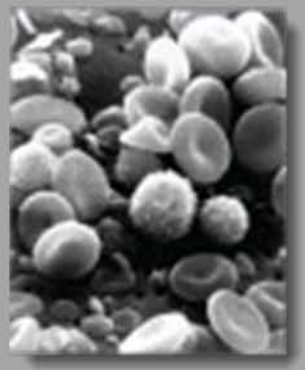


12th Annual Canadian Blood Services International Symposium

Plasma: Transfuse it, Fractionate it or Forget it?

Canadian Blood Services
it's in you to give

Controversies in Plasma Transfusion

"In a controversy, the instant we feel anger we have already ceased striving for the truth, and have begun striving for ourselves."

- Budda

Walter (Sunny) Dzik, MD
Co-Director, Blood Transfusion Service
Massachusetts General Hospital,
Boston, MA

3 Controversies regarding Plasma Therapy

#1 Prophylaxis prior to invasive procedures

#2 Treatment of VKA-related bleeding

#3 Up-front Treatment of coagulopathy of trauma

Case: A 56 yo man, chronic alcohol use, known HCV is admitted to the ICU.

BP 100/50; pulse 105; 37 C (low dose pressors)

Confused. Ascites, edema, splenomegaly.

A laparoscopic liver biopsy is required for OLTx.

Hb = 9.0; WBC=3,400; Plts = 45,000

INR = 1.9; aPTT= 44; Fibrinogen= 130; D-dimer 3+

You are consulted:

Based on his lab tests, how much FFP should be given to correct the coagulopathy prior to laparoscopic biopsy ?

Select ONE of the following for this patient

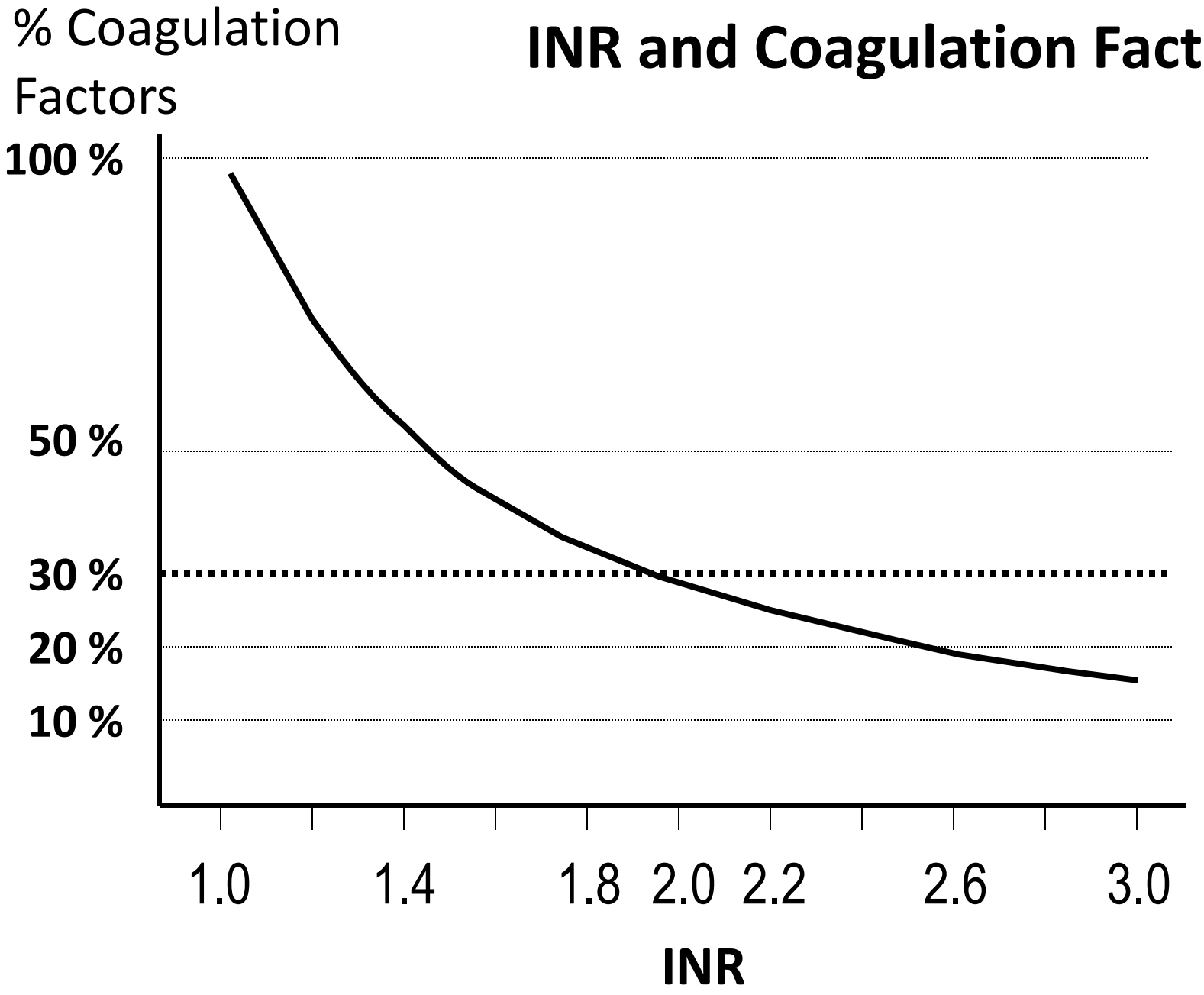
A. Pre-biopsy: 2- 4 units FFP

B. Pre-biopsy: No role for pre-procedure FFP;
If he bleeds, give 4-factor PCC @ 25-50 IU/kg.

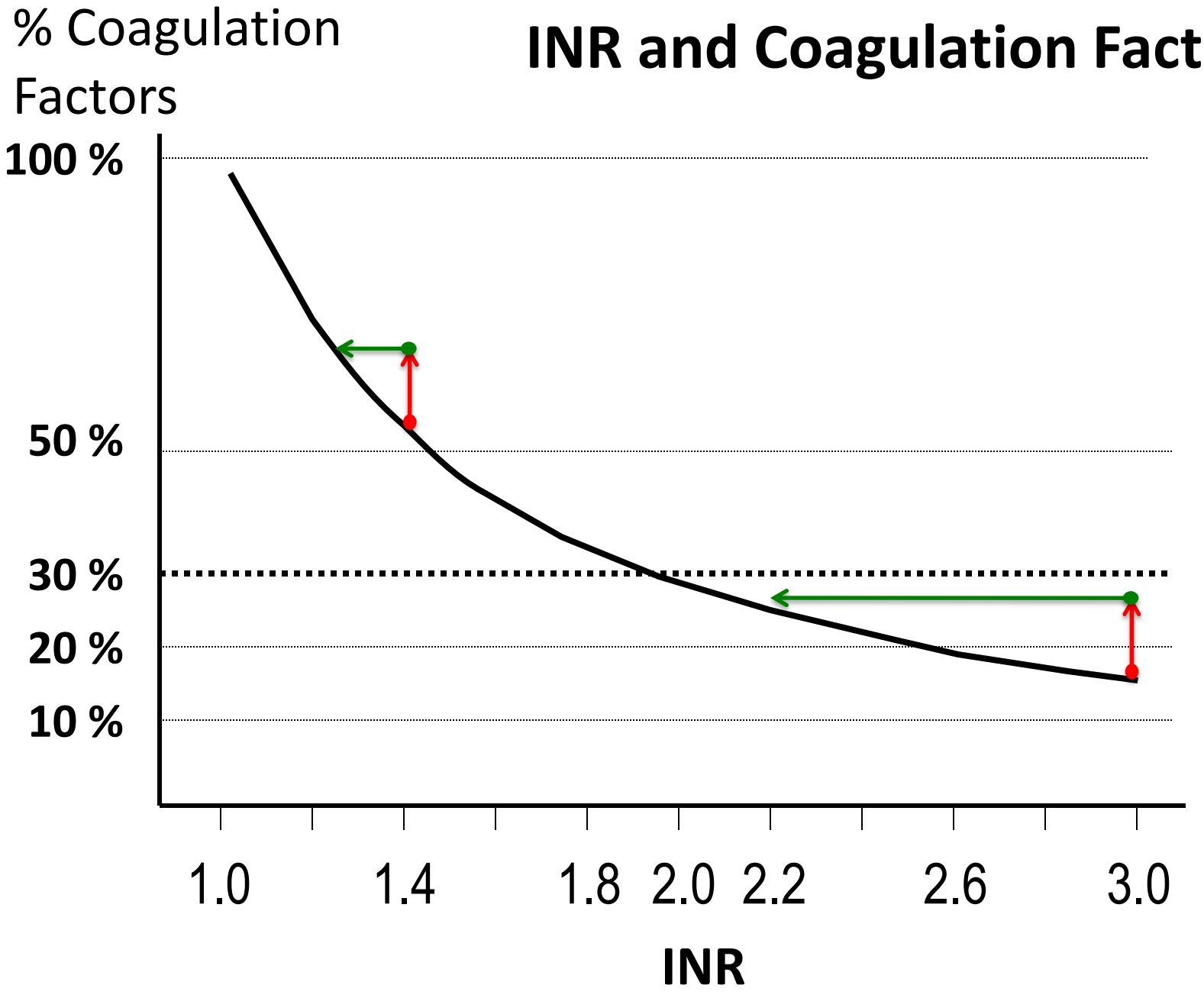
C. Pre-biopsy: No role for pre-procedure FFP;
No role for 4-factor PCC for bleeding

D. Pre-biopsy: 2 – 4 units FFP;
Use r7a for bleeding.

INR and Coagulation Factors



INR and Coagulation Factors



Toward Rational FFP Transfusion:
Effect on Coagulation Test Results

- Retrospective cohorts at U of Oklahoma.

- Test group:

140 adults receive 236 transfusions FFP

39 pediatric patients receive 59 transfusions FFP

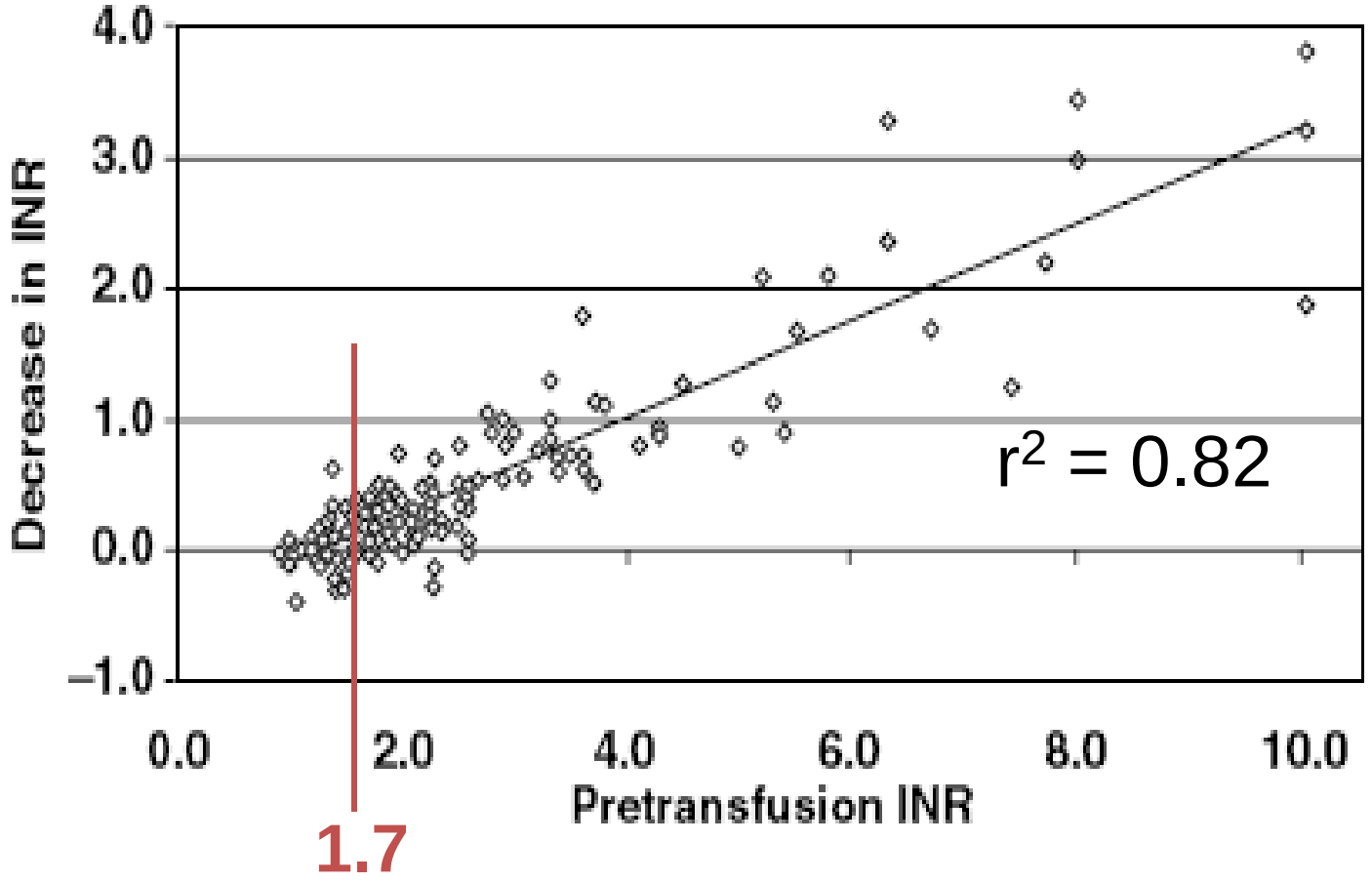
- Control group:

Patients with INR < 1.6 who were not transfused

All patients get follow-up INR @ ~ 4-8 hrs

Holland and Brooks, Am J Clin Path 2006; 126: 133.

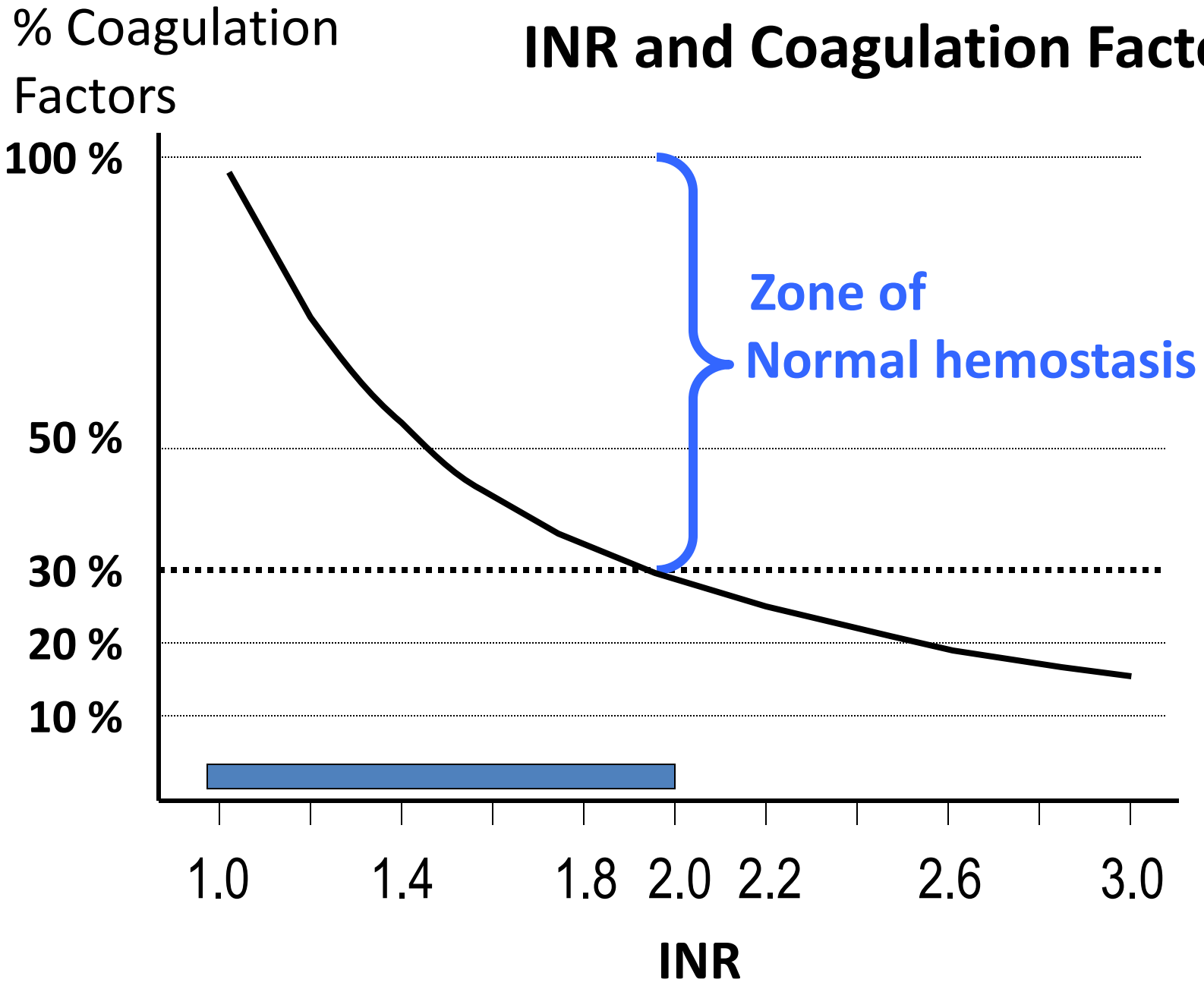
INR Change per 2 units FFP



Decrease = 0.37 [pre-Tx INR] – 0.47

Holland and Brooks, Am J Clin Path 2006; 126: 133.

