Update in Bleeding Disorders

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UNC

SCHOOL OF MEDICINE

Blood Research Center

Disclosures

Commercial Interest	Nature of Relevant Financial Relationship (Include all those that apply)	
	What was received	**For what role**
Takeda	• Honoraria	• Speaking
Takeda	• Research Grant	• PI on research grant

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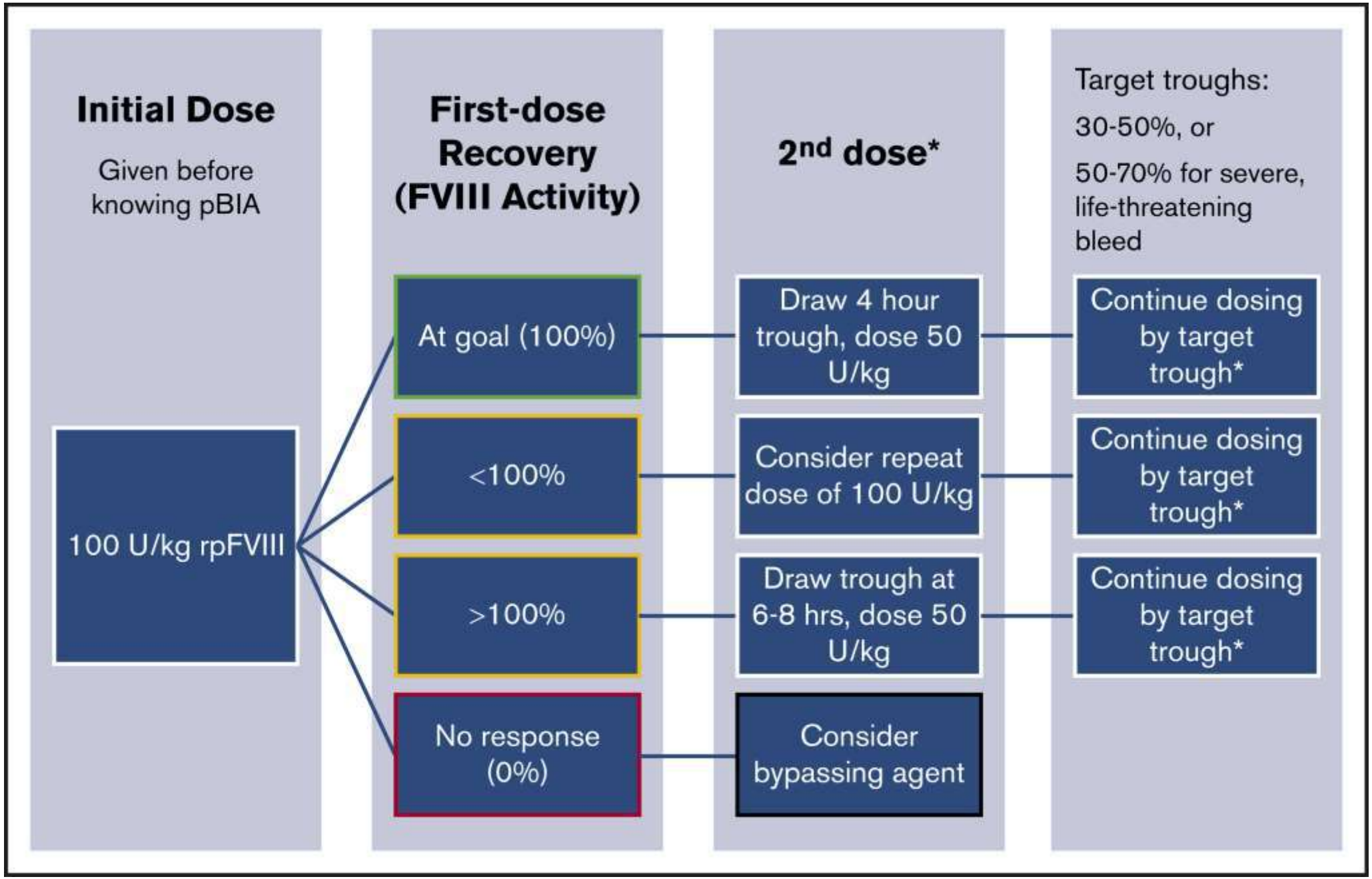
Outline

- Acquired Hemophilia
- ITP
- Von Willebrand Disease
- Hemophilia

Case 1

- A 78 yo man with coronary artery disease, insulin-dependent diabetes, hypertension,and emphysema presented with gross hematuria and an elevated aPTT at 78 sec.
- The patient was found to have acquired hemophilia A, with a Factor VIII level of 1% and a Bethesda titer of 104.
- The patient was treated with recombinant porcine FVIII for 6 days, with excellent bleed resolution, according to UNC protocol, which uses less rpFVIII than current package insert.
- Immunosuppression with Rituximab was also started



Ellsworth P, et al. Blood Adv, 2020, 4:6240

Case 1

- Unfortunately, the patient's hematuria recurred within 2 weeks. He also had a left forearm hematoma. His repeat Bethesda titer was lower at 68. He had not developed a porcine inhibitor titer. He was treated again with rpFVIII. He completed his course of 4 doses of Rituximab.
- After insurance approval, prophylaxis with emicizumab was started.
- No further episodes of hematuria occurred

Emicizumab

- Bispecific antibody binding FIXa and FX, thus mimicking the action of FVIIIa
- Approved for patients with hemophilia A, with or without inhibitors to FVIII
- Approved to give SQ once weekly at a load of 3 mcg/kg/week x 4 weeks, then 1.5 mcg/kg/week
- Publications
  - Knoebl P et al. Blood. 2020 Aug 7 epub PMID: 32766881
  - Al-Banaa K et al Am J Case Rep. 2019 20:1046
  - Tiede A et al J Thromb Haemost. 2020
  - Möhnle P et al. Transfus Med Hemother. 2019 6(2):121
  - Hess KJ Am J Case Rep. 2020
  - Dane KE et al. Res Pract Thromb Haemost. 2019 Apr 9;3(3):420-423
  - Ganslmeier M. et al Haemophilia. 2020

