

Novel Prediction Equations for Absolute Risk Assessment of Total Cardiovascular Disease Incorporating Cardiovascular- Kidney-Metabolic Health:

A Scientific Statement From the AHA



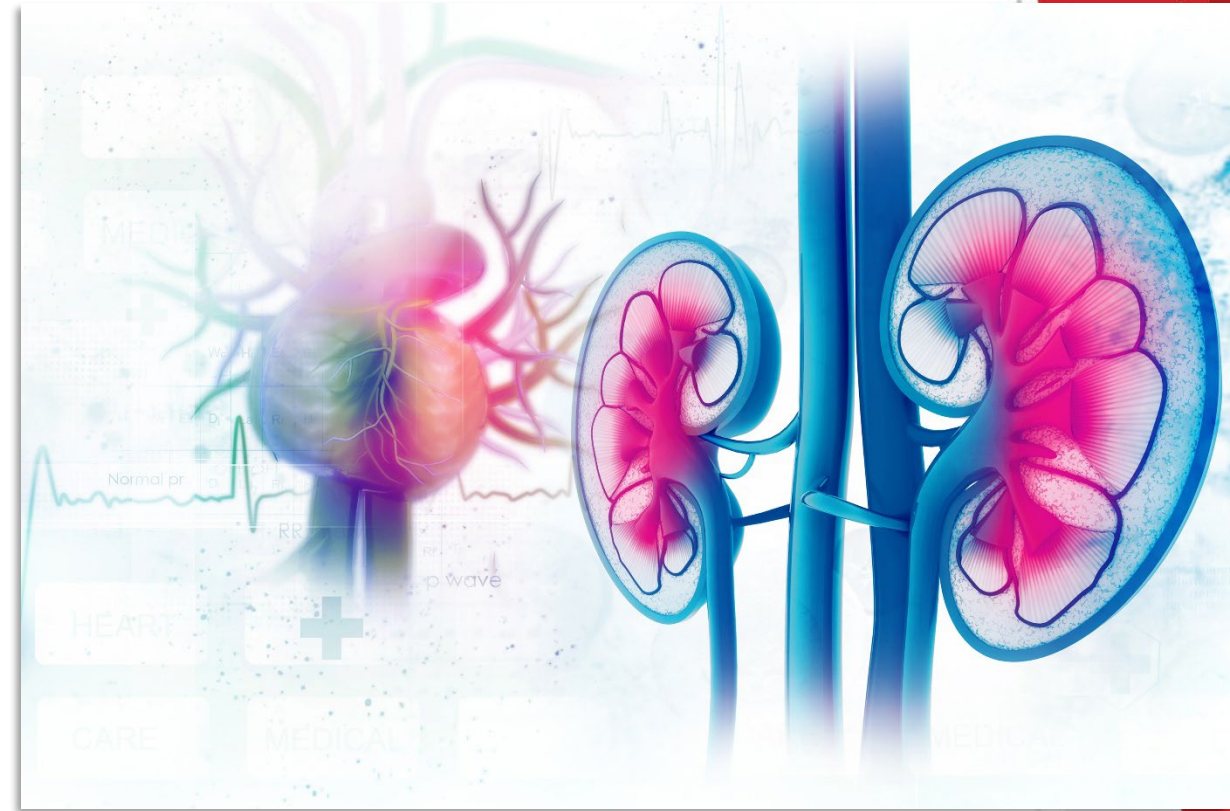
American
Heart
Association.

Definition of Cardiovascular-Kidney-Metabolic Syndrome (CKM)

- » A systemic disorder characterized by pathophysiologic interactions among metabolic risk factors, chronic kidney disease, and the cardiovascular system, leading to multi-organ dysfunction and a high rate of adverse cardiovascular outcomes.
- » CKM syndrome includes both individuals at risk for cardiovascular disease due to the presence of metabolic risk factors and/or chronic kidney disease, and individuals with existing cardiovascular disease that is potentially related to or complicates metabolic risk factors and/or chronic kidney disease.
- » The increased likelihood of CKM syndrome and its adverse outcomes is further influenced by unfavorable conditions for lifestyle and self-care resulting from policies, economics, and the environment.

