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Prediction of Heart Failure in Patients with CKD

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KDIGO — March 22, 2024

Disclosures: Scientific advisor to Healthy.io and SomaLogic

Prediction of Heart Failure in CKD

- Background – Staging & Risk prediction in CKD (ckdpcrisk.org)
- **Cardiovascular risk prediction** – ASCVD (CHD, stroke), **HF**, CVM
  - AHA PREVENT (Circulation 2024) includes
    - HF risk prediction
    - eGFR and ACR
- Future directions – Biomarker strengths and limitations

Classification & Staging of CKD (KDIGO 2012)

- Cause (C)
- GFR (G)
- Albuminuria (A)

				Albuminuria Categories, Description and Range		
				A1	A2	A3
				normal to mildly increased	moderately increased	severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR Categories, Description and Range (mL/min/ 1.73 m^2)	G1	normal or high	>90			
	G2	mildly decreased	60-89			
	G3a	mildly to moderatel y decreased	45-59			
	G3b	moderatel y to severely decreased	30-44			
	G4	severely decreased	15-29			
	G5	kidney failure	<15			

Risk Categories (Heat Map)

NFK KDOQI 2002

KDIGO 2012 guidelines

KDIGO 2023 Update

Prediction – Individualized Estimate from a Multivariable Model

Levey AS, Grams ME, Inker LA. N Engl J Med 2022;386:2120-8.

Table 2. Predictive Instruments Using GFR and Albuminuria.*

Instrument and Target Population	Outcome	Interval from Risk Prediction to Outcome	Hazard Ratio†		No. of Predictors	Predicted Risk in Target Population‡		Recommended Risk Threshold for Clinical Actions§
			GFR ~30ml	ACR 8-fold		1st decile	10th decile	
		years				*percent*		*percent*
KFRE: GFR <60 ml/min/1.73 m²	KFRT	2	29	2.6	4	<0.1	93	>10: Multidisciplinary care >20–40: Dialysis access and transplantation evaluation
	KFRT	5	29	2.6	4	<0.1	100	>5: Nephrology referral
CKD with Severely Decreased GFR: GFR <30 ml/min/1.73 m²	KFRT CVD Death	2 2 2	4.1 0.9 1.3	3.9 1.2 1.0	9 9 9	0.8 3.8 2.6	42 34 36	Same as for KFRE; high risk of CVD and death influences overall management
KFRT Risk Tool for Kidney Donor Candidates: GFR ≥60 ml/min/1.73 m² and ACR <300 mg/g	KFRT	Lifetime	2.3	2.6	10	0.1	6.0	<1–2: Acceptable donor candidate
CKD Progression Calculator:								
GFR ≥60 ml/min/1.73 m², no DM	40% GFR decline	3	1	2.4	12	0.2	7.8	>1–4: Use medications to slow kidney-disease progression, more frequent monitoring
GFR ≥60 ml/min/1.73 m², DM	40% GFR decline	3	1.4	2.3	12	0.4	18	
GFR <60 ml/min/1.73 m², no DM	40% GFR decline	3	2.7	2.3	12	1.4	42	
GFR <60 ml/min/1.73 m², DM	40% GFR decline	3	1.6	2.6	12	1.2	65	>5: Consider multiple medications to slow disease progression
Incident GFR <60 Calculator:								
GFR ≥60 ml/min/1.73 m², no DM	GFR <60 ml/min/1.73 m²	5	13	1.4	9	0.1	46	>5: Measure albuminuria if not done, use medications to slow disease progression
GFR ≥60 ml/min/1.73 m², DM	GFR <60 ml/min/1.73 m²	5	6.9	1.4	11	2.1	68	
SCORE plus Kidney Variables Calculator: general population free of CVD	Death from CVD	10	3.0	1.6	7	0.6	27	>5: Improves risk prediction beyond SCORE¶
PCE plus Kidney Variables Calculator: general population free of CVD	ASCVD event	10	1.7	1.3	11	0.3	54	Same as for SCORE plus Kidney Variables Calculator

CVD

RISK MODELS
ckdpc.risk.org

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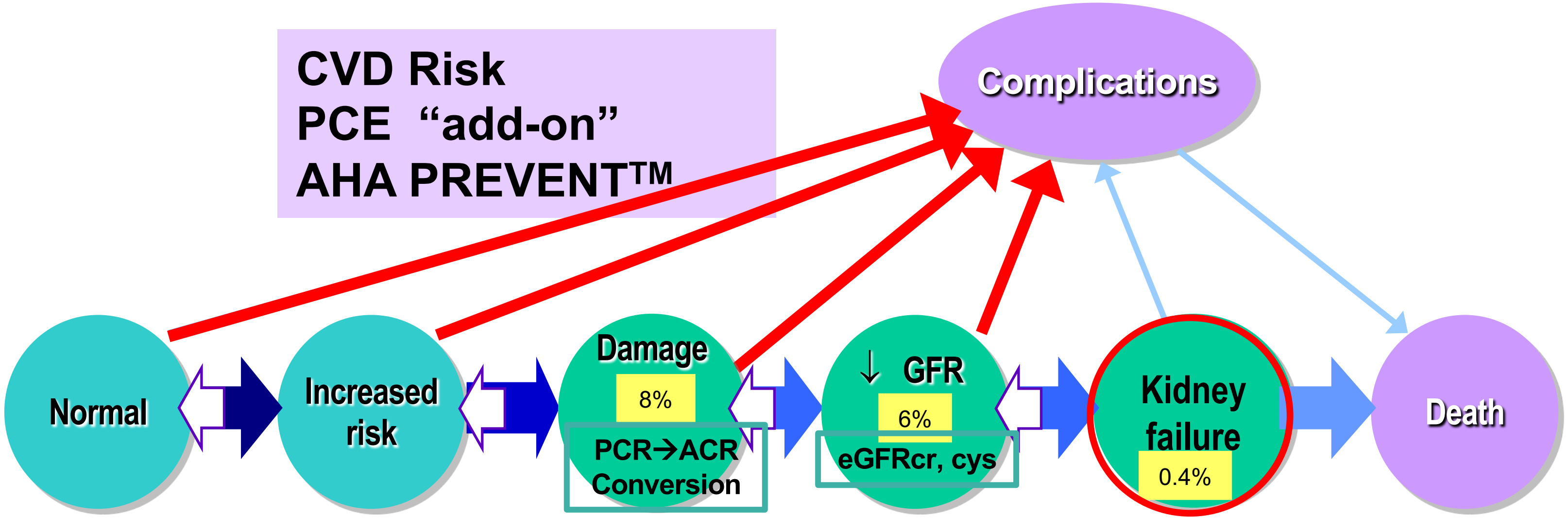
CKD: Risk Prediction & Equations (ckdpcrisk.org)



Risk of KFRT among Kidney Donor Candidates

Risk of incident eGFR<60

Risk of 40% decline in eGFR

(Diabetes Care 2022)

Risk of albuminuria

eGFR <60

Kidney Failure Risk Eqn. (KFRE)

eGFR <30

CKD G4+ risk of KFRT, CVD, Death

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Review: N Engl J Med June 2, 2022;386:2120-8

Predicting CKD Progression: HF is a Risk Factor

CKD ⇄ HF

Outcome: ≥40% eGFR decline in 3 years

Population: No Diabetes eGFR>60

Earlier & More Common than Kidney Failure

KFRE does not work at eGFR>60

	No Diabetes	
	Model 1	Model 2
Age, per 10 years	1.59 (1.50, 1.69)	1.45 (1.36, 1.54)
Male sex	0.97 (0.88, 1.07)	0.87 (0.79, 0.95)
eGFR, 5 mL/min/1.73 m^2	1.02 (1.00, 1.05)	1.03 (1.02, 1.05)
lnACR*	1.59 (1.50, 1.68)	1.52 (1.44, 1.61)
SBP, per 20 mmHg		1.36 (1.28, 1.44)
Antihypertensive medication use		1.30 (1.12, 1.51)
SBP × HTN medications		0.89 (0.83, 0.96)
History of HF	(strong risk factor)	2.87 (2.48, 3.32)
History of CHD		1.51 (1.36, 1.67)
History of Afib		1.12 (0.91, 1.38)
Current smoker		1.46 (1.20, 1.79)
Former smoker		1.20 (1.10, 1.31)
BMI, per 5 kg/m^2		1.04 (1.01, 1.08)

Higher risk at older age (opposite to KFRE)

Baseline eGFR is less important (vs. strongest in KFRE)

ACR is important (similar to KFRE)

2.5 in DM; also in eGFR<60 +/- DM (HR~1.6)

Development: 19 cohorts with 181,618; Median C-stat 0.739
Validation: 18 cohorts 236,284 participants; Median C-stat 0.743

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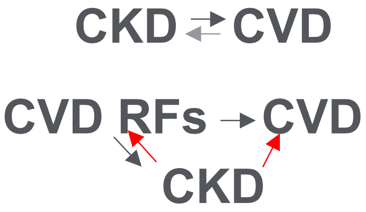
Diabetes Care. 2022 ;45:2055-2063

Predicting CVD Incidence: CKD is a Risk Factor



Background:

- Multivariable equations are recommended by guidelines to assess absolute risk of cardiovascular disease (CVD).
  - SCORE2 (in Europe predicts myocardial infarction, stroke, and CVD mortality.)
  - Pooled Cohort Equation (in US predicts ASCVD = CHD + Stroke)

Limitations:

- **HF excluded**
- B/W race-specific, older data (higher CVD risk), limited geography

New Equation (2023):

- **AHA Predicting Risk of CVD EVENTs (PREVENT™) Equation**
- Addresses all of the limitation above (include HF, newer data, consider eGFR, ACR, A1c, SDI)

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Development and Validation of the American Heart Association Predicting Risk of Cardiovascular Disease EVENTs (PREVENT) Equations

Sadiya S. Khan, MD, MSc, Kunihiro Matsushita, MD, PhD, Yingying Sang, MSc, Shoshana H Ballew, PhD, Morgan E. Grams, MD, PhD, Aditya Surapaneni, PhD, Michael Blaha MD, MPH, April P. Carson, PhD, Alexander R. Chang, MD, MS, Elizabeth Ciemins, MPH, PhD, Alan S. Go, MD, Orlando M. Gutierrez, MD, Shih-Jen Hwang, PhD, Simerjot K. Jassal, MD, MAS, Csaba P. Kovesdy, MD, Donald M. Lloyd-Jones, MD, ScM, Michael G. Shlipak, MD, MPH, Latha P. Palaniappan, MD, MS, Laurence Sperling, MD, Salim S. Virani, MD, PhD, Katherine Tuttle, MD, Ian J. Neeland, MD, Sheryl L. Chow, PharmD, Janani Rangaswami, MD, FAHA, Michael J. Pencina, PhD, Chiadi E. Ndumele, MD, PhD, Josef Coresh, MD, PhD
For the **Chronic Kidney Disease Prognosis Consortium** and the American Heart Association Cardiovascular-Kidney-Metabolic Science Advisory Group

Circulation 2024 (6):430-449. (ePub 2023) PMID: 37947085

PREVENT™ Online Calculator

https://professional.heart.org/en/guidelines-and-statements/prevent-calculator

Novel Prediction Equations for Absolute Risk Assessment of Total Cardiovascular Disease Incorporating Cardiovascular-Kidney-Metabolic Health: A Scientific Statement From the American Heart Association. Circulation. 2024;PMID: 37947094

American Heart Association.

