Original Article

High Initial Cardiovascular Events in ESRD Patients on Maintenance Dialysis: A Case-Crossover Study of Taiwan's National Health Insurance Database

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Objectives: Dialysis is the most common final resort of treatment for patients with end-stage renal disease (ESRD). However, the incidence of acute cardiovascular events among patients with ESRD on maintenance dialysis has not been fully addressed.

Methods: We conducted a case-crossover study using the Longitudinal Health Insurance Database, with the control period defined as 1-15 days before first dialysis, and the case periods defined as 1-15, 16-30, 31-45, 46-60, 61-75, 76-90 days after the first dialysis. Conditional logistic regression models were used to assess the effect of dialysis on the incidence of cardio-cerebrovascular diseases, including cerebrovascular diseases, ischemic heart disease, arrhythmias, atrial fibrillation, congestive heart failure, and hypertension.

Results: A total of 47,436 participants were included in this study. Dialysis decreased the incidence of arrhythmias, atrial fibrillation, congestive heart failure, and hypertension in the case period totaling 90 observation days after the patients' first dialysis. Dialysis increased the incidence of cerebrovascular diseases and ischemic heart diseases 15 days after the patients' first dialysis, OR = 2.40 (95% CI, 1.42-4.04) and OR = 2.04 (95% CI, 1.25-3.33), respectively.

Conclusions: This study indicates high incidence of initial cardiovascular events in ESRD patients on maintenance dialysis, although these events were significantly reduced after maintenance dialysis. Dialysis could also dramatically reduce the incidence of arrhythmias, atrial fibrillation, congestive heart failure, and hypertension after initiation of dialysis therapy with an observation period of 90 days.

Key words: cerebrovascular disease, dialysis, end-stage renal disease, ischemic heart disease

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Introduction

End-stage renal disease (ESRD) is associated with an increased incidence of cardiovascular disease, especially coronary artery disease, heart failure, peripheral artery diseases, and arrhythmia.[1-5] Dialysis therapy is the most common final life-sustaining treatment for patients with ESRD. In addition, from the data of the United States Renal Data System: USRDS 2007 Annual Data Report, cardiac arrest and cardiac arrhythmias account for about 25% of the major causes of death of patients with dialysis. However, to the best of our knowledge, the incidence of acute cardiocerebrovascular events among patients with ESRD on maintenance dialysis remains poorly addressed.

Taiwan is currently facing a severe problem: not only does Taiwan have the highest incidence and prevalence of ESRD out of some 30 countries reported in the United States Renal Data System (USRDS), but the incidence is also two- to three-fold higher than that of most European countries.[6,7] The Taiwan National Health Insurance (NHI) program is a comprehensive and universal health insurance program in which up to 99% of Taiwan's inhabitants are enrolled. In this study, using data retrieved from the Longitudinal Health Insurance Database (LHID) from January 1, 1997 to December 31, 2007, we performed a case-crossover study to investigate the incidence of initial cardiovascular events in ESRD patients on maintenance dialysis. This timeframe should make it possible to elucidate the transient effect of dialysis on the risk of acute events.[8,9] The use of case-crossover design may provide more reliable data because the same subjects, who were investigated at adjacent time points, served as their own controls, thereby minimizing the confounding effects of both known and unknown variables among the study patients.

Materials and Methods

National health insurance in Taiwan

In 1995, the National Health Insurance (NHI) scheme, a government-run insurer with a single-payer insurance system, was established in Taiwan with the goal of ensuring health coverage for the entire population and avoiding social problems caused by poverty and disease. The characteristics of NHI include payroll-related premiums shared between employers, employees and the government, fee-for-service under the global budget and the requirement of co-payment for medication, ambulatory and inpatient care.

