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Cardiovascular Disease Risk Prediction: Lessons for Arthritis

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Disclosures

- Dr. Lloyd-Jones has no relationships with industry/ relevant conflicts of interest to disclose
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  - NIH, AHA, CMMS

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Using Clinical Decision Rules in CVD Prevention

Clinical Decision Rules

- What do we use them for?
  - Diagnosis, prognosis, treatment decisions
- Why do we need them?
  - Signs and symptoms rarely pathognomonic
  - Risk factors (almost) never deterministic
  - Need prior probability for test/treat decisions (Bayes)
    - Test or treat all? None? Some?
  - Enrich the pool for cost-effective treatment
  - Patients and clinicians are very poor at estimating risk/probability and net benefit of therapy

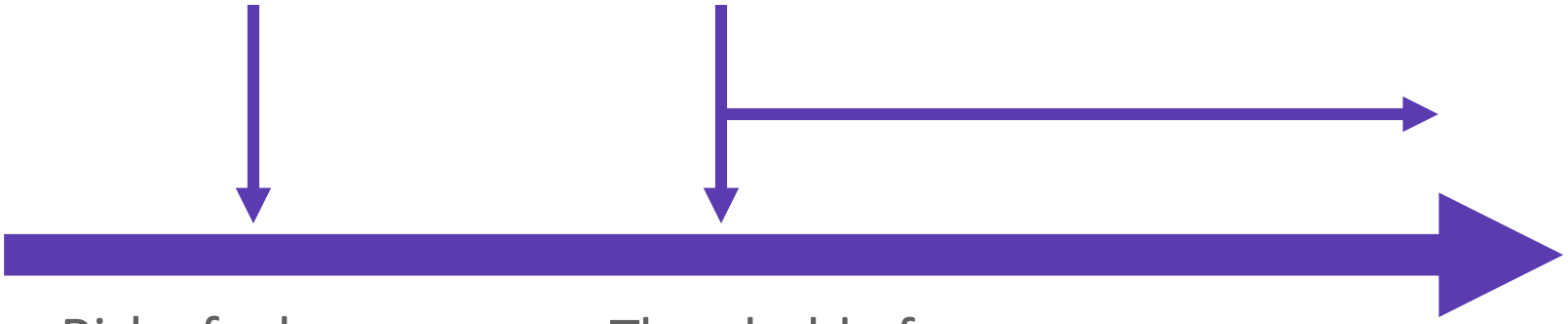
Treatment Thresholds

Finding net benefit

Where does your patient fall?

And how do you know?

Net harm | **Marginal benefit** | **Net benefit**



Risk of adverse Event from Rx

Threshold of treatment benefit

Risk of disease

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Why Do We Estimate Risk?

- Clinical/academic interest
  - Understand mechanisms of disease
  - Prognosis: assess comparative risks for different diseases or death
  - Identify risk factors/novel targets for therapy
  - Assess relative contributions of risk factors to disease incidence
  - Compare risks of disease with potential benefits and harms of therapies

Patients substantially overestimate and underestimate risk

- 1557 primary care patients asked to estimate risk on a continuous scale of 0% to 100%

Perceived 10-year risk compared to actual 10-year risk	Patients (%)

- Mean absolute differences between perceived and actual predicted 10-year risk were:
  - 22.9% (95% CI 21.8–24.0%) for MI
  - 24.6% (23.4–25.8%) for stroke

Physicians overestimate and underestimate risk

- 79 physicians at all levels at 3 university hospitals
- Surveyed re: 12 primary prevention scenarios
  - Overestimation (MD estimate >1.5x actual risk)
  - Underestimation (MD estimate <0.67x actual risk)
- Only 24% of physicians' risk estimates were accurate
  - Physicians overestimated absolute risk 32% to 92% of the time
  - Physicians made larger errors in patient scenarios involving patients with high total or LDL-c levels

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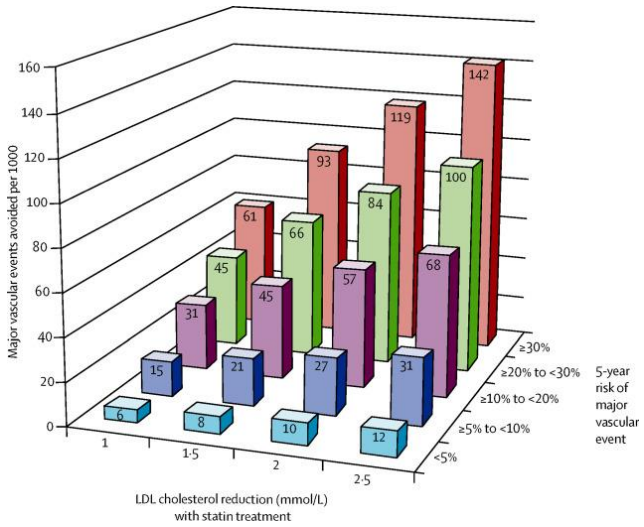
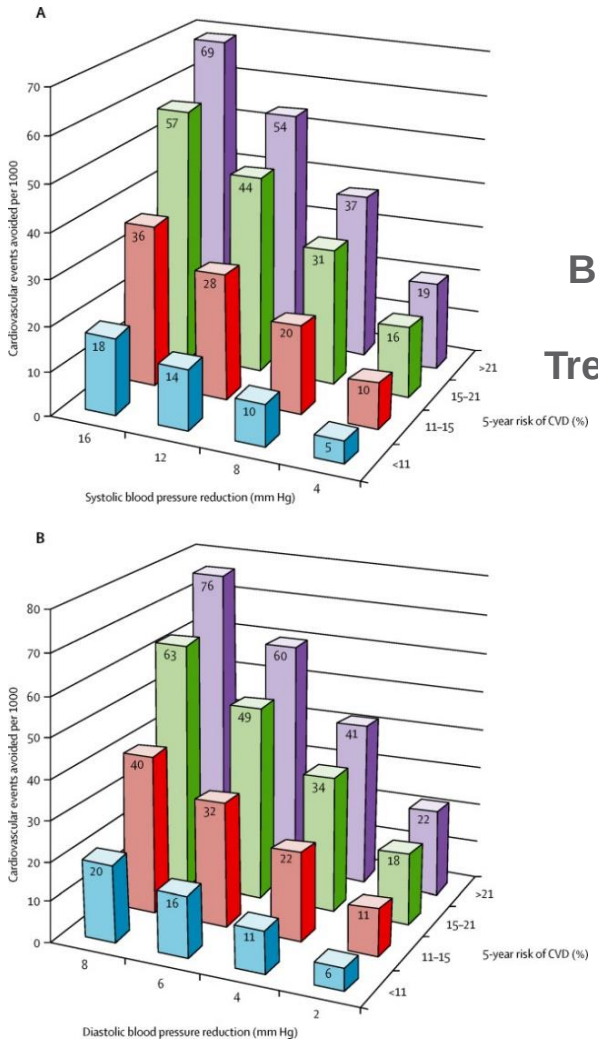
Why Do We Estimate Absolute Risk?

- Relative risk is poorly understood by clinicians and patients
  - Problem of the referent group
- Understand absolute risk for prognosis
- Improve communication and motivate lifestyle change/adherence to therapy
- Identify treatment-eligible individuals at sufficiently high risk to merit treatment and expect net cost-effective benefit
- Directly compare benefits/harms of therapy

Rationale for Absolute Risk Estimation

Cholesterol Treatment Trialists





Blood Pressure Lowering Treatment Trialists

- **Allows identification of patients at sufficient risk to merit treatment with higher likelihood of net individual and societal benefit**
- **Allows direct comparison of potential benefits and harms from drug therapy**

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CTT, Lancet 2012
BPLTTC, Lancet 2014
Lloyd-Jones et al., Circ and JACC 2019

Evidence Base for Risk Estimation

- Providing CVD risk score data had statistically significant but modest effects on:
  - Initiation/intensification of BP and cholesterol medications
  - Levels of CVD risk factors
  - Estimated 10-year CVD risk at follow-up
- Harm very unlikely
- Use of validated, quantitative risk assessment scores appears to be appropriate, safe, and moderately efficacious in helping to control risk factors … with the potential for additional value to improve decision-making.
- (Especially true if therapy is expensive - early statins, early PCSK9i)

Risk scoring for the primary prevention of cardiovascular disease (Review)

Karmali KN, Persell SD, Perel P, Lloyd-Jones DM, Berendsen MA, Huffman MD

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Karmali et al., Cochrane Reviews 2017
Lloyd-Jones et al., Circ and JACC 2019

What is Probability and How Do We Estimate It?

- Probability (likelihood) is a measure or estimation of how likely it is that something will happen or that a statement is true (Wikipedia)
- Most often, we return to $y = mx + b$

  y = outcome or diagnosis

  x = predictor variable(s)

  m = weight for each predictor variable

  b = intercept (underlying disease risk)
- Transform relative hazards/odds ratios into absolute probabilities

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How Do We Know if a Risk Score "Works"?

How Do We Measure the Performance of a Screening/Risk Prediction Test?

We should use:

- Sensitivity/specifity/predictive value
- Discrimination
  - Area under the ROC curve (AUC; C statistic)
  - Discrimination slope
- Calibration
  - Hosmer/Lemeshow and GND tests
- Informativeness criteria
  - AIC, BIC
- Likelihood ratios (LR+ and LR-)
- Brier score
- Reclassification (NRI, IDI)

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Example – Risk Prediction and Clinical Decision Making in Primary Prevention of ASCVD

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Geriatric Society, the American Society of Preventive Cardiology, and the Preventive Cardiovascular Nurses Association

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American Heart Association.

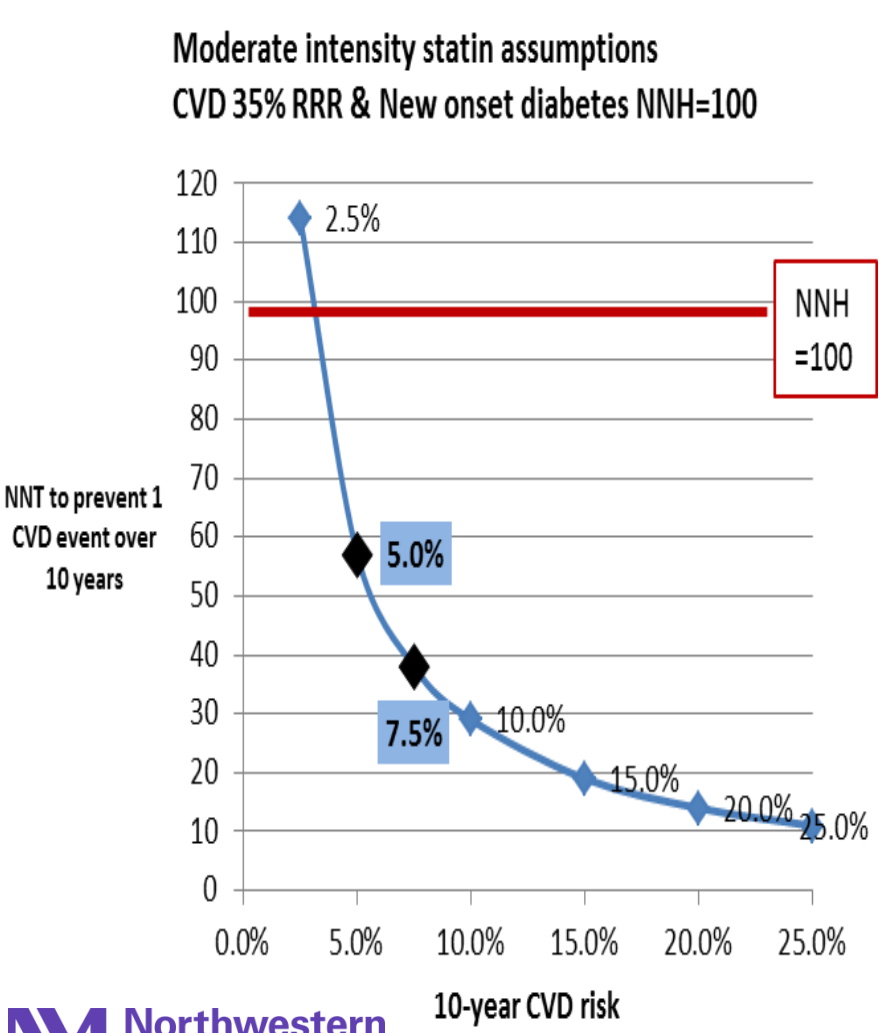
Current Paradigm for CVD Prevention

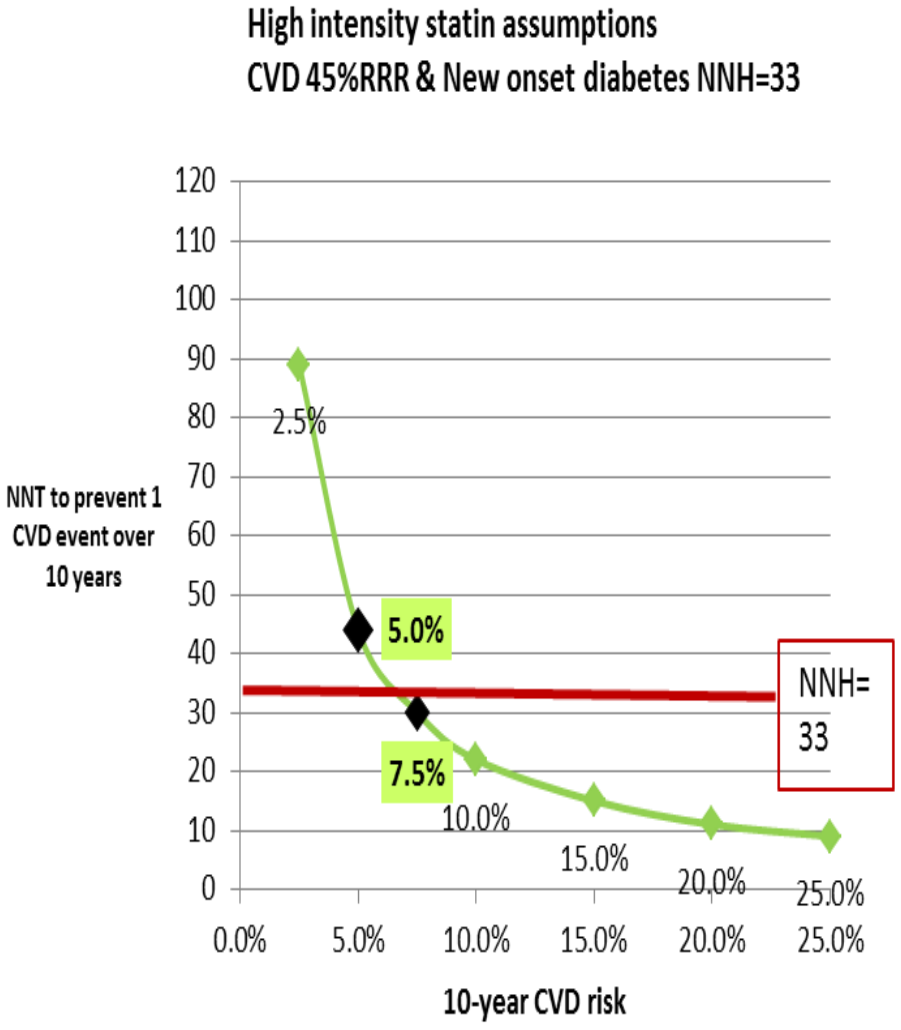
- "The intensity of prevention efforts should match the absolute risk of the patient"
  - Those at low risk should receive appropriate lifestyle counseling to remain so as long as possible
  - Those at high risk should alter lifestyle and receive early evidence-based drug therapy
  - Those at "intermediate risk" should be considered for further testing to further risk stratify for net benefit of drugs
- This latter implies sequential testing (Bayesian framework) which fits well with medical decision making

Scaling the Net Benefits

- Interventions with similar relative risk reductions across risk strata (like statins) provide the greatest absolute risk reduction in those with the highest pretreatment risk
- Thus, determination of absolute risk and expected absolute risk reduction is necessary to adequately assess the risk-benefit ratio of an intervention for an individual patient as well as for health policy
- And we should weigh the expected benefit against potential harms, to understand *net benefit*

What About Diabetes Risk with Statins?





