



Clinical Evidence of Platelet Dose

Nancy M Heddle MSc., FCSMLS(D)

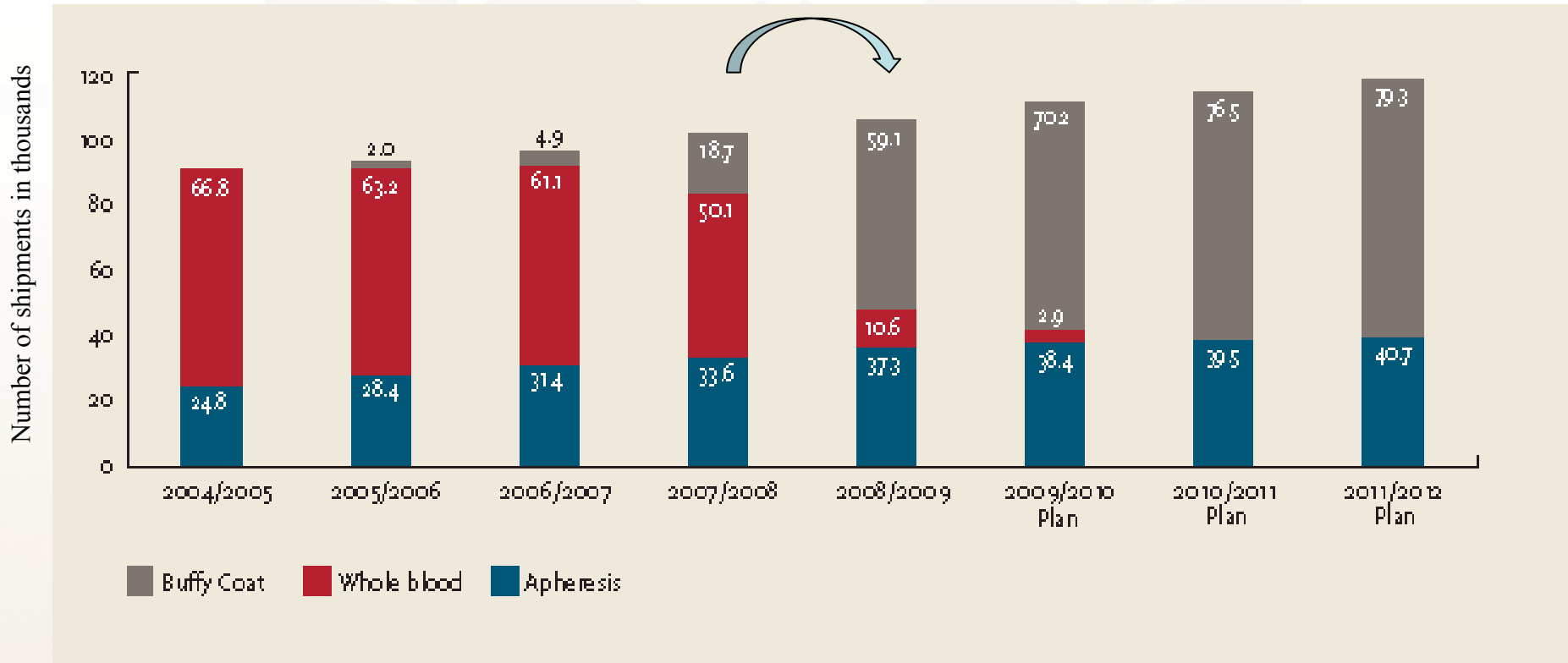
Associate Professor

Department of Medicine

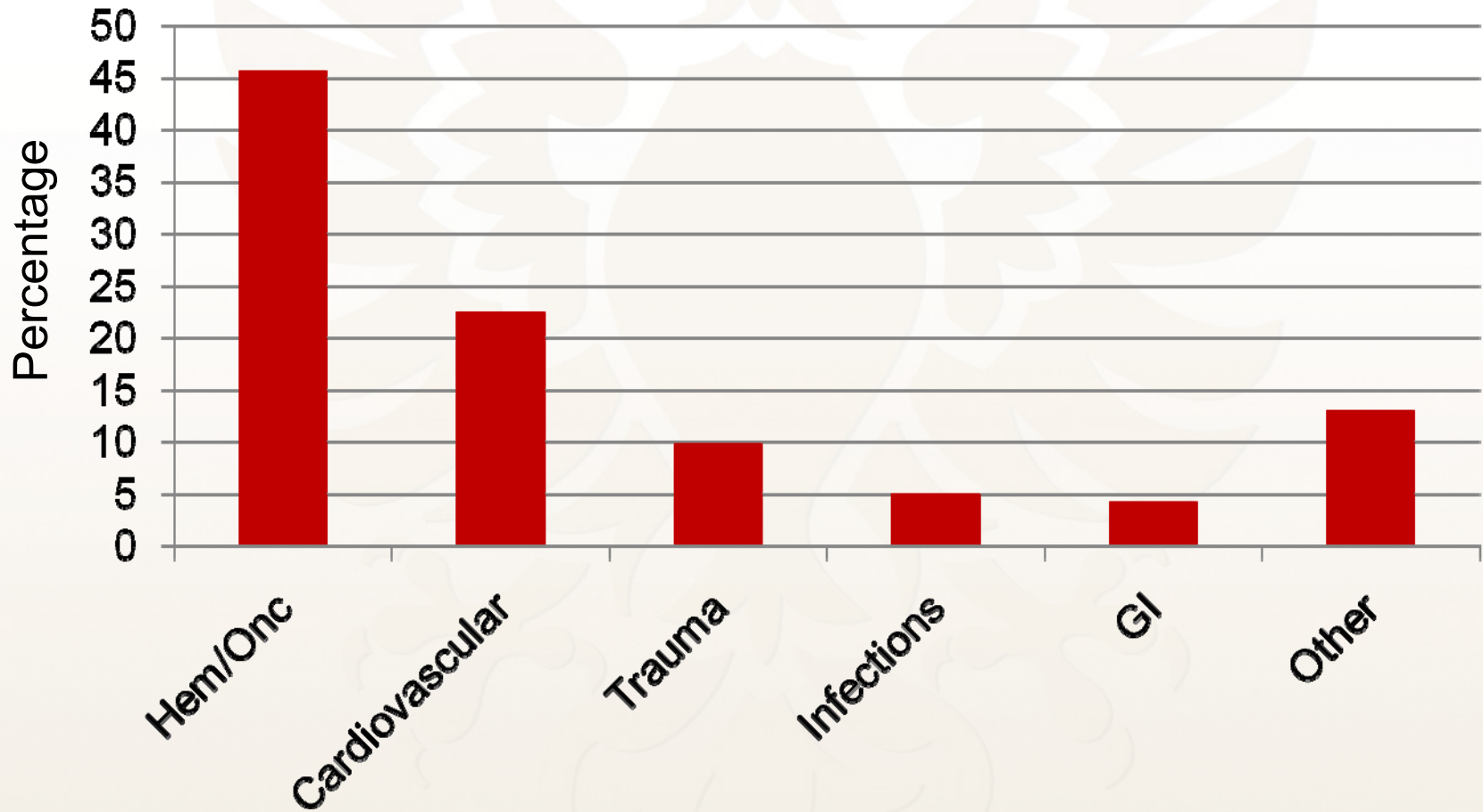
McMaster University

Platelet Doses in Thousand

4.5% increase



Who uses platelets?



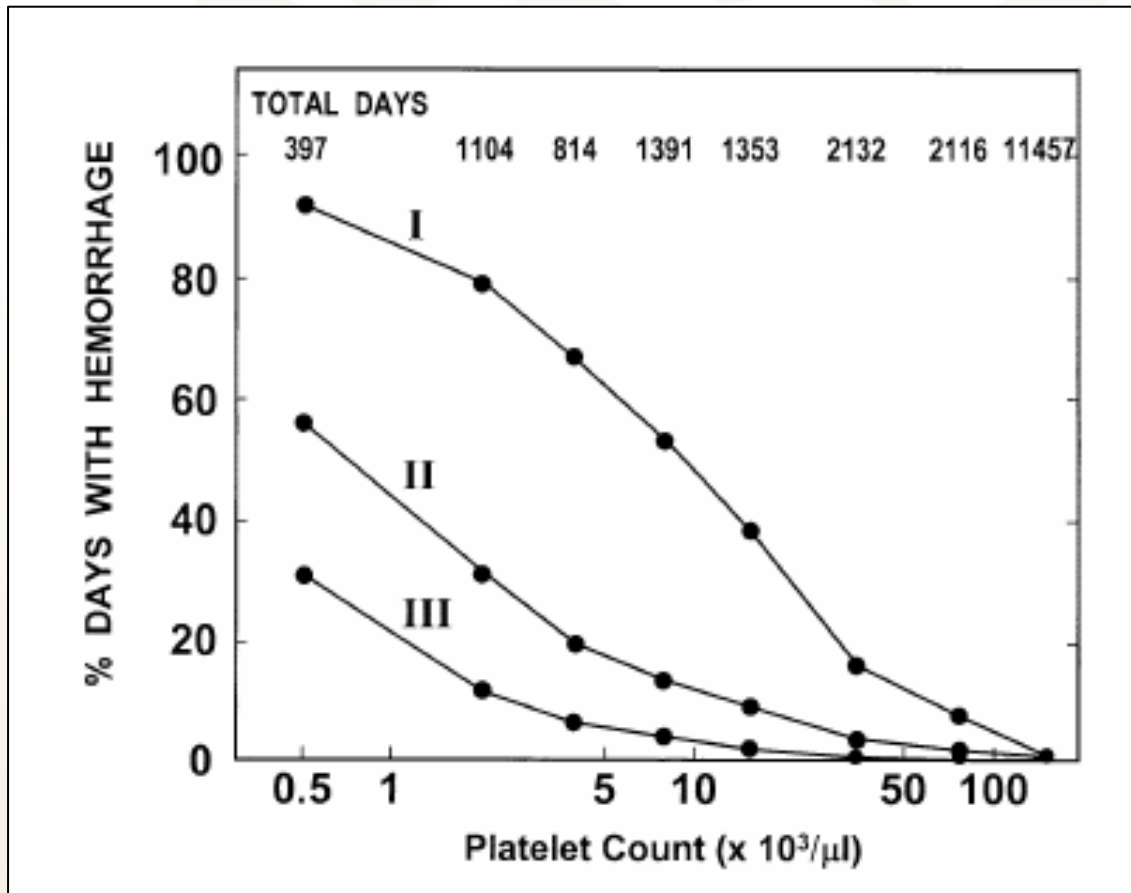
