

1/ 🗳️🗣️ Hey, #Nephtwitter, #Medtwitter, today we will discuss CKM syndrome based on the @Kireports blog. Have you heard about #cardio-#kidney-#metabolic (CKM) connection? Let's start with a poll

What percentage of American adults have at least one CKM risk factor?

a) 30%

b) 50%

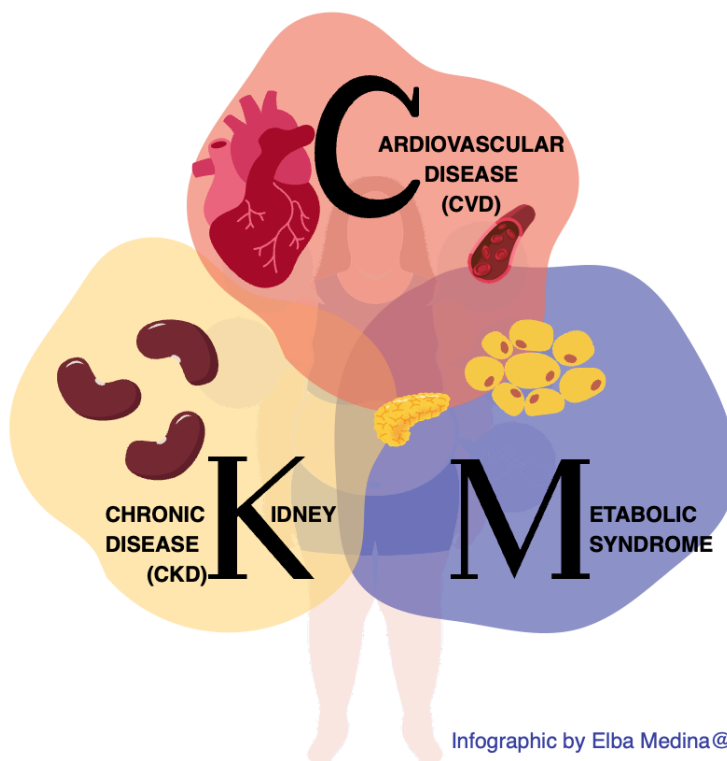
c) 70%

d) 90%

2/ We'll be talking about Combination of Cardiovascular, Kidney, and Metabolic Diseases in a Syndrome Named Cardiovascular-Kidney-Metabolic, With New Risk Prediction Equations.

[https://www.kireports.org/article/S2468-0249\(24\)01757-1/fulltext](https://www.kireports.org/article/S2468-0249(24)01757-1/fulltext). @MassyZiad

The American Heart Association proposed this concept @American_Heart @AHAScience



3/ Let's start by talking about CKM syndrome.

→ ~30-60% with HF have moderate or severe kidney damage

→ ~40% with DM have CKD

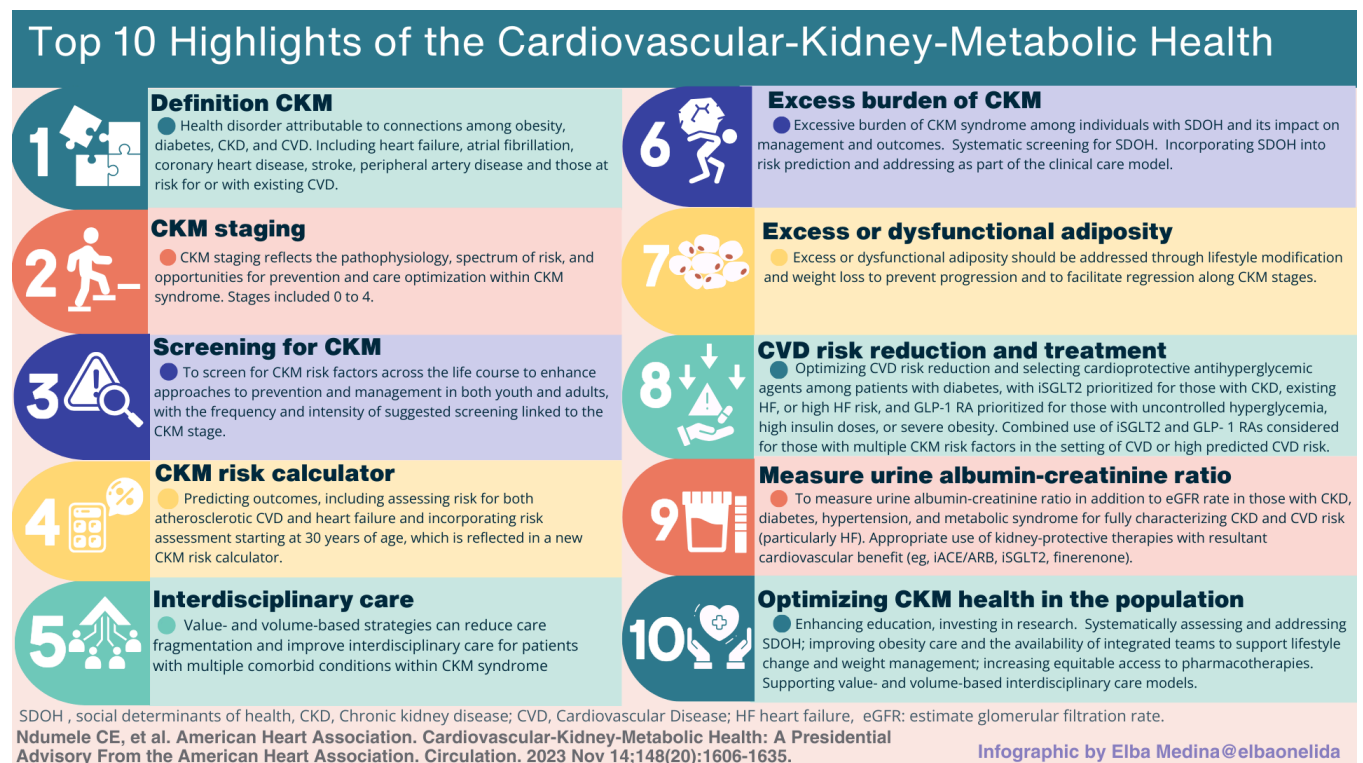
→ ~10% have isolated T2DM with no associated cardiovascular or kidney disorder