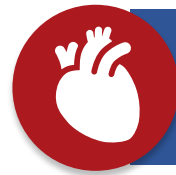
Definition of CKM Syndrome Simplified

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

Existing Risk-Based Recommendations in AHA/ACC Guidelines for Primary Prevention



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

For adults 40 to 75 years of age, clinicians should routinely assess traditional cardiovascular risk factors and calculate 10-year risk of ASCVD by using PCEs. (1)

In adults at borderline risk or intermediate risk, it is reasonable to use additional risk-enhancing factors to guide decisions about preventive interventions. (2a)

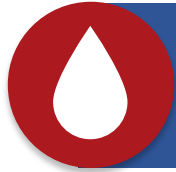
For adults 20-39 years of age, it is reasonable to assess traditional ASCVD risk factors at least every 4-6 years. (2a)

For adults 20 to 39 years of age, and for those 40 to 59 years of age who have < 7.5% 10-year ASCVD risk, estimating lifetime or 30-year ASCVD risk may be considered. (2b)

Abbreviations: ACC indicates American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; GDMT, guideline-directed medical therapy; HF, heart failure; HFSA, Heart Failure Society of America; and PCE, pooled cohort equation.

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Existing Risk-Based Recommendations in AHA/ACC Guidelines for Blood Cholesterol



2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

For adults 40 to 75 years of age, clinicians should routinely assess traditional cardiovascular risk factors and calculate 10-year risk of ASCVD by using PCEs. (1)

For the primary prevention of clinical ASCVD in adults 40–75 years of age without diabetes with an LDL-C level of 70–189 mg/dL, the 10-year ASCVD risk of a first “hard” ASCVD event should be estimated by using the race- and sex-specific PCE, and adults should be categorized as being at low risk, borderline risk, intermediate risk, and high risk. (1)

In adults 40–75 years of age with LDL-C 70–189 mg/dL who are at a 10-year ASCVD risk of $>$ or $=$ 7.5%, CKD not treated with dialysis or kidney transplantation is a risk-enhancing factor and initiation of a moderate-intensity statin combined with ezetimibe can be useful. (2a)

For clinical decision-making in adults of different races and ethnicities, it is reasonable for clinicians to review racial and ethnic features that can influence ASCVD risk to adjust choice of statin or intensity of treatment. (2a)

Clinicians should consider conditions specific to women, such as premature menopause and history of pregnancy-associated disorders, when discussing lifestyle intervention and potential for benefit of statin therapy. (1)

Abbreviations: AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA, American Academy of Physician Assistants; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; NLA, National Lipids Association; NMA, National Medical Association; PCE, pooled cohort equation; PCNA, Preventive Cardiovascular Nurses Association; and SBP, systolic blood pressure.



Existing Risk-Based Recommendations in AHA/ACC Guidelines for High Blood Pressure



2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher, and for primary prevention in adults with an estimated 10-year ASCVD risk or 10% or higher and an average SBP of 130 mmHg or higher or an average DBP of 80 mmHg or higher. (1)

Use of BP-lowering medications is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-ASCVD risk <10% and an SBP of 140 mmHg or higher or a DBP of 90 mmHg or higher. (1)

Abbreviations: AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA, American Academy of Physician Assistants; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; NLA, National Lipids Association; NMA, National Medical Association; PCE, pooled cohort equation; PCNA, Preventive Cardiovascular Nurses Association; and SBP, systolic blood pressure.

