

Risico gestuurde trombocyten transfusies – tijd voor een andere benadering?

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Ons huidige probleem

- Op een gemiddelde hematologie afdeling heeft:
- **50%** van de patiënten een graad 2 of ernstigere bloeding op **15 – 30%** van de dagen met een trombocyten getal tussen 0 en 80
- **5%** van de patiënten een graad 3/4 bloeding op **< 1%** van het aantal dagen
- Tot dusver is er nog geen beleid/product studie geweest, welke een significante verandering bereikt heeft in deze percentages

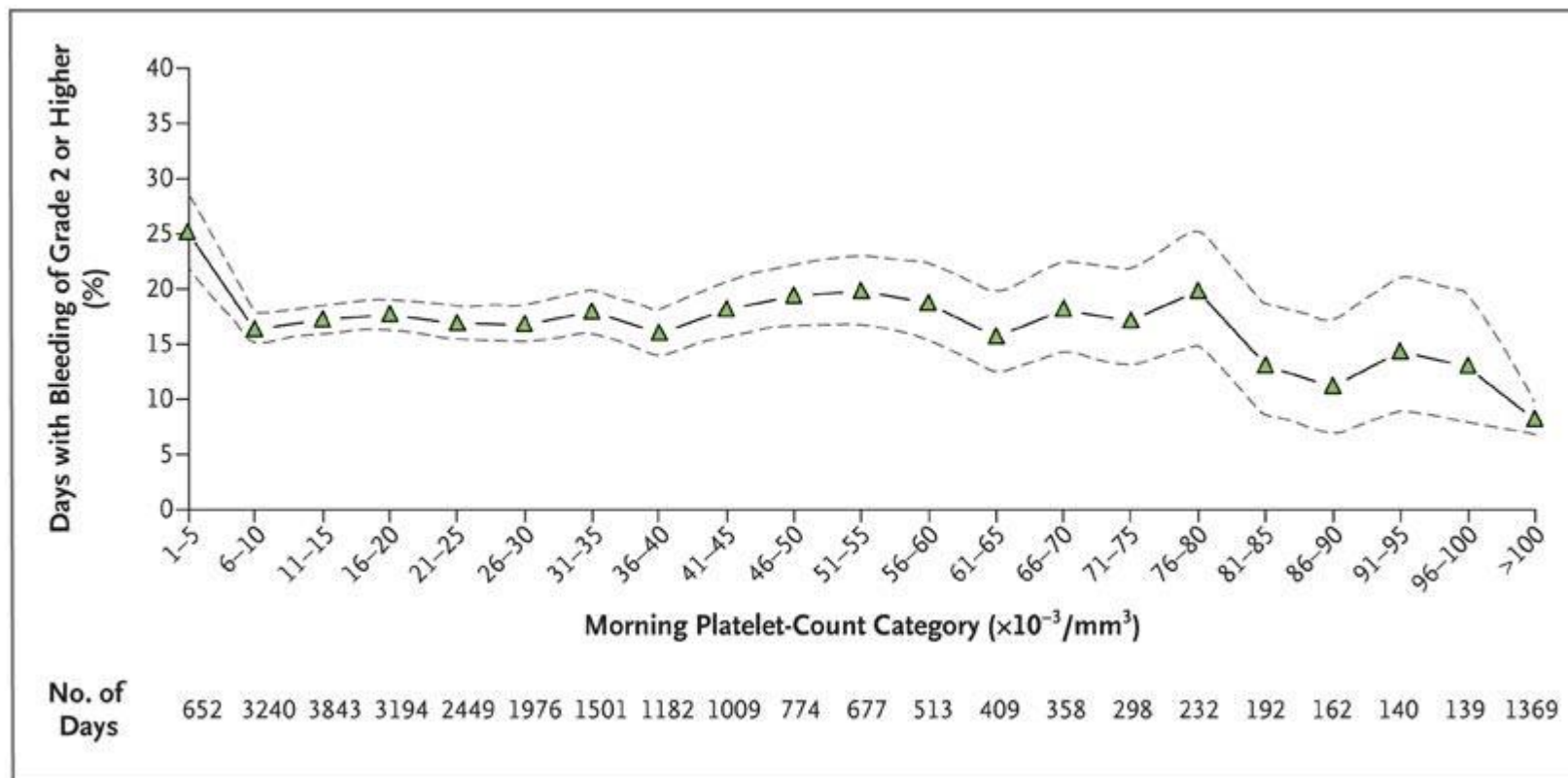
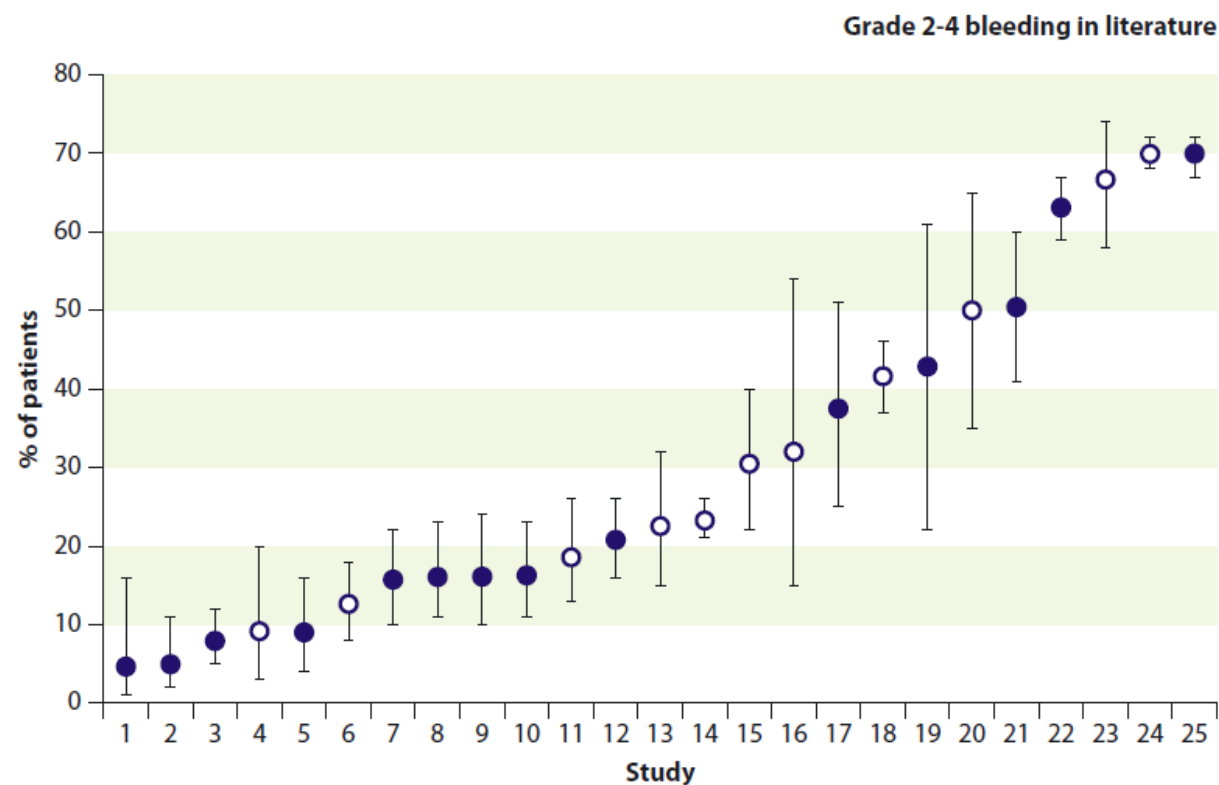


