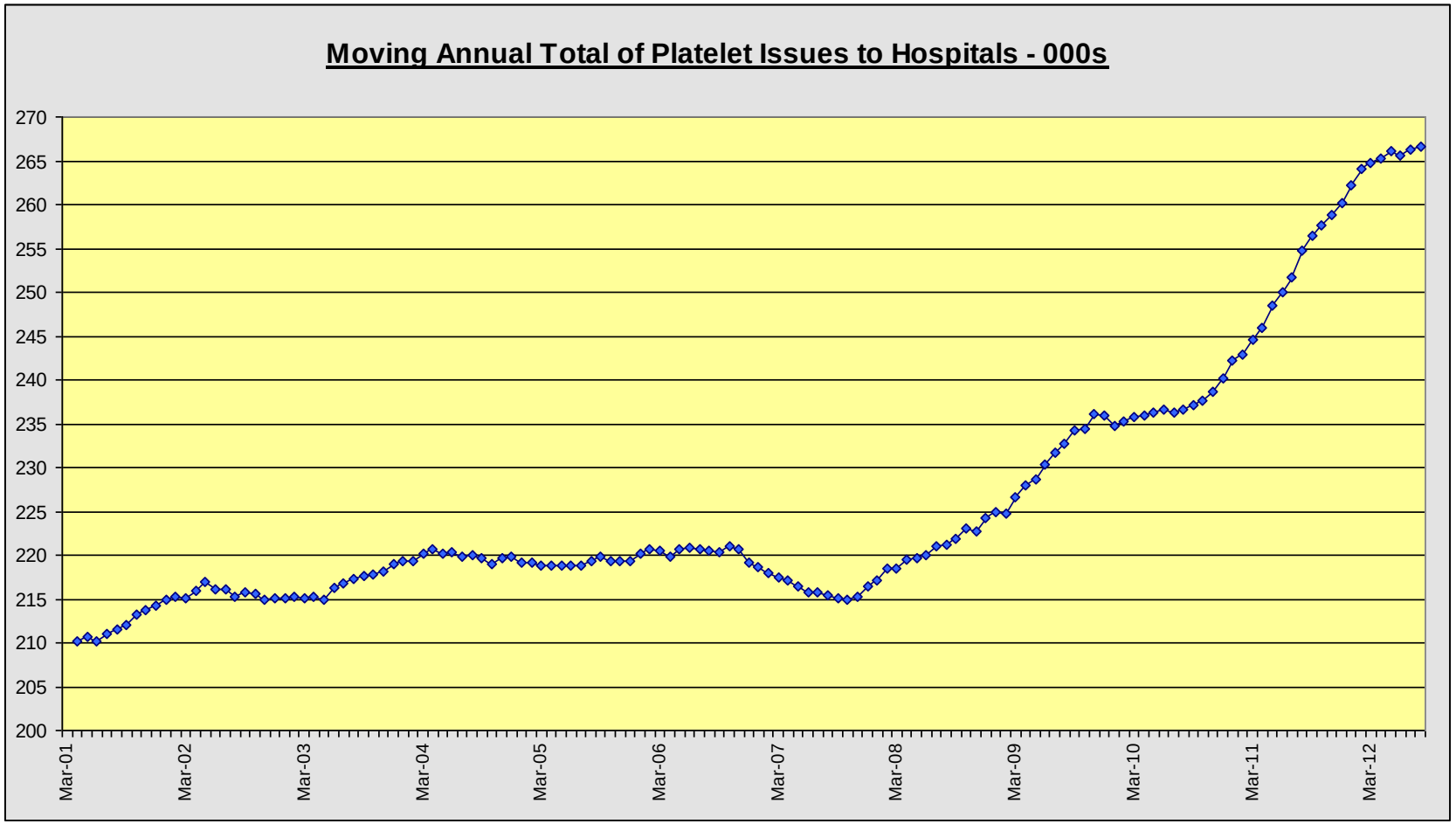
Home truths.....