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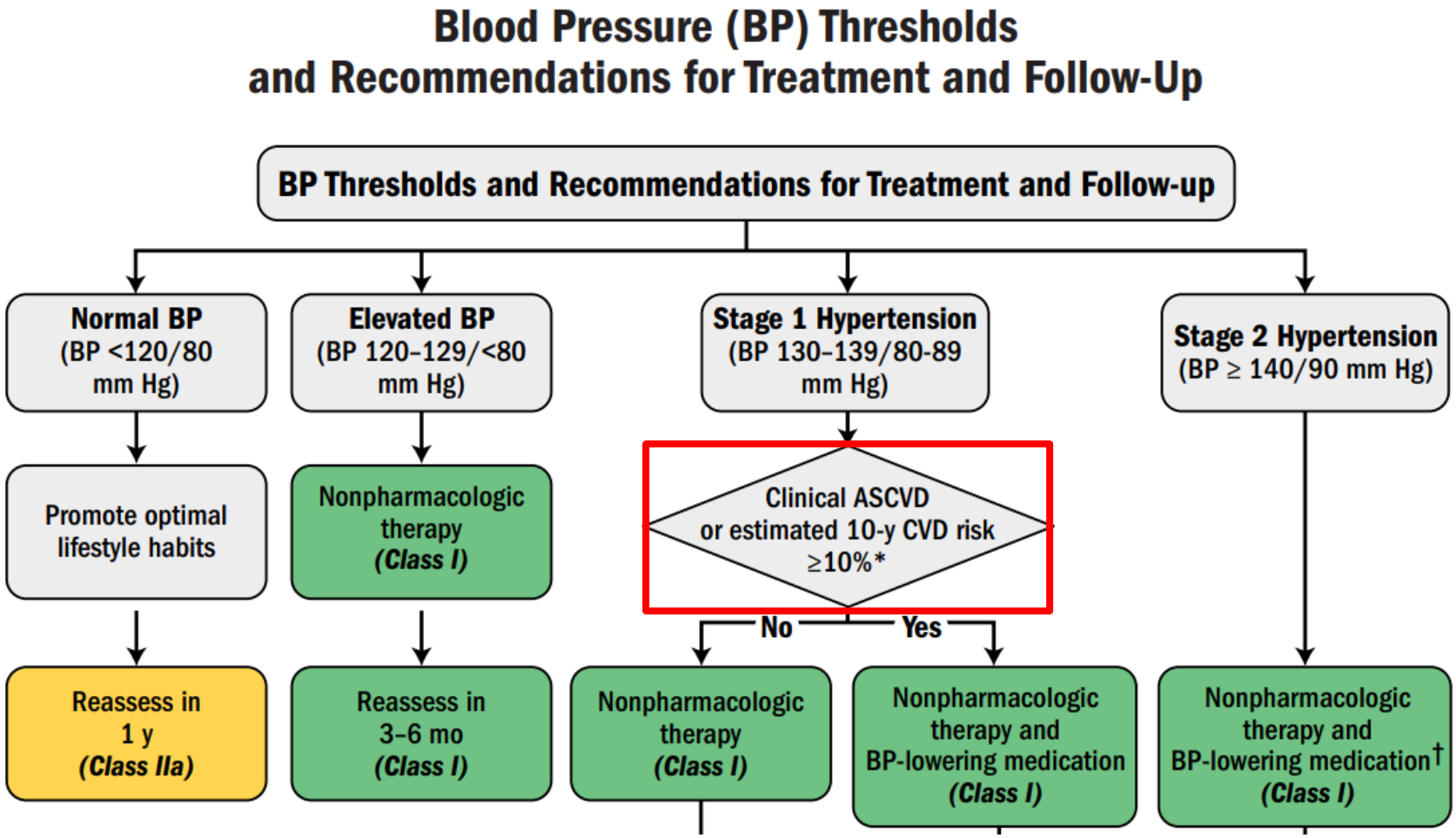
2017 ACC/AHA Hypertension Guidelines



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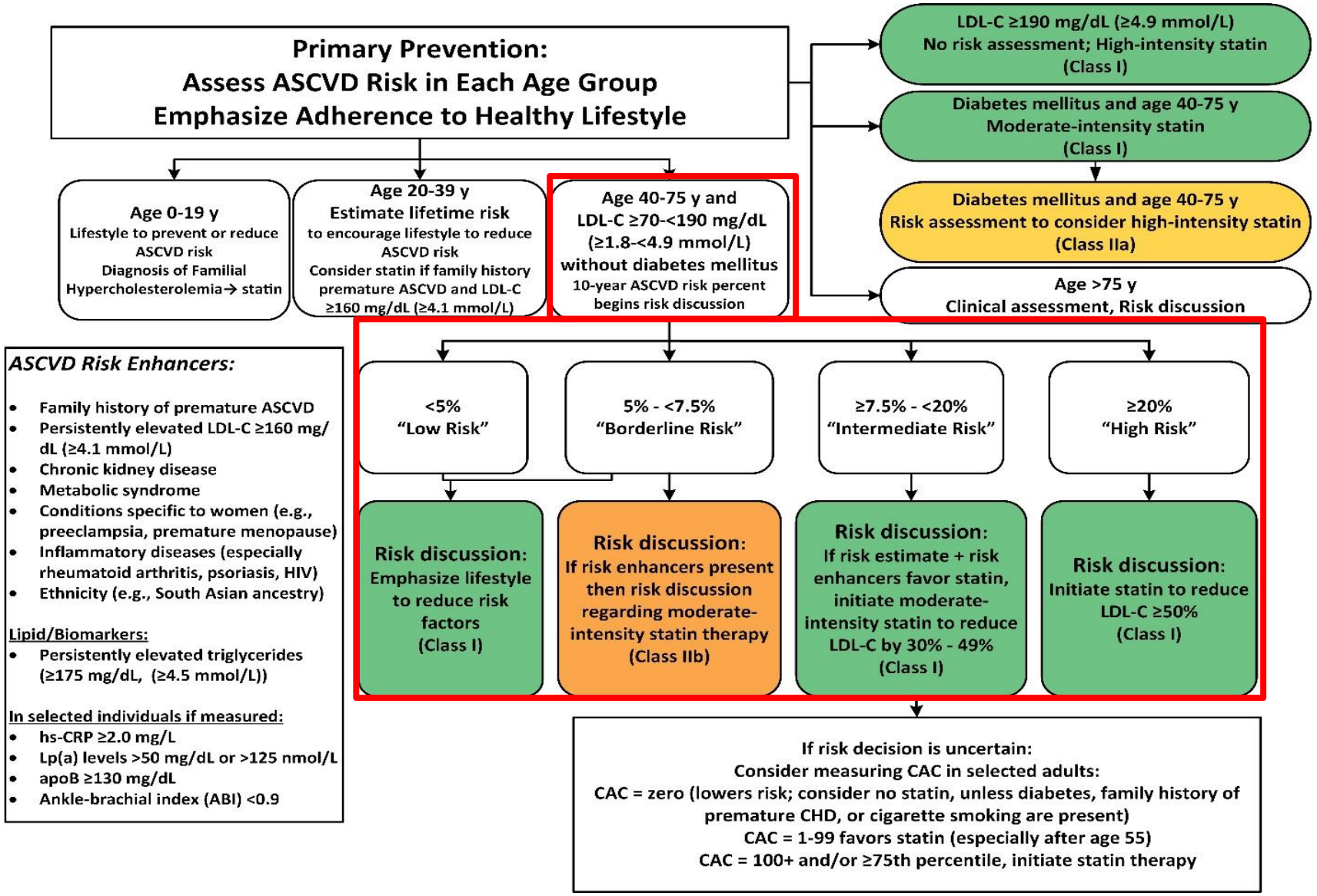
2018 AHA/ACC/Multi-Specialty Cholesterol Guidelines



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL.

PUBLISHED BY ELSEVIER

AHA/ACC SPECIAL REPORT

Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease

A Special Report From the American Heart Association and American College of Cardiology

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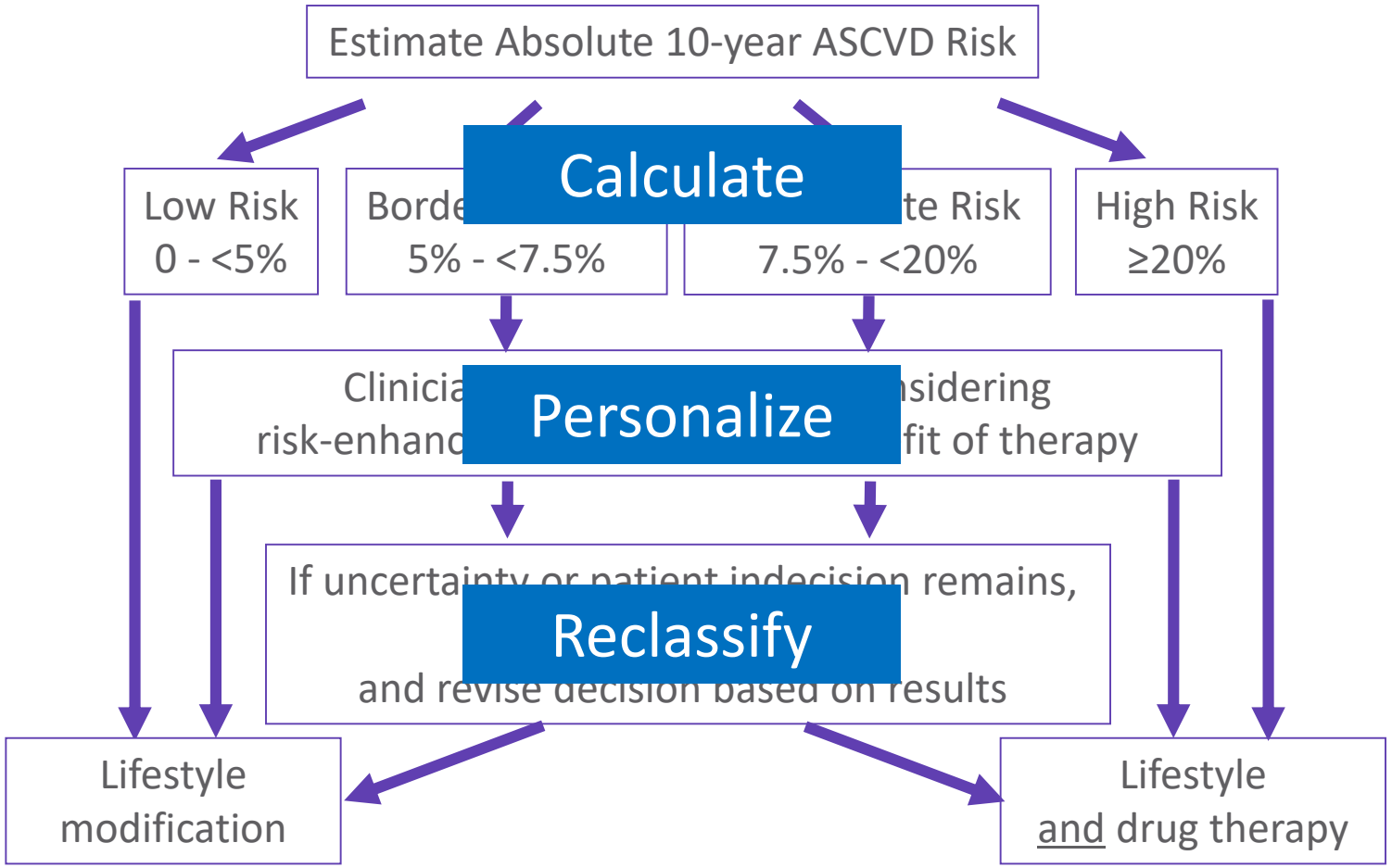
Lloyd-Jones et al. *Circulation* 2019; *JACC* 2019

Approach to Risk Assessment in 1º Prevention: CPR



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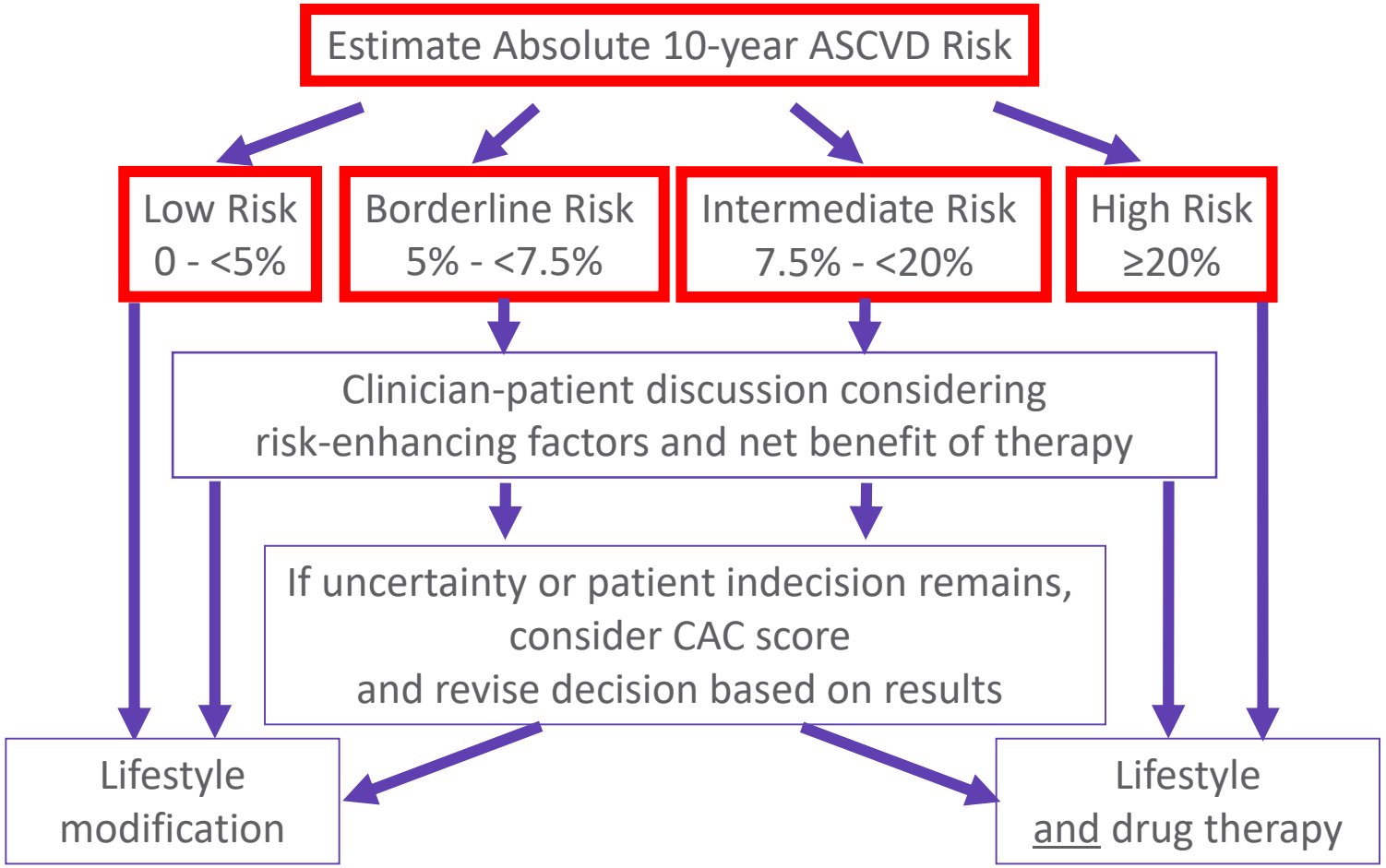
C = Calculate: Estimate 10-Year and Lifetime Risks