→ #Cardio, #kidney and #metabolic disease are the pandemic of 21st century

4/ So why is important !?

≥25% of patients are affected by CKM syndrome which is associated with premature mortality🔥! Look at the Presidential Advisory from the American_Heart @AHAScience @ChiadiNdumele

<https://www.ahajournals.org/doi/10.1161/CIR.000000000001184>



5/ What is the objective 🎯?

The integration 🌱 of #CKM syndrome was to create an integrated staging system that is useful for clinical management, prevention, and research purposes for optimizing @CKMH

(#Cardiovascular-#Kidney-#Metabolic- Health) 🧠 🔥

Definitions of CKM health stages

CKM health stages	Definition
STAGE 0 No CKM health risk factors	Individuals without: <ul style="list-style-type: none"> Overweight/obesity Metabolic risk factors (HTA, hypertriglyceridemia, MetS, diabetes) CKD or subclinical/clinical CVD
STAGE 1 Excess and/or dysfunctional adiposity	Individuals with: <ul style="list-style-type: none"> Overweight/obesity, abdominal obesity, or dysfunctional adipose tissue BMI 25 kg/m² (or 23 kg/m² if Asian ancestry) Waist circumference ≥88/102 cm in women/men (or if Asian ancestry, ≥80/90 cm in women/men) Fasting blood glucose ≥100-124 mg/dl or HbA1c between 5.7% and 6.4% Individuals without: <ul style="list-style-type: none"> Other metabolic risk factors or CKD
STAGE 2 Metabolic risk factors and CKD	Individuals with: <ul style="list-style-type: none"> Metabolic risk factors: hypertriglyceridemia (≥135 mg/dl), HTA, MetS, diabetes, (nonmetabolic etiologies of hypertension) or CKD (nonmetabolic etiologies)
STAGE 3 Subclinical CVD in CKM	Subclinical: <ul style="list-style-type: none"> ASCVD or HF among individuals with excess dysfunctional adiposity, other metabolic risk factors, or CKD HF diagnosed by ↑ cardiac biomarkers or by echocardiographic parameters, with combination indicating highest HF risk. Very high-risk CKD (G4 or G5 CKD or very high risk per KDIGO classification) ASCVD to be principally diagnosed by coronary artery calcification (subclinical atherosclerosis by coronary catheterization/CT angiography also meets criteria) Risk equivalents of subclinical CVD High predicted 10-y CVD risk
STAGE 4 Clinical CVD in CKM	Clinical: <ul style="list-style-type: none"> CVD (coronary heart disease, heart failure, stroke, peripheral artery disease, AFib) among individuals with excess/ dysfunctional adiposity, other metabolic risk factors, or CKD Stage 4a: no kidney failure Stage 4b: kidney failure present

HTA, hypertension; METs, metabolic syndrome; CKD, chronic kidney disease; BMI, body mass index; CKM, cardiovascular-kidney-metabolic; ASCVD, atherosclerotic cardiovascular disease; CT computed tomography; CVD, cardiovascular disease; KDIGO, Kidney Disease Improving Global Outcomes; HF, heart failure; AFib, atrial fibrillation

