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Original research article

Cardiovascular comorbidities in a United States patient population with hemophilia A: A comprehensive chart review

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ABSTRACT

Purpose: Previous retrospective claims database analyses reported increased prevalence and earlier onset of cardiovascular comorbidities in patients with versus without hemophilia A. A comprehensive chart review was designed to further investigate previous findings.

Methods: This retrospective chart review study was conducted at Henry Ford Health System (Detroit, MI, USA). Baseline demographics, bleeding events, treatment parameters, coexisting diseases, hemophilia-associated events, Charlson Comorbidity Index score, and prevalence of 12 cardiovascular risk factors and associated diseases were compared between hemophilia A and control cohorts. *P* values from a chi-square test for categorical variables and a *t* test for continuous variables were calculated. Because of small sample sizes (N = 0–90, most < 50), statistical differences between cohorts were also assessed using absolute standardized difference.

Results: Both groups were well matched by age, race, healthcare payer, and study year. The Charlson Comorbidity Index score was similar between groups. Prevalence of bleeds, hepatitis B and C, and HIV/AIDS was higher in the hemophilia cohort. Hemophilia A severity was severe, moderate, mild, or unknown in 52.7%, 10.8%, 10.8%, and 25.7% of patients, respectively. Prevalence of 12 cardiovascular risk factors and diseases was numerically higher in the control cohort, but differences were statistically significant ($P \leq 0.05$) only for diabetes and hyperlipidemia. Meaningful statistical differences using standardized differences were not reached for venous and arterial thrombosis and atrial fibrillation.

Conclusions: This retrospective chart review did not confirm statistically significant differences in cardiovascular comorbidities and their earlier onset in hemophilia A versus controls. Results suggest numerically higher comorbidities in controls.

1. Introduction

The availability of replacement factor products and improvements in treatment strategies over time have led to an increase in life expectancy of patients with hemophilia; consequently, the incidence of age-related comorbidities has increased in this population [1,2]. To date, there have been conflicting data in the literature regarding the risks of cardiovascular (CV) comorbidities in patients with hemophilia A compared with the general population. Some studies have reported lower mortality from CV diseases and/or decreased atherogenesis in patients with hemophilia because of the potentially protective effect of chronically low factor VIII (FVIII) activity on thrombus formation [2,3]. Conversely, other reports indicate comparable or higher CV comorbidities in patients with hemophilia compared with the general population [4–6]. One such study, conducted in light of conflicting reports regarding CV risk in hemophilia, specifically assessed the CV risk profile (via QRISK®2) of 709 patients aged ≥30 years in the Netherlands or United Kingdom [5]. Most CV risk factors were lower (obesity and hypercholesterolemia) or similar (diabetes and smoking) for patients with hemophilia versus the age-matched general population; however, patients with hemophilia had a higher prevalence of hypertension (49% vs 40%) along with a significantly higher 10-year QRISK2 risk overall (8.9% vs 6.7%) and in all age groups > 40 years. One aspect to consider in reviewing previous studies is the nature of controls employed. These vary among age-matched [2,4]; World Federation of Hemophilia, national or state databases [3,5,7,8], and

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uncontrolled [6] methods.

We previously conducted a retrospective claims database analysis showing a higher prevalence of CV comorbidities in male patients with hemophilia A compared with a general male population with similar patient characteristics [1]. Data for that study were derived from the MarketScan Neptune, NJ Commercial and Medicare Supplemental Research databases (Ann Arbor, MI) from January 1, 2007, to December 31, 2009. The prevalence of CV comorbidities including hemorrhagic stroke, ischemic stroke, arterial thrombosis, and venous thrombosis was statistically significantly higher in the hemophilia A cohort compared with the control population of patients without hemophilia [1]. CV comorbidities showed earlier onset in hemophilia A versus the general patient population. Of special concern were the elevated incidences of stroke and arterial and venous thrombosis in the hemophilia A cohort aged < 40 years; specifically, significant differences versus controls were noted in age groups 0–17 and 18–29 years for hemorrhagic stroke, and 0–17 years for ischemic stroke. To confirm these findings, the PharMetrics® LifeLink claims database (IMS Health Inc., Danbury, CT) was used to evaluate patient records available from January 1, 2008, to December 31, 2011 [9]. The structure of the study cohorts and the inclusion criteria were similar to those used previously in the MarketScan database analysis [1]. This second retrospective study using the PharMetrics LifeLink database confirmed the result seen previously in the MarketScan database analysis demonstrating an increased prevalence and earlier onset of CV comorbidities in patients with hemophilia A compared with the general patient population [9]. The findings from the two commercial database reviews needed to be confirmed by comprehensive chart review to determine next steps in the evaluation of CV risk factors in US patients with hemophilia A.

Therefore, the primary study objective was to confirm and explore the prevalence of CV risk factors and diseases in a comprehensive chart review, potentially to verify the findings of 2 claims database reviews. Additional objectives included exploring the prevalence of atrial fibrillation and its relationship to hypertension, as well as stroke and its relationship with both hypertension and venous thrombosis.

