



# haemostasis registry

Scott Dunkley – Steering committee



**MONASH** University  
Medicine, Nursing and Health Sciences

# Haemostasis Registry

- Department of Epidemiology & Preventive Medicine, Monash University
- All cases of rFVIIa use for critical bleeding in participating hospitals  
(ie outside haemophilia)
- Funded through unrestricted Education Grant from Novo Nordisk Pharmaceuticals

# Aims

**investigate**

the safety, efficacy and dosing of rFVIIa in areas of critical bleeding,

**monitor**

the extent, indications for, dosages and appropriateness of use

**generate**

information to assess cost-effectiveness and to support clinical use

**publish**

based on analyses of local experience

**provide**

data for physicians, hospitals and Regulatory Authorities

# Haemostasis Registry

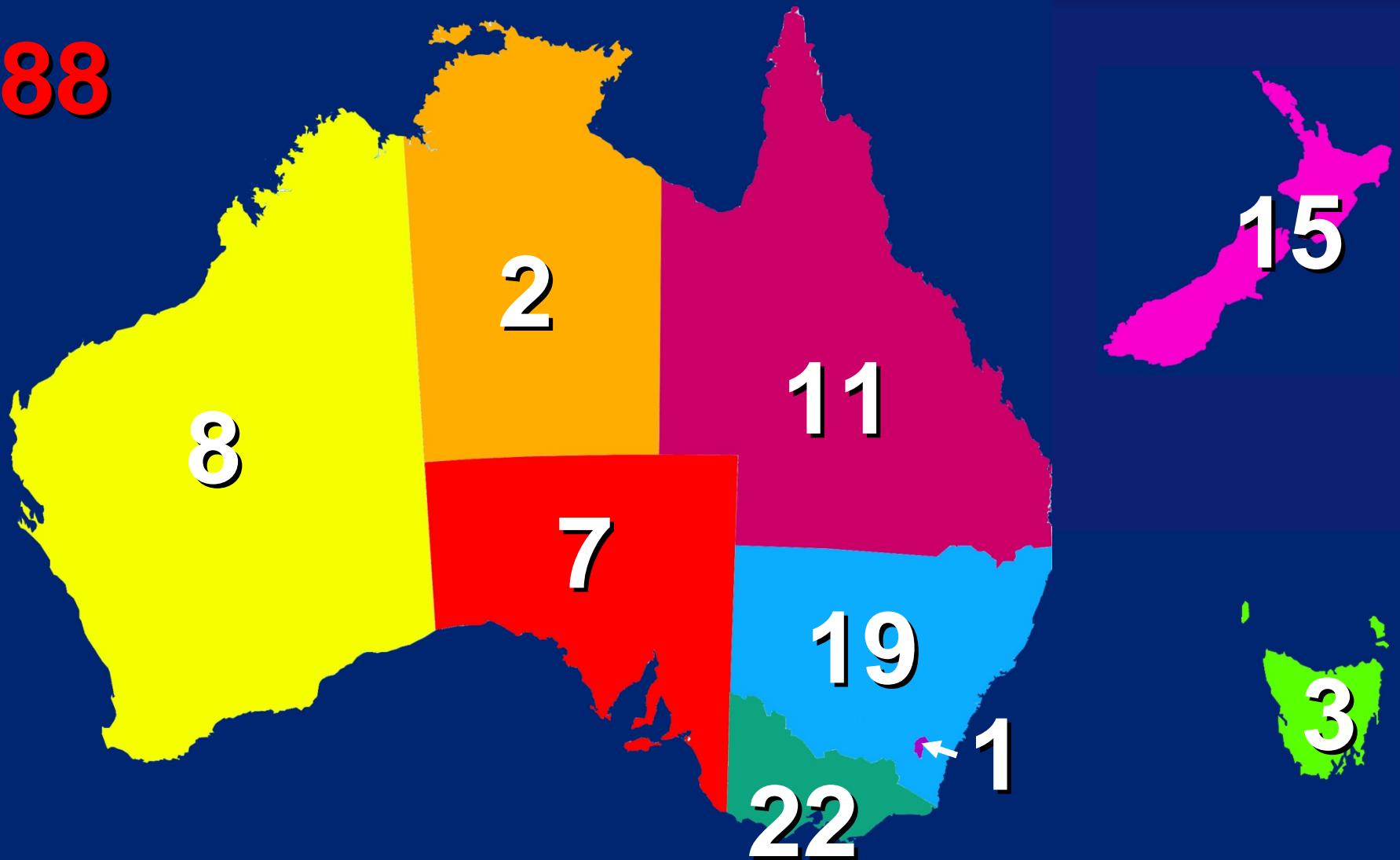
- Commenced Data Collection May 2005 (including retrospective cases), to date have obtained ethical approval from 88 hospitals and submitted ethics applications to a further 6 ethics committees
- Includes all major users of rFVIIa in Australia and New Zealand and hospitals in all states/territories of Australia and New Zealand
- As at 19 March 2008 have received 1712 cases

# Method

- Local Investigators at each participating hospital are responsible for identifying cases and data collection
- required to submit ALL cases
  - routine audit conducted
- Data submitted by web based data entry system
- Data quality monitored through
  - automatic range, consistency and completeness tests,
  - manual verification of text fields
  - random audit of 5% cases against source material