the clinical use of components in the UK

Platelets, FFP, Cryoprecipitate

Jonathan Wallis

E&N.Wales Platelet use over 12 years



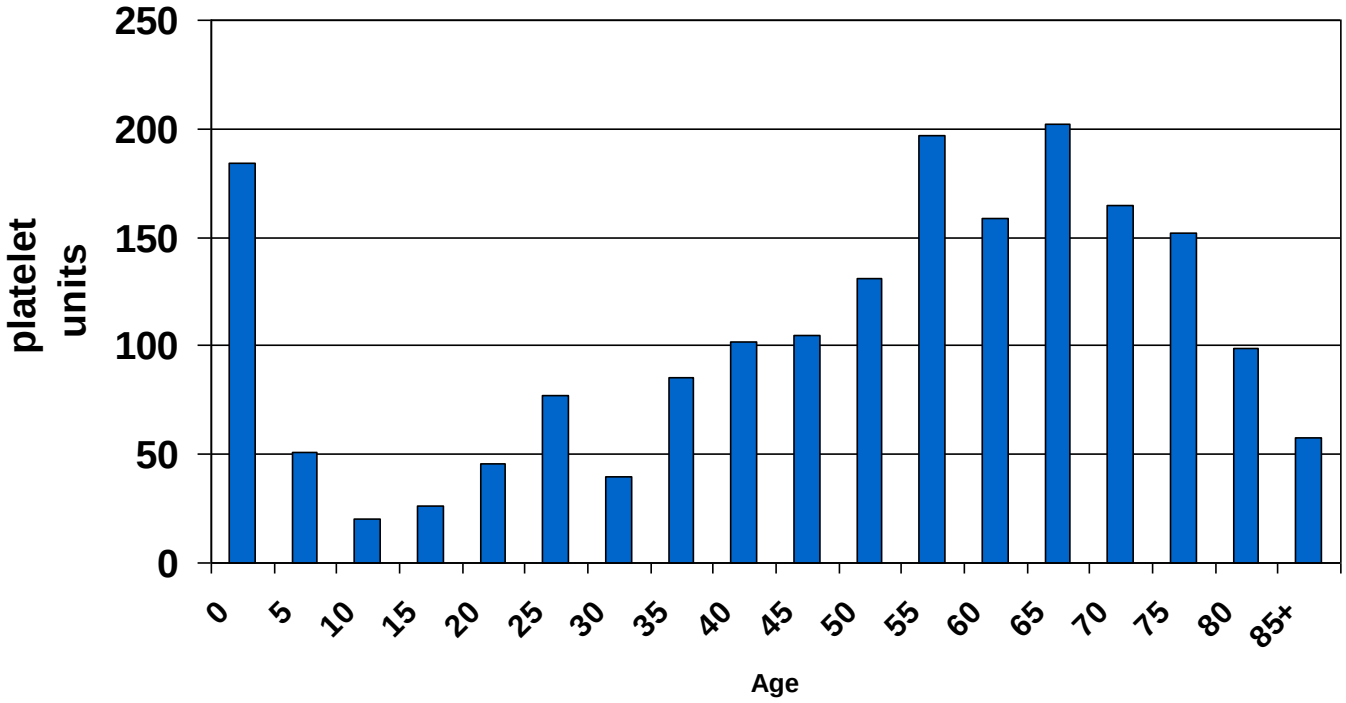
23% increase in demand over 4 years

Observational study in Northern region

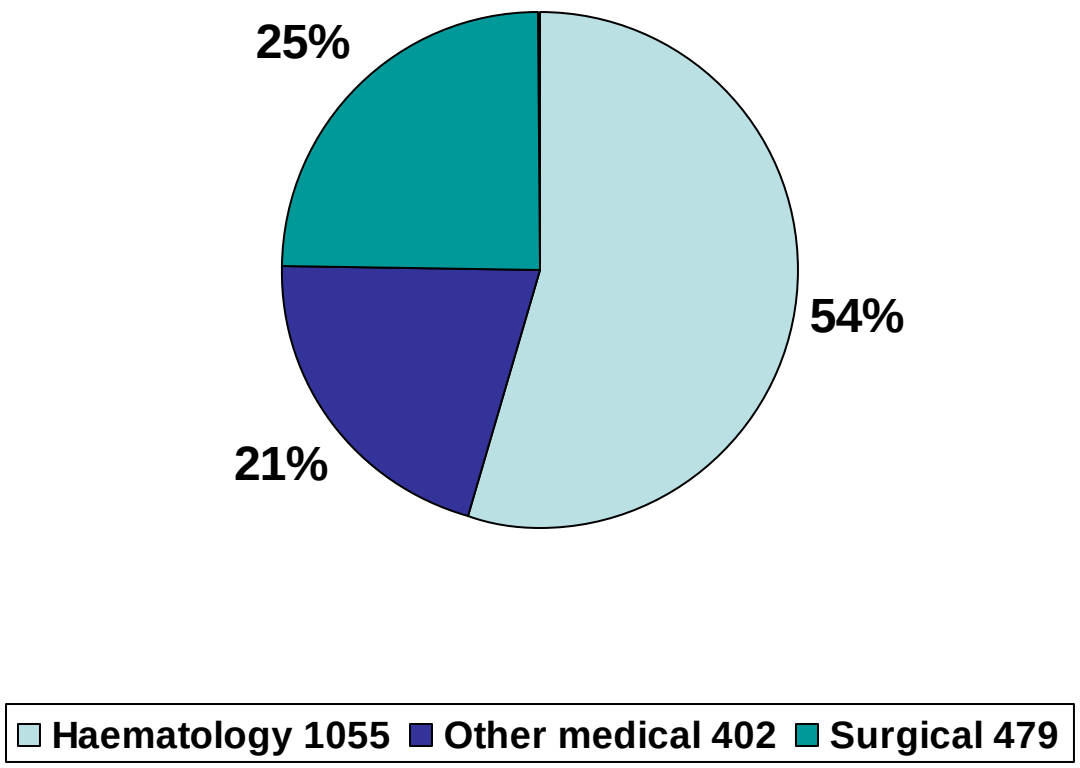
Thanks to Hazel Tinegate
Andrew Charlton SpR, Adil Iqbal Chair of NRTC, Denise Watson and all regional hospitals

