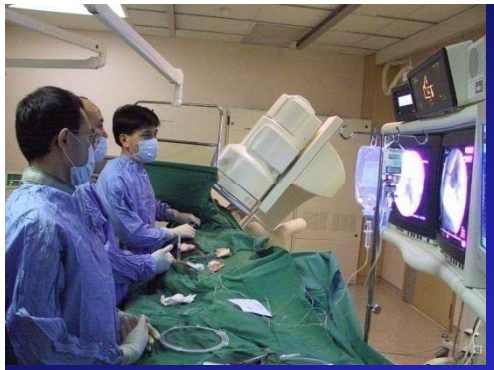

Angioplasty Summit- TCTAP 2010
Innovations in 2011:
Now and the Future

Update on ACS/AMI: Have We Made Any Progress? What's Next?

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Acute Coronary Syndromes

- Encompasses a broad and heterogenous population from atypical chest pain, non specific electrocardiographic changes, and normal biomarkers to patients with large ST-segment elevation, myocardial infarction, and cardiogenic shock

- Diversity in clinical presentation challenges physicians at each step of treatment in terms of diagnosis of ACS, appropriate risk stratification, therapeutic decision making and monitoring response to therapy

Contents

- Risk Stratification
- Biomarkers
- Optimal Adjunctive pharmacotherapy
- Invasive vs conservative Therapy

ACS Risk Stratification

- Current guidelines recommend calculating risk scores to evaluate risk and guide treatment decisions accordingly
- Clinicians tend to underestimate risk based on clinical evaluation. Poor correlation between physician-estimated risk and risk determined by conventional risk models
- Current risk scores include TIMI, GRACE and PURSUIT. All offered better discrimination in terms of predicting outcomes compared with physicians' estimation

Global Registry of Acute Coronary Events

- 100 hospitals in 14 countries
  - Europe, North & South America, Australia, New Zealand

GRACE In-hospital Mortality Risk Model

- 8 major risk factors identified from GRACE cohort of 11,389 ACS patients
  - age, initial serum creatinine, systolic blood pressure, heart rate, initial cardiac enzyme elevation (trop I/T > ULN, CK-MB or CK >2 X ULN), Killip class, ST-segment deviation (ST elevation or depression ≥ 1mm) and cardiac arrest at presentation

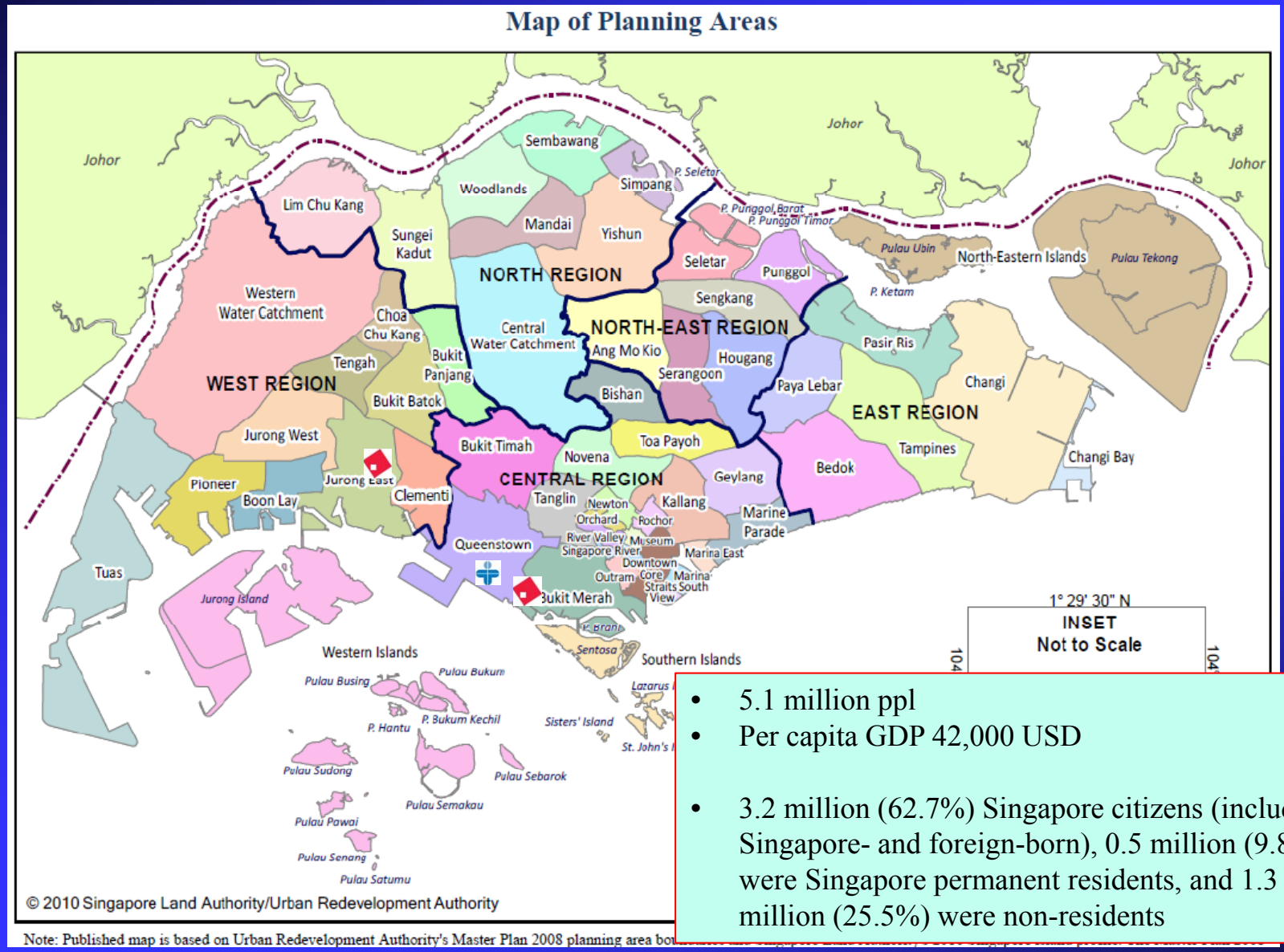
- Risk score to estimate in-hospital mortality
  - Calibrated using β coefficients of the 8 risk factors
  - *C*-index = 0.84

- *C*-index ≥ 0.79 in 2 non-Asian validation cohorts
  - GUSTO IIb (n=12 142)[1] and MINAP (n=100,686)[2]

- No independent validation studies in Asian countries

1 Granger CB, Arch Int Med 2003 2 Gale CP, Heart 2008

City-State of Singapore



- 5.1 million ppl
- Per capita GDP 42,000 USD

- 3.2 million (62.7%) Singapore citizens (including Singapore- and foreign-born), 0.5 million (9.8%) were Singapore permanent residents, and 1.3 million (25.5%) were non-residents

Baseline Characteristics: GRACE vs SMIR Cohort

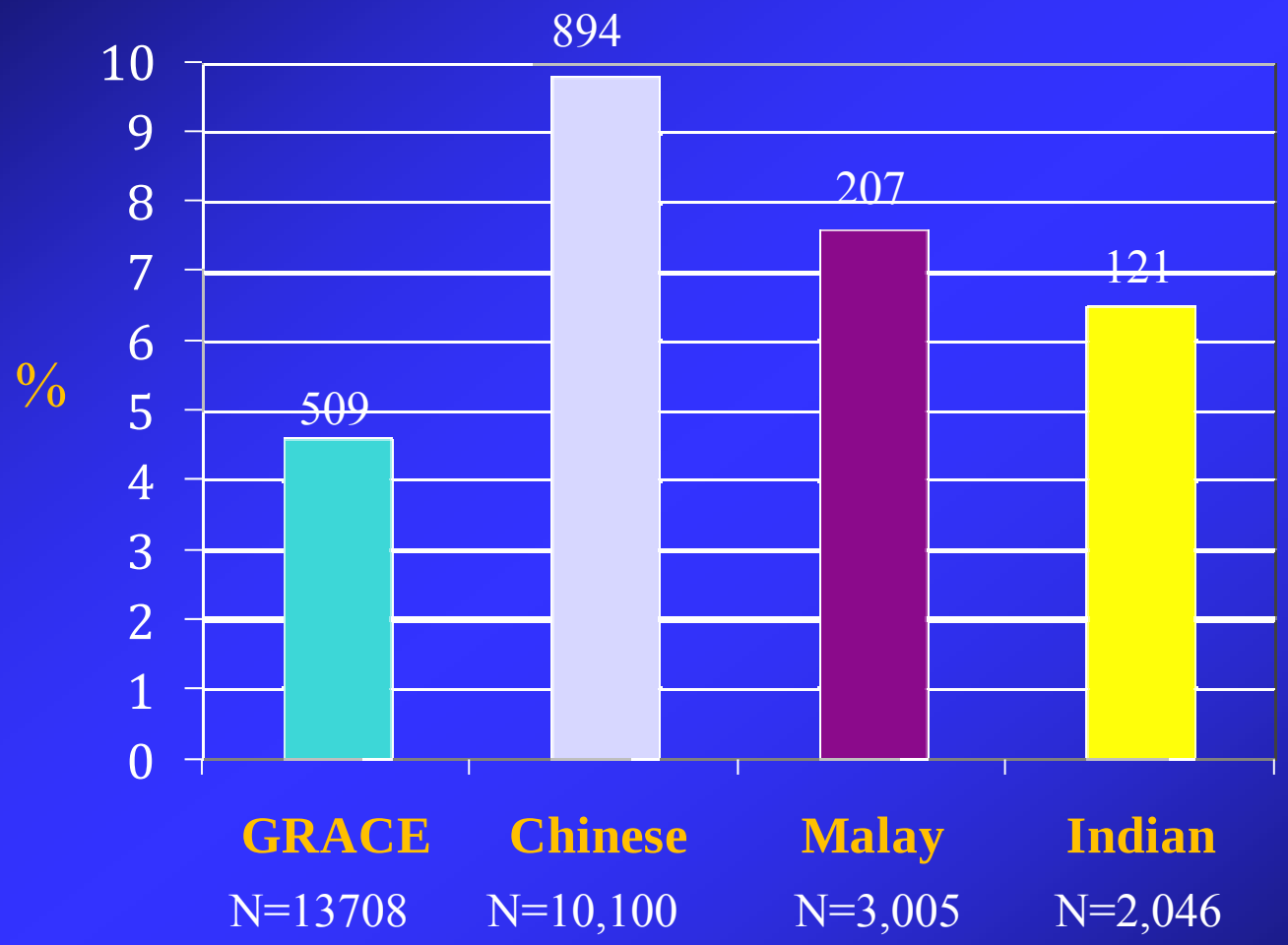
	GRACE (n=11,389)	SMIR Cohort		
		Chinese (n=10,100)	Malay (n=3,005)	Indian (n=2,046)
Age, years	66 (56-75)	64 (54 – 74)	61 (51 – 71)	58 (49 – 70)
Women, %	34	29	27	23
FHx of premature CAD, %	NA*	11	15	22
Diabetes mellitus, %	23	35	42	51
Hypertension, %	58	61	55	54
Hyperlipidemia, %	44	50	46	52
Prior MI, %	32	11	11	15
Prior PCI, %	14	4	4	8
Prior CABG, %	13	3	2	5
Renal Failure, %	7	6	7	4

