Surgical experience from four phase III studies (HAVEN 1–4) of emicizumab ▼ in persons with haemophilia A (PwHA) with or without FVIII inhibitors

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. These should be reported to the Regulatory authorities in your country according to your national requirements.

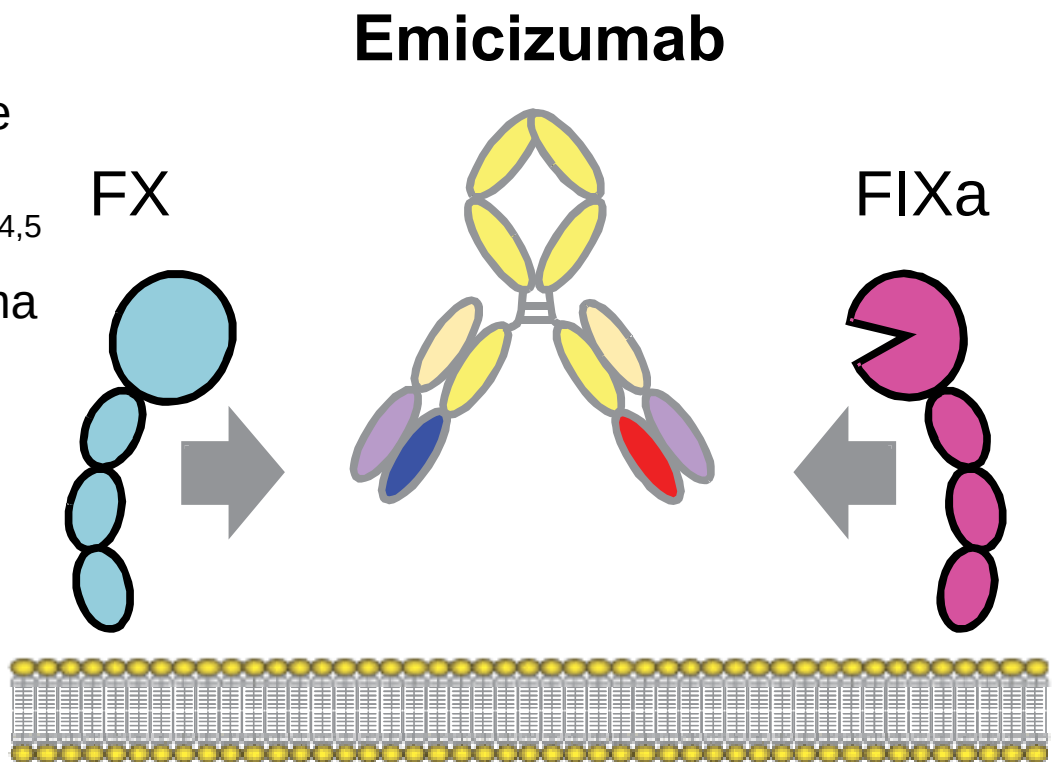
Disclosures

- Disclosures for Elena Santagostino

Consultant	Bayer, Shire, Takeda, Pfizer, Novo Nordisk, CSL Behring, Sobi, Bioverativ, Roche, Grifols, Kedrion, Octapharma, Uniqure, Spark
Speaker bureaus	Bayer, Shire, Takeda, Pfizer, Novo Nordisk, CSL Behring, Sobi, Bioverativ, Roche, Grifols, Kedrion, Octapharma
Employee, shareholder, grant/research support, paid instructor, etc	No relevant conflicts of interest to declare

Emicizumab: a humanised bispecific monoclonal antibody

- Bridges activated FIX and FX to replace the function of missing activated FVIII in PwHA, restoring haemostasis[1]
- Does not induce FVIII inhibitors as it shares no sequence homology with FVIII[2,4–6]
- Is administered subcutaneously with high bioavailability[2,4,5]
- Has a long half-life, enabling effective steady-state plasma concentrations throughout the dosing interval[6]
- Is approved for routine prophylaxis in PwHA of all ages, with or without FVIII inhibitors[2,4,5]
- Can be given QW, Q2W or Q4W[4–7]

