
Minneapolis Heart Institute Foundation
GRAND ROUNDS

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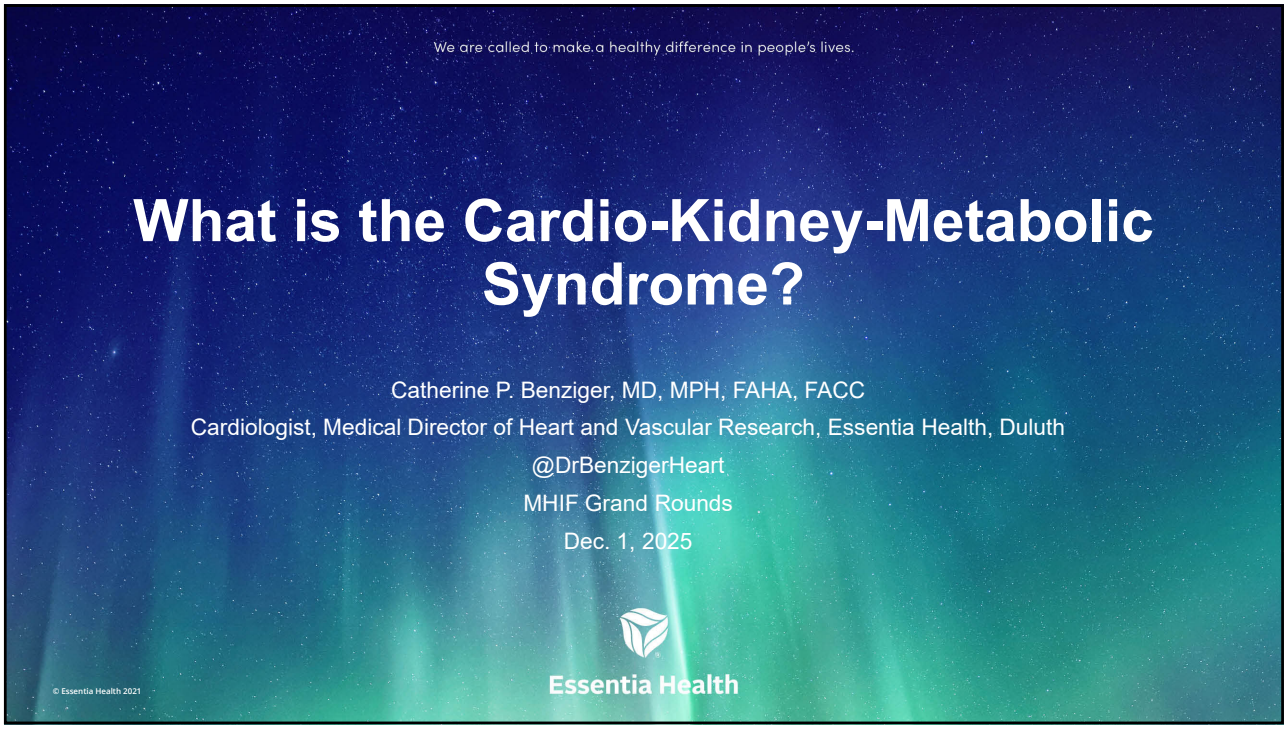
We are called to make a healthy difference in people's lives.
What is the Cardio-Kidney-Metabolic Syndrome?
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MHIF Grand Rounds
Dec. 1, 2025
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We are called to make a healthy difference in people's lives.

Disclosures

Consultant, Novartis

National Lead, Victorion-1-prevent study, Novartis

Site PI, AstraZeneca, Amgen, Novartis, Lilly

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Overview

- Define cardio-kidney-metabolic stages
- Describe screening and management
- When do you need to refer to a specialist?

Circulation
Volume 148, Issue 20, 14 November 2023; Pages 1606-1635
https://doi.org/10.1161/CIR.0000000000001184

American Heart Association.

AHA PRESIDENTIAL ADVISORIES

Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association

Ref: Ndumele et al. Circulation 2023;148(20):1606-1635.

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We are called to make a healthy difference in people's lives.

Case: 65-year-old female with recent STEMI

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Case 1: 65-year-old obese female

- History of ST-elevation myocardial infarction (STEMI) 1 month ago
  - Percutaneous coronary intervention (PCI) to right coronary artery (RCA)
- New diagnosis type 2 diabetes mellitus
- Hypercholesterolemia
- Obesity (BMI 35 kg/m^2)
- Moderate peripheral arterial disease (PAD)
- Tobacco abuse (1/2 ppd)
- Feeling well, no complaints
- **"What can I do to improve my health and reduce risk of another cardiovascular event?"**

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Vital signs: HR 82, BP 139/89, 264 lbs. BMI 35

Exam was unremarkable.

Recent labs:

- WBC 6.3, hemoglobin 12.4, platelets 285
- Basic metabolic panel:

136	101	20	136
4.3	27	1.4	

- Hemoglobin A1C 8.4%
- LDL-c 168, HDL-c 27, TG 375
- EKG: NSR, HR 82, LVH
- Echocardiogram:
  - Moderate concentric left ventricular hypertrophy
  - LVEF 65%
  - Grade 2 diastolic dysfunction with dilated left atrium and elevated filling pressures

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Case

Medications

- Aspirin 81mg
- Clopidogrel 75mg
- Atorvastatin 80mg
- Metformin 1000mg BID
- Glipizide 5mg

No known drug allergies

Past Social and Family History

- Married, two adult children
- Denies alcohol use
- Smoked ½ ppd since age 16, quit after MI
- Father had CAD in his 60s

What optimization of risk factors and medication changes would you consider?

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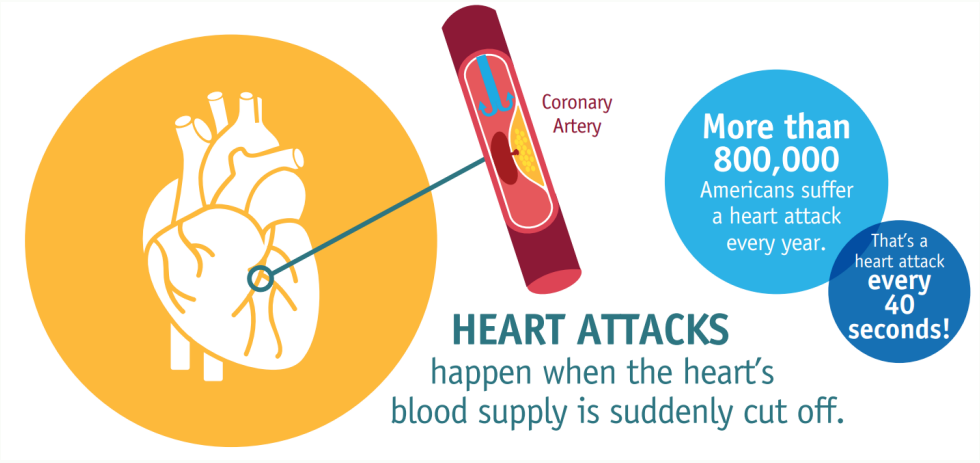
Heart Attacks



Ref: Z19023 - Heart Attack Infographic Update (cardiosmart.org)

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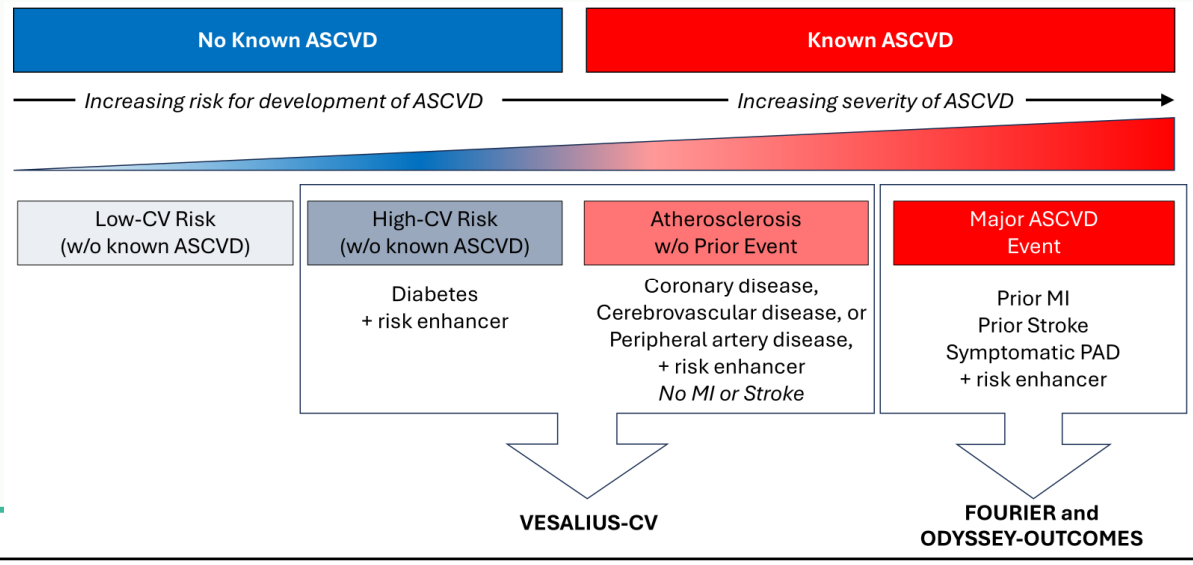
ASCVD Continuum



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Disease Prevention

LDL goal <100

LDL goal <55

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Cardio-Kidney-Metabolic Syndrome

- A health disorder attributed to the connections among **obesity, diabetes, chronic kidney disease** (CKD) and leading to **multiorgan dysfunction** and high rate of adverse cardiovascular disease outcomes

✓Define it

✓Stage and Screen for it

✓Use risk assessment (AHA PREVENT) tools

✓Assess social determinants of health

✓Prevent and Manage

Ref: Ndumele et al. Circulation 2023;148(20):1606-1635.

