The Role of Biomarkers in Cardiovascular Disease

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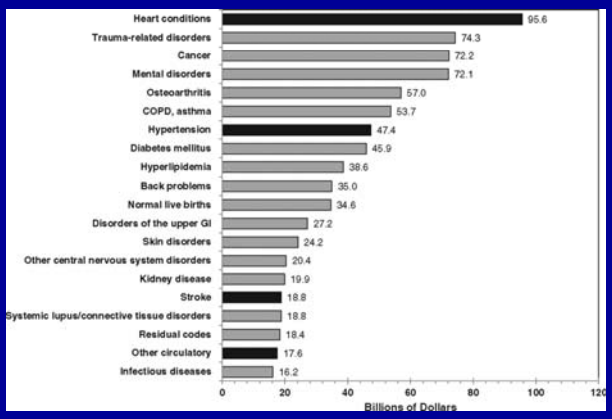
February 1, 2013

Scope of the Problem: Mortality

- CVD is the leading cause of death among women in the United States
  - Regardless of race or ethnicity
- In 2009, > 400,000 deaths
  - More deaths than stroke, COPD, lung cancer, and breast cancer combined

Go et al, Circulation 2013

Scope of the Problem: Morbidity



- In 2009, total cost of CVD and stroke ~ $312.6 billion
- Accounts for 15% of total health costs

Go et al, Circulation 2013

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What is the role for biomarkers?

- 1980 to 2002: age-adjusted CVD mortality decreased in men and women
- Morbidity and mortality remains high
  - Existing therapies are static: pharmacologic, device-based and interventional

- Use of cardiac biomarkers may improve outcomes by allowing for personalized or biologically-based care

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What is a biomarker?

- Indicator of disease:
  - Trait: risk factor/ marker
    - *Antecedent*
  - State: preclinical or clinical
    - *Screening*
    - *Diagnostic*
  - Rate: progression
    - *Staging*
    - *Prognostic*

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What Makes a Cardiac Biomarker Useful?

- Goal: improve ability of clinician to optimize care of patient
- Characteristics:
  - Accurate, reproducible, available, interpretable
  - Known normal distribution and abnormal values
  - Acceptable to patient
  - Predicts outcome of interest
  - Adds to existing clinical and laboratory assessment
  - Knowledge of levels changes management

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Biomarkers in CVD states

- Coronary heart disease: Troponin
- Heart failure: NT-proBNP
- Emerging biomarkers: Galectin-3, sST2, proneurotensin

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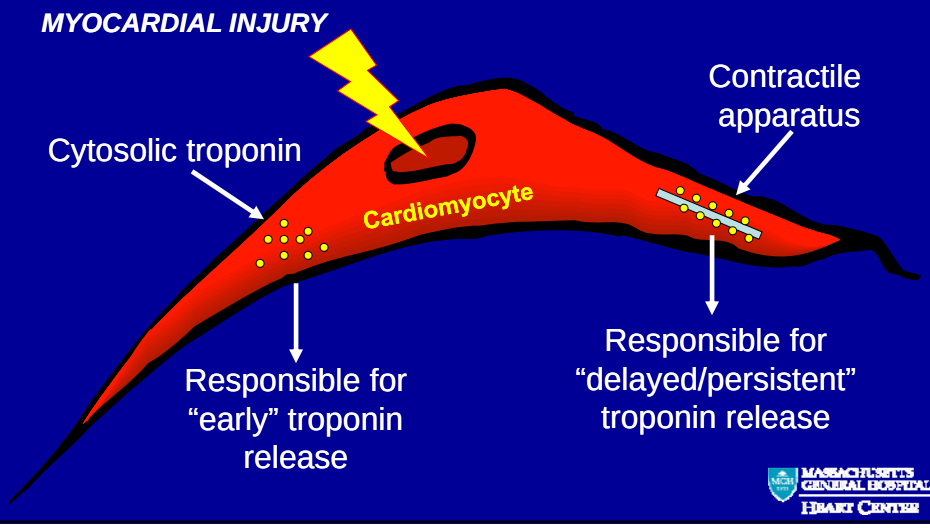
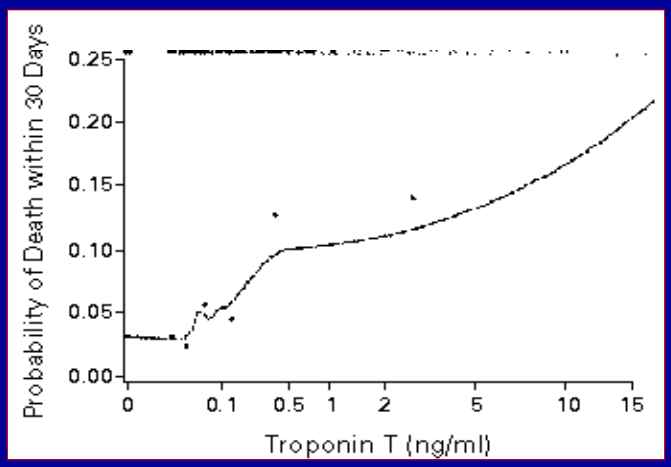
Two-compartment troponin biology



cTnT Levels are Associated with Outcomes in ACS



Ohman et al, NEJM 1996

Diagnosis of MI

- Detection of rise/fall of cTnI or cTnT
  - At least one value > 99th percentile of the URL
- Evidence of myocardial ischemia with at least one of the following:
  - Symptoms
  - ECG changes (new ischemia, Q waves)
  - Imaging evidence of new loss of myocardium or new RWMA

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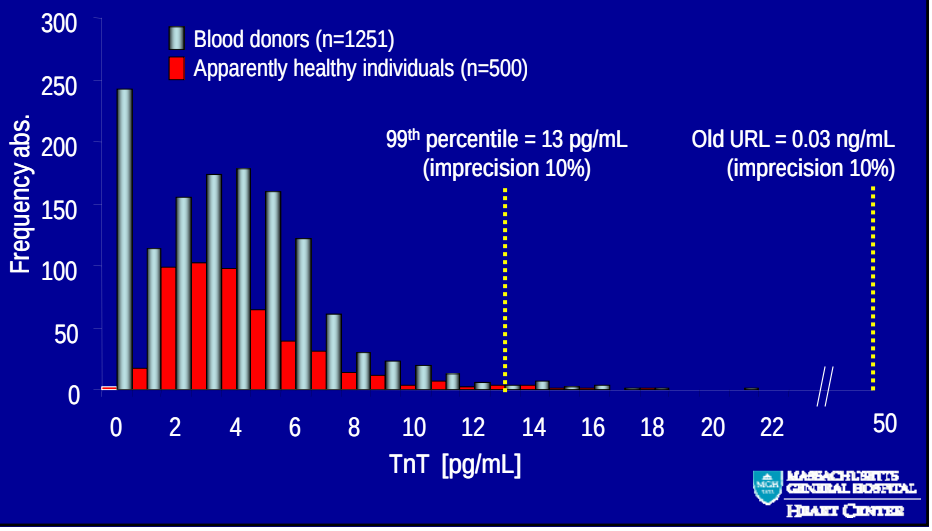
99th Percentile for Troponin T



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Sex Differences in 99th Percentile Values for cTnI and cTnT

- cTnI in healthy males > females
  - Differences between assays
- cTnT in healthy males similar to females
  - Single assay
- Role of assay imprecision?