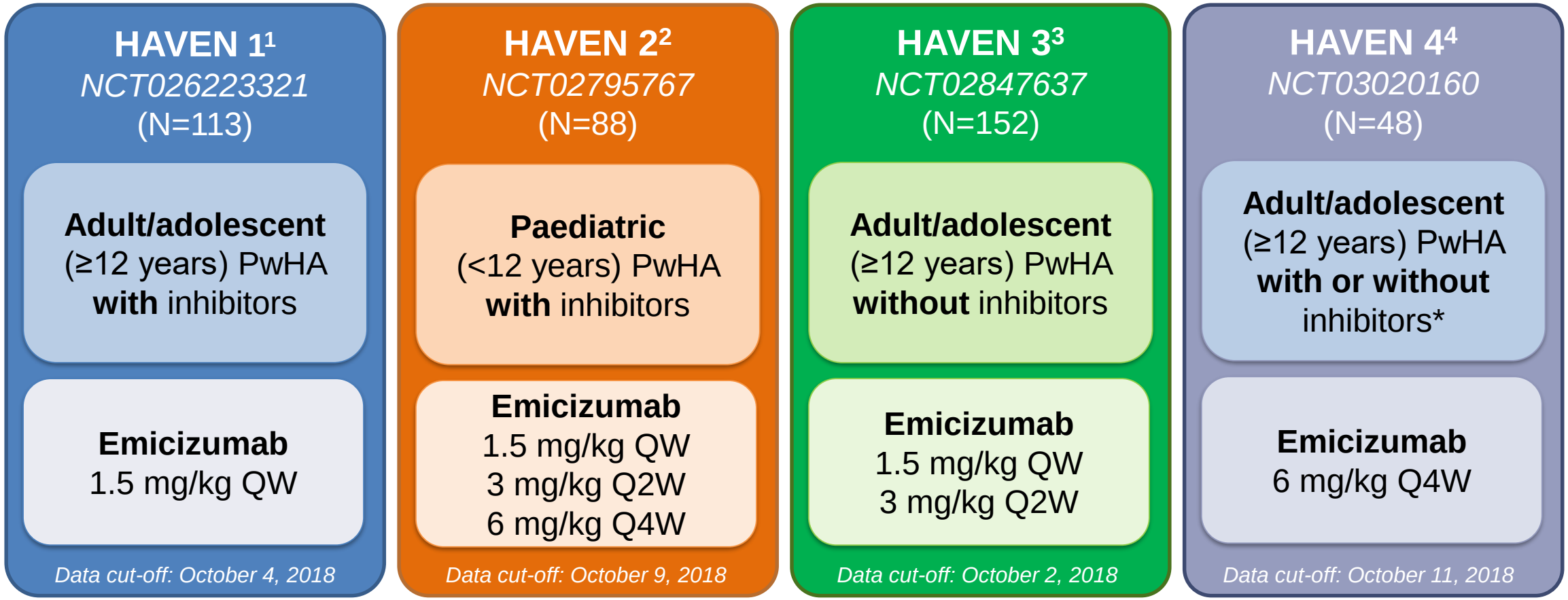


- Management and outcomes of patients who underwent surgical procedures during emicizumab studies are of clinical interest
- Herein we describe the surgical experience across the HAVEN programme

F, factor; PwHA, persons with haemophilia A; QW, once weekly
Q2W, every 2 weeks; Q4W, every 4 weeks

1. Kitazawa T, et al. Thromb Haemost 2017;117:1348–57; 2. Kitazawa T, et al. Nat Med 2012;18:1570–4; 3. Sampei Z, et al. PLoS One 2013;8:e57479; 4. Oldenburg J, et al. N Engl J Med 2017;377:809–18; 5. Mahlangu J, et al. N Engl J Med 2018;379:811–22
6. US Emicizumab PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761083s002s004lbl.pdf Accessed May 13, 2019
7. Pipe S, et al. Lancet Haematol 2019; doi: 10.1016/S2352-3026(19)30054-7

HAVEN study participants and emicizumab dosing regimens



*Five participants had FVIII inhibitors and 43 participants did not have FVIII inhibitors at study entry
A loading dose of 3 mg/kg QW for 4 weeks was applied to all regimens, followed by the maintenance dosing regimens listed

