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Estimating the risk of myocardial infarction in persons with hemophilia A using a machine-learning approach with US claims data

Imi Faghmous,[1] Carlos Flores,[2] Kati Sarouei,[3] Tiffany Chang,[3] Anisha M Patel,[3] Cami S Sima,[3] Peter Kuebler[3]

[1]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [2]Genesis Research, Hoboken, NJ, USA; [3]Genentech, Inc., South San Francisco, CA, USA

INTRODUCTION

- Epidemiological studies in the literature provide conflicting conclusions regarding the risk of myocardial infarction (MI) in people diagnosed with congenital hemophilia A (HA). Furthermore, a survey of studies highlighted potential methodological limitations across a wide array of publications.[1–5]
- As a result, the question of whether HA provides protection from MI remains debated.
- The aim of this study was to assess the risk of MI in people with hemophilia A (PwHA) compared with individuals with no evidence of HA.

METHODS

Pharmaco-epidemiological approach

- Initially, a traditional pharmaco-epidemiological approach was conducted using the US Truven MarketScan Commercial Database and/or Medicare Supplemental Database.
- A cohort of PwHA was identified based on the following criteria:
  - A confirmed diagnosis of congenital HA between Jan 1, 2000 and Sept 30, 2017;
  - ≥3 claims for HA within 365 consecutive days; and
  - Continuous enrollment with insurance coverage for the 6 months after first diagnosis of HA.
- All individuals were also required to be male, and have no evidence of a diagnosis of von Willebrand disease (VWD), hemophilia B, acquired HA, or MI prior to their first HA diagnosis.
- A cohort of individuals with no evidence of HA in the study period was then randomly selected from the MarketScan database and frequency matched to the HA cohort by age, sex, insurance type, region, enrollment length, diabetes status, and hypertensive status at a 1:3 ratio.
- High relative risk estimations using the pharmaco-epidemiological approach prompted further investigations considering concomitant medications.
- These results led to the revision of methods underlying cohort identification to the machine-learning approach.

Machine-learning approach

- For this approach, the inclusion criteria for the study were further refined to include persons with:
  - ≥1 medical or pharmacy claim for factor VIII (FVIII) therapy, activated prothrombin complex concentrate, or activated factor VIIa therapy; or
  - ≥1 medical or pharmacy claim for FVIII/VWD therapy and no diagnosis of VWD; or
  - ≥1 medical or pharmacy claim for desmopressin and ≥1 medically-attended visit with a diagnosis of HA in the same claim line; or
  - ≥1 medically-attended visit with a HA diagnosis.
- The earliest date for fulfilling any of these inclusion criteria was deemed the individual's index date.
- Participants also had to have 6 months of continuous insurance enrollment prior to study entry in order to participate.
- An HA classification algorithm[6], set to 98.5% specificity and 77.8% sensitivity was adapted and applied to the aforementioned refined cohort.
- A cohort of individuals with no evidence of HA in the study period was once again selected using the same selection criteria and frequency matching as per the pharmaco-epidemiological approach.
- A Poisson regression model was then fitted to estimate the adjusted incidence rate ratio (IRR); the model was adjusted for all baseline covariates as well as human immunodeficiency virus and hepatitis C status, with age as a time-varying covariate.

RESULTS

Pharmaco-epidemiological approach

- Based on the defined criteria, 3337 people with congenital HA were identified (**Table 1**)
  - The crude incidence rate of MI in this cohort was estimated to be 1.08 (95% confidence interval [CI]: 0.88–1.30) per 100 person-years (**Table 3**)
  - Relative to the matched cohort of individuals with no evidence of HA (n=16,606), an unadjusted IRR of 1.71 (95% CI: 1.66–1.73) was yielded (**Table 3**).
- These high relative risk estimations prompted further investigations into concomitant medications, which revealed evidence of misclassification bias with a large proportion of participants having been prescribed anticoagulants and a low frequency of hemophilia drug utilization.

Machine-learning approach

- The use of the machine-learning approach identified 3154 individuals with a ≥90% probability of being true PwHA; ten were excluded as they had a previous history of MI, leaving a final cohort of 3144 PwHA (**Table 2**).
- The crude incidence rate of MI was calculated to be 0.25 (95% CI: 0.15–0.34) and 0.22 (95% CI: 0.18–0.27) per 100 person-years in the HA and non-HA population (n=15,673), respectively, yielding an unadjusted IRR of 1.14 (95% CI: 1.07–1.16; **Table 3**).
- The adjusted IRR was estimated to be 1.31 (95% CI: 0.85–2.00; p=0.22), indicating that there was no evidence to suggest a difference in the rate of MI in the HA population versus a matched non-HA control (**Table 3**).

Table 1. Pharmaco-epidemiological approach: participant disposition.

