Alternatives to platelet transfusion

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SW regional transfusion meeting 07/06/2023

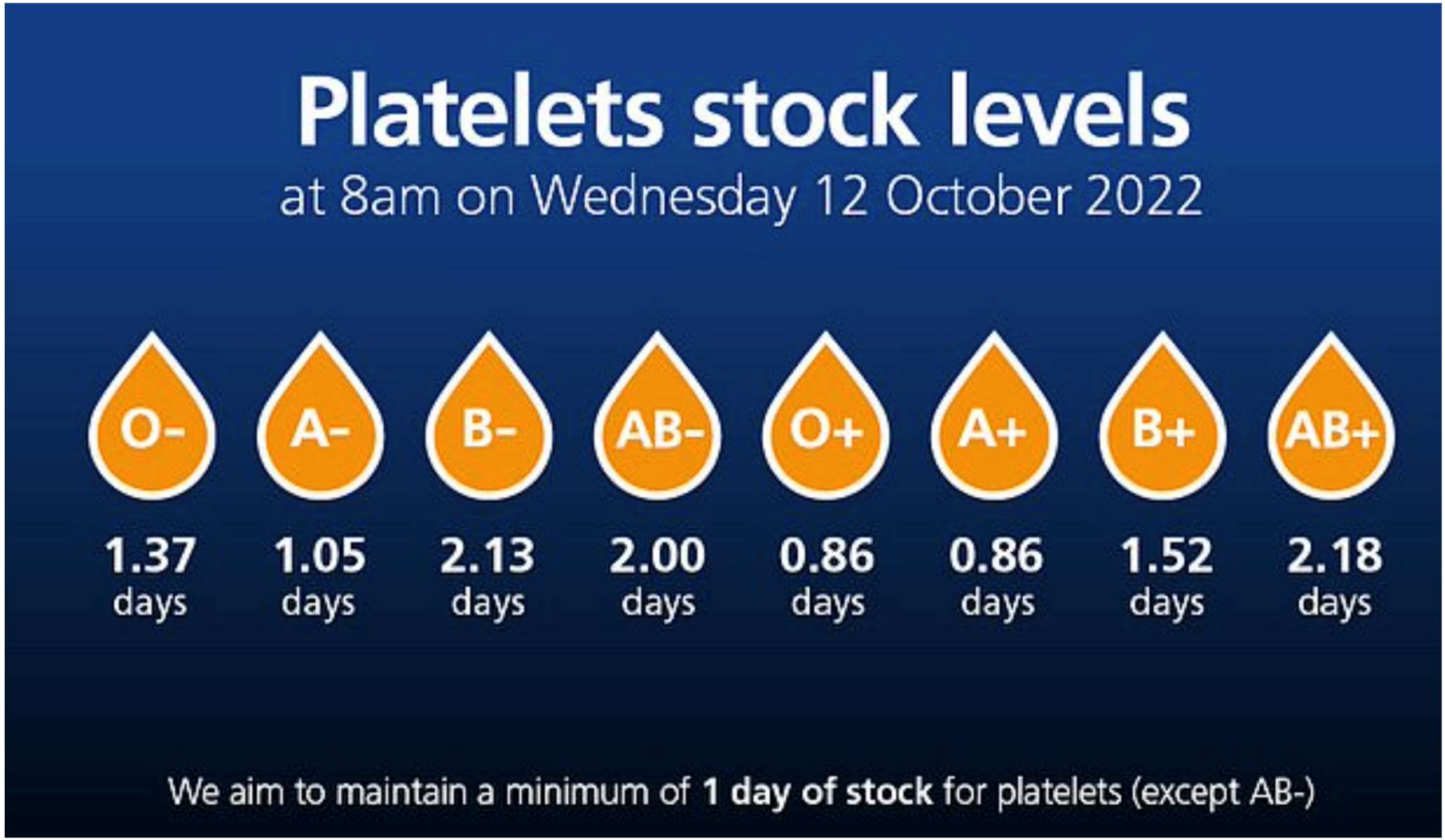
Talk outline

- Why consider alternatives to platelets?
- Evidence for platelet transfusion
- Alternative agents
  - Thrombopoietin mimetics
  - Desmopressin
  - Tranexamic acid
  - Adjunct measures
  - Therapies under investigation

