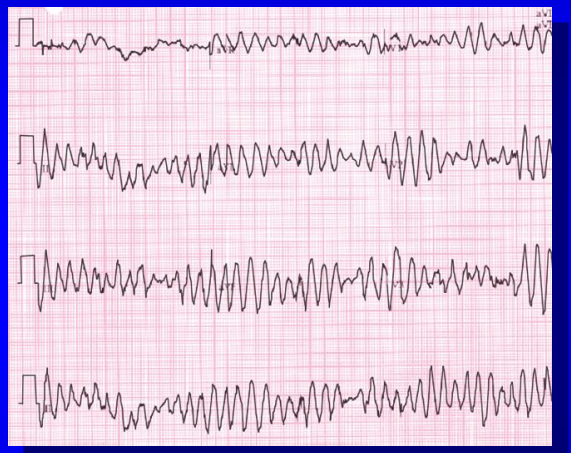
Biomarkers of Sudden Death



James L. Januzzi, Jr, MD, FACC, FESC
Associate Professor of Medicine
Harvard Medical School
Roman W. DeSanctis Endowed Clinical Scholar
Director, Cardiac ICU
Massachusetts General Hospital

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER

Disclosures

- Grants: Roche Diagnostics, Siemens, Critical Diagnostics, Thermo Fisher, Singulex, BG Medicine, NHLBI

- Consulting: Roche Diagnostics, Critical Diagnostics, BG Medicine, Zensun, Amgen, Novartis

The Public Health Dilemma

- Public health burden: ~ 400,000 SCDs/year in US:
  - SCD accounts for over 50% of all cardiac deaths and 15 to 20% of total mortality.
- Majority of SCDs occur in “low-risk” populations
- Results of treatment are poor:
  - Overall survival to hospital discharge for resuscitated SCD ranges from 2-5% in most major urban centers to 15-26% in cities with advanced EMS systems.

LVEF as Sole Risk Stratifier for SCD

- LVEF lacks sensitivity since the majority of patients who suffer a cardiac arrest will have an LVEF > 0.35.
- LVEF lacks specificity for predicting SCD as compared to other modes of cardiovascular death, thus limiting the effectiveness of the ICD.
- Difficult/expensive to implement as a screening strategy in the general population.

Other predictors of SCD risk are needed.

Challenges to Biomarker Studies of SCD

Prospective Samples:

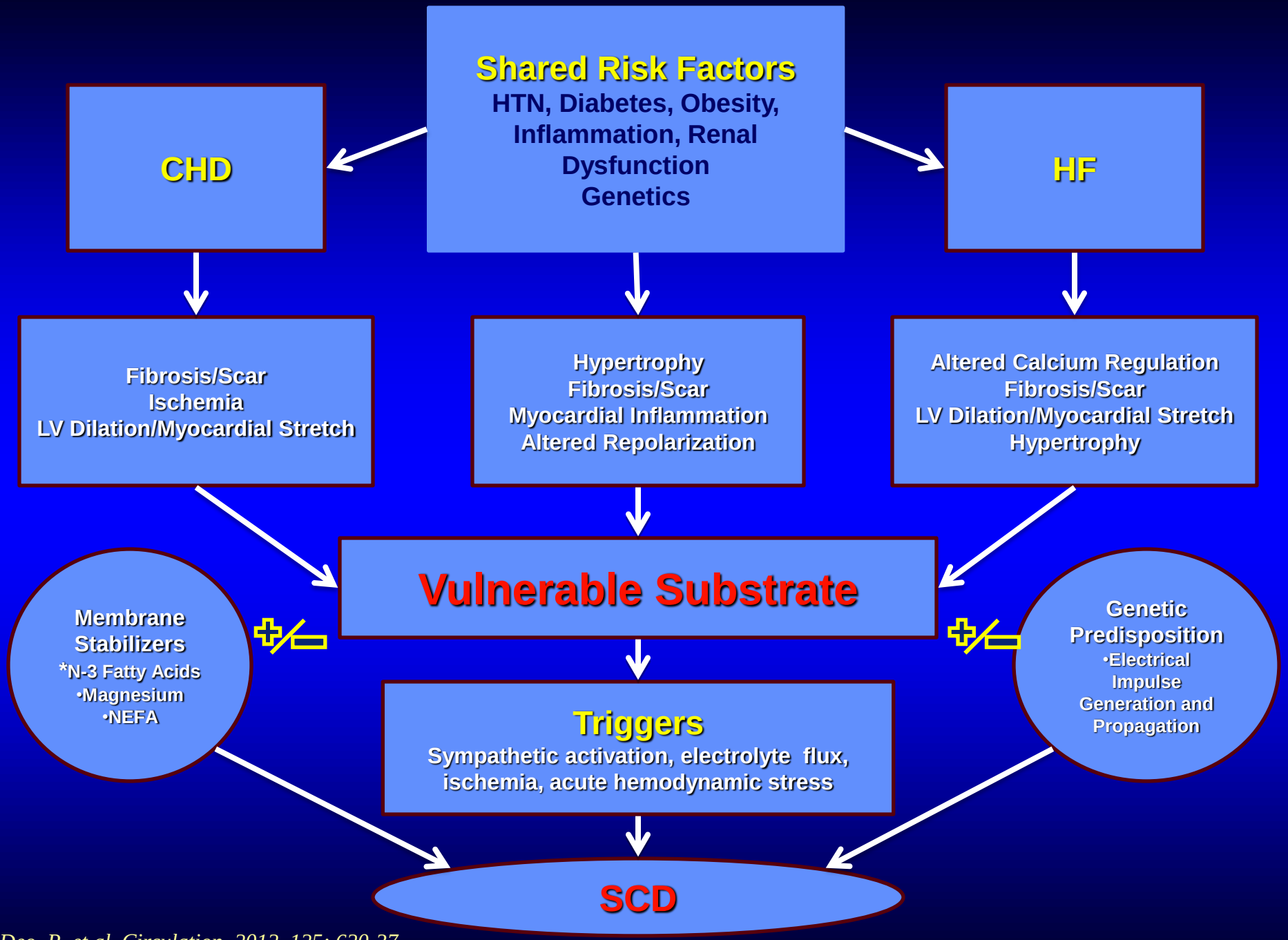
- Blood collection prior to death/event
- Likely altered by the preceding cardiac arrest and/or death
- Samples are finite

Sudden Cardiac Death/Arrhythmic Event is a Rare Event

- Individual studies generally have low numbers of events
- Large sample sizes needed for replication and modeling

Biomarkers reflect processes that are RISKS for SCD

- **There is no biomarker specific for arrhythmia (yet)**



Deo, R, et al. Circulation, 2012. 125: 620-37.

Biomarkers

Potential Candidate Pathways

- Inflammation
- Myocardial Dysfunction and Fibrosis
- Renin-Angiotensin-Aldosterone System
- Membrane Stabilization
- Metabolic Markers
- Renal Dysfunction

Selected biomarkers in these pathways have been associated with fatal CHD events to a greater degree than non-fatal events

CRP, Lipids, Homocysteine and SCD among Healthy Men

97 SCDs/ 192 controls

	Relative Risk (95%CI) by Quartile				
Variable	**1**	**2**	**3**	**4**	**P, Trend**
C-reactive protein	1.0	1.12 (0.51-2.46)	1.19 (0.55– 2.61)	2.78 (1.35-5.72)	< 0.001
Total cholesterol	1.0	1.50 (0.73 - 3.06)	1.38 (0.70 - 2.74)	1.43 (0.70 - 2.95)	0.37
LDL cholesterol	1.0	1.59 (0.80 - 3.15)	0.91 (0.44 - 1.89)	1.48 (0.75 - 2.91)	0.56
HDL cholesterol	1.0	0.72 (0.36 - 1.45)	0.65 (0.33 - 1.25)	0.63 (0.31 - 1.26)	0.17
Triglycerides	1.0	0.87 (0.43 - 1.77)	1.03 (0.52 – 2.04)	1.01 (0.52 – 1.97)	0.87
TC/HDL-C ratio	1.0	1.07 (0.51 - 2.26)	1.24 (0.61 - 2.50)	1.89 (0.92 – 3.86)	0.06
Homocysteine	1.0	0.73 (0.38 - 1.45)	0.61 (0.29 - 1.28)	1.06 (0.51 – 2.20)	0.98

