Medizinische Hochschule Hannover

FRANZISKUS HOSPITAL gem. GmbH

Akademisches Lehrkrankenhaus der Medizinischen Hochschule Hannover

Role of fibrinogen concentrate in coagulation management in complex cardio-vascular surgery

Niels Rahe-Meyer
Clinic for Anaesthesiology and Intensive Care Medicine

In major blood loss, fibrinogen deficiency develops first

Haemostatic factor	Critical level	Blood loss (%)
Platelets	**50 x 10^3/mm^3**	**230**

Hiippala ST et al. Anesth Analg 1995; 81: 360-5.

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Factor II	20	201
Factor V	25	229
Factor VII	20	236

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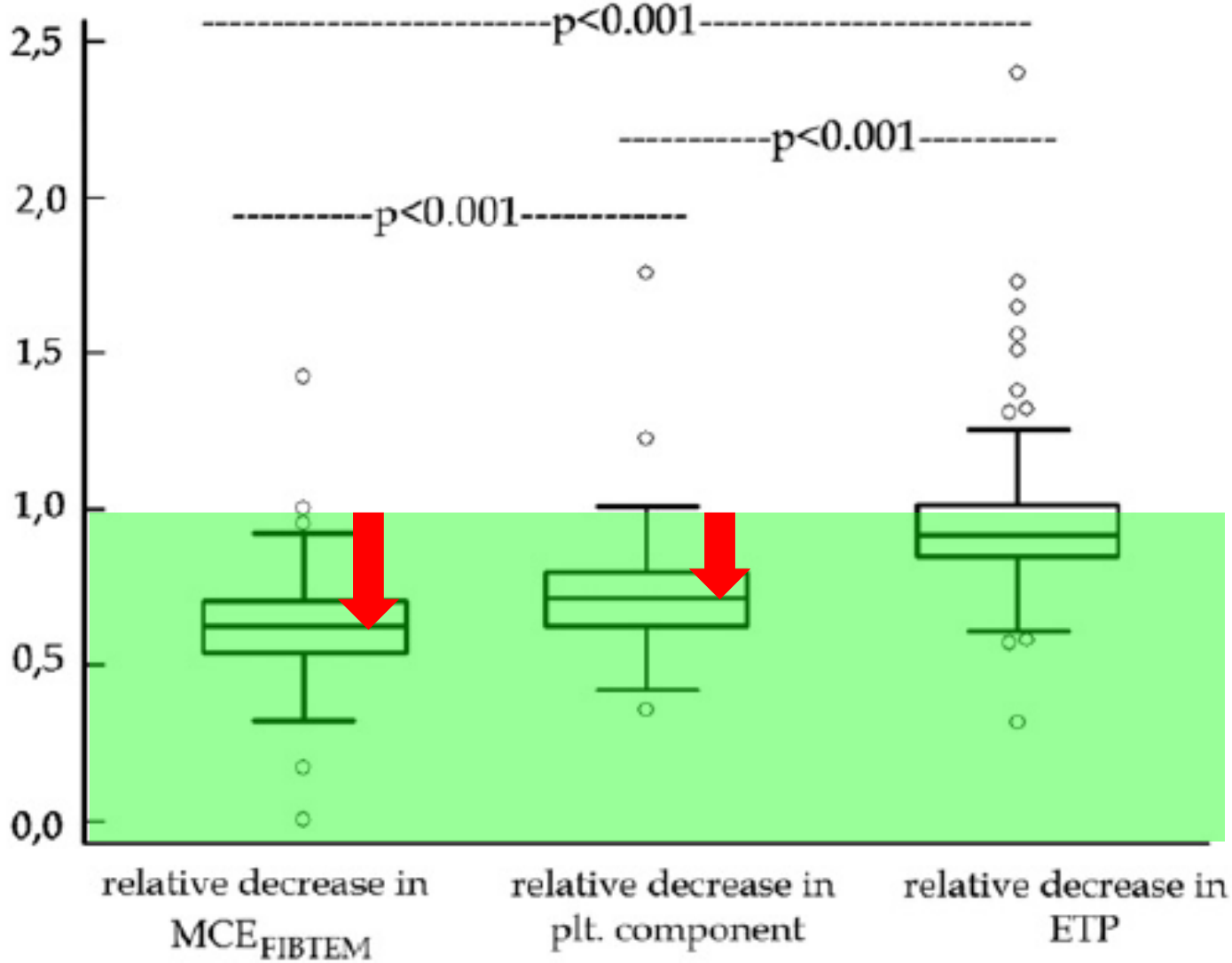
Factor II	20	201
Factor V	25	229
Factor VII	20	236
Fibrinogen	1.0 g/L	142

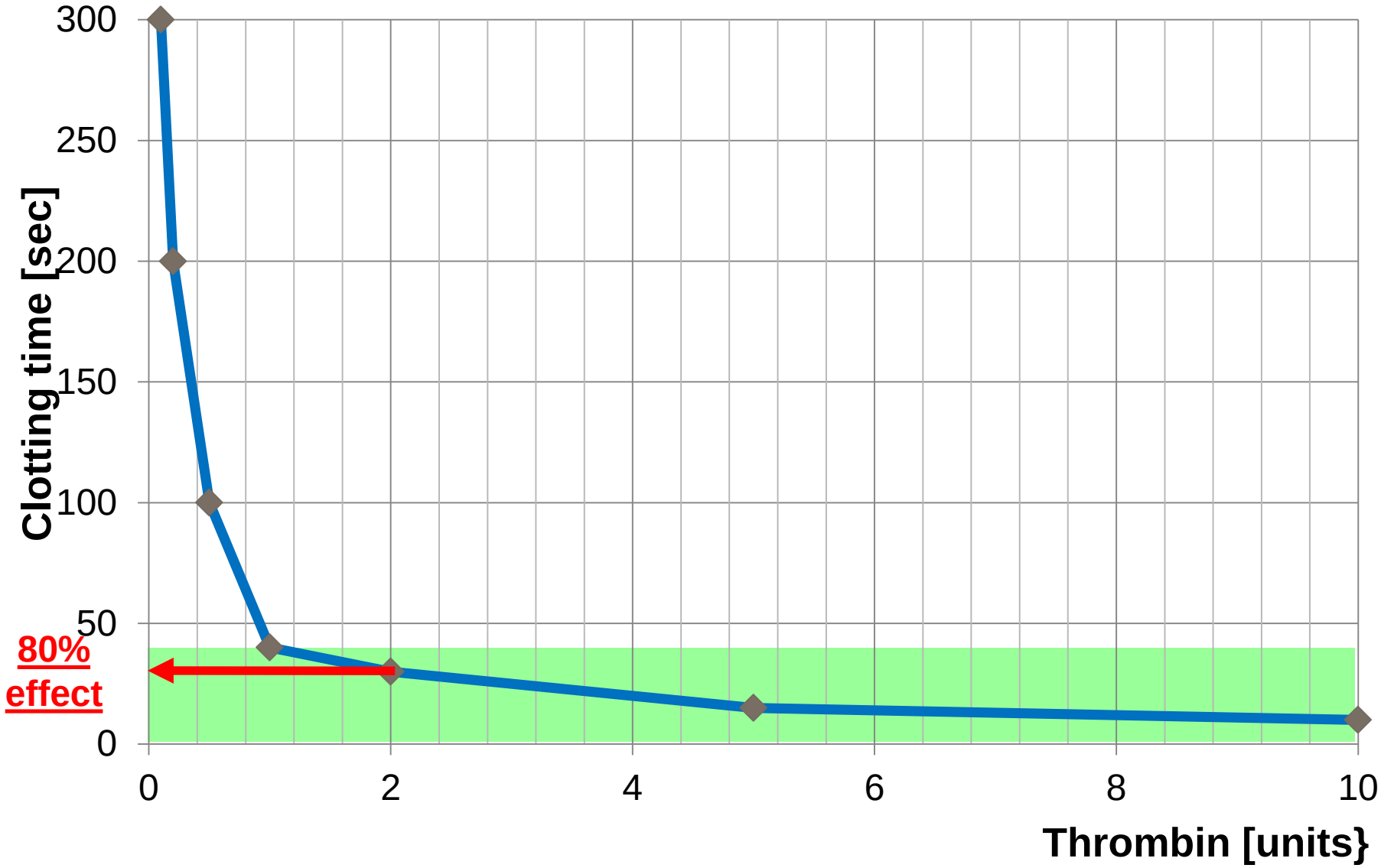
Hiippala ST et al. Anesth Analg 1995; 81: 360-5.