INR and Coagulation Factors



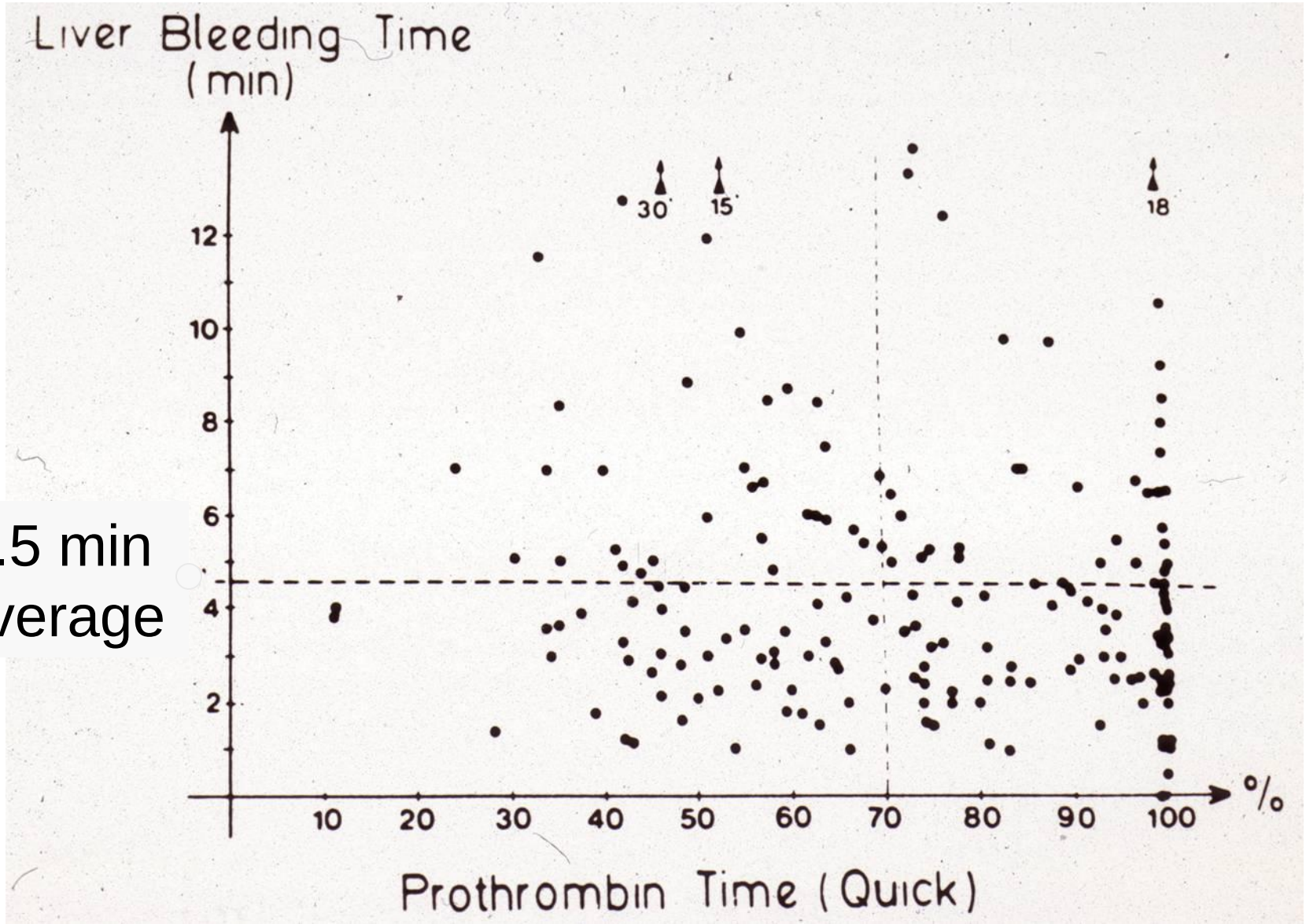
Closed Liver Biopsy: Abnormal Coags

- 200 patients: liver biopsy
- All had abnormal coags
- No pre-procedure FFP

- Insert Laparoscope.. biopsy..watch liver bleed !
- Measure the time the liver bleeds

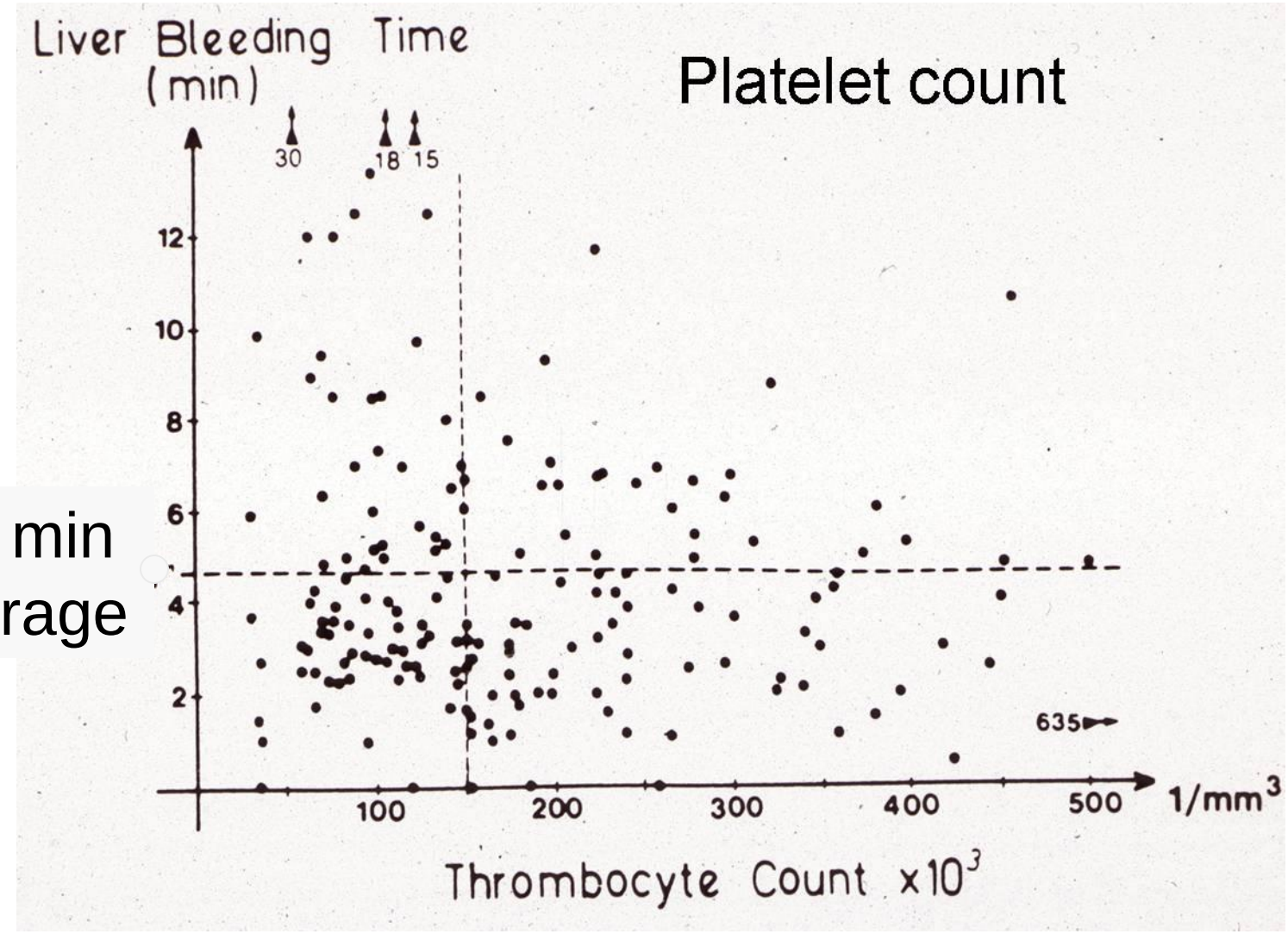
Ewe. Digestive Dis Sciences 1981; 26: 388

Coagulation time (% activity)



4.5 min
Average

Ewe. Digestive Dis Sciences 1981; 26: 388



4.5 min
Average

No correlation between pre-biopsy Platelet count or PT and duration of bleeding after liver biopsy.

Ewe. Digestive Dis Sciences 1981; 26: 388

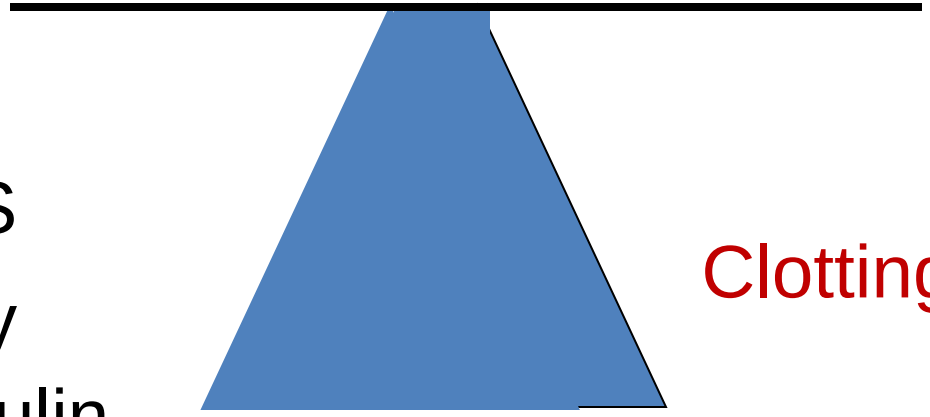
Retrospective Studies of INR Prior to Liver Biopsy

Procedure	Reference	"N"	Outcome	Comment
Liver BX	McGill. Gastro 1990;99:1390	9212	Clinical bleeding only	PT/PTT not predictive
Liver BX laparoscopic	Ewe. Dig Dis Sci 1981;26:388	200	Direct observation of liver bleed time	PT/PTT not predictive
Liver BX	Mcvay. Am J Clin Path 1990; 94:747	177	Hematocrit fall; RBC transfusion	PT/PTT not predictive
Liver BX	Boberg. Thromb Haemost 99;81:378	219	Hg fall > 2 g/dL	PT/PTT not predictive
Liver BX	Carturelli. Liver 1993;13:270	85	Ultrasound	PT/PTT not predictive
Liver BX laparoscopic	Dillon. J Gastro Hepatol 1994;9:269	51	Direct observation of liver bleed time	PT/PTT not predictive
Liver BX	Makris. Br J Heme 1992;81:51 (absr)	104	CT scan	PT/PTT not predictive
Liver Bx	Terjung. Digestion 2003; 67: 138-45	629	Hg fall > 2 g/dL; Abnl ultrasound	PT/PTT not predictive

Normally, a *stable balance*...

Anti-coagulation

Pro-coagulation



Protein C & S activated by Thrombomodulin

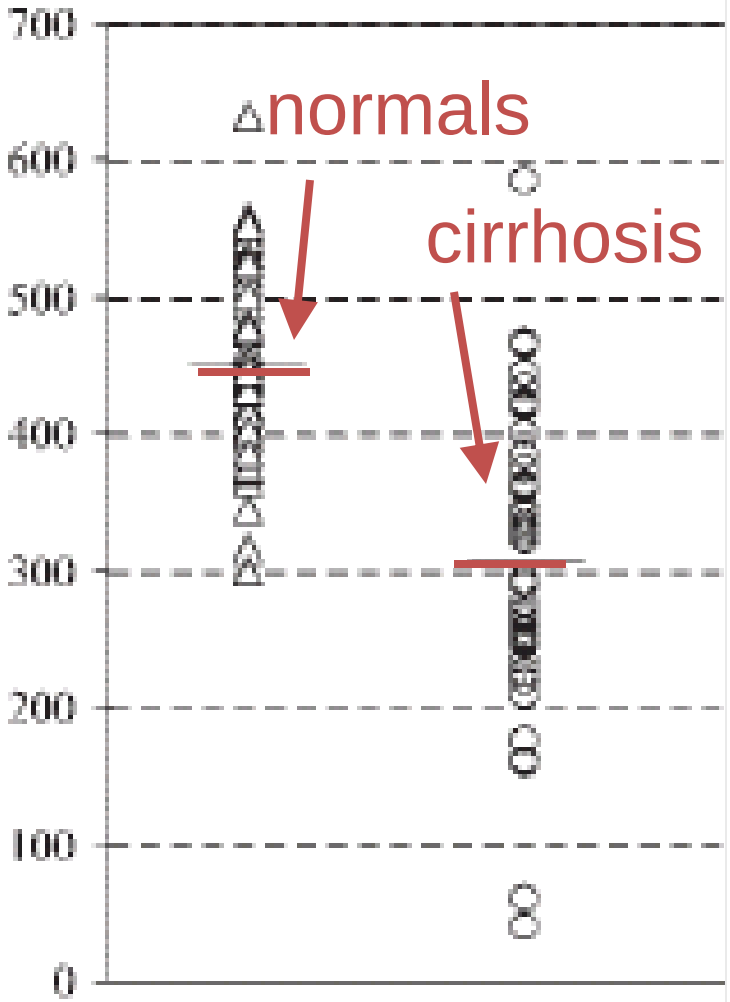
Clotting factors

...but Lab Tests (INR, aPTT) only examine 'pro-coagulants'

Thrombin generation

Endogenous thrombin potential

(Units/min)



