CADILLAC Study

Blood Transfusion after Myocardial Infarction: Friend, Foe or double-edged Sword?

Georgios I. Papaioannou, MD, MPH, FACC, FSCAI

Athens Medical Center

Cardiac Catheterization Laboratory

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GP IIb/IIIa Inhibitors during STEMI: CADILLAC Study

2082 patients with STEMI within 12 hrs
ASA+Heparin+Plavix/Ticlid (load)
2.5-4.0 mm vessels

- PTCA n=518
- PTCA+Abciximab n=528
- Stenting n=512
- Stenting+Abciximab n=524

Outcome	PTCA (N=518)	PTCA plus Abciximab (N=528)	Stenting (N=512)	Stenting plus Abciximab (N=524)	P Value
At 6 months (cumulative)					
Death	4.5	2.5	3.0	4.2	0.23
Reinfarction	1.8	2.7	1.6	2.2	0.64
Disabling stroke	0.2	0.2	0.4	0.4	0.88
Revascularization of ischemic target vessel	15.7	13.8	8.3‖	5.2**	<0.001
Composite end point	20.0	16.5	11.5††	10.2‡‡	<0.001
Target-vessel revascularization for any reason	16.9	14.8	8.9‡‡	5.7**	<0.001

Hypothesis: Stenting was superior to PTCA and not inferior to PTCA+Abciximab with respect to composite end point. P values compare abciximab vs. non-abciximab groups.

N Engl J Med 2002;346:957-66.

CADILLAC: 30 Days Results

Outcome	PTCA (N=518)	PTCA plus Abciximab (N=528)	Stenting (N=512)	Stenting plus Abciximab (N=524)	P Value
		percent			
At 30 days					
Death	2.5	1.1	2.2	2.7	0.31
Reinfarction	0.8	0.8	1.0	0.8	0.97
Disabling stroke	0.2	0.0	0.2	0.2	0.79
Revascularization of ischemic target vessel	5.6	3.4	3.2	1.6†	0.004
Composite end point	8.3‡	4.8	5.7	4.4	0.02
Other adverse events					
Target-vessel revascularization for any reason	6.0	3.6	3.4§	1.6†	0.002
Subacute thrombosis	1.9	0.8	1.0	0.0	0.01
Hemorrhagic complication					
Severe	0.6	0.4	0.2	0.8	0.58
Moderate	2.5	2.3	4.3	2.5	0.18
Intracranial hemorrhage	0.0	0.0	0.0	0.2	0.99
Thrombocytopenia (<100,000 cells/mm³)	1.4¶	4.0	2.6	4.0	0.02
Blood-product transfusion	3.7	5.1	4.1	5.0	0.62

N Engl J Med 2002;346:957-66.

Reanalysis: **CADILLAC Study-**Prognostic Impact of Blood Transfusion After Primary Angioplasty for Acute Myocardial Infarction

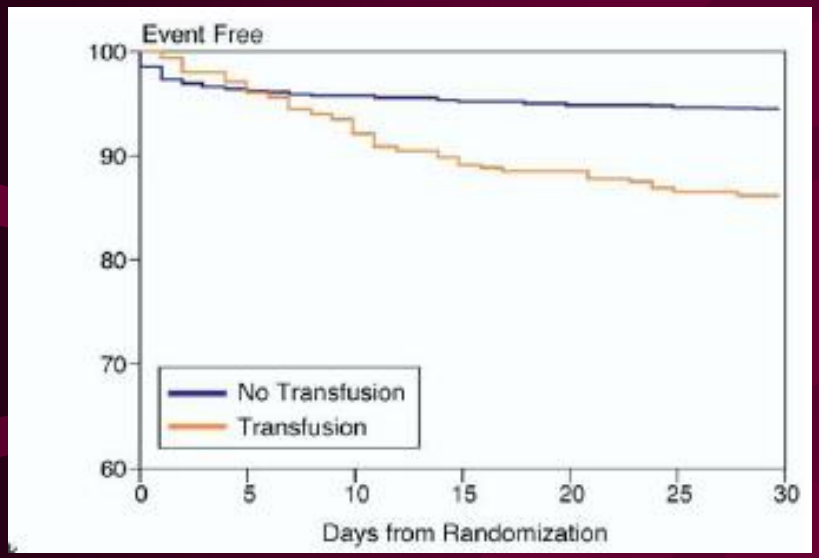
Background

- Bleeding is the most important non-cardiac complication in patients undergoing PCI
- Limited data are available to guide transfusion therapy in patients with chronic anemia and/or active hemorrhage
- Current treatment of CAD and MI involves both catheter based and pharmacological interventions