As the enrollment in the NHI was mandatory, by December 2008, there were 22.918 million individuals enrolled in the program nationwide, indicating a coverage rate of 99.5%. This marked a substantial increase in coverage when compared with enrollment coverage of 92% at the NHI launch in 1995. The Bureau of the NHI (BNHI) contracts with almost 93.3% of medical institutions nationwide, thereby providing the public with comprehensive medical benefit coverage, such as hospitalization, day care for the mentally ill and social rehabilitation. The registration of all seriously disabled database (SDD) cases, such as chronic renal disease and cancer is required by the Bureau of the NHI before certification for SDD can be granted. By 2008, there were 790,621 individuals with SDD certificates, which constituted 3.4% of the total population.

Data sources

This study used a sampling cohort dataset obtained from National Health Insurance Research Database (NHIRD), which includes details of outpatient, ambulatory and hospital inpatient care, as well as dental services. The National Health Research Institutes use a systematic sampling approach to randomly select a representative database of 1,000,000

patients from the year 2000 registry of all NHI enrollees (NHI 2000).[10] We retrospectively identified and included all maintenance dialysis patients who had survived for more than 3 months from 2002 through 2007 in Taiwan. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital. Because the patient identifiers in this national dataset were scrambled to the public and only meant for research purposes in Taiwan, the study was exempted from the requirement for written or verbal consents from patients. According to the National Health Research Institutes, there were no significant differences in age, sex, or health care costs between the sampled group and all enrollees in NHI 2000.[11] This dataset therefore gives researchers access to comprehensive demographic data, including gender, date of birth, and income level as well as health care data, including date of admission or discharge, clinical diagnoses (up to five coexisting diagnoses listed on one claim record), medical procedures (up to five diagnostic or therapeutic procedures), expenditures, detailed drug prescriptions, and in-hospital deaths. The NHI lists diagnoses according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).[12]

Study subjects and definition

This case-crossover study recruited patients aged 30-95 years in 2002. Because anyone insured in need of maintenance dialysis should be issued a SDD certificate for dialysis to waive the deduction, all patients in the NHI dataset were screened, and the study cohort included those who met all the following criteria: 1) having SSD certificate for chronic dialysis (Code: 585, XX); and 2) having been prescribed with either hemodialysis (code: 58001C, 58019C, 58020C, 58021C, 58022C, 58023C, 58024C, 58025C, 58026C, 58027C, 58029) or peritoneal dialysis (PD) (total 347 PD solution codes) in the first 4 consecutive calendar months after being issued the SDD certificate for chronic dialysis. All patients who did not receive dialysis therapy regularly or received dialysis therapy less than 2 times per week were excluded in our study. The study index date was the patient's first maintenance dialysis date. The observation period in this study was 15 days before to 90 days after the index dialysis date. Cardiovascular events were defined as those that occurred prior to dialysis commencement with at least one hospitalization or 2 ambulatory visits within one year, including cerebrovascular diseases (ICD-9-CM codes 434.91), ischemic heart disease (ICD-9-CM codes 410-414), arrhythmias (ICD-9-CM codes 427.9), atrial fibrillation (ICD-9-CM codes 427.31), congestive heart failure (ICD-9-CM codes 428.0), and hypertension (ICD-9-CM codes 401–405).

Case-crossover design

We conducted a case-crossover study with the study index dialysis date being the patient's first day of maintenance dialysis. The control period was defined as 1-15 days before the index dialysis date, and the case periods were defined as 1-15, 16-30, 31-45, 46-60, 61-75, and 76-90 days after the index dialysis date. The observation period in this study was from 15 days before the index dialysis date to 90 days after the index dialysis date. In this case-crossover design, we compared the patient's medical claims during the control period to those within the case periods. Because we used the same patient for comparison, we were able to avoid between-subject risk-factor differences, both measured and unmeasured.[13]

Statistical analysis

A descriptive analysis was carried out to describe the socio-demographic and clinical characteristics of the study subjects. Descriptive statistics such as means, standard deviations, and proportions were used where appropriate. Conditional logistic regression models

were used to assess the effect of dialysis on the incidence of cardiovascular diseases, including cerebrovascular diseases, ischemic heart disease, arrhythmias, atrial fibrillation, congestive heart failure, and hypertension. All statistical tests were carried out by using SAS 9.2. A two-sided p value < 0.05 was considered significant.