1. Oldenburg J, et al. N Engl J Med 2017;377:809–18; 2. Young G, et al. ASH 2018; oral presentation #623
3. Mahlangu J, et al. N Engl J Med 2018;379:811–22; 4. Pipe SW, et al. Lancet Haematol 2019; doi: 10.1016/S2352-3026(19)30054-7

Methods

- Unplanned surgeries and elective minor procedures were allowed in the HAVEN programme
- Surgical procedures were managed per the investigator's discretion
- Data are pooled across studies for all participants who received emicizumab treatment (N=399)* to describe their surgical experiences
  - Procedures were categorised as minor or major as defined by Santagostino *et al*.[1]
  - Details of procedures, FVIII utilisation, adverse events and bleeds were captured prospectively[2–5]
- Analysis objectives:
  - Type and number of procedures performed
  - Perioperative use of FVIII or BPA
  - Occurrence of surgery-related bleeds or adverse events

*One participant in HAVEN 1 discontinued prior to treatment
BPA, bypassing agent

1. Santagostino, et al. Haemophilia 2015;21:34–40; 2. Oldenburg J, et al. N Engl J Med 2017;377:809–18
3. Young G, et al. ASH 2018; oral presentation #623; 4. Mahlangu J, et al. N Engl J Med 2018;379:811–22
5. Pipe SW, et al. Lancet Haematol 2019; doi: 10.1016/S2352-3026(19)30054-7

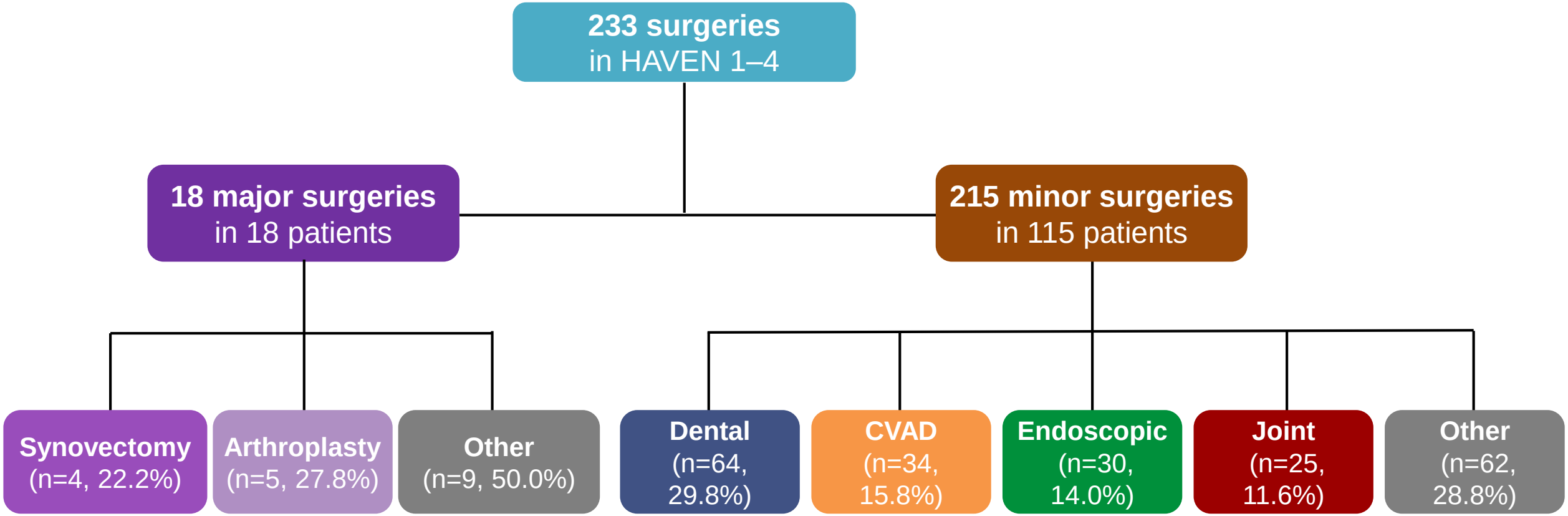
Characteristics of patients who underwent surgical procedures