JACC Intv 2009;2:624-632

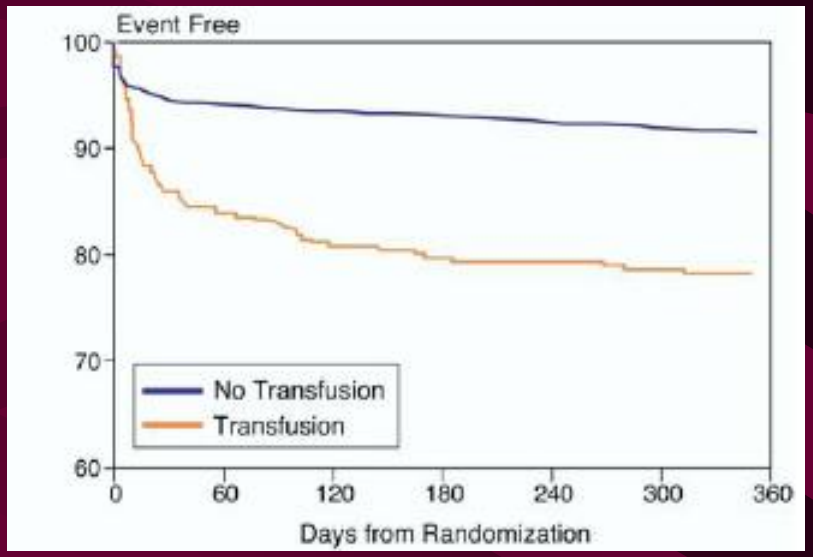
GUSTO IIb -Thrombolysis in STEMI

30 days – **All cause mortality**



13.7% vs. 5.5% - p<0.01

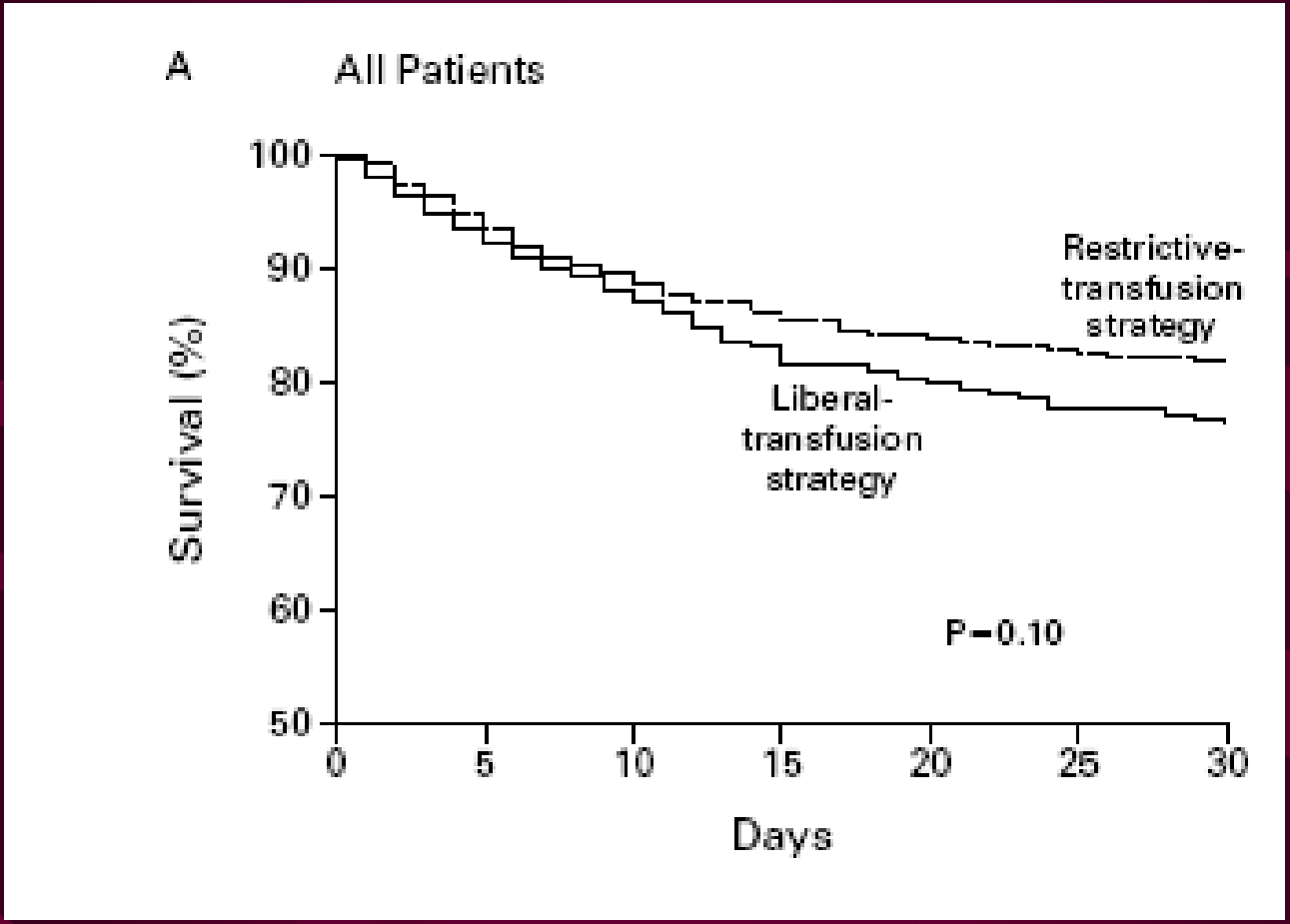
1 year – All cause mortality



21.8% vs. 8.7% - p<0.01

JACC Intv 2009;2:46-53

TRICC Study - Transfusion Requirement in Critical Care



N Engl J Med 1999;340:409-417

STEMI CT Database (>1000 patients)

Variable	Odds Ratio	P value
Recurrent infarction	10	0.001
TIMI bleeding	8.9	0.003
Endotracheal intubation	6.5	0.04
Baseline anemia	5.5	0.03
IABP	5	<0.001
Age	1.1	0.02

Papaioannou et al. Am J Cardiol 2004;94(Suppl):240.

Baseline Characteristics - CADILLAC

Table 1. Baseline Clinical Characteristics and Angiographic Features According to Blood Transfusion Administration

	Red Blood Cell Transfusion (n = 82)	No Transfusion (n = 1,978)	p Value
Clinical characteristics			
Male sex	47.6%	74.1%	<0.0001
Age, yrs	67.5 [58–74]	59 [50–68]	<0.0001
Diabetes mellitus	23.2%	24.3%	0.13
Hypertension	57.3%	47.7%	0.09
Hyperlipidemia	42.7%	37.6%	0.35
Current smoking	34.1%	43.7%	0.09
Prior myocardial infarction	7.3%	14.0%	0.10
Prior percutaneous coronary intervention	6.1%	11.4%	0.15
Prior coronary bypass surgery	3.7%	1.9%	0.21
Prior stroke or transient ischemic attack	4.9%	2.9%	0.30