Fibrin formation is more impaired than thrombin generation and platelets immediately following cardiac surgery



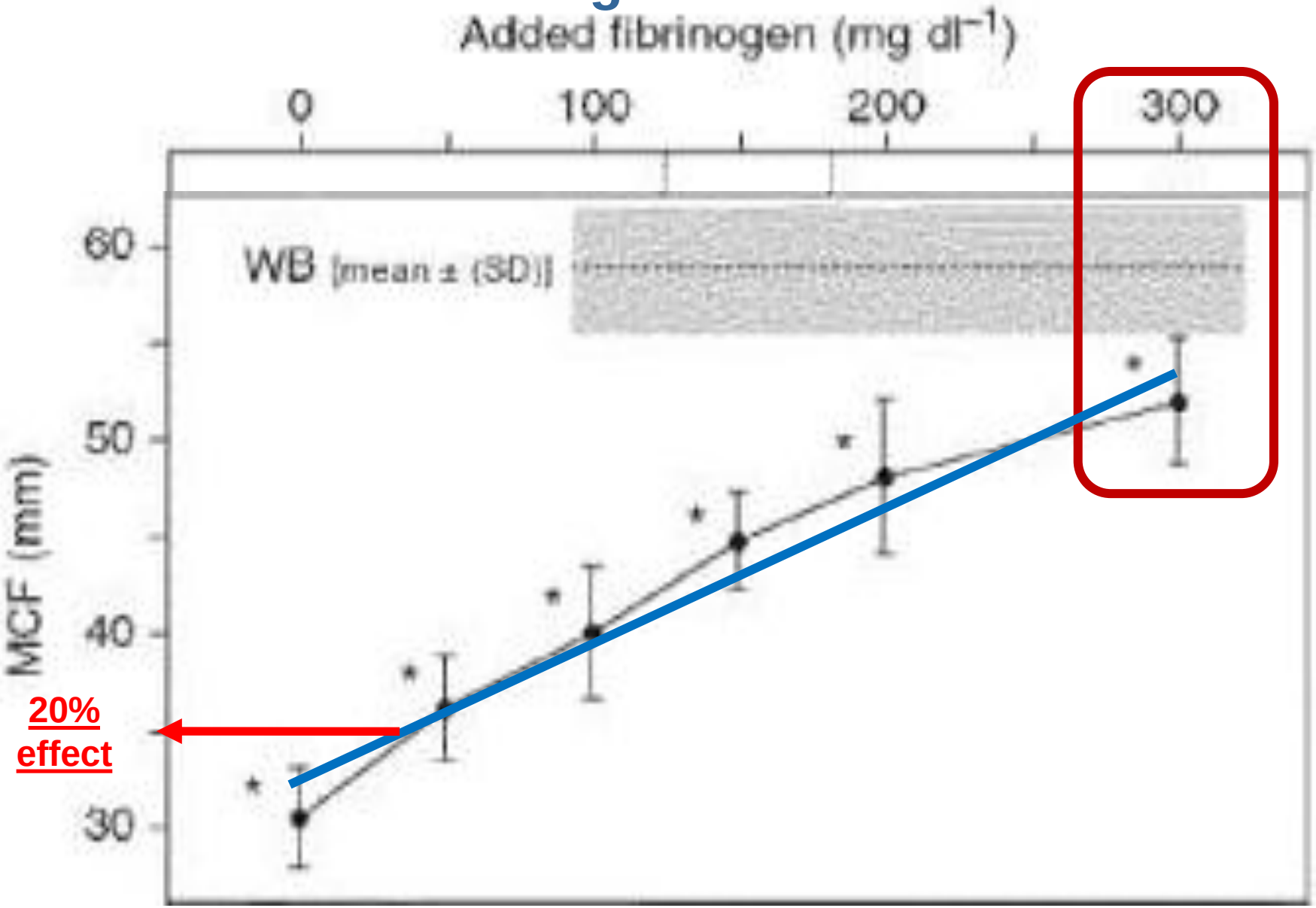
Solomon C et al.
Thromb Res 2011;
128: 277

Effect of thrombin dose on clotting time



Jaques *J Physiol* 1941

Effect of fibrinogen level on clot firmness



Bolliger D et al. Br J Anaesth 2009; 102: 793-9

What is the target?

Vance G. Nielsen, MD*
Jerrold H. Levy, MD†

Fibrinogen and Bleeding: Old Molecule—New Ideas

- **Increases in fibrinogen increase plasma clot strength linearly up to 300 mg/dl**
- **Plasma clot strength is equal to whole blood at 625 mg/dl**

Nielsen VG & Levy JH. Anesth Analg 2007; 105: 902-3

Correlation blood loss – pre-operative fibrinogen, CABG, RCT, placebo-controlled double blind, n=20

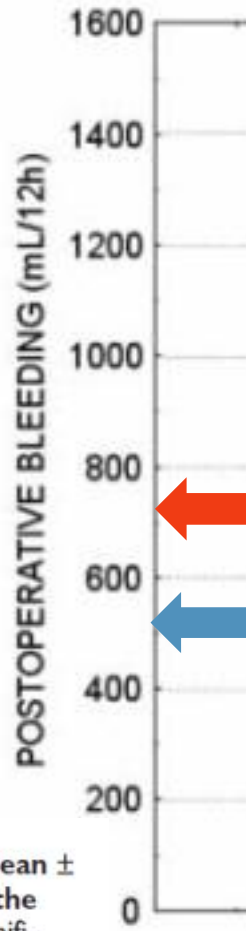


Figure 2: Postoperative bleeding (mean ± SD) in the FIB group (n=10) and in the control group (n=10). There was a significant difference between the mean value in the two groups (p=0.010, Student t-test).

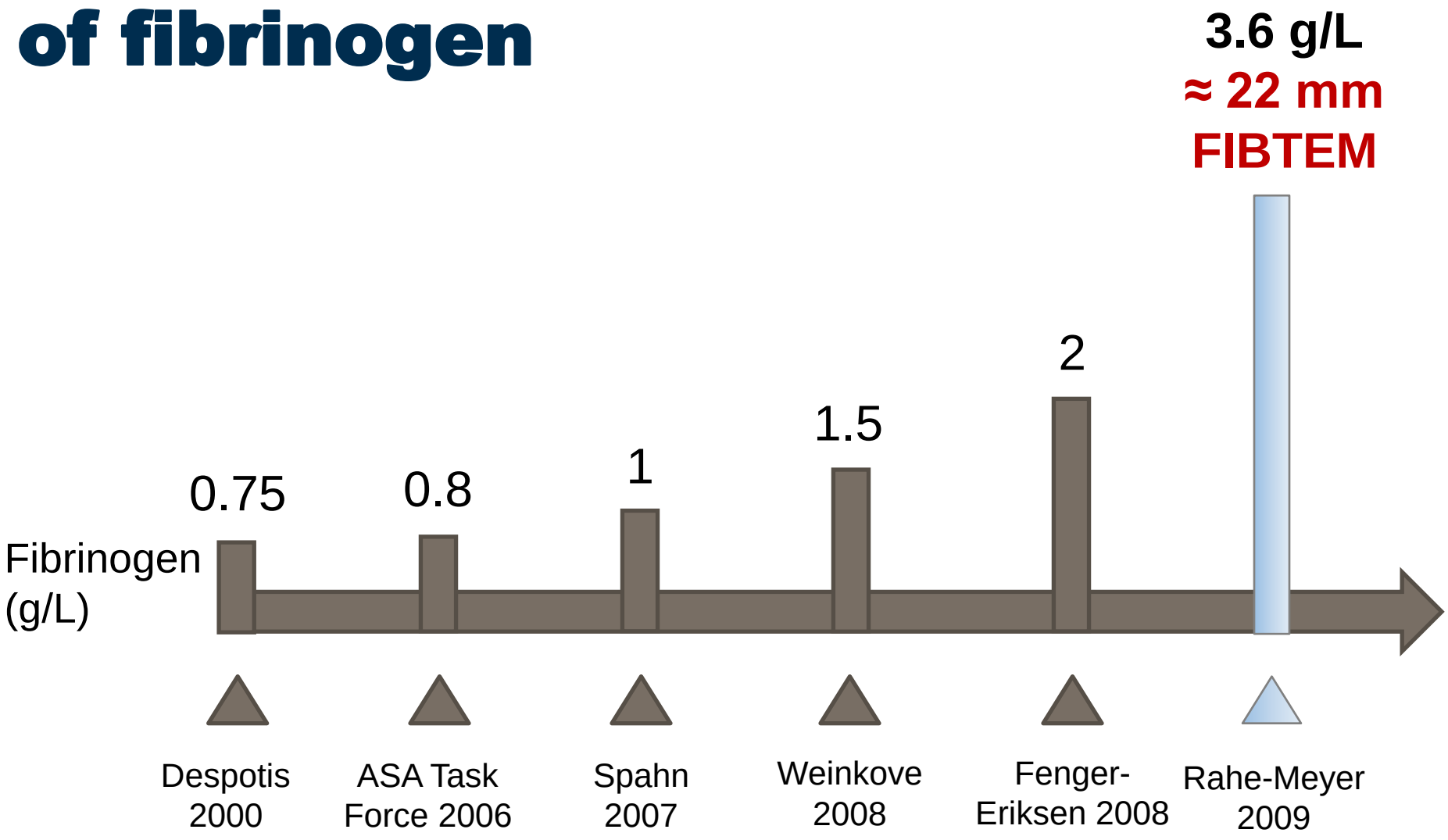
Karlsson M et al. Thromb Haemost 2009; 102: 137-44

Study design RCT

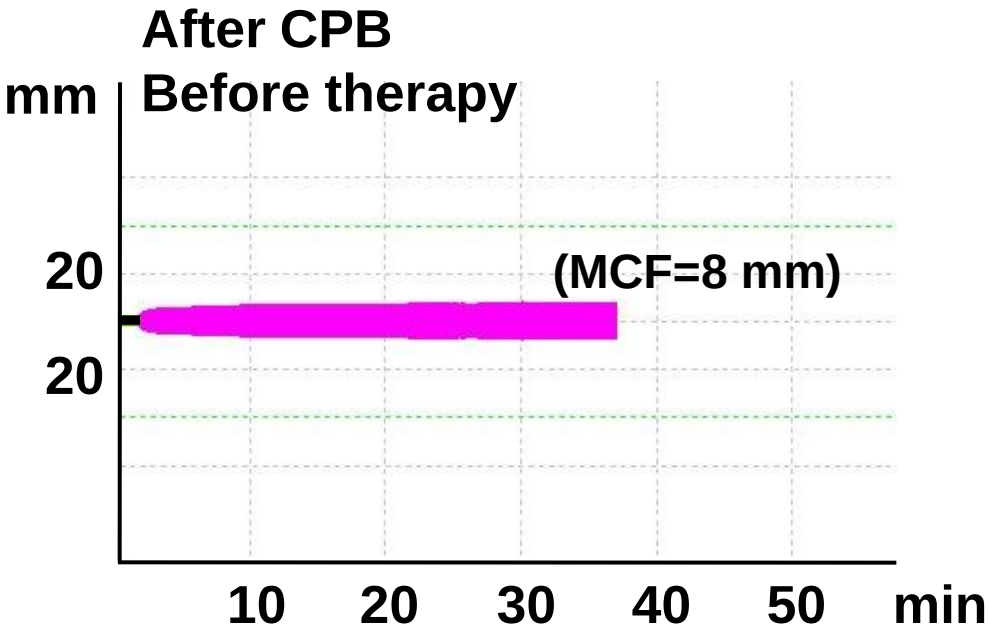
- Study sponsored by CSL Behring
- Monocentric, 61 patients
- Elective TAAA, ascending aorta, aortic arch
- Double-blinded/placebo controlled
- Strict coagulation treatment algorithm, with the trigger of peri-operative bleeding
- Individually dosed high level fibrinogen