Figure 1: Figure 1 shows reported percentages of patients with grade 2 – 4 bleeding complication. The error bars reflect the 95% confidence interval. The filled markers represent randomised controlled trials, whereas the open markers represent observational studies. 1 = Blumberg et al¹⁴; 2 = Sensebe et al⁵; 3 = Kerkhoffs et al⁷; 4 = Oka et al¹⁶; 5 = Tinmouth et al¹⁷; 6 = Gil-Fernandez et al¹⁸; 7 = Zumberg et al¹⁹; 8 = Kerkhoffs et al⁶; 9 = Mirasol²⁰; 10 = Diedrich et al²¹; 11 = Wandt et al²²; 12 = Rebullia et al¹²; 13 = Gmur²³; 14 = Nevo et al⁹; 15 = Wandt et al²⁴; 16 = Sagmeister et al²⁵; 17 = Murphy et al²⁶; 18 Pihush et al²⁷; 19 = Higby et al²⁸; 20 = Navarro et al²⁹; 21 = Heddle et al⁵; 22 = McCullough et al¹³; 23 = Lawrence et al³⁰; 24 = Friedmann et al³¹; 25 = Slichter et al⁴.



Maar

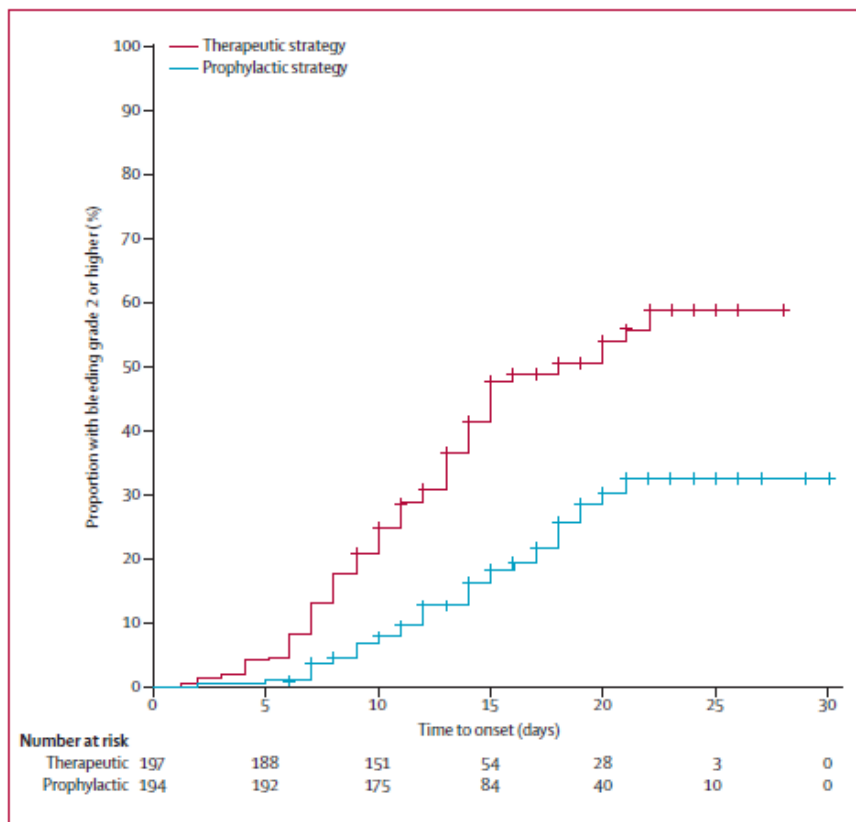
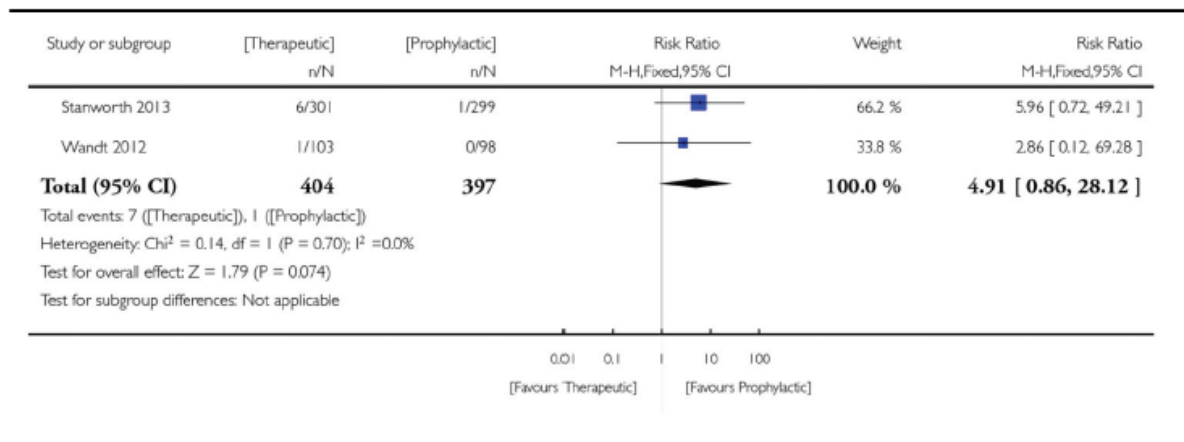