Existing Risk-Based Recommendations in AHA/ACC Guidelines for Heart Failure

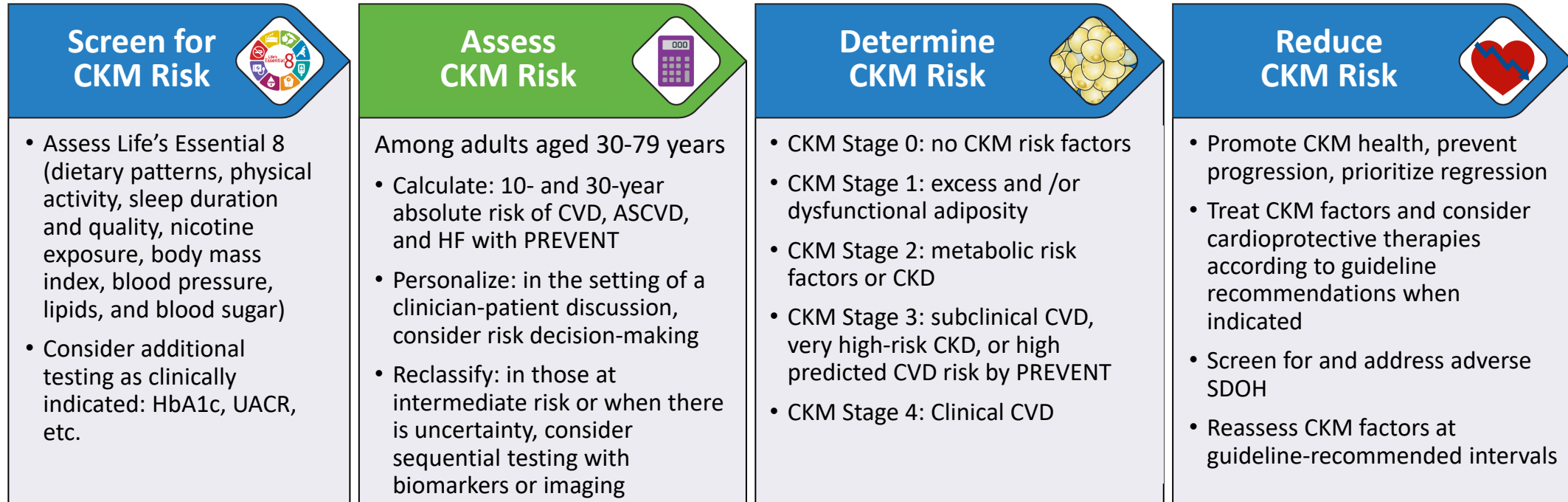


2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure

In the general population, validated multivariable risk scores can be useful to estimate subsequent risk of incident HF. (2a)

For patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing GDMT, can be useful to prevent the development of left ventricular dysfunction or new-onset HF. (2a)

Conceptual Framework: Integrating PREVENT into CKM Staging



Abbreviations: ASCVD indicates atherosclerotic cardiovascular disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; HF, heart failure; PREVENT, Predicting Risk of CVD Events; SDOH, social determinants of health; SGLT2i, sodium glucose co-transporter 2 inhibitor; and UACR, urine albumin-to-creatinine ratio.

Conceptual Framework: Integrating PREVENT into CKM Staging

Screen for CKM Risk

- Assess Life's Essential 8 (dietary patterns, physical activity, sleep duration and quality, nicotine exposure, body mass index, blood pressure, lipids, and blood sugar)
- Consider additional testing as clinically indicated: HbA1c, UACR, etc.



Abbreviations: CKM indicates cardiovascular-kidney-metabolic; HbA1c, hemoglobin A1c; PREVENT, Predicting Risk of CVD Events; and UACR, urine albumin-to-creatinine ratio.

Conceptual Framework: Integrating PREVENT into CKM Staging

Assess CKM Risk

Among adults aged 30-79 years

- Calculate: 10- and 30-year absolute risk of CVD, ASCVD, and HF with PREVENT
- Personalize: in the setting of a clinician-patient discussion, consider risk decision-making
- Reclassify: in those at intermediate risk or when there is uncertainty, consider sequential testing with biomarkers or imaging



Abbreviations: ASCVD indicates atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HF, heart failure; and PREVENT, Predicting Risk of CVD Events.

Conceptual Framework: Integrating PREVENT into CKM Staging

Determine CKM Risk

- CKM Stage 0: no CKM risk factors
- CKM Stage 1: excess and /or dysfunctional adiposity
- CKM Stage 2: metabolic risk factors or CKD
- CKM Stage 3: subclinical CVD, very high-risk CKD, or high predicted CVD risk by PREVENT
- CKM Stage 4: Clinical CVD



Abbreviations: CKM indicates cardiovascular-kidney-metabolic; CKD, chronic kidney disease; CVD, cardiovascular disease; and PREVENT, Predicting Risk of CVD Events.

