

How to use antithrombotics in patients with renal impairment ?

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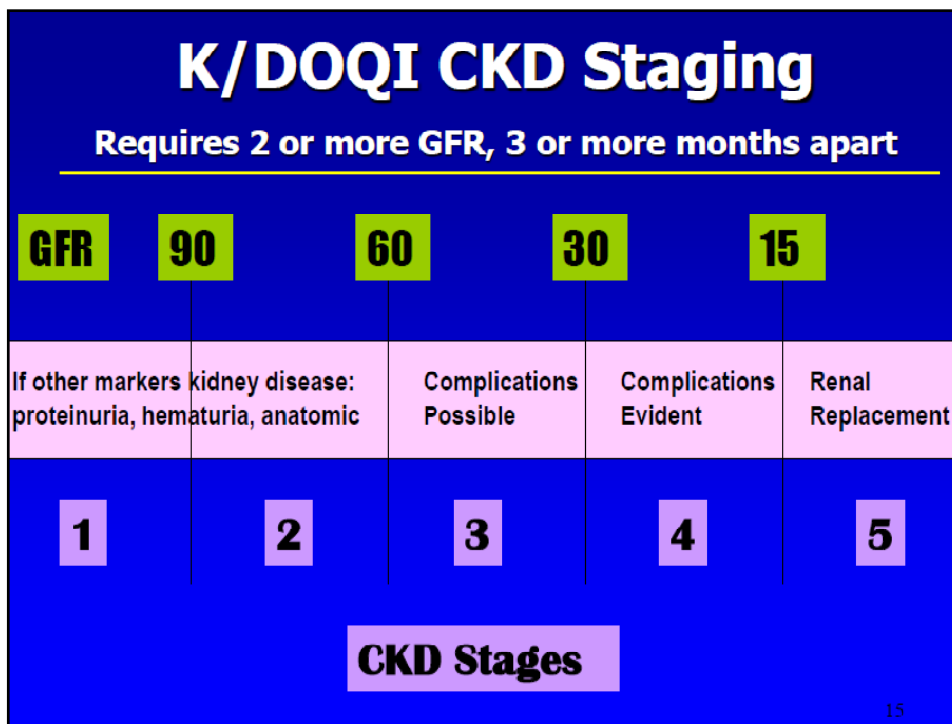
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Facts

- Patients with CKD have higher risk of CVD
- CVD risk factors exacerbate CKD
- 20 % of dialysis patients die each year from CV complications
- Patients with CAD and concomitant renal impairment are usually under treated
- CKD patients are usually excluded from CV trials