Figure 2: Time to onset of bleeding of grade 2 or higher in all patients

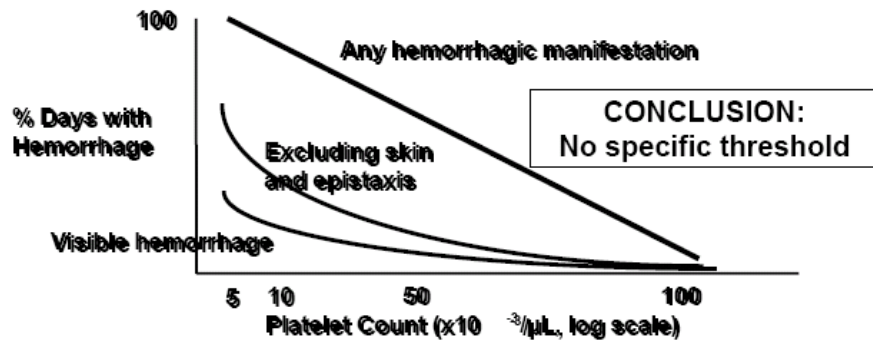
Lancet 2012; 380: 1309-16



Profylaxe lijkt te helpen!

Echter de klassieke trigger....

Relationship of thrombocytopenia to hemorrhage



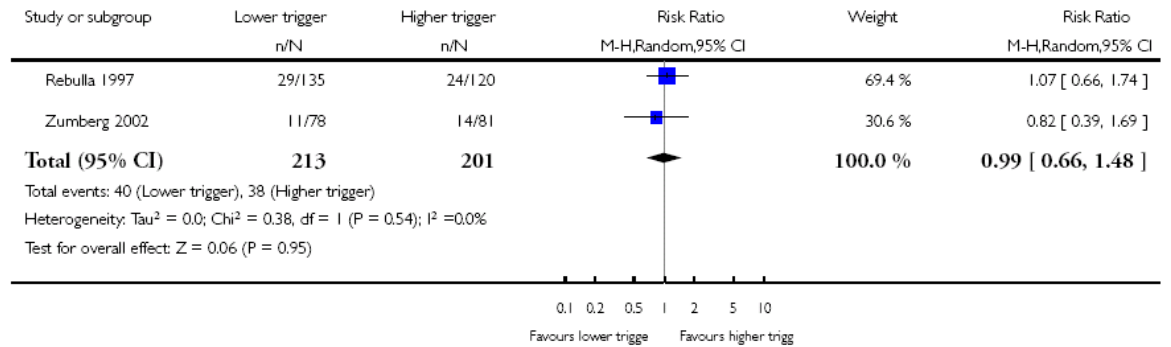
Gaydos *et al.* NEJM 1962;266:905-9

Analysis 2.4. Comparison 2 Prophylactic platelet transfusion at one trigger level versus another trigger level, Outcome 4 Numbers of participants with major or more severe bleeding events.

Review: Prophylactic platelet transfusion for haemorrhage after chemotherapy and stem cell transplantation

Comparison: 2 Prophylactic platelet transfusion at one trigger level versus another trigger level

Outcome: 4 Numbers of participants with major or more severe bleeding events



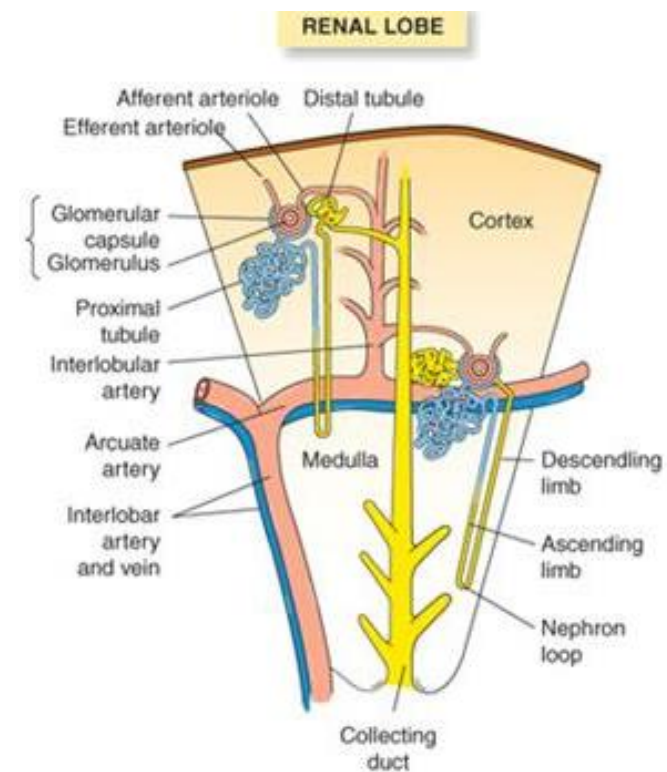
LAAT ONS IN DE STEEK.....

