The Stratification of Short-Term and Long-Term CVD Risks:
The Impact of Conventional Risks and Biomarkers

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Disclosures

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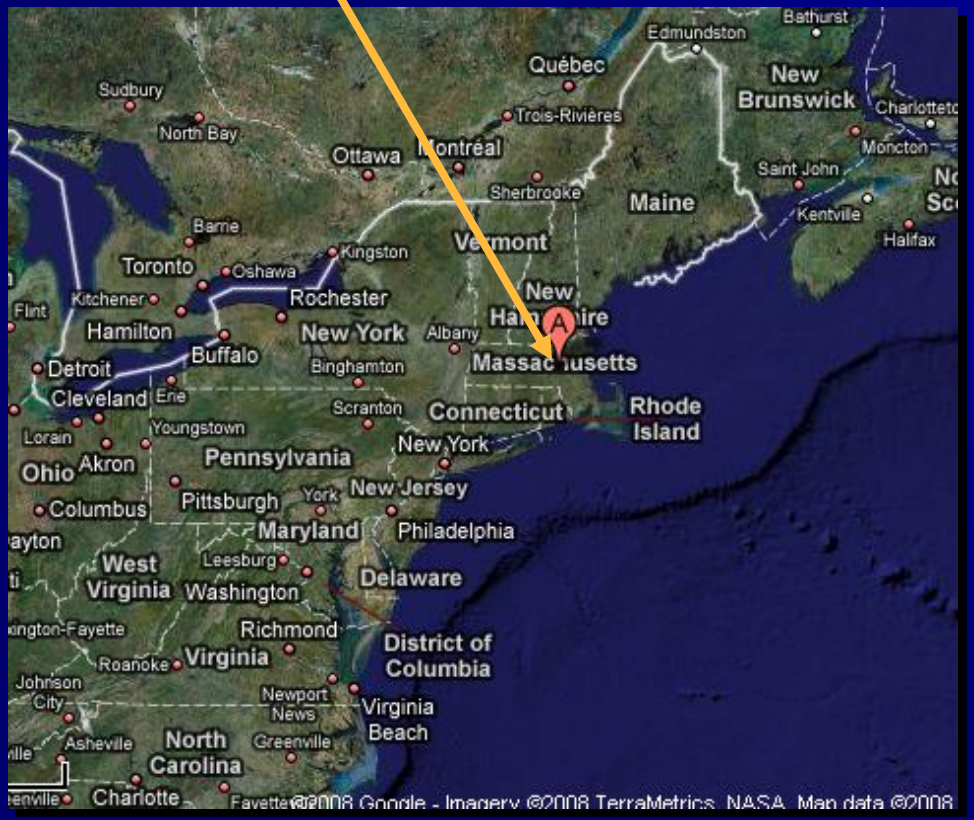
- Organizations: Society of Cardiovascular Patient Care, Journal of the American Heart Association
- Full listing see w*ww.dcri.duke.edu/research/coi.jsp*

Framingham Heart Study

Framingham, MA (pop 67,000)



- 1948: 5,209 healthy residents, age 30-60 years enrolled
- First major CV study to recruit women
- Extensive medical follow up every 2-4 yrs
- 1971: 5,124 children (and their spouses) enrolled in the "Offspring Study"

Conventional Risk Factors for Cardiovascular Disease

Modifiable

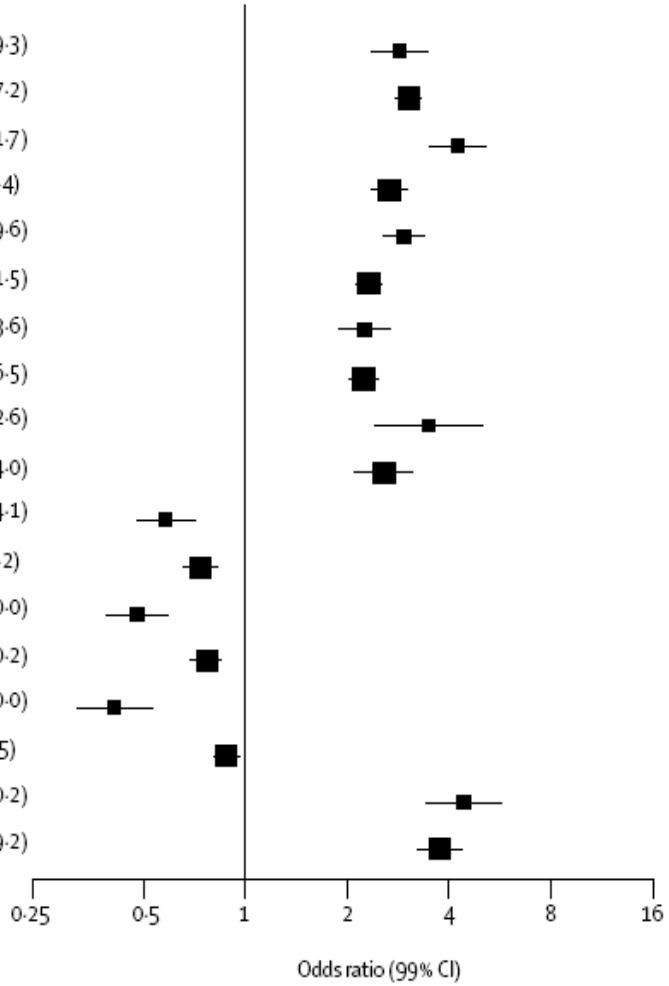
- Cholesterol
- Hypertension
- Smoking
- Diabetes
- Obesity
- Sedentary Lifestyle