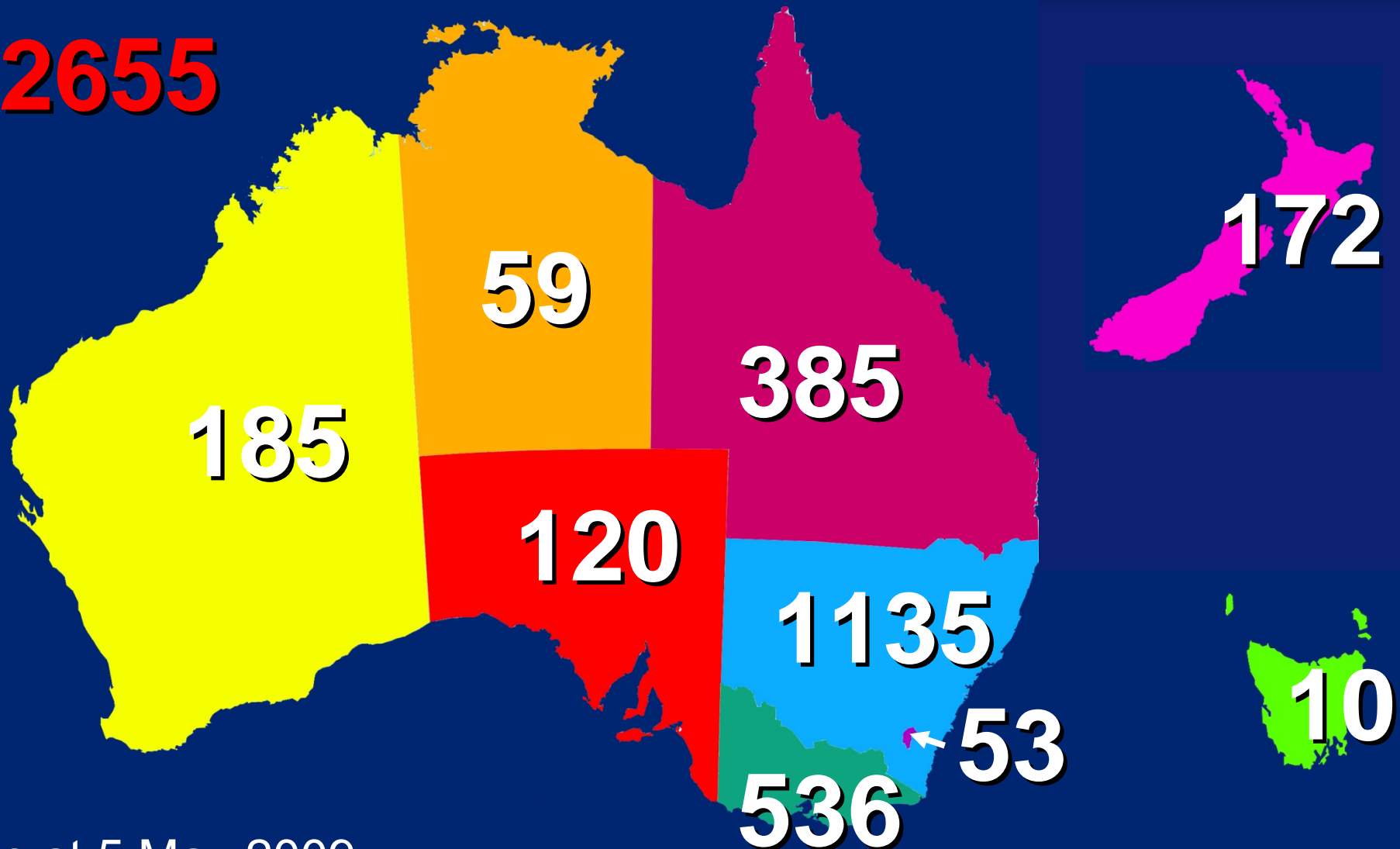
# Participating Hospitals

88



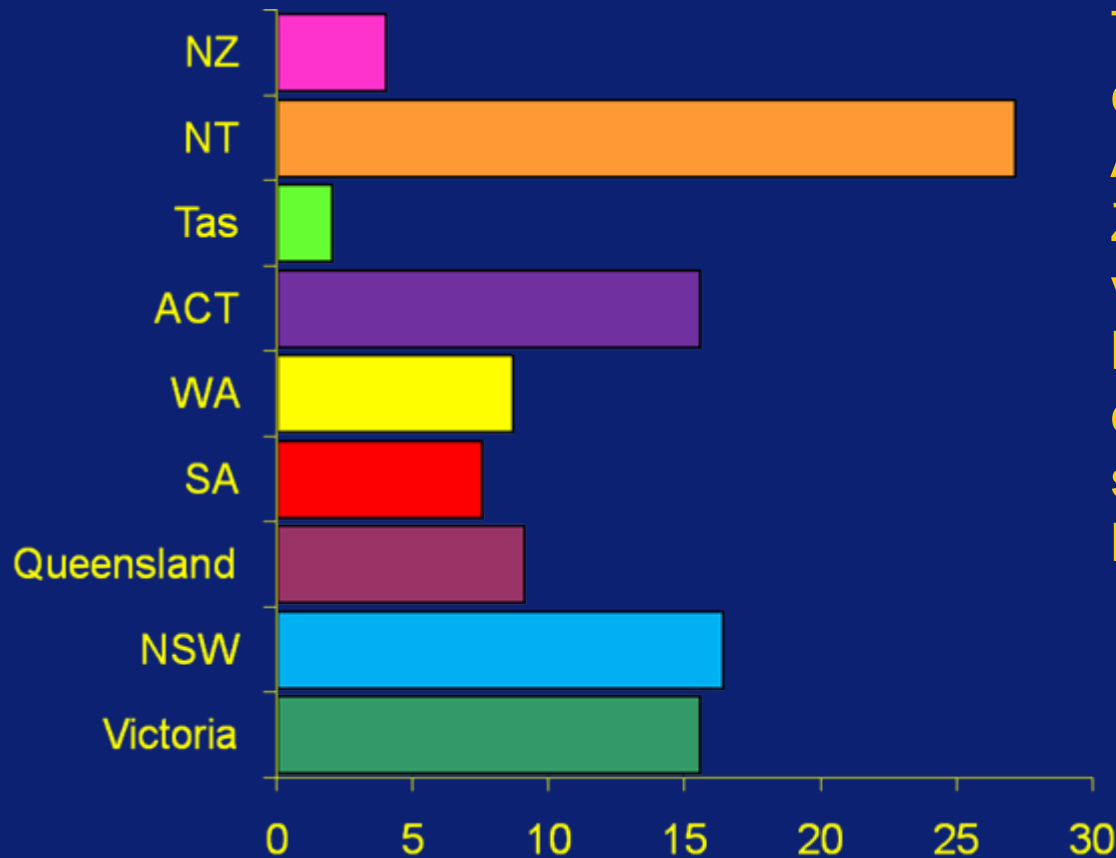
# Cases Submitted

**2655**



as at 5 May 2009

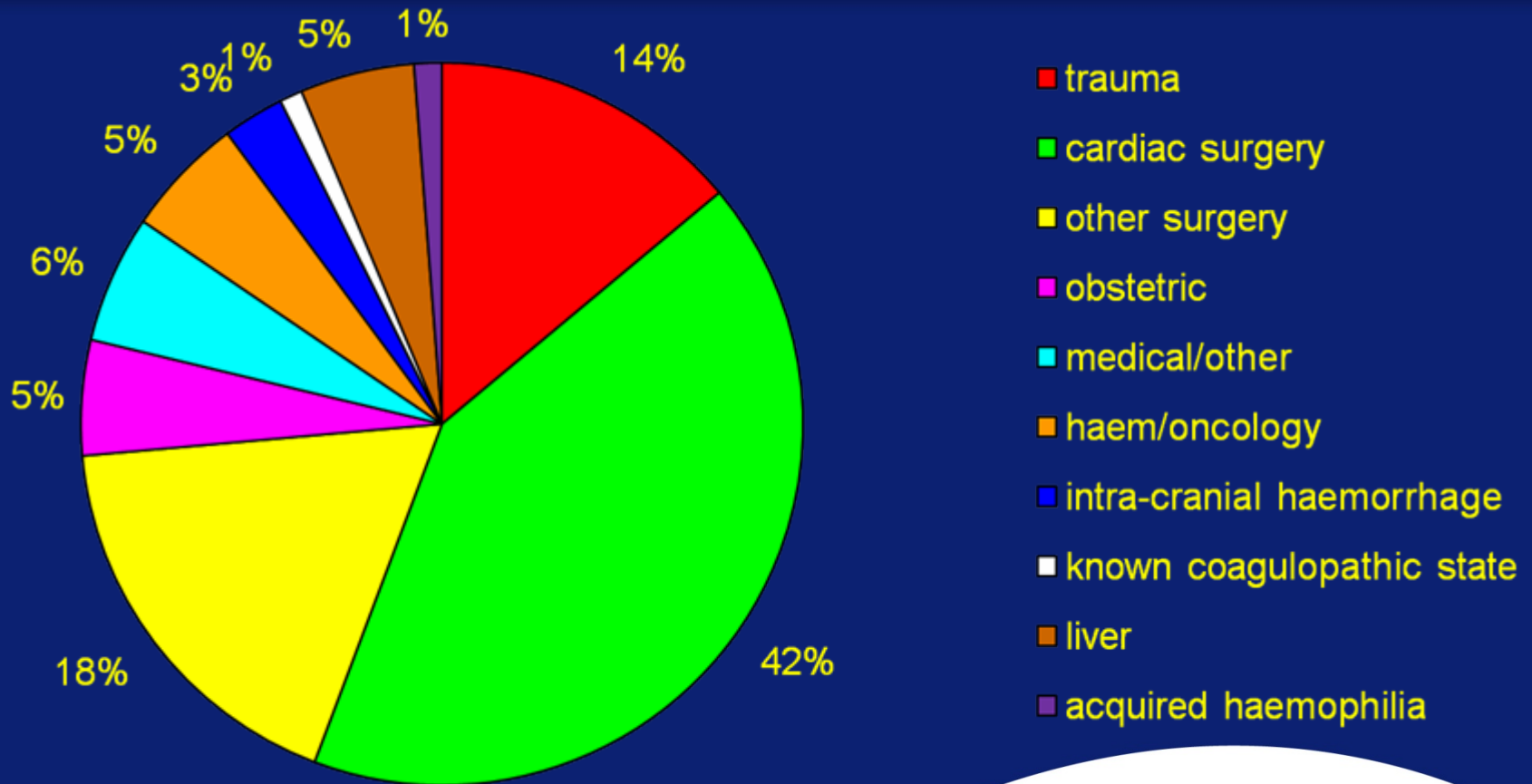
# Cases by Geographic Region



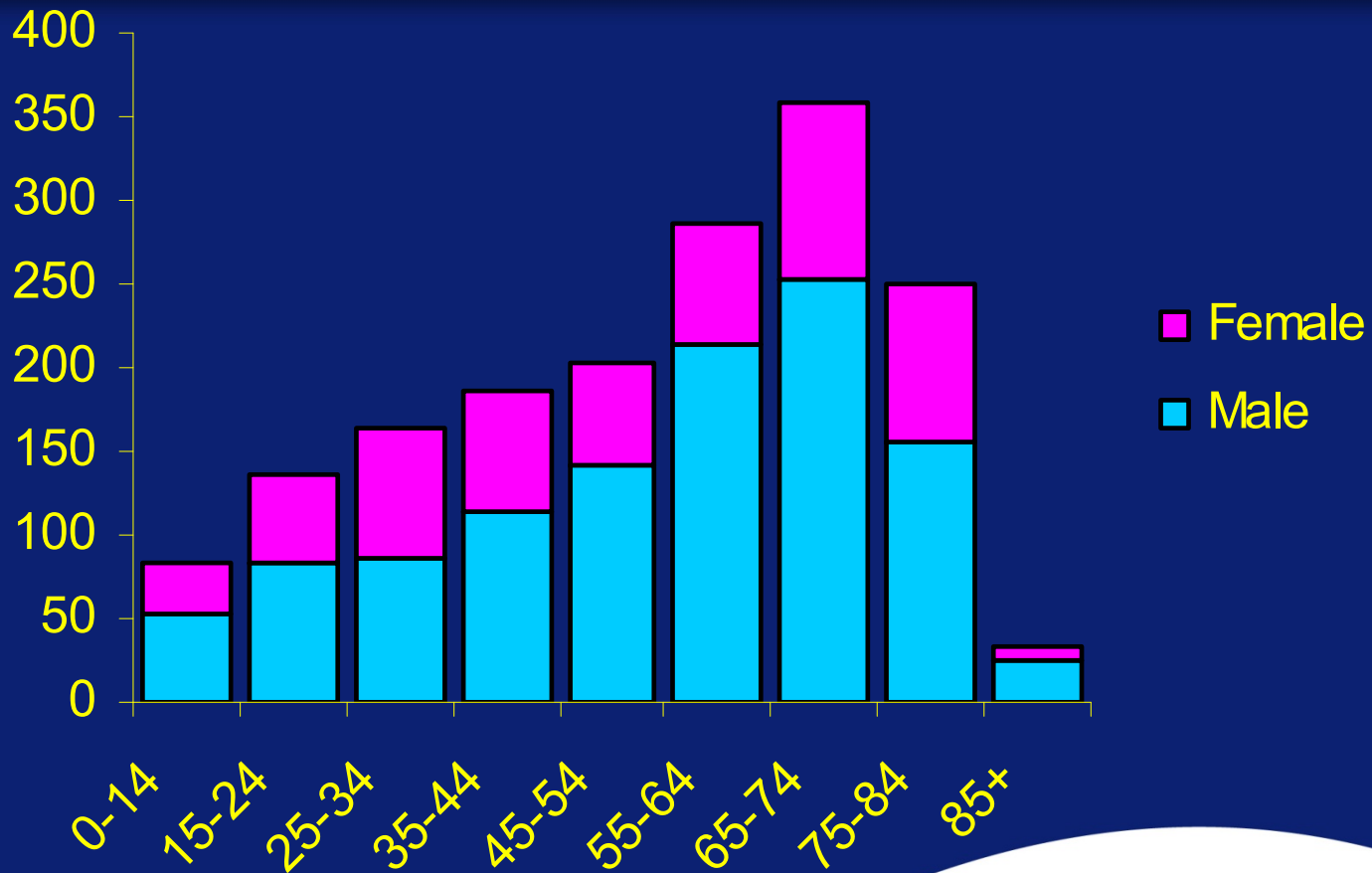
The number of cases varied considerably between different Australian States and New Zealand. Reasons for this variability include availability of blood components, population demographics and transport of some patient types across state boundaries.