Mail Online

NHS is dangerously short of blood: Service declares first ever 'amber alert' with just TWO DAYS' worth of supplies - meaning health bosses will have to CANCEL routine ops like hip replacements

Amber alert


Platelets stock levels
at 8am on Wednesday 12 October 2022
O-
1.37 days
A-
1.05 days
B-
2.13 days
AB-
2.00 days
O+
0.86 days
A+
0.86 days
B+
1.52 days
AB+
2.18 days
We aim to maintain a minimum of 1 day of stock for platelets (except AB-)

Why talk about alternatives to platelet transfusion?

- National blood shortages
- Efficacy of platelet transfusion (might other agents be more effective?)
- Risks of platelet transfusion
- Costs of platelet transfusion
- Convenience

Amber alert

NHS Blood and Transplant

Summary of Guidelines for the Use of Platelet Transfusions in a Platelet Shortage

British Society for Haematology Guideline (2016) Adults

British Society for Haematology Guideline (2016 & 2020 addendum) Children, Neonates

Platelet transfusion: principles, risks, alternatives and best practice

Platelet transfusions are an essential component in the management of selected patients with thrombocytopenia. However, they need to be used judiciously as they are a limited resource and are not risk free

Prior to prescribing a platelet transfusion consider:

What is the indication for transfusion in this patient?

Are there any alternatives which could be used instead?

Is the patient aware of the benefits, harms and alternatives to a platelet transfusion?

Possible alternatives to platelet transfusion:

- Apply surface pressure after superficial procedures and correct surgical causes for bleeding
- Surgical patients expected to have at least a 500 ml blood loss (or >10% blood volume in children), use tranexamic acid (TXA) unless contraindicated
- Trauma patients who are bleeding or at risk of bleeding, early use of TXA
- Severe bleeding replace fibrinogen if plasma concentration less than 1.5 g/L
- Anti-platelet agents - discontinue or if urgent procedure/bleeding use TXA if risk/benefit would support
- Uraemia with bleeding or pre-procedure – dialyse, correct anaemia, consider desmopressin
- Inherited platelet function disorders - specialist haematology advice required. Consider desmopressin
- Chronic Bone Marrow Failure (BMF) with bleeding – consider TXA

Amber alert guidelines

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https://nationalbloodtransfusion.co.uk/sites/default/files/documents/2023-03/Summary%20BSH%20platelet%20guideline%20appendix%20update%202022%20Amber%2006%2001%202023.pdf

Red alert guidelines

Possible alternatives to platelet transfusion:

- Postpone any procedures or surgery that may require a platelet transfusion that are not urgent
- Can the procedure be changed to one with a low risk of bleeding e.g. from percutaneous to trans-jugular liver biopsy?
- Apply surface pressure after superficial procedures and correct surgical causes for bleeding
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https://nationalbloodtransfusion.co.uk/sites/default/files/documents/2023-03/Summary%20BCSH%20platelet%20guideline%20appendix%20update%202022%20Red%2006%2001%202023_.pdf

Why transfuse platelets?

- Prophylaxis
  - Prevention of spontaneous bleeding due to severe thrombocytopenia (typically platelet count <10 $x10^9$/L)
  - Prevention of bleeding prior to invasive procedures (typically platelet count <50 $x10^9$/L, although different thresholds depending on procedure)
- Treatment
  - Treatment of acute haemorrhage
  - [?reversal of antiplatelet drug effect or platelet dysfunction]