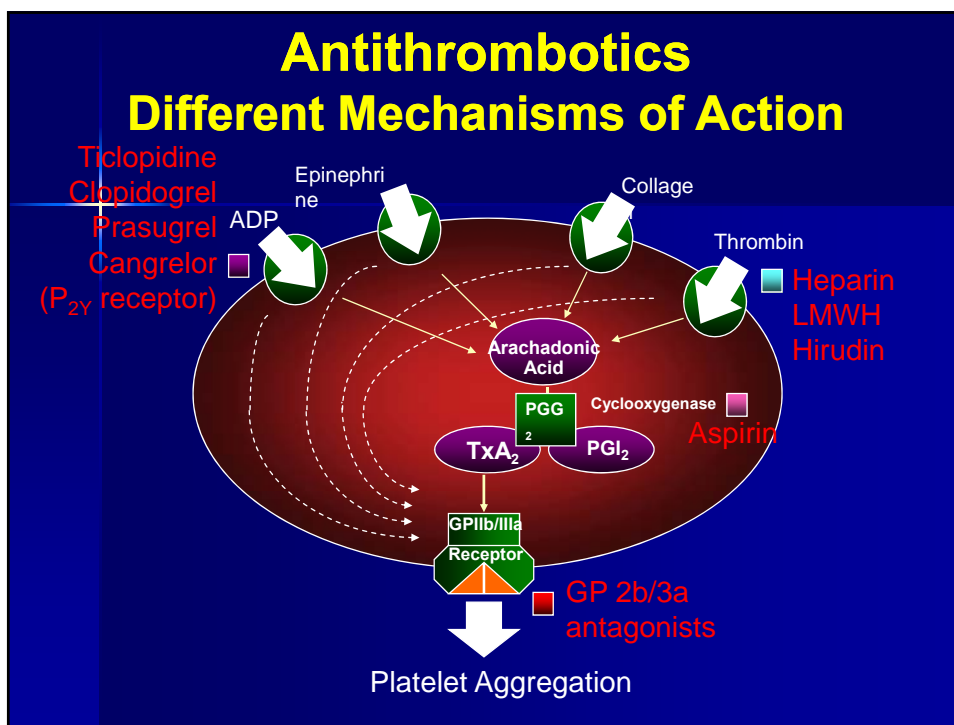
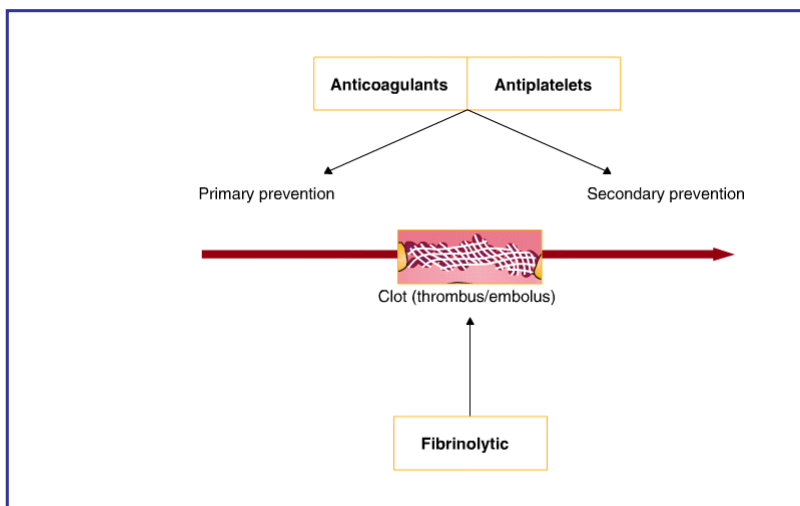


Antithrombotics and renal impairment Magnitude of the problem

Renal impairment is associated with :

- More severe and diffuse atherothrombosis
- More frequent co morbidities ,polypharmacy
- Higher mortality
- Higher spontaneous bleeding risk
- Higher transfusion rate
- Excess dosing of kidney excreted drugs
- Protein binding alteration