History of peripheral vascular disease	6.1%	2.6%	0.07
History of gastrointestinal bleeding	6.1%	0.9%	0.002
History of genitourinary bleeding	0.0%	0.2%	1.00
Killip class ≥2	17.1	10.4%	0.07
Body mass index, kg/m^2	25.9 [25.8–28.7]	27.3 [28.8–30.5]	0.005
Baseline anemia	36.6%	10.8%	<0.0001
Baseline hemoglobin, g/dl	13.1 [11.8–14.5]	14.7 [13.6–15.6]	<0.0001
Baseline hematocrit, %	38.7 [34.4–43.0]	43.1 [40.1–45.9]	<0.0001
Baseline platelet count, ×10^3 cells/mm^3	248 [193–307]	230 [193–272]	0.04
Baseline creatinine clearance, ml/min	64 [46–92]	89 [67–113]	<0.0001
Chronic renal insufficiency, %	38.0%	17.3%	<0.0001
ST-segment elevation or left bundle branch block	86.8%	88.0%	0.72
Symptom to balloon inflation, h	4.4 [3.4–7.8]	4.0 [2.9–6.1]	0.05
Angiographic features			
Single-vessel disease	43.9%	52.0%	0.17
Double-vessel disease	28.0%	33.3%	0.34
Triple-vessel disease	28.0%	14.7%	0.002
Left ventricle ejection fraction, %	45 [35–55]	50 [40–56]	0.07
Infarct-related artery			
Left anterior descending artery	37.8%	36.7%	0.91
Left circumflex artery	19.5%	17.2%	0.55
Right coronary artery	42.7%	45.8%	0.65
Medications on admission			
Aspirin	23.2%	27.4%	0.45
Thienopyridine	2.4%	2.6%	1.0
ACE inhibitor or ARB	18.3%	9.0%	0.01
Beta-blocker	7.3%	15.1%	0.06
Calcium-channel blocker	34.1%	14.8%	<0.0001
Statin	17.1%	11.6%	0.15