- Across HAVEN 1–4, 126/399 (31.6%) participants who received emicizumab had at least one surgery

Characteristic	HAVEN 1 N=38	HAVEN 2 N=27	HAVEN 3 N=45	HAVEN 4 N=16	Total N=126
Number of patients who underwent					
1 surgical procedure, n (%)	21 (55.3)	25 (92.6)	25 (55.6)	12 (75.0)	83 (65.9)
2 surgical procedures, n (%)	6 (15.8)	2 (7.4)	8 (17.8)	2 (12.5)	18 (14.3)
>2 surgical procedures, n (%)	11 (28.9)	0	12 (26.7)	2 (12.5)	25 (19.8)
Median duration of emicizumab exposure (IQR), weeks	101.7 (84.1–127.1)	79.1 (67.1–102.1)	89.1 (80.3–97.1)	68.1 (68.1–72.1)	86.3 (75.1–102.1)
Median age (IQR), years	31.5 (17.0–46.0)	7.0 (5.0–8.0)	44.0 (29.0–53.0)	46.5 (35.5–57.5)	33.5 (13.0–49.0)

IQR, interquartile range

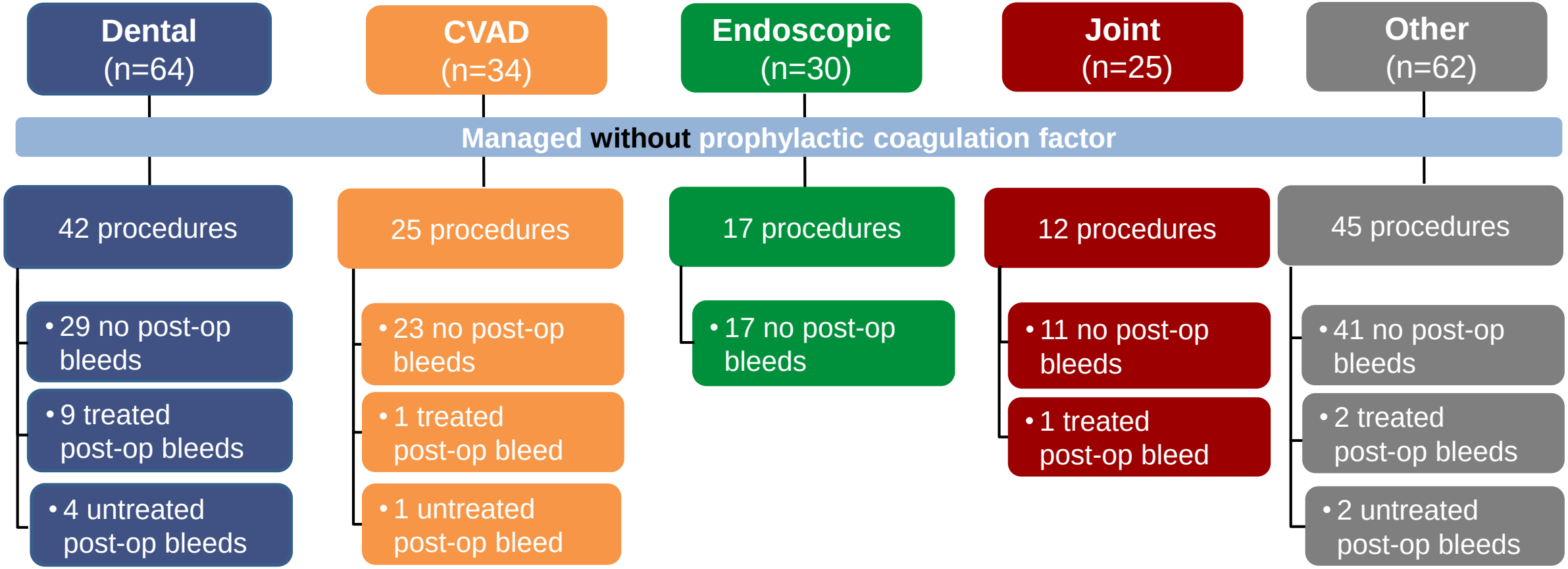
Types of surgeries



n refers to the number of surgeries. Patients with both minor and major surgeries are counted in both categories
CVAD, central venous access device

