Association of Hemophilia A Inhibitor Status and Patient-Reported Outcomes with Work Productivity and Health-related Quality of Life

Megan Ullman, MA, MPH[1], Marilyn J. Manco-Johnson, MD[2], Jonathan C. Roberts, MD[3], Nicole Crook, RN[4], Rahul Khairnar, PhD[5], Marquita Decker-Palmer, PhD[5], Randall Curtis, MBA[6], Judith Baker, DrPH, MHSA[4], Amit Soni, MD[4], Joanne Wu, MD, MS[7], Michael B. Nichol, PhD[7]

[1]Gulf States Hemophilia & Thrombophilia Center, University of Texas Health Science Center at Houston, TX; [2]University of Colorado Anschutz Medical Campus, Aurora, CO; [3]Bleeding & Clotting Disorders Institute, Peoria, IL; [4]The Center for Comprehensive Care & Diagnosis of Inherited Blood Disorders, CA; [5]Genentech Inc., South San Francisco, CA; [6]Factor VIII Computing, CA; [7]University of Southern California, CA.

INTRODUCTION

- Persons with hemophilia A (PwHA) suffer from recurrent bleeds, especially hemarthrosis, resulting in joint damage.
- Hemophilia inhibitor status impacts bleeding, which is associated with acute and chronic pain.

OBJECTIVES

- To compare (1) patient-reported outcomes (bleed rate, pain, and joint health), work productivity and activity impairment (WPAI) and (2) health-related quality of life (HRQoL) by inhibitor status.
- Investigate the correlation of patient-reported outcomes with WPAI and HRQoL.

METHODS

- **Study Design**
  - Study enrolled PwHA (FVIII activity level <5%) aged ≥ 2 years with and without inhibitors at a 1:2 ratio, 2019-2021.
  - Participants from 4 geographically diverse U.S. Hemophilia Treatment Centers were classified into 3 groups.
    1) Active inhibitor: FVIII inhibitor titer>1.0 BU six months prior to enrollment.
    2) Tolerized inhibitor: history of inhibitor titer >1.0 BU plus past Immune Tolerance Induction (ITI), and/or use of factor VIII for prophylaxis at enrollment.
    3) No inhibitor
  - Parents/adult participants completed a survey at enrollment to collect sociodemographic and clinical characteristics, self-reported bleeds in the last month, pain, and joint stiffness (5-item Stiffness Impact—a part of HealthMeasures).
  - We also measured WPAI and HRQoL using the EuroQoL EQ-5D-3L.
  - Clinical chart review documented hemophilic severity, inhibitor level and treatment regimen.

- **Statistical Analysis**
  - Patient-reported data were compared across three groups using Chi-square tests for categorical variables and generalized linear models for continuous variables.
  - Association of bleeds, pain, and joint stiffness with HRQoL and WPAI were assessed using Pearson correlation.

ACKNOWLEDGMENTS

Table 1. Participants' Characteristics

Variable	Total (N=80)	Active inhibitor (n=9, 11.3%)	Tolerized inhibitor (n=22, 27.5%)	No inhibitor (n=49, 61.3%)	P Value*
Mean (SD) age	24.9 (14.3)	21.9 (19.1)	16.3 (9.5)	29.3 (13.5)	0.001
Age group: Adults (%)	53 (66.3)	5 (55.6)	9 (40.9)	39 (79.6)	<0.01
Hemophilic severity (%)					0.13
Moderate	10 (12.5)	0 (0.0)	1 (4.5)	9 (18.4)	
Severe	70 (87.5)	9 (100.0)	21 (95.5)	40 (81.6)	
Prophylactic treatment (%)	70 (87.5)	9 (100.0)	21 (95.5)	40 (81.6)	0.13
Had bleeds in last month (%)	39 (48.8)	6 (66.7)	5 (22.7)	28 (57.1)	0.01
Chronic pain level (SE)[†,‡]		2.02 (0.88)	1.13 (0.64)	2.34 (0.44)	>0.06
EQ VAS (SE)[†,§]		71.32 (5.50)a	84.96 (3.99)b	86.49 (2.77)b	<0.02
EQ-5D index score (SE)[†,§]		0.79 (0.07)a	0.96 (0.05)b	0.90 (0.04)a,b	0.03