Presentation Characteristics: GRACE vs SMIR Cohort

	GRACE (n=11,389)	SMIR cohort		
		Chinese (n=10,100)	Malay (n=3,005)	Indian (n=2,046)
HR, beats/min	76 (65-90)	80 (69 – 93)	80 (70 – 97)	80 (70 – 96)
Systolic BP, mm Hg	140 (120-160)	130 (114 – 150)	130 (113 – 150)	132 (117 – 150)
Cardiac arrest, %	NA*	1	1	2
ST elevation, %	35	47	46	48
ST deviation, %	54	64	62	60
Positive initial biomarkers, %	32	87	88	88
Killip Class ≥II, %	17	33	34	32
GRACE risk score	NA*	144 (119 – 173)	138 (115 – 167)	131 (109 – 160)

*NA = data not available

Unadjusted Inhospital Mortality



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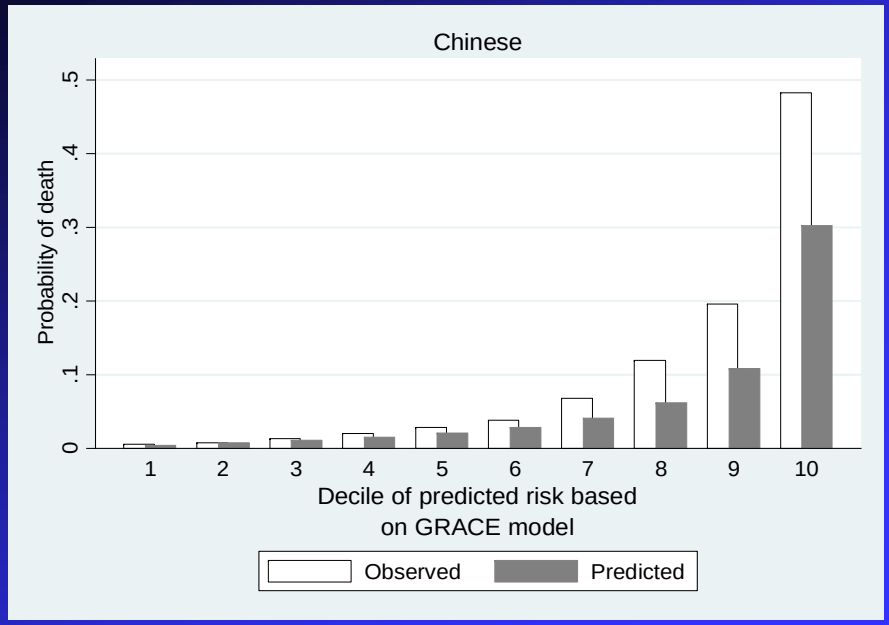

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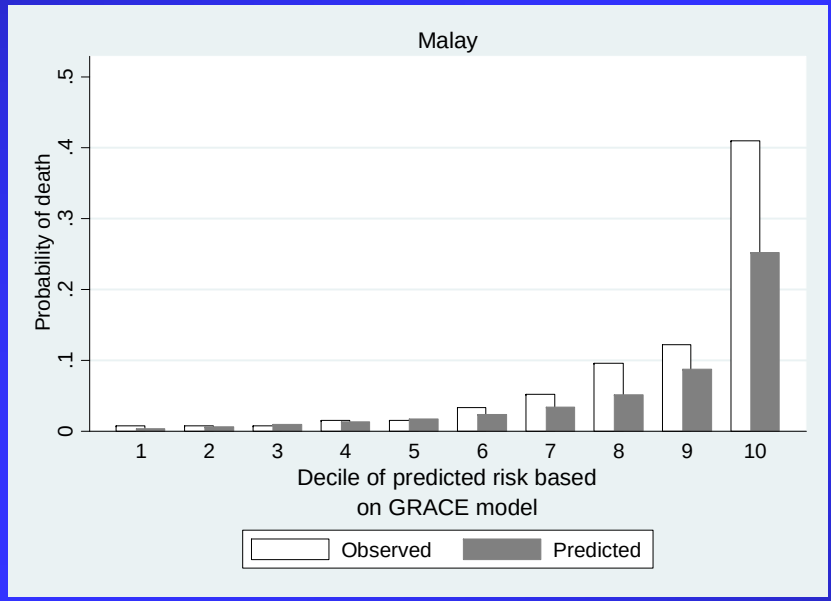

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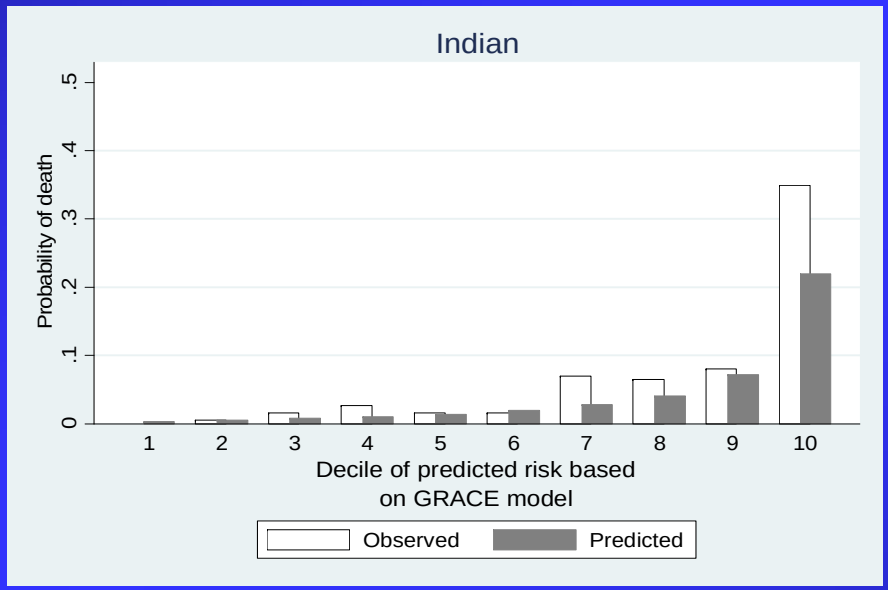


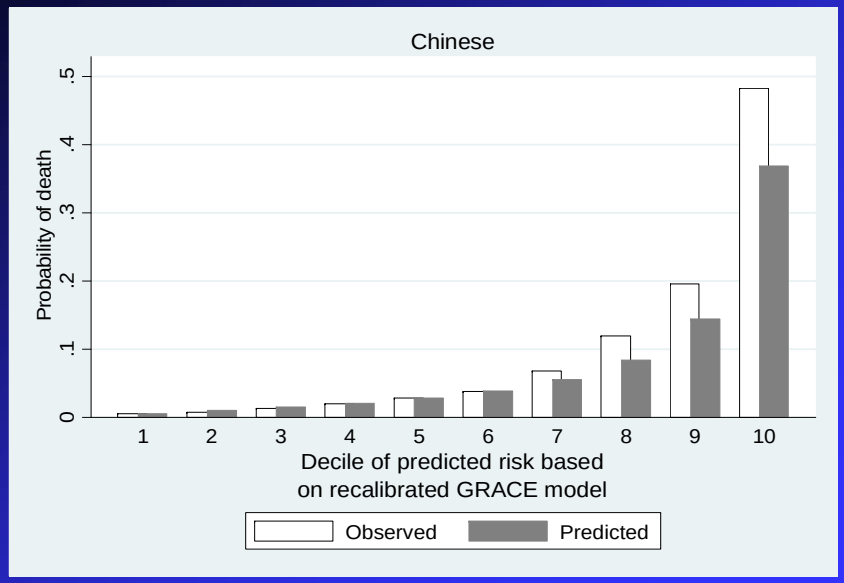
Original Grace Model: Predicted vs Observed

Recalibration of the GRACE Score

- Retaining original regression coefficients
- Substitute the original score constants with constants derived using mean-centered values of risk factors from the Singapore cohort

$$P = \frac{\exp(f[x, M])}{1 + \exp(f[x, M])}$$

A



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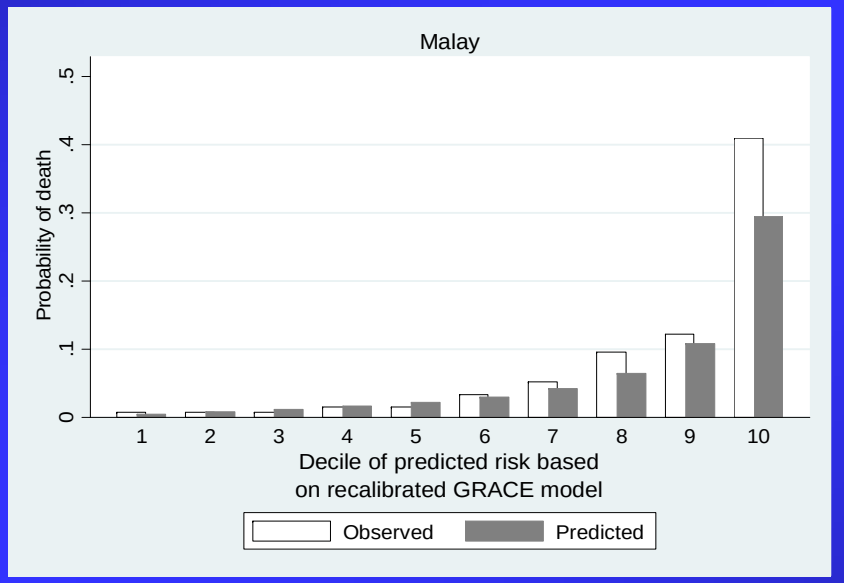

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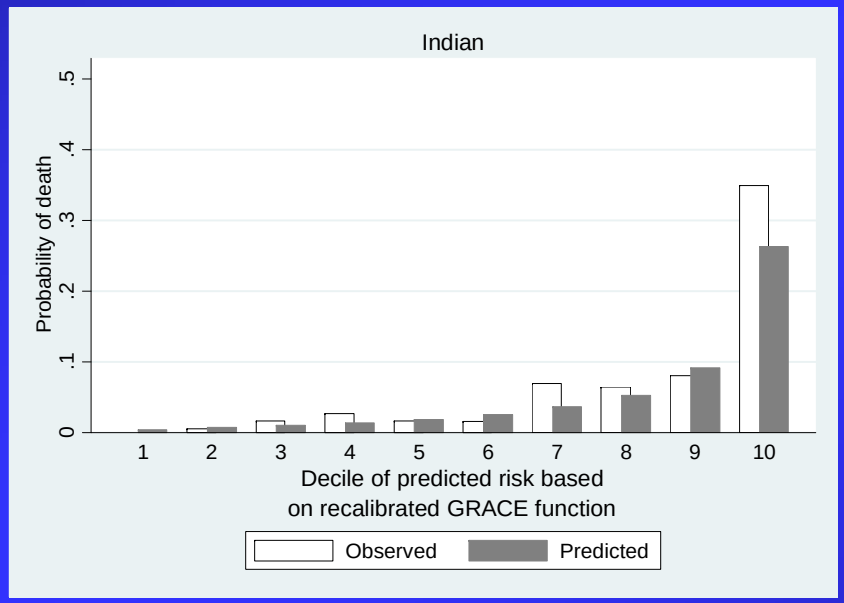