Spectrum of Absolute Cardiovascular Disease Risk Across the Cardiovascular-Kidney-Metabolic Stages

CKM Stages	Stage 0	Stage 1	Stage 2	Stage 3
CVD Risk	Low risk	Low risk to Borderline to intermediate risk	Borderline to intermediate risk	High risk

Low risk
 Borderline to intermediate risk
 High risk

Abbreviations: CKM indicates cardiovascular-kidney-metabolic; and CVD, cardiovascular disease

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Conceptual Framework: Integrating PREVENT into CKM Staging

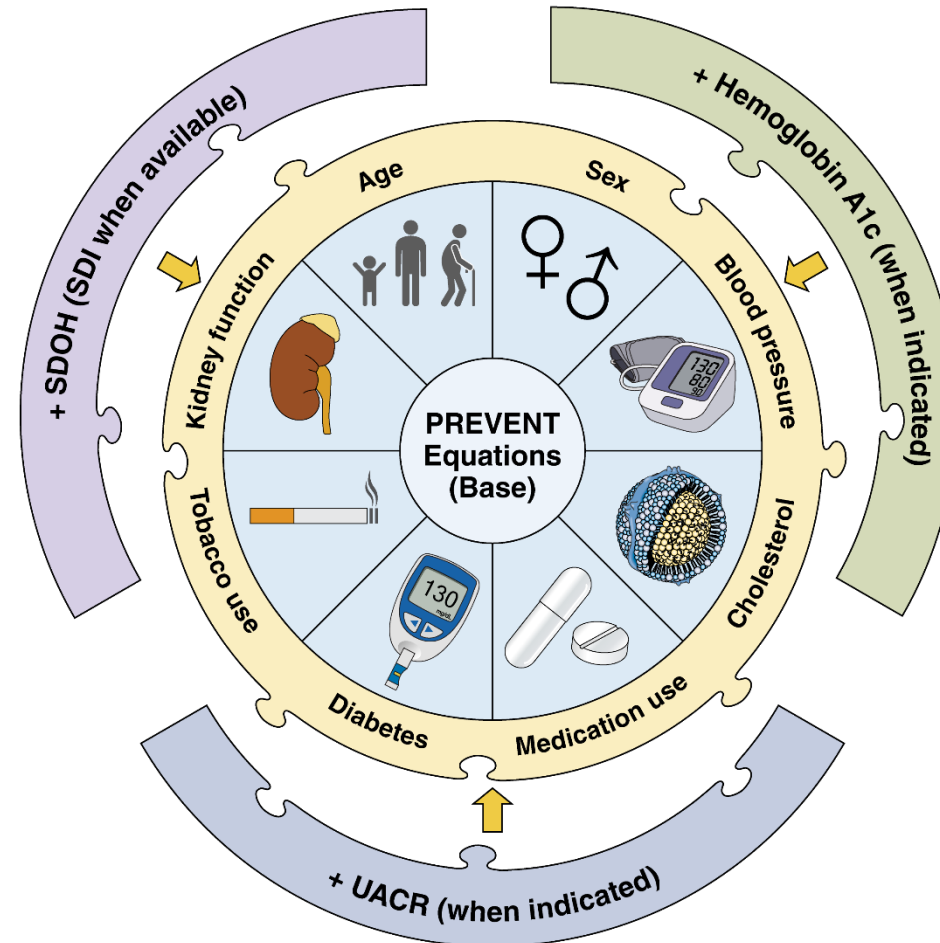
Reduce CKM Risk

- Promote CKM health, prevent progression, prioritize regression
- Treat CKM factors and consider cardioprotective therapies according to guideline recommendations when indicated
- Screen for and address adverse SDOH
- Reassess CKM factors at guideline-recommended intervals



Abbreviations: CKM indicates cardiovascular-kidney-metabolic; PREVENT, Predicting Risk of CVD Events; and SDOH, social determinants of health.

Predicting Risk of CVD EVENTS (PREVENT) Base Model and Additional Equations

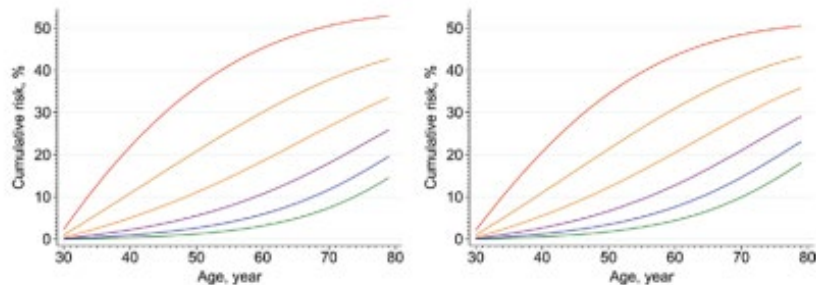


Abbreviations: CVD indicates cardiovascular disease; PREVENT, Predicting Risk of CVD Events; SDI, social deprivation index; SDOH, social determinants of health; and UACR urine albumin-to-creatinine ratio.