Table 2. Meta-Analyzed Sex-Specific Hazard Ratios (95% CIs) of Traditional Cardiovascular Risk Predictors for Total Cardiovascular Disease and Cardiovascular Disease Subtypes in Derivation Samples

Risk factor	Total CVD		ASCVD		Heart failure	
	Female N=1 839 828	Male N=1 442 091	Female N=1 839 828	Male N=1 442 091	Female N=1 839 828	Male N=1 442 091
Cardiovascular disease risk factors in the PREVENT-CVD primary model						
Non–HDL-C per 1 mmol/L	1.03 (0.99–1.07)	1.07 (1.03–1.11)	1.12 (1.07–1.17)	1.17 (1.13–1.21)	*	*
HDL-C per 0.3 mmol/L	0.85 (0.84–0.87)	0.91 (0.89–0.93)	0.86 (0.85–0.88)	0.89 (0.87–0.92)	*	*
SBP <110 per 20 mm Hg (U-shape)	0.78 (0.69–0.88)	0.63 (0.54–0.72)	0.91 (0.80–1.04)	0.73 (0.61–0.86)	0.63 (0.56–0.71)	0.49 (0.44–0.56)
HF ↑ SBP ≥110 per 20 mm Hg	1.43 (1.37–1.50)	1.40 (1.35–1.45)	1.44 (1.38–1.50)	1.39 (1.34–1.44)	1.44 (1.37–1.51)	1.45 (1.39–1.50)
↑ Diabetes	2.39 (2.31–2.48)	2.18 (2.08–2.29)	2.35 (2.23–2.47)	2.10 (1.98–2.23)	2.86 (2.72–3.01)	2.56 (2.41–2.71)
↑ Current smoking	1.74 (1.55–1.96)	1.59 (1.43–1.76)	1.67 (1.46–1.91)	1.53 (1.38–1.70)	1.84 (1.60–2.12)	1.70 (1.48–1.95)
BMI <30, per 5 kg/m² (U-shape)	*	*	*	*	0.98 (0.94–1.03)	0.93 (0.88–0.99)
↑ BMI ≥30, per 5 kg/m²	*	*	*	*	1.35 (1.28–1.41)	1.46 (1.38–1.54)
↑ eGFR <60, per −15 mL/min per 1.73 m²	1.94 (1.86–2.03)	1.86 (1.78–1.94)	1.75 (1.66–1.84)	1.59 (1.53–1.66)	2.26 (2.16–2.36)	2.19 (2.03–2.36)
eGFR ≥60, per −15 mL/min per 1.73 m² (flat)	1.04 (1.01–1.07)	1.01 (0.99–1.03)	1.04 (1.01–1.07)	1.01 (0.99–1.03)	1.05 (1.01–1.09)	1.02 (0.98–1.06)

Cardiovascular disease risk factor treatment status
Antihypertensive use
Statin use
Treated SBP ≥110 mm Hg per 20 mm Hg
Treated non–HDL-C per 1 mmol/L

Age–risk factor interactions per 10 y older

Hazard ratios centered at age 55 years

Stronger in younger, weaker in older age

American Heart Association.

Table 2. Meta-Analyzed Sex-Specific Hazard Ratios (95% CIs) of Traditional Cardiovascular Risk Predictors for Total Cardiovascular Disease and Cardiovascular Disease Subtypes in Derivation Samples

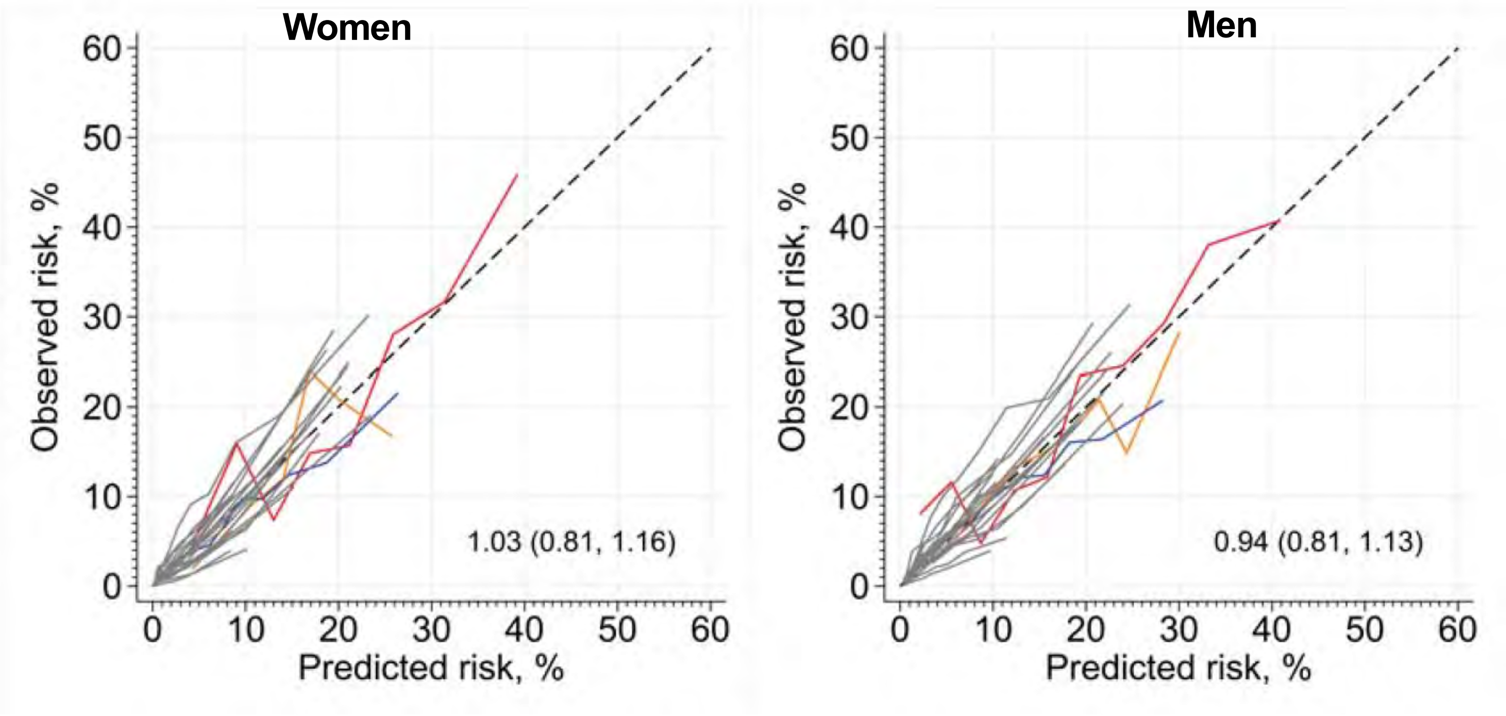
Risk factor	Total CVD		ASCVD		Heart failure	
	Female N=1 734 246	Male N=1 356 397	Female N=1 734 246	Male N=1 356 397	Female N=1 734 246	Male N=1 356 397
Cardiovascular disease risk factors in the PREVENT-CVD primary model						
…all risk factors and age interactions included but not shown						
eGFR <60, −15 mL/min per 1.73 m^2	1.72 (1.64–1.81)	1.61 (1.53–1.69)	1.58 (1.48–1.69)	1.42 (1.36–1.49)	1.96 (1.85–2.07)	1.83 (1.69–1.97)
…						
Kidney function						
Ln UACR, mg/g, per 1 ln unit	1.19 (1.17–1.22)	1.21 (1.20–1.23)	1.16 (1.14–1.19)	1.17 (1.15–1.19)	1.23 (1.21–1.26)	1.27 (1.24–1.29)
No UACR available†	1.02 (0.98–1.07)	1.12 (1.07–1.18)	1.01 (0.96–1.05)	1.07 (1.02–1.13)	1.04 (0.98–1.11)	1.19 (1.13–1.25)
Glycemic status						
HbA1c in diabetes, per 1%	1.14 (1.06–1.23)	1.13 (1.07–1.19)	1.14 (1.05–1.23)	1.11 (1.05–1.18)	1.20 (1.12–1.28)	1.17 (1.10–1.24)
HbA1c no diabetes, per 1%	1.15 (1.14–1.16)	1.11 (1.10–1.12)	1.15 (1.14–1.17)	1.12 (1.10–1.14)	1.18 (1.16–1.20)	1.13 (1.12–1.15)
No HbA1c available†	0.99 (0.94–1.05)	0.97 (0.93–1.02)	1.00 (0.95–1.06)	0.99 (0.94–1.03)	1.00 (0.94–1.06)	0.97 (0.91–1.04)
SDI‡ decile categories						
SDI 1–3	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
SDI 4–6	1.15 (1.07–1.24)	1.09 (1.00–1.20)	1.16 (1.08–1.24)	1.08 (0.97–1.20)	1.14 (1.02–1.26)	1.13 (1.02–1.25)
SDI 7–10	1.26 (1.15–1.38)	1.33 (1.23–1.43)	1.26 (1.16–1.38)	1.32 (1.23–1.43)	1.27 (1.15–1.40)	1.42 (1.26–1.59)
No SDI available†	1.20 (1.13–1.27)	1.16 (1.10–1.24)	1.18 (1.12–1.24)	1.16 (1.09–1.23)	1.20 (1.12–1.29)	1.19 (1.10–1.29)

HF

External Validation: Calibration Plots for All CVD

	Derivation Sample		Validation Sample	
	Female	Male	Female	Male
N, participants	1,839,828	1,442,091	1,894,882	1,435,203
N, cohorts	25	25	21	21

REGARDS
CRIC
Rancho B.
OLDW



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PREVENT Model –Discrimination & Calibrationin Validation Sample (n~3.2 Million)

Models	Total CVD		ASCVD		Heart failure	
	Female	Male	Female	Male	Female	Male
Base PREVENT model						
No. of cohorts	21	21	21	21	21	21
No. of participants	1 894 882	1 435 203	1 894 882	1 435 203	1 894 882	1435 203
No. of events	50 324	46 804	31 277	31 328	27 931	23 707
C-statistic (IQI)	0.794 (0.763 to 0.809)	0.757 (0.727 to 0.778)	0.774 (0.743 to 0.788)	0.736 (0.710 to 0.755)	0.830 (0.816 to 0.850)	0.809 (0.777 to 0.827)
Calibration slope (IQI)	1.03 (0.81 to 1.16)	0.94 (0.81 to 1.13)	1.09 (0.93 to 1.33)	1.04 (0.95 to 1.19)	1.00 (0.55 to 1.15)	0.89 (0.49 to 1.07)

Good discrimination & calibration – overall & in subgroups

Slightly improved discrimination vs. PCE & by adding eGFR, ACR, A1c, SDI

Good calibration for all CVD subtypes (vs. PCE ASCVD predicted ~2 x observed)

Ndumele, C.E. et al., Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. 2023. *Circulation*.