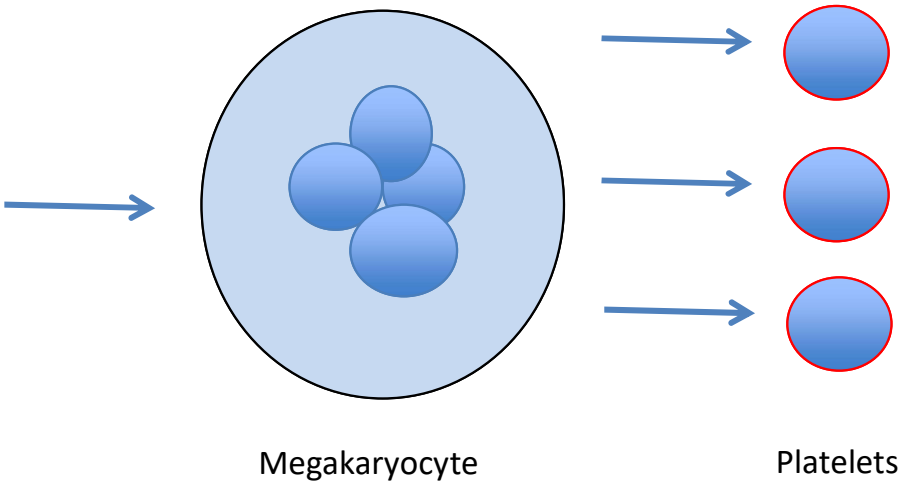
Three examples of platelet transfusion evidence

Trial	Setting	Comparator	Outcome
TOPPS trial	Haematological malignancy	Transfuse platelets if count <10 x10^9/L (prophylaxis) vs only if bleeding (no prophylaxis)	Bleeding 151/300 (50%) patients in the no-prophylaxis group, as compared with 128/298 (43%) in the prophylaxis group
PATCH trial	Intracerebral haemorrhage and on antiplatelet drugs	One adult dose of platelets vs standard care	Odds of death or dependence higher with platelet transfusion: odds ratio 2·05, 95% CI 1·18-3·56; p=0·0114
Van Barle et al.	Central line insertion	Platelet transfusion at 50 x10^9/L (transfusion group) vs 10 x10^9/L (no transfusion group)	Bleeding in 9/188 (4.8%) in the transfusion group and 22/185 (11.9%) in the no-transfusion group

Stanworth et al. N Engl J Med 2013;368(19):1771-80
Baharoglu et al. Lancet 2016;387(10038):2605-13
Van Barle et al. N Engl J Med 2023;388(21):1956-65