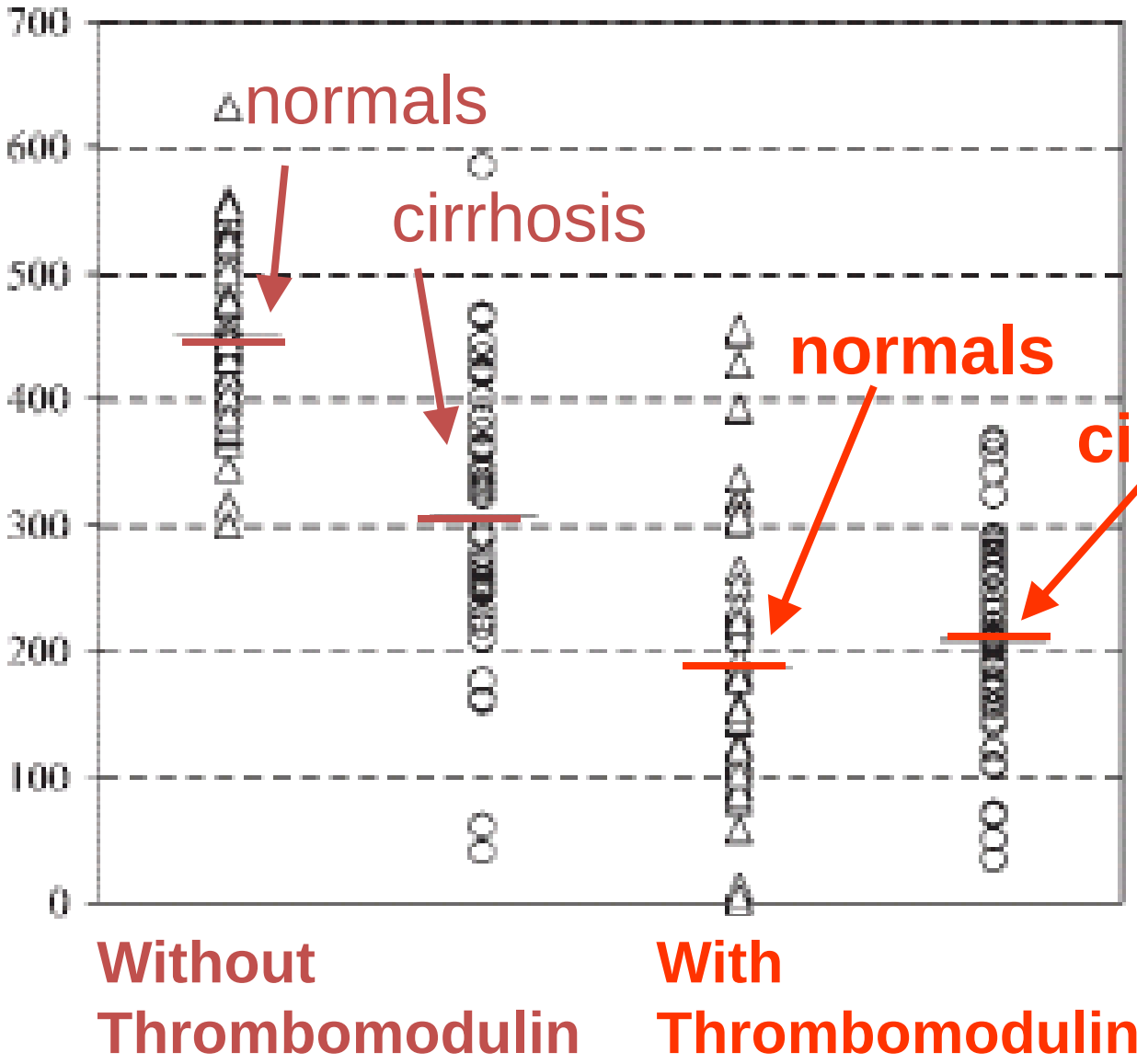
Without Thrombomodulin

Pier Mannucci Hepatology 2005; 41: 553-558

Thrombin generation with TM is normal in cirrhosis

Endogenous thrombin potential

(Units/min)



Pier Mannucci Hepatology 2005; 41: 553-558

Defects in Liver Disease:

Unstable, re-balanced hemostasis

Pro-coagulation

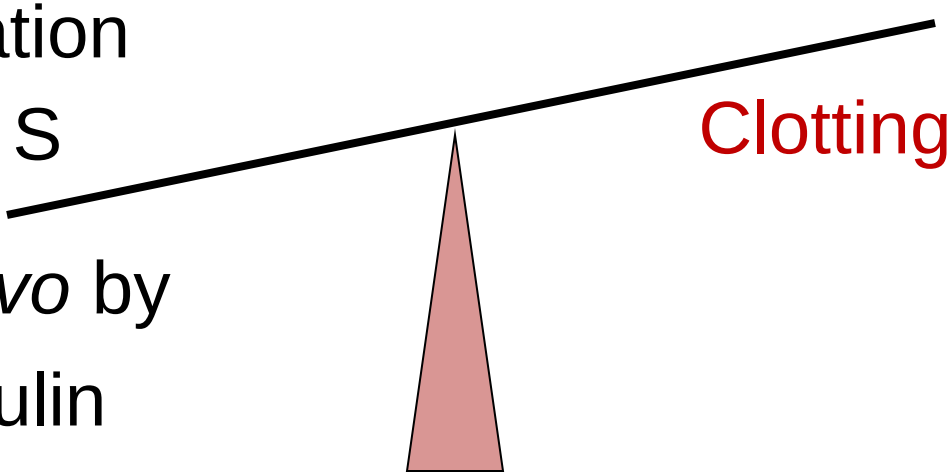
Anti-coagulation

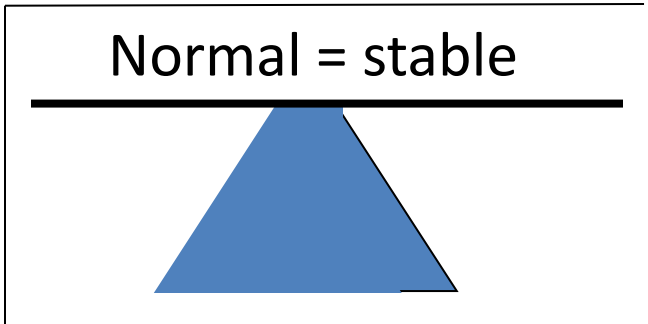
Protein C & S

Clotting factors

activated *in vivo* by

Thrombomodulin





Pier Mannucci Hepatology 2005; 41: 553-558

FFP prior to procedures: ICU

- Prospective, randomized multi-center trial
- ICU patients, INR 1.5-3.0:
  - FFP 12 mL/kg *versus* No-Rx
  - Central venous line, trach, chest tube, abscess drainage
- Endpoints:
  - INR "correction"
  - Lung injury
  - Post-procedure bleeding outcomes

Muller MC et al. Transfusion 2014 (epub ahead of print).

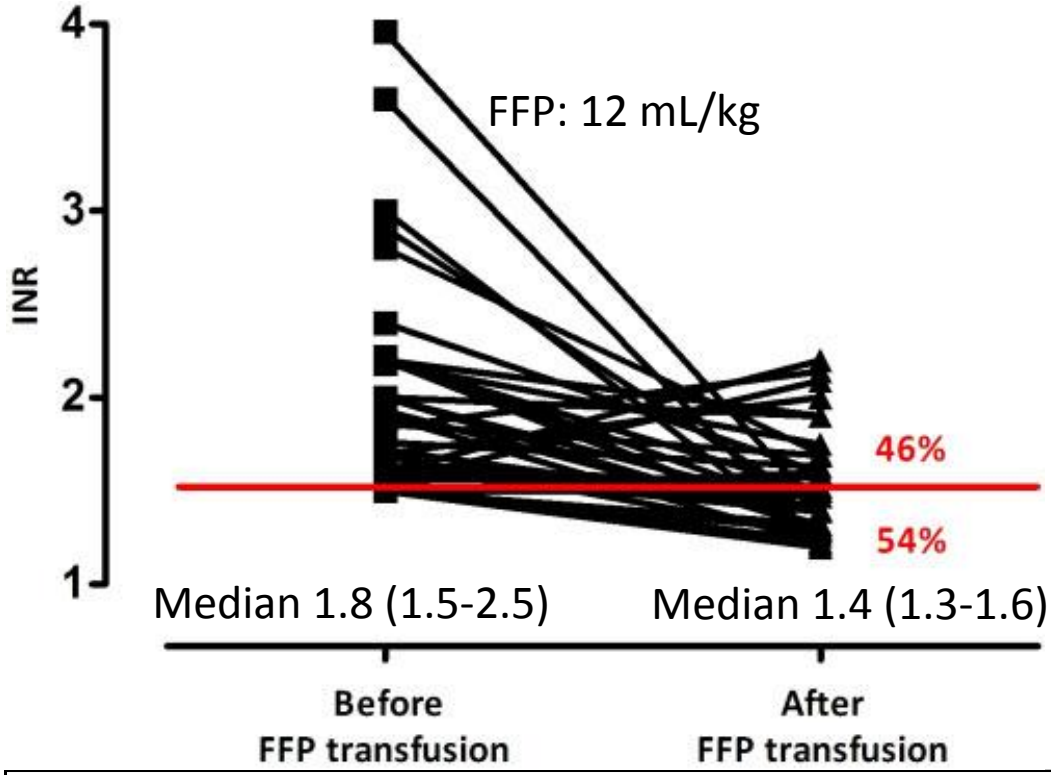
FFP Prophylaxis in ICU: Study Design

- Exclusions:
  - Overt bleeding (1.6 Hb drop)
  - Hemodynamic instability
  - Platelets < 30,000/uL
  - VKA
  - Activated protein C
  - Abciximab
  - Tirofiban, ticlopidine
  - PCC, Heparin
  - History of factor deficiency
  - History of bleeding disorder

- Major Bleeding:
  - Hb drop > 2 g/dL
  - >= 2 RBCs
  - > 20 mmHg systolic
  - > 20 heart rate
  - Need intervention
- Minor Bleeding:
  - Increase hematoma
  - Oozing at site

Muller MC et al. Transfusion 2014 (epub ahead of print).

FFP prior to procedures: Results



INR: 1.8 → 1.4

TABLE 3. Bleeding rates in randomized patients

	FFP transfusion (n = 38)	No FFP transfusion (n = 38)
Fatal bleeding	0	0
Major bleeding	0	1
Minor bleeding	8	5
No bleeding	30	32

* Data are expressed as number.

No effect of FFP

38 in each arm

Muller MC et al. Transfusion 2014 (epub ahead of print).

Take home messages...

- Coagulation tests were NEVER designed to identify patients at increased risk of bleeding following a procedure.
- Mild-moderate prolongations of the INR do not indicate a clinical hemostatic defect and are NOT CORRECTED by FFP.
- No clinical study has ever shown that prophylactic transfusions, triggered by a laboratory test, achieve benefit.

Controversy #2: Treatment of bleeding related to vitamin-K antagonists

True or False ?

1. RCTs in Europe and Canada demonstrate that PCCs are superior to FFP for hemostasis in the setting bleeding due to vitamin-K antagonists.

2. When used for the emergency treatment of vitamin K antagonists, 4-factor PCCs carry at least a 5 fold lower rate of side-effects than FFP.

CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Executive Summary

CHEST 2012; 141(2)(Suppl):7S–47S

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

*Gordon H. Guyatt, MD, FCCP; Elie A. Akl, MD, PhD, MPH; Mark Crowther, MD; David D. Gutterman, MD, FCCP; Holger J. Schünemann, MD, PhD, FCCP; for the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel**

9.3 Treatment of Anticoagulant-Related Bleeding

9.3. For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with four-factor prothrombin complex concentrate rather than with plasma. (Grade 2C)

4 factor PCCs vs FFP

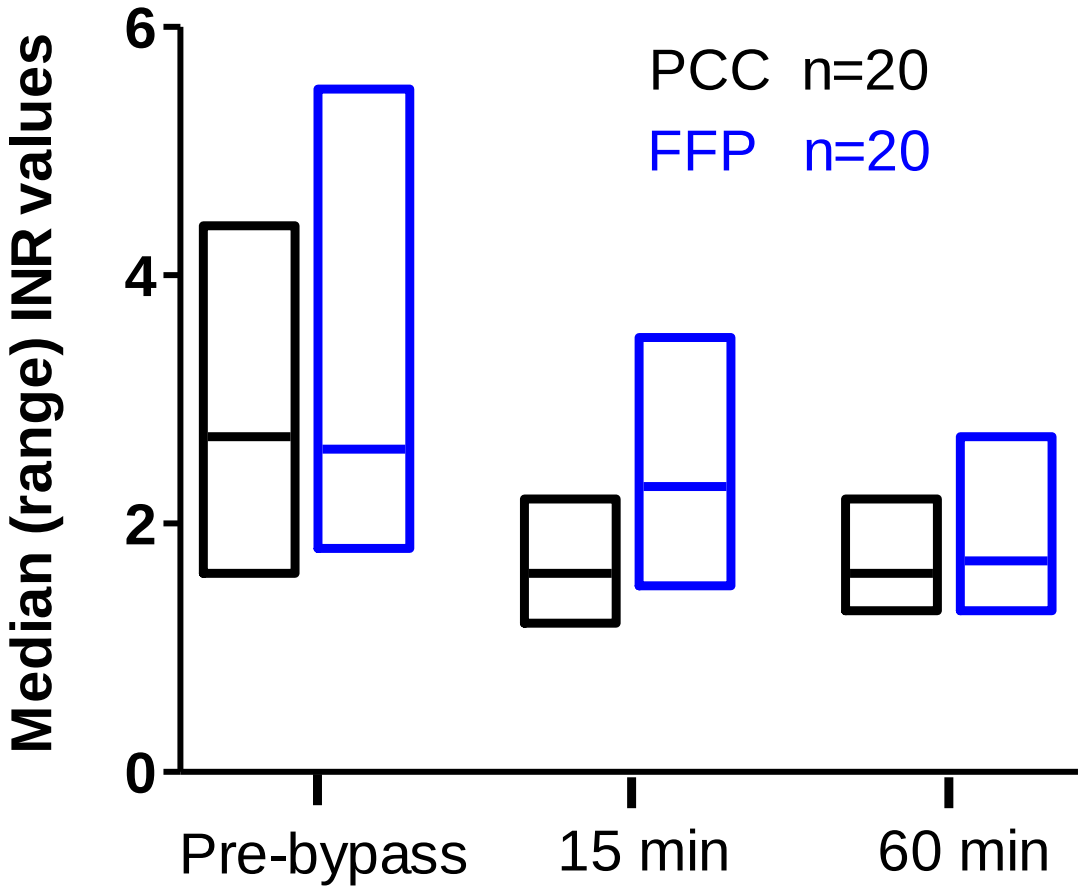
Author	Design	Sample size	Patients	Endpoint
Fredriksson 1992	Retrospective	PCC n=10 FFP n=7	ICH	Δ INR
Markis 1997	Retrospective	PCC n=29 FFP n=12	ICH	Δ INR
Cartmill 2000	Retrospective	PCC n=6 FFP n=6	ICH	Δ INR
Demeyere 2010	Prospective, randomized	PCC n=18 FFP n=20	Cardiac surgery	Δ INR
Sarode 2013	Prospective, randomized	PCC n=98 FFP n=104	E.R.	Hemostasis Δ INR

40 patients: cardiac surgery

*All on warfarin.

*Randomized: FFP vs 4-factor PCC (Cofact)

* No vitamin K.



FFP: 2 units (400 mL) at start of bypass plus 400 mL at end.

PCC: 40 mL at start of bypass plus 40 mL at end.

FFP: 400 mL x 2 = ~ 800 IU units of each factor.

PCC: 565 IU/mL x 40 x 2 = 45,200 IU units of each factor.

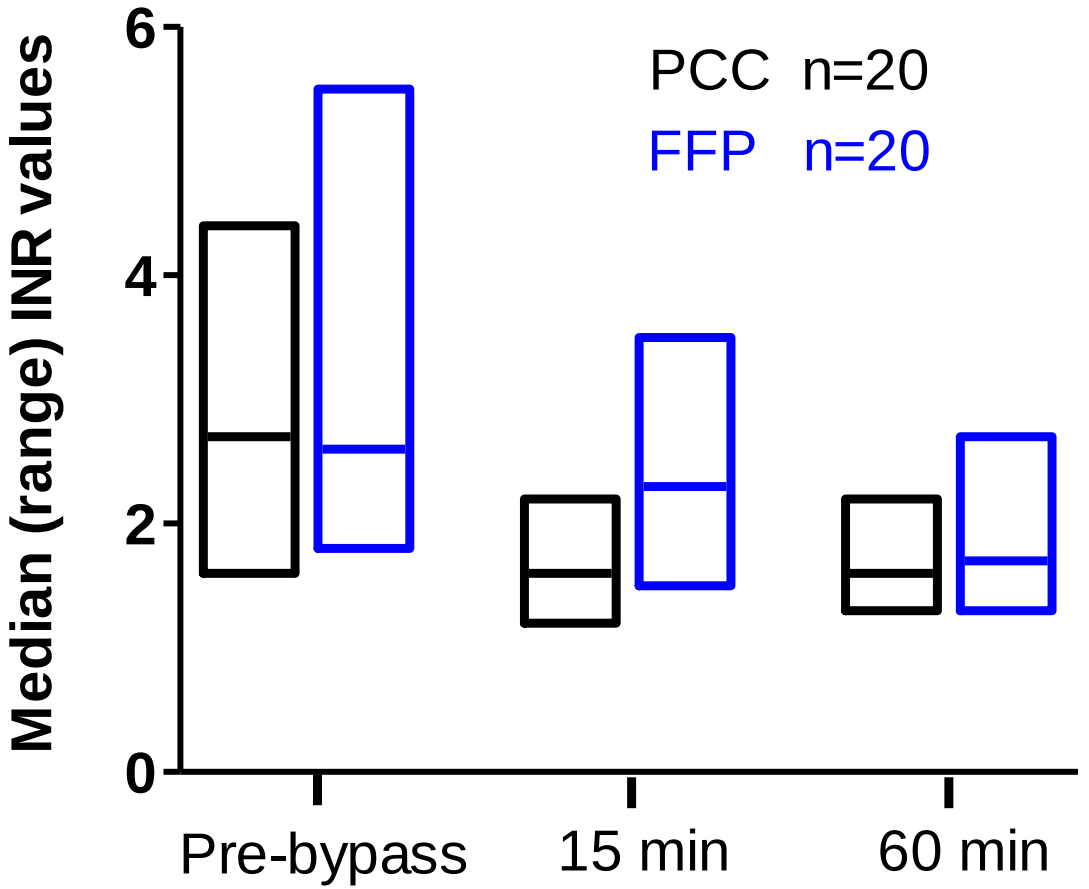
Demeyere et al. Vox Sanguinis 2010; 99: 251–260

40 patients:
cardiac surgery

*All on warfarin.

