An Insight into Clinical Outcomes in Mild, Moderate, and Severe Hemophilia A (HA): A Preliminary Analysis of the CHESS II Study

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The CHESS II study collected real-world data on the burden-of-illness in adult PwHA without FVIII inhibitors

- The previous CHESS I study captured the annualized **economic and psychosocial burden of severe hemophilia**[1] and the CHESS PAEDS study assessed the **burden-of-illness of moderate and severe hemophilia** in the pediatric population[2]
  - Both studies were conducted in five European countries (France, Germany, Italy, Spain, UK)[1,2]

- However, there is a **paucity of data** on the clinical burden of HA across disease severity, especially **in mild and moderate HA**

- **Aim of this interim analysis**
  - To examine **clinical outcomes by disease severity** in adult PwHA without current FVIII inhibitors in relation to treatment strategy, in eight European countries (Denmark, France, Germany, Italy, Netherlands, Romania, Spain, and the UK)

CHESS, Cost of Haemophilia Across Europe: a Socioeconomic Survey; CHESS PAEDS, Cost of Haemophilia across Europe – a Socioeconomic Survey in a paediatric population;
HA, hemophilia A; PwHA, persons with hemophilia A.

1. O'Hara J, et al. Orphanet J Rare Dis. 2017;12:106;
2. O'Hara J, et al. ISTH 2019: OC 70.1.

HA severity classification is based on the amount of FVIII clotting factor activity in the person's blood

- HA, a congenital bleeding disorder caused by a deficiency in FVIII, is characterized by uncontrolled bleeding and musculoskeletal dysfunction[1]

	HA severity		
	Mild	**Moderate**	**Severe**
% of patients[2]	23–30%	17–18%	51–59%
% FVIII level[3]	5–<40%	1–<5%	<1%
Bleeding episodes[3]	• Severe bleeding with major trauma or surgery • Spontaneous bleeding is rare	• Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery	• Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge

- Residual FVIII activity level accounts for ~70% of the bleeding phenotype, the remaining ~30% are potentially related to unexplained individual variables; thus some patients do not exhibit a bleed phenotype as traditionally expected based on their FVIII level[4]

1. Mannucci PM & Tuddenham EG. N Engl J Med. 2001;344:1773–9;
2. CDC. Registry report on males with haemophilia 2014–2017. Diagnosis & severity. Available at: https://www.cdc.gov/ncbddd/hemophilia/communitycounts/registry-report-males/diagnosis.html. [Accessed May 2020];
3. WFH. Guidelines for the management of haemophilia. 2012. Available at: https://www1.wfh.org/publications/files/pdf-1472.pdf. [Accessed May 2020]; 4. Mancuso ME, et al. J Thromb Haemost. 2018;16:2106–2110.

F, factor; HA, hemophilia A.

For this interim analysis, 12 months of retrospective data were captured from physicians and patients

1. Physician recruitment

- **120** hematologists/hemophilia healthcare providers recruited from Denmark, France, Germany, Italy, Netherlands, Romania, Spain, UK

2. Physician profiling

- Physicians completed workload survey and attitudinal profile online

3. Patient profiling

- **787** web-based case report forms (CRFs) for treated patients ≥18 years old completed by physicians
  - This included patient's medical history, consultations, clinical information, and healthcare resource utilization
  - **628** PwHA were recruited, **580** of which were included in the analysis; mild HA (**n=97**), moderate HA (**n=199**), severe HA (**n=284**)

4. Patient perspective

- Paper-based PPIE questionnaire, covering non-medical costs, work impairment, and health status, was completed by the patients

HA, hemophilia A; PPIE, patient and public involvement and engagement; PwHA, persons with hemophilia A.

