Optimizing Transfusion Support In MDS Patients

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Disclosures

- Research funding and honoraria Celgene
- Research funding Takeda
- Research funding Otsuka

Agenda

- Burden, prognosis and risks of anemia and RBC Transfusion dependence
- How patients are currently transfused
- 'Restrictive' vs. 'Liberal Transfusions'
- Bleeding and Platelet Transfusions in MDS

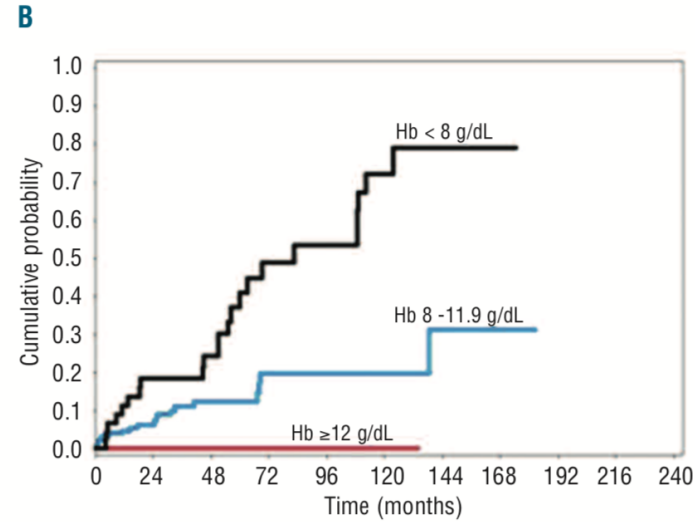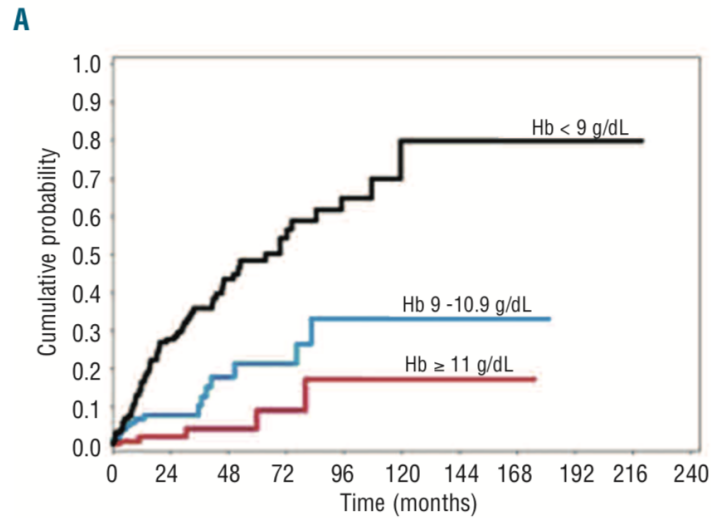# 6 US cross-sectional surveys of 101 hematologists 2005-2007: n=4514

Recently Diagnosed: n=670
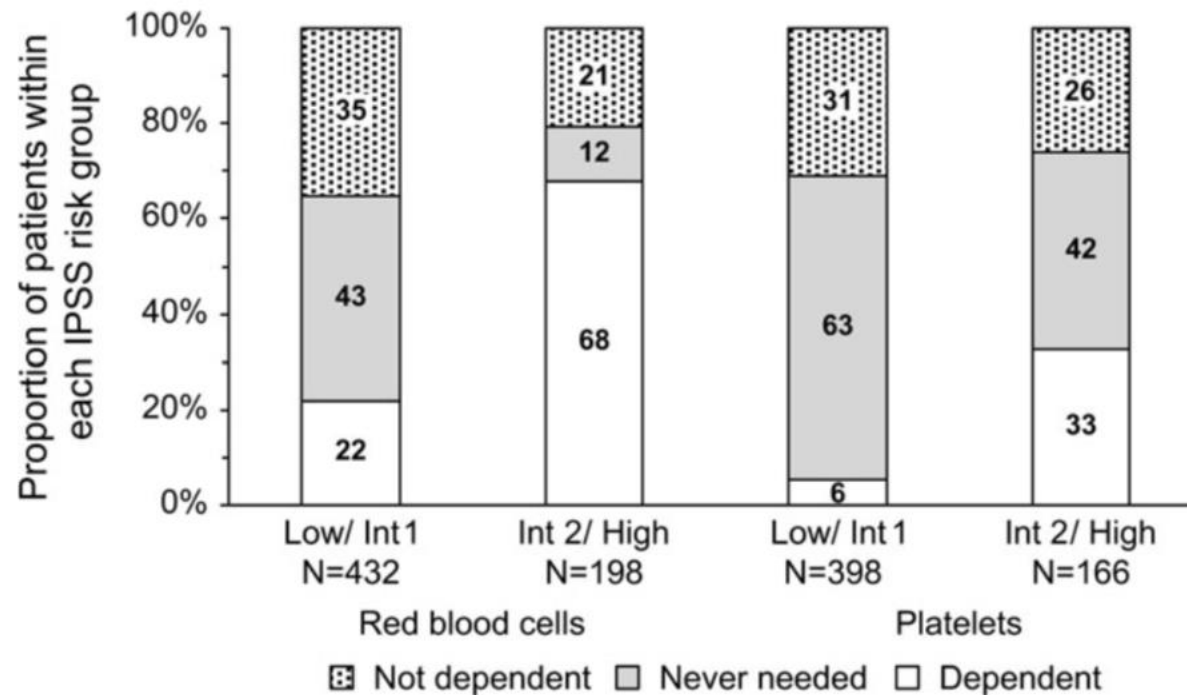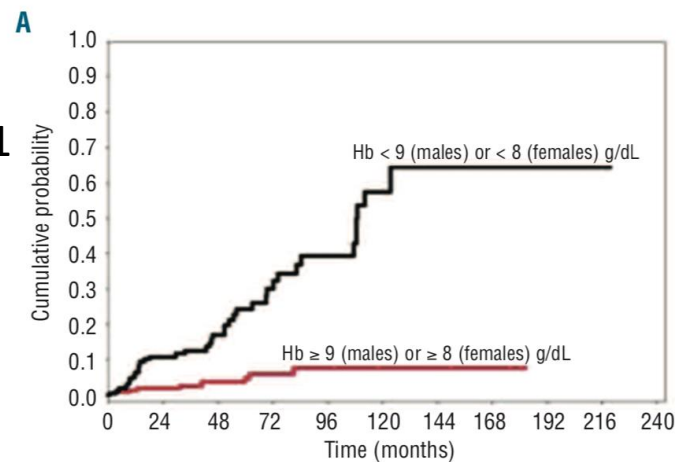

EL-Net Lower Risk:
29% TD at Diagnosis-18 months

Sekeres M et al. JNCI 2008

Probability of non-Leukemic Death Increases with Anemia in Men (A) and Women (B)
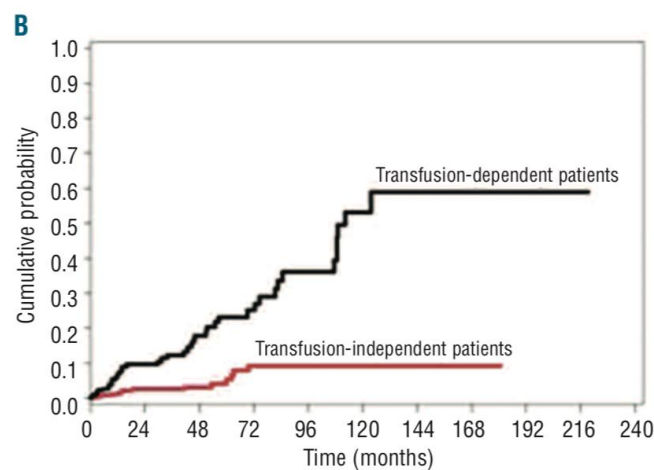

Probability of Developing Cardiac Disease and Death Increases with Anemia and TD (> 1 units/8 weeks x 16 weeks)

HR 3.85, P < .0001

(HR 2.88, *P*<0.001)

Malcovati L et al. Haematologica 2011

Dynamic assessment of RBC-transfusion dependency improves the prognostic value of the IPSS-R in MDS patients
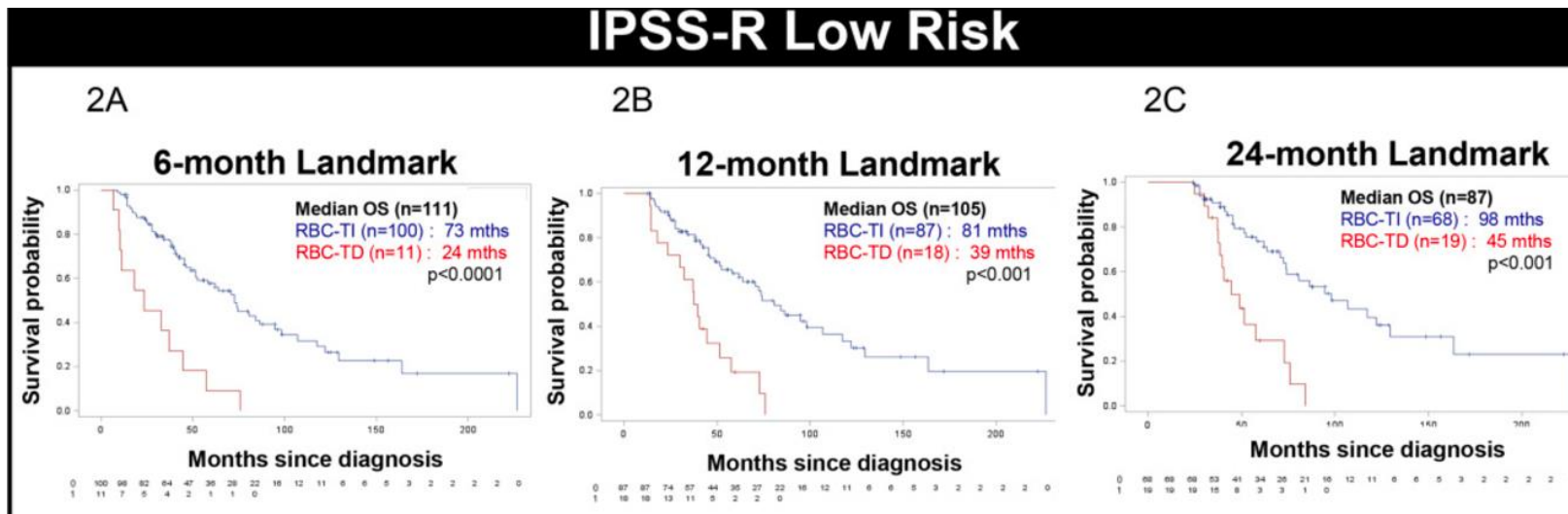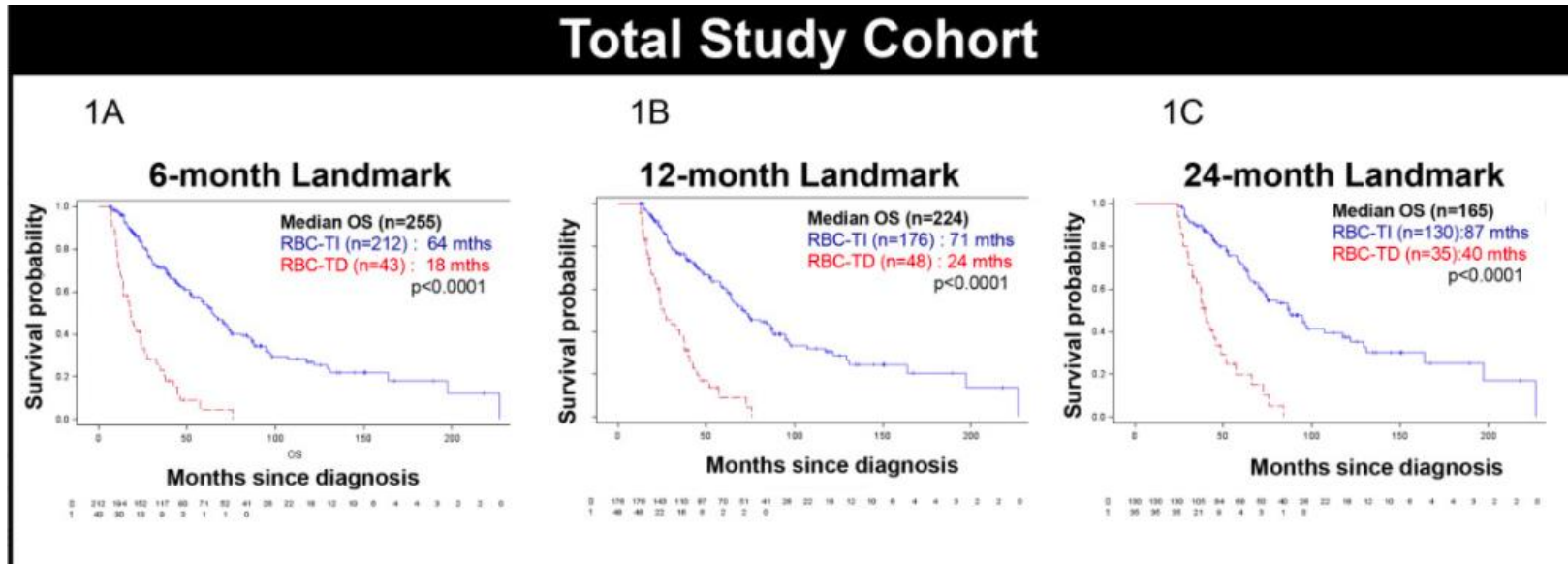
Transfusion dependence upstages lower risk disease