Methods

Target plasma level of fibrinogen



ROTEM® FIBTEM-guided administration of fibrinogen concentrate



CPB, cardiopulmonary bypass; MCF, maximum clot firmness

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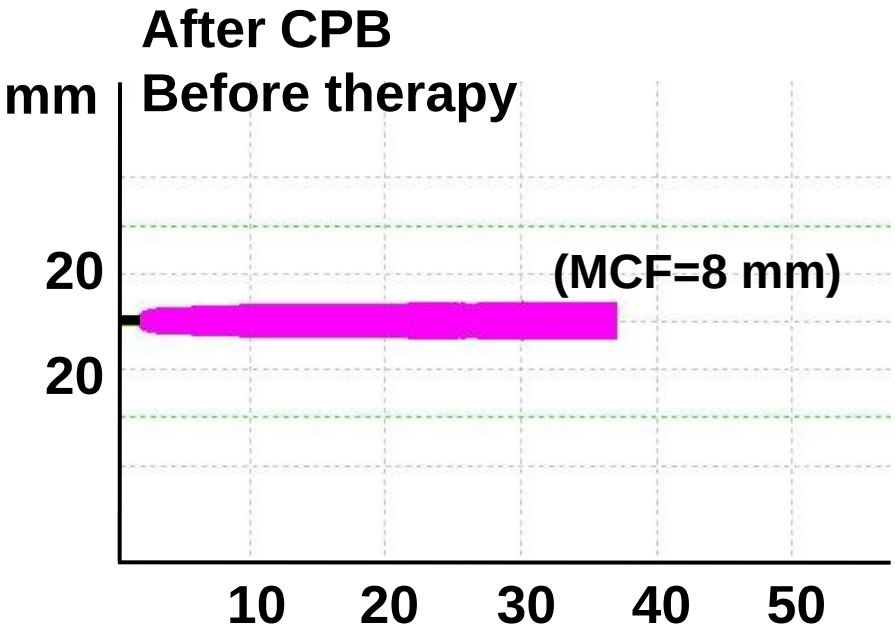

7 g 22 mm 8 mm

$$\text{Fibrinogen dose [g]} = \frac{(\text{target} - \text{FIBTEM MCF [mm]}) \times (\text{bodyweight [kg]}/70)}{2}$$

CPB, cardiopulmonary bypass; MCF, maximum clot firmness

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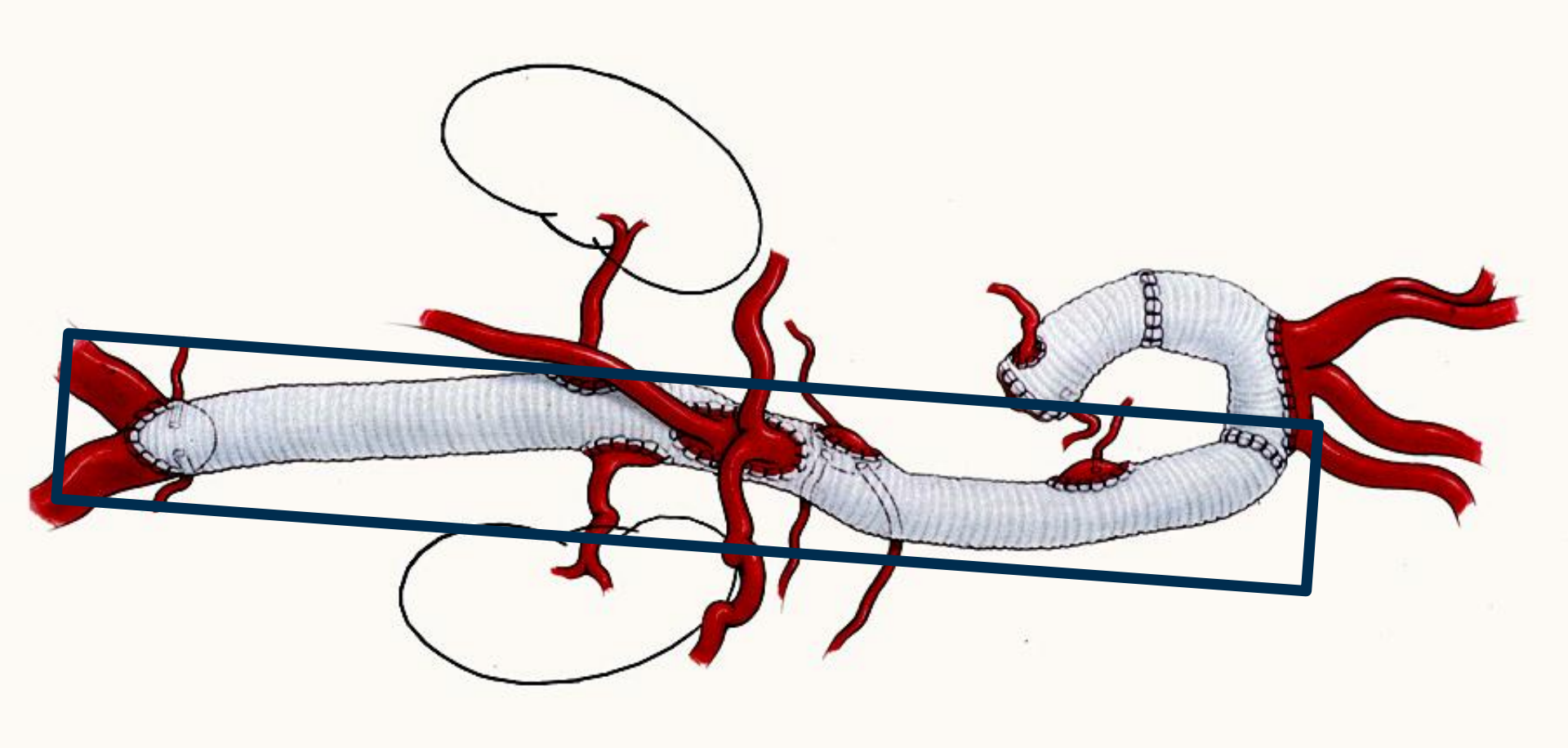
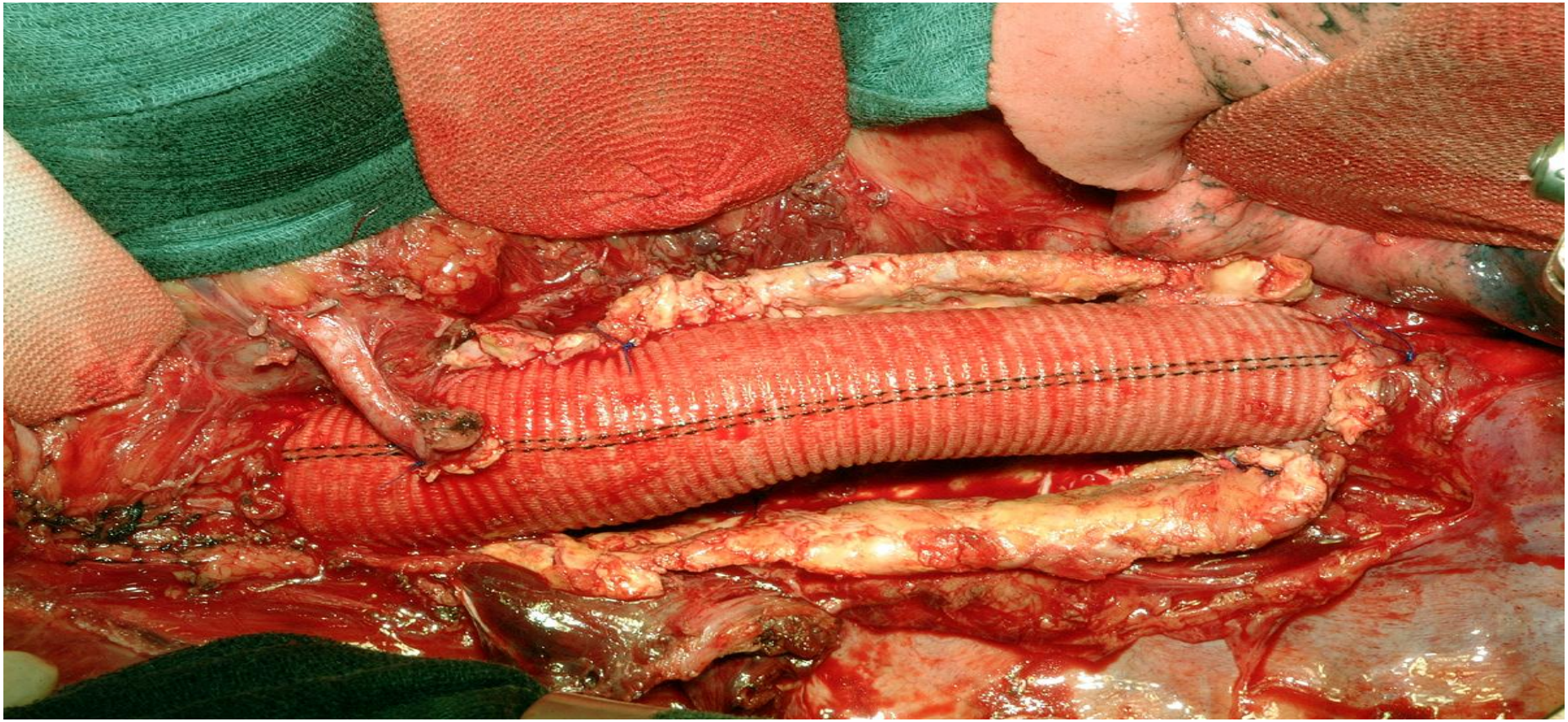
Thoraco-abdominal aorta