Data are presented as percentages and as median [interquartile range].
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

Procedural Results - CADILLAC

Table 2. Procedural Results According to Blood Transfusion Administration

	Red Blood Cell Transfusion (n = 82)	No Transfusion (n = 1,978)	p Value
TIMI flow			
Baseline			
Grade 0 or 1	70.4%	67.8%	0.71
Grade 2	7.4%	10.2%	0.57
Grade 3	22.2%	22.0%	1.0
Final			
Grade 0 or 1	6.3%	1.1%	0.003
Grade 2	7.5%	2.8%	0.03
Grade 3	86.3%	96.1%	0.0004
Reference diameter, mm			
Baseline	2.8 [2.5–3.3]	3.0 [2.6–3.3]	0.06
Final	2.9 [2.5–3.2]	3.0 [2.6–3.4]	0.048
Minimal luminal diameter, mm			
Baseline	0 [0–0.8]	0 [0–0.7]	0.64
Final	2.6 [2.5–2.9]	2.7 [2.4–3.0]	0.74
Diameter stenosis, %			
Baseline	100 [71–100]	100 [75–100]	1.0
Final	10 [0–19]	11 [4–18]	0.52
Stent implanted			
Per randomization	48.8%	49.8%	0.91
As bail-out for complications	7.3%	8.1%	1.00
Abciximab administered			
Per randomization	57.6%	50.5%	0.26
As bail-out for complications	9.8%	2.6%	0.002
Volume of contrast media, ml	300 [240–360]	295 [211–375]	0.79
Procedural success	76.9%	92.8%	<0.0001
Procedure duration, h	1.20 [0.90–1.80]	1.02 [0.78–1.35]	0.0005

Data are presented as percentages and as median [interquartile range].
TIMI = Thrombolysis In Myocardial Infarction.

