcome measures consisted of the incidence of hospital admission due to any cause, cardiovascular disease, and respiratory disease, respectively, based on physician diagnoses. The incidence of admission due to cardiovascular diseases was identified with respect to coronary heart disease or stroke (ICD-9: coronary heart diseases: 410–414, heart failure: 428, cerebrovascular disease: 430–435, 437, 438; ICPC-2: cardiovascular or cerebrovascular disease: K74-K77, K84, K90, K91, K99). The respiratory diseases captured in the system included chronic obstructive airway disease, asthma, pneumoconiosis and other lung diseases that are major complications of pulmonary hypertension or complications that are commonly seen among patients on ACEIs (ICD-9: 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; ICPC-2: R79, R95, R96). The proportions of new-onset cardiovascular and respiratory diseases were captured from the hospitalization information system of the Hospital Authority.

The variable tested for association with the outcomes was the medication prescribed (lisinopril vs. perindopril). We controlled for age, sex, socioeconomic status (SES), service types (inpatient vs. specialist outpatient vs. general outpatient), the Proportion of Days Covered (PDC) as a measure of medication adherence, and the number of comorbidities. As a proxy measure of SES, we classified patients into recipients and non-recipients of social security allowance. We categorized comorbidities into “cardiovascular diseases”, “respiratory diseases”, “renal diseases” and “diabetes or impaired glucose tolerance”, based on the respective ICD-9 and ICPC-2 codes. [22] The interval-based PDC has been recognized as an internationally accepted metric to evaluate

medication adherence in database research. [23-25] The PDC was derived from dividing the time period with prescriptions by the total period of follow-up. For patients who died within 2 years after the index prescription, the PDC was estimated by adopting the time period between the index date and the death date. The medication adherence was regarded as high (PDC ≥0.80) or low (PDC <0.80) according to international standard. [25-27]

Statistical Analysis

The demographic and clinical characteristics of patients prescribed lisinopril vs. perindopril were compared by Pearson's Chi-square tests for categorical variables and Student's t-tests for continuous variables. We tabulated the incidence of hospital admissions due to any cause, cardiovascular disease and respiratory disease, respectively, across different independent variables. The Kaplan-Meier method with the log-rank test was adopted to compare the difference between lisinopril users vs. perindopril users in their incidence of cause-specific hospital admission. A Cox proportional hazard regression analysis [28] was modelled to compare the mortality rates of the two drug groups, adjusting for age, sex, SES, service types, the PDC, and the number of comorbidities. Three models were constructed for admissions due to any cause, cardiovascular disease and respiratory diseases, respectively, where hazard ratios and the corresponding 95% confidence intervals (95% CI) were evaluated. The medication dosages were controlled in additional regression analyses to detect for differences in hazard ratios.

To minimize the influence of treatment indication bias caused by different baseline characteristics of the two drug groups, we performed propensity score matching which was incorporated into the Cox proportional hazard models. The score was estimated by a logistic regression model with ACEIs prescribed against age, sex, service types, and SES. The probability of prescribing lisinopril compared with perindopril was predicted according to the baseline characteristics of each patient. A propensity score was assigned for each patient. The Cox proportional hazard analyses adjusted for

147 the propensity scores and other confounding factors. This standardized methodology to minimize
148 indication bias has been utilized by other studies. [29-31] All tests of significance were two-tailed,
149 where *p* values less than 0.05 were regarded as statistically significant. We performed all statistical
150 analyses with the Statistical Package for Social Sciences (version 16.0, Chicago, IL).

Results

Participant characteristics

The baseline characteristics of all patients were presented in **Table 1**. Their average age was 64.5 years (SD 15.0), and 49.2% were female subjects. There was no significant difference in age and gender between users of perindopril and lisinopril. Slightly more patients who received lisinopril were recipients of public financial assistance (17.4% vs. 14.8%, $p<0.001$). Higher proportion of lisinopril users attended specialist out-patient clinics (37.3% vs. 32.0%, $p<0.001$) when compared with perindopril users. Patients prescribed lisinopril had higher medications adherence at 6 months (PDC $\geq$ 0.80: 34.8% vs. 30.2%), 1 year (48.9% vs. 41.7%) and 2 years (36.0% vs. 28.8%, all $p<0.001$). Lisinopril users were prescribed higher dosages (>5 mg/day: 14.8% vs. 7.2%, $p<0.001$) **(Table 1)**.

