Tapering Thrombopoietin Receptor Agonists in Primary Immune Thrombocytopenia: Recommendations Based on the RAND/UCLA Modified Delphi Panel Method

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Disclosures

This study was funded by Novartis. **JM Despotovic, RF Grace, C Kruse, MP Lambert, HA Liebman, RM Lyons, KR McCrae, V Pullarkat, and JS Wasser** signed research agreements with PHAR and received honoraria from Novartis for their participation on the panel; these panel members were not aware of the identity of the sponsor during the study or manuscript development. Novartis did not provide input on study design, methods, results, or interpretation of findings.

Authors report the following additional conflicts of interest:

- **A Cuker** has served as a consultant to Synergy CRO and his institution has received research support on his behalf from Alexion, Bayer, Novartis, Novo Nordisk, Pfizer, Sanofi, Spark, and Takeda. He did not receive an honorarium for his work on the panel.
- **JM Despotovic** has served as a consultant to Amgen, Novartis, and Dova, and her institution has received research support on her behalf from Novartis and Amgen.
- **RF Grace** has served on an Advisory Board for Dova, and has received institutional research funding from Agios, Pfizer, and Novartis.
- **C Kruse** has served as a consultant to Novartis and UCB; Platelet Disorder Support Association (PDSA) has received consultancy support and honoraria on her behalf from Amgen, and funding on her behalf from Amgen, Argenx, CSL Behring, Dova, Momenta, Novartis, Octapharma, Pfizer, Principia, Rigel, and UCB; and has served on the board of Thrombosis & Hemostasis Societies of North America.
- **MP Lambert** has served on an Advisory Board for Dova, Principia, and Novartis; has served as a consultant to Dova, Principia, Novartis, Shionogi, Educational Concepts in Medicine, Octapharma, Bayer, and Argenix; has received honorarium from ClinGen; has served as a Medical Advisor to Platelet Disorder Support Association (PDSA), 22qSociety, ITP Australia, CdLS Foundation, and RDMD ITP study; and has received institutional research funding from Sysmex, Novartis, AstraZeneca, and Octapharma.
- **HA Liebman** has served as a consultant to Genzyme, BMS, Rigel, Janssen, Portola, and Principia Biopharma, and has received research funding from Amgen, Rigel, Novartis, Kezar, and Argenix. His wife (Dr. Ilene Weitz) has served as a consultant to Alexion.
- **RM Lyons** has no additional conflicts.
- **KR McCrae** has served as a consultant to Rigel and Dova.
- **V Pullarkat** has served as a consultant to and received honoraria from Amgen, Novartis, and Dova.
- **JS Wasser** has served as a speaker for Novartis; his institution has received research funding on his behalf from Pfizer, Merck, and Incyte; and he has served as a consultant to Amgen. He and his wife have equity ownership in Merck, Biogen, Pfizer, and Eli Lilly.
- **D Beenhouwer, SN Gibbs, I Yermilov, and M Broder** report other from Novartis during the conduct of the study; other from AbbVie, other from Akcea, other from ASPC, other from Amgen, other from AstraZeneca, other from BMS, other from Boston Scientific Corporation, other from Celgene, other from Eisai, other from Ethicon, other from GRAIL, other from Helsinn, other from Illumina, other from Innovation and Value Initiative, other from Ionis, other from Jazz , other from Kite, other from Novartis, other from Otsuka, other from Pathnostics , other from PhRMA, other from Prothena , other from Sage, other from Verde Technologies, other from Genentech, Inc. , other from Greenwich Biosciences, Inc., other from Mirum Pharmaceuticals, Inc., grants and other from Dompe US, Inc., other from Sanofi US Services, Inc., other from Sunovion Pharmaceuticals, Inc. outside the submitted work.