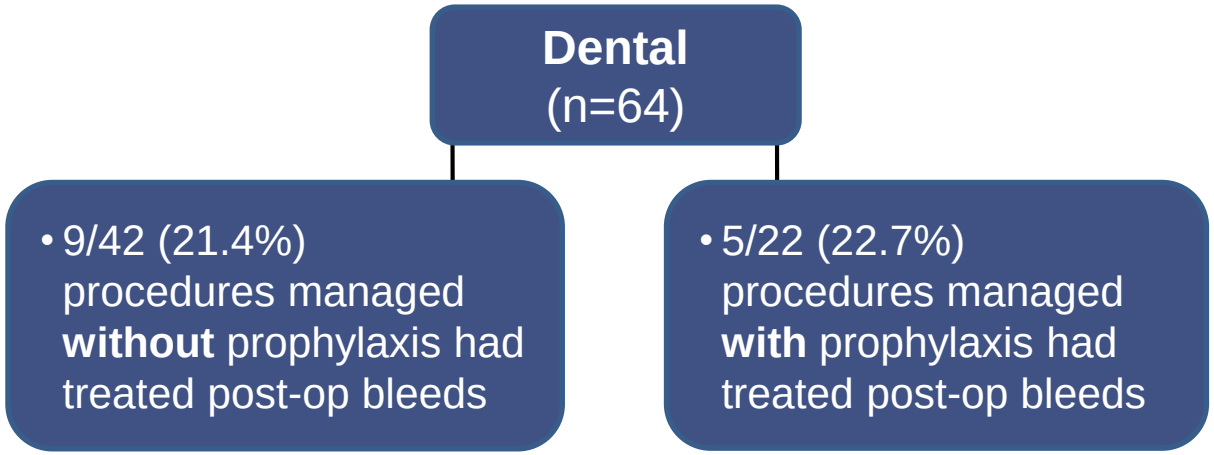
The majority of minor surgeries/procedures were managed without prophylactic coagulation factor and were not associated with treated bleeds

- Of the 141 (65.6%) minor surgeries/procedures managed without prophylactic coagulation factor, 128/141 (90.8%) did not result in treated post-operative bleeds



Post-op, post-operative
n refers to the number of surgeries

The majority of minor dental surgeries/procedures were managed without prophylaxis and were not associated with bleeds

