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Regular Article

# Prevalence and risk factors of atherothrombotic events among 1054 hemophilia patients: A population-based analysis

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ABSTRACT

*Introduction:* Reports on the prevalence and risk factors of atherothrombotic events (AEs) are conflicting in persons with hemophilia (PWH).
*Methods:* This study evaluated the prevalence and risk factors of AEs among 1054 male hemophilia patients, using data collected from Taiwan's National Health Insurance Research Database between 1997 and 2010, by comparing variable to those of an unaffected 10540 age- and gender-matched general population.
*Results:* The proportions of all AEs among PWH, including 26 ischemic stroke, 29 coronary artery disease and 5 peripheral arterial disease were comparable to those in the general population. The mean age at diagnosis of AE among PWH was younger than that in the general population: 49.0 (95% CI, 43.6-54.5) and 55.8 years (95% CI, 54.5-57.0), P = 0.019, respectively. PWH with Chronic Obstructive Pulmonary Disease (COPD), hypertension, and hyperlipidemia were associated with greater risk for the occurrence of AEs, with hazard ratios (95% CI) of 3.42 (1.25-9.38), 4.15 (2.11-8.17), and 2.84 (1.39-5.79), respectively. PWH who needed replacement therapy had a lower risk of AEs than those who did not need, with a hazard ratio (95% CI) of 0.41 (0.21-0.81).
*Conclusions:* The study indicated the prevalence of AEs among PWH was comparable to that of the general population. AEs appeared at an earlier age among PWH. COPD, hypertension, and hyperlipidemia were risk factors for AEs. PWH who needed replacement therapy may have a lower risk of AEs.


## Introduction

Hemophilia A and B are inherited bleeding disorders resulting from the absence or deficiency of coagulation factors. Since the introduction of clotting factor concentrates, regular prophylaxis and more comprehensive hemophilia care have led to an increased life expectancy of persons with hemophilia (PWH) [1,2]. Therefore, age-related disorders are emerging issues in PWH [3–6]. Cardiovascular diseases (CVDs) in particular are increasingly being reported in the hemophilia populations. Several studies have investigated the incidence, prevalence and mortality of CVDs among PWH [7–17]. Although some cohort studies have reported a reduced mortality caused by ischemic heart disease among PWH [11,12], it remains controversial as to whether hemophilia is associated with a decrease, increase or no change in the risk of atherothrombotic events (AEs) in comparison to that of the general population. Several reports on the prevalence of known risk factors for AEs are also conflicting among PWH [7,10,13,14,18–21]. In addition, few studies have investigated whether clotting factor concentrate use, higher prevalence rates of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infection, and hemophilic arthropathy contribute to the development of atherothrombosis in the hemophilia population. This study analyzed a population-based database to compare the

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prevalence of AEs between PWH and the general population, and investigate the risk factors for AEs among PWH.

## Patients and Methods

### *Data Sources*

The data was obtained from the National Health Insurance Research Database (NHIRD) in Taiwan. The National Health Insurance (NHI) program in Taiwan was introduced in 1995. It provides comprehensive medical care, including inpatient and outpatient care for nearly one hundred percent of Taiwan's population of around 23 million people. The Bureau of National Health Insurance (BNHI) in Taiwan includes hemophilia in the list of catastrophic illnesses. Each newly diagnosed case of hemophilia A or B must be certified by a clinician, and is eligible to receive free treatment with clotting factor concentrates. Anonymized data in NHIRD are made publicly available for research purposes. In this study, the retrieved data were verified by linking each encrypted personal identification number with the patient's catastrophic illness certificate. Each NHIRD patient files includes an encrypted personal identification number, date of birth, date of enrollment, and medical claims. In cooperation with the Bureau of NHI, the National Health Research Institute (NHRI) in Taiwan randomly sampled a representative database of 1,000,000 subjects from the year 2005 registry of all NHI enrollees using a systematic sampling method for research purposes, in order to establish a database known as the Longitudinal Health Insurance Database (LHID). There were no statistically significant differences in age, gender, or healthcare costs between the general population and the study group. These databases have previously been used for epidemiological research, and the information provided regarding prescription use, diagnoses, and hospitalizations is of high quality [22,23]. The accuracy of diagnosis of major diseases in the NHIRD, such as stroke and diabetes, has been validated [24,25].