- 1937 platelet units surveyed over 8 weeks
- 4.41 units per 1,000 population
  - Compares to 4.93 /1,000 for all E&NW
  - Compares to 36 RCs /1000
- Mean recipient age = 57 yrs
- Male to female 1.4:1
- 68% prophylactic use with no planned procedure

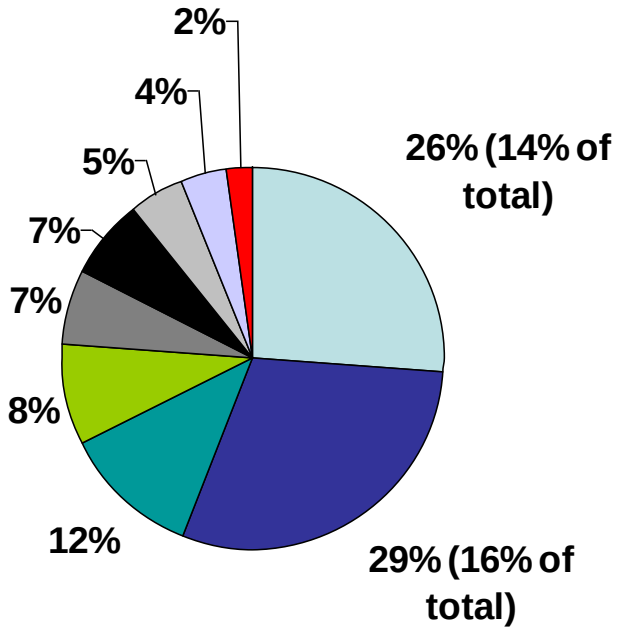
N.Region platelet use by recipient age



N. Region platelet use by broad speciality