Alternate strategies to transfusing platelets for thrombocytopenic patients

1. Increase platelet production

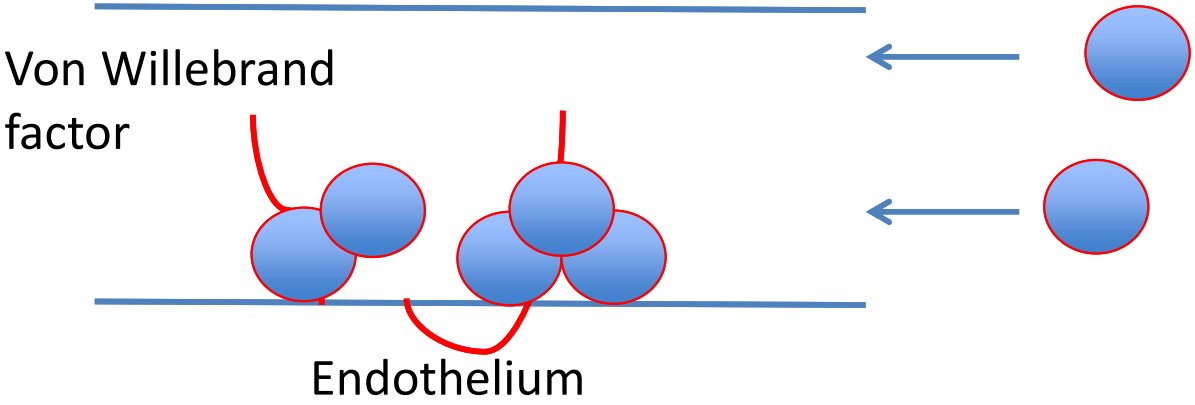


Thrombopoietin mimetics
e.g. romiplostim,
eltrombopag or
avatrombopag

2. Artificial alternatives to platelets

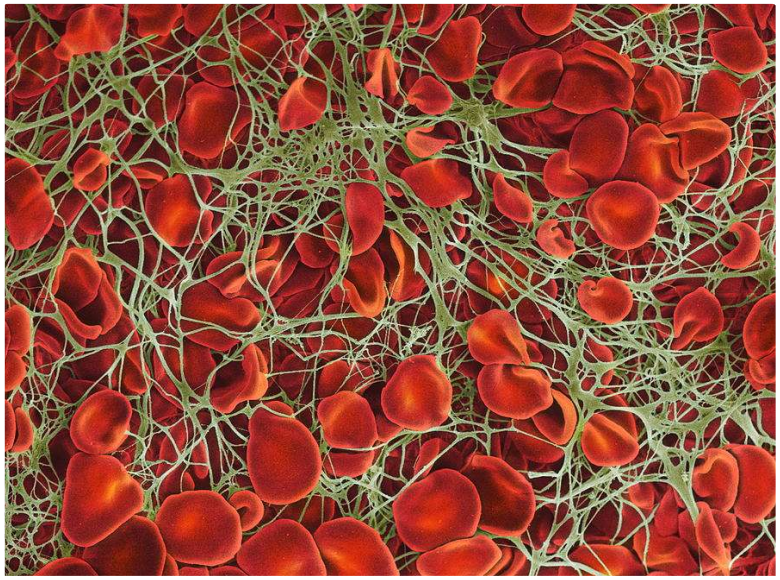
Artificial platelet membranes
Lyophilised platelets
Liposomes with inserted platelet receptors

3. Increase platelet adhesion to endothelium



Desmopressin (DDAVP)

4. Optimise fibrin formation

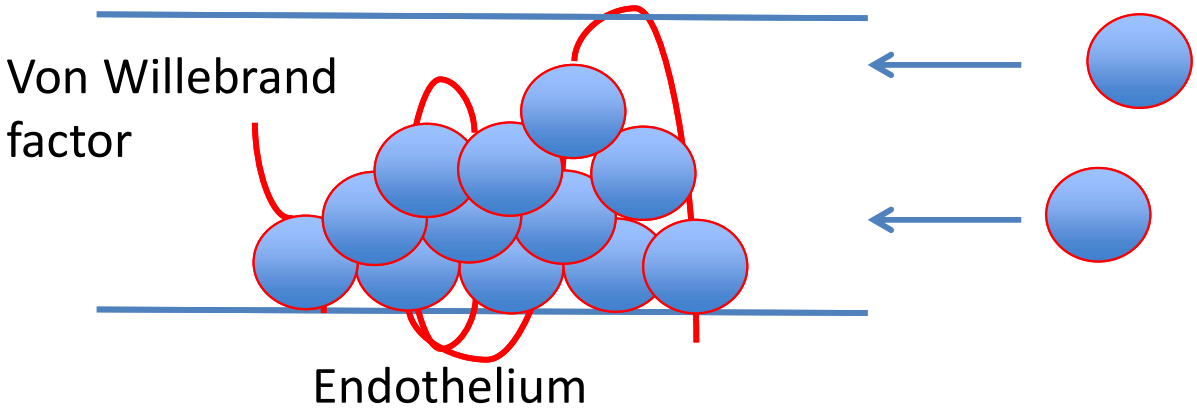


Increase fibrin production
Fibrinogen concentrate
Recombinant factor VIIa
Fresh frozen plasma

Increase fibrin cross-linkage
Recombinant factor XIII

Decrease fibrin breakdown (fibrinolysis)
Tranexamic acid
Epsilon aminocaproic acid
Aprotinin