- HF included

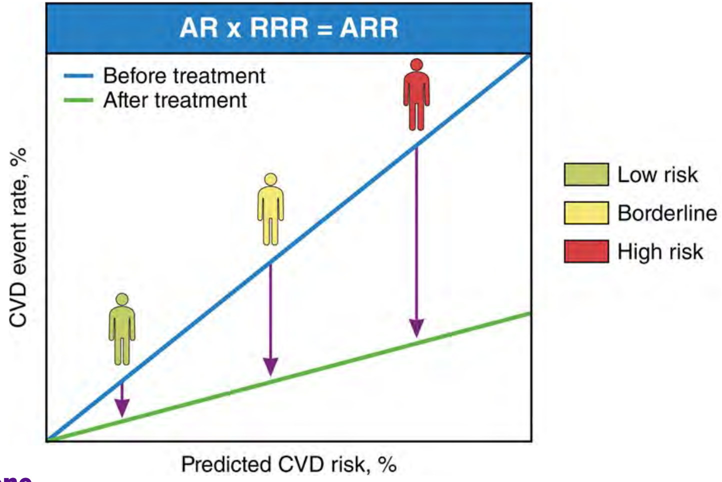
- **eGFR in the Base PREVENT model**
- **ACR optional**

Key Takeaways of the AHA PREVENT Equations
1. Include a large, contemporary, and diverse sample of US adults for derivation and external validation
2. Predict the risk of total or global CVD as a composite of atherosclerotic cardiovascular disease and heart failure as well as for each CVD subtype separately
3. Broaden the outcome to include prediction of heart failure
4. Remove race from risk prediction acknowledging that race is a social construct and not a biological predictor
5. Lower the age to begin risk prediction as early as age 30 years and capture a greater proportion of the adult life course
6. Provide risk estimates for CVD over a 10-year and 30-year time span
7. Offer optional models that incorporate add-on measures of kidney and metabolic health when indicated given the growing burden of cardiovascular-kidney-metabolic (CKM) syndrome
8. Include a measure of place-based social disadvantage (social deprivation index [SDI]) to acknowledge the role of social determinants of health in cardiovascular disease risk

Cohort consortium informs clinical practice guidelines

American Heart Association PREVENT™

Higher predicted (absolute risk, AR) often identifies greater treatment benefit (absolute risk reduction, ARR)



What's to come:

1. Evaluate Net Benefit in Trials
2. Equity evaluation
3. *Implementation by AHA*
   - *Anticipate use in **guidelines***
4. Integration into **EMR** and clinical practice
   - *Clinical decision support (CDS)*
   - *Replace PCE (e.g. in national EPIC)*

HF risk prediction including eGFR and ACR

Khan et al. *Circulation* 148: 1982–2004 (2023)
Corresponding – ckdpc@nyulangone.org

Future Directions

- The recent AHA PREVENT risk equations help determine who is at high risk but focused on:
  - Traditional cardiovascular risk factors
  - People without any CVD

- NT-pro-BNP and hs-troponin levels might provide additional risk information over traditional risk factors and within a broader patient population

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Research Questions

- What is the added value of NT-pro-BNP as a heart failure risk factor across a range of cohorts and patient characteristics (age, sex, BMI, eGFR, prevalent CHD/stroke (ASCVD), DM)?

- Does hs-troponin add additional information after NT-pro-BNP?

- Are NT-pro-BNP and hs-troponin levels across cohorts and measurement methods relatively uniform allowing for harmonization?

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Biomarkers & HF: Statistical Analysis

- Key Exposures:
  - NT-pro-BNP (undetectable imputed at 2.5 pg/mL = 0.5*detectable) continuous
    - Continuous, log2 (NT-por-BNP)
    - <> 125 ng/L
  - TnT categories: undetectable, low, high (>=99th percentile)
- Cox PH analysis
  - Follow-up time scale (adjusted for age)
  - Combining men and women
  - Test interactions: Sex , age, BMI categorical (<30/>30), eGFR (< > 60), ACR (< > 30), DM, ASCVD
  - Cohort-specific & meta-analysis
- Uniformity of biomarker levels across cohorts
  - Compare levels adjusted for risk factors (age, sex, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, anti-hypertensive use, statin use, diabetes, BMI (knot at 30), eGFR (spline knot at 60), ACR, ASCVD)

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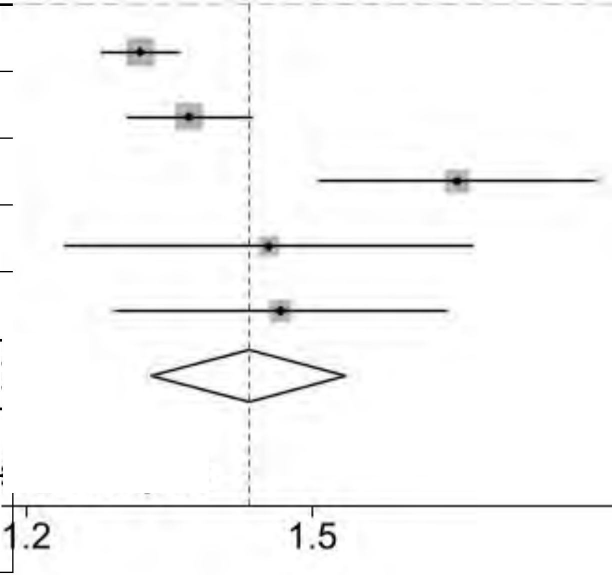
Adjusted Hazard Ratio of Heart Failure per 2-fold higher NT-pro-BNP

Study	**Hazard Ratio** Adj. HR, per 2 fold higher NTproBNP	C-statistic Adj. Model	Δ in C-statistic Adding NT-pro-BNP
1	**1.31 (1.27, 1.35)**	0.752	**0.016 (0.011, 0.020)**
2	**1.36 (1.30, 1.43)**	0.774	**0.030 (0.020, 0.040)**
3	**1.68 (1.51, 1.87)**	0.781	**0.065 (0.038, 0.093)**
4	**1.45 (1.24, 1.70)**	0.767	**0.035 (0.009, 0.060)**
5	**1.46 (1.28, 1.67)**	0.679	**0.052 (0.020, 0.083)**
Meta-analysis	**1.43 (1.32, 1.54)**		**Range: 0.016 to 0.065**

Results are similar when adjusted for PREVENT base risk score

Further addition of hs-TNT does not improve the C-statistic much (~0.004, only statistically significant in one study)



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Adjusted for age, sex, SBP, BP meds, smoking, DM, BMI, eGFR, ACR, prevalent CHD/stroke (ASCVD)

NT-Pro-BNP: No Consistent Interactions

Log2 NTproBNP	1	2	3	4	5
NTproBNP in men (example)	**1.33 (1.28, 1.39)**	**1.34 (1.26, 1.42)**	**1.64 (1.47, 1.84)**	**1.36 (1.12, 1.64)**	**1.46 (1.28, 1.67)**
Interactions (*NTproBNP): **Female**	0.96 (0.91, 1.02)	1.06 (0.97, 1.15)	1.18 (0.89, 1.57)	1.21 (0.89, 1.63)	
Age	**1.08 (1.02, 1.13)**	1.02 (0.97, 1.07)	0.96 (0.84, 1.09)	1.07 (0.90, 1.26)	
BMI	**0.92 (0.88, 0.96)**	0.97 (0.93, 1.01)	**0.81 (0.72, 0.91)**	0.98 (0.81, 1.20)	1.37 (0.82, 2.29)
Diabetes	**0.92 (0.86, 0.97)**	**0.91 (0.83, 0.99)**	**0.70 (0.57, 0.86)**	0.86 (0.63, 1.17)	0.84 (0.59, 1.18)
eGFR (-15 ml/min)	0.97 (0.92, 1.03)	0.95 (0.90, 1.01)	0.95 (0.82, 1.10)	0.85 (0.65, 1.13)	1.68 (0.63, 4.51)
lnACR	**1.02 (1.01, 1.04)**	**0.97 (0.95, 0.99)**	0.97 (0.93, 1.02)	0.99 (0.89, 1.10)	1.02 (0.93, 1.12)

Adjusted for age, sex, SBP, BP meds, smoking, DM, BMI, eGFR, ACR, prevalent CHD/stroke (ASCVD)

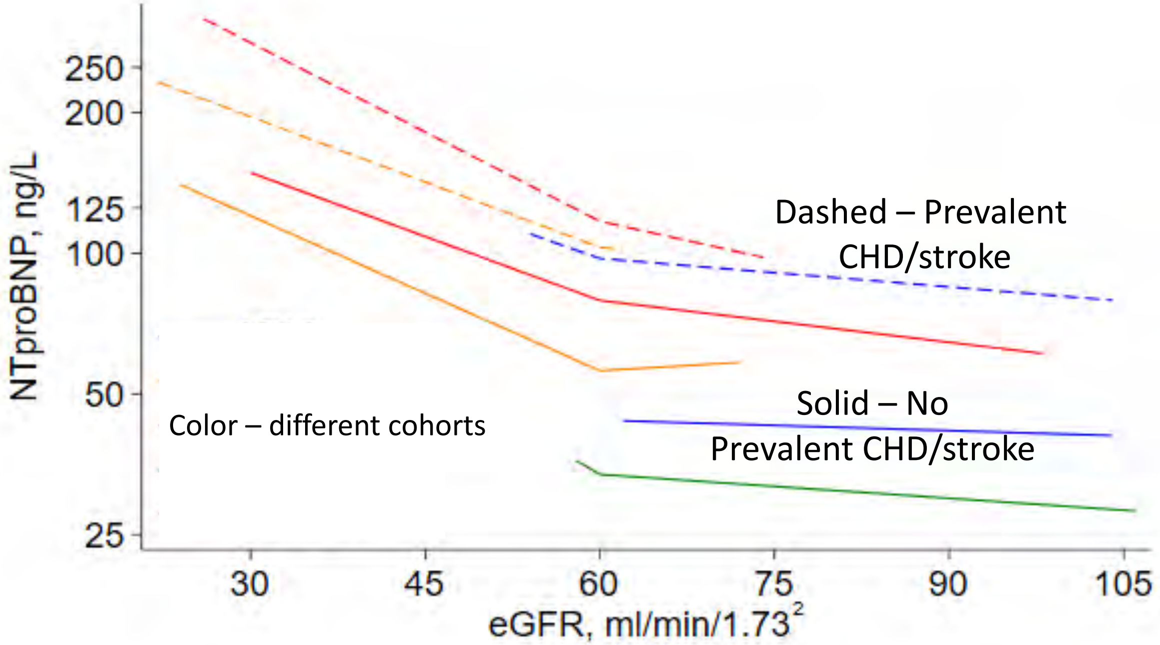
NT-Pro-BNP: Inconsistency across cohorts