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C = Calculate: Tools for Risk Estimation

- Pooled Cohort Equations – App or Online (or EHR programmable)
- ACC ASCVD Risk Estimator Plus (online/app)
  - http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/
- AHA ASCVD Risk Calculator (online/app)
  - http://static.heart.org/riskcalc/app/index.html#!/baseline-risk

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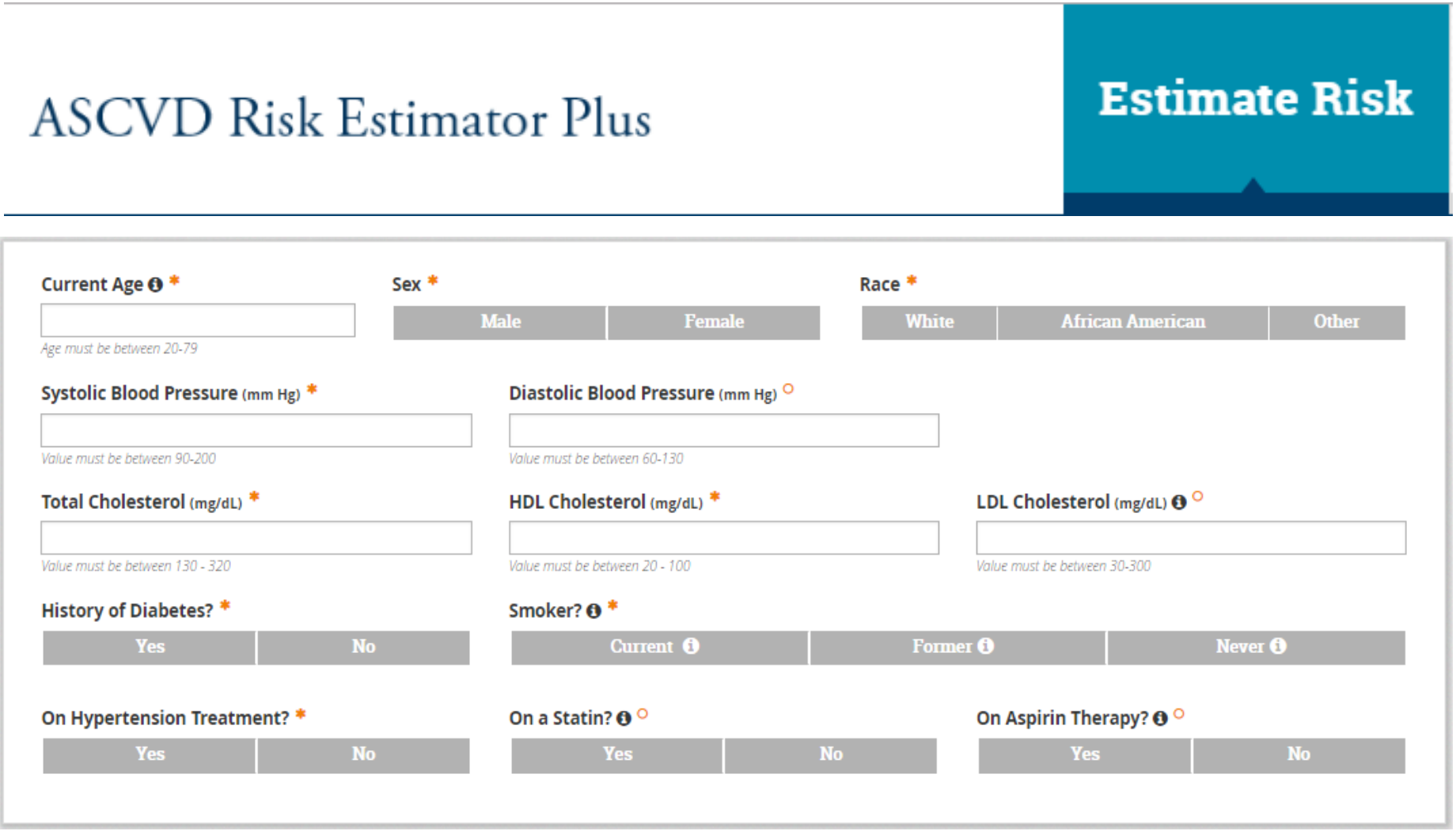
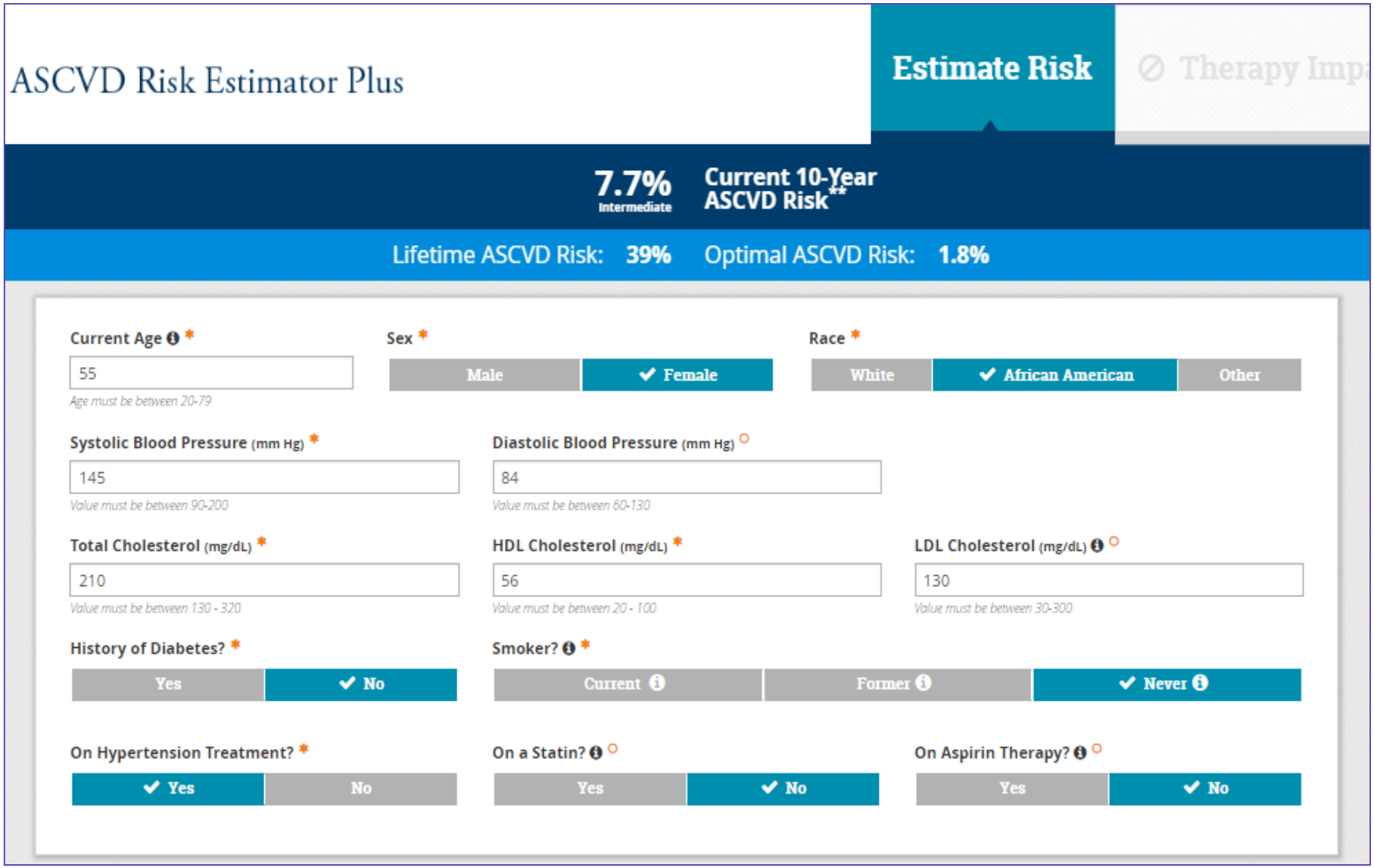
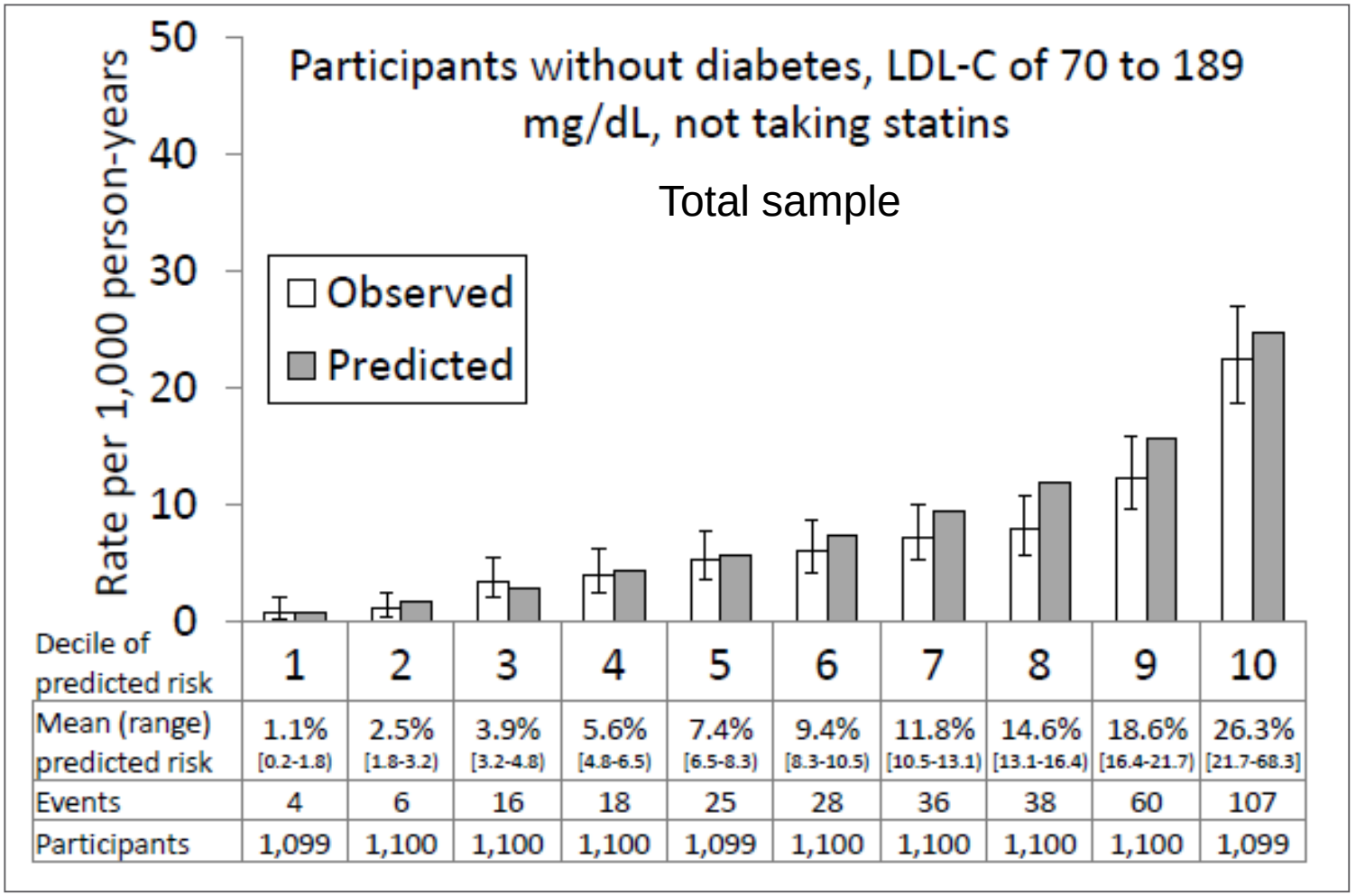
ASCVD Risk Estimator Plus



ASCVD Risk Estimator Plus



External Validation: REGARDS*



Decile of predicted risk	1	2	3	4	5	6	7	8	9	10
Mean (range) predicted risk	1.1% [0.2-1.8)	2.5% [1.8-3.2)	3.9% [3.2-4.8)	5.6% [4.8-6.5)	7.4% [6.5-8.3)	9.4% [8.3-10.5)	11.8% [10.5-13.1)	14.6% [13.1-16.4)	18.6% [16.4-21.7)	26.3% [21.7-68.3]
Events	4	6	16	18	25	28	36	38	60	107
Participants	1,099	1,100	1,100	1,100	1,099	1,100	1,100	1,100	1,100	1,099

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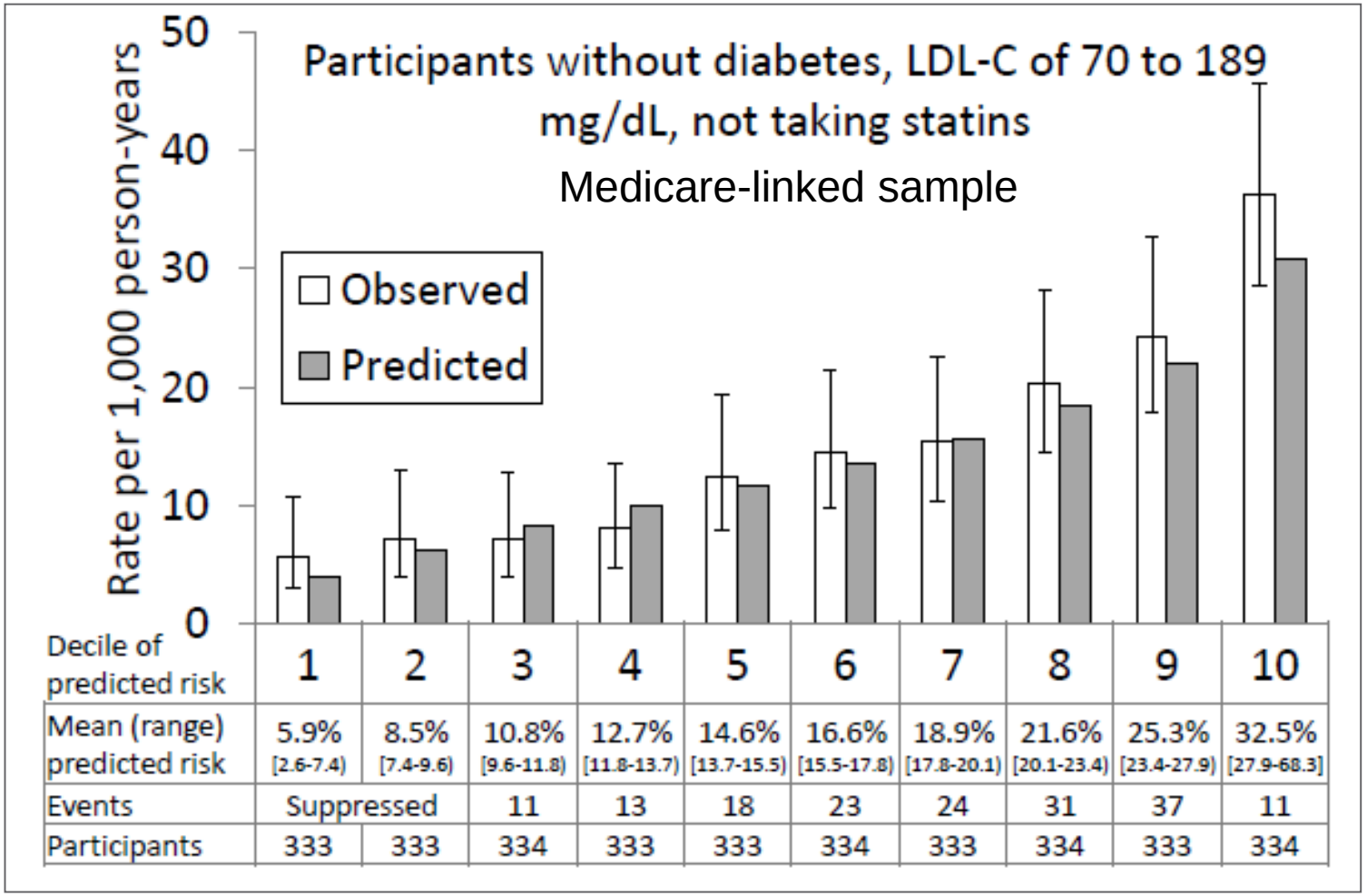
*5-year follow up
Muntner et al, JAMA 2014

