

Troponins (and Natriuretic Peptides)

Current Status and Gaps in Evidence Base

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Diagnostic Criteria for MI

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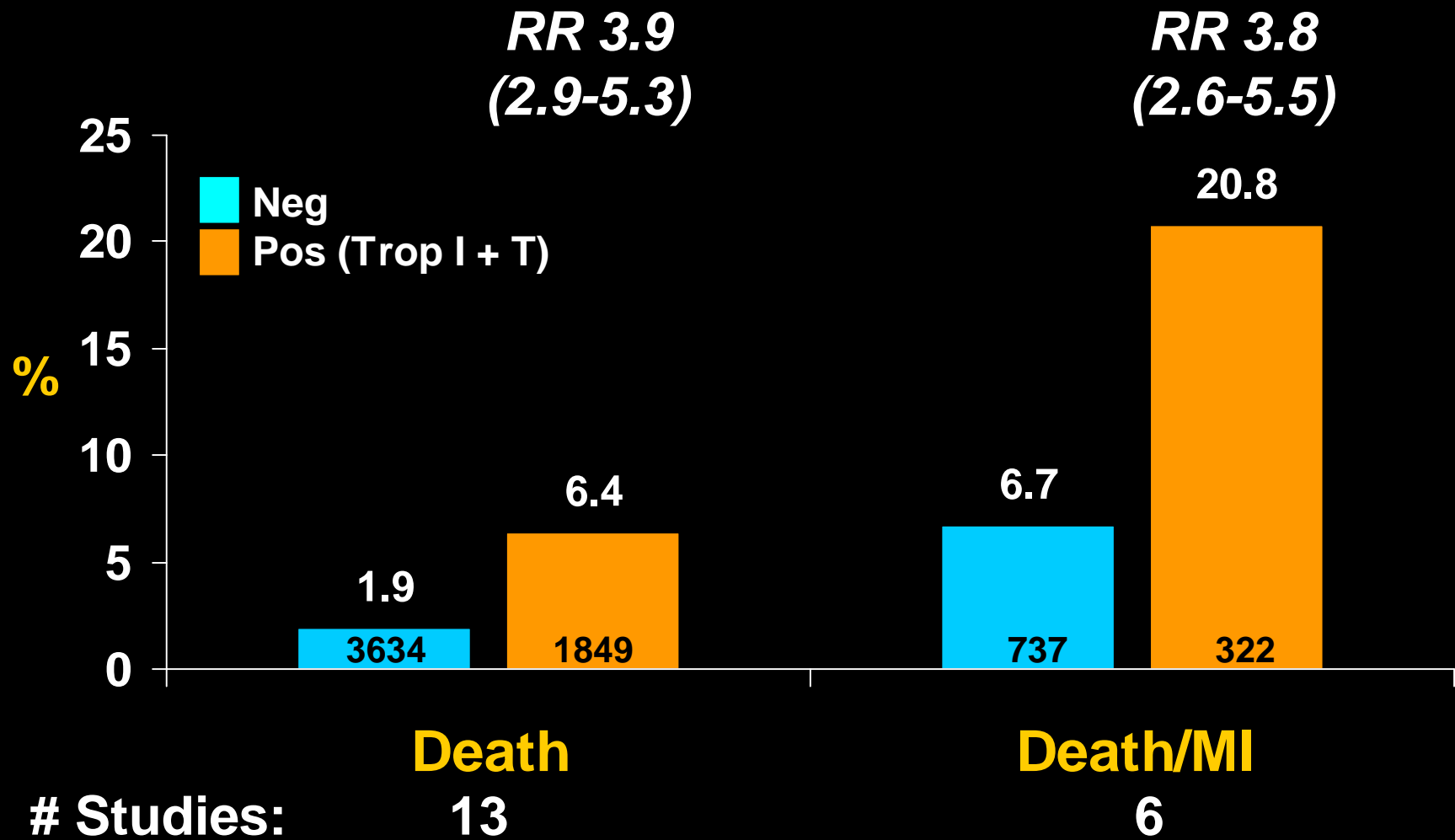
Myocardial Infarction Redefined—A Consensus
Document of The Joint European Society of
Cardiology/American College of Cardiology
Committee for the Redefinition of Myocardial Infarction
The Joint European Society of Cardiology/
American College of Cardiology Committee**

Biomarker indicators of MI

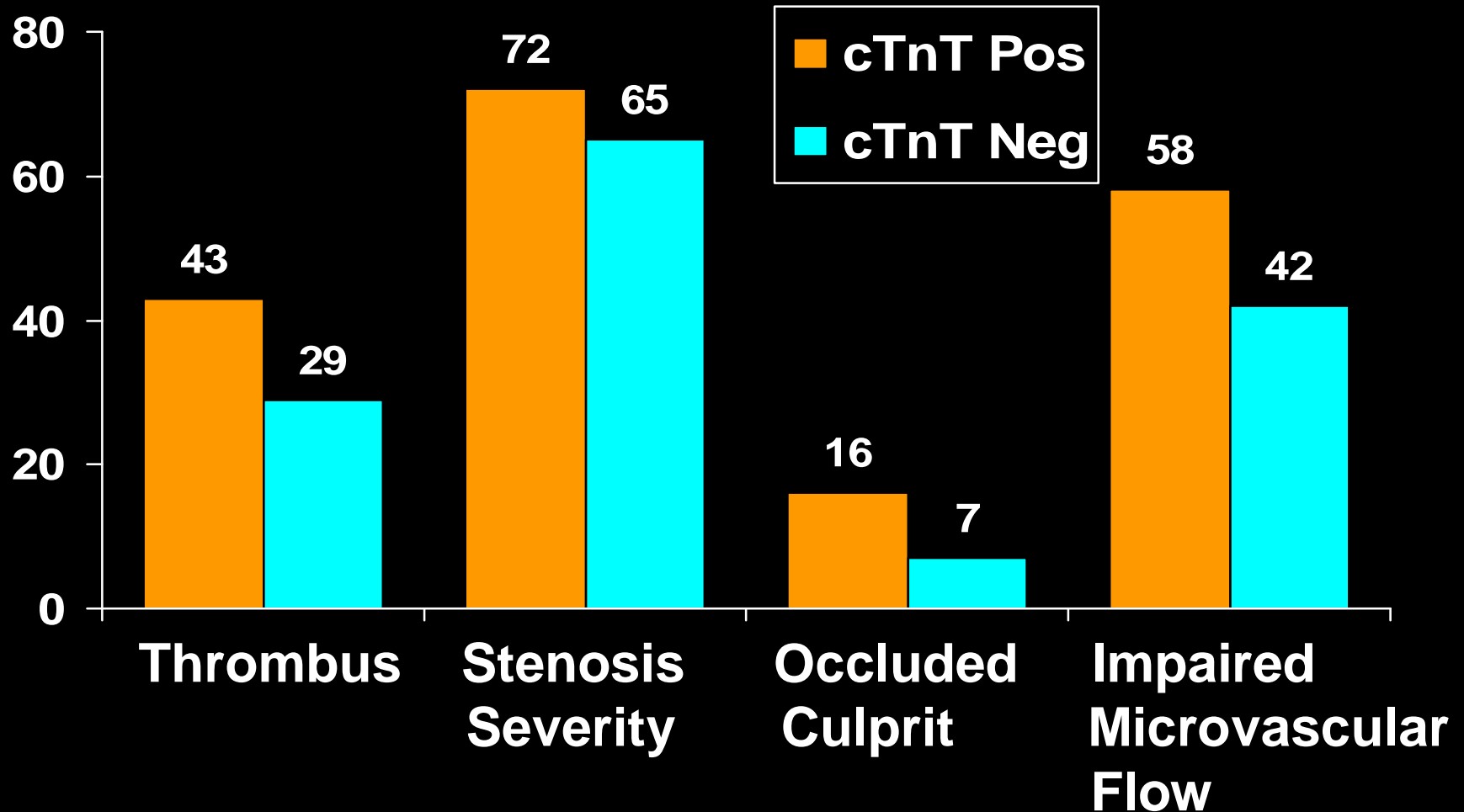
- Troponin is preferred biomarker for dx of MI
- cTnT or cTnI > 99th %ile on any determination
- CK-MB > 99th %ile on two successive measurements or > 2X ULN on any sample

Prognostic Value of Pos. Troponin Test in ACS

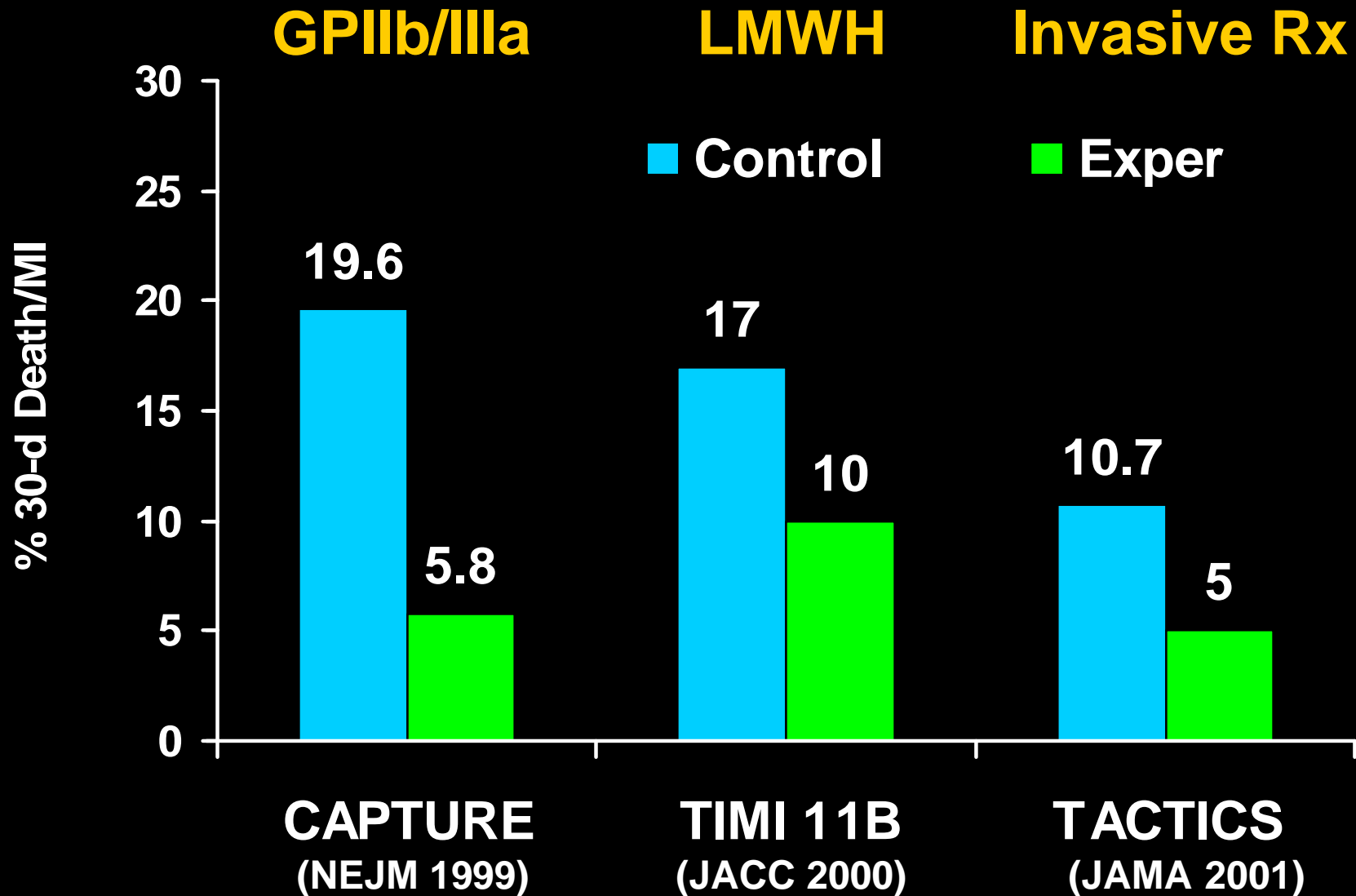
ACC/AHA Guidelines for UA/NSTEMI JACC 36:970, 2000