Results

In the Taiwan National Health dataset from 2002 through 2007, we identified 47,436 patients having survived for more than 3 months after their first dialysis. The clinical characteristics of the subjects are shown in Table 1. Their mean age was 61.2 ± 14.2 years. The gender ratio was close to 1:1 (Male: 49.2%). Hypertension, diabetes, and cerebrovascular diseases were noted in 75%, 52%, and 13% of patients, respectively, while 33% were diagnosed with cardiac disorders, and 20% with gout. Forty-one percent of the patients did not have fixed salary, and only 32% of the patients had more than twenty thousand NTD income per month.

Table 2 shows the results of the association between dialysis and cardiovascular diseases. Although there were 20 patients who suffered from cerebrovascular diseases in the control period, 48 patients with newly-diagnosed cerebrovascular diseases were found in the first case period (1-15 days after the patient's first dialysis). Dialysis was associated with the incidence of cerebrovascular diseases within 15 days of the patients' first dialysis, OR = 2.40 (95% CI, 1.42-4.04). Even though this association was still significant in the fourth case period (46-60 days after patient's first dialysis), OR = 1.80 (95% CI, 1.04-3.11), the amplitude was highest during the first case period. Furthermore, the association between dialysis and ischemic heart disease was similar to that for cerebrovascular disease with a high odd ratio (OR = 2.04, 95% CI, 1.25-3.33) when comparing the control period with the first case period (i.e., the first 1-15 days after the first dialysis).

Table 1. Demographic and clinical characteristics of the subjects (N = 47,436)

Variable	Mean ± SD or n (%)
Age (years)	61.26 ± 14.20
Gender (male)	23352 (49.23)
Residence (urban)	34310 (72.33)
Incomes (New Taiwan dollar/Month)	
without fixed salary	19848 (41.84)
< 20000	11958 (25.21)
≥ 20000	15630 (32.95)
Comorbidities	
Diabetes mellitus	24688 (52.04)
Hypertension	35857 (75.59)
Cardiovascular diseases	15668 (33.03)
Cerebrovascular diseases	6336 (13.36)
Gout	9549 (20.13)

The beneficial effect of dialysis was also found in the first 1-15 days after the first dialysis for the other four cardiovascular diseases. However, the effect reached an early plateau for arrhythmias and atrial fibrillation. Interestingly, the beneficial effect of dialysis was found to increase steadily during the whole study period for congestive heart failure and hypertension (Table 2 & Fig. 1).

Discussion

Cardiovascular disease is one of the major comorbidities among ESRD patients and accounts for more than half of all the deaths among this population.[14-17] Although dialysis is the most common life-sustaining treatment for patients with ESRD, accelerated cardiovascular disease, cardiac arrhythmias, and cerebrovascular disease are frequently noted in patients under dialysis.[16,18] In addition, the mortality among dialysis patients is much higher in relatively young patients than that in their age-and sex-matched counterparts without CKD.[19,20]

Table 2. Association of dialysis (n = 47436) with the incidence of cardiovascular diseases in Taiwan, 2002-2007

