AATS ANNUAL MEETING 93RD 2013

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Platelet Activity Measured by a Rapid Turnaround Assay Identifies CABG Patients at Increased Risk for Bleeding and Transfusion Complications Following Clopidogrel Administration

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- No disclosures and no off-label indications to declare

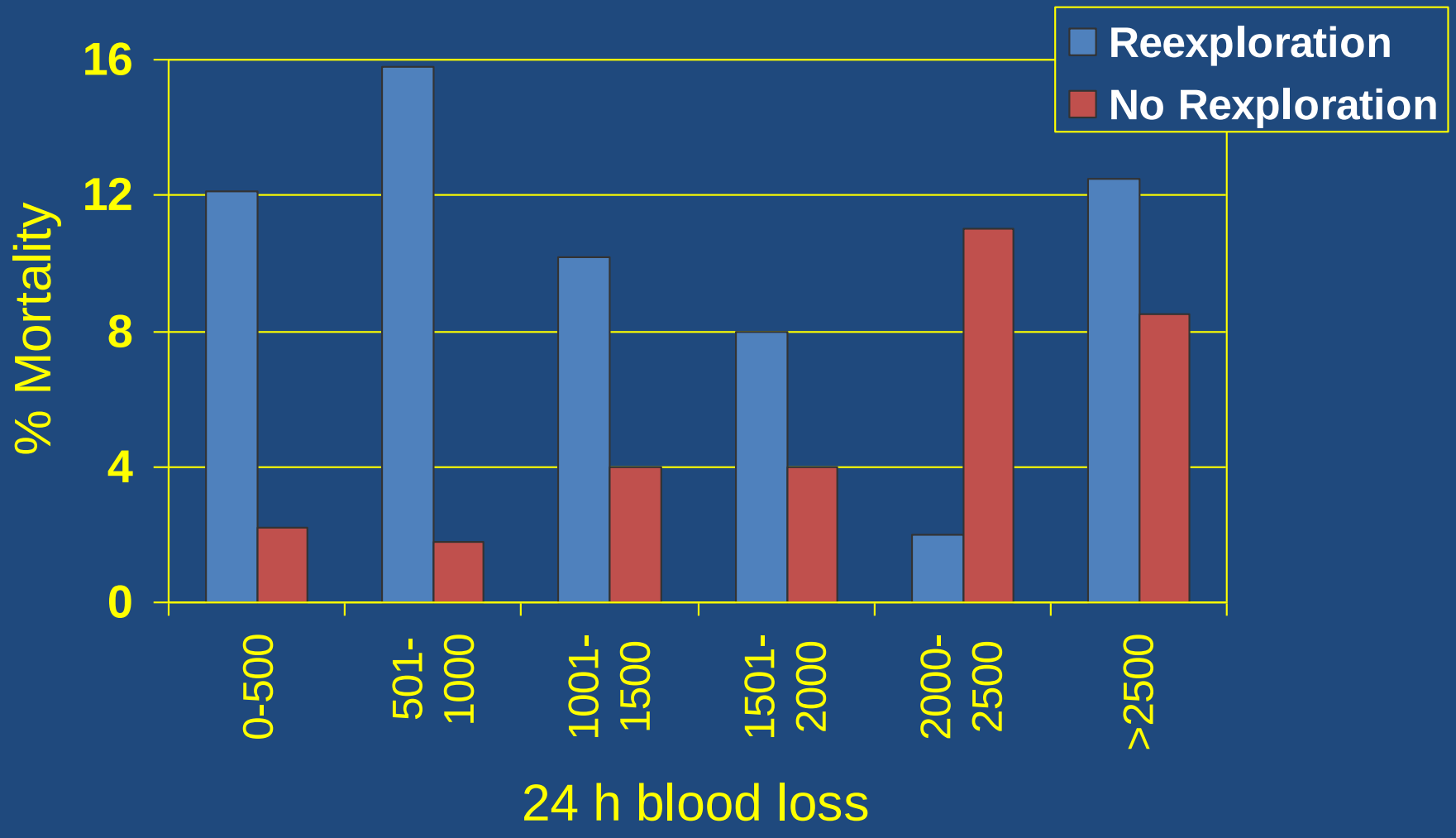
Introduction

An estimated 21% of patients who have undergone PCI will subsequently undergo coronary bypass surgery (CABG), and nearly 13% of CABG patients will present for surgery while receiving clopidogrel or another ADP inhibitor .