Apple et al, Clin Chem 2012

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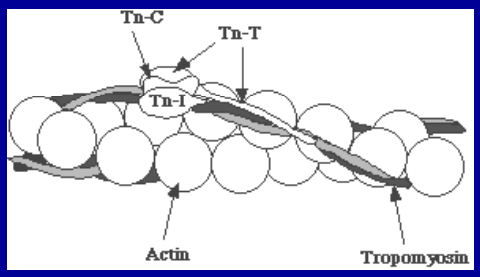
Newer 'high sensitivity' troponin assays

- New assays for troponin
- Extreme precision (i.e. <10% co-efficient of variation) at the 99th percentile for a normal patient population



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Sex Differences in 99th Percentile Values for hs-cTnI and hs-cTnT

- hs-cTnI in healthy males > females
- hs-cTnT in healthy males > females

Apple et al, Clin Chem 2012

Risk Factors Associated with Detectable hs-cTn

- Age
- Sex (male > female)
- Race (black > others)
- Lower eGFR
- History of HF
- Increased LV mass and LV thickness
- Hypertension
- Diabetes mellitus

de Lemos et al, JAMA 2010

hsTn Elevation in Apparently Healthy

- cTnI and cTnT are 100% specific for heart
  - High-sensitivity assay detects cTn in nearly all presumably healthy subjects
  - May reflect detection of ***subclinical disease***
  - Indirect assessment of CV health
    - Structural/functional changes, CAD severity
    - Relevance of gender differences

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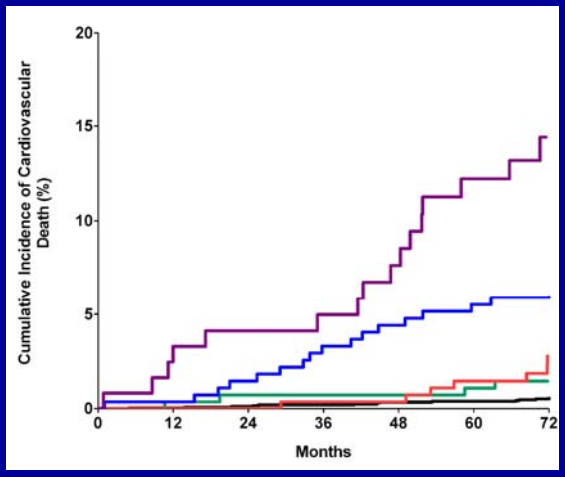
Association with CV Mortality



de Lemos et al, JAMA 2010

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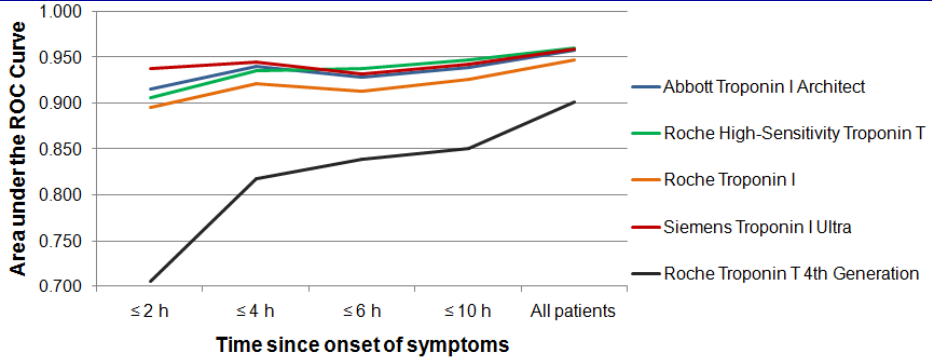
Highly Sensitive Troponins Improve the Early Diagnosis of AMI



hs-Tn + ECG + History → Rule out ↑ + Rule in ↑

Reichlin et al, NEJM 2009

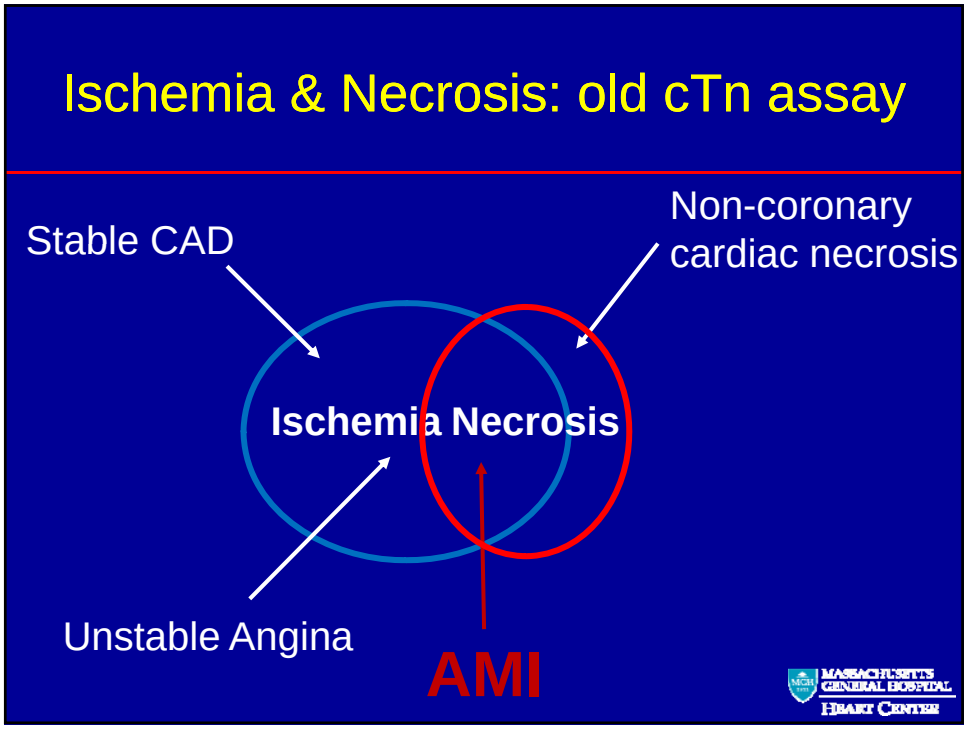
hsTnT is Superior to cTnT for Diagnostic Evaluation of Chest Pain