Platelet Use Hematology/Oncology

Cancer



**Prophylactic
Therapeutic**

Relationship Between Hemorrhage and Plt Count in Non-Transfused Thrombocytopenic Patients



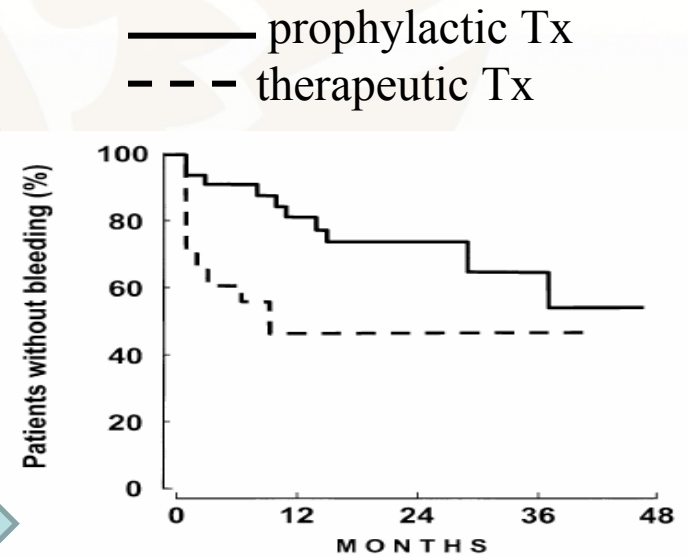
I = All hemorrhagic complications
II = Skin bleeding & epistaxis
III = Grossly visible hemorrhage

