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Original Article

Different impact of aspirin on renal progression in patients with predialysis advanced chronic kidney disease with or without previous stroke

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ABSTRACT

Background: The benefit of reducing the risk of stroke against increasing the risk of renal progression associated with antiplatelet therapy in patients with advanced chronic kidney disease (CKD) is controversial.
Methods: We enrolled 1301 adult patients with advanced CKD treated with erythropoiesis stimulating agents from January 1, 2002 to June 30, 2009 from the 2005 Longitudinal Health Insurance Database in Taiwan. All of the patients were followed until the development of the primary or secondary endpoints, or the end of the study (December 31, 2011). The primary endpoint was the development of ischemic stroke, and the secondary endpoints included hospitalization for bleeding events, cardiovascular mortality, all-cause mortality, and renal failure. The adjusted cumulative probability of events was calculated using multivariate Cox proportional regression analysis.
Results: Adjusted survival curves showed that the usage of aspirin was not associated with ischemic stroke, hospitalization for bleeding events, cardiovascular mortality or all-cause mortality, however, it was significantly associated with renal failure. In subgroup analysis, aspirin use was associated with renal failure in the patients with no history of stroke (HR, 1.41; 95% CI, 1.14–1.73), and there was a borderline interaction between previous stroke and the use of aspirin on renal failure (interaction $p = 0.0565$).
Conclusions: There was no significant benefit in preventing ischemic stroke in the patients with advanced CKD who received aspirin therapy. Furthermore, the use of aspirin was associated with the risk of renal failure in the patients with advanced CKD without previous stroke.

1. Introduction

Patients with chronic kidney disease (CKD) had high risk of cerebrovascular disease [1]. A meta-analysis of 21 studies reported that a increased 43% risk of incident cerebrovascular disease in patients with CKD (estimate glomerular filtration rate (eGFR) < 60 mL/min/1.73 m2) [2]. Furthermore, the risk of stroke is especially high in dialysis patients. One study in Taiwan revealed that there were increased risks of cerebrovascular events (three-fold of ischemic stroke and six-fold of hemorrhagic stroke) in mora than 80,000 dialysis patients [3]. Antiplatelet agents have been shown to prevent death, myocardial infarction and ischemic stroke in high risk patients [4,5]. The HOT study reported that aspirin therapy produced a significant risk reduction in major cardiovascular events (66%) and mortality (49%) in hypertensive CKD patients [6]. Other studies also have reported that the antiplatelet therapy had benefit effect on reducing cardiovascular death and all-cause mortality in patients with renal failure [7,8].

Aspirin is widely used for preventing cerebrovascular disease in patients with CKD [9,10]; however its use is often based on data obtained from patients with normal renal function because patients with CKD have been mostly excluded from the major clinical trials [5,11]. Previous literatures reported that antiplatelet therapy had no benefits on reducing risk of ischemic stroke in patients with renal failure [7,8,12–14]. In addition, patients with CKD had complex disturbance on hemostasis

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coagulation and platelet dysfunction [15,16]. There is still controversial about the risks and benefits about chronic use of aspirin in advanced CKD patients who have bleeding tendency [17]. Furthermore, aspirin therapy increases renal deterioration in CKD patients by inhibiting renal prostaglandins [9]. A retrospective study advocated that low-dose aspirin (<100 mg) was significantly associated with the increased risk of renal failure ($p = 0.042$) in patients with CKD [8]. Therefore, the purpose of this study was to evaluate the efficacy for ischemic stroke reduction and safety for renal progression about aspirin agents in patients with predialysis stage 5 CKD (eGFR <15 mL/min/1.73 m2).

2. Materials and methods

2.1. Data source

The coverage rate of Taiwan National Health Insurance Research Datasets (NHIRD) was about 99% of 23 million people. This study used the 2005 Longitudinal Health Insurance Database (LHID), which is comprised of 1 million beneficiaries randomly sampled from the registry for beneficiaries of the NHIRD in 2005. The LHID contains secondary data provided for research purposes, in which the data are anonymized. This study was approved by the Institutional Review Board of Chung-Shan Medical University Hospital, Taiwan.

The LHID includes demographic and outpatient or hospitalization medical claims data including International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) diagnostic codes, costs and prescriptions. The Inclusion criteria were patients with CKD (ICD-9 CM:585.x) who received erythropoiesis stimulating agent (ESA) treatment, and the index date was defined as the date of the 31st day after the first ESA prescription from January 1, 2002, to June 30, 2009. The exclusion criteria were receiving renal replacement therapy before ESA treatment, incomplete demographic data, age not between 20 and 100 years, those who died or required long-term hemodialysis within 30 days after the index date, and those who received antiplatelet drugs other than aspirin within 30 days after the index date. In total, 1301 patients with stage 5 CKD were enrolled into analysis (Fig. 1).