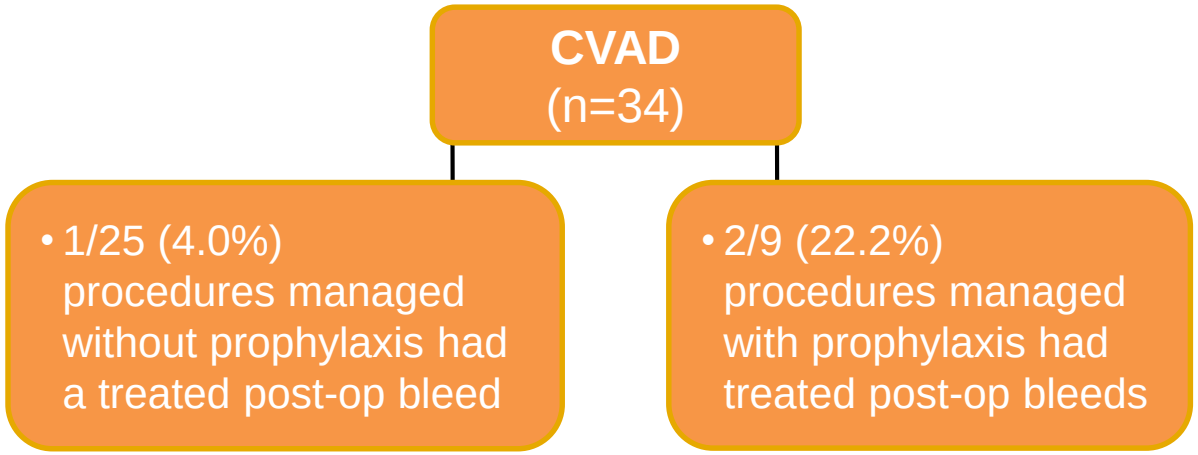


- An anti-fibrinolytic was used in 43 dental procedures in 28 patients

	rFVIIa	Standard FVIII*	EHL FVIII*
# prophylactic doses/surgery, median (IQR)	1.0 (1–1)	1.0 (1–1)	1.0 (1–1)
Prophylactic cumulative dose/surgery, median (IQR)	83.4 μg/kg (83.4–106.8)	25.4 U/kg (24.8–38.9)	42.1 U/kg (36.8–47.4)
# treatment doses for post-op bleeds/surgery, median (IQR)	2.5 (2–4)	2.5 (2–3)	1.0 (1–1)
Cumulative dose for post-op bleeds/surgery, median (IQR)	248.6 μg/kg (166.9–347.8)	56.3 U/kg (32.5–77.3)	42.7 U/kg (37.9–47.4)

n refers to the number of surgeries; *Among PwHA without inhibitors
EHL, extended half-life; rFVIIa, recombinant activated FVII

The majority of CVAD minor surgeries/procedures were managed without prophylactic coagulation factor and were not associated with bleeds