Analyte, cut-point	Sens	Spec	PPV	NPV
hsTnT, 13 pg/mL	62%	89%	38%	96%
cTnT, 0.01 ng/mL	49%	97%	67%	95%
cTnT, 0.03 ng/mL	35%	99%	72%	93%

hsTnT ~30% of ACS patients were reclassified from UA to NSTEMI by hsTnT

NRI and IDI analyses demonstrate significant *improvement* in diagnostic accuracy with hsTnT

Januzzi et al, Circulation 2010


Ischemia & Necrosis: old cTn assay
Stable CAD
Non-coronary cardiac necrosis
Ischemia Necrosis
Unstable Angina
AMI
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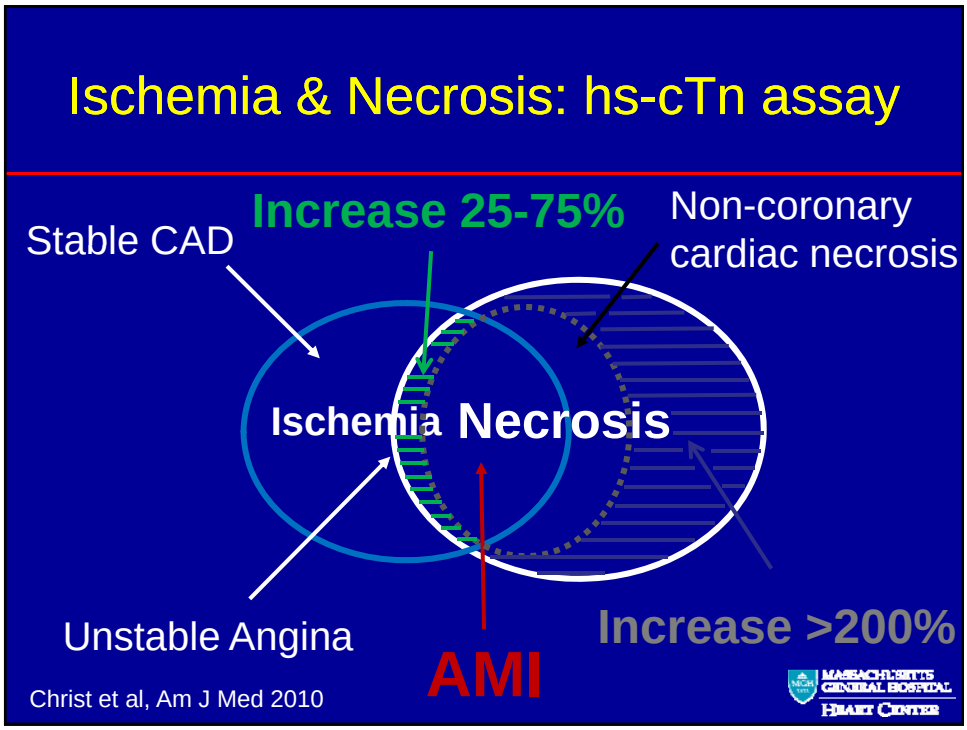
Ischemia & Necrosis: hs-cTn assay
Increase 25-75%
Stable CAD
Non-coronary cardiac necrosis
Ischemia Necrosis
Unstable Angina
AMI
Increase >200%
Christ et al, Am J Med 2010
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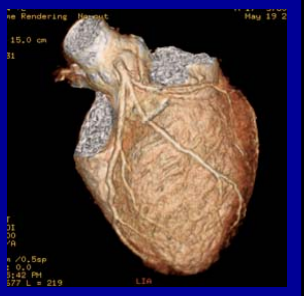
Application of hsTn for differential dx

What's the problem?

cTn_{AMI} = $cTn_{Myocarditis}$ = $cTn_{Tachycardia}$ = cTn_{AHF} etc.

- hsTnT strongly associated with the presence and severity of CAD, as well as cardiac structure and function…

  …independent of a diagnosis of ACS



Januzzi et al, Circulation 2010

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Non-ACS Troponin Elevation

- A real false positive
- Normal variants?
- Pericarditis
- Severe illness
  - Sepsis
- Blunt chest trauma
- Radiofrequency ablation
- DC Cardioversion
- Transplant rejection
- Aortic dissection
- Myocarditis
- Pulmonary embolism
- Myocardial abscess
- CHF and LVH
- Arrhythmias and LVH
- Idiopathic CMP
- Chemotherapy or other toxic/metabolic insults
- Cirrhosis
- Renal failure

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Biomarkers in CVD states

- Coronary heart disease: Troponin
- Heart failure: NT-proBNP
- Emerging biomarkers: Galectin-3, sST2, proneurotensin

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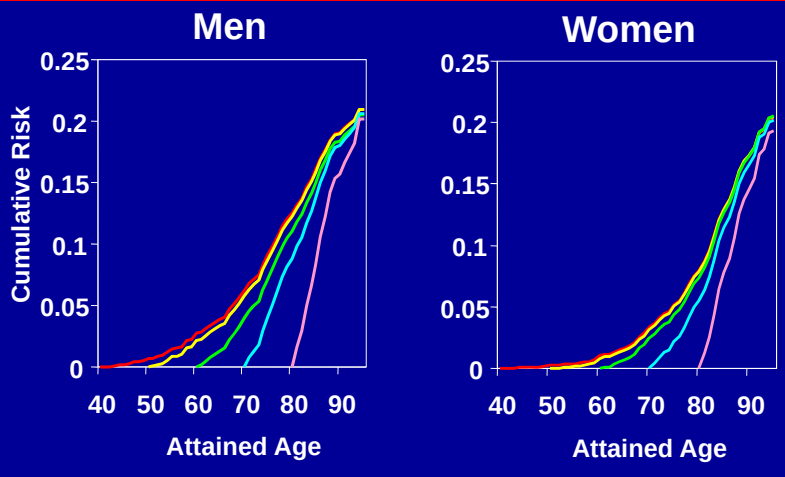
Why should we care about heart failure?

Lifetime Risk for CHF by Sex and Age



Lloyd-Jones et al, Circulation 2002

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Assessment of Heart Failure

No gold standard for the evaluation of HF exists!