### *Identification of Study Cohorts*

In this study, we used the registration files and original claims data of catastrophic illness patients in NHIRD between 1997 and 2010 to conduct the analysis. Male cases of hemophilia A and B were identified by the International Classification of Diseases Ninth Revision (ICD-9) codes 286.0 and 286.1. In order to evaluate relative risks, data of the general male population between 1997 and 2010 were retrieved from the LHID by matching the month of birthday and Charlson Comorbidity Index with a ratio of 1:10. A total of 1099 patients with hemophilia A or B were eligible for inclusion in this analysis. Forty-five patients with missing data were excluded during matching to the 10540 individuals without coagulation disorders; thus, 1054 PWH comprising 885 patients with hemophilia A and 169 with hemophilia B, were included in the final analysis (Fig. 1).

### *Definition*

Urbanization levels in Taiwan are divided into four strata in Taiwan's National Health Research Institute publications; level 1 indicates "most urbanized" communities and level 4 indicates the "least urbanized" communities. Patients with CVDs including coronary artery disease (CAD) (myocardial infarction and angina pectoris), cerebrovascular disease (hemorrhagic stroke and ischemic stroke), peripheral arterial disease, deep vein thrombosis, and pulmonary embolism were identified by ICD-9 codes (see Table 1S in supplementary material). Comorbidities, including hypertension, hyperlipidemia, chronic obstructive pulmonary disease (COPD), diabetes, heart failure, atrial fibrillation, hepatitis B virus (HBV), HCV or HIV infection, and hip and/or knee replacement, were also identified by ICD-9 codes (Table IS in supplementary material) from the medical claims in NHIRD. Because patients' clotting factor levels were not recorded in the NHIRD, hemophilia severity was generally classified into two groups according to the use of clotting factor concentrates. Patients who needed replacement therapy were defined as PWH who needed to receive clotting factor concentrates in daily life other than the perioperative period of invasive procedure or surgery. The remaining patients were referred as patients who did not need replacement therapy. The latter group represented patients with mild hemophilia who received treatment with desmopressin acetate or clotting factor concentrates only during the peri-operative period. PWH who needed bypassing agents represented

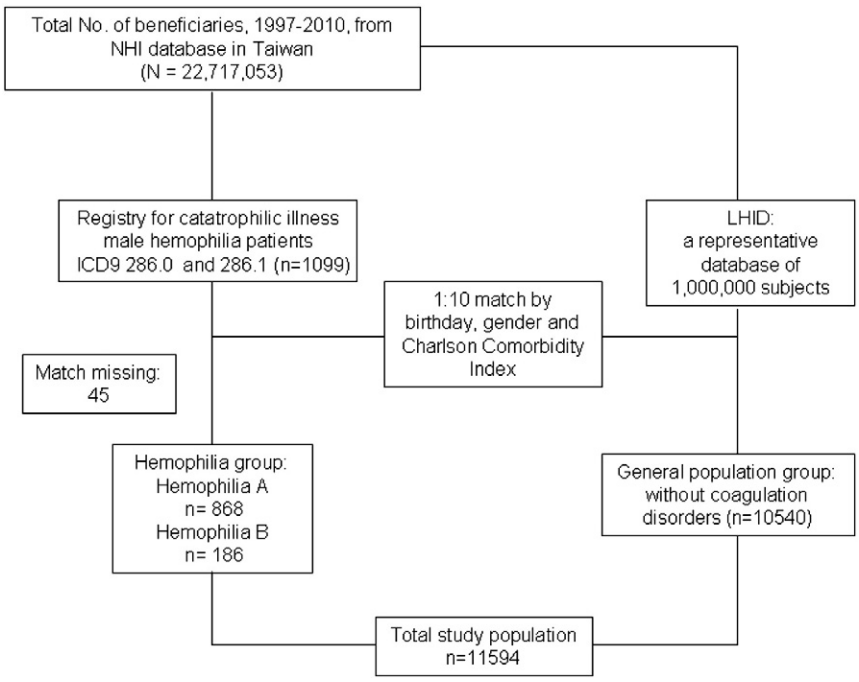


**Fig. 1. Study design flowchart.** NHI, National Health Insurance; ICD-9, International Classification of Diseases, ninth revision; LHID, Longitudinal Health Insurance Database.