Background & objective

- Thrombopoietin Receptor Agonists (TPO-RAs), such as romiplostim, eltrombopag, and avatrombopag, are approved for the treatment of primary immune thrombocytopenia (ITP).[1]

- While it was previously thought that patients would need to remain on TPO-RAs indefinitely, case reports and cohort studies have shown that some patients are able to maintain a hemostatic platelet count off all treatment after discontinuing their TPO-RA.[2-12]

- We convened a panel of experts to develop consensus on:
  - When it is appropriate to consider tapering TPO-RAs in children and adults with persistent or chronic primary ITP
  - How to taper patients off therapy
  - How to monitor patients after discontinuation
  - How to restart therapy in the event of relapse

RAND/UCLA modified Delphi panel method

- We convened a diverse panel of 9 hematologists and 1 patient representative.

- We developed and reviewed evidence from 12 case reports,[13-24] 11 cohort studies,[2-12] and 2 clinical trial analyses[25-26] on the cessation of TPO-RA treatment in adults and children with ITP.

- The panel was double-blinded while work was ongoing: The sponsor did not know the identity of the non-chair experts and the non-chair experts did not know the identity of the sponsor until publications of the work were drafted.

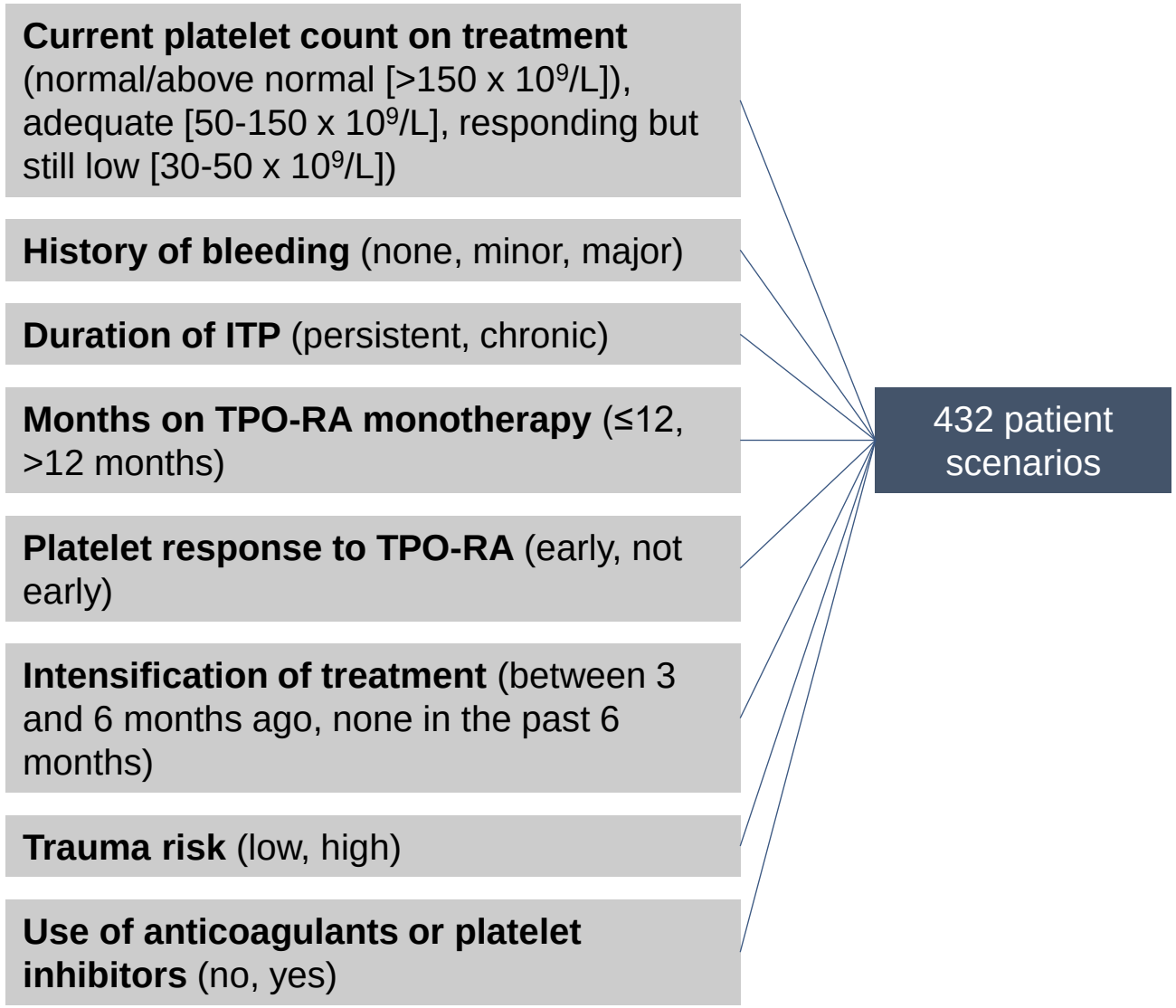
6 adult hematologists

3 pediatric hematologists

1 patient representative

Rating form development & patient scenarios