Gaydos et al., NEJM 1962: 266; 905-909,

Prophylactic versus Therapeutic Platelet Transfusions (RCTs)

Study	Population	Sample Size
Higby* (Trans 1974)	Adults AML	21
Solomon** (Lancet 1978)	Adults ALL	31
Murphy*** (AJH 1982)	Children	56

TOTAL 108



Murphy S, Am J Hematol 12: 347-356, 1982

*3 units/m²; trigger 30 x 10⁹/L versus platelet poor plasma

**Dose not stated ; Trigger 20 x 10⁹/L versus 50% drop in plt count and count < 20 x 10⁹/L

***4 units/m²; trigger 20 x 10⁹/L versus therapeutic only

Objectives

- Focus of platelet dose
- 2 recent trials (design & results)
 - SToP (**S**trategies for **T**ransfusion of **P**latelets)
 - PLADO (**P**latelet **D**ose Study)
- Outcome - WHO Bleeding \geq Grade 2
 - What we have learned from SToP
 - A new bleeding scale
 - A new conceptual model moving forward

Platelet Dose Studies

Author/ DATE	# Pts	# Tx	Design	Treatment Arms	Outcomes
Norol 1998	69	207	Crossover	Medium, High Very high	Increments Transfusion Interval
Klumpp 1999	45	158	Crossover	Lower vs Higher	Increments Transfusion interval
Goodnough 2001	120	166	Parallel RCT	Low vs High	Increments
Tinmouth 2004	111	311	Parallel RCT	Low vs Standard	Bleeding
Sensebe 2005	96	96	Parallel RCT	Standard vs High	Increments, transfusion interval, bleeding
Heddle 2009	129	878	Parallel RCT	Low vs Standard	Bleeding
Slichter 2010	1272	6031	Parallel RCT	Low, Medium High	Bleeding



SToP Study Design

Eligible Patients



Informed Consent

Strata
•Centre
•Diagnosis (2)



Target:
150-299 x 10⁹



Low Dose

Standard Dose

Daily Assessment for Bleeding

Target:
300-600 x 10⁹

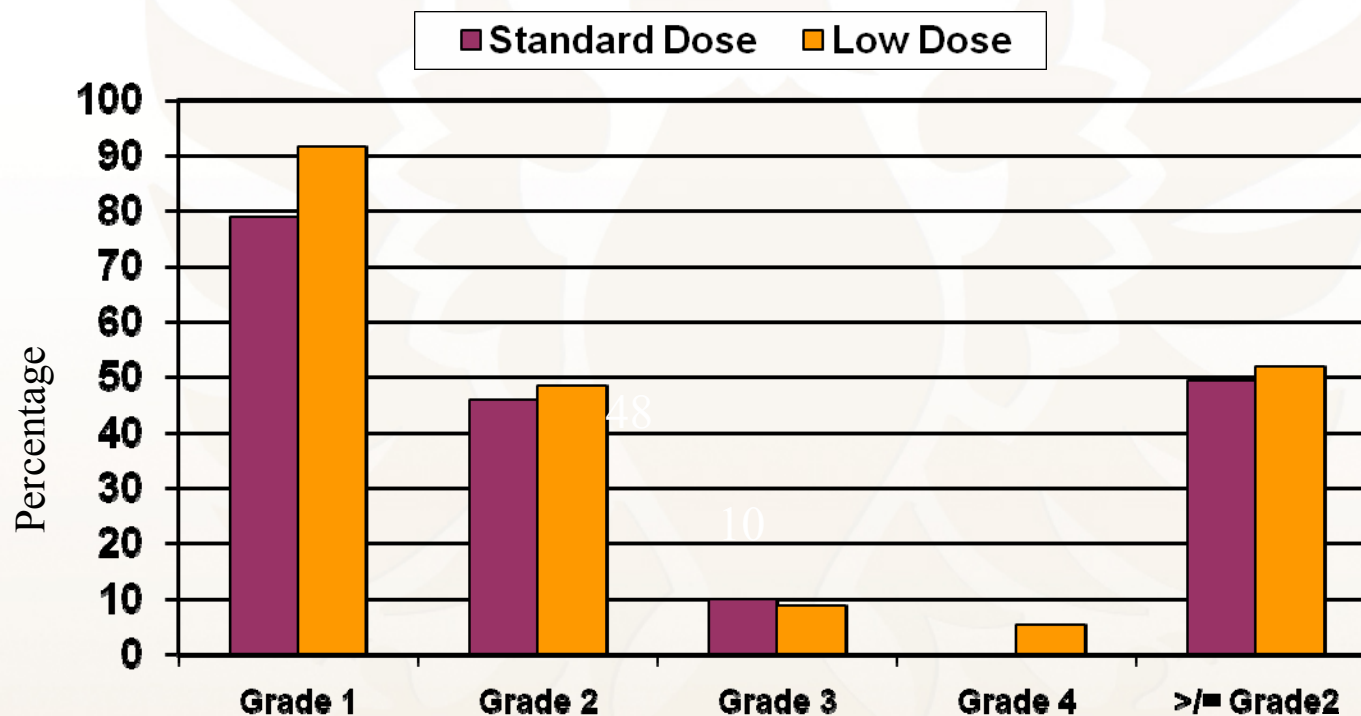
Primary Outcome
% Patients bleeds (≥ Grade 2)
Secondary Outcomes
Bleeding – Recurrent event analysis
Product utilization/donor exposures
Duration of thrombocytopenia