Recalibrated GRACE Model: Predicted vs Observed

Conclusions

- Proper validation before applying external risk models to previously untested populations
- Need for individualized geographic and population-specific risk models to address over or underestimation of risk
- Recalibration an alternative method to optimize risk stratification

Contents

- Risk Stratification
- Biomarkers
- Optimal Adjunctive pharmacotherapy
- Invasive vs conservative Therapy

Novel BioMarkers

Many biomarkers reflecting variety of pathophysiologic pathways:

- Markers of Ischemia and inflammation
  (ischemia-modified albumin, heart fatty acid binding protein, myeloperoxidase)

- Vascular dysfunction
  (matrix metalloproteinase-9, pregnancy-associated plasma protein A0, Biomechanical stress (copeptin, ST2, growth-differentiation factor [GDF]-15)

- Hemostasis (fibrinogen, plasminogen activator inhibitor-1)

- Lipid metabolism (lipoprotein-associated phospholipase A2)

Most are unlikely to reach widespread clinical use
Few shown to consistently improve on established markers

Established Novel Markers

Biomarkers		Diagnosis				
		ACS (Without Evidence of Myocardial Necrosis)	MI	Prognosis	Clinical Implications	Monitor Therapy
Troponin	Necrosis	+++	+++	+++	+++	
Natriuretic peptides	Ventricular stress	+		+++	++	+
Creatine kinase-myocardial bound	Necrosis	++	++	+++	++	
Myoglobin	Necrosis	++	+		+	
High-sensitivity troponin	Necrosis/ischemia	++	++	++		
Ischemia-modified albumin	Ischemia	+		+		
Fatty acid binding protein	Ischemia	+		++		
Growth differential factor-15	Ischemia/reperfusion	++		++	+	
C-reactive protein	Inflammation: nonspecific marker	++		+++		+
Pregnancy-associated plasma protein-A	Inflammation: matrix metalloproteinase-9/plaque instability	+				
Myeloperoxidase	Inflammation: neutrophil activation, reactive oxygen species	+		++		
ST2	Inflammation: regulatory protein in times of myocardial stress	+		+		
Lysosomal phospholipase A2	Cholesterol trafficking	+		++	+	
Copeptin	Stress: vasopressin prohormone	+		+		
Soluble CD40 ligand	Platelet activation	+		+		
Fibrinogen	Thrombosis	+		++		
Plasminogen activator inhibitor-1	Endogenous fibrinolytic system	+				
D-Dimer	Thrombosis	+		+		
Platelet aggregation	↓ Response to antiplatelet therapy			++	++	+
CYP2C19 polymorphism	↓ Response to clopidogrel			++	++	
Metabolite profile	Early signs of metabolic dysregulation	+	+			

ACS = acute coronary syndrome; MI = myocardial infarction; + = limited or contradictory evidence; ++ = compelling but not conclusive evidence; +++ = strong/validated evidence for use.

Scirica BM et al J Am Coll Cardiol 2010; 55: 1403-15

Cardiac Troponins

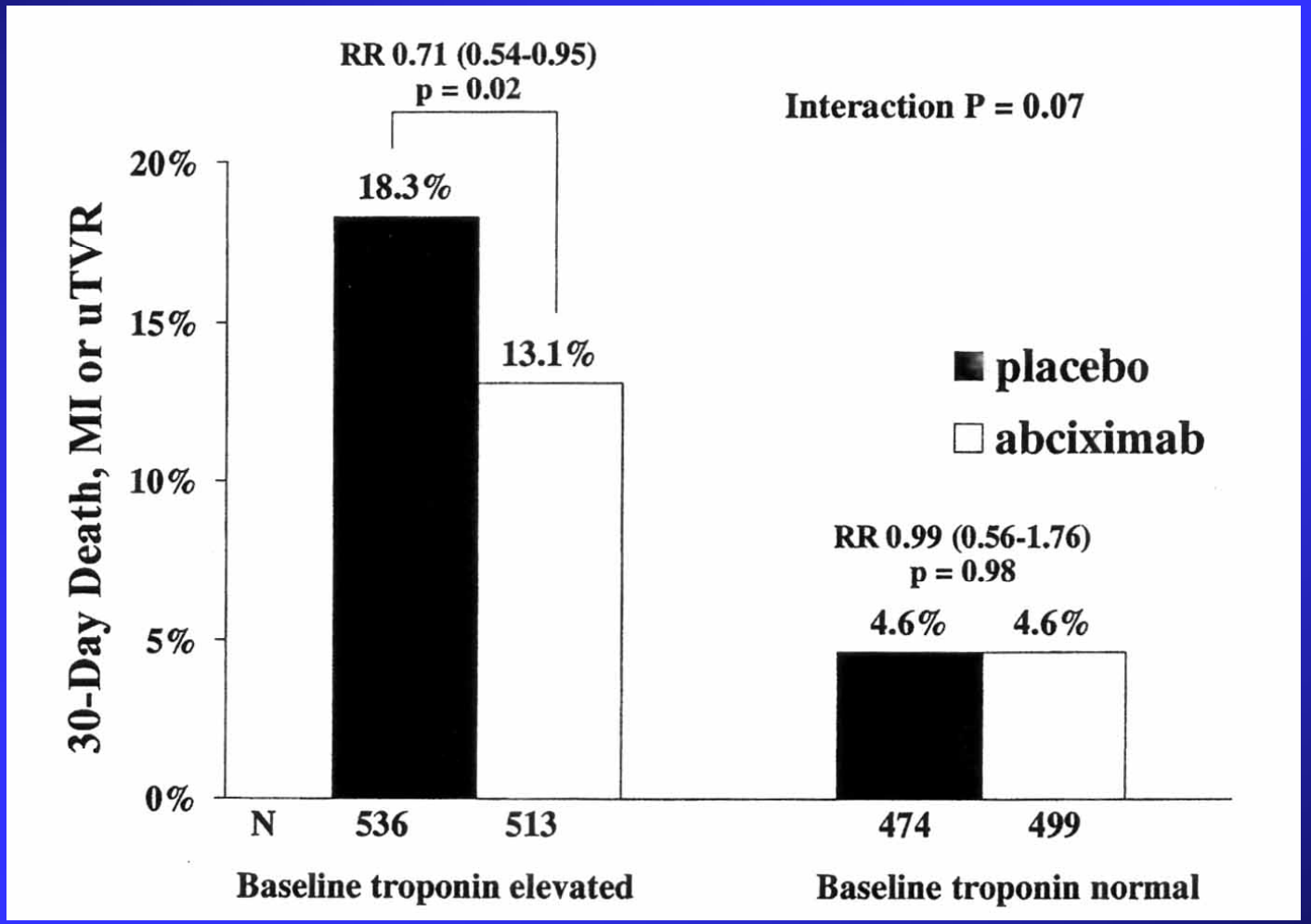
- Elevated concentration of cardiac troponin is central to universal definitions of MI
- Values that are above the 99th percentile of normal population should be considered as an indication of myocardial necrosis
- Assay should have precision of <10% coefficient of variation at 99th percentile level

Confusions

- Multiple commercially available assays, each with an individual decision limit based on assay's performance
- Many laboratories still report several cut points, often labeling them as "normal', 'indeterminate'
- Widespread use of troponin in broader population- clinically challenging

ISAR-REACT 2 Trial

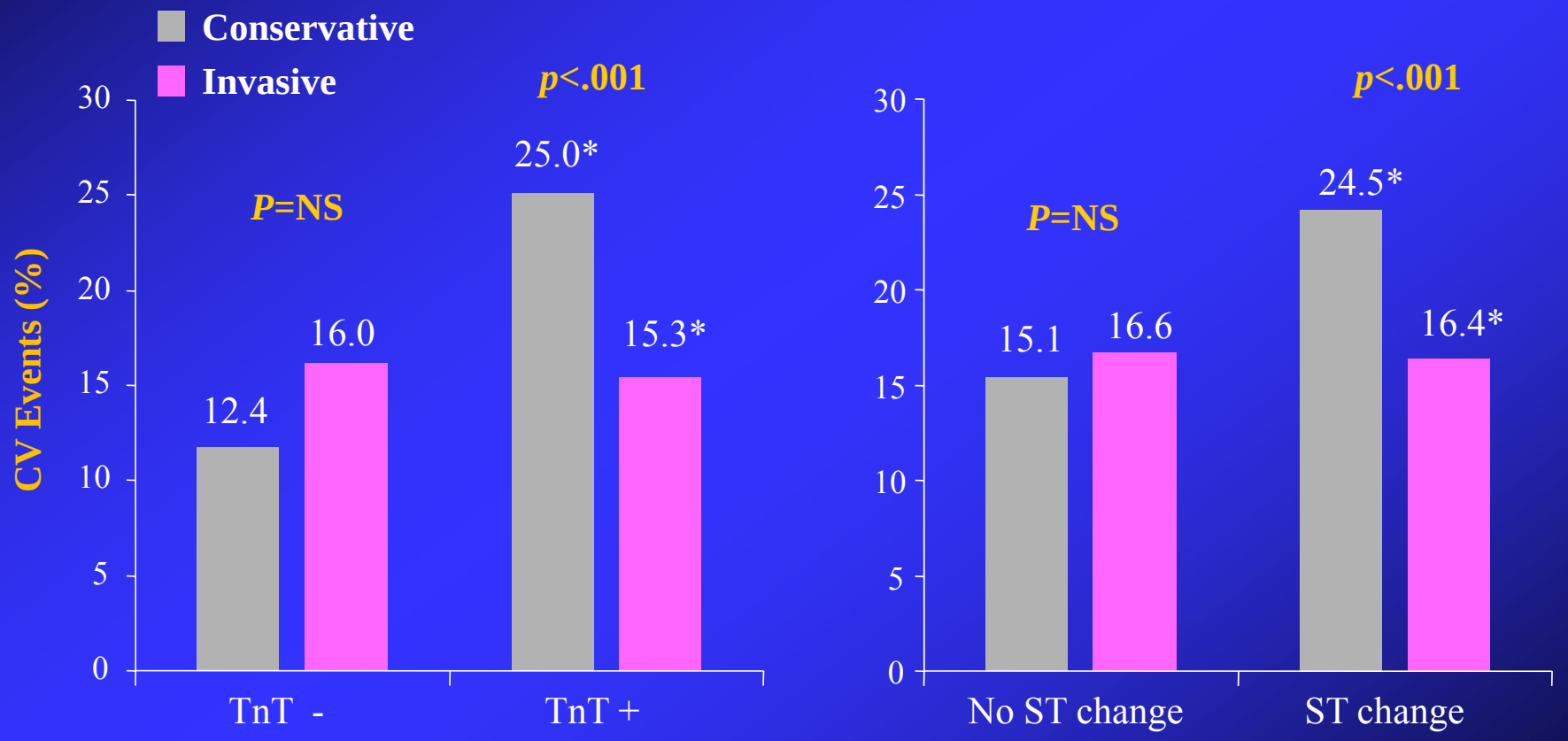
2022 pts, all given clopidogrel 600mg at least 2 hrs before procedure as well as 500mg of oral or intravenous aspirin