*Randomized: FFP vs 4-factor PCC (Cofact)

* No vitamin K.



Chest Tube Drainage			
	PCC	FFP	p-value
1 hr	67 ±46	97 ±54	ns
4 hr	133 ±73	163 ±89	ns
24 hr	439 ±247	471 ±294	ns

4-factor PCC versus FFP for Coumadin Reversal

Company-sponsored Prospective RCT

200 patients on coumadin with acute bleeds.

All receive vitamin K.

INR	PCC N = 98	FFP N = 104
2 to < 4	25 IU/kg	10 mL/kg
4 to < 6	35	12
> 6	50	15

	PCC n= 98	FFP n= 104
Age	69.8 (29 – 96)	69.8 (26 - 92)
Baseline INR	3.9	3.6
Non-visible GI	55	58
Visible	16	21
Intracranial	12	12
Other	15	13

Sarode et al, Circulation 2013;128(11):1234-43.

Results: 4 factor PCC vs FFP

INR < 1.3 at 30 minutes

PCC was superior to FFP for rapid correction of laboratory test.

PCC N = 98	**FFP** N = 104	PCC - FFP
62% (53 – 72%)	10 % (4 – 15%)	53 % (40 – 66%)

Hemostatic Efficacy at 24 hours

PCC was *"not inferior"* to FFP for hemostatic efficacy.

PCC N = 98	**FFP** N = 104	PCC - FFP
71	68	--
72% (64 – 81%)	65 % (56 – 74%)	7.1 % (-6 – 20%)

Sarode et al, Circulation 2013;128(11):1234-43.

Adverse Events

	PCC N = 103	**FFP** N = 109	p-value
Any SAE	32	26	n.s.
Thrombosis	8	6	n.s.
Fluid overload	5	14	0.054
Death at 45 days	10	5	0.18

Kcentra licensed by FDA for warfarin reversal in May 2013.

Controversy #2:
FFP for reversal of VKA-related bleeding

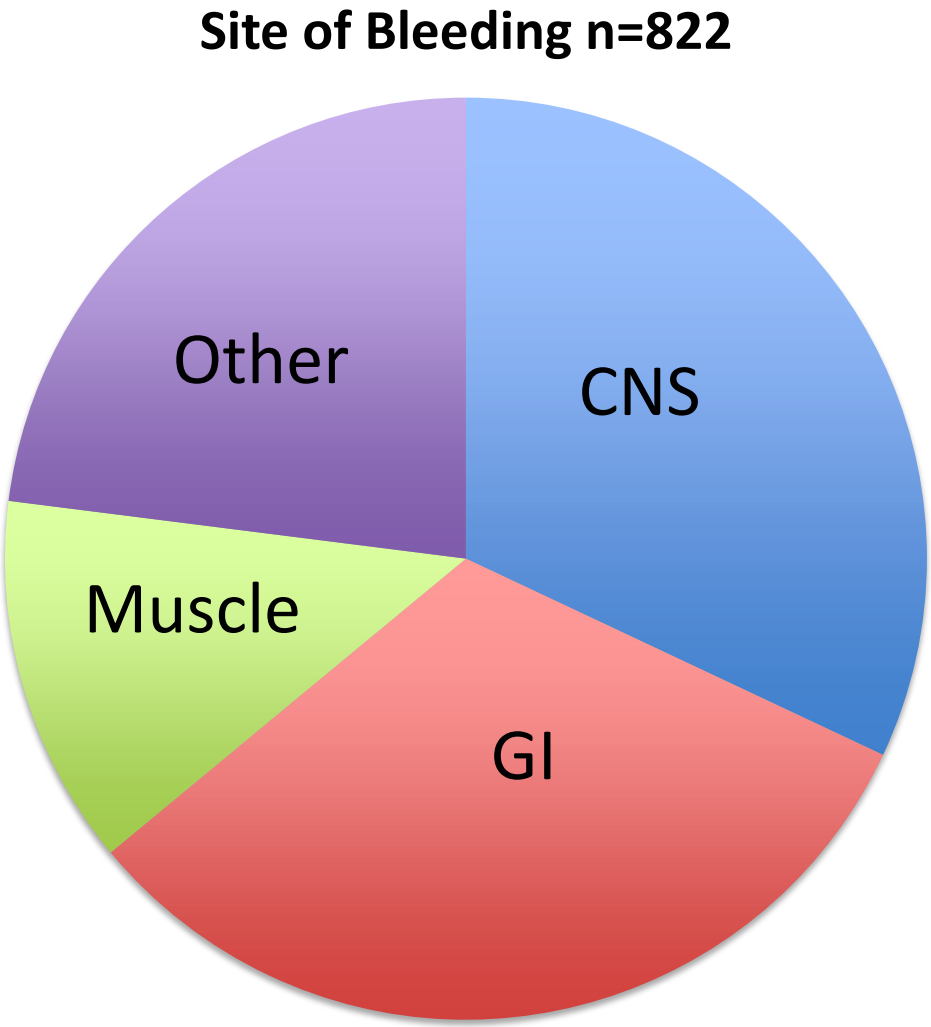
- In some areas, 4-factor PCCs have virtually replaced FFP for Rx of VKA-related bleeding.
- This practice change is largely driven by data on INR correction rate.
- Canadian Society pays pharmaceutical houses for this practice change.
- Is there evidence of clinical benefit to patients ?

VKA-associated bleeding: 44 E.R.'s (France)

822 VKA-treated patients with severe hemorrhage.

Overall cohort:
7-day mortality was 13%

CNS cohort:
7-day mortality was 33%



Tazarourte K et al. Critical Care 2014:18; R81

CNS bleeds: 4-factor PCC vs FFP
Does 4-factor PCC improve outcomes?

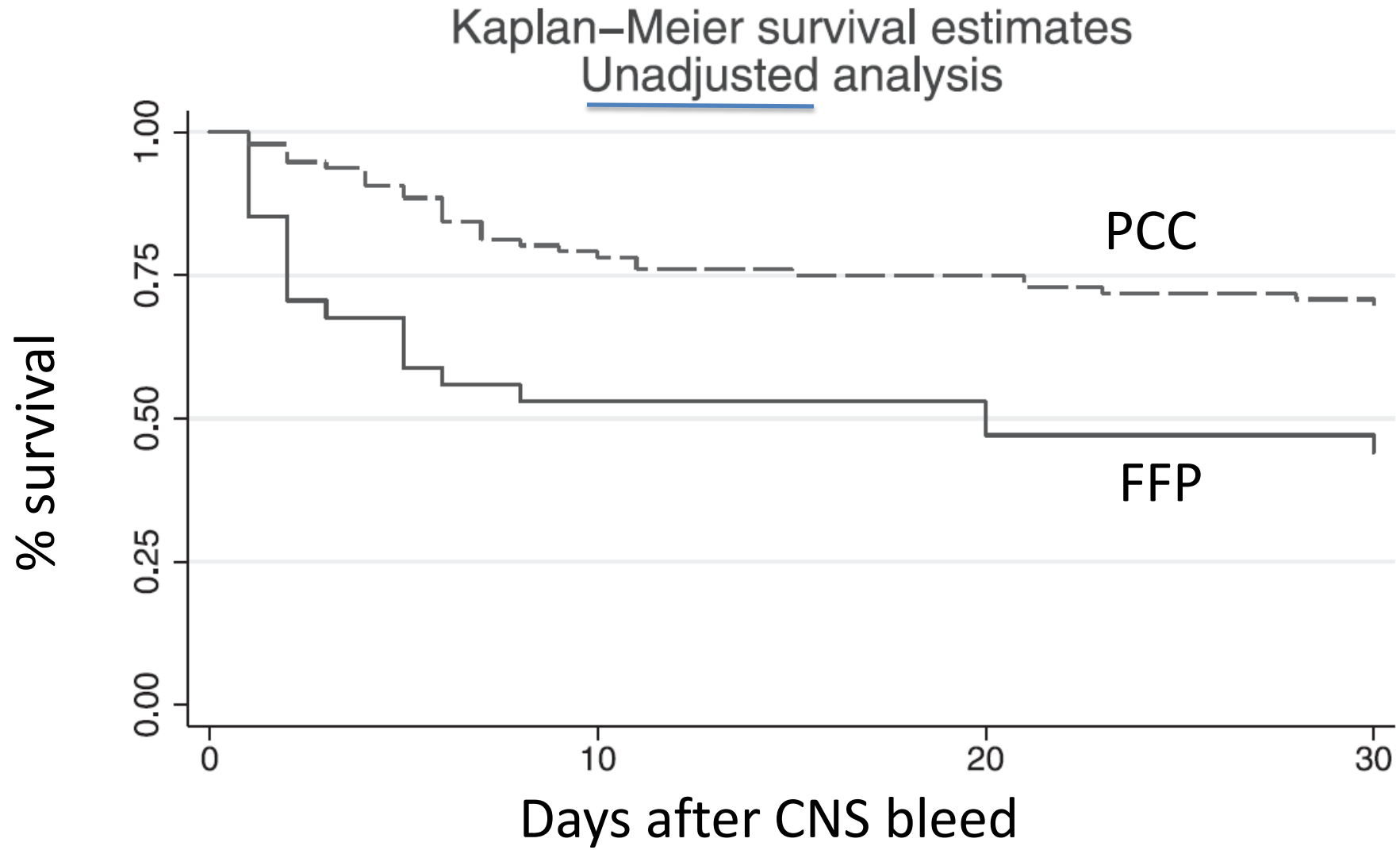
- Retrospective multicenter study (3 nations)
- N = 135 with VKA-associated intra-cranial bleeds.
- Comparison of outcomes in:
  - Canada (FFP and vit K were used)
  - Netherlands & Sweden (4 factor and vit K were used)
- Factors affecting outcome were collected to adjust comparisons.
- Endpoint: 30 day all-cause mortality.

Majeed A et al. Thromb Haemostasis 2014; 111.233-239.

Clinical outcomes in CNS bleeding: 4-factor PCC vs FFP

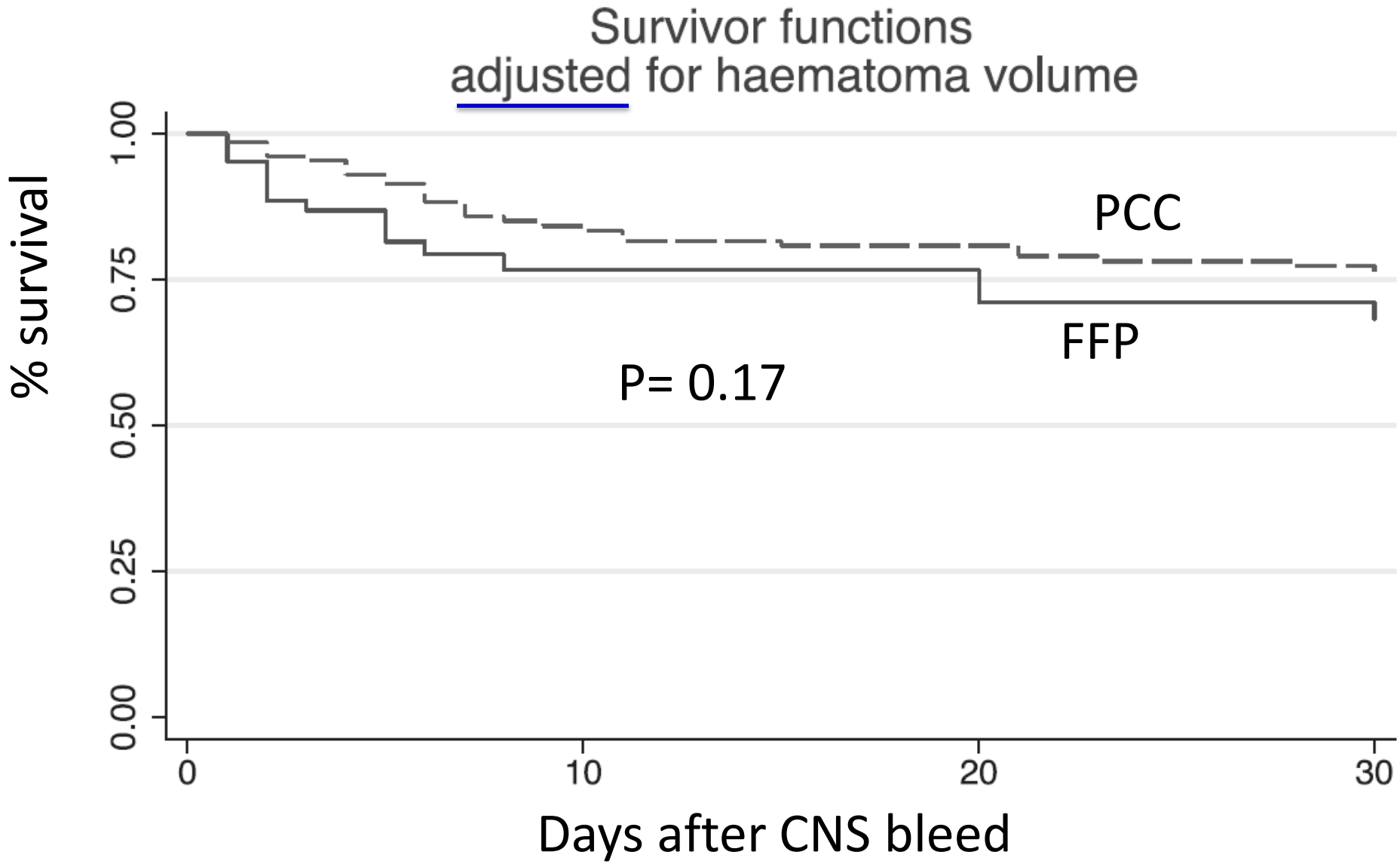
	4-factor PCC n=100	FFP n=35	P-value
Age (mean)	73.4	72.8	p=ns
Atrial fibrillation	61%	51%	p=ns
Presenting INR	3.0 (1.5-9.3)	2.9 (1.9-7.7)	p=ns
Anti-platelet Rx	7%	26%	0.008
Diabetes	18%	40%	0.008
Intra-ventricular bleed	32%	60%	0.004
Initial bleed volume cm^3	36	64	0.021
Time from symptoms to infusion (hours)	4 (2.1 – 8)	15.5 (8.5-24.5)	<0.001

Majeed A et al. Thromb Haemostasis 2014; 111.233-239.



Majeed A et al. Thromb Haemostasis 2014; 111.233-239.

PCC's provided no survival advantage



Majeed A et al. Thromb Haemostasis 2014; 111.233-239.

Adjusting for other factors did not change conclusion

Step	Covariates included	Odds ratio	p-value
0	No adjustment	0.4 (0.18-0.87)	0.021
1	Volume of bleed	0.55 (0.23-1.30)	0.17
2	Volume of bleed Location of bleed	0.48 (0.19-1.22)	0.12
3	Volume of bleed Location of bleed Age	0.49 (0.19-1.24)	0.13

"In summary, although the reversal of VKA coagulopathy with PCC in intra-cerebral hemorrhage is more rapid, this treatment does not seem to reduce the 30-day all cause mortality compared to plasma."

Majeed A et al. Thromb Haemostasis 2014; 111.233-239.

PCC's: an expensive form of FFP ?

Off-label use ….