- We collaboratively developed the rating form.
- Part I included 432 patient scenarios based on 8 patient characteristics to assess the appropriateness of tapering therapy.
- Part II included the different ways to taper TPO-RAs (12 items), how to monitor patients after discontinuation (11 items), and how we restart therapy (5 items).



Conducted two rounds of ratings, before and after a meeting

- We independently rated each item in the rating form on a 1 to 9 scale.
- Discussed our ratings during a virtual meeting on March 18-19, 2020.

How appropriate is it to recommend tapering (with the aim of discontinuing) TPO-RAs in a patient with these characteristics?	**Inappropriate**, I would not recommend tapering treatment in this patient because the risks of discontinuing treatment outweigh the benefits	**I'm not sure** (e.g., due to inadequate data) or the risks and benefits of discontinuing treatment in this patient seem roughly balanced	**Appropriate**, I would recommend tapering treatment in this patient because the benefits of discontinuing treatment outweigh the risks

Analyzed median ratings and differences in distributions

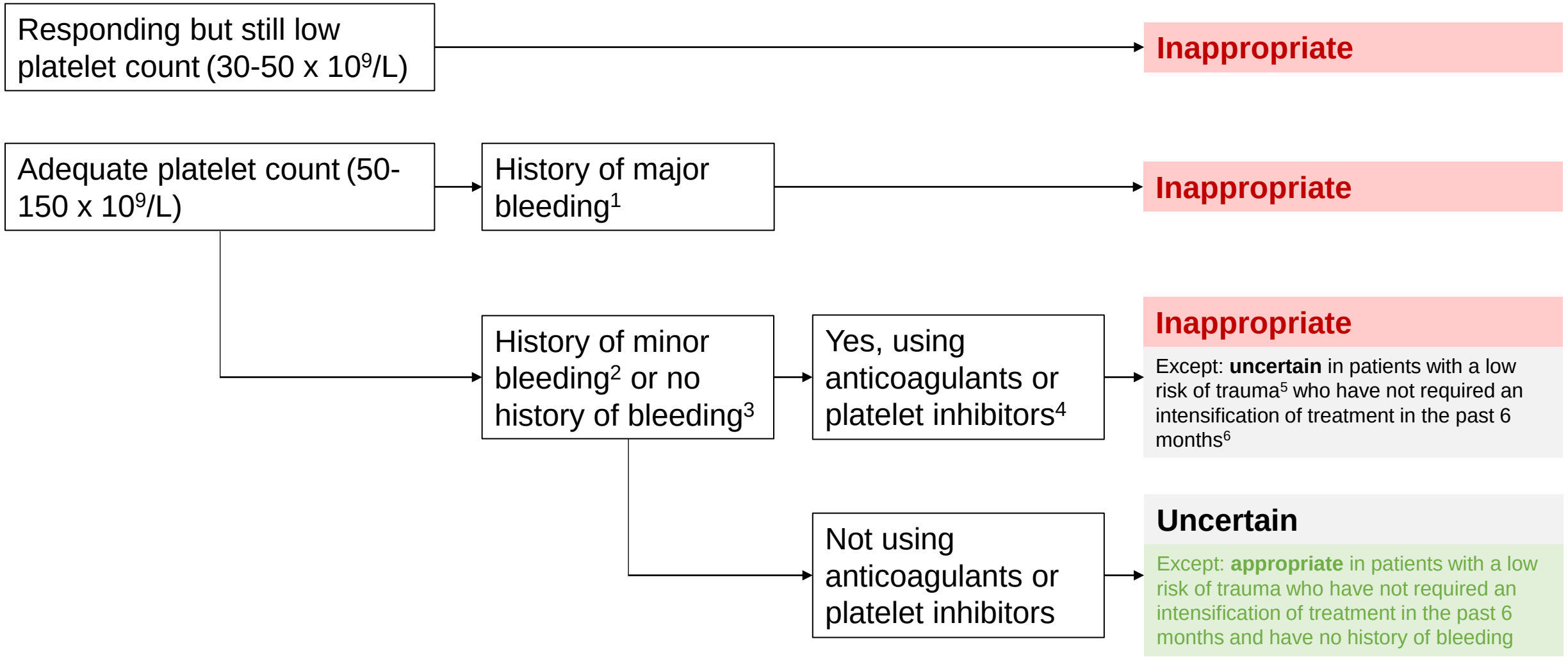
- Median ratings were calculated for each item and classified into 4 groups.
- We conducted Chi-squared tests to determine which characteristics had a statistically significant impact on ratings (defined as $p<0.05$).
- The proportion of items with disagreement decreased from 20% to 10% following the panel meeting.