3. Increase platelet adhesion to endothelium



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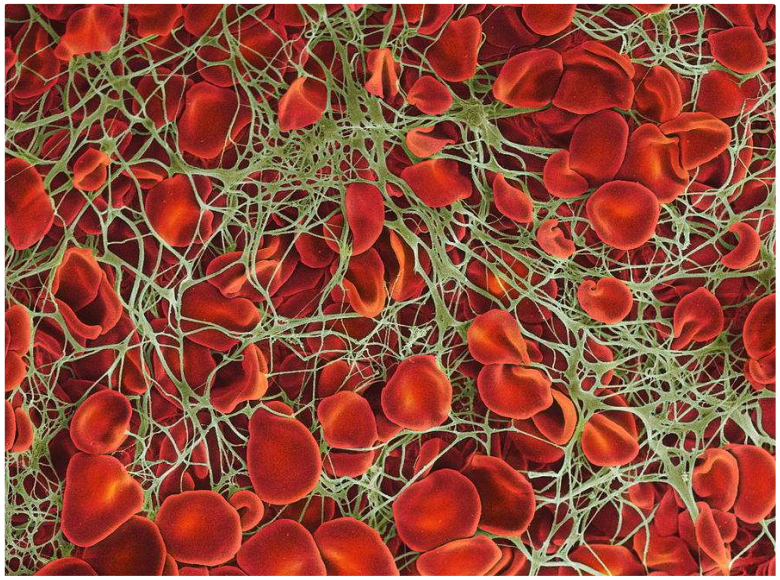

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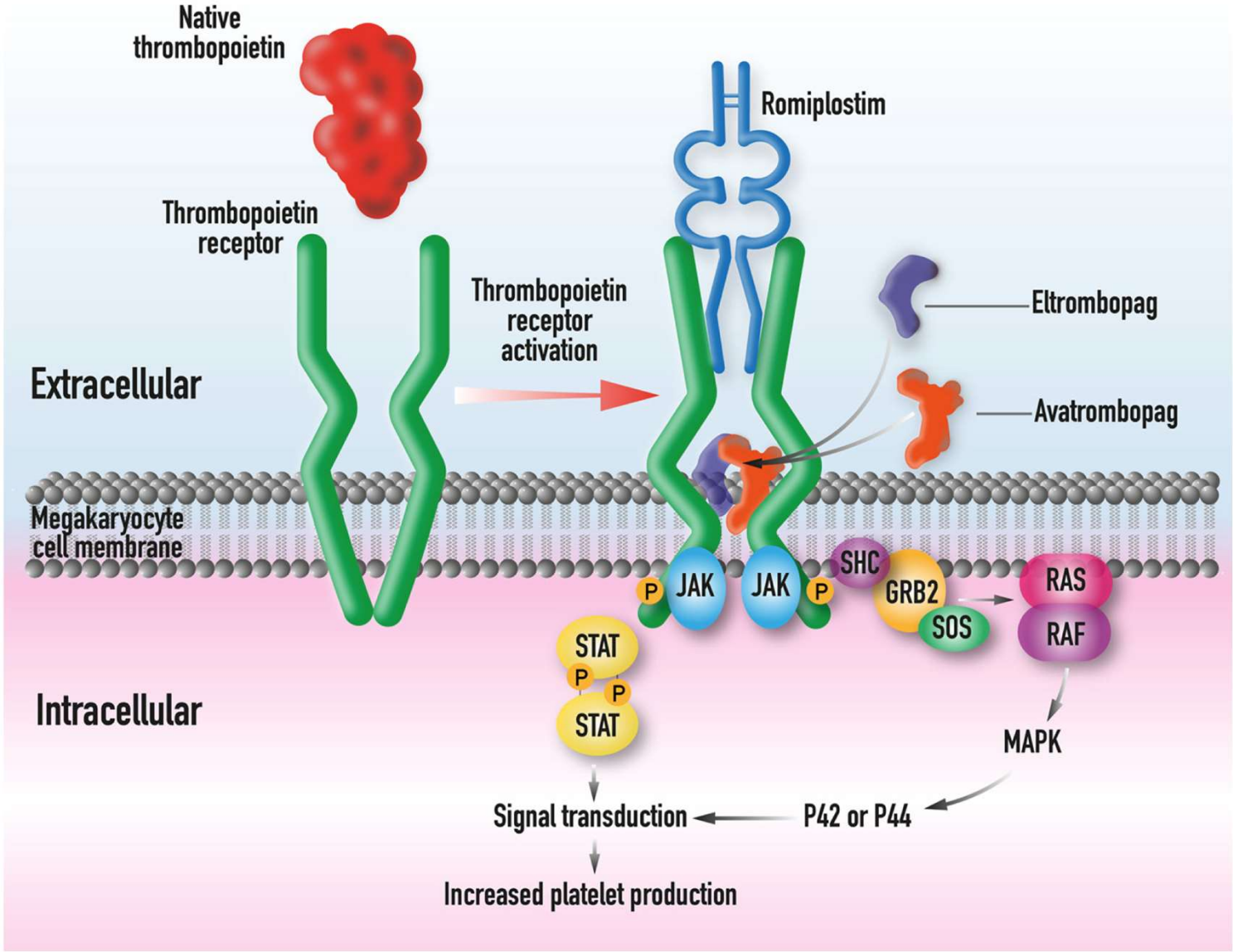
Thrombopoietin mimetics