Albert CM, et al. Circulation, 2002: 2595-2599

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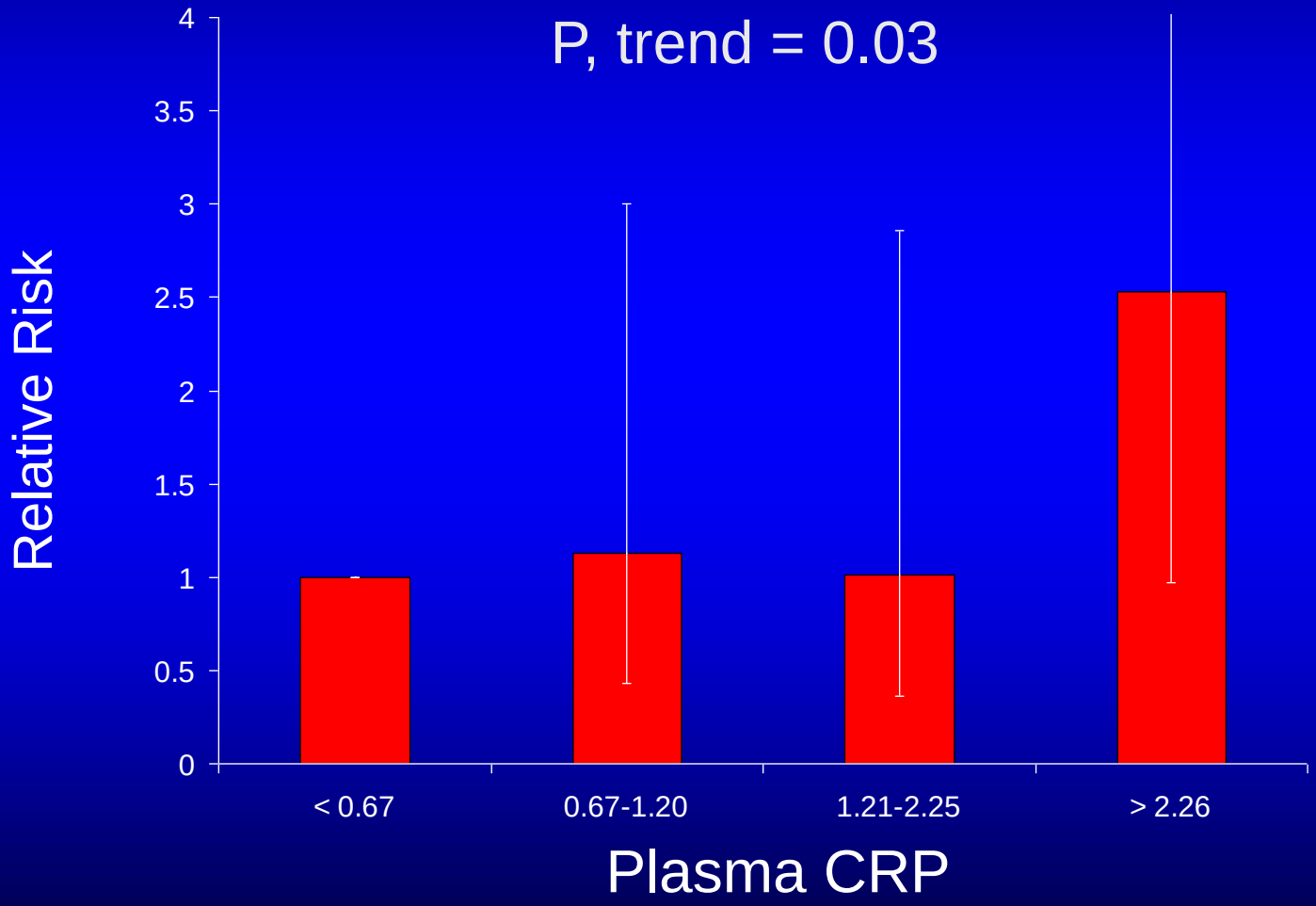
CRP and Sudden Cardiac Death



Albert CM, et al. Circulation, 2002: 2595-2599

Inflammatory Markers and SCD versus NSCD
The Prime Study

Table 3. Adjusted HRs and 95% Confidence Intervals of Study Outcomes by Thirds of hs-CRP, Fibrinogen, and IL-6. The PRIME Study

	Sudden Death (n=50)	Nonsudden Coronary Death (n=34)	Nonfatal CHD (n=580)
Hs-CRP (mg/L)			
1st tertile (≤1.51)	1	1	1
2nd tertile (≤3.70)	1.96 (0.75–5.08)	0.80 (0.20–3.17)	1.17 (0.87–1.57)
3rd tertile (>3.70)	1.27 (0.51–3.17)	1.86 (0.50–6.95)	1.48 (1.10–1.99)
P for trend	0.58	0.14	0.017
1-SD log (0.98)	1.04 (0.71–1.52)	1.79 (0.96–3.36)	1.16 (1.03–1.32)
Fibrinogen (g/L)			
1st tertile (≤2.89)	1	1	1
2nd tertile (≤3.46)	0.75 (0.32–1.78)	1.86 (0.52–6.62)	0.96 (0.73–1.28)
3rd tertile (>3.46)	1.90 (0.76–4.75)	6.04 (1.37–26.71)	1.32 (0.99–1.75)
P for trend	0.16	0.017	0.011
1-SD log (0.26)	1.22 (0.84–1.78)	1.64 (1.03–2.61)	1.16 (1.04–1.31)
IL-6 (pg/mL)			
1st tertile (≤0.06)	1	1	1
2nd tertile (≤0.48)	1.82 (0.68–4.85)	2.16 (0.60–7.75)	1.25 (0.93–1.68)
3rd tertile (>0.48)	3.06 (1.20–7.81)	2.97 (0.84–10.49)	1.53 (1.13–2.06)
P for trend	0.02	0.095	0.021
1-SD log (2.94)	1.57 (1.06–2.35)	1.72 (0.99–2.27)	1.16 (1.02–1.31)

HRs were estimated by conditional logistic regression that accounted for matching variables (age, centre, and baseline examination date) and that were adjusted for BMI, smoking status, diabetes, HDL, and Total-C.

Nested case control among 9771 asymptomatic European men

50 SCD
34 NSCD

Only IL-6 predicted SCD

Empana J-P et al. *Arterioscler Thromb Vasc Biol*. 2010

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NT-proBNP, hsCRP, and lipids and SCD risk among women

Higher NT-proBNP is associated with SCD in apparently healthy women

	Multivariable Relative Risk (95%CI) by Quartile				
Variable	**1**	**2**	**3**	**4**	**P, Trend**
NT-proBNP	1.0	1.33 (0.58 – 3.02)	1.34 (0.58 – 3.10)	2.37 (0.97 – 5.80)	0.05
hs-CRP	1.0	1.18 (0.51 – 2.72	1.10 (0.45 – 2.65)	1.30 (0.54 – 3.14)	0.60
TC /HDL-C ratio	1.0	1.01 (0.42 – 2.43)	1.38 (0.54– 3.53)	1.34 (0.49– 3.66)	0.57
LDL cholesterol	1.0	1.37 (0.59 – 3.20)	1.66 (0.66 – 4.20)	1.36 (0.53 – 3.51)	0.57
HDL cholesterol	1.0	0.81 (0.37 – 1.76)	1.08 (0.49 – 2.39)	1.25 (0.53 – 2.93)	0.53
Triglycerides	1.0	0.85 (0.37 – 1.93)	0.81 (0.32- 2.03)	1.46 (0.56 – 3.83)	0.31

Korngold,E..Albert,CM. Circulation 2009; 119:2868-76

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NT-proBNP vs hsCRP and SCD in women in Nurses' Health Study

Higher NT-proBNP is associated with SCD in apparently healthy women

Biomarker	RR (95% CI) per 1-SD in Log Variable	*P*-value	RR (95%CI) for values above the 80th percentile	*P*-value	RR (95%CI) for Clinical Cut-Points*	*P*-value
NT-proBNP						
Model 1 (age, fasting)	1.32 (1.01 - 1.71)	0.04	1.50 (0.83 - 2.71)	0.18	3.60 (1.43 - 9.10)	0.007
Multivariable Model**	1.49 (1.09 -2.05)	0.01	1.99 (0.97 - 4.12)	0.06	5.68 (1.78 -18.2)	0.003
hsCRP						
Model 1 (age, fasting)	1.33 (1.03 - 1.70)	0.03	1.57 (0.92 - 2.68)	0.10	1.40 (0..87-2.24)	0.17
Multivariable Model**	1.17 (0.85 - 1.61)	0.34	1.49 (0.76 - 2.93)	0.25	1.05 (0.58-1.91)	0.86

* hsCRP (>3.0 mg per liter) and NT-pro-BNP (> 389 pg/mL)

**Controlled simultaneously for age, smoking, and fasting status, history of hypertension, history of diabetes, alcohol consumption (<0.1 g, 0.1-14.9, 15.0 to 29.9, 30+), parental history of myocardial infarction prior to age 60, body-mass index (<25 kg/m2, 25-30 kg/m2, >=30 kg/m2), physical activity (quintiles of metabolic equivalent (MET-hours)), current postmenopausal hormone use, GFR, aspirin use>=22 days/month, plasma NT-proBNP, hsCRP, triglyceride, and TC/HDL-Ratio levels

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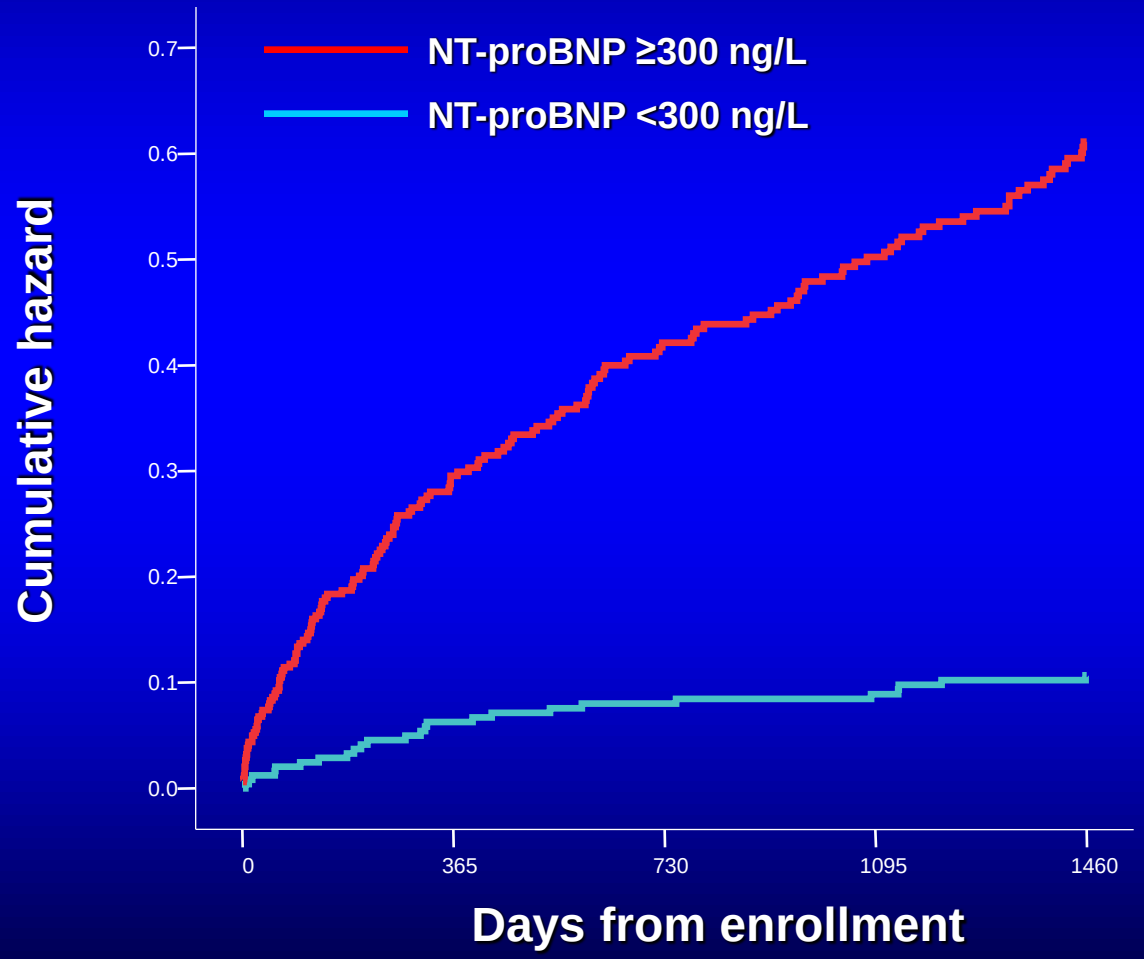
Korngold,E..Albert,CM. Circulation 2009; 119:2868-76