History and Physical

Laboratory Testing

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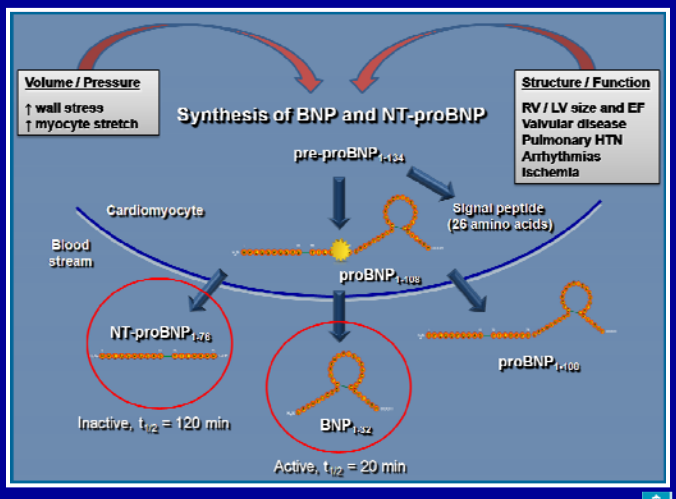
What is NT-proBNP?



Motiwala and Januzzi, Cardiol Rev 2012

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Natriuretic Peptides: Major Clinical Utilities

- To supplement clinical judgment
  - Acute evaluation and diagnosis
  - Grading HF severity
- To provide prognostication using processes not obvious at the bedside
- To offer unique information regarding therapeutic intervention
  - To judge therapeutic success
  - To guide therapy?

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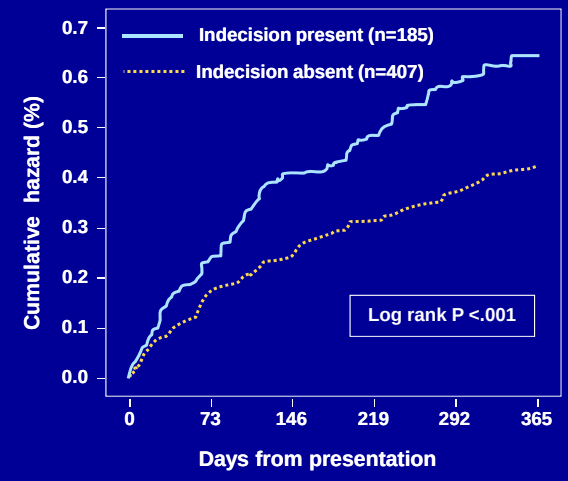
Diagnostic Uncertainty in Dyspnea is Associated with Poor Prognosis



31% of subjects in PRIDE were judged uncertainly by the managing physician re: likelihood for HF as cause of dyspnea

Their prognosis was significantly worse, with higher rates of death and re-hospitalization and longer lengths of stay

Green et al, Arch Intern Med 2008

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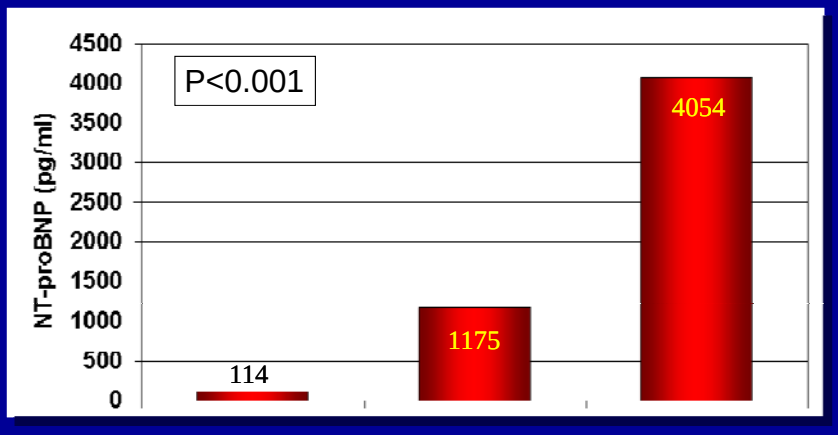
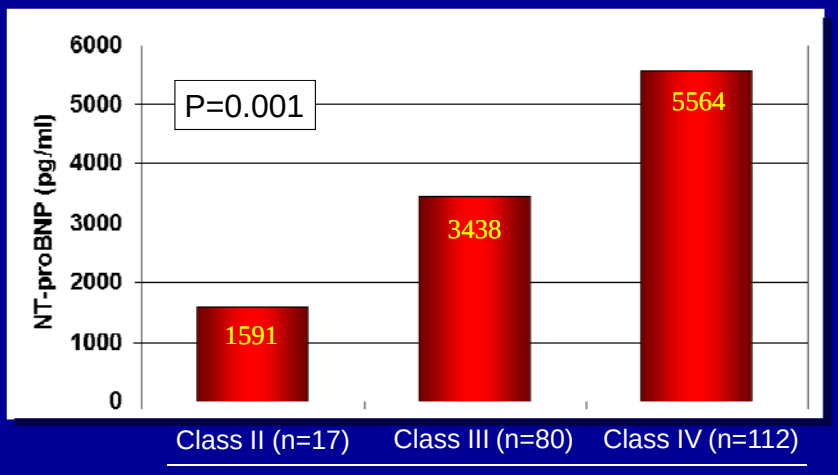
NT-proBNP Levels are Higher in Acute Heart Failure



Januzzi et al, Am J Cardiol 2005

NT-proBNP Levels are Associated with Symptoms



Januzzi et al, Am J Cardiol 2005

Know the Differential Diagnosis of an Elevated NP

- Unrecognized HF
- Prior HF
- LVH
- Valvular heart disease
- Atrial fibrillation
- Advancing age
- Myocarditis
- ACS
- Pulmonary hypertension
- Congenital heart disease
- Anemia
- Pulmonary embolism
- Cardiac surgery
- Sleep apnea
- Critical illness
- Sepsis
- Burns
- Renal failure
- Toxic-metabolic insults

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Know the Differential Diagnosis of an Unexpectedly Low NP

- Obesity
- Non-systolic heart failure
- Mild acute heart failure
- Isolated right heart failure
- Partially treated heart failure