Kastrati A et al JAMA 2006; 295: 1531-8

Benefit of Invasive Strategy by Troponin and ST-Segment Changes

Death, MI, Rehosp ACS at 6 Months



Morrow DA. JAMA 2001; 286: 2405-2412;
Cannon CP N Engl J Med. 2001;344:1879-1887

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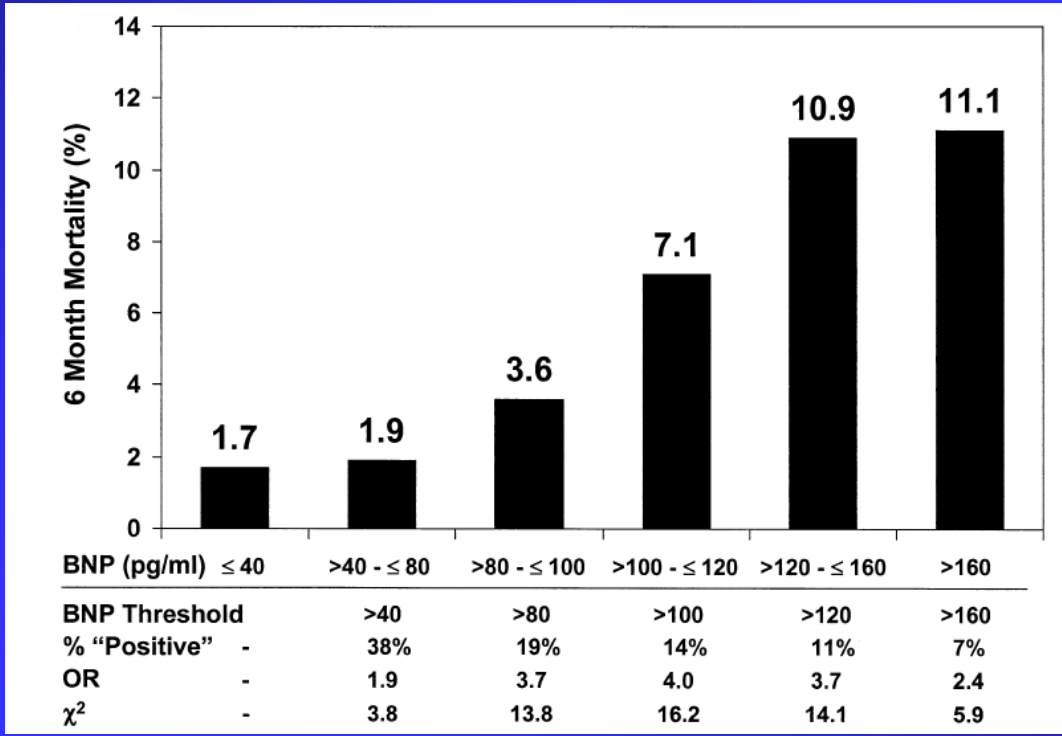
Natriuretics Peptides

- Released from ventricular myocardium in response to stress
- Elevated in heart failure, pul hypertension, pul embolism, cardiac arrhythmias, and cardiac ischemia

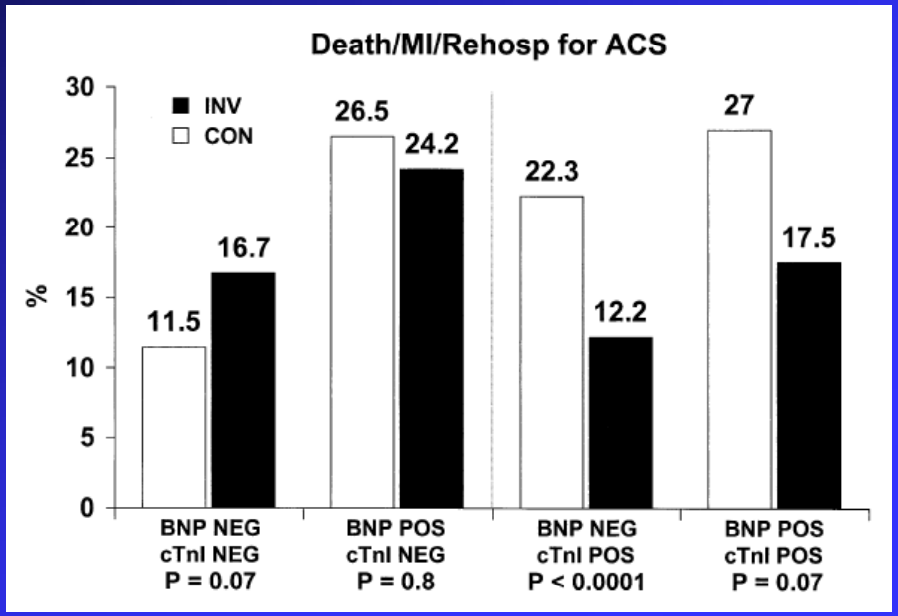


BNP (pg/ml)	≤ 40	>40 - ≤ 80	>80 - ≤ 100	>100 - ≤ 120	>120 - ≤ 160	>160
BNP Threshold		>40	>80	>100	>120	>160
% "Positive"	-	38%	19%	14%	11%	7%
OR	-	1.9	3.7	4.0	3.7	2.4
χ^2	-	3.8	13.8	16.2	14.1	5.9

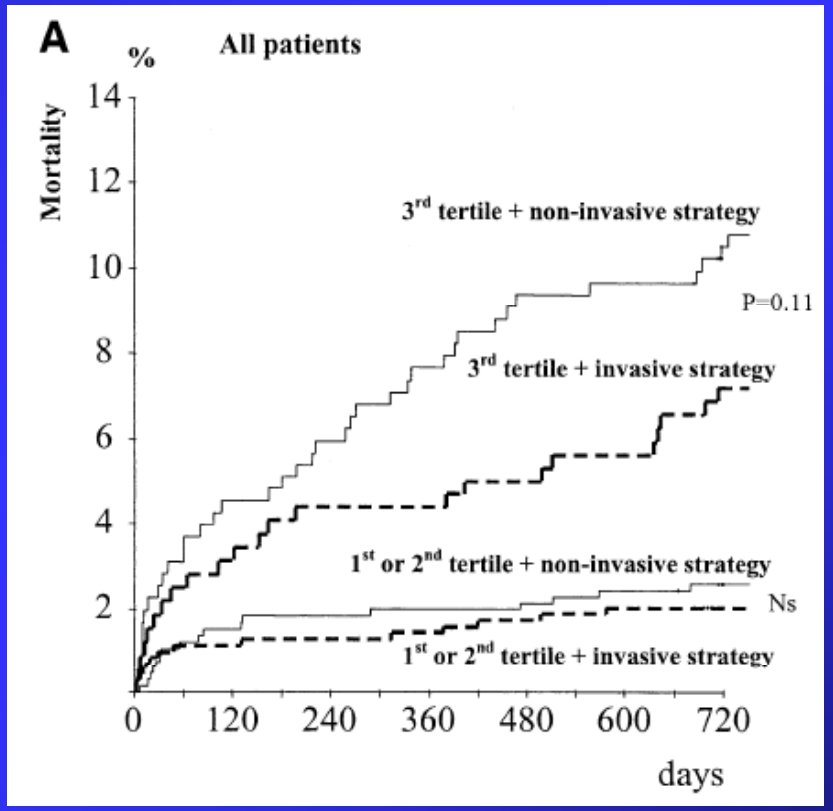
Higher mortality at 6 months with elevated BNP in patients with NSTE-ACS

Morrow DA et al J Am Coll Cardiol 2003; 41: 1264-72

No Benefit of Early Invasive vs Medical Therapy In ACS Patients with Elevated NPs



Morrow DA et al J Am Coll Cardiol 2003



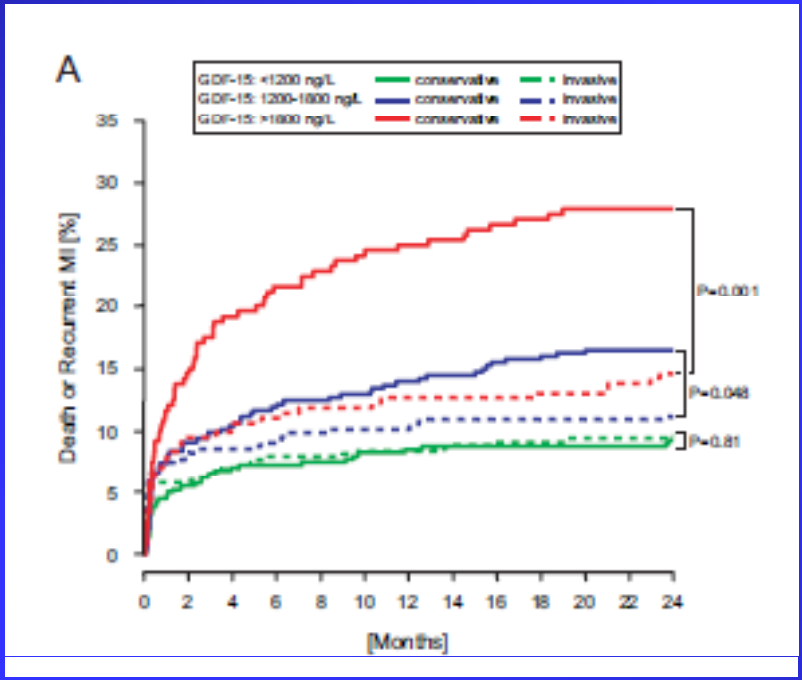
Jernberg T et al J Am Coll Cardiol 2003

No clear clinical implications of how an elevated NP level should guide specific therapy of treatment in ACS

GDF (Growth Differentiation Factor)-15: Most Promising !