12 pts with AHA from University of Vienna

- Newly diagnosed, 6 men, 6 women, all with bleeding
  - 8 with severe bleeding (organ-, limb- or life-threatening, drop in hemoglobin levels >2 g/dL, or need for ≥2 red blood cell transfusions)
  - 6 - associated major surgery and bleeding from surgical wounds.
  - 5 - deep muscle hematomas
  - 10 - superficial muscle hematomas
  - 1 with retroperitoneal bleeding
  - all patients had extended skin hematomas
- median age 74 years (range, 51-87 years)
- Comorbidities
  - older age (6 patients were older than 75 years);
  - 1 had extensive chronic inflammatory bowel disease, heavily pretreated with >10 abdominal surgeries and long-term immunosuppression, complicated by pulmonary tuberculosis;
  - 5 patients had metabolic syndrome with adiposity, diabetes, and hypertension;
  - 2 had active infections (peritonitis, tuberculosis, large infected abdominal wound); 6 had severe arteriosclerosis, coronary heart disease, femoral arterial bypass grafting, and atrial fibrillation.
- Labs
  - FVIII <1 (<1 to 1.5)
  - Inhibitor titer 22.3 (9-80)

Hemostatic Treatment

- All 8 with severe bleeding got bypassing agents
- Assessment by independent board of coagulationists
  - 5 patients had insufficient response to bypassing therapy,
  - 1 had an adverse event to bypassing therapy,
  - 3 had social reasons as additional factors limiting the use of approved hemostatic therapy.
  - Five patients had very high inhibitor titers >60 BU/mL, 4 of them after recent surgery,
- A conclusion that conventional AHA therapy seemed to be associated with a high rate of complications, and that emicizumab plus reduced-intensity immunosuppression could be a better option, led to a shared decision-making process between physicians and patients.
- Decision for Emicizumab plus rituximab

Therapy

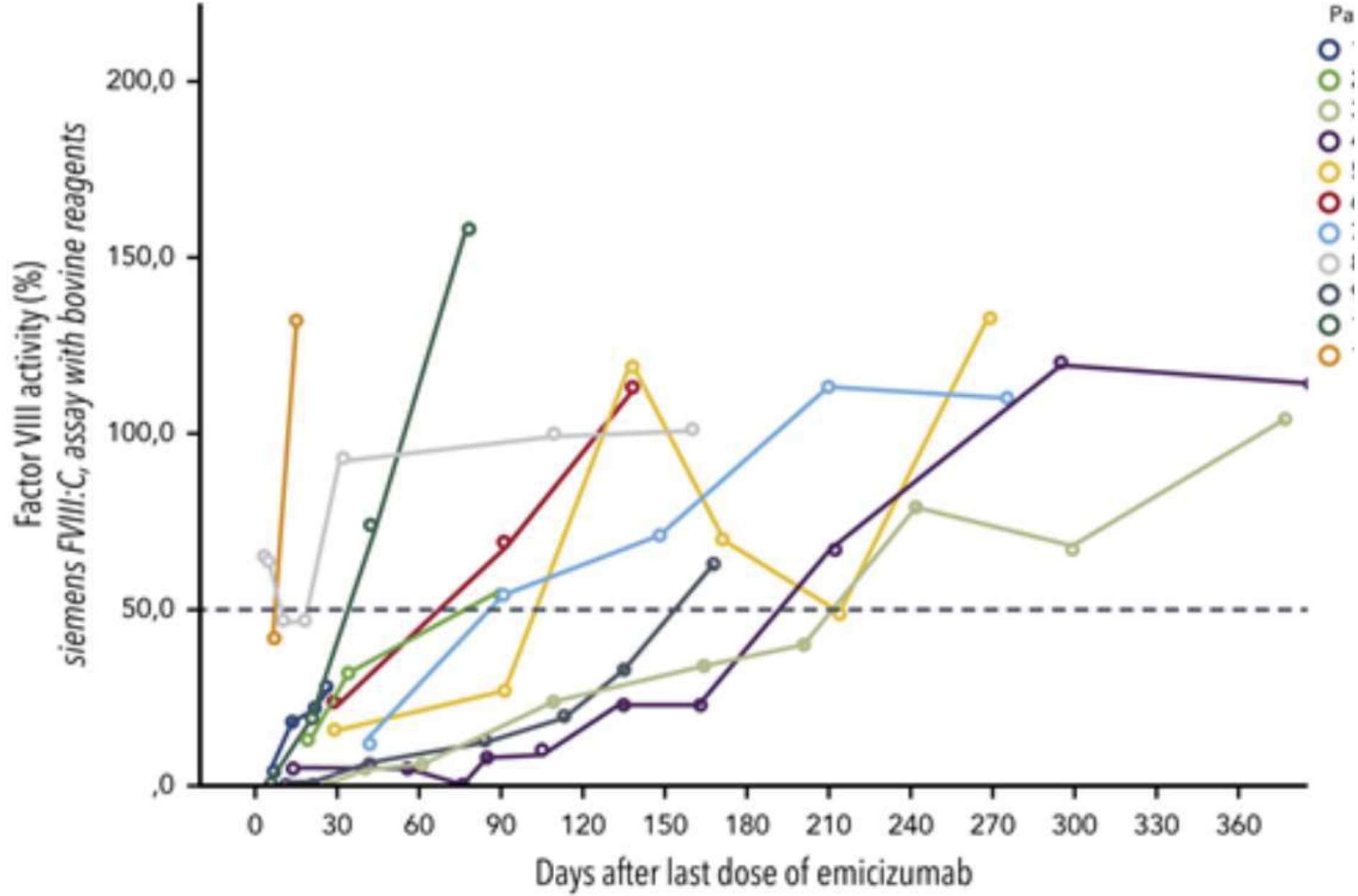
- After stopping APCC for at least 48 hours (and switching to rhFVIIa in bleeding patients), the first dose of emicizumab was applied subcutaneously (target dose of 3 mg/kg). Thereafter, rhFVIIa was continued at a lower dose until visible hemostatic response.
- To try to keep total dose down, Emicizumab was therefore continued weekly at 3 mg/kg BW for 2 to 3 additional doses, and dose reduction (to 1.5 mg/kg) and interval prolongation to up to 4 weeks were performed when FVIII:h exceeded 10% (representing approximately emicizumab plasma concentrations of 20 µg/mL)
- In 10 patients, initial immunosuppression was started with a short course of corticosteroids[5] (prednisone, 1 mg/kg BW for 1 week, followed by dose tapering over the following 2 weeks). Two patients had uncontrolled diabetes and did not receive steroids. As an attempt to reduce the intensity and adverse effects of immunosuppression, all patients were treated with off-label rituximab after consenting to this therapy (in 11 patients within 1 week of diagnosis, 1 patient with a low inhibitor titer started rituximab after 18 weeks because of missing remission).