NT-proBNP and mortality in HF



***P* <.0001**

Januzzi, et al., Clin Chem 2010

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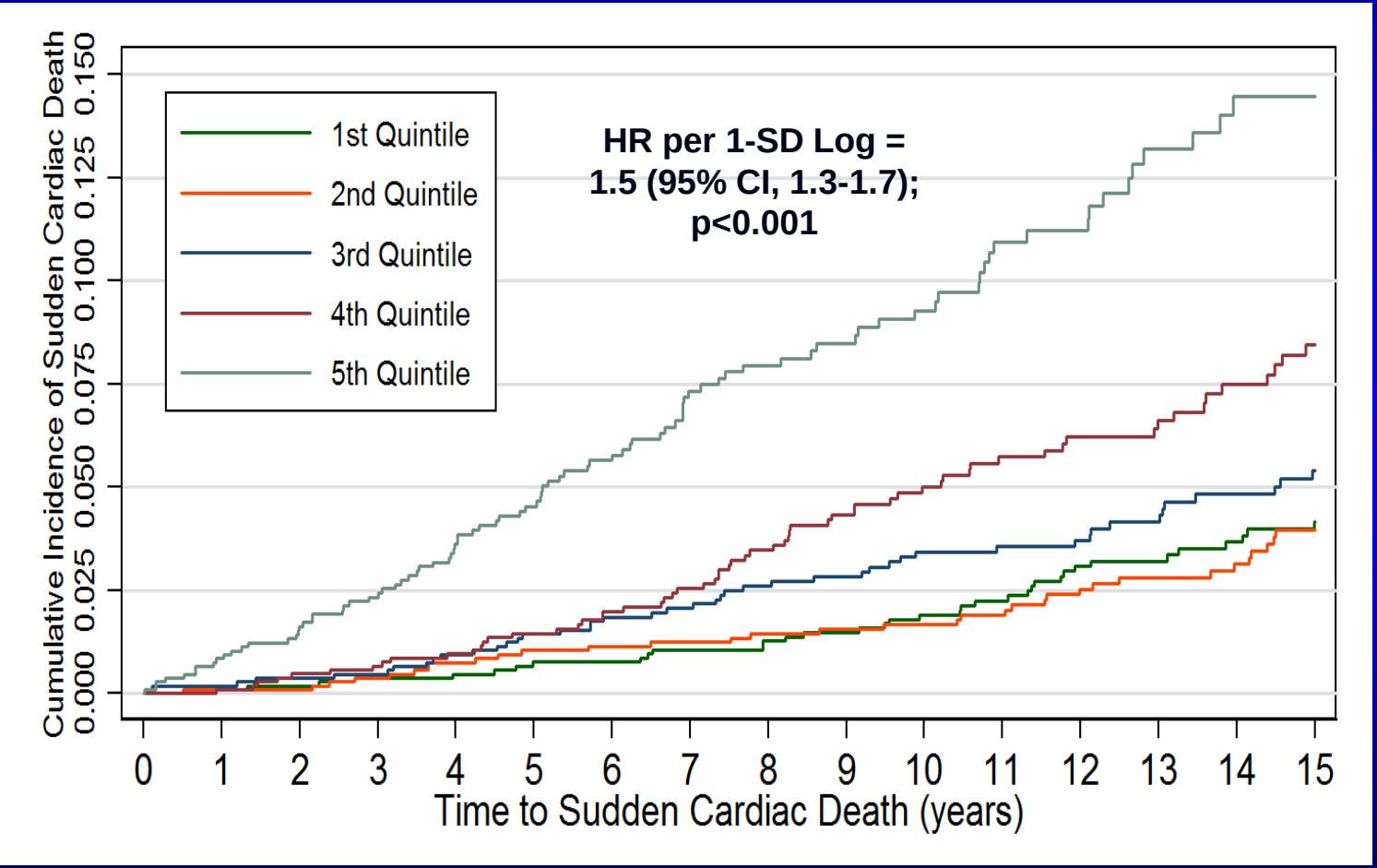
NT-proBNP and SCD among the Elderly:

The Cardiovascular Health Study



Patton, KK et al. Heart Rhythm 2011

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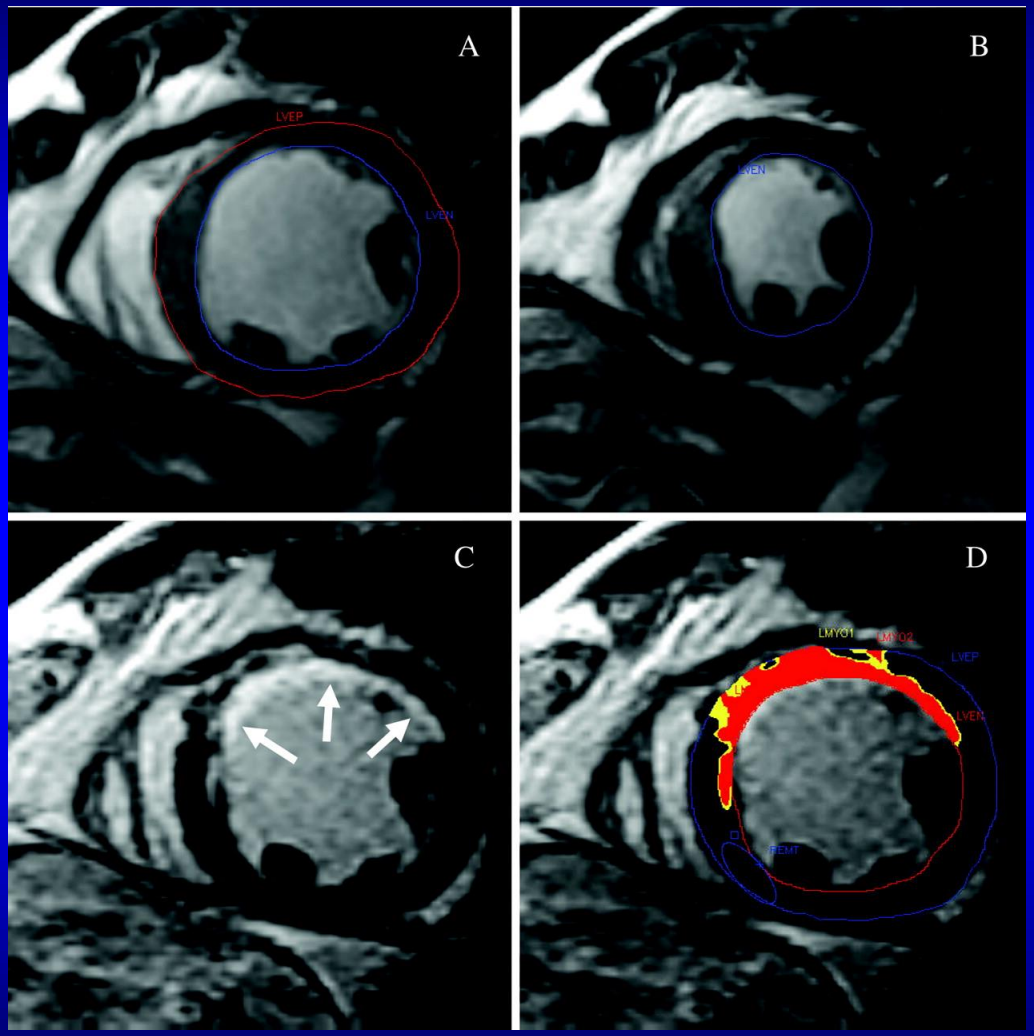
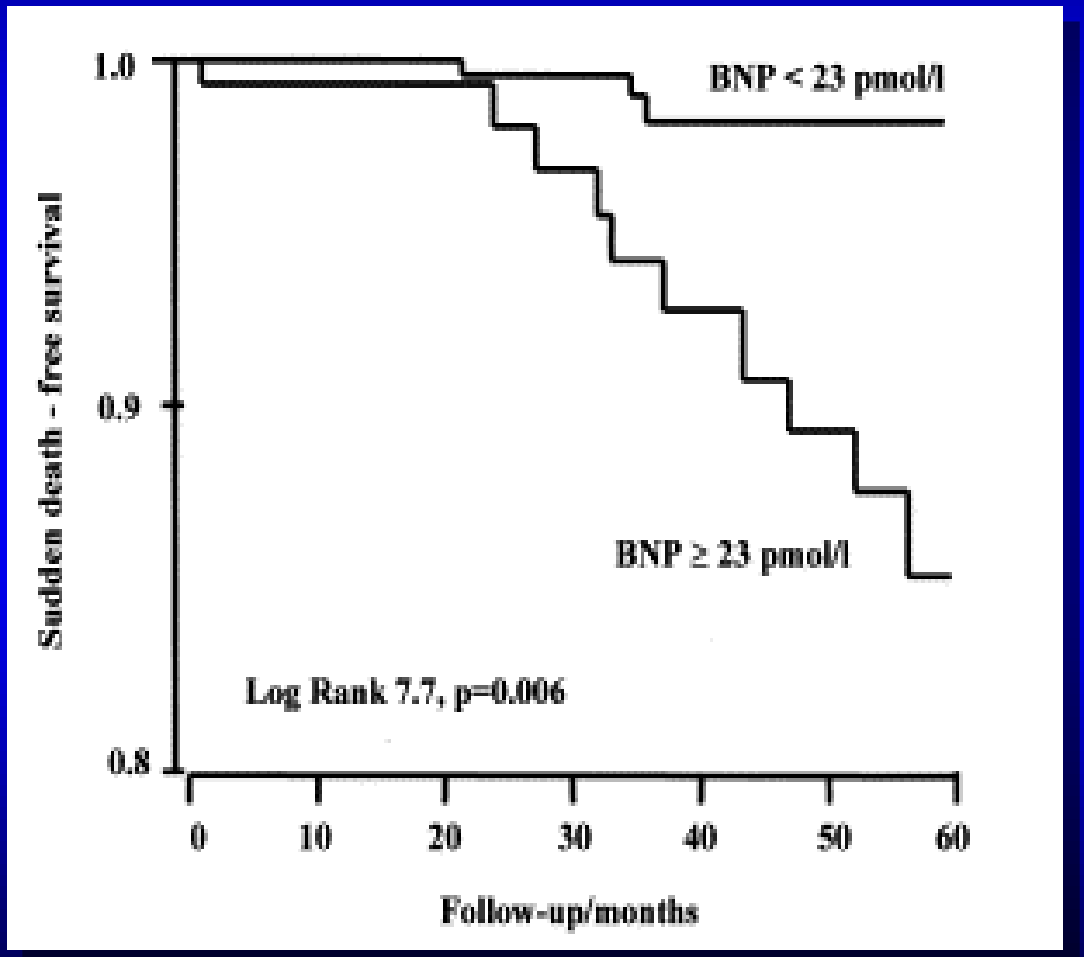
Peri-Infarct Zone and Post–MI Mortality