Nadir Hematocrit Values in Patients Received RBC Transfusion

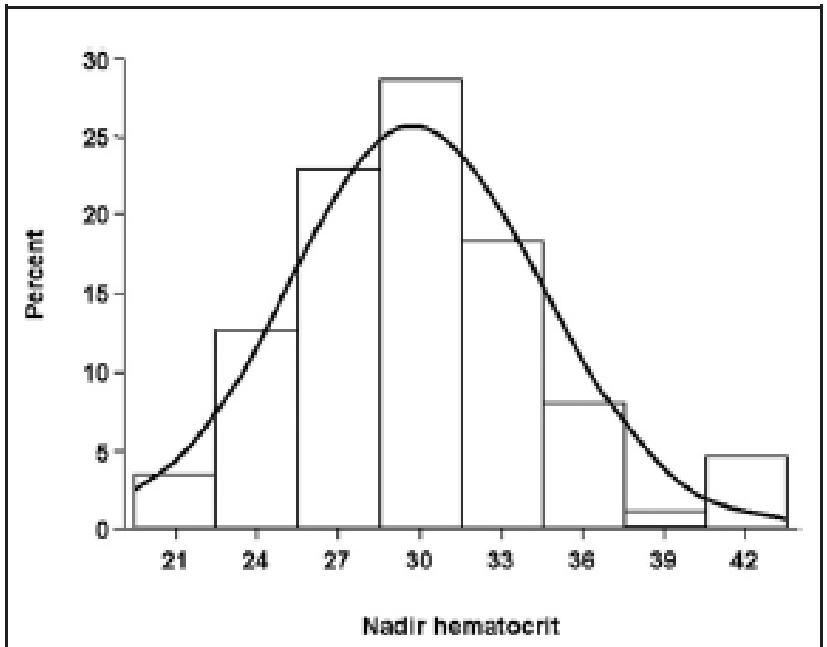


Figure 1. Histogram of In-Hospital Nadir Hematocrit Values in Patients Receiving an RBC Transfusion

The mean ± standard deviation nadir hematocrit in patients who received transfusion was 29.9 ± 4.65%. In more than one-half of transfused patients (53.7%), nadir hematocrit was >30%.

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KM Estimates of Adverse Events at 1 Year