Relation of cTnT to Epicardial and Microvasculature Perfusion in TACTICS



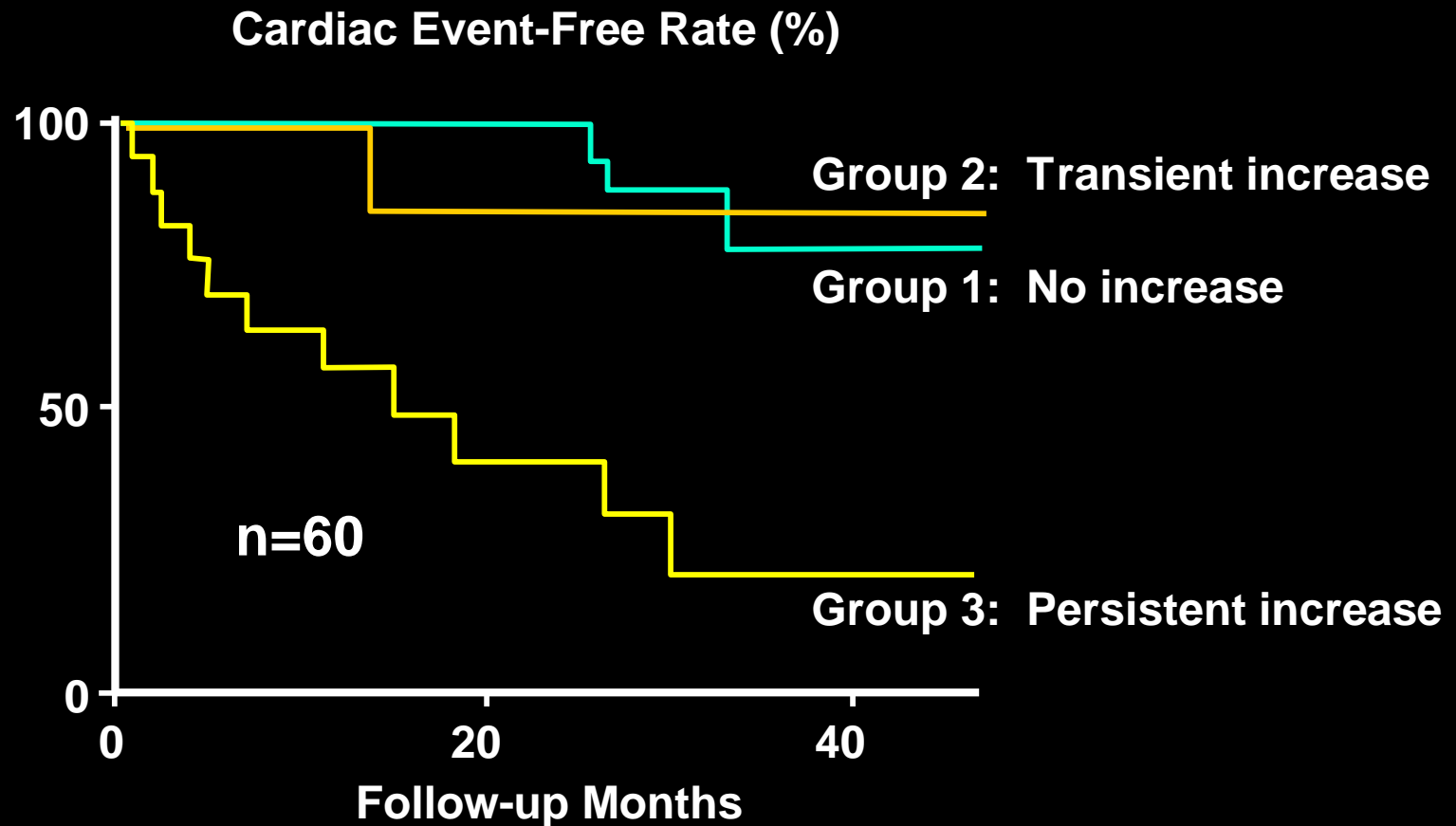
Troponins in Clinical Decision-Making



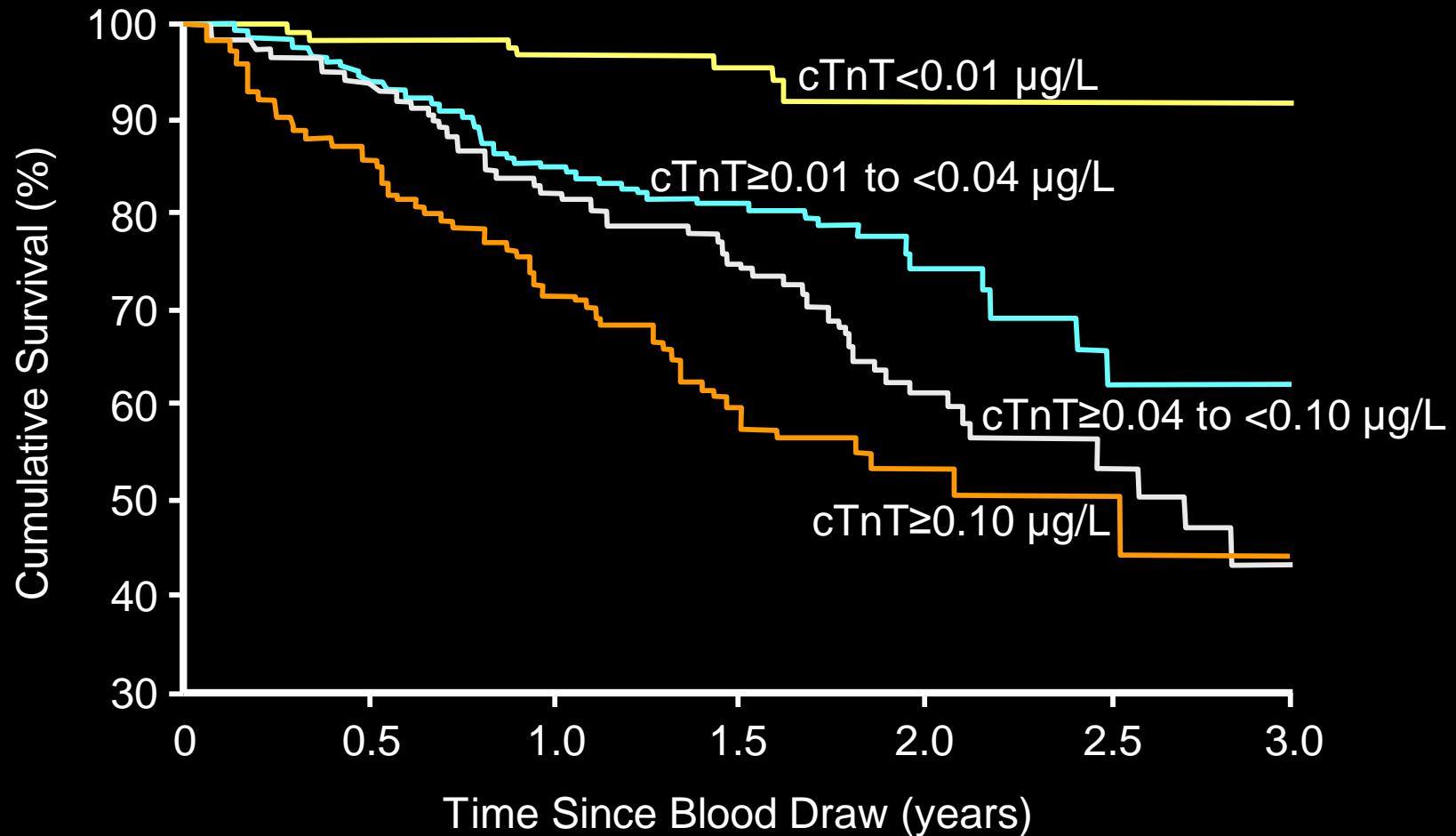
Non-ACS ↑ of Cardiac Troponins

- **Pulmonary embolism**
- **Congestive Heart Failure**
- **Sepsis**
- **Renal Failure**
- **Chronic CAD/LVH/LVSD**

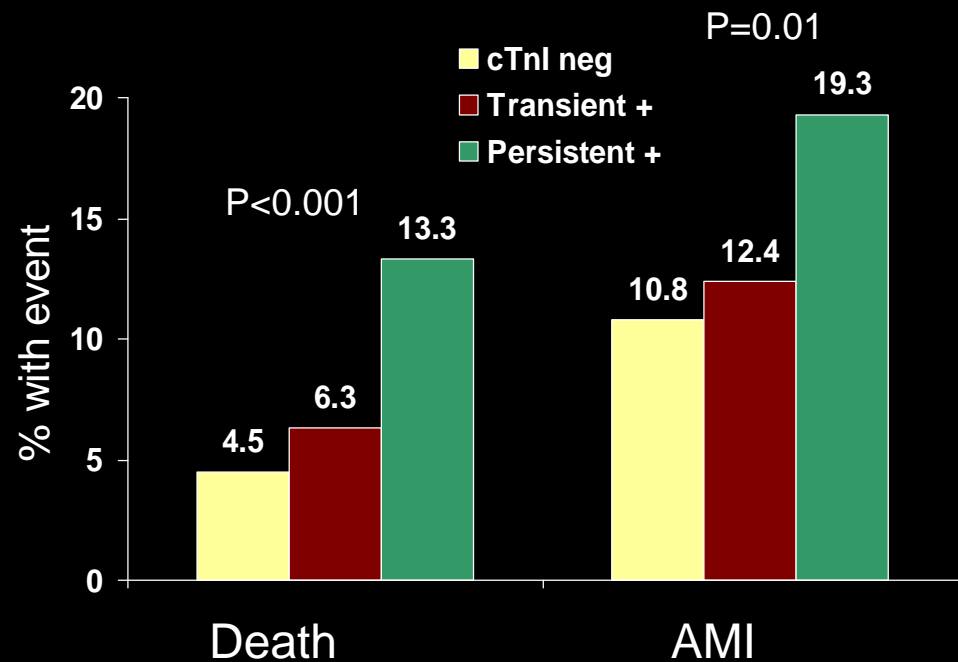
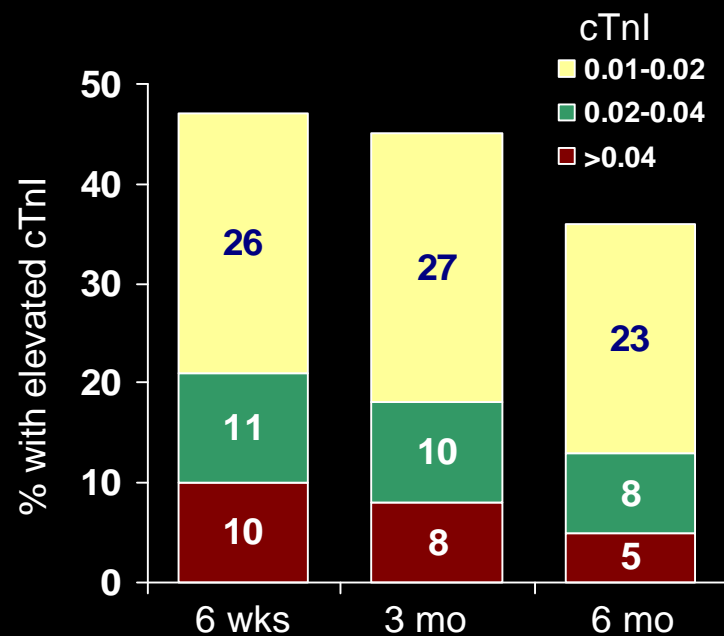
Troponin T in Heart Failure