Infographic by Elba Medina @elbaonelida

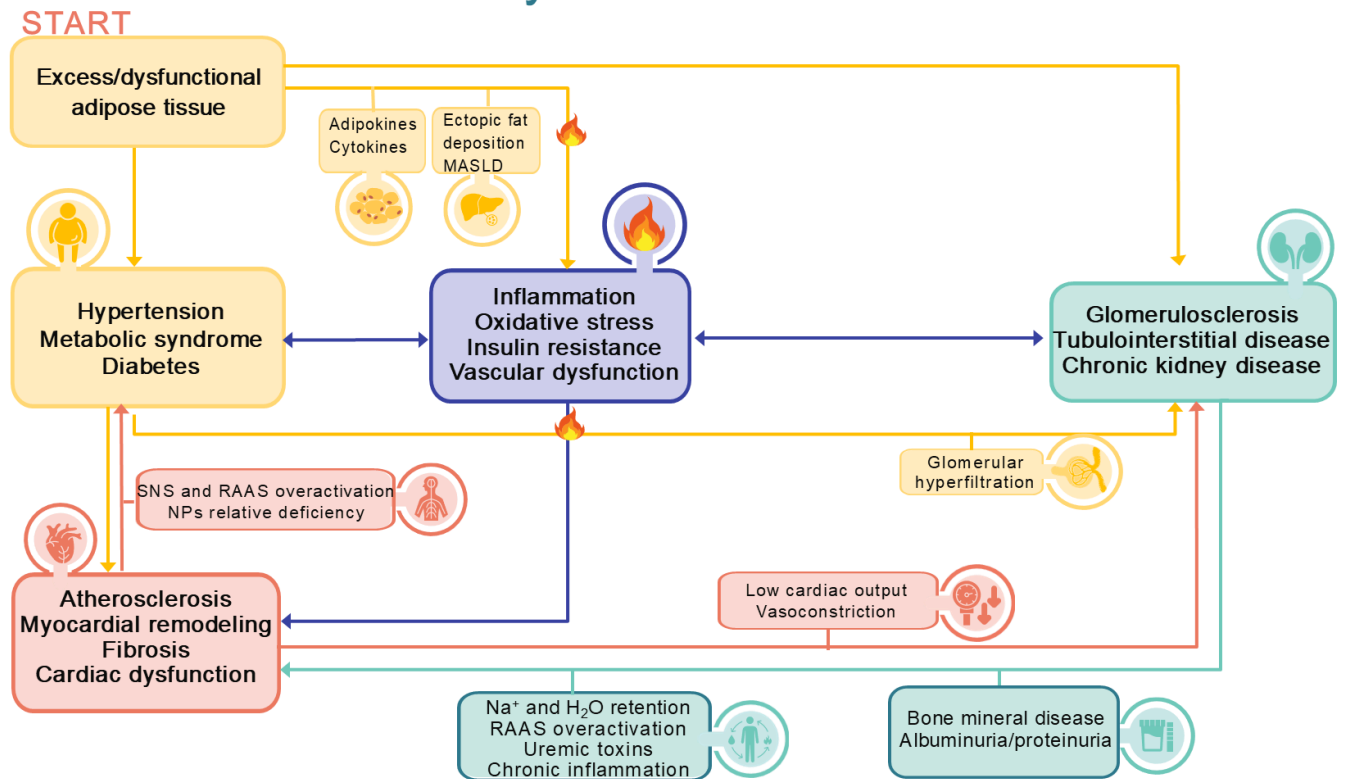
6/ In the pathophysiology of CKM syndrome a variety of interconnected factors are involved:

- ✳ Insulin resistance, hyperglycemia
- ✳ RAAS
- ✳ AGEs
- ✳ Oxidative stress
- ✳ Dyslipidemia and lipotoxicity
- ✳ Mitochondrial dysfunction
- ✳ Chronic (micro) inflammation
- ✳ Potentially uremic toxins

7/ #CKM syndrome most commonly originates from **excess adipose tissue**, dysfunctional adipose tissue, or both 🔥 with consequences not just limited to the known systems but also affect other organs interconnectedness.

Check out this infographic created by @elbaonelida

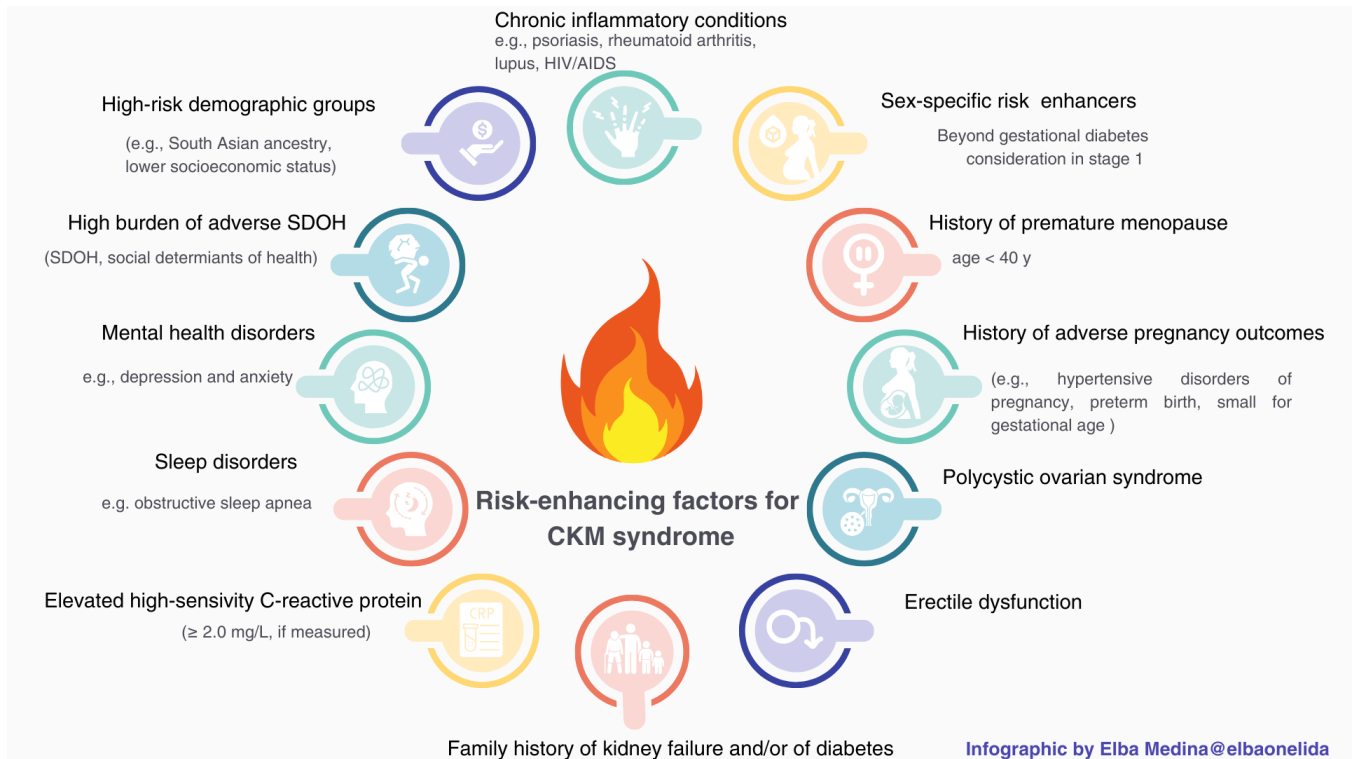
Cardio-Kidney-Metabolic interconnections



