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Cardiovascular mortality in hypertensive patients newly prescribed perindopril vs. lisinopril: A 5-year cohort study of 15,622 Chinese subjects

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ABSTRACT

Background: Perindopril and lisinopril are two common ACE inhibitors prescribed for management of hypertension. Few studies have evaluated their comparative effectiveness to reduce mortality. This study compared the all-cause and cardiovascular related mortality among patients newly prescribed ACE inhibitors.
Methods: All adult patients newly prescribed perindopril or lisinopril from 2001 to 2005 in all public clinics or hospitals in Hong Kong were retrospectively evaluated, and followed up until 2010. Patients prescribed the ACE inhibitors for less than a month were excluded. The all-cause mortality and cardiovascular-specific (i.e. coronary heart disease, heart failure and stroke) mortality were compared. Cox proportional hazard regression model was used to assess the mortality, controlling for age, sex, socioeconomic status, patient types, the presence of comorbidities, and medication adherence as measured by the proportion of days covered. An additional model using propensity scores was performed to minimize indication bias.
Results: A total of 15,622 patients were included in this study, in which 6910 were perindopril users and 8712 lisinopril users. The all-cause mortality (22.2% vs. 20.0%, $p < 0.005$) and cardiovascular mortality (6.5% vs. 5.6%, $p < 0.005$) were higher among lisinopril users than perindopril users. From regression analyses, lisinopril users were 1.09-fold (95% C.I. 1.01–1.16) and 1.18-fold (95% C.I. 1.02–1.35) more likely to die from any-cause and cardiovascular diseases, respectively. Age-stratified analysis showed that this significant difference was observed only among patients aged >70 years. The additional models controlled for propensity scores yielded comparable results.
Conclusions: The long-term all-cause and cardiovascular related mortality rates of lisinopril users was significantly different from those of perindopril users. These findings showed that intra-class variation on mortality exists among ACE inhibitors among those aged 70 years or older. Future studies should consider a longer, large-scale randomized controlled trial to compare the effectiveness between different medications in the ACEI class, especially among the elderly.

1. Introduction

Hypertension is a chronic disease requiring long-term care, and is one of the common health problems worldwide [1,2]. Around 30% of the adult population around the globe suffer from hypertension [3,4]. The number of hypertensive patients is rising drastically due to aging population. The increasing patient volume can cause financial burden to a healthcare system. In Hong Kong, around 10% of the adult population is reported to have hypertension, but approximately half of the hypertensive population does not realize that they suffer from the disease [5]. Hypertension was well documented to be associated with an increased risk of cardiovascular diseases. Previous literature showed that around 54% of stroke and 47% of ischemic heart disease are attributable to hypertension [6]. Hypertension can also exacerbate the vascular complications of diabetes, including renal disease and retinopathy [7].

Lifestyle modifications are recommended to hypertensive patients in the early stage, but medication is necessary for those who have

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uncontrolled blood pressure despite lifestyle changes. The effectiveness of antihypertensive therapies to protect against stroke and heart attack was well recognized in a meta-analysis [8]. According to the US National Health and Nutrition Examination Survey, the number of adult patients on hypertensive medication increased from around 60% in 2001 to 80% in 2010 [9]. However, the proportion of hypertensive patients with optimal blood pressure control was found to be low in many countries, partly due to poor medication adherence [10–12]. Treatment effectiveness, absence of adverse effects, and patient satisfaction are important to achieve better drug adherence.

The choice of antihypertensive treatment, particularly for the first-line agent, should be made with caution as it could significantly affect clinical outcomes [13]. Existing guidelines, including those of the National Institute for Health and Clinical Excellence (NICE), the updated Eighth Joint National Committee (JNC 8th), and the reappraisal of the European hypertension guidelines in 2008 all recommended angiotensin-converting-enzyme (ACE) inhibitors as one of the preferred first-line agent for management of arterial hypertension [14–17]. Nevertheless, there have not been explicit recommendations on which ACE inhibitor is more preferred.

The effectiveness of ACE inhibitors was reported in a few studies [18–20], and the intra-class pharmacokinetic differences were also reported among the ACE inhibitors [21]. The comparative benefit of ACE inhibitors on mortality was addressed in Western populations [22,23], yet none was conducted among Chinese patients. It is well recognized that the pharmacological actions of antihypertensive agents differ according to ethnicity. In Hong Kong, ACE inhibitors were found to be one of the most commonly prescribed first-line hypertensive treatments in the entire population, and perindopril and lisinopril were among the most popular prescriptions [24]. The objective of this study is to compare the effectiveness of the two ACE inhibitors, perindopril and lisinopril, on prevention of all-cause mortality and cardiovascular deaths in a large Chinese population.