Antithrombotics



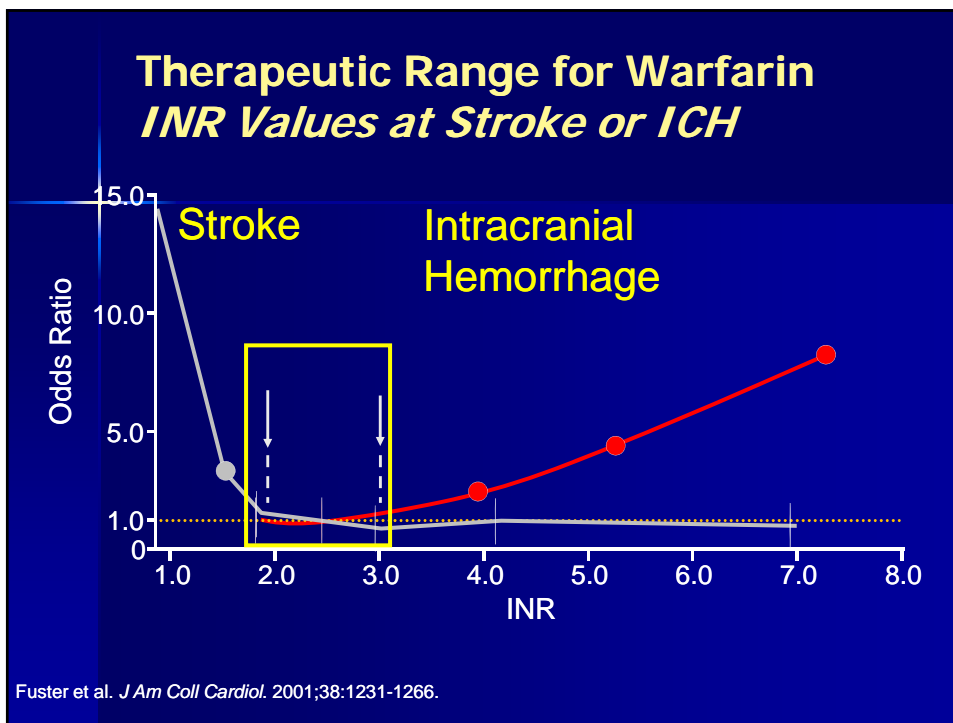
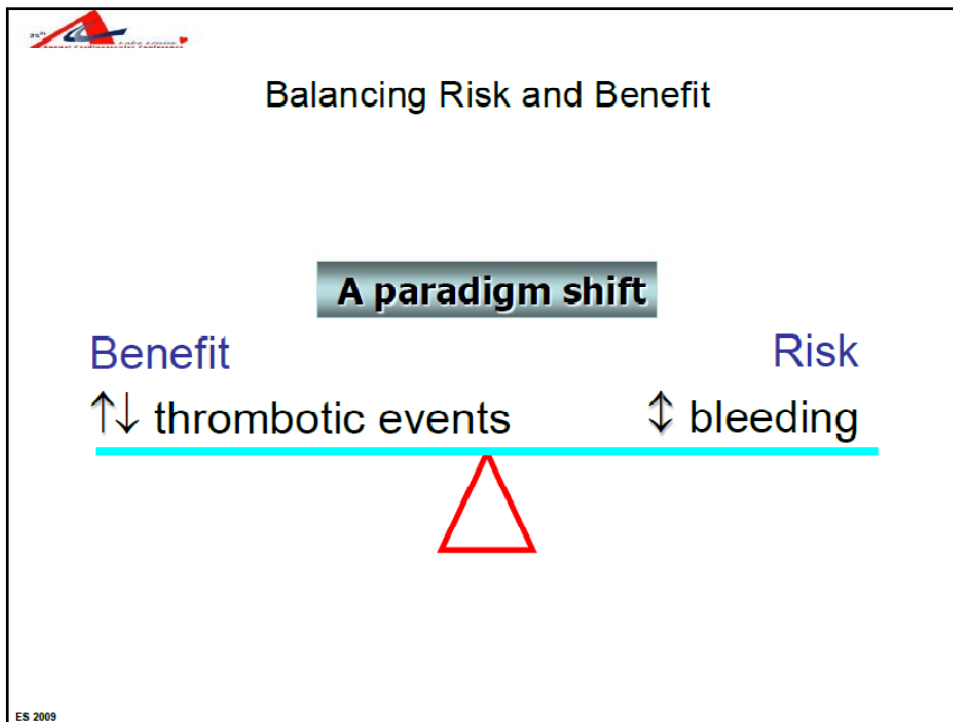


TABLE 2. Renal Clearance of New Anticoagulants

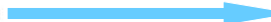
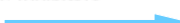


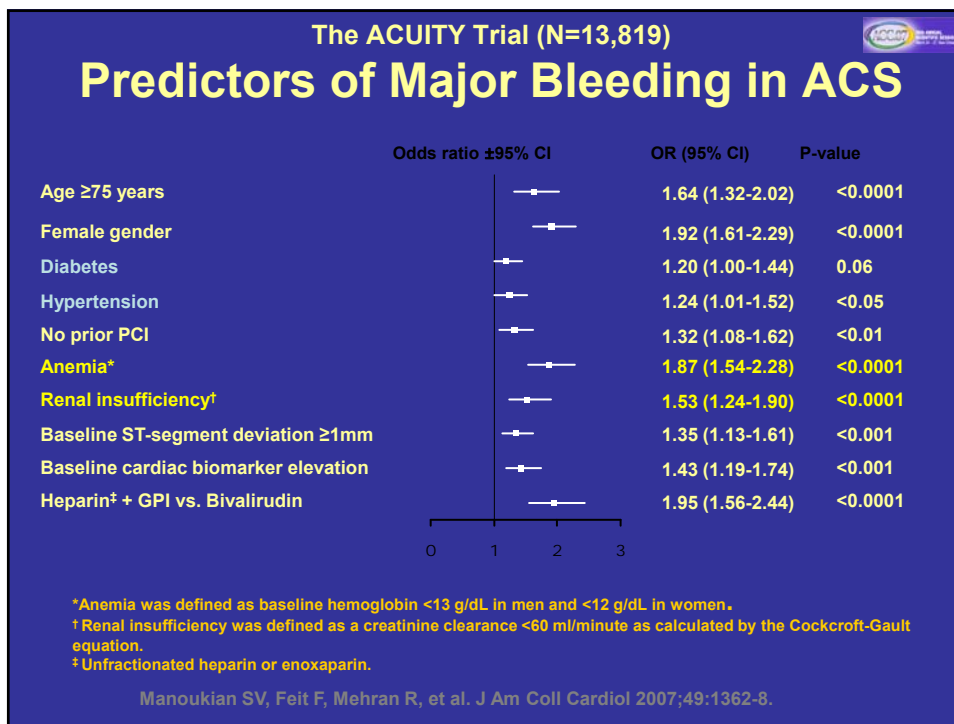
	Nonrenal	Partial Renal (≤50%)	Predominantly Renal (>50%)
Parenteral			
UFH 	X
LMWH	(X)
Direct thrombin inhibitors
Argatroban 	X
Bivalirudin	...	X	...
Hirudin	(X)
Factor IXa inhibitors
Factor IXa aptamer 	X
Factor Xa inhibitors
Fondaparinux	(X)
Oral			
Warfarin 	X
Direct thrombin inhibitors
Dabigatran	(X)
Factor Xa inhibitors
Rivaroxaban	(X)
Apixaban	...	X	...