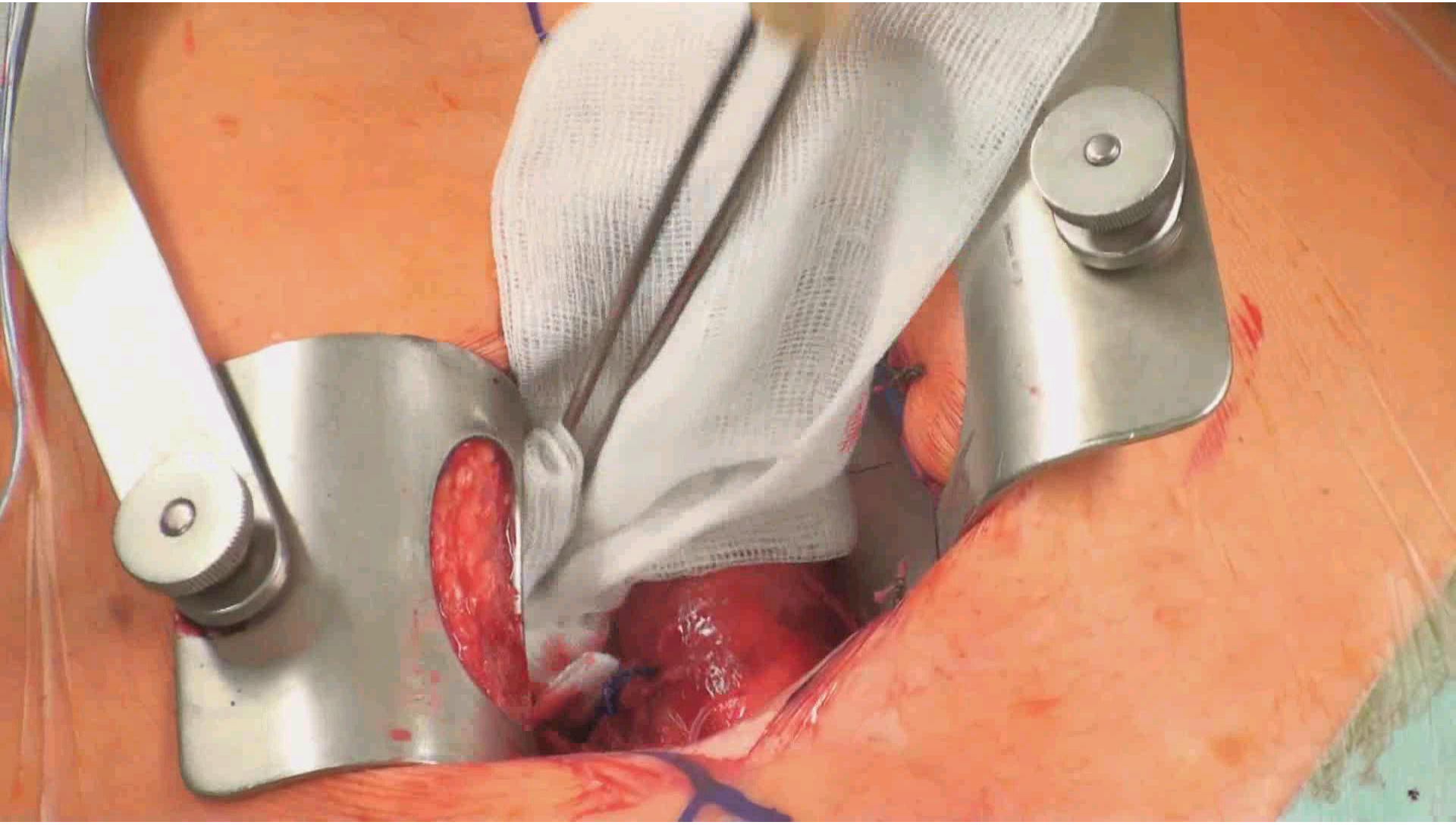
Standardized treatment trigger 5–min bleeding mass

1. After weaning from CPB
2. After heparin reversal (protamine)
3. After surgical haemostasis

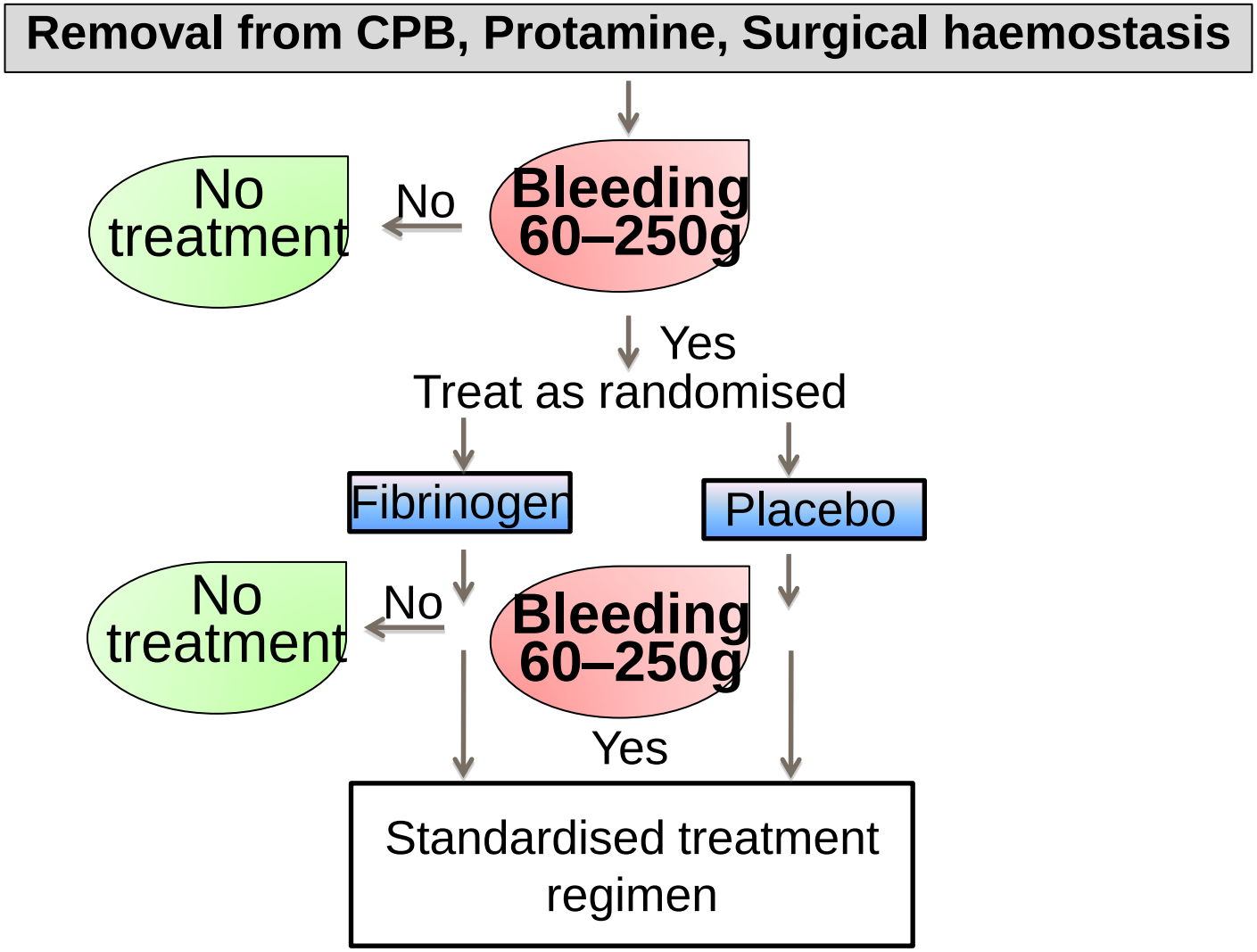
Intra-operative bleeding after protamin and surgical haemostasis