- Member of transforming growth factor family released by myocytes during ischemia and reperfusion

- Elevated levels associated with increased risk of death and MI in patients with chest pain and NSTE-ACS, independent of ECG changes, troponin level, or NP level



2079 pts with NSTE-ACS followed up for 2 years

Invasive strategy preferential in pts with an increased concentration

Wollert KC et al Circulation 2007; 166: 1540-8

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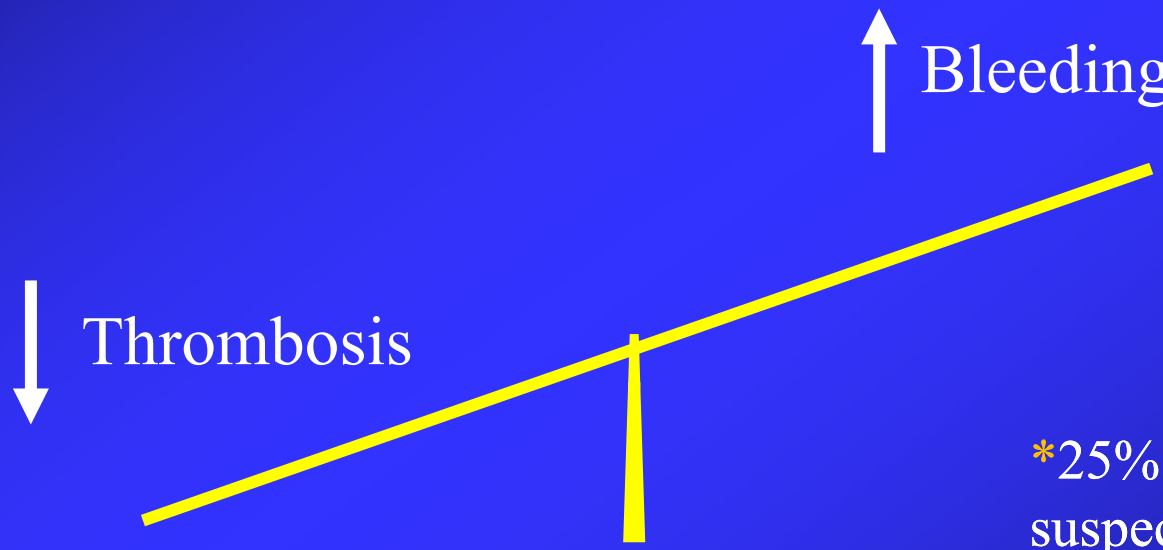
Balance Between Antithrombotic Efficacy and Bleeding

More potent platelet inhibition =



*25% confirmed or suspected GI source

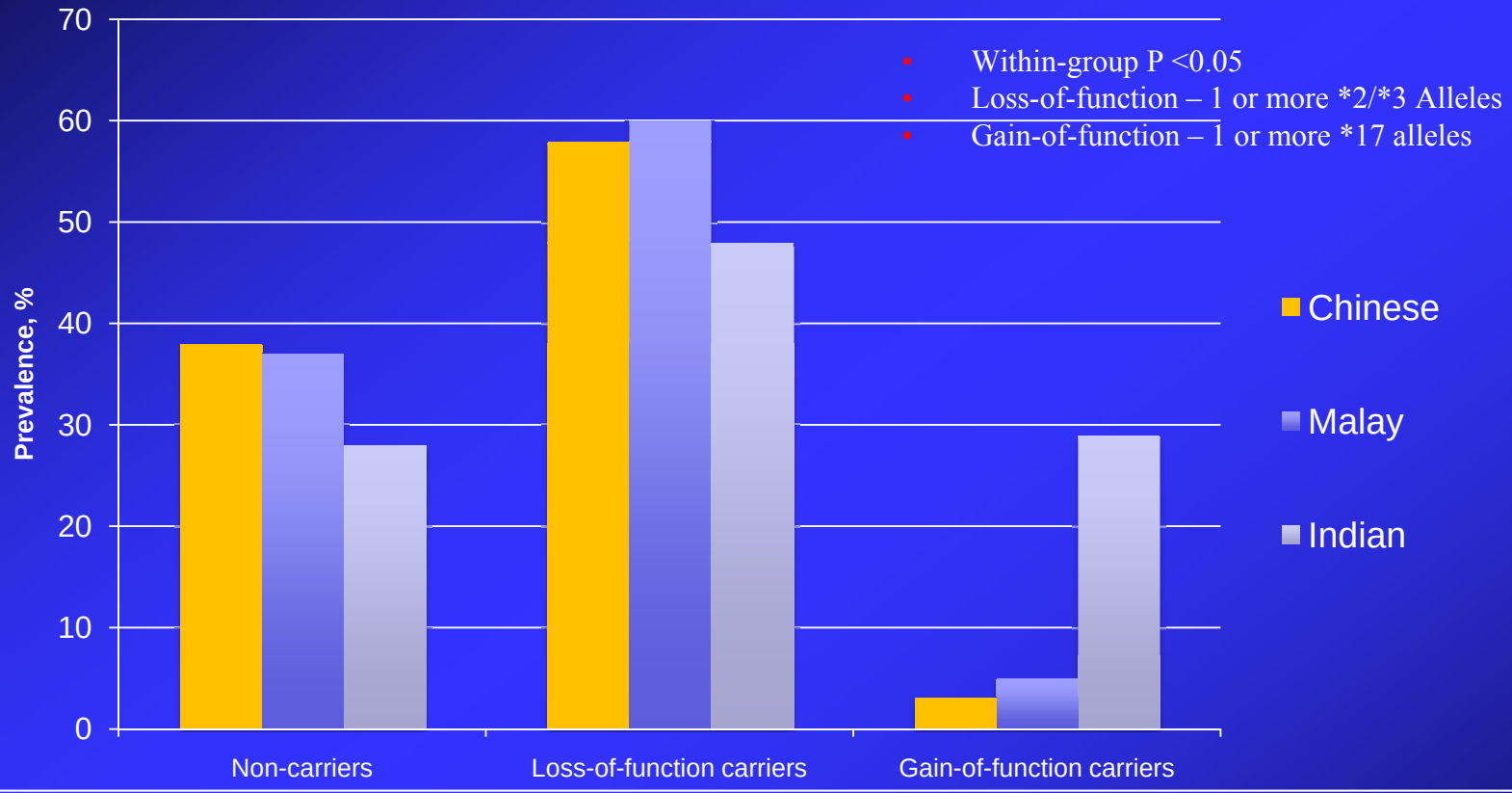
Types of P2Y12 Receptor Antagonists

	Ticlopidine [3]	Clopidogrel [22]	Prasugrel [23] (C-747, LY640315)	Cangrelor [24] (AR-C69931MX)	AZD6140 [12]
Drug class	Thienopyridine	Thienopyridine	Thienopyridine	ATP analogue	ATP analogue Cyclo-pentyl-triazolo-pyrimidine
Chemical activity (prodrug versus metabolically active)	Prodrug	Prodrug	Prodrug	Direct acting	Direct acting
Reversibility	Irreversible	Irreversible	Irreversible	Reversible	Reversible
Route of administration	Oral	Oral	Oral	Intravenous	Oral
Time to peak effect	500-mg oral dose: 5 days	300 mg: 6 h	1 h	Several minutes	120–240 min
Drug elimination half-life	24–36 h after a single oral dose and up to 96 h after 14 days of repeated dosing	7.2–7.6 h	3.7 h (active plasma metabolite R-138727)	5–9 min	12 h
Duration of action	5–10 days	5–10 days	5–10 days	1 h	24 h

ATP: adenosine triphosphate.

Chan et al Acute Coronary Syndromes 2007;8(4):114–21

Prevalence of CYP2C19 Polymorphisms in 300 Asian Subjects



Chinese and Malay subjects demonstrated an East Asian genotype with a high prevalence of CYP2C19*2 and *3 loss-of-function polymorphisms and low prevalence of the CYP2C19*17 gain-of-function polymorphism. In contrast, Indian subjects demonstrated a South Asian genotype, with a lower prevalence of loss-of-function polymorphisms but a higher prevalence of the *17 gain-of-function polymorphism

Why is Bleeding Bad?

- The mechanism through which bleeding influences future ischemic events is poorly understood

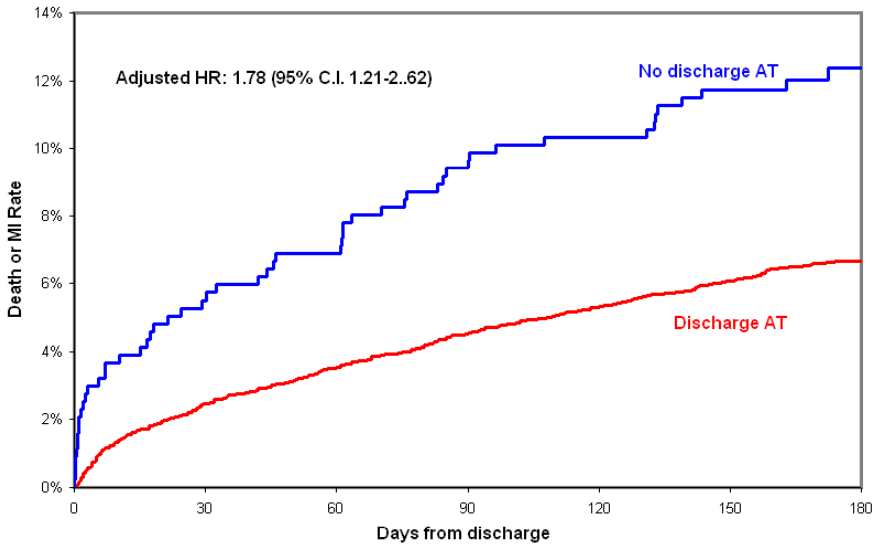
- Discontinuation of antiplatelet therapy (AT) after bleeding may be a possible mechanism as patients who bleed are often taken off their AT, and may remain without AT at discharge

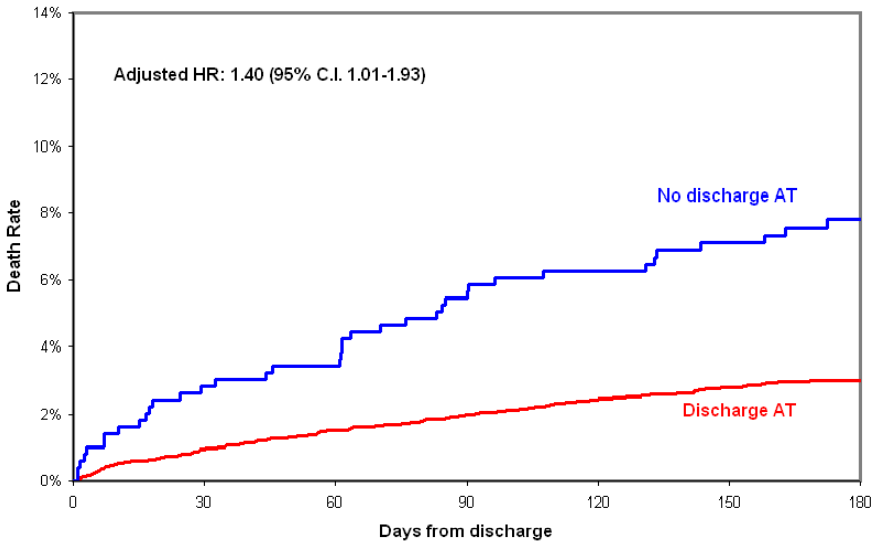
- Practice guidelines recommend continuing AT in patients with mild bleeding or restarting therapy as soon as possible in patients with more severe bleeding

  Class I recommendation, level of evidence C

Cumulative Event Rates: Discharge vs No Discharge Antiplatelet Therapy

- 8,582 ACS patients with in-hospital bleeding from a total of 26,451 patients enrolled in 4 randomized trials (PURSUIT, PARAGON-A, PARAGON-B, SYNERGY)
- Bleeding definitions: GUSTO or modified GUSTO bleeding