Hiwase D. AJH 2017

EL-NET: RBC transfusion dose density influences PFS in lower risk MDS: landmark year 1, 516/1267 transfused
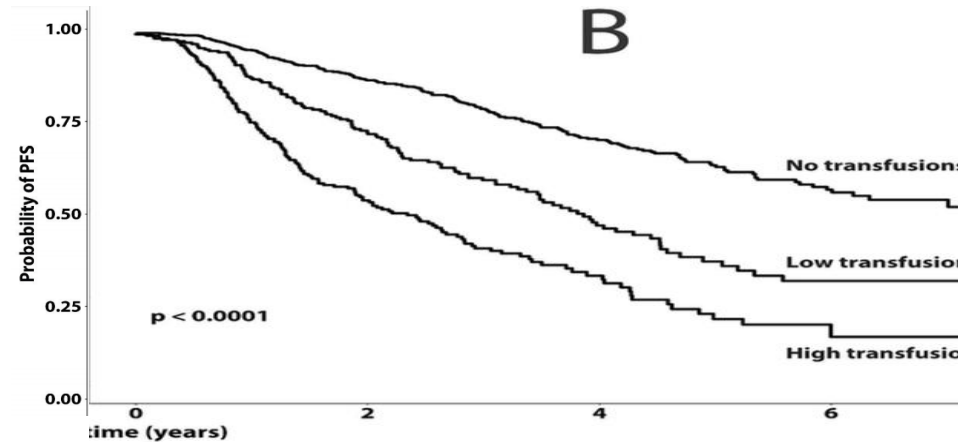
Low: < 0.87 u/m

High: ≥ 0.87 u/m
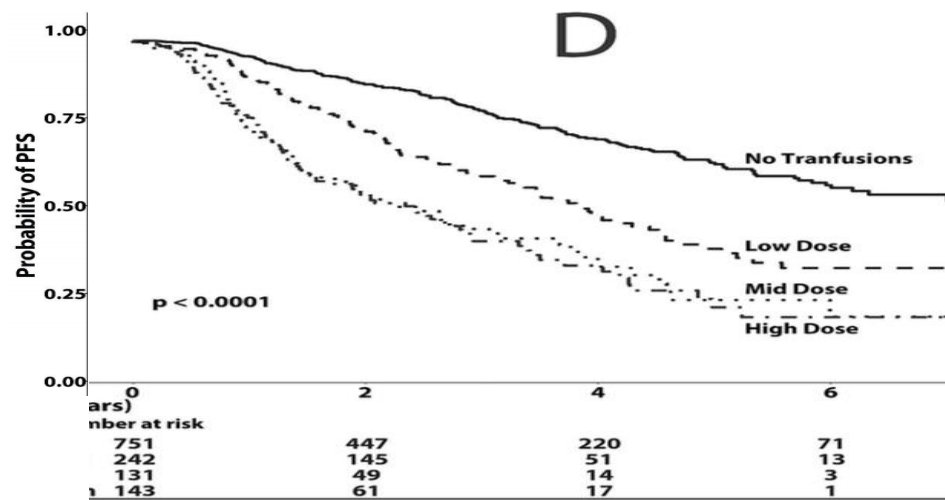
Low: >0-0.75 u/m   IWG 2006: TI

Mid: 0.75-1.75 u/m   IWG 2018: LTB

High: > 1.75 u/m   IWG 2018: HTB

de Swart L et al. Haematologica 2019

EL-NET: 1683 patients
QOL by Transfusion Dependence

MVT Analysis:
TD
Age > 75
Female sex
MDS CI
Hgb < 10 g/L

- No
- Yes

Stauder, R. Leukemia 2018
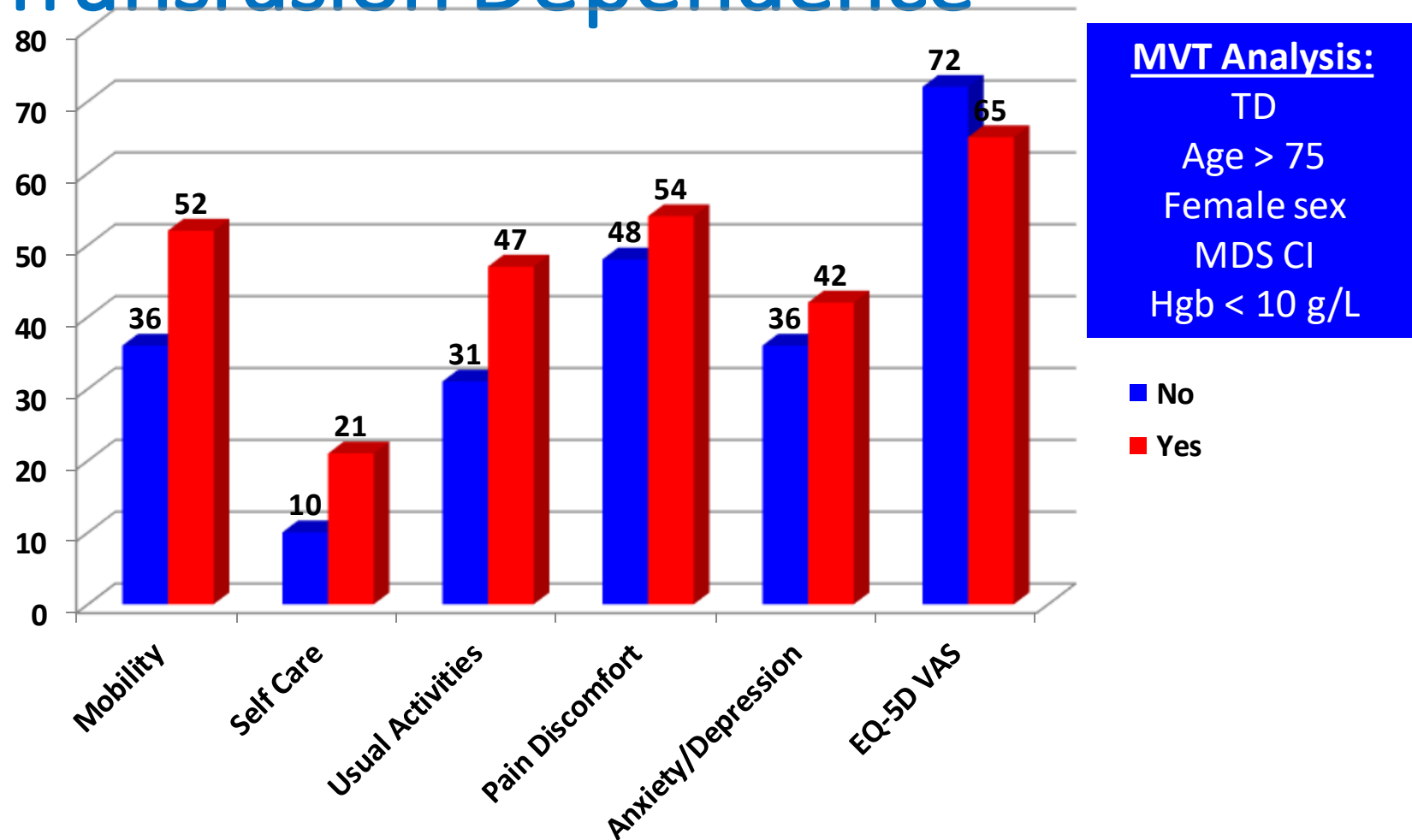
Risks of Red Blood Cell Transfusions

- Cost/convenience
- Iron overload
- TACO and TRALI
- Infections
- Alloimmunization (15-20%)

South Australia: n=817
11% alloimmunized
70% after 20 units
50% by 6 months

65% vs 18% auto antibodies

Lower rates of allo immunization:
Disease modifying therapy (HDC/ALLO>HMA)
Higher risk disease

Singhal D et al. Haematologica 2017

N=176 TD MDS patients (2001-2014)
- **Median 39 units**

17% allo-immunization rate overall
87%: RH and Kell
Median # to first ab: 16 units

Prophylactic RH/Kell matching decreased allo-immunization by 68% (19 to 6%) and 100% for RH/Kell (0 vs 18%)