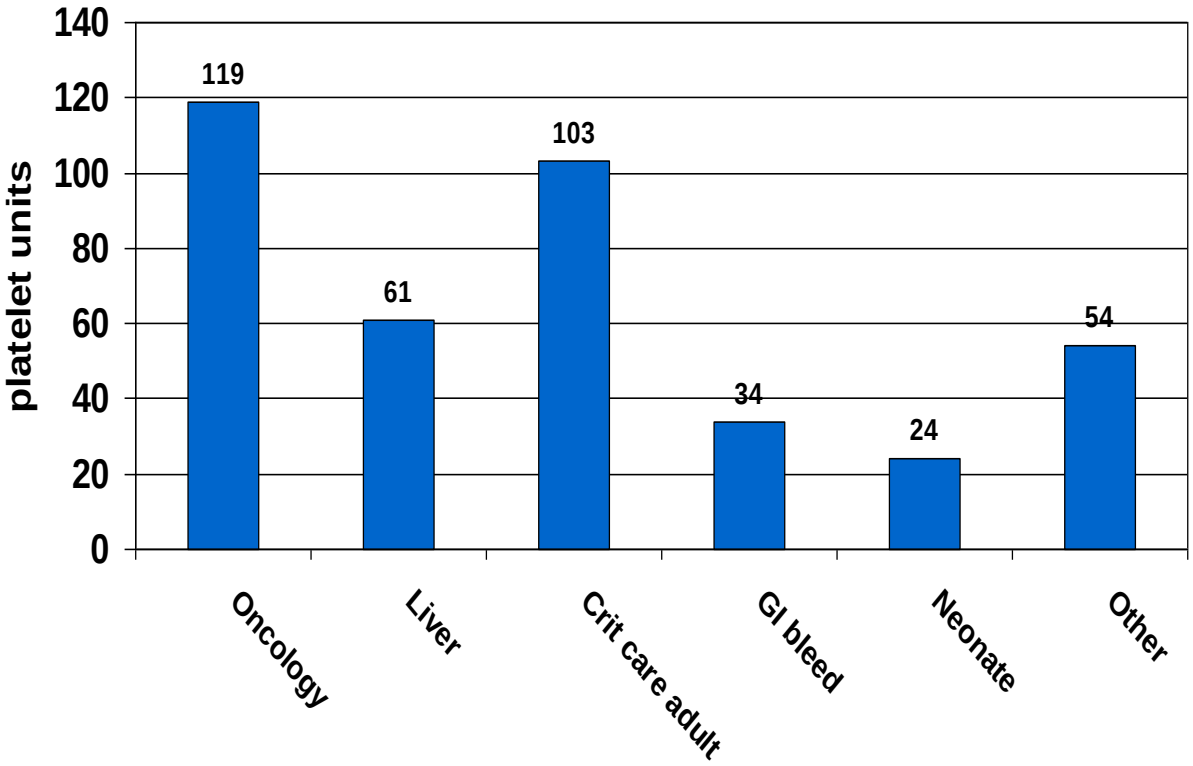


Haematology use: 54% of total



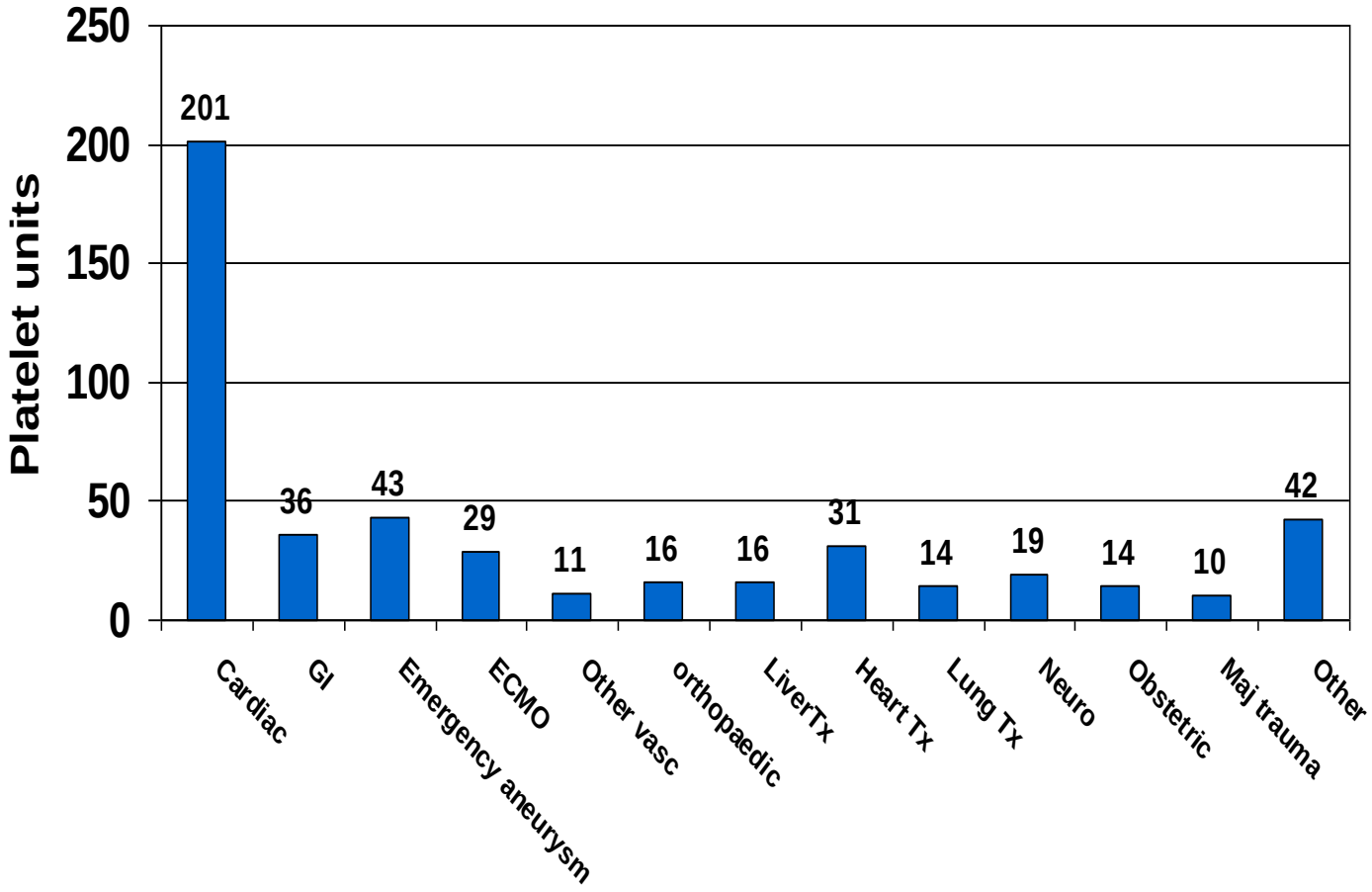
Transplant, 271	AML, 310	MDS, 123
NHL, 87	ALL, 69	Myeloma, 68
CLL, 48	Aplastic, 41	Other (ITP, HD), 24

Medical platelet use



Approx 5% of total use in oncology and 5% in critical care

Platelet use in surgical specialities (25% of total)