Standardized treatment trigger
5–min bleeding mass

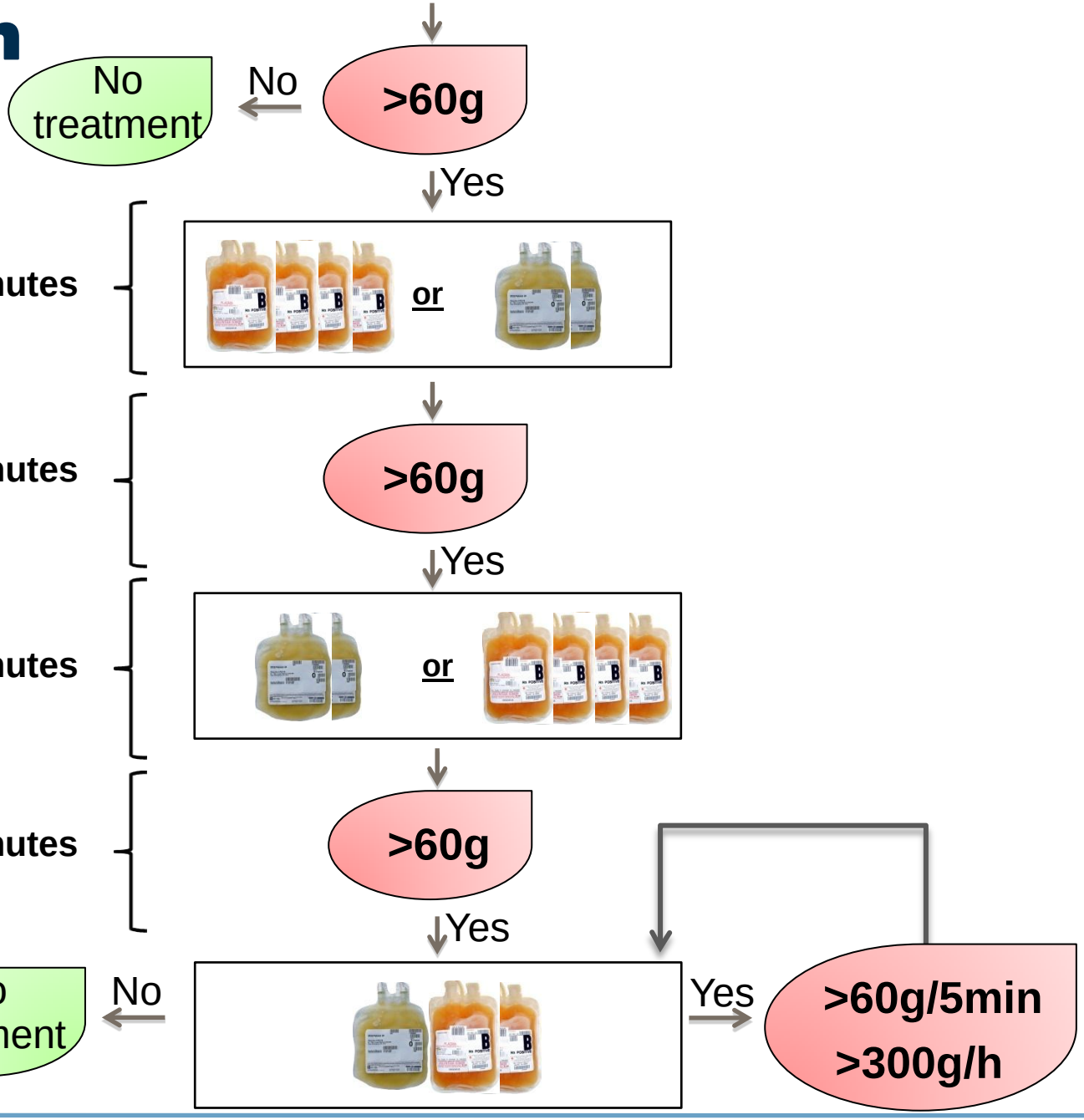


Algorithm



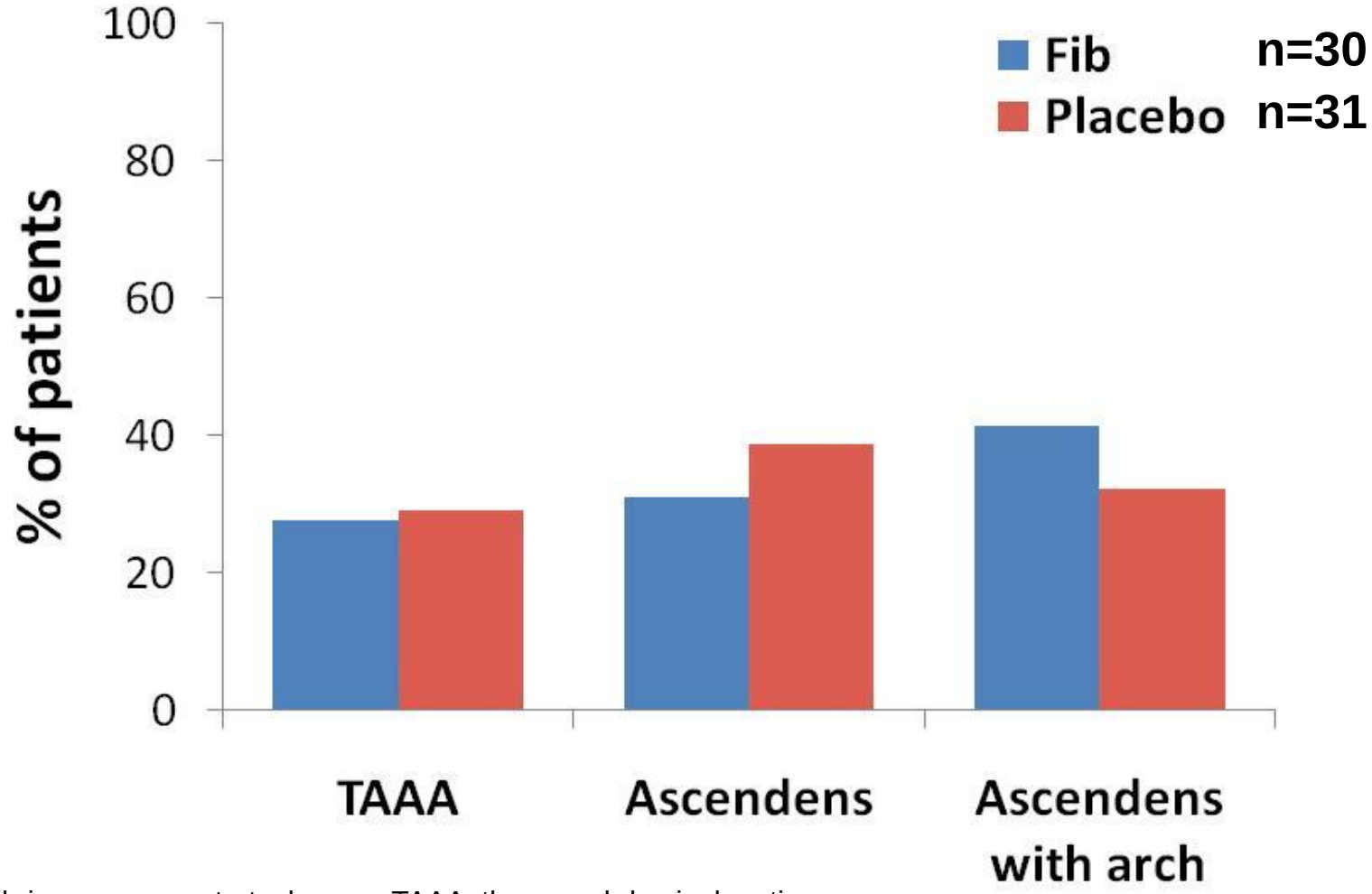
CPB, cardiopulmonary bypass

Algorithm


>60g
No
No treatment
Yes
5 minutes
or
5 minutes
>60g
Yes
5 minutes
or
5 minutes
>60g
Yes
5 minutes
No
No treatment
Yes
>60g/5min
>300g/h

Results

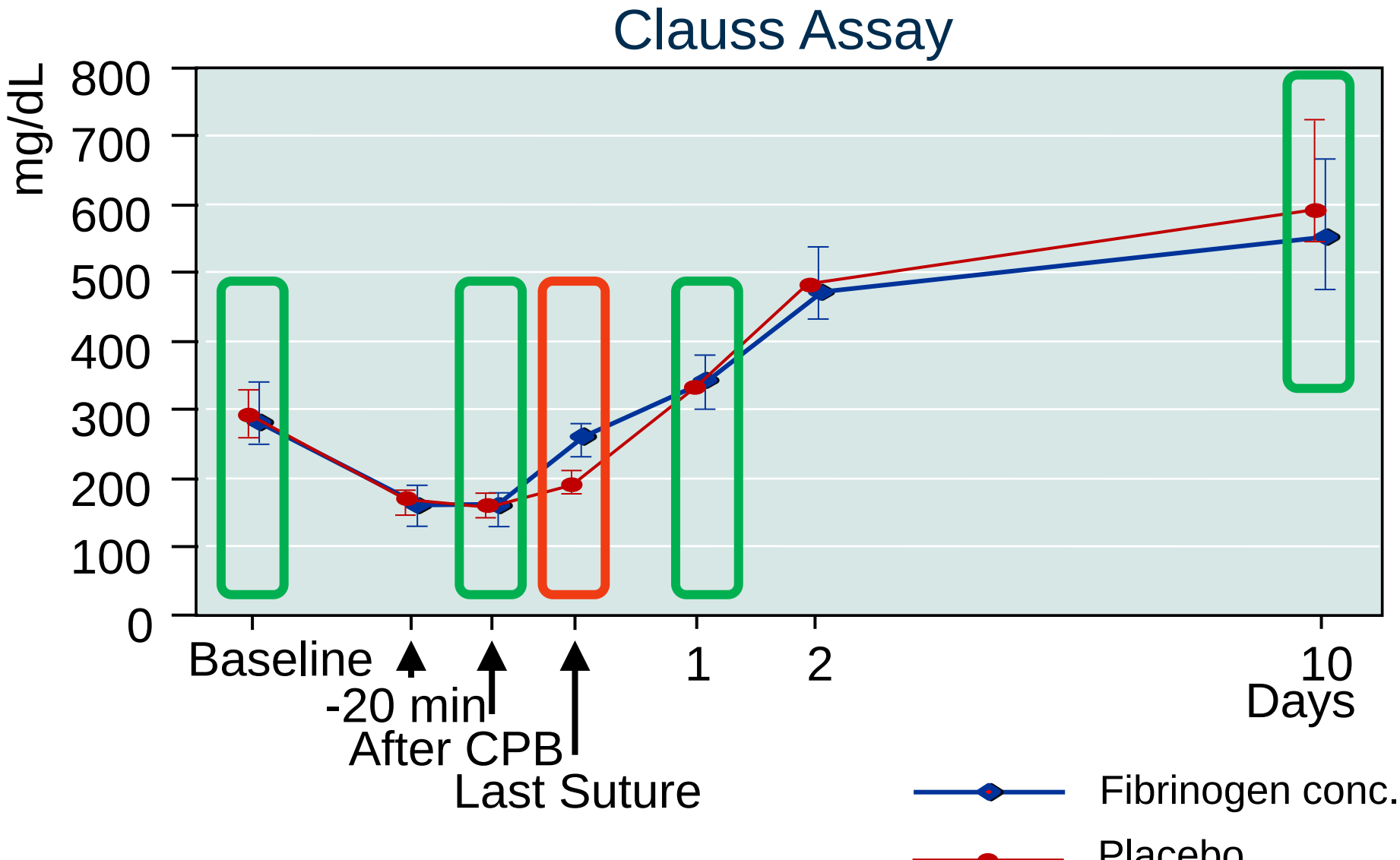
Distribution of operations



Fib, fibrinogen concentrate, human; TAAA, thoraco-abdominal aortic aneurysm

Rahe-Meyer et al. Manuscript accepted: Anesthesiology

Fibrinogen levels over time



Solomon C et al. Manuscript submitted

Safety

Adverse events

AEs	Fib (n = 29)	Placebo (n = 32)
Overall	**24** (82.8%)	**27** (84.4%)
Serious	**5** (17.2%)	**5** (15.6%)
Fatal	**1** (3.4%)	**4** (12.5%)