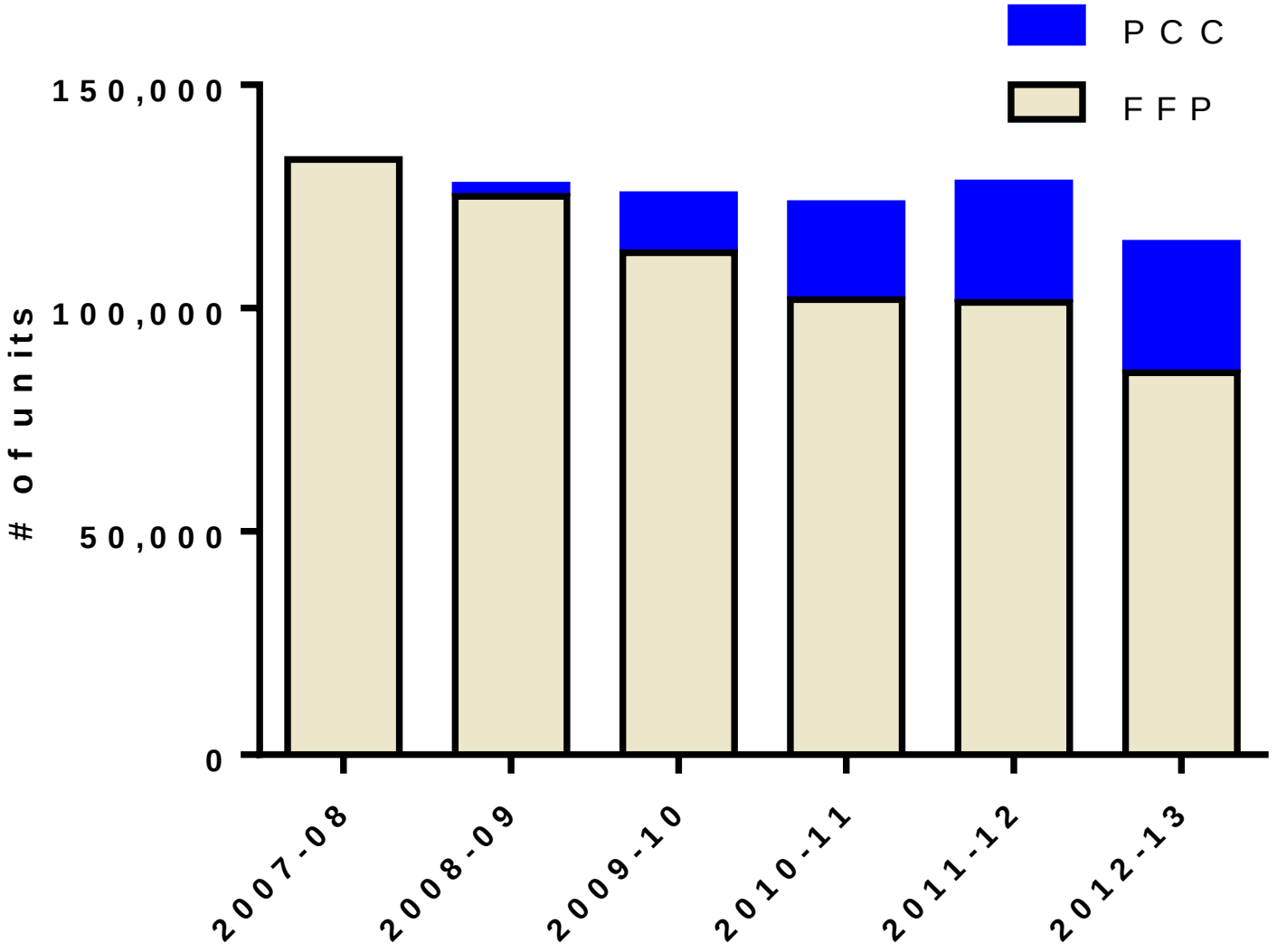
- Single center review (Montreal)
- Patients with advance liver disease, n=51
- 80% cirrhosis
- PCC given for bleeding (55%) or prior to procedure (40%)
- INR corrected to < 1.3 in only 10% of patients
- 6% of patients had thromboembolic events

Conclusion:

PCC is ***not indicated*** for control of bleeding in liver disease.

Richard-Carpentier et al. ASH Abstract #2400 in 2013.

FFP market share in Canada



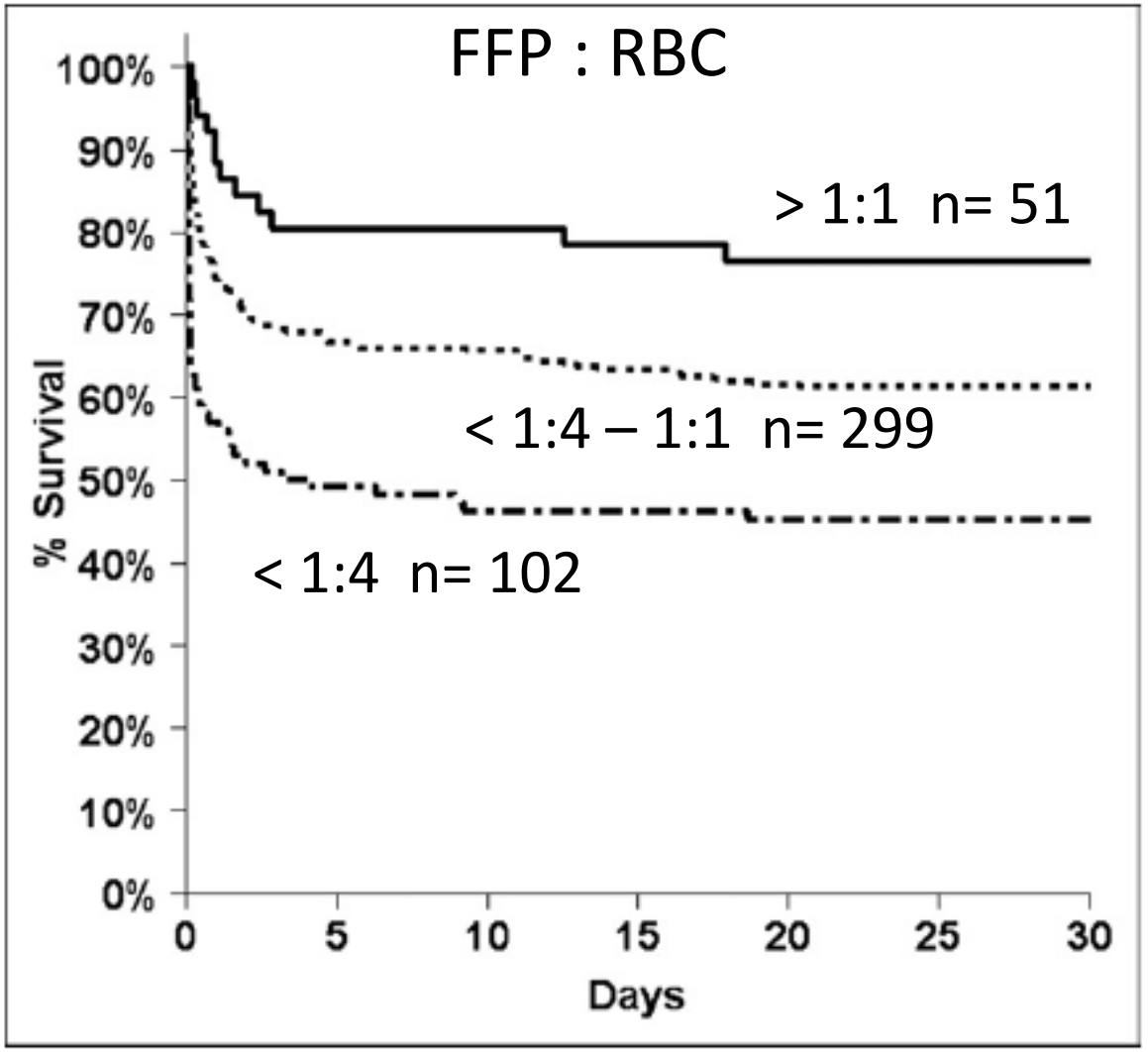
Unpublished information, kindly provided by Dr Peter H Pinkerton

Controversy #3: Aggressive use of FFP in trauma and rapid bleeding.

Photo credit: N.Y. Times, Nov 6, 2007

Does a high ratio of FFP to RBC improve survival ?

Retrospective review of 452 patients receiving >10 units RBCs in 24 hours.



Survival

Zink KA, Am J Surg 2009; 297: 565

Reducing the FFP to RBC ratio: no effect in the UK

2012 retrospective from Royal London Hospital: before vs after use of more aggressive massive hemorrhage protocol*

Patients receiving > 10 RBCs	2007-08 (n=40)	2008-09 (n=56)	p-value
Age	37 (25-51)	34 (26-60)	0.33
ISS	32 (9 – 54)	29 (22-41)	0.72
Admit to ICU	25 (63%)	37 (66%)	0.66
FFP:RBC	1:3	1:2	0.003
Mortality ?			

* Did NOT include routine use of anti-fibrinolytics

Khan S et al. Injury Nov 2012 epub ahead of print.

Reducing the FFP to RBC ratio: no effect in the UK

2012 retrospective from Royal London Hospital: before vs after use of more aggressive massive hemorrhage protocol*

Patients receiving > 10 RBCs	2007-08 (n=40)	2008-09 (n=56)	p-value
Age	37 (25-51)	34 (26-60)	0.33
ISS	32 (9 – 54)	29 (22-41)	0.72
Admit to ICU	25 (63%)	37 (66%)	0.66
FFP:RBC	1:3	1:2	0.003
Mortality	22 (55%)	32 (57%)	0.84

* Did NOT include routine use of anti-fibrinolytics

Khan S et al. Injury Nov 2012 epub ahead of print.

Spill-over of 1:1 ratios to non-trauma surgery

- Retrospective review, 2008-2012.
- All MGH surgical patients with ≥ 20 RBCs in 24 hrs.
- Low ratio: < 1 FFP for each 1.5 RBCs
- High ratio: ≥ 1 FFP for each 1.5 RBCs

Finding: n=265 received ≥ 20 RBCs in 24 hrs

Trauma = 38 68% got high ratio

Non-trauma= 227 79% got high ratio

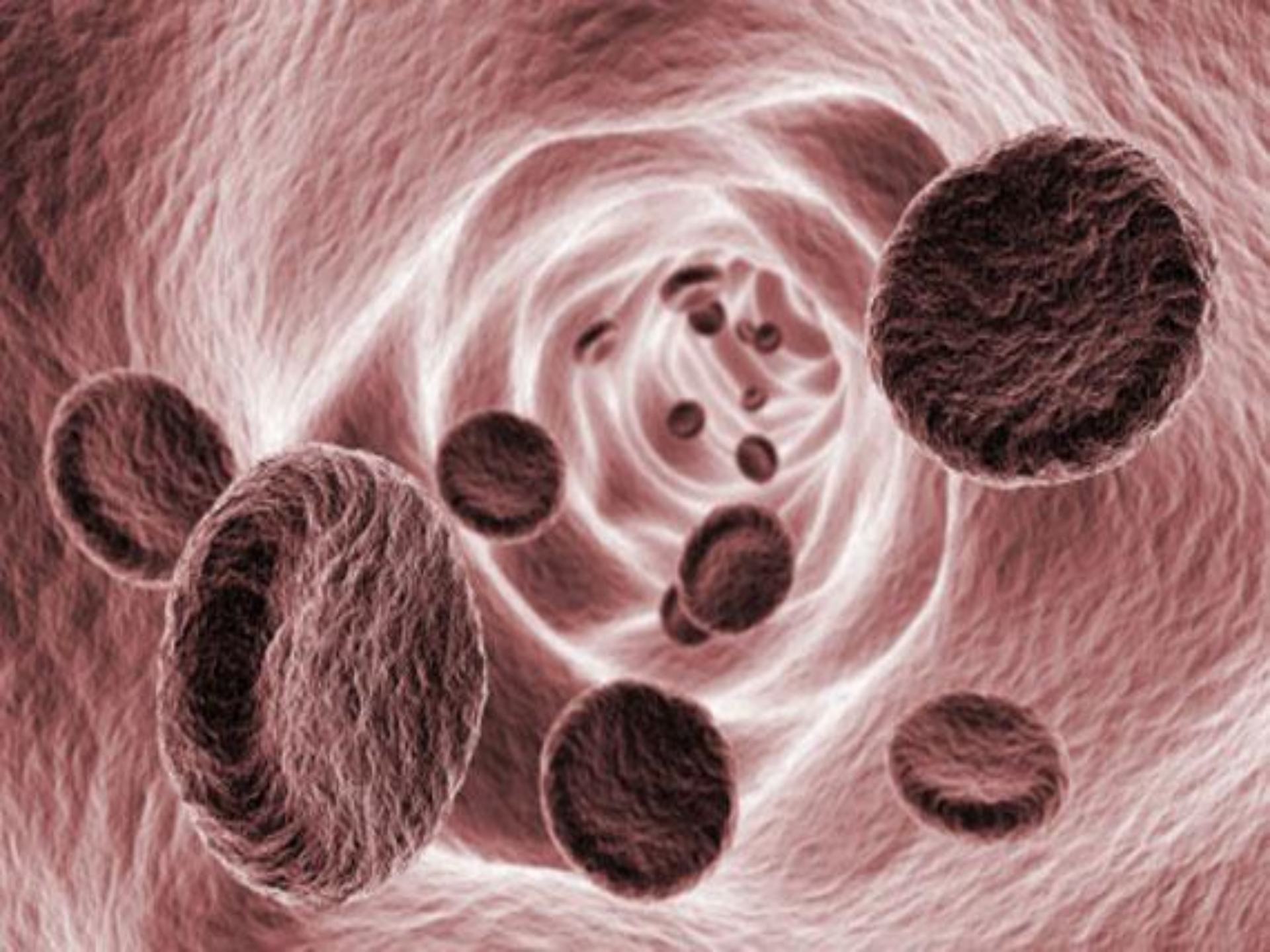
Non-trauma:

General surgery, cardiac, ortho, transplant.

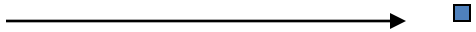
Spill-over of 1:1 ratios to non-trauma surgery: Outcomes

Units per patient	Low FFP:PRBC ratio (N=47) Median (Q1-Q3)	High FFP:PRBC ratio (N=180) Median (Q1-Q3)	p-value
PRBC	34.3 (25.5 – 50)	32.2 (24 – 43.7)	0.277
FFP	20 (13 – 26.5)	30 (22.5 – 42)	0.001
Platelets	36 (18 – 69)	42 (24 – 72)	0.194
Cryoprecipitate	10 (2 – 20)	10 (0 – 20)	0.714

	Low FFP:PRBC ratio (N=47)	High FFP:PRBC ratio (N=180)	p-value
Survival N (%)	28 (59.6)	111 (61.7)	0.79
LOS (mean ± SD)	22.8 ± 24.2	25.3 ± 27.6	0.4
Survivors' LOS	32.6 ± 23.7	31.6 ± 23.4	0.4
Discharge home N (%)	10 (21.3)	64 (35.6)	0.79
Days from transfusion to death (median, IQR)	1 (0 – 3)	2 (0 – 5.5)	0.31



What is the largest surface in the body ?

Skin 1.5-2 m^2 

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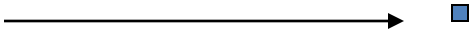
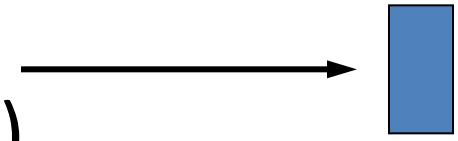
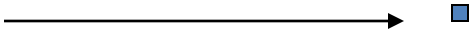
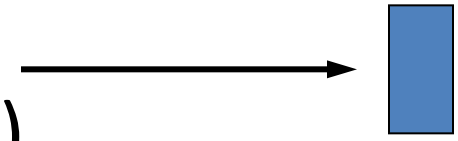
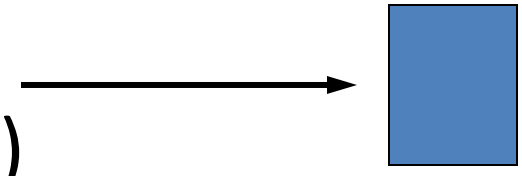
Skin 1.5-2 m^2 

Alveoli 100 m^2
(< 1 tennis court) 

What is the largest surface in the body ?