Cardiac Troponin in Patients With ESRD



Persistent cTn Elevation post ACS



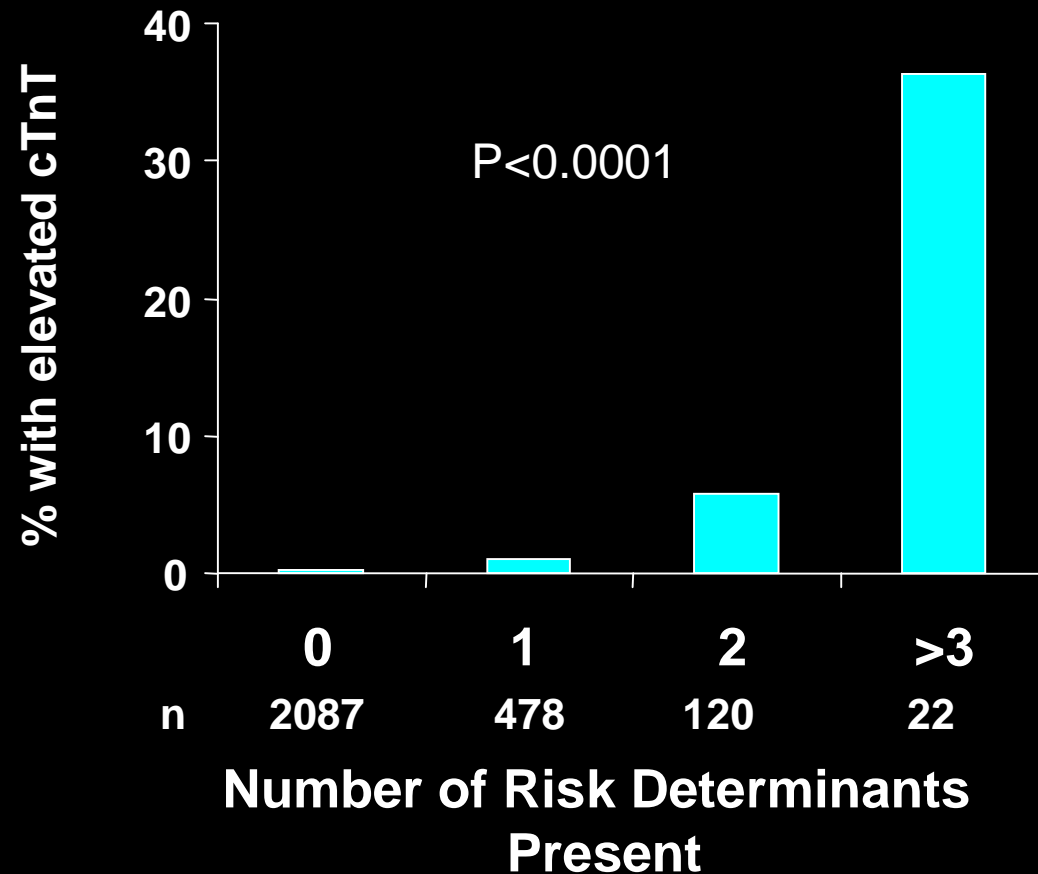


Troponin Elevation in the General Population

The Dallas Heart Study

0.7% prevalence of cTnT > 0.01 mg/L

Risk Determinant	Odds Ratio
Diabetes	4.6
LV Hypertrophy	5.4
Congestive Heart Failure	5.3
Chronic Kidney Disease	20.4



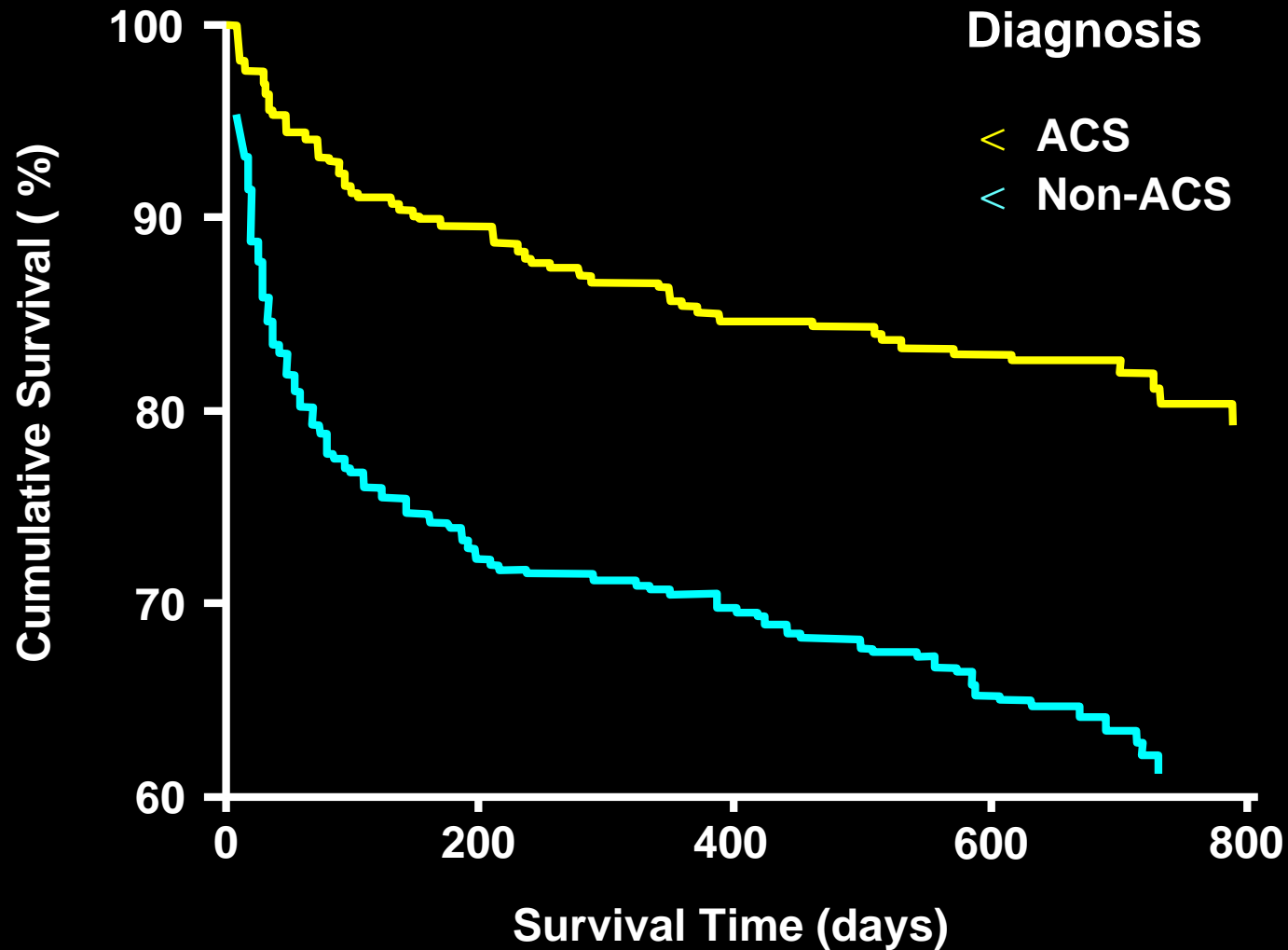
Positive Predictive Value for the Diagnosis of ACS in Different Patient Profiles

Patient Profile	Troponin Levels		
	Any Positive Result	0.1-1.0 ng/mL	>1.0 ng/mL
All patients	56 (52-60)	48 (43-53)	76 (69-82)
Age < 70 y and creatinine < 1.13 mg/dL	78 (72-84)	73 (65-80)	89 (79-95)
Age < 70 y and creatinine ≥ 1.13 mg/dL	44 (35-55)	40 (29-52)	59 (36-79)
Age > 70 y and creatinine < 1.13 mg/dL	52 (42-63)	42 (31-54)	90 (68-99)
Age > 70 y and creatinine ≥ 1.13 mg/dL	37 (29-45)	27 (20-37)	59 (43-73)