SToP – Stopped Early

- Sample size: approximately 600 patients
- Stopping rule
 - DSMB may stop the study if:
 - Absolute difference in the cumulative frequency of grade 4 bleeding exceeds 5%
 - After a minimum of 50 patients enrolled in each group
- DSMB requested the study be stopped after 129 patients were enrolled
 - Grade 4 Bleeding Low dose – 5.2%
 - Grade 4 Bleeding Standard dose – 0%

SToP Study Analysis

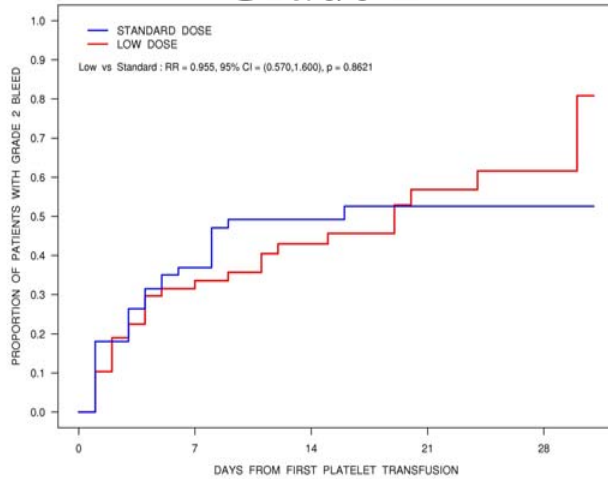
% of Patients with Bleeding (Grade 2, 3 & 4)



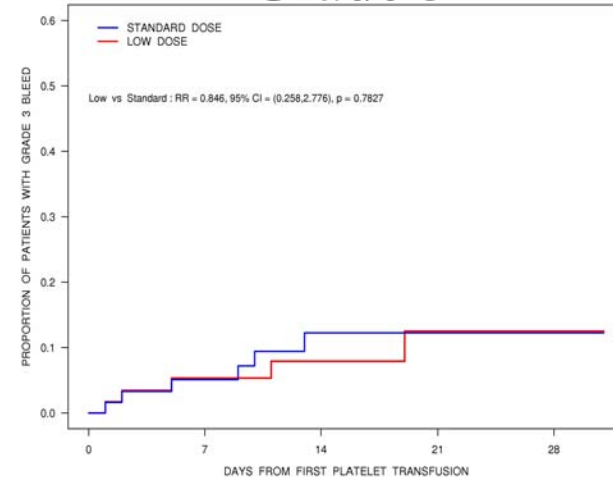
Secondary Outcome	Standard Dose Platelet (n=61)	Low Dose Platelets (N = 58)
Percentage of days with bleeding (proportion) \geq Grade 2	8.5 (73/854)	12.1 (111/918)