Per  
100,000  
residents

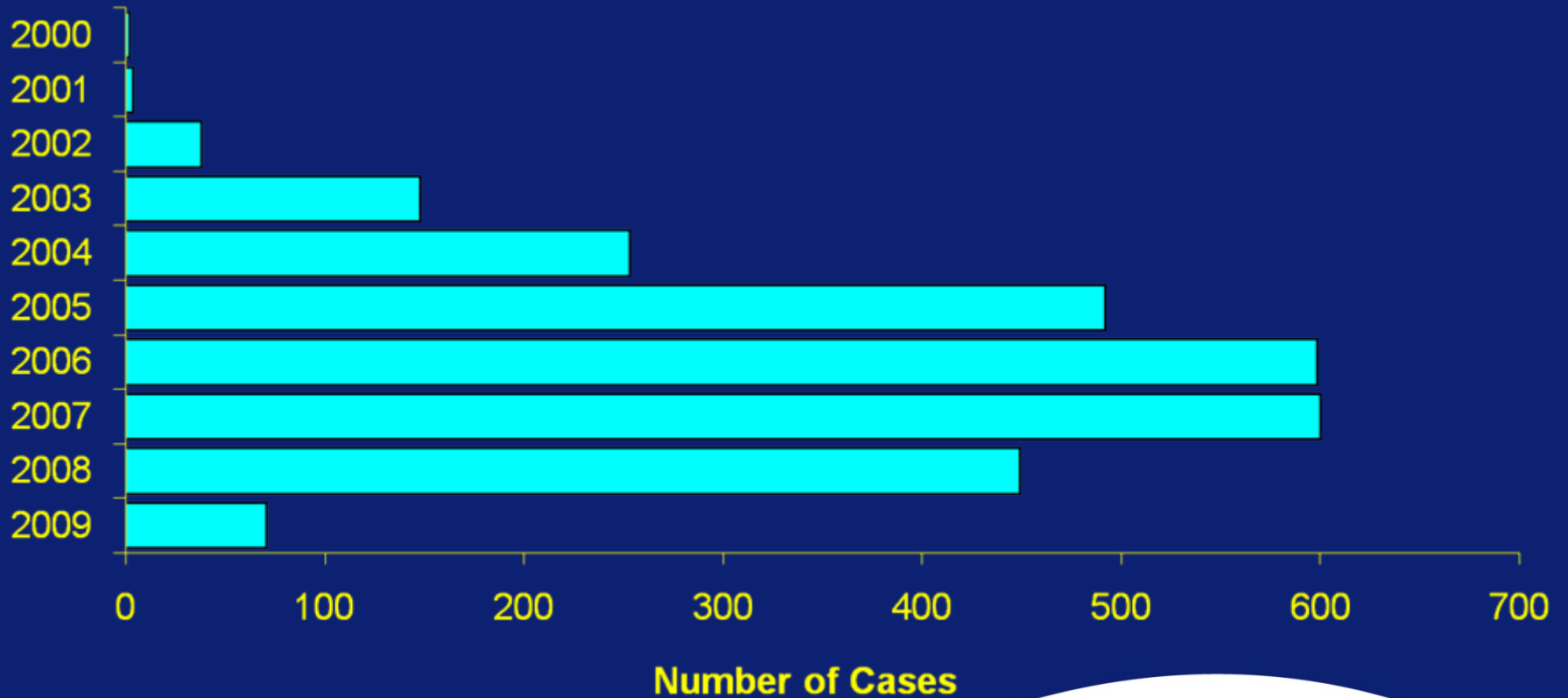
# Cases by Presentation



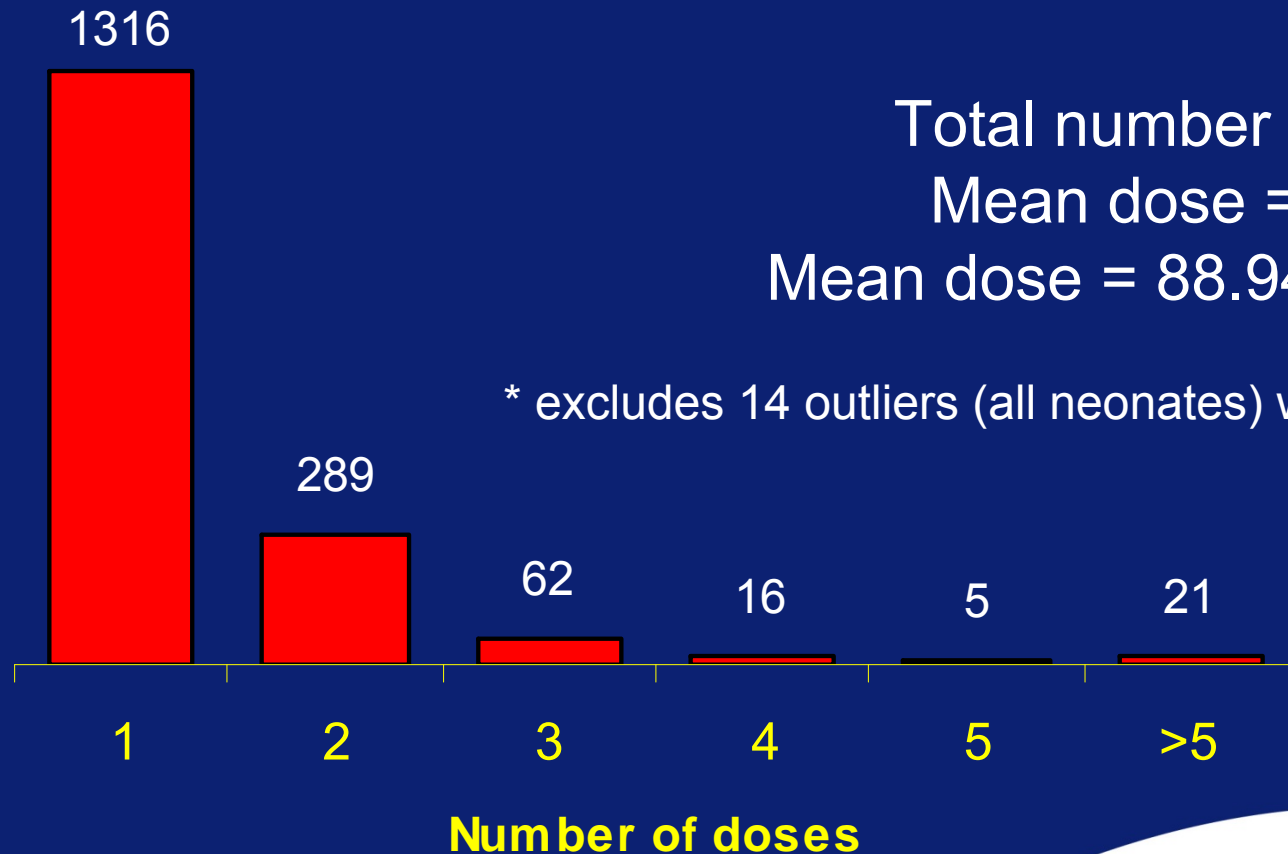
# Gender and Age



# Year



# Dose



$n = 1712$

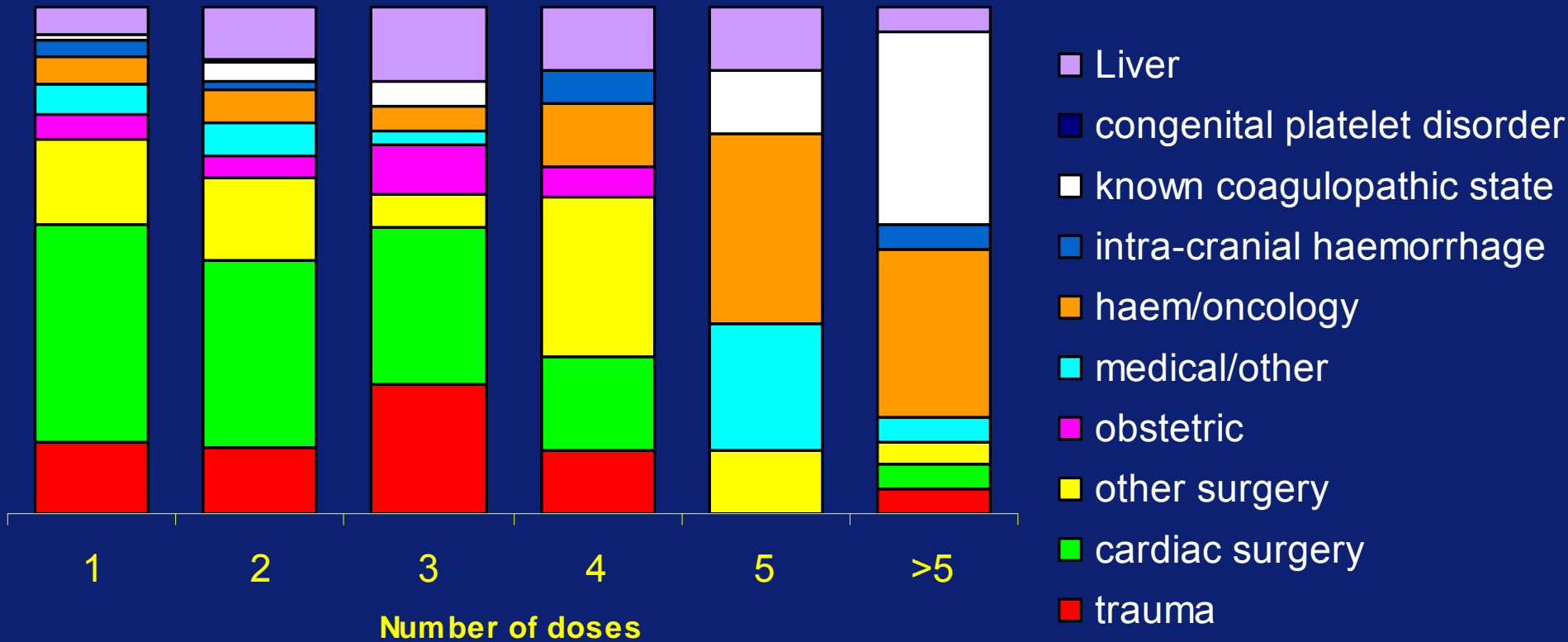
Total number of doses = 2513

Mean dose =  $6.30 \pm 2.62$  mg

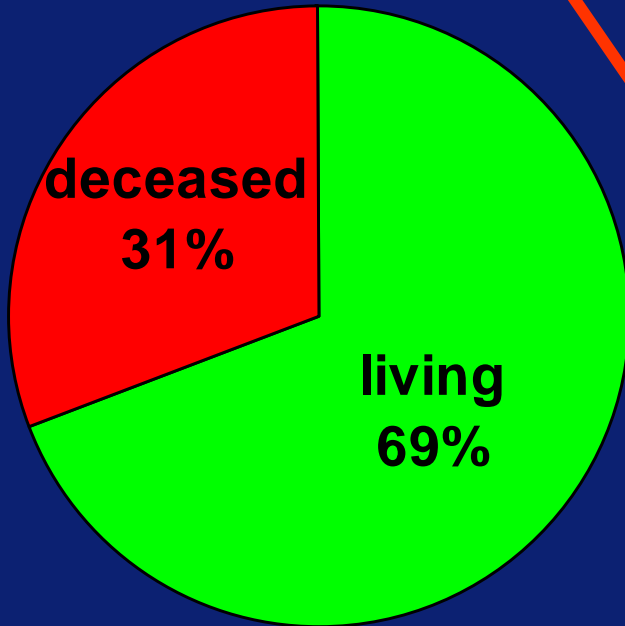
Mean dose =  $88.94 \pm 32.06$   $\mu\text{g}/\text{kg}^*$

\* excludes 14 outliers (all neonates) with dose  $> 400$   $\mu\text{g}/\text{kg}$