A. Death

B. Reinfarction

C. TVR

D. Stroke

E. MACE

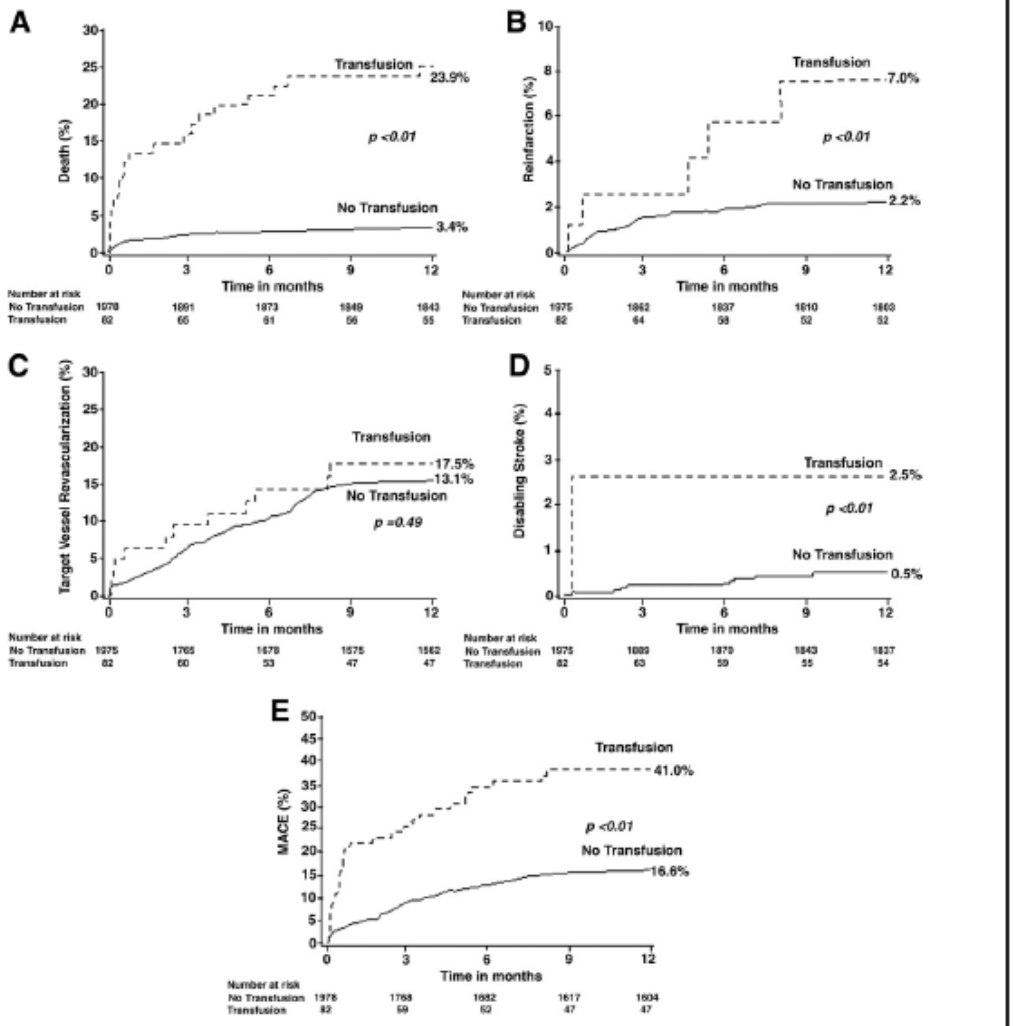

Figure 2. Kaplan-Meier Estimates of Adverse Events at 1 Year

Cumulative adverse event rates during 1 year of follow-up in patients undergoing primary percutaneous coronary intervention for acute myocardial infarction stratified by red blood cell transfusion. (A) Death; (B) reinfarction; (C) target vessel revascularization; (D) disabling stroke; and (E) composite major adverse cardiovascular events (MACE).

Outcomes in Patients transfused according to bleeding status

Table 3. Clinical Outcomes at 30 Days and 1 Year in Patients Receiving Red Blood Cell Transfusions According to Whether Overt Moderate or Severe Bleeding Was Present

	Transfusion in the Setting of Major Bleeding (n = 33)	Transfusion Without Major Bleeding (n = 49)	p Value
Mortality			
30 days	6.1%	18.4%	0.11
1 yr	19.0%	29.3%	0.26
Disabling stroke			
30 days	3.1%	2.3%	0.83
1 yr	3.0%	2.3%	0.83
Reinfarction			
30 days	0.0%	4.4%	0.23
1 yr	7.9%	7.2%	0.90
Target vessel revascularization			
30 days	0.0%	8.9%	0.05
1 yr	7.9%	17.3%	0.19
Composite adverse events			
30 days	9.1%	30.6%	0.02
1 yr	28.6%	45.0%	0.09

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Multivariate Analysis

Table 4. Multivariable Predictors of Mortality at 30 Days and 1 Year

	Hazard Ratio (95% Confidence Interval)	p Value
30-day mortality		
Renal insufficiency	5.96 (2.73–13.03)	<0.0001
Left anterior descending artery infarct vessel	5.06 (2.32–11.02)	<0.0001
Blood transfusion	4.71 (1.97–11.26)	0.0005
Propensity to transfusion	1.60 (1.04–2.45)	0.032
Hypertension	2.91 (1.24–6.81)	0.014
1-year mortality		
Blood transfusion	3.16 (1.66–6.03)	0.0005
Left anterior descending artery infarct vessel	2.41 (1.47–3.96)	0.0005
Renal insufficiency	2.60 (1.42–4.74)	0.002
Killip class 2 or 3	2.28 (1.30–4.02)	0.004
Baseline minimal luminal diameter	0.44 (0.24–0.81)	0.0008
Age	1.03 (1.01–1.06)	0.015
Propensity to transfusion	1.43 (1.03–1.99)	0.033

Principal findings – CADILLAC Study

- RBC transfusion was administered to 3.9% of patients despite the absence of clinically overt moderate or severe bleeding
- Baseline anemia was the strongest independent predictor of RBC transfusion
- Patients received RBC transfusion had worse clinical characteristics, angiographic and clinical outcomes
- After adjustment RBC transfusion but not anemia remained the most powerful independent predictor of 30 days and 1 year mortality
- Prognosis among those who received RBC transfusion was worse in those without associated moderate or severe bleeding