Events of special interests:

- **Thromboembolic or haemorrhagic**
- **Re-operation because of bleeding**
- **Allergic or other reactions to IMP or transfusion (TRALI)**
- **Organ failure or paraplegia**

Data given as number of patients (%); AEs, adverse events; Fib, fibrinogen concentrate

Rahe-Meyer et al. Manuscript accepted: Anesthesiology

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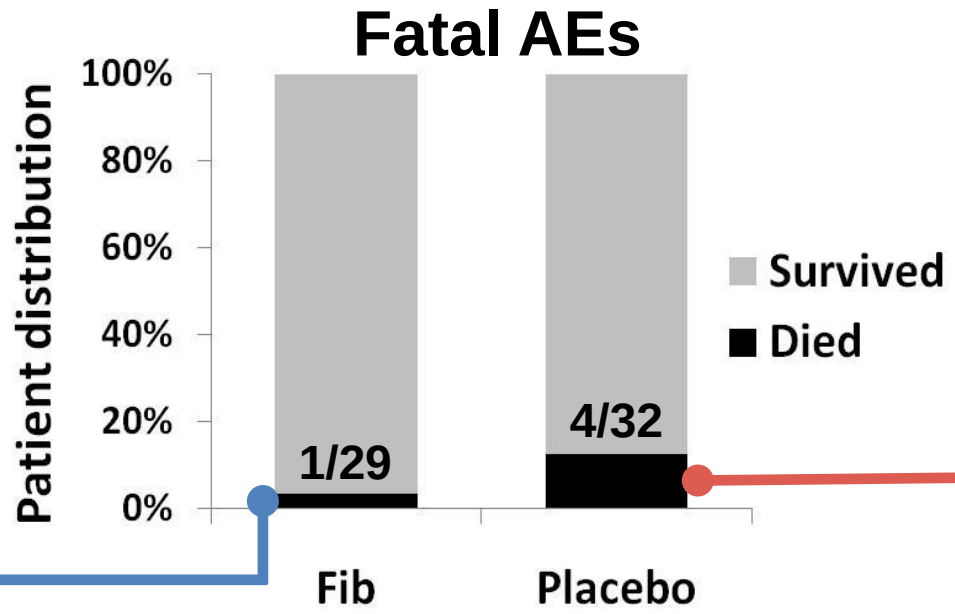
Myocardial infarction
Day 30



Operative haemorrhage
Day 0

Cardio-respiratory arrest
Day1

Cerebral haemorrhage
Day 1

Cerebral Infarction
Day 1

Data given as number of patients (%); AEs, adverse events; Fib, fibrinogen concentrate

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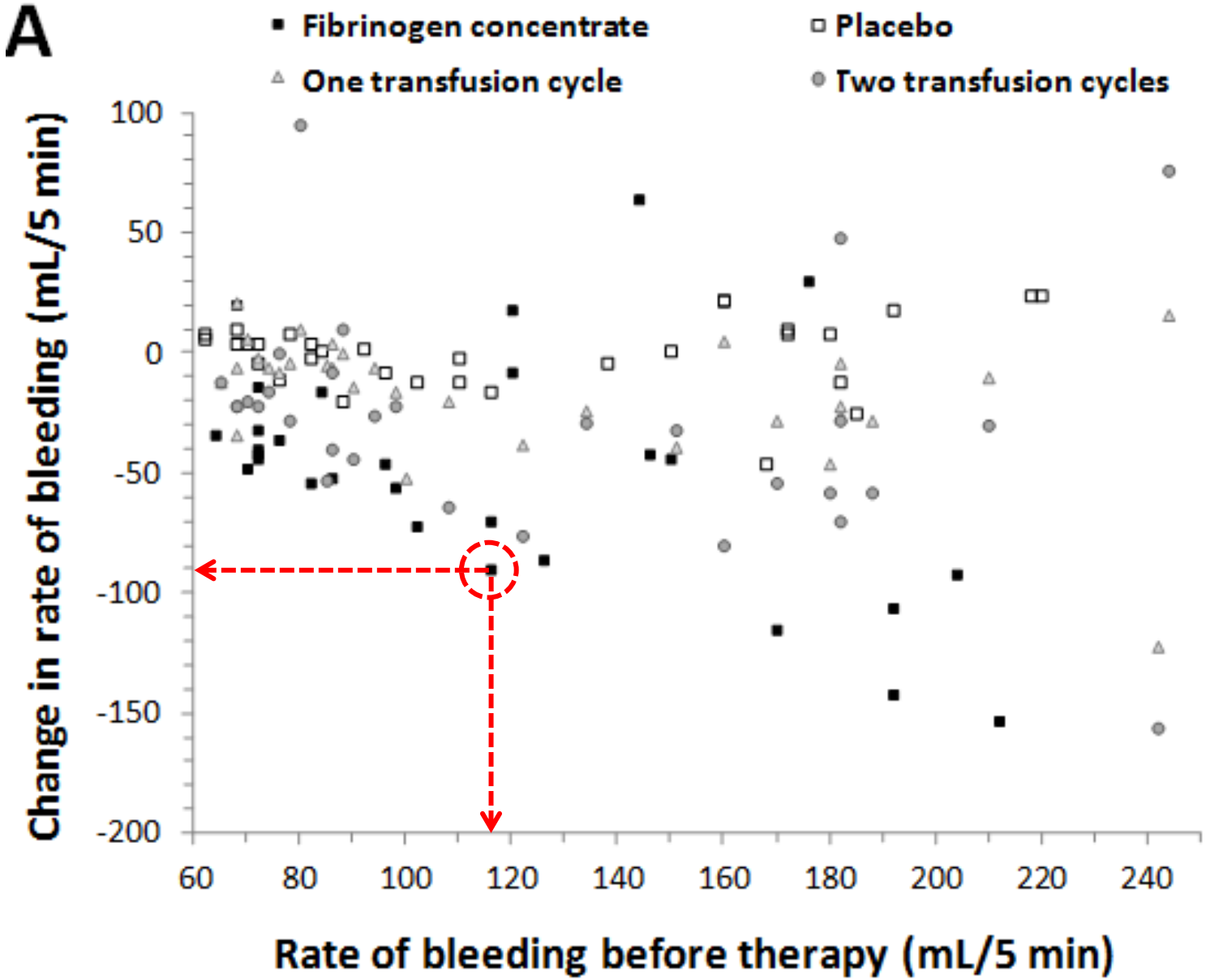
Reduction of bleeding by treatment



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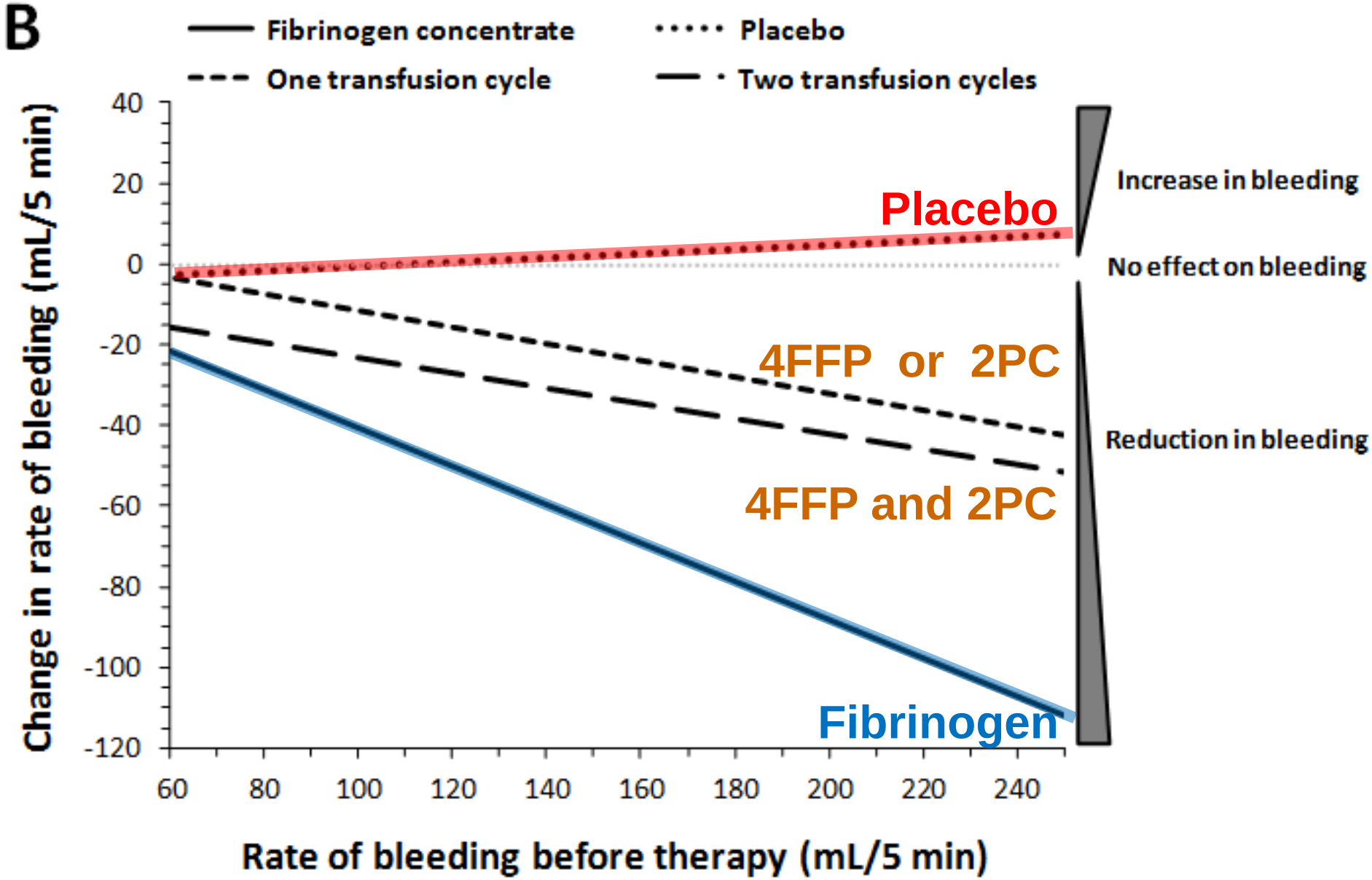
Reduction of bleeding by treatment