Diseases	Odds-ratio (95% CI[a])	*p* value	Control[b]		Case[c]		
			n	%	n	%	Case period
Cerebrovascular disease	2.40 (1.42-4.04)	0.001	20	0.04	48	0.10	1-15
	1.80 (1.04-3.11)	0.035			36	0.08	16-30
	1.44 (0.82-2.55)	0.206			29	0.06	31-45
	1.80 (1.04-3.11)	0.035			36	0.08	46-60
	1.35 (0.76-2.40)	0.313			27	0.06	61-75
	1.60 (0.92-2.80)	0.099			32	0.07	76-90
Ischemic heart disease	2.04 (1.25-3.33)	0.004	24	0.05	49	0.10	1-15
	1.17 (0.68-2.01)	0.580			28	0.06	16-30
	0.71 (0.38-1.32)	0.281			17	0.04	31-45
	0.63 (0.33-1.19)	0.153			15	0.03	46-60
	0.38 (0.17-0.81)	0.012			9	0.02	61-75
	0.63 (0.33-1.19)	0.153			15	0.03	76-90
Arrhythmias	0.50 (0.32-0.79)	0.003	56	0.12	28	0.06	1-15
	0.63 (0.41-0.95)	0.029			35	0.07	16-30
	0.61 (0.40-0.93)	0.022			34	0.07	31-45
	0.61 (0.40-0.93)	0.022			34	0.07	46-60
	0.46 (0.29-0.74)	0.001			26	0.05	61-75
	0.57 (0.37-0.88)	0.012			32	0.07	76-90
Atrial fibrillation	0.56 (0.32-1.00)	0.051	32	0.07	18	0.04	1-15
	0.47 (0.25-0.87)	0.015			15	0.03	16-30
	0.31 (0.15-0.64)	0.001			10	0.02	31-45
	0.31 (0.15-0.64)	0.001			10	0.02	46-60
	0.38 (0.19-0.73)	0.004			12	0.03	61-75
	0.31 (0.15-0.64)	0.001			10	0.02	76-90
Congestive heart failure	0.62 (0.50-0.76)	< 0.001	243	0.51	150	0.32	1-15
	0.29 (0.22-0.38)	< 0.001			71	0.15	16-30
	0.37 (0.29-0.47)	< 0.001			90	0.19	31-45
	0.28 (0.21-0.36)	< 0.001			67	0.14	46-60
	0.24 (0.18-0.32)	< 0.001			59	0.12	61-75
	0.21 (0.16-0.28)	< 0.001			51	0.11	76-90
Hypertension	0.51 (0.45-0.58)	< 0.001	688	1.45	351	0.74	1-15
	0.30 (0.25-0.35)	< 0.001			205	0.43	16-30
	0.20 (0.16-0.24)	< 0.001			135	0.28	31-45
	0.20 (0.17-0.24)	< 0.001			138	0.29	46-60
	0.18 (0.15-0.22)	< 0.001			125	0.26	61-75
	0.12 (0.09-0.15)	< 0.001			81	0.17	76-90

[a]Confidence interval; [b]Control period: 1-15 days before to the patients' first dialysis; [c]Case periods: 1-15, 16-30, 31-45, 46-60, 61-75, 76-90 days after to the patients' first dialysis.

On the other hand, the effect of dialysis on the incidence of cardiovascular disease among ESRD patients remains uncertain. Therefore, this study aimed at investigating the influence of dialysis on the incidence of cardiovascular disease in patients with ESRD.

It has been suspected that subclinical myocardial ischemia could result from dialysis due to intradialytic hypotension.[21,22] In addition, transient dialysis-induced ST segment depression and troponin elevation have been previously reported.[21,23,24] Singh et