Clopidogrel use is associated with up to a 7-fold risk for re-operation and a 50% increase in number and incidence of RBC transfusions.

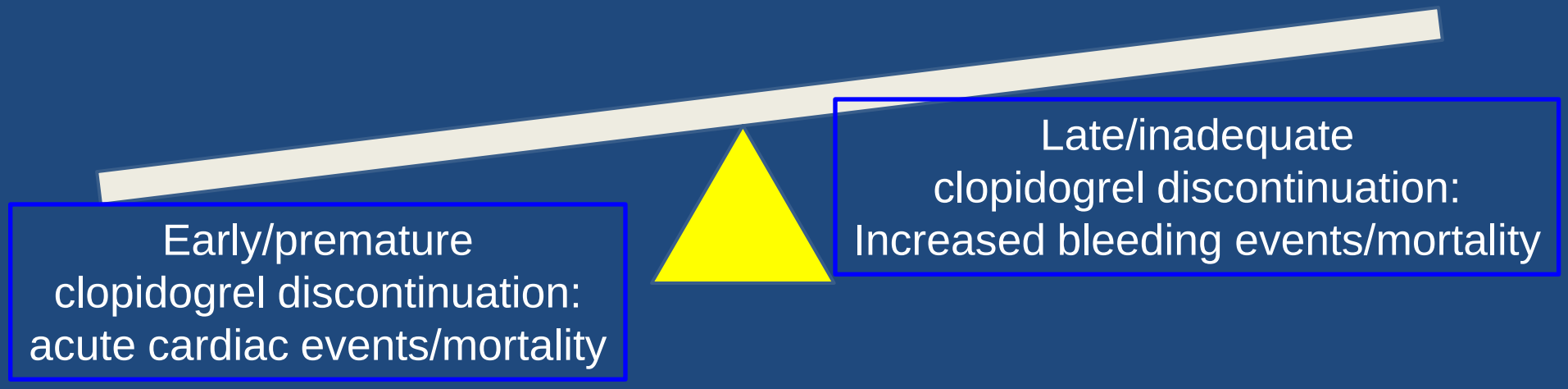
Although current guidelines recommend clopidogrel withdrawal 5-7d prior to open heart surgery, premature clopidogrel withdrawal may be associated with increased mortality rate and acute coronary events, especially in ACS patients.