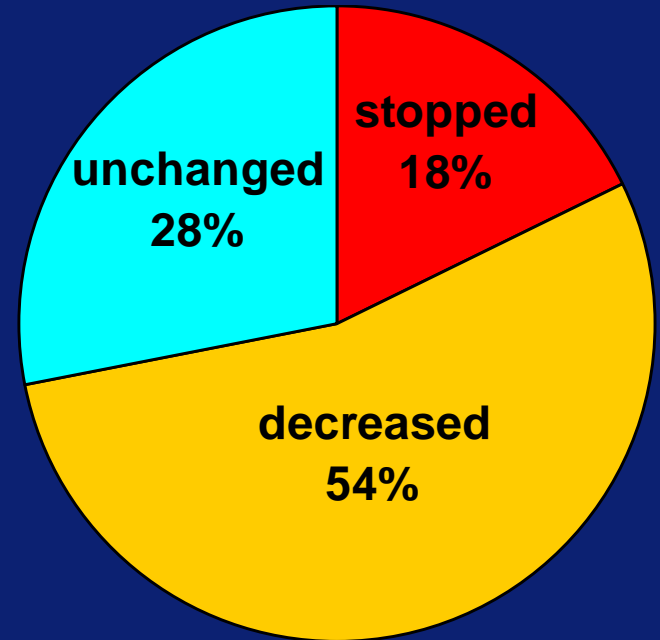
# Number of Doses



# Final Effect on Bleeding



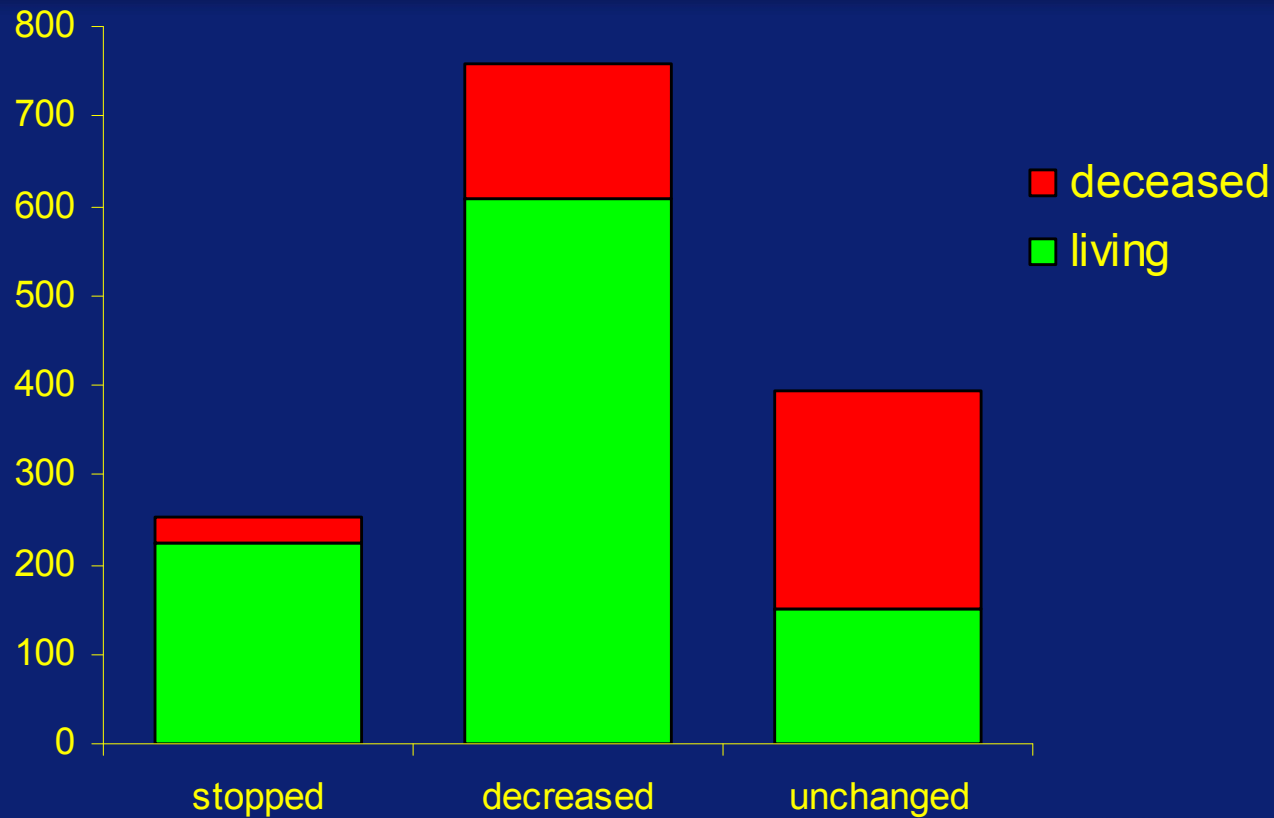
28 Day Mortality



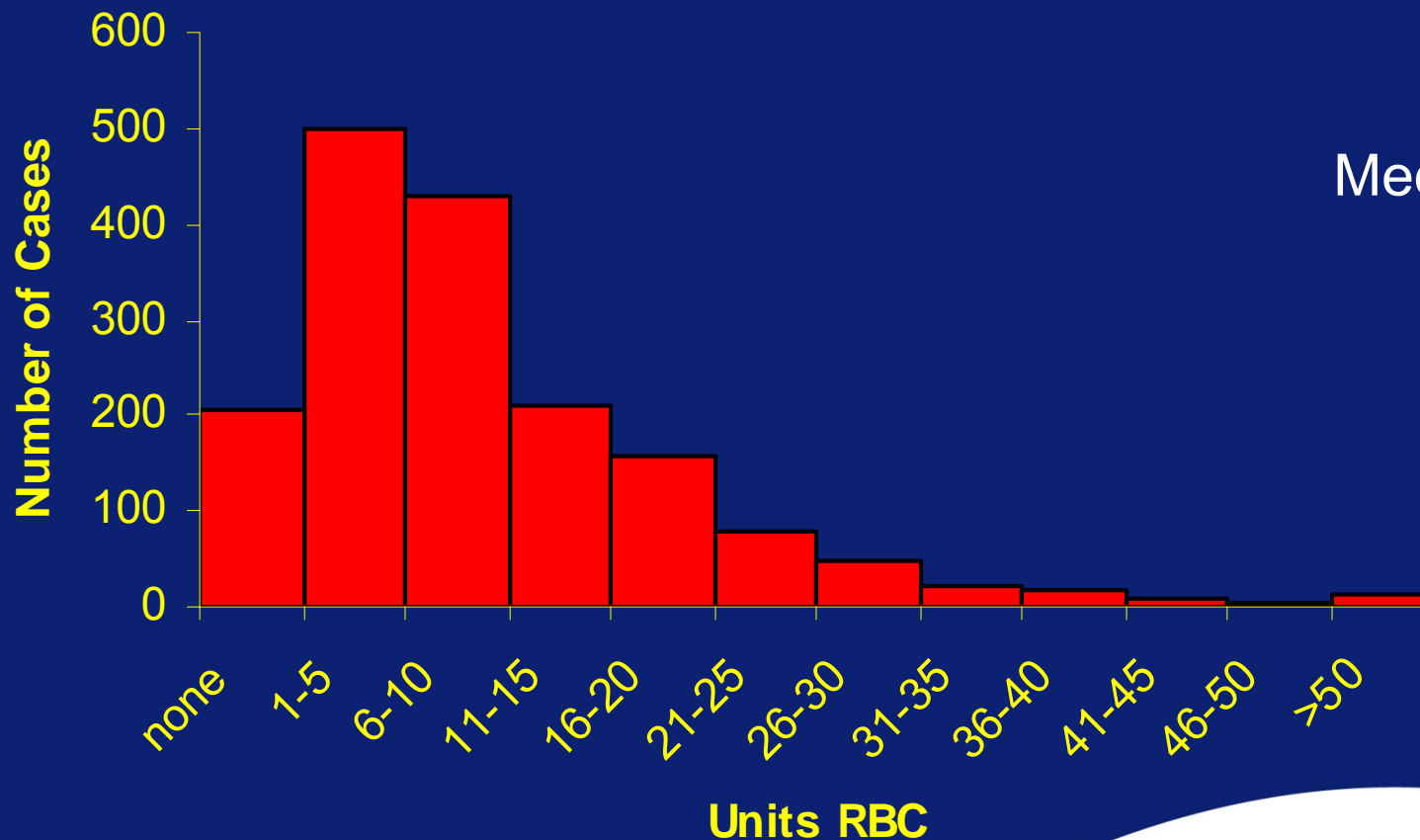
# Efficacy

- Cardiac 84%
- Obstetrics 68%
- Trauma 59%
- Medical 52%

# Effect on Bleeding vs 28 Day Mortality

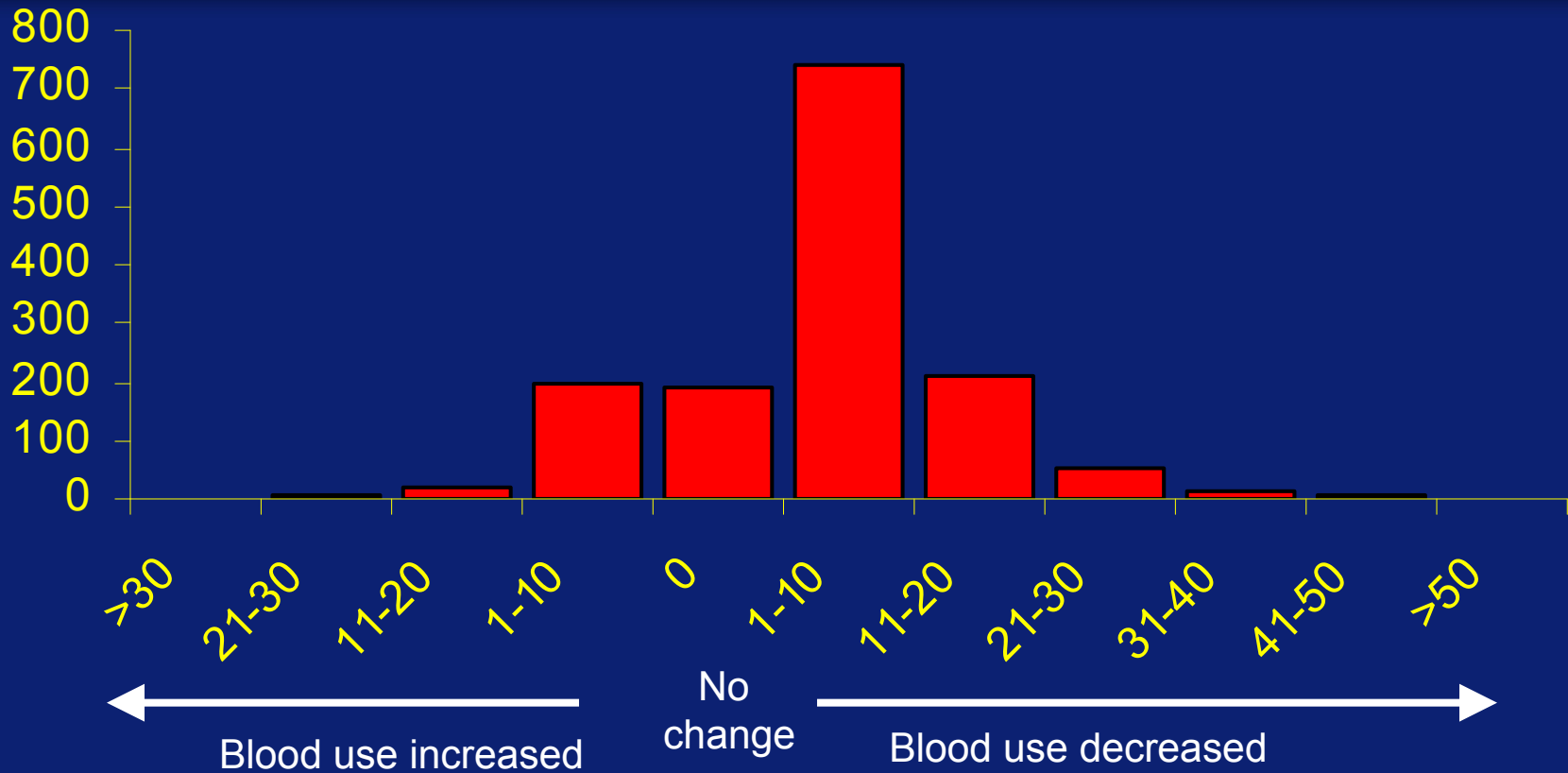


# RBC use before rFVIIa

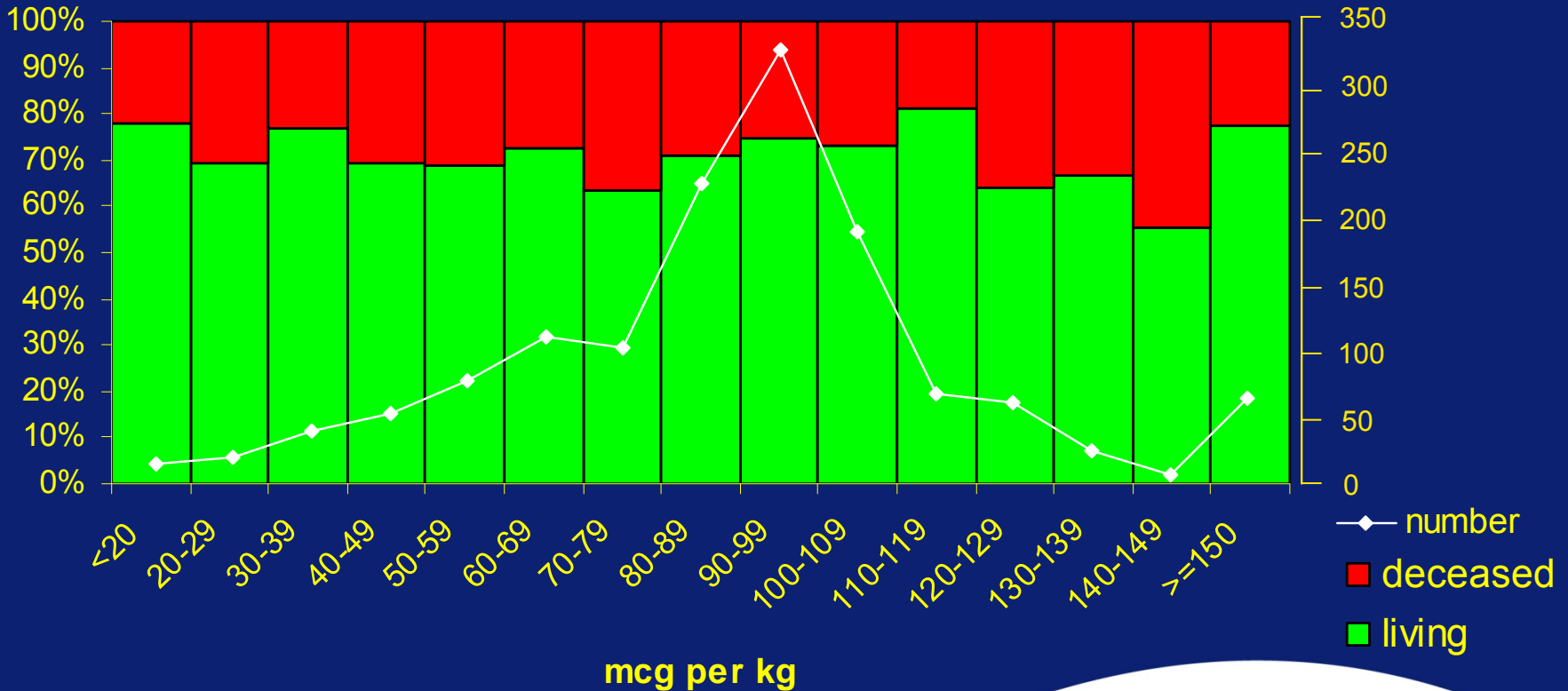


$n = 1701$   
Median = 7 units  
IQR 3 - 14  
Range 0 - 78

# $\Delta$ RBC before and after Dose 1 rFVIIa



# Size of Dose and Outcome



# Adverse Events

	<b>Total AEs</b>	<b>Thromboembolic AEs</b>
Definitely Linked	1	0
Probably Linked	6	4
Possibly Linked	78	45
<b>Sub Total</b>	<b>85 = 5.0%</b>	<b>49 = 2.8%</b>
Unlikely to be Linked	344	56
Not Linked	457	35
Unable to Assess	22	4
<b>Total</b>	<b>823 = 48%</b>	<b>95 = 5.5%</b>

# Adverse Events

When adjusted for procedure type, Haemostasis Registry cases do not show any significant difference in rates of thromboembolic events compared to the ASCTS Cardiac Surgery Database.

CVA/TIA	OR 0.75	95% CI 0.50-1.11 – <i>N.S.</i>
AMI	OR 0.67	95% CI 0.31-1.41 – <i>N.S.</i>
PE	OR 0.87	95% CI 0.25-2.98 – <i>N.S.</i>

# Univariate Analyses

	Effect on Bleeding p-value	Mortality p-value
Dose (or timing)	0.481	0.502
Temperature	0.03	0.08
pH	<0.001	<0.001
Platelet Level	0.04	<0.001
Fibrinogen Level	0.06	0.185
Units RBC	<0.001	<0.001
Age	0.15	0.230
Gender	0.811	0.22
Type of Surgery	0.171	0.11
Time to Dose	0.547	0.415
PT/INR	<0.001	0.001
Place of Admin	0.096	0.06

# Multivariate Analyses

Variables showing a significant univariate association were entered into the multivariate analyses.

pH and platelet count were identified as independent predictors of both patient response and mortality.

Patients with pH less than 7.2 were significantly less likely to respond to rFVIIa (OR = 0.31, 95% CI = 0.16-0.60) and were more likely to die (OR = 9.46, 95% CI = 4.95-18.07) than those with normal pH.