% (n)	Median ≥7-9 without disagreement	Median ≥4-<7 without disagreement	Median 1-<4 without disagreement	Disagreement (≥2 ratings of 1-3 and ≥2 ratings of 7-9
First-round	13% (59)	15% (68)	52% (241)	20% (92)
Second-round	14% (66)	24% (110)	52% (237)	10% (47)

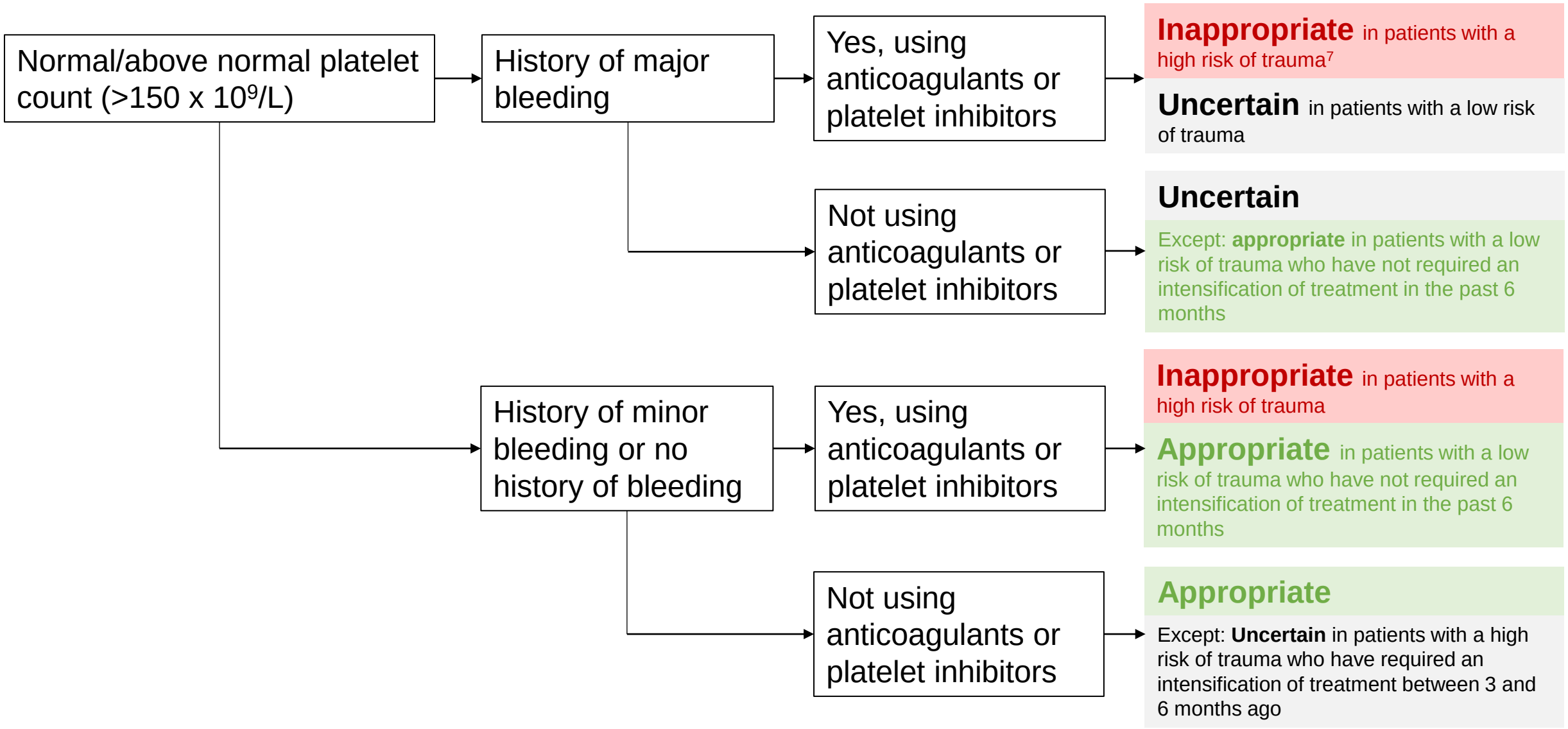
Five characteristics significantly impacted ratings

Characteristics included in patient scenarios	p-value
Platelet count (normal/above normal [>150 x 10^9/L]), adequate [50-150 x 10^9/L], responding but still low [30-50 x 10^9/L])	<0.001
History of bleeding (none, minor, major)	0.001
Intensification of treatment (between 3 and 6 months ago, none in the past 6 months)	<0.001
Trauma risk (low, high)	<0.001
Use of anticoagulants or platelet inhibitors (no, yes)	<0.001
Duration of ITP (persistent, chronic)	0.427
Months on TPO-RA monotherapy (≤12, >12 months)	0.964
Platelet response to TPO-RA (early, not early)	0.881

Consensus about when to taper TPO-RAs



Consensus about when to taper TPO-RAs



Example consensus statements about how to taper TPO-RAs

- It is inappropriate to discontinue TPO-RA monotherapy without tapering.

- Eltrombopag and romiplostim can be tapered by decreasing the dose periodically to the minimum available dose but maintaining the time interval between doses.

- It is appropriate to measure the platelet count soon after the patient has discontinued treatment (e.g., within 1-2 weeks) and with decreasing frequency over time assuming a successful clinical taper.

- In many cases, it is appropriate to consider restarting therapy when the patient's platelet count is $<30 \times 10^9$/L and shows any signs of bleeding beyond skin manifestations. Thresholds for restarting therapy may be different for patients with different characteristics.

Conclusions

- We used a validated methodology to develop the first set of consensus statements from US clinical experts on tapering TPO-RA monotherapy in patients with persistent or chronic primary ITP.

- The guidance reflects areas of greatest agreement among a panel of experts based on currently available limited evidence.

- These consensus statements could serve as a guide for clinical care and could inform the design and development of clinical trials that prospectively test the safety of tapering TPO-RA monotherapy in patients with ITP.

Thank you

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