Impact of Bleeding in Cardiac Surgery



Moulton MJ. J Thorac Cardiovasc Surg 1996; 111: 1037-46

Clopidogrel Withdrawal Risk/Benefit Ratio



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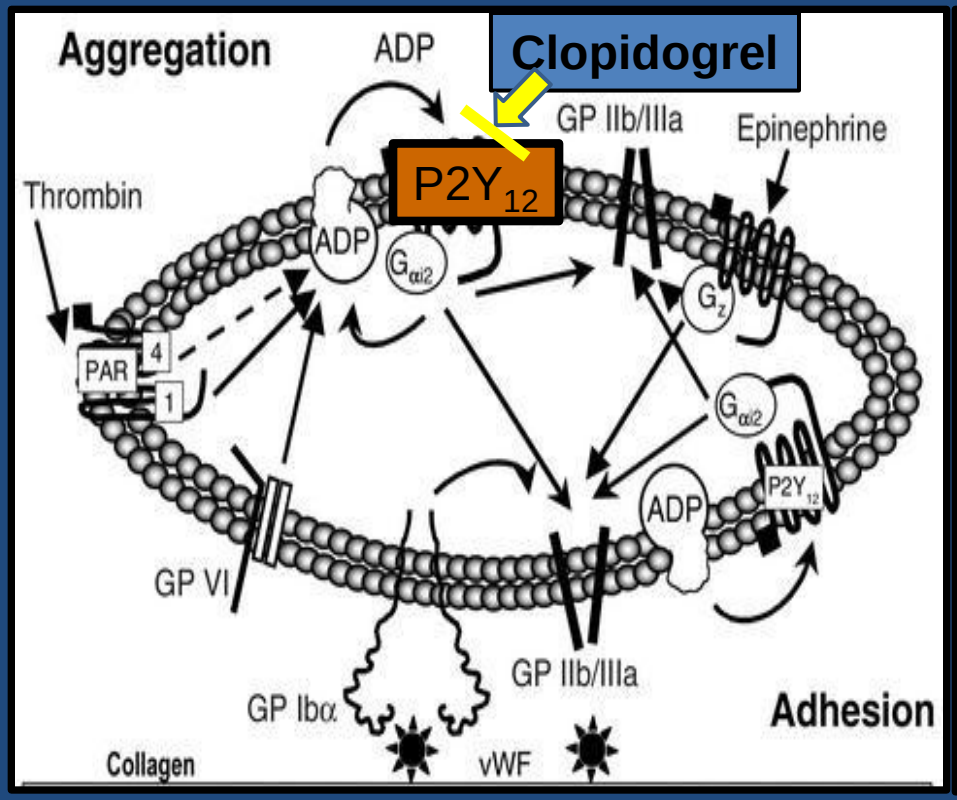
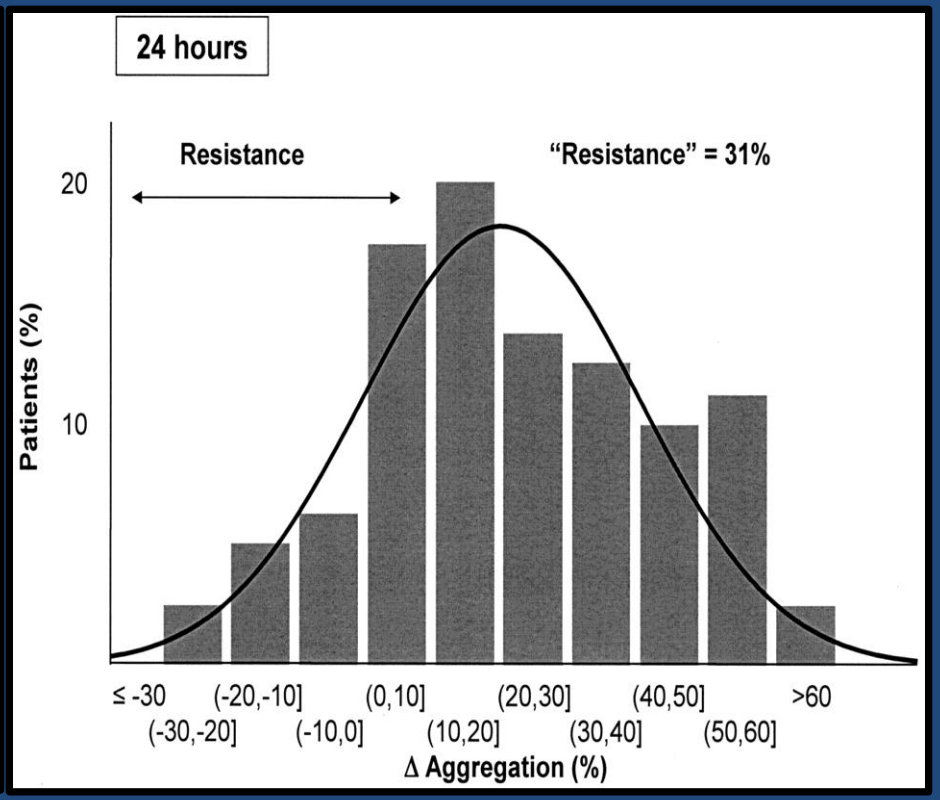
Clopidogrel Response Variability





Andre P *et al*. *J Clin Invest*. 2003;112: 398-406
O'Donoghue M , Wiviott S D Circulation 2006

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Hypothesis

Whereas the heteregeneity of response to clopidogrel administration makes levels of platelet inactivation unpredictable, a more accurate means of assessing the risk/benefit and accurate timing of clopidogrel discontinuation is desirable to minimize both bleeding/transfusion and increased mortality risks.