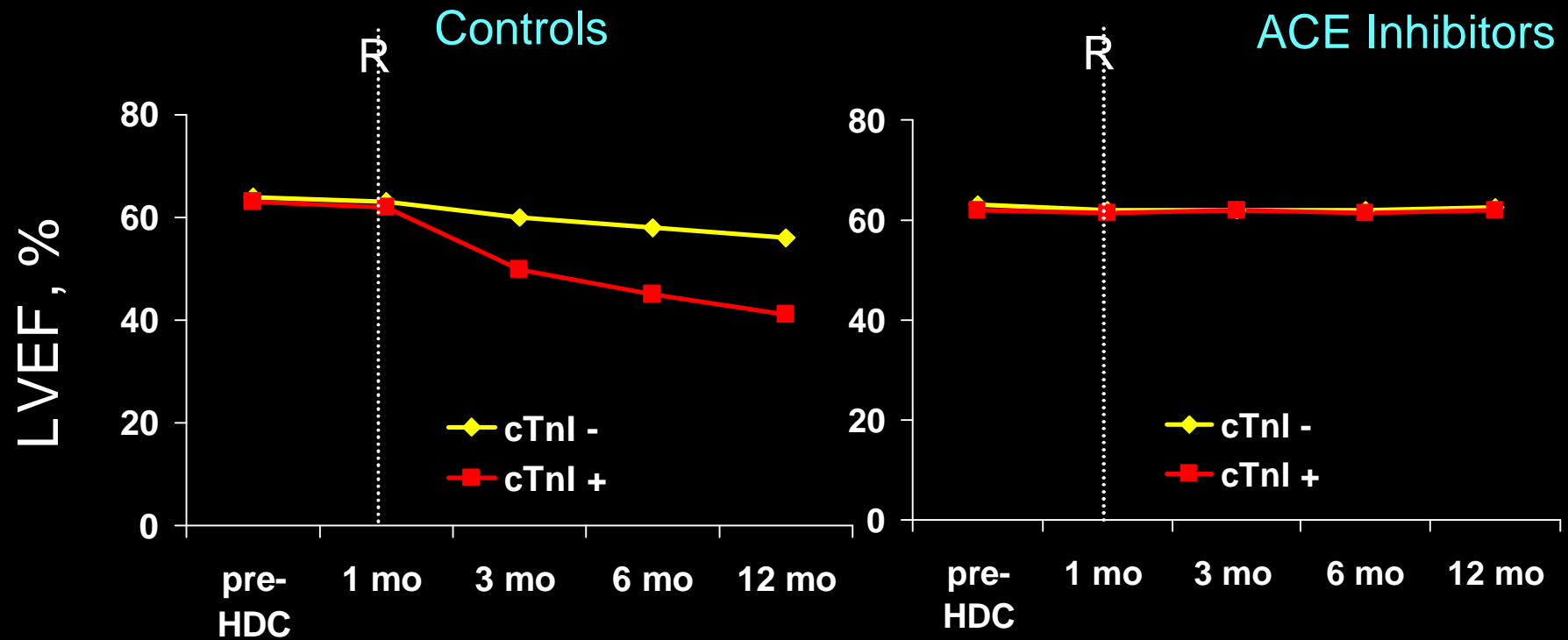
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Survival Curves According to Principal Diagnosis

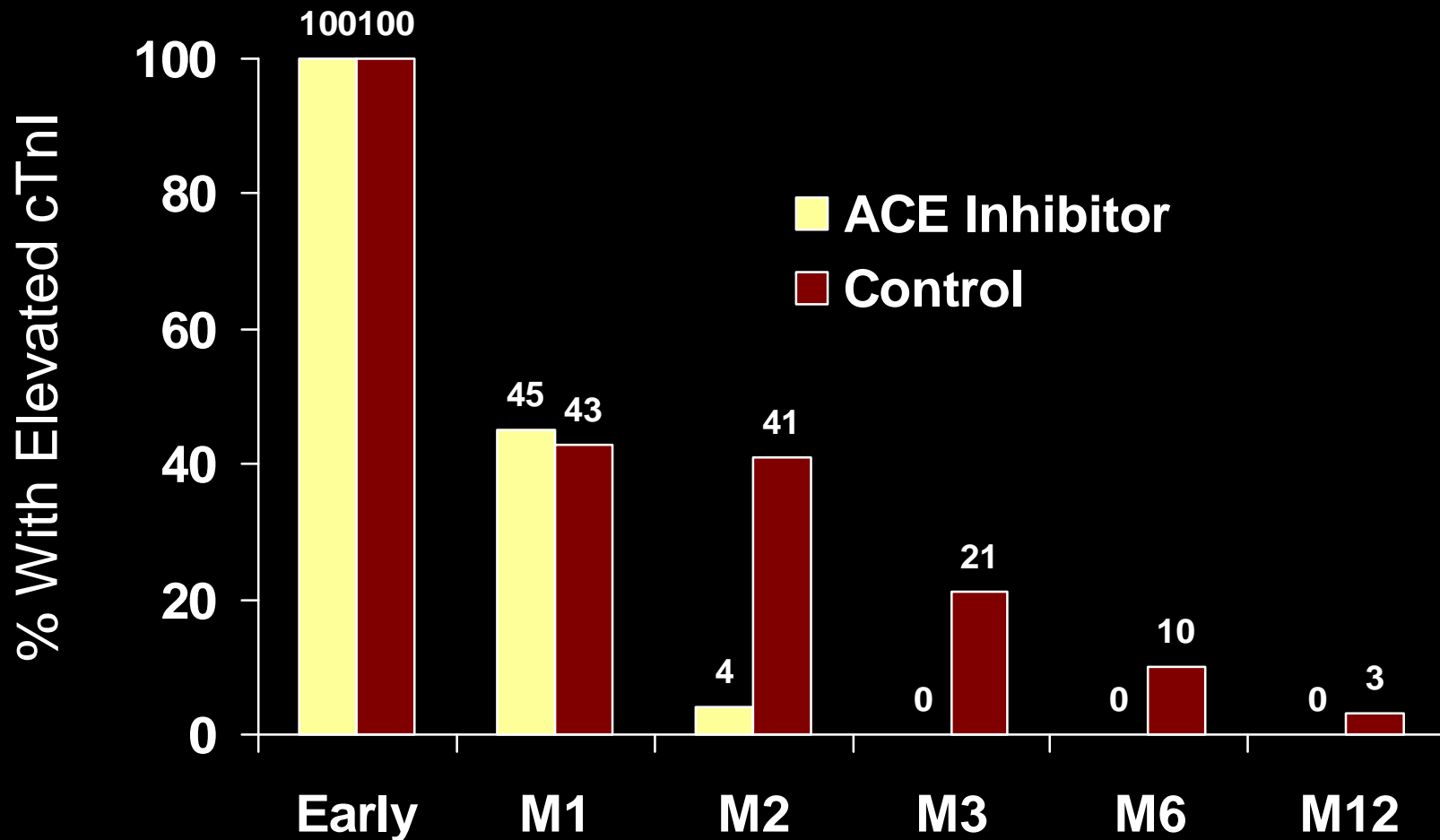


cTnI in Cancer Chemotherapy



*cTnI increased in 114/473 pts receiving high dose chemo

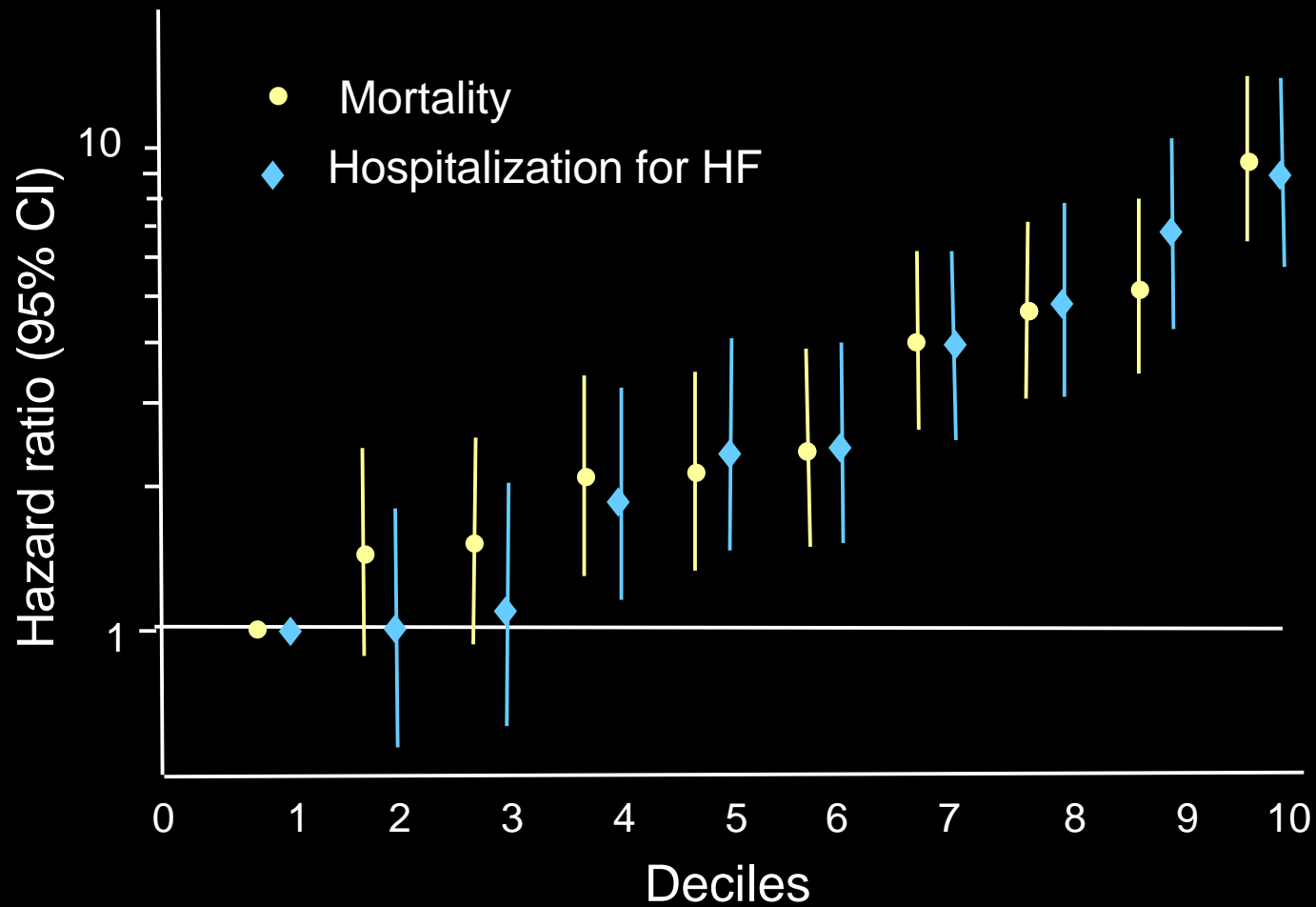
cTnI in Cancer Chemotherapy



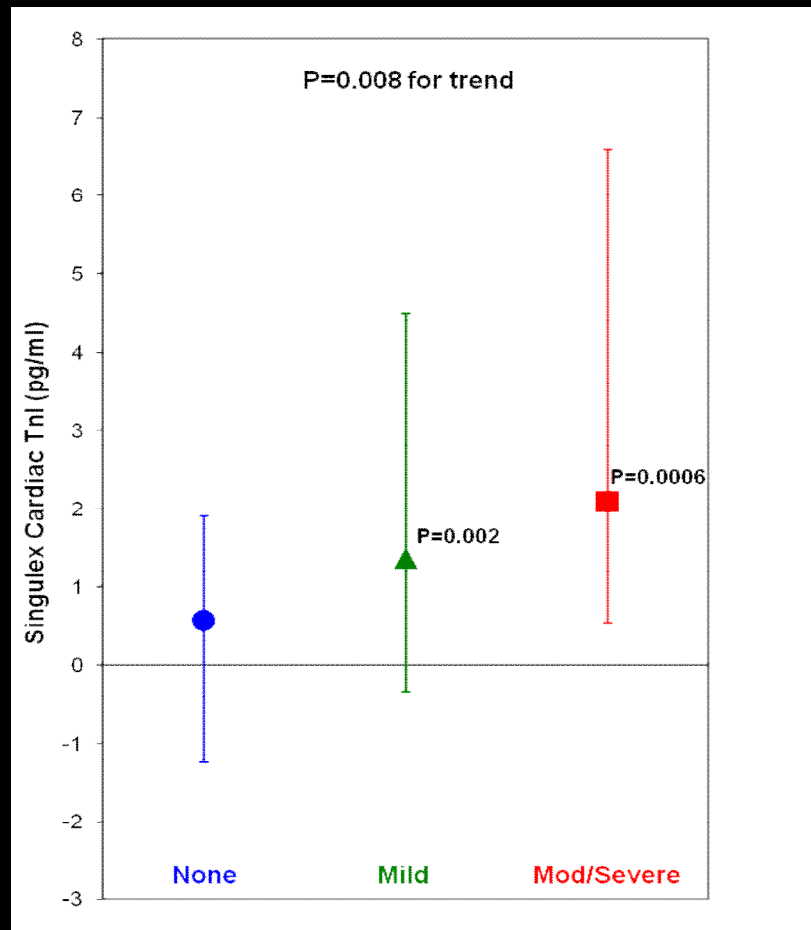
The next opportunity (and challenge)

