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Effectiveness of and risk associated with aspirin therapy in hemodialysis patients with a background of antiplatelet factor 4/heparin complex antibody detection

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ABSTRACT

Background: The optimal prevention measures against hemodialysis (HD)-associated complications, including all-cause thrombotic events and death, are unclear.
Methods: This prospective study was designed to assess the effect of aspirin on prevention of HD-associated complications. Patients were divided into four groups according to platelet factor-4/heparin-complex (PF4/H) antibody detection and aspirin prescription: Group 1, antibody(−)/aspirin(+); Group 2, antibody(−)/aspirin(−); Group 3, antibody(+)/aspirin(+); and Group 4, antibody(+)/aspirin(−). Adverse events were compared among all four groups. Cox hazard regression was performed to analyze the effects of anti-PF4/H antibody and aspirin on thrombosis and death.
Results: This study included 648 patients undergoing HD; 142 were positive for anti-PF4/H antibodies, and 229 had received aspirin before enrollment. During the 4-year follow-up period, 138 patients developed thrombosis, and 63 of these events were anti-PF4/H antibody-associated. A total of 112 patients died; 75 died of coronary heart disease (CHD). Group 4 had a significantly higher incidence of total and anti-PF4/H antibody-associated thrombosis events as well as total and CHD-associated death than did the other three groups. Aspirin had a preventive effect against all adverse events in anti-PF4/H antibody-positive patients, but not in antibody-negative patients. Group 1 patients with baseline D-dimer levels of <0.6 μg/mL developed more hemorrhagic events than did patients in the other groups.
Conclusions: Aspirin prevention of thrombosis and death in patients undergoing HD might require consideration of the anti-PF4/H antibody status. In antibody-positive individuals, taking aspirin could improve the prognosis and therefore might be recommended. In antibody-negative individuals, prevention was minimal and the bleeding risk was obviously increased; thus, aspirin should be avoided or at least require careful evaluation prior to aspirin treatment.

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Introduction

Thrombotic complications, especially myocardial and cerebral infarction, strongly influence the prognosis of patients undergoing hemodialysis (HD) [1,2]. This has been confirmed by studies performed in Western countries [3,4]. Similarly, in China, myocardial and cerebral infarction is considered to be the main reason for hospitalization of patients undergoing HD. Unfortunately, the factors that play key roles in the development of thrombosis in these patients remain unclear. Heparin-induced thrombocytopenia (HIT), a serious complication of heparin exposure, is characterized by thrombocytopenia and subsequent thrombosis [5,6]. HIT is an immune-mediated syndrome involving the generation of antibodies to platelet factor 4–heparin complex (PF4/H). Among HD patients who develop anti-PF4/H antibodies, only a subset generate anti-PF4/H antibody-induced thrombocytopenia, and only some of these patients subsequently develop thrombosis [7,8]. However, some patients develop thrombosis even without thrombocytopenia [9]. Classic HIT rarely occurs in HD patients; vascular complications occur more frequently [10,11]. One author reported that 28.5% of anti-PF4/H antibody-positive HD patients developed thrombosis, while only 8.7% of those without anti-PF4/H antibodies developed

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thrombosis [12]; these findings are supported by other studies [13,14]. However, some researchers have reported conflicting results [15,16]. Additionally, the development of anti-PF4/H antibodies in asymptomatic HD patients has been suggested as a potential risk factor for mortality [17]. Aspirin, a commonly used antiplatelet agent, can decrease the incidence of chronic cardiovascular diseases, especially myocardial and cerebral infarction [18,19]. In the present study, we analyzed the ability of aspirin to prevent thrombotic events and mortality in patients with polyspecific anti-PF4/H antibodies.

The aim of the study was to answer the following questions: (1) Can aspirin successfully decrease the incidence of severe thrombotic events and improve patients' survival? If so, is this effect associated with the anti-PF4/H antibody level? (2) Is long-term aspirin administration safe for the bleeding risk in HD patients?

Methods

Participants and Aspirin Prescription

This study was approved by the Ethics Committee of Health Department of Beijing Military Region. Three hospitals participated in the study: (1) Beidaihe Sanatorium of Beijing Military Region; (2) Affiliated Hospitals of Harbin Medical University; (3) General Hospital of Beijing Military Region. The inclusion criteria were an age of >18 years, no plans to undergo peritoneal dialysis or renal transplantation, no administration of antiplatelet agents other than aspirin, and the ability to undergo regular follow-up. All patients provided written informed consent. In total, 790 patients met all of the above criteria and were recruited from September to November 2009. A total of 108 patients (13.7%) had disobeyed the designed therapeutic schedule and failed to complete the study. Follow-up was completed in November 2013, at which time 112 patients had died. A total of 648 patients provided the complete information; 34 were excluded because they were missing important clinical data.