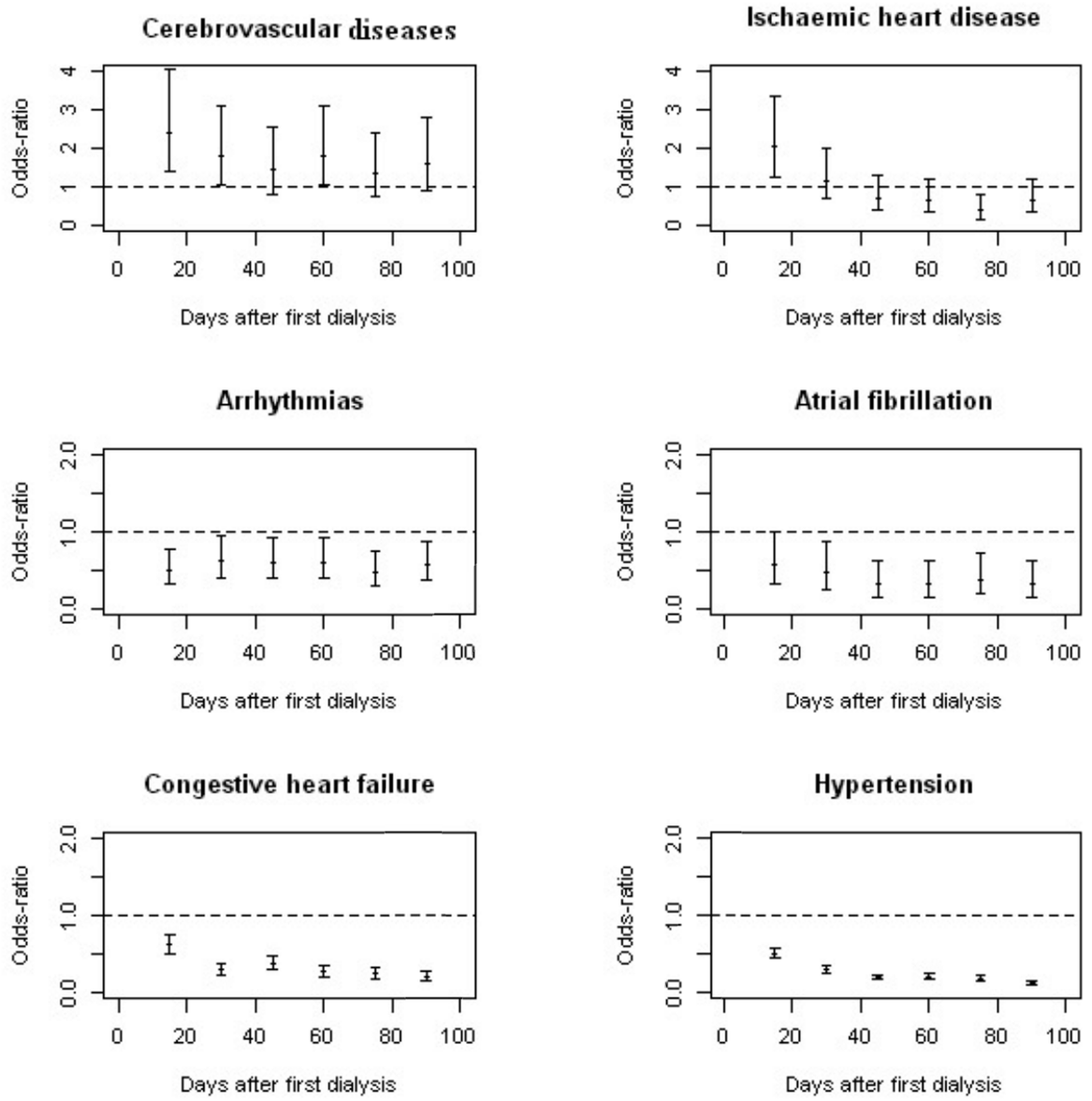

Fig. 1 Effect of dialysis (n = 47,436) on the incidence of cardiovascular diseases in Taiwan, 2002-2007. Control period was defined as 1-15 days before the patients' first dialysis, and the case periods were defined as 1-15, 16-30, 31-45, 46-60, 61-75, 76-90 days after the patients' first dialysis.

al. further used sestamibi single-proton emission computer tomography to demonstrate perfusion defects during dialysis.[25] However, whether dialysis can induce clinical myocardial ischemia or cerebral vascular ischemia after the initiation of dialysis therapy requires elucidation. Of the 47,436 ESRD patients in our study, within 15 days after initiation of the first dialysis, 48 patients suffered from newly diagnosed ischemic cerebral diseases and 49 patients had newly diagnosed ischemic heart diseases. The odd ratio of dialysis being associated with the incidence of cerebrovascular diseases and ischemic heart diseases 15 days post patients' first dialysis was significantly higher than that 15 days before the initiation of dialysis (Table 2 and Fig. 1). Clinically, although anuria, severe acidosis, hyperkalemia or other critical uremic conditions are well-documented indications for dialysis, the

results of the present study suggest that dialysis-related increase in cardio-cerebrovascular risk has to be taken into account and to be explained to the patient before initiation of dialysis.