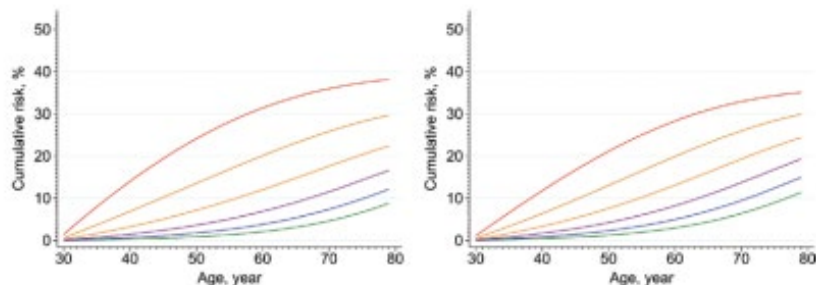
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Cumulative Incidence of Cardiovascular Disease Based on Risk

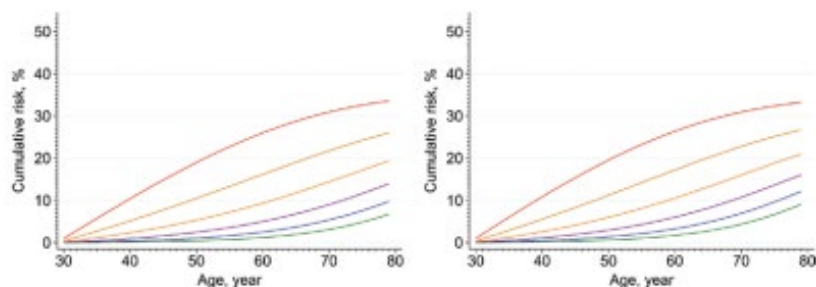
All cardiovascular disease, women on the left and men on the right



Atherosclerotic cardiovascular disease, women on the left and men on the right



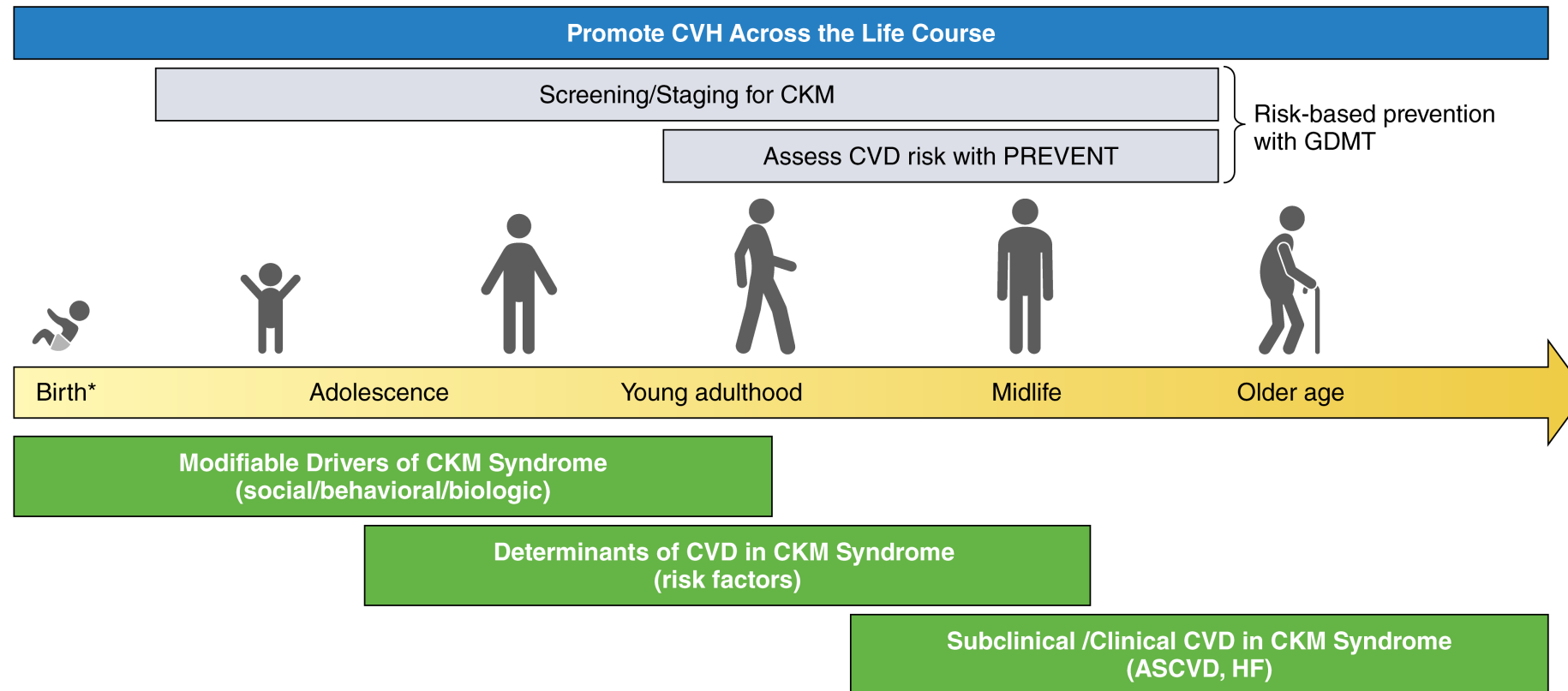
HF, women on the left and men on the right