Note: Data are presented as number (column percentage) for categorical variables, or mean (SD or SE) for continuous variables. *P values were calculated from chi-square tests for categorical variables and analysis of variances for continuous variables to test the variables' association with inhibitor status. a, b For each row, covariates adjusted mean with different symbols (a,b) across the inhibitor status categories statistically significantly differ from one another (P<0.05). The P value for each row is the maximum for all significant comparisons or the minimum across all nonsignificant comparisons. ‡Chronic pain was measured by a question: During the past month, how would you describe your chronic pain level in general on a scale of 0 (no pain) to 10 (worst possible pain)? §EQ VAS is a visual analog scale in which respondents indicate their overall health at the time of the survey. On the VAS, 0 indicates the worst imaginable health and 100 indicates the best imaginable health. The EQ-5D index score was derived from weighted values that represent the U.S. societal perspective, and ranged from 0 (a health state equivalent to death) to 1 (perfect health). Abbreviation: SD, standard deviation; SE, standard error.

Figure 1. Bleeds and Joint Stiffness
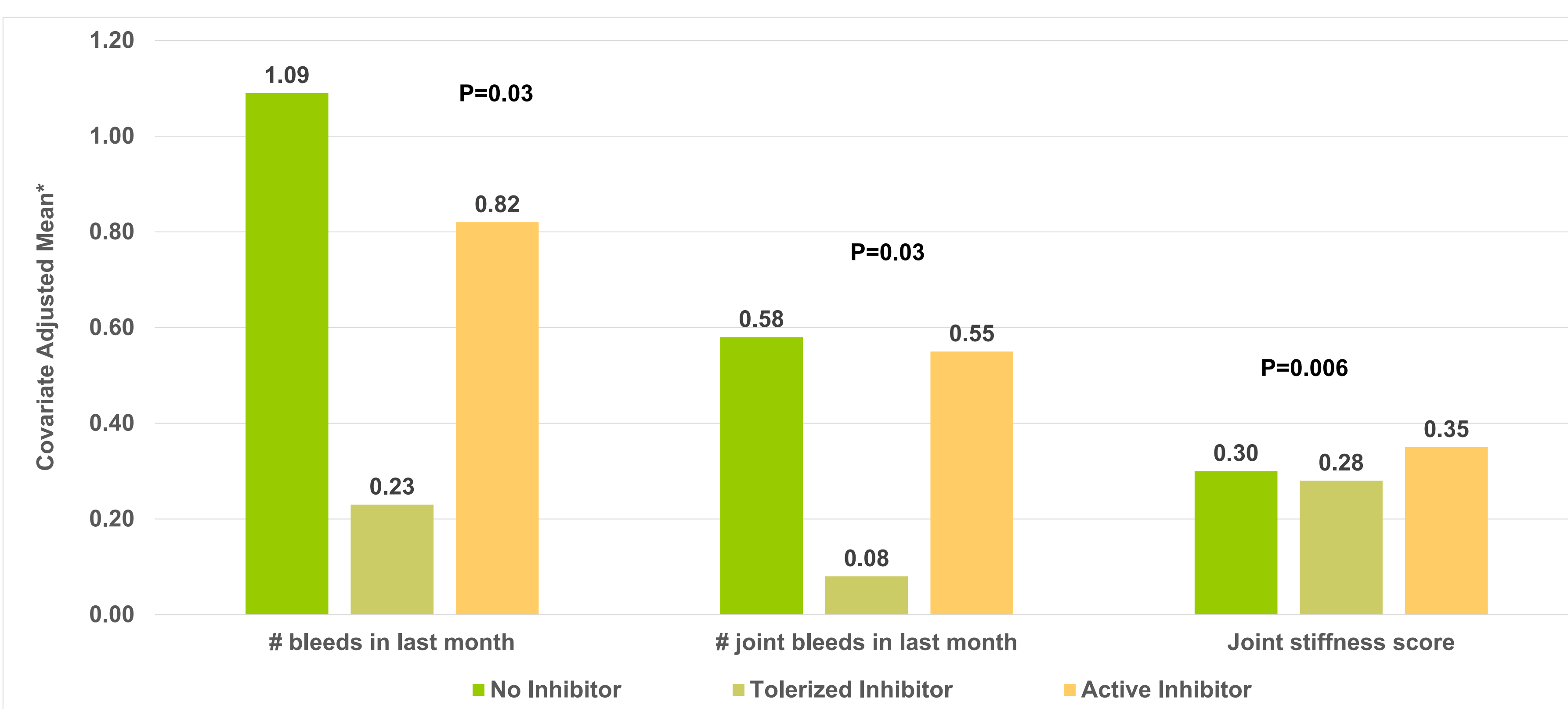
Note: Joint stiffness was measured using 5-item instrument of stiffness impact short form from the HealthMeasures Measurement Systems. Joint stiffness score was standardized to have a mean of 50 and standard deviation of 10. In order to present the data on the same scale, the scores were divided by 100. *Covariates included age, hemophilic severity, and prophylactic treatment.