2. Methods

2.1. Data source

The present study covered the entire population of Hong Kong, which was more than seven million as of 2012. All patient records for this study were extracted from electronic clinical databases, known as the Clinical Management System. These databases captured patients' demographic information, prescription details, and clinical diagnoses in the form of the International Classification of Diseases (ICD-9 and ICD-10) or the International Classification of Primary Care (ICPC-2). It served as the sole portal of clinical data entry in all public inpatient and outpatient settings across different regions in Hong Kong, including Kowloon, Hong Kong Island, and the New Territories. This networked system allowed physicians to review patient history at each patient visit in different locations. All drug prescriptions must be entered into the system by the attending physicians, and were cross-checked by dispensers or pharmacists as a standard procedure. Any changes of prescriptions after the initial consultation were also recorded. This database had also been described in previous publications [24–33]. The database was previously validated and demonstrated a high level of completeness on the socio-demographic information (100%) and prescription profiles (99.8%) [27]. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was not necessary as all subjects were anonymized. The ethics clearance of the study was obtained from 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

All patients who were newly prescribed perindopril or lisinopril as their antihypertensive agents at any public inpatient and outpatient settings between the calendar years 2001 and 2005 were included. The date of the first drug prescription record was defined as the index date. Patients who received any other antihypertensive medications before the index date, whose ACE inhibitor prescriptions lasted for less than a month, and who switched to another antihypertensive treatment after the index date were excluded in this study. Comorbidities including cardiovascular risk factors and medical conditions were extracted from the system, as indicated by the respective ICPC-2 or ICD-10 codes. All patients were followed up until death or the end of study period in 2010, whichever came earlier.

2.3. Outcome variables and covariates

All-cause mortality was the primary outcome and mortality due to cardiovascular diseases (CVD), including coronary heart disease, heart failure and stroke, was the secondary outcome of this study. The cause of death was defined according to the primary cause of illness by the physician-in-charge, and was registered in the death certificate. The ICD-10 was adopted to identify the causes of mortality in the system: I20.0 to I25.9 for coronary heart disease, I50.0 to I50.9 for heart failure, and I60.0 to I69.9 for stroke. The majority of deaths occurred in public hospitals in Hong Kong, which allows accurate case ascertainment. A number of previous studies have utilized deaths in a hospital as a proxy of patient mortality, especially for Chinese populations in which death usually occurs in hospitals [34,35].

The independent variables in this study were the subtype of ACE inhibitors, age, gender, socioeconomic status, patient types (inpatient, specialist outpatient, or general outpatient), the number of comorbidities, and proportion of days covered (PDC) by the ACE inhibitor. The socioeconomic status was classified by the recipients of public financial assistance, known as comprehensive social security-assistance (CSSA) in Hong Kong. The list of comorbidities was categorized into "diabetes or impaired glucose tolerance", "cardiovascular diseases", "respiratory diseases" and "renal diseases", according to the ICPC-2 and ICD-10 codes. The coding details were presented in a previous study [36]. Besides, the interval-based measure of PDC is an internationally accepted metric for assessing drug adherence in large database analysis [37–39]. It refers to the number of days with medication divided by the total number of days in the follow-up period. For patients who died during the follow-up period, the time period between the index date and the death date was used to estimate the PDC. Drug adherence was divided into three levels, namely: high (PDC $\geq$ 0.70), intermediate (PDC = 0.40–0.69) or low (PDC < 0.40), according to an internationally recognized classification system [40–42].

2.4. Statistical analysis

The mortality rate across different independent variables was compared. Difference in categorical variables was evaluated using Pearson's Chi-square test. The Kaplan–Meier method with the log-rank test was used to compare the difference in mortality rates between perindopril and lisinopril users. Cox proportional hazard regression model [43] was used to compare the mortality rates, controlling for age, sex, socioeconomic status, patient types, the number of comorbidities, and medication adherence as reflected by the PDC. Hazard ratios with 95% CIs were estimated. Models were independently run for all-cause mortality and mortality due to CVD.

A propensity score was developed to further minimize the influence of treatment indication bias due to different baseline characteristics of patients, and further adjusted the Cox proportional hazard models for mortality comparison. The scores were estimated

Table 1
Baseline characteristics among lisinopril and perindopril users.

	Lisinopril users (n = 8,712)	Perindopril users (n = 6,910)	Overall (n = 15,622)
Age			
<49	1713 (19.7%)	1238 (17.9%)	2951 (18.9%)
49–59	1808 (20.8%)	1433 (20.7%)	3241 (20.8%)
60–69	1838 (21.1%)	1487 (21.5%)	3325 (21.3%)
≥70	3353 (38.5%)	2752 (39.8%)	6105 (39.0%)
Sex			
Male	4367 (50.1%)	3542 (51.3%)	7909 (50.6%)
Female	4345 (49.9%)	3368 (48.7%)	7713 (49.4%)
Public financial assistance			
Non-recipients	7212 (82.8%)	5905 (85.5%)	13117 (84.0%)
Recipients	1500 (17.2%)	1005 (14.5%)	2505 (16.0%)
Patient type			
In-patient	2573 (29.5%)	2189 (31.7%)	4762 (30.5%)
Specialist outpatient	3493 (40.1%)	2441 (35.3%)	5934 (38.0%)
General outpatient	2222 (25.5%)	2055 (29.7%)	4277 (27.4%)
Others (e.g. A&E, day hospital, community/rehab program)	424 (4.9%)	225 (3.3%)	649 (4.1%)
Presence of co-morbidities			
0	2445 (28.1%)	2427 (35.1%)	4872 (31.2%)
1	4777 (54.8%)	3560 (51.5%)	8337 (53.4%)
2	1323 (15.2%)	829 (12.0%)	2152 (13.8%)
3	167 (1.9%)	94 (1.4%)	261 (1.67%)
Drug adherence			
<0.4 PDC	1988 (22.8%)	1589 (23.0%)	3577 (22.9%)
0.4–0.7 PDC	2713 (31.3%)	1812 (26.2%)	4525 (29.0%)
>0.7 PDC	4011 (46.0%)	3509 (50.8%)	7520 (48.1%)