High sensitivity troponin testing

HS-cTnT in VAL-HEFT



HS-cTnI in Reversible Ischemia



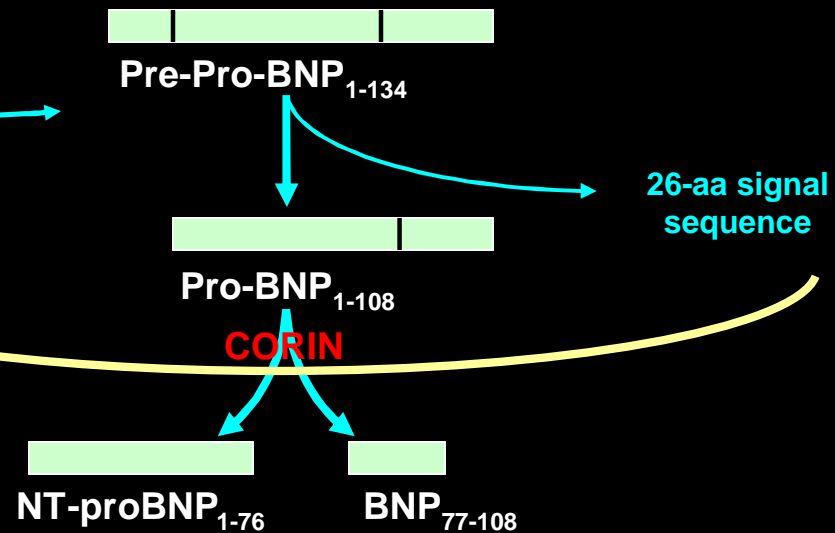
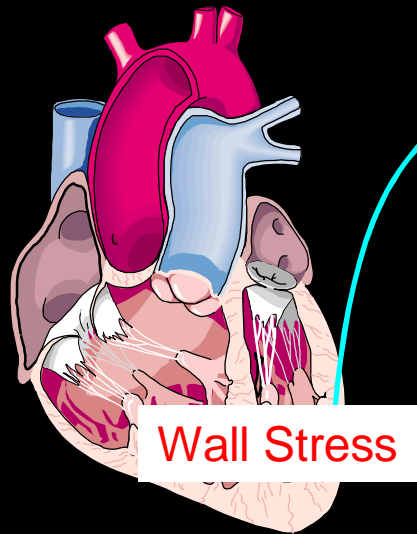
Troponin –Bottom Line

- As a diagnostic marker, specific for myocyte injury but not ischemic mechanism
 - Must be interpreted in clinical context
 - Rise and fall pattern *probably* helpful
 - Implications differ procedural vs nonprocedural
- Valuable for risk assessment but therapeutic implications only defined for unambiguous ACS
- In non-ACS cases
 - Often a *chronic* marker
 - Adverse prognostic indicator
 - Therapeutic implications not clear
- High(er) sensitivity assays coming
 - Will this “soften” our hard endpoints?
 - New challenges when we “risk enrich” trial populations using cTn
 - Transition from qualitative to quantitative marker

Future Uses and Evidence Needed

- MI diagnostic marker (surrogate for CV death)
 - Is the case weakening as the assays get more sensitive?
 - ? Long term implications of small MIs vs bleeding
- Cardiac safety marker
 - Need evidence linking ≥ 2 interventions (drugs) that causes acute and/or chronic elevation with subsequent heart failure and/or cardiac death
- Chronic disease monitoring
 - Need evidence demonstrating that “turning off” troponin release is associated with reverse remodeling and favorable outcomes
- Targeting therapy
 - Need subgroup analyses from trials outside ACS

BNP and NT-proBNP



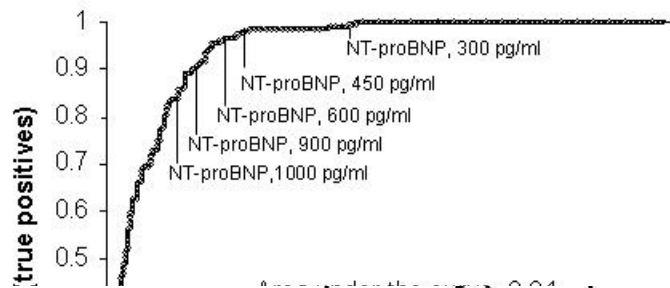
The WBC count for the
Cardiologist?

Clinical Uses of BNP/NT-proBNP

- **Diagnostic**
 - CHF (systolic and diastolic)
 - Detect asymptomatic LV dysfunction
- **Prognostic Assessment**
 - CHF or LV dysfunction
 - RV processes
 - ACS
- **Population screening**
- **Therapeutic**
 - Assess response to CHF Rx
 - Guide CHF Rx

High NPV but Moderate PPV for HF Diagnosis

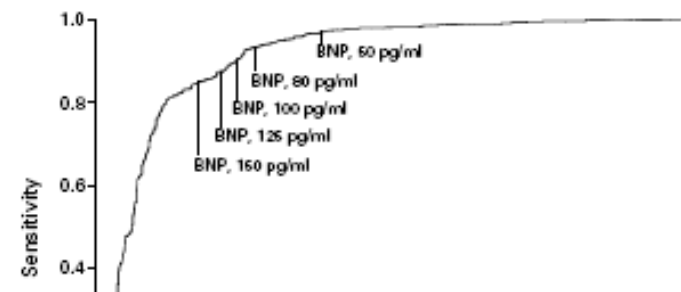
PRIDE



Cut Point	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
300 pg/ml	99%	68%	62%	99%
450 pg/ml	98%	76%	68%	99%
600 pg/ml	96%	81%	73%	97%
900 pg/ml	90%	85%	76%	94%
1000 pg/ml	87%	86%	78%	91%

300 pg/ml	99%	68%	62%	99%	79%
450 pg/ml	98%	76%	68%	99%	83%
600 pg/ml	96%	81%	73%	97%	86%
900 pg/ml	90%	85%	76%	94%	87%
1000 pg/ml	87%	86%	78%	91%	87%

Breathing Not Properly



BNP pg/ml	SENSITIVITY	SPECIFICITY	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE
	(95 percent confidence interval)			
60	97 (96-98)	62 (59-66)	71 (68-74)	96 (94-97)
80	93 (91-96)	74 (70-77)	77 (75-80)	92 (89-94)
100	90 (88-92)	76 (73-79)	79 (76-81)	89 (87-91)
125	87 (85-90)	79 (76-82)	80 (78-83)	87 (84-89)
160	85 (82-88)	83 (80-86)	83 (80-86)	85 (83-88)
80	93 (91-96)	74 (70-77)	77 (75-80)	92 (89-94)
100	90 (88-92)	76 (73-79)	79 (76-81)	89 (87-91)
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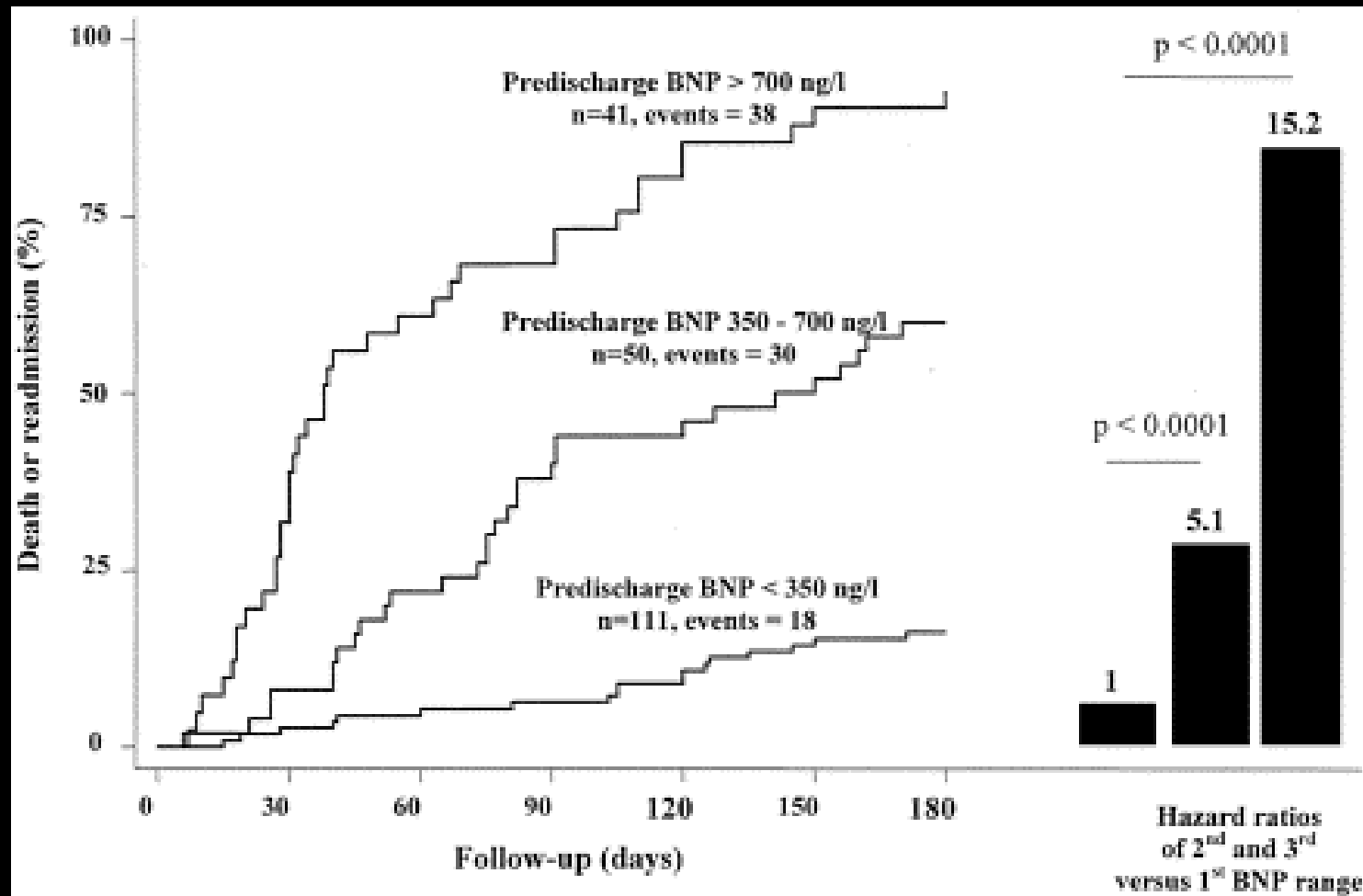
Figure 3. Receiver-Operating-Characteristic Curve for Various Cutoff Levels of B-Type Natriuretic Peptide (BNP) in Differentiating between Dyspnea Due to Congestive Heart Failure and Dyspnea Due to Other Causes.