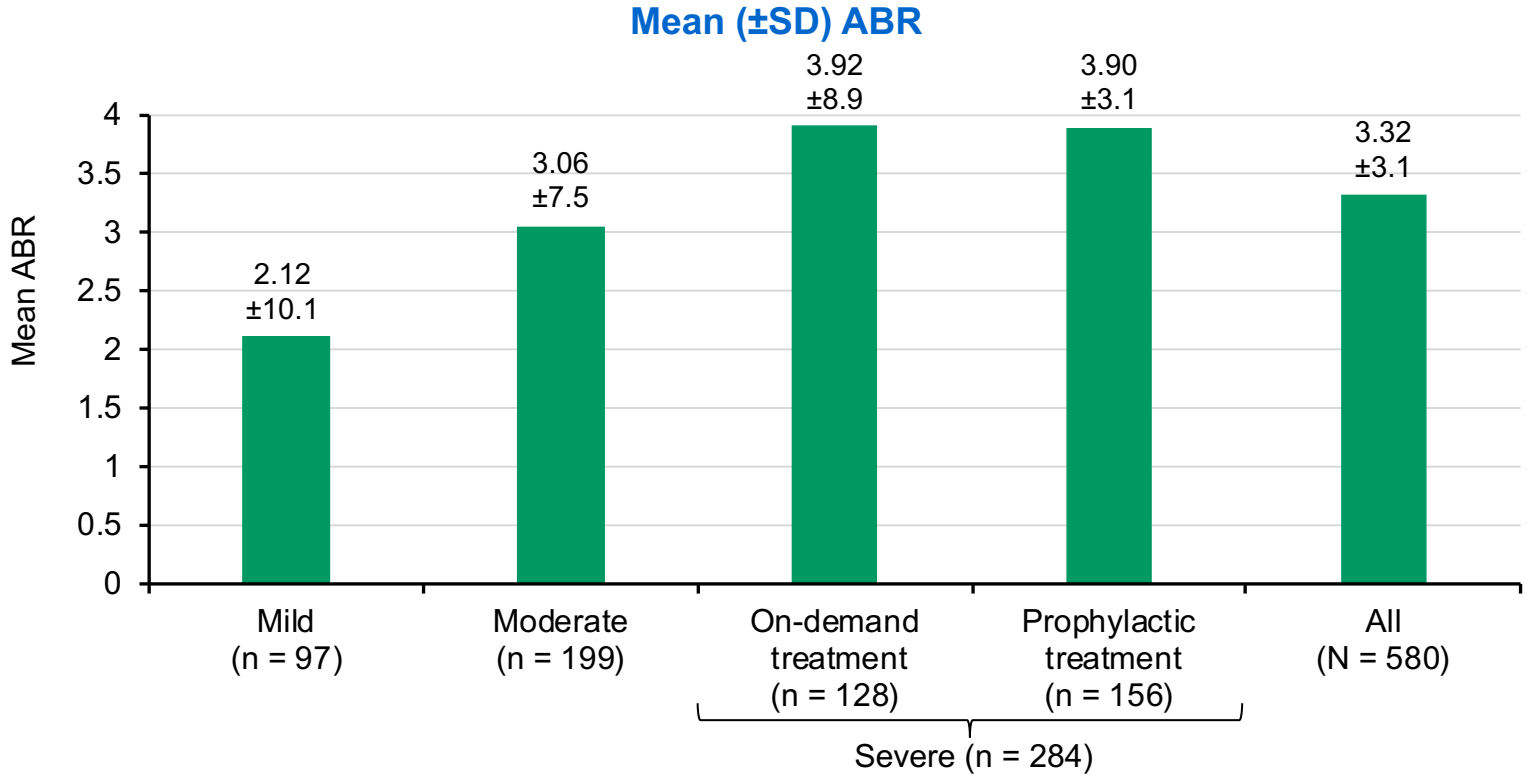
Baseline demographics and characteristics

- Bleed data were available for 580 PwHA without current FVIII inhibitors

	Mild HA (n = 97)	Moderate HA (n = 199)	Severe HA (n = 284)		All (N = 580)
			Prophylactic treatment	On-demand treatment	
Mean age (SD), years	39.41 (14.8)	38.82 (15.1)	38.33 (14.5)	35.91 (12.8)	38.15 (14.4)
Mean BMI (SD), kg/m²	24.59 (2.4)	24.59 (3.0)	24.92 (2.9)	24.33 (2.5)	24.62 (2.8)
Treatment strategy, n (%)					
Prophylaxis*	2 (2)	17 (9)	156 (55)		175 (30)
On-demand†	26 (27)	62 (31)	128 (45)		216 (37)
No treatment	69 (71)	120 (60)	0		189 (33)

*Includes both primary prophylaxis, where treatment has always been prophylactic, and secondary prophylaxis, where treatment was previously episodic or 'on-demand', and currently prophylactic;
†Includes both primary on-demand, where treatment has always been episodic or 'on-demand'; and secondary on-demand, where treatment was previously prophylactic and is currently episodic or 'on-demand'.
BMI, body mass index; HA, hemophilia A; PwHA, persons with hemophilia A; SD, standard deviation.