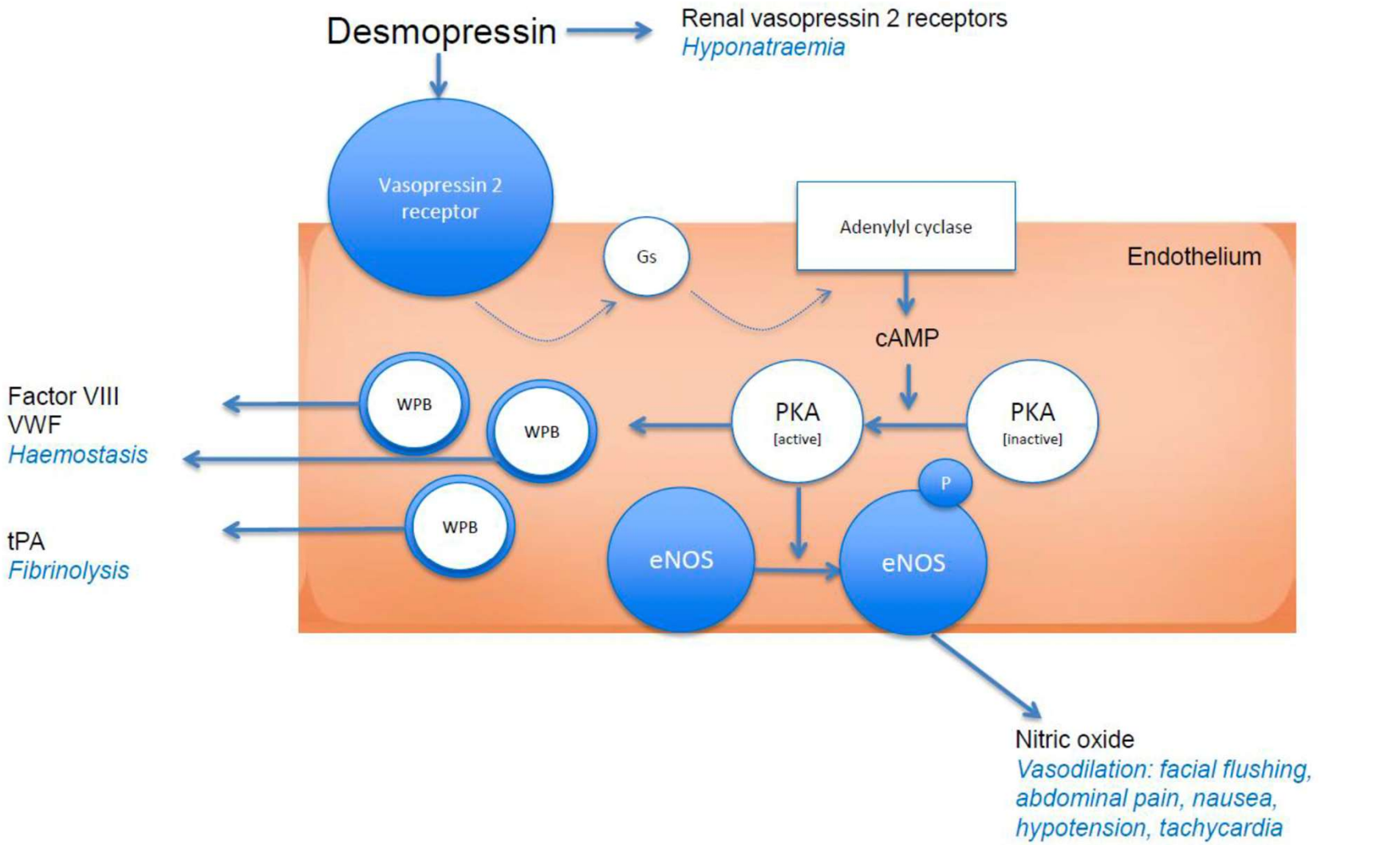


Provan & Semple. eBioMedicine 2022;76;103820

Thrombopoietin mimetic licensed indications

Cause of thrombocytopenia	Avatrombopag	Eltrombopag	Romiplostim
Immune thrombocytopenia	Yes	Yes	Yes
Chronic liver disease before procedures	Yes	-	-
Hepatitis C [to allow antiviral therapy]	-	Yes	-
Aplastic anaemia	Ongoing trials	Yes	Ongoing trials
Chemotherapy	Ongoing trials	Ongoing trials	Ongoing trials
Inherited thrombocytopenia	-	Ongoing trials	Ongoing trials
Myelodysplastic syndrome	-	Trials completed	Trials completed

https://www.medicines.org.uk/emc/product/11837/smpc#gref
https://www.medicines.org.uk/emc/product/7819/smpc
https://www.medicines.org.uk/emc/product/567/smpc#gref
Clinicaltrials.gov