Not Modifiable

- Age
- Sex
- Family History

Risk Factors for Heart Attack: A Global View

Risk Factor	Sex	Control (%)	Case (%)	Odds ratio (99% CI)	PAR (99% CI)
Smoking	F	9·3	20·1	2·86 (2·36–3·48)	15·8% (12·9–19·3)
	M	33·0	53·1	3·05 (2·78–3·33)	44·0% (40·9–47·2)
Diabetes	F	7·9	25·5	4·26 (3·51–5·18)	19·1% (16·8–21·7)
	M	7·4	16·2	2·67 (2·36–3·02)	10·1% (8·9–11·4)
HTN	F	28·3	53·0	2·95 (2·57–3·39)	35·8% (32·1–39·6)
	M	19·7	34·6	2·32 (2·12–2·53)	19·5% (17·7–21·5)
Obesity	F	33·3	45·6	2·26 (1·90–2·68)	35·9% (28·9–43·6)
	M	33·3	46·5	2·24 (2·03–2·47)	32·1% (28·0–36·5)
Psych Index	F	–	–	3·49 (2·41–5·04)	40·0% (28·6–52·6)
	M	–	–	2·58 (2·11–3·14)	25·3% (18·2–34·0)
Fruits / Veges	F	50·3	39·4	0·58 (0·48–0·71)	17·8% (12·9–24·1)
	M	39·6	34·7	0·74 (0·66–0·83)	10·3% (6·9–15·2)
Exercise	F	16·5	9·3	0·48 (0·39–0·59)	37·3% (26·1–50·0)
	M	20·3	15·8	0·77 (0·69–0·85)	22·9% (16·9–30·2)
Alcohol	F	11·2	6·3	0·41 (0·32–0·53)	46·9% (34·3–60·0)
	M	29·1	29·6	0·88 (0·81–0·96)	10·5% (6·1–17·5)
Lipids	F	14·1	27·0	4·42 (3·43–5·70)	52·1% (44·0–60·2)
	M	21·9	35·5	3·76 (3·23–4·38)	53·8% (48·3–59·2)



INTERHEART Study; Yusuf, et al. Lancet 2004

Risk Factor Conundrum

- Not all patients with conventional risk factors have a heart attack or die of heart disease
- Some patients who have heart attacks or die from heart disease do not have *any* known risk factors
- Unfortunately, our ability to identify high risk individuals is limited
  - Primary risk:
    - Framingham, C-index = 0.69 in men and 0.72 in women

How Can Biomarkers Help?

- “Biomarkers” broadly are the output of any modality used to characterize and classify human health and disease and responses to various interventions and perturbations
- Examples of Biomarkers
  - Biospecimens
    - Routine and Advanced
  - Imaging
  - Electrocardiography
- Must add incremental information about risk to conventional risk factors

Biomarkers Add to Clinical Estimates of Risk

hsCRP and the Framingham Risk Score

NATIONAL CHOLESTEROL EDUCATION PROGRAM
Third Report of the Expert Panel on
Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

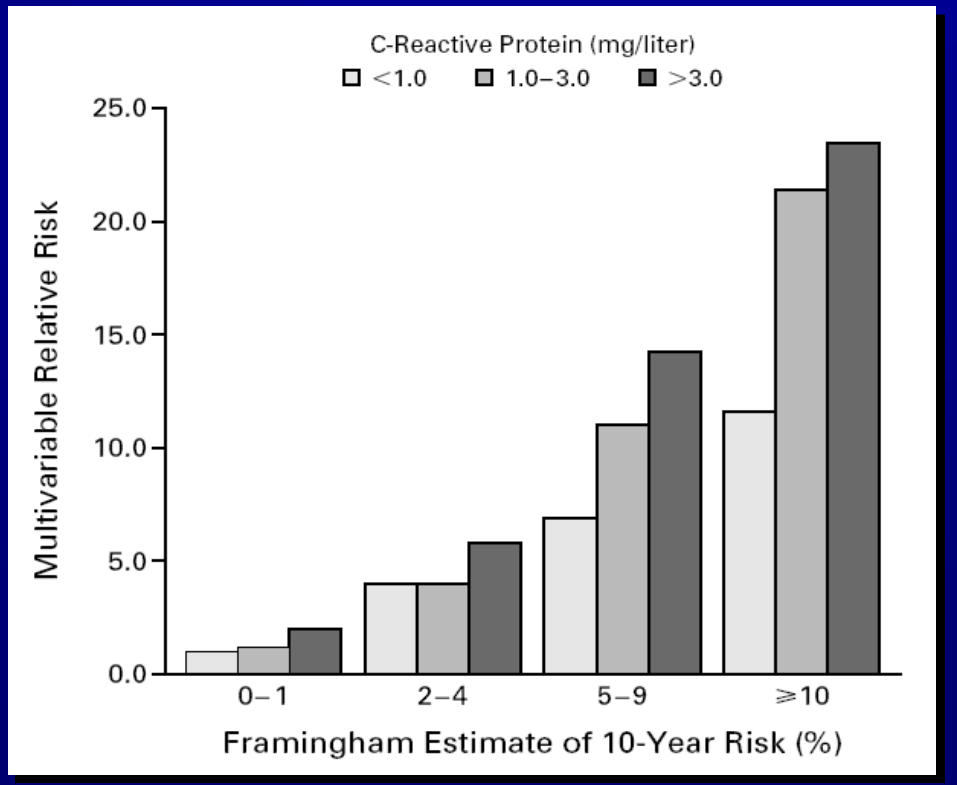
Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

The risk assessment tool below uses recent data from the Framingham Heart Study to estimate 10-year risk for "hard" coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes. Use the calculator below to estimate 10-year risk.

Age:	54 years
Gender:	X Female ○ Male
Total Cholesterol:	154 mg/dL
HDL Cholesterol:	84 mg/dL
Smoker:	X No ○ Yes
Systolic Blood Pressure:	136 mm/Hg
Currently on any medication to treat high blood pressure.	○ No X Yes