OPLOSSING

- Epidemiologie en identificeren van risico factoren/voorspellers
- Biomarkers
- Nieuwe interventies - onderzoek

Does (micro)albuminuria precede bleeding in thrombocytopenia

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Introduction: PREPAREs

the search for bedside labtest, the prediction of bleeding ?

- PREPAREs trial: Pathogen Reduction Evaluation & Predictive Analytical Rating Score
 - Randomized multicenter trial (the Netherlands, Canada, Norway)
 - Mirasol treated platelet products for clinical efficacy
 - Primary endpoint: clinical non inferiority of pathogen reduced platelet products : bleeding WHO grade ≥ 2
 - Secondary outcome measures:
 - ✓CCI
 - ✓Transfusion requirements
 - ✓HLA immunization
 - ✓In vitro measures (patient and product) and linking this to bleeding symptoms
 - ✓Etc.etc.

Introduction: platelets and maintenance of endothelial integrity; markers for endothelial damage

- Prevention of endothelial thinning/fenestration requires a certain amount of platelets
- “platelet type bleeding” reflects functional platelet deficiency on the vascular endothelial level
- Glomerular filtration barrier is formed by the endothelium in the glomeruli
- Primary urine is virtually protein free
- Conditions associated with endothelial damage predispose to microalbuminuria: diabetes mellitus, sepsis, inflammatory states, ...
- C-reactive protein (CRP) :
 - inflammation marker
 - inverse relationship between CRP levels and endothelial function

Kitchens 1975 Blood; Slichter 1978).

Nachman NEJM 2008

Introduction: definition of albuminuria /risk factor in cardiovascular disease

Definition of albuminuria

	Collection of urine (mg albumin/24 hours)	(early morning) urinary portion albumin/creatinine ratio (g/mol)
Microalbuminuria	30-300	2,5-30
Macroalbuminuria	>300	>30

- (micro) albuminuria is associated with all cause mortality

(ref: Lancet. 2010 Jun 12;375(9731):2073-81 Chronic Kidney Disease Prognosis Consortium, Matsushita K ea)

- (micro) albuminuria is associated with increased risk of cardiovascular disease

(ref: J Am Soc Nephrol. 2006 Aug;17(8):2106-11. Microalbuminuria and risk for cardiovascular disease: Analysis of potential mechanisms. Stehouwer CD, Smulders YM.)

- (micro) albuminuria can be seen in patients with haematological malignancies and intensive chemotherapy (pilot study JL Kerkhoffs)

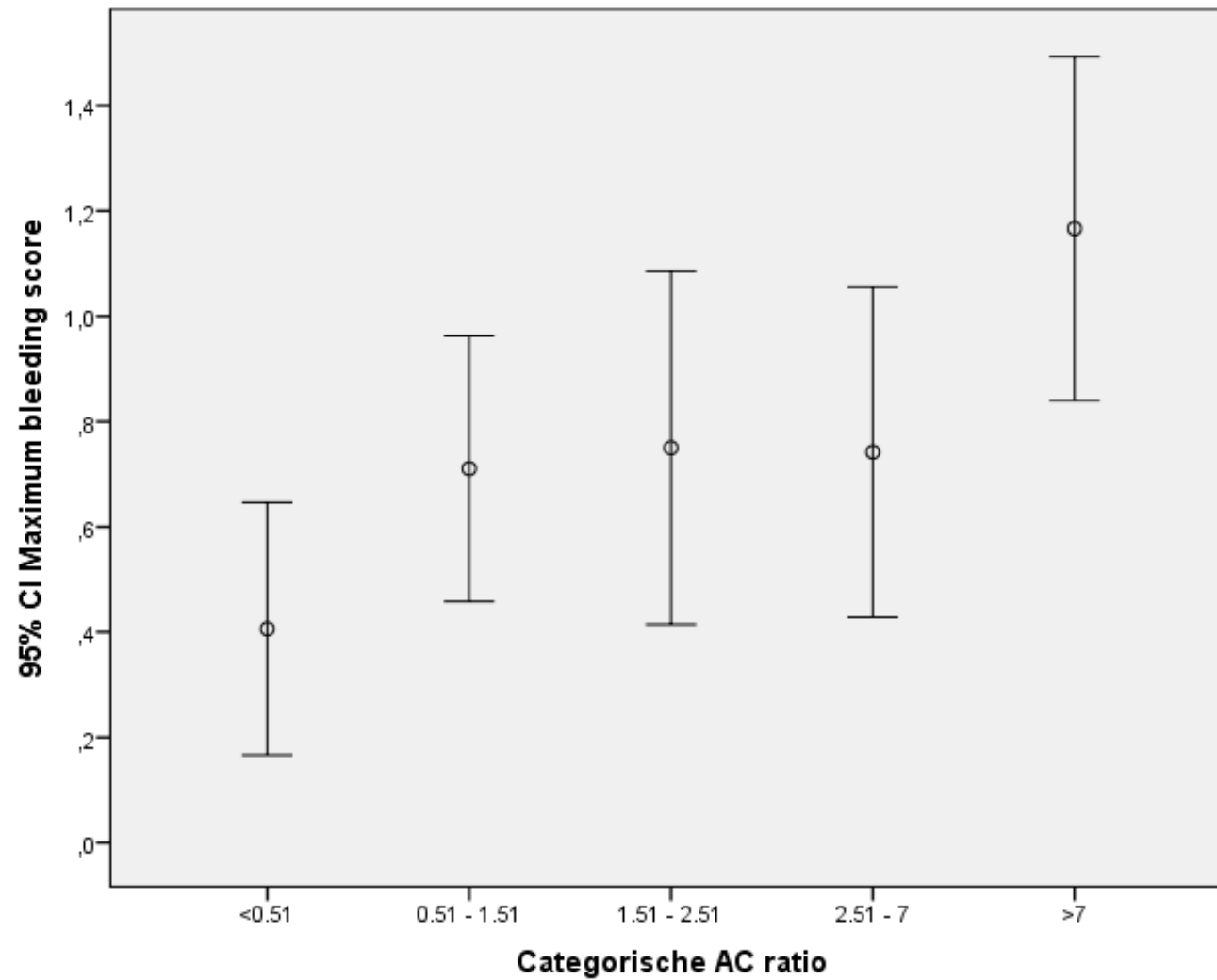
PREPAREs and “endothelopathy”