Profile of admissions due to any cause, cardiovascular disease and respiratory disease

Table 2 shows the participant characteristics according to cause-specific hospital admissions. Among patients who were still survived, the proportion of subjects admitted to hospitals 6 months within the date of index prescription due to any cause, cardiovascular disease and respiratory disease was 12.2%, 7.6% and 3.1%, respectively. Patients admitted due to any cause (age $\geq$70 years; 58.5% vs. 36%), cardiovascular disease (65.9% vs. 36.5%), and respiratory disease (77.6% vs. 37.5%) were older than those not admitted. For all types of admissions, there was a higher proportion of male patients and recipients of public financial assistance **(Table 2)**. When compared with patients who were not admitted, those admitted due to any cause (57.5% vs. 56.6%) and respiratory disease (58.5% vs. 56.7%) had higher proportions taking lisinopril, as well as having PDC $\geq$0.80. At 12 months, the proportion of patients admitted due to any cause, cardiovascular and respiratory disease was 20.4%, 11.3% and 4.9%. The corresponding figures at 24 months were 31.1%, 16.1% and 7.1% **(Table 3)**. Among admissions due to any cause and respiratory diseases, the majority were lisinopril users. The admission rate at 24 months within the date of index

prescription due to any cause, cardiovascular disease and respiratory disease among lisinopril vs. perindopril users was 24.8% vs. 24.8%, 13.7% vs. 14.0% and 6.9% vs. 6.3%, respectively.

Comparison between lisinopril and perindopril

Unadjusted and adjusted Cox proportional hazard regression analyses with propensity score matching were performed to compare the disease-specific admission rates between lisinopril and perindopril **(Table 4)**. From regression analysis, lisinopril users were significantly more likely to be admitted due to respiratory diseases (adjusted hazard ratios [AHR]=1.25, 95% C.I. 1.08 to 1.43, p=0.002 at 12 months; AHR=1.17, 95% C.I. 1.04 to 1.31, p=0.009 at 24 months) and any cause (AHR=1.12, 95% C.I. 1.05 to 1.19, p<0.001 at 24 months) than perindopril users.

Discussion

Statement of Major Findings

The present study included more than 20,000 patients newly prescribed ACEIs and compared the incidence of hospital admission between patients who received lisinopril and perindopril, where indication bias was controlled by propensity score matching. It was found that the odds of hospital admission was significantly higher among lisinopril users when compared with perindopril users at 24 months due to any cause (by 12%) and respiratory diseases (by 17%). These findings supported an intra-class difference in the pharmacological benefits within the ACEI drug group.

Relationship with Literature and Explanation of Findings

ACEIs are the only drug class recommended for all of the compelling indications listed in the JNC 7 guideline. Lisinopril and perindopril are commonly prescribed. They belong to the carboxyl-containing ACEIs with identical duration of action (24 hours), and both were eliminated via the kidneys. [32] Lisinopril has a longer serum half-life (11-12 hours) than perindopril (3-10 hours). There have been very few studies which directly compared the effectiveness of lisinopril and perindopril on reducing the incidence of cardiovascular and respiratory disease-related admissions. A meta-analysis of randomized controlled trials of ACEI therapy for any cardiovascular outcomes [12] showed that the effect size of perindopril was higher than that of the combined ACEI class. The risk reduction of composite cardiovascular endpoints was 18% for perindopril users but was lowered to 5% only if perindopril was excluded from the analysis. The authors concluded that the survival benefits differed according to different ACEIs prescribed. This statement was corroborated by another study conducted by Comini and colleagues, who compared the effectiveness of five ACEIs (enalapril, perindopril, quinapril, ramipril, and trandolapril) at equihypotensive doses on increasing endothelial nitric oxide synthase protein expression and activity in the aorta and cardiac myocytes. [33] A highly significant effect was observed with

perindopril when compared with other ACEIs, which provided further evidence in favor of the differential effects of ACEI therapy. Hence, the clinical benefits associated with these medications might not solely reflect a class effect extending their benefit beyond BP-lowering effect. In addition, Pilote and colleagues performed two retrospective studies using linked hospital discharge and prescription databases in Canada. They found that patients older than 65 years who suffered from an acute myocardial infarction were significantly less likely to die if they were prescribed ramipril compared with those on other ACEIs (enalapril, fosinopril, captopril, quinapril, and lisinopril). [34] They also showed that elderly patients who had heart failure had higher mortality rate 30 days after hospital discharge among those prescribed captopril or enalapril compared with Ramipril. [35] Together with our previous studies which showed that hypertensive patients who received lisinopril were more likely than perindopril users to die from cardiovascular disorders or be admitted due to renal disease or diabetes, [13, 36] the conclusion of this study was compatible with those from existing literature. The difference in their effectiveness to reduce respiratory disease and all-cause admissions might be due to their different pharmacokinetic and pharmacodynamics activities. Also, this study reported that patients prescribed perindopril had lower medication adherence levels than lisinopril users. The exact mechanism where they confer different effects is yet to be explored. Our study is unique as it included patients with ethnicities that have not been previously studied. It is known that the pharmacological responses to different antihypertensive drugs differ according to different ethnicities [37] – hence our findings allow the conclusions of previous studies to be more generalizable.