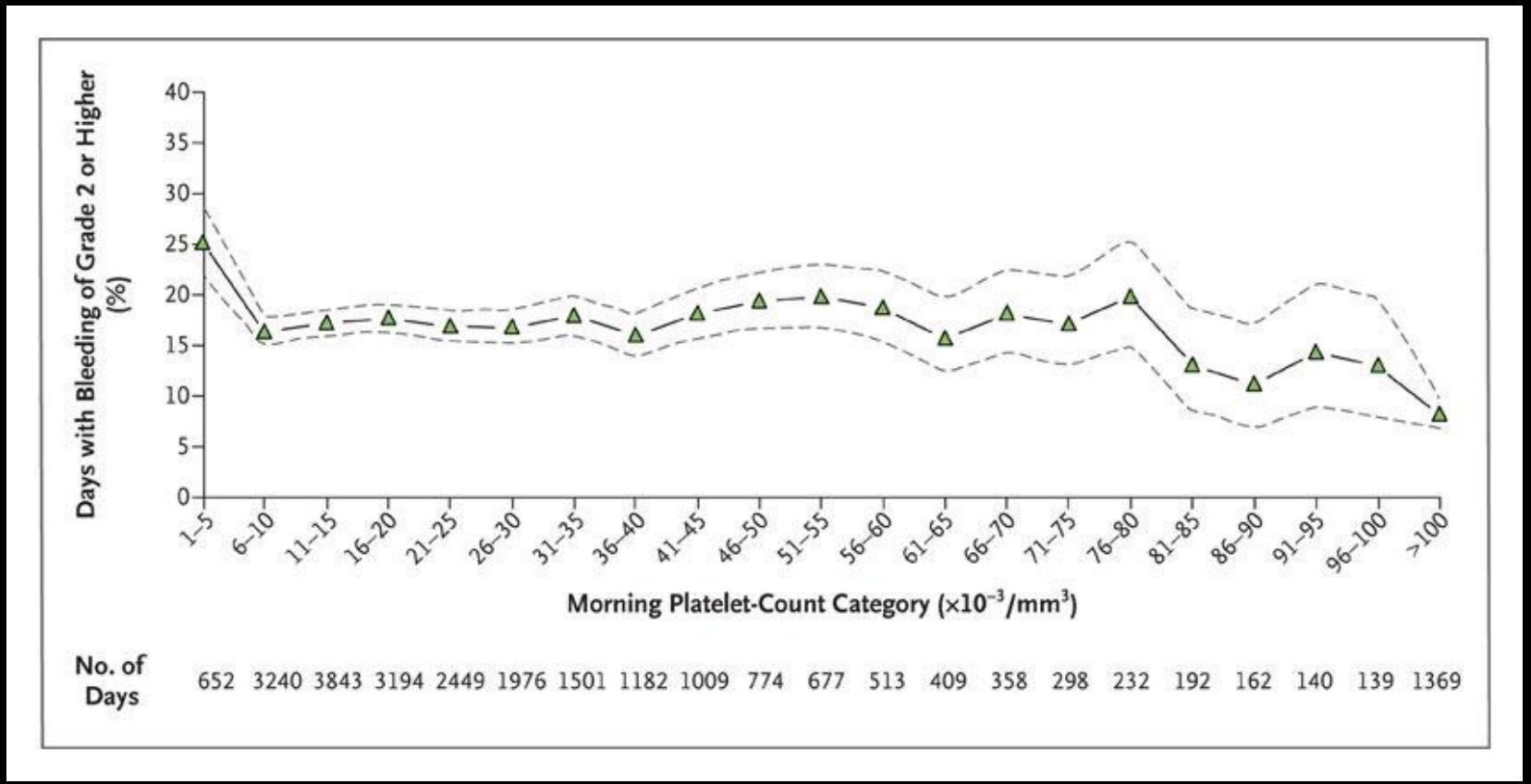
Cardiac use is 10% of all platelet use

Evidence for platelet use

- Cardiac surgery: No studies or trials showing benefit of platelet transfusion

- GI bleeding: No trials showing benefit of platelet transfusion

Days with Bleeding of Grade 2 or Higher in All Three Treatment Groups, According to Morning Platelet-Count Categories



Slichter SJ et al. N Engl J Med 2010;362:600-613

PLADO study
Slichter SJ et al. N Engl J Med 2010;362:600-613

- Doses between 1.1×10^{11} and 4.4×10^{11} /M2
  - No effect on the incidence of bleeding
- Low doses of platelets
  - decreased total number of platelets transfused
  - increased number of transfusions

Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study

Hannes Wandt, Kerstin Schaefer-Eckart, Knut Wendelin, Bettina Pilz, Martin Wilhelm, Markus Thalheimer, Ulrich Mahlknecht, Anthony Ho, Markus Schaich, Michael Kramer, Martin Kaufmann, Lothar Leimer, Rainer Schwerdtfeger, Roland Conradi, Gottfried Dölken, Anne Klenner, Mathias Hänel, Regina Herbst, Christian Junghanss, Gerhard Ehninger, for the Study Alliance Leukemia

Summary

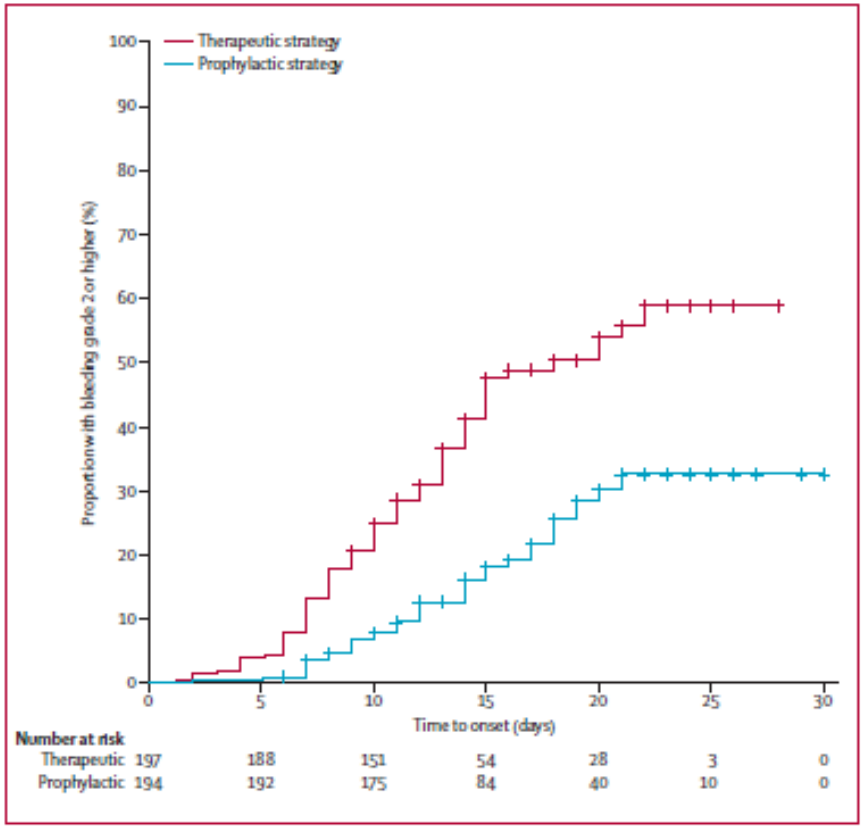


Figure 2: Time to onset of bleeding of grade 2 or higher in all patients

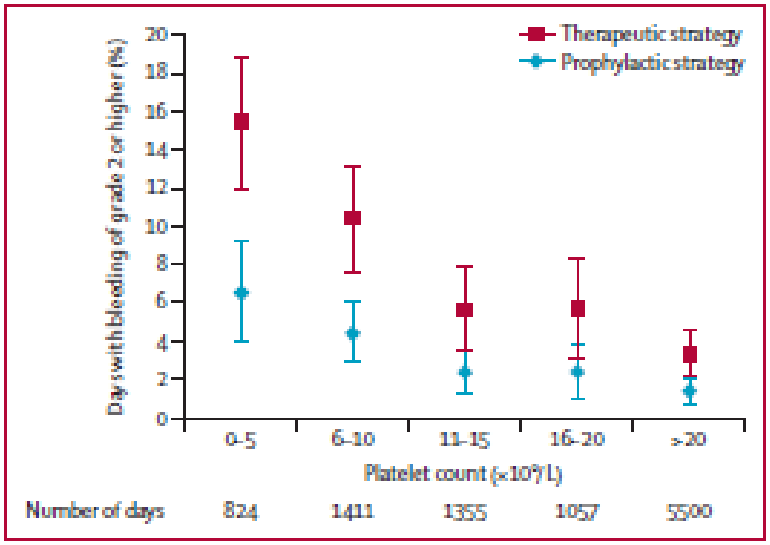


Figure 3: Days with bleeding of grade 2 or higher in both transfusion groups by categories of morning platelet count
Error bars show 95% CI. Data are based on the 10 147 days during the study period in which patients had a morning platelet count, and on information about bleeding of grade 2 or higher.