Calculate 10-Year Risk

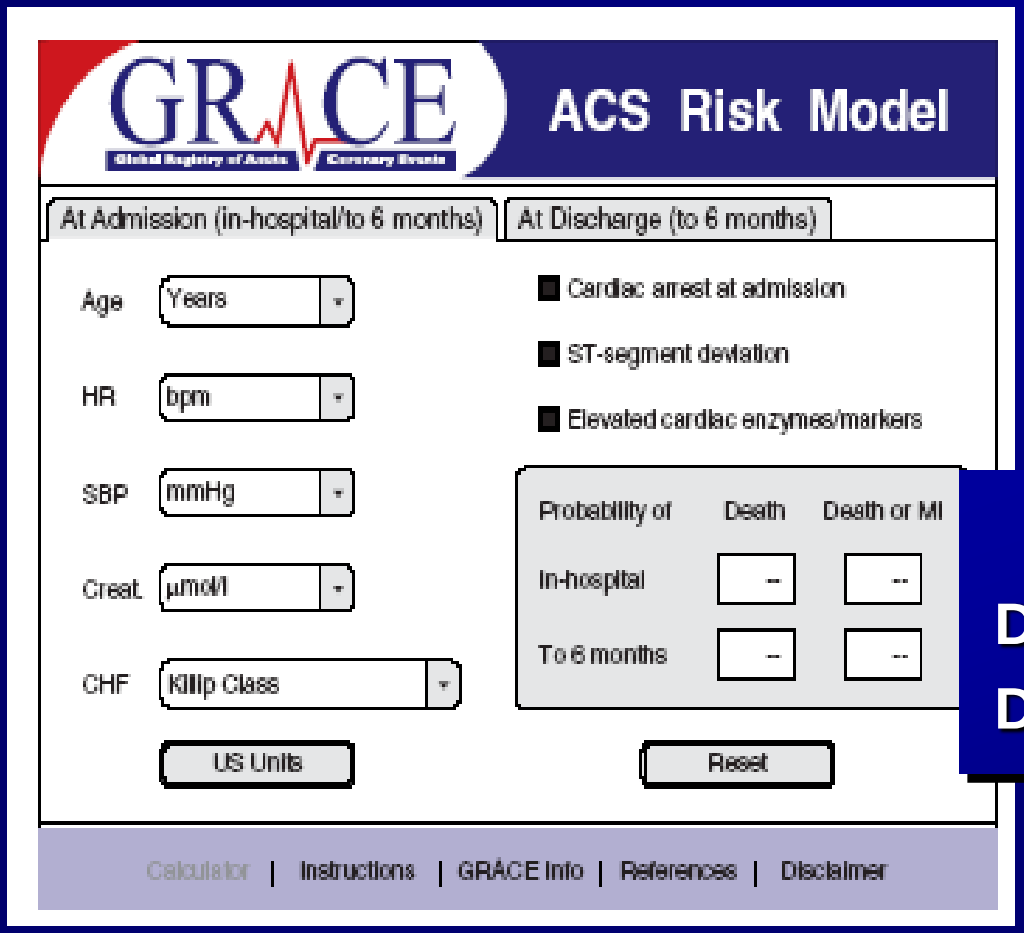
< 1%



Ridker, et al. NEJM 2002

How Can Biomarkers Help?

Secondary Risk After Heart Attack



GRACE risk score

C-index = 0.84

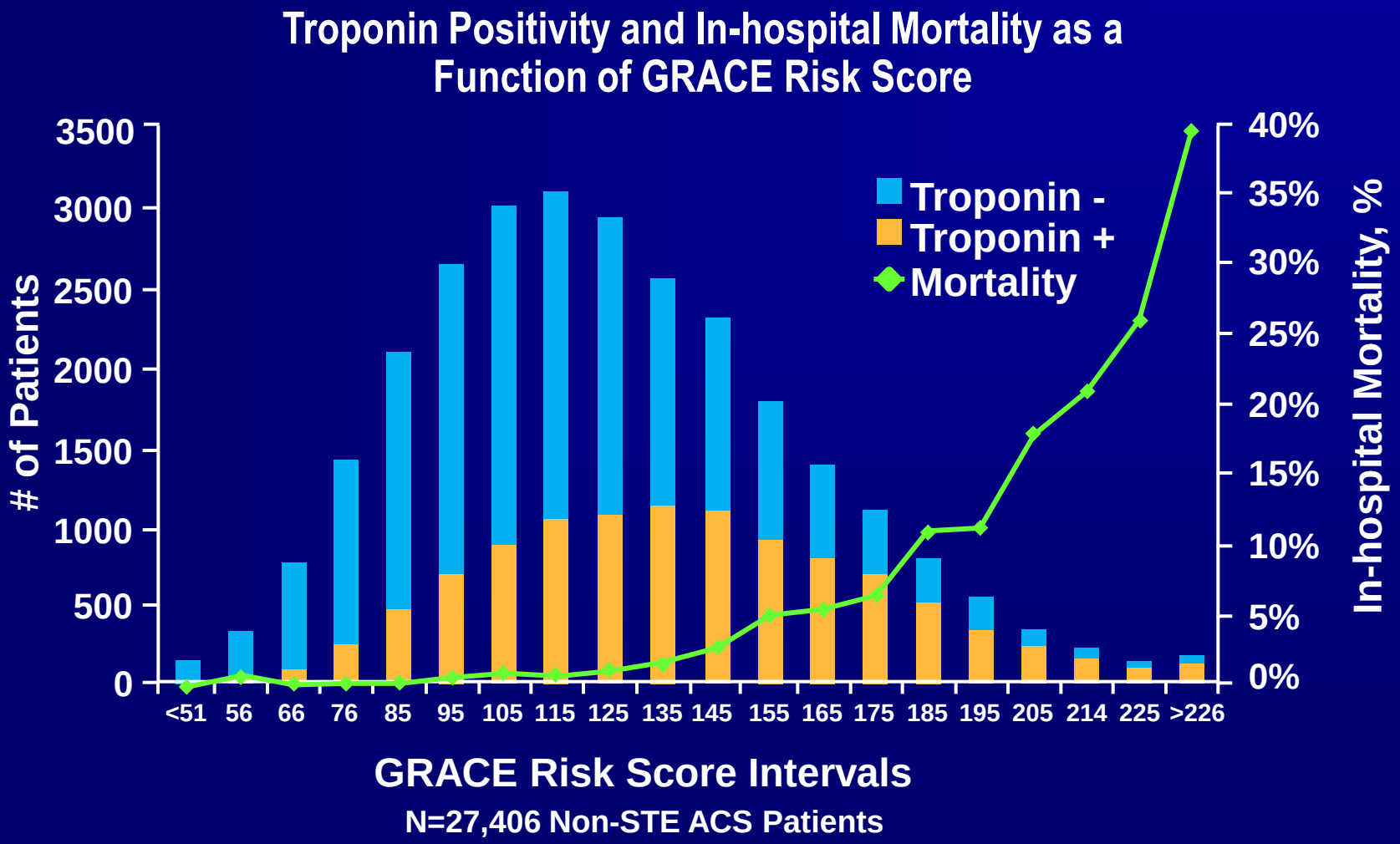
	In-hosp	6 mo
Death	**20%**	**30%**
Death/MI	**30%**	**50%**

www.statcoder.com/grace.htm

Granger et al *Archives Int Med* 2003

Short-term Risk Stratification Post-ACS

Troponin Alone is Not Enough



Steg, Fitzgerald, Fox, AJM 2009

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

David C. Goff, Jr, Donald M. Lloyd-Jones, Glen Bennett, Sean Coady, Ralph B. D'Agostino, Sr, Raymond Gibbons, Philip Greenland, Daniel T. Lackland, Daniel Levy, Christopher J. O'Donnell, Jennifer Robinson, J. Sanford Schwartz, Susan T. Shero, Sidney C. Smith, Jr, Paul Sorlie, Neil J. Stone and Peter W.F. Wilson