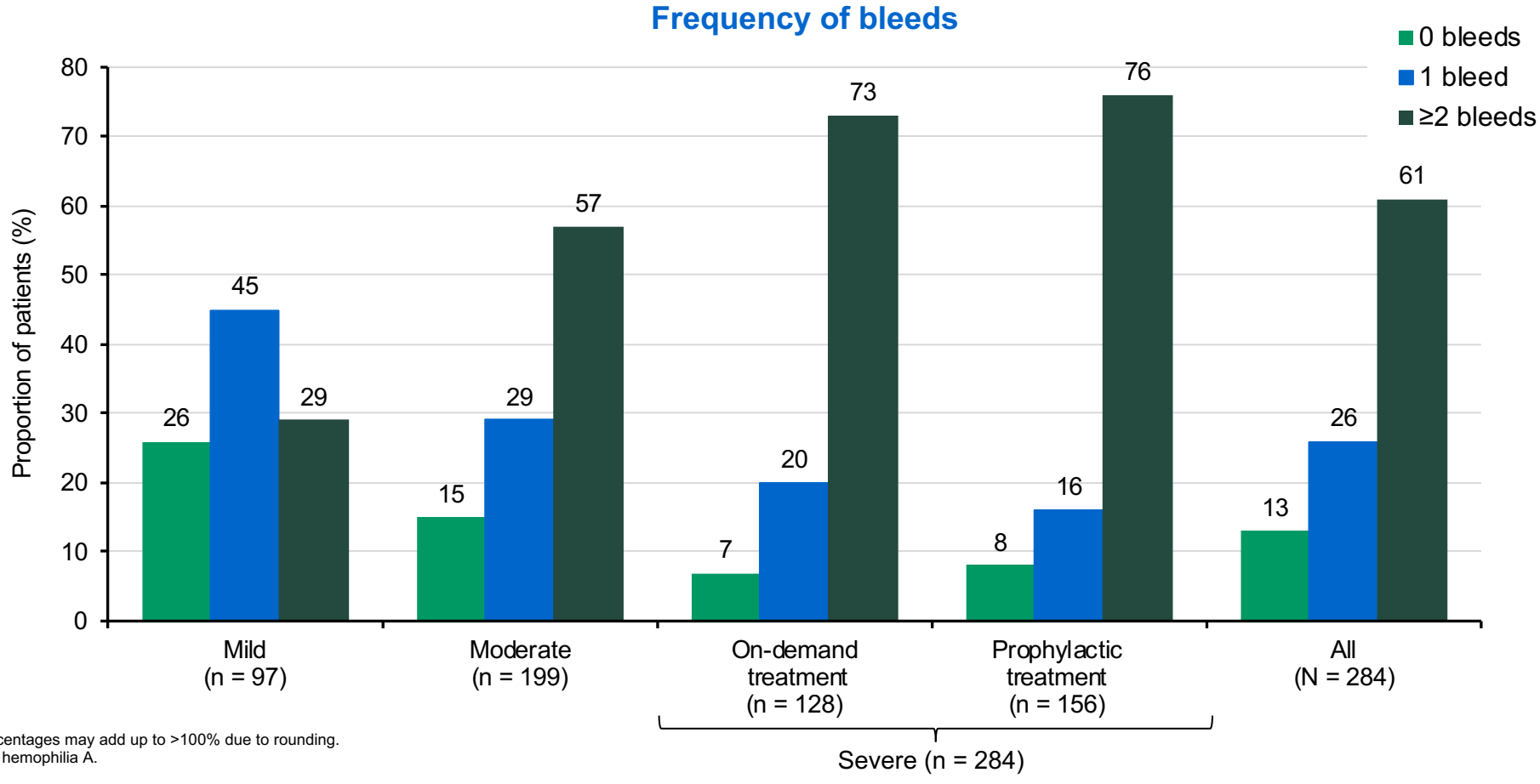
The mean ABR was >2 in PwHA without FVIII inhibitors in all disease severity categories



Median ABR (IQR)	1 (2)	2 (3)	3 (3)	3 (3)

