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Risk of major cardiovascular events among incident dialysis patients: A Korean national population-based study

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ABSTRACT

Background: Dialysis patients are at high risk for cardiovascular diseases, but until now there have been no detailed analyses of the incidences among Asian patients initiating dialysis. The aims of this study were to determine the incidence rates of major adverse cardiac and cerebrovascular events (MACCE) and to compare them between incident HD patients and PD patients.
Methods: We included all patients who had started dialysis between January 1, 2005 and December 31, 2008 in Korea, and analyzed 30,279 eligible patients [22,892 hemodialysis (HD) patients and 7387 peritoneal dialysis (PD) patients] by intention-to-treat. Median follow-up was 21.5 months.
Results: The crude incidence rates were as follows: MACCE, 182 per 1000 patient-years (PY); major adverse cardiac events (MACE), 138/1000 PY; all-cause mortality, 116/1000 PY; non-fatal acute myocardial infarction (AMI), 18/1000 PY; target vessel revascularization (TVR), 17/1000 PY; and non-fatal stroke, 60/1000 PY. When comparing all baseline covariate-adjusted relative risks between HD and PD patients, HD is overall superior to PD in terms of MACCE. Further examined by each endpoint, all-cause mortality, non-fatal AMI, and TVR occurred significantly more frequently in patients on PD than in those on HD, whereas non-fatal hemorrhagic stroke occurred significantly more frequently in patients on HD than in those on PD.
Conclusions: The incidence of MACCE may be different from Western dialysis patients. HD is overall superior to PD in terms of MACCE as an initial dialysis modality. Underlying mechanisms differentially affecting cardiovascular outcomes by dialysis modality remain to be further elucidated.

1. Introduction

Cardiovascular disease (CVD) is the most common cause of morbidity, disability, and mortality in end-stage renal disease (ESRD) patients initiating dialysis therapy, accounting for 33% of hospitalizations, 37% of rehospitalizations, and 41% of deaths [1–3]. The risk of developing cardiovascular events among dialysis patients is estimated to be roughly 10 to 20 times higher than that of the general population [4] in parallel with their high mortality risk [5]. This may be due not only to high prevalence of traditional risk factors such as diabetes, hypertension, and dyslipidemia that begin to progress from the early stage of chronic kidney disease, but also to non-traditional uremia-related or dialysis-related factors, including hemodynamic overload, increased oxidative stress, dialysate impurities, and inadequate dialysis [1,6]. To date, a substantial number of articles have focused mainly on prevalence, risk factors, and mortality outcomes of CVD in dialysis patients [7–9]. However, no study has produced detailed descriptive or comparative analyses of incidence rates of major cardiovascular events between patients receiving either hemodialysis (HD) or peritoneal dialysis (PD), particularly in a large-scale, Asian population-based national cohort.

The main purposes of this study were (1) to determine the incidence rates of major cardiovascular events, both as widely-accepted comprehensive composite endpoints, in terms of "major adverse cardiac and

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cerebrovascular events" ("MACCE"), including major adverse cardiac events (MACE), composed of all-cause mortality, non-fatal acute myocardial infarction (AMI), and target vessel revascularization (TVR) [including percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG)], and non-fatal stroke [10,11], and as separate cardiovascular endpoints and, (2) to compare the incidence rates of major cardiovascular events between incident HD patients and PD patients as a whole or subgroups based on age, comorbidities, and dialysis vintage using the Korean Health Insurance Review and Assessment Service (HIRA) database, a nationwide, population-based dataset.

2. Methods

2.1. Data source and study population

We used the Korean HIRA database. The organization of this database and its use for analysis has been described in Supplementary methods, and more details were provided elsewhere [12]. The institutional review board at the HIRA approved the survey of the study population.

The comorbidities of the participants were identified by reviewing their medical history during the year before initiation of dialysis therapy. We initially screened all incident dialysis patients who had started dialysis therapy between January 1, 2005 and December 31, 2008 in Korea. Among them, we first identified and only included patients who started dialysis during the study period and remained on the dialysis therapy for at least three months, without an occurrence of MACCE. The reasons why we excluded the patients who experienced MACCE within less than 90 days from the date of dialysis initiation were as follows: 1) most of the acutely ill patients who need urgent initiation of dialysis start dialysis preferentially with HD. Therefore, if analyzed based on the true initial dialysis modality, there is a high probability that the results could be biased against HD. 2) MACCE occurring in the first 90 days is considered to be affected more by the pre-existing comorbidities than by the dialysis modality per se. 3) Even the patients, who choose PD as the final dialysis modality, are usually treated initially by temporary HD. Therefore, we only included the patients who had MACCE-free survival within the first 90 days after initiation of dialysis treatment and remained on 'chronic dialysis'.

Next, we excluded patients who were younger than 18 years of age. Finally, our study included 30,279 eligible patients.