Emicizumab monitoring

- Normal 1 stage aPTT and FVIII assays are absolutely not reliable
- Chromogenic assay using human reagents may give some idea of emicizumab effect
- Chromogenic assay using bovine reagents will pick up patient's own endogenous FVIII or any exogenous recombinant human FVIII (but not porcine)

- Initial hemostatic therapy started 1 day (1-29 days) after initial bleeding (median, range).
- 3 patients were initially treated with APCC 50 U/kg every 6 hours) and switched to rhFVIIa 90 µg/kg every 2 hours because of insufficient response or adverse effects.
- 7 patients received initial hemostatic therapy with rhFVIIa.
- The first dose of emicizumab (= day 0) was given 3 days (1-13 days) after start of initial hemostatic therapy (median dose, 2.7 mg/kg; range, 1.7-3.5 mg/kg).
- A median of 5 doses of emicizumab were given (range, 3-9 doses), the last dose after a median of 31 days (range, 12-175 days) (Table 3). One patient needed repetitive small surgery to close her abdominal wound, and was treated prophylactically with additional rhFVIIa injections before and after such surgery.

- Even in patients with severe bleeding or surgical wounds, a clinically impressive improvement of bleeding was observed within 3 days (IQR, 3-4 days; range, 2-15 days); 1 patient had mild bleeding associated with small surgical interventions, as mentioned. Also, in the 5 patients with insufficient response to bypassing therapy, bleeding stopped within the first 4 days. No new or breakthrough bleeding events were observed after day 2. Thus, even low emicizumab plasma concentrations seem to protect from bleeding in patients with AHA.


Factor VIII activity (%)
siemens FVIII:C, assay with bovine reagents
200,0
150,0
100,0
50,0
,0
0
30
60
90
120
150
180
210
240
270
300
330
360
Days after last dose of emicizumab
Pa

AEs

- In a 61-year-old male patient (with a history of severe chronic inflammatory bowel disease for several years), neutropenic sepsis occurred 64 days after start of immunosuppressive therapy with steroids and rituximab, and 20 days after his last dose of emicizumab. He recovered following broad-spectrum antimicrobial therapy and administration of filgrastim. At this time, his FVIII:h level had already exceeded 50%, indicating remission of AHA. One month later (45 days after his last dose of emicizumab), he was admitted to another hospital with a recurrent exacerbation of his chronic inflammatory bowel disease, bowel perforation and peritonitis. The patient rapidly deteriorated and died of this event, which was considered not associated with the applied therapy for AHA, but due to his preexisting chronic bowel disease.
- Immunosuppressive therapy was otherwise well tolerated, without any side effects to rituximab or steroids, and no infections or metabolic disturbance in the other 11 patients.
- A 79-year-old female patient experienced minor stroke on day 16 on emicizumab during comedication with repetitive single doses of 90 µg/kg rhFVIIa prior to the change of a vacuum assisted closure (VAC) suction system for her large abdominal wound with signs of infection (FVIII:h at this time was 10%, equivalent to emicizumab plasma concentration of about 20 µg/mL,[31] and FVIII:b was <1%). She had had inflammation, repetitive surgery with general anesthesia, repetitive rhFVIIa injections, and emicizumab, adiposity, immobilization, and a higher age, as thromboembolic risk factors. rhFVIIa was stopped, emicizumab was continued for 5 more weeks (4 additional doses) after that stroke without worsening of the neurologic situation. No antiplatelet therapy or other anticoagulation was given. She recovered without any sequelae.
- Five days before start of emicizumab, an 87-year-old male patient developed non-ST elevation myocardial infarction after 6 days on APCC therapy. He was switched to rhFVIIa for 4 days before emicizumab was started. No anti-platelet therapy was given. He recovered completely.

Conclusions

- Which patients with AHA to consider for emicizumab/Rituxan use?
  - Older, more frail, contra-indications to bypassing therapy, high titer inhibitor, multiple admissions
- Considerations
  - Do not use emicizumab with FEIBA
  - Special monitoring is required to detect remission
  - Once emicizumab is on board, use of recombinant porcine FVIII is more difficult, since levels cannot be accurately measured
  - There may be insurance issues
  - We don’t know how to treat breakthrough bleeds or surgeries

Case 2

- A 24 yo man with a h/o CVID and childhood ITP has been maintained on eltrombopag, 75 mg qd for the past 7 years. His platelet count varies between 10 and 60. He is variably adherent to the eltrombopag diet, since his favorite foods are milk, cheese, and ice cream.
- He has previously failed rituximab, vincristine, and splenectomy

bjh research paper

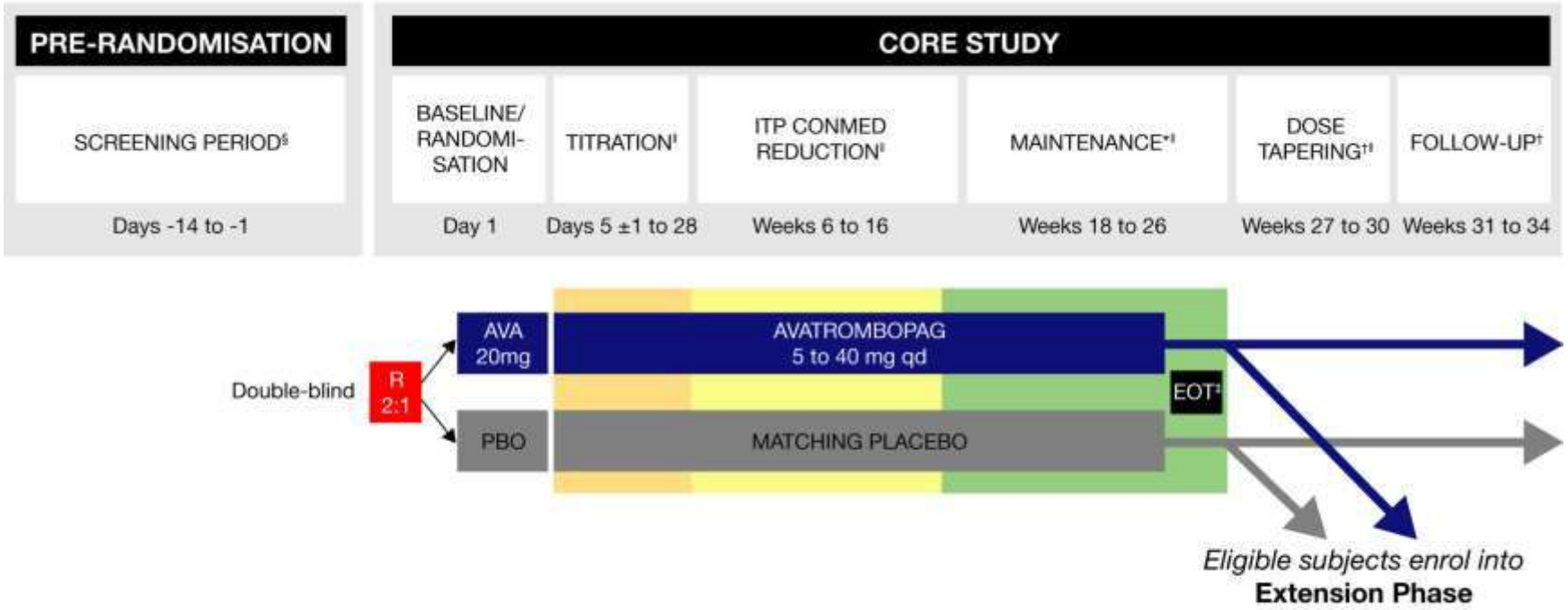
Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia

Wojciech Jurczak ✉, Krzysztof Chojnowski, Jiří Mayer, Katarzyna Krawczyk ... See all authors

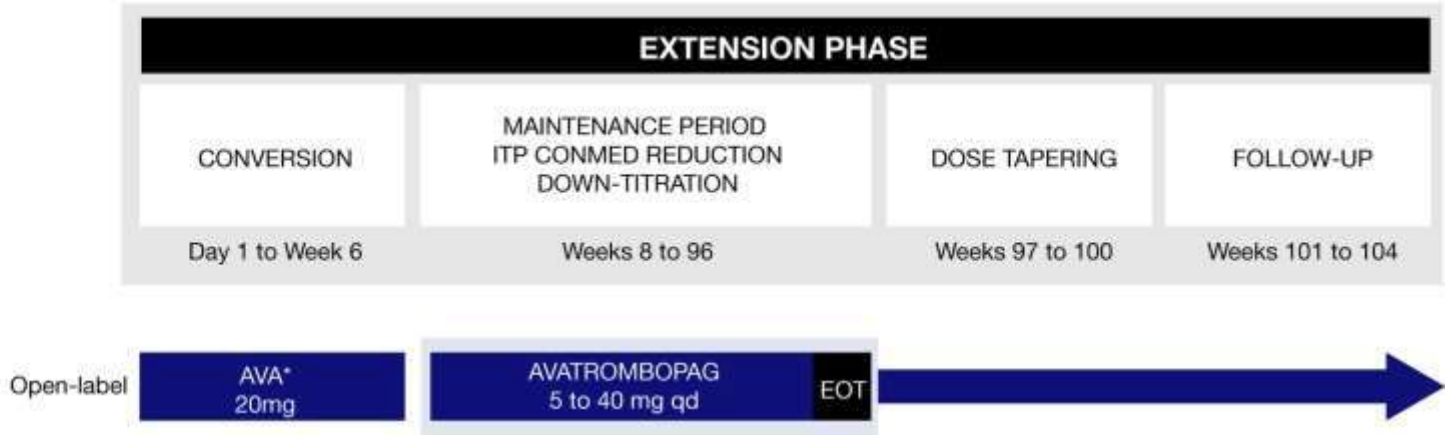
First published: 07 September 2018 | https://doi.org/10.1111/bjh.15573 | Citations: 22