Chan et al Am Heart J 2010; 160: 1056- 1064

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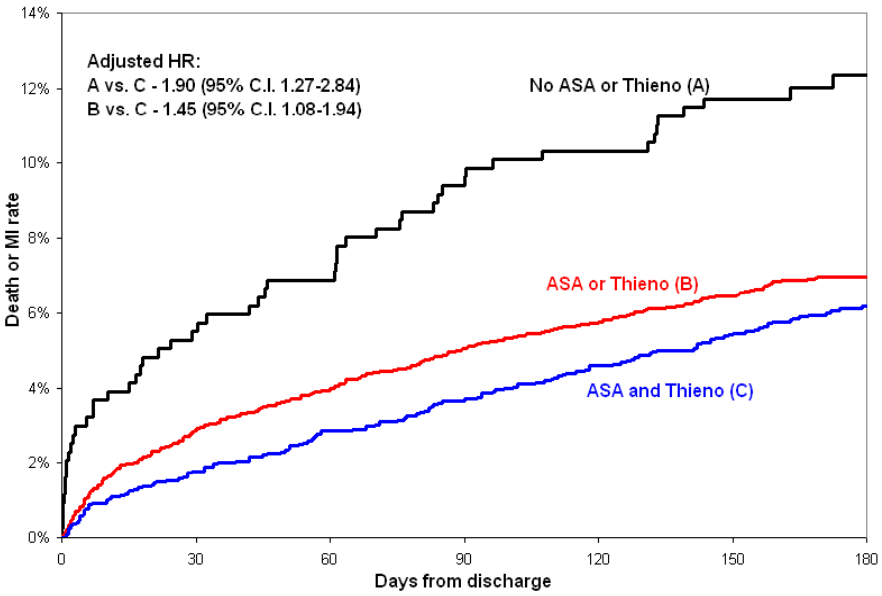
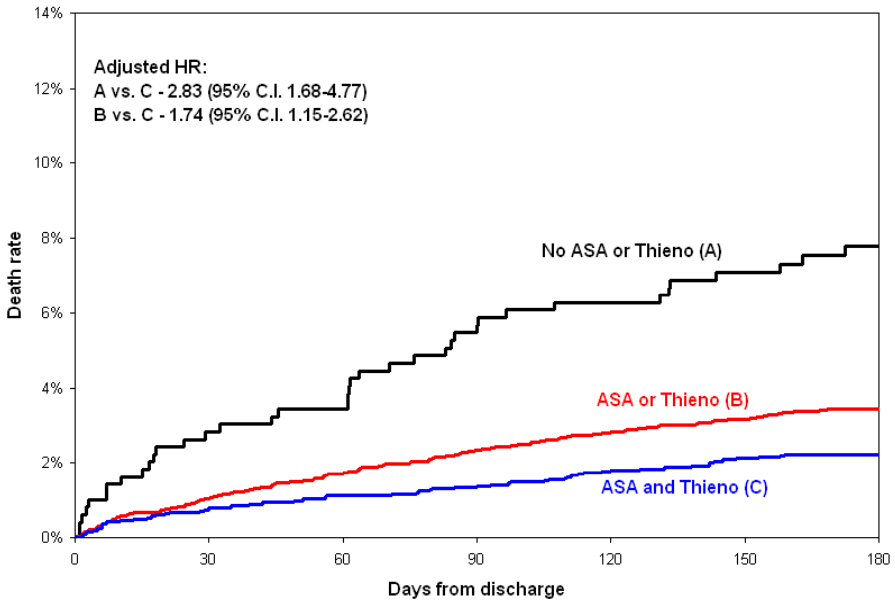
Cumulative Events as Function of Discharge Antiplatelet Intensity





Chan et al Am Heart J 2010; 160: 1056- 1064

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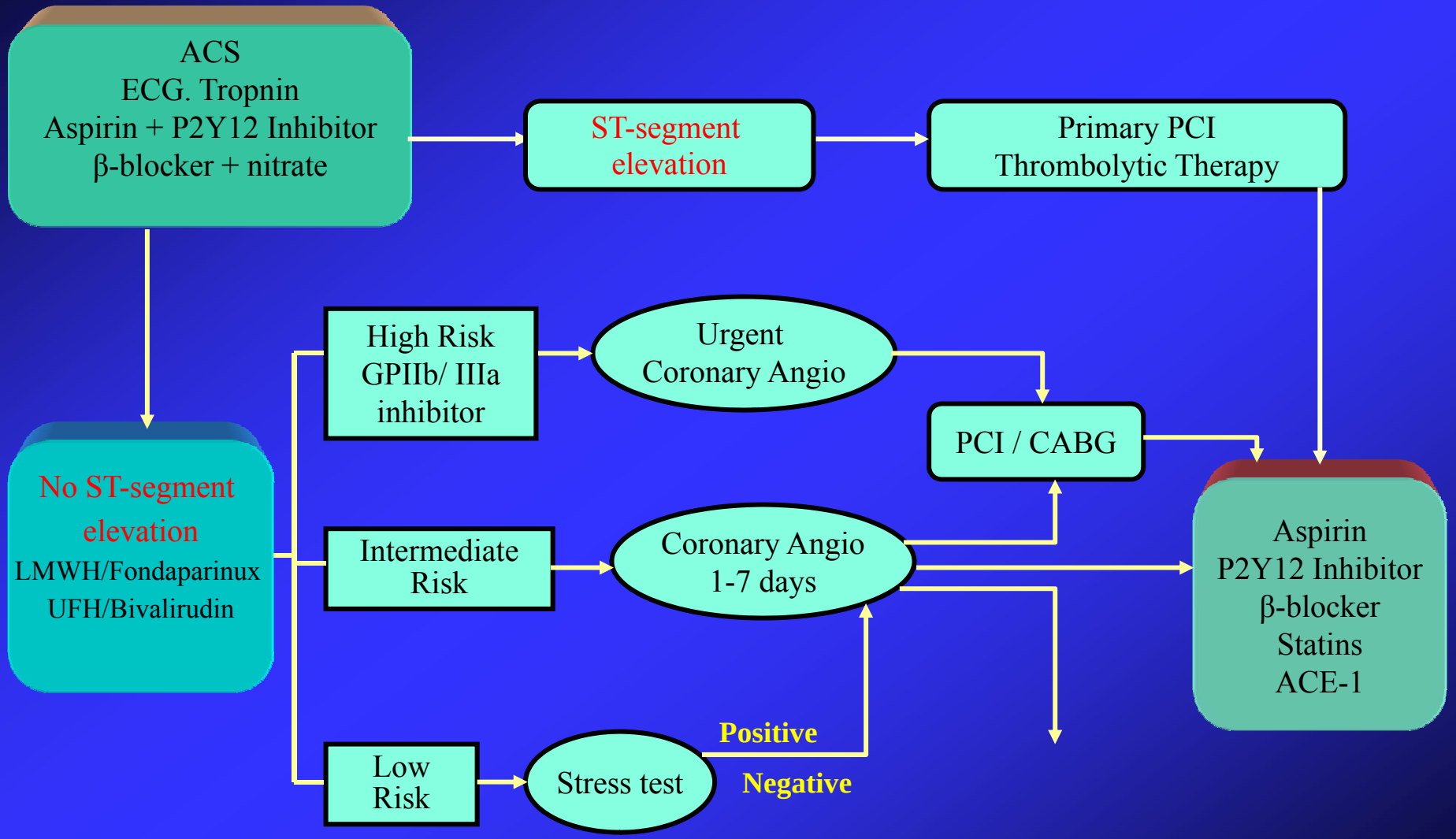
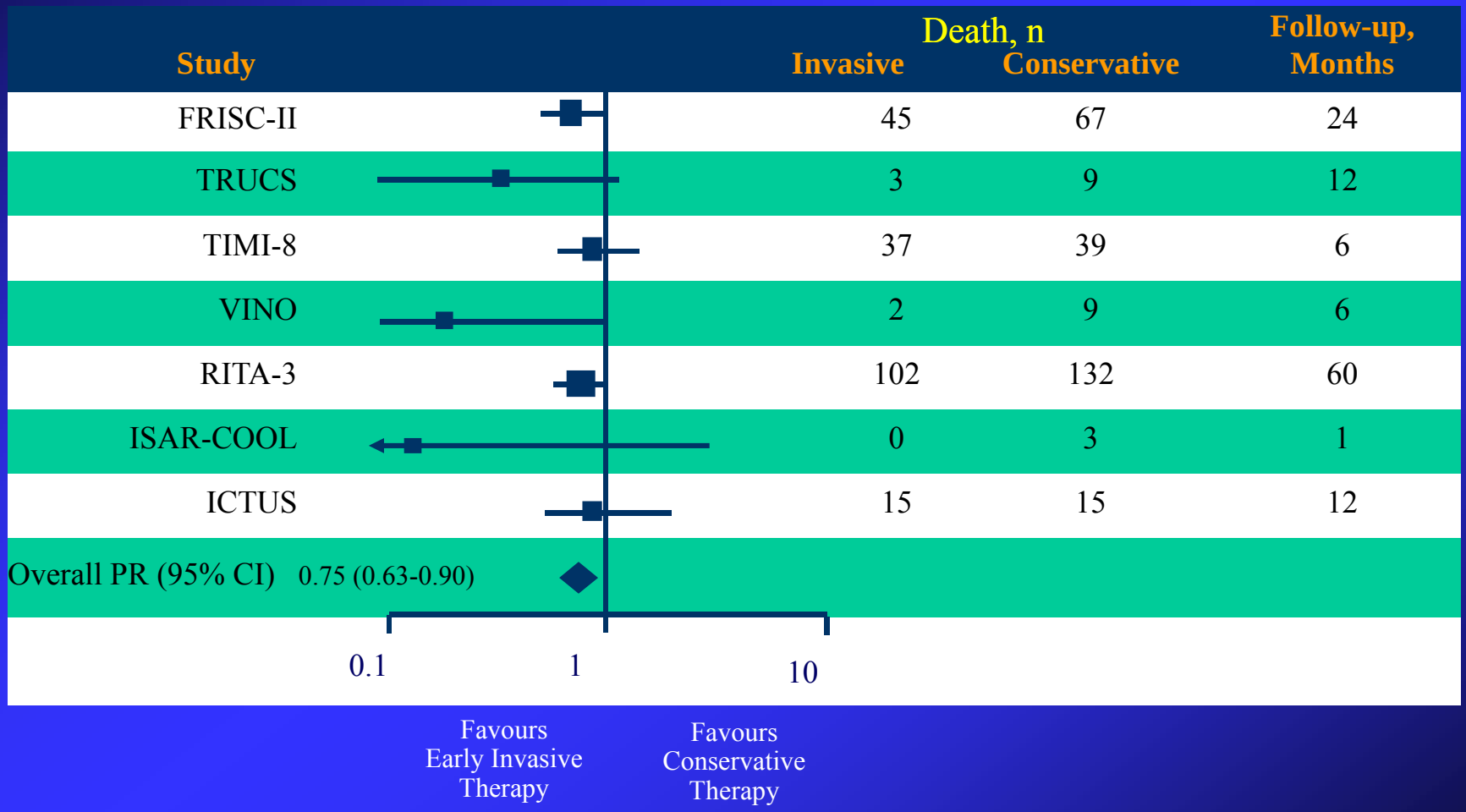
Algorithm in Treatment of ACS/AMI



Relative Risk of Outcomes With Early Invasive Versus Conservative Therapy in UA/NSTEMI