Adjusted HR=1.42 per 10% increase in ($\%MDE_{periphery}$). *P*=0.005



Yan, A. T. et al. Circulation 2006;114:32-39

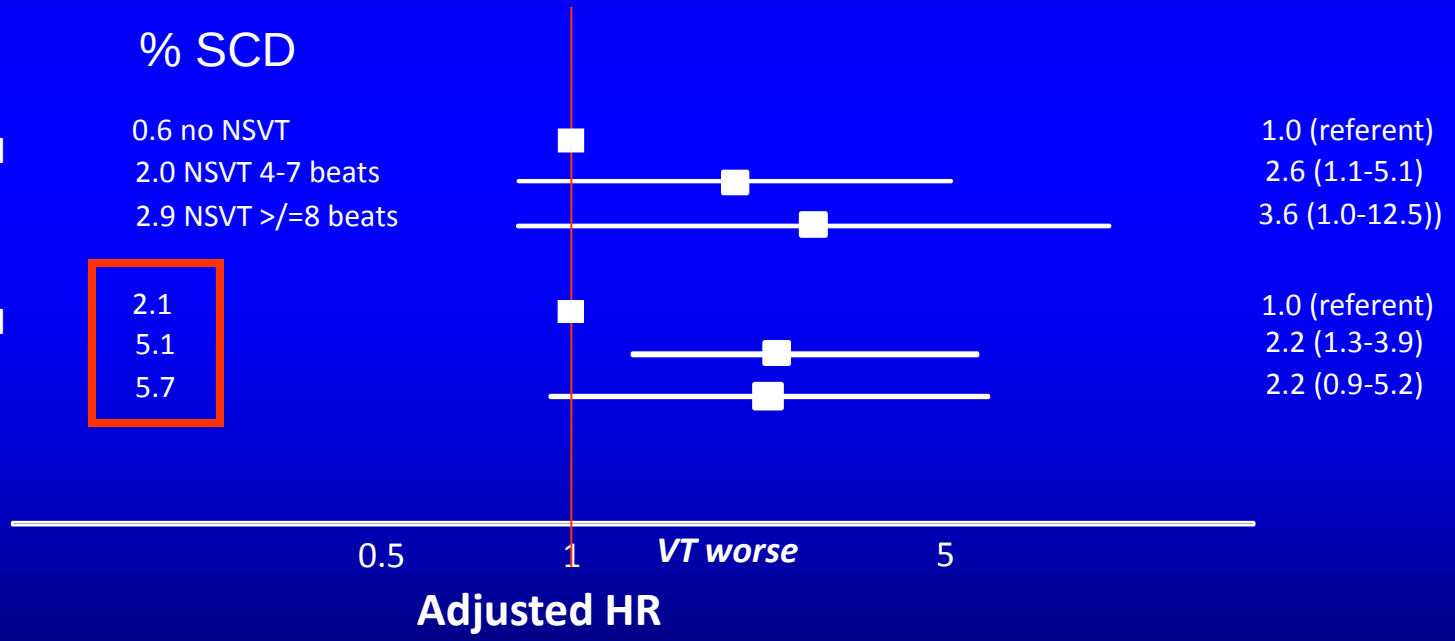
Predictive Value of BNP for SCD Post-MI



Tapanainen JM. et al. JACC 2004

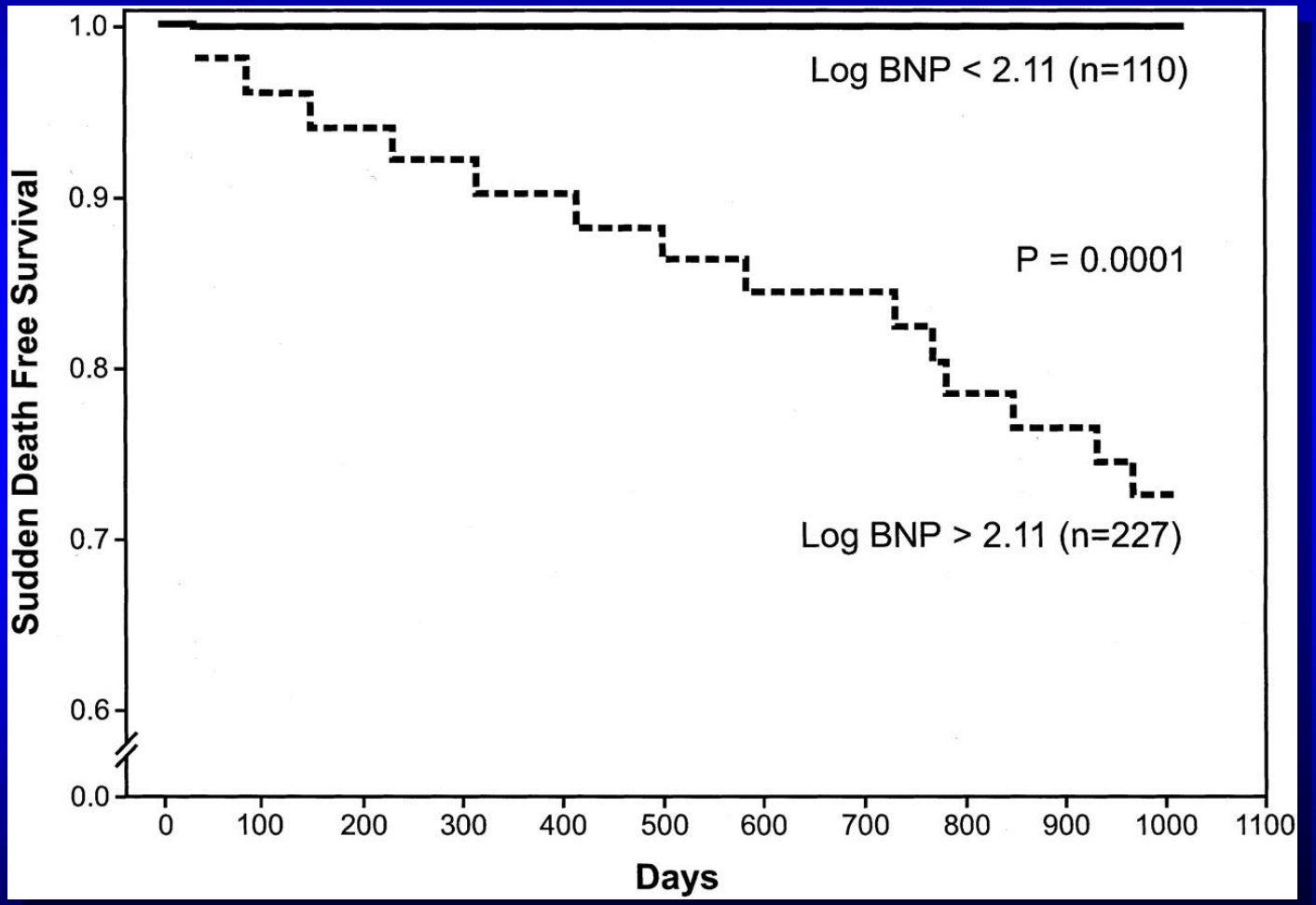
Predictive Value of BNP for SCD in ACS: MERLIN TIMI 36

Although the relative risk for SCD was similar with higher incidence of VEA, when BNP was elevated, the ABSOLUTE risk was 2x higher



Scirica et al, Circulation 2010

B-Type Natriuretic Peptide Predicts Sudden Death in Patients With Chronic Heart Failure

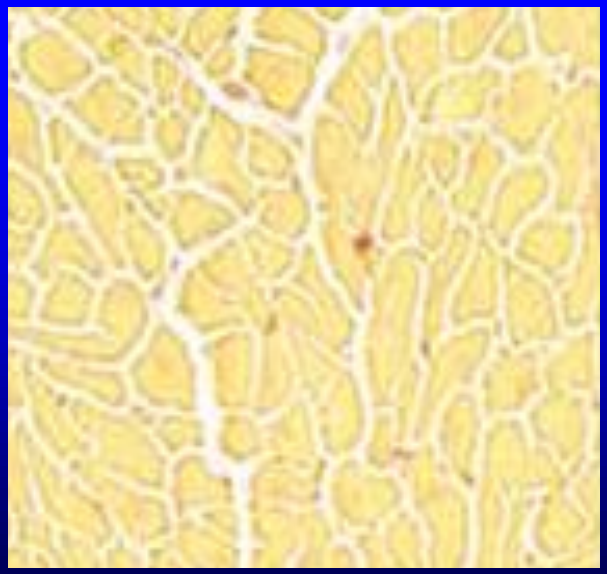


Berger, R. et al. Circulation 2002;105:2392-2397

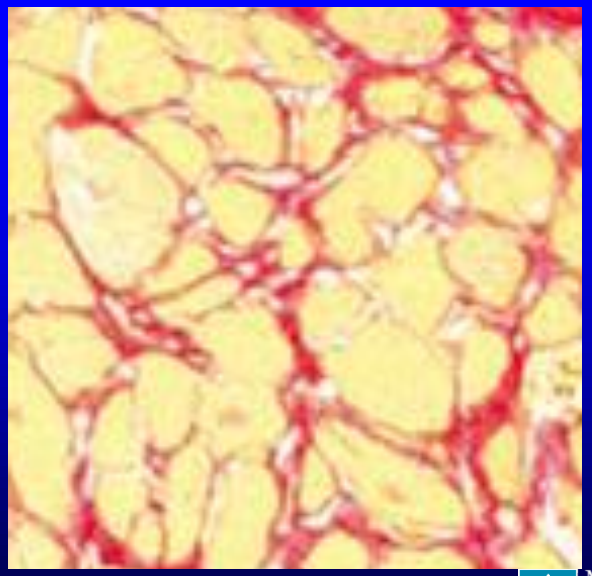
ST2 plays a role in reducing cardiomyocyte hypertrophy and fibrosis