Volume 183, Issue 3
November 2018
Pages 479-490

(A) Core study design

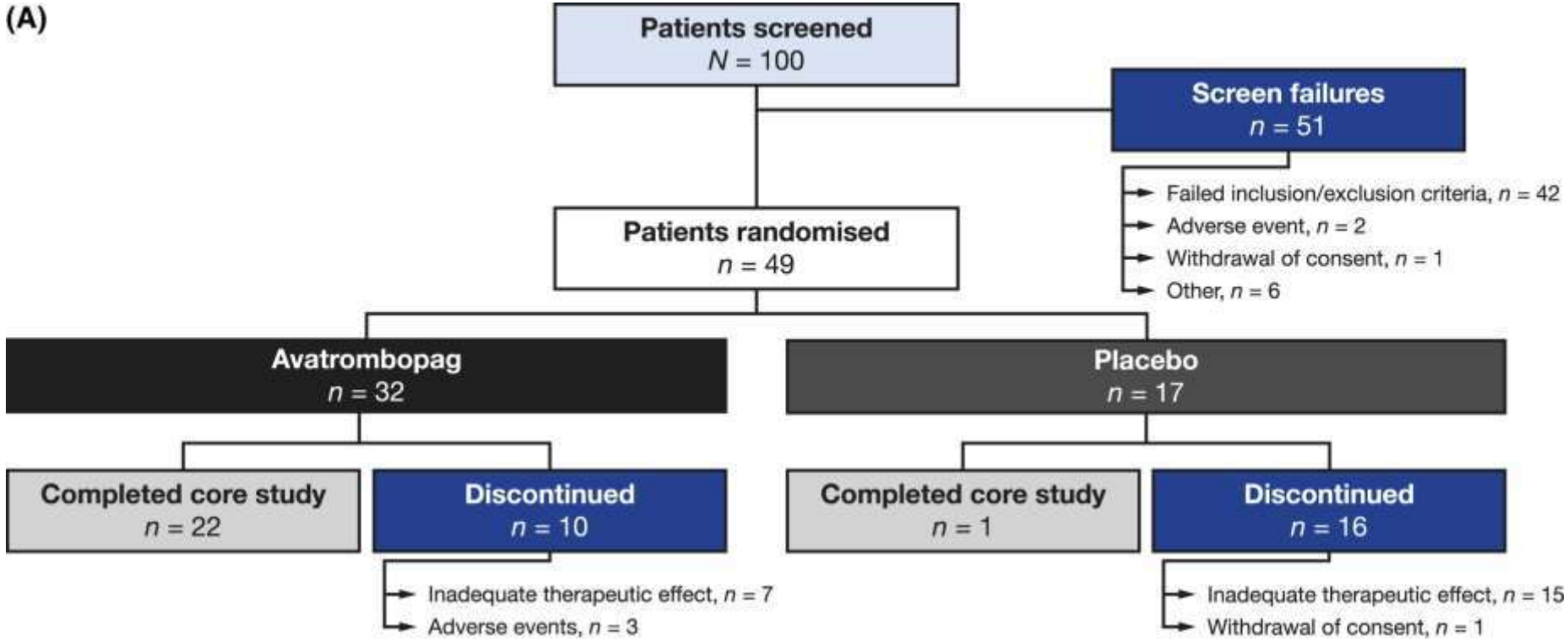


(B) Extension phase design

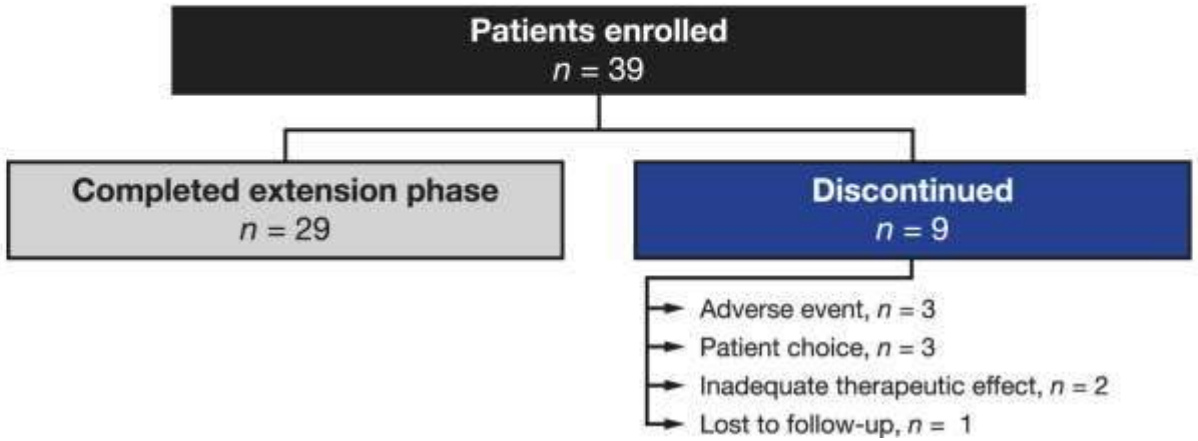


British Journal of Haematology, Volume: 183, Issue: 3, Pages: 479-490, First published: 07 September 2018, DOI: (10.1111/bjh.15573)

(A)



(B)



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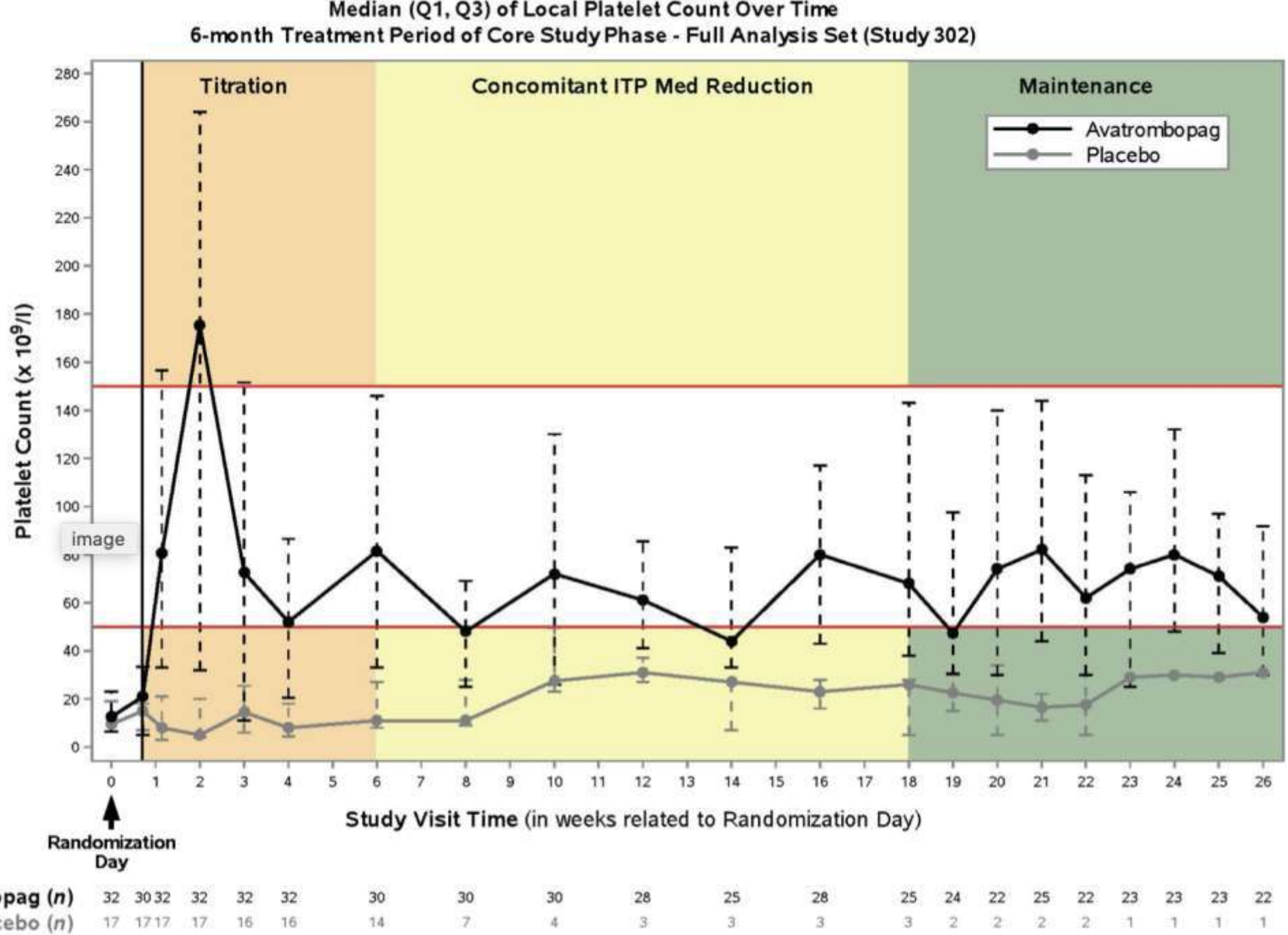
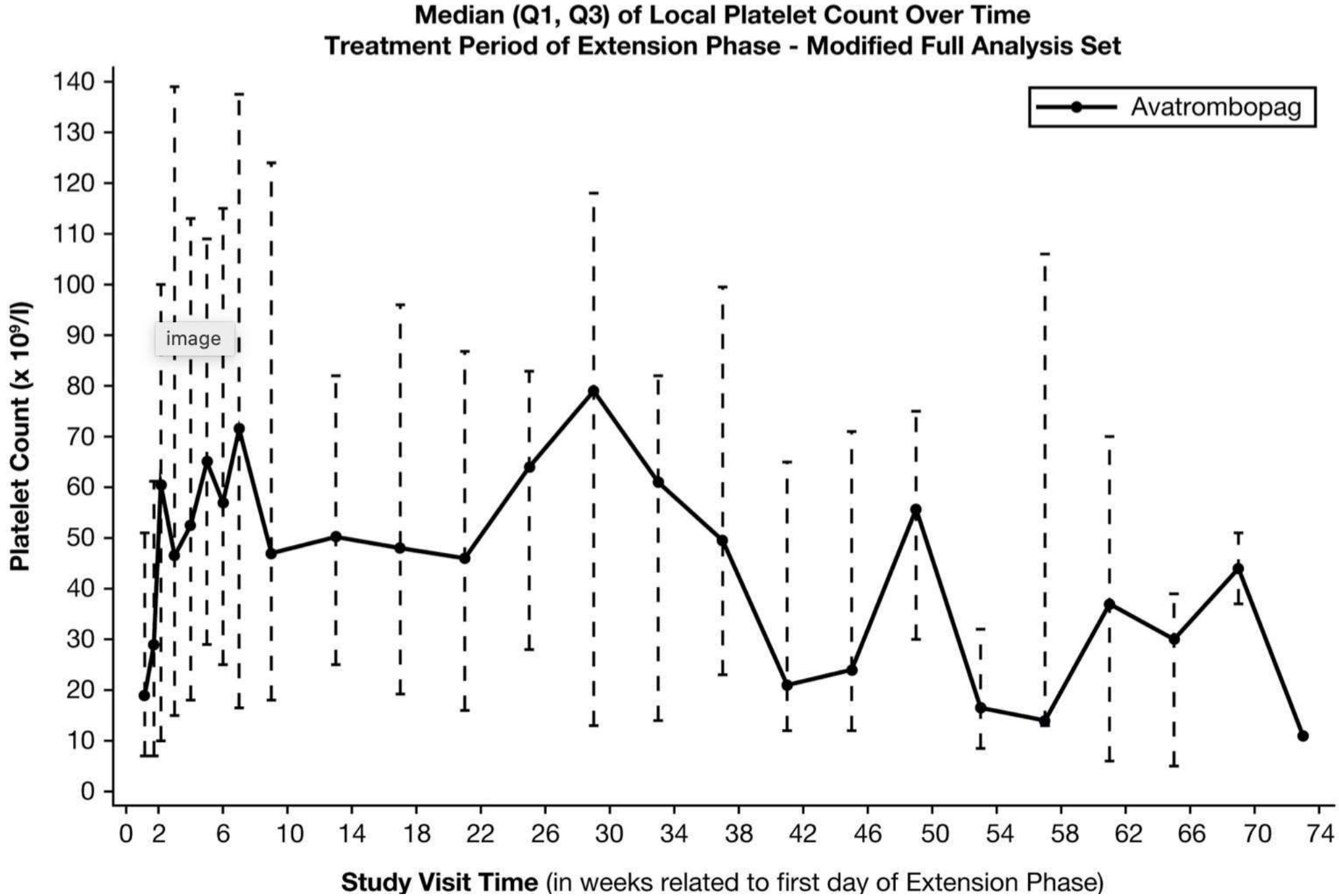
(A)