MASLD, Metabolic dysfunction-associated steatotic liver disease; SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone; NPs, natriuretic peptides

Infographic by Elba Medina @elbaonelida

8/ Numerous risk factors cover a diversity of predisposing conditions for CKM syndrome influence its severity as well as related adverse outcomes.



09/ There are social determinants at multiple levels of influence, affect the likelihood of #cardiovascular-#kidney, #metabolic (CKM) syndrome and of consequent adverse outcomes.

@CircAHA @ChiadiNdumele

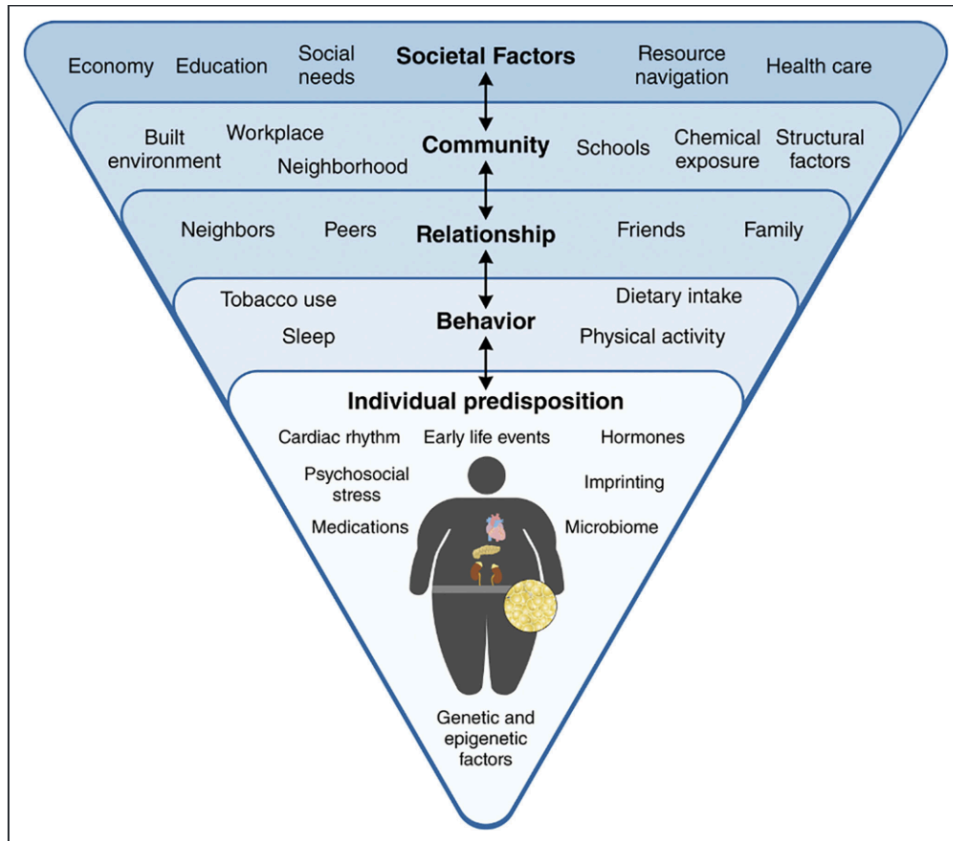


Figure 2. Socioecological framework for CKM syndrome. Social determinants at multiple levels of influence, including at societal, community, interpersonal and individual behavioral levels, affect the likelihood of cardiovascular-kidney-metabolic (CKM) syndrome and of consequent adverse outcomes. Individual biological predisposition, nested within these multiple levels of social influence, further affects CKM syndrome development and related outcomes.