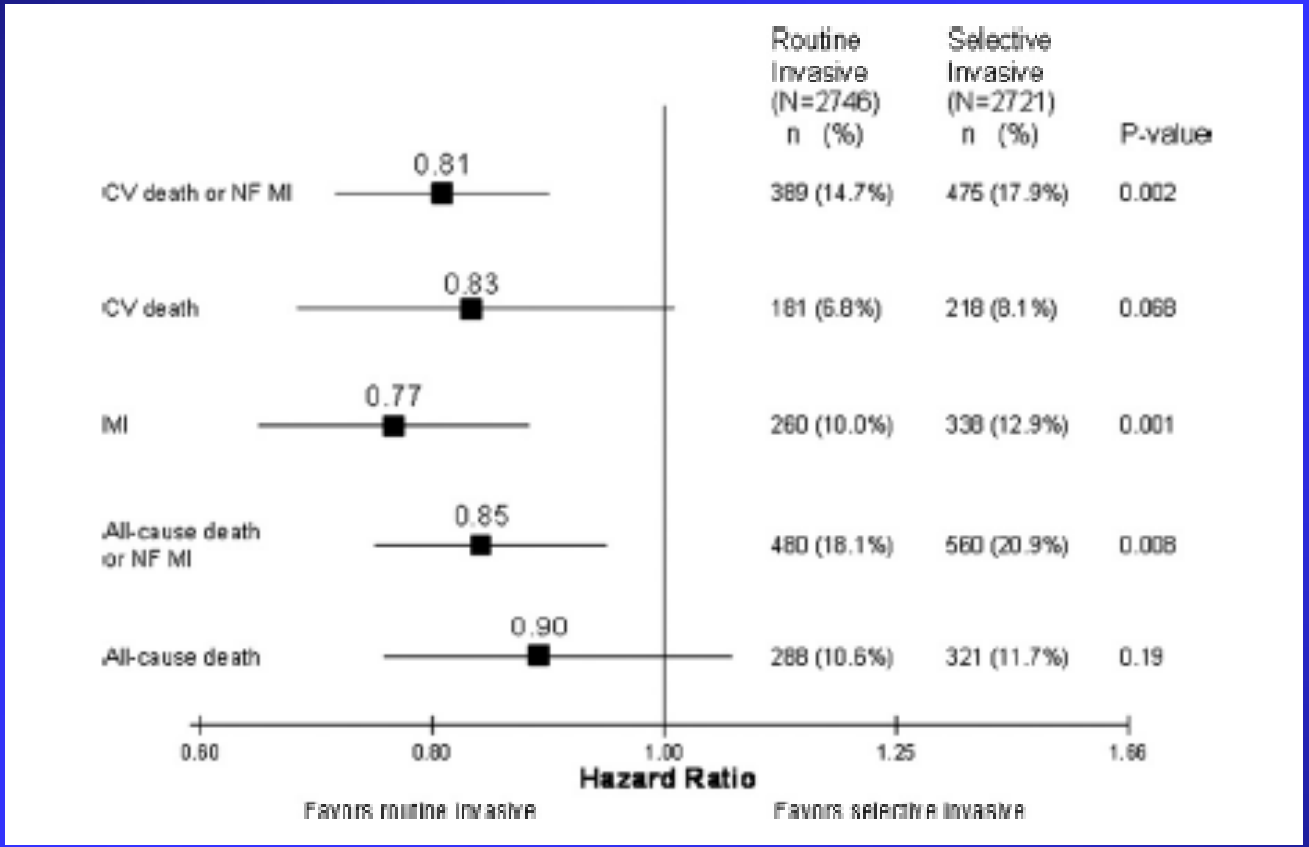


Anderson et al J Am Coll Cardiol 2007; 50: e1-157

National University Health System

Outcomes at 5-Years Comparing Routine vs Selective Invasive Strategies from Meta-Analysis of 3 Trials

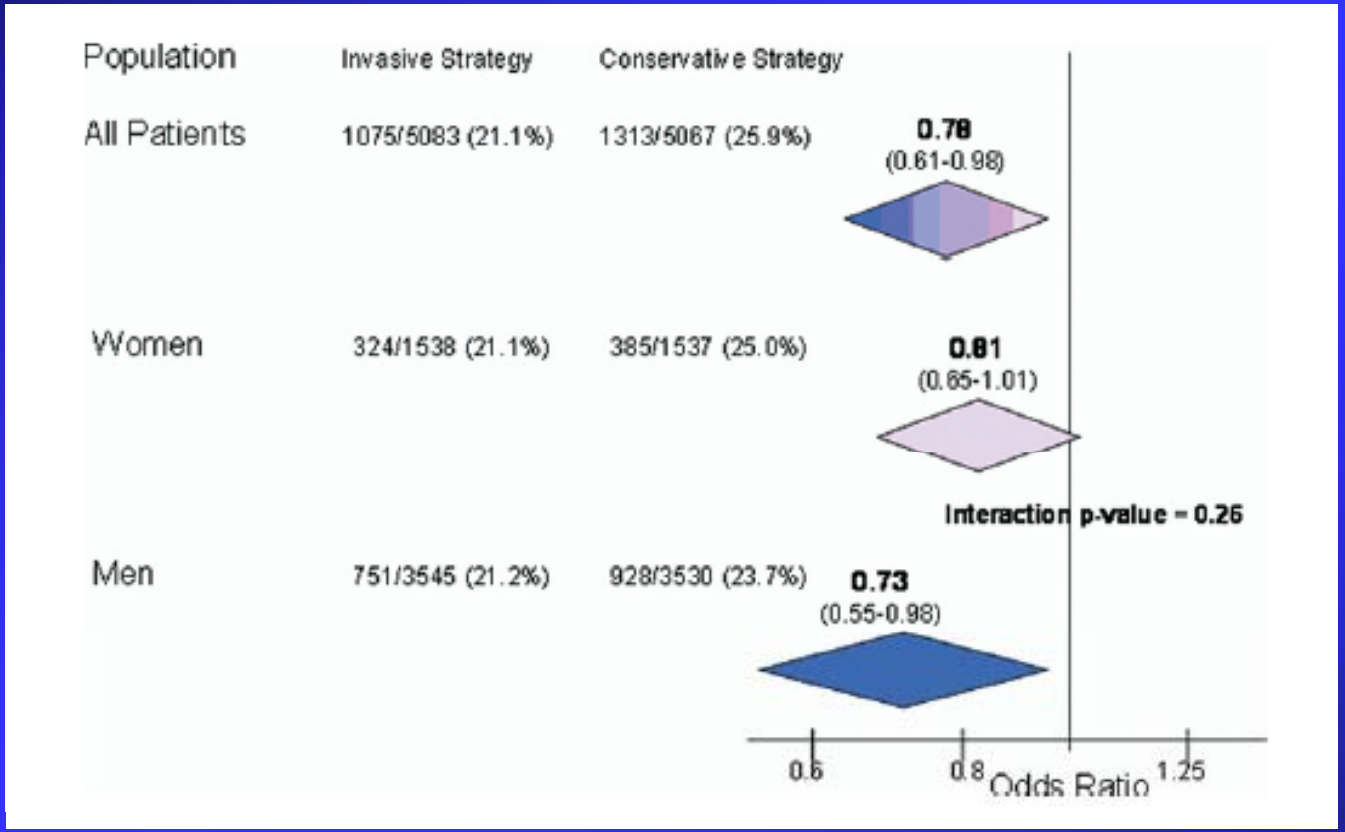
Individual patient data obtained from FRISC-II, ICTUS and RITA-3, n=5467



Conclusion: A RI strategy reduces long-term rates of cardiovascular death or MI and the largest absolute effect in seen in higher risk patients

Early Invasive vs Conservative Therapy In Men and Women With UA/NSTEMI

8 trials involving 3075 women and 7075 men

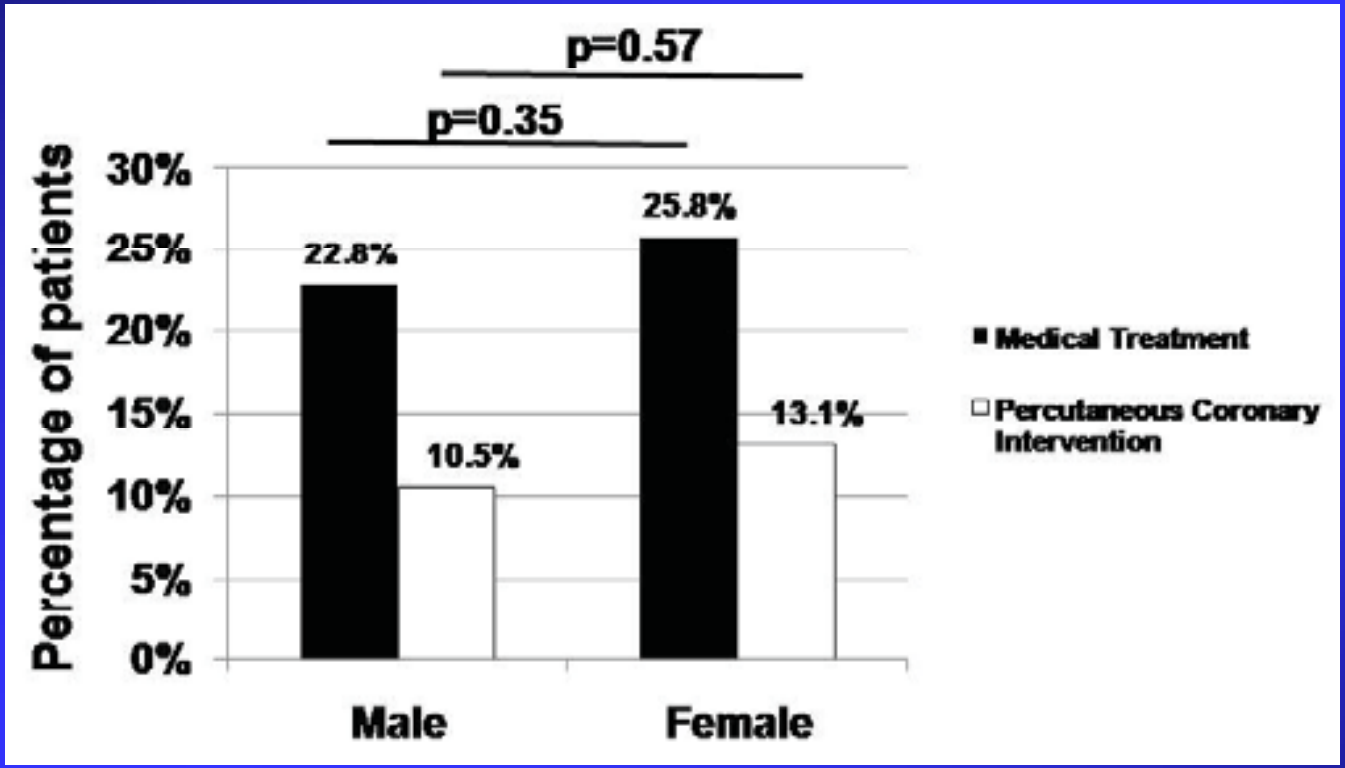


Among women who had a positive biomarker at baseline, an invasive strategy reduced the odds of an event by 33%, whereas in biomarker-negative women , there was only a 6% reduction (interaction p=0.08)

O' Donoghue M et al JAMA 2008; 300: 71-80

Patients with MACE At 1 Year (Stratified by Gender and Management strategies)