- Research questions:
 1. Do patients with hypoproliferative thrombocytopenia develop microalbuminuria
 2. Is microalbuminuria –when it occurs- related to bleeding complications and/or refractoriness to platelet transfusions
 3. Is elevated CRP –when it occurs- related to bleeding complications and/or refractoriness to platelet transfusions

Results table 1: patient-numbers and measurements

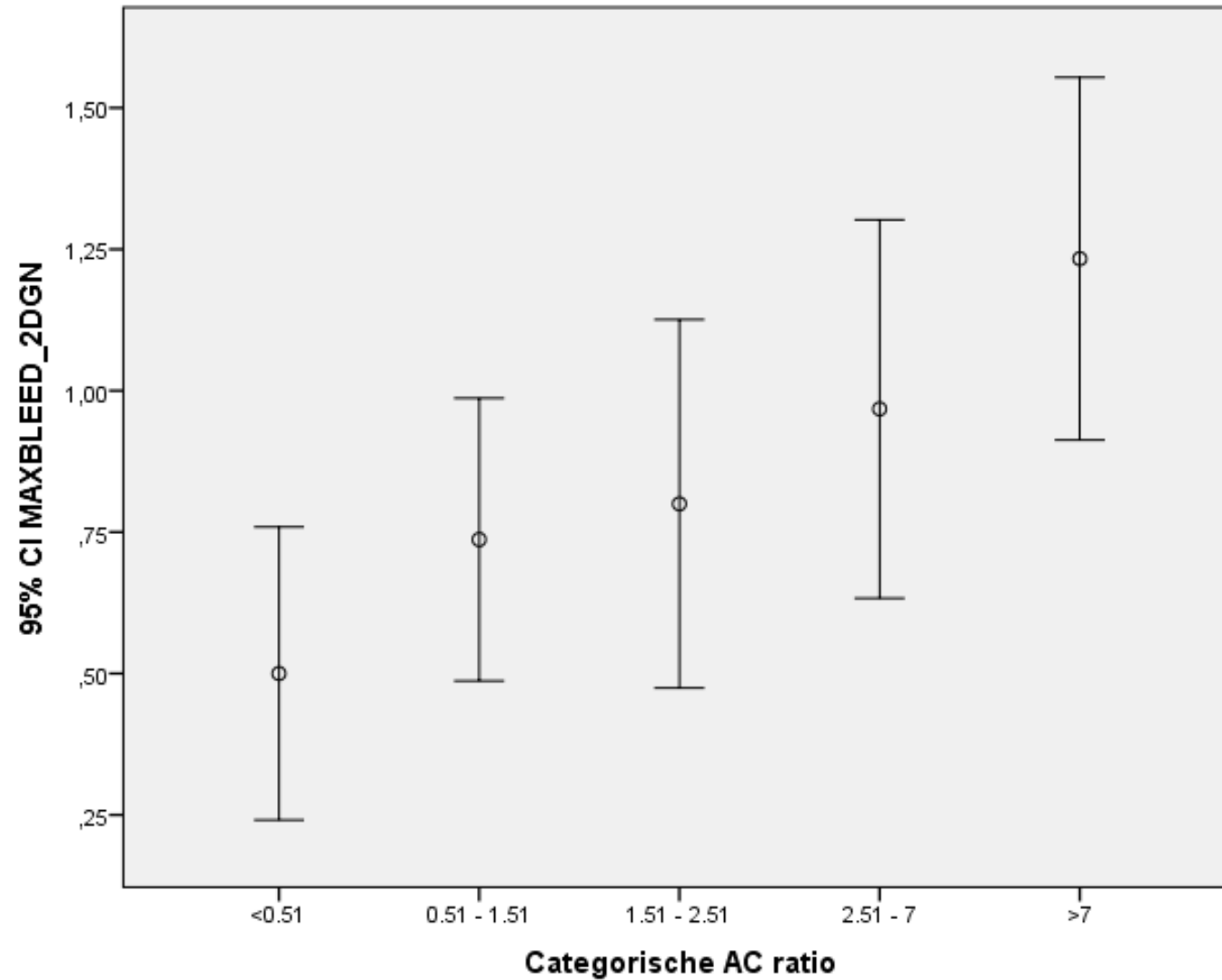
Table 1	
Patients	41
days per patient	8-35
Total bleeding days	646
no bleeding	341 (53%)
bleeding grade 1	181 (28%)
bleeding grade ≥ 2	124 (19%)
Total days CRP measured	140
CRP value mg/L (median IQR)	38 (9-109)
Total days alb/creat ratio (g/mol)	151
AC ratio (median IQR)	1,7 (0,7-4,8)
AC ratio first week	1,5
AC ratio second week	3,85