Independent Determinants of BNP in patients with Heart Failure

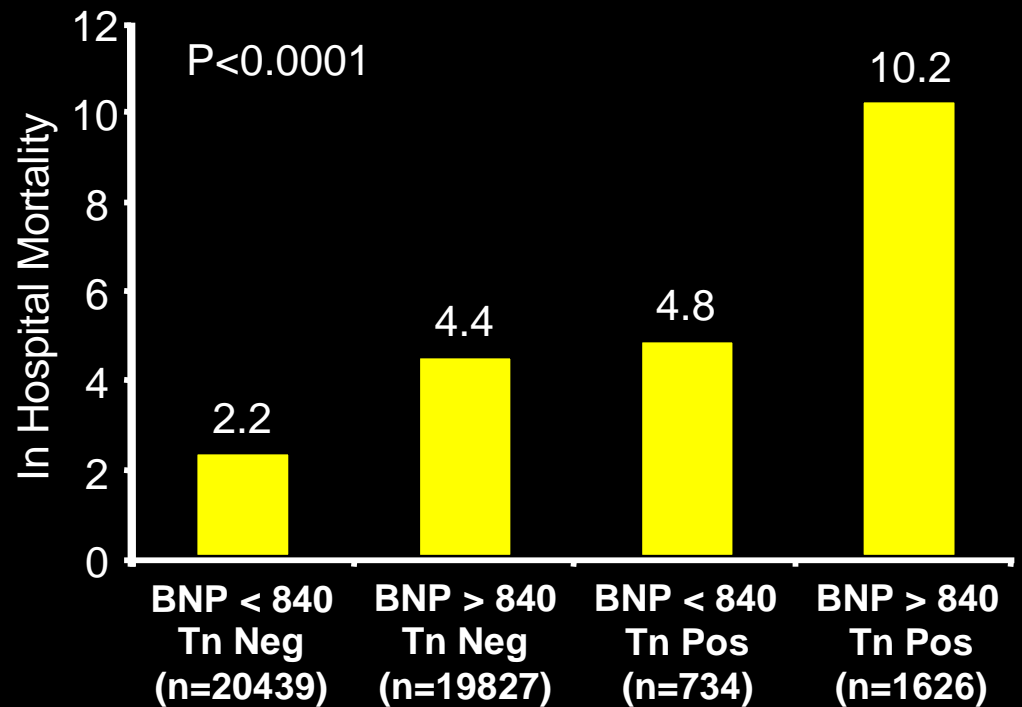
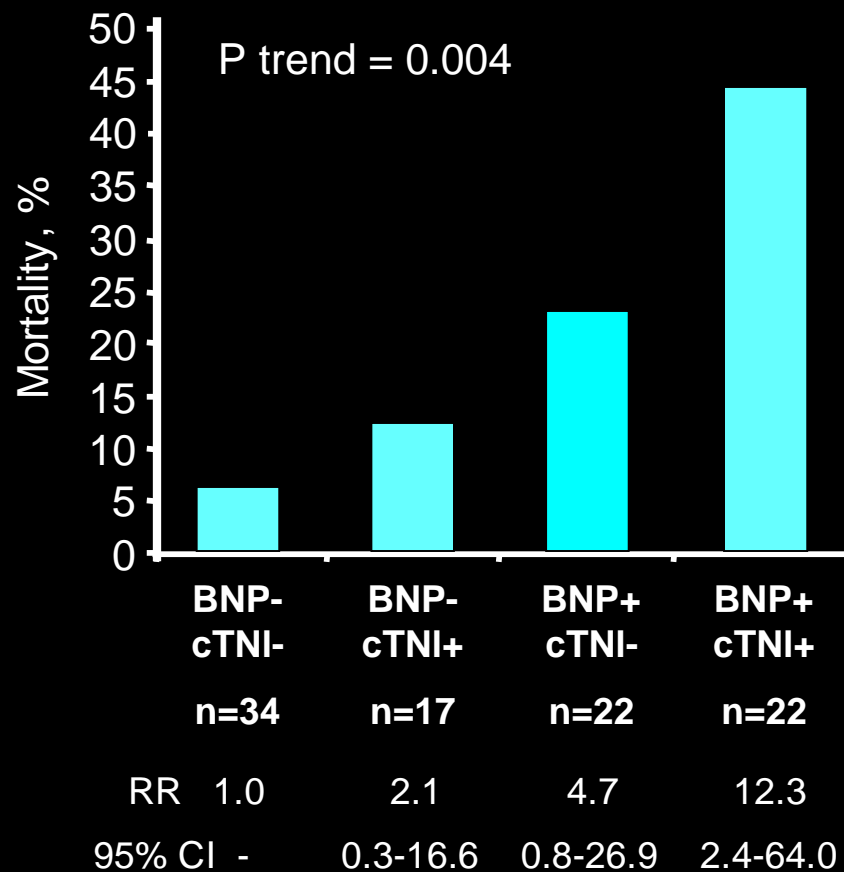
- Diastolic indices
- Filling pressures
- LVEF
- RVSF
- MR severity
- Age
- ClCr

Model fit R=0.8; n=108

Pre-Discharge BNP and Prognosis

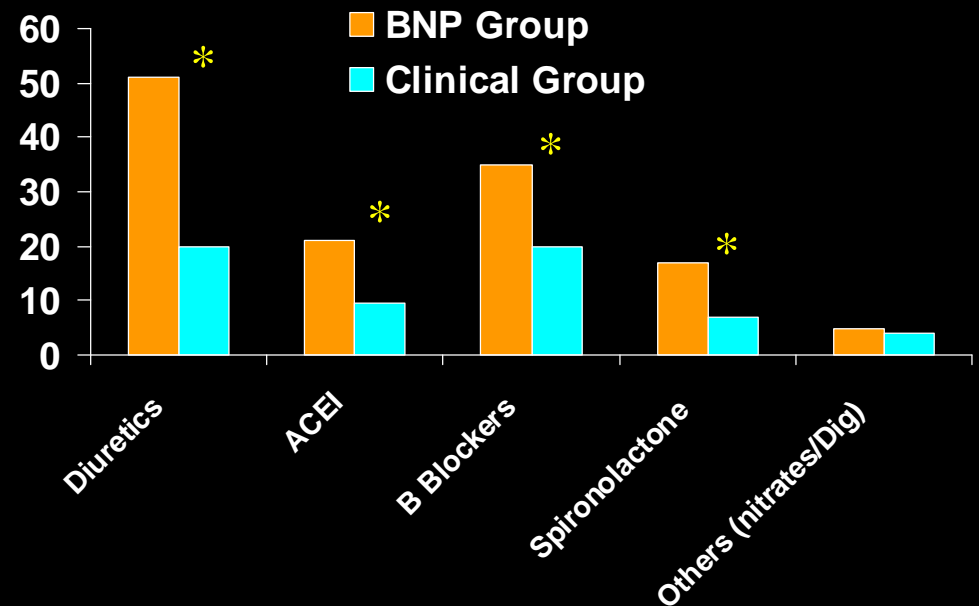
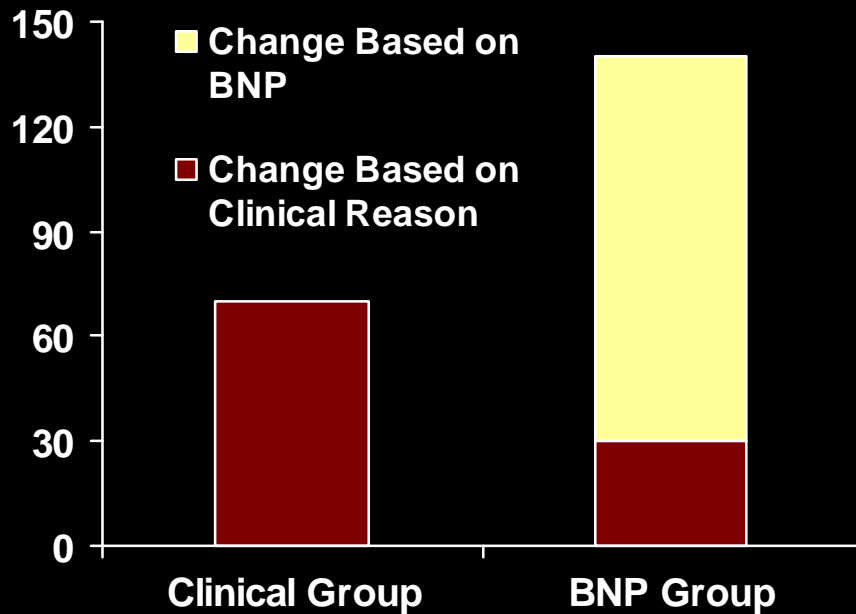