External Validation: REGARDS*



Decile of predicted risk	1	2	3	4	5	6	7	8	9	10
Mean (range) predicted risk	5.9% [2.6-7.4]	8.5% [7.4-9.6]	10.8% [9.6-11.8]	12.7% [11.8-13.7]	14.6% [13.7-15.5]	16.6% [15.5-17.8]	18.9% [17.8-20.1]	21.6% [20.1-23.4]	25.3% [23.4-27.9]	32.5% [27.9-68.3]
Events	Suppressed		11	13	18	23	24	31	37	11
Participants	333	333	334	333	333	334	333	334	333	334

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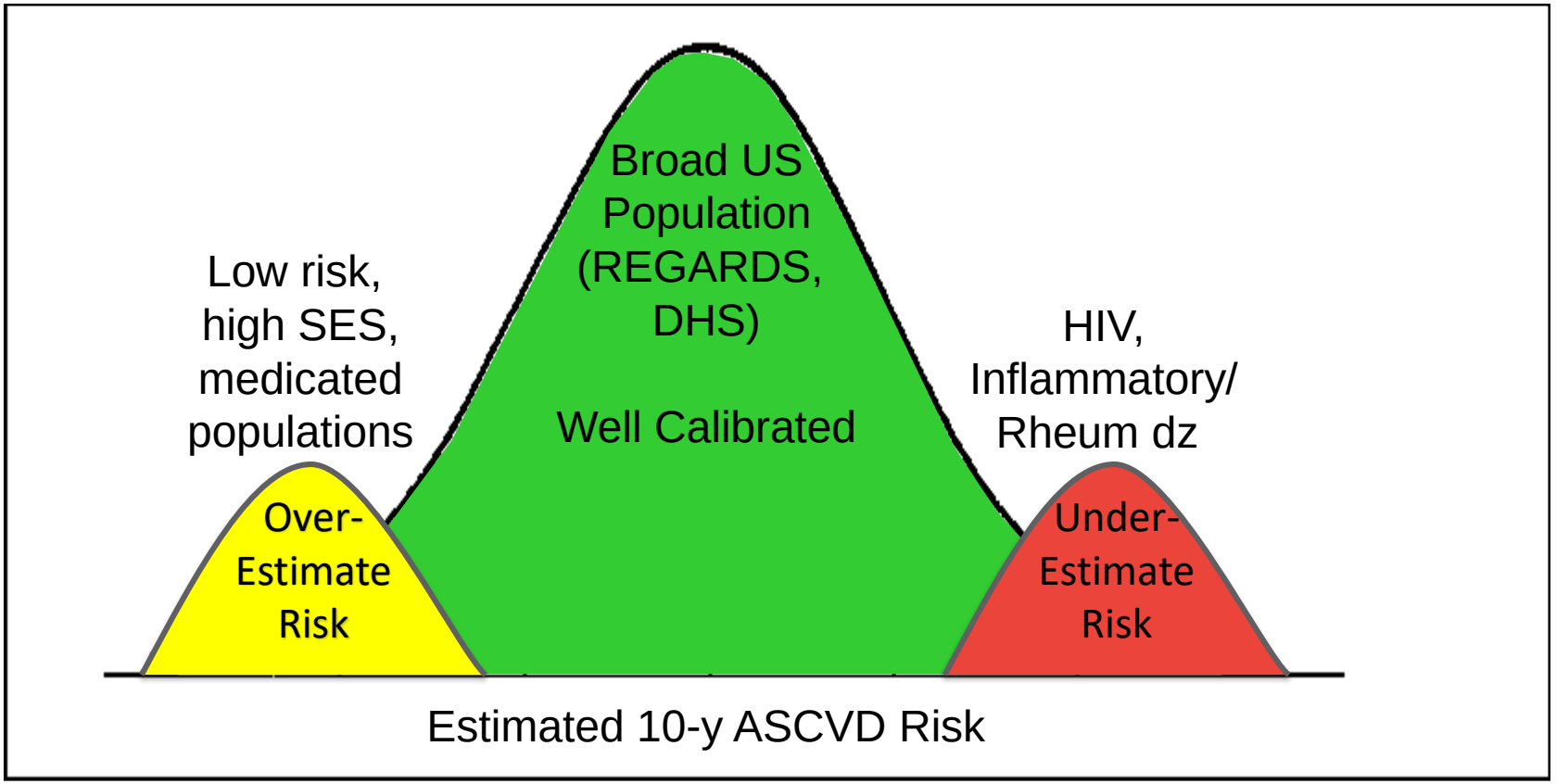
*5-year follow up
Muntner et al, JAMA 2014

Performance of Pooled Cohort Equations in Diverse Population Samples: Predictable



Patient-Clinician Discussion

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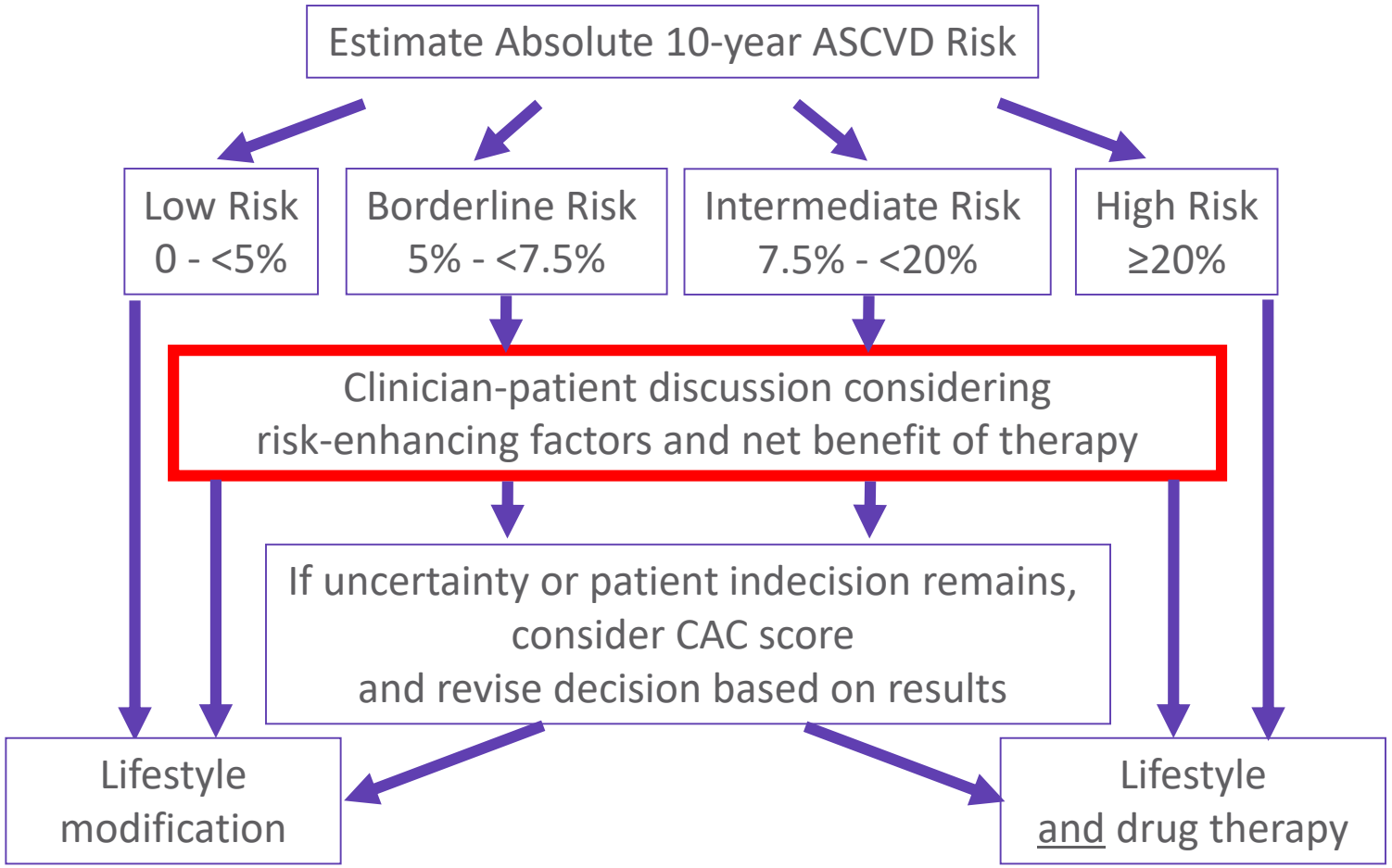
P = Personalize: Refine Risk for Individual Patients



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P = Personalize: Refine Risk for Individual Patients

Risk-Enhancing Factors for Clinician–Patient Risk Discussion

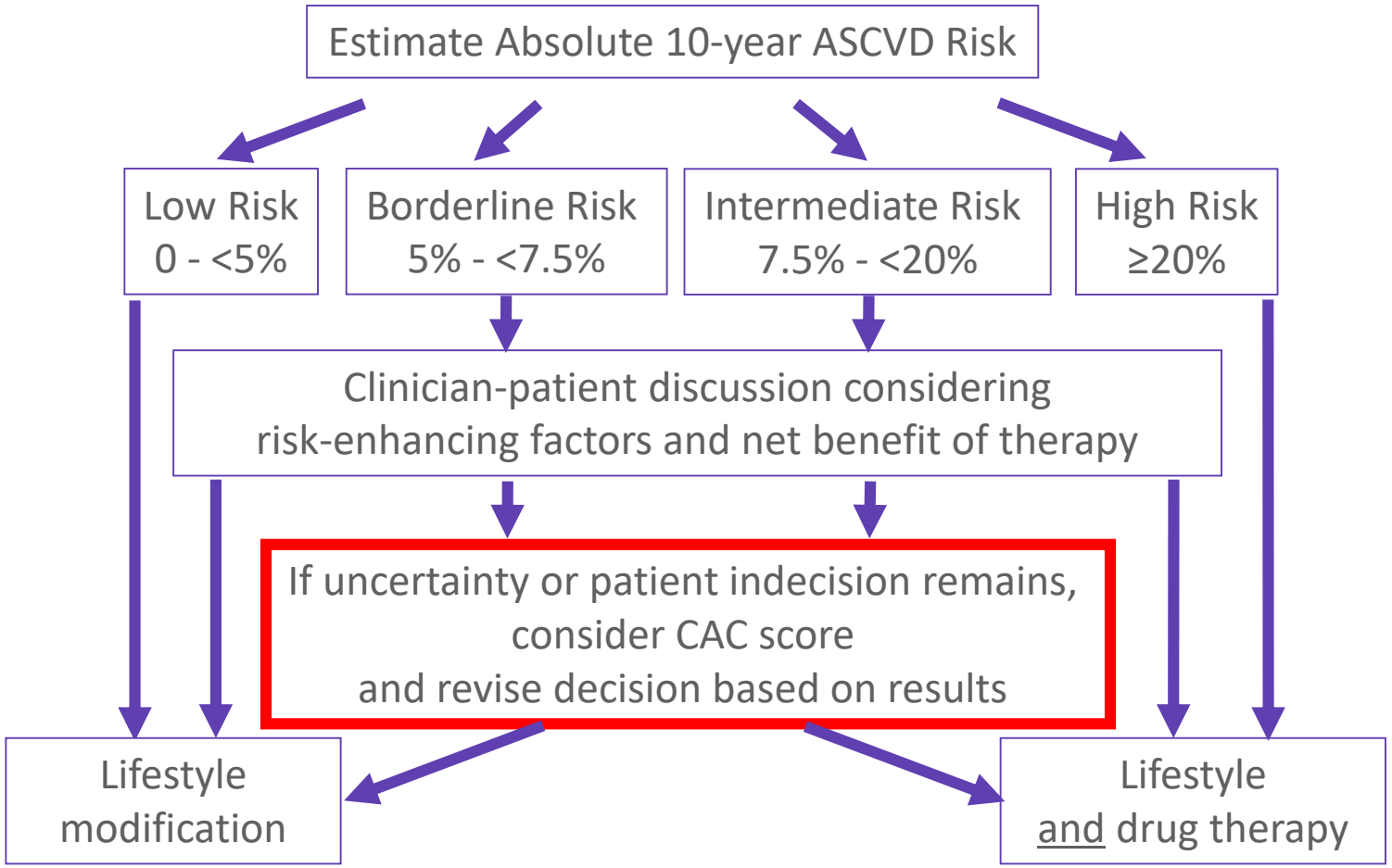
- **Family history of premature ASCVD**; (males, age <55 y; females, age <65 y)
- **Primary hypercholesterolemia** (LDL-C, 160-189 mg/dL [4.1- 4.8 mmol/L]; non-HDL-C 190-219 mg/dL [4.9-5.6 mmol/L])*
- **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis)
- **Chronic kidney disease** (eGFR 15-59 mL/min/1.73 m^2 with or without albuminuria, not treated with dialysis or kidney transplantation)
- **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS
- **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as pre-eclampsia**
- **High-risk race/ethnicities** (e.g. South Asian ancestry)
- **Lipid/biomarkers**: Associated with increased ASCVD risk

-Persistently* elevated, primary hypertriglyceridemia (≥175mg/dL);

-If measured:

  - **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L
  - **Elevated Lp(a)** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥ 50 mg/dL or ≥125 nmol/L constitutes a risk enhancing factor especially at higher levels of Lp(a)
  - **Elevated apoB** ≥130 mg/dL - A relative indication for its measurement would be triglyceride ≥ 200 mg/dL. A level ≥ 130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk enhancing factor
  - **ABI (ABI)** <0.9