2. Methods

This was a retrospective chart review study evaluating the prevalence of CV risk factors and diseases among patients diagnosed with hemophilia A and control patients without evidence of a hemophilia diagnosis from a single healthcare system. The study was approved by the local institutional review board. The study was approved by the Henry Ford Health System Institutional Review Board on 07-13-2015, IRB #9783. The study is currently active within the IRB with the latest approval dates from 6-7-2018 through 6-6-2019.

Data for this study were derived from medical records from the Henry Ford Health System (HFHS). The HFHS is a large, vertically integrated healthcare system in Detroit, Michigan. As a nonprofit corporation consisting of Henry Ford Hospital, 30 medical centers, and more than 1000 physicians in 40 medical specialties, HFHS provides care for approximately 800,000 southeastern Michigan residents. The Health Alliance Plan (HAP), a health maintenance organization owned and operated by HFHS, currently enrolls more than 500,000 individuals from more than 3000 employers in the Detroit metropolitan area. A subset of the patient cohort is insured under HAP, which allows investigators to evaluate all medical and pharmaceutical claims as well as detailed clinical information derived from electronic medical records including laboratory values, vital statistics, and diagnostic testing.

Comorbidities were classified using the Charlson Comorbidity Index [10], a method of estimating risk of death from comorbid disease [11].

2.1. Study cohorts and analysis

The target patients were those with a hemophilia A diagnosis (cases) and a matched general population of patients without hemophilia A (controls). Patients meeting all of the proposed inclusion criteria were selected into the study cohort: male sex; evidence of hemophilia A diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code of 286.0) between January 1, 1995 and December 31, 2014; and evidence of receipt of FVIII treatment between January 1, 1995, and December 31, 2014. The 12-month period preceding a patient's last visit (index date) captured in the HFHS served as the study year.

Patients meeting any of the following criteria were excluded from the study cohort: female sex, diagnosis of von Willebrand disease, and receipt of factor IX any time during the study period. Each hemophilia A patient was matched to 3 general population controls based on age during the study year, race, study year, and health plan (private vs Medicare/Medicaid). The hemophilia A patients and controls were also required to have continuous activity in the health system, which was defined as having ≥1 additional visit at the HFHS ≥ 12 months and ≤18 months prior to the index date. This ensured equal opportunity to identify CV diseases and risk factors. Patient eligibility was verified via the medical records, and variables such as demographic characteristics, hemophilia characteristics (hemophilia A patients only), CV risk factors and diseases, and other pertinent patient characteristics were abstracted. Demographic characteristics included age, race, study year, HAP insurance, and insurance payer. Non-CV comorbidities were identified from the HFHS database and included hepatitis B and C, hepatocellular carcinoma, HIV/AIDS, port placement, and joint replacement. The prevalence rates of 12 CV comorbidities and associated risk factors were tabulated. CV medications and procedures were also quantified. *P* values generated from a chi-square test for categorical variables and a *t* test for continuous variables were reported. To address the small sample size, statistical differences between the cohorts were also assessed using absolute standardized difference (SDiff), where a value ≥0.10 was considered statistically meaningful. Standardized differences measure the effect size between two groups [12]. Compared with a *t* test or Wilcoxon rank-sum test, they are independent of sample size. Thus, their use can be recommended for comparing baseline covariates in clinical trials as well as matched studies. The SDiff (d_i) was calculated as: $\boldsymbol{d_i} = \frac{100 \times |\boldsymbol{x_{Ai}} - \boldsymbol{x_{Bi}}|}{\sqrt{(\boldsymbol{s^2_{Ai}} - \boldsymbol{s^2_{Bi}})/2}}$

3. Results

3.1. Demographics

The hemophilia A group comprised 74 patients versus 222 in the control group. Baseline demographics are shown in Table 1. The hemophilia and control groups were generally well balanced. Although there was a higher percentage of Medicaid patients in the hemophilia A group, the total percentage of patients with government insurance (61%) was the same in both groups (Table 1). The demographics of the population studied in this review revealed higher percentage of African Americans than in a similar published study [7]. The results did not change when the data were analyzed excluding the African-American patients.

3.2. Clinical characteristics

The overall clinical characteristics between the groups are shown in Table 2. With respect to non-CV comorbidities, the prevalence rates of hepatitis B (4.1% vs 0.5%), hepatitis C (14.9% vs 0.5%), and HIV/AIDS (14.9% vs 2.7%) were significantly higher in the hemophilia A group. The incidence of hepatocellular carcinoma was not significantly different between the groups (1.4% vs 0.0%). HIV/AIDS was the most prevalent comorbidity in both groups. The Charlson Comorbidity Index score [11] indicated a higher comorbidity burden for the hemophilia A patients versus controls based on the SDiff (1.91 ± 3.05 vs 1.48 ± 2.10; SDiff = 0.1618; $P = 0.27$). The bleeding events, as