Strengths and Limitations

This is the first study of this scale which included a large number of patients newly prescribed two commonly used ACEIs in the whole territory of Hong Kong, using a validated and comprehensive database. [14] The standardized prescription and dispensing practices which were under regular

audit in the public healthcare system enhanced the robustness of the present analysis. The use of ICD-9 and ICPC-2 as internationally recognized strategies for disease coding, and the ability of the electronic pharmacy system to include medication details in all clinic visits at different geographical regions provide an accurate source of data. However, some limitations should be addressed here. Firstly, the inherent assumption of database analysis where patients were actually taking the prescribed medications needs to be taken into account. Hence we have also incorporated PDC as a universally accepted metric into the Cox regression models. [23-25] Also, the follow-up period of this study was up to two years – and it is unknown whether the observed differences in hospital admission between the two groups could be sustained in the long term. Thirdly, there exist heterogeneity in the baseline characteristics of patients between the two drug groups, and critics might argue that indication bias could influence the results against the null hypothesis. Therefore we have attempted to address this concern employing propensity score matching, which has been widely used internationally for analyzing administrative databases. [30, 36] It should also be noted that the two medications have exactly the same compelling indications and contraindications, and both were available in all the public clinics where the choice of prescription was up to the physicians-in-charge. Finally, due to the non-randomized nature of assigning subjects into the two groups, some residual confounders that were not captured by the database might introduce bias, including previous comorbidities, prior experience of hospital admission, lifestyle habits after clinical consultations, and concomitant medications taken by the patients.

Conclusions

This study reported intra-class difference of ACEIs with respect to their effectiveness to reduce all-cause and respiratory disease admissions, among hypertensive patients who received their first-ever antihypertensive medications. The better outcomes seen in perindopril vs. lisinopril provide an important clinical implication to both researchers and physicians. Lisinopril alone may not be

adequate to represent the entire ACEI class in interpretation of existing trials, which almost exclusively used lisinopril as “representative of ACEIs”. Future studies should be performed to compare the effectiveness of different drugs within the ACEI class on patient-oriented outcomes by rigorously designed trials, preferably in patients of different races. The hypothesis where one ACEI is superior to another should be further tested prospectively, as it also exerts an impact on the formulation of future clinical guidelines on recommendation of antihypertensive treatments.

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Authors' contributions: MCSW (principal investigator) and HHXW conceived of the study design and provided overall guidance. Data analysis was mainly done by WWST and CSKC, and all authors contributed to literature search and interpretation of the data. MCSW wrote the first draft, and DKLC and HHXW contributed to the subsequent revisions of the manuscript. All authors contributed to the feedback on study results and writing of the final report. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table Legends

Table 1: Characteristics of study participants (N=20,252)

Table 2: Profiles of patient admission at 6 months

Table 3: Incidence of hospital admission at 12 months and 24 months according antihypertensive agents and medication adherence

Table 4: Hospital admissions due to any cause, cardiovascular disease and respiratory disease at 6 months, 12 months and 24 months after the index prescription date with propensity score matching

Table 1 Characteristics of study participants (N=20,252)

	Overall (n=20,252)	Perindopril users (n=8,731)	Lisinopril users (n=11,521)	p
Age				
<49	3,523 (17.4%)	1,460 (16.7%)	2,063 (17.9%)	0.177
49-59	3,986 (19.7%)	1,729 (19.8%)	2,257 (19.6%)	
60-69	4,340 (21.4%)	1,881 (21.5%)	2,459 (21.3%)	
≥ 70	8,403 (41.5%)	3,661 (41.9%)	4,742 (41.2%)	
Sex				
Male	10,292 (50.8%)	4,430 (50.7%)	5,862 (50.9%)	0.841
Female	9,960 (49.2%)	4,301 (49.3%)	5,659 (49.1%)	
Public financial assistance				
Non-recipients	16,952 (83.7%)	7,436 (85.2%)	9,516 (82.6%)	<0.001
Recipients	3,300 (16.3%)	1,295 (14.8%)	2,005 (17.4%)	
Service type				
In-patient	6,553 (32.4%)	2,907 (33.3%)	3,646 (31.6%)	<0.001
Specialist outpatient	7,091 (35.0%)	2,798 (32.0%)	4,293 (37.3%)	
Accident & Emergency	128 (0.6%)	63 (0.7%)	65 (0.6%)	
General outpatient	5,739 (28.3%)	2,731 (31.3%)	3,008 (26.1%)	
Others	741 (3.7%)	232 (2.7%)	509 (4.4%)	