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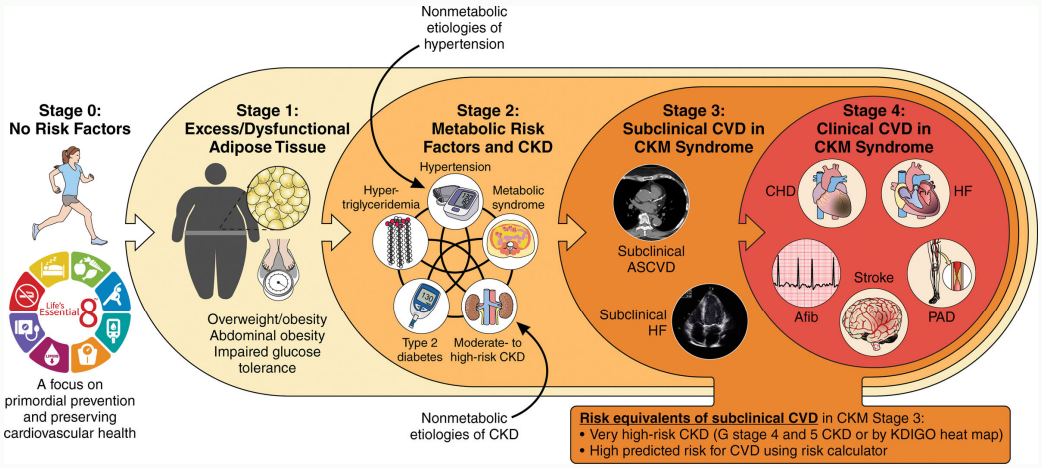
Stages of CKM syndrome



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At Risk Patients for ASCVD

1 in 3 US adults

~136.8 million with CKM

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Goal 1. Lifestyle modifications for all

AHA Life's Essential 8

Ref: https://www.heart.org/en/healthy-living/healthy-lifestyle/lifes-essential-8

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Goal 2: BP control

Treat to goal <130/80 mmHg

- Screen for secondary causes
- Low sodium diet
- Optimize meds ("A+C+D+MRA")
  - ACEi or ARB
  - CCB (long-acting)
  - Thiazide-type diuretic (chlorthalidone > HCTZ)
  - MRA
- Consider renal denervation

2025 AHA/ACC Hypertension guidelines

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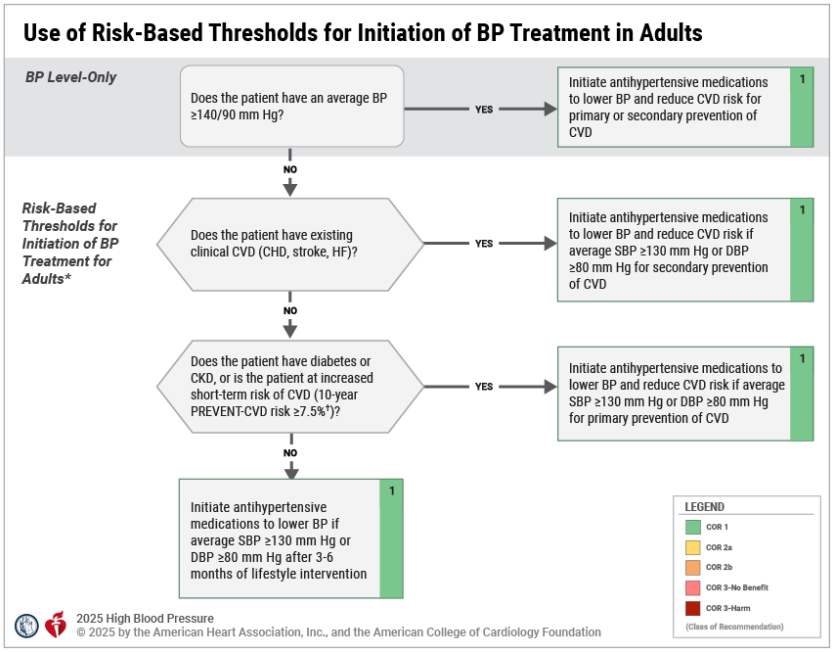
Use of Risk-Based Thresholds for Initiation of BP Treatment in Adults



BP indicates blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; HF, heart failure; PREVENT, Predicting Risk of cardiovascular EVENTs; and SBP, systolic blood pressure.

*In older adults who may be frail or have a limited life expectancy, a clinician-patient assessment of potential benefits and harms of BP lowering should be pursued to align care with patient goals.

†Increased short-term or 10-year risk is defined as a 10-year predicted risk for CVD events of ≥7.5% using PREVENT.

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Routine Tests for Hypertension

• Complete blood count
• Serum sodium, potassium, calcium
• Serum creatinine with estimation of glomerular filtration rate (eGFR; based on the 2021 CKD-EPI Creatinine Equation)
• Lipid profile
• Fasting blood glucose or Hemoglobin A1c
• Thyroid-stimulating hormone (TSH)
• Urinalysis
• Urine albumin-to-creatinine ratio; urine protein-to-creatinine ratio
• ECG

ECG indicates electrocardiogram.

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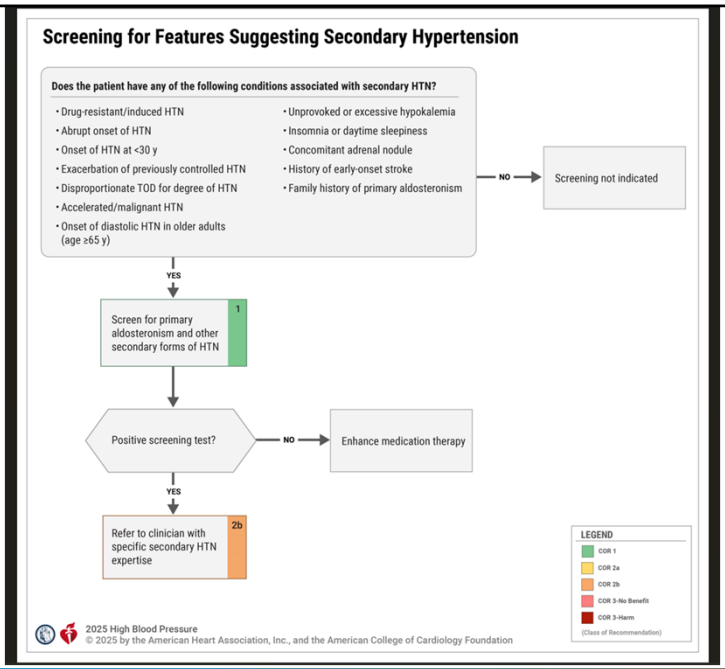
Screening for Features Suggesting Secondary Hypertension



HTN indicates hypertension; and TOD, target organ damage (eg, cerebrovascular disease, hypertensive retinopathy, left ventricular hypertrophy, left ventricular dysfunction, heart failure, coronary artery disease, chronic kidney disease, albuminuria, peripheral artery disease).

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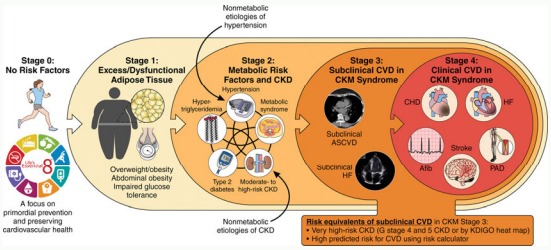
CKM adulthood screening

- **Screening for health-related social needs**
- **Obesity**
  - Measure BMI and waist circumference **annually**
- **Screening for MetS components** (elevated blood pressure, elevated triglycerides, low HDL cholesterol, and hyperglycemia):
  - **Annually** for those with stage 2 CKM
  - Every **2-3 years** for those with stage 1 CKM or history of gestational diabetes
  - Every **3-5 years** for those with stage 0 CKM



Ref: Ndumele et al. Circulation 2023;148(20):1606-1635.

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CKM adulthood screening

- **Liver disease:** Screening for advanced liver fibrosis related to MASLD every 1–2 years for individuals with diabetes, prediabetes, or ≥2 metabolic risk factors **using the FIB-4 index**
- **Kidney Disease:** Assessment of **UACR** along with serum creatinine/cystatin C for accurate KDIGO staging
  - **Annually** for those with stage 2 CKM or higher
  - More frequently for those with higher KDIGO risk
- **Coronary artery calcium (CAC) screening** reasonable in those with intermediate 10-y ASCVD risk (5-20%) to guide intensification of preventive therapies
- Subclinical HF screening with echocardiogram and/or cardiac biomarkers likely based on age/comorbidities/risk score

CKD is classified based on:
Cause (C)*
GFR (G)†
Albuminuria (A)†

GFR categories (mL/min per 1.73 m²) Description and range				Albuminuria categories Description and range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30–299 mg/g 3–29 mg/mmol	A3 Severely increased ≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer‡ 3	Treat and refer‡ 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

Ref: Ndumele et al. Circulation 2023;148(20):1606-1635.