RESULTS

- Among 80 PwHA enrolled, 9 (11%) had active inhibitors, 22 (27.5%) had tolerized inhibitors, and 49 (61.3%) had no inhibitors (Table 1).
- Mean age of the non-inhibitor group (29.3±13.5) was older than the tolerized inhibitor group (16.3±9.5 years, p<0.05) or the active inhibitor group (21.9±19.1, p>0.05) (Table 1).
- The non-inhibitor group had a lower rate of severe hemophilia (81.6%) or prophylactic treatment (81.6%) than those in the active (100%) or tolerized groups (95.5%, p=0.13) (Table 1).
- Larger proportions of participants with active inhibitors (66.7%) and no inhibitors (57.1%) reported having bleeds in the last month compared to those with tolerized inhibitors (22.7%, p=0.01) (Table 1).
- Participants without inhibitors had a greater mean number of bleeding episodes (1.09±standard error (SE) 0.26 vs. 0.23±0.38, p=0.03), specifically joint bleeds (0.58±0.16 vs. 0.08±0.24, p=0.03,) than the tolerized group (Figure 1).
- Those with active inhibitors reported significantly higher mean joint stiffness scores (35.1±2.6 vs. 27.5±1.9, p=0.006) (Figure 1) or higher proportion of joint pain (77.8% vs. 54.5%, p=0.23) than the tolerized group.
- Mean EQ-5D index score was significantly lower in the active inhibitor group (0.79±SE (0.07) than in the tolerized group (0.96±0.05, p=0.03) (Table 1).
- Joint bleeding, chronic pain, and joint stiffness were negatively correlated with the EQ-5D visual analogue scale, and index scores (all correlation coefficients |r|>0.43, all p<0.001).
- Number of bleeds and the joint stiffness score in children were positively correlated with their parents' level of impairment while working (r=0.41, p=0.04; r=0.62, p=0.001) and overall work impairment (r=0.41, p=0.046; r=0.60, p=0.002).
- Joint bleeding, chronic pain, and joint stiffness in adults were positively correlated with WPAI including proportion of work time missed (r=0.31, p=0.03; r=0.39, p=0.006; r=0.48, p=0.0004), overall work impairment (r=0.37, p=0.007; r=0.41, p=0.003; r=0.42, p=0.002), and activity impairment (r=0.33, p=0.02; r=0.63, p<0.0001; r=0.59, p<0.0001), respectively.

LIMITATIONS & CONCLUSION

- The study sample was skewed toward a younger age in the tolerized inhibitor group, making age a possible confounding factor.
- Better outcomes observed in the tolerized group might be due to younger age rather than inhibitor status.
- PwHA in the active and no inhibitor groups experienced greater clinical burden as measured by bleeds compared to the tolerized group.
  - This may be due to more consistent adherence to treatment regimens among tolerized PwHA so as to prevent inhibitor recurrence.
- Those with an active inhibitor displayed lower HRQoL scores than the tolerized inhibitor group.
- Bleeds, chronic pain and joint stiffness were inversely correlated with HRQoL, resulting in lower work productivity and activity.