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Goals of the "New Risk Model"

- **Useful in practice**
  - Derived from information readily available in primary practice
- **Numerous multivariable risk scores**
  - None tested in RCTs
  - Dated populations
- **Focus on absolute risk (rather than relative)**
  - Better predictor/assessment of risk

Goff DC, et al. Circulation 2013

Development of the "New Risk Model"

- State-of-the-art statistical methods to derive and internally validate the Pooled Cohort Equations
  - Sex-and race-specific estimates of 10-year risk for **hard** ASCVD (Death, MI, or **STROKE**)
    - African-American and Caucasian men and women ages 40 to 79 years
- Risk assessment equations include
  - Age
  - Total and HDL-cholesterol
  - Systolic BP (treated or untreated status)
  - Diabetes
  - Current smoking status

Goff DC, et al. Circulation 2013

Summary of the New Risk Model

Risk Score				Risk Factors/Covariates Included														Cardiovascular Disease Events								
																					Hard CVD including cardiac failure					
																					Hard ASCVD					
																					Hard CHD					
																			Total CHD							
																		Total CHD including revascularization								
Study Group	Study and Region	Data Source	Publication Year	Age	Sex	Total Chol	LDL-Chol	HDL-Chol	CRP	Systolic BP	BP Rx	Diabetes	HbA1c*	Smoking	Family Hx CVD†	Body Mass Index	Social	Region	Coronary Revasc	Angina Pectoris	Unstable Angina	Myocardial Infarct	CHD Death	Stroke	Stroke Death	Cardiac Failure	TIA
Pooled Cohort (current)	CARDIA, Framingham, ARIC, CHS,USA	EAF, EAM AAF, AAM		x	x	x		X		x	x	x		x								X	x	x	x		

- Derived from more ethnically diverse populations
  - ARIC, Framingham (original and offspring), CHS and CARDIA
- Uses hard cardiac endpoints
  - CHD death, MI, stroke
- C-index 0.713 (AA men) to 0.818 in AA women
- Calibration lowest in white men; best in AA women

Goff DC, et al. Circulation 2013

Other Risk Models

Risk Score				Risk Factors/Covariates Included														Cardiovascular Disease Events								
																					Hard CVD including cardiac failure							
																					Hard ASCVD						
																					Hard CHD						
																			Total CHD							
																		Total CHD including revascularization								
Study Group	Study and Region	Data Source	Publication Year	Age	Sex	Total Chol	LDL-Chol	HDL-Chol	CRP	Systolic BP	BP Rx	Diabetes	HbA1c*	Smoking	Family Hx CVD†	Body Mass Index	Social	Region	Coronary Revasc	Angina Pectoris	Unstable Angina	Myocardial Infarct	CHD Death	Stroke	Stroke Death	Cardiac Failure	TIA
Framingham CHD (56)	Framingham MA, USA	EAF, EAM	1998	x	x	x	x	X		x		x		x						x	x	X	x				
ATP III (25)	Framingham MA, USA	EAF, EAM	2001	x	x	x		X		x	x			x								X	x				
Framingham Global (57)	Framingham MA, USA	EAF, EAM	2008	x	x	x		X		x	x	x		x								X	x	x	x	x	
PROCAM (58)	Muenster, Germany	EM	2002	x			x	X		x		x		x	x							X	x				
QRISK (59)	QRESEARCH, United Kingdom	EF, EM	2007	x	x	x		X		x	x			x	x	x	x‡	x	x	x	x	X	x	x	x		x
Reynolds Men (60)	Phys Health Study USA	EAF	2008	x		x		X	x	x				x	x				x			X	x	x	x		
Reynolds Women (61)	Women's Health Study USA	EAM	2007	x		x		X	x	x			x	x	x				x			X	x	x	x		
EUROSCORE (62)	12 cohorts Europe	EF, EM	2003	x	x	x		X		x				x				x					x		x		

Goff DC, et al. Circulation 2013

Risk Assessment Recommendations
Conventional Risk Factors

- Class 1, LOE B

Table 4. Summary of Recommendations for Risk Assessment

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
1. The race- and sex-specific Pooled Cohort Equations* to predict 10-year risk for a first hard ASCVD event should be used in nonHispanic African Americans and nonHispanic Whites, 40 to 79 years of age.	B (Moderate)	N/A	I	B (4-8)

- Limited evidence in other populations (Asian, Hispanic…non-US!)
  - May overestimate 10-yr risk in Asian and Hispanic Americans
  - May underestimate 10-yr risk in American Indians

2. Use of the sex-specific Pooled Cohort Equations for nonHispanic Whites may be considered when estimating risk in patients from populations other than African Americans and nonHispanic Whites.	E (Expert Opinion)	Appendix 2 CQ2/ES1	IIb	C

Goff DC, et al. Circulation 2013

Adding Biomarkers to Conventional Risks

- Biomarkers must contribute incremental information to conventional risk factors