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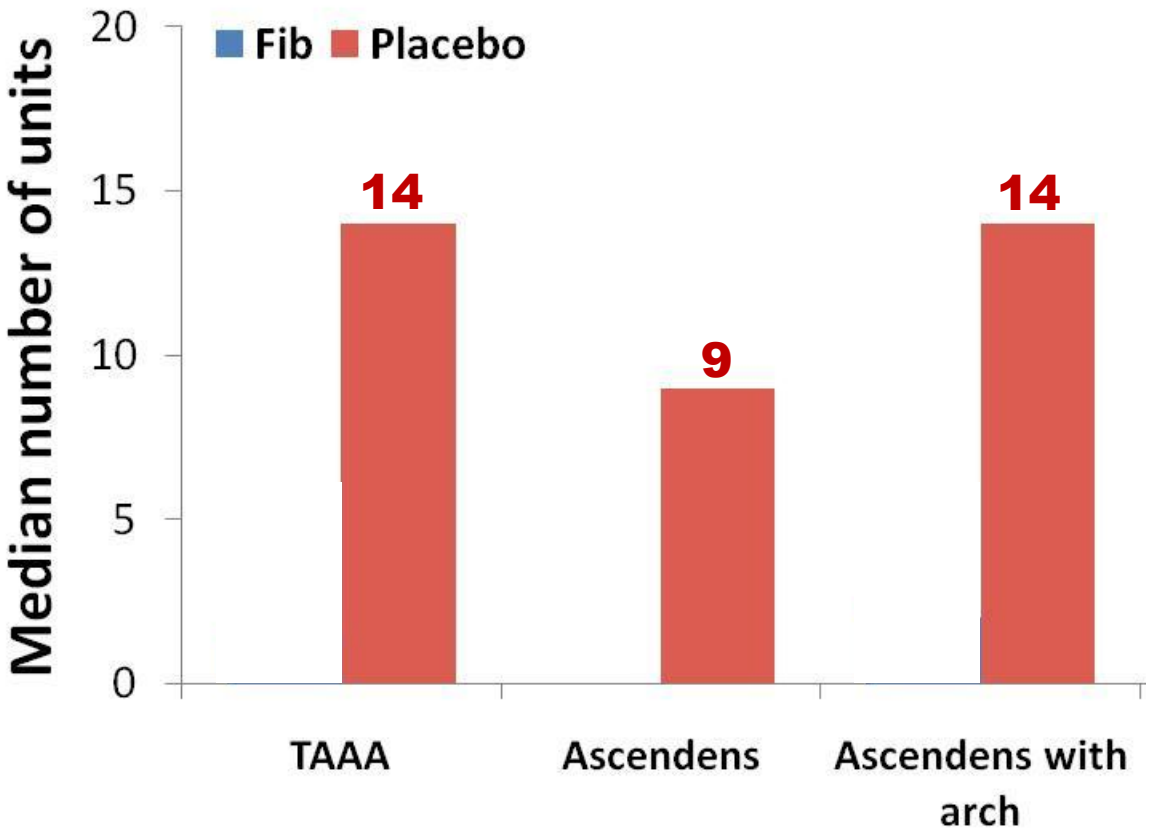
Total of units of allogeneic blood (RBC, FFP, PC) within 24 h



Fib, fibrinogen concentrate; TAAA, thoraco-abdominal aortic aneurysm

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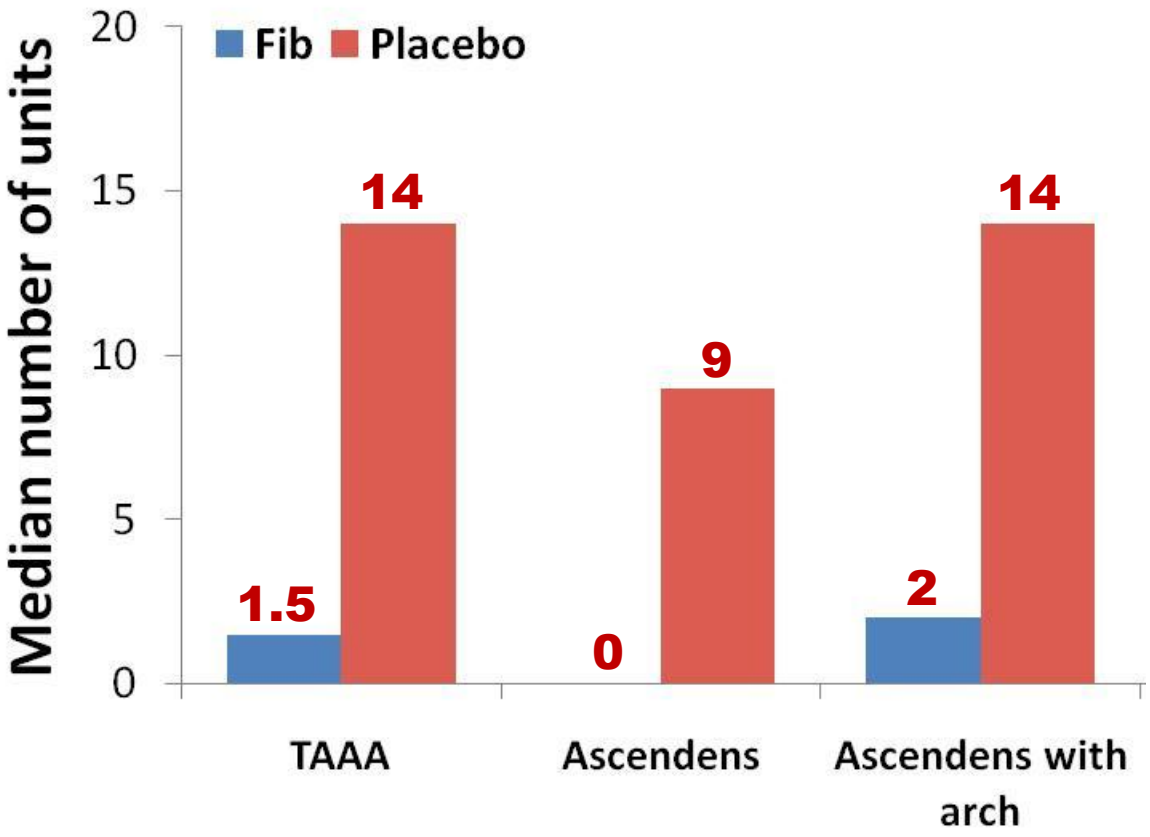

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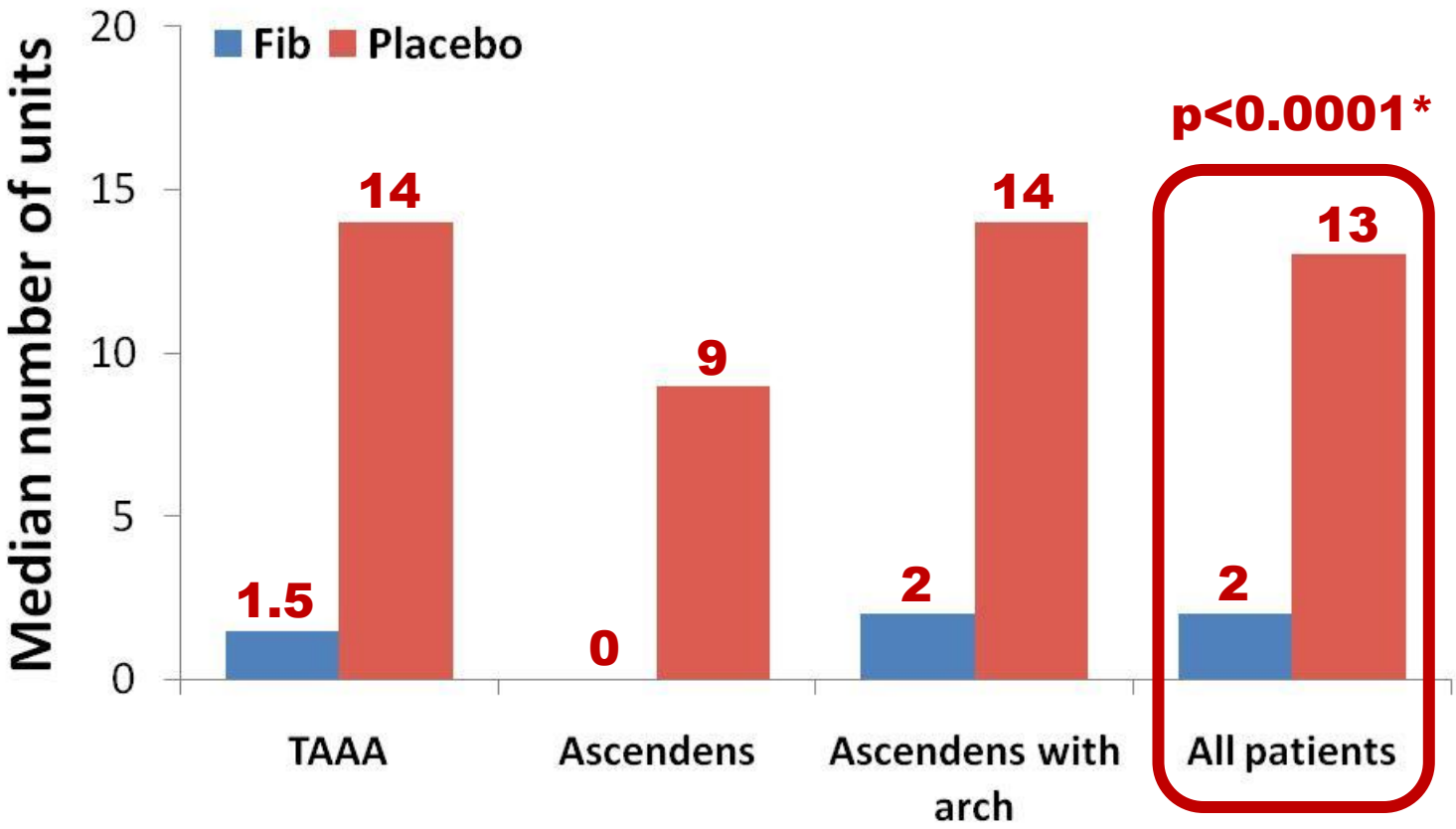