DOI: (10.1111/bjh.15573)

(B)


Median (Q1, Q3) of Local Platelet Count Over Time
Treatment Period of Extension Phase - Modified Full Analysis Set
Avatrombopag
Platelet Count (x 10⁹/l)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
0 2 6 10 14 18 22 26 30 34 38 42 46 50 54 58 62 66 70 74
Study Visit Time (in weeks related to first day of Extension Phase)

Avatrombopag

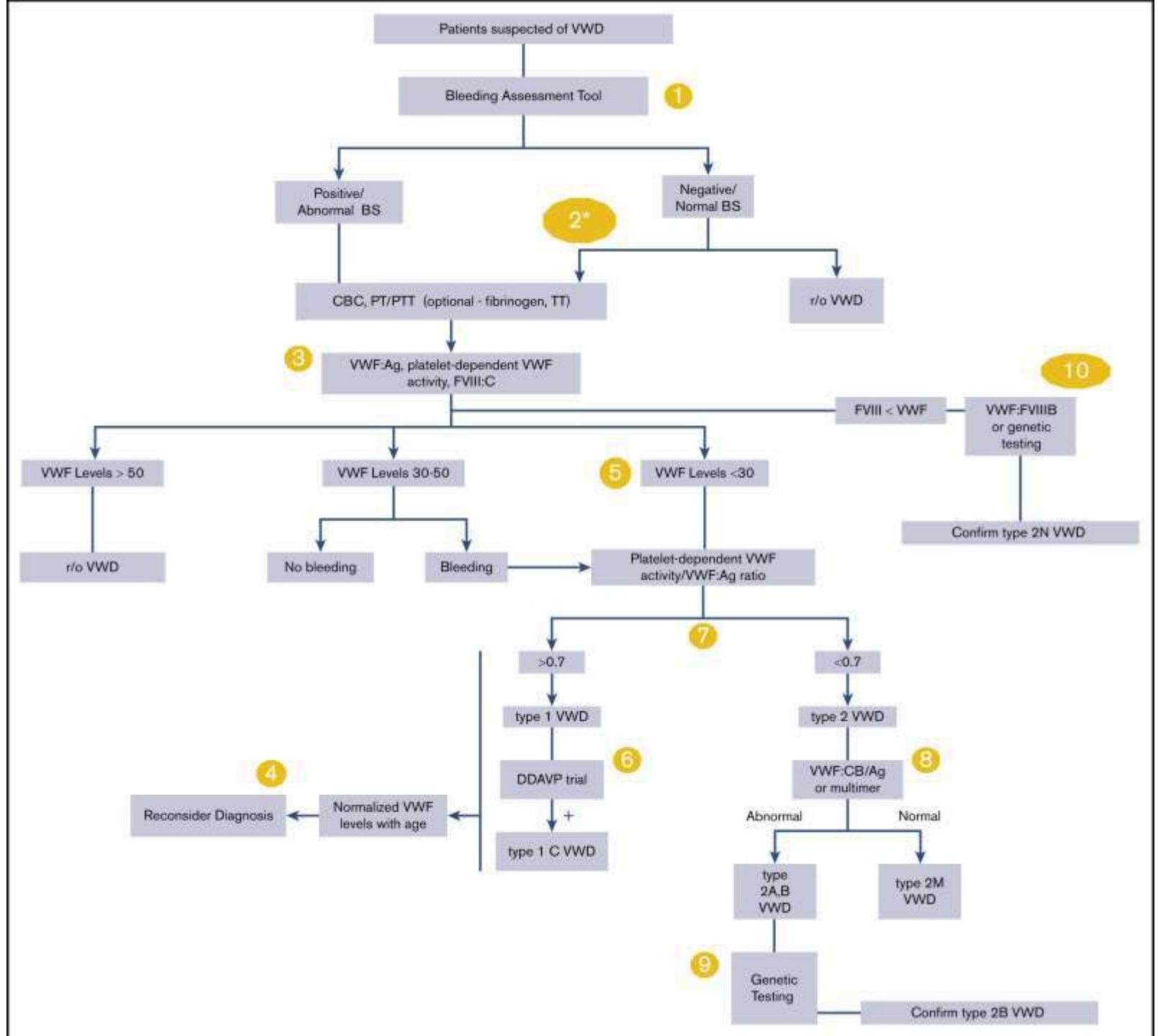
- AEs
  - headache, contusion, upper respiratory tract infection, arthralgia, epistaxis, fatigue, gingival bleeding and petechiae, with exposure-adjusted incidence rates that were all comparable with, or lower than, placebo
- FDA approval for chronic ITP June 2019