Time to First Bleed

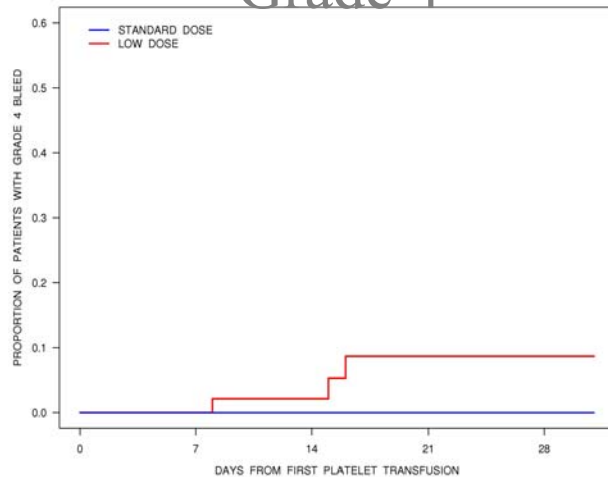
Grade 2



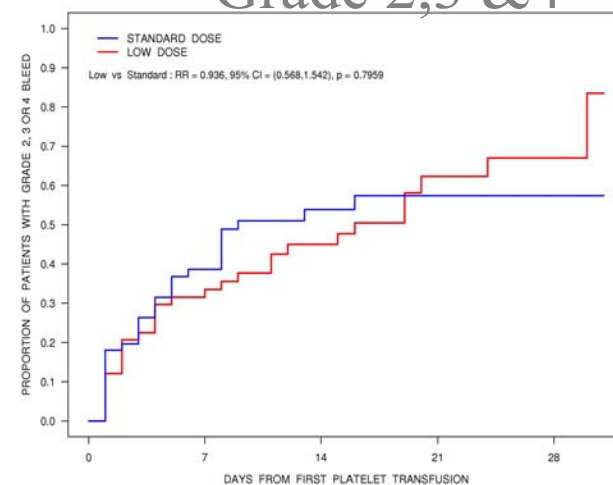
Grade 3



Grade 4

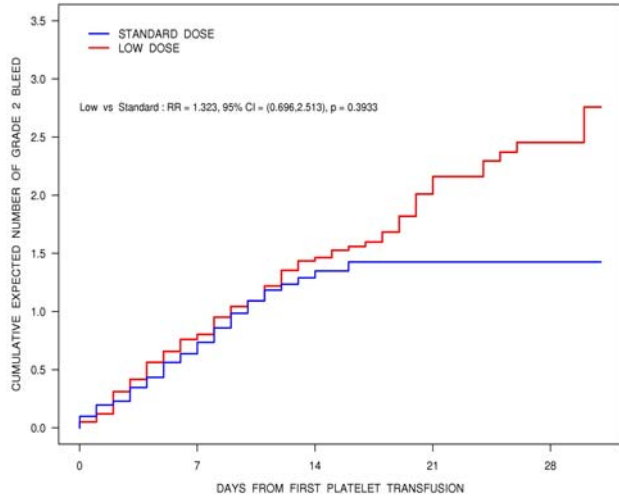


Grade 2,3 &4

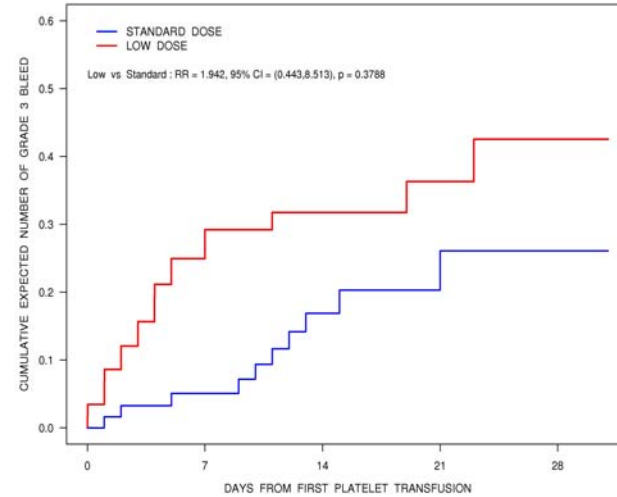


Recurrent Event Analysis

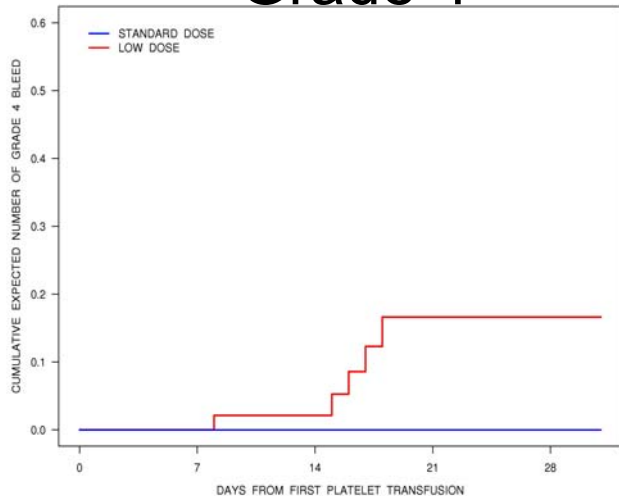
Grade 2



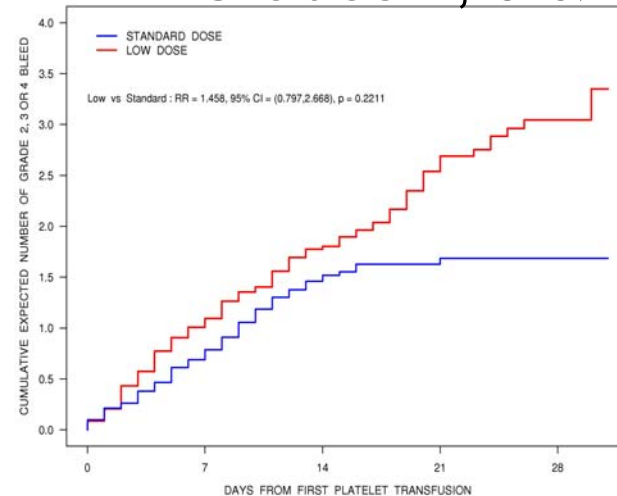
Grade 3



Grade 4

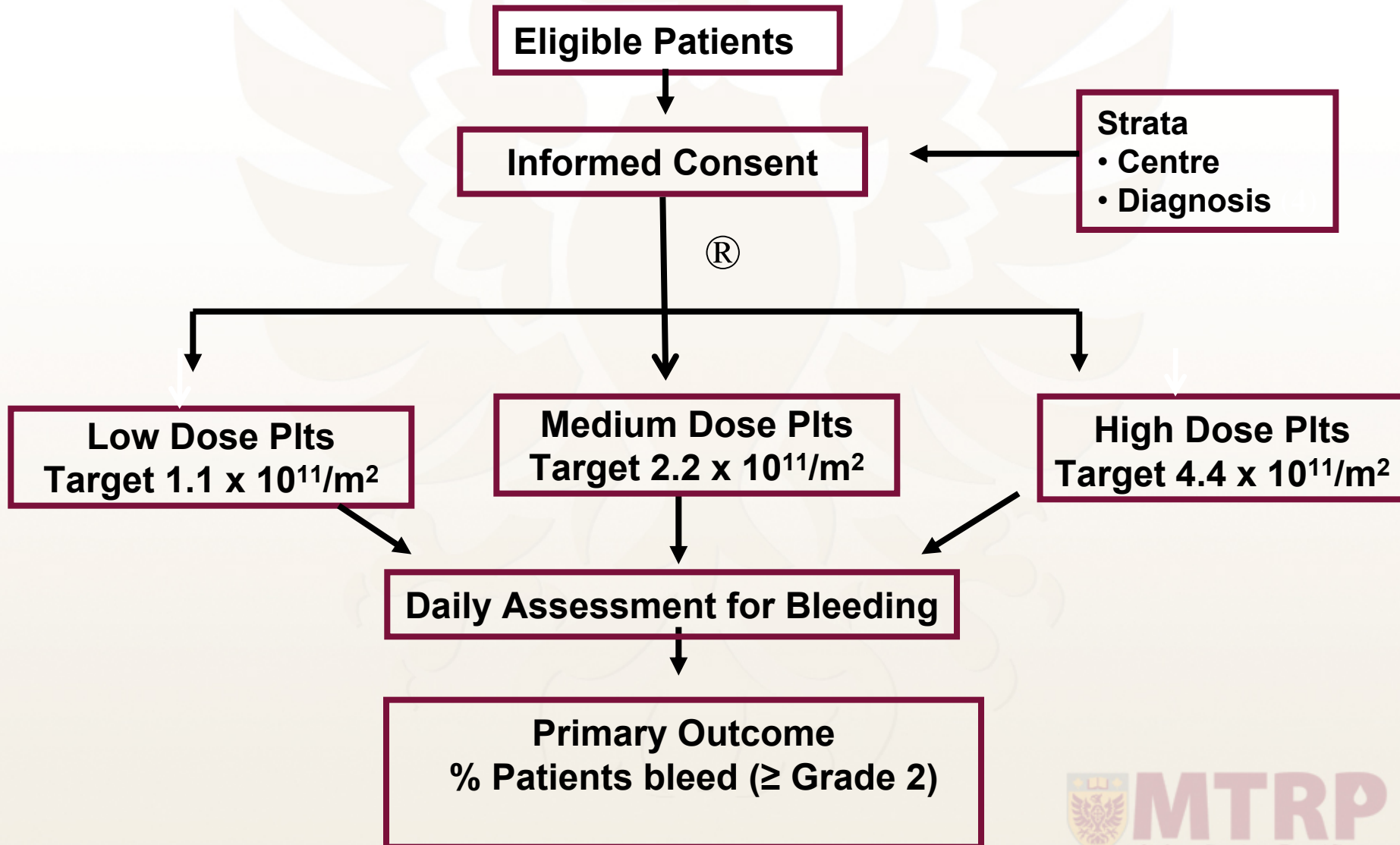


Grades 2, 3 & 4



PLADO Study Design

Slichter et al., NEJM 2010



PLADO Results

Outcome	% of patients		
	LOW n = 417	MEDIUM n = 423	HIGH n = 432
Bleeding \geq Grade 2	71	69	70
No Bleeding or Grade 1	30	32	30
Grade 2	58	59	60
Grade 3	9	7	8
Grade 4	3	2	2
Death from Hemorrhage (# Pts)	1	1	1

All P values were not significant

Designed as a superiority study – 85% power to detect an absolute difference of 12.5%
3 comparisons with adjustment of P value

PLADO Results

Outcome	% of patients		
	LOW n = 417	MEDIUM n = 423	HIGH n = 432
Red Cell Tx ≥ 1 Transfusion	95	92	92
Median	4	4	4
IQR	2 - 8	2 - 8	2 - 8
Platelet Tx (Total #)	2547*	1912*	1572*
Median	5	3	3
IQR	3 - 9	2 - 6	2 - 6
Platelet Increment x 10 ³ /mm ³			
Median	10*	19*	38*
IQR	5 - 17	11 - 30	22 - 54
Post Transfusion CCI (4 hours)			
Median	10	10	11
IQR	5 - 15	6 - 16	6 - 15

*P < 0.001


Designed as a superiority study – 85% power to detect an absolute difference of 12.5%
3 comparisons with adjustment of P value

PLADO Conclusions

- Low dose leads to:
 - An increased number of transfusions
 - A decreased number of platelets transfused
 - No increased risk of bleeding
- Anticipated that the study will change practice

SToP and PLADO

Non-Inferiority/Superiority Design

- SToP–non inferiority
 - No reason to think bleeding would be lower but hypothesized it would not be higher
 - Non-inferiority study requires some benefit
 - Society
 - Patient (less harm)
 - Hypothesis
 - Fewer platelet transfusions, donor exposures & adverse effects