Abnormalities in ST2 experimentally result in severe cardiac remodeling and heart failure

Intact sST2

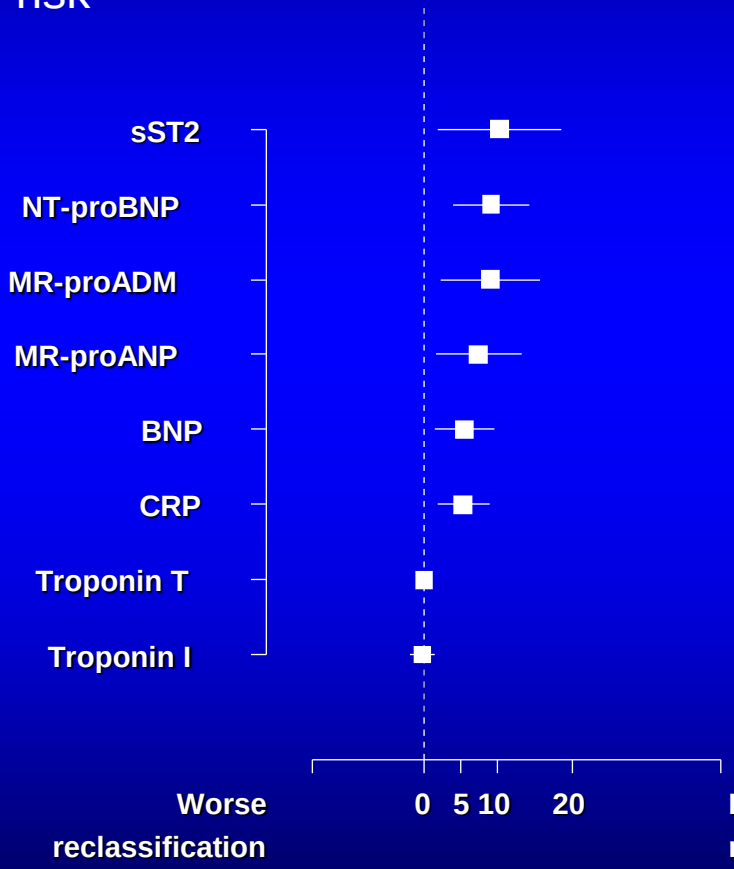


sST2 knock out



Multiple biomarkers in ADHF:
the GREAT Network Analysis

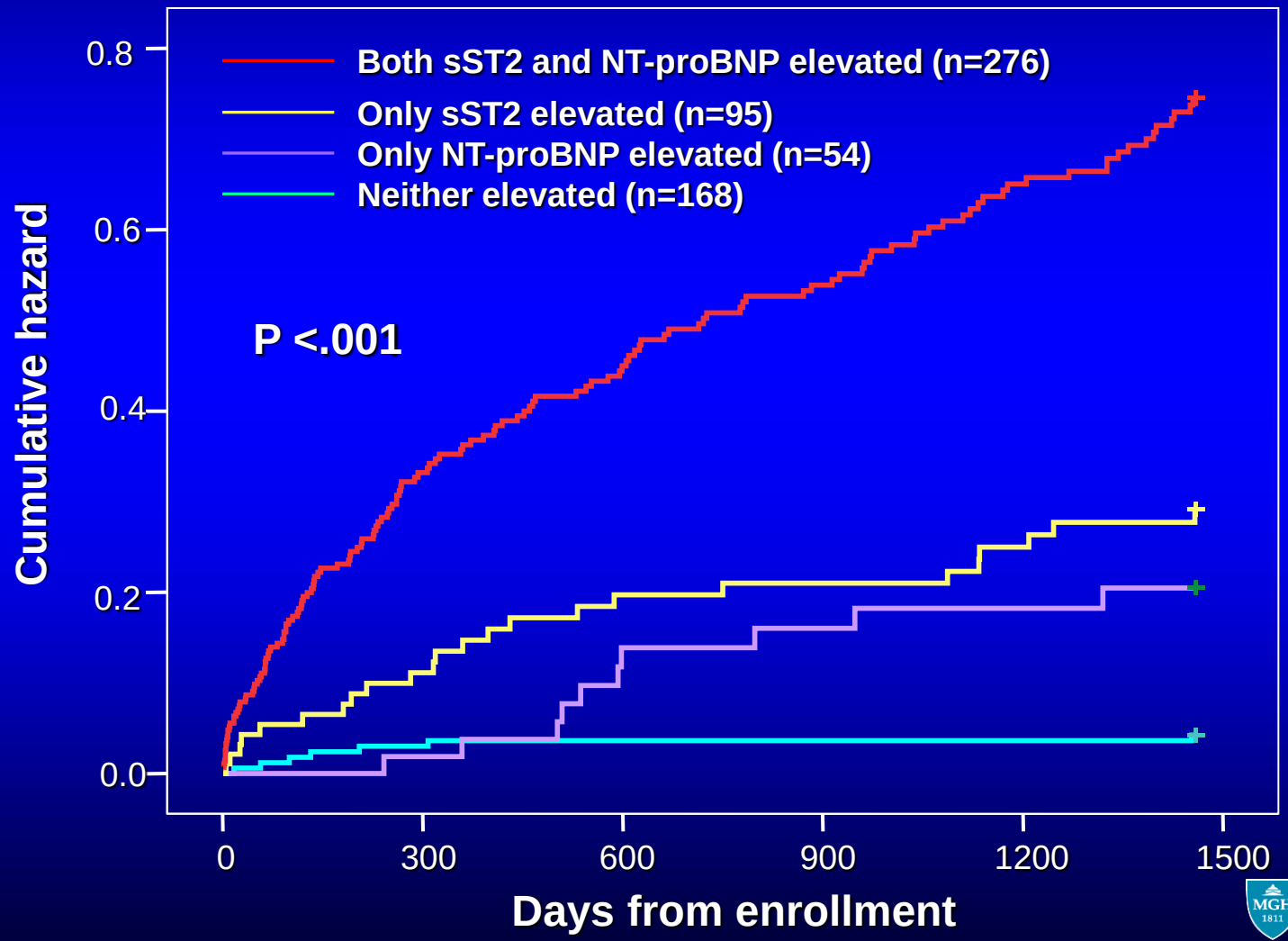
365 day risk



	NRI [95% CI]	IDI [95% CI]
sST2	10.3 [1.9 ; 18.7]	0.048 [0.028 ; 0.067]
NT-proBNP	9.1 [4.0 ; 14.1]	0.025 [0.016 ; 0.034]
MR-proADM	9.1 [2.4 ; 15.8]	0.042 [0.028 ; 0.057]
MR-proANP	7.4 [1.6 ; 13.2]	0.028 [0.014 ; 0.041]
BNP	5.5 [1.5 ; 9.4]	0.020 [0.012 ; 0.027]
CRP	5.3 [1.9 ; 8.8]	0.011 [0.005 ; 0.016]
Troponin T	0.0 [-0.9 ; 1.0]	0.000 [-0.001 ; 0.002]
Troponin I	-0.2 [-1.8 ; 1.5]	0.000 [-0.001 ; 0.002]

Lassus, et al, Int Jour Cardiol, 2013

Additive value of ST2 to NT-proBNP in long term prognosis



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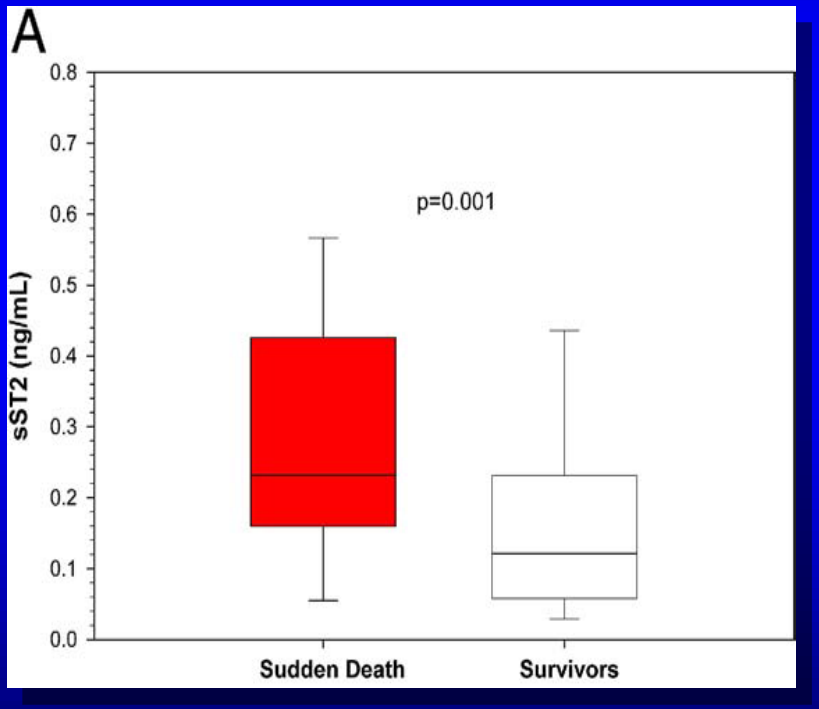
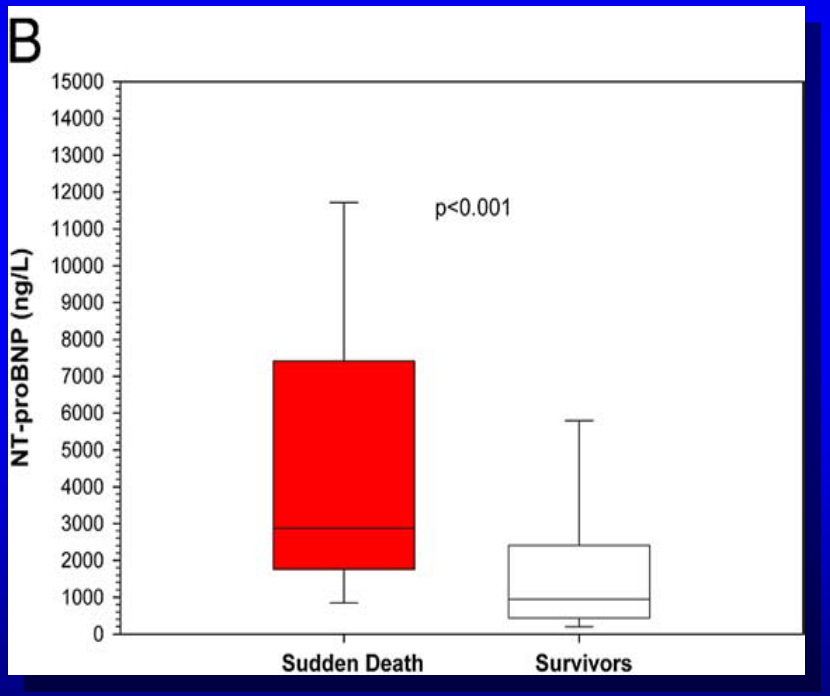
Soluble ST2 and NT-proBNP and SCD in Heart Failure