WANDT *et al*. LANCET
Published on-line Aug 7th 2012

Wandt et al: Key findings

- More serious/fatal bleeds in therapeutic group
- Fatal intra-cerebral bleeds limited to AML treatment
  - One had platelets >10 x 10’9/L
  - Other had invasive fungal infection and should have received platelets under protocol
- 6 cerebral haemorrhages found in therapeutic group
  - Only mildly symptomatic
  - Found due to protocol CT for headaches
- 1/3rd reduction in platelet use in therapeutic vs proph arm

Conclusion

- Limited duration thrombocytopenia may be managed with a therapeutic strategy
- Longer duration is better managed with prophylactic strategy
- Bleeding not closely correlated with inverse of actual platelet count
- Will TOPPS trial confirm??

What do I want?
What do I really really want?

1. Function , Recovery , Survival

Dose x Recovery x Survival = Platelet Days

- 2x 10’11x 1.0 x 5 days = 10x 10’11 platelet days

- Eg
  - Dose x 0.9 x 0.9 = 0.81 x dose platelet days
  - Dose x 0.7 x 0.7 = 0.49 x dose “
  - Dose x 0.6 x 0.6 = 0.36 x dose “

Platelets age at 1/3 rd of normal rate in storage at 21 C

2. Universal platelets?

- Group O platelets
- Suspended in group AB plasma +/- PAS
- Leucodepleted
- Pathogen inactivated?
- Provided for use within 48 hrs of donation

Fresh frozen Plasma: 300,000 units/yr in UK

Country	Single donor FFP	Pooled FFP	FFP per 1000
France	65%	33%	4.0
Portugal	5%	95%	5.9
Holland	60%	40%	6.2
Spain	100%		6.2
Ireland	5%	95%	6.4
UK	94%	6%	6.4
Norway		100%	7.1
Belgium		100%	8.8
Greece	100%		9.6
Finland	100%		9.6
Denmark	100%		10.2
Italy	94%	6%	11.3
Germany	72%	28%	12.0
United States			12.7

2009 national audit of FFP

with thanks to John Grant-Casey

Q6 What was the underlying medical or surgical condition?	Age 16+ years[1] National (4635)	
Warfarin reversal	**14%**	669
Disseminated Intravascular Coagulopathy (DIC)	**3%**	148
Massive haemorrhage (as defined in your hospital)	**13%**	590
Cancer	**10%**	451
Liver disease	**19%**	886
Cardiac surgery	**13%**	587
Other surgery	**21%**	974
Trauma	**3%**	158
Other*	**18%**	812