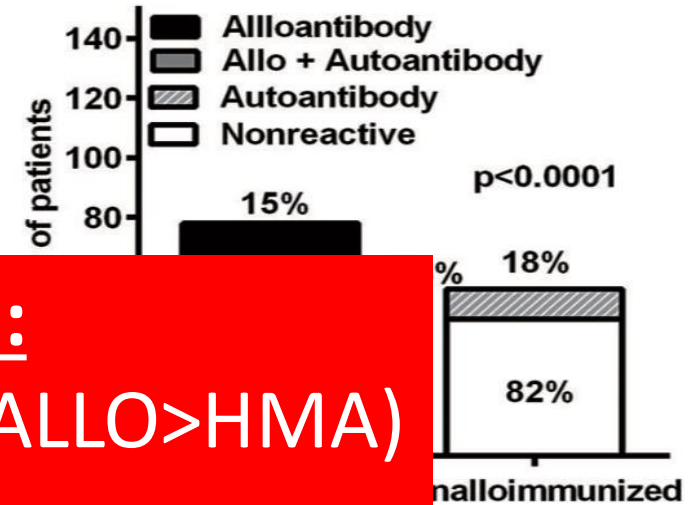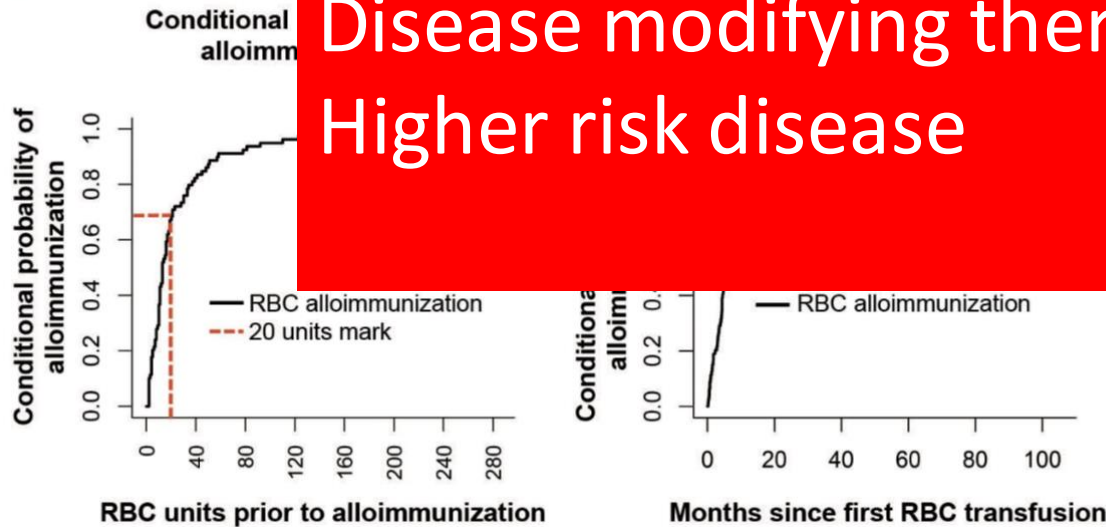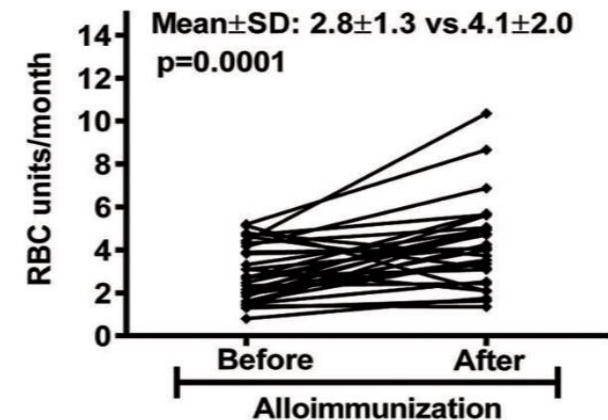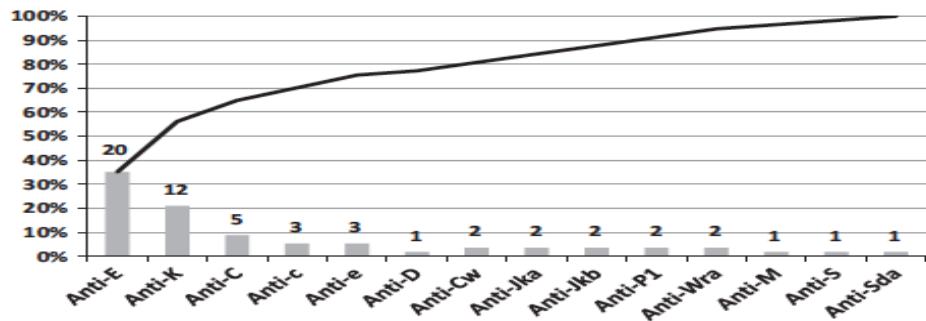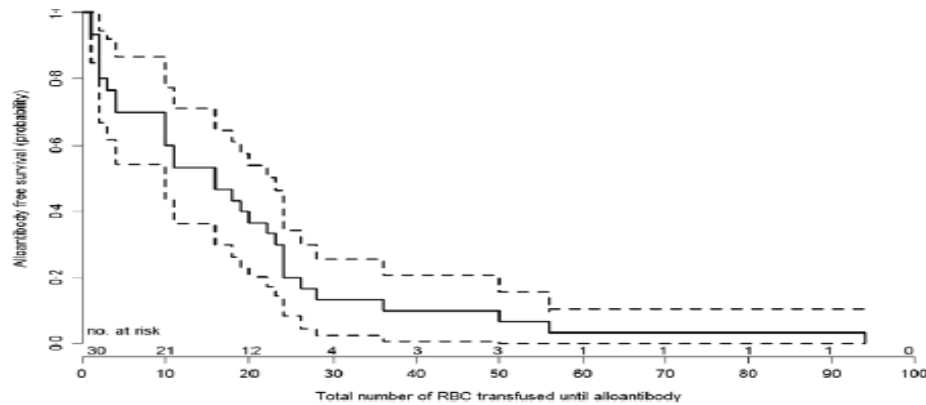|	Prophylactic antigen matching		
	All patients (N = 176)	PAM (N = 32)	No PAM (N = 144)
Ever phenotyped (%)	77 (44)	32 (100)	45 (31)
Phenotyped prior to first transfusion (%)	35 (20)	32 (100)	3 (2)
Location of transfusion (%)			
PAM institution	73 (41)	27 (84)	46 (63)
PAM & non-PAM institutions	12 (7)	0 (0)	12 (100)
Non-PAM institutions	91 (52)	5 (16)	86 (95)
New alloantibody (%)	30 (17)	2 (6)	28 (19)
New Rh/K alloantibody (%)	26 (15)	0 (0)	26 (18)
New non-Rh/K alloantibody (%)	10 (6)	2 (6)	8 (6)

PAM, prophylactic RhCE and K antigen matching.

Lin, Y. et al Vox Sang, 2017,112:79-86

Impact of red blood cell transfusion strategies in haemato-oncological patients: a systematic review and meta-analysis: Favors Restrictive
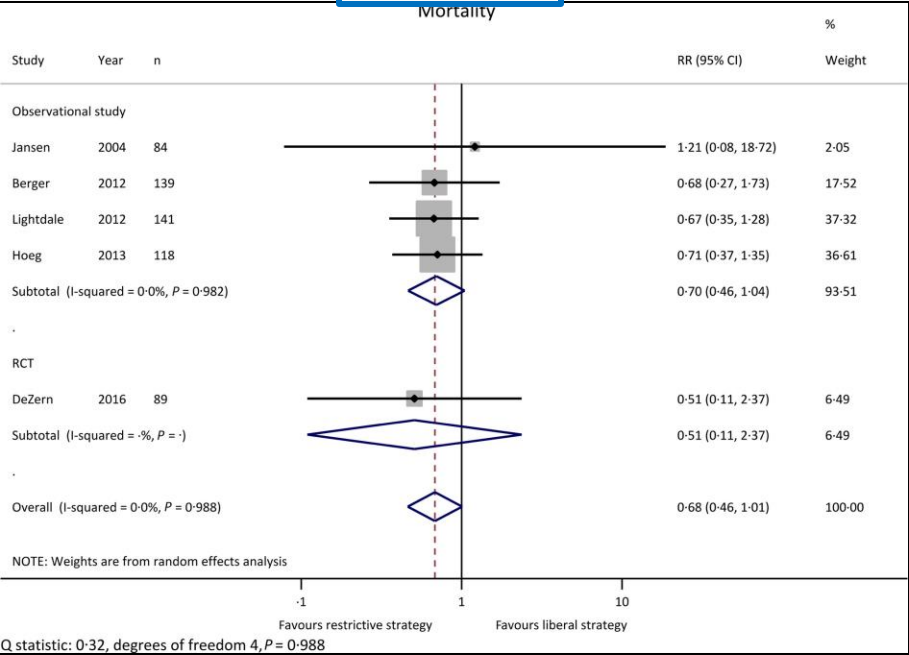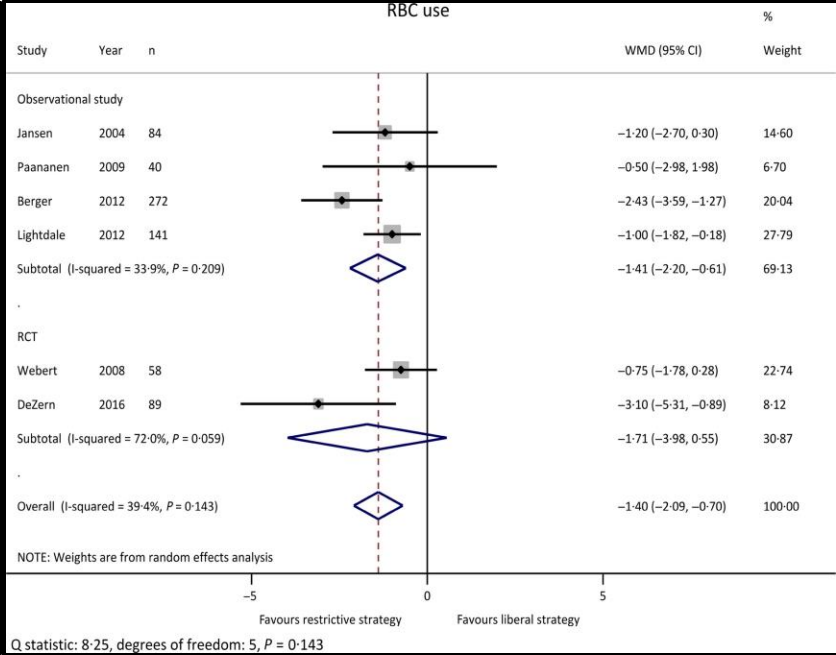
Mortality | RBC Use | Plt use
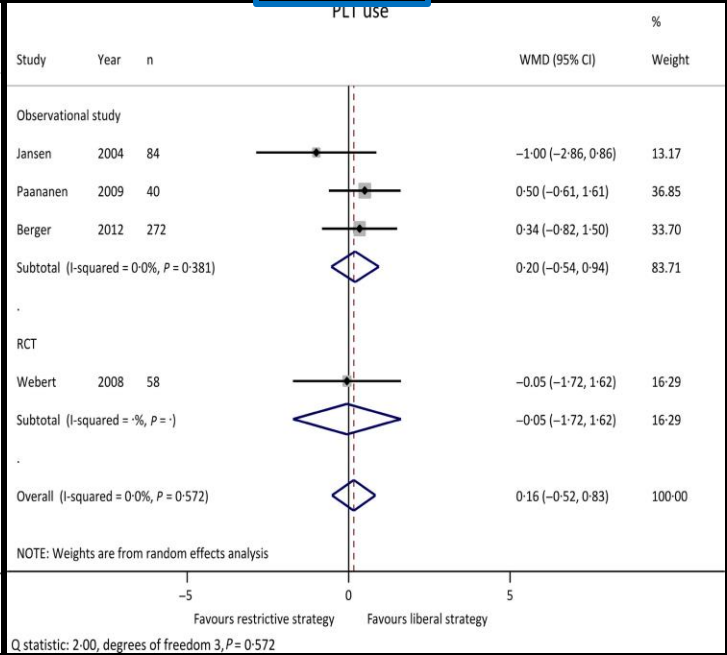
Mainly cohort studies
Mainly in patients receiving chemotherapy/ASCT

Hoeks M et al. British Journal of Haematology 2017

PROS and CONS of Liberal Transfusions

Iron Overload

Improved QOL: Fatigue and Physical function

Frequent Visits, $$

Decreased Dyspnea

TACO, TRALI, ATR

Less Cardiac Morbidity/mortality?