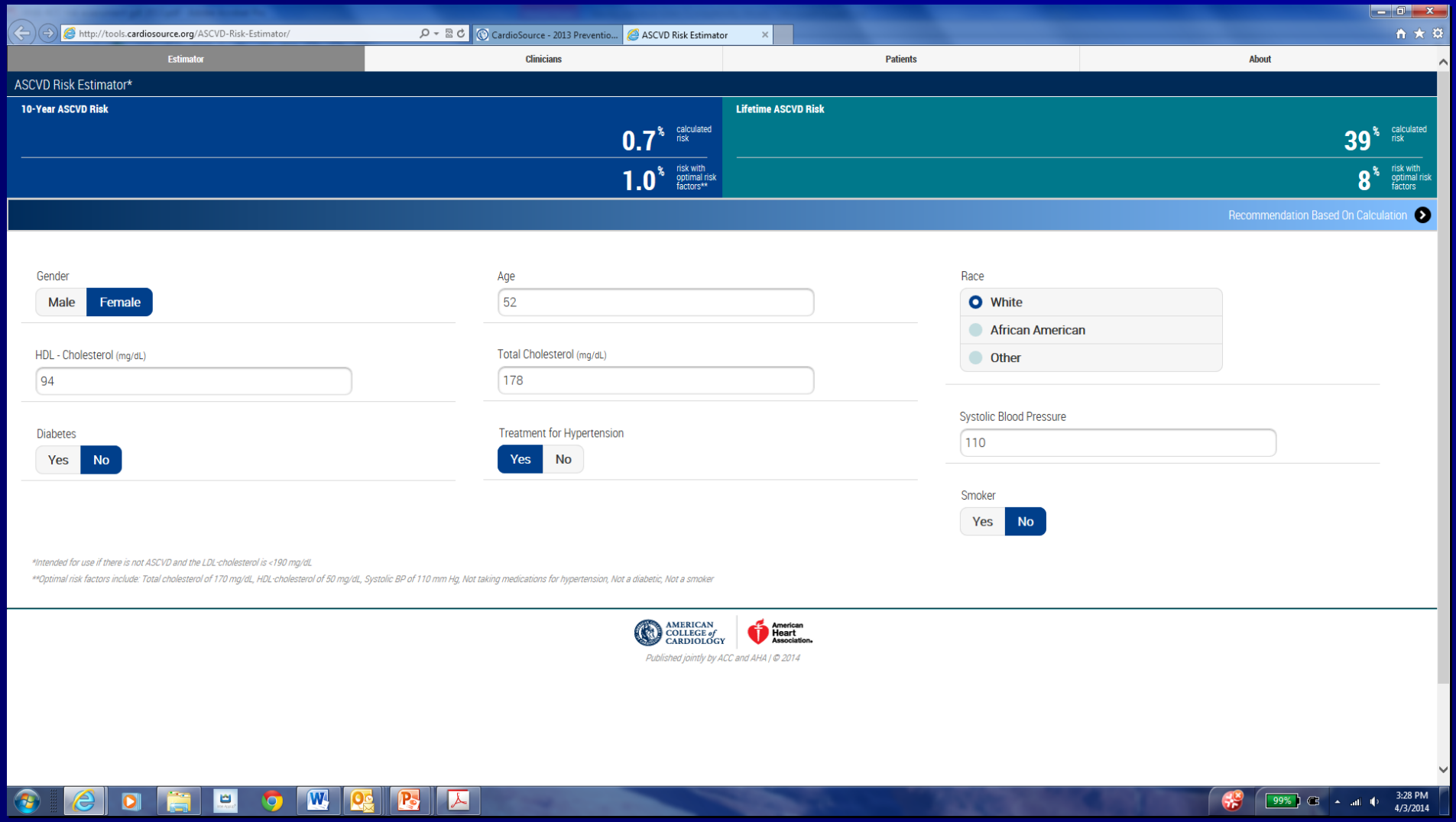
Table 4. Summary of Recommendations for Risk Assessment

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
3. If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of 1 or more of the following—family history, hs-CRP, CAC score, or ABI—may be considered to inform treatment decision making.	E (Expert Opinion)	Appendix 1	IIb†	B (9-17)
4. The contribution to risk assessment for a first ASCVD event using ApoB, CKD, albuminuria, or cardiorespiratory fitness is uncertain at present.	N (No Recommendation For or Against)	Appendix 1	N/A	N/A
5. CIMT is not recommended for routine measurement in clinical practice for risk assessment for a first ASCVD event.	N (No Recommendation For or Against)	Appendix 1	III: No Benefit†	B (12,16,18)

Goff DC, et al. Circulation 2013

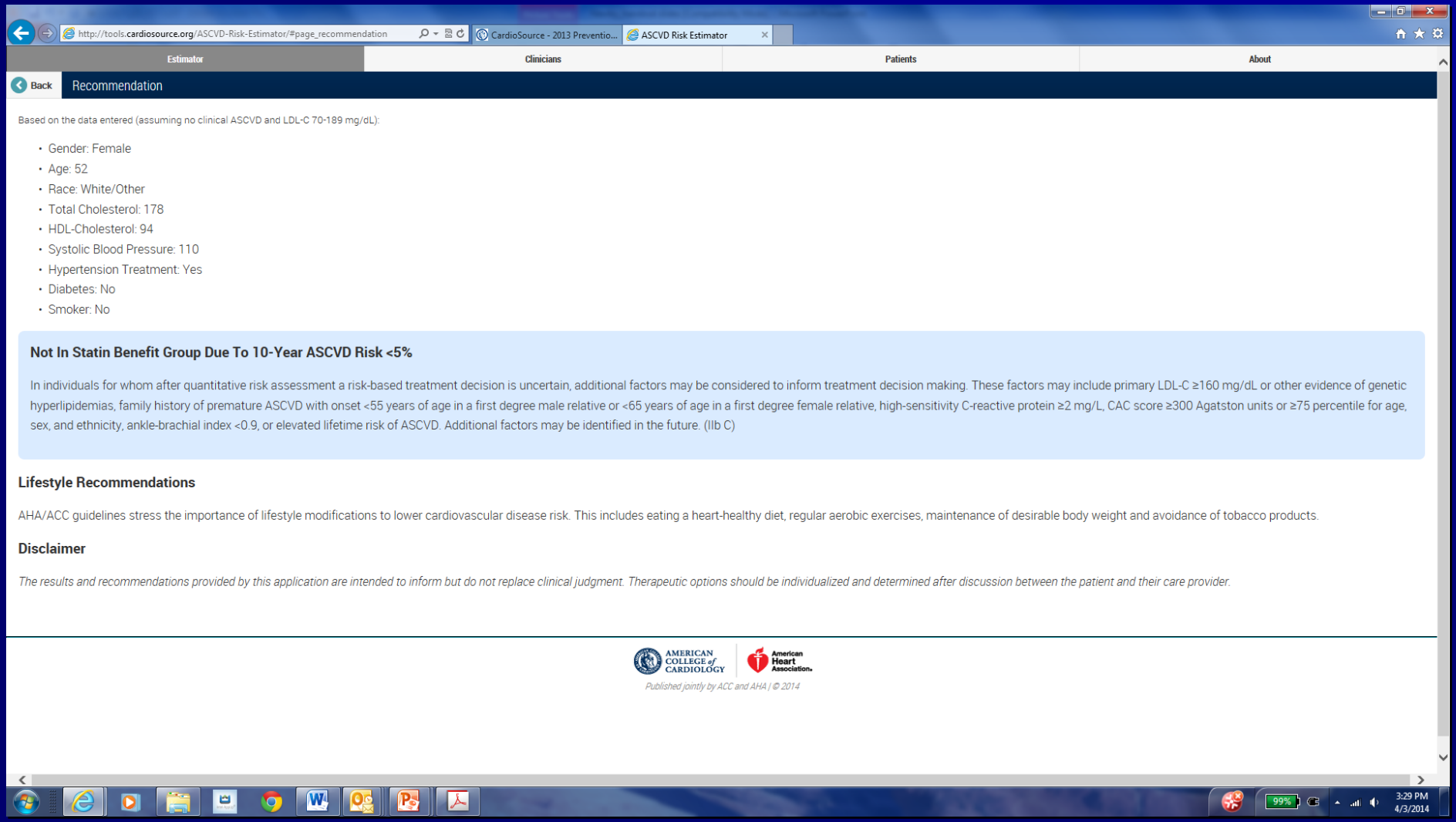
The ACC/AHA Risk Assessment Gdl Calculator