Hypothesis: Pre-op platelet aggregometry could be used to stratify bleeding/transfusion risk in patients receiving clopidogrel prior to CABG .

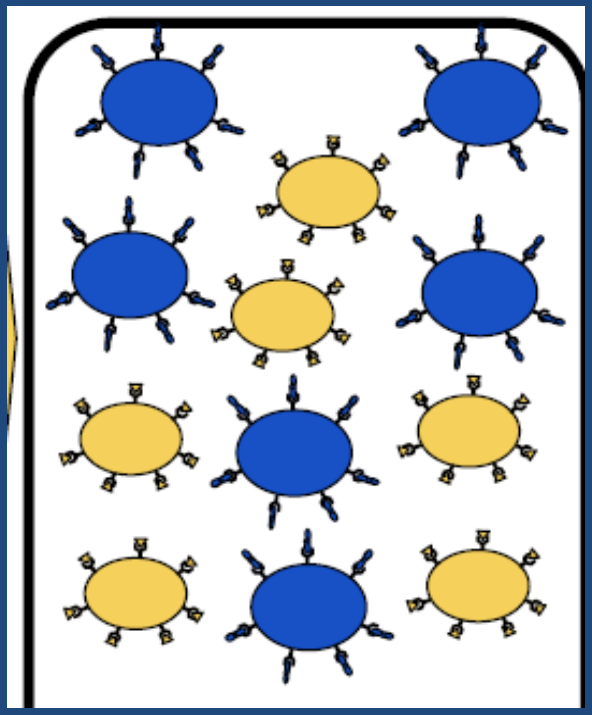
Study Design

- Retrospective analysis of de-identified records for all patients undergoing (on or off-pump) "CABG-only" procedure at our institution from January, 2010 to June, 2011 (n=366)

- Patients excluded were those with:
  - An excessive risk for bleeding/transfusion, as per STS guidelines:
    - Evidence of liver failure or renal dysfunction (n = 38)
  - Non-aspirin/clopidogrel glycoprotein IIb/IIIa inhibitor use (n = 8)
  - Clopidogrel use without $P2Y_{12}$ testing (n=18)
  - Incomplete records (n=26)

- Pre-operative platelet function was assayed within 24 hours of surgery.

$P2Y_{12}$ Receptor Blockade Assay



$P2Y_{12}$ receptor blockade assay
VerifyNow® system (Accumetrics)

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Descriptive Characteristics of Clopidogrel-treated CABG Population

Descriptive Characteristics	All (n=149)		"Normal" Function (PRU >=237; n=85)		"Abnormal" Function (PRU 0-236; n=64)	
Gender (female)	29	19%	19	22%	10	16%
Age (median, IQ)	65	(58, 73)	66	(58, 73)	63.5	(57, 73)
BSA (median, IQ)	2	(1.9, 2.2)	2	(1.9, 2.2)	2	(1.9, 2.2)
Race						
Caucasian	135	91%	74	87%	61	95%
Black/ African American	3	2%	3	4%	0	0%
Hispanic	7	5%	3	4%	4	6%
Priority						
Elective	1	1%	1	1%	0	0%
Emergent	3	2%	3	4%	0	0%
Urgent	145	97%	81	95%	64	100%
Diabetes mellitus	59	40%	38	45%	21	33%
Aspirin	105	70%	63	74%	42	66%
Peripheral vascular disease	13	9%	5	6%	8	13%
Off pump procedure	59	40%	30	35%	29	45%
Abnormal (low) hematocrit*	106	71%	66	78%	40	63%

*p=0.043

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Bleeding/Transfusion as a Function of Platelet Reactivity: Standard Criteria

Patient Characteristics	All		Group A "Normal" Function		Group B "Abnormal" Function		p-value
	(n=149)		(PRU >237; n=85)		(PRU 0-237; n=64)		
Red blood cell transfusion	63	42%	39	46%	24	38%	0.305
Coagulation factor transfusion	64	43%	29	34%	35	55%	0.012
High chest tube output*	62	42%	29	34%	33	52%	0.033
Bleeding/transfusion composite outcome**	92	62%	45	53%	47	73%	0.011