Adapted with permission from *Kaufmann et al. J Thromb Haemost 2003; **1**: 682-9*. Desmopressin binds to endothelial vasopressin 2 receptors. This stimulates exocytosis of Weibel-Palade bodies (WPBs), leading to release of Von Willebrand Factor (VWF), factor VIII and tissue plasminogen activator (tPA).

Desmopressin

- Usually given at 0.3 mcg/kg subcutaneously or intravenously
- Meta-analysis for patients with platelet dysfunction undergoing surgery showed reduced major bleeding and reduced transfusion requirements with no increase in thrombosis
- Trials completed and in press for desmopressin vs placebo for:
  - Thrombocytopenia and undergoing invasive procedures (DRIVE)
  - Intracerebral haemorrhage and taking antiplatelet drugs (DASH)

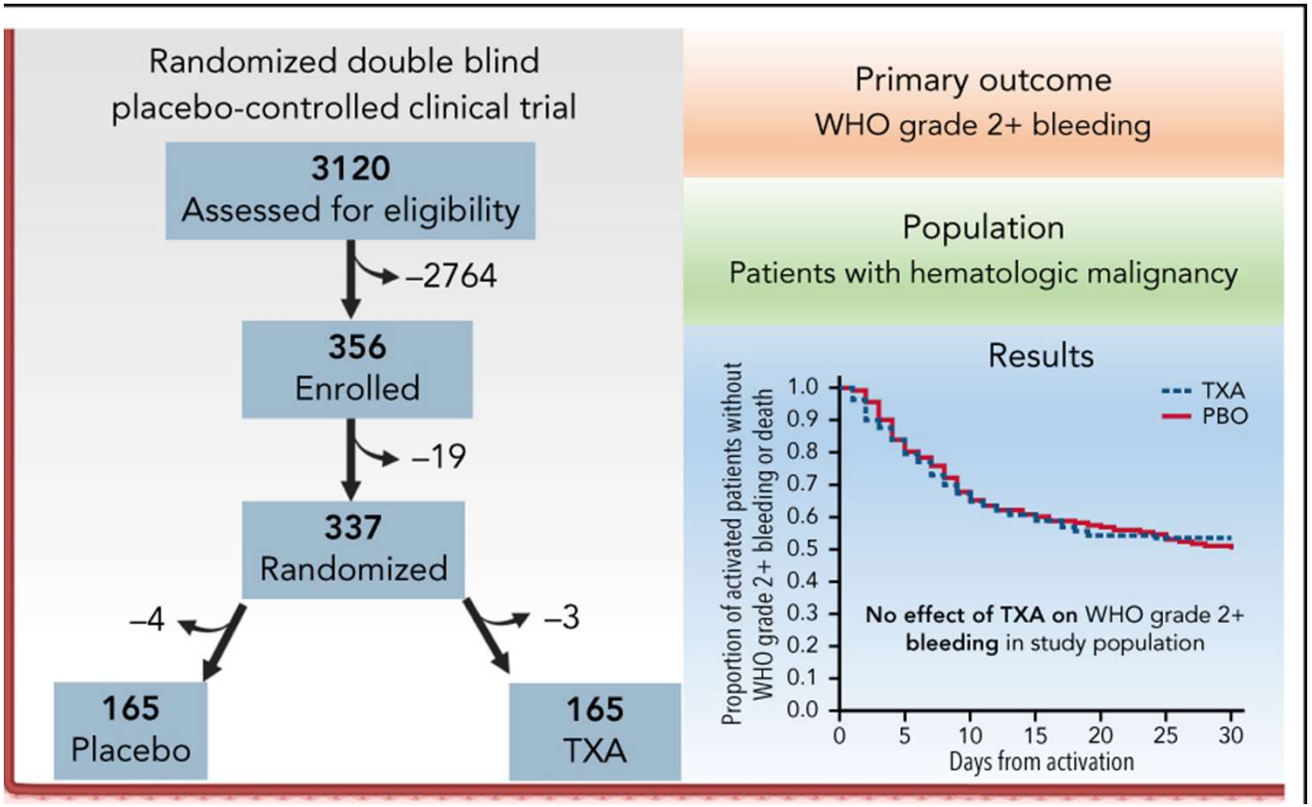
Desborough et al. J Thromb Haemost 2017;15(2):263-72
Desborough et al. Cochrane Database Syst Rev 2017;7(7):CD001884
Desborough et al. DRIVE: ISRCTN12845429
Desborough et al. DASH: ISRCTN67038373