*p<0.0001 for treatment difference using the unstratified Hodges-Lehmann point estimate and corresponding non-parametric confidence intervals; Fib, fibrinogen concentrate; TAAA, thoraco-abdominal aortic aneurysm

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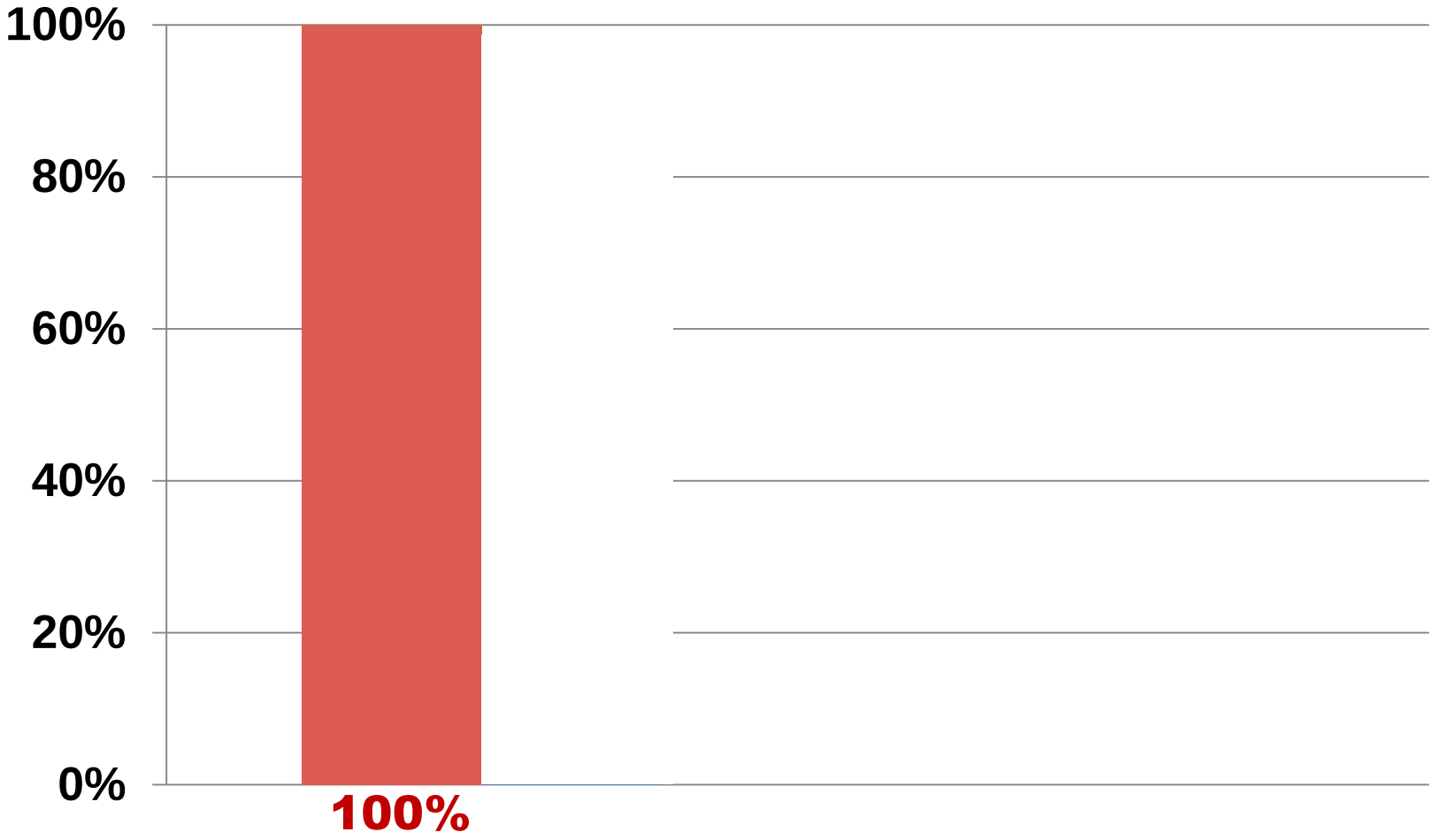
Secondary endpoint

Patients with transfusion



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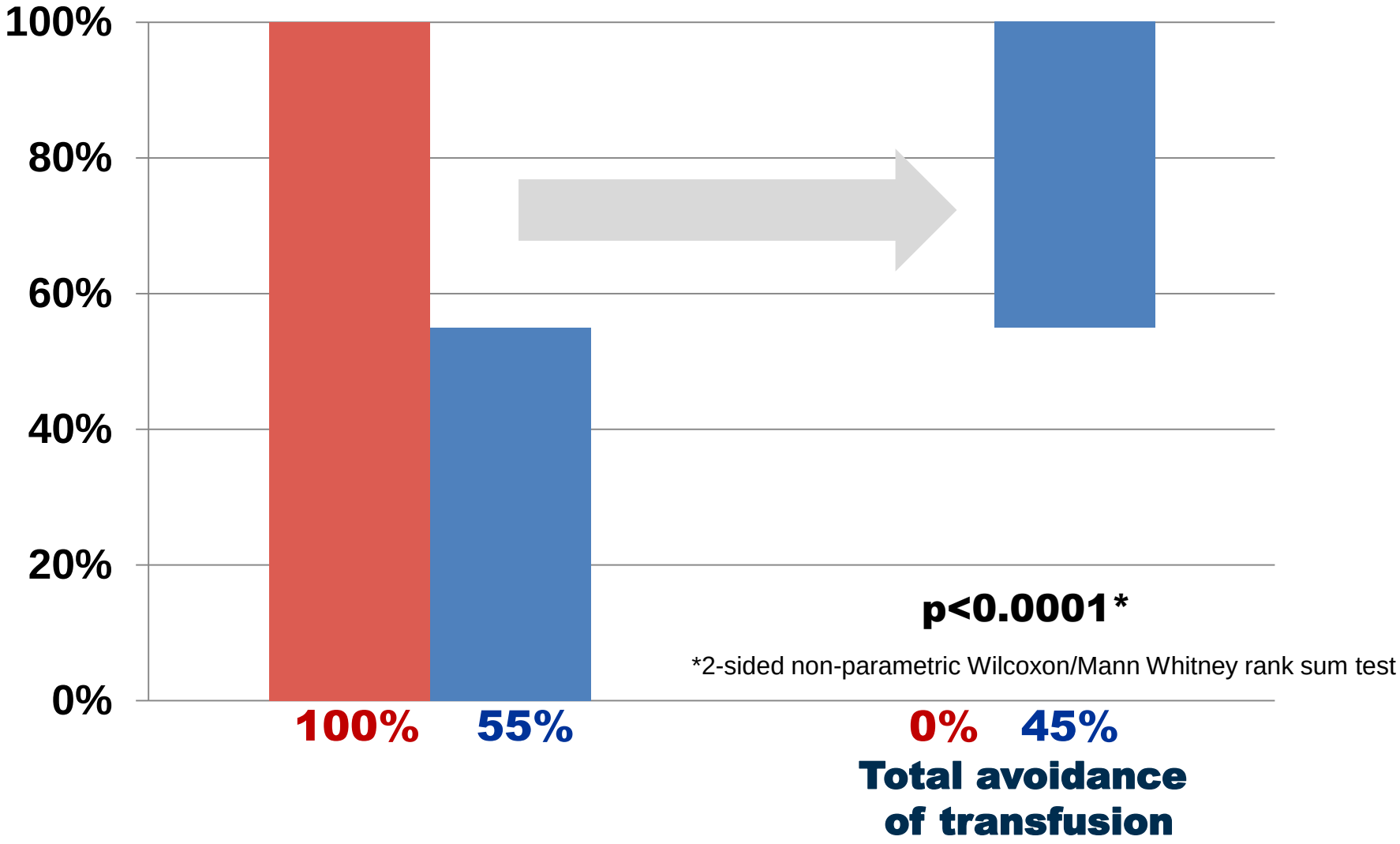

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Conclusions

ESA guidelines:
Management of severe perioperative bleeding
(publication anticitpated end of 2012)

Fibrinogen concentrate infusion guided by point-of-care viscoelastic coagulation monitoring may be used to reduce perioperative blood loss in complex cardiovascular surgery (level of evidence 1+; grade of recommendation B).