Skin 1.5-2 m^2 

Alveoli 100 m^2
(< 1 tennis court) 

Gut 250 m^2
(> 1 tennis court) 

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Skin 1.5-2 m^2

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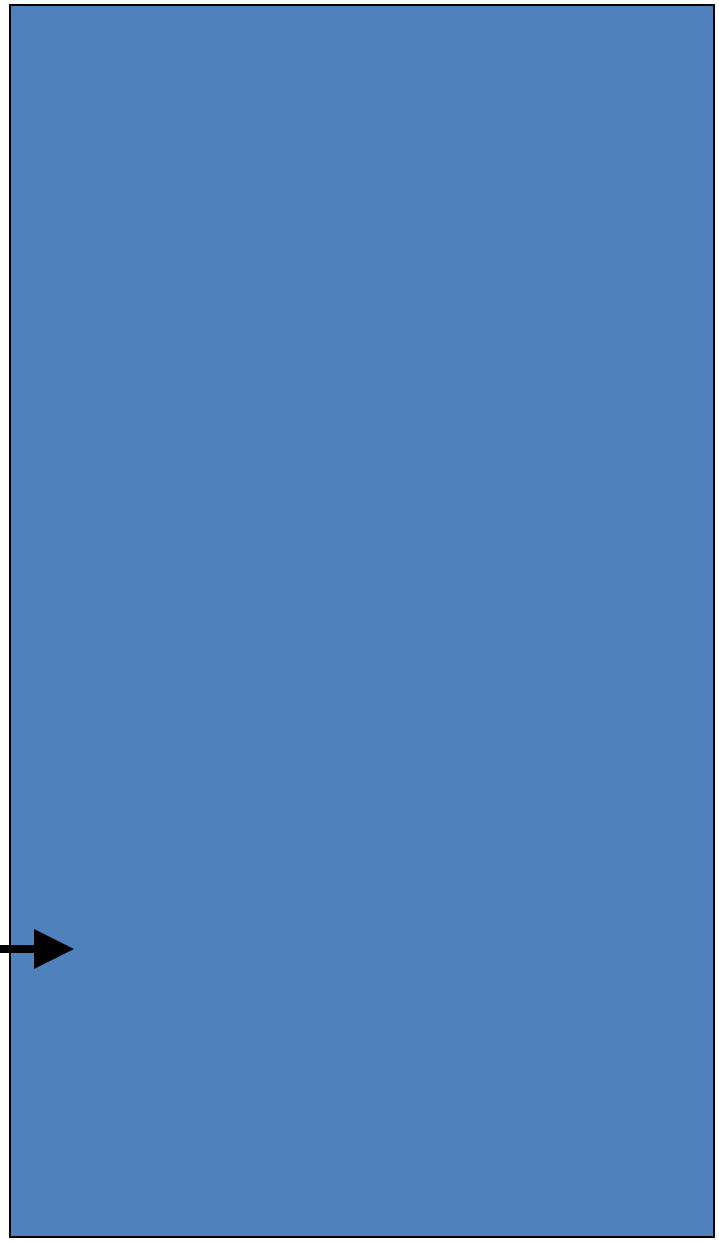
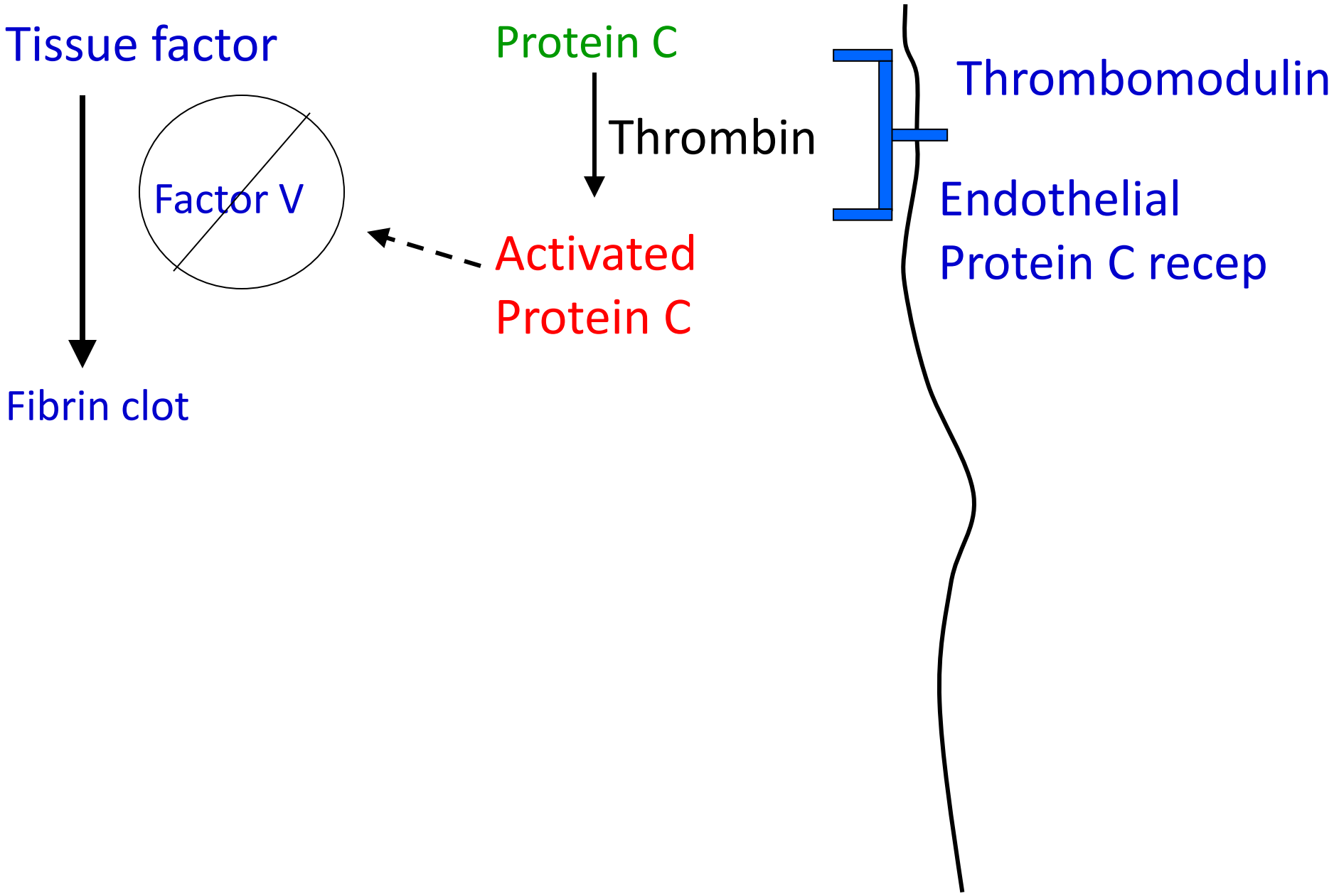
(< 1 tennis court)

Gut 250 m^2
(> 1 tennis court)

Endothelium: 1,000 m^2
1 Trillion cells; (Football field)



Coagulopathy of Trauma: an Endothelial Response...



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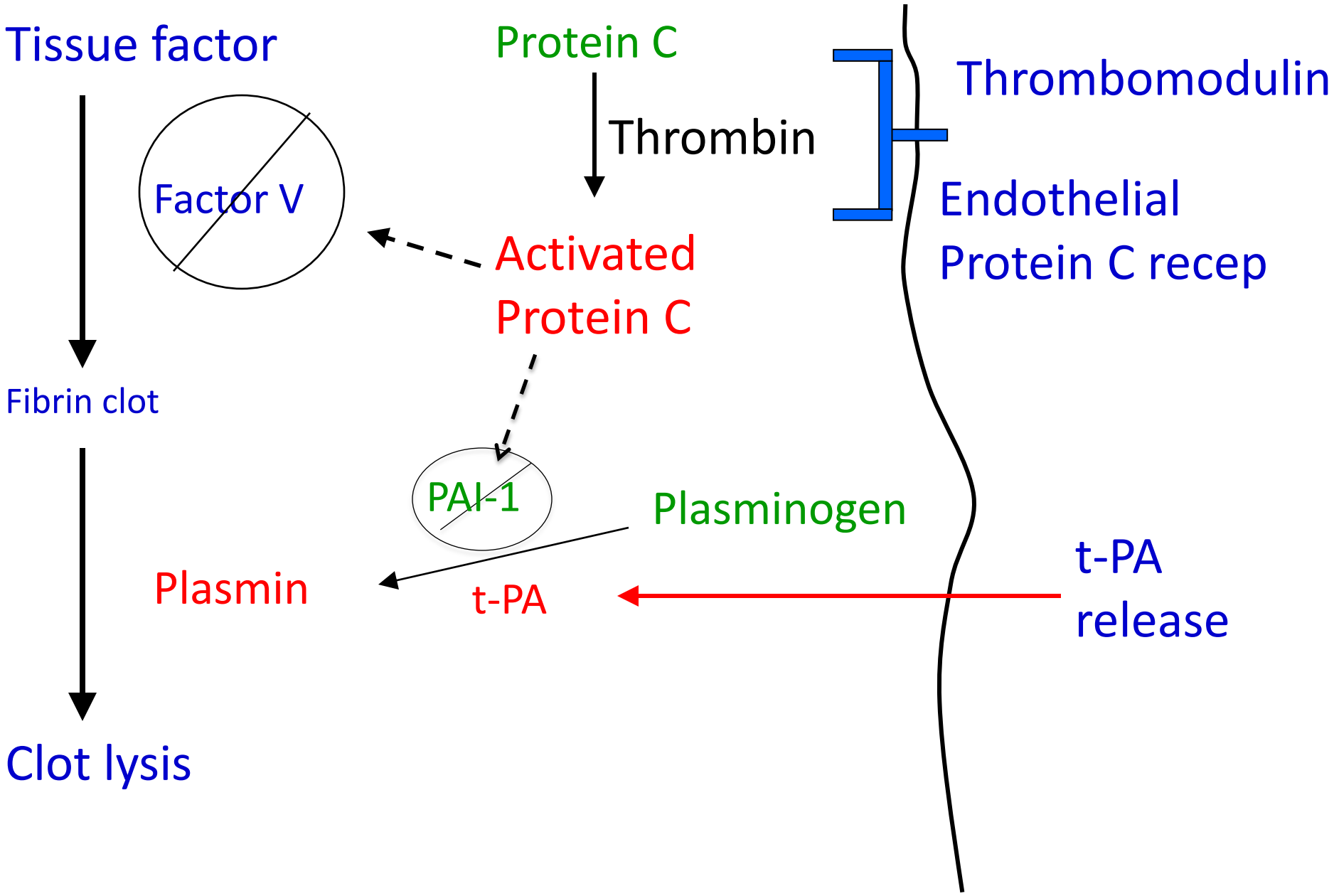
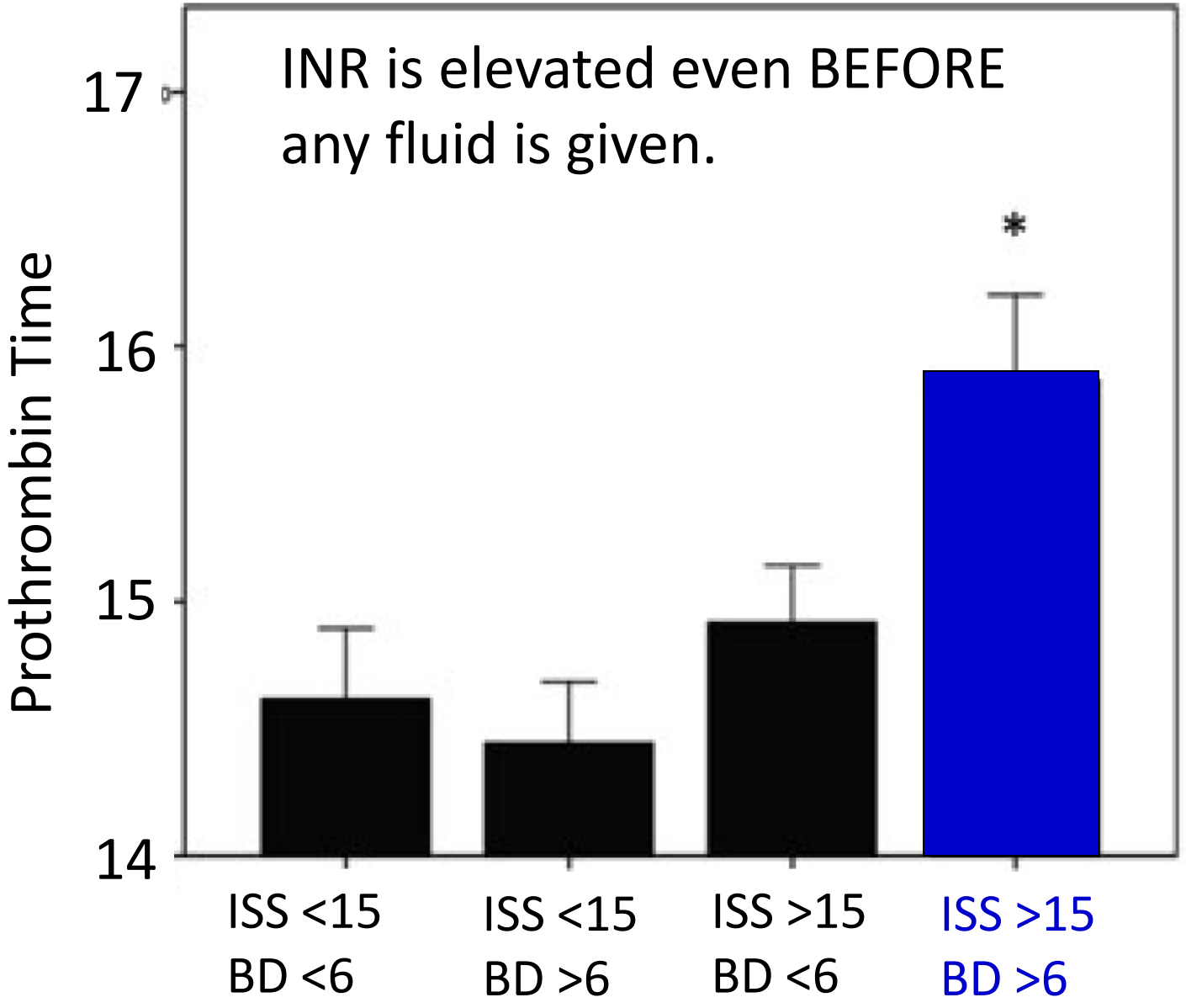
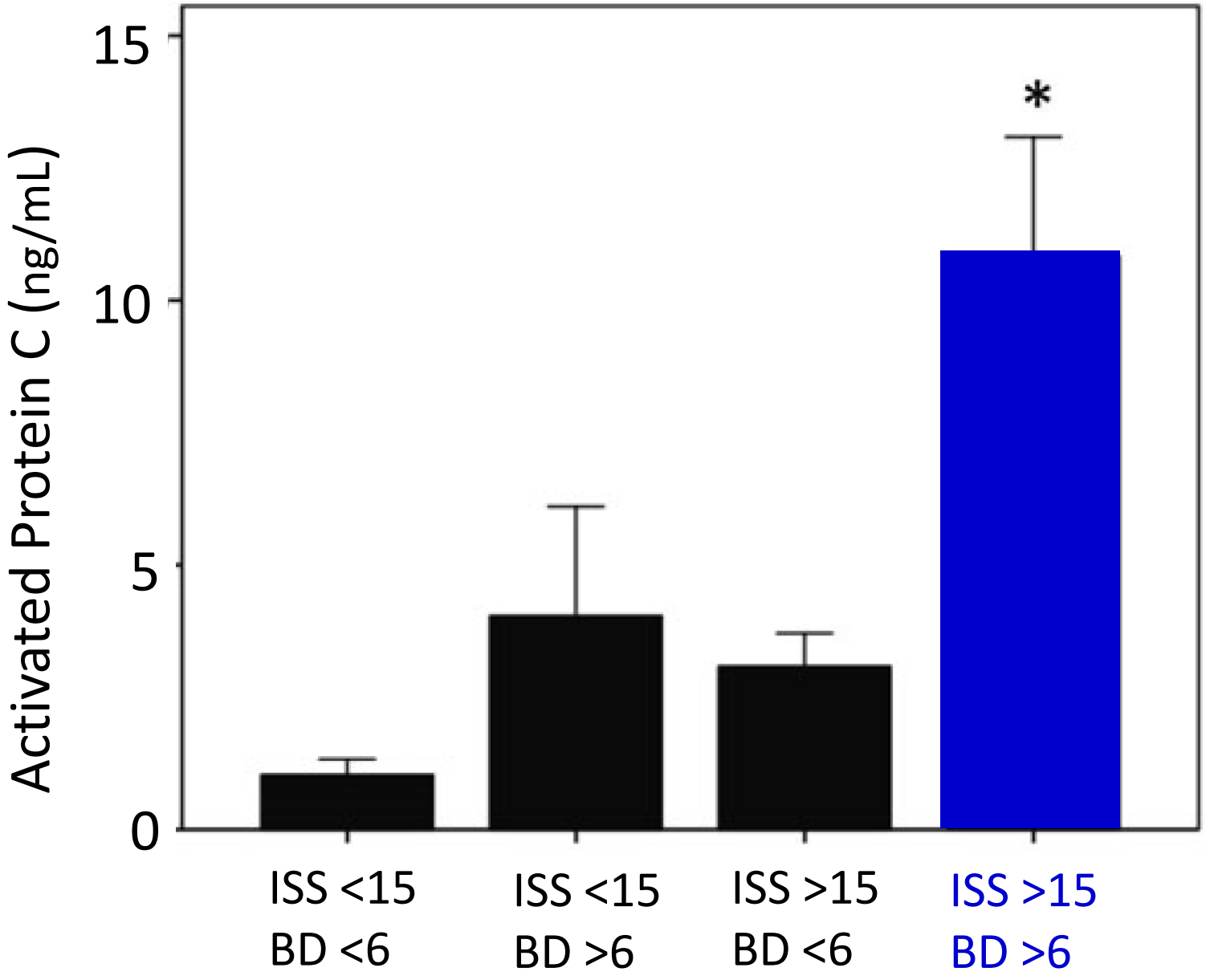