- All risk factors optimal
- 1 Risk factor elevated
- 2 Risk factors elevated
- 3 Risk factors elevated
- 4 Risk factors elevated
- 5 Risk factors elevated

Optimal risk factor levels defined as non-high-density lipoprotein cholesterol 3.5 mmol/L or 135 mg/dL; systolic blood pressure 120 mmHg; no diabetes, nonsmoking, no use of antihypertensives or statins, and estimated glomerular filtration rate 90 mL/min-1.73 m⁻². Elevated risk factor levels were defined as non-high density lipoprotein cholesterol 5.5 mmol/L or 213 mg/dL; systolic blood pressure 150 mmHg, diabetes, current smoking, and estimated glomerular filtration rate 45 mL-min-1.73 m⁻² with average risk of all combinations displayed when >1 risk factor was elevated. Models were adjusted for competing risk of non cardiovascular death. HF indicates heart failure

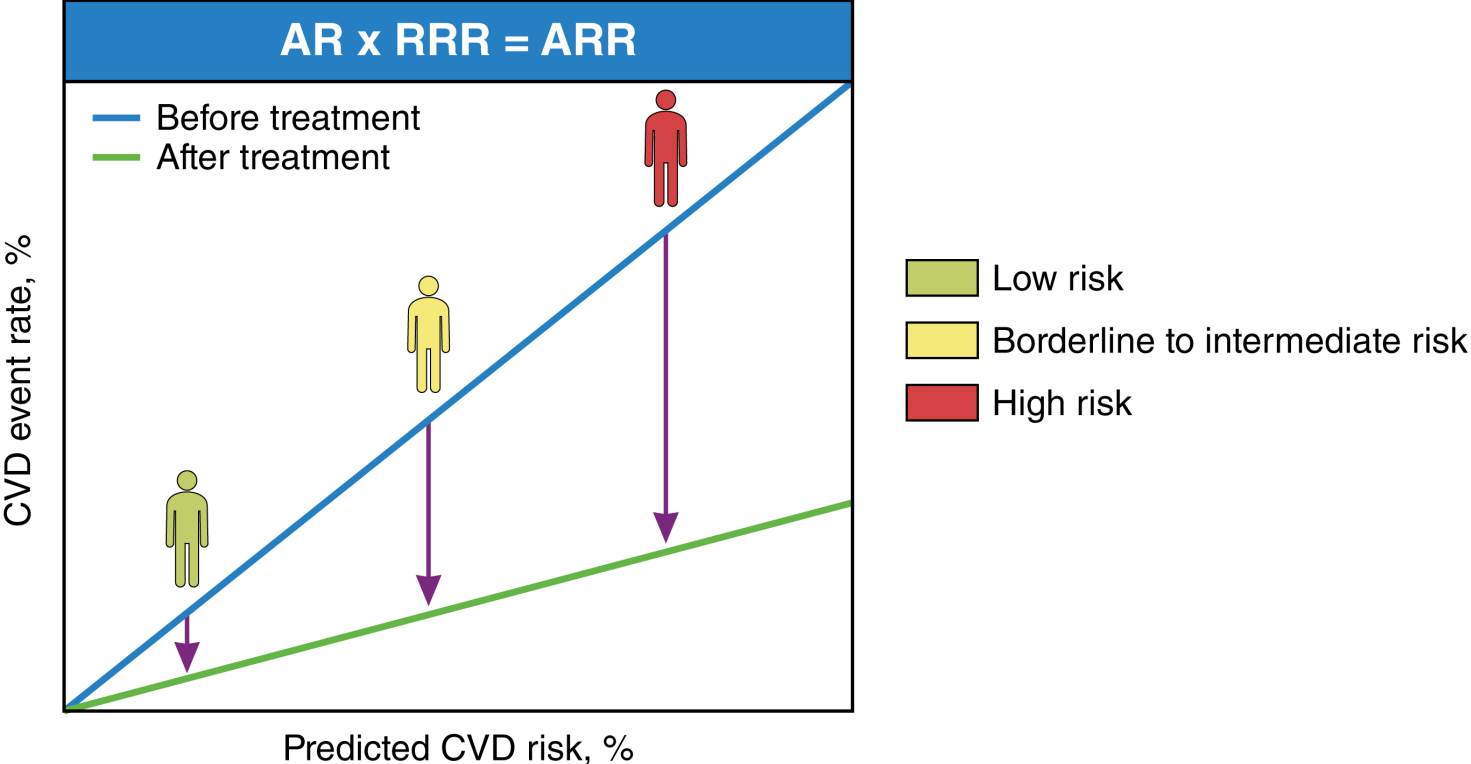
A Life Course Approach to the Promotion of CVH, Staging of CKM Health, and Risk Assessment: Drivers, Determinants, And Disease