Table 5. Incidence of Hospital Stroke and Major Bleeding Stratified by Renal Function

	Normal Renal Function (n = 8,937)	Moderate Renal Dysfunction (n = 2,924)	Severe Renal Dysfunction (n = 459)
Primary PCI (n = 3,350)			
Stroke, %	0.2 (p = 0.04)	1.3 (p = 0.71)	1.4 (p = 0.77)
Major bleeding, %	2.7 (p < 0.001)	6.8 (p < 0.001)	7.3 (p = 0.23)
Fibrinolysis (n = 3,723)			
Stroke, %	1.2 (p = 0.004)	1.7 (p = 0.53)	2.7 (p = 0.64)
Major bleeding, %	1.9 (p = 0.02)	3.4 (p = 0.11)	8.2 (p = 0.12)
No reperfusion (n = 5,247)			
Stroke, %	0.6	1.3	1.9
Major bleeding, %	1.4	2.5	4.2

N = 12,320. p values are given with "no reperfusion" as the reference group and are adjusted for GRACE risk score.
Abbreviations as in Table 3.

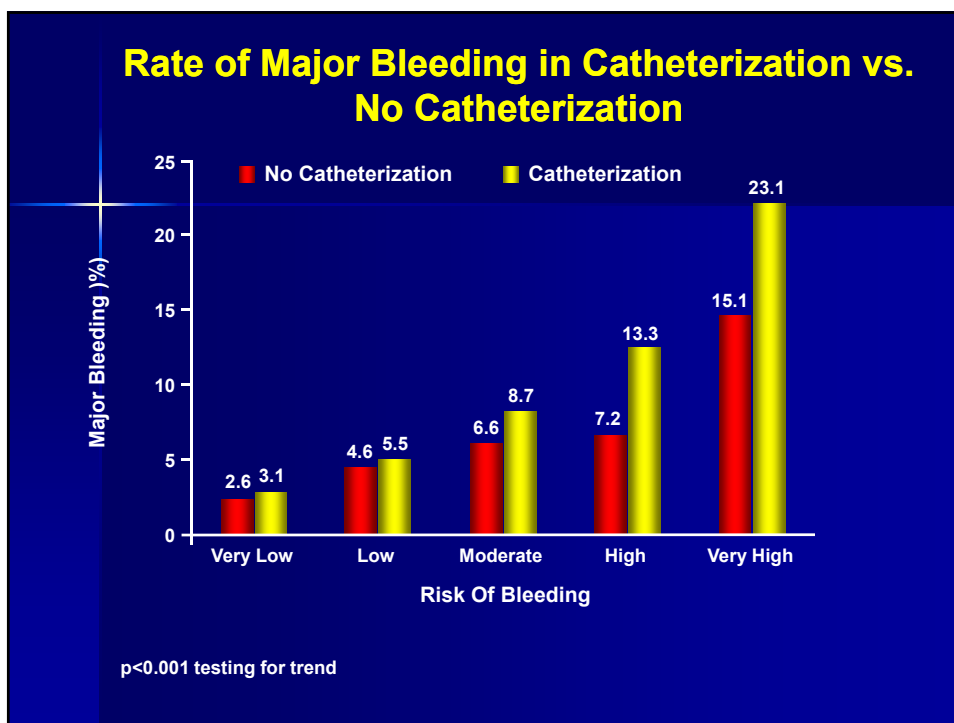
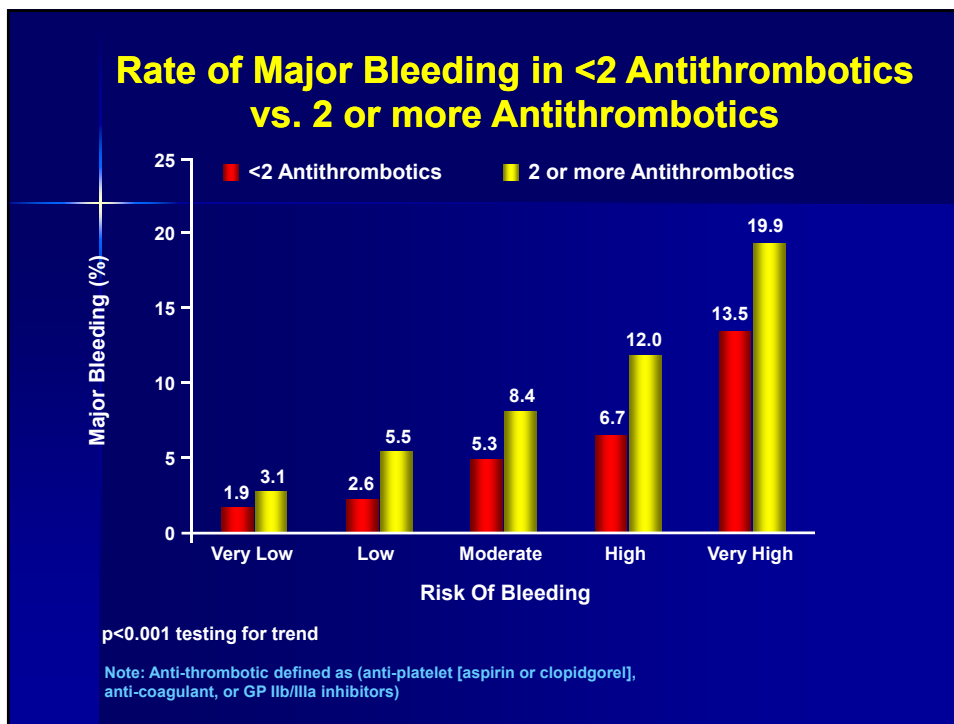