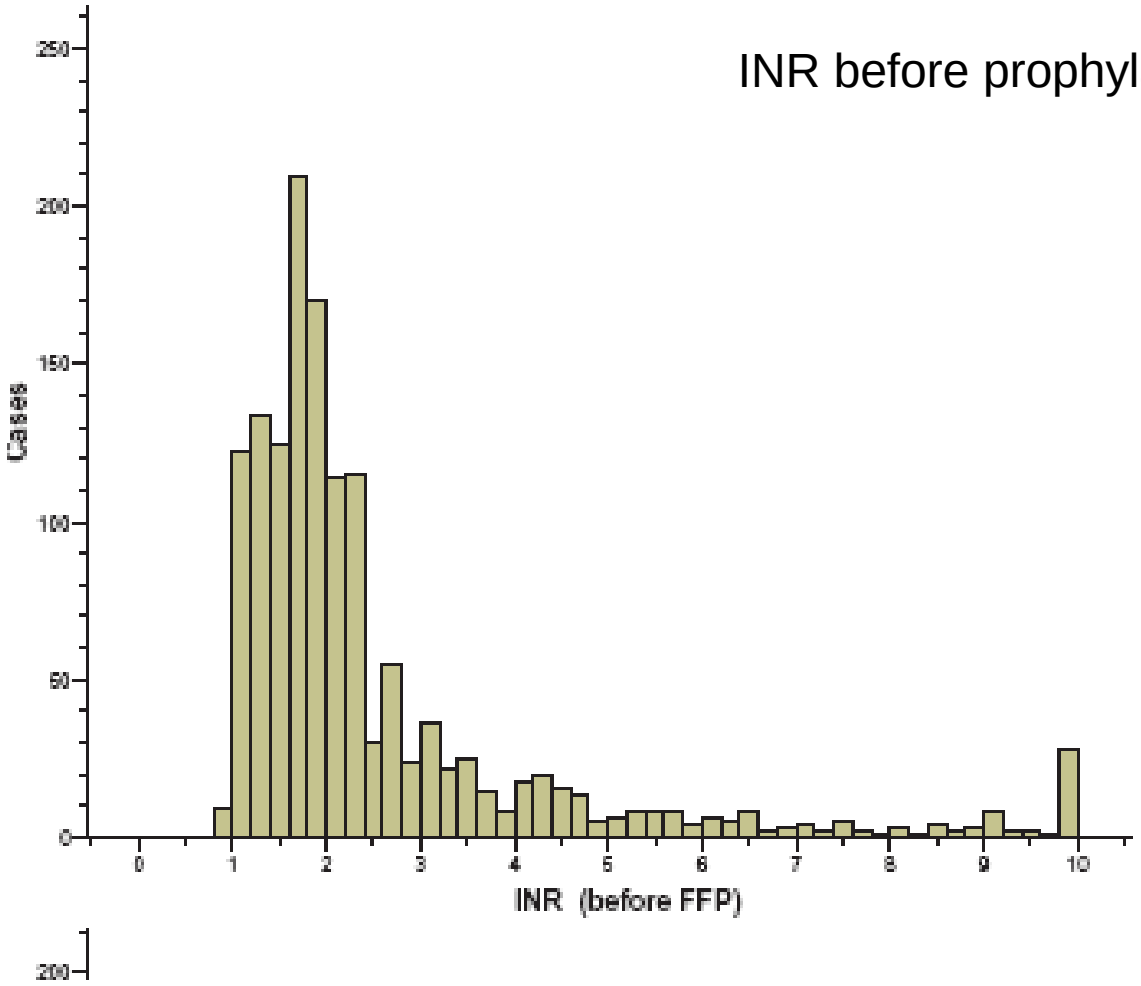
Use in Newcastle Jan-Aug 2012

Ward speciality	4094 units
Cardiac surgery	24%
ITU	20%
Liver disease	15%
Other surgery	13.2%
Trauma	7.5%
Renal/TTP	5%
Paed ITU	3.8%
Medicine	3.7%
Haem/Onc	2.2%
Obs/Gynae	1.4%
NK and Other	4%
Warfarin reversal	0%

Q8 Which (one) of these best describe the reasons for giving this initial FFP transfusion?	Age 16+ years National (4635)
Bleeding	54%
Before invasive procedure or surgery, with abnormal coagulation	23%
During invasive procedure or surgery, with abnormal coagulation but no bleeding	8%
Abnormal coagulation with no bleeding	12%
Other	1%
Not documented / not known / blank	2%

Stanworth, SJ., Grant-Casey, J., Lowe, D.,Laffan, M., New, H., Murphy, M., and Allard, S. (2011) The use of fresh-frozen plasma in England: high levels of inappropriate use in adults and children, *Transfusion,* **51,** 62-70

INR before prophylactic FFP



FFP use

- Practice could be improved
  - FFP use in ITU
- Evidence of benefit is lacking in many situations
- Alternative agents are gaining popularity
  - Prothrombin complex concentrate
- Increased use in major haemorrhage
  - Retrospective studies
  - Prospective study planned
  - ?more important than red cells

“How do you like your plasma in the morning??”

- Pre-thawed
  - Shelf life of 3-5 days?
  - Freeze dried?
- Male donor/HLA Ab tested
- Group AB
- Pooled ?
- Pathogen inactivated?
- Concentrated?

Cryoprecipitate

Approximately 11,000 adult doses issued per year in England

= 1 adult dose per 7 litres FFP

Cryoprecipitate for transfusion: which patients receive it and why. A study of patterns of use across three regions of England.

Tinegate, Allard, Grant-casey, Hennem, ,Kilner, Rowley, Seeney, Stanworth

Transfusion Medicine 2012; 22: 356-61

Table 2. Main clinical scenario and indication for cryoprecipitate use: adults

Clinical Scenario	Total number (%)	Haemorrhage (%)	Prophylaxis (%)
Cardiac surgery	102 (32)	97 (36)	5 (9)
Trauma	38 (12)	37 (14)	1 (2)
Haem/Onc excl APML	37 (12)	21 (8)	16 (29)
Liver failure	26 (8)	14 (5)	12 (22)
Vascular surgery	24 (7)	24 (9)	0
GI bleed	26 (8)	23 (9)	3 (5)
Critical care	23 (7)	16 (6)	7 (13)
Surgical	18 (6)	16 (6)	2 (4)
Obstetrics	14 (4)	13 (5)	1 (2)
Renal Failure	6 (2)	3 (1)	3 (5)
Acute promyelocytic leukaemia	6 (2)	2 (1)	4 (7)
Thrombolytic therapy *	1 (<1)	0	1 (2)
Other medical *	1 (0)	1 (0)	0
Total	**322**	**267**	**55**

* Bleeding indication missing from one case within this category

Findings

- Wide variation in Cryo: Red cell use between different hospitals and different regions
  - 0.1 – 4.9 units per 100 red cells
- Variation in fibrinogen level pre transfusion
  - Not measured / <1g/L / 1.5g/L
- Variation in measurement of fibrinogen
  - Clauss / Derived
- Are there alternatives?

“No Cryo for me, I’ll use fibrinogen.....”

- Is Fibrinogen concentrate enough?
- Do factors VIII & XIII, vWf, and fibronectin matter?
- Freeze dried cryo?

Conclusions

- Considerable international and national variation in use of blood components
- Room for improved use according to current guidelines
- Room for improved products