*High chest tube output: 12 hr output > 437 ml

**High chest tube output OR coagulation factor transfusion

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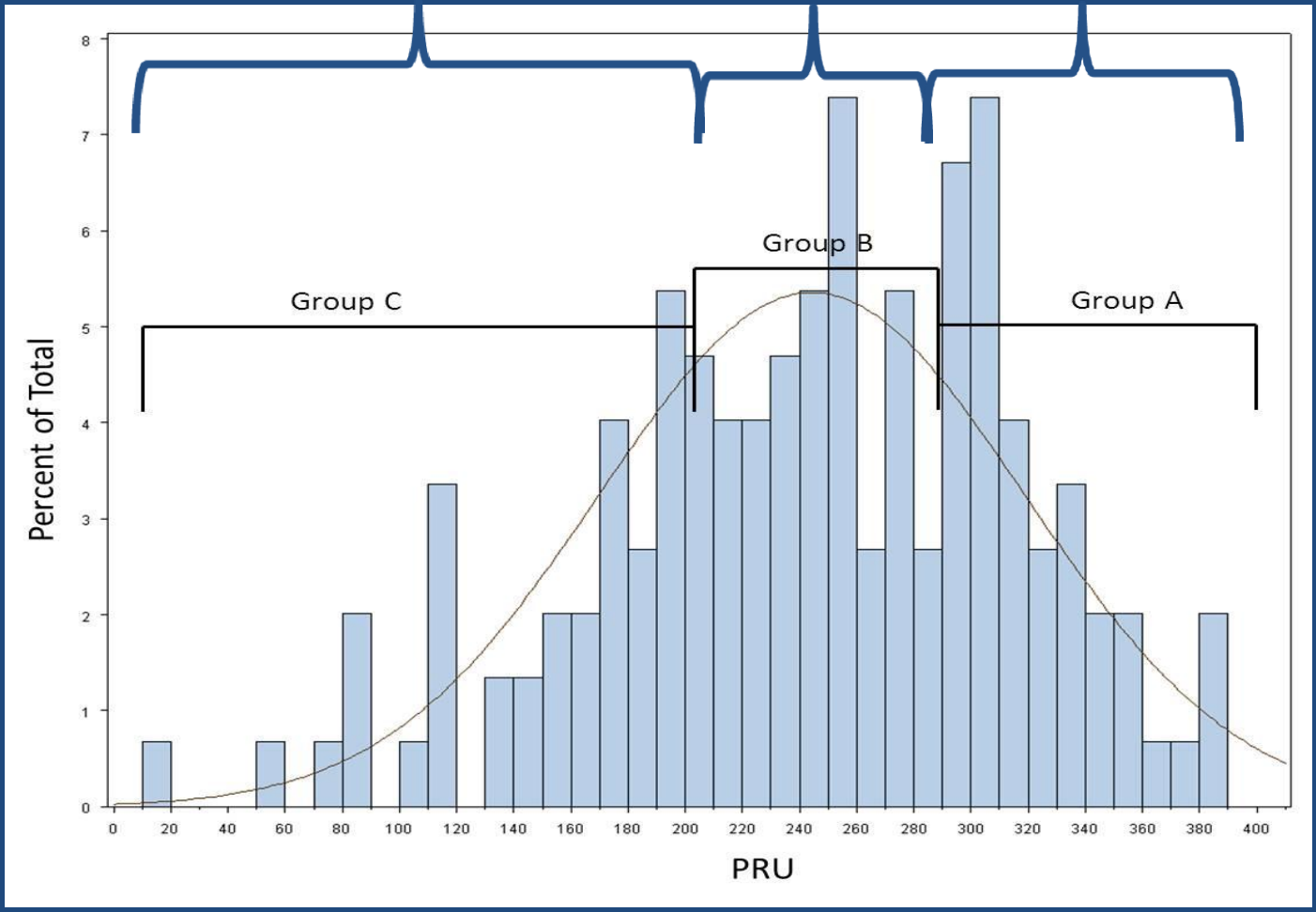
Stratification of Risk According to Heterogeneity of PRU Response