Abbreviations: *Risk for poor CKM may begin before birth with adverse exposures in utero (eg, gestational diabetes). ASCVD indicates atherosclerotic cardiovascular disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; CVH, cardiovascular health; GDMT, guideline-directed medical therapy; and HR, heart failure



Estimating the Expected Treatment Benefit (ARR) Based on Absolute Risk and Relative Risk Reduction of Treatment of Treatment



Abbreviations: AR indicates absolute risk; ARR, absolute risk reduction; RRR, relative risk reduction; and CVD, cardiovascular disease;



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Key Gaps and Future Directions in Cardiovascular Disease Risk Prediction and Risk-Based Prevention

Areas of Research

Key Gaps and Unanswered Questions

SDOH

- What are the individual- and place-based SDOH factors with predictive utility in models for CVD risk prediction?
- What are the best approaches to analyze and integrate multi-level SDOH factors for CVD risk prediction?
- How should we address SDOH to reduce risk of CVD associated with CKM risk?
- Identify approaches to measurement of key SDOH factors in the clinical setting.

Novel Predictors and Outcomes

- Incorporate prediction of CKD progression as a risk factor and modifiable target for CVD risk-based prevention.
- Evaluate the clinical utility of prediction of CVD risk factors or subclinical CVD.
- Investigate the predictive utility of broad-based predictors or aggregate scores for CVD.
- Determine cost effectiveness of diagnostic imaging in risk-enriched populations to identify subclinical CVD to improve accuracy of staging.

Abbreviations: CKM indicates cardiovascular-kidney-metabolic; CKD, chronic kidney disease; CVD, cardiovascular disease; and SDOH, social determinants of health.

Key Gaps and Future Directions in Cardiovascular Disease Risk Prediction and Risk-Based Prevention

Areas of Research

Key Gaps and Unanswered Questions

Interventional and Implementation Research

- Determine the risk threshold at which net benefit is favorable for each cardioprotective therapy that treat CVD risk factors, address underlying risk, and prevent progression of CKD.
- Define strategies to implement Life's Essential 8 as a framework to measure, modify, and monitor CKM health.
- Conduct randomized clinical trials in young adults to inform interventions at earlier ages and prevent onset of CVD risk factors or subclinical disease.

Dissemination and Implementation Research

- Integration of PREVENT into EMRs to support widespread utilization of risk assessment.
- What are the best strategies to optimize CVD risk factor control among those at increased predicted risk of CVD?
- Can pharmacist-delivered health system intervention or in a community-based intervention improve risk factor control among those at increased predicted risk of CVD?

Abbreviations: CKM indicates cardiovascular-kidney-metabolic; CKD, chronic kidney disease; CVD, cardiovascular disease; EMR, electronic medical record; and PREVENT, Predicting Risk of CVD Events.

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