A Hypothetical Patient



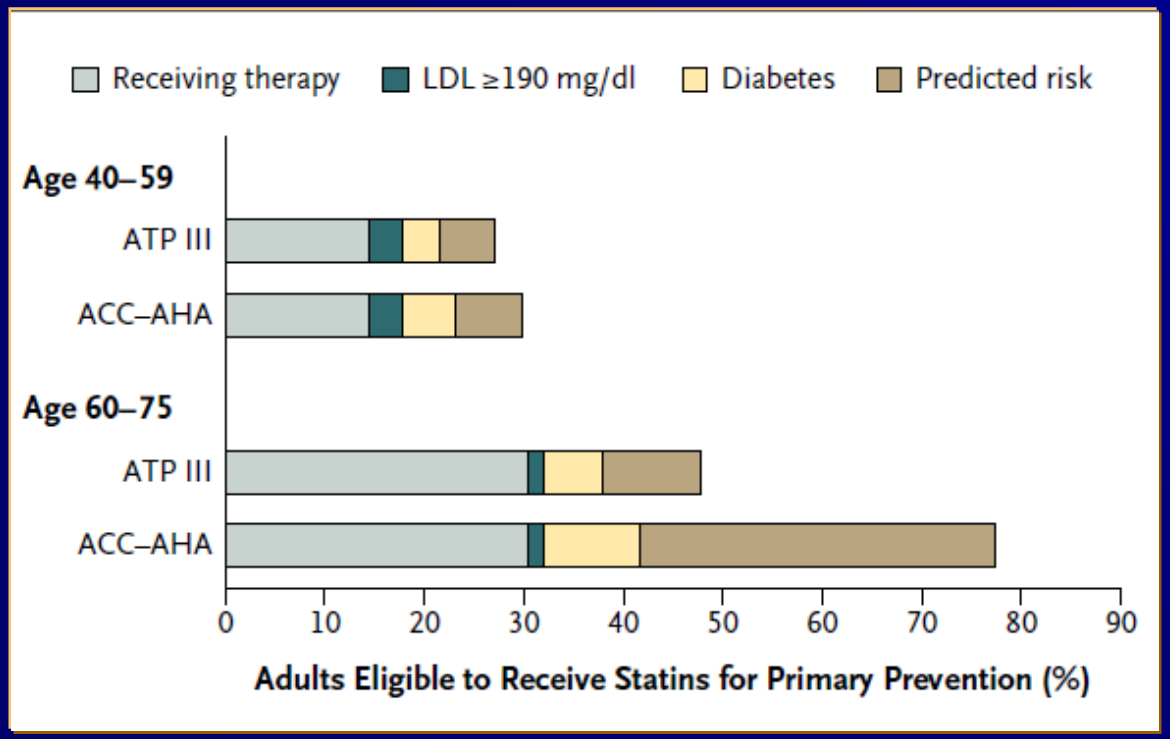
http://tools.cardiosource.org/ASCVD-Risk-Estimator/#page_recommendation

A Hypothetical Patient



http://tools.cardiosource.org/ASCVD-Risk-Estimator/#page_recommendation

What Does This Mean for Statin Treatment?



Pencina MJ, et al. N Engl J Med 2014

- FRS and Pooled Cohort Model identify similar percentages of new individuals eligible to receive statin therapy (19.7% and 24.0%, respectively)
- Increase sensitivity for CV events among eligible by 16.8%, but decrease specificity by 9.2%
- Potentially prevent additional 475,000 CV events over 10 yrs in incremental 1.9 mil Rxd

What is on the Horizon for Biomarkers as Adjuncts to Conventional Risk Assessment?

- Potential uses of hsTn as an adjunct to short and long term risk stratification in populations
  - Select high risk individuals for treatment or trials
  - Monitor treatment
    - Chronic CAD
    - Hypertension
    - Transplant