More Infections
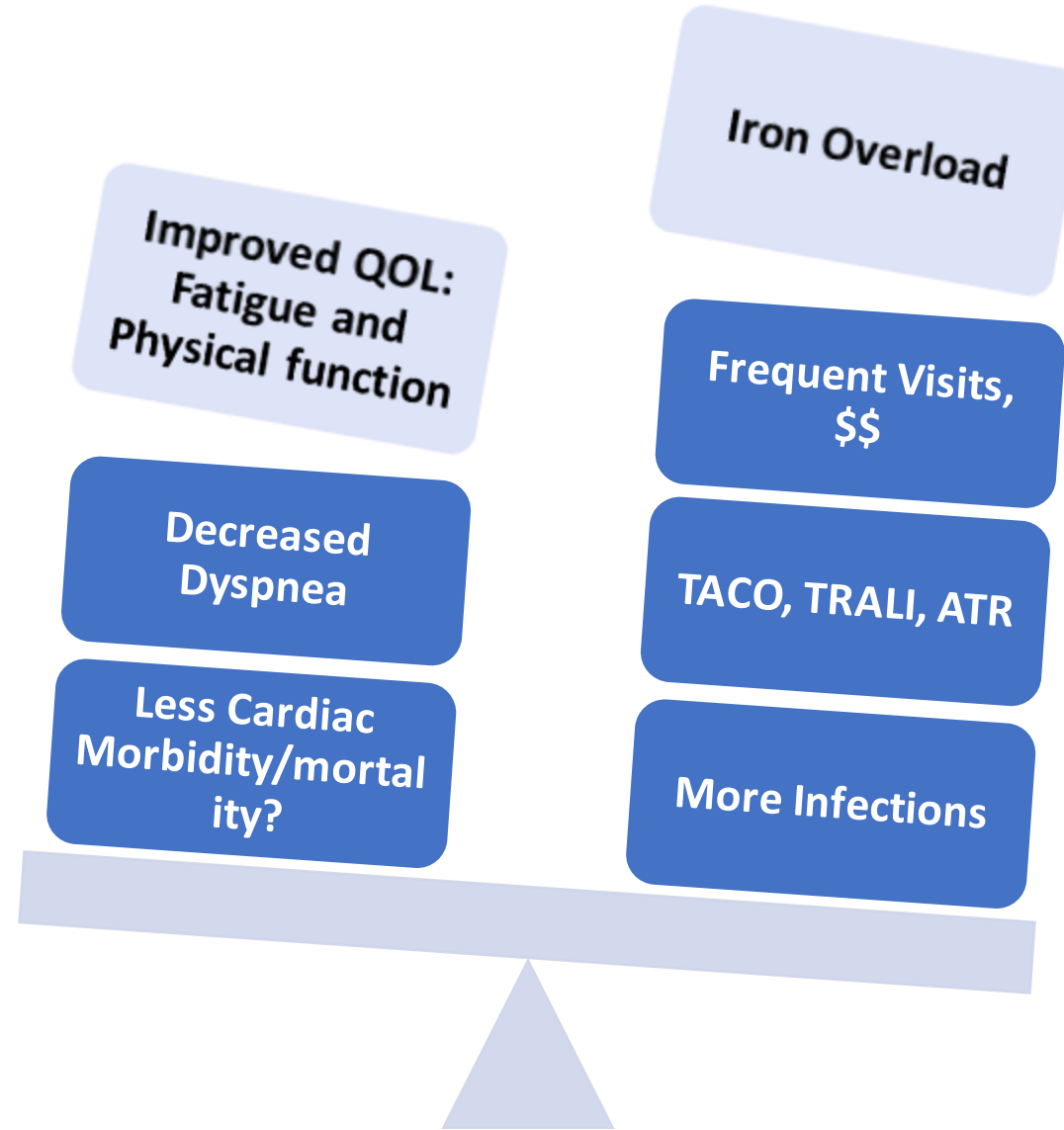
Audit of RBC Transfusions: US, Canada, UK

- Questions?
  - How are MDS patients being transfused?
  - How can we best meet our patients needs?
- Dissemination:
  - ❑ MDS Foundation, AAMAC
  - ❑ Leukemia Lymphoma Society Canada,
  - ❑ MDS-CAN registry,
  - ❑ University of York and the UK MDS patient forum
- 712 respondents (475 TD); 75% US

Starkman, Buckstein et al. Blood 132(Suppl_1):3092-3092

Audit results (n=475)

- Risk: Lower 45%, Higher 27%, not known: 27%

- Became TD at or within 6 months of diagnosis: 51%

- Visited transfusion clinic/4 weeks: 1-2 x: 63%

- # units/4 weeks: median 2

- Felt better after 1-2 days: 53%
  - Never felt better: 7%

- Felt worse for 1-2 days: 20%

- Time to organize transfusion: 65% 1-2 days, same day 24%
  - Of 75% non same day, 30% wished for same day X match

Audit results: Median Hgb Threshold 80 g/L
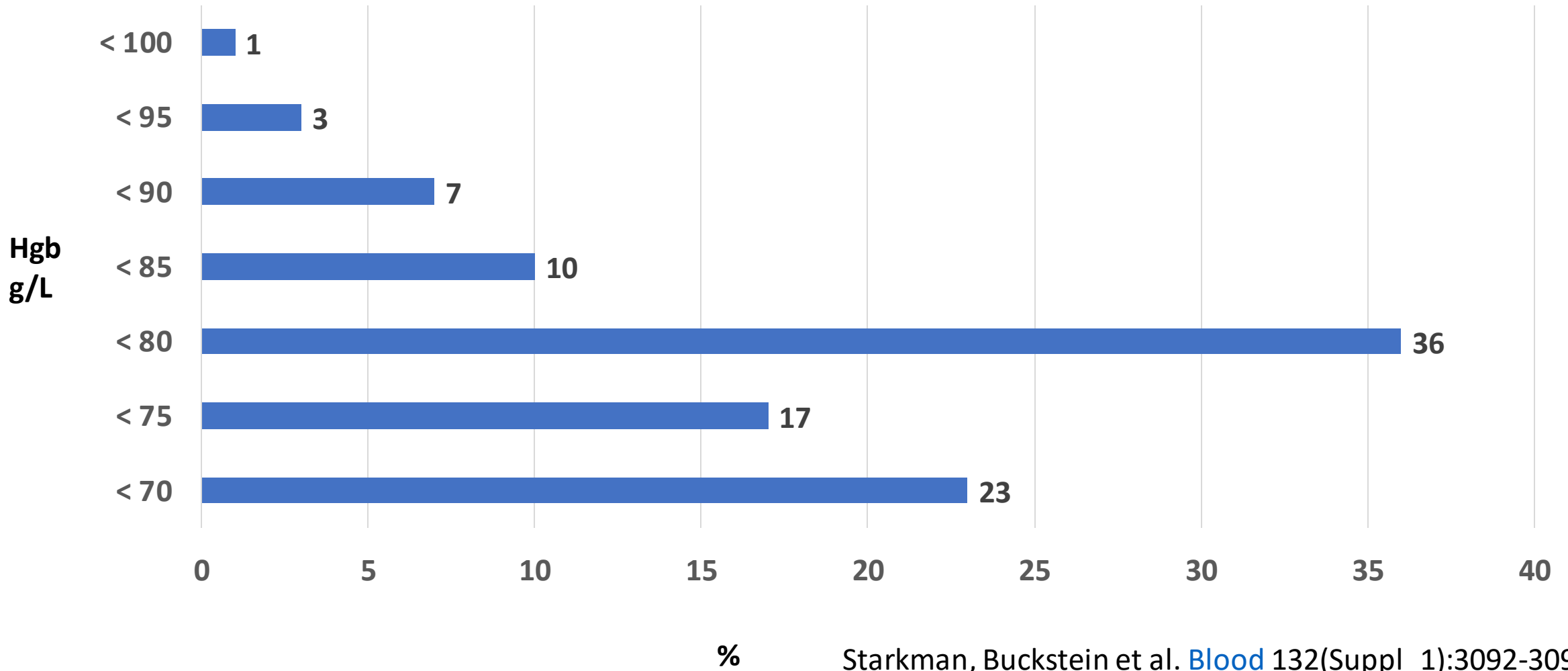
Q55: I would prefer to get my blood transfused at a higher threshold than my physician currently uses.

- Answ

What Threshold?
66% chose
Hgb ≤ 85 or higher

24% chose
Hgb of < 95-100

40%

152 (43.30%)

95 (27.07%)

47 (13.39%)

36 (10.26%)

21 (5.98%)