10/ CKM syndrome includes the 2 major parameters of CKD progression risk: glomerular filtration rate and albuminuria. A more severe urinary albumin-to-creatinine ratio (uACR) was associated with increased rates of all 10 adverse outcomes @goKDIGO

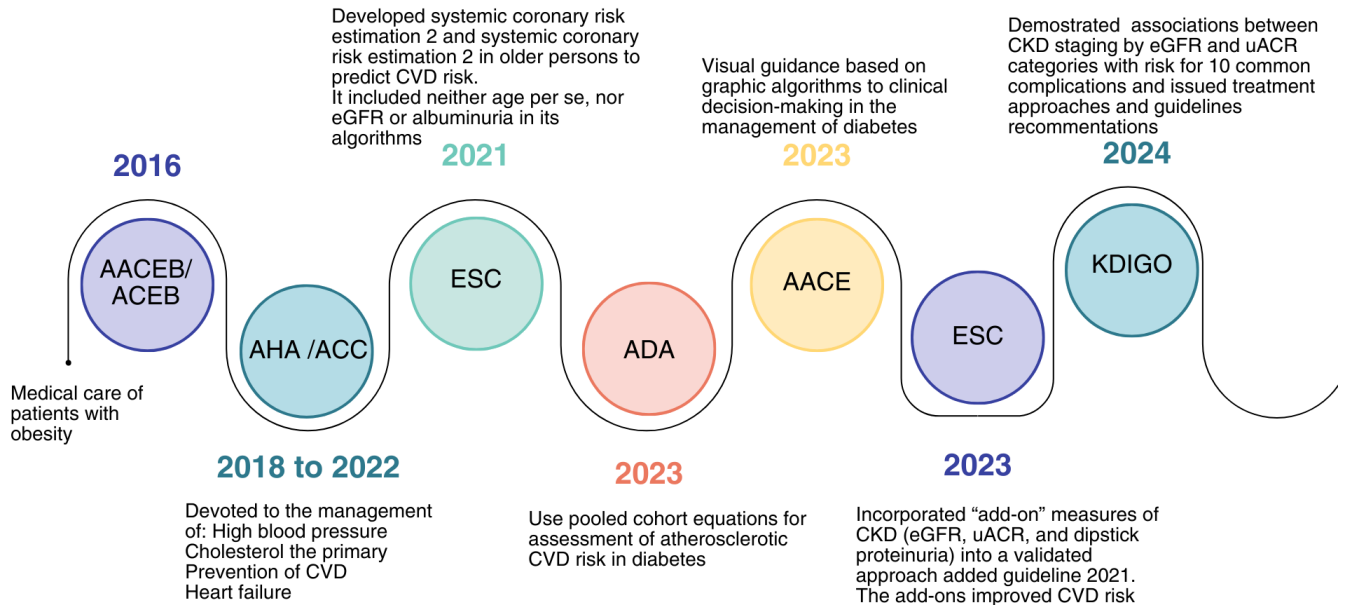
Associations of CKD staging by eGFRcr-cys and ACR categories and risks for 10 common complications by age in multivariable-adjusted analyses

Age <65					Age 65+					ADJUSTED VARIABLES INCLUDED
eGFRcr-cys	ACR, mg/g				eGFRcr-cys	ACR, mg/g				
	<10	10-29	30-299	300+		<10	10-29	30-299	300+	
	All-cause mortality					All-cause mortality				age
105+	0.99	1.2	1.5	2.4	105+	1.2	1.4	1.9	3.5	sex
90-104	ref	1.3	1.5	2.5	90-104	ref	1.2	1.4	2.0	systolic blood pressure
60-89	1.2	1.6	2.0	2.9	60-89	1.2	1.5	1.8	2.3	smoking status (current, former, or never)
45-59	2.1	2.7	2.9	4.5	45-59	1.6	2.0	2.4	2.9	total cholesterol
30-44	2.7	3.8	4.2	5.6	30-44	2.0	2.4	3.2	4.1	cancer
<30	5.2	4.0	7.1	8.6	<30	3.4	4.1	5.1	6.5	systolic blood pressure
	Cardiovascular mortality					Cardiovascular mortality				high-density lipoprotein cholesterol
105+	0.95	1.4	1.7	4	105+	1.1	1.5	2.0	12	body mass index
90-104	ref	1.6	1.8	3.5	90-104	ref	1.4	1.4	3.4	use of antihypertensive medications
60-89	1.3	1.7	2.3	3.9	60-89	1.2	1.7	2.2	3.1	medical history of diabetes
45-59	2.5	4.0	4.6	6.0	45-59	1.7	2.4	3.0	4.3	stroke
30-44	3.1	6.6	5.3	7.1	30-44	2.4	3.1	4.5	5.8	coronary heart disease
<30	6.0	5.5	9.4	12	<30	5.7	5.2	5.1	7.8	atrial fibrillation
	Kidney failure replacement therapy					Kidney failure replacement therapy				peripheral artery disease
105+	0.57	0.77	2.3	12	105+	2.0	1.0	2.1		heart failure
90-104	ref	1.4	3.9	11	90-104	ref	1.9	4.7	10	chronic obstructive pulmonary disease
60-89	1.9	3.7	8.3	33	60-89	1.4	2.6	6.2	19	
45-59	7.0	16	28	100	45-59	3.7	7.9	16	42	
30-44	22	34	109	210	30-44	14	14	46	137	
<30	335	267	419	625	<30	87	364	241	406	