Large between cohort variation

Beyond CVD risk factors

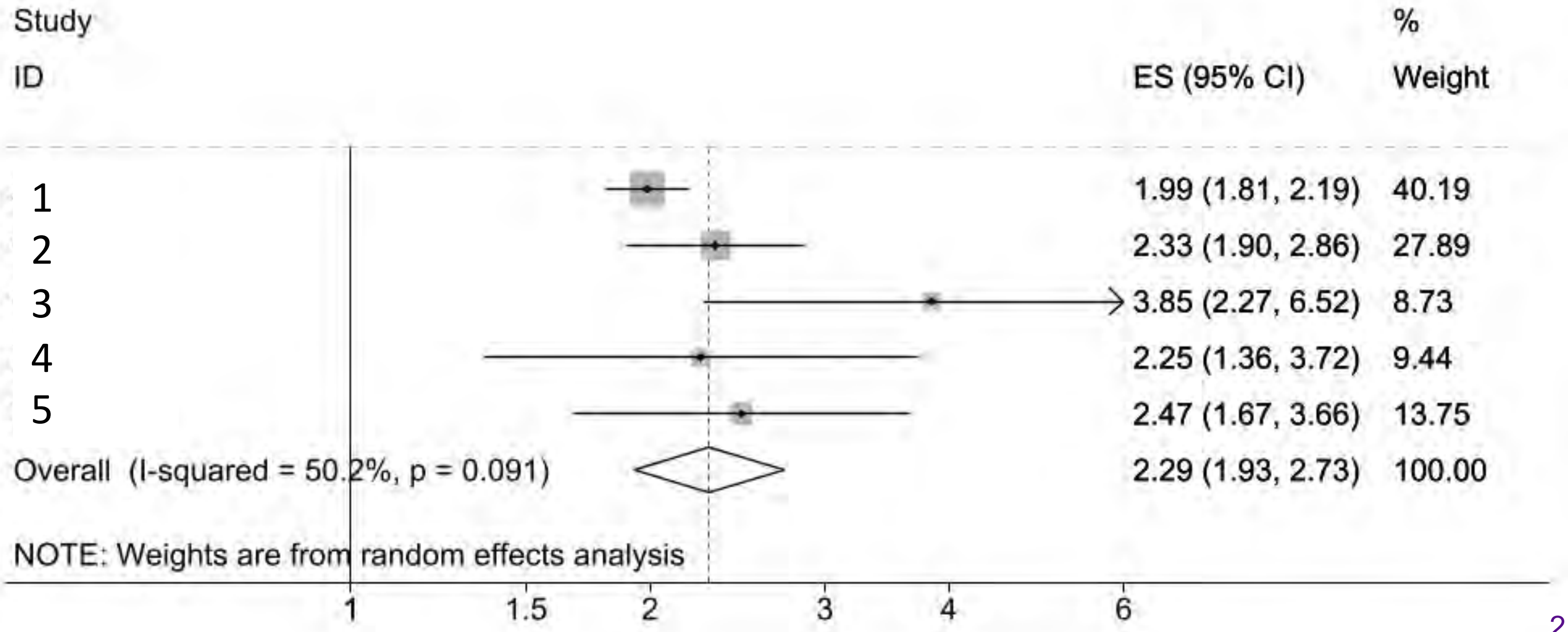
- Higher levels
  - Prevalent CHD/stroke
  - Lower eGFR
- Adjustment to age 55, male, SBP 130, BMI 25, no DM, no smoking, ACR 30

Absolute cutoffs may mean different things in different cohorts/settings



NT-Pro-BNP: 125 ng/L Threshold

- Consistent relative hazards for <>125 ng/L -- despite variable levels across cohorts



Adjusted for age, sex, SBP, BP meds, smoking, DM, BMI, eGFR, ACR, prevalent CHD/stroke (ASCVD)

NT-Pro-BNP: 125 ng/L Threshold

- Consistent relative hazards for <>125 ng/L -- despite variable levels across cohorts

Study	HR BNP ≥ 125 Vs. <125	C-statistic, base	Δ in C-statistic
1	**1.99 (1.81, 2.19)**	0.752	**0.012 (0.008, 0.016)**
2	**2.33 (1.90, 2.86)**	0.774	**0.014 (0.006, 0.021)**
3	**3.85 (2.27, 6.52)**	0.781	**0.026 (0.008, 0.044)**
4	**2.25 (1.36, 3.72)**	0.767	**0.024 (0.005, 0.042)**
5	**2.47 (1.67, 3.66)**	0.679	**0.036 (0.006, 0.065)**

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Adjusted for age, sex, SBP, BP meds, smoking, DM, BMI, eGFR, ACR, prevalent CHD/stroke (ASCVD)

Conclusions: Prediction of Heart Failure in CKD

- **Background** – CKD staging & risk prediction in CKD (ckdpcrisk.org) are well developed with multiple tools ready for wider application
- **Cardiovascular risk prediction** – ASCVD (CHD, stroke), **HF**, CVM
  - AHA PREVENT (Circulation 2024; US cohorts) includes
    - HF risk prediction
    - eGFR and ACR
- **Future directions** – Biomarker: NT-pro-BNP is a consistent risk factor across a wide range of cohorts and subgroups (including CKD) despite **some calibration issues**
  - Could be used to identify patients who may benefit from early treatment of HF risk factors; as well as inclusion in future clinical trials of HF therapies in CKD.

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Thank you

CKD Prognosis Consortium (NKF & KDIGO)
Steering committee: J Coresh (co-PI), M Grams (co-PI), K Matsushita (CVD), S Ballew, A Levey, R Gansevoort, Juan-Jesus Carrero, Michael Shlipak, Dorothea Nitsch
Analysis leaders: Y Sang, A Surapaneni

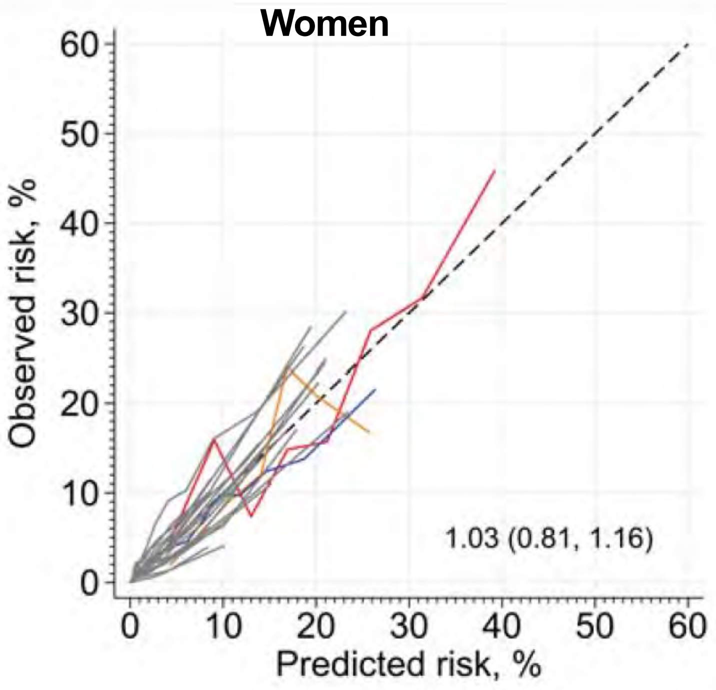
CKD-EPI Collaboration (eGFR)
Lesley Inker & Andrew Levey

Johns Hopkins & NYU Langone Health co-investigators & staff

External Validation: Calibration Plots for All CVD

	Derivation Sample		Validation Sample	
	Female	Male	Female	Male
N, participants	1,839,828	1,442,091	1,894,882	1,435,203
N, cohorts	25	25	21	21

REGARDS
CRIC
Rancho B.
OLDW



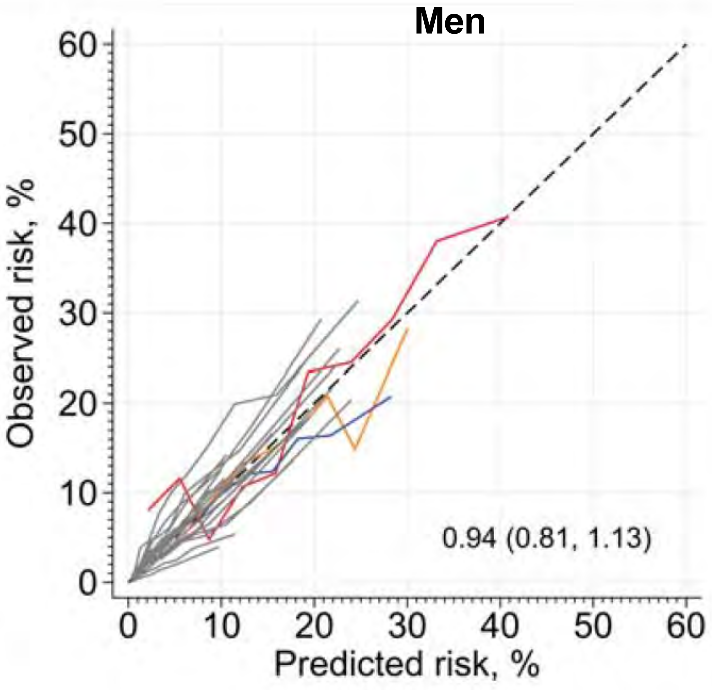


Table 1. Individual-level participant baseline characteristics of derivation and validation samples stratified by sex for prediction of total cardiovascular disease and cardiovascular disease subtypes.