203 Major Trauma patients in San Francisco...



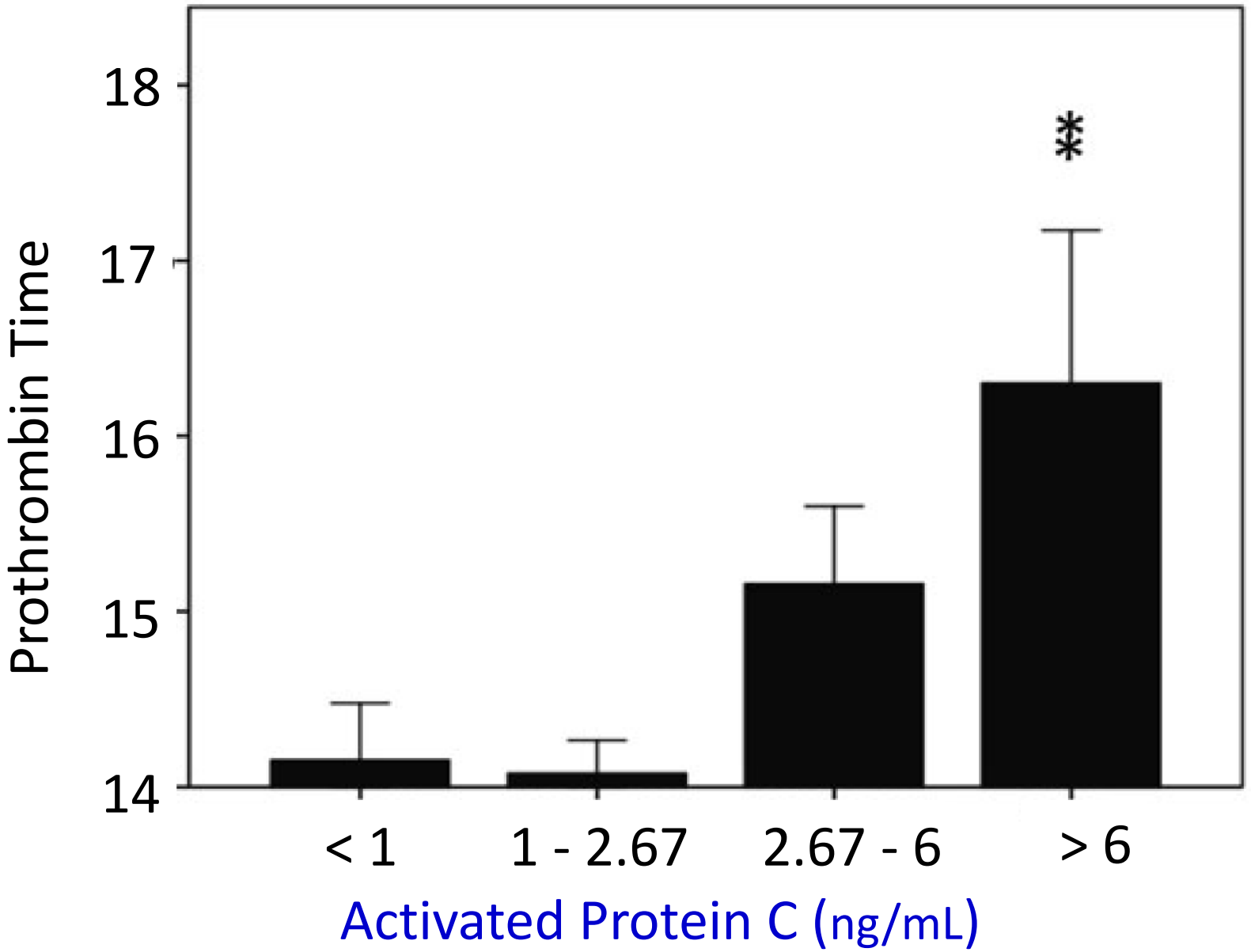
Cohen MJ et al. Ann Surg 2012; 255: 379-385.

Activated Protein C levels rise....



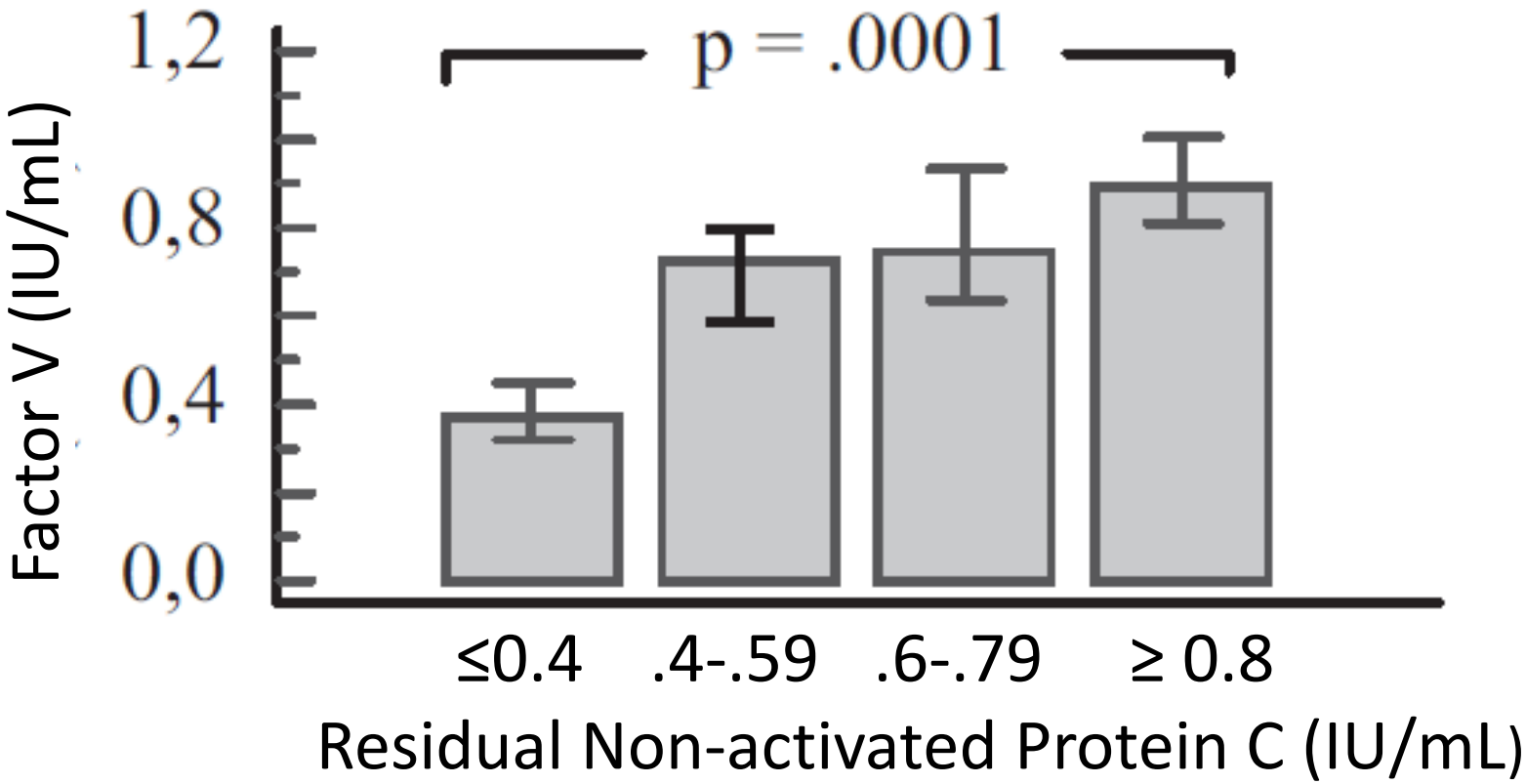
Cohen MJ et al. Ann Surg 2012; 255: 379-385.

Protein C activation → elevated INR



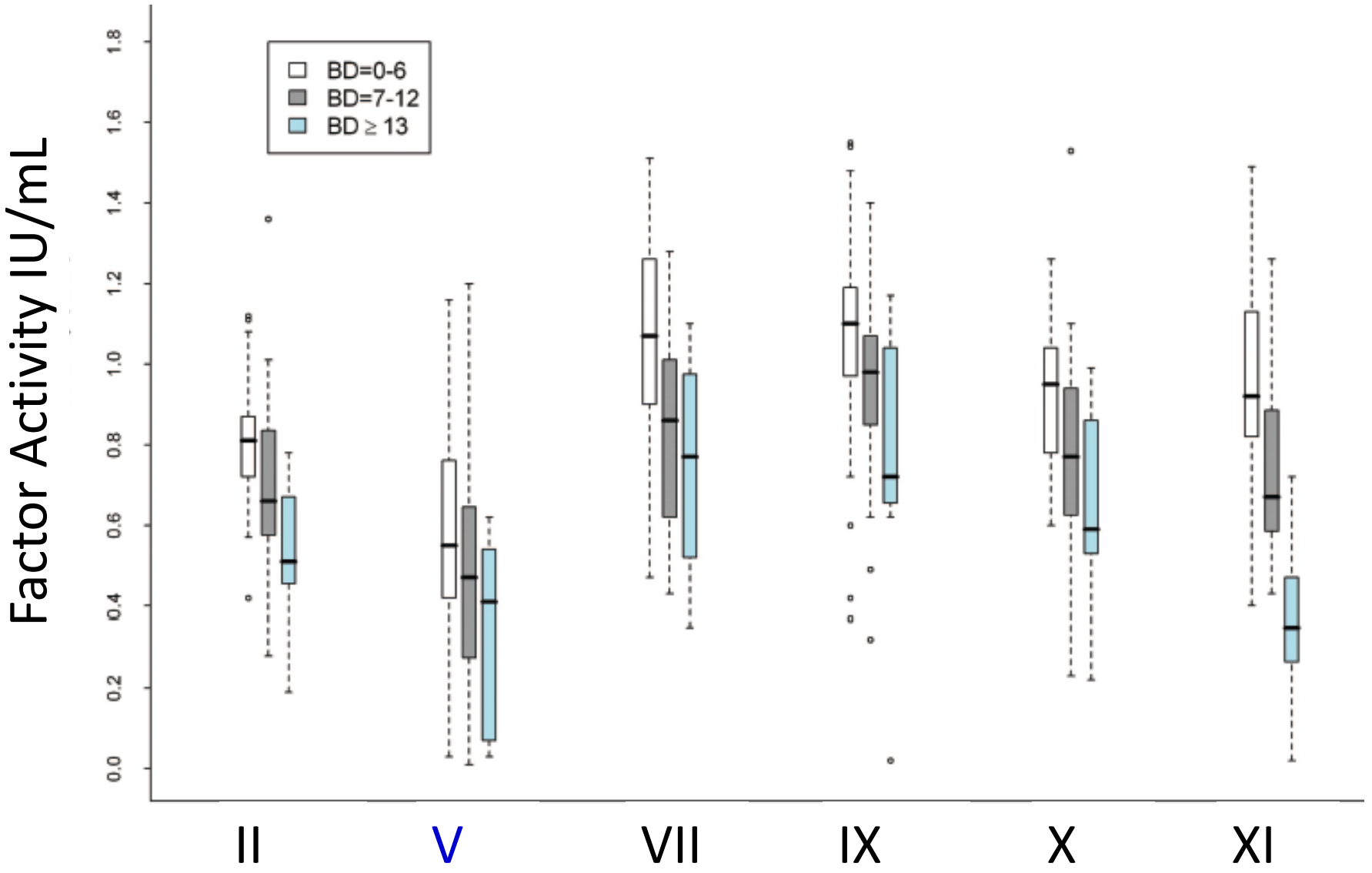
Cohen MJ et al. Ann Surg 2012; 255: 379-385.

In trauma, activated protein C reduces factor V



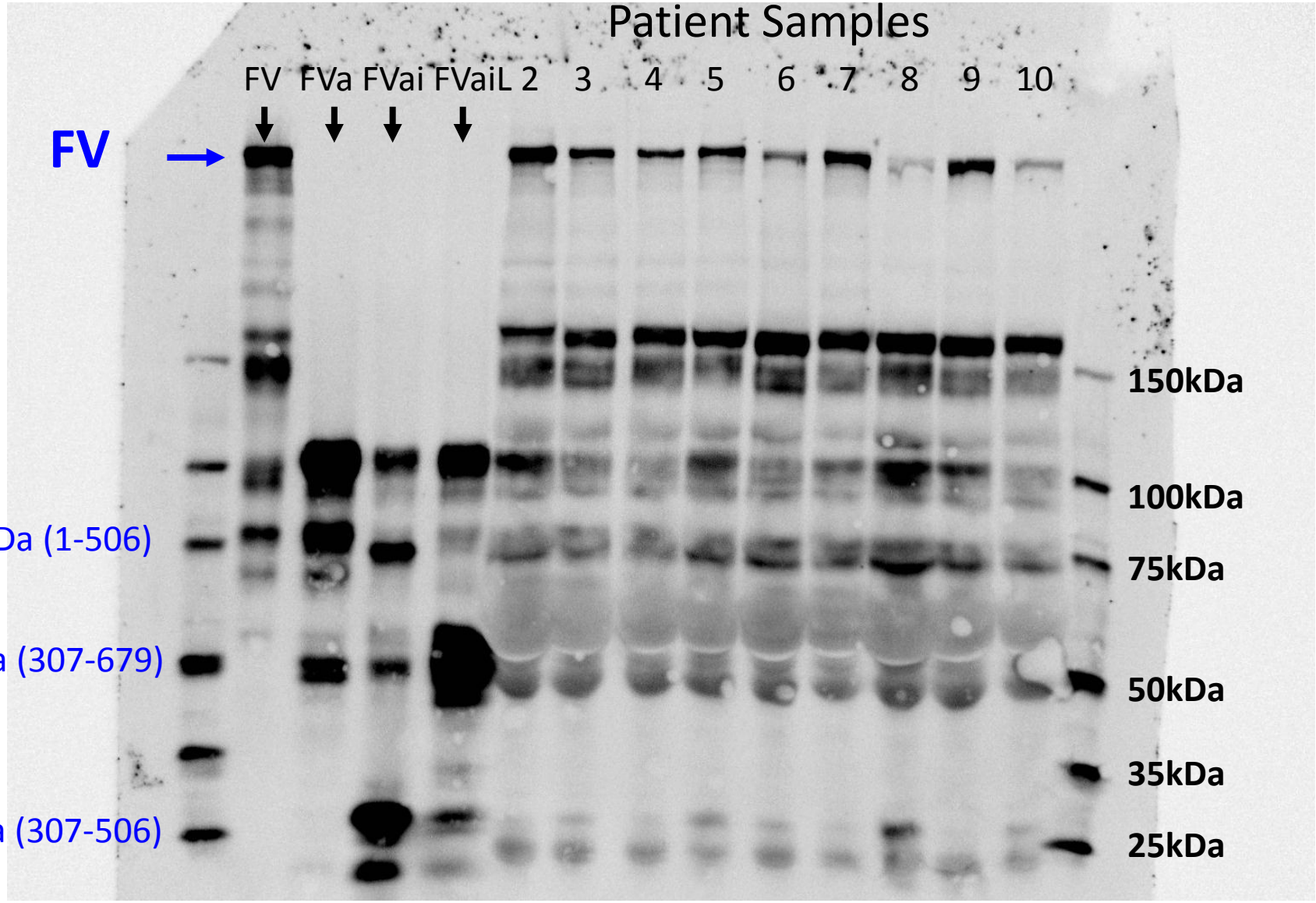
Floccard et al. Injury 2012 43:26-32.