The patients were divided into four groups according to initial anti-PF4/H antibody positivity and aspirin prescription: Group 1, antibody(−)/aspirin(+); Group 2, antibody(−)/aspirin(−); Group 3, antibody(+)/aspirin(+); and Group 4, antibody(+)/aspirin(−) (Fig. 1). Notably, the study was observational: aspirin therapy was initiated prior to inclusion of patients and not as a function of the study design. A total of 229 patients had received aspirin before enrollment: 38 had developed thrombosis within the last year, 41 had intermittent angina pectoris or transient ischemia attaches, 46 were evaluated as having a high thrombosis risk although they lacked obvious symptoms, 35 had developed frequent arteriovenous fistula embolism and failure (>3 times/year), 48 had unstable atherosclerosis plaques and needed

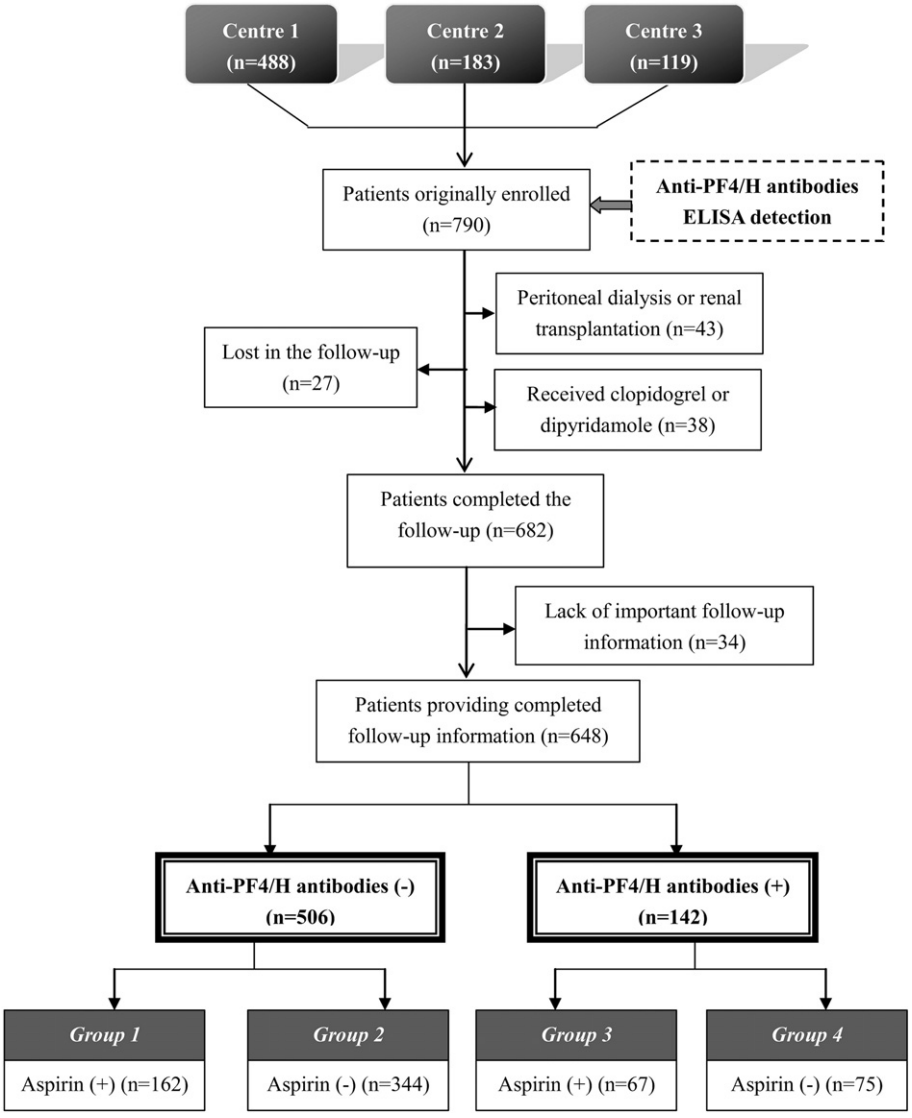

Fig. 1. Enrollment and grouping of hemodialysis patients.

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