R = Reclassify Risk in Selected Patients



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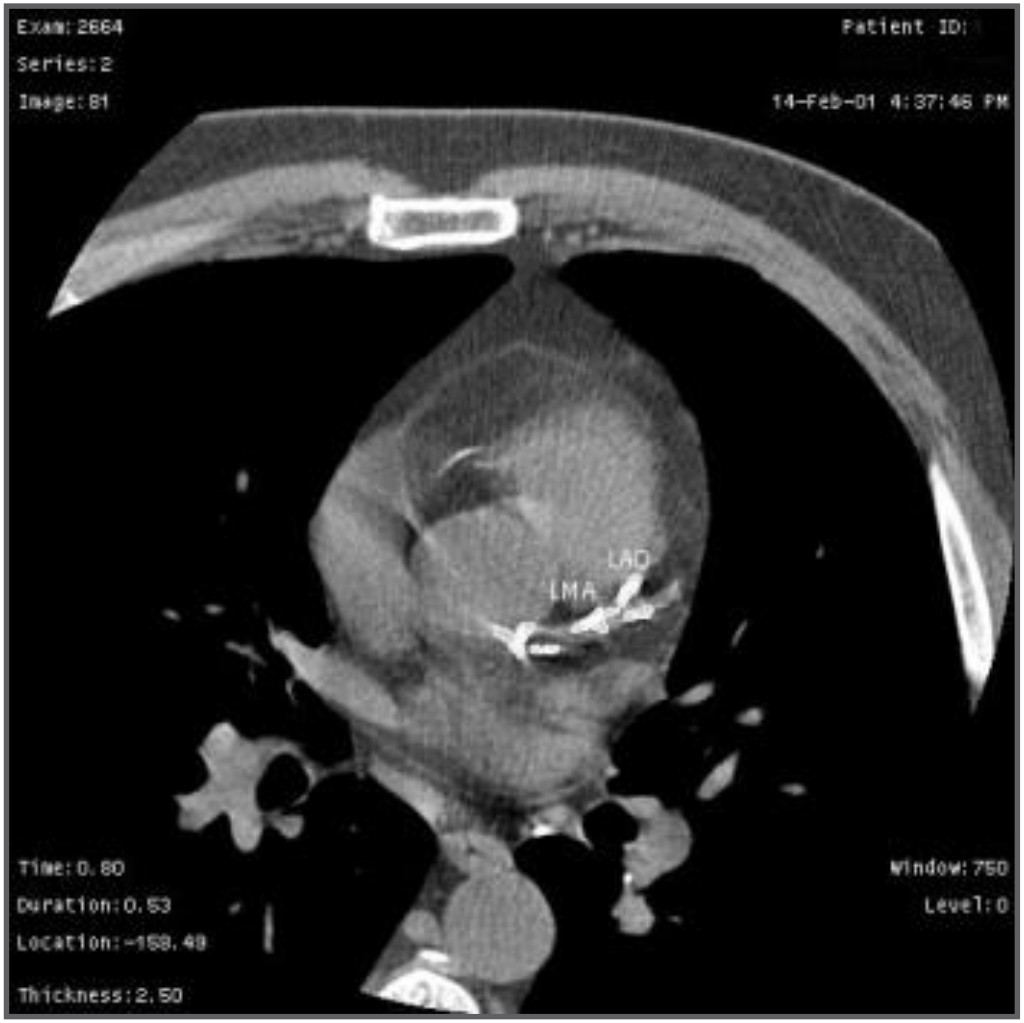
Coronary Artery Calcification

Powerful Marker of Plaque Burden



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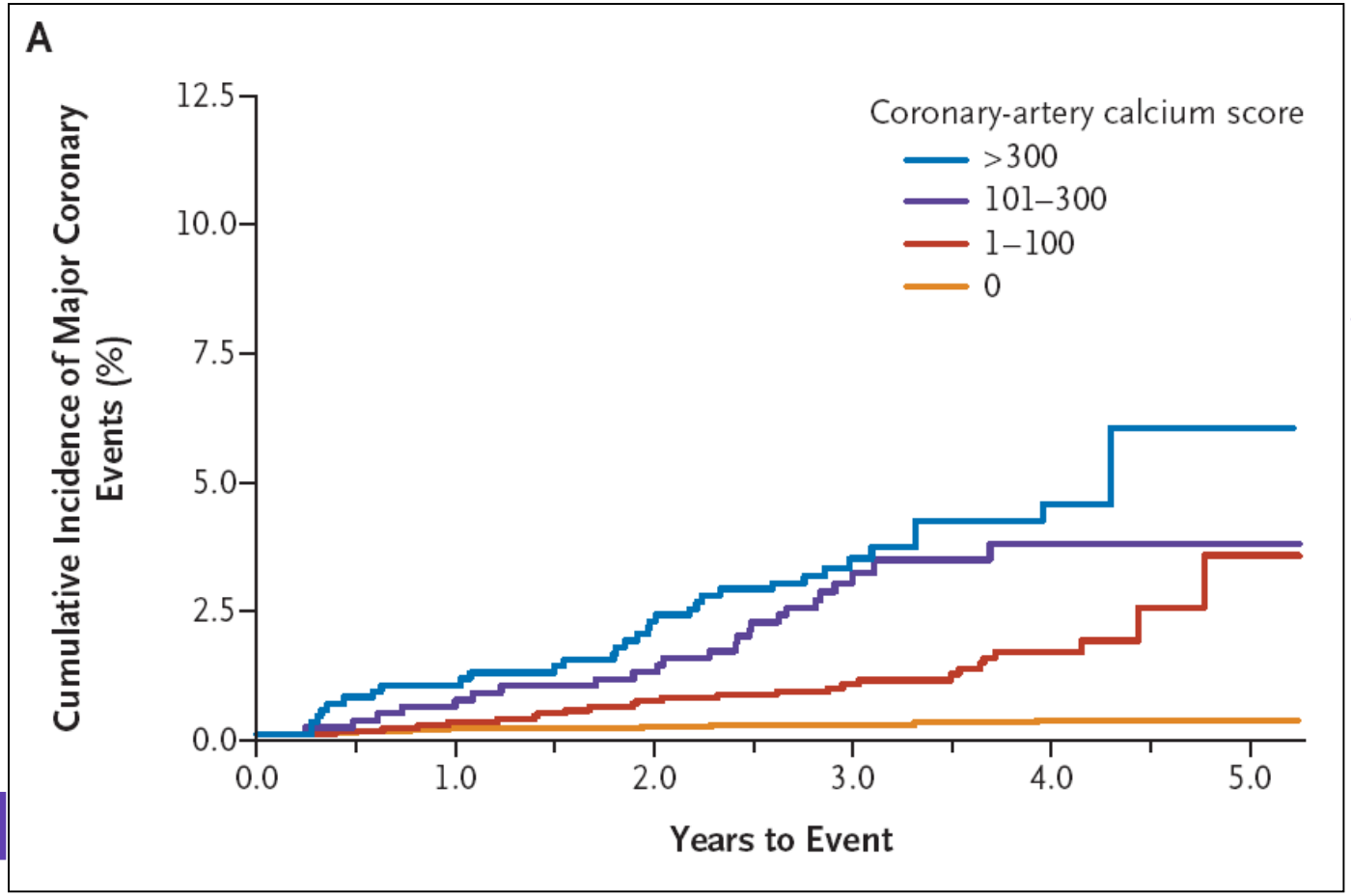
Screening for Coronary Calcium

MESA Study (Detrano, NEJM 2008)



RF-Adj HR

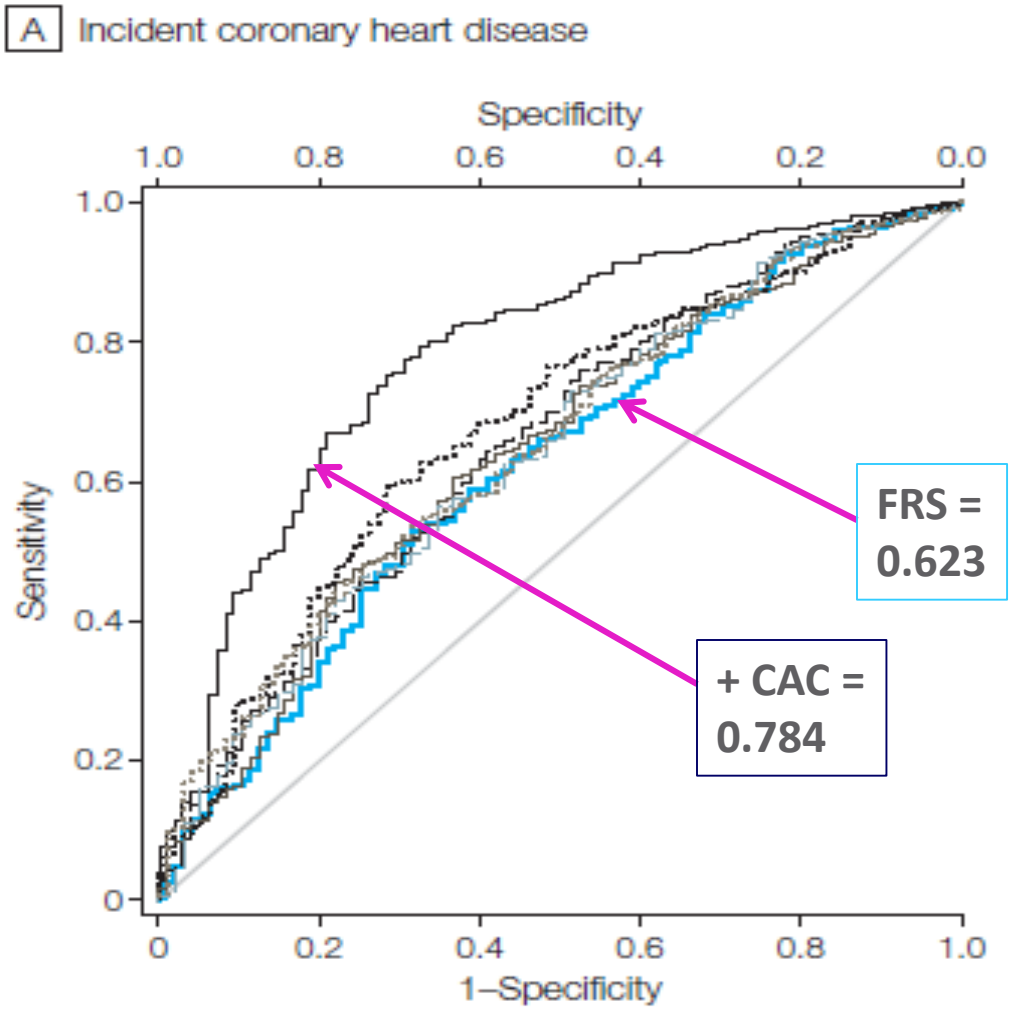
6.84

7.08

3.89

1.0 (ref)

ROC Curves Showing Area Under Curve for Incident CHD: MESA



NOTE: Reasonably large increase in AUC with CAC

Yeboah J. JAMA 2012; 308:788-95.

NRI for Incident CHD with Addition of Novel Risk Marker to FRS: MESA

Variable	% Reclassified	Risk Category, No. of Events FRS Events (n = 94) FRS Nonevents (n = 1236) Low	Intermediate	High	% Net Correct Reclassification	NRI
FRS plus carotid IMT						.102
Events	7.4	0	87	7	7.4	
Nonevents	5.3	50	1170	16	2.8	
FRS plus CAC						.659
Events	51.1	12	46	36	25.5	.
Nonevents	54.9	589	557	90	40.4	
FRS plus brachial FMD						.024
Events	0.0	0	94	0	0	
Nonevents	3.2	35	1196	5	2.4	
FRS plus ABI						.036
Events	4.3	1	90	3	2.1	
Nonevents	4.0	34	1186	16	1.5	
FRS plus high-sensitivity CRP						.079
Events	4.3	0	90	4	4.3	
Nonevents	5.2	54	1172	10	3.6	
FRS plus family history						.160
Events	8.5	0	86	8	8.5	
Nonevents	11.2	116	1097	23	7.5	

NRI for FRS + CAC = 0.659

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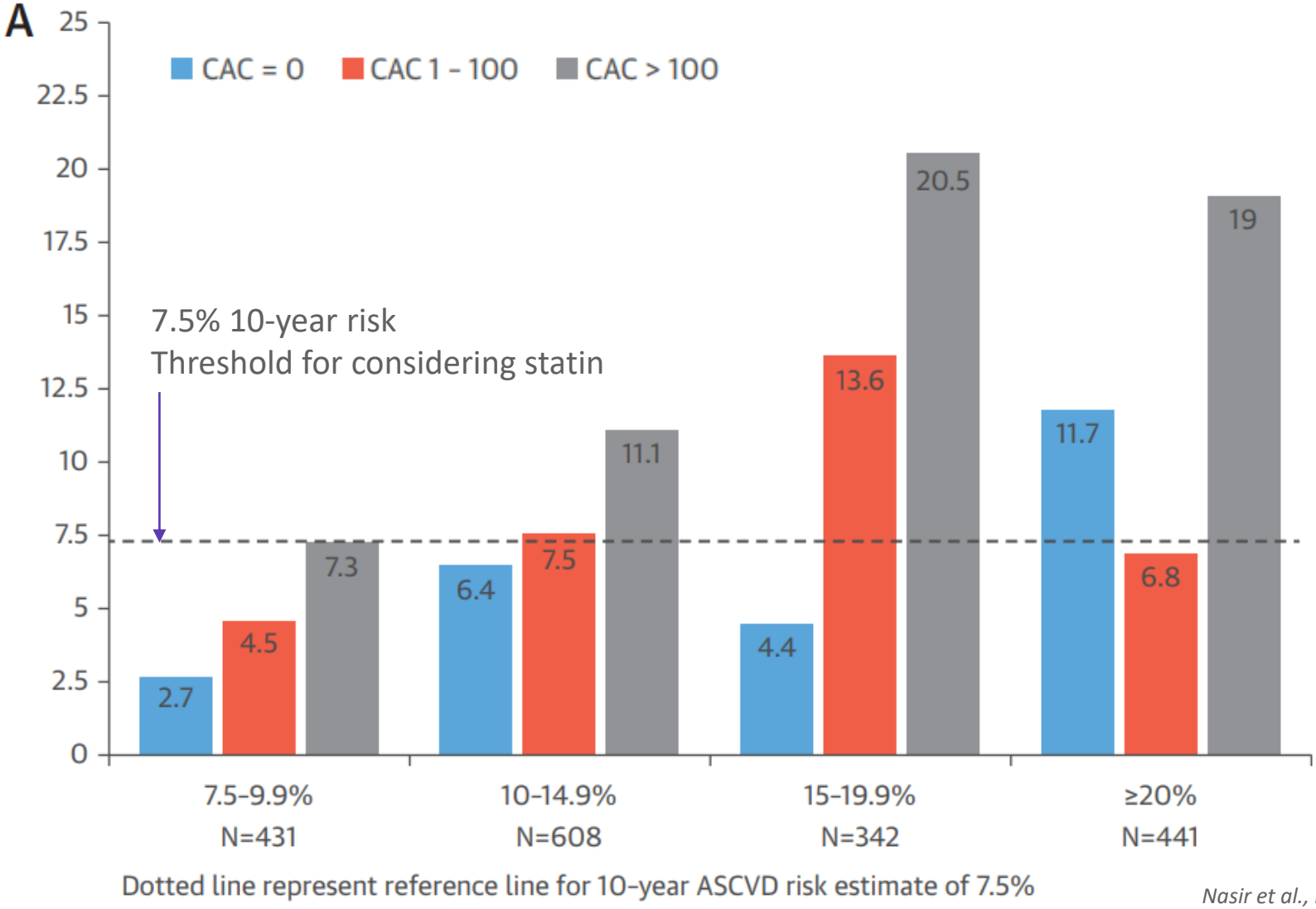
Yeboah J. JAMA 2012;308:788-95