Factor V is the most affected



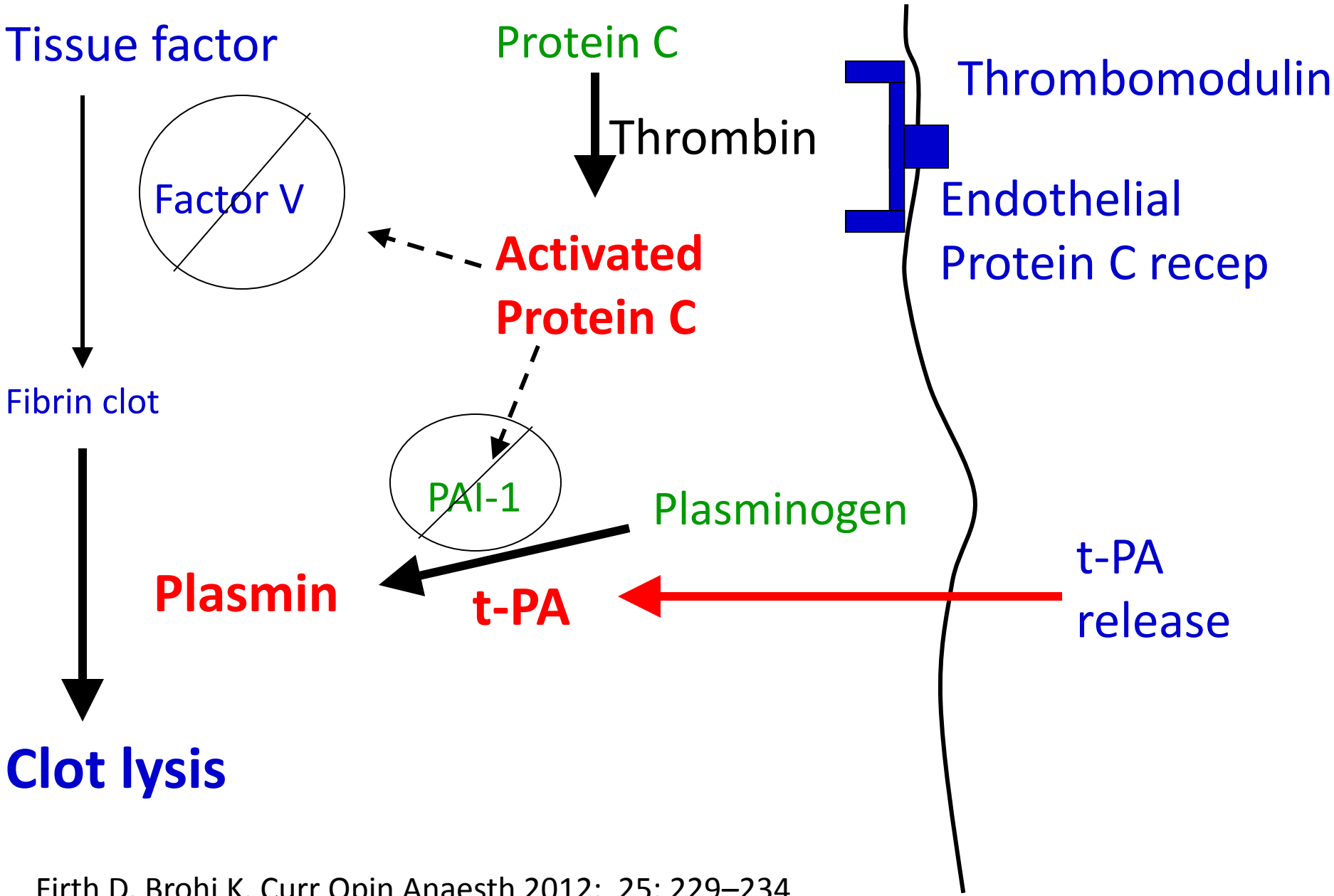
Jansen et al. *J Trauma.* Nov 2011;71(5 Suppl 1):S435-440.

aPC is the culprit: cleaves FV at Arg^{306} & Arg^{506}



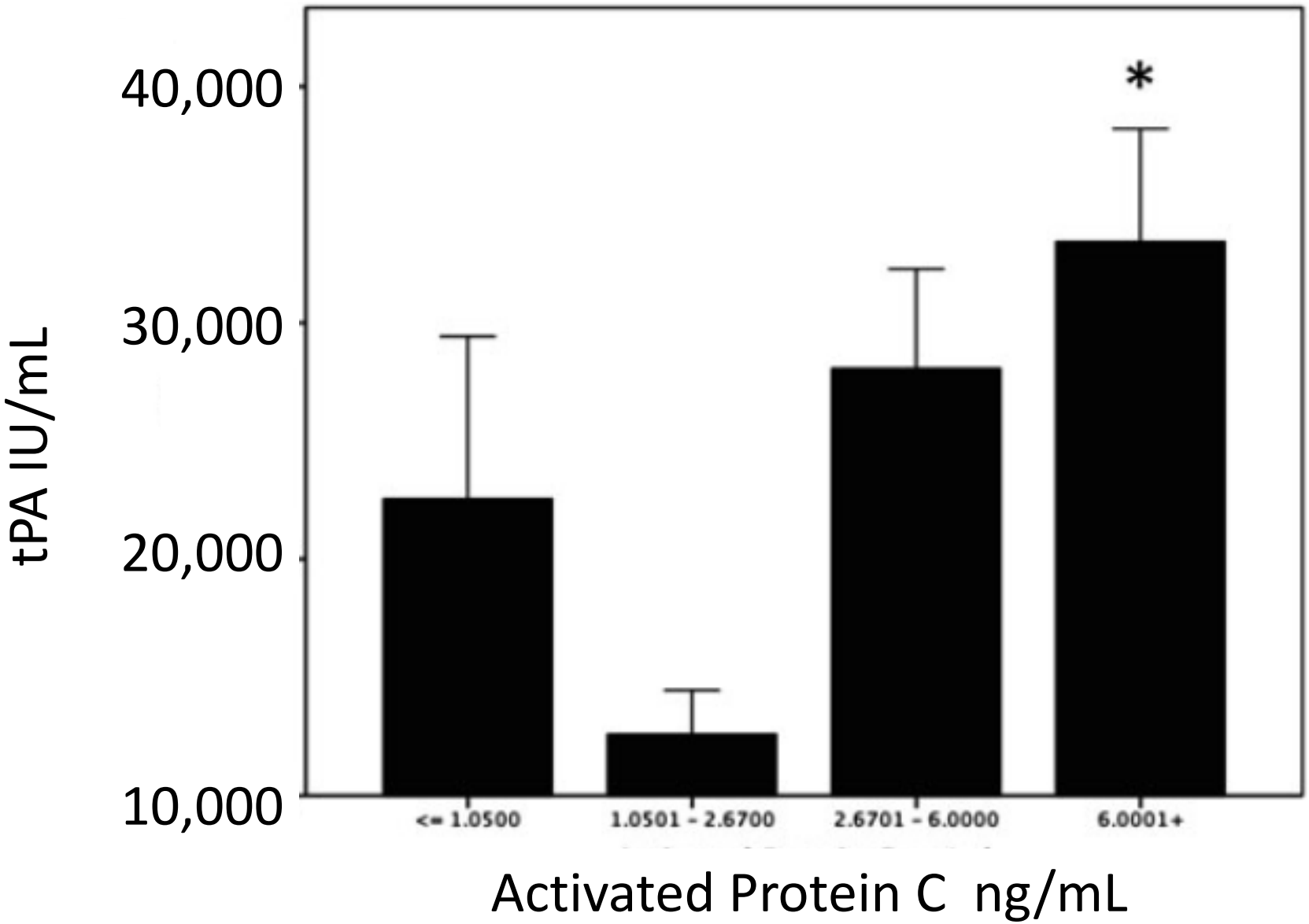
Courtesy of Jeannie Callum, Sunnybrook, CA

Endothelial Response to Injury and Shock



Firth D, Brohi K. Curr Opin Anaesth 2012; 25: 229–234

tPA activity increases with aPC



Cohen et al. Ann Surg 2012 Feb;255(2):379-85.

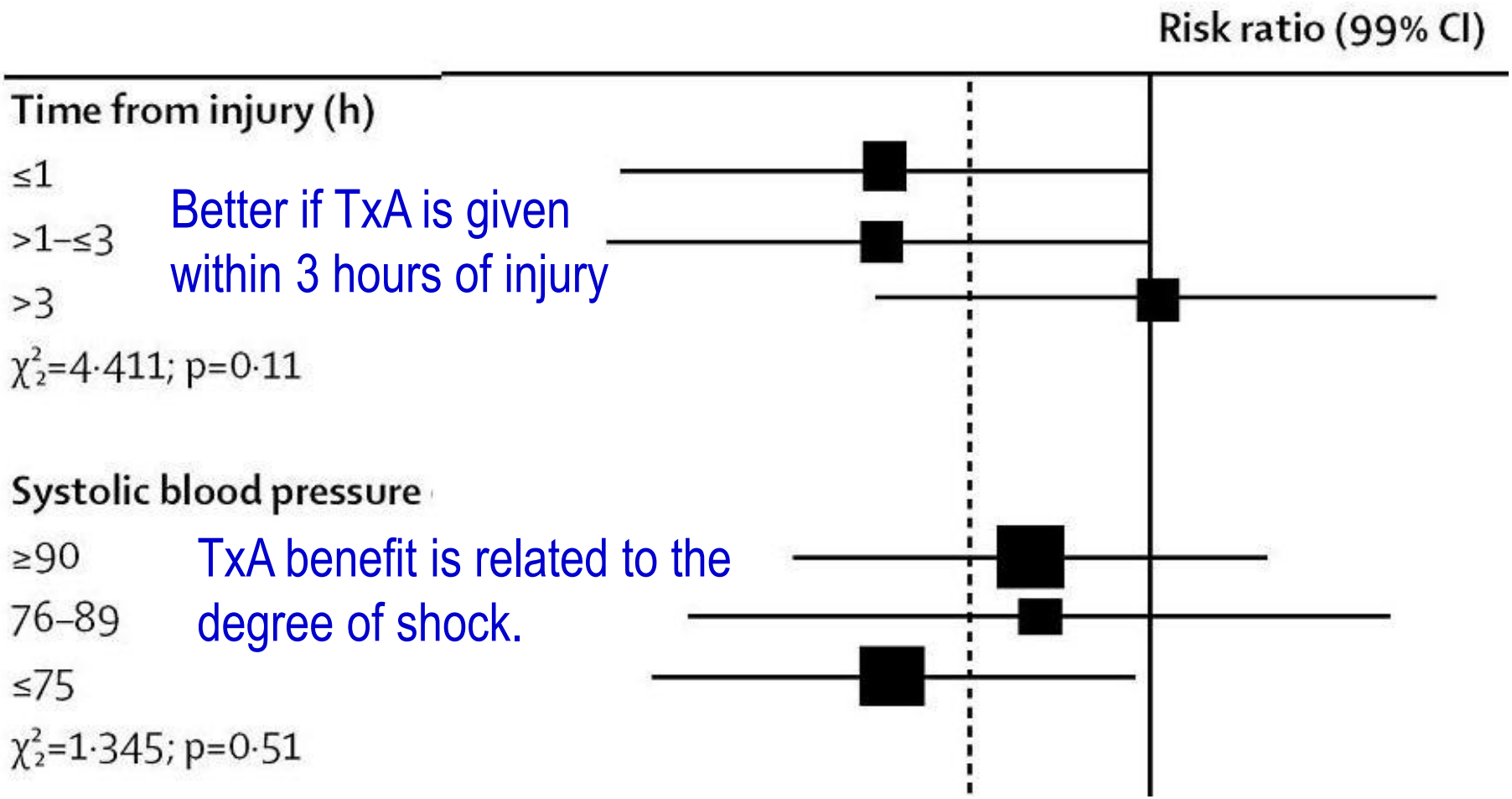
CRASH-2

- Multicenter, prospective randomized trial
- 274 hospitals in 40 countries.
- n = 20,211injured patients randomized to:
  - tranexamic acid: 1 gm bolus & 1 gm in 8 hrs
  - vs, placebo infusion.
- Primary outcome: Death in hospital within 4 weeks
  - Tranexamic: 14.5%
  - Placebo: 16%

  } $p < 0.0035$
- Secondary outcome: bleeding-related death
  - Tranexamic: 4.9%
  - Placebo: 5.7

  } $p < 0.0077$

CRASH-2



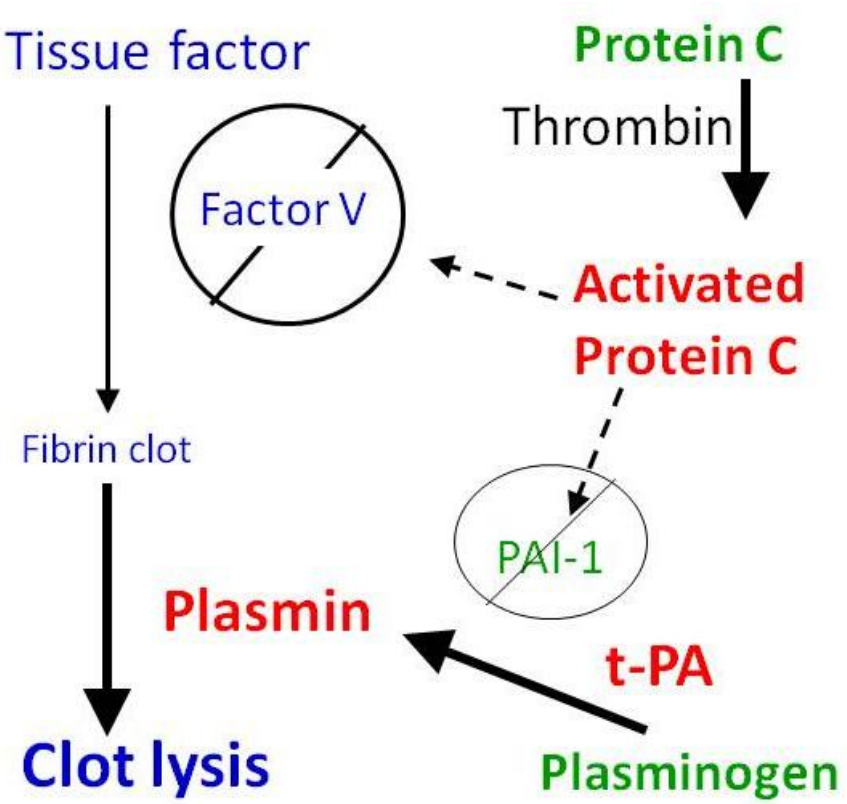
CRASH-2 Lancet 2010

Implications of the 'endothelial model'

1. The initial coagulopathy is not due to "lack of factors".

2. Up front FFP may actually be detrimental by supplying more Protein C & Plasminogen.

3. Inhibitors of fibrinolysis should be effective as an "up front" therapy.



4. A chemical inhibitor of activated Protein C might transform coagulopathy of shock.

Plasma Therapy: What would Budda say ?

Controversy	FFP: Good or Bad ?	Recent New Insights	Trials Needed	Long range solution
FFP as prophylaxis				
Rx of VKA-related bleeding				
Rx of coagulopathy of trauma				

Plasma Therapy: Where are we ?

Controversy	FFP: Good or Bad ?	Recent New Insights	Trials Needed	Long range solution
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Rx of coagulopathy of trauma	? Harmful; ? Wasteful; ? Helpful	Callum; Cohen: (Not a deficiency)	Await PROPPR trial	Need an inhibitor of activated protein C