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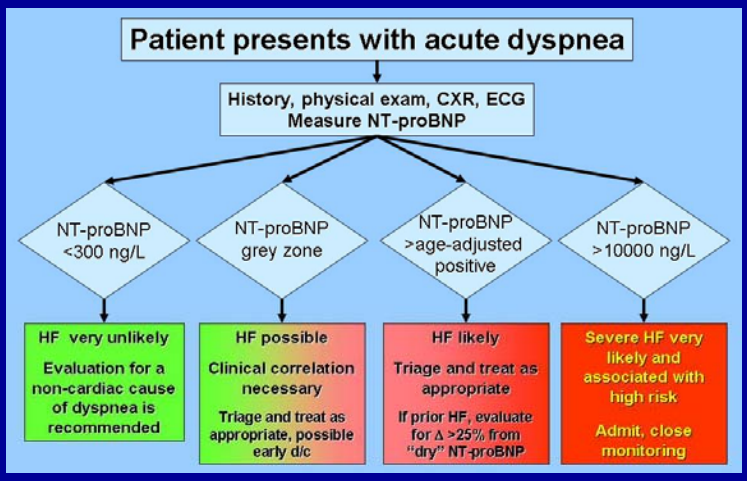
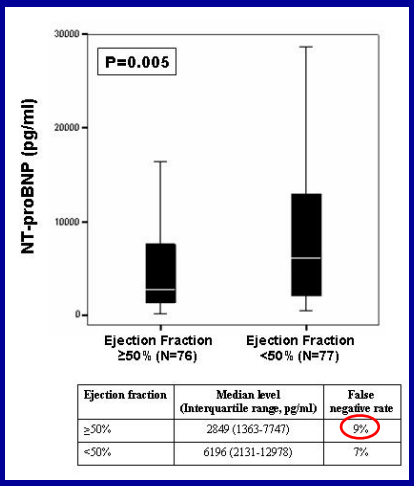
Logical use of natriuretic peptide values

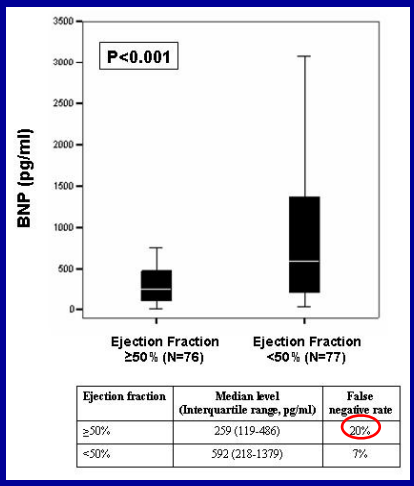


Januzzi et al, Am J Cardiol 2008

NP values are Lower in HFpEF



Ejection fraction	Median level (Interquartile range, pg/ml)	False negative rate
≥50%	2849 (1363-7747)	9%
<50%	6196 (2131-12978)	7%



Ejection fraction	Median level (Interquartile range, pg/ml)	False negative rate
≥50%	259 (119-486)	20%
<50%	592 (218-1379)	7%

O'Donoghue et al, J Card Fail 2005

Sex Differences in NT-proBNP and BNP Levels

- Healthy: female > men
  - Lower BMI
  - Lower androgen (testosterone) levels
- Disease: female < male
  - Increased incidence of HFpEF

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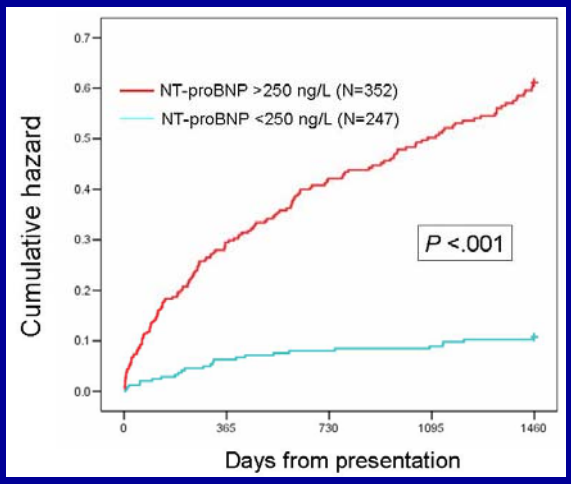
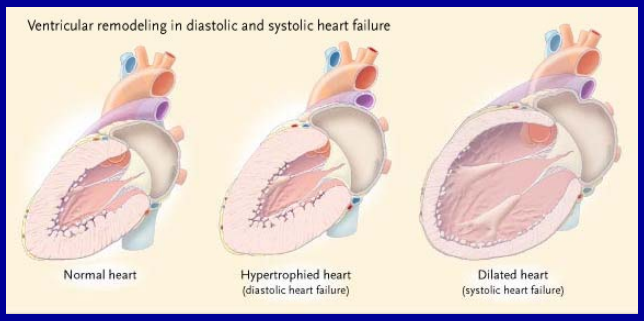
NPs are Associated with Long-term Risk of Death in Dyspneic Patients



A single natriuretic peptide measurement at presentation offers prognostic value out to over 4 years!

Rehman et al, in preparation

Remodeling in ACS and HF



- Remodeling is not felt
- Remodeling is not detectable with physical exam, until too late
- Imaging can see remodeling, but only too late
- Predicting remodeling with imaging is imperfect

Higher NT-proBNP is Associated with Risk for Remodeling

Remodeling index	Hazard ratio*	95% CI	P value
Increase in LVEDVi	1.43	1.10-1.86	0.007
Increase in LVESVi	1.54	1.10-1.91	0.01
Fall in LVEF	1.53	1.12-1.89	0.02

*Hazard ratio refers to risk for remodeling per log-unit of NT-proBNP at the end of the study.

NT-proBNP was entered as log-transformed due to non-normality. Model adjusted for baseline log-transformed NT-proBNP, age, diabetes, ischemic heart disease and New York Heart Association Symptom Severity.

Weiner et al, Eur J Heart Fail 2012

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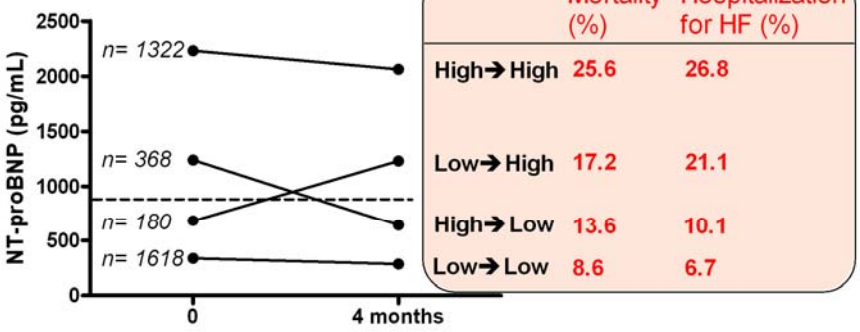
Serial NP Measurements are Useful for Prognostication in Chronic HF



	Mortality (%)	Hospitalization for HF (%)
High → High	25.6	26.8
Low → High	17.2	21.1
High → Low	13.6	10.1
Low → Low	8.6	6.7

Masson et al, J Am Coll Cardiol 2008

Val-HeFT Heart Center

"Shouldn't we be maximizing all heart failure meds in all patients?"