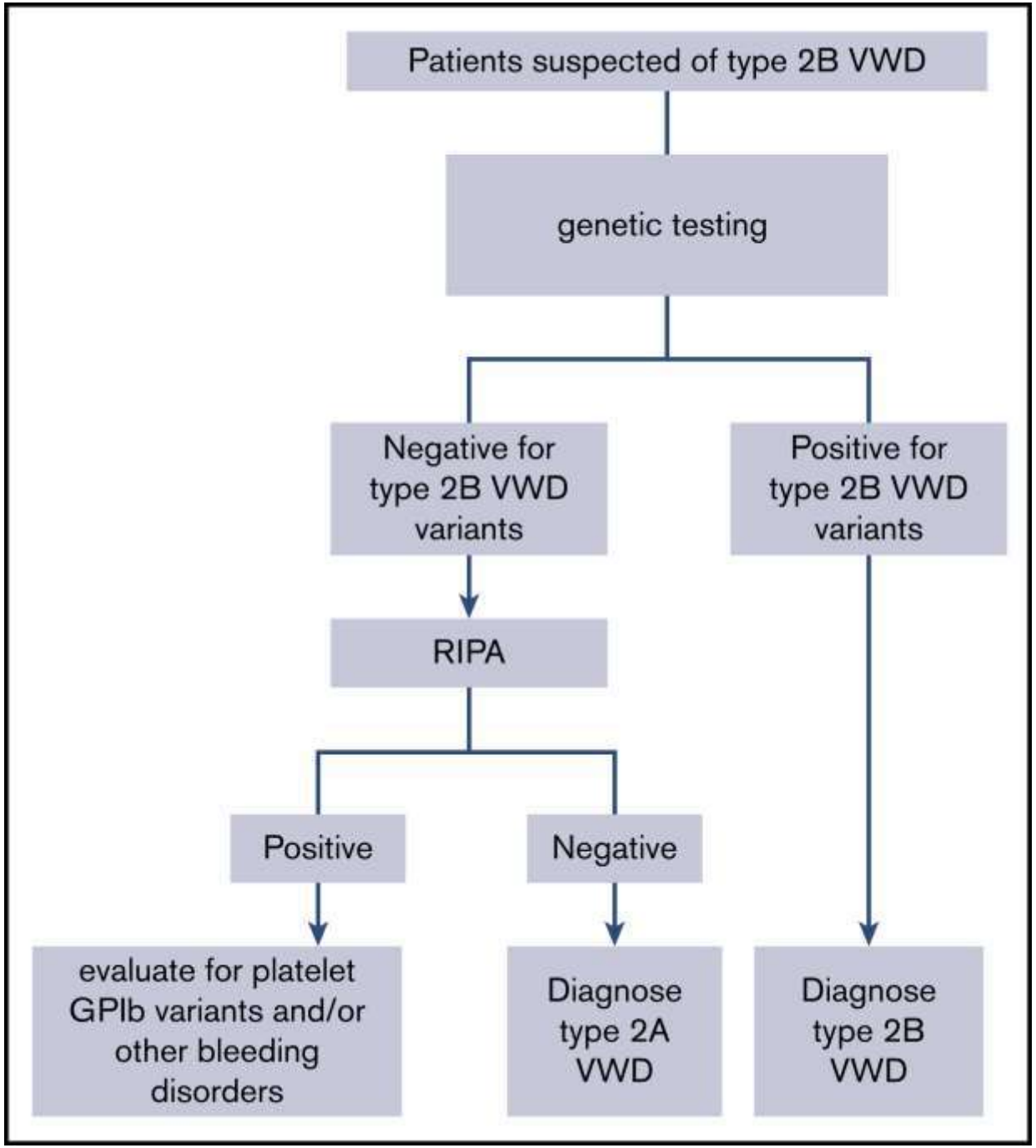
Dose	Dose Level
40 mg Once Daily	6
40 mg Three Times a Week *AND* 20 mg on the Four Remaining Days of Each Week	5
20 mg Once Daily*	4
20 mg Three Times a Week	3
20 mg Twice a Week *OR* 40 mg Once Weekly	2
20 mg Once Weekly	1