■ Strongly Disagree ■ Disagree ■ Neutral ■ Agree ■ Strongly Agree

Starkman, Buckstein et al. Blood 132(Suppl_1):3092-3092
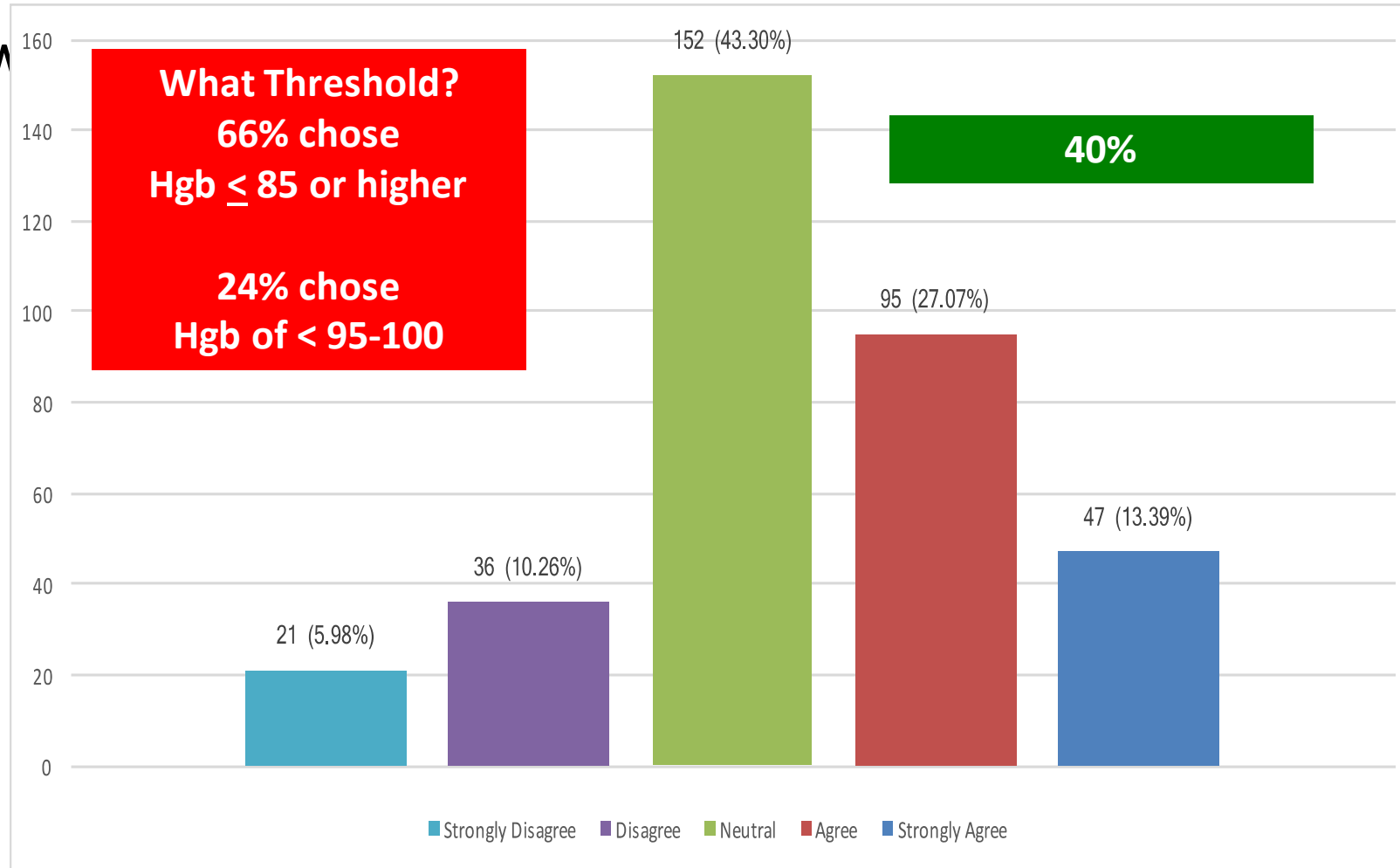
Q52: The ability to check blood counts with a machine at home to determine when another transfusion is needed before experiencing symptoms due to low blood levels would improve my quality of life.
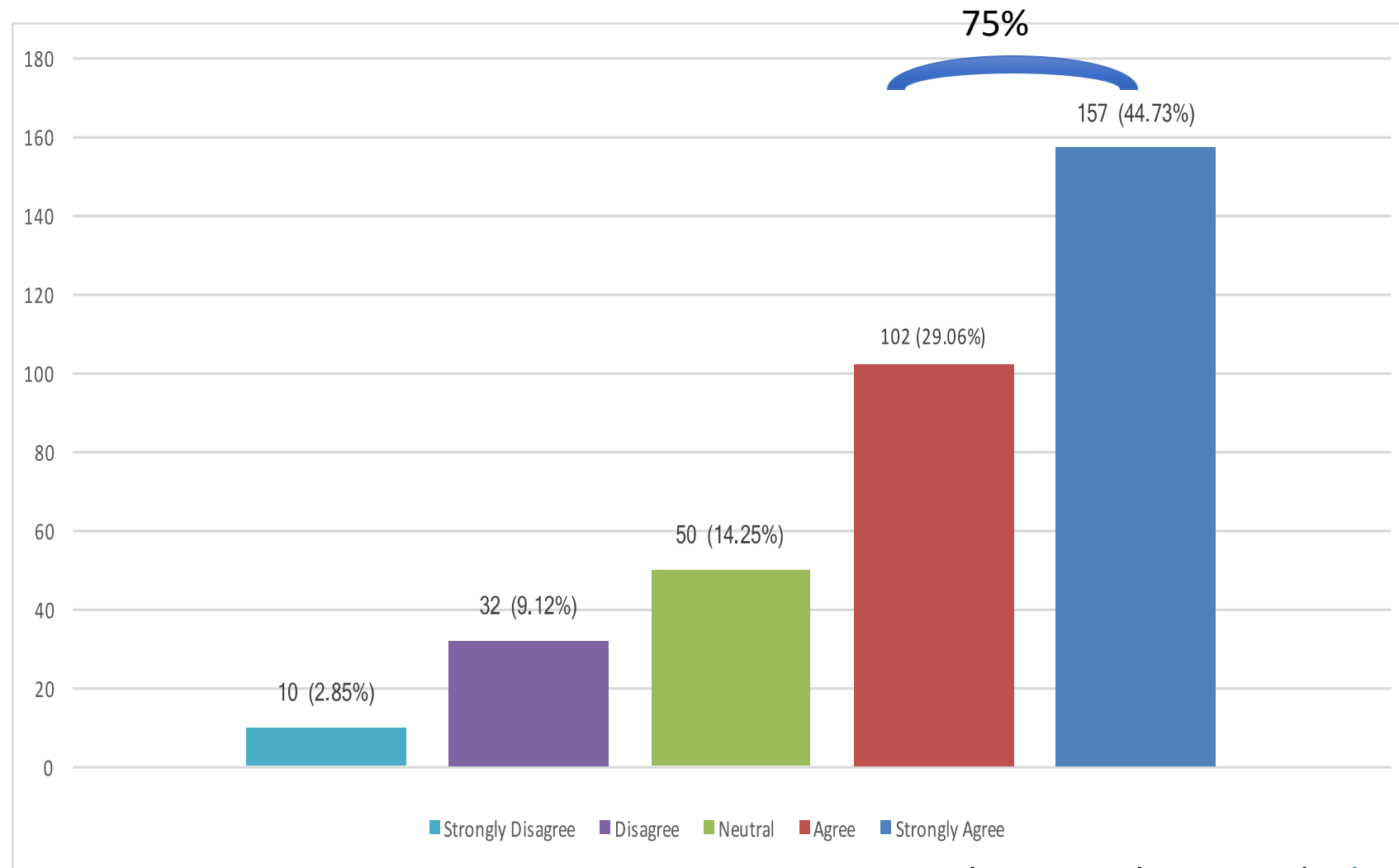
Do transfusions improve QOL (FACT-AN)?

N=15

50 to 58
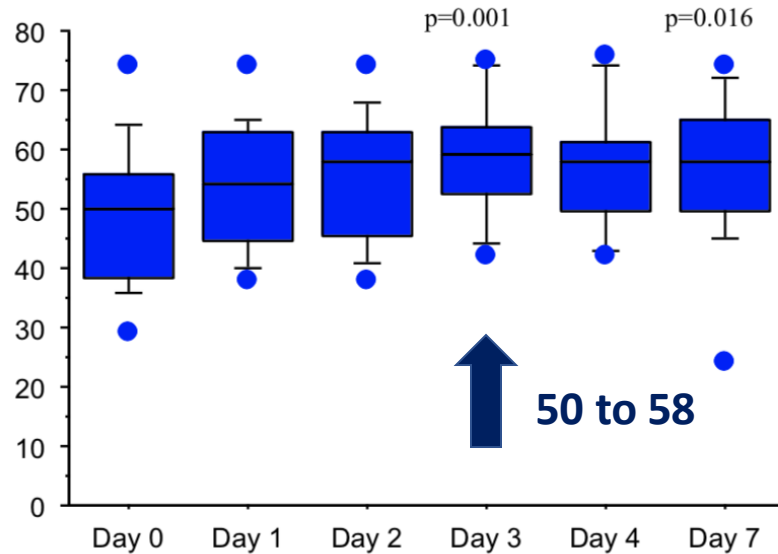
Fig. 1. The total FACT-An score for 15 patients before and after blood transfusion (day 0–7). Scores at day 3 (median 59) and day 7 (median 58) were compared with scores at day 0 (median 50). Data are presented as medians with 25th and 75th percentile ranges in the boxes. The whiskers represent the 10th and 90th percentiles and dots are outliers.
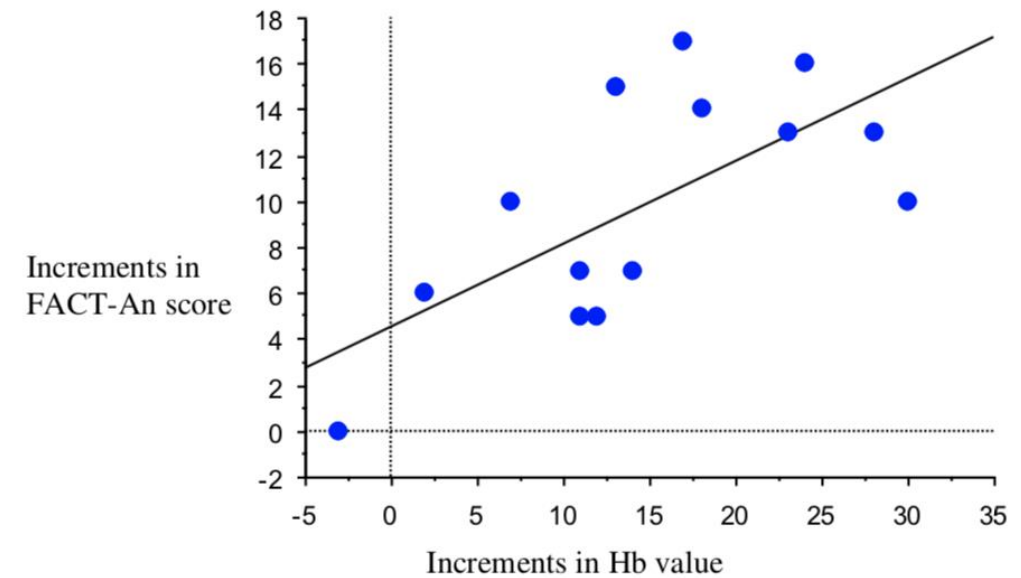
Fig. 2. The association between increments in the FACT-An score and the Hb value (day 0 to 3) as analyzed by Spearman's rank-order correlation ($n = 14$). The correlation coefficient was large (r_s 0.66, p 0.02).