- Even for the skilled HF specialist with resources for close follow up, the ***addition*** of NP measurement is valuable
- The majority of heart failure care is not in the hands of heart failure specialists.
- Opportunities exist for achieving guideline-derived medical therapy goals

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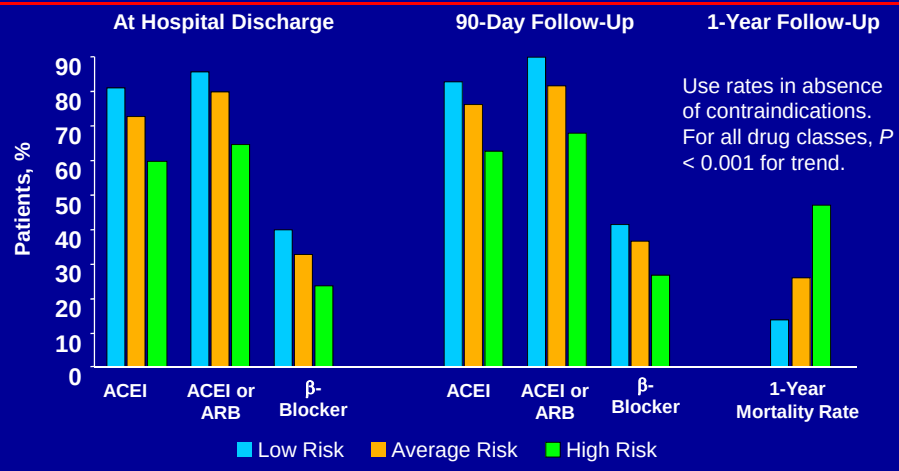
Risk-Treatment Mismatch in HF: Canadian EFFECT Study



Lee et al, JAMA 2005

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Therapies with Effects on B-Type Natriuretic Peptide Levels

Therapy	Effect on BNP/NT-proBNP
Diuresis	↓
ACE-I	↓
ARB	↓
β-blockers	Some transiently ↑, most ↓
Aldosterone antagonists	↓
BiV pacing	↓
Exercise	↓
Rate control of AF	↓
BNP infusions	↓ N-BNP, ↑BNP then ↓

Characteristics of "guided therapy" trials

- Well tolerated
- Up-titration of therapies more often seen in biomarker guided arm
- When a low target was selected and natriuretic peptide lowering was achieved, better outcomes were observed

Januzzi, J Card Fail 2011

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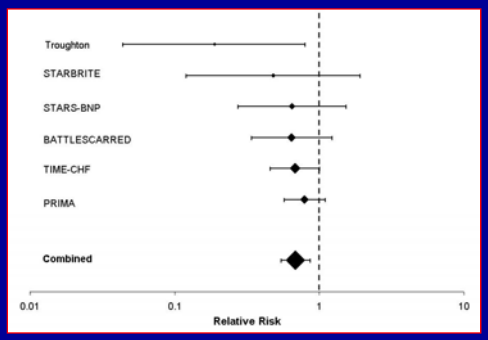
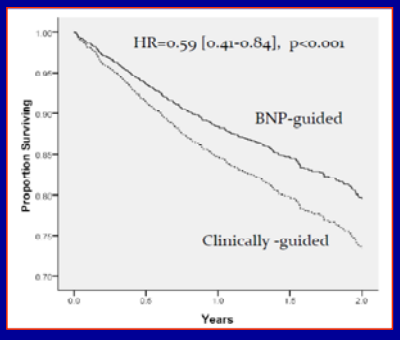
Guided therapy Combined Analyses Demonstrate Benefit

Meta analysis of publication data



Felker et al, Am Heart Journal 2009

Pooled patient data from all available trials



Troughton et al, ESC 2011

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Biomarkers in CVD states

- Coronary heart disease: Troponin
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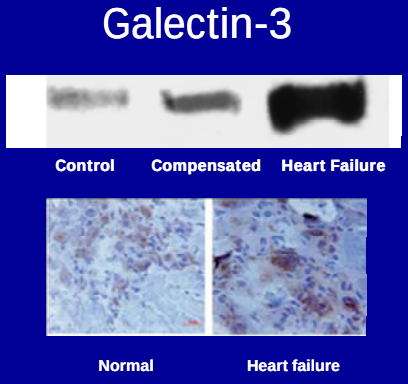
- Emerging biomarkers: Galectin-3, sST2, proneurotensin

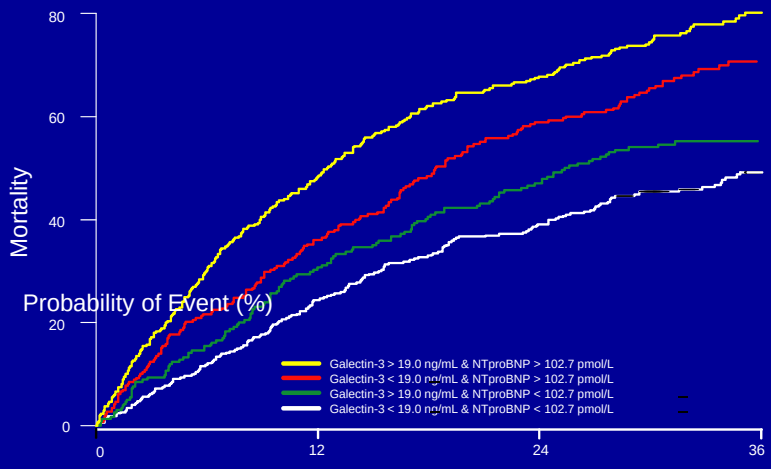
Galectin-3 in HF
Scientific Discovery

- In animal models of HF, galectin-3 is highly expressed in failing versus functionally compensated hearts
- Intrapericardial administration of galectin-3 significantly increases LV collagen content and reduces LV EF