Reclassification of Risk by CAC

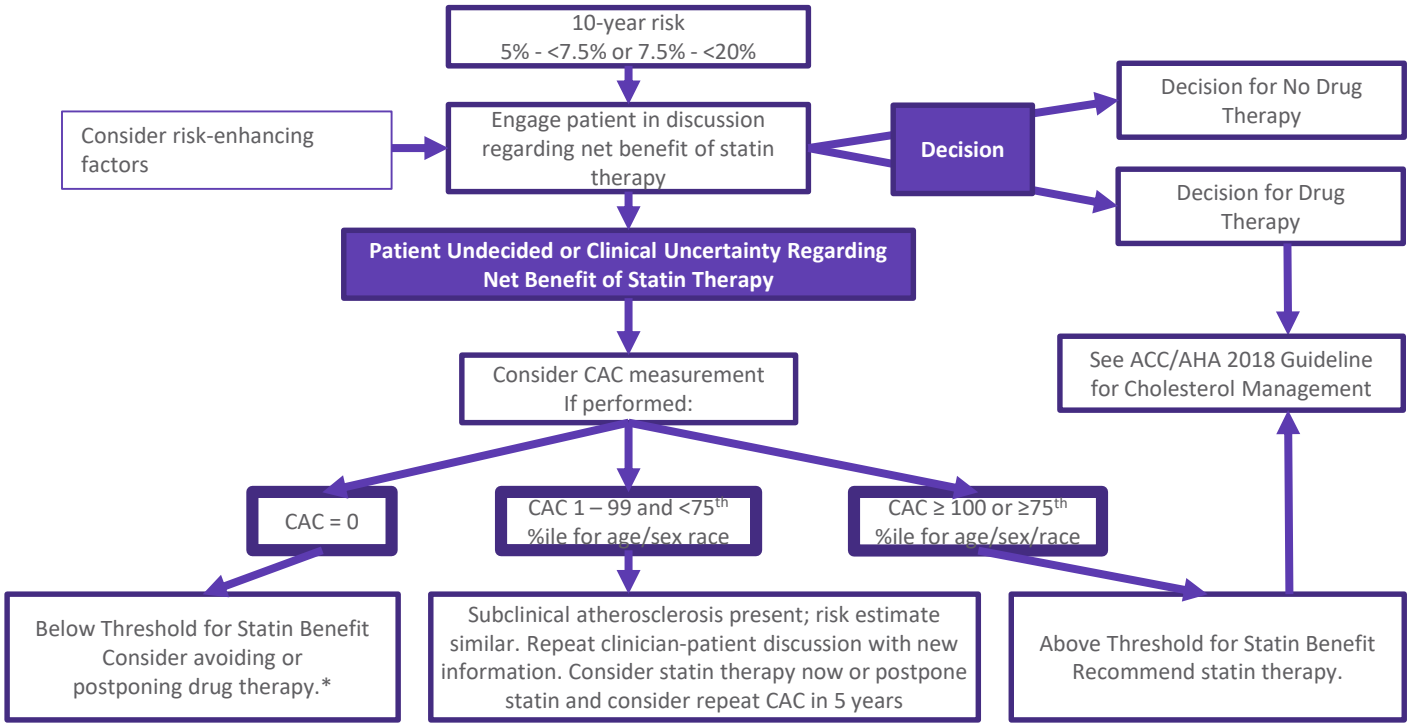
Example: MESA Study



Dotted line represent reference line for 10-year ASCVD risk estimate of 7.5%

Nasir et al., MESA Study, JACC 2015

R = Reclassify Risk in Selected Patients



*Clinicians and patients may not wish to postpone therapy in patients with a CAC score of 0 and diabetes mellitus, heavy current cigarette smoking, or strong family history of premature ASCVD.

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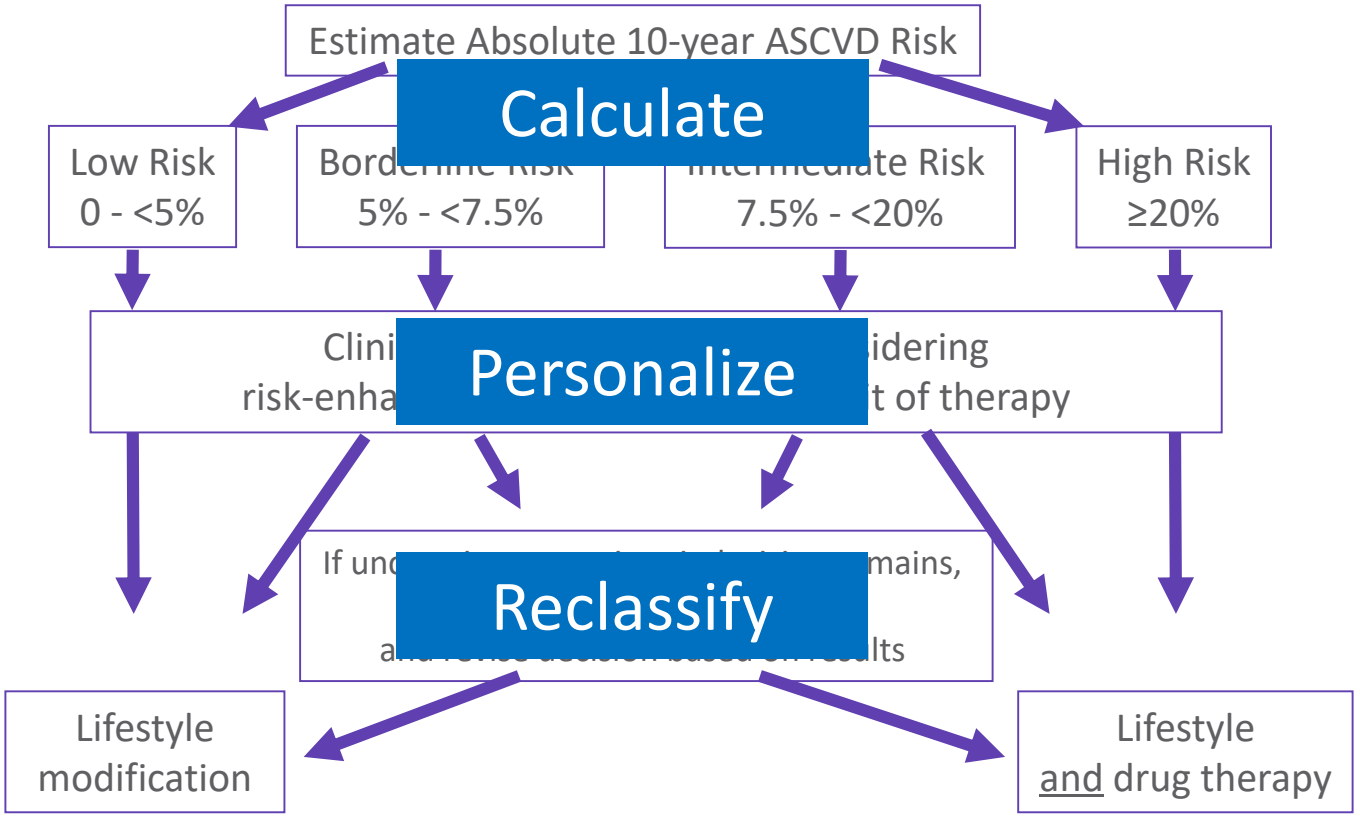
Approach to Risk Assessment in 1º Prevention: CPR



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Machine Learning

Cardiovascular Event Prediction by Machine Learning

The Multi-Ethnic Study of Atherosclerosis

Bharath Ambale-Venkatesh, Xiaoying Yang, Colin O. Wu, Kiang Liu, W. Gregory Hundley, Robyn McClelland, Antoinette S. Gomes, Aaron R. Folsom, Steven Shea, Eliseo Guallar, David A. Bluemke, João A.C. Lima

Table 1. A List of the Markers That Were Used for Prediction in This Study

Traditional risk factors, demographics, anthropometry, site
Age, sex, race, body mass index, body surface area, waist/hip ratio, systolic blood pressure, diastolic blood pressure, pulse pressure, diabetes mellitus, smoking status, pack-years, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, triglycerides, heart rate, creatinine, site, waist circumference, hip circumference, fasting glucose
Medication use
All hypertension, angiotensin-converting enzyme, angiotensin-II receptor blockers, lipid control, statins, β-blockers, calcium channel blockers
Atherosclerotic markers—computed tomography, carotid ultrasonography
Coronary Artery Calcium score, ankle-brachial index, common and internal carotid artery intima media thickness, maximum carotid stenosis
Questionnaire
Family history of heart attacks, alcohol use, no. of drinks per week, emphysema, asthma, arthritis, cancer, liver disease, education level, economic status/income, exercise metabolic equivalents
Magnetic resonance imaging markers
Left ventricular (LV) mass, LV end-diastolic volume, LV end-systolic volume, LV ejection fraction, LV mass/volume ratio, LV stroke volume, LV sphericity index at end diastole and end systole, LV cardiac output, LV end-diastolic wall thickness, LV end-systolic wall thickness, ascending aortic distensibility, descending aortic distensibility, pulse wave velocity, maximum ascending aortic area, maximum descending aortic area, aortic arch distance, maximum left atrial (LA) volume, minimum LA volume, maximum LA strain, total LA ejection fraction, passive LA ejection fraction, active LA ejection fraction, right ventricular (RV) mass, RV end-diastolic volume, RV end-systolic volume, RV ejection fraction, RV stroke volume
Laboratory Biomarkers
Interleukin-2 soluble receptor, plasmin-antiplasmin complex, D-dimer, Factor VIII, NT-proBNP (N-Terminal Pro-B-Type Natriuretic Peptide), cardiac troponin-T, C-reactive protein, interleukin-6, fibrinogen, homocysteine, tissue necrosis factor-α soluble receptor
Electrocardiographic main
PR duration, QRS duration, QT duration, P axis, QRS axis, T axis, Minnesota codes, ECG LV hypertrophy by cornell voltage and novacode, heart rate variability short-term and overall components, Cornell voltage
ECG all
P-, P′-, Q-, R-, R′-, S-, S′-, T-, and T′-wave duration, amplitude, area, and intrinsicoid; middle and end of ST-segment amplitudes; amplitude at the point of 60 ms from J point; STJ amplitude; total QRS area, balance, deflection balance, intrinsicoid; for each of the leads (aVL, aVr, aVF, I, II, III, V_1, V_2, V_3, V_4, V_5, V_6)

Circ Res 2017

Cardiovascular Event Prediction by Machine Learning

The Multi-Ethnic Study of Atherosclerosis

Bharath Ambale-Venkatesh, Xiaoying Yang, Colin O. Wu, Kiang Liu, W. Gregory Hundley, Robyn McClelland, Antoinette S. Gomes, Aaron R. Folsom, Steven Shea, Eliseo Guallar, David A. Bluemke, João A.C. Lima

- Performance of ML models with shotgun phenotypes
- Better than sequential testing?

	DTH	STRK	CHD	CVD	HF	AF
No. of variables						
RSF with all covariates	735	735	735	735	735	735
RSF with top-20 covariates	20	20	20	20	20	20
AIC-Cox with forward selection	13	9	5	6	5	6
Cox with top-20 RSF covariates	20	20	20	20	20	20
LASSO-Cox with top-20 RSF covariates	19	17	19	19	10	15
AIC-Cox backward selection with top-20 RSF covariates	16	12	13	13	11	12
Concordance index at 12 y						
RSF with all covariates	0.86	0.77	0.81	0.81	0.84	0.82
RSF with top-20 covariates	0.84	0.75	0.80	0.80	0.84	0.75
AIC-Cox with forward selection	0.78	0.70	0.74	0.74	0.78	0.79
Cox with top-20 RSF covariates	0.80	0.66	0.75	0.76	0.81	0.78
LASSO-Cox with top-20 RSF covariates	0.80	0.67	0.75	0.76	0.82	0.78
AIC-Cox Backward Selection with top-20 RSF covariates	0.80	0.68	0.75	0.76	0.80	0.78

Circ Res 2017

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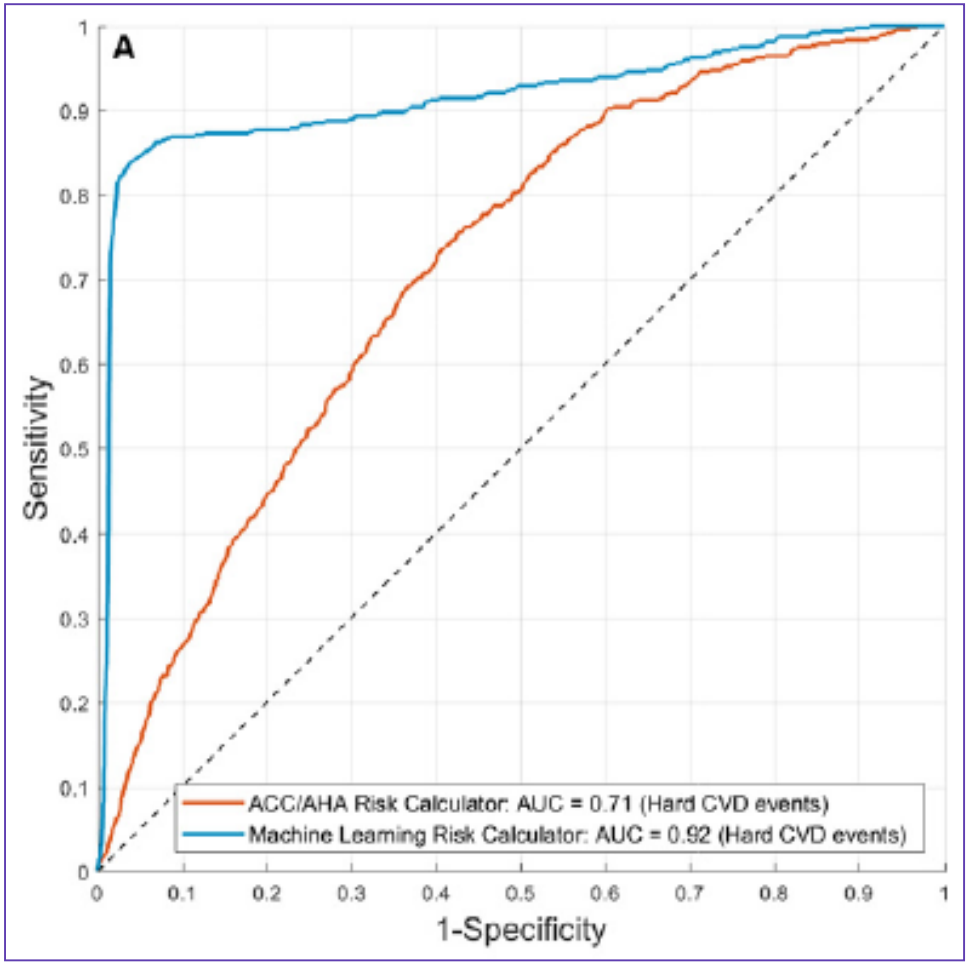
Machine Learning Outperforms ACC/AHA CVD Risk Calculator in MESA

Ioannis A. Kakadiaris, PhD; Michalis Vrigkas, PhD; Albert A. Yen, MD; Tatiana Kuznetsova, MD; Matthew Budoff, MD; Morteza Naghavi, MD