Numbers reflect the adjusted hazard ratio compared with the reference cell. The colors were determined for each outcome separately using the following rule: the percentile shaded the darkest green color corresponds to the proportion of cells in the grid without CKD (e.g., 6 of 24 cells), and the percentile shaded the darkest red color corresponds to proportion expected to be at highest risk (e.g., 5 of 24 cells). In this manner, the numbers of green and red cells are consistent across outcomes, but the patterns are allowed to differ. ref, reference cell. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Cr, creatinine; cys, cystatin C; ACR, albumin-to-creatinine ratio. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024 Apr;105(4S):S117-S314.

11/ Over the years, risk prediction and risk-based prevention guidelines have been created, to improve the prediction and care of obesity, diabetes, and hypertension ! @American_Heart @AHAScience, @goKDIGO, @ACCinTouch, @AmDiabetesAssn, @escardio

Risk Prediction and Risk-Based Prevention Guidelines



AACE, American Association of Clinical Endocrinology; AAACEB, American Association of Clinical Endocrinologists Board of Directors; ACEB, American College of Endocrinology Board of Trustees; AHA, American Heart Association; ACC, American College of Cardiology; ESC, European Society of Cardiology; ADA, American Diabetes Association; KDIGO, Kidney Disease: Improving Global Outcomes; CVD, cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; uACR, urine albumin-to-creatinine ratio.

Infographic by Elba Medina @elbaonelida

12/ There are calculators for calculated 10y and lifetime risk of atherosclerotic cardiovascular disease (ASCVD) [ASCVD Risk Estimator + \(acc.org\)](https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/therapy/)



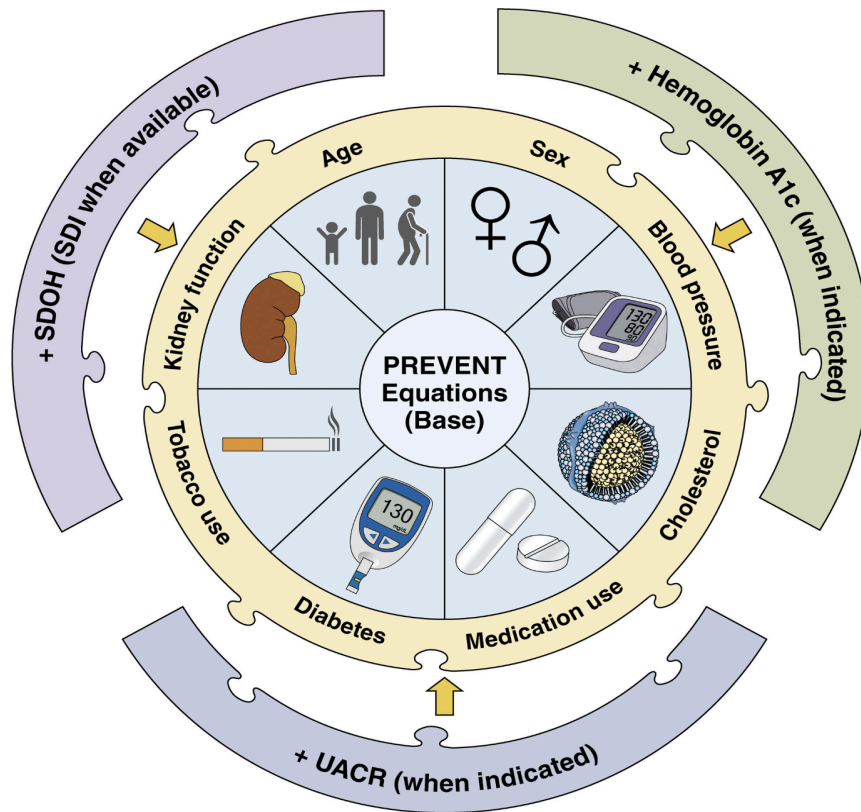
<https://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/therapy/>

13/PREVENT equation Absolute Risk Assessment of Total Cardiovascular Disease Incorporating Cardiovascular-Kidney-Metabolic Health This should be used for primary prevention patients only

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

<https://gph.is/g/aX836BO>

14/ PREVENT Equation originated with a derivation and validation cohort from a sample of >6 million people that provided CVD risk of total CVD (and CVD subtypes) estimates over periods of 10 and 30 years.



<https://www.ahajournals.org/doi/epub/10.1161/CIR.0000000000001191>

15/ Notwithstanding the benefits PREVENT equations, were observed several limitations:

Limitations of PREVENT equation

The authors used electronic medical records/based data sets

Excluded people with extreme clinical values of systolic blood pressure, serum total, and HDL cholesterol, or BMI.

The long baseline time period of the included data sets, spanning more than 3 decades, might have led to differences in risk factor prevalence and treatment modalities.

The authors used age as the time scale for model development as the time scale.