Troponin and BNP in Heart Failure



Peacock F from the ADHERE Registry

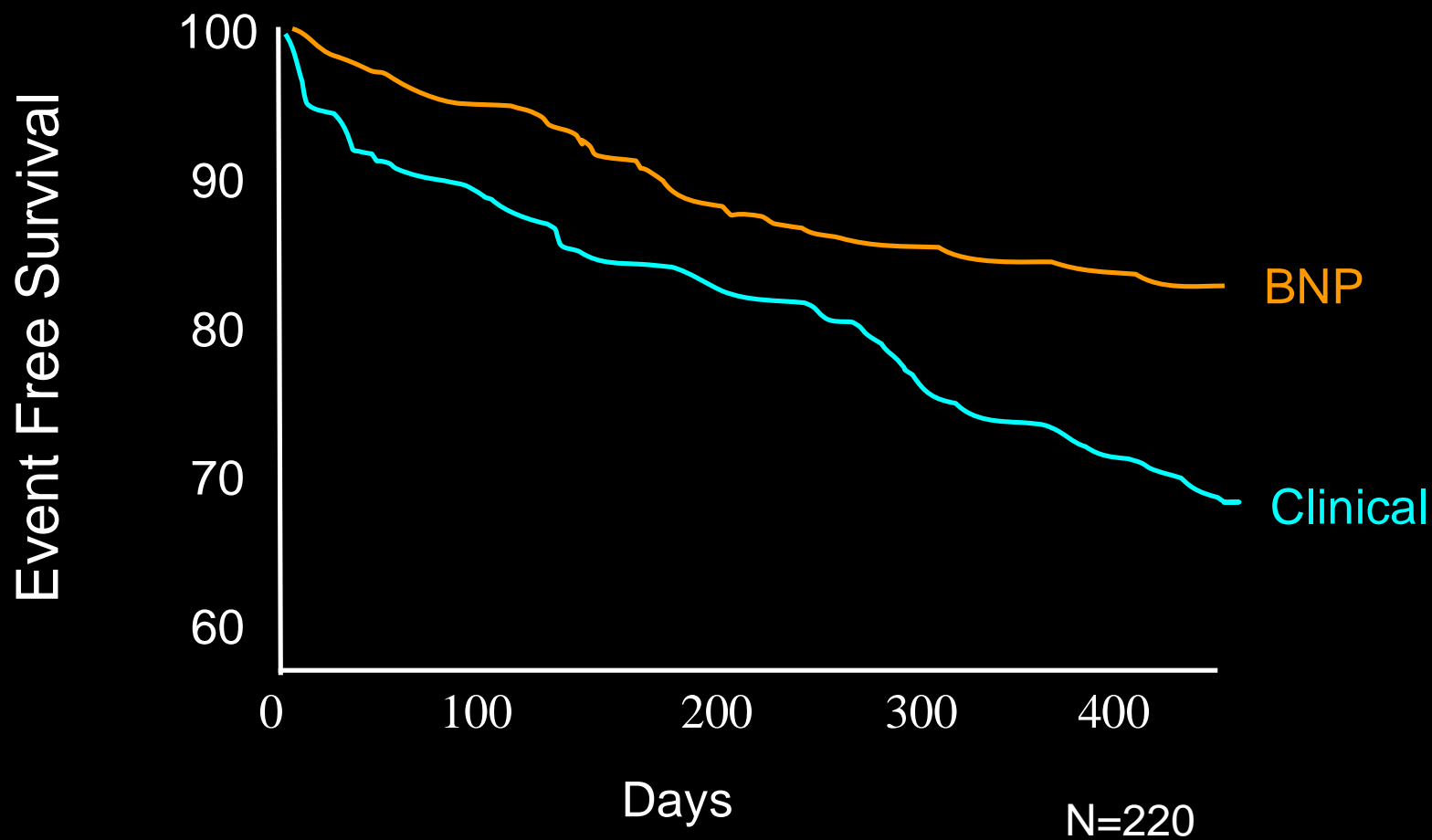
STARS-BNP



N=220

* P<0.05

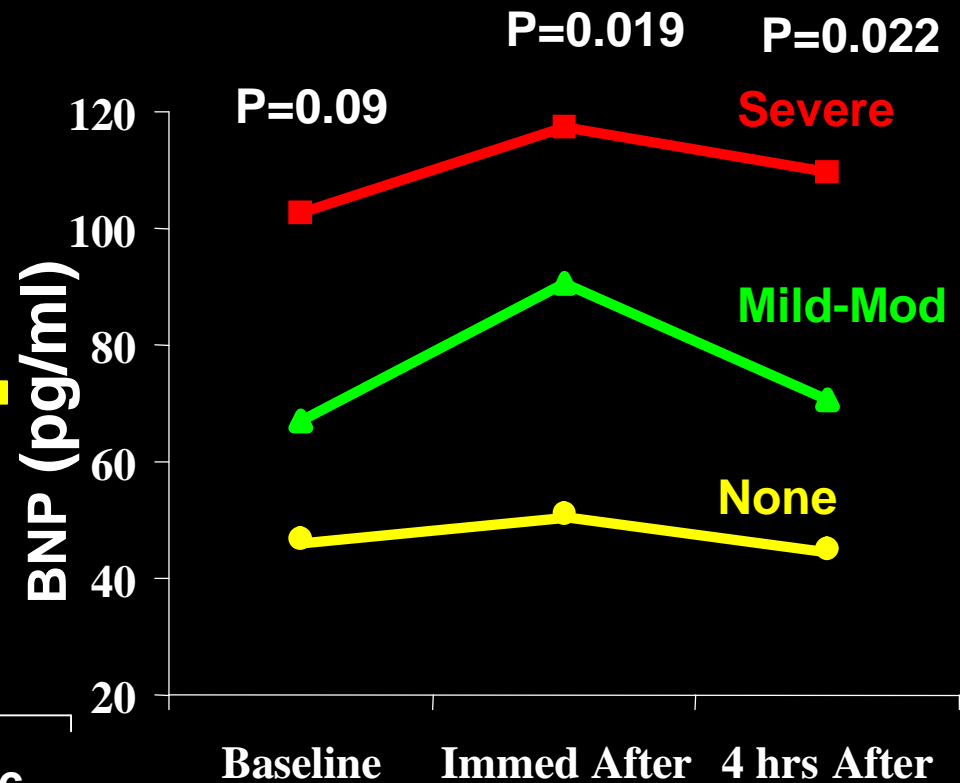
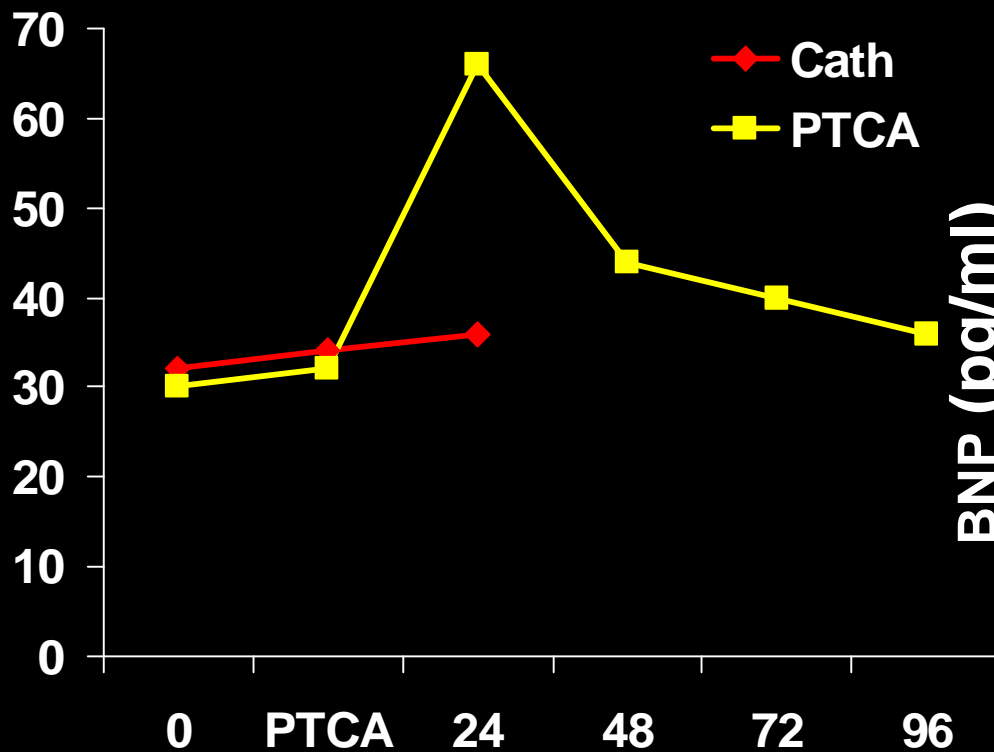
STARS-BNP



Challenges with BNP titration trials

- What is the goal?
 - Lowest BNP possible (individual goal)
 - Same arbitrary BNP goal for all subjects
 - Maintain BNP in a desired range
- High reference change values
 - 50 to > 100%
- BNP level reflects multiple pathological processes
 - What is the most appropriate therapeutic maneuver?
- Safety
 - Renal function
 - Electrolyte balance