- True, but…
- Fixed vs flexible treatment threshold



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JAHA 2019

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Polygenic Risk Scores

Polygenic Risk Scoring

- GWAS-based risk scores offered no additional utility
- Newer whole-genome genotyping techniques may allow for comprehensive polygenic risk assessment to include rare variants

nature genetics

LETTERS

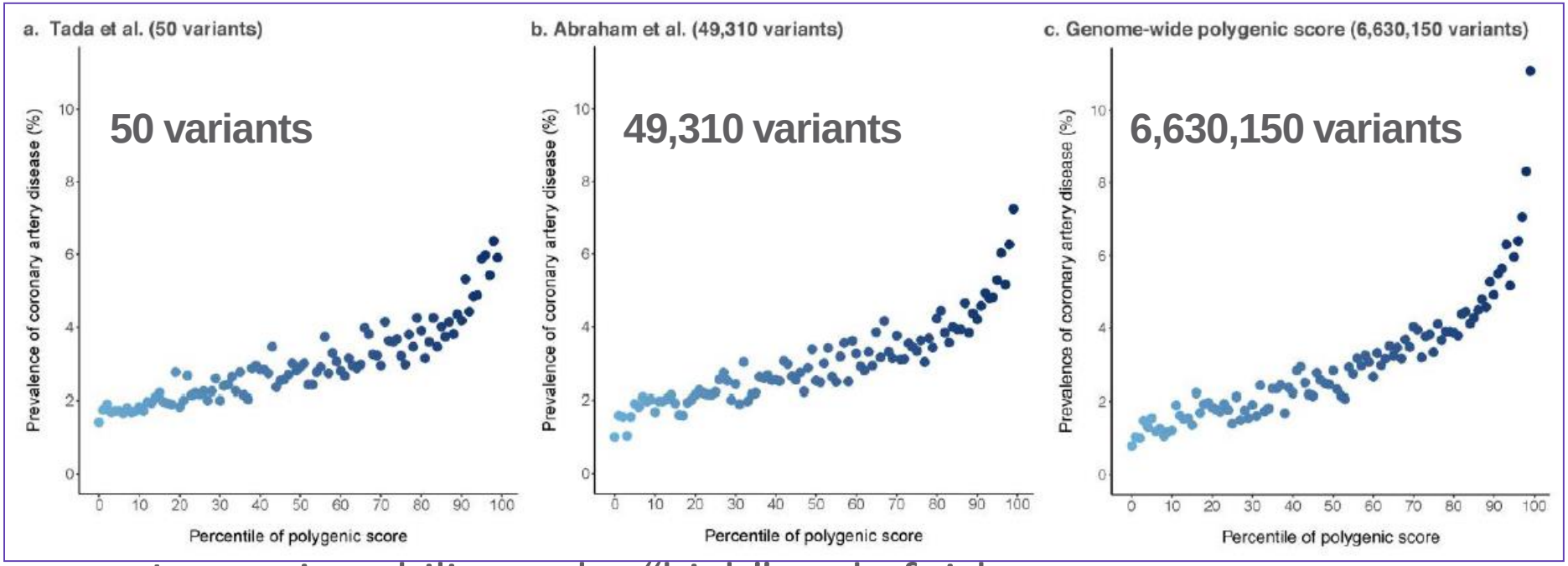
https://doi.org/10.1038/s41588-018-0183-z

Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

Amit V. Khera[1,2,3,4,5], Mark Chaffin[4,5], Krishna G. Aragam[1,2,3,4], Mary E. Haas[4], Carolina Roselli[4], Seung Hoan Choi[4], Pradeep Natarajan[2,3,4], Eric S. Lander[4], Steven A. Lubitz[2,3,4], Patrick T. Ellinor[2,3,4] and Sekar Kathiresan[1,2,3,4*]

Nature Genetics 2019

Polygenic Risk Scoring



- Improving ability at the "high" end of risk
- But not high risk
- And not risk, but prevalence
- More work to do

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Nature Genetics 2019

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Newer Directions in Long-Term and Competing Risks for CVD

Rationale: Lifetime Risk Estimation

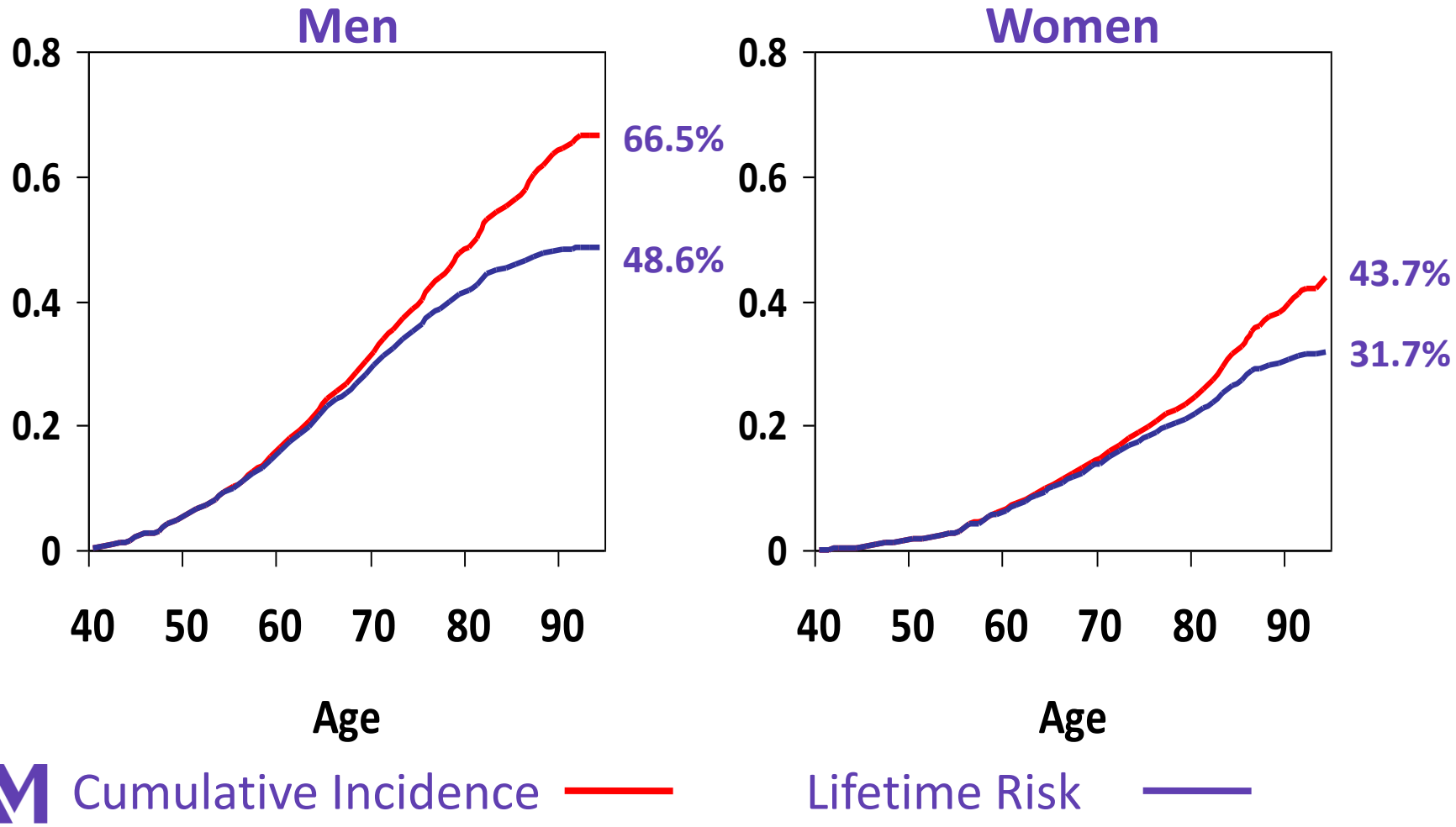
- Reliance solely on estimates of *short-term* absolute risk to communicate risk and make treatment decisions is problematic
  - Atherosclerosis is a life course disease
  - Any single risk factor can produce cumulative damage and high risk if left untreated for years
  - Almost all men <50 and women <70 are considered to be at "low" short-term risk *regardless of risk factor burden*

AHA Prevention Conference V, Circulation 2000; Cavanaugh-Hussey, Prev Med 2008; Marma, Circ CQO 2010

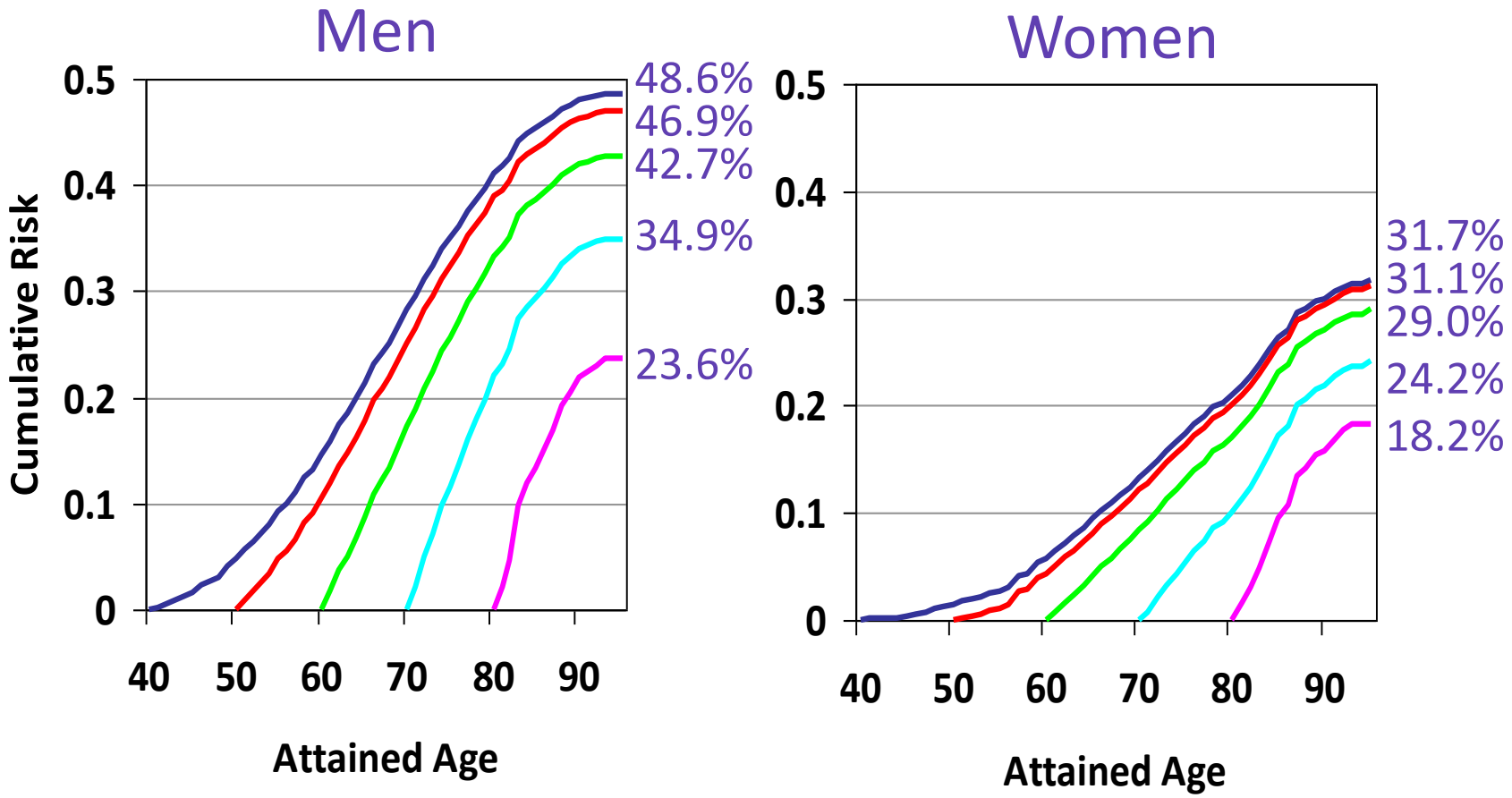
Rationale: Lifetime Risk Estimation

- Lifetime risk
  - The absolute cumulative risk of an individual developing a given disease before death
  - Accounts for risk of disease of interest, remaining life expectancy, and competing causes of death
  - Reflects real-life risks and population burden of disease better than Kaplan-Meier cumulative incidence
  - Allows for comparison of disease burden now and in future
  - May provide adjunctive information for individual risk assessment

KMCI vs. Lifetime Risk for CHD
Age 40



Lifetime Risk for CHD by Age and Sex



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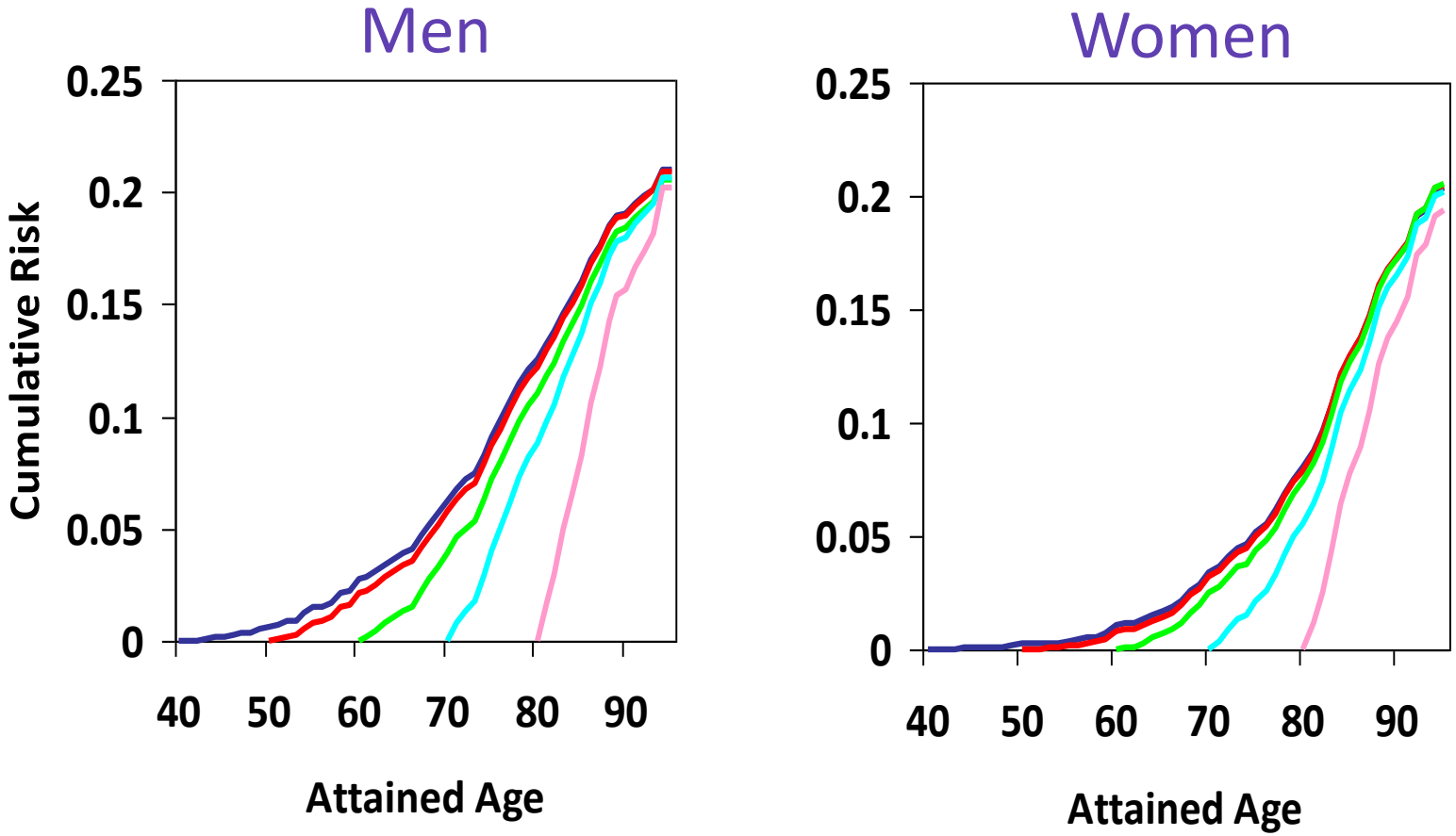
Lloyd-Jones et al. Lancet 1999;353:89.