Clinical Outcomes as a Function of PRU Distribution Cut-off Stratification

Outcome	High Function (PRU >290; n=175)*		Intermediate Function (PRU 200-290; n=61)		Low Function (PRU<200; n=40)		p value
RBC transfusion	67	38%	22	36%	17	43%	0.808
Coagulation factor transfusion	51	29%	25	41%	26	65%	<0.0001
High chest tube output **	53	30%	27	44%	22	55%	0.0057
High chest tube output OR coagulation factor transfusion	77	44%	39	64%	32	80%	<0.0001
Adverse clinical event***	71	41%	21	34%	16	40%	0.694

*Includes high PRU clopidogrel treated patients (n=48) and “no clopidogrel controls (n=127)
** High chest tube output: 12 hr output > 437 ml
***30d post-op mortality, reoperation for bleeding, post-operative length of stay > 1 standard deviation from mean, readmission within 30d of primary hospital discharge

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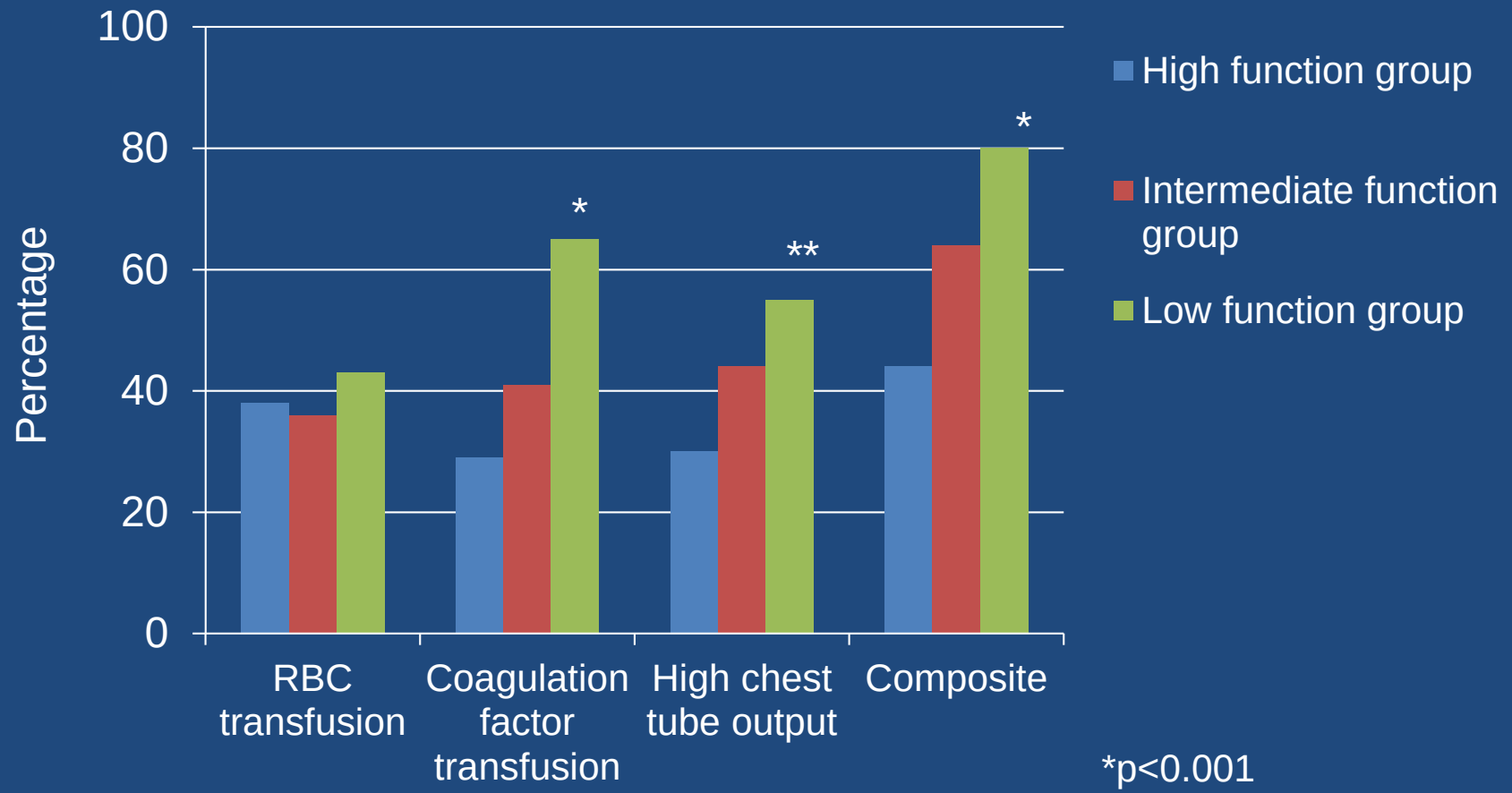
Clinical Outcomes as a Function of PRU Strata