Cardiac Surgery patients were more likely to respond to rFVIIa (OR = 2.30, 95% CI = 1.10-4.59) than trauma patients.

Medical patients were more likely to die than trauma patients (OR = 4.1, 95% CI = 1.7-9.6) as were haematology/oncology patients (OR = 7.2, 95% CI = 2.3-22.3).

# Lessons

- cause and effect relationship ?
- substrate levels for efficacy – adequate plt, fibrinogen..
- non-laboratory parameters of coagulation (temp., pH)
- sick patients (pH, INR) do worse
- don't wait too long (RBC transfusion)(OT vs ICU)
- our patients received a standard dose

# “Older” Massive Transfusion Protocol

## **After 6 units of packed RBC and ongoing bleeding**

- Give 4 units of FFP
- 10 units cryoprecipitate
- 4 unit equivalent of platelets



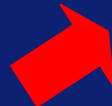
## **If further bleeding continues**

- Transfuse PC to keep Hb > 80g/L
- Give 4 units of FFP for every 4U PC

And transfuse:

- 4U Platelets – if platelets < 50 x 10<sup>9</sup>/L  
or 100 x 10<sup>9</sup>/L with DIC or head injury
- 10U Cryoprecipitate – if fibrinogen < 1.2
- FFP – if INR > 1.5 or APTT > 45

Repeat bloods ~ every 60 minutes



## **With “massive transfusion” and ongoing bleeding**

**Priority must be given to  
correct the triad of  
hypothermia, acidosis and  
coagulopathy**

**Consider the use of rVIIa**

# “New” blood bank driven PC:plasma equivalent Massive Transfusion Protocol

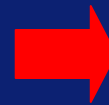
## **Activate massive transfusion protocol**

- Trauma with life threatening haemorrhage
- Expected replacement of > 1 BV / 24h
- **4 unit of RBC**



## **Blood product ‘shipments’**

- Each shipment contains 4U PC and 4U FFP
- 1 ‘pooled’ platelet with 2<sup>nd</sup> shipment (and alternate thereafter)
- 10U cryoplate with 3<sup>rd</sup> shipment (and alternate thereafter)