Lifetime Risk for CHF by Age and Sex



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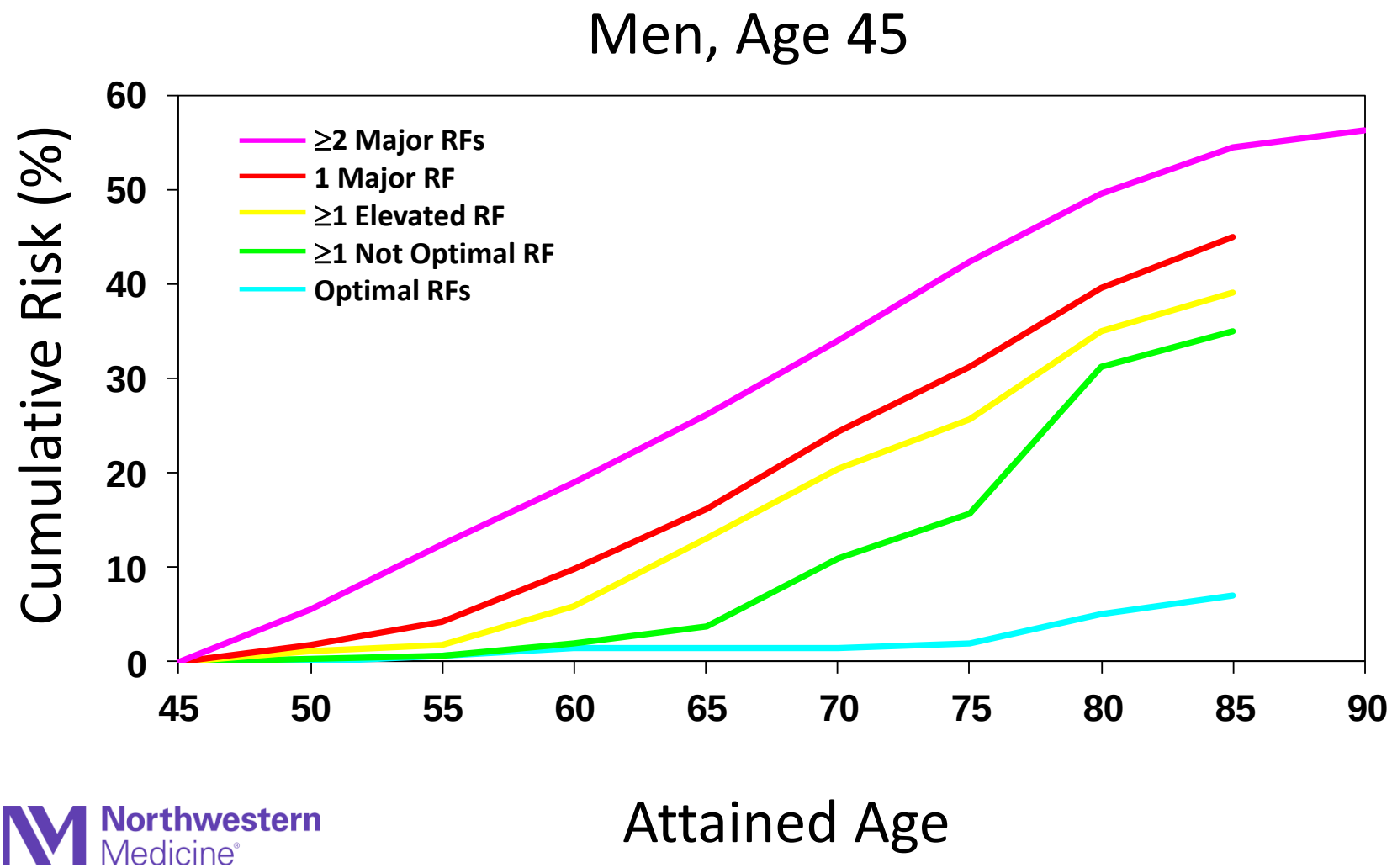
Lloyd-Jones et al. *Circulation* 2002

Lifetime Risks for All ASCVD
Cardiovascular Lifetime Risk Pooling Project



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Berry et al, NEJM 2012

Compression of Morbidity

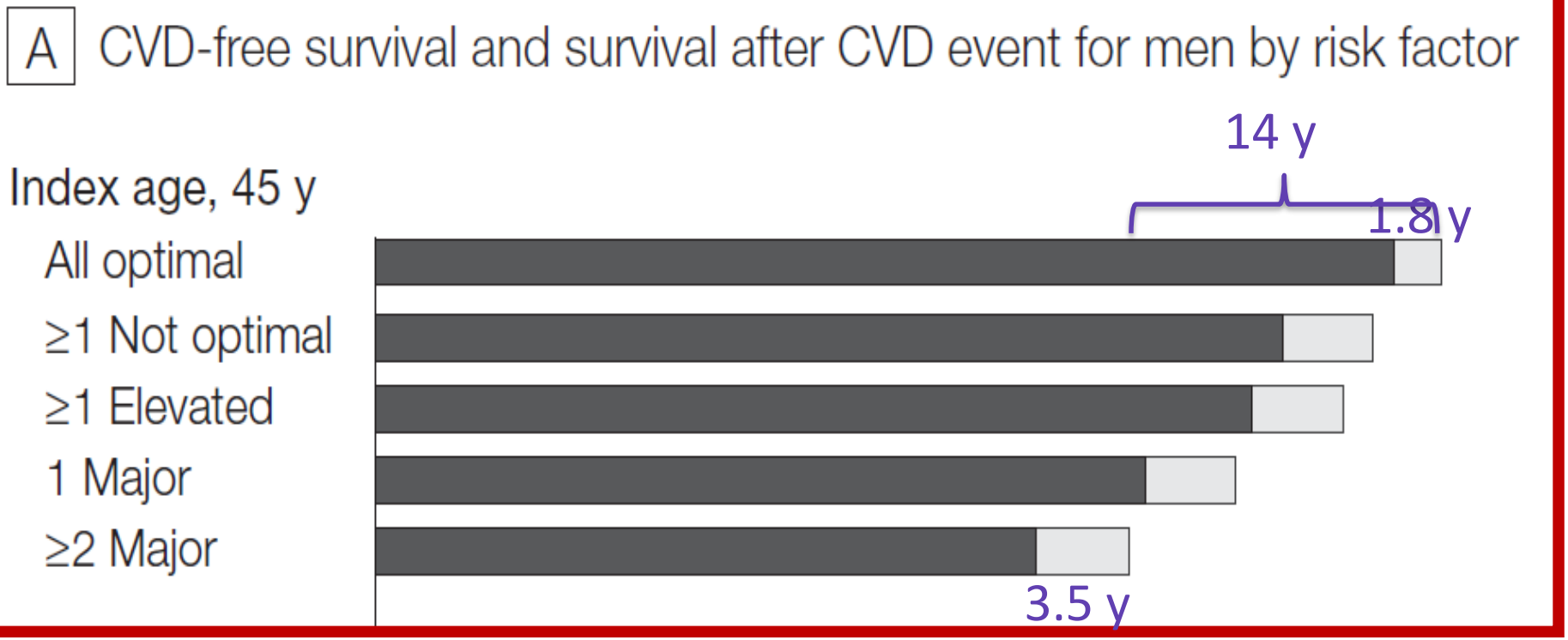
Figure 2. CVD-Free Survival and Survival After CVD Events for Men and Women by Index Age and Aggregate Risk Factor Burden

A CVD-free survival and survival after CVD event for men by risk factor

Index age, 45 y

B CVD-free survival and survival after CVD event for women by risk factor

Index age, 45 y

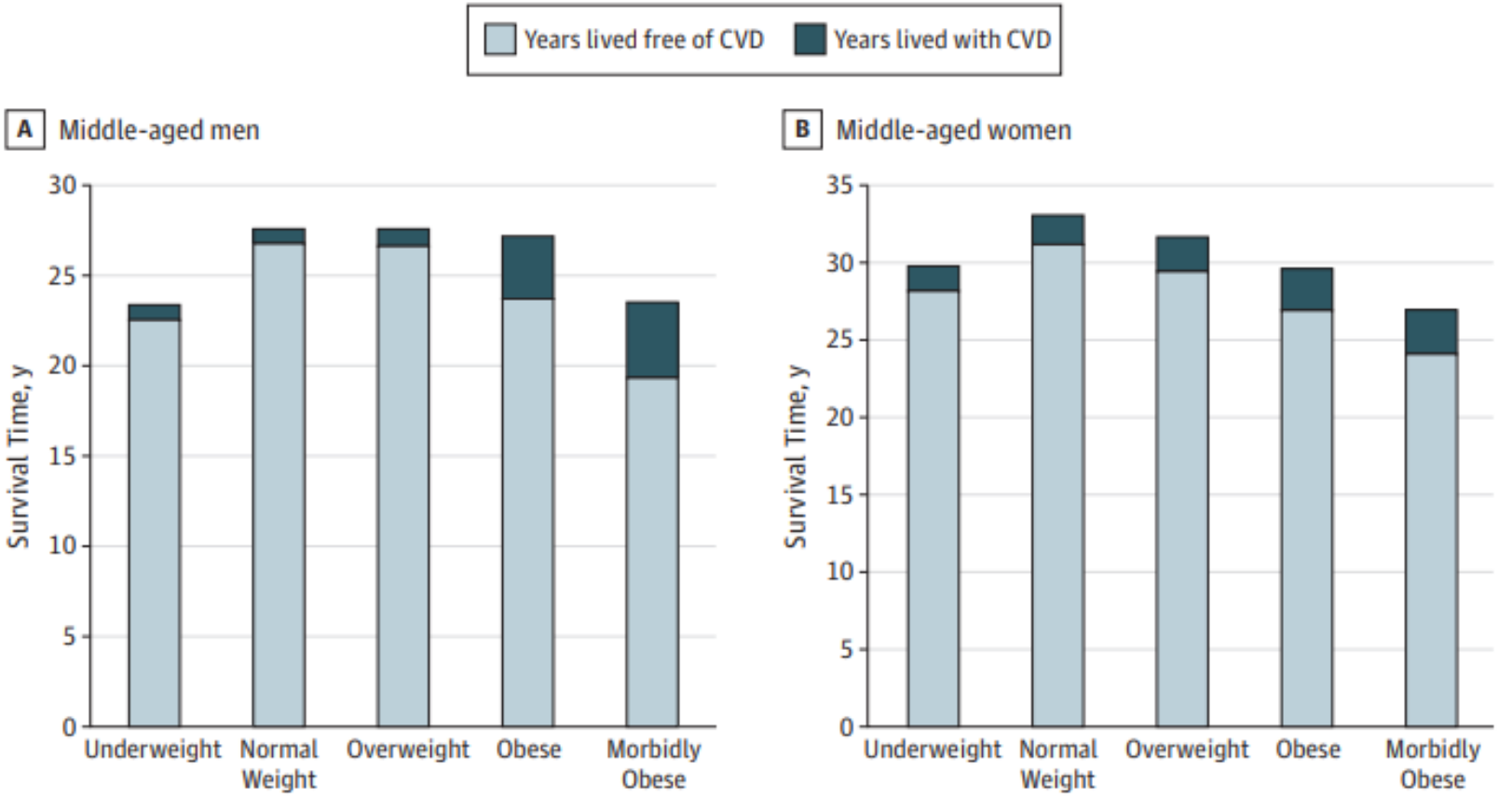


CVD indicates cardiovascular disease.

Wilkins, JAMA 2012

BMI and Compression of Morbidity

Figure 2. Years Lived Free of and With Cardiovascular Disease (CVD) Among Middle-aged Individuals



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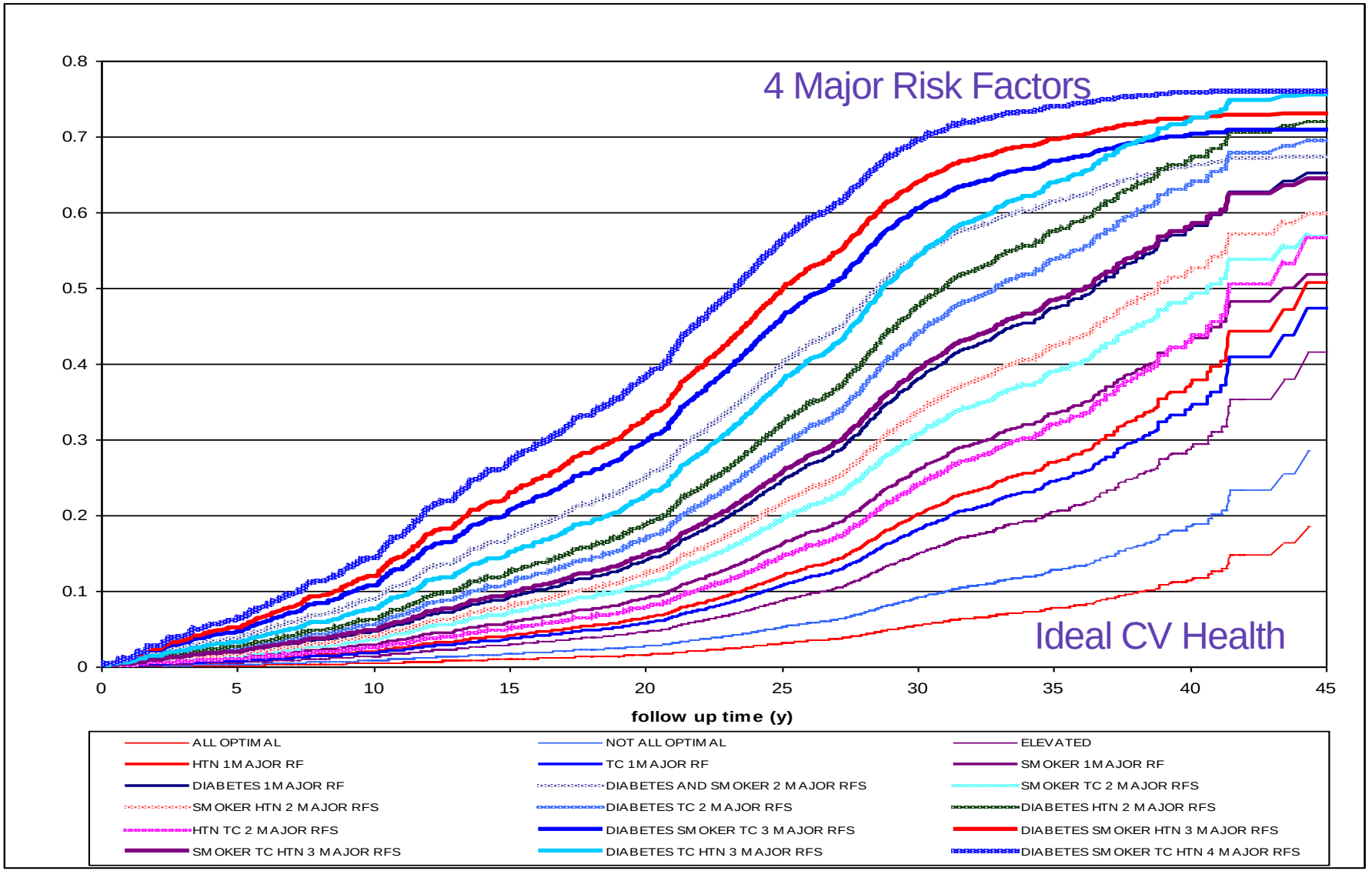
Competing Cox Methodology

- Lets the outcomes compete to be first, rather than considering them one at a time
- Provides robust estimates of hazards and cumulative incidences for multiple endpoints simultaneously
  - And gives a total cumulative incidence for events through the end of follow up

Lifetime Risk for a Cardiovascular Event
Female, Age 45



Summary/Take Home Points

- Risk scores can assist with more precise prognostication of patients and improved decision making for net clinical benefit
- Combinations of risk factors/markers can improve discrimination
- Discrimination, calibration, and (maybe) NRI help describe utility of risk scores
- Additional biomarkers/sequential testing strategies need to be specific and strongly and independently associated with outcomes (and are best if they are specific markers of disease or target organ damage)
- Newer risk score modeling approaches can improve discrimination and calibration at the cost of complexity/utility(?)
  - At least at present

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Questions?