Ryblom H et al. Eur J Nursing 2014

Therapeutic impact of red blood cell transfusion on anemic outpatients: the REDDS-III RETRO study
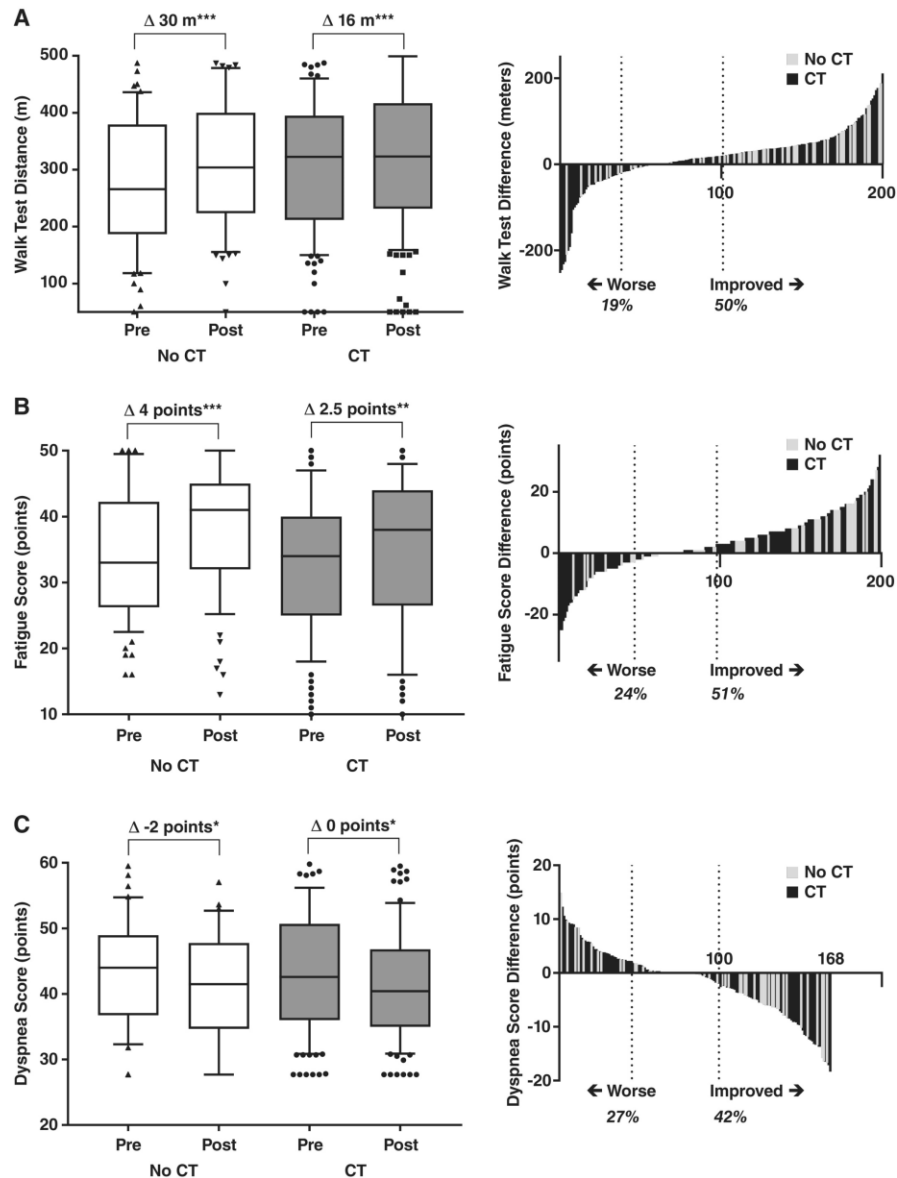
85% Hematologic cancers, n=208
Pre Tx Hgb 77 g/L (74-79 IQR)
1 week post transfusion:87 g/L (81-94)

70% had clinical improvement in either fatigue, walk distance or both
6 minute walk test improved median of 20 m (significant)
Fatigue (FACIT-F) improved 3 points (significant)
Dyspnea did not improve

Most predictive of benefit:
Not being on chemotherapy
Worst levels of fatigue and dyspnea
Receiving 2 units instead of 1
Post transfusion Hgb of > 80 g/L (6 minute walk)

Lezin E. et al. Transfusion 2019

Does it take more blood to remain at higher baseline?

- N=36 (19 TI and 17 TD)

- All treated with DARB 300 ug/week +/- GCSF until 16 weeks to target hgb 120 g/L
  - Not at target: transfused

- 56% responded (75% TI and 50% TD)

- 13 were transfused to target hgb at week 16 and maintained for 8 weeks at this level

- Transfusion rate in previously transfused did

  not exceed pre-study

Nilsson Ehle et al. Eur J Haematol 2011
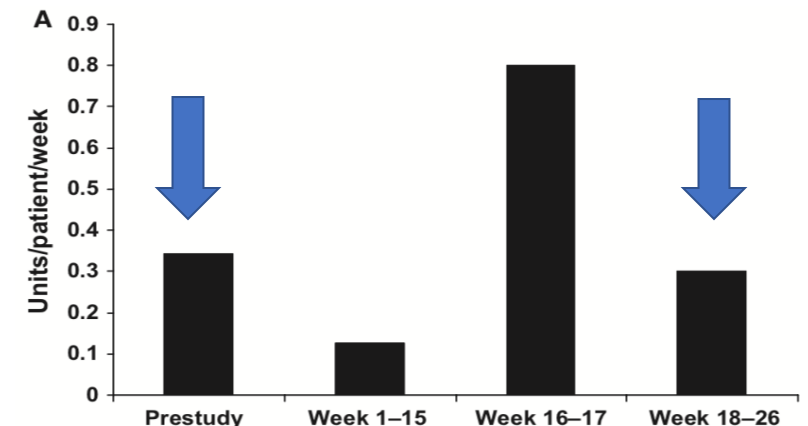
Red blood cell transfusion thresholds and QoL in myelodysplastic syndromes: a pilot, feasibility study (REDDS-1)

Inclusion:
- MDS > 18 yrs
- < 20% marrow blasts
- TD (1 u/8 weeks)
- LE > 6 months

Exclusion:
- ESAs
- Disease modifying agents
- Active bleeding or hemolysis

Test: liberal strategy

TDMDS

Group 1

Group 2

Standard: restrictive strategy

- Feasibility
- HrQoL
- Outcomes

Stanworth S et al. BJH 2019
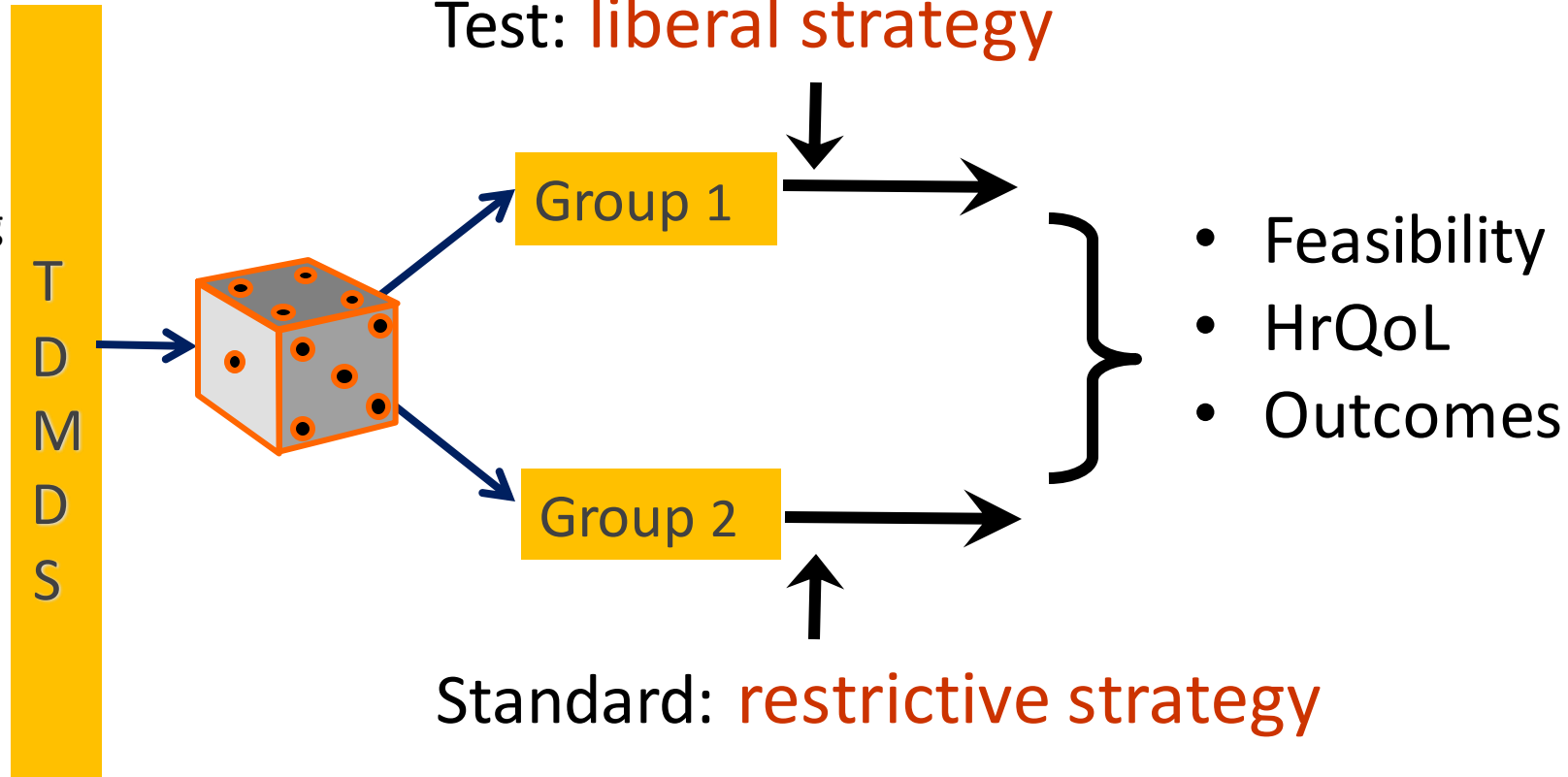
Outcomes

Primary

To **evaluate protocol adherence** when implementing a restrictive and a liberal red cell transfusion strategy

- **% of pre-transfusion Hb concentrations being below the target range** of the assigned red cell transfusion strategy

- **Achievement of at least a 20g/L difference** between the mean pre-transfusion Hb in the liberal and restrictive strategy groups

Secondary

- Number of patients ineligible due to screening failure or workload of department

- Enrolment rates

- % compliance with completing QoL

- Ability of patients to remain blinded to the treatment arm

- Proportion of transfusions and patients with all transfusions given correctly, according to the algorithm

- Magnitude of change in physical functioning, fatigue, dyspnoea and global health scores on the EORTC QLQ-C30 and in descriptive part EQ-5D-5L

- Numbers of adverse events (cardiac and thromboembolic events) and transfusion reactions

- Overall utilisation of blood during study period

Study transfusion algorithm

Consent & Enrol
6 week run-in period
Hb level target ≥100 g/L

Randomise: Hb ≥ 100g/L achieved?

No
Patient not randomised

Yes: **Randomise**, then
Continue allocated RBC transfusion policy until end of week 12

Restrictive arm: Target Hb 85-100g/L

Liberal arm: Target Hb 110-125g/L

Next clinic, measure pre-transfusion Hb:

Hb < 70g/L, transfuse 2⊙, return 1/52,
Hb 70- 79g/L, transfuse 2⊙, return 2/52
Hb 80 – 85g/L, transfuse 1⊙, return 2/52
Hb > 85 no transfusion, return 2/52

Next clinic, measure pre-transfusion Hb:

Hb < 95 g/L, transfuse 2⊙, return 1/52,
Hb 95 - 104g/L, transfuse 2⊙, return 2/52
Hb 105-110 g/L, transfuse 1⊙, return 2/52
Hb > 110 g/l no transfusion, return 2/52

Stanworth S et al. BJH 2019

Primary Outcome Results

Outcome	Restrictive (n=20)	Liberal (n=18)	Overall (n=38)
Number of participants with at least 1 transfusion	16	18	34
Proportion of pre-transfusion haemoglobin concentrations being below the target range of the assigned red cell transfusion strategy % (exact 95% CI)	86 (75-94)	99 (95-100)	94 (90-97)

As compliance is ≥70% in both arms, the study was declared feasible
4 patients in restrictive arm did not get transfused

Primary Outcome Results

Outcome	Restrictive (n=20)	Liberal (n=18)	Overall (n=38)	p-value
Pre-transfusion haemoglobin concentration (g/L)[1] Mean (standard deviation)	80 (6)	97 (7)	91 (10)	<0.0001
Difference in mean pre-transfusion haemoglobin concentrations (liberal – restrictive) (g/L) Difference (95% CI)	16.7 (14.6-18.8)			
[1] t-test for equality of means				