Prevalence of Detectable cTn and cTn >99th Percentile in Community Population

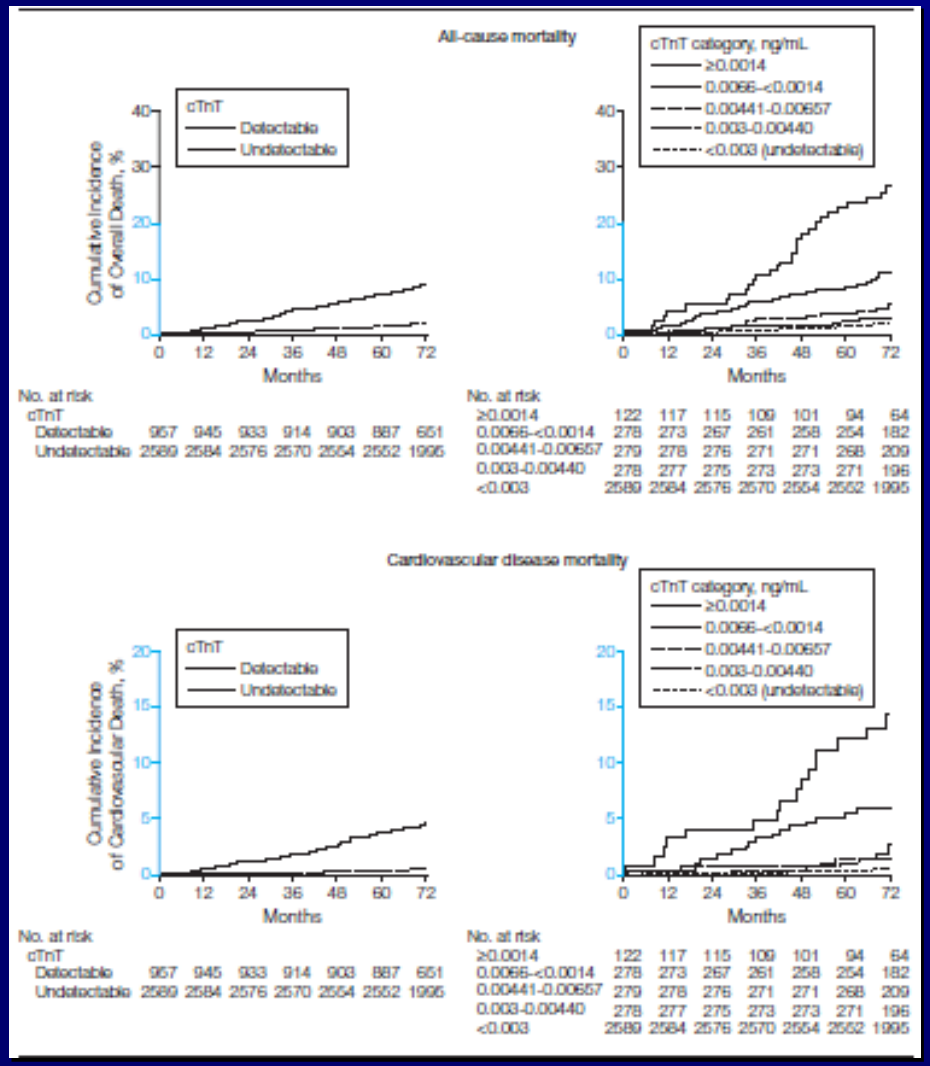
Group	Sample Size, No.	cTnT Level, ng/mL ≥0.003 No. (%)	≥0.003 Sample Weight–Adjusted Prevalence, % (95% CI)	≥0.014 No. (%)	≥0.014 Sample Weight–Adjusted Prevalence, % (95% CI)
Overall population	3546	957 (27.0)	25.0 (22.7-27.4)	122 (3.4)	2.0 (1.5-2.6)
Restricted population					
Without CHD	3428	891 (26.0)	24.2 (21.8-26.5)	103 (3.0)	1.8 (1.2-2.4)
Without cardiovascular disease	3277	813 (24.8)	23.7 (21.3-26.1)	82 (2.5)	1.9 (1.0-2.0)
Without cardiovascular disease or CKD[a]	3222	773 (24.0)	23.1 (20.7-25.5)	65 (2.3)	1.2 (0.8-1.7)
Without cardiovascular disease, CKD, or subclinical heart disease	2554	510 (20.0)	19.3 (16.8-21.8)	43 (1.7)	1.1 (0.6-1.7)
Without cardiovascular disease, CKD, subclinical heart disease, diabetes, or hypertension[b]	1854	292 (15.7)	16.2 (13.3-19.1)	16 (0.9)	0.6 (0.1-1.0)
Age, y[c]					
30-<40	1156	172 (14.9)	14.0 (11.2-16.9)	20 (1.7)	1.0 (0.4-1.7)
40-<50	1152	279 (24.2)	22.1 (18.1-26.2)	24 (2.1)	0.8 (0.3-1.3)
50-<60	846	343 (40.5)	37.4 (32.4-42.3)	56 (6.6)	4.6 (2.6-6.6)
60-65	247	138 (55.9)	57.6 (47.0-68.2)	22 (8.9)	5.2 (2.2-8.2)
Sex[d]					
Men	1565	670 (42.8)	37.1 (33.3-41.0)	85 (5.4)	2.8 (1.9-3.7)
Women	1981	287 (14.5)	12.9 (10.6-15.2)	37 (1.9)	1.3 (0.6-2.0)
Self-reported race/ethnicity[e]					
Black	1628	599 (32.8)	34.4 (30.6-38.3)	94 (5.1)	4.7 (3.2-6.3)
White	1042	246 (23.8)	25.4 (21.8-29.0)	21 (2.0)	1.8 (0.9-2.7)
Hispanic	601	101 (16.8)	19.0 (14.5-23.5)	7 (1.2)	0.7 (0.1-1.3)
Other	75	9 (12.0)	8.7 (2.0-15.5)	0	0

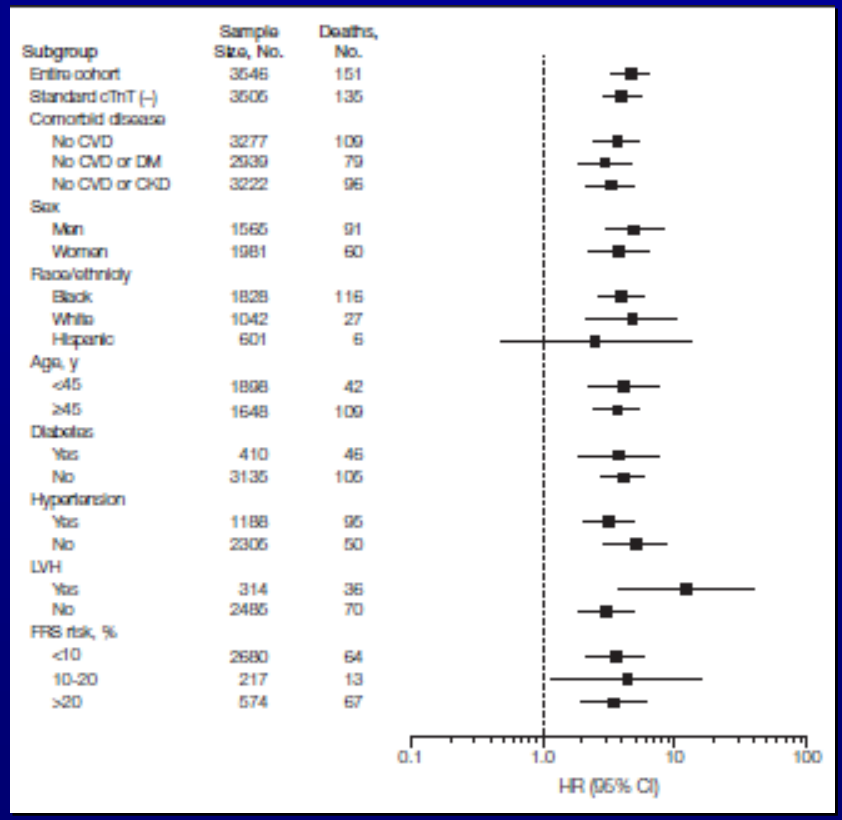
Dallas Heart Study

- Multiethnic, population based cohort Dallas County
- N=6101 (n=3546 with cTnT levels)
- All assayed with hs-cTnT assay (Roche Diagnostics; LOD 0.003 ng/mL; 99th percentile 0.014 ng/mL)