	Derivation Sample		Validation Sample	
	Female	Male	Female	Male
N, participants	**1,839,828**	**1,442,091**	**1,894,882**	**1,435,203**
N, cohorts	**25**	**25**	**21**	**21**
Age, years, mean (SD)	53 (13)	52 (12)	52 (13)	52 (12)
Race and Ethnicity, %				
White	78%	80%	78%	80%
Black	10%	8.0%	10%	8.2%
Hispanic	6.0%	5.3%	4.2%	3.7%
Asian	2.6%	2.5%	2.7%	2.2%
Other/Missing*	4.1%	4.6%	4.9%	5.5%
Cardiovascular Risk Factors/Predictors in PREVENT-CVD Primary Model				
SBP, mm Hg	123 (16)	127 (15)	123 (16)	128 (15)
Total cholesterol, mmol/L	5.0 (0.8)	4.9 (0.8)	5.0 (0.8)	4.9 (0.8)
Non-HDL-C, mmol/L	3.4 (0.8)	3.6 (0.8)	3.5 (0.8)	3.6 (0.8)
HDL-C, mmol/L	1.5 (0.4)	1.2 (0.3)	1.5 (0.4)	1.2 (0.3)
BMI*, kg/m^2	29 (5)	29 (4)	28 (5)	29 (4)
Diabetes, %	10%	12%	11%	13%
Current smoking, %	5.8%	6.2%	4.7%	4.9%
Anti-hypertensive treatment, %	23%	27%	24%	29%
Statin treatment, %	14%	17%	14%	17%
eGFR, mean (SD), mL/min/1.73 m^2	91 (19)	91 (17)	91 (18)	91 (17)
Add-on Risk Factors/Predictors in Sequential Models				
UACR, median (IQI), mg/g**	8 (8-12)	8 (8-12)	8 (8-12)	8 (8-11)
HbA1c, mean (SD), %	7.3 (1.8)	7.6 (1.9)	7.2 (1.8)	7.6 (1.9)
SDI decile, median (IQI)***	4 (2-7)	3 (2-6)	4 (2-7)	4 (2-6)
Outcomes				
Mean follow-up time	4.8 (3.1)	4.6 (3.0)	5.0 (3.2)	4.8 (3.2)
Total CVD events	53258	53403	54365	50489
ASCVD events	31812	34691	33969	33933
HF events	30957	28393	30287	25679
Deaths	84289	80897	82555	76783

Development and Validation of PREVENT^{TM} (pending) Equations: Methods

Derivation: 25 datasets (3,281,919 participants) between 1992-2017.

Primary outcome: CVD (atherosclerotic CVD [ASCVD] **and heart failure [HF]**).

Predictors: Traditional risk factors (smoking status, systolic blood pressure, cholesterol, anti-hypertensive or statin use, diabetes) and estimated glomerular filtration rate [**eGFR**].

Models: Sex-specific, developed on the age-scale, and adjusted for **competing** risk of non-CVD **death**.

Analyses: In each dataset and meta-analyzed.

- Discrimination was assessed using Harrell's C-statistic.
- Calibration was calculated as the slope of the observed vs. predicted risk by decile.

Equations: Sequential equations to predict each CVD subtype (ASCVD, HF)

- Equations with **additional** predictors (urine albumin-to-creatinine ratio [**UACR**], hemoglobin A1c [**HbA1c**]), and social deprivation index [**SDI**])

External validation: 3,330,085 participants from 21 additional datasets.

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PREVENT^{TM} Equations

Results:

6,612,004 adults included, mean (SD) age was 53 (12) years and 56% were female.

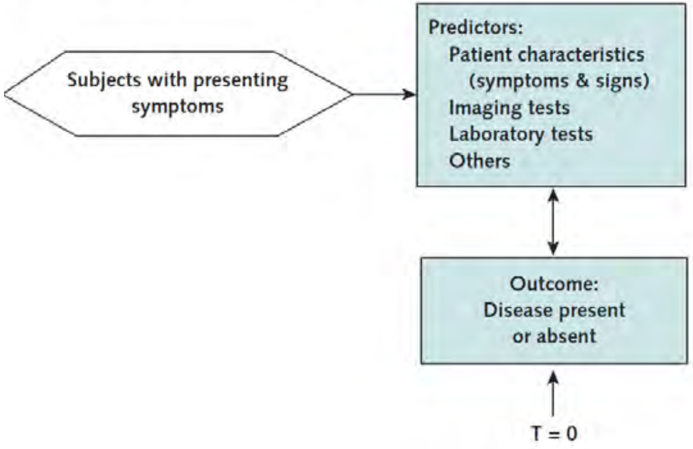
Follow-up: mean (SD) 4.8 (3.1) years; 211,515 incident total CVD events.

External validation

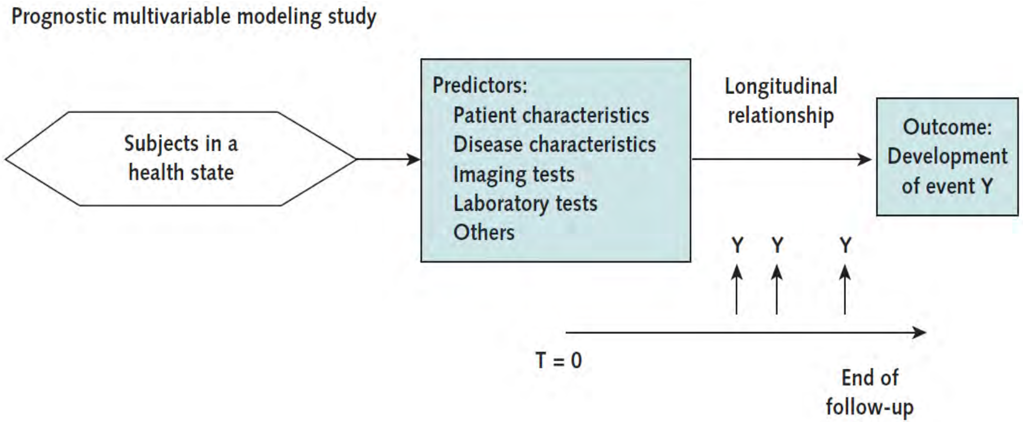
- Median C-statistics for CVD were 0.794 (interquartile interval [IQI]: 0.763-0.809) in female and 0.757 (0.727-0.778) in male participants.
  improved by eGFR, improved on PCE (by a little)
- Calibration slopes were 1.03 (IQI 0.81 -1.16) and 0.94 (0.81-1.13) among females and males
  Lower ASCVD calibration than PCE (slope ~0.5); all CVD closer to PCE ASCVD
- Similar estimates for discrimination and calibration for ASCVD- and HF-specific models.
- The improvement in discrimination was small but statistically significant when UACR, HbA1c, and SDI were added together to the base model to total CVD (ΔC-statistic [IQI] 0.004 [0.004, 0.005] and 0.005 [0.004, 0.007] among females and males, respectively).

Prediction – Individualized Estimate from a Multivariable Model
Diagnostic vs. Prognostic (harder to predict the future)

Diagnostic: Cross-sectional



Prognosis: Prospective Risk Modeling



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Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the **TRIPOD statement**. Ann Intern Med 2015;162: 55-63.

Development of Risk Prediction Models

Consideration	Comments
1. Population at risk	Identify persons at risk to whom the model will be applied on the basis of demographic characteristics, health status, location, and clinical context.
2. Outcome of interest	Use well-curated data, with outcomes that reflect the primary focus of care.
3. Time horizon	Starting point and duration of follow-up should align with goals of interventions.
4. Predictors	Decisions about choices and number of predictors should take into account ease and time of collection, possible bias, model stability, and interpretation (e.g., understanding what outputs the model produces and identifying key predictors and their association with outcome).

Consideration	Comment
5. Mathematical model	Balance performance with ability to understand, implement, and maintain the model. Burden of proof is placed on the more complex models. Be transparent and avoid black-box solutions.
6. Model evaluation	Rigorously evaluate the model using data different from those used for development and collected in a setting that mirrors clinical application.
7. Translation to CDS **(clinical decision support)**	To translate model into CDS, determine intended use and what should be displayed. Separate evaluation of the CDS tool is necessary, including comparison with current practice (ideally, randomized).
8. Clinical implementation	Incorporation into clinical workflows with training, performance engineering, monitoring, and updating, when necessary, is required.

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Pencina, Goldstein and D'Agostino, NEJM 2020:1583-1586
TRIPOD statement. Ann Intern Med 2015;162: 55-63.

Age-related diseases can be prevented

Vascular health is central to optimal aging

Inter-connected function of the:

- Heart, kidney, brain & muscles

Life's essential 8 (keys to prevention):

- No smoking, good sleep, diet & exercise
- Optimal blood glucose, lipids & pressure
- Ideal weight

Huge potential to prevent chronic diseases

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Cohort consortium informs clinical practice guidelines

Chronic kidney disease heatmap

	Urine albumin to creatinine ratio, mg/g				
Overall	<10	10-29	30-299	300-999	≥1000
eGFR, mL/min/1.73 m² using creatinine alone	All-cause mortality: 82 cohorts 26 444 384 participants; 2 604 028 events				
≥105	1.6	2.2	2.9	4.3	5.8
90-104	Reference	1.3	1.8	2.6	3.1
60-89	1.0	1.3	1.7	2.2	2.8
45-59	1.3	1.6	2.0	2.4	3.1
30-44	1.8	2.0	2.5	3.2	3.9
15-29	2.8	2.8	3.3	4.1	5.6
<15	4.6	5.0	5.3	6.0	7.0

Grams, Coresh *et al.* for CKD Prognosis Consortium
JAMA 330(13):1266-1277 (2023)

Lower kidney filtration and higher urine protein **predict higher risk** of 10 adverse outcomes in **27 million people**.

→ KDIGO guidelines 2024

→ Ckdpcrisk.org – implemented into more EMRs

CKD Prognosis Consortium

International consortia inform clinical practice guidelines

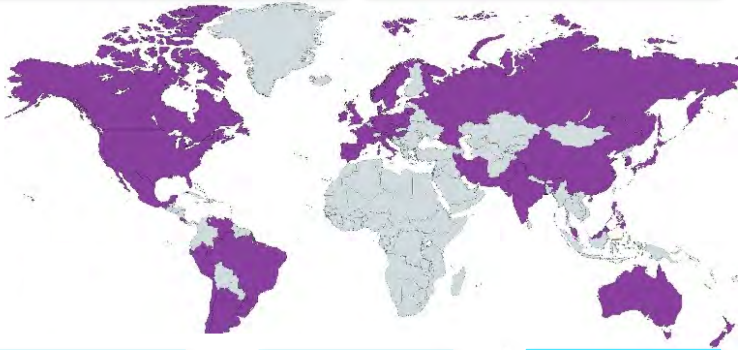
CKD Prognosis Consortium

Chronic Kidney Disease Prognosis Consortium (CKD-PC)

Co-PIs: Morgan Grams (Precision Medicine) & Josef Coresh (OAI)
Operations Director: Shoshana Ballew

>100 cohorts

>30 million participants



- Move from prognosis to **clinical practice guidelines**
- **Establish risk scores** for chronic kidney disease, cardiovascular disease (AHA PREVENT™) and heart failure