ST2



NT-proBNP



Pascual-Figal DA. et al. JACC 2009

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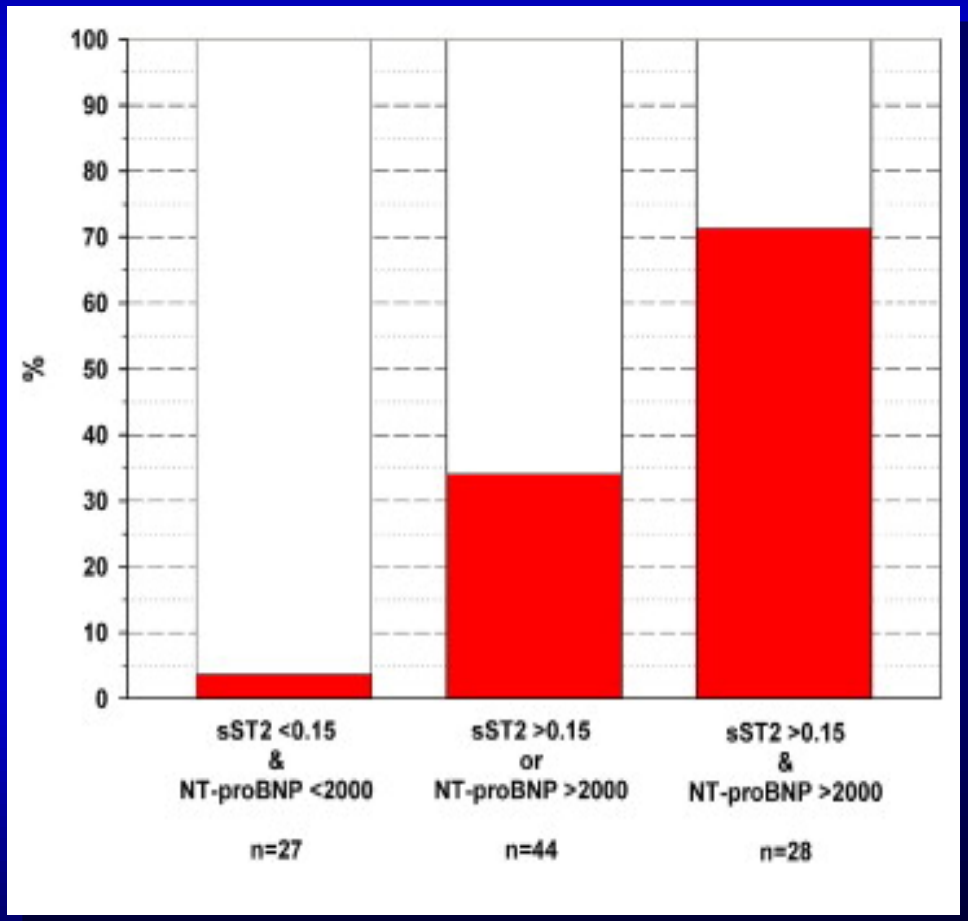
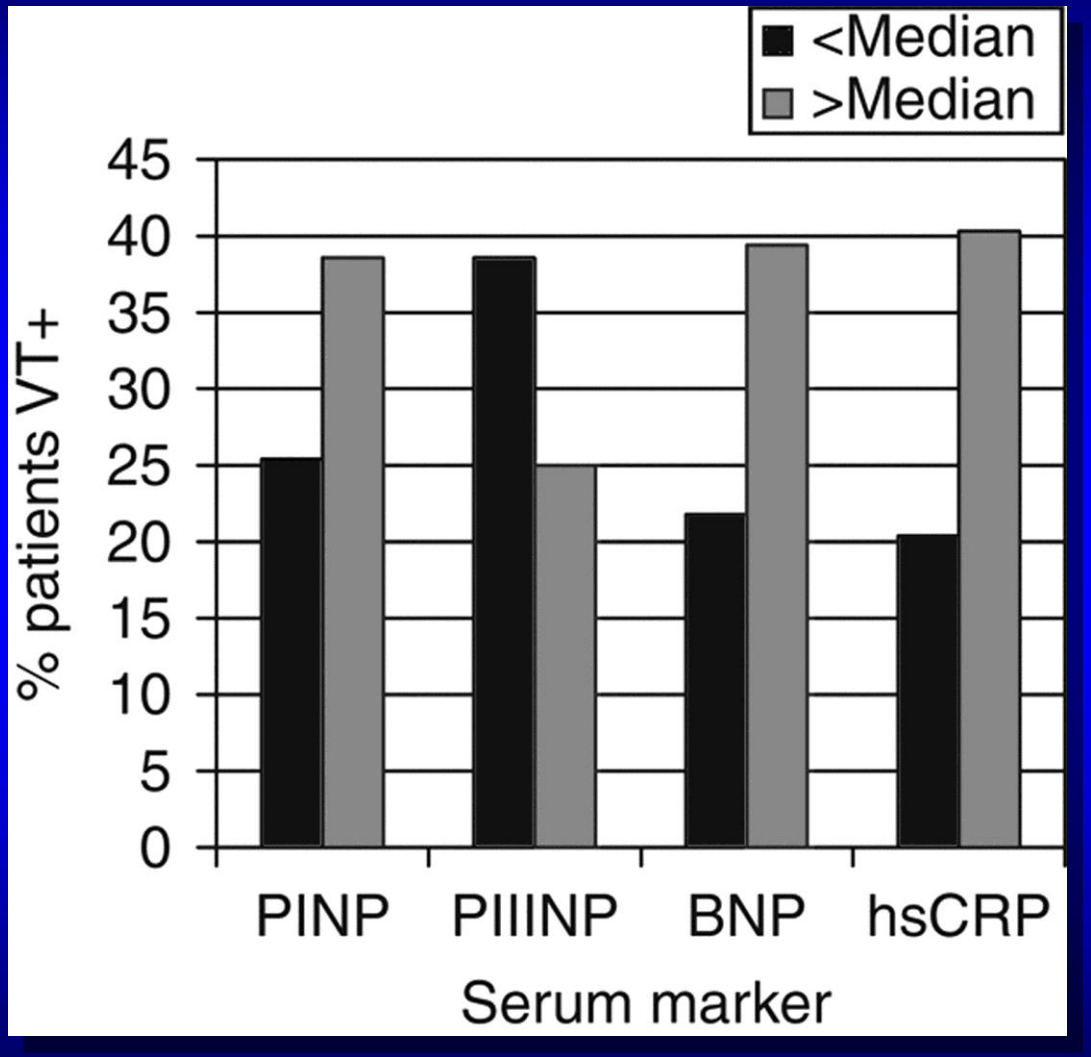