Sharma et al, Circulation 2004

Joint effect of NT-proBNP and galectin 3 in chronic heart failure



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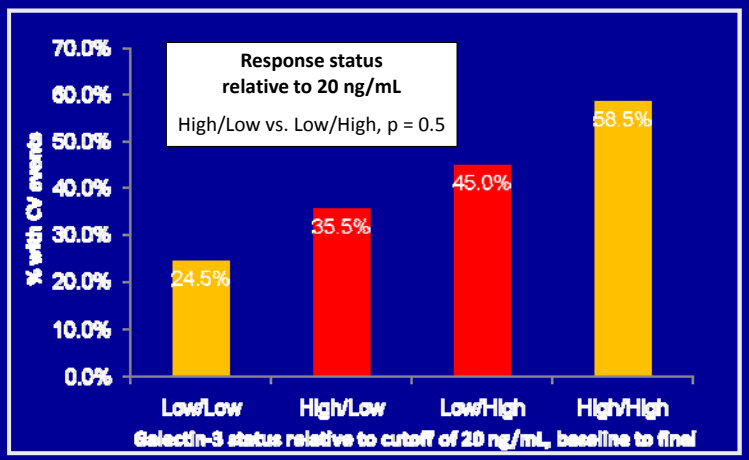
Galectin-3 Levels are Associated with Outcomes in HF



Motiwala et al, submitted

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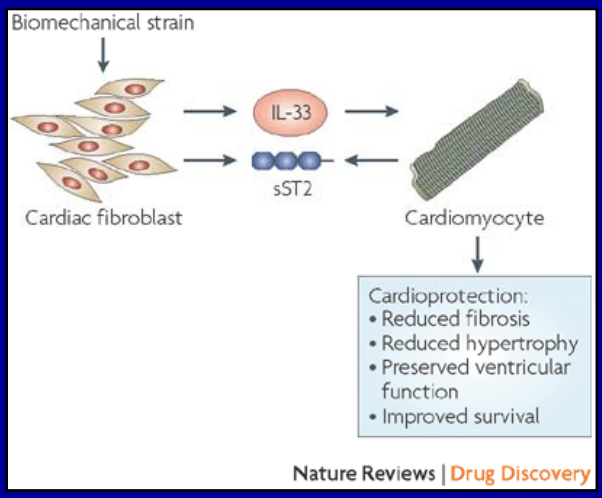
What is ST2?



Kakkar and Lee, Nat Rev Drug Discov 2008

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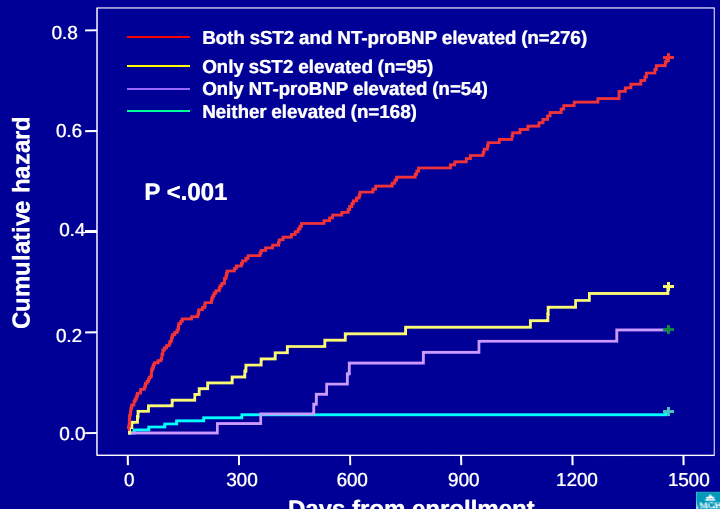
sST2 is Additive to NT-proBNP for Long Term Prognosis



Januzzi et al, Clin Chem 2010

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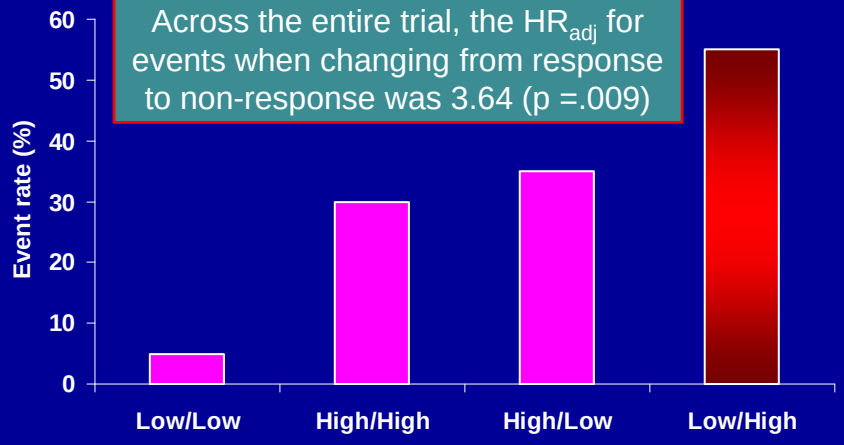
Ramification of change in ST2 in PROTECT: 3 months

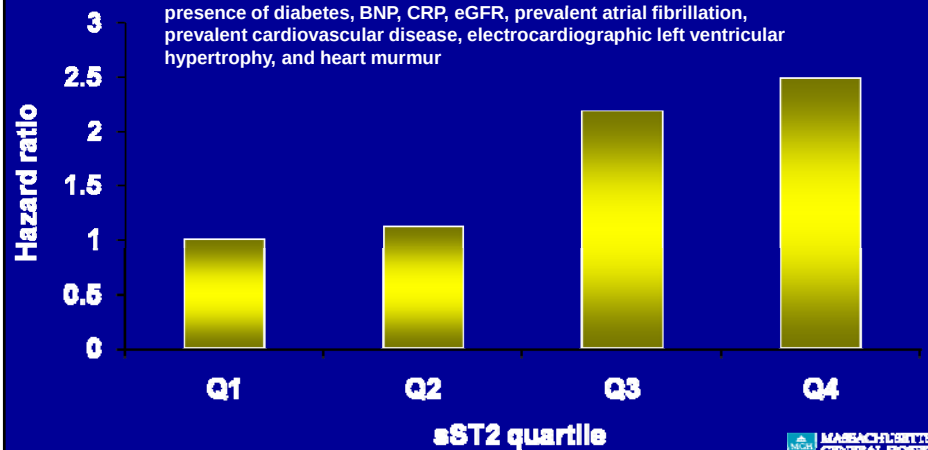
Across the entire trial, the HR_{adj} for events when changing from response to non-response was 3.64 (p =.009)



Gaggin et al, submitted

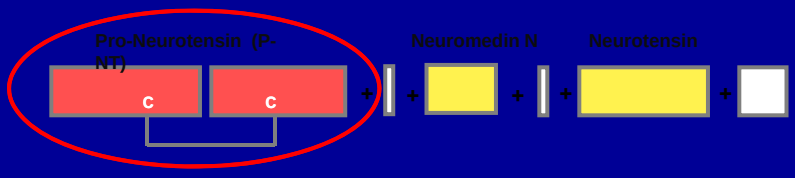
ST2 Predicts HF in Community Cohort

*Adjusted for : age, gender, BMI, systolic blood pressure, hypertension therapy, total cholesterol, HDL cholesterol, regular cigarette smoking, presence of diabetes, BNP, CRP, eGFR, prevalent atrial fibrillation, prevalent cardiovascular disease, electrocardiographic left ventricular hypertrophy, and heart murmur



Wang et al, Circulation 2012

What is (Pro-) Neurotensin (P-NT)?