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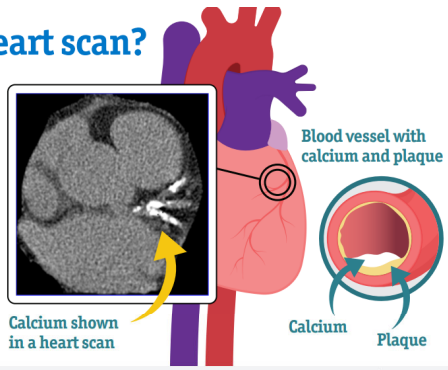
What is a CAC scan?

Ref: Z22057 CardioSmart CAC Infographic_V9 copy

What is a calcium heart scan?

A test that **measures the amount of calcium in the heart's arteries.** It's:

- Done with a CT scan of the heart (low radiation)
- Most helpful if there is some question about your chances (risk) of developing heart disease, for example:
  - You may have some risk factors
  - Other tests haven't given clear answers



WHAT THE TEST RESULTS MEAN

You'll get a score, or number, that shows:

Amount of calcium:	None	Mild	Moderate	Severe
	0	1-99	100-299	300 or more
Chance of heart disease, heart attack or stroke is:	Low			High

The more calcium in the arteries, the greater your risk of a heart attack or stroke.

TALK WITH YOUR TEAM

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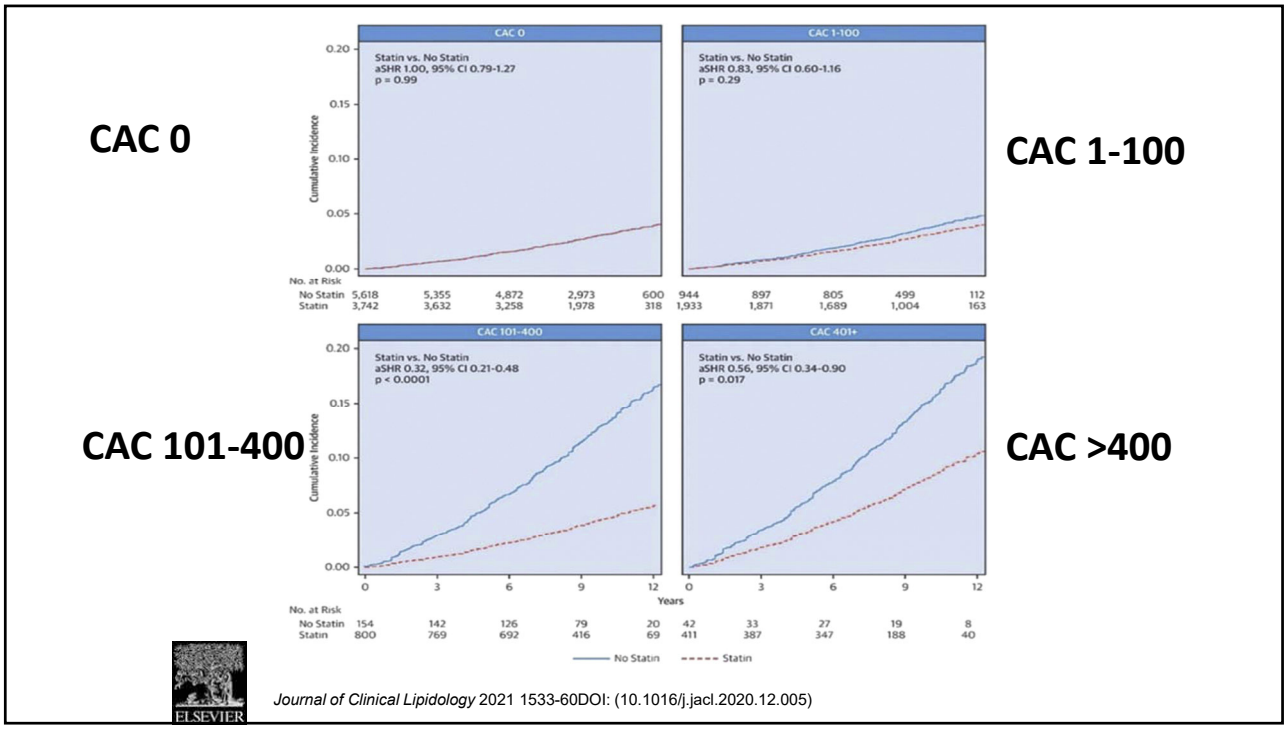

Journal of Clinical Lipidology 2021 1533-60DOI: (10.1016/j.jacl.2020.12.005)

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Calculate the PREVENT risk score

Sex ◉ Male ○ Female
Age 64 years
Total Cholesterol 197 mg/dL
HDL Cholesterol 58 mg/dL
SBP 120 mmHg
BMI 26.5
eGFR 80
Diabetes ◉ No ○ Yes
Current Smoking ◉ No ○ Yes
Anti-hypertensive medication ○ No ◉ Yes

AHA PREVENT Risk Calculator predicts 10- and 30-year risk of CVD and CVD subtypes (ASCVD, HF, CHD, stroke) in patients aged 30-79 without known CVD

Interpretation of Risk Estimates:
10-year risk for CVD is categorized as:

- Low risk (<5%)
- Borderline risk (5% to 7.4%)
- Intermediate risk (7.5% to 19.9%)
- High risk (≥20%)

Full model

The following three predictors are optional for further personalization of risk assessment. When they are clinically indicated or available, please click on yes and enter the value

UACR ◉ No ○ Yes
HbA1C ◉ No ○ Yes
Zip Code (for estimating social deprivation index [SDI]) ○ No ◉ Yes
55808
Calculate Reset
◉ Risk of CVD ○ Risk of ASCVD ○ Risk of Heart Failure
This individual has an estimated 10-year risk of CVD = 11.4%
The risk estimates were calculated using the model that included SDI based on zip code

PREVENT Online Calculator - Professional Heart Daily | American Heart Association

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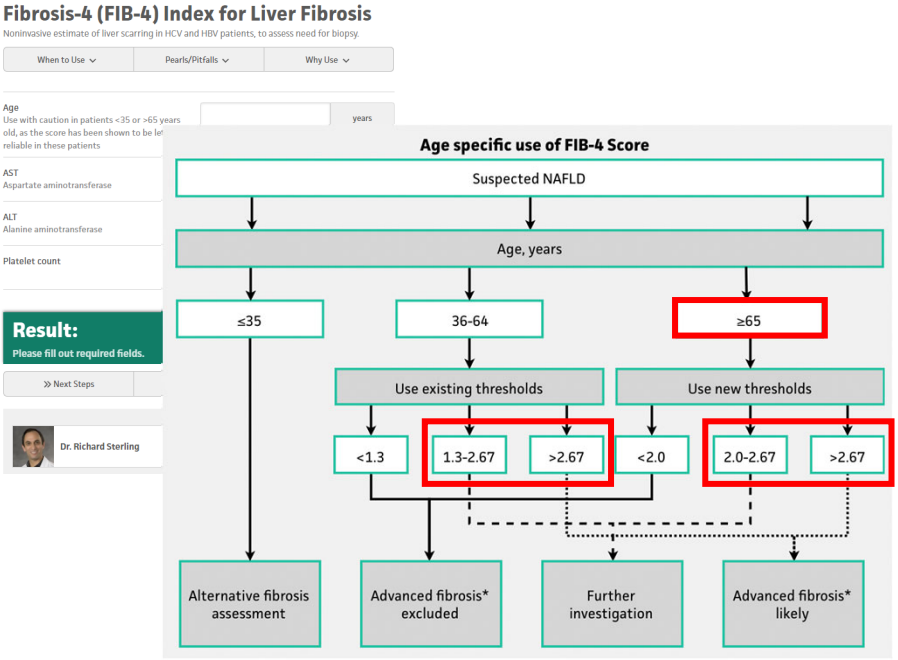
FIB-4 index

1. Age
2. AST
3. ALT
4. Platelets

FIB-4 Score > 1.3 (or >2.0 if >=65 years) needs fibroscan and/or referral to hepatology



Ref: McPherson et al. AJG 2016.

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Heat map for CKD classification

Need both serum creatinine/eGFR and urine albumin/creatinine ratio (UACR)

CKD is classified based on:
Cause (C)*
GFR (G)†
Albuminuria (A)†

GFR categories (mL/min per 1.73 m²) Description and range				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
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Low risk (if no other markers of kidney disease, no CKD)
High risk
Moderately increased risk
Very high risk

Ref: Ndumele et al. Circulation 2023;148(20):1606-1635.

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Assess for risk enhancing factors for CKM syndrome

Ref: Ndumele et al. Circulation 2023;148(20):1606-1635.

Risk-Enhancing factors for Cardio-Kidney-Metabolic Syndrome
Chronic inflammatory conditions (eg, psoriasis, rheumatoid arthritis, lupus, HIV/AIDS)
High-risk demographic groups (eg, South Asian ancestry, lower socioeconomic status)
High burden of adverse social determinants of health
Mental health disorders (eg, depression and anxiety)
Sleep disorders (eg, obstructive sleep apnea)

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Assess for risk enhancing factors for CKM syndrome

Ref: Ndumele et al. Circulation 2023;148(20):1606-1635.