Pascual-Figal DA. et al. JACC 2009

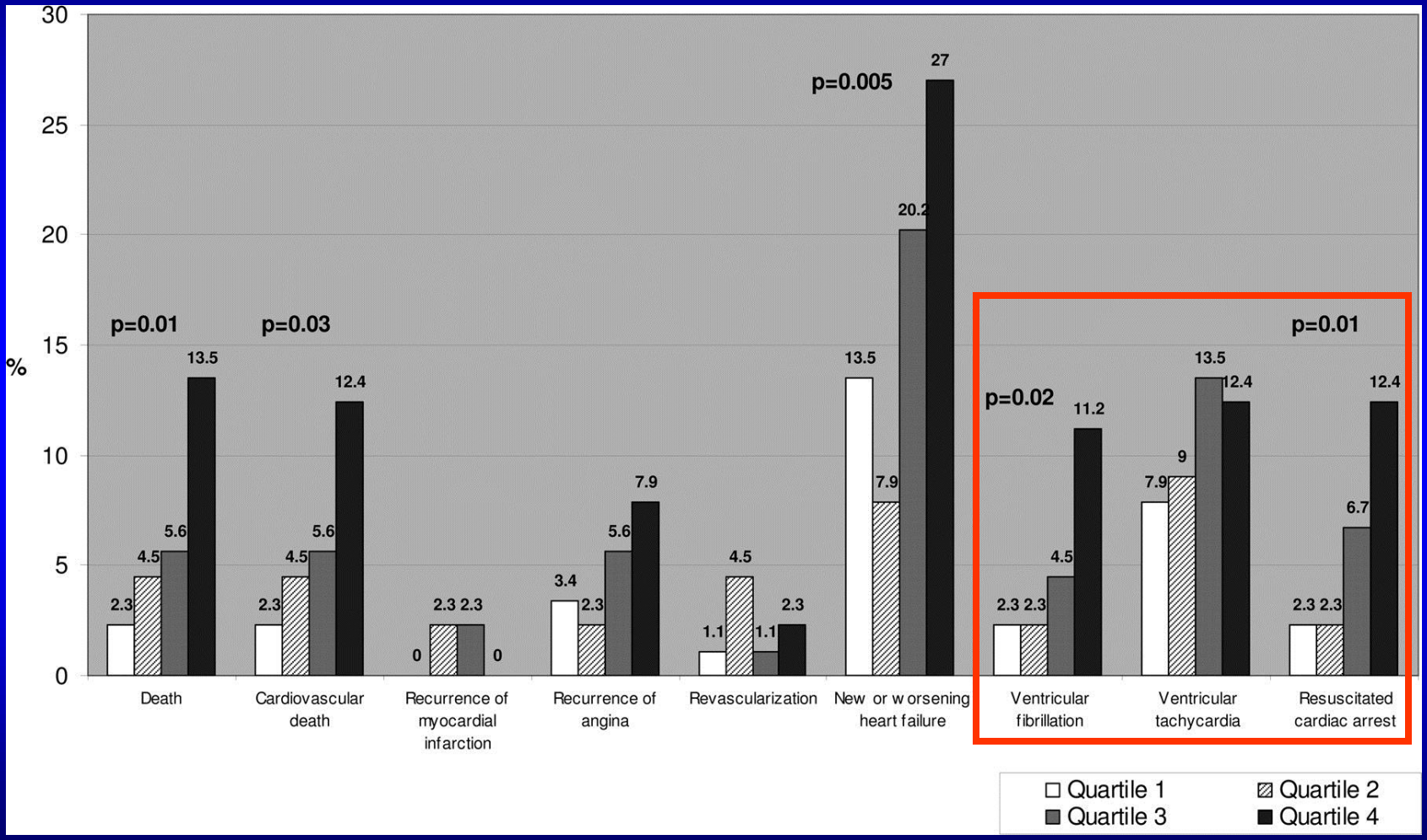
Biomarker Predictor of ICD discharges for VT/VF



Biomarker patterns consistent with fibrosis, myocyte stretch, or inflammation are associated with VT/VF

Blangy, H. et al. Europace 2007 9:724-729;

Events Post-MI Mortality and Aldosterone Levels



Beygui, F. et al. Circulation 2006;114:2604-2610

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Biomarkers

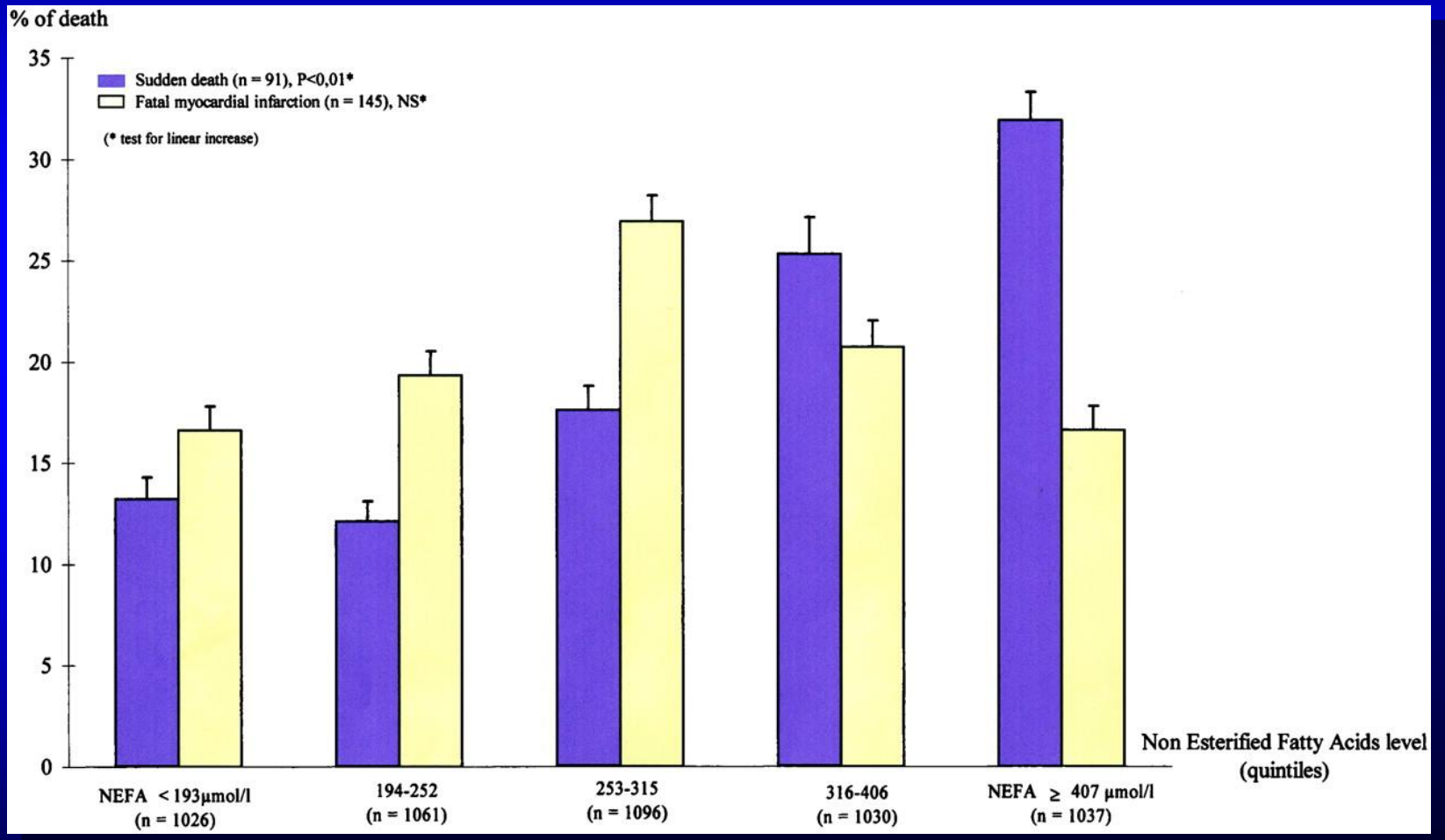
Potential Candidate Pathways

- Inflammation
- Myocardial Dysfunction and Fibrosis
- Renin-Angiotensin-Aldosterone System
- Membrane Stabilization
- Metabolic Markers
- Renal Dysfunction

Selected biomarkers in these pathways have been associated with fatal CHD events to a greater degree than non-fatal events

Risk of Sudden Death versus Fatal Myocardial Infarction According to Circulating NEFA level

Paris Prospective Study



Jouven, X. et al. Circulation 2001;104:756-761

Relative Risk of SCD According to Blood Long Chain n-3 Fatty Acid Level

N-3 Fatty Acid Level	Relative Risk	95% CI
≤ 4.35	1.0	Referent
4.35 – ≤ 5.15	0.55	(0.18 – 1.70)
5.15 - ≤ 6.09	0.28	(0.09 – 0.87)
> 6.09	0.19	(0.05 – 0.71)