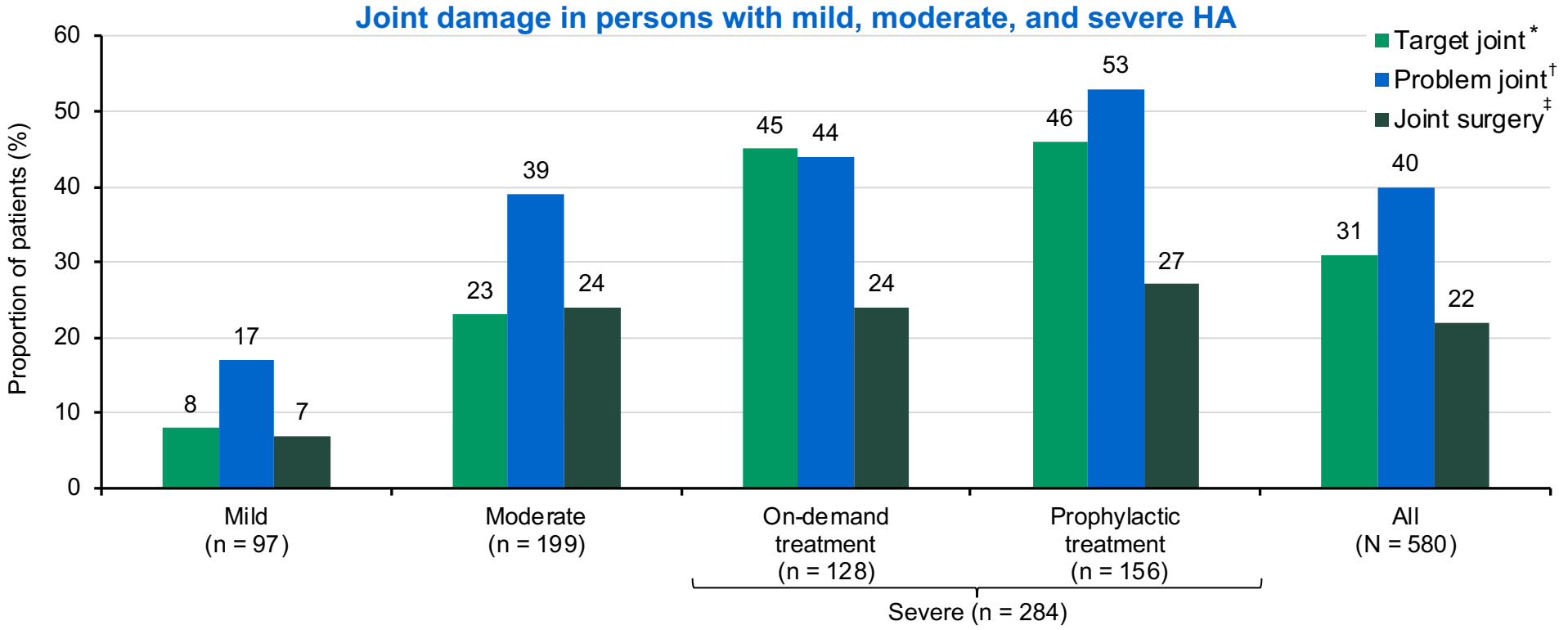
ABR is for the past 12 months.
ABR, annualized bleed rate; IQR, interquartile range; PwHA, persons with hemophilia A; SD, standard deviation.

The majority of patients with moderate and severe HA had ≥2 bleeds a year



Percentages may add up to >100% due to rounding.
HA, hemophilia A.

Patients with moderate and severe HA receiving on-demand treatment had similar incidences of problem joints and joint surgery



*A joint in which ≥3 spontaneous bleeds have occurred within a consecutive 6-month period. Where there have been ≤2 bleeds into the joint within a consecutive 12-month period the joint is no longer considered a target joint[1]; †Problem joint: any joint that has been permanently damaged as a result of patients bleeding disorder, with or without persistent bleeding; a problem joint can be defined as having chronic joint pain and/or limited range of movement due to compromised joint integrity (i.e. chronic synovitis and/or hemophilic arthropathy)[2]; ‡Target joint surgery includes: arthrocentesis (joint aspiration), arthrodesis (joint fusion), arthroplasty (joint reconstruction/replacement), arthroscopy (joint examination/repair via endoscope), and synovectomy (removal of synovium)[1].

HA, hemophilia A.

1. Blanchette VS, et al. J Thromb Haemost 2014:12:1935–9;
2. O'Hara J, et al. Haemophilia 2019;25(S1):P154.

Conclusions

- The CHESS II study addresses the **lack of available data on clinical outcomes across disease severity**, and is one of the **largest datasets in mild/moderate HA available to date**; the data presented here are from an interim analysis, with further data on a larger sample to follow
- These data demonstrate that **all PwHA experience bleeds regardless of disease severity**; they also highlight the **unmet need in patients with mild and moderate disease severity**
- **Persons with mild and moderate HA appear to exhibit a clinical burden indicated by their ABR and frequency of bleeds**
  - The majority of patients with moderate disease experienced ≥2 bleeds, which may lead to irreversible, long-term joint damage
- In patients with severe disease, **mean ABR and frequency of bleeds were similar**, **regardless of treatment regimen**
- The proportions of patients with **problem joints and the incidence of surgeries** to affected joints were **similar in patients with moderate and severe HA receiving on-demand treatment**, indicating that HA may have a similar impact on quality of life in these patients

ABR, annualized bleed rate; HA, hemophilia A; PwHA, persons with hemophilia A.

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