Drug adherence (PDC at 6 months)				
<0.80	13,610 (67.2%)	6,097 (69.8%)	7,513 (65.2%)	<0.001
≥ 0.80	6,642 (32.8%)	2,634 (30.2%)	4,008 (34.8%)	
Drug adherence (PDC at 1 year)				
<0.80	10,970 (54.2%)	5,086 (58.3%)	5,884 (51.1%)	<0.001
≥ 0.80	9,282 (45.8%)	3,645 (41.7%)	5,637 (48.9%)	
Drug adherence (PDC at 2 years)				
<0.80	13,591 (67.1%)	6,214 (71.2%)	7,377 (64.0%)	<0.001
≥ 0.80	6,661 (32.9%)	2,517 (28.8%)	4,144 (36.0%)	
Drug dosage (mg/day)				
0-2.5	12,389 (61.2%)	5,798 (66.4%)	6,591 (57.2%)	<0.001
>2.5-5.0	5,526 (27.3%)	2,300 (26.3%)	3,226 (28.0%)	
>5.0-7.5	240 (1.2%)	148 (1.7%)	92 (0.8%)	
>7.5-10	1,069 (5.3%)	151 (1.7%)	918 (8.0%)	
>10	1,028 (5.1%)	334 (3.8%)	694 (6.0%)	

PDC: Proportion days covered with the lisinopril and perindopril. The percentages are across rows. The p values represent the comparison between the perindopril and lisinopril groups using Pearson chi-square tests.

Table 2 Profiles of patient admission at 6 months

	All-cause		Cardiovascular disease		Respiratory disease	
	Not Admitted	Admitted	Not Admitted	Admitted	Not Admitted	Admitted
Mean Age (S.D.)	63.3	66.2	63.3	67.6	63.5	68.8
Age	n=16664	n=2323	n=17539	n=1448	n=18393	n=594
≤ 49	3,249 (19.5%)	239 (10.3%)	3,417 (19.5%)	71 (4.9%)	3,472 (18.9%)	16 (2.7%)
50-59	3,636 (21.8%)	297 (12.8%)	3,774 (21.5%)	159 (11%)	3,905 (21.2%)	28 (4.7%)
60-69	3,779 (22.7%)	428 (18.4%)	3,943 (22.5%)	264 (18.2%)	4,118 (22.4%)	89 (15%)
≥ 70	6,000 (36%)	1,359 (58.5%)	6,405 (36.5%)	954 (65.9%)	6,898 (37.5%)	461 (77.6%)
Sex						
Male	8346 (50.1%)	1244 (53.6%)	8796 (50.2%)	794 (54.8%)	9259 (50.3%)	331 (55.7%)
Female	8318 (49.9%)	1079 (46.4%)	8743 (49.8%)	654 (45.2%)	9134 (49.7%)	263 (44.3%)
Public financial assistance						
Non-recipients	14355 (86.1%)	1667 (71.8%)	15010 (85.6%)	1012 (69.9%)	15652 (85.1%)	370 (62.3%)
Recipients	2309 (13.9%)	656 (28.2%)	2529 (14.4%)	436 (30.1%)	2741 (14.9%)	224 (37.7%)
Service type						
In-patient	3779 (22.7%)	1652 (71.1%)	4234 (24.1%)	1197 (82.7%)	4934 (26.8%)	497 (83.7%)
Specialist outpatient	6493 (39%)	506 (21.8%)	6812 (38.8%)	187 (12.9%)	6932 (37.7%)	67 (11.3%)
Accident & Emergency	113 (0.7%)	10 (0.4%)	120 (0.7%)	3 (0.2%)	121 (0.7%)	2 (0.3%)
General outpatient	5589 (33.5%)	122 (5.3%)	5670 (32.3%)	41 (2.8%)	5689 (30.9%)	22 (3.7%)
Others (e.g. day hospital, community	690 (4.1%)	33 (1.4%)	703 (4%)	20 (1.4%)	717 (3.9%)	6 (1%)