Risk-Enhancing factors for Cardio-Kidney-Metabolic Syndrome Cont.
Sex-specific risk enhancers (beyond gestational diabetes; stage 1 CKM)
History of premature menopause (age <40 y)
History of adverse pregnancy outcomes (eg, hypertensive disorders of pregnancy, preterm birth, small for gestational age)
Polycystic ovarian syndrome
Erectile dysfunction
Elevated high-sensitivity C-reactive protein (≥2.0 mg/L if measured)
Family history of kidney failure; family history of diabetes

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CKM pediatric and adolescence screening (<21 years)

Ref: Ndumele et al. Circulation 2023;148(20):1606-1635.

- **Obesity**: Screening for overweight and obesity using sex- and age-specific CDC growth charts: annually
- **Blood pressure**: starting at age 3 years, annually for children with no risk factors; at every health encounter for children with overweight/obesity, diabetes, kidney disease, or structural heart disease
- **Mental and Social:** Mental and behavioral health screening, SDOH screening for all children
- **Cholesterol**: universal fasting lipid panel recommended:
  - Once between 9-11 years of age and then again 17-21 years of age
  - Screening is advised beginning at 2 years of age if a family history is suggestive of either early CVD or significant primary hypercholesterolemia.
- **Glucose**: check FPG/OGTT/HbA1c, ALT: starting at 9-11 years of age
  - If normal, may repeat every 2-3 years for all children with obesity
  - If normal, may repeat every 2-3 years for children with overweight if additional risk factors present (family history of obesity-related diseases, elevated blood pressure or lipid levels, tobacco use)

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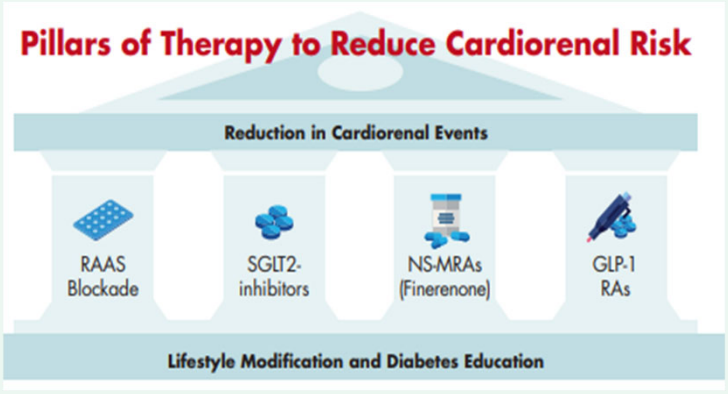
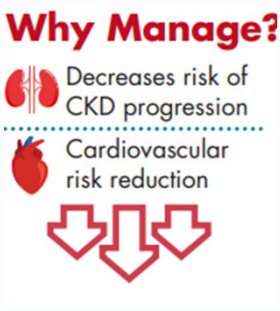
Goal 3. Management of diabetes-related kidney disease



- ✓ Check UACR annually
- ✓ If >30mg/g, start ARB



Ref: Infographics | American Diabetes Association

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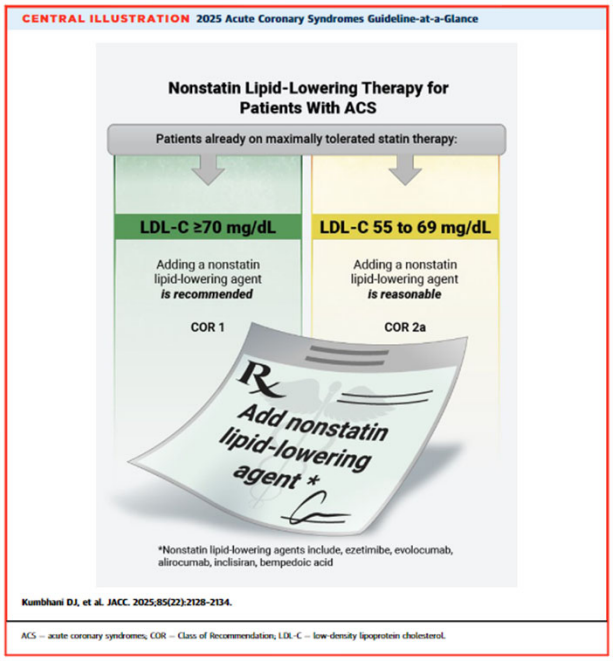
Goal 4. Lipid lowering therapy

- Start high-intensity statin (atorvastatin 80mg or rosuvastatin 20mg)
- Add ezetimibe (zetia) 10mg PO daily
- Add PCSK9 inhibitor (evolocumab 140mg/mL SC q 2 weeks or alirocumab 75mg SC q 2 weeks)



LDL goal as low as possible (<55 if known ASCVD/ ACS)

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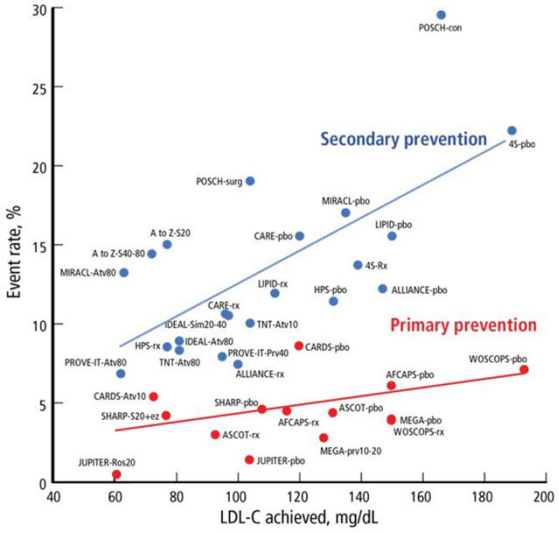
CV benefit with lower LDL

Scatter plot with best-fit lines of major lipid trials (statin and nonstatin trials) for both primary and secondary prevention of coronary heart disease events.



Marc S. Sabatine CCJM 2016;83:181-186

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FOURIER Trial- Evolocumab (Repatha)

Outcomes, LDL-c levels over time and adverse events

Primary endpoint: CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization

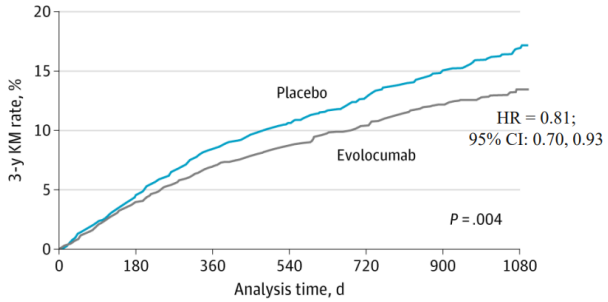

Table 3. Adverse Events and Laboratory Test Results.

Outcome	Evolocumab (N = 13,769)	Placebo (N = 13,756)
Adverse events — no. of patients (%)		
Any	10,664 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)
Injection-site reaction*	296 (2.1)	219 (1.6)
Allergic reaction	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results — no. of patients/total no. (%)		
Aminotransferase level >3 times the upper limit of the normal range	240/13,543 (1.8)	242/13,523 (1.8)
Creatine kinase level >5 times the upper limit of the normal range	95/13,543 (0.7)	99/13,523 (0.7)

* The between-group difference was nominally significant (P<0.001).
† The total numbers of patients were 8337 in the evolocumab group and 8339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.

Evolocumab reduced the risk for MACE vs. placebo (9.8% vs 11.3%; HR, 0.85; 95% CI, 0.79 to 0.92; *P* < .001)

Gencer et al. *JAMA cardiology* 2020;5:952-957

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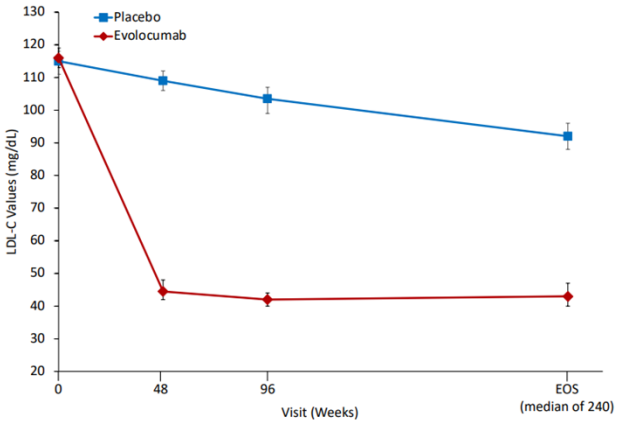
VESALIUS-CV- Evolocumab (Repatha)

Figure S2: Low-Density Lipoprotein (LDL) cholesterol levels over time.

Median with nonparametric rank-based 95% confidence intervals for LDL-C values by treatment arm in the lipid sub-study.