Results



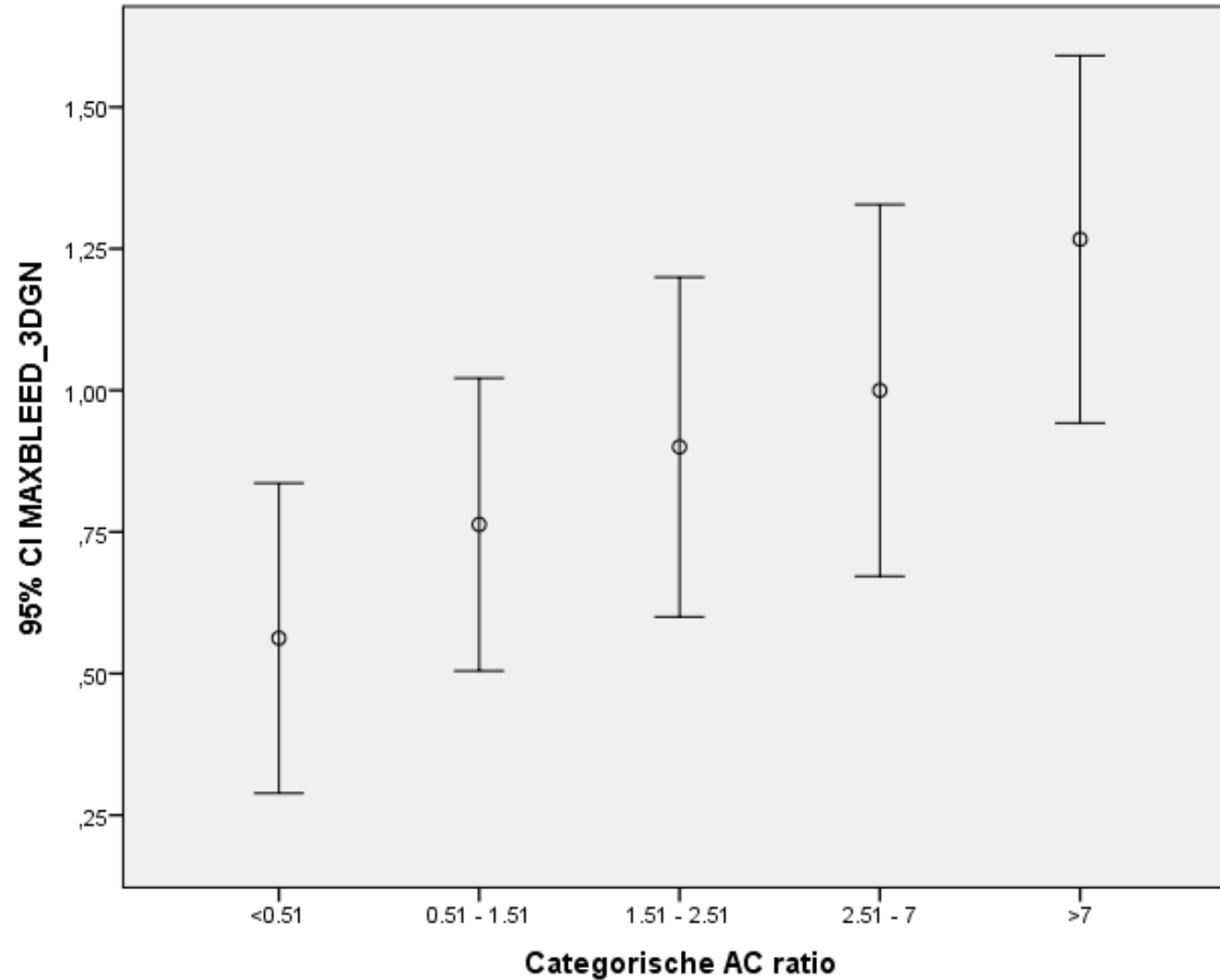
AC ratio = albumin/creatinine ratio g/mol