de Lemos JA, et al. JAMA 2010

Mortality According to Troponin Levels with High Sensitivity Assay





de Lemos JA, et al. JAMA 2010

High Sensitivity Troponin Assays in Older Adults

Cardiovascular Health Study

N=4221

Age >65 at enrollment; 2-3 years follow-up

HS cTnT (Roche Diag: LOD 0.003 ng/mL; 99th perc. 0.014 ng/mL)

66.2% of subjects had baseline detectable cTn

	cTnT Concentration, pg/mL				
	<3.00 (n = 1427)	3.00-5.44 (n = 697)	5.45-8.16 (n = 700)	8.17-12.94 (n = 697)	>12.94 (n = 700)
Heart failure	(n = 311)	(n = 180)	(n = 235)	(n = 237)	(n = 316)
Incidence rate (95% CI), per 100 person-years	1.6 (1.4-1.8)	2.1 (1.8-2.4)	3.0 (2.6-3.4)	3.4 (3.0-3.8)	6.4 (5.8-7.2)
Hazard ratio (95% CI)					
Unadjusted	1 [Reference]	1.33 (1.11-1.60)	1.96 (1.65-2.31)	2.27 (1.91-2.69)	4.83 (4.12-5.66)
Adjusted for demographic factors[a]	1 [Reference]	1.21 (1.01-1.46)	1.71 (1.44-2.03)	1.79 (1.50-2.14)	3.52 (2.95-4.21)
Adjusted for demographic and traditional risk factors[b]	1 [Reference]	1.13 (0.93-1.36)	1.41 (1.18-1.69)	1.47 (1.22-1.77)	2.48 (2.04-3.00)
Adjusted for demographic factors, traditional risk factors, and NT-proBNP and CRP	1 [Reference]	1.09 (0.90-1.32)	1.27 (1.06-1.52)	1.24 (1.03-1.50)	1.84 (1.51-2.24)
Cardiovascular death	(n = 222)	(n = 153)	(n = 204)	(n = 239)	(n = 285)
Incidence rate (95% CI), per 100 person-years	1.1 (0.9-1.2)	1.6 (1.4-1.9)	2.3 (2.0-2.7)	3.0 (2.6-3.4)	4.8 (4.3-5.4)
Hazard ratio (95% CI)					
Unadjusted	1 [Reference]	1.59 (1.30-1.96)	2.34 (1.93-2.82)	3.14 (2.61-3.77)	5.93 (4.96-7.08)
Adjusted for demographic factors[a]	1 [Reference]	1.41 (1.14-1.73)	1.92 (1.58-2.33)	2.24 (1.84-2.71)	3.80 (3.12-4.64)
Adjusted for demographic and traditional risk factors[c]	1 [Reference]	1.35 (1.10-1.67)	1.66 (1.36-2.02)	1.91 (1.57-2.33)	2.91 (2.37-3.58)
Adjusted for demographic factors, traditional risk factors, and NT-proBNP and CRP	1 [Reference]	1.30 (1.05-1.60)	1.45 (1.19-1.78)	1.58 (1.29-1.93)	2.10 (1.70-2.60)

deFilippi C, et al. JAMA 2010

Outcomes According to Changes in High-Sensitivity Troponin Levels

	All Participants With Baseline cTnT (n = 2918)		Participants With Detectable Baseline cTnT Only (n = 1797)		
	Undetectable at Follow-up (n = 1036)	Detectable at Follow-up (n = 1882)	>50% Increase (n = 393)	Change ≤50% (n = 1157)	>50% Decrease (n = 247)
Heart failure	(n = 182)	(n = 625)	(n = 155)	(n = 366)	(n = 56)
Incidence rate (95% CI), per 100 person-years	1.5 (1.3-1.7)	3.7 (3.5-4.0)	5.3 (4.5-6.2)	3.5 (3.1-3.8)	2.0 (1.5-2.6)
Hazard ratio (95% CI)					
Unadjusted[a]	1 [Reference]	2.06 (1.70-2.50)	1.73 (1.44-2.10)	1 [Reference]	0.57 (0.43-0.76)
Adjusted for demographic factors[b]	1 [Reference]	1.82 (1.50-2.21)	1.67 (1.38-2.02)	1 [Reference]	0.65 (0.49-0.86)
Adjusted for demographic and traditional risk factors[c]	1 [Reference]	1.70 (1.39-2.07)	1.61 (1.32-1.97)	1 [Reference]	0.73 (0.54-0.97)
Adjusted for demographic factors, traditional risk factors, and NT-proBNP and CRP	1 [Reference]	1.55 (1.26-1.90)	1.40 (1.14-1.71)	1 [Reference]	0.74 (0.55-1.00)
Cardiovascular death	(n = 142)	(n = 534)	(n = 140)	(n = 321)	(n = 48)
Incidence rate (95% CI), per 100 person-years	1.1 (0.9-1.3)	2.8 (2.6-3.1)	4.1 (3.5-4.8)	2.6 (2.4-3.0)	1.6 (1.2-2.1)
Hazard ratio (95% CI)					
Unadjusted[a]	1 [Reference]	1.94 (1.56-2.41)	1.79 (1.47-2.19)	1 [Reference]	0.57 (0.42-0.77)
Adjusted for demographic factors[b]	1 [Reference]	1.63 (1.31-2.04)	1.72 (1.40-2.11)	1 [Reference]	0.68 (0.50-0.93)
Adjusted for demographic and traditional risk factors[d]	1 [Reference]	1.57 (1.25-1.95)	1.65 (1.35-2.03)	1 [Reference]	0.71 (0.52-0.97)
Adjusted for demographic factors, traditional risk factors, and NT-proBNP and CRP	1 [Reference]	1.39 (1.12-1.74)	1.38 (1.11-1.71)	1 [Reference]	0.75 (0.55-1.02)

deFilippi C, et al. JAMA 2010