LDL-c -55%;
median 45mg/dL
at 48 weeks

Ref: Bohula E. et al NEJM 2025

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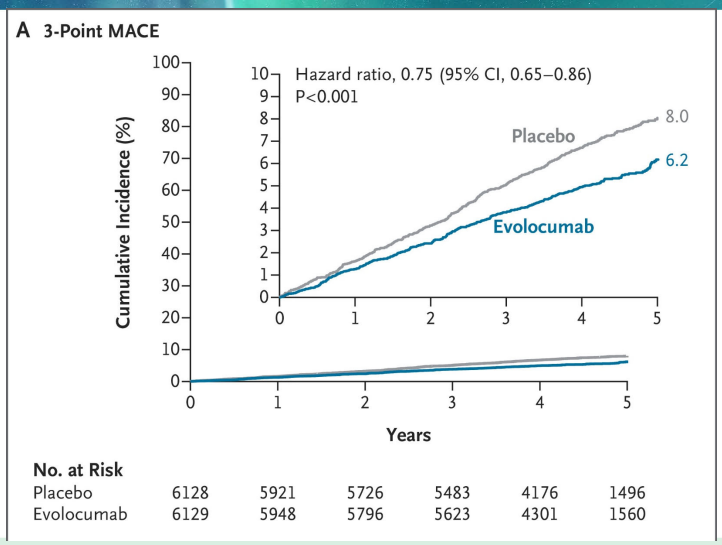
VESALIUS-CV



25% RRR

LDL-c -55%; median 45mg/dL at 48 weeks

Ref: Bohula E. et al NEJM 2025

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Goal 4. Optimize lipid lowering therapy

	Bempedoic acid (nexletol)	Ezetimibe (zetia)	CETPi Obicetrapib	PCSK9i Enlicitide	PCSK9i laroprovstat	PCSK9i Inclisiran	PCSK9i alirocumab/ evolocumab
% LDL-C reduction	-18%	-20%	-30%	-58%	-51%	-50%	-55-60%
% lipoprotein(a) reduction	0%	0%	-50%	-20%	-20%	-20%	-25%
% ApoB reduction	<10%	<10%	20%	49%	43%	40%	45%
% HS-CRP reduction	-25-40%	0%	0%	0%	0%	0%	0%
Mode of admin.	Oral daily	Oral daily	Oral daily	Oral daily	Oral daily	SC 2x/year	SC 26x/year
			BROADWAY	**CORALreef lipids, Outcomes**	**PURSUIT; AZURE-CVOT**	**V2P, V1P trials**	**FOURIER, ODYSSEY, VESALIUS trials**

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LDL "Bad" Cholesterol + HDL "Good" Cholesterol + TRIGLYCERIDES/5 = TOTAL CHOLESTEROL

How well do you know your statin therapy?

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering†	≥50%	30%–49%	<30%
Statins	**Atorvastatin (40 mg‡) 80 mg** **Rosuvastatin 20 mg (*40 mg***	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg§**	Simvastatin 10 mg
	…	**Pravastatin 40 mg** (80 mg) **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 1–4 mg	**Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg

Grundy et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary. JACC Nov 2018

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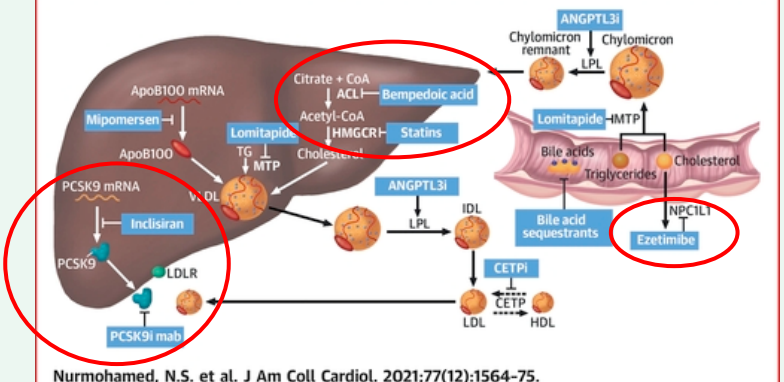
Approach to lipid lowering therapy

CENTRAL ILLUSTRATION: Working Mechanisms of Low-Density Lipoprotein Cholesterol Lowering Therapies



Nurmohamed, N.S. et al. J Am Coll Cardiol. 2021;77(12):1564-75.

LDL as low as possible <55 if high risk for ASCVD or established ASCVD:

- Start high-intensity statin (atorvastatin 80mg or rosuvastatin 20mg)
- Add ezetimibe (zetia) 10mg PO daily
- Add PCSK9 inhibitor (especially if Lp(a) is >125 nmol/L)
- Evinacumab (Evkeeza) infusion monthly for HeFH (LDL-independent)
- Consider trials

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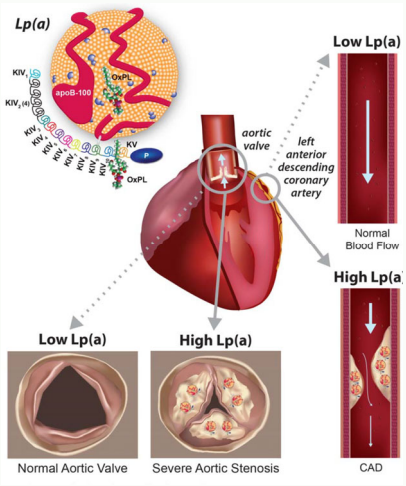
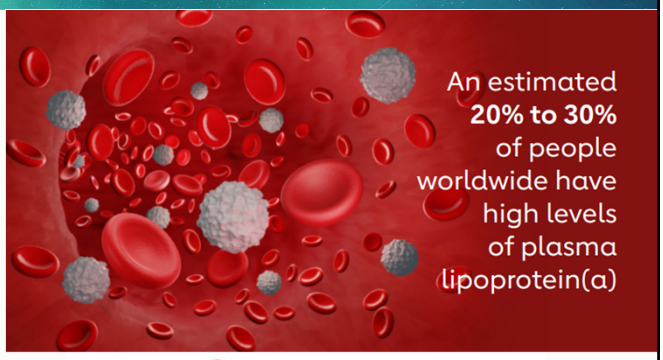
Check lipoprotein(a) once





Black people have the highest Lp(a) levels, followed by South Asians, Hispanics and East Asians. American Indians have the lowest.[11]

Ref: Journal Of Lipid Research Cover March 2016

Ref: Lp(a): A Toolkit for Health Care Professionals (heart.org)

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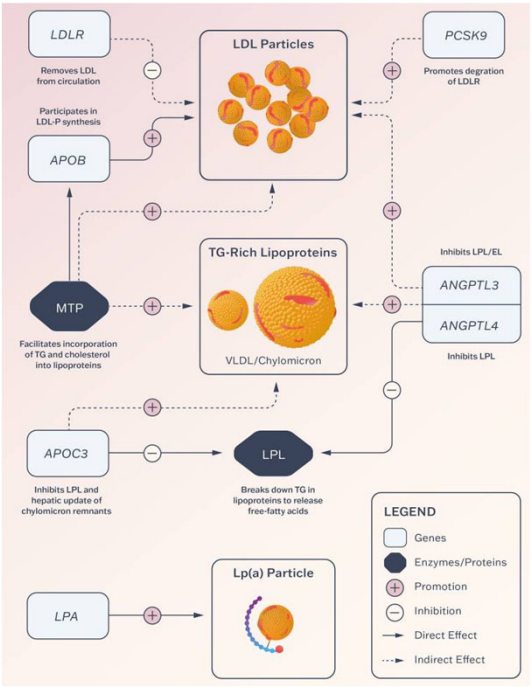
Targetable genes in lipoprotein disorders

Gurevitz et al. EHJ 2025;46:3420-3433



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Targetable genes in lipoprotein disorders

Gurevitz et al. EHJ 2025;46:3420-3433

Table 1 Genetic targeted therapies for lipoprotein disorders

Pathway	Agent	Mode of action	Frequency of administration	Main efficacy endpoints	Cardiovascular outcome data
PCSK9	Inclisiran	siRNA	Biannually	LDL-C reduction up to 50%	Phase 3 CVOT are ongoing (ORION-4, VICTORION 2-PREVENT)[56]
ANGPTL3	Vupanorsen	ASO	Monthly	Triglycerides reduction up to 53%	Phase 2 completed (TRANSLATE-TIMI 70),[57] program discontinued.
	Zodasiran	siRNA	Monthly	Triglycerides reduction up to 74%, LDL-C reductions up to 48%	Phase 2 in patients with mixed hyperlipidaemia completed (ARCHES-2)[58,59] Phase 2 in HoFH interim data presented (GATEWAY).[57] Phase 3 in HoFH was launched.[60]
	Solbinsiran	siRNA	Monthly	Triglycerides reduction up to 86%	Phase 1 completed.[61] Phase 2b study (PROLONG-ANG3, NCT05256654) completed but not published yet.
ANGPTL4	Lipisense	ASO	Weekly	Triglycerides reduction up to 48% total cholesterol reductions up to 56%, reduced atherosclerotic lesion size (−86%)	Preclinical studies in mice were completed, phase 1 completed.[62] Phase 2a in patients with severe HTG and T2DM is underway.