**rFVIIa 90µg/kg**

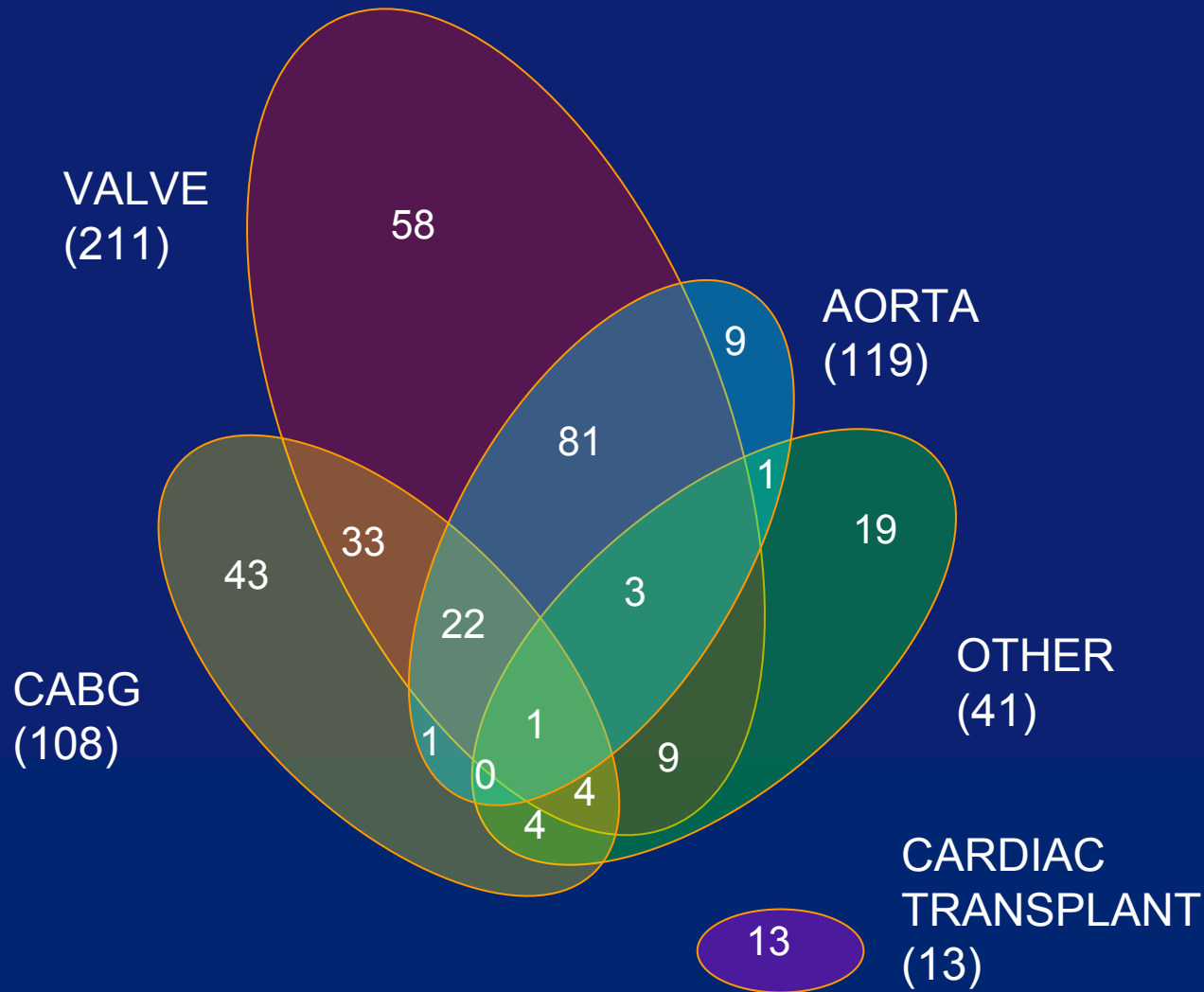
Suggested after 10units PC

haemostasis registry

**Correct the triad of hypothermia, acidosis and coagulopathy**  
Repeat bloods ~ every 60 minutes  
Platelets >50 x 10<sup>9</sup> /L  
or 100 x 10<sup>9</sup> /L with DIC or head injury  
Fibrinogen > 1g/L  
Calcium supplements if < 1.0mmol/L

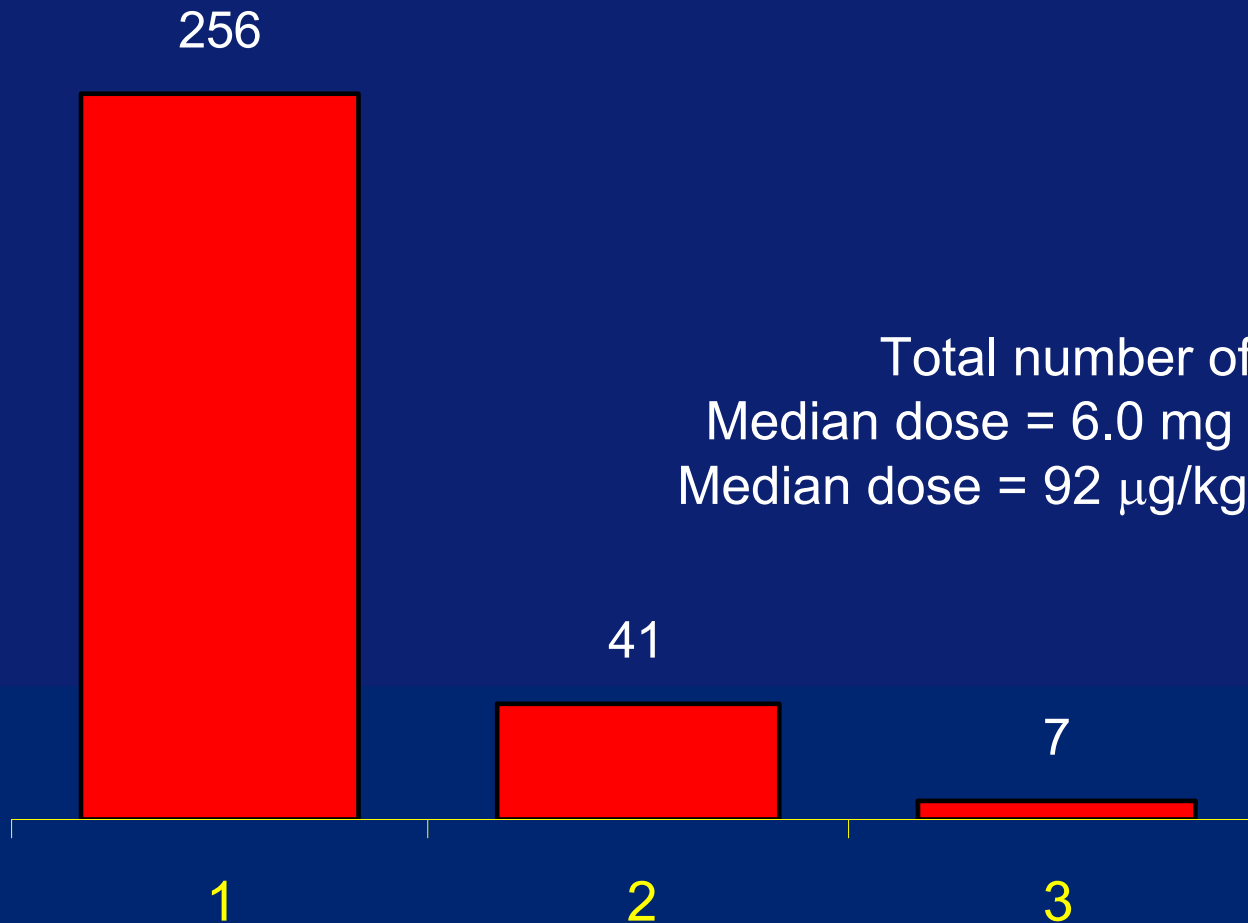


# Type of Cardiac Surgery



# Cardiac doses

Dunkley, et al. Ann Thorac Surg 2008



$n = 304$

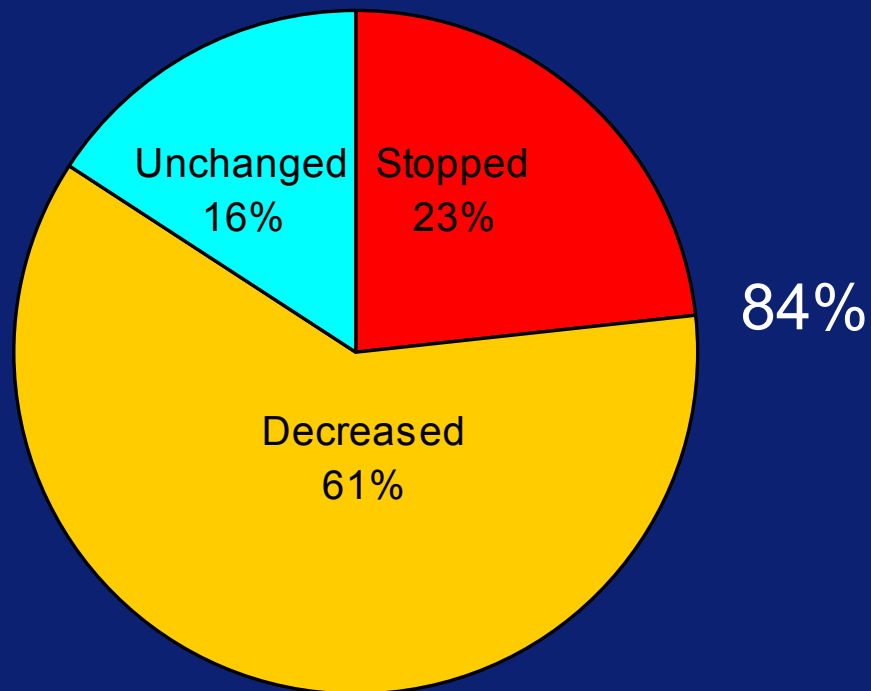
Total number of doses = 359

Median dose = 6.0 mg (IQR 4.8-8.4)

Median dose = 92  $\mu\text{g}/\text{kg}$  (IQR79-103)

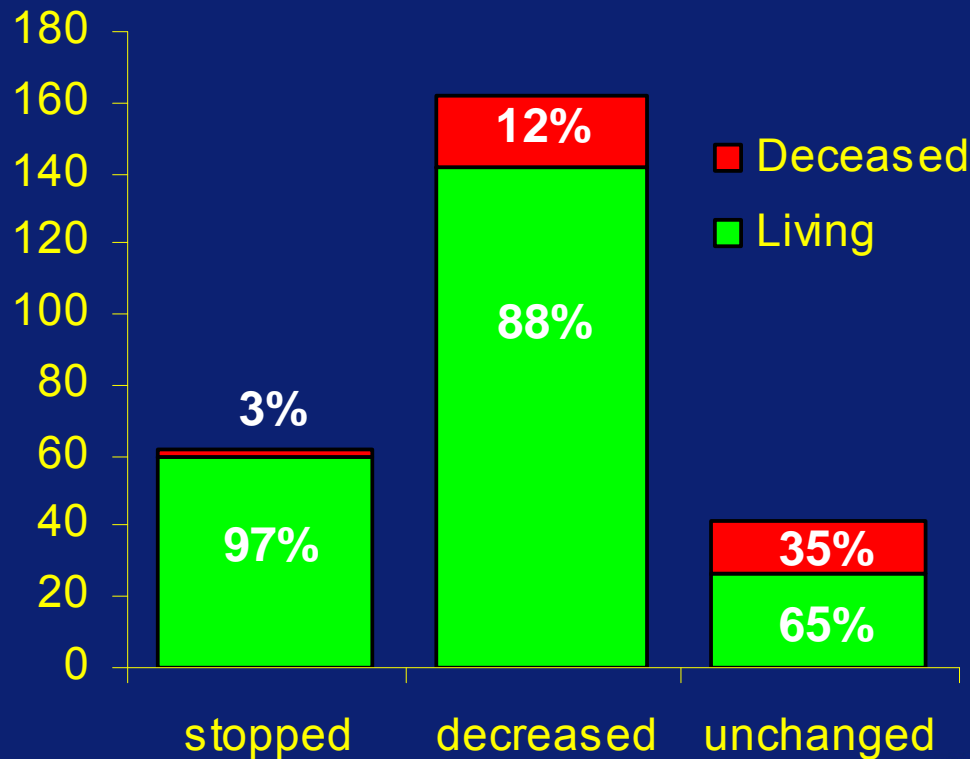
# Effect on Bleeding (cardiac)