2.2. Outcome definitions

The primary clinical endpoint of interest for our study was the development of a MACCE as a composite endpoint, which includes MACE and non-fatal stroke; MACE includes all-cause mortality, non-fatal AMI, and TVR that includes PCI and CABG. Non-fatal stroke includes both non-fatal ischemic stroke and non-fatal hemorrhagic stroke. These conditions were determined using insurance claims recorded in the HIRA database. For assessing event-free survival, we considered the dialysis modality at day 90 to be the initial dialysis modality and used day 90 as the starting point (day 0). That is, the patients analyzed in this study were left-censored for the first event-free 90 days after dialysis initiation, and they were right-censored on December 31, 2009.

2.3. Statistical analysis

In all analyses, an intention-to-treat principle was adopted. The crude incidence rates were calculated by dividing the number of patients with a given event by the person-years of follow-up, which were expressed as cases per 1000 patient-years; confidence intervals were estimated based on a Poisson distribution.

In comparison analyses between HD and PD, baseline characteristics were compared using an independent *t*-test for continuous variables and Pearson's Chi-square test for categorical variables. In estimation of the adjusted relative risks of composite endpoints and each separate endpoint, multivariate Poisson regression analyses, which were adjusted for all the baseline covariates listed in Table 1, were used. If the Poisson assumption that variance is equal to the mean was not met, we instead used a negative binomial model. To further compare the MACCE-free survival between HD and PD patients, we calculated the propensity scores based on a logistic regression to predict the probability of choosing a specific dialysis modality using a list of baseline covariates (Table 1); thereby, we next conducted weighted Cox proportional hazard models to evaluate the hazard ratios for the events between the two modalities by using inverse probability of treatment weighting (IPTW) [13]. Weights were calculated as the inverse of the propensity score for PD patients and the inverse of (1 − propensity score) for HD patients.

There was no missing data on baseline characteristics of participants and their outcomes. All statistical tests were evaluated using a two-tailed 95% confidence interval, and $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using the statistical package SAS 9.1 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Baseline characteristics of the subjects

A total of 30,279 eligible patients who started dialysis therapy between January 1, 2005 and December 31, 2008 were analyzed. At the initiation of dialysis treatment, the mean patient age was 56.3 ± 14.0 years; 41.7% of the patients were females, and 48.9% of the patients had diabetes. The numbers of incident HD and PD patients were 22,892 (75.6%) and 7387 (24.4%), respectively. A detailed description and comparison of the baseline characteristics between incident HD and PD patients are shown in Table 1.

During the follow-up period, 5.1% (1540/30,279) of participants have switched their dialysis modality after a median of 8.5 months of treatment on initial modality. Stratified by modality, 1.7% (386/22,892) of the patients who started dialysis on HD were transferred to PD after a median of 2.3 months; 15.6% (1154/7387) of the patients who started dialysis on PD were transferred to HD after a median of 11.6 months.

3.2. Crude incidence rates of MACCE

During the median follow-up of 21.5 months (range, 0.0–57.0 months), 11,053 (36.5%) of all incident dialysis patients had experienced MACCE. When stratified by dialysis modality, 8404 (36.7%) of HD patients and 2649 (35.9%) of PD patients had experienced MACCE, respectively. The one-, two-, and three-year cumulative incidences of MACCE were 21.1%, 32.3%, and 40.5%,

Table 1
Baseline characteristics of the participants.

Variables	All incident dialysis patients (N = 30,279)	Incident HD patients (N = 22,892)	Incident PD patients (N = 7387)	*P*-values (HD vs. PD patients)
Age (years)	56.3 ± 14.0	57.2 ± 14.0	53.7 ± 13.7	<0.001
Females (vs. males)	12,626 (41.7)	9359 (40.9)	3267 (44.2)	<0.001
National Health Insurance (vs. Medical Aid)	26,204 (86.5)	19,736 (86.2)	6468 (87.6)	0.003
Diabetes mellitus	14,812 (48.9)	11,154 (48.7)	3658 (49.5)	0.235
Comorbidities other than DM				
Any cardiovascular disease*	8279 (27.3)	6282 (27.4)	1997 (27.0)	0.494
Myocardial infarction	864 (2.9)	594 (2.6)	270 (3.7)	<0.001
Congestive heart failure	4315 (14.3)	3165 (13.8)	1150 (15.6)	<0.001
Peripheral artery disease	1726 (5.7)	1344 (5.9)	382 (5.2)	0.024
Cerebrovascular accident	3089 (10.2)	2473 (10.8)	616 (8.3)	<0.001
Chronic pulmonary disease	4846 (16.0)	3705 (16.2)	1141 (15.4)	0.132
Connective tissue disease	843 (2.8)	640 (2.8)	203 (2.7)	0.829
Peptic ulcer disease	4396 (14.5)	3401 (14.9)	995 (13.5)	0.003
Liver disease	3326 (11.0)	2582 (11.3)	744 (10.1)	0.004
Cancer	1869 (6.2)	1565 (6.8)	304 (4.1)	<0.001

Age is expressed as mean ± SD, and all other data are expressed as number (%).

* Any cardiovascular disease comprises myocardial infarction, congestive heart failure, peripheral artery disease, and cerebrovascular accident.

HD, hemodialysis; PD, peritoneal dialysis; DM, diabetes mellitus.