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Targetable genes in lipoprotein disorders

Gurevitz et al. EHJ 2025;46:3420-3433

APOC3	Volanesorsen	ASO	Weekly	Triglycerides reduction up to 77% (APPROACH) in FCS and 71% in MCS (COMPASS)	Phase 3 laboratory trials completed[63] [approved in Europe for FCS], CVOT not planned.
	Olezarsen	ASO	Monthly	Triglycerides reduction up to 53% in moderate HTG with high cardiovascular risk or severe HTG, and 43% in FCS	Phase 3 FCS study completed.[64] FDA has accepted for Priority Review the NDA for FCS. Phase 2b in moderate HTG and high CV risk completed.[65] Phase 3 is ongoing.[66]
	Plozasiran	siRNA	Monthly	Triglycerides reduction of up to 62% in mixed hyperlipidaemia, 57% in severe HTG and 80% in chylomicronemia	Phase 2 trials completed;[67,68] Phase 3 in FCS completed;[69] Phase 3 in mixed hyperlipidaemia and severe HTG enrolling (MUIR, SASHTA, CAPITAN).[70–72]
LPA	Pelacarsen	ASO	Monthly	Lp(a) reduction up to 92%	Phase 3 CVOT (HORIZON-Lp(a)) and phase 3 aortic valve stenosis (CAVS) are ongoing.[73,74]
	Olpasiran	siRNA	Quarterly	Lp(a) reduction up to 101.1% (placebo-adjusted)	Phase 3 CVOT is ongoing (OCEAN(a)).[75]
	Lepodisiran	siRNA	Biannually or annually	Lp(a) reduction up to 100.5% (placebo-adjusted)	Phase 3 CVOT is ongoing (ACCLAIM).[76]
	Zerlasiran	siRNA	Every 16 or 24 weeks	Lp(a) reduction up to 98% (APOLLO)	Phase 2 is completed (ALPACAR-360).[77]

ANGPTL3, angiopoietin-Like 3; ANGPTL4, angiopoietin-Like 4; APOC3, apolipoprotein C-III; ASO, antisense oligonucleotide; CV, cardiovascular; CVOT, cardiovascular outcomes trial; FCS, familial chylomicronemia syndrome; FDA, U.S. Food and Drug Administration; HTG, hypertriglyceridaemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular events; MCS, mixed chylomicronemia syndrome; NDA, new drug application; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA; T2DM, type 2 diabetes mellitus.

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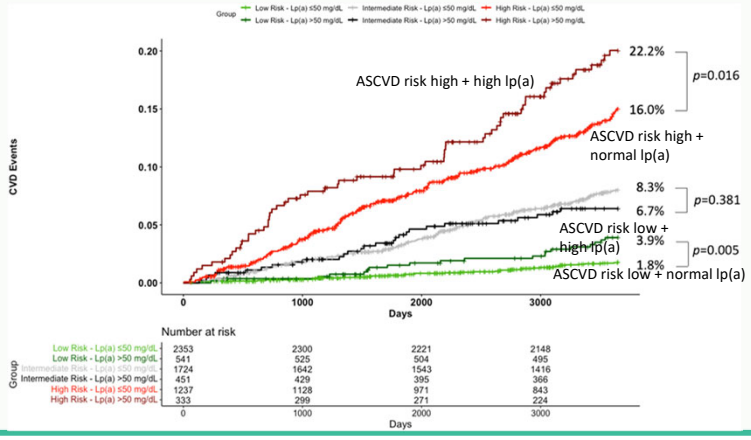
Remember to check Lipoprotein(a) once

Lp(a) can prognosticate future ASCVD risk

MESA Study:
Lp(a) >50mg/dL improves 10-year ASCVD pooled cohort equation risk prediction

Elevated **lp(a) >125 nmol/L**



Bhatia et al. Atherosclerosis 2023

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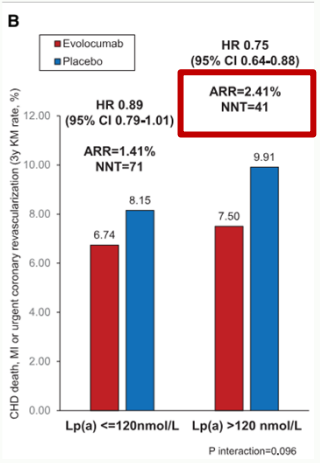
Current Therapies for Lp(a)

PCSK9 inhibitors (monoclonal antibody/siRNA)

- **Evolocumab** – FOURIER trial (-26.9%, absolute reduction -11 nmol/L) (figure)
- **Alirocumab** – ODYSSEY trial (−23%, absolute reduction 5mg/dL)
- **Inclisiran** - Meta-analysis (-17.95%)

Other (niacin, estrogen, etc.)

Lipoprotein Apheresis



Ref: Bittner V et al JACC 2020; 75(2): 133-144

Ref: O'Donoghue et al Circ 2019; 139(12): 1483-1492

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Future Therapies

Second-generation ASO targeting apo(a) mRNA

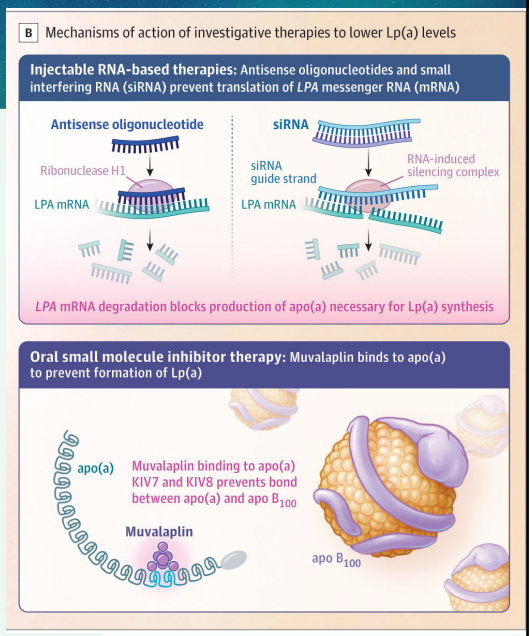
- Pelacarsen – lowers 35-80%

Silencing RNA targeting apo(a) mRNA

- Lepodisiran – lowers 41-94%
- Olpasiran – lowers 70-90%
- Zerlasiran – lowers 46-98%

Small molecule binding apo(a)

- Muvalaplin (oral) – lowers 50-65%



Ref: Nicholls et al JAMA 2023;330;(11):1042-1053.

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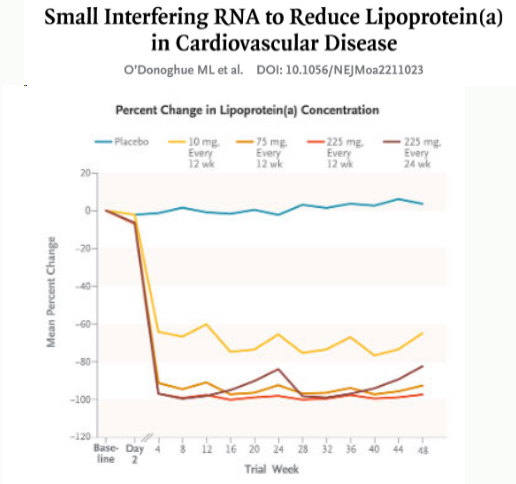
Olpasiran - OCEAN(a) trial

- siRNA reduces lp(a)
- N=281 patients with Lp(a) >150 nmol/L with ASCVD
- 10mg, 75mg or 225mg S.C. q 12 weeks
- Endpoint: % change Lp(a) at 36 weeks



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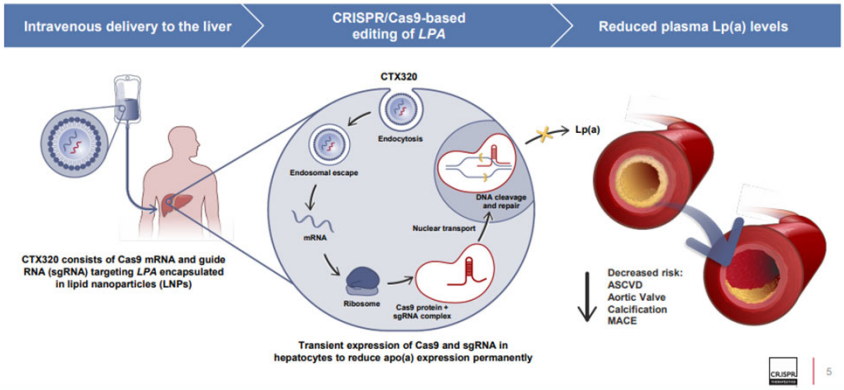
Future Therapies

CRISPR Cas9 mRNA targeting LPA



CRISPR CTX320

- Durable 95% reduction in lp(a) in non-human primates at 1 year
- Phase 1 trial in process

Ref: PowerPoint Presentation

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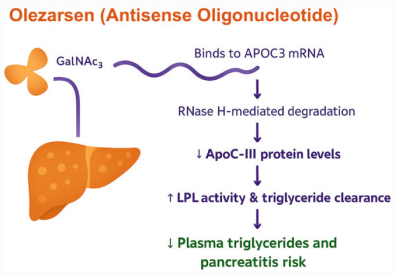
What about triglycerides?

TG-lowering therapies

- Icosapent ethyl (vascepa) 2g BID if DM or ASCVD and TG >150
- Olezarsen (Tryngolza) – ASO to apoC3 approved for FCS and severe high TG (>500mg/dL), pancreatitis
- Plozasiran (Redemplo) – siRNA to apoC3 for FCS, recent FDA approval 11/2025



Ref: Khan et al Ann Med Surg 2025 Sept 4;87(11):7802-06

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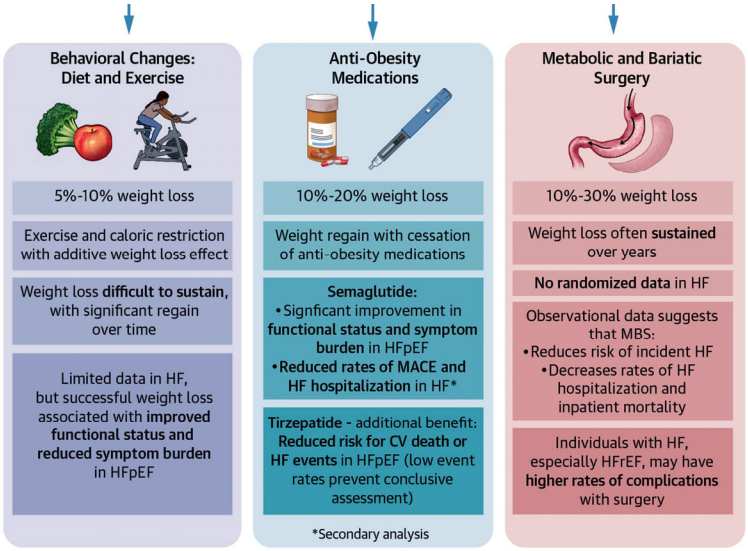
Goal 5. Weight loss strategies

- Goal 10-15% body weight reduction



Kittleson MM. et al. JACC. 2025;86(20):1953-3.