	People with congenital HA (n=3337)	Matched cohort of individuals without HA (n=16,606)	Overall (N=19,943)
Sex, male, n (%)	3337 (100)	16,606 (100)	19,943 (100)
Age, n (%)			
<18 years	1189 (35.6)	5945 (35.8)	7134 (35.8)
18–35 years	873 (26.2)	4365 (26.3)	5238 (26.3)
36–45 years	312 (9.3)	1560 (9.4)	1872 (9.4)
46–55 years	341 (10.2)	1702 (10.2)	2043 (10.2)
56–65 years	331 (9.9)	1643 (9.9)	1974 (9.9)
66–75 years	131 (3.9)	595 (3.6)	726 (3.6)
≥76 years	160 (4.8)	796 (4.8)	956 (4.8)
US region, n (%)			
Northeast	599 (18.0)	2985 (18.0)	3584 (18.0)
North central	813 (24.4)	4054 (24.4)	4867 (24.4)
South	1244 (37.3)	6171 (37.2)	7415 (37.2)
West	617 (18.5)	3079 (18.5)	3696 (18.5)
Unknown	64 (1.9)	317 (1.9)	381 (1.9)
Insurance, n (%)			
MarketScan CCAE	3034 (90.9)	15,170 (91.4)	18,204 (91.3)
MarketScan Medicare*	303 (9.1)	1436 (8.6)	1739 (8.7)
Enrollment length, years			
Mean (SD)	4.28 (3.56)	4.57 (3.61)	4.52 (3.60)
Median (Q1, Q3)	3.00 (1.83, 5.59)	3.42 (2.00, 6.00)	3.33 (2.00, 6.00)
Evidence of diabetes†			
No	2991 (89.6)	14,912 (89.8)	17,903 (89.8)
Yes	346 (10.4)	1694 (10.2)	2040 (10.2)
Evidence of hypertension†			
No	2483 (74.4)	12,375 (74.5)	14,858 (74.5)
Yes	854 (25.6)	4231 (25.5)	5085 (25.5)

CCAE, Commercial Claims and Encounters; HA, hemophilia A; SD, standard deviation.
*Includes supplemental and coordination of benefits data only. †During enrollment.

Table 2. Machine-learning approach: participant disposition.

	People with congenital HA (n=3144)	Matched cohort of individuals without HA (n=15,673)	Overall (N=18,817)
Sex, male, n (%)	3144 (100)	15,673 (100)	18,817 (100)
Age, n (%)			
<18 years	1353 (43.0)	6527 (41.6)	7880 (41.9)
18–35 years	963 (30.6)	4939 (31.5)	5902 (31.4)
36–45 years	310 (9.9)	1560 (10.0)	1870 (9.9)
46–55 years	275 (8.7)	1399 (8.9)	1674 (8.9)
56–65 years	157 (5.0)	824 (5.3)	981 (5.2)
66–75 years	49 (1.6)	221 (1.4)	270 (1.4)
≥76 years	37 (1.2)	203 (1.3)	240 (1.3)
US region, n (%)			
Northeast	693 (22.0)	3451 (22.0)	4144 (22.0)
North central	903 (28.7)	4497 (28.7)	5400 (28.7)
South	760 (24.2)	3796 (24.2)	4556 (24.2)
West	718 (22.8)	3580 (22.8)	4298 (22.8)
Unknown	70 (2.2)	349 (2.2)	419 (2.2)
Insurance, n (%)			
MarketScan CCAE	3047 (96.9)	15,213 (97.1)	18,260 (97.0)
MarketScan Medicare*	97 (3.1)	460 (2.9)	557 (3.0)
Enrollment length, years			
Mean (SD)	4.07 (3.37)	3.62 (3.16)	3.69 (3.20)
Median (Q1, Q3)	3.00 (1.67, 5.33)	2.67 (1.34, 4.75)	2.75 (1.42, 4.75)
Evidence of diabetes†			
No	2943 (93.6)	14,691 (93.7)	17,634 (93.7)
Yes	201 (6.4)	982 (6.3)	1183 (6.3)
Evidence of hypertension†			
No	2560 (81.4)	12,791 (81.6)	15,351 (81.6)
Yes	584 (18.6)	2882 (18.4)	3466 (18.4)

CCAE, Commercial Claims and Encounters; HA, hemophilia A; SD, standard deviation.
*Includes supplemental and coordination of benefits data only. †During enrollment.

Table 3. Comparison of incidence rates and unadjusted and adjusted IRRs using both approaches.

	Crude incidence rate		Unadjusted IRR	Adjusted IRR
	People with congenital HA	Matched cohort of individuals without HA		
Pharmaco-epidemiological approach (95% CI)	1.08 (0.88–1.30)	0.63 (0.57–0.71)	1.71 (1.66–1.73)	NA
Machine-learning approach (95% CI)	0.25 (0.15–0.34)	0.22 (0.18–0.27)	1.14 (1.07–1.16)	1.31 (0.85–2.00)

CI, confidence interval; HA, hemophilia A; IRR, incidence rate ratio; NA, not applicable.

CONCLUSIONS

- To our knowledge, this represents the largest real-world data study investigating MI in the HA population.
- This study highlights the importance of validating cohort selection methods.
- While every effort was taken to mitigate for the effects of confounders and bias, the results should be interpreted in the context of the limitations of a secondary data use study.
- No evidence of a different risk of MI in PwHA relative to non-HA counterparts was observed in this analysis; however PwHA should be made aware of cardiovascular risks and have access to services to reduce actionable cardiovascular risk factors (e.g. support to stop smoking, reduce hypertension, treat obesity etc.).

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DISCLOSURES

IF: employment (F. Hoffmann-La Roche Ltd); **CF**: no disclosures to report; **KS**: employment (Genentech, Inc.); **TC, AP, CS, PK**: employment (Genentech, Inc.), equity ownership interests (F. Hoffmann-La Roche Ltd/Genentech, Inc.).

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