Dose 1



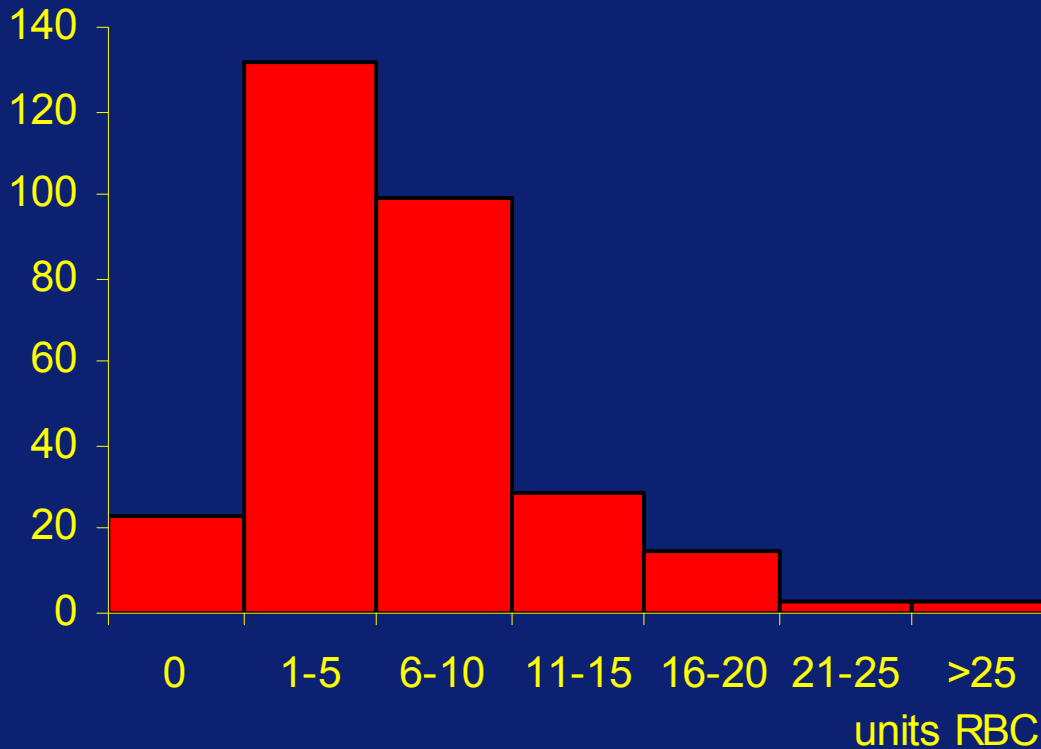
# Effect vs Outcome (28 day)

## cardiac subgroup



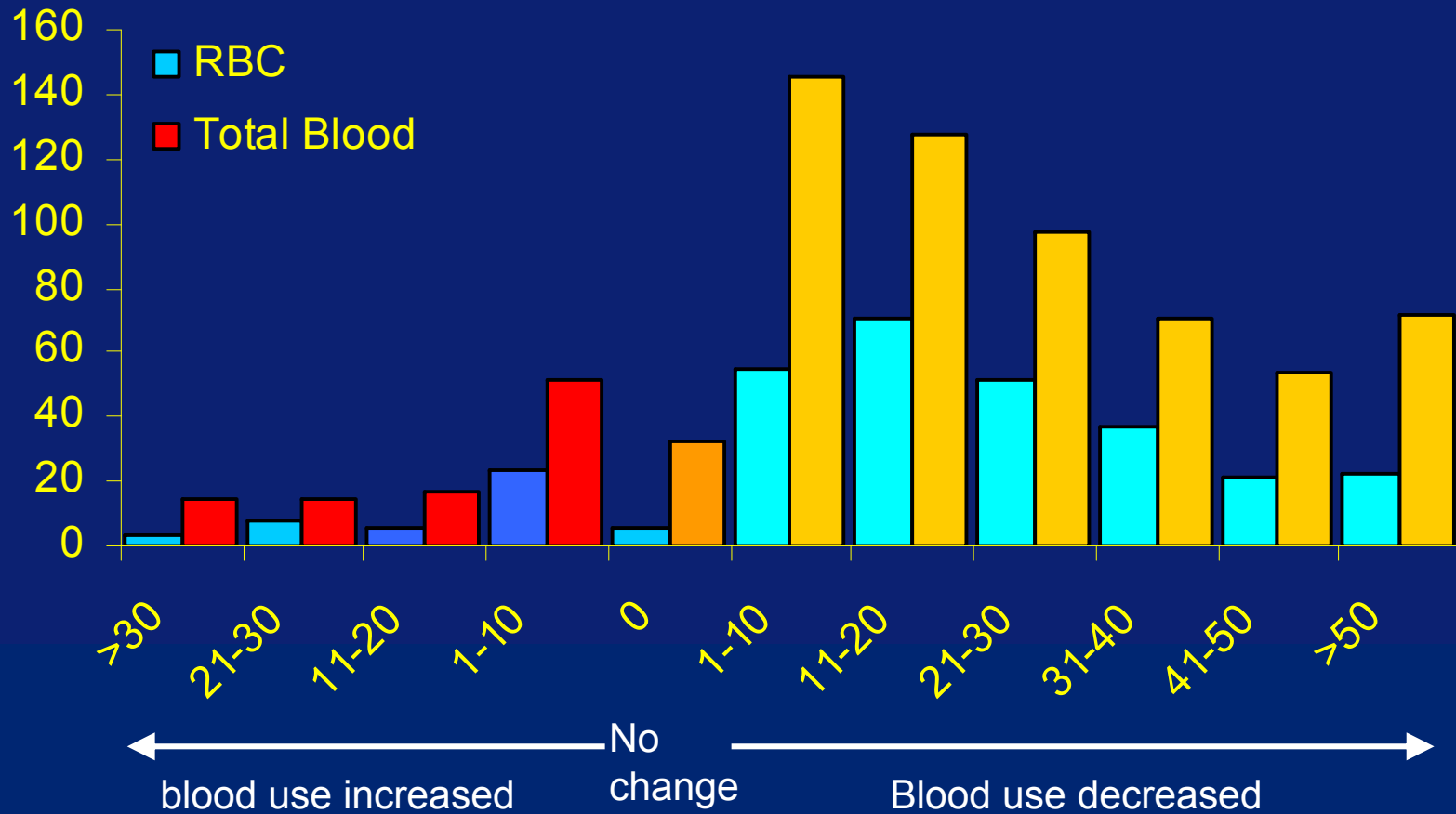
$\chi^2_2 = 22.9, p < 0.001$

# RBC before rFVIIa (cardiac)



$n = 304$   
Median = 5 units  
IQR 3 - 9  
Range 0 - 44

# Δ Total Blood Products before & after rFVIIa dose 1 (cardiac)



# Guidelines for Management of Critical Bleeding and Coagulopathy in Cardiac Surgery

## Appropriate Surgical Interventions:

- Identify and manage surgical bleeding

## Medical Interventions:

- Maintain haemodynamic stability; prevent and reverse hypothermia; prevent and reverse acidosis; heparin reversal; warfarin reversal

Suggest antifibrinolytic agents (aprotonin ,tranexamic acid)

### Early treatment in Theatre

Continued Bleeding with inability to close chest

Not responsive to 'small volume' coagulopathy correction

- usually 10 U cryoprecipitate
- 1 U 'pooled' platelets
- +/- 2 units FFP



rFVIIa, 50 µg/kg  
(rounded to whole vial)



If no response in 20 minutes.

Consider 2nd dose of rFVIIa (100 µg/kg)  
And repeat 'standard' coagulopathy correction

### Late Salvage in ICU/Theatre

Correct coagulopathy. Using 'standard' dose correction

Usually 4 U FFP, 1 U 'pooled' platelets, 10 U cryoprecipitate



If bleeding continues: With 5 units PC transfusion OR >200ml/hr chest drainage



SURGICAL REVIEW

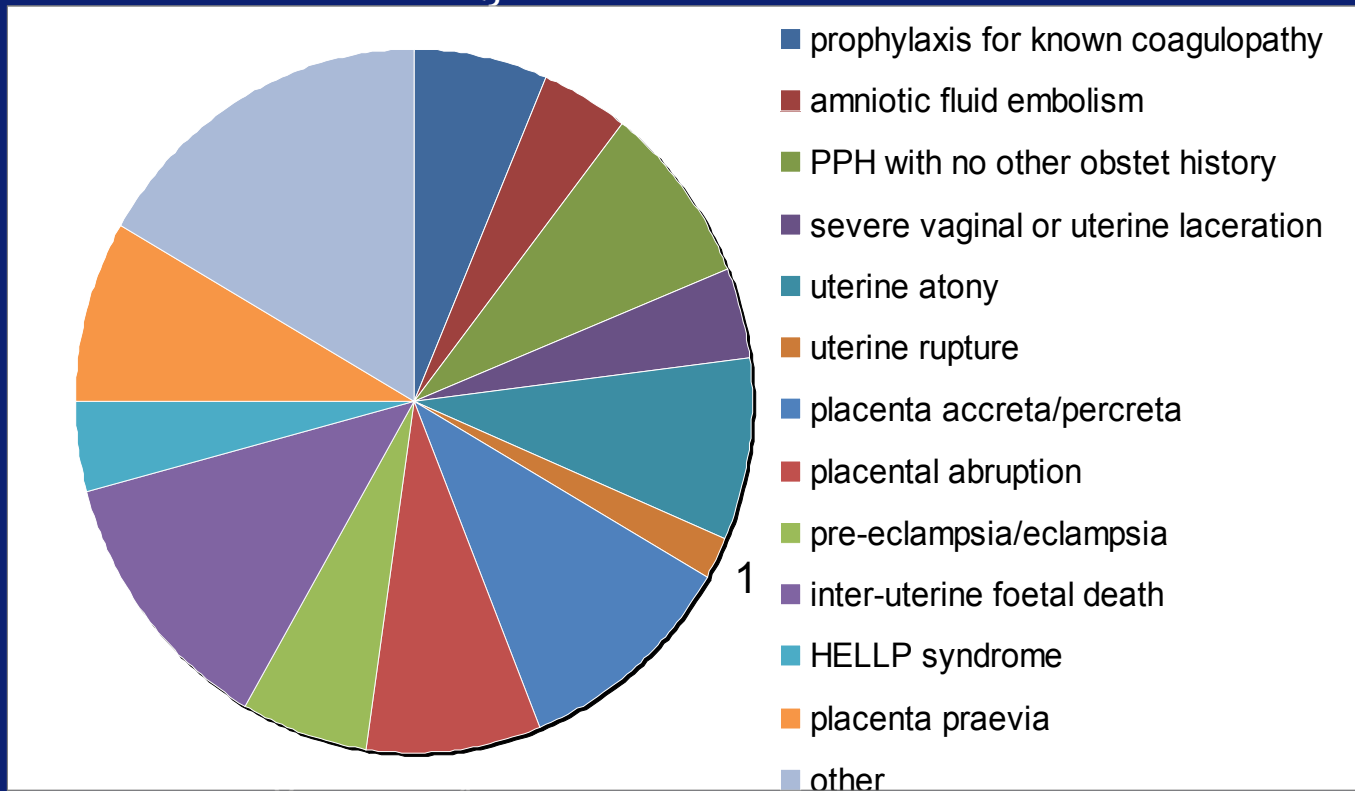
(If non-surgical coagulopathic bleeding)



rFVIIa, 100 µg/kg  
(rounded to whole vial)