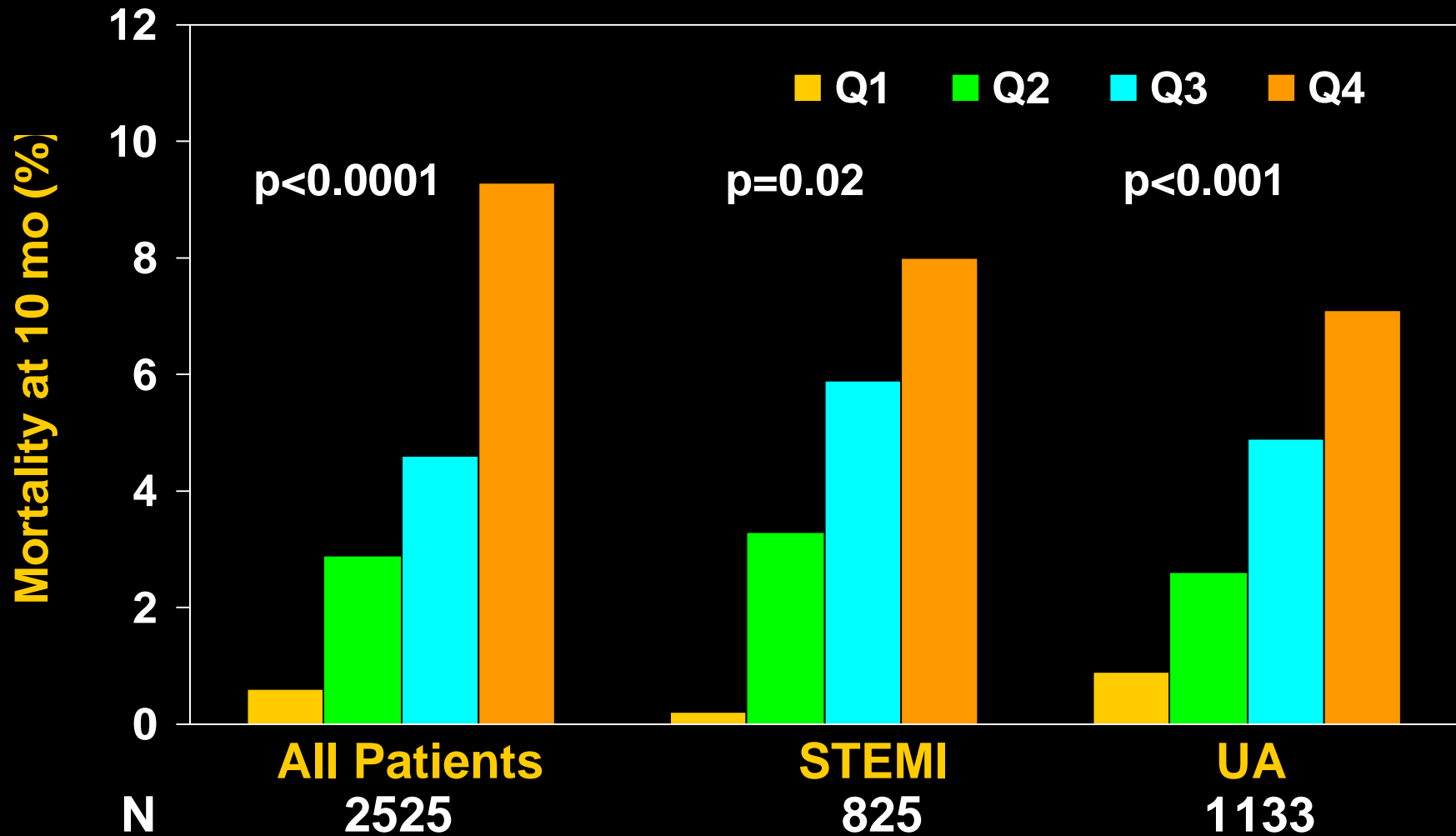
Ischemia as a Stimulus for BNP release



Tateishi et al. *Clin Card* 2000;23:776-80

Sabatine *JACC* 2004; 44:1988-95

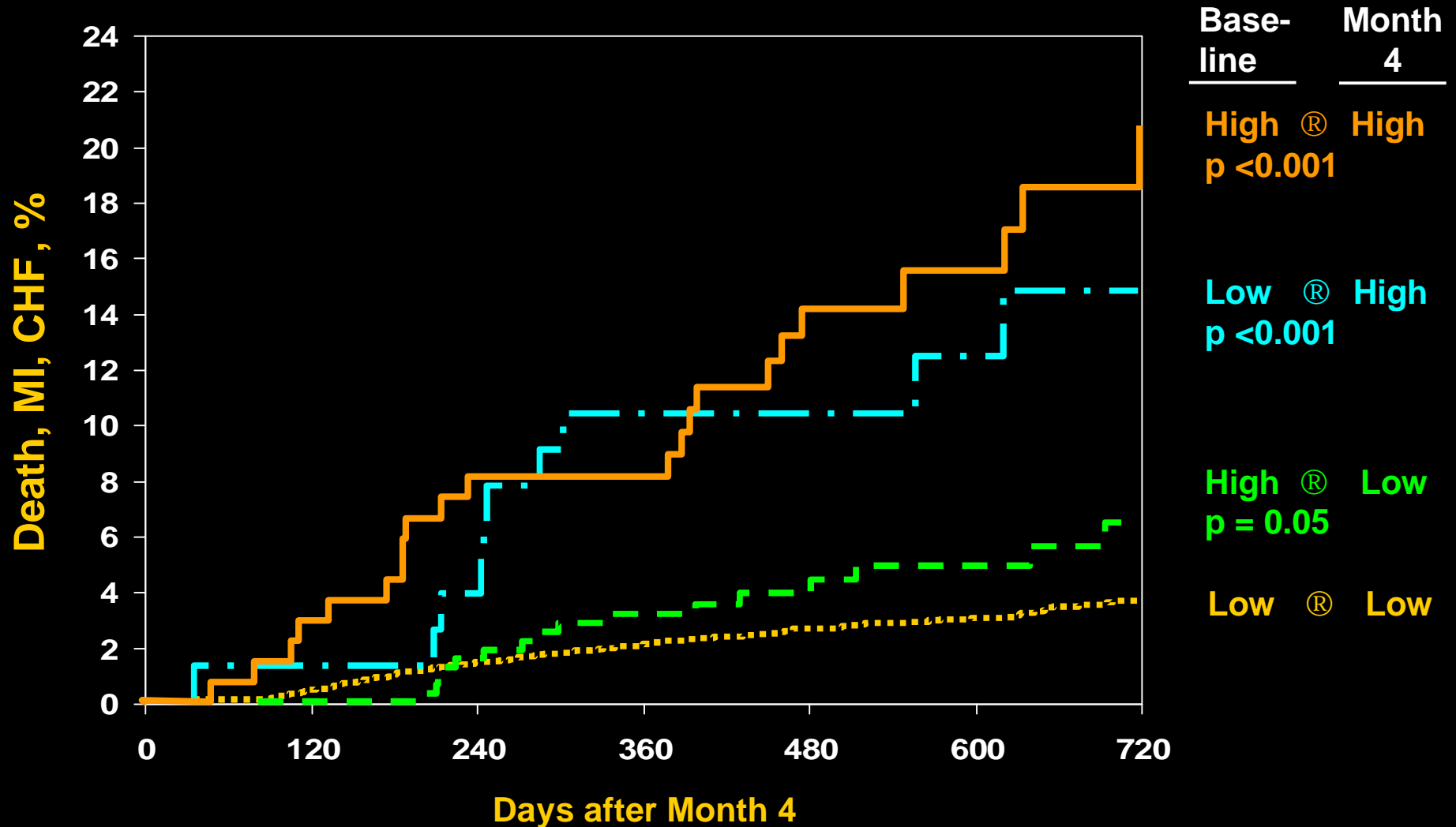
BNP & Risk of Death OPUS-TIMI 16 Trial



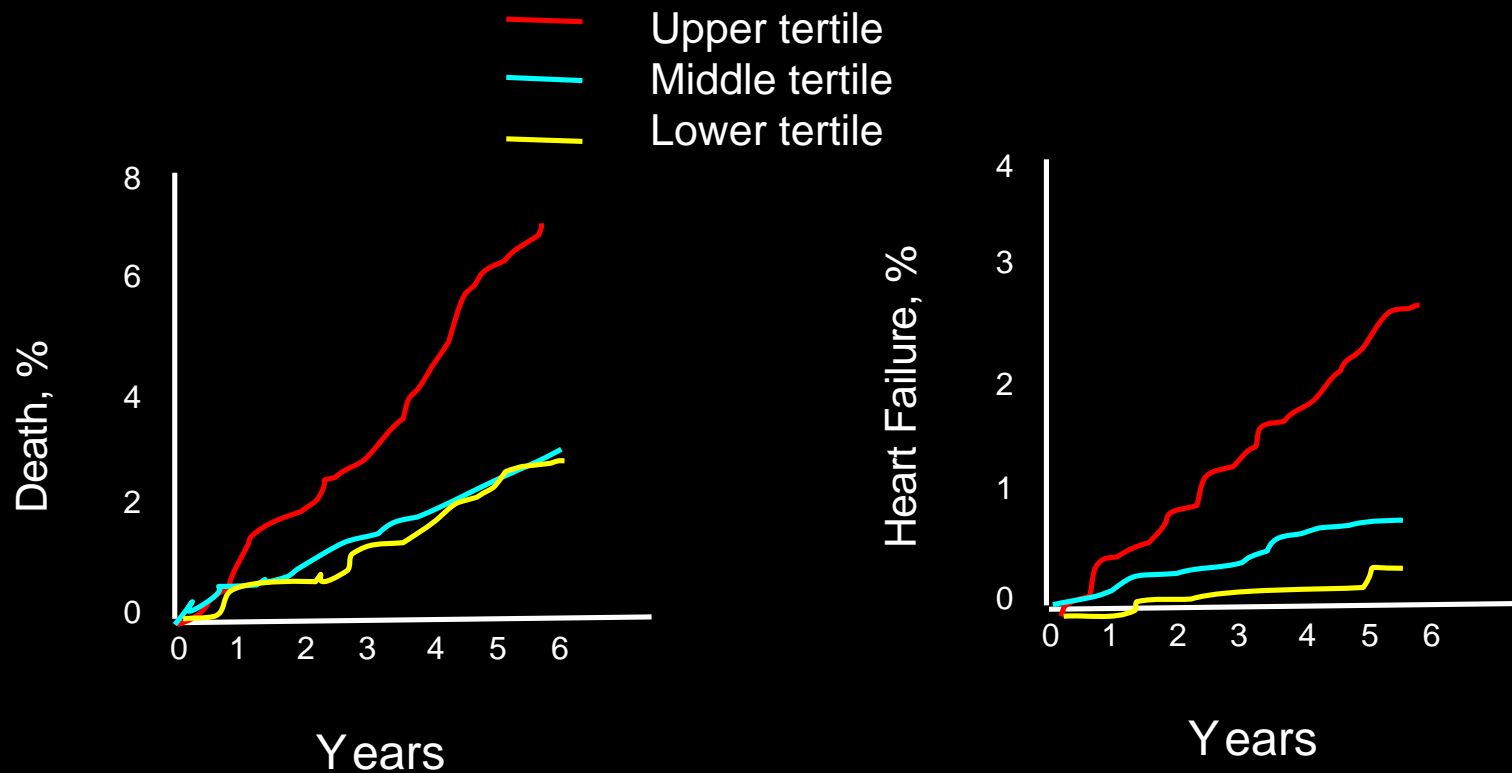


Clinical Relevance of Achieved BNP in Patients with ACS

A to Z Trial



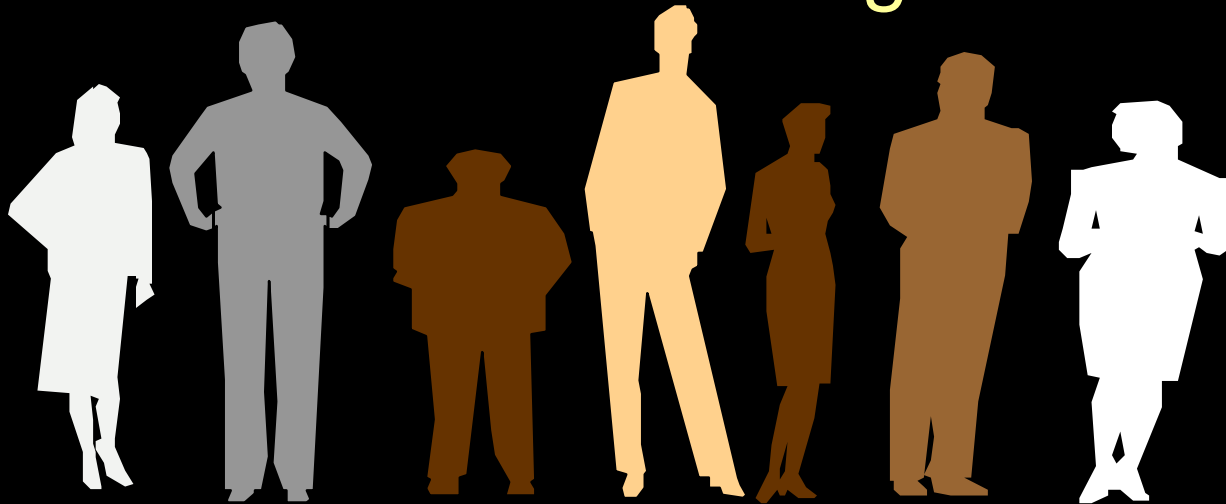
BNP for Population Screening



Wang et al. *NEJM* 2004;350:647-54

Understanding noncardiac sources of variation in BNP

A prerequisite to cardiac screening and chronic disease monitoring



Noncardiac sources of variation in BNP/NT-proBNP

- Sex
- Body composition
- Renal function
 - Greater influence with NT-proBNP
- Thyroid hormone

BNP –the bottom line

- Helpful in CHF diagnosis
 - Low value accurate to rule out decompensated CHF
 - Intermediate values nonspecific
 - High values need to be interpreted with “dry weight” BNP
- Powerful prognostic factor in multiple disease states, including CHF and ACS
 - Therapeutic implications poorly defined
- **Integrative** indicator of multiple cardiac (and noncardiac) pathological process
 - Nonspecific and relatively crude—thus will be difficult to use as a trigger for specific therapeutic responses
- Future Roles
 - Disease monitoring
 - Population Screening
 - Will need to fully understand non-cardiac sources of variability

Future Uses and Evidence Needed

- “Hardening” the heart failure endpoint
 - I think we have enough evidence now
- Cardiac safety marker (+/- cTn)
 - Some beneficial therapies increase BNP
- Chronic disease monitoring/BNP as a therapeutic target
 - Multiple titration trials underway
- BNP as a trial endpoint
 - Avante-Garde trial
 - Nonspecificity, high variability a problem
 - Will not be a surrogate, even if the trials work!