 - PLADO – appears to be superiority
 - Rationale not clear
 - Results showed bleeding was the same with each dose
 - What is the benefit?
- 

RESULTS

Measure	SToP Study Dose		PLADO Study Dose		
	Low	Standard	Low	Medium	High
# of PLT Tx Episodes	533	325	2547	1912	1572
Mean # of PLT Tx Episodes/thrombocytopenic day ⁺⁺	9.5 ±7.8	5.3 ±3.3			
# of PLT Donor exposures ⁺	1524	1354			
Interval between PLT Tx	1.8* (1.1)	2.8* (1.8)	1.1** (0.7 – 2.1)	1.9** (0.9 – 3.1)	2.9** (1.2 – 4.7)
Median # Plt Tx/Patient (IQR)			5 (3 – 9)	3 (2 – 6)	3 (2 – 6)
Total # of PLTs Tx (x10 ¹¹)			9.25	11.25	19.63

⁺⁺ P<0.001; ⁺ P = 0.335; * Mean (SD); ** Median (IQR)

Dispensing Platelets Like Pills



Differences between SToP and PLADO – Why?

Characteristic	STOP	PLADO
Frequency of Bleeding	49.2 – 51.7%	69 – 71%
Patient Population		
Acute leukemia	86.6 %	45 %
Lymphoma	5.9 %	27 %
Myeloma	0.0 %	12%
Age range	Adults only	Adults & Pediatric
Methodology for grading bleeding	Adjudication	Electronic Algorithm,

Grade 1:

- Petechiae, oropharyngeal bleeding
- epistaxis (<1 hour)
- purpura < 1" diameter.
- Stool occult blood (trace to 1+)
- Urine hemoglobin (trace to 1+)
- Retinal hemorrhage without visual impairment.
- Abnormal vaginal bleeding

Grade 2:

- Melena, hematemesis, hemoptysis, hematuria, hematochezia, and abnormal vaginal bleeding **not requiring red cell Tx**
- Epistaxis or oropharyngeal bleeding >1 hour
Stool occult blood (moderate or 2+ and greater)
Urine hemoglobin (moderate or 2+ and greater)

WHO Classification

Grade 1: Minor

Grade 2: Mild Blood Loss

Grade 3: Gross Blood Loss

Grade 4: Debilitating Blood Loss

Grade 3:

- Melena, hematemesis, hemoptysis, hematuria, abnormal vaginal bleeding, hematochezia, epistaxis, and oropharyngeal **bleeding requiring red cell tx**

Bleeding from invasive sites

CNS bleeding noted on CT without clinical consequences.