Individual-level social determinants of health were not routinely available in all data sets

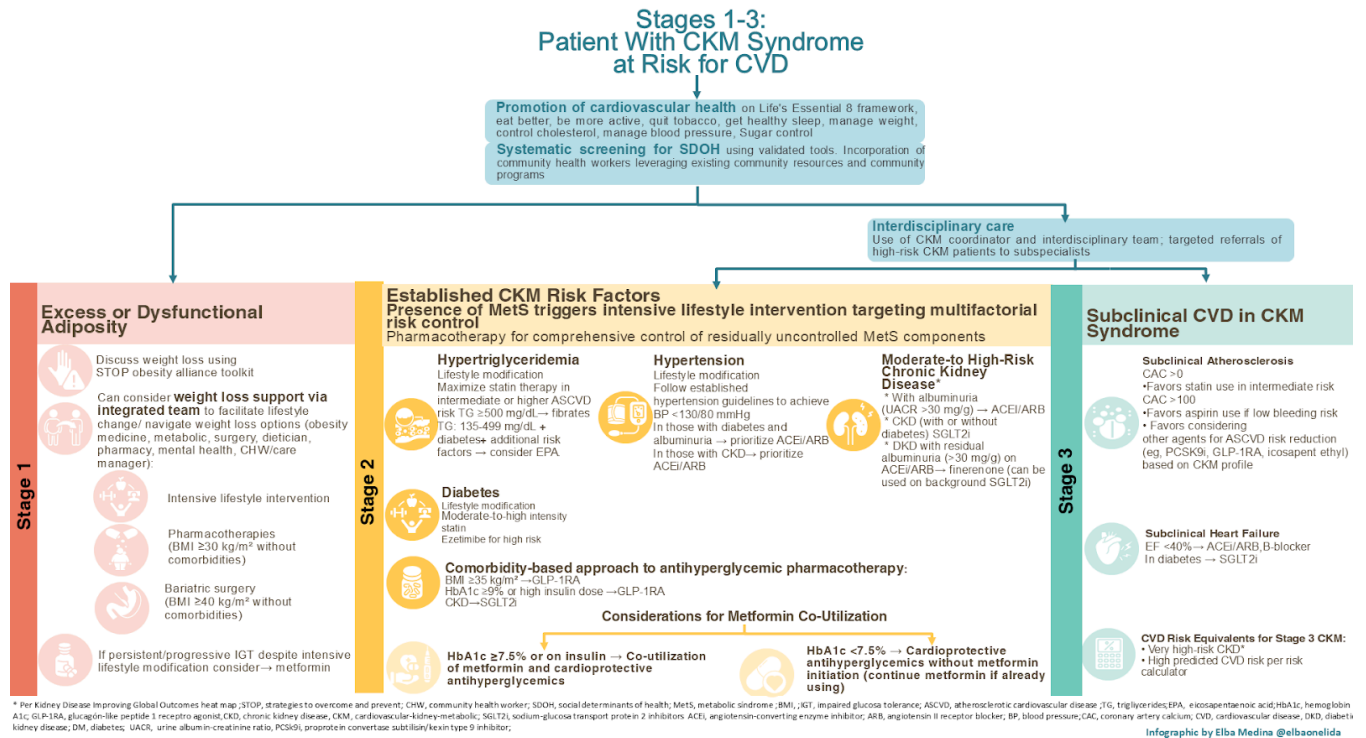
The PREVENT model development did not include a variety of well-known biomarkers of target organ damage.

Separate modeling was used for total CVD and its components in the development of PREVENT equations.

Valid only for individuals aged 35 to 79 years in the US.

16/ knowing the result of the PREVENT equation of risk may assist and guide clinicians and patients in shared decision-making for interventions targeting lifestyle behaviors and consideration of pharmacotherapies
 =Earlier and more appropriate treatment
 =Prevention of CKM factors

17/ #CKM (#cardio-#kidney-#metabolic syndrome) treatment algorithm Stages 1-3 Patient with CKM syndrome at Risk of CVD.



18/ What do you think is the treatment of patient in Stage 4 with multiples comorbidities in the setting of Diabetes and CVD ?

- A) Co-utilization of SGLT2i and GLP-1 RA
- B) SGLT2i
- C) GLP-1 RA
- D) Lifestyle modification

19/ Here is #CKM (#cardio-#kidney-#metabolic syndrome) treatment algorithm Stage 4 Patient with CKM syndrome with Existing CVD.

Stage 4: Patient With CKM Syndrome With Existing CVD

Promotion of cardiovascular health with an emphasis on Life's Essential 8 framework: eat better, be more active, quit tobacco, get healthy sleep, manage weight, control cholesterol, manage blood sugar, manage blood pressure
Systematic screening for SDOH using validated tools, incorporation of community health workers and care navigators into the care team, leveraging existing community resources and community programs
Interdisciplinary care - Use of CKM coordinator and interdisciplinary team, targeted referrals of high-risk patients with CKM to subspecialists

HF: GDMT for all patients
ASCVD: Aspirin and high-intensity statin for all patients, consider addition of ezetimibe and PCSK9i based on LDL level/goals or presence of high-risk ASCVD

