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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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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 were 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% CI 1.08 to 1.43, $p = 0.002$ at 12 months; AHR = 1.17, 95% CI 1.04 to 1.31, $p = 0.009$ at 24 months) and all causes (AHR = 1.12, 95% CI 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.

1. 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

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

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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 the 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; meanwhile, the major international guidelines [3–5] do not offer explicit recommendations on any specific ACEI agent over another within the same drug group. 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.

2. Methods

2.1. 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.

2.2. 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.

2.3. Outcome 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 ($PDC \geq 0.80$) or low ($PDC < 0.80$) according to international standards [25–27].

2.4. 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