Some Secondary Outcomes

	Restrictive (n=20)	Liberal (n=18)	Overall (n=38)
Total number of RBC transfusions after randomisation	58	105	163
Total number of occasions RBC transfusion indicated by algorithm	38	94	132
Number of RBC units transfused Per participant Median (IQR) Per participant per 4 weeks Median (IQR)	6 (4-7) 3 (2-3)	11 (8-14) 4 (3-5)	8 (5-11) 3 (3-4)
Number of days between transfusions Median (IQR)	14 (11-21)	14 (7-14)	14 (7-15)

Amplitude of variation in haemoglobin concentration (post-hoc)
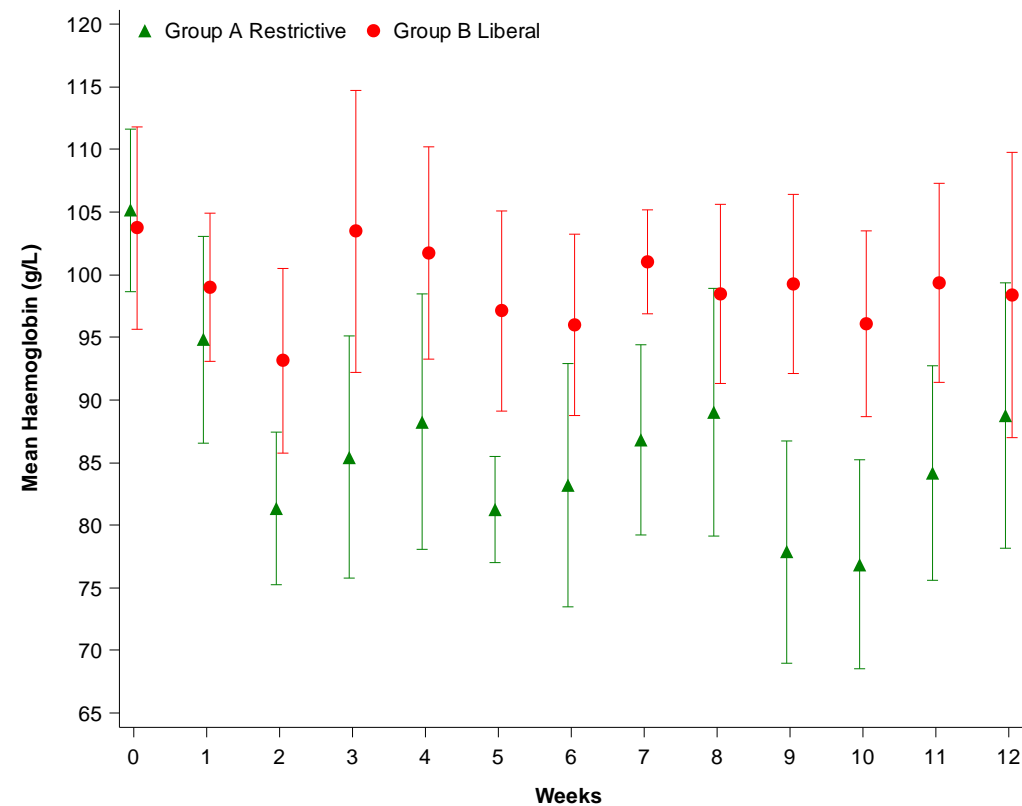
	Restrictive (n=20)	Liberal (n=18)
Median (IQR) adjusted sum of squares per participant	72 (47-116)	34 (32-58)

Patient reported outcome parameters (post-hoc): standardised area under the curve - median and IQR

- 72-75% successfully blinded
- 50% Liberal vs 30% restrictive reported improved fatigue

	Restrictive (n=20)	Liberal (n=18)	Overall (n=38)
EQ-5D-5L: Descriptive part (Higher=better)	0.76 (0.51-0.81)	0.83 (0.69-0.86)	0.78 (0.68-0.86)
EORTC: Physical functioning (Higher=better)	61 (50-86)	69 (48-94)	68 (50-86)
EORTC: Global health scores (Higher=better)	63 (60-75)	70 (53-87)	68 (56-76)
EORTC: Fatigue (Lower=better)	38 (33-54)	34 (14-66)	37 (21-63)
EORTC: Dyspnoea (Lower=better)	42 (31-64)	25 (1-77)	40 (12-67)

Thrombocytopenia in MDS

- < 100 x 10^9/L: 40-65%
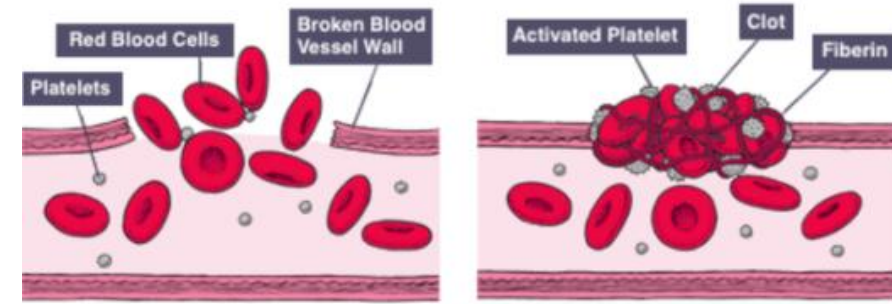
- < 20 x 10^9/L: 17% (increased bleeding and IPSS-R scores)

- Bleeding COD: 13-24% of patients
  - MDS CAN: 30/581: 5%

- Correlation between actual plt counts and bleeding non-linear (n=2924, 10 y)
  - 12% patient days grade 2 bleeds
  - 1.3% patient days grade 3+ bleeds

John's Hopkins
Heme/Oncology patients, plt < 50

Bleeding score = 2

Severe bleeding (score = 3 or 4)

% of patient-days

Platelet Count, per mm3
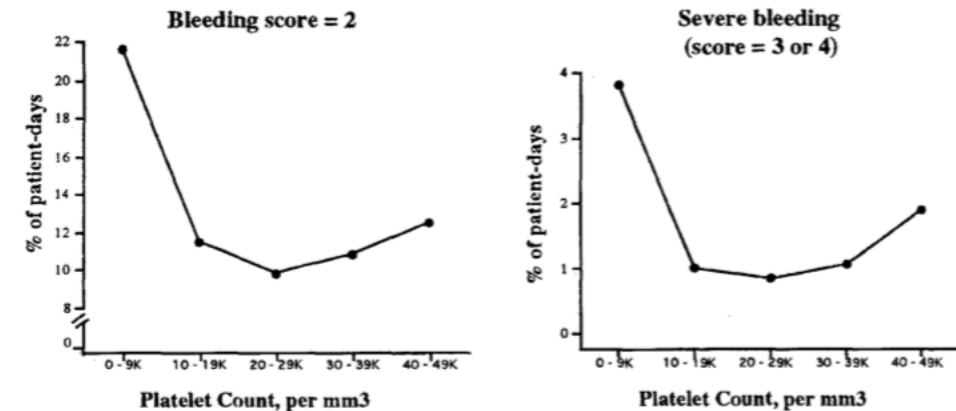
Fig 1. Relationship between bleeding and first morning platelet count shown as the percentage of patient days with each level of bleeding. (The scale on the vertical axis changes with each bleeding level.)

Kantarjian H. Cancer 2007; Neukirchen J et al. 2009; Friedman A. Transf Med Reviews 2002

From where does the practice of prophylactic plt transfusions originate? Inpatients!

Source	n	Age	Scenario	Intervention	Results	P
Wandt H Lancet 2012 Open label RCT Germany	397	16-80	AML and ASCT	Therapeutic Versus Prophylactic (Plt < 10 x 10^9/L)	WHO bleeding 2+: 42 vs 19% WHO bleeding 4+: 5 vs 1% Effect only in AML not ASCT	<.001 .01
Stanworth S NEJM 2013 Open label non inferiority RCT UK and Australia TOPPS	600	16+	AML and ASCT	Therapeutic Versus Prophylactic (Plt < 10 x 10^9/L)	WHO bleeding 2+ 50 vs 43% Who bleeding 3 or 4 2 vs 1% WHO bleeding 2+ ASCT 45 vs 47%	.06 for non-inferiority 0.13 NS

Risks and disadvantages of platelet transfusions

- Allo-immunization and refractoriness: 5-11%

- Bacterial contamination 1/1000-3000

- Febrile reactions and urticaria

- Cost

- Time/inconvenience

- Lack of donors!

Retrospective cohort study of thrombocytopenia management and outcomes….

- Retrospective audit Sunnybrook MDS patients enrolled in MDS-CAN

- Persistent severe thrombocytopenia(PST)
  - Plt count < 20 x 10^9/L for minimum of 50% lab tests over 8 weeks

- Prophylactic platelets (PROPH) if given within a recurrent interval of 2 weeks

- Therapeutic platelets (THERA) given less frequently

- WHO bleeding scale highest grade assigned once per visit/hospitalization

- Patients assigned to one of 4 groups based on **maximal treatment strategy** to prevent bleeding

Vijenthura A et al. Leuk Res 2019

Duration of thrombocytopenia (weeks)