P, trend = 0.007

Albert CM, et al. N Engl J Med, 2002; 346:1113-8

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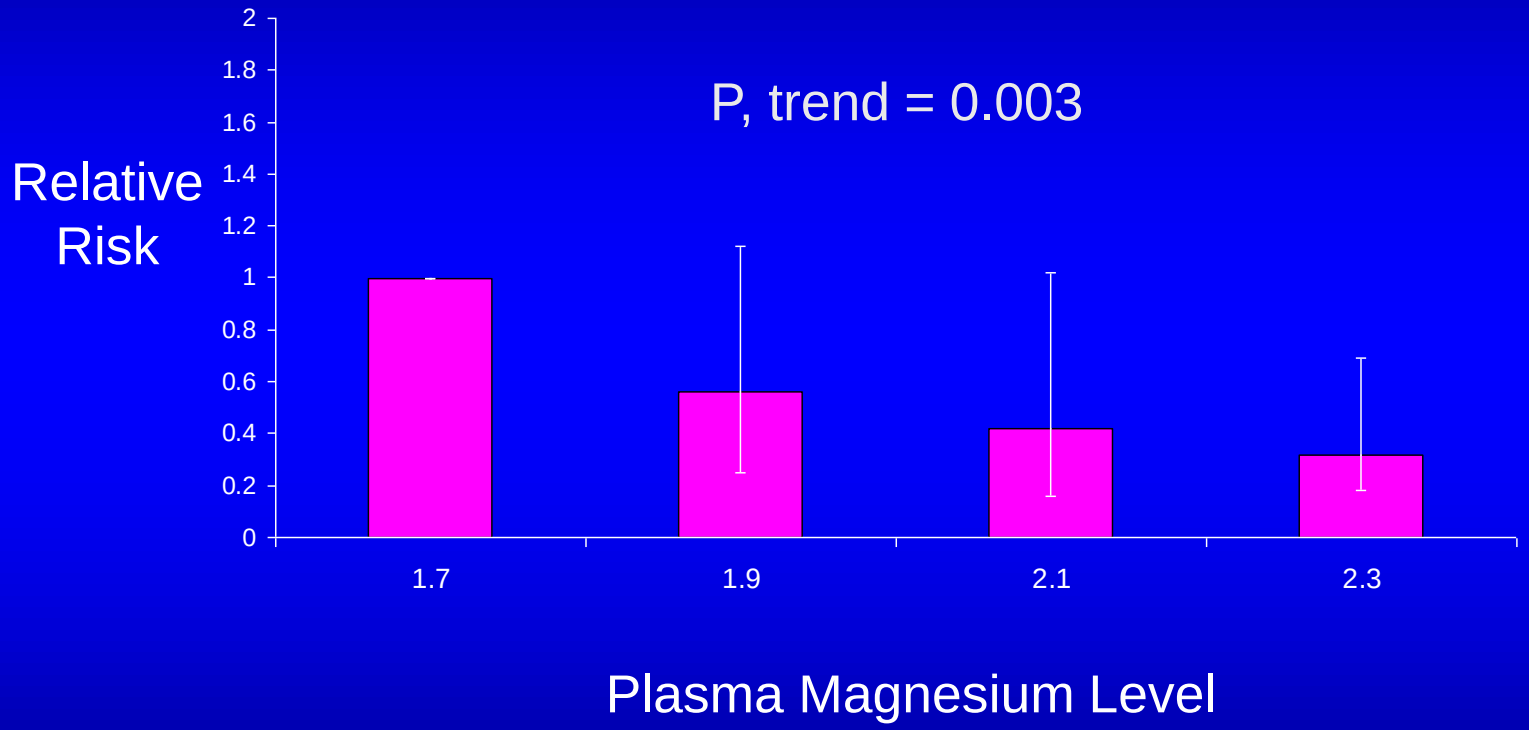
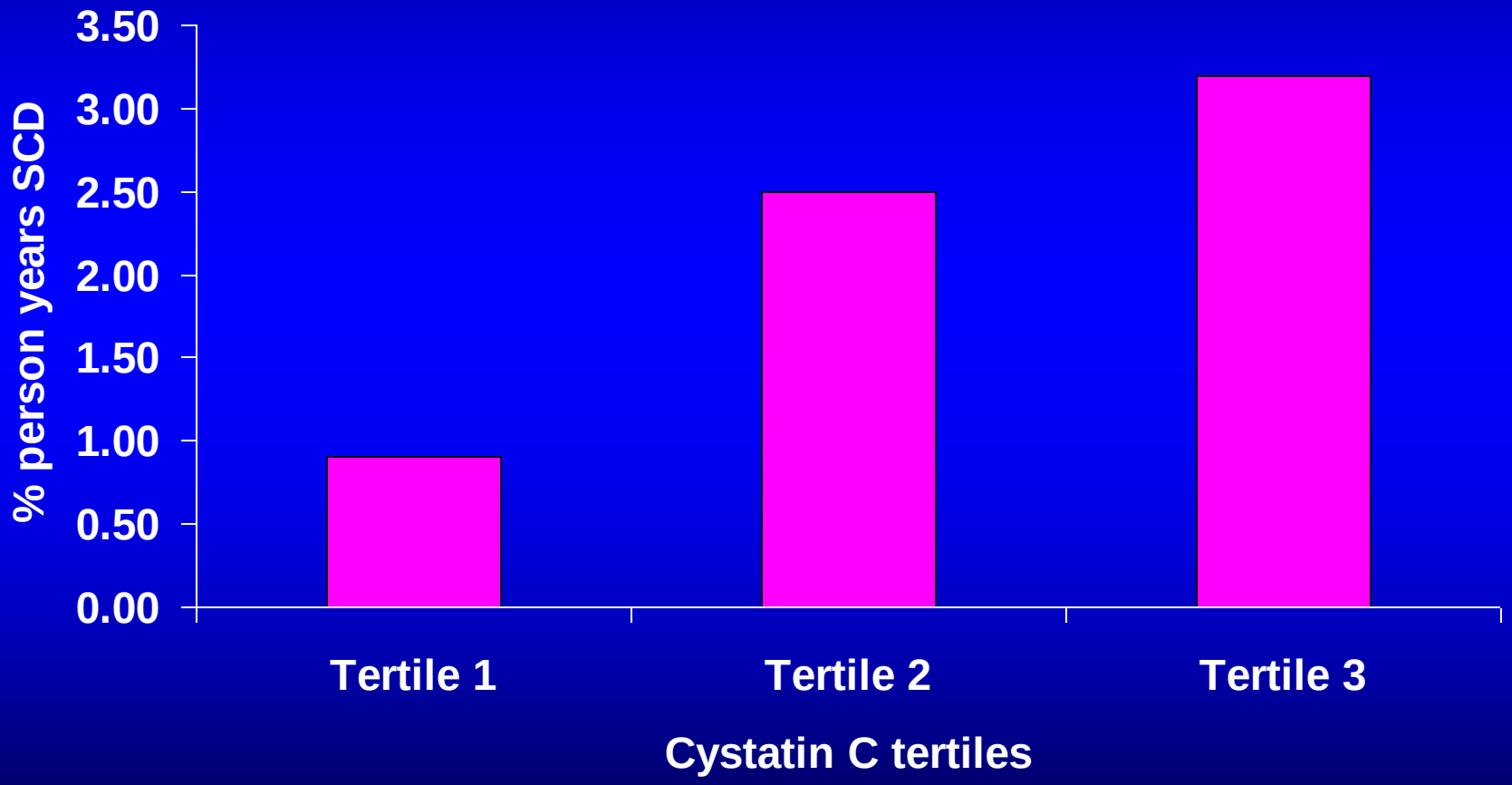
Plasma Magnesium and Sudden Cardiac Death



* Model adjusted for: matching factors, aspirin use, BMI, physical activity, alcohol, history of diabetes, history of hypertension, family history of MI, hormone therapy, intake of Mg, K, Ca, marine n-3 fat, vitamin D, total:HDL cholesterol, GFR, CRP, NT-proBNP

Chiuve et al. Am J Clin Nut 2011

Cystatin C and SCD Risk in the Elderly



Deo R et al. Circ Cardiovasc Qual Outcomes 2010.

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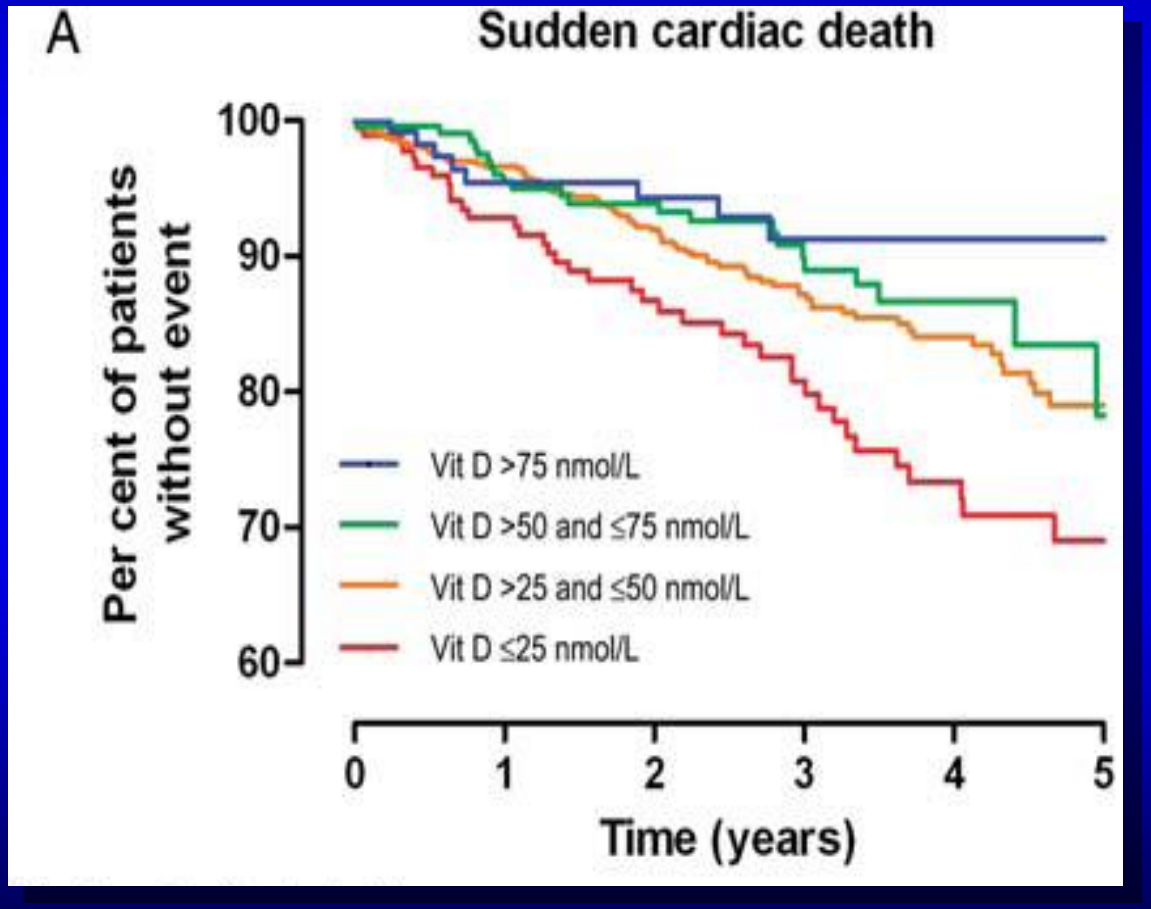
Vitamin D and SCD in Hemodialysis Patients



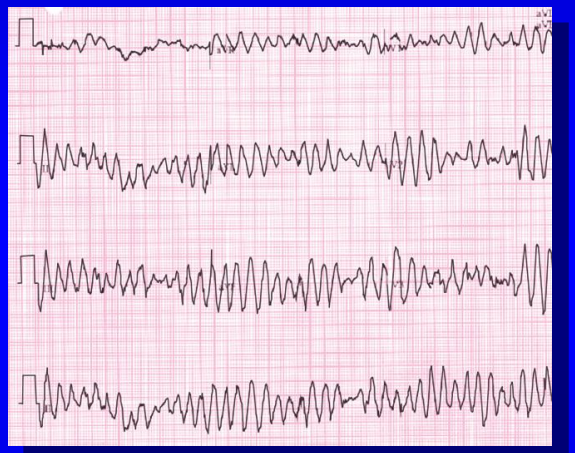
Low vitamin D was associated with SCD in patients with uniformly severe CKD

Drechsler C et al. European Heart Journal 2010

Conclusion

- Advancements in SCD prevention will require improved markers to identify the “pro-arrhythmic” substrate
- Biomarkers may be promising for SCD prediction
- Likely, prediction will involve a combination of markers (genes, proteins, metabolic markers, and imaging)
- Surrogate endpoints are useful for raising hypotheses, but hard SCD endpoints will be needed to definitively test hypotheses
- Large populations at different levels of SCD risk will be needed to accumulate the necessary SCD endpoints and to allow for replication of the results

Biomarkers of Sudden Death



James L. Januzzi, Jr, MD, FACC, FESC
Associate Professor of Medicine
Harvard Medical School
Roman W. DeSanctis Endowed Clinical Scholar
Director, Cardiac ICU
Massachusetts General Hospital

MASSACHUSETTS GENERAL HOSPITAL
HEART CENTER