Collaborative Opportunities

- Leverage data for research into dementia, aging & cancer
- National & global EMR research

ckdpc@nyulangone.org

Morgan Grams

Josef Coresh

Shoshana Ballew

Definition of CKM Syndrome Simplified

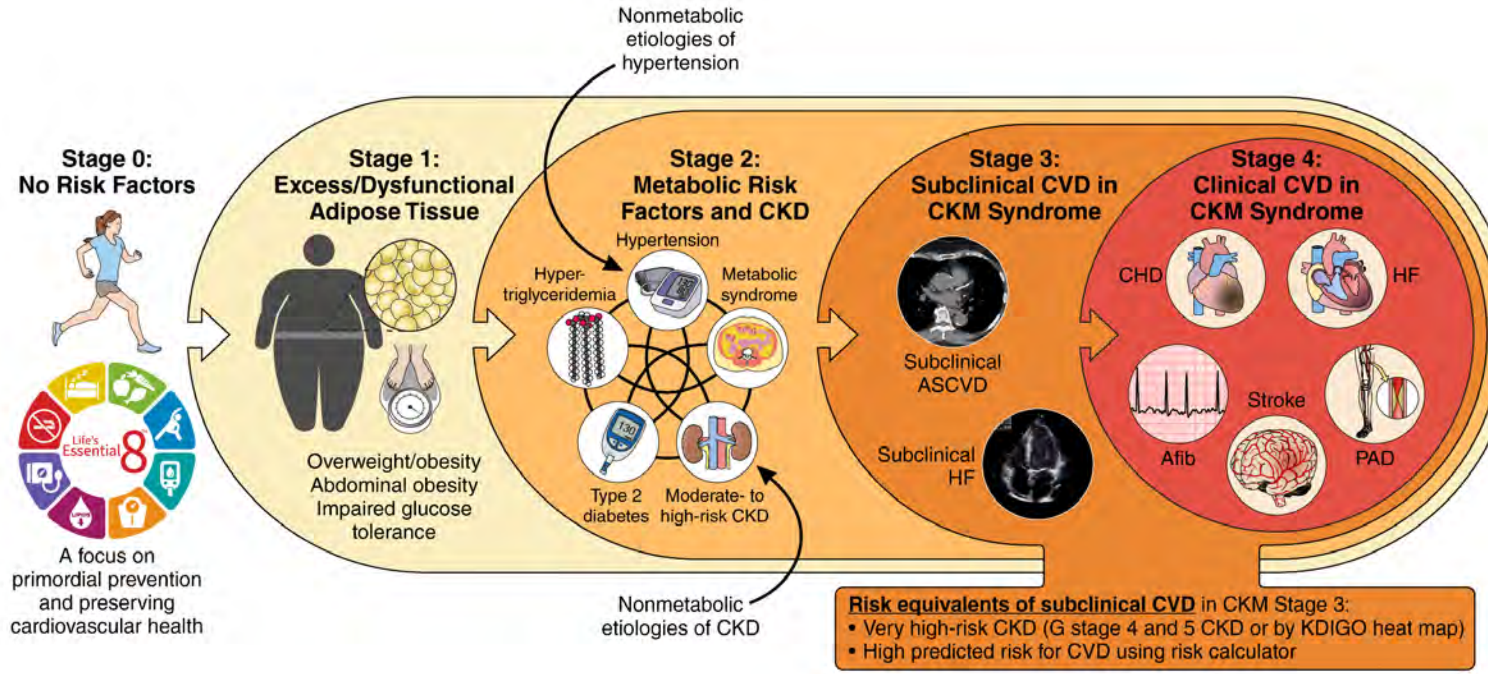
Cardiovascular-kidney-metabolic (CKM) syndrome
is a health disorder due to connections among heart disease, kidney disease, diabetes, and obesity leading to poor health outcomes.

Abbreviations: CKM indicates Cardiovascular-Kidney-Metabolic.

American Heart Association.

Ndumele, C.E. et al., Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. 2023. *Circulation*.

Stages of Cardiovascular-Kidney-Metabolic Syndrome



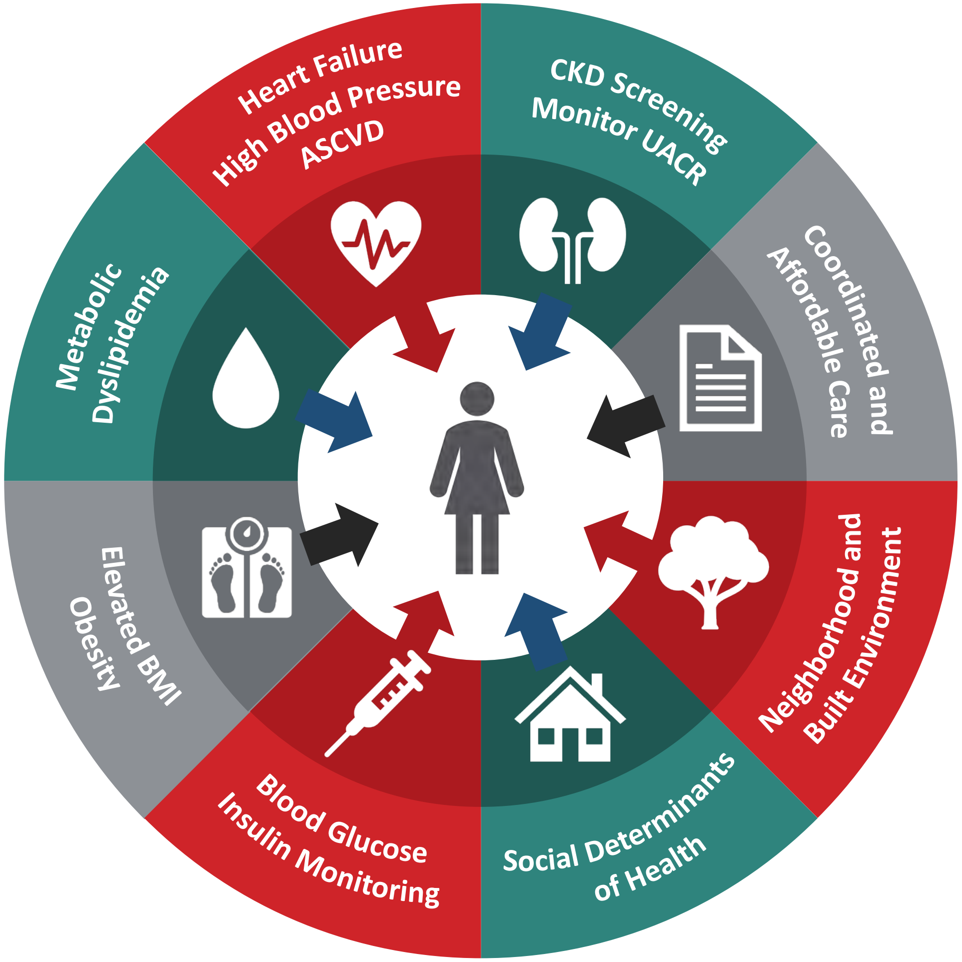
Abbreviations: Afib indicates atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease: CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; HF, heart failure; KDIGO, Kidney Disease Improving Global Outcomes; and PAD, peripheral artery disease.

American Heart Association.

Ndumele, C.E. et al., Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. 2023. *Circulation*.

Cardiovascular-Kidney-Metabolic Syndrome

Patient-Centered Implementation Focus



Abbreviations: ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; and UACR, urine albumin-creatinine ratio.

American Heart Association.

Ndumele, C.E. et al., Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. 2023. *Circulation*.

Table S5D. Meta-analyzed calibration slope (IQI) for the base model with and without eGFR

	Base without eGFR		Base	
Subgroup	**Development**	**Validation**	**Development**	**Validation**
	Total CVD			
Overall	1.07 (0.84, 1.28)	1.02 (0.80, 1.21)	1.06 (0.81, 1.23)	1.00 (0.81, 1.14)
Men	1.07 (0.89, 1.28)	0.96 (0.79, 1.14)	1.06 (0.89, 1.25)	0.94 (0.81, 1.13)
Women	1.08 (0.85, 1.28)	1.05 (0.80, 1.17)	1.06 (0.82, 1.21)	1.03 (0.81, 1.16)
eGFR <60	1.34 (1.04, 1.75)	1.29 (0.98, 1.48)	1.10 (0.87, 1.35)	1.02 (0.83, 1.22)
eGFR <45	1.55 (1.19, 1.99)	1.53 (1.03, 1.67)	1.11 (0.89, 1.30)	1.04 (0.73, 1.22)

Under-predict (O>E)

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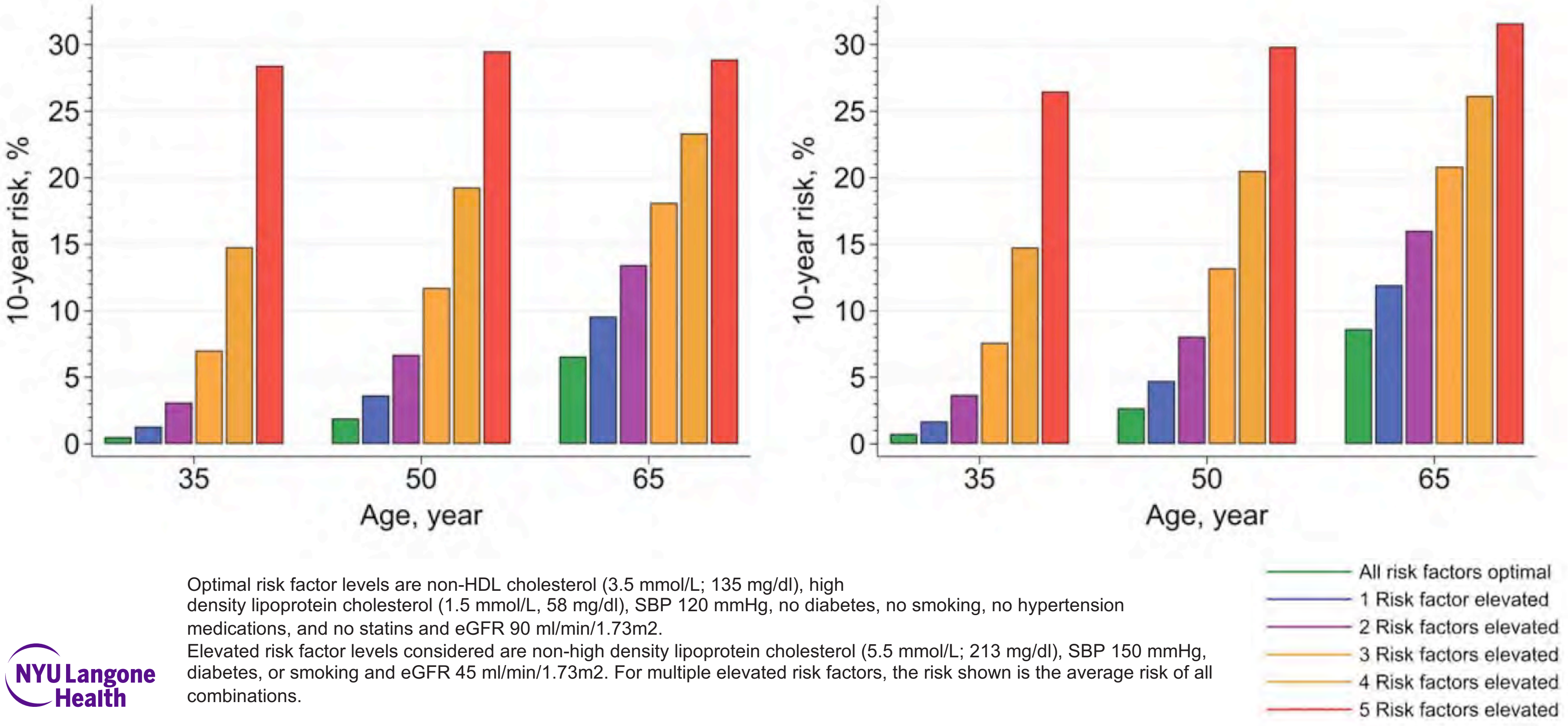
All CVD 10-Year Risk by Sex, Age and Number of Elevated Risk Factors