Legend: No treatment, TXA alone, TXA+PROPH, PROPH alone, ✖ Grade 3 or 4 bleed
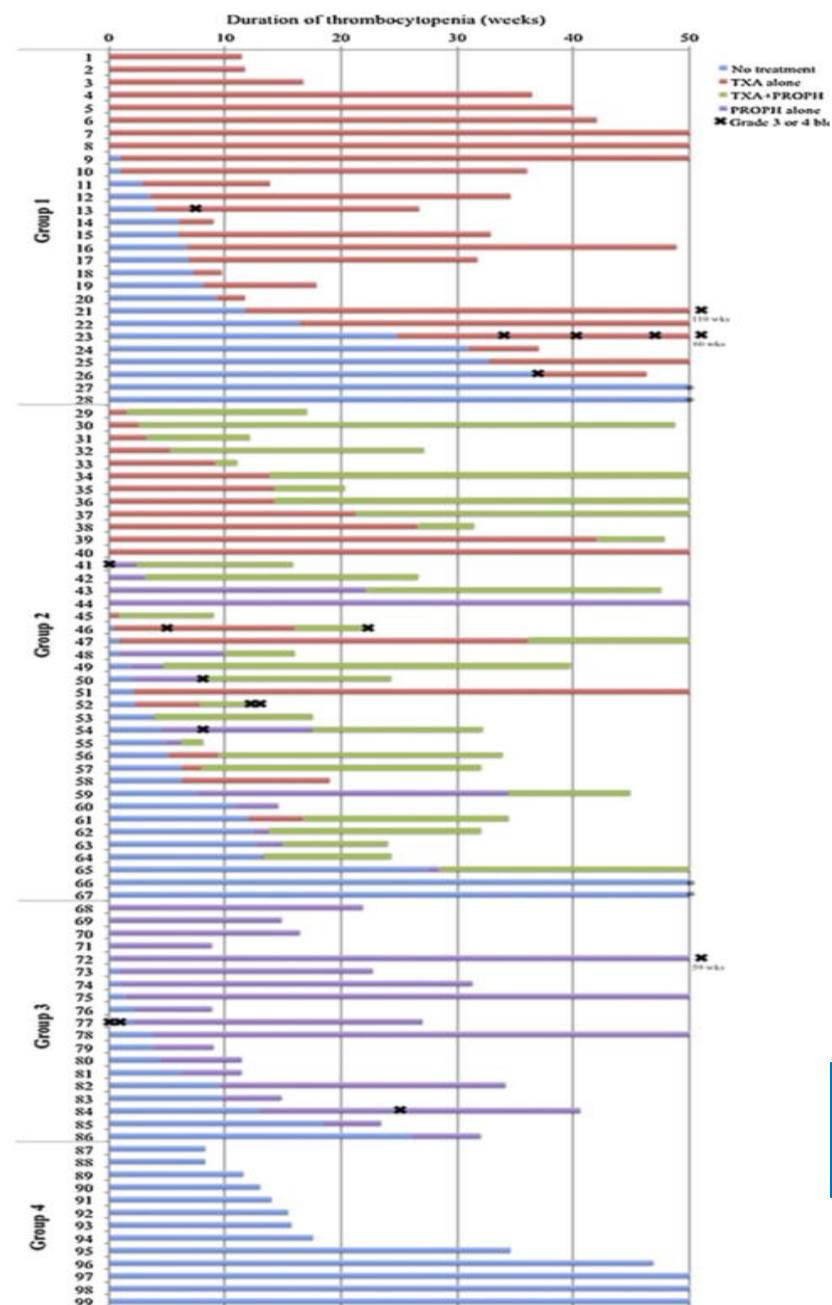
N=99	1: TXA alone N=28	2. TXA + PROPH N=39	3. PROPH N=19	4. No Rx N=13	P value
Age	71	72	74	72	.97
OS (95% CI)	1.2 (0.7-2.4)	0.7 (0.5-1.2)	0.6 (0.3-1.3)	2.5 (0.9-7.4)	.04
IPSSR-H/VH	44%	68%	77%	50%	0.13
Time from dx to DST (y)	1.2	0.5	1.2	1.0	0.8
Median plt	13	10	13	13	0.3
% plt < 10 x 10^9/L	36%	50%	36%	23%	0.2
Time to 1st bleed	10 w	5 w	3 w	5 w	.04
Therapeutic plts	32%	-	-	23%	.01
#plt tx/4w (IQR)	0 (0-0.1)	2.2 (1.4-3)	3.1(2.2-5)	0 (0-0.3)	<.0001

- **Median duration of PST was 27 weeks; median plt 12 (IQR 9-16)**
- **71% in groups 1 and 4 received no plt transfusions**

Vijenthura A et al. Leuk Res 2019

Bleeding grades according to treatment group
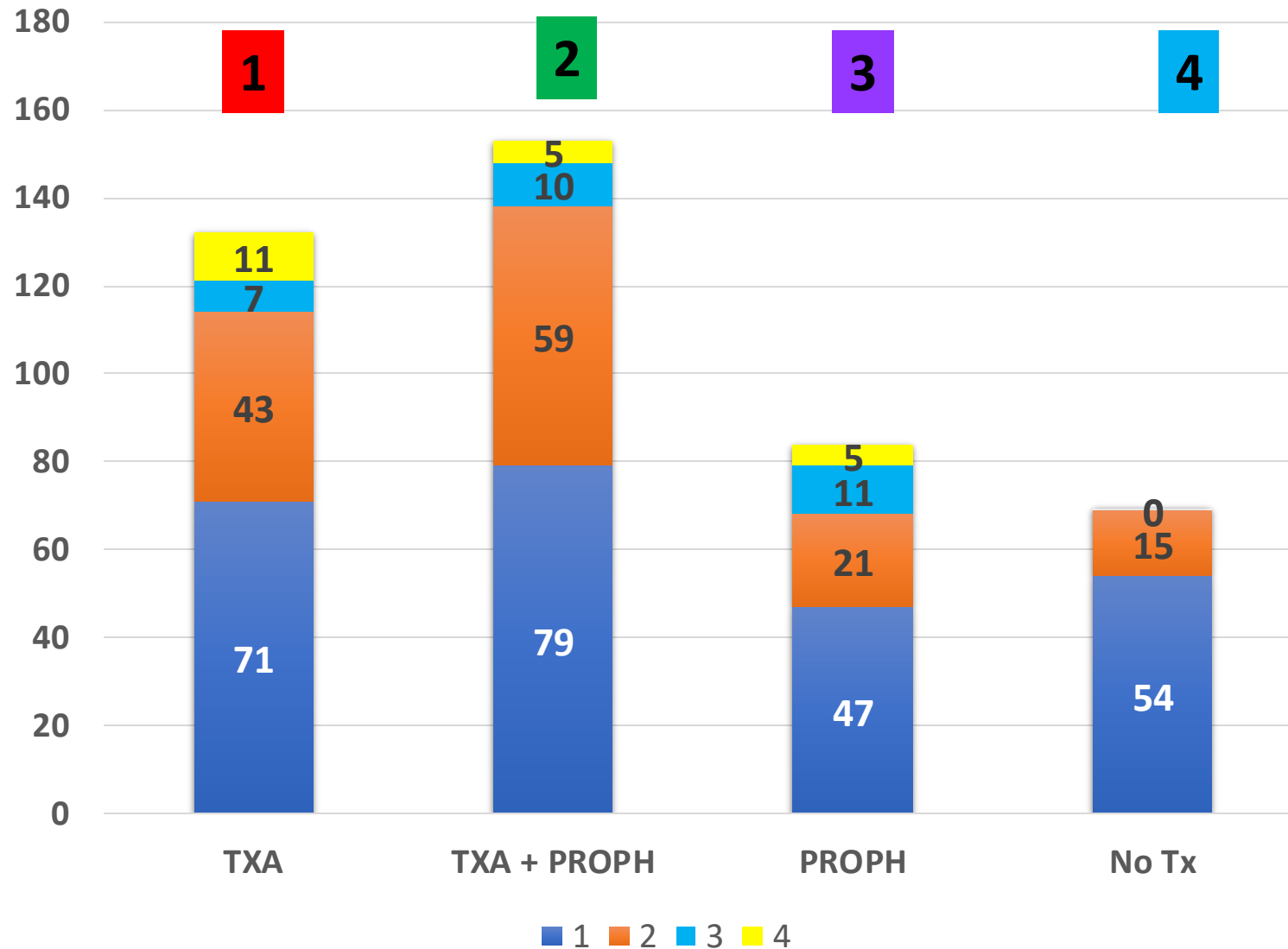
- **Trend to more grades 1-2 bleeding in groups 1 and 2**

- **Of 12 patients with grades 3-4 bleeding, 6/8 in groups 2 and 3 were plt refractory**

- **9% overall died of hemorrhage (n=9)**
  - **Alloimmunized/refractory**
  - **Plts > 10**
  - **Prophylactic treatment**

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

Original Articles

Guidance on Platelet Transfusion for Patients With Hypoproliferative Thrombocytopenia

See Editorial, pages 1–2

Susan Nahirniak [a,*], Sherrill J. Slichter [b], Susano Tanael [c], Paolo Rebulla [d], Katerina Pavenski [e], Ralph Vassallo Mark Fung [g], Rene Duquesnoy [h], Chee-Loong Saw [i], Simon Stanworth [j], Alan Tinmouth [k], Heather Hume [l], Arjuna Ponnampalam [m], Catherine Moltzan [n], Brian Berry [o], Nadine Shehata [p], for the International Collaboration for Transfusion Medicine Guidelines (ICTMG)

VOLUME 36 · NUMBER 3 · JANUARY 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Charles A. Schiffer, Kari Bohlke, Meghan Delaney, Heather Hume, Anthony J. Magdalinski, Jeffrey J. McCullough, James L. Omel, John M. Rainey, Paolo Rebulla, Scott D. Rowley, Michael B. Troner, and Kenneth C. Anderson

Cochrane Library

Cochrane Database of Systematic Reviews

Comparison of a therapeutic-only transfusion policy for people with congenital or acquired bone marrow failure disorders (Review)

Malouf R, Ashraf A, Hadjinicolaou AV, Doree C, Hopewell S, Estcourt LJ

Patients with chronic, stable, severe thrombocytopenia, such as individuals with myelodysplasia or aplastic anemia, who are not receiving active treatment may be observed without prophylactic transfusion, reserving platelet transfusions for episodes of hemorrhage or during times of active treatment (Type of recommendation: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Schiffer A et al. JCO 2018

Cochrane Database of Systematic Reviews 2018

Guidelines for the use of platelet transfusions

Lise J. Estcourt,[1] Janet Birchall(Writing Group Chair)[2], Shubha Allard(BCSH Task Force Member)[3], Stephen J. Bassey,[4] Peter Hersey,[5] Jonathan Paul Kerr,[6] Andrew D. Mumford,[7] Simon J. Stanworth[8] and Hazel Tinegate[9] on behalf of the British Committee for Standards in Haematology

- A **no prophylaxis** platelet transfusion strategy should be used for patients with asymptomatic chronic bone marrow failure (including those taking low dose oral chemotherapy or azacitidine) (2B)

- Prophylactic platelet transfusion should be given to patients with chronic bone marrow failure receiving intensive treatment (1B)

- Patients with chronic bleeding of WHO grade 2 or above **require individual management according to the severity of their symptoms** and signs. A strategy of prophylaxis (e.g. twice a week) should be considered (2C)

BJH 2016

Summary

- Anemia is common in MDS and more than 50% become TD

- Anemia and TD are associated with decreased OS, LFS, impaired QOL

- The link between plt count and bleeding in stable outpatients is poorly established
  - Rates of severe or fatal bleeding are low

- We may be ***undertransfusing*** RBC

- We may be ***overtransfusing*** Plts

- Randomized trials are feasible and needed

Thank You

MDS-CAN

Our Patients

Crashley Estate

Location	PI Name	Institution
Vancouver	Dr. Thomas Nevill	Vancouver General Hospital
	Dr. Heather Leitch	St. Paul's Hospital
Edmonton	Dr. Nancy Zhu	University of Alberta Hospital
Calgary	Dr. Michelle Geddes	Tom Baker Cancer Centre
Saskatoon	Dr. Mohammed Elemary	Saskatchewan Cancer Agency
Winnipeg	Dr. Versha Banerji	CancerCare Manitoba
Montreal	Dr. April Shamy	Jewish General Hospital
	Dr. John M. Storring	McGill University Health Centre
Ottawa	Dr Mitchell Sabloff & Dr. Grace Christou	The Ottawa Hospital
Quebec City	Dr. Robert Delage	CHU de Québec
Hamilton	Dr. Brian Leber	Juravinski Cancer Centre
Toronto	Dr. Karen Yee Dr Shabbir Alibhai	Princess Margaret Hospital
	Dr. Rena Buckstein	Odette Cancer Centre
Halifax	Dr. Mary-Margaret Keating	QEII Health Sciences Centre
Moncton	Dr. Eve St-Hillaire & Dr. Nicholas Finn	Dr. Georges-L. Dumont Regional Hospital

UNIVERSITY OF TORONTO

Hematology Site Group @ Sunnybrook Health Sciences/OCC	
Kevin Imrie MD	Signy Chow MD
David Spaner MD PhD	Lisa Chodirker MD
Richard Wells MD DPhil	Eugenia Piliotis MD
Matthew Cheung MD	Neil Berinstein MD
Lee Mozessohn MD	Jeannie Callum MD and Yulia Lin MD