Results



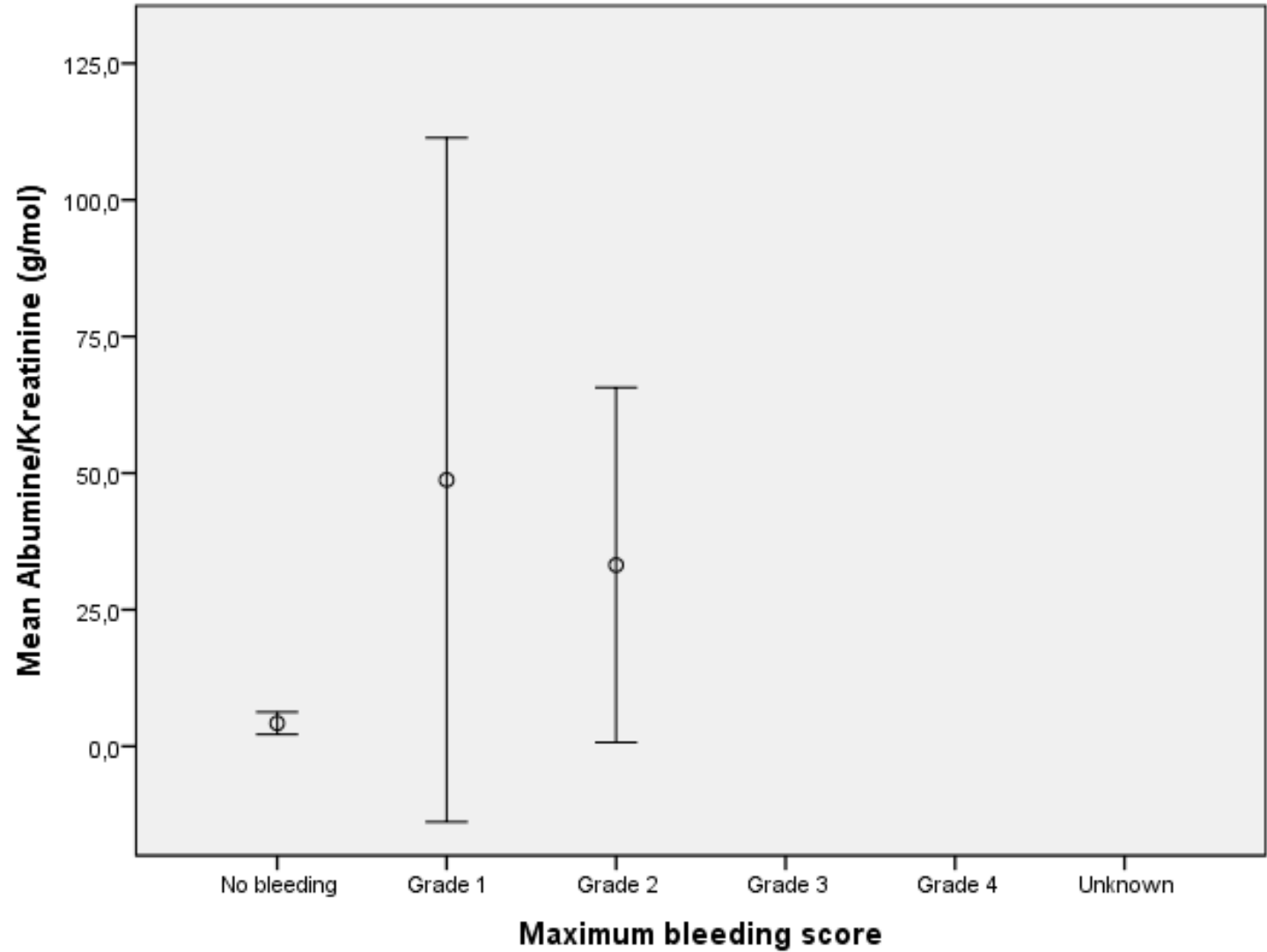
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Results



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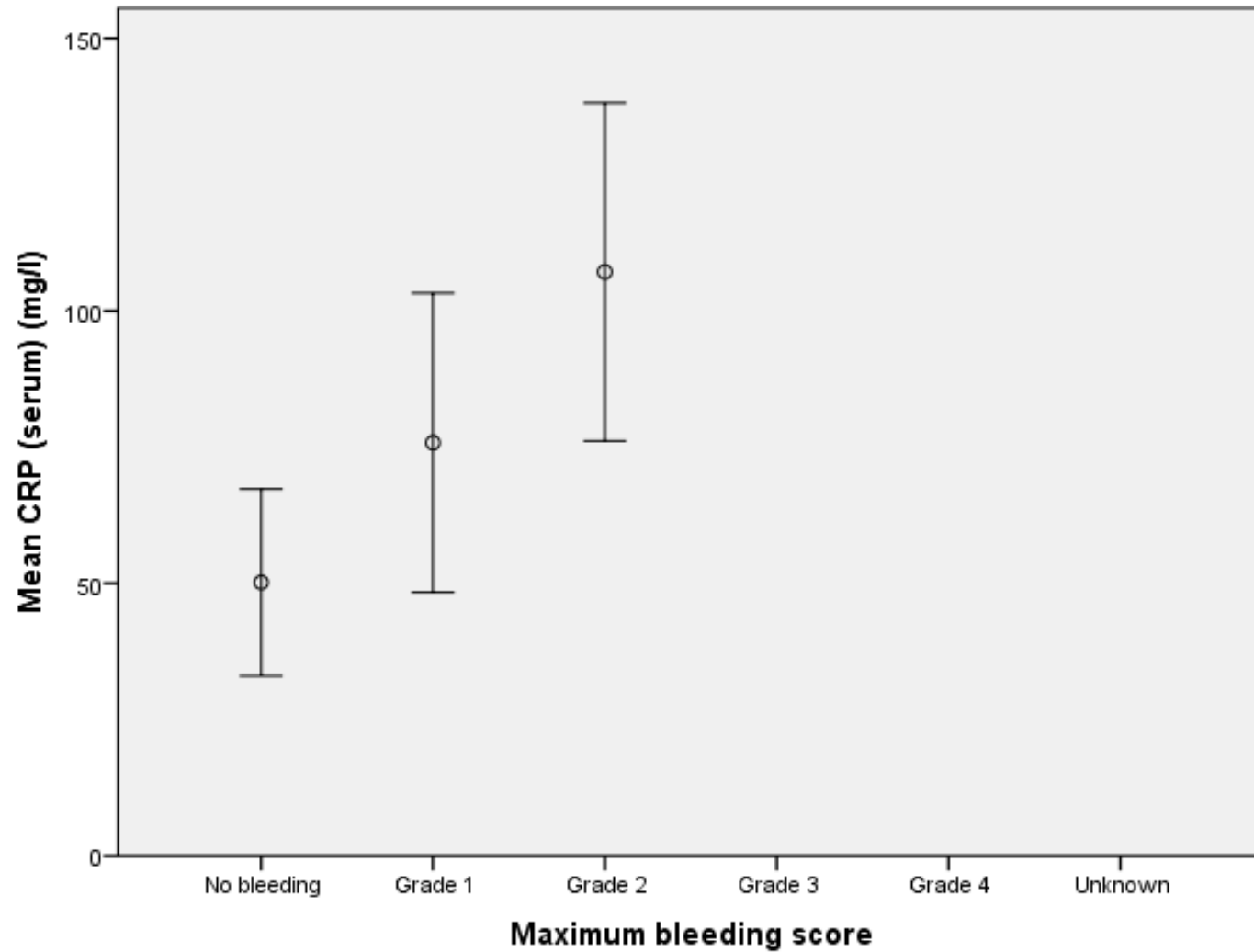
Results