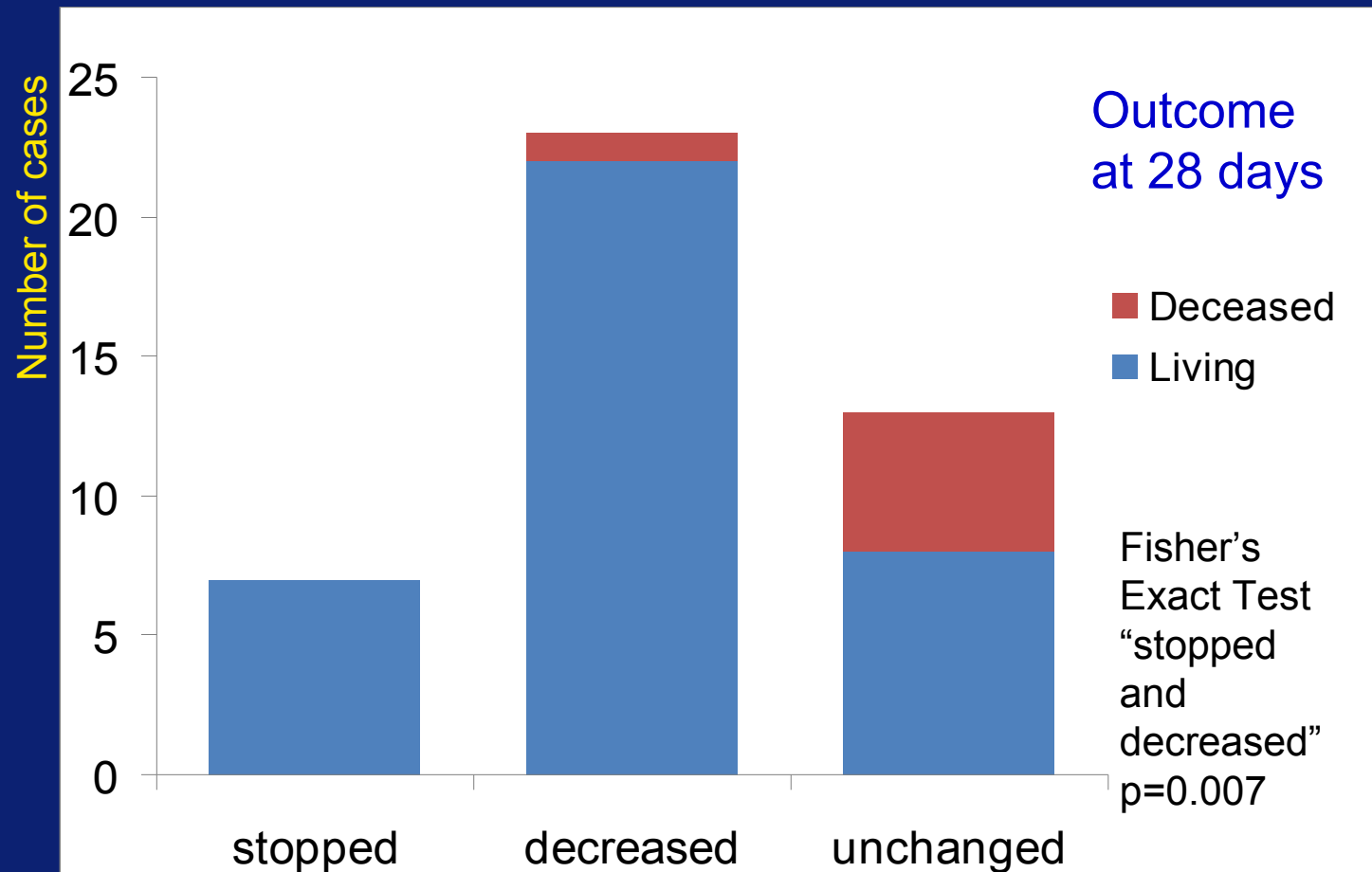


# Obstetric Category



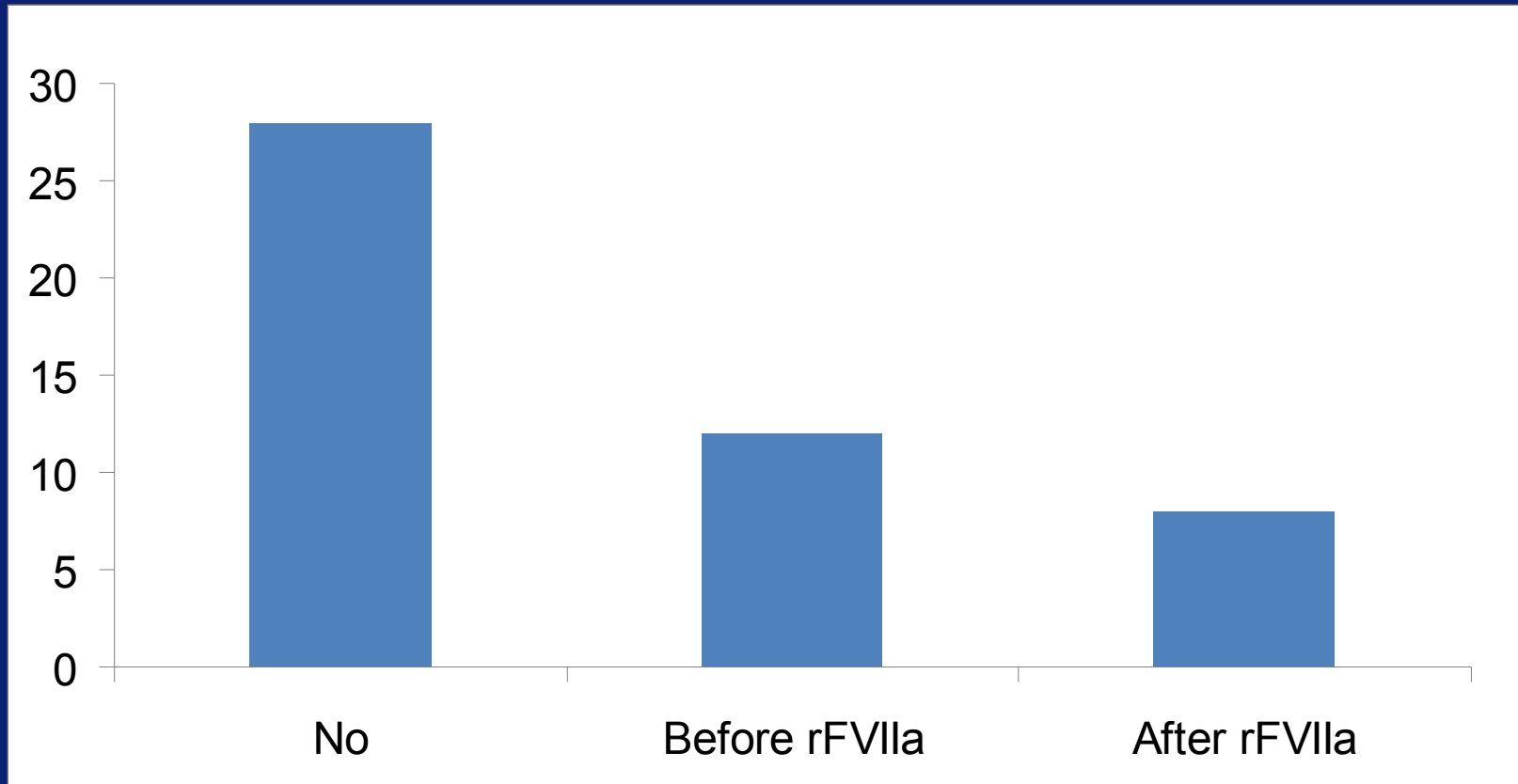
$n = 48$

# Effect on Bleeding vs Outcome



	Total adverse events	Thrombotic adverse events
Definitely linked	0	0
Probably linked	0	0
Possibly linked	0	0
Unlikely to be linked	8	1 (CVA)
Not linked	6	0
Unable to assess	1	1 (DVT)
total	15 (31%)	2 (4%)

# Use related to hysterectomy



# Management of Critical Bleeding in Postpartum Haemorrhage

## Appropriate Medical Interventions:

- Active resuscitation to maintain haemodynamic stability; prevent and/or reverse hypothermia; prevent and/or reverse acidosis
- Treat cause, uterine massage/compression, uterotonic agents
- Coagulation studies and attempt to treat coagulopathy

## Appropriate Surgical Interventions:

- EUA and repair, uterine tamponade, B-Lynch suture, arterial ligation, radiological arterial embolisation

Persistent bleeding unresponsive to directed therapy

- Perform surgical assessment
- Repeat coagulation studies

Treat bleeding and reverse coagulopathy \*

Initial:  
4 U PRBC

Subsequent:

- 1) 4 U PRBC+ 4 U FFP+ platelets
- 2) 4 U PRBC + 4 U FFP + platelets + 8 U cryoprecipitate

If uncontrolled bleeding continues after 8-12 U PRBC have been given and before performing a hysterectomy give rFVIIa, 90 µg/kg

If no response after 20 minutes. repeat rFVIIa 90µg/kg



If life-threatening bleeding continues:  
**HYSTERECTOMY**

# Conclusion

- rFVIIa increasingly used in Australia
- Overall efficacy is good, but improved by patient selection and pre-treatment
- Cardiac subgroup is unique with high efficacy correlating with survival, possibility of smaller doses, good economic outcome
- The role in PPH has been identified by the Australian Government
- In the absence of RCT, data-bases remain important to help guide treatment

# Acknowledgements

- Dr Louise Phillips (Haemostasis Registry Project Manager)
- Monash University, Department of Epidemiology and Preventive Medicine
- Haemostasis Registry Steering Committee
- Local Investigators and Data Collectors at participating hospitals



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