Tranexamic acid randomized trial evidence

Setting	Mortality	Thrombotic events	Seizures
Trauma[1]	Reduced	No change	No change
Post-partum haemorrhage[2]	Reduced	No change	No change
Surgery[3]	Reduced	No change	No change but increased in some studies when high doses used[3,4]
Traumatic brain injury[5]	Reduced	No change	No change
Intracerebral haemorrhage[6]	No change	No change	No change
Gastrointestinal haemorrhage[7]	No change	Increased	Increased

1. CRASH-2 trial collaborators. *Lancet* 2010;376:23–32. 2. WOMAN trial collaborators. *Lancet* 2017;389:2105–16. 3. Ker K, et al. *BMJ* 2012;344:e3054. 4. Myles PS, et al. *N Engl J Med* 2017;376:136–48. 5. CRASH-3 trial collaborators. *Lancet* 2019;394:1713–23. 6. Sprigg N et al. *Lancet* 2018;391:2107–15. 7. HALT-IT trial collaborators. *Lancet* 2020;395:1927–36.

Tranexamic acid and thrombocytopenia



- UK systematic review 2016
  - Limited data and unable to make recommendation
- A-TREAT (see graphic above)
  - No difference in bleeding events with tranexamic acid vs placebo
- TREATT
  - UK study – results awaited

Estcourt et al. Cochrane Database Syst Rev 2016;3(3):CD009733
Gernsheimer et al. Blood 2022;140(11):1254-62
Estcourt et al. TREATT: ISRCTN73545489

Adjuncts

- Correction of other clotting defects (e.g. hypofibrinogenaemia)
- Treatment of sepsis
- Prolonged pressure on wounds
- Correction of anaemia [possibly]

Desborough et al. Br J Haematol 2016;175(3):381-92
Desborough et al. Haemost Thromb 2017;117(5):889-98

Agents in development or that have been investigated

Agent
Refrigerated platelets
Cryopreserved platelets
Lyophilised platelets
Haemostatic particles
Liposomes
Engineered nanoparticles
Infusible platelet membranes
Platelets generated from stem cells

Summary

- Potential alternatives to platelet transfusion are:
  - 1. Not to transfuse (in many cases, outcomes are similar)
  - 2. Thrombopoietin mimetics (although only licensed for a small number of conditions)
  - 3. Tranexamic acid (although no evidence of benefit in severe thrombocytopenia)
  - 4. Desmopressin (no clear evidence of benefit with trials underway)