Error Bars: 95% CI

Bleeding score: WHO grading

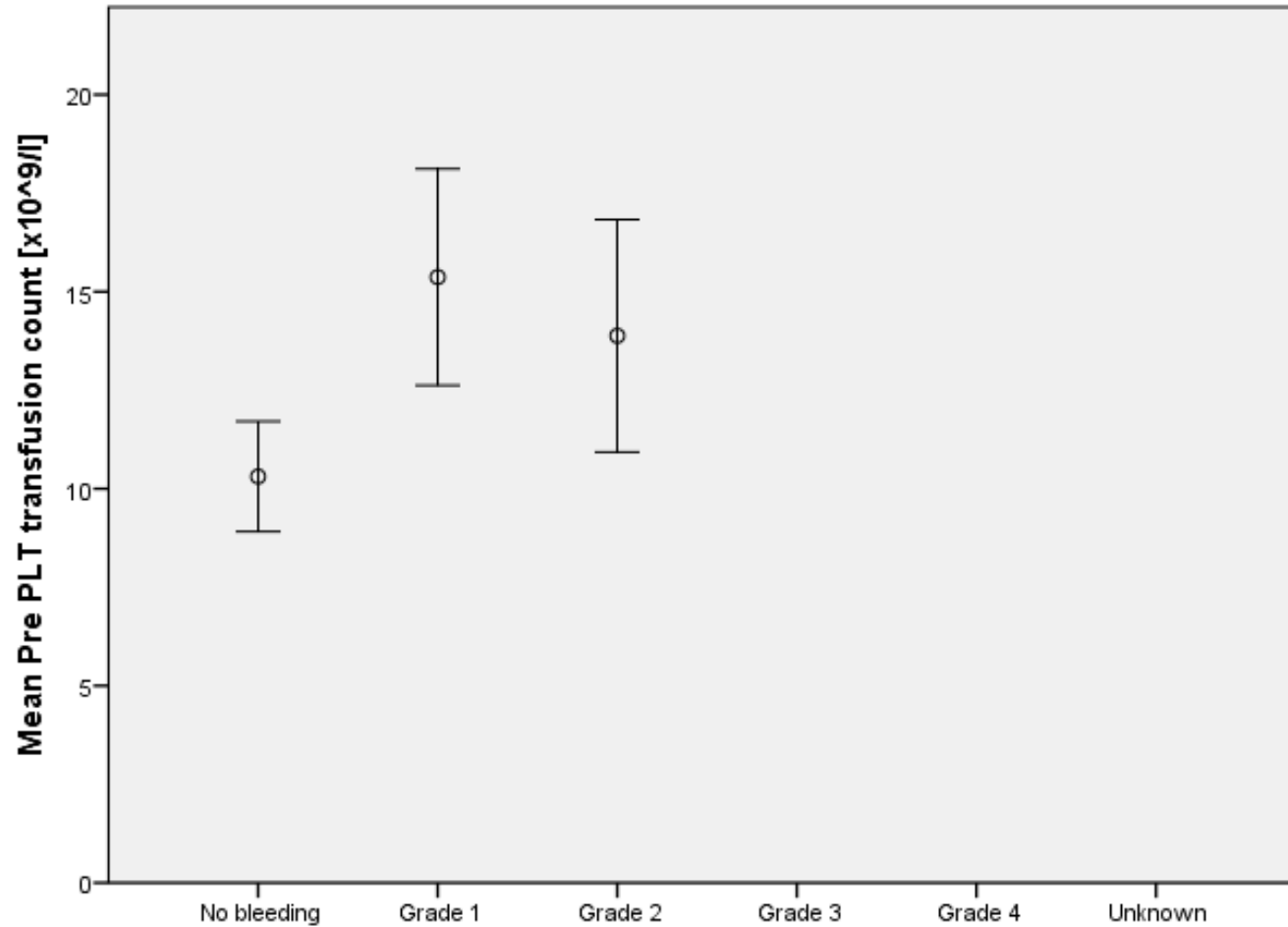
Results



Error Bars: 95% CI

Bleeding score: WHO grading

Results



Error Bars: 95% CI

Bleeding score: WHO grading



Conclusion and discussion

- During thrombocytopenia → microalbuminuria and CRP possible markers of endothelopathy ?
- Cause: chemotherapy ?, infection/inflammation? Thrombocytopenia?
- In this pilot: **no albuminuria and low CRP → no bleeding**
- What do we need for further analysis ? **568 patienten, 110000 observatie dagen**
 - Data completion
 - Other important variables: disease type, conditioning regimen, gender, presence of fever and even the randomisation arm (mirasol platelets or normal platelets), CCI's,.....
 - Positive and negative predictive value of these laboratory tests

Studie voorstel (eventueel als zijstudie van een HOVON studie)

- Onderverdelen patienten in **high risk** of **standard risk** op bloedingen
- Standard risk patiënten krijgen therapeutische transfusies bij stijging CRP/albuminurie randomisatie tussen continueren therapeutisch versus switch naar profylaxe.
- High risk patienten krijgen profylaxe en bij stijging CRP/albuminurie randomisatie tussen continueren profylaxe + tranexaminezuur of verhoging naar trigger van 10 naar bv 50
- Eindpunt: aantal dagen met graad 3 / 4 bloeding