A second retrospective database analysis confirms prior findings of apparent increased cardiovascular comorbidities in hemophilia A in the United States

To the Editor: The availability of replacement factor products and improvements in treatment strategies over time have led to increased life expectancy of patients with hemophilia; consequently, the incidence of age-related comorbidities has increased in this population [1,2]. There have been conflicting published data regarding the risks of cardiovascular (CV) comorbidities in patients with hemophilia 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 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 controls; 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.

We previously conducted a retrospective claims database analysis showing a higher prevalence of CV comorbidities in male patients with hemophilia compared with a general male population with similar patient characteristics [1]. Data for that study were derived from the MarketScan® Commercial and Medical 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]. Moreover, 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. To confirm these findings, the current study was conducted in a second population of patients in the United States using a similar design but a different commercial database.

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. Fully adjudicated medical and pharmaceutical claims for >70 million unique patients from >80 health plans across the United States (~25 million covered lives per year) were analyzed.

The structure of the study cohorts and the inclusion criteria were similar to those used previously in the MarketScan database analysis [1]. The presence of hemophilia A was determined by an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 286.0 for ≥1 inpatient discharge diagnosis or ≥2 primary or secondary outpatient claims on two different dates. Male patients continuously enrolled in the health plan for ≥1 year were included. The hemophilia A cohort was matched with a general health population cohort at a 1:3 ratio. Cardiovascular comorbidities were determined using ICD-9-CM codes on database claims pertaining to hemorrhagic stroke, ischemic stroke, coronary artery disease, myocardial infarction, hypertension, hyperlipidemia, arterial thrombosis, and venous thrombosis (including pulmonary embolism).

The prevalence of CV comorbidities was compared between matched cohorts. Statistical significance was calculated by Fisher exact test and was denoted by a P value threshold of 0.05. Statistical analyses were conducted using SAS (Cary, NC).

The study included 4,200 men (hemophilia population, $n = 1050$; general health population, $n = 3{,}150$). Approximately 40% of the study population was aged ≥40 years, and 379 patients were aged ≤17 years. The prevalence of CV comorbidities during the follow-up period was significantly higher in the hemophilia cohort compared with the general health population cohort (Table I). Statistical significance was reached for all analyzed outcomes. In both cohorts, the most frequently observed comorbidities were hypertension (21.3% and 13.2% in hemophilia and general health populations, respectively; difference, 8.1%; $P < 0.0001$) and hyperlipidemia (15.0% and 12.0%; difference, 3.0%, $P = 0.016$). The largest between-cohort differences were seen for the less prevalent comorbidities; in particular, the hemophilia cohort had incidences of ischemic stroke, myocardial infarction, and arterial thrombosis that were more than twice as high as those in the general health population, whereas the prevalence rates were 7 times higher for hemorrhagic stroke and 16 times higher for venous thrombosis. Across age groups, more patients had venous access devices than controls (4.19% vs. 0.38%). The between-cohort differences obtained using the PharMetrics database analysis were similar to those in the previously published MarketScan database analysis [1].

The increased prevalence of CV comorbidities observed in the hemophilia cohort was consistent across most age groups. With the exception of hyperlipidemia, in which significance was reached only in the group aged 50–59 years, significantly higher comorbidity rates were observed in at least three age groups for each CV comorbidity. Additionally, the onset of CV comorbidities was generally earlier in the hemophilia cohort compared with the general health cohort.

The similar findings in both claims database analyses now await further confirmation. Possible explanations for these findings include a higher proportion of patients with milder bleeding phenotypes in the hemophilia patient sample who may have less protection from thrombosis than those with more severe bleeding phenotypes. Further study seems warranted.

Commercial claims databases have limitations, including potential coding errors and misclassification of patient characteristics and/or medications because of limitations in the eligibility period. Data from commercial claims databases do not necessarily take into account all disease- and treatment-related variables, including hemophilia severity, presence of other CV risk factors.

In conclusion, this second retrospective study of claims databases using the PharMetrics LifeLink database confirms the increased prevalence and earlier onset of CV comorbidities in patients with hemophilia A compared with the general patient population reported previously in the MarketScan database analysis [1]. The findings for stroke and thrombosis (venous and arterial) are of particular concern. If confirmed by chart review, the results support further evaluation of CV risk factors in US patients with hemophilia and establishing screening for CV comorbidities in patients beginning at an earlier age than recommended for the general population.

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TABLE I. Cardiovascular Comorbidities in Patients With Hemophilia A

	PharMetrics Integrated Database				MarketScan Database [1]			
Comorbidities, %	Hemophilia (n = 1,050)	General health (n = 3,150)	Difference	P value[a]	Hemophilia (n = 2,506)	General health (n = 7,518)	Difference	P value[a]
Hemorrhagic stroke	1.4	0.2	1.2	<0.0001	2.0	0.5	1.5	<0.001
Ischemic stroke	4.1	1.7	2.4	<0.0001	4.7	2.7	2.0	<0.001
Coronary artery disease	8.9	5.2	3.7	<0.0001	10.7	5.8	4.9	<0.001
Myocardial infarction	1.4	0.6	0.8	0.013	0.8	0.3	0.5	0.003
Hypertension	21.3	13.2	8.1	<0.0001	22.6	15.5	7.1	<0.001
Hyperlipidemia	15.0	12.0	3.0	0.016	15.9	11.9	4.0	<0.001
Arterial thrombosis	9.6	3.7	5.9	<0.0001	12.1	5.9	6.2	<0.001
Venous thrombosis[b]	4.9	0.3	4.6	<0.0001	4.4	1.1	3.3	<0.001

[a] Hemophilia versus general health population; Fisher exact test.
[b] Including pulmonary embolism.

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Author Contributions

All authors designed the study and interpreted the data. Mr Kamalakar contributed to data acquisition. All authors contributed to the development of the manuscript, reviewed each draft, and approved the final draft.

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