Optimal risk factor levels are non-HDL cholesterol (3.5 mmol/L; 135 mg/dl), high density lipoprotein cholesterol (1.5 mmol/L, 58 mg/dl), SBP 120 mmHg, no diabetes, no smoking, no hypertension medications, and no statins and eGFR 90 ml/min/1.73m2.
Elevated risk factor levels considered are non-high density lipoprotein cholesterol (5.5 mmol/L; 213 mg/dl), SBP 150 mmHg, diabetes, or smoking and eGFR 45 ml/min/1.73m2. For multiple elevated risk factors, the risk shown is the average risk of all combinations.

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Statement on Risk Prediction Includes PREVENT™ (pending) Risk Scenarios

10-year CVD risk in Women

			Diabetes (No)																							
			Whites												Blacks											
			Current Smoking (No)						Current Smoking (Yes)						Current Smoking (No)						Current Smoking (Yes)					
			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic		
Age	Total Chol	HDL Chol	100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160
40	160	65	0%	0%	0%	0%	0%	1%	1%	1%	1%	1%	2%	2%	0%	0%	0%	1%	1%	3%	0%	0%	1%	1%	3%	5%
		55	0%	0%	0%	0%	1%	1%	1%	1%	2%	2%	2%	3%	0%	0%	1%	1%	2%	4%	0%	1%	1%	2%	4%	8%
		45	0%	0%	1%	1%	1%	1%	1%	2%	3%	3%	4%	5%	0%	1%	1%	1%	3%	7%	0%	1%	2%	3%	6%	13%
	200	65	0%	0%	0%	0%	1%	1%	1%	2%	2%	2%	3%	4%	0%	0%	1%	1%	2%	3%	0%	1%	1%	1%	3%	7%
		55	0%	1%	1%	1%	1%	1%	1%	2%	3%	3%	4%	5%	0%	0%	1%	1%	2%	5%	0%	1%	2%	2%	5%	10%
		45	1%	1%	1%	1%	1%	2%	2%	3%	4%	4%	6%	7%	0%	1%	1%	2%	4%	8%	0%	1%	3%	3%	8%	15%
	240	65	0%	1%	1%	1%	1%	1%	2%	2%	3%	3%	4%	5%	0%	0%	1%	1%	2%	4%	0%	1%	1%	2%	4%	8%
		55	1%	1%	1%	1%	1%	2%	2%	3%	4%	4%	6%	7%	0%	0%	1%	1%	3%	6%	0%	1%	2%	2%	6%	11%
		45	1%	1%	1%	1%	2%	3%	3%	4%	6%	6%	8%	10%	0%	1%	2%	2%	5%	9%	1%	2%	3%	4%	9%	18%
50	160	65	0%	1%	1%	1%	1%	2%	1%	2%	3%	3%	3%	4%	0%	1%	2%	2%	3%	5%	1%	2%	3%	3%	6%	11%
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		45	1%	1%	1%	1%	2%	2%	2%	3%	4%	4%	5%	7%	1%	2%	3%	3%	5%	9%	2%	3%	6%	6%	10%	17%
	200	65	1%	1%	1%	1%	2%	2%	2%	3%	3%	3%	5%	6%	1%	1%	2%	2%	4%	7%	1%	2%	4%	4%	8%	13%
		55	1%	1%	1%	1%	2%	3%	2%	3%	4%	4%	6%	7%	1%	1%	3%	3%	5%	8%	1%	3%	5%	5%	10%	16%
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60	160	65	2%	2%	3%	3%	4%	5%	3%	5%	6%	6%	8%	11%	2%	3%	5%	4%	7%	10%	4%	6%	10%	8%	13%	18%
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	200	65	2%	3%	4%	3%	5%	6%	4%	5%	7%	7%	10%	13%	2%	4%	6%	5%	8%	12%	5%	8%	12%	10%	15%	22%
		55	2%	3%	4%	4%	5%	7%	4%	6%	8%	8%	11%	14%	3%	4%	7%	6%	9%	13%	5%	8%	13%	11%	17%	24%
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	240	65	2%	3%	4%	4%	5%	7%	4%	6%	8%	8%	11%	14%	3%	5%	7%	6%	9%	14%	5%	9%	14%	12%	18%	25%
		55	2%	3%	5%	4%	6%	8%	5%	7%	9%	9%	13%	16%	3%	5%	8%	7%	10%	15%	6%	10%	15%	13%	20%	28%
		45	3%	4%	5%	5%	7%	9%	6%	8%	11%	11%	14%	18%	3%	6%	9%	8%	12%	17%	7%	11%	17%	14%	22%	31%
70	160	65	5%	8%	10%	10%	14%	17%	9%	12%	16%	16%	21%	27%	6%	9%	11%	9%	12%	15%	12%	16%	22%	17%	22%	28%
		55	6%	8%	10%	10%	14%	18%	9%	13%	17%	17%	22%	28%	6%	8%	11%	9%	12%	15%	12%	16%	21%	17%	22%	27%
		45	6%	8%	11%	11%	15%	19%	9%	13%	17%	17%	23%	29%	6%	8%	11%	9%	11%	15%	11%	16%	21%	16%	21%	27%
	200	65	6%	8%	11%	11%	14%	18%	9%	13%	17%	17%	23%	29%	7%	11%	14%	11%	14%	18%	14%	20%	26%	20%	27%	33%
		55	6%	8%	11%	11%	15%	19%	10%	13%	18%	18%	23%	29%	7%	10%	14%	11%	14%	18%	14%	20%	26%	20%	26%	33%
		45	6%	9%	12%	12%	15%	20%	10%	14%	18%	18%	24%	30%	7%	10%	14%	10%	14%	18%	14%	19%	25%	20%	26%	32%
	240	65	6%	9%	11%	11%	15%	19%	10%	14%	18%	18%	24%	30%	9%	12%	16%	13%	17%	21%	17%	23%	30%	24%	31%	38%
		55	6%	9%	12%	12%	16%	20%	10%	14%	19%	19%	25%	31%	9%	12%	16%	12%	17%	21%	17%	23%	30%	23%	30%	37%
		45	7%	9%	12%	12%	16%	21%	11%	15%	19%	19%	25%	32%	9%	12%	16%	12%	16%	21%	16%	22%	29%	23%	30%	37%

			Diabetes (Yes)																							
			Whites												Blacks											
			Current Smoking (No)						Current Smoking (Yes)						Current Smoking (No)						Current Smoking (Yes)					
			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic			Untreated Systolic			Treated Systolic		
Age	Total Chol	HDL Chol	100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160	100	120	140	120	140	160
40	160	65	0%	0%	1%	1%	1%	1%	1%	2%	3%	3%	3%	4%	0%	1%	1%	1%	3%	6%	0%	1%	2%	3%	6%	12%
		55	0%	1%	1%	1%	1%	1%	2%	3%	3%	3%	5%	6%	0%	1%	2%	2%	5%	10%	1%	2%	4%	4%	9%	18%
		45	1%	1%	1%	1%	2%	2%	3%	4%	5%	5%	7%	9%	0%	1%	3%	3%	7%	15%	1%	2%	6%	6%	14%	28%
	200	65	0%	1%	1%	1%	1%	2%	2%	3%	4%	4%	5%	7%	0%	1%	1%	2%	4%	8%	0%	1%	3%	3%	8%	15%
		55	1%	1%	1%	1%	2%	2%	3%	4%	5%	5%	7%	9%	0%	1%	2%	2%	6%	12%	1%	2%	4%	5%	11%	22%
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		45	12%	16%	21%	21%	28%	35%	18%	25%	33%	32%	42%	50%	16%	23%	29%	23%	30%	37%	30%	40%	50%	41%	51%	60%
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		45	12%	17%	22%	22%	29%	36%	19%	27%	34%	34%	43%	52%	19%	26%	34%	27%	35%	42%	35%	46%	56%	47%	57%	67%

Simplified Models

Excellent regression approximation of the full competing risks (CDV and mortality) models

R-square ~0.999 for logit of risk

Conclusions: The PREVENT equations accurately and precisely predicted risk for incident CVD and its subtypes in a large, diverse, and contemporary sample of US adults using routinely available clinical variables. Further addition of kidney, metabolic, and social predictors marginally improved risk discrimination but may refine risk estimation in higher-risk subgroups.