- Grade 4:** Debilitating bleeding including retinal bleeding with visual impairment, non-fatal CNS bleeding with neurologic signs and symptoms, bleeding associated with hemodynamic instability, and fatal bleeding from any source.

Adjudication Process

- Adjudicators blinded to the bleeding Grade assigned by RA
- Data provided:
 - Spreadsheet with all lab and transfusion data
 - DBA and interventions CRF
 - Specific Guidelines
 - Assign a WHO Bleeding Score
 - Indicate the site of bleeding (9 sites)
- Disagreement
 - Data sent to 3rd adjudicator ...
 - Consensus

Results of Adjudication (SToP)

Reviewed by Adjudicator	Daily Bleeding Assessments with Evidence of Bleeding (N=1150)					
	WHO Grade of Bleeding Number (%)		Organ Site of Bleeding Number (%)		Grade + Organ Site Number (%)	
	Agreement	No Agreement	Agreement	No Agreement	Agreement	No Agreement
1 and 2	791	359 (31.2)	955	195 (17.0)	707	443 (38.5)
3	313	46 (4.0)	163	32 (2.8)	341	102 (8.9)
4	38	8 (0.7)	30	2 (0.2)	68	34 (3.0)
5	3	5 (0.4)	0	2 (0.2)	16	18 (1.6)

Grade Agreement: Adjudicators versus Bedside

WHO Bleeding Grade Assigned
by Adjudicator

WHO Bleeding Grade Assigned
by Study Personnel
(at the bedside)

	0	1	2	3	4	Total
1	24 (2.09%)	880 (76.52%)	79 (6.87%)	11 (0.96%)		994
2		37 (3.22%)	95 (8.26%)	6 (0.52%)		138
3			1 (0.09%)	11 (0.96%)		12
4			1 (0.09%)		5 (0.43%)	6
Total	24	917	176	28	5	1,150

Impact on Results - Adjudicators versus Bedside

WHO Bleeding Grade	Number of patients with bleeding by WHO Grade (%)			
	Adjudicated Grade**		Bedside Grade	
	Standard-dose N=61	Low-dose N=58	Standard-dose N=61	Low-dose N=58
Grade 1	48 (78.7)	53 (91.4)	49 (80.3)	53 (91.4)
Grade 2	28 (45.9)	28 (48.3)	20 (32.8)	23 (39.7)
Grade 3	6 (9.8)	5 (8.6)	2 (3.3)	2 (3.4)
Grade 4	0 (0.0)	3 (5.2)	0 (0.0)	4 (6.9)
≥ Grade 2	30 (49.2)	30 (51.7)	21 (34.4)	25 (43.1)*

14.8%

8.6%

* p=0.3320 for comparison standard 21/61 vs. low 25/58.

**final adjudicated grade

Other issues raised by adjudicators

Issues

Bleeding obvious from drop in hemoglobin but no red cells transfused

New vision impairment but no consult note re: investigation

Distinguishing prophylactic from therapeutic Tx

Multiple platelet Tx/day – didn't fit the definition of Grade 3 bleeding

Vaginal bleeding – normal/abnormal

Repeat days with petechiae, bruising, ecchymosis, mucocutaneous bleeding – are these old or new?

Do we really know what we are doing?



Picture compliments of Dr David Diltz

Development of the Bleeding Severity Measurement Scale (BSMS)

Identification of patient population

- Patients with non-immune thrombocytopenia secondary to bone marrow failure

Item generation and reduction

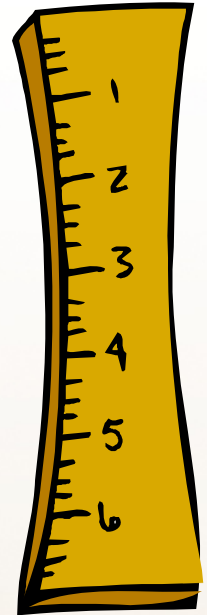
- Literature review; review of existing scales that measure bleeding;
- Expert opinion.
- Redundant or inappropriate items eliminated and those describing the same phenomenon were grouped.

Review of items and formatting the scale

- Items reviewed by consensus groups – modification
- Categorical response sets were created.
- Review to ensure that response sets accurately captured bleeding severity.

Evaluation of psychometric properties

- Raters used the scale
- Applied to bleeding and non bleeding patients



The Bleeding Severity Measurement Scale

Bleeding Grade				Description of Bleeding
0	No Bleeding			No bleeding.
1	Not clinically significant bleeding	a	Trace bleeding	Minimal bleeding or bleeding detectable by laboratory measures only. Bleeding does not have <u>any</u> impact on the patient or the level of care provided to the patient.
		b	Mild bleeding	Non-clinically significant bleeding. Bleeding does not have <u>any</u> impact on the patient or the level of care provided to the patient.
2	Clinically significant bleeding	a	Serious bleeding	Bleeding directly resulting in one or more of the following: <ul style="list-style-type: none"> ▪ Significant pain (requiring medical treatment or intervention) ▪ Need for interventions (including transfusion, surgery, invasive procedures, administration of medication, etc.) ▪ Need for invasive investigations or increased monitoring
		b	Serious bleeding causing significant morbidity	Any bleeding meeting one or more of the following criteria: <ul style="list-style-type: none"> ▪ All central nervous system bleeding ▪ Any bleeding resulting in hemodynamic instability (tachycardia [increase in resting heart rate by at least 20 bpm] OR hypotension [decrease in systolic and/or diastolic BP by at least 20 mmHg]) ▪ Bleeding resulting in vision loss ▪ Bleeding resulting in significant morbidity
		c	Fatal bleeding	Any bleeding directly contributing to the patient's death.