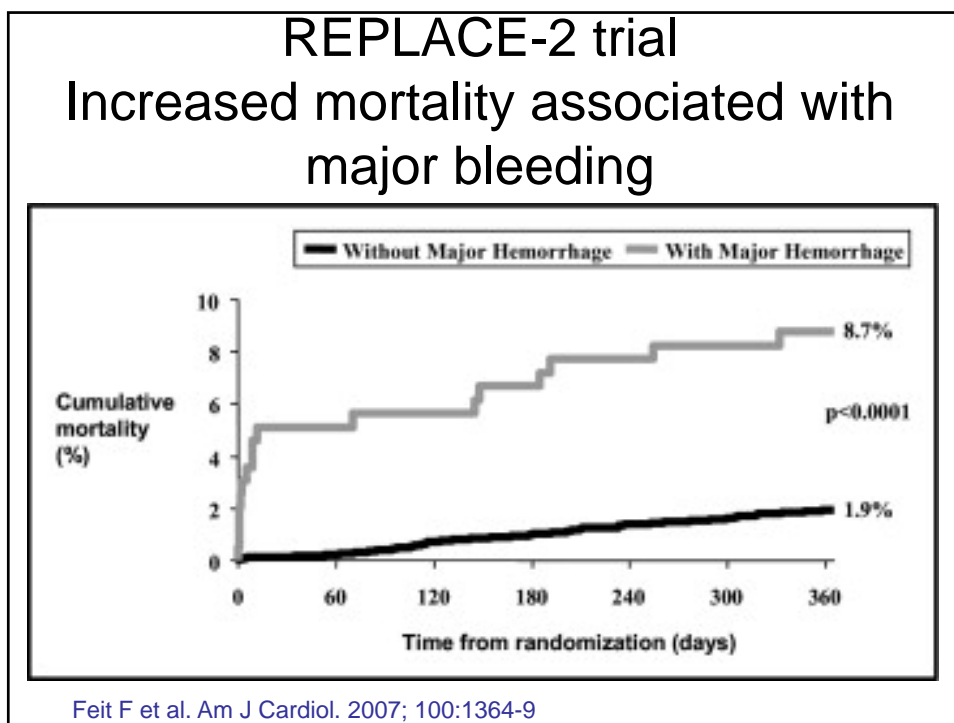
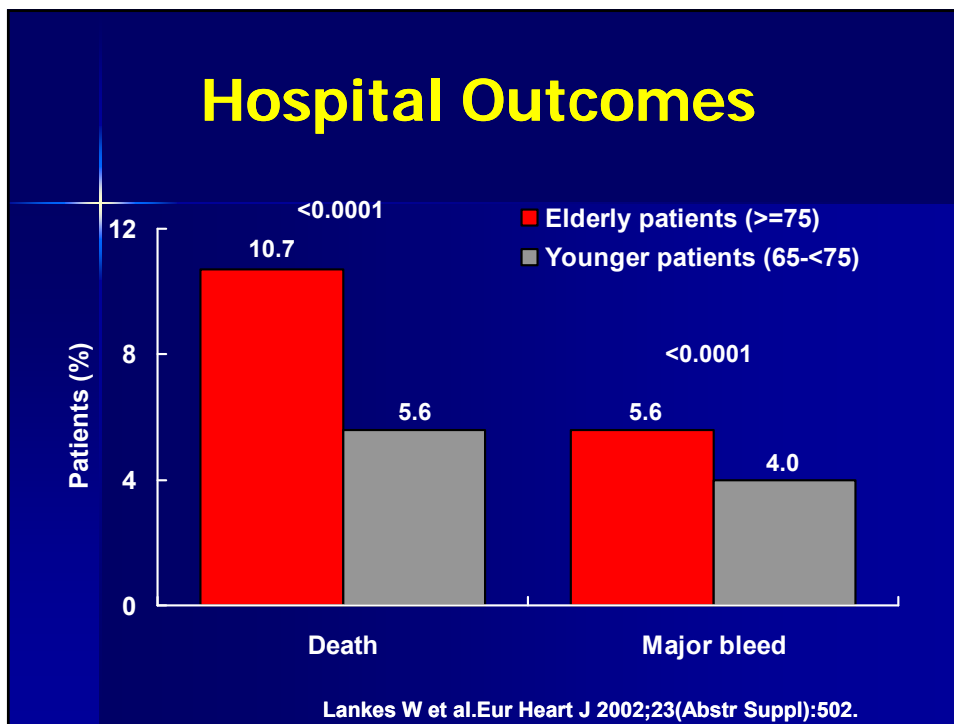
The REPLACE-2 Trial (N=6,010):