1353 patients (62.2% male) with NSTEMI were studied bet 2000 and 2005



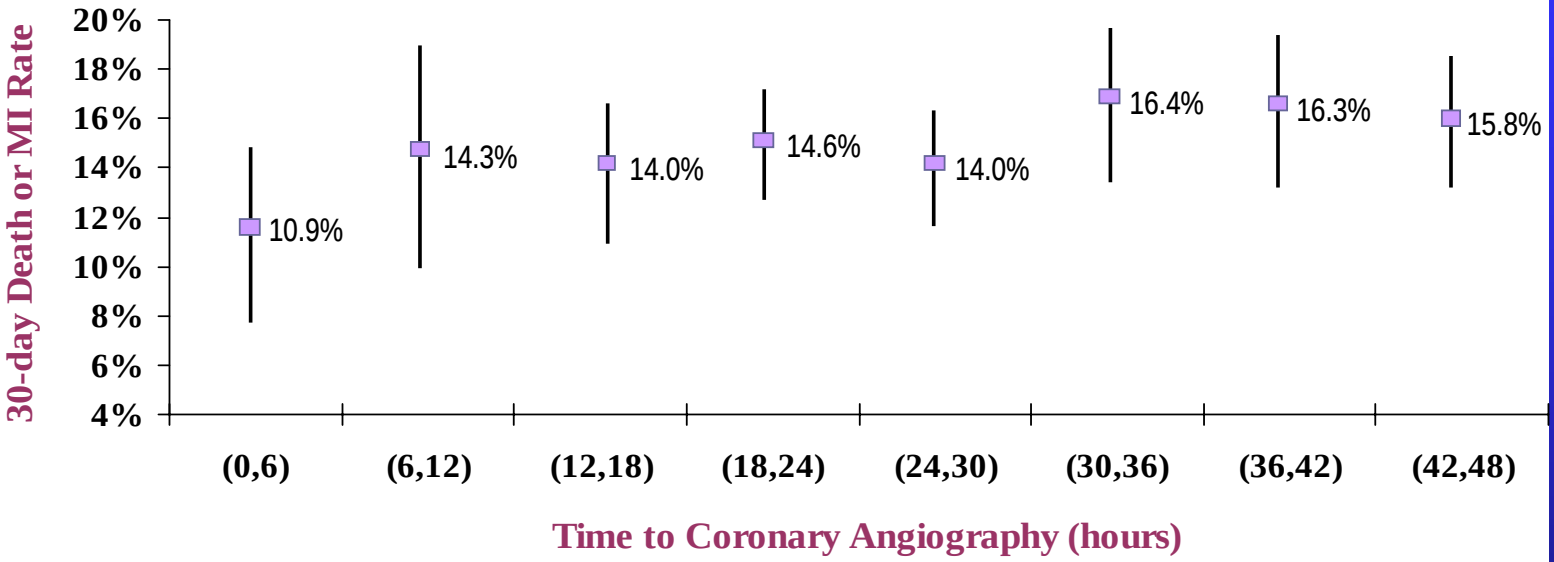
While there is a gender based difference in the rate of revascularisation among patients with NSTEMI, women benefit from an invasive approach as much as men, despite their advanced age, with similar rates of mortality and recurrent MI at 1-year follow-up.

LC Lee, HC Tan et al Ann Acad Med 2010

What Is The Optimal Timing of Angiography and Revascularisation?

SYNERGY: Time to Coronary Angiography and Outcomes Among Pts With High Risk NSTE-ACS

- 10027 pts with NSTE-ACS grouped by 6-hour intervals of time from hospital admission to coronary angiography
- Primary endpoints: 30-day death or MI, in-hospital TIMI and GUSTO bleeding & blood transfusion



Conclusion: Significantly lower rates of death or MI as time interval from presentation to angiography decreased, with an adjusted ratio of 0.56 for angiography performed < 6 hr compared with pts who received angiography at any later time or never received angiography

ABOARD (Angioplasty to Blunt the Rise of Troponin in ACS Randomised for an Immediate or Delayed Intervention)

352 patients with NSTE-ACS and TIMI 3 flow at 13 French centres bet August 2006 and September 2008 receive intervention either immediately or on the next working day (between 8 and 60 hrs after enrollment)

End Point	Intervention Strategy, No. (%)		P Value
	Immediate (n = 175)	Delayed (n = 177)	
Peak troponin I during index hospitalization, median (IQR), ng/mL (primary end point)	2.1 (0.3-7.1)	1.7 (0.3-7.2)	.70
Death, MI, or urgent revascularization at 1 mo, (key secondary end point)	24 (13.7)	18 (10.2)	.31
Death (all-cause)	5 (2.9)	2 (1.1)	.28
MI	16 (9.1)	8 (4.5)	.09
Non–CABG-related	15 (8.6)	8 (4.5)	.12
Post-CABG	1 (0.6)	0 (0)	.50
Urgent revascularization	6 (3.4)	10 (5.6)	.32
PCI	5 (2.9)	7 (4.0)	.57
CABG	1 (0.6)	3 (1.7)	.62
Death, MI, urgent revascularization, or recurrent ischemia at 1 mo	37 (21.1)	38 (21.5)	.94
Recurrent ischemia with or without urgent revascularization at 1 mo	21 (12.0)	33 (18.6)	.08
Major bleeding at 1 mo	7 (4.0)	12 (6.8)	.25
Non–CABG-related	4 (2.3)	9 (5.1)	.26
CABG-related	3 (1.7)	3 (1.7)	>.99
Transfusion ≥2 units	6 (3.4)	10 (5.6)	.32
Transfusion ≥5 units	2 (1.1)	2 (1.1)	>.99
Thrombocytopenia	5 (2.9)	8 (4.5)	.41
Non-CABG	4 (2.3)	7 (4)	.54
Post-CABG	1 (0.6)	1 (0.6)	>.99

Abbreviations: CABG, coronary artery bypass graft; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Conclusions: No difference in peak troponin or clinical ischemic composite in pts randomsied to immediate vs delayed (average 21 hr) intervention

2009 ACC/AHA/SCAI PCI Guideline Update

Class IIa

It is reasonable for initially stabilised ***high-risk*** patients with GRACE risk score >140 to undergo an early invasive strategy within 12 to 24 hrs of admission

For patients ***not at high risk***, an early invasive approach is also reasonable (Level of Evidence B)

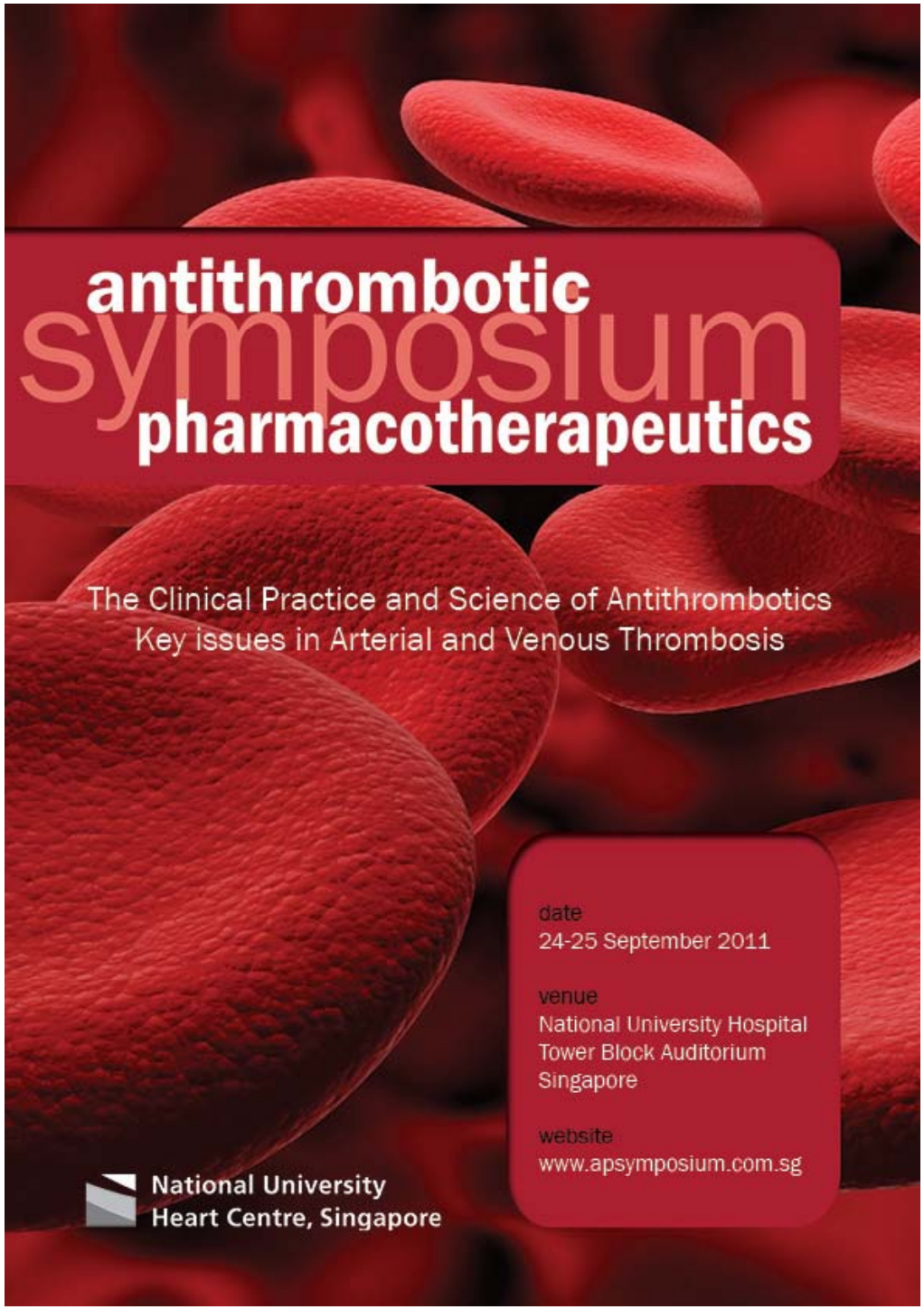
Conclusions

- Risk model prediction is useful tool but proper validation needed before applying external risk models to previously untested populations

- With a growing number of biomarkers associated with adverse clinical outcomes, challenge lies in the identification of one that can be integrated with imaging and diagnostic modalities to improve the prediction of death and cardiovascular complications in a cost-effective manner

- Significant differential prevalence of genetic CYP2C19 polymorphism present in Asian ethnic groups. Bleeding remains a challenge in pharmacologic therapy of ACS

- Current trend of more frequent and earlier use of angiography and revascularisation are expected to continue with existing evidence



THEME

The Clinical Practice and Science of Antithrombotics. Key issues in Arterial and Venous Thrombosis

SYMPOSIUM HIGHLIGHTS

- State-of-the-art lectures addressing contemporary clinical issues in antithrombotic drug use
- How-to-series illustrating the decision-making process from experts
- Workshops to provide up-to-date skills for pharmacists, nurses and clinical trial coordinators involved with antithrombotic drug use
- Platelet Function Testing workshop addressing technical knowledge and clinical application
- Interactive case presentations: Submit your challenging clinical cases for awards and prizes

TARGET AUDIENCE

Cardiologists, Haematologists, Cardiothoracic Surgeons, Medical Trainees, Pharmacists, Nurses, and Industry Delegates

WEBSITE

www.apsymposium.com.sg

ENQUIRY

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