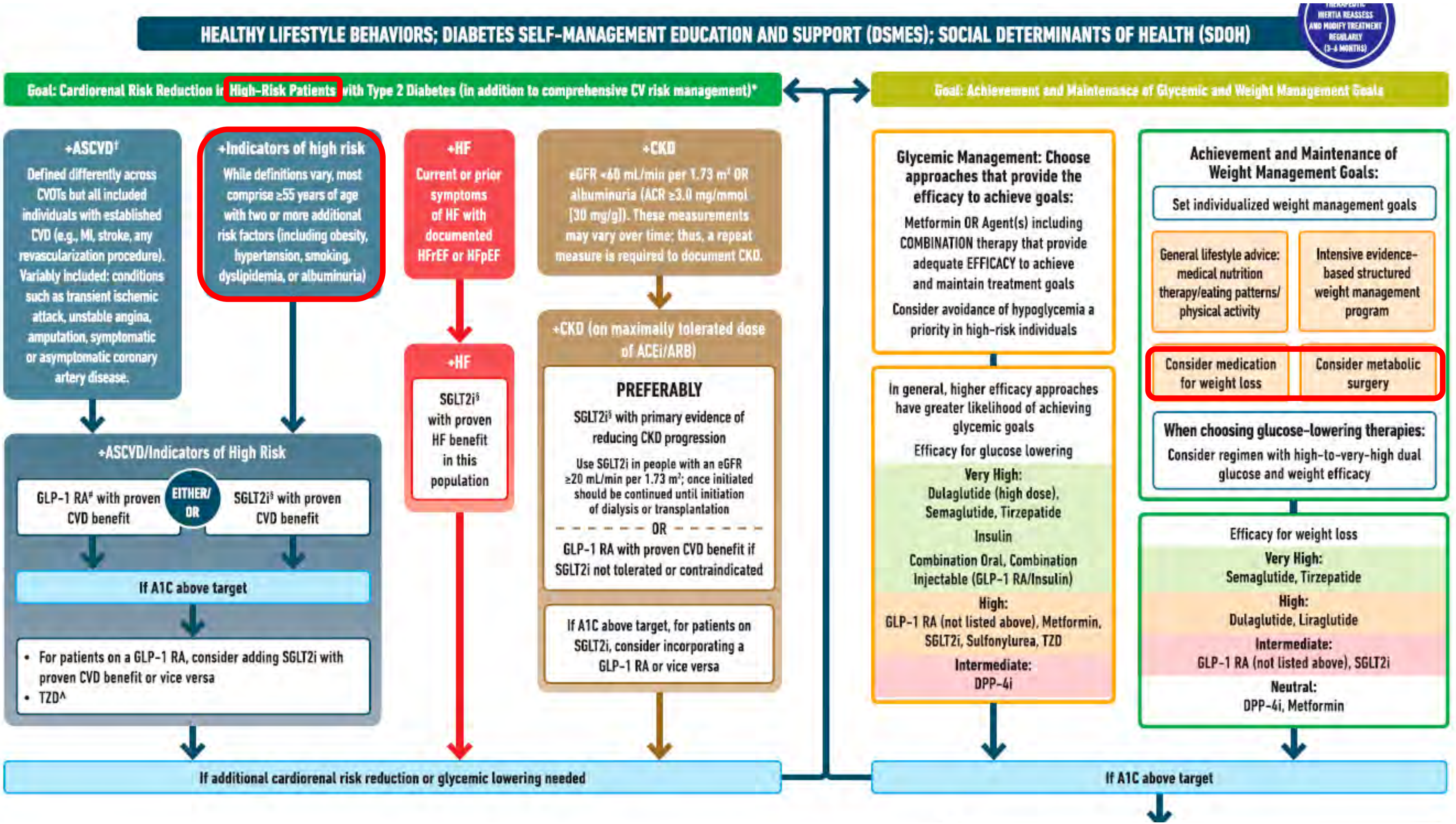
Funding American Heart Association, US National Kidney Foundation, NIDDK, and NHLBI

American Heart Association.

Ndumele, C.E. et al., Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. 2023. *Circulation*.

Improving Patient Management

Populations → Outcomes (Progression/Complications) → Risk Factors (eGFRs, ACR, PCR) → Available Tools → Patient Management


HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)
INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)
Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (in addition to comprehensive CV risk management)*
Goal: Achievement and Maintenance of Glycemic and Weight Management Goals
+ASCVD†
Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, any revascularization procedure). Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease.
+Indicators of high risk
While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria)
+HF
Current or prior symptoms of HF with documented HFrEF or HFpEF
+CKD
eGFR <60 mL/min per 1.73 m² OR albuminuria (ACR ≥3.0 mg/mmol [30 mg/g]). These measurements may vary over time; thus, a repeat measure is required to document CKD.
+ASCVD/Indicators of High Risk
GLP-1 RA# with proven CVD benefit
EITHER/OR
SGLT2i§ with proven CVD benefit
If A1C above target
For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit or vice versa
TZD^
+HF
SGLT2i§ with proven HF benefit in this population
+CKD (on maximally tolerated dose of ACEi/ARB)
PREFERABLY
SGLT2i§ with primary evidence of reducing CKD progression
Use SGLT2i in people with an eGFR ≥20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation
OR
GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated
If A1C above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa
If additional cardiorenal risk reduction or glycemic lowering needed
Glycemic Management: Choose approaches that provide the efficacy to achieve goals:
Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
Consider avoidance of hypoglycemia a priority in high-risk individuals
In general, higher efficacy approaches have greater likelihood of achieving glycemic goals
Efficacy for glucose lowering
Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide
Insulin
Combination Oral, Combination Injectable (GLP-1 RA/Insulin)
High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD
Intermediate:
DPP-4i
Achievement and Maintenance of Weight Management Goals:
Set individualized weight management goals
General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity
Intensive evidence-based structured weight management program
Consider medication for weight loss
Consider metabolic surgery
When choosing glucose-lowering therapies:
Consider regimen with high-to-very-high dual glucose and weight efficacy
Efficacy for weight loss
Very High:
Semaglutide, Tirzepatide
High:
Dulaglutide, Liraglutide
Intermediate:
GLP-1 RA (not listed above), SGLT2i
Neutral:
DPP-4i, Metformin
If A1C above target

Summary

- **Risk prediction can help guide clinical action**
- **Important to check**
  - Discrimination
  - Calibration
  - Thresholds
    - Match thresholds to treatment recommendations
    - Consider likely benefits (risk reduction), harms and costs
- New therapies for kidney and cardiovascular risk reduction
  - ACEI, ARB, Statins, Diuretics, CCBs
  - → SGLT2, GLP1, MRAs
- May benefit from careful upated risk estimates (include HF in CVD and consider CKD) and thresholds

dd

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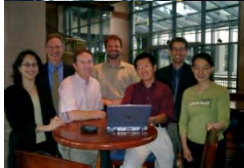
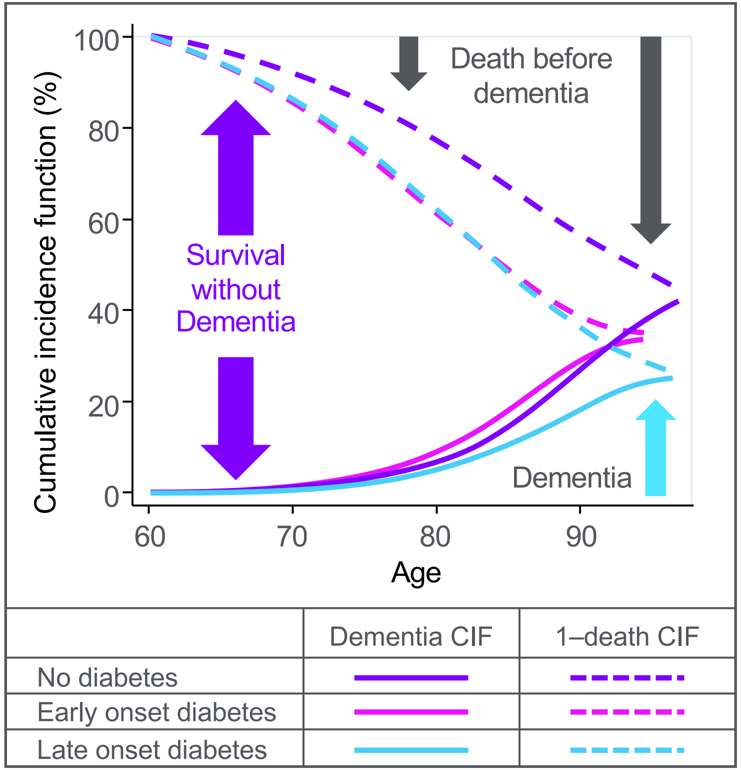
Thank you!



“Competition” between diabetes, dementia, and death risk



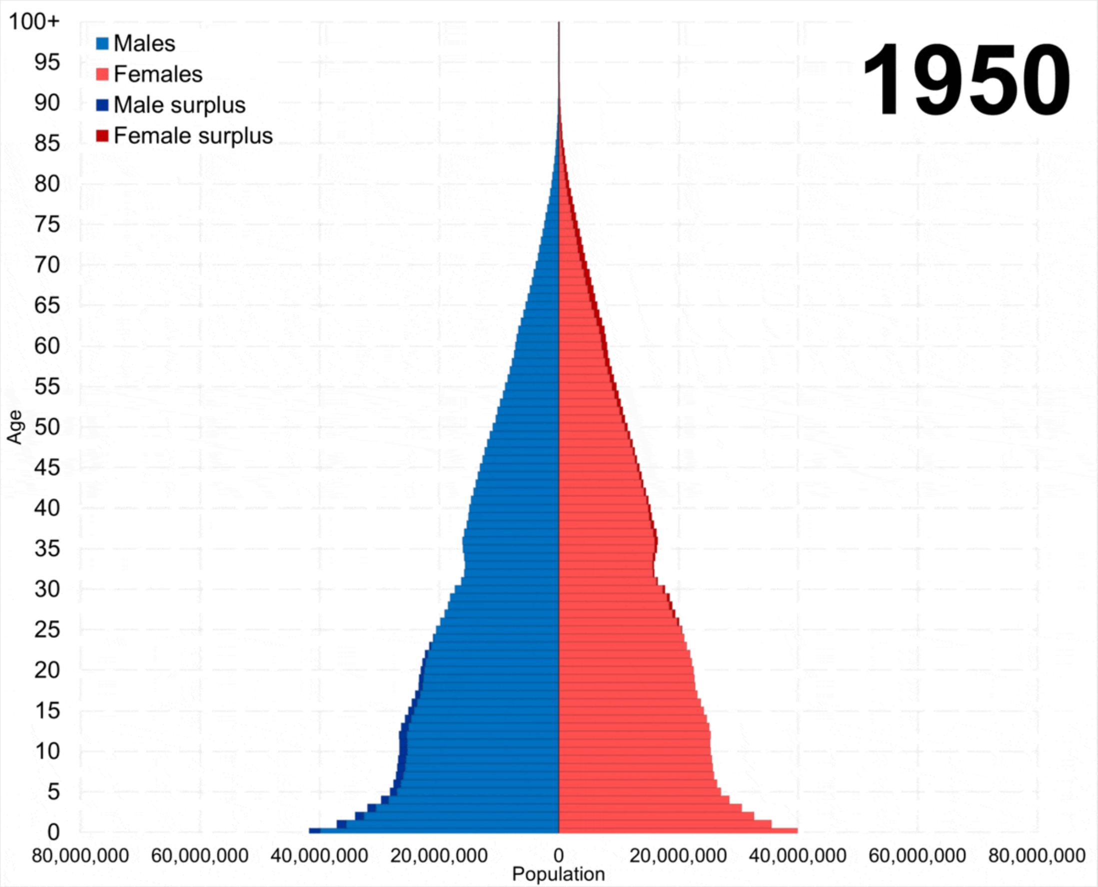
Preventing and delaying the onset of diabetes can reduce the risk of dementia

Collaborative Opportunities

- Diabetes prevention
- Estimating late-life impact of mid- and early-life intervention

Hu J … Coresh J (in preparation)

Population pyramid of the world from 1950-2200



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