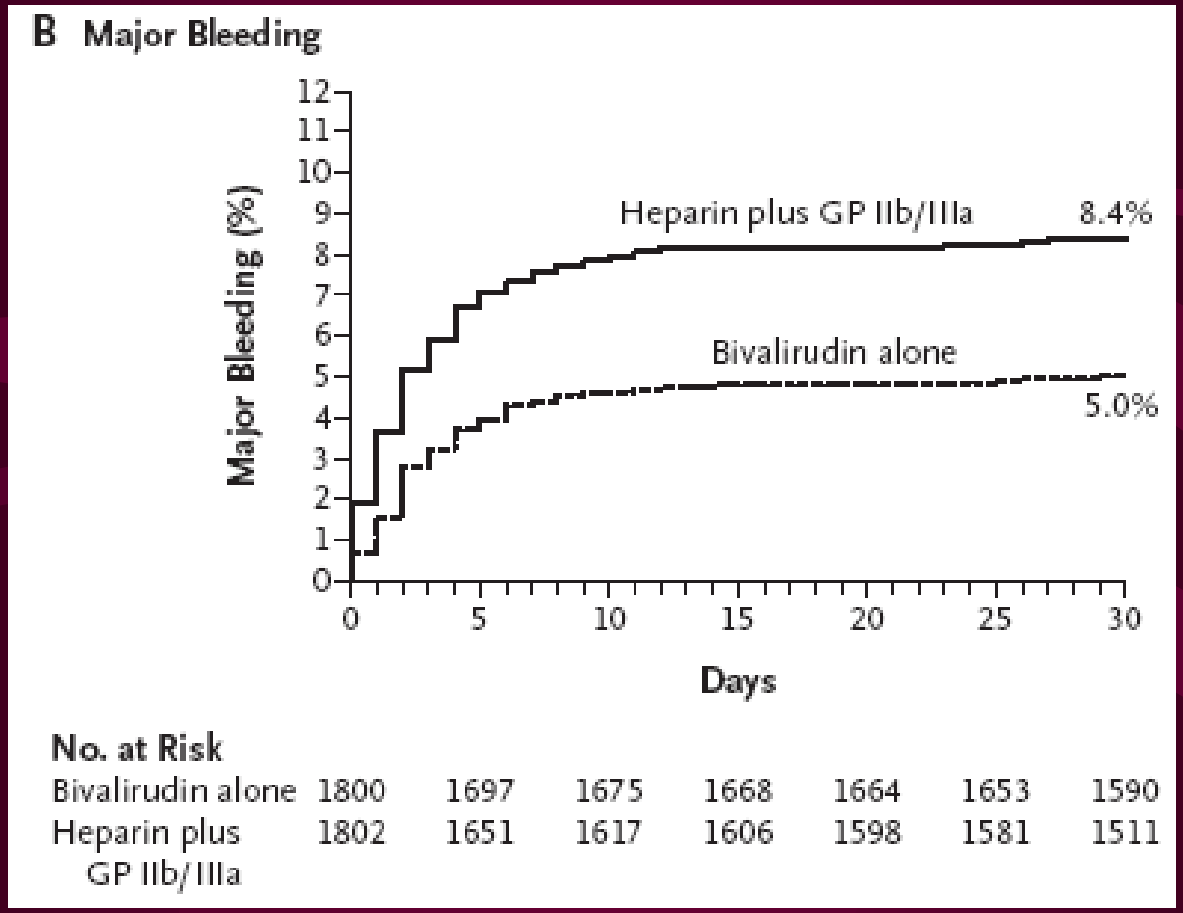
Issues

- Post hoc analysis of prospectively collected data
- Transfusion was a post randomization event
- Anemia cause was never investigated
- Potential effect of discontinuation of antithrombin and antiplatelet therapy due to bleeding
- Lack of a cause-effect explanation and mechanism (causality and plausibility - key in statistics)

Strategies that diminish bleeding risk

- Role of newer anticoagulants (?DTIs)
- Dose adjustment (gender, body mass index, renal function etc) – measurement of ACT (heparin)
- Meticulous puncture technique (femoral)
- Radial access
- Restrictive indication strategy for blood transfusion whenever appropriate

DTIs – HORIZONS MI



NEJM 2008;358:2218-2230

Radial Access – MORTAL Study

- 32,000 patients underwent PCI in BC-Canada from 1999-2005
- RA was associated wit 50% reduction of transfusion rate
- RA had an ARR of 1% and RRR of 17% in 1 year mortality (NNT 100 patients)

Heart 2008:94;1019-1025

Conclusion

- Anemia and bleeding are important predictors of an adverse outcome in patient undergoing elective or emergent PCI
- Blood transfusion may be associated with adverse outcomes too – lack of a causal mechanism
- Manipulation of pharmacological and non-pharmacological strategies to diminish access site bleeding risk
- Restrictive transfusion policies appears warranted till more studies are available