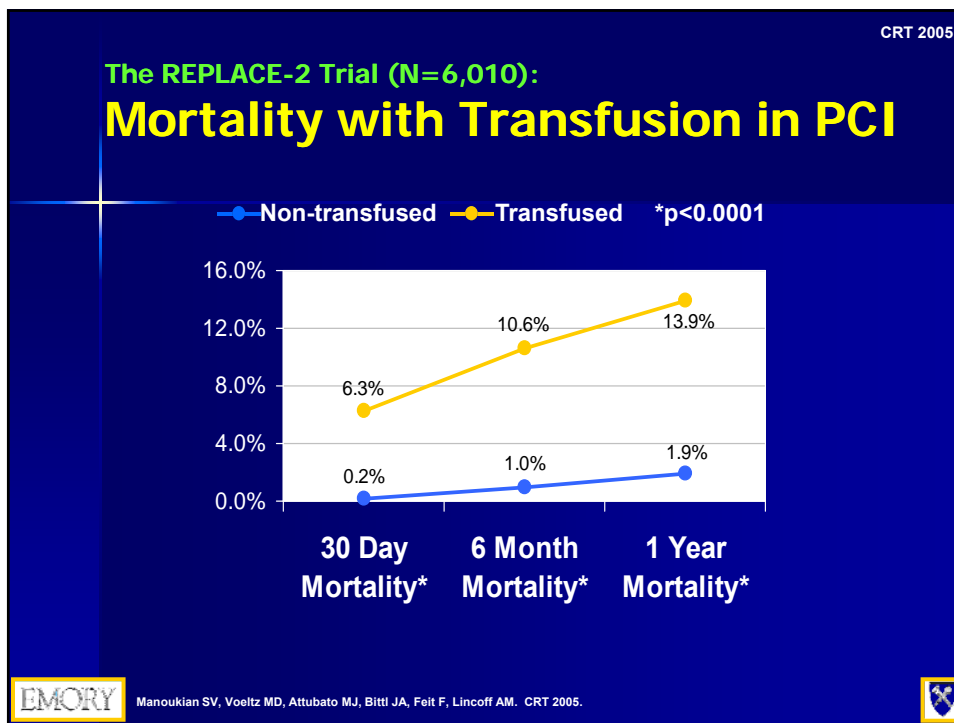
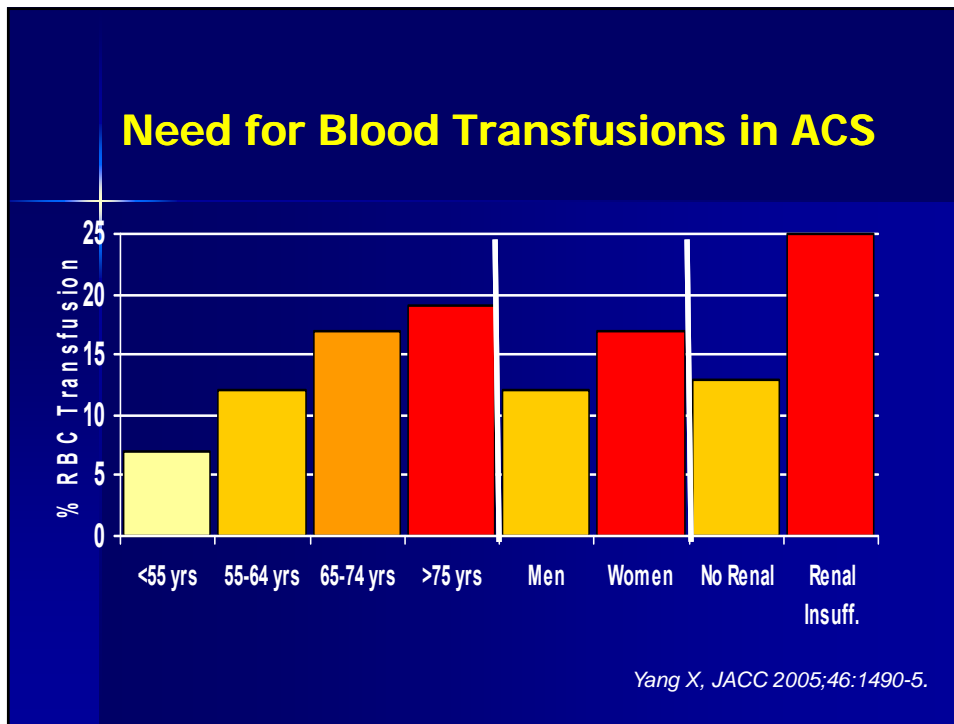
Predictors of Major Bleeding in PCI

Variable	OR	95% CI	p-value
<i>Baseline risk factors</i>			
Age ≥ 75	1.482	1.01, 2.18	0.045
Gender (Female)	1.535	1.12, 1.10	0.007
Creatinine Clearance	1.008	1.00, 1.01	0.006
Anemia	1.403	1.02, 1.94	0.040
Prior Angina	1.589	1.08, 2.35	0.02
Prior PCI	0.629	0.45, 0.88	0.007
Prior Thienopyridine	0.601	0.39, 0.93	0.023
<i>Peri-procedural risk factors</i>			
Treatment Group (Heparin + GPI vs. bivalirudin)	1.969	1.37, 2.84	0.0003
Provisional GPI received	2.679	1.59, 4.51	0.0002
Procedure Duration >1h	2.049	1.22, 3.45	0.007
Time to Sheath Removal >6h	1.614	1.06, 2.45	0.024
Intensive Care Unit stay (days)	1.25	1.18, 1.32	<0.0001
Intra-aortic Balloon Pump	8.705	3.43, 22.07	<0.0001