CV = cardiovascular; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; MACE = major adverse cardiac events; MBS = metabolic and bariatric surgery.

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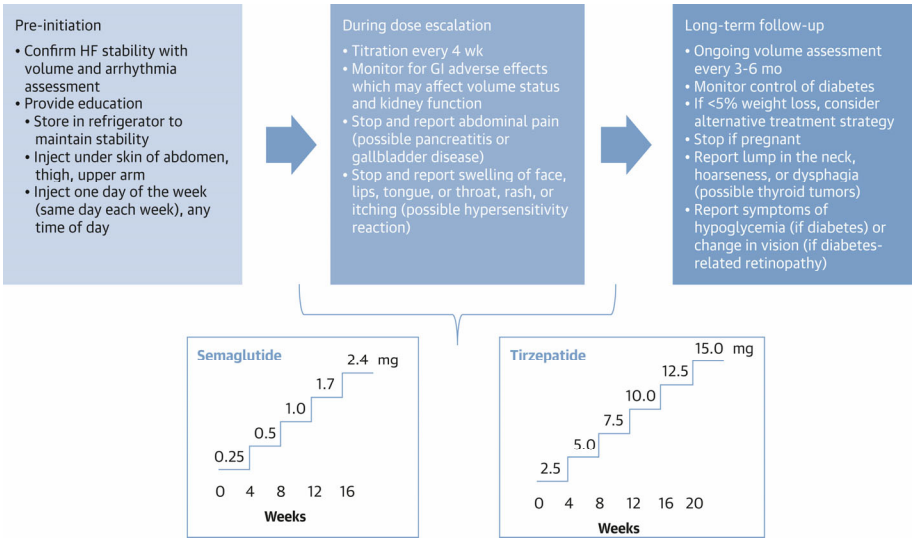
Goal 5. GLP1 therapy

- Provide education
- Dose escalation every 4 weeks
- Monitor for GI side effects. If tolerated, get to goal dose
- Set goal/target weight



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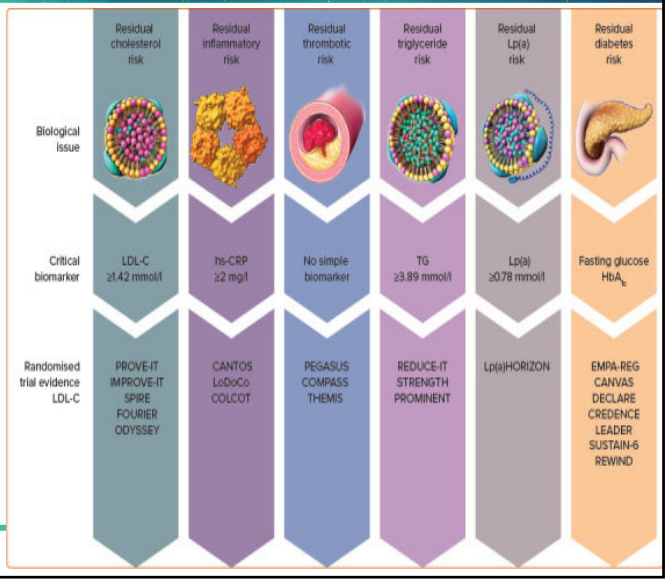
Summary of Key Contemporary Residual Risk Pathways in Secondary Prevention of ASCVD

Lipid Biomarkers
- LDL-C
- Triglycerides
- Apolipoprotein B
- Lipoprotein(a)

Cardiac Injury/Wall Stress
- High sensitivity Troponin
- Natriuretic peptides

Inflammatory Markers
- hsCRP (>2.0mg/L)



Lawler et al. 2020 Eur Heart J. 2021;42:113–31.

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We are called to make a healthy difference in people's lives.

How do we address all of these CKM issues?

Essentia Health

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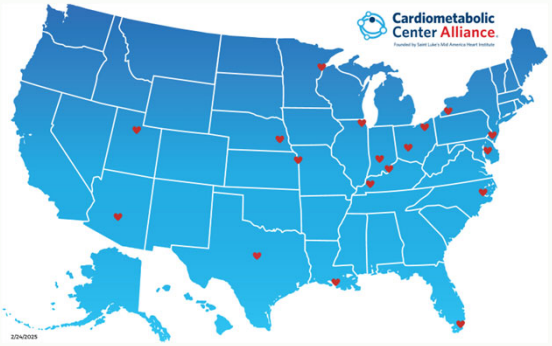
Cardiometabolic clinic

Cardiometabolic Center Alliance (CMCA) is a proven, collaborative approach to treating cardiometabolic conditions in a holistic manner, providing team-based, comprehensive care specifically tailored to each patient.



Home - Cardiometabolic Center Alliance (cardiometabolicalliance.org)

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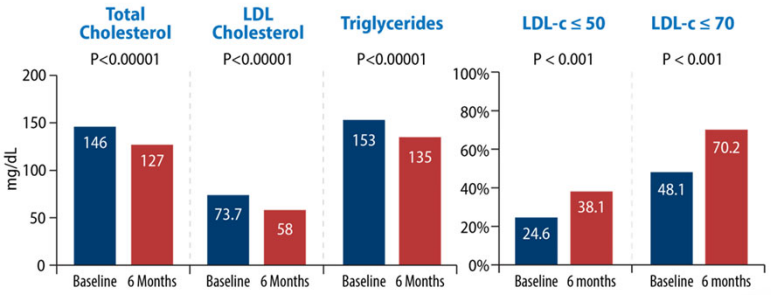
Cardiometabolic clinic- lipid for DM2

Baseline and 6-Month Follow-Up Lipid Measures and 6-Month LDL-c Goal Achievement



Ref: 1937-LB: Coordinated Approach to Improve Quality of Care and Address Disparities in Patients with Cardiometabolic Disease—Analysis from the Cardiometabolic Center Alliance Registry | Diabetes | American Diabetes Association (diabetesjournals.org)

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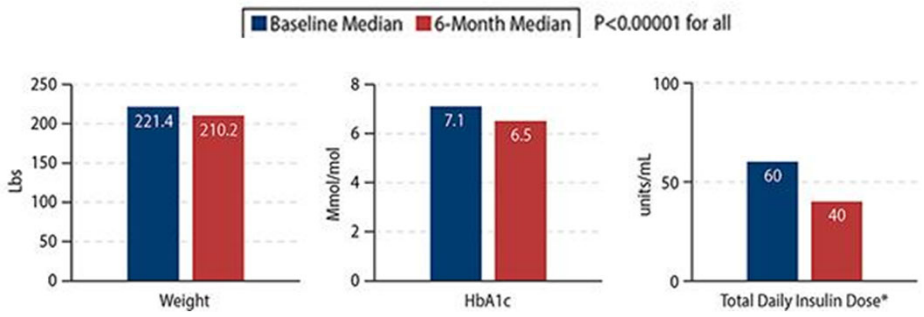
Cardiometabolic clinic - weight, A1c, insulin for DM2



Ref: 1937-LB: Coordinated Approach to Improve Quality of Care and Address Disparities in Patients with Cardiometabolic Disease—Analysis from the Cardiometabolic Center Alliance Registry | Diabetes | American Diabetes Association (diabetesjournals.org)

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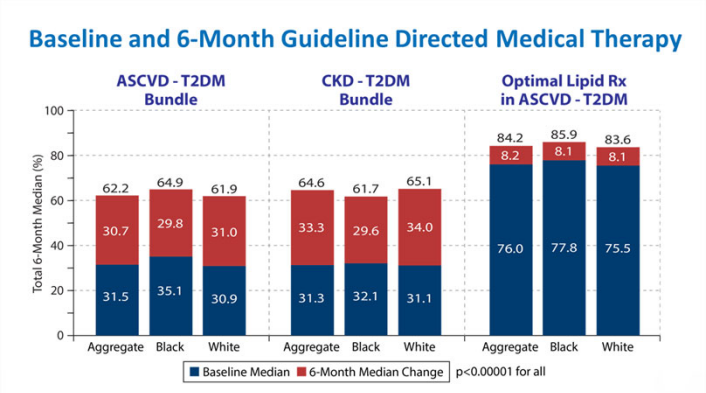
Cardiometabolic clinic- GDMT for DM2



Ref: 1937-LB: Coordinated Approach to Improve Quality of Care and Address Disparities in Patients with Cardiometabolic Disease—Analysis from the Cardiometabolic Center Alliance Registry | Diabetes | American Diabetes Association (diabetesjournals.org)

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Cardiometabolic clinic scorecard

Optimized Patient Care Scorecard

When striving to improve target outcomes and optimize therapeutic agents to reduce cardiovascular risk, this form can help clinicians identify potential opportunities or highlight goals that have been achieved in an individual's care plan. It may be customized to organizational workflow and additional reference material can be found here: Optimized GDMT in the Setting of CKM Syndrome.