	Management of Other CKM Risk Factors Presence of metabolic syndrome triggers intensive lifestyle intervention targeting multifactorial risk control Pharmacotherapy for comprehensive control of residually uncontrolled MetS components
<div style="display: flex; align-items: center;"> <div style="writing-mode: vertical-rl; transform: rotate(180deg); font-weight: bold; margin-right: 5px;">Stage 4:</div> <div style="flex: 1;"> <p>Management of Excess or Dysfunctional Adiposity</p> <p>Discuss weight loss using STOP obesity alliance toolkit</p> <p>Weight loss support via integrated team to facilitate lifestyle change/navigate weight loss options (obesity medicine, metabolic surgery, dietician, pharmacy, mental health, CHW/care manager):</p> <ul style="list-style-type: none"> • Intensive lifestyle intervention • Pharmacotherapies (BMI ≥27 kg/m²) • Bariatric surgery (BMI ≥35 kg/m²) <p>If persistent/progressive IGT despite intensive lifestyle modification → consider metformin</p> </div> </div>	<div style="display: flex; align-items: center;"> <div style="writing-mode: vertical-rl; transform: rotate(180deg); font-weight: bold; margin-right: 5px;">Stage 4:</div> <div style="flex: 1;"> <p>Hypertriglyceridemia</p> <ul style="list-style-type: none"> • Maximize lifestyle modification and statin therapy • Fibrates for ≥500 mg/dL • Consider EPA for TG: 135-499 mg/dL for patients with diabetes and additional risk factors <p>Hypertension</p> <ul style="list-style-type: none"> • Follow established hypertension guidelines to achieve BP <130/80 mmHg • In diabetes or CKD prioritize ACEi/ARB; consider steroidal MRA for resistant hypertension avoid CCB in HF/EF • African American patients with HF/EF → prioritize hydralazine + isosorbide dinitrate after 4 pillars of GDMT <p>Chronic Kidney Disease</p> <ul style="list-style-type: none"> • With albuminuria (UACR >30 mg/g) → ACEi/ARB • ARNI preferred in HF/EF • In CKD (in those with/without diabetes) • DKD with residual albuminuria SGLT2i* (UACR >30 mg/g) on ACEi/ARB → finerenone* (can be used on background SGLT2i) <p>Diabetes</p> <ul style="list-style-type: none"> • Lifestyle modification • Co-utilization of metformin with cardioprotective antihyperglycemics if HbA1c ≥7.5% <p>In ASCVD</p> <p>To reduce MACE → Either SGLT2i* or GLP-1RA To reduce HF hospitalizations → SGLT2i*</p> <p>GLP-1RA/SGLT2i based on:</p> <ul style="list-style-type: none"> BMI ≥35 kg/m² → GLP-1RA HbA1c ≥9% or high insulin dose → GLP-1RA CKD → SGLT2i Concomitant HF → SGLT2i* <p>In HF</p> <p>To reduce HF hospitalizations and CV mortality → SGLT2i* Avoid → thiazolidinediones, DPP4i</p> <p>SGLT2i for all patients with HF +</p> <ul style="list-style-type: none"> • BMI ≥35 kg/m² → add GLP-1RA • HbA1c ≥9% or high insulin dose → add GLP-1RA • Diabetes with multiple comorbidities → add GLP-1RA • Albuminuria → consider adding finerenone‡ <p>Multiple comorbidities in the setting of Diabetes and CVD → Consider co-utilization of SGLT2i* and GLP-1RA</p> </div> </div>

*SGLT2i can be safely initiated for patients with estimated glomerular filtration rate (eGFR) ≥20 ml·min⁻¹·1.73 m⁻². †Metformin can be also be used in patients with eGFR ≥30 ml·min⁻¹·1.73 m⁻² and without unstable or decompensated HF. ‡Finerenone can likely be initiated on background SGLT2i for those with eGFR >25 ml·min⁻¹·1.73 m⁻² and potassium <5 mEq/L. †STOP, strategies to overcome and prevent; CHW, community health worker; SDOH, social determinants of health; MetS, metabolic syndrome; BMI, BMI; iGT, impaired glucose tolerance; ASCVD, atherosclerotic cardiovascular disease; TG, triglycerides; EPA, eicosapentaenoic acid; HbA1c, hemoglobin A1c; GLP-1RA, glucagon-like peptide 1 receptor agonist; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; SGLT2i, sodium-glucose transport protein 2 inhibitors; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; DPP4i, ‡GDMT, guideline-directed medical therapy; HF/EF, heart failure with reduced ejection fraction; CVD, cardiovascular disease; DKD, diabetic kidney disease; DM, diabetes; UACR, urine albumin-creatinine ratio; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; ARNI, angiotensin receptor/neprilysin inhibitor; angiotensin receptor/neprilysin inhibitor; DPP4i, dipeptidyl peptidase 4 inhibitor; MACE, major adverse cardiovascular event.

InfoGraphic by Elba Medina @elbaonelida

20/ This has been a Xtorial by @elbaonelida POD3 Glomke3pers @NSMCInternship NephEdC 2024 Interns. Thank your for reading our KI Reports Community blog

[CKM Syndrome: Finally recognizing the connection between the heart, kidney & metabolic syndrome](#)