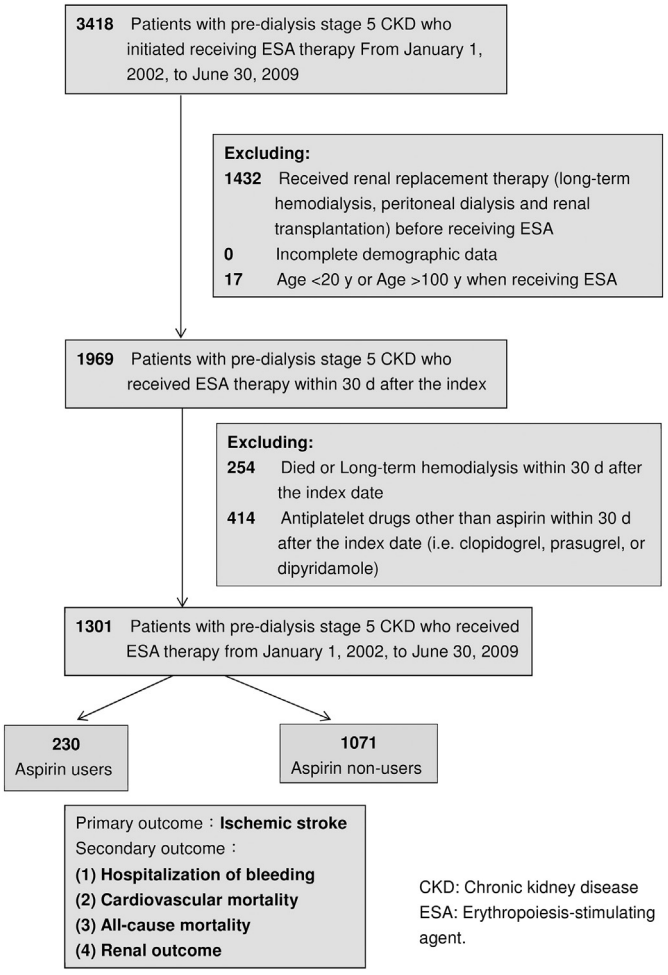

Fig. 1. Flowchart of Patient Selection.

2.2. Use of erythropoiesis-stimulating agents

The ESA prescription was performed by The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) clinical practice guideline. ESA type were erythropoietin (Eprex®; Janssen, Recormon®; Roche) darbepoetin alfa (Aranesp®; Kirin) and methoxy polyethylene glycol-epoetin beta (Mircera®; Roche). The dosage of ESA prescription was performed with maximum dose of 20,000 U per month in erythropoietin, 100 mcg per month in darbepoetin alfa and methoxy polyethylene glycol-epoetin beta.

2.3. Aspirin exposure assessment

The prescription records were used to identify which medications were used, and the Anatomical Therapeutic Chemical (ATC) classification system was used to classify the types of drugs. The patients who received low-dose aspirin (≤100 mg/day) therapy within 30 days after the initial ESA treatment were defined as aspirin users, and the other patients as nonusers.

2.4. Comorbidities

We considered the comorbidities which may have confounded the association between aspirin use and outcomes. Comorbidities were confirmed by at least two clinical visits or one admission in the year before the index date, and the baseline comorbidities included hypertension (ICD-9 CM 401–405), diabetes mellitus (ICD-9 CM 250.0–250.7), congestive heart failure (ICD-9 CM 428), ischemic heart disease (ICD-9 CM 410–414), atrial fibrillation (ICD-9 CM 427.31), previous stroke (ICD-9 CM 430–438), peripheral artery disease (ICD-9 CM 443.9, 441, 785.4, V43.4 or Procedure 38.48), and peptic ulcer disease (ICD-9 CM 531–534). In addition, we calculated the Charlson Comorbidity Index score (CCIs) [18] to evaluate the impact of the comorbidities in a variety of disease conditions.

2.5. Medications

The NHIRD contains comprehensive data on prescriptions, and we identified the drugs of interest using ATC codes. The drugs of interest were defined as those that the patients used 30 days before or after the first ESA prescription, and included anticoagulants, antilipemic agents, non-selective non-steroidal anti-inflammatory drugs, proton pump inhibitors, selective serotonin reuptake inhibitors and corticosteroids.

2.6. Composite outcomes

The primary outcome of this study was ischemic stroke (ICD-9-CM 433–436), and there were four secondary outcomes: hospitalization/death due to bleeding (gastrointestinal bleeding (ICD-9-CM 531–535, 578.9), intracranial bleeding (ICD-9-CM 430–432), urinary tract bleeding (ICD-9 CM 596.7, 599.7), airway bleeding (ICD-9 CM 784.7, 784.8, 785.5, 786.3), cardiovascular death (angina pectoris (ICD-9 CM 413.9), myocardial infarction (ICD-9 CM 410, 412), ischemic heart disease (ICD-9 CM 410–414), atrial fibrillation (ICD-9 CM 427.31), heart failure (ICD-9 CM 428), cerebrovascular disease (ICD-9 CM 430–438), all-cause

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