The importance of cardiac arrhythmias in CKD is currently well established.[26] Electrocardiographic abnormalities, such as QT prolongation, are frequently found in ESRD patients and have been proven to be associated with elevated mortality and sudden cardiac death in this patient population.[27,28] In the past decade, several studies have also shown associations of atrial arrhythmias, especially atrial fibrillation, with chronic renal disease, especially in ESRD patients.[18,29-31] Different explanations and risk factors of the cardiac arrhythmias in uremia patients have been suggested (e.g., presence of cardiac valvular calcification, conduction defect, previous ischemic cerebral diseases, failing heart, hypertension, hypocalcemia, autonomic nerve dysfunction, rapid changes in electrolyte plasma concentrations during dialysis and cardiac hypertrophy[29,32-36]), but the exact mechanism remains unknown.

From these studies, the prevalence and threat of cardiac arrhythmias has been notably higher in ESRD and dialysis patients. However, the effect of dialysis on the prevalence of cardiac arrhythmias in this patient population is unknown. In our study, the beneficial effect of dialysis on arrhythmias and atrial fibrillation occurred in the immediate 1-15 days after first dialysis, but quickly leveled off in the study period and even had no significant beneficial effect after one year of follow-up (results not shown). Through the correction of electrolyte imbalance and fluid status, it is reasonable to speculate that the patient's heart function and cardiac electrical activity would be improved after the initiation of dialysis. However, after a period of progression of both underlying diseases and cardiorenal syndrome, the protective effect of dialysis against cardiac arrhythmias waned.[37,38]

On the other hand, the prevalence of hypertension and heart failure in our patients was significantly lower during the case periods compared to that in the control period in this study (Table 2, Fig. 1), indicating that the beneficial effect of dialysis was found to continue steadily over the study period. Correcting and stabilizing the fluid status and sodium levels of the patient is the cornerstone in the treatment of hypertension and heart failure. In ESRD patients, sodium and water are always retained in the vessels and cause hypertension and congestive heart symptoms. Dialysis corrects electrolyte levels and eliminates excess water, thereby reducing blood pressure and heart burden. Our data showed that, as long as dialysis continues, sodium level and water status as well as the risk of hypertension and heart failure were controlled.

Our analysis nonetheless has certain limitations. First, we did not examine the influence of other therapeutic interventions on the risk of cardiovascular disease. For example, phosphate binder use and dialysate calcium levels were not examined in this analysis as they were not available in the dataset. Moreover, we were unable to demonstrate the difference between hemodialysis and peritoneal dialysis in terms of their associations with the occurrence of cardiovascular disease due to the insufficient number of patients undergoing peritoneal dialysis. The role that these factors play in the development of cardiovascular disease warrants further exploration. Second, though the case-crossover design could automatically control for all time-invariant confounders, it is likely that our results were still confounded by time-variant factors, such as electrolyte imbalance, acute psychiatric distress, and drug-drug interaction, which could all independently trigger cardiovascular disease but were not available in our study. Third, the case-crossover design might be vulnerable to changes in prescription patterns over time. However, the time-trend bias would be limited due to the

narrow time window of this study. Fourth, we did not take into account several important lifestyle risk factors of cerebral- and cardiovascular diseases such as obesity, cigarette smoking, or alcohol drinking because of their unavailability in this study. Furthermore, since patients who died before initiation of dialysis and those received only one dialysis were excluded, survival bias may have affected our results. However, because this was a case-crossover study, this bias would have been trivial. Finally, since we studied a population largely consisting of people of Han Chinese descent, our results may not be generalizable to non-Asians.

In conclusion, this study used a unity case-crossover design to determine the acute effect of dialysis on the incidence of cardiovascular diseases. The results demonstrated that dialysis could dramatically reduce the incidence of arrhythmias, atrial fibrillation, congestive heart failure, and hypertension in patients with ESRD within 90 days after their first dialysis. On the other hand, there was an initial elevation in the incidence of cardiovascular events in patients under maintenance dialysis. Further large-scale prospective studies are thus warranted to investigate the risks and benefits of the first dialysis therapy to help physicians make appropriate recommendations for patients without a previous history of cardiovascular or cerebrovascular diseases.

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