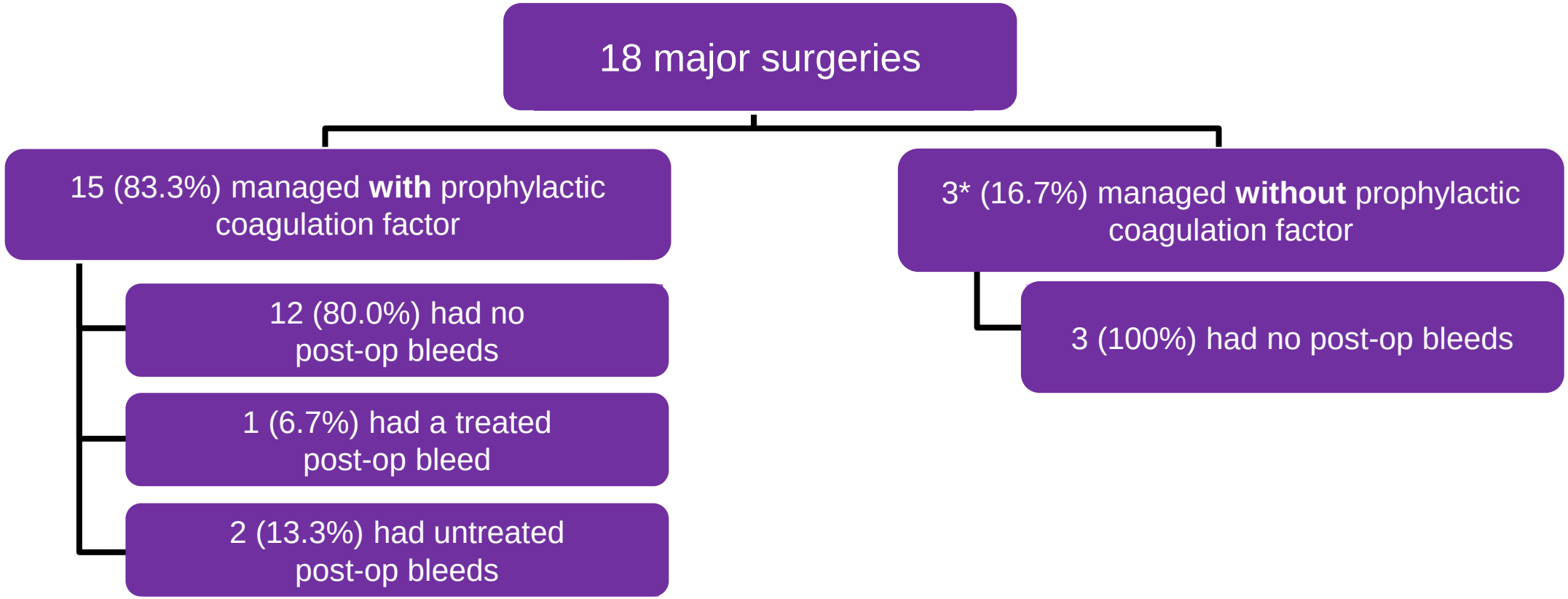


	rFVIIa
# prophylactic doses/surgery rFVIIa, median (IQR)	1.0 (1–2)
Prophylactic cumulative dose/surgery of rFVIIa, median (IQR)	119.0 mg/kg (86.5–168.7)
# treatment doses of rFVIIa for post-op bleeds/surgery, median (IQR)	1.0 (1–6)
Cumulative dose for post-op bleeds/ surgery of rFVIIa, median (IQR)	94.6 mg/kg (81.0–306.5)

- An anti-fibrinolytic was used in 12 CVAD procedures in 12 patients

No patients without inhibitors were managed with FVIII prophylaxis for CVAD procedures; n refers to the number of surgeries

The majority of major surgeries were managed with prophylactic coagulation factor and did not result in post-operative bleeds



- Major orthopaedic surgeries managed with prophylactic coagulation factor included arthroplasty (n=5), and synovectomy (n=3)

*Synovectomy (n=1), open reduction of fracture (n=1), and muscle suture (n=1)

Major surgeries: arthroplasty

	Ankle arthroplasty	Hip arthroplasty[1]		Hip arthroplasty	Hip arthroplasty	Knee arthroplasty
Type of prophylaxis	Standard rFVIII	rFVIIa	pdFVIII	rFVIIa	EHL FVIII	rFVIIa
Cumulative dose						
Only pre-operative	65.9 U/kg	98.4 μg/kg	–	89.7 μg/kg	78.6 U/kg	357.7 μg/kg
Cumulative dose post-procedure	395.6 U/kg	3688.5 μg/kg	751.4 U/kg	4756.4 μg/kg	864.3 U/kg	7064.1 μg/kg
Number of doses in the first 7 days post-procedure, n	11	11	5	33	22	52
Total post-op days on prophylaxis or treatment	19	17	7	23	16	29
Bleed due to surgery	No	Yes		No	No	No
Additional medication	–	Standard FVIII; antifibrinolytic therapy[1*]		Antifibrinolytic therapy	–	Antifibrinolytic therapy
Adverse events of special interest	No TE or TMA	No TE or TMA		No TE or TMA	No TE or TMA	No TE or TMA

*Recorded as an untreated bleed, however upon further investigation, this bleed was managed with coagulation factor

EHL, extended half-life; pdFVIII, plasma-derived FVIII; TE, thromboembolic event; TMA, thrombotic microangiopathy

1. Santagostino E, et al. Haematologica 2019; 104:xxxx (Epub ahead of print)

Major surgeries: synovectomy*

	Synovectomy	Synovectomy	Arthrofibrosis + chrondroplasty + joint debridement + synovectomy
Type of prophylaxis	Standard rFVIII	Standard rFVIII	rFVIIa
Cumulative dose			
Only pre-operative	55.0 U/kg	106.7 U/kg	170.2 μg/kg
Cumulative dose post-procedure	192.6 U/kg	–	4087.8 μg/kg
Number of total doses post-procedure, n	4	–	49
Total post-op days on prophylaxis or treatment	3	–	15
Bleed due to surgery	No	No	Yes
Additional medication	–	–	–
Adverse events of special interest	No TE or TMA	No TE or TMA	No TE or TMA

*There was one additional major surgical case of synovectomy, which was managed without prophylaxis

Conclusions

- Minor and major surgeries were performed safely in PwHA receiving emicizumab prophylaxis while participating in the HAVEN programme
- The majority of minor surgeries/procedures (141/215, 65.6%) were performed without prophylactic coagulation factor, and of those, >90% did not result in a treated post-operative bleed
  - Emicizumab alone may provide adequate haemostatic coverage for patients undergoing certain types of minor surgeries
- 18 major surgeries (including orthopaedic) performed mostly with additional prophylactic coagulation factor, resulting in 1 treated bleed
- No major or minor surgery/procedure in PwHA with or without inhibitors resulted in death, thrombosis, new FVIII inhibitor development, or unexpected bleed

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