*p<0.001
**p<0.01

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Adjusted Logistic Regression Analysis of Outcomes as a Function of PRU Strata*

Bleeding Outcomes	Odds Ratio	95% CI	P Value	C Index
High chest tube output **	1.72	(1.23, 2.42)	0.002	0.625
High function group	1.0	--	--	--
Intermediate function group	2.08	(1.12, 3.86)	0.02	
Low function group	2.73	(1.34, 5.57)	0.006	
Coagulation factor transfusion	2.08	(1.47, 2.94)	<0.0001	0.65
High function group	1.0	--	--	--
Intermediate function group	1.95	(1.04, 3.63)	0.037	
Low function group	4.46	(2.13, 9.33)	<0.0001	
High chest tube output OR coagulation factor transfusion	2.36	(1.61, 3.47)	<0.0001	0.666
High function group	1.0	-	-	
Intermediate function group	2.67	(1.43, 4.97)	0.02	
Low function group	5.08	(2.19, 11.77)	0.0002	

*Model adjusted for increased pre-operative use of aspirin found in Group II

** High chest tube output: 12 hr output > 437 ml

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Conclusions

Anti-platelet agent responsiveness requires careful monitoring in patients undergoing CABG after receiving clopidogrel, as a wide range of bleeding and transfusion risks are associated with prior clopidogrel dosing.

Point of care platelet functional testing can be used to monitor levels of anti-platelet effects and assist in timing of clopidogrel discontinuation to minimize bleeding risks.

Compared to arbitrary timelines, this strategy might better balance bleeding and (stent) thrombosis risks in patients undergoing CABG after anti-platelet agents.

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Clinical Outcomes as a Function of Platelet Reactivity: Standard Criteria

Descriptive Characteristics	All (n=149)		Group A Normal Function (PRU >=237; n=85)		Group B Abnormal Function (PRU 0-236; n=64)	
Reoperation for bleeding	3	2%	1	1%	2	3%
Prolonged length of stay*	36	24%	22	26%	14	22%
Readmission (30 day)	21	14%	11	13%	10	16%
Mortality (30 day)	4	3%	1	1%	3	5%
Composite**	57	38%	33	39%	24	38%

*Prolonged post-op length of stay (> 6 days [1 SD])

**30d post-op mortality, reoperation for bleeding, post-operative length of stay > 1 SD from mean, readmission within 30d of primary hospital discharge

Transfusion as a Function of Platelet Reactivity: Standard Criteria

Transfusion Characteristics	ALL (n=149)			Group A (PRU>=237; n=85)			Group B (PRU 0-236; n=64)		
	n	%	Median (IQ)*	n	%	Median (IQ)	n	%	Median (IQ)
Any transfusion	85	57%	3 (2, 6)	48	57%	3 (2, 5)	37	58%	4 (2, 6)
Red blood cells	63	42%	2 (1, 3)	39	46%	2 (1, 3)	24	38%	2 (1, 3)
Platelets	57	38%	2 (1, 3)	24	28%	2 (1, 3)	33	52%	2 (1, 2)
Fresh frozen plasma	33	22%	2 (2, 3)	16	19%	2 (2, 2.5)	17	27%	2 (2, 3)

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