Applying the Webert Scale to SToP Data

Primary Category	Secondary Category	# Patients (%)
No Bleeding		18 (15.1)
Bleeding – Not Significant	Overall	101 (84.9)
	a) Trace	?
	b) Mild	?
Bleeding - Significant	Overall	47 (39.5)
	a) Serious	44 (37.0)
	b) Serious causing morbidity	3 (2.5)
	c) Fatal	0 (0.0)



**IS BLEEDING (\geq GRADE 2)
A GOOD OUTCOME?**

Composite and Surrogate Outcomes

Surrogate Outcomes

- Why are they used?
 - Easier to measure
 - Feasibility (reasonable sample size)
- Requirements for a surrogate:
 - Can be accurately measured
 - The effect of the intervention on the surrogate end point should predict the effect on the clinical outcome. (This implies a much stronger condition than correlation).

Composite Outcomes

- Why are they used?
 - Selected for statistical efficiency
- Requirements for a composite outcome:
 - Associated with the primary objective
 - Biologically plausible
 - Meaningful to patients & clinicians
 - Translated into clinically important long term outcomes
 - Ideally – of equal value

Bleeding: A Composite and Surrogate

Grade 3 Bleeding

Clinically relevant:
- Patient morbidity
- Utilizes additional resources

Bleeding

Grade 4 Bleeding

Clinically Relevant:
- Morbidity
- Mortality

Grade 2 Bleeding

Surrogate Outcome:
- Little or no clinical relevance
- Associated with thrombocytopenic bleeding

Grade 2
Bleeding

Grade 2

■ Grade 3

■ Grade 4

Bleeding: A surrogate and composite

How good is it?

Requirements	Requirement met Yes/No
Grade 2 bleeding as a surrogate	
The effect of the intervention on the surrogate end point (Grade 2 bleeding) should predict the effect on the clinical outcome (Grade 3 and 4 bleeding)*.	No
Can Grade 2 bleeding be accurately measured?	No
Bleeding as a Composite (\geq Grade 2)	
Associated with the primary objective	Partially
Biologically plausible	Yes
Meaningful to patients & clinicians	No
Translated into clinically important long term outcomes	No
Are all parts of the composite of equal value?	No

*This implies a much stronger condition than correlation



If Bleeding \geq Grade 2 is not
the right outcome

WHAT IS?

Why do we give Prophylactic Platelet Transfusions?

We want to prevent bleeding.

Why?



Platelet Transfusions

A Conceptual Model

We want to prevent or stop bleeding.

Why?

We want to prevent:

- Death
- Permanent Morbidity
- Temporary Morbidity
 - mild to severe
- Avoid utilization of additional resources

} Quality of Life

Which of these are the most important?

Depends on the perspective:

- Patient's
- Physician's
- Funder
- Society's

Blending the Conceptual Model and the Webert Bleeding Scale

CONCEPTUAL MODEL We want to avoid bleeding to prevent:	WEBERT BLEEDING SCALE						Descriptors
	Primary Category			Secondary Categories Clinically Significant			
	No Bleed	Not Sig (1)	Clin Sig (2)	Serious	Serious + Morbidity	Fatal	
Death			★			★	Mortality
Permanent Morbidity			★		★		Stroke, Blind
Temporary Morbidity			★	★	★		Nose bleed, GI bleed, vision impairment
Utilization of additional resources			★	★	★		RBCs, Plts, procedures, interventions
% of Patients from SToP			39.5	37.0	2.5	0.0	

Options

- **Just use mortality due to bleeding**
 - sample size would be huge!
- **Composite: mortality from bleeding + permanent morbidity**
 - infrequent event resulting in a large sample size,
 - suffers methodologically from the events having unequal frequencies, and
 - assumes that death is equivalent to stroke or permanent loss of sight!
- **Composite: interventions + procedures (economic/resource utilization – Webert Clin Sig – Serious category)**
 - Monitor harm (permanent morbidity/mortality from bleeding)
- **Weighted composite**
 - Require considerable thought and would still be hard for people to interpret.
- **Quality of Life**
 - Patient's perspective, Need appropriate scale
- **Use all cause mortality**
 - this approach considers platelet transfusion as supportive care NOT a treatment).

Where do we go from here?



A Therapeutic Platelet Transfusion Strategy is Safe and Feasible... RESULTS

Wandt et al, BMT 2006; 37:387-392

Bleeding	Prospective Cohort No Prophylactic Tx # (%)	Matched Controls Prophylactic Tx # (%)
No Bleeding	114/140 (81)	47/60 (78)
Grade 1	28/140 (20)	1/60 (1)
Grade 2	26/140 (19)	12/60 (20)
Grade 3	0	0
Grade 4	0	0

Are Prophylactic Plt Tx Necessary?

Details	Wandt (Germany)	Stanworth (UK)
Design	Parallel RCT, Non Inferiority	
Patients	AML Autologous PBSCT	Acute Leukemia Allo & auto SCT
Tx Arms	Prophylactic at trigger of 10 Therapeutic only when bleeding or clinically unstable	Prophylactic Therapeutic when Bleeding (WHO \geq Grades 2)
Primary Outcome	% of patients with clinically significant bleeding (WHO \geq Grades 2)	% of pts with WHO \geq Grades 2 up to 30 days following randomization

Safety remains to be established

Final Comments

- 7 RCTs conducted
- Optimal platelet dose is still unknown
- WHO Bleeding \geq Grade 2 is not a good outcome
 - Weibert scale will be a validated alternative
- Focus on breakthrough bleeding?
- Abandoning prophylactic platelet transfusions remains to be seen
- Surgical/medical populations have been ignored to-date

Future of Platelet Transfusions

»» Remains to be seen