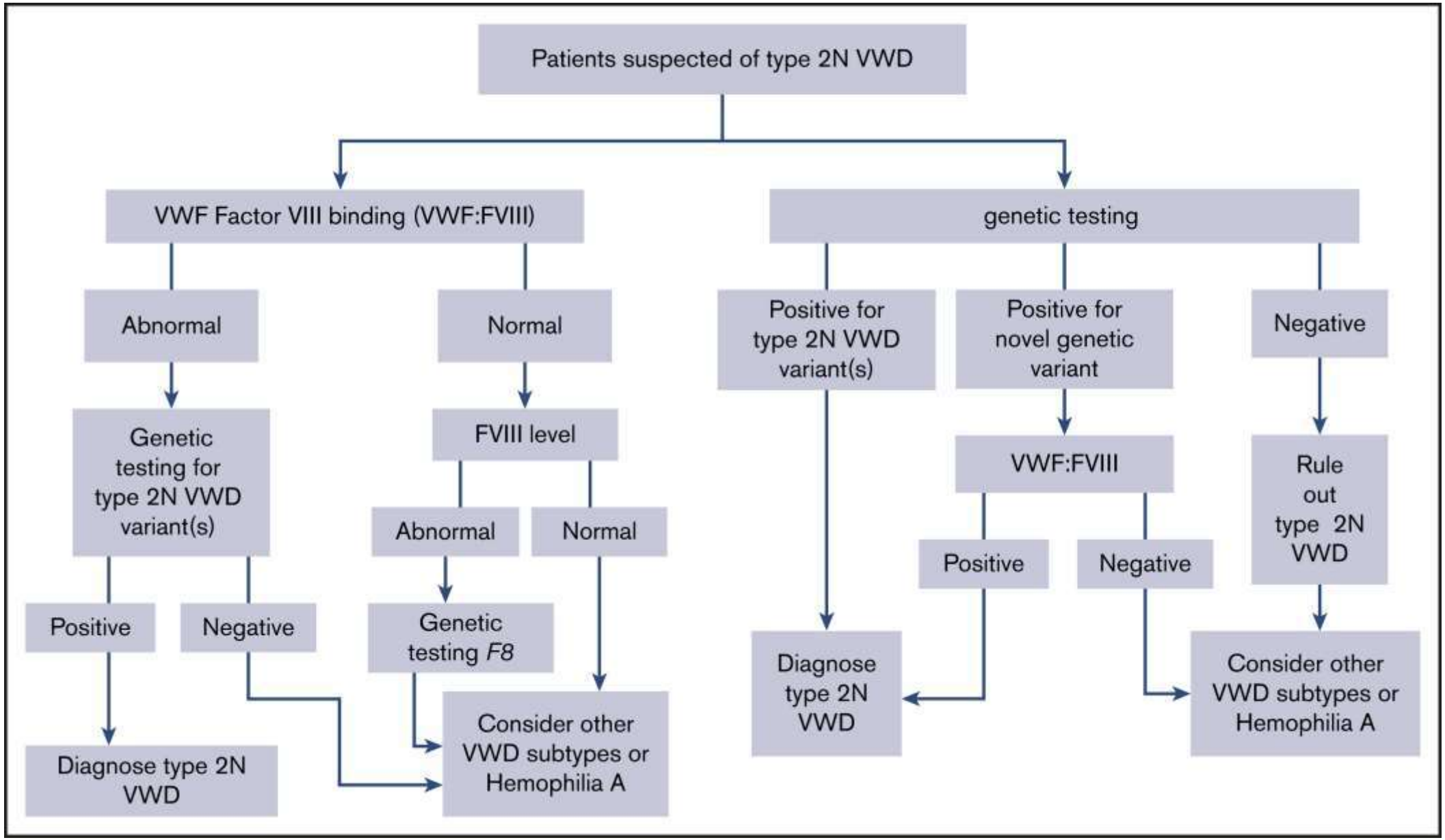
Platelet Count (x10^9/L)	Dose Adjustment or Action
Less than 50 after at least 2 weeks of DOPTELET	• Increase *One Dose Level* per Table 3. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
Between 200 and 400	• Decrease *One Dose Level* per Table 3. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
Greater than 400	• Stop DOPTELET. • Increase platelet monitoring to twice weekly. • When platelet count is less than 150 x10^9/L, decrease *One Dose Level* per Table 3 and reinitiate therapy.
Less than 50 after 4 weeks of DOPTELET 40 mg once daily	• Discontinue DOPTELET.
Greater than 400 after 2 weeks of DOPTELET 20 mg weekly	• Discontinue DOPTELET.

The ASH/ISTH/NHF/WFH Guidelines for VWD Diagnosis

Blood Adv (2021) 5 (1): 280–300.


Patients suspected of VWD
Bleeding Assessment Tool
1
Positive/ Abnormal BS
Negative/ Normal BS
2*
CBC, PT/PTT (optional - fibrinogen, TT)
r/o VWD
3
VWF:Ag, platelet-dependent VWF activity, FVIII:C
10
FVIII < VWF
VWF:FVIIIB or genetic testing
Confirm type 2N VWD
VWF Levels > 50
VWF Levels 30-50
5
VWF Levels <30
r/o VWD
No bleeding
Bleeding
Platelet-dependent VWF activity/VWF:Ag ratio
7
>0.7
<0.7
type 1 VWD
type 2 VWD
6
DDAVP trial
8
VWF:CB/Ag or multimer
4
Reconsider Diagnosis
Normalized VWF levels with age
+
type 1 C VWD
Abnormal
Normal
type 2A,B VWD
type 2M VWD
9
Genetic Testing
Confirm type 2B VWD




Patients suspected of type 2N VWD
VWF Factor VIII binding (VWF:FVIII)
genetic testing
Abnormal
Normal
Positive for type 2N VWD variant(s)
Positive for novel genetic variant
Negative
Genetic testing for type 2N VWD variant(s)
FVIII level
VWF:FVIII
Rule out type 2N VWD
Abnormal
Normal
Positive
Negative
Positive
Negative
Genetic testing *F8*
Diagnose type 2N VWD
Consider other VWD subtypes or Hemophilia A
Diagnose type 2N VWD
Consider other VWD subtypes or Hemophilia A

Case 3

- A 36 yo woman with type 1 VWD, responsive to desmopressin needs tooth extraction. She would normally take her Stimate nasal spray as well as tranexamic acid before her procedure
- Stimate nasal spray has been on manufacturer's recall and is not expected to be available until at least 2022
- What are options?

Options to replace intranasal DDAVP

- DDAVP given parenterally
  - 0.3 mcg/kg given IV at infusion center
  - Or 0.3 mcg/kg by SQ administration (no more than 1 cc per injection)
- Factor concentrate
  - At infusion center or by home nursing

Gene Therapy for hemophilia

- Hemophilia A
  - Valoctocogene roxaparvovec FDA approval DENIED—more data needed, given falling F8 levels seen in the phase I/II trial
- Hemophilia B
  - Promising data in a number trials for hemophilia B gene therapies

Watch this space