program)						
ACE Inhibitor						
Perindopril	7225 (43.4%)	987 (42.5%)	7541 (43%)	671 (46.3%)	7967 (43.3%)	245 (41.2%)
Lisinopril	9439 (56.6%)	1336 (57.5%)	9998 (57%)	777 (53.7%)	10426 (56.7%)	349 (58.8%)
Drug adherence (PDC at 6 months)						
<0.80	11229 (67.4%)	1238 (53.3%)	11702 (66.7%)	765 (52.8%)	12151 (66.1%)	316 (53.2%)
≥ 0.80	5435 (32.6%)	1085 (46.7%)	5837 (33.3%)	683 (47.2%)	6242 (33.9%)	278 (46.8%)

PDC: Proportion of Days Covered as a measure of medication adherence

Table 3 Incidence of hospital admission at 12 months and 24 months according antihypertensive agents and medication adherence

	All-cause		Cardiovascular disease		Respiratory disease	
	Not Admitted	Admitted	Not Admitted	Admitted	Not Admitted	Admitted
12 months						
Medication	15764	3223	17054	1933	18106	881
Perindopril	6870 (43.6%)	1342 (41.6%)	7345 (43.1%)	867 (44.9%)	7864 (43.4%)	348 (39.5%)
Lisinopril	8894 (56.4%)	1881 (58.4%)	9709 (56.9%)	1066 (55.1%)	10242 (56.6%)	533 (60.5%)
Drug adherence (PDC) at 12 months						
<0.80	8094 (51.3%)	1620 (50.3%)	8741 (51.3%)	973 (50.3%)	9241 (51%)	473 (53.7%)
≥ 0.80	7670 (48.7%)	1603 (49.7%)	8313 (48.7%)	960 (49.7%)	8865 (49%)	408 (46.3%)
24 months						
Medication	14488	4499	16358	2629	17730	1257
Perindopril	6384 (44.1%)	1828 (40.6%)	7064 (43.2%)	1148 (43.7%)	7697 (43.4%)	515 (41%)
Lisinopril	8104 (55.9%)	2671 (59.4%)	9294 (56.8%)	1481 (56.3%)	10033 (56.6%)	742 (59%)
Drug adherence (PDC) at 24 months						
<0.80	9352 (64.5%)	2974 (66.1%)	10567 (64.6%)	1759 (66.9%)	11443 (64.5%)	883 (70.2%)
≥ 0.80	5136 (35.5%)	1525 (33.9%)	5791 (35.4%)	870 (33.1%)	6287 (35.5%)	374 (29.8%)

PDC: Proportion Days Covered as a measure of medication adherence

Table 4 Hospital admissions due to any cause, cardiovascular disease and respiratory disease at 6 months, 12 months and 24 months after the index prescription date with propensity score matching

	Cardiovascular disease				Respiratory disease				All cause			
	Crude HR (95% C.I.)	**P**	**Adjusted HR (95% C.I.)**	**P**	**Crude HR (95% C.I.)**	**P**	**Adjusted HR (95% C.I.)**	**P**	**Crude HR (95% C.I.)**	**P**	**Adjusted HR (95% C.I.)**	**P**
12-months												
Perindopril	1.000 (referent)		1.000 (referent)		1.000 (referent)		1.000 (referent)		1.000 (referent)		1.000 (referent)	
Lisinopril	0.926 (0.847, 1.013)	0.092	0.925 (0.845, 1.013)	0.091	1.169 (1.021, 1.338)	0.024	**1.245 (1.084, 1.429)**	**0.002**	1.064 (0.992, 1.141)	0.083	1.058 (0.986, 1.135)	0.120
24-months												
Perindopril	1.000 (referent)		1.000 (referent)		1.000 (referent)		1.000 (referent)		1.000 (referent)		1.000 (referent)	
Lisinopril	0.973 (0.901, 1.051)	0.493	0.977 (0.904, 1.056)	0.56	1.101 (0.984, 1.232)	0.092	**1.166 (1.040, 1.307)**	**0.009**	1.118 (1.054, 1.187)	<0.001	**1.116 (1.051, 1.185)**	**<0.001**

Crude HR, Crude Hazard Ratios; Adjusted HR, Adjusted Hazard Ratios

* The propensity scores were matched for age, sex, public financial assistance, service type, initial dosage, and Proportion Days Covered (PDC).