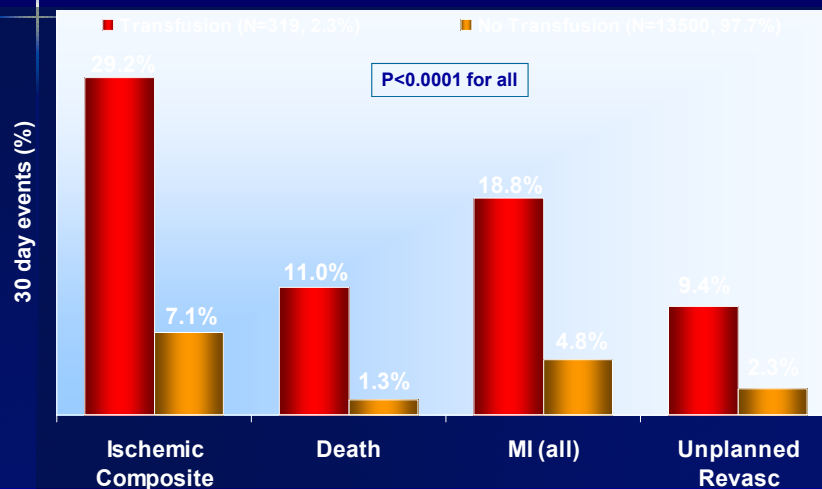
EMORY Feit F, Voeltz MD, Attubato MA, et al. Unpublished.







Results: The ACUTY Trial (N=13,819) Transfusion and Events in ACS



How Might Bleeding and transfusion Increase Long-term mortality ?

- Hemodynamic compromise
- Hyperadrenergic state
- Transfusion – induced microcirculatory disorder, NO depletion, immunologic effects
- Inflammatory response
- Discontinuation of antithrombotics

Risk of bleeding and mortality with antithrombotics in CKD patients

- Old age
- Female sex
- DM
- Anemia
- Transfusion
- Excess antithrombotics
- Reduced **GFR**

Antithrombotics and renal impairment

ESC ,2007-NHS , 2009 recommendations

- The GFR should be done for every patient
- Generally ,patient with CKD should receive the same first line treatment as any other patient (in the absence of contraindications)
- Patients with CrCl < 60ml/min , at high risk of further ischemic events and should be submitted to invasive evaluation whenever possible

Antithrombotics and renal impairment

ESC ,2007-NHS ,2009 recommendations

- Reperfusion : Primary angioplasty is preferable because of gradual risk of bleeding ?
- Aspirin and clopidogrel : No contraindications for their uses
- Prasugrel : Careful monitoring of the dose is recommended
- GP IIb/IIIa inhibitors : Dose adaptation is needed with eptifibatide and tirofiban, 50 % dose reduction is recommended with Cr Cl <30 ml/min. Careful evaluation of the bleeding risk is recommended for abciximab

Antithrombotics and renal impairment

ESC ,2007 -NHS,2009 recommendations

- Anticoagulants : In patients with CrCL<30ml/min ,dose adjustment is necessary with some anticoagulants ,while others are contraindicated :
 - *UFH is recommended instead of LMWH when Cr Cl < 30 ml/ min , otherwise monitoring for anti- factor xa activity is required*
 - *Fondaparinux is renally excreted and should be used with caution in patients with Cr Cl 30 to 50 ml/min*
 - *Enoxaparin ,bivaluridin and fondaparinux are contraindicated in ESRD*

Antithrombotics and renal impairment

ESC ,2007-NHS ,2009 recommendations

Warfarin : No contraindication for its use ,however in moderate or high risk AF ,it should be used alone even in the presence of concomitant CVD

Evidence does not support the use of combination of warfarin and aspirin in patients with ACS ,post MI or stable CAD Warfarin alone is effective as aspirin in preventing ischemic events in patients with IHD

Take home message

- **CKD and CAD are usually coexisted**
- **The use of antithrombotics in patients with CKD is a challenging issue**
- **GFR is the gold standard test for CKD evaluation**
- **Low GFR ,old age ,female sex , DM ,anemia ,transfusion and aggressive antithrombotics are major predictors of bleeding and mortality in CKD patients receiving antithrombotics**
- **According to the GFR , dose adjustment of some antithrombotics is recommended ,while other drugs are contraindicated**