- Neurotensin is a satiety hormone


nature publishing group

ARTICLES
INTEGRATIVE PHYSIOLOGY

Peripheral and Central Administration of Xenin and Neurotensin Suppress Food Intake in Rodents

Jennifer H. Cooke[1], Michael Patterson[1], Sejal R. Patel[1], Kirsty L. Smith[1], Mohammad A. Ghatei[1], Stephen R. Bloom[1] and Kevin G. Murphy[1]

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Sites of Synthesis and Function

Central nervous system

→ Amygdala

→ Hypothalamus

SATIETY, HYPOTHERMIC, ANTINOCICEPTIVE

Gastrointestinal tract

→ enteroendocrine cells (N-cells) in the mucosa of ileum, jejunum, colon and duodenum

STIMULATION OF GROWTH, SECRETION

INHIBITION OF MOTILITY, SATIETY (?)

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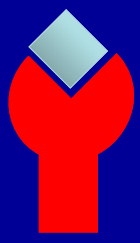
Neurotensin Has 3 Different Receptors in Humans



NTSR1

G-coupled

Breast cancer progression (trophic and antiapoptotic)

NTSR2

G-coupled

NTSR3

Not G-coupled (=SORT1)

One of the major human CAD susceptibility gene variants

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P-NT Strongly Interacts With Gender on Risk of Incident CVD

Sample size / first events	HR per 1 SD (95% CI)	P-value
All (4362 / 519)	1.17 (1.07-1.27)	<0.001
Women (2559 / 224)	1.33 (1.17-1.51)	<0.001
Men (1803 /295)	1.06 (0.95-1.19)	0.310

Adjusted for age, sex, use of antihypertensive medication, systolic blood pressure, BMI, current smoking, diabetes mellitus and fasting concentrations of HDL and LDL

Melander et al, JAMA 2012

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P-NT Strongly Predicts CVD in Women

Q1 (of P-NT)	Q2 HR (95% CI)	Q3 HR (95% CI)	Q4 HR (95% CI)	P trend
1.0 (ref)	0.91 (0.59-1.41)	1.58 (1.08-2.30)	1.65 (1.13-2.41)	0.001

Adjusted for age, sex, use of antihypertensive medication, systolic blood pressure, BMI, current smoking, diabetes mellitus and fasting concentrations of HDL and LDL

Melander et al, JAMA 2012

P-NT Predicts New-Onset Diabetes Mellitus in Women

Sample size / first events	HR per 1 SD (95% CI)	P-value
Women non-DM (2200 / 74)	1.41 (1.12-1.77)	0.003
Women non-IFG (1950 / 38)	1.47 (1.08-2.00)	0.014

Adjusted for age, use of antihypertensive medication, systolic blood pressure, BMI, waist circumference, prevalent cardiovascular disease, current smoking and fasting concentrations of glucose, HDL, LDL, triglycerides and insulin

Melander et al, JAMA 2012

P-NT Predicts Breast Cancer (113 first events)

Q1 (of P-NT)	Q2 HR (95% CI)	Q3 HR (95% CI)	Q4 HR (95% CI)	P trend
1.0 (ref)	1.32 (0.70-2.50)	1.89 (1.03-3.46)	2.80 (1.59-4.92)	<0.001

Adjusted for age, use of antihypertensive medication, use of hormone replacement therapy, ever use of oral contraceptives, educational level, age at menarche, age at first child birth, number of children, menopausal status, systolic blood pressure, BMI, diabetes mellitus, current smoking, prevalent cardiovascular disease, heredity for cancer, and fasting concentrations of HDL, LDL and insulin

Melander et al, JAMA 2012

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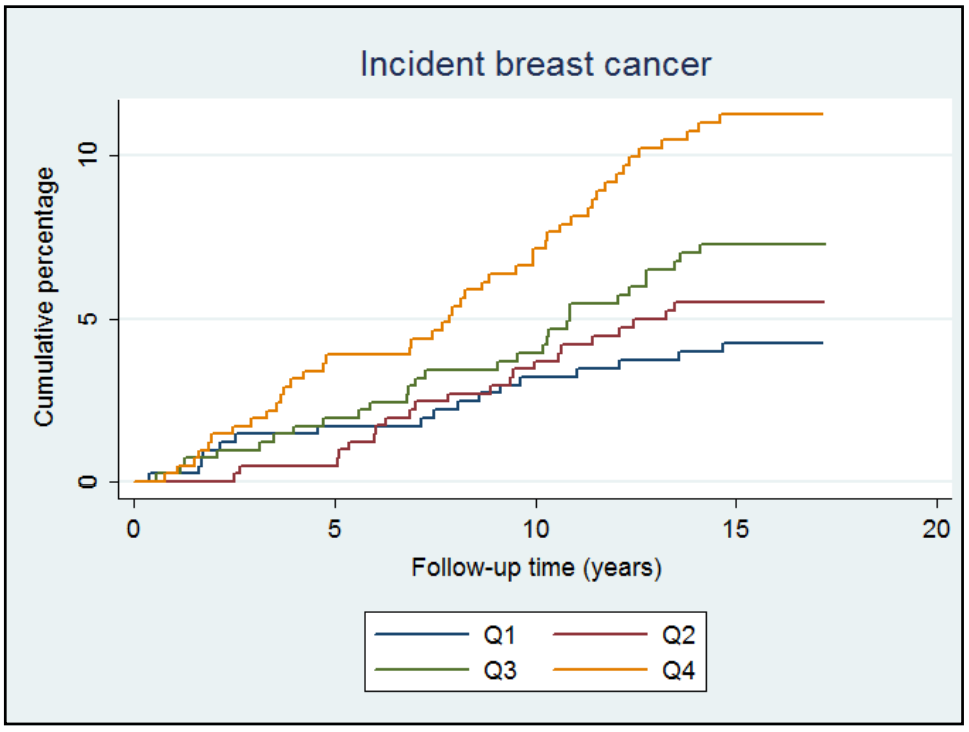

P-NT/Neurotensin Might Be Broad Markers of Women's Health Risk

- Associations with DM, CVD, death and breast cancer
- Identification of women at high risk (>20%) in absence of traditional risk factors
- Can this change management and therapeutic choices?

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