Patient		Date of Birth		Visit Date	
Labs & Testing	**Result**	**Date**	**Standard Goal[1]**	**Notes**	
Glycemic Management	HbA1c			< 7%	
	Time in Range			> 70% TIR	
	Time Below Range			< 4% time <70 mg/dL < 1% time <54 mg/dL	
Cardiovascular Risk	LDL-C			□ < 55 mg/dL □ < 70 mg/dL	
	BP			< 130/80 mmHg	
	BNP/NTproBNP			Screen for HR/prevent worsening	
	LP(a)			Screen for high risk	
Kidney Risk	eGFR			Screen for/prevent decline in eGFR	
	UACR			Screen/reduce ≥30% (if uACR ≥300)	
Liver Risk	Fib-4			Screen for liver disease	
Weight Management	Weight			If indicated, reduction of □ 5% □ 10%	
	BMI			< 25 kg/m²	
	Waist Circumference			women < 35 in men < 40 in	

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Optimized GDMT for cardio-metabolic disease

	Targets to Reduce Cardiovascular Risk[1]			
	Weight Management	**Glycemic Management**	**Blood Pressure Management**	**Lipid Management**
Goals[4]	≥10-15% weight loss, improve body mass index & waist circumference	A1c <7.0%, TIR >70%, or individual goal & absence of hypoglycemia	BP <130/80 or individual goal	LDL <55 (very high risk) or <70 (high risk) Triglycerides <150 HDL >40 non–HDL ≤130
Optimized Medication Therapy[1]	GLP-1ra	Agents that provide adequate efficacy; based on person centered treatment factors	ACE-I or ARB[5] Thiazide-type diuretic Dihydropyridine calcium channel blocker Resistant: SMRA	High intensity statin or maximally tolerated statin +/- ezetimibe or PCSK9i/inclisiran --- Consider: Bemp Acid Icosapent Ethyl
Device or surgery	Metabolic surgery[12]	CGM	ABPM	
CPGs[1]	AACE '19 AGA '22 ADA '23	AACE '22 ADA '23	ACC/AHA '17 ESC/ESH '18 ADA '23	AHA/ACC '18 ESC/EAS '19 ADA '23

Targets Met?

Continue to monitor ← Yes, to both

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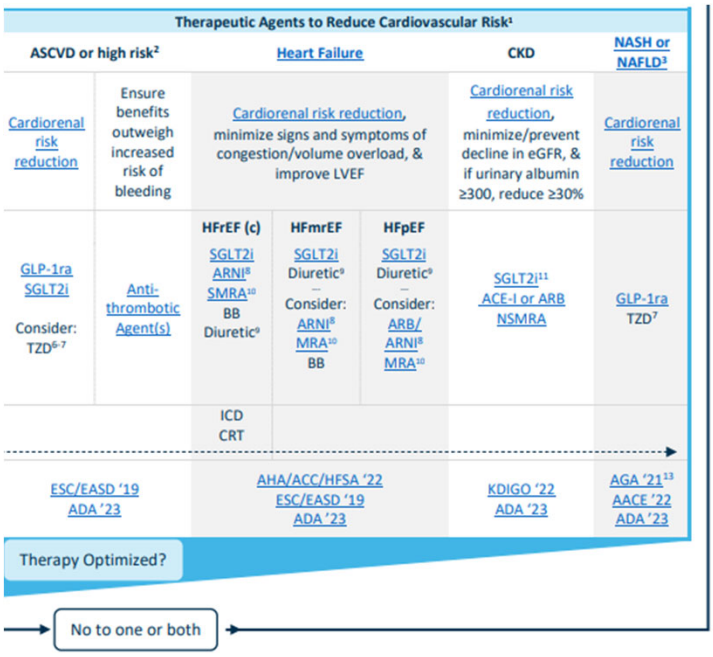
Optimized GDMT for cardio-metabolic disease



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Cardio-kidney-metabolic health initiative

American Heart Association.
Cardiovascular-Kidney-Metabolic Health Initiative™

Why Now? Collaboration Is Our Most Powerful Tool for Change

- Quality Improvement Consultation
- Professional & patient-facing resources
- Measurement & tracking support
- Collaboration with peer sites locally & across the US
- Recognition & model sharing opportunities
- Project participation stipend

AHA CKM Health Initiative

- Began in 2024
- Within 4 years, 150 certified health care centers and reach over 265,000 patients
- Education
- Registries
- Recognition program

CKM Health Groundbreakers | American Heart Association

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65-year-old obese female STEMI s/p PCI to RCA, DM2, HLD, PAD, tobacco abuse, obesity

- ST-elevation myocardial infarction (STEMI)
  - Labs: HS-CRP
  - Consider colchicine 0.6mg daily if >2mg/dL
  - DAPT x 12 mo, aspirin 81mg lifelong, beta blocker
- Hypertension
  - BP goal <130/80mmHg
  - Optimize therapy with meds "A+C+D+MRA"
  - Consider RDN if SBP >150mmHg on 3+ meds
- Diabetes mellitus, type 2
  - Labs: repeat A1c, CMP, CBC, microalbumin
  - Calculate FIB-4 score, refer for Fibroscan if score >2
  - Start SGLT2i, GLP1-RA
  - Stop glipizide
  - Start ARB (e.g. irbesartan 150mg), consider finerenone (karendia) 10mg if microalbumin >30, K<5.5

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65-year-old obese female STEMI s/p PCI to RCA, DM2, HLD, PAD, tobacco abuse, obesity

- Hypercholesterolemia, high triglycerides
  - Labs: repeat fasting lipid panel, lipoprotein(a), apolipoprotein B (on treatment goal same as LDL)
  - LDL goal <55 given ACS, DM.
    - High-intensity statin, ezetimibe, and PCSK9i (evolocumab/ alirocumab/ inclisiran)
  - After LDL at goal, get TG to goal <150
    - Start icosapent ethyl (vascepa 2g BID) if TG >150
    - Consider TG-lowering therapy if >500
- Obesity (BMI 35 kg/m^2)
  - State BMI and category
  - Recommend GLP1-RA or dual agonist (tirzepatide)
  - Aim to lose 10-15% BW, referral to weight management/dietician, cardiac rehab
  - Refer to sleep medicine to eval OSA
- Smoking
  - Congratulate on quitting smoking!
  - Refer to tobacco treatment specialist if ongoing use, set quit date, offer patches or gum

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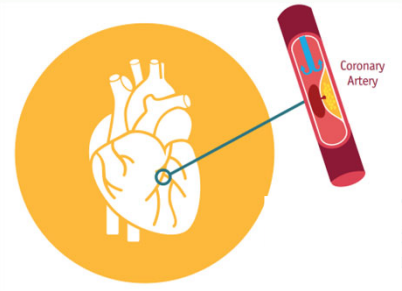
Consider referral to cardiometabolic clinic

- **Type 2 diabetes mellitus with:**
  - Prior atherosclerotic cardiovascular disease
  - Prior cerebrovascular disease
  - Prior peripheral arterial disease
  - Prior heart failure
  - Prior chronic kidney disease



Home - Cardiometabolic Center Alliance (cardiometabolicalliance.org)

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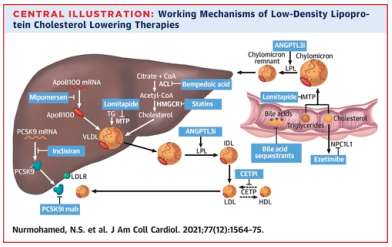
Consider referral to cardiometabolic clinic

- Baseline LDL-C ≥190 mg/dL
- Intolerance to at least 2 (preferably 3) statin therapies
- ASCVD and baseline LDL-C ≥190 mg/dL who did not achieve ↓ LDL-C ≥50% and LDL-C <70 mg/dL



Ref: Familial Hypercholesterolemia | CDC

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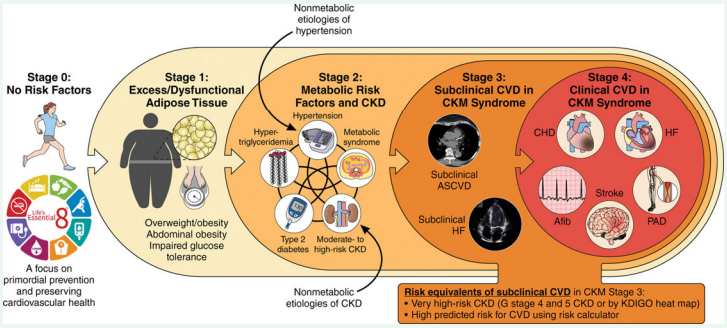
Summary

Stage CKM syndrome



- Heart healthy lifestyle for all
- Get BP, BMI, lipids and A1c to goal
- Screen for CKD, liver disease, sleep apnea
- Use guideline-directed therapy
- Refer to cardiometabolic and lipid specialists

Ref: Ndumele et al. Circulation 2023;148(20):1606-1635.

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We are called to make a healthy difference in people's lives.

Thank you

Whatever you do today, have a great day!

Catherine.Benziger@essentiahealth.org

Essentia Health

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