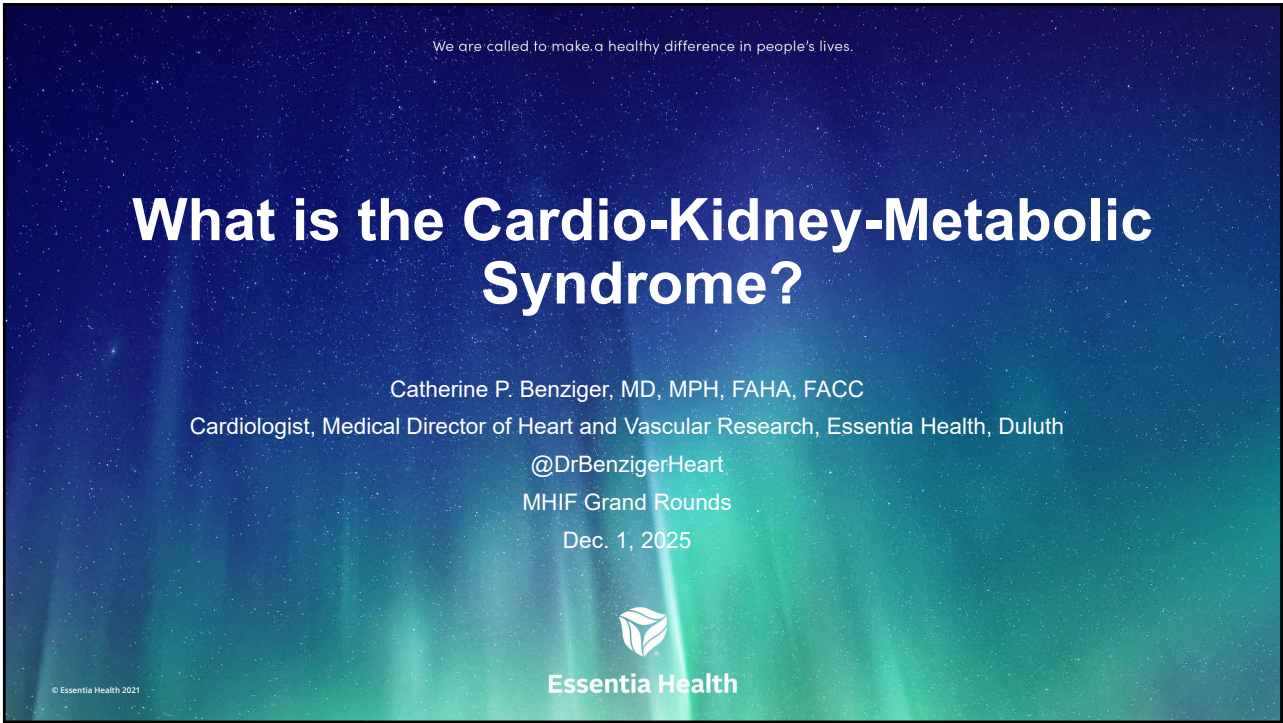




1




2

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



Essentia Health

© Essentia Health 2021

3

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>

AHA PRESIDENTIAL ADVISORIES

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



© Essentia Health 2021

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

4

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

Case: 65-year-old female with recent STEMI



Essentia Health

© Essentia Health 2021

5

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/m²)
- 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?”**

© Essentia Health 2021

6

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

© Essentia Health 2021

7

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?

© Essentia Health 2021

8

4 of 33

Heart Attacks

HEART ATTACKS happen when the heart's blood supply is suddenly cut off.

More than **800,000** Americans suffer a heart attack every year.

That's a heart attack **every 40 seconds!**

Coronary Artery

© Essentia Health 2021

Ref: [Z19023 - Heart Attack Infographic Update \(cardiosmart.org\)](#)

9

ASCVD Continuum

No Known ASCVD **Known ASCVD**

Increasing risk for development of ASCVD Increasing severity of ASCVD

Low-CV Risk (w/o known ASCVD)	High-CV Risk (w/o known ASCVD)	Atherosclerosis w/o Prior Event	Major ASCVD Event
	Diabetes + risk enhancer	Coronary disease, Cerebrovascular disease, or Peripheral artery disease, + risk enhancer <i>No MI or Stroke</i>	Prior MI Prior Stroke Symptomatic PAD + risk enhancer
	VESALIUS-CV		FOURIER and ODYSSEY-OUTCOMES

10

Disease Prevention



© Essentia Health 2021

LDL goal <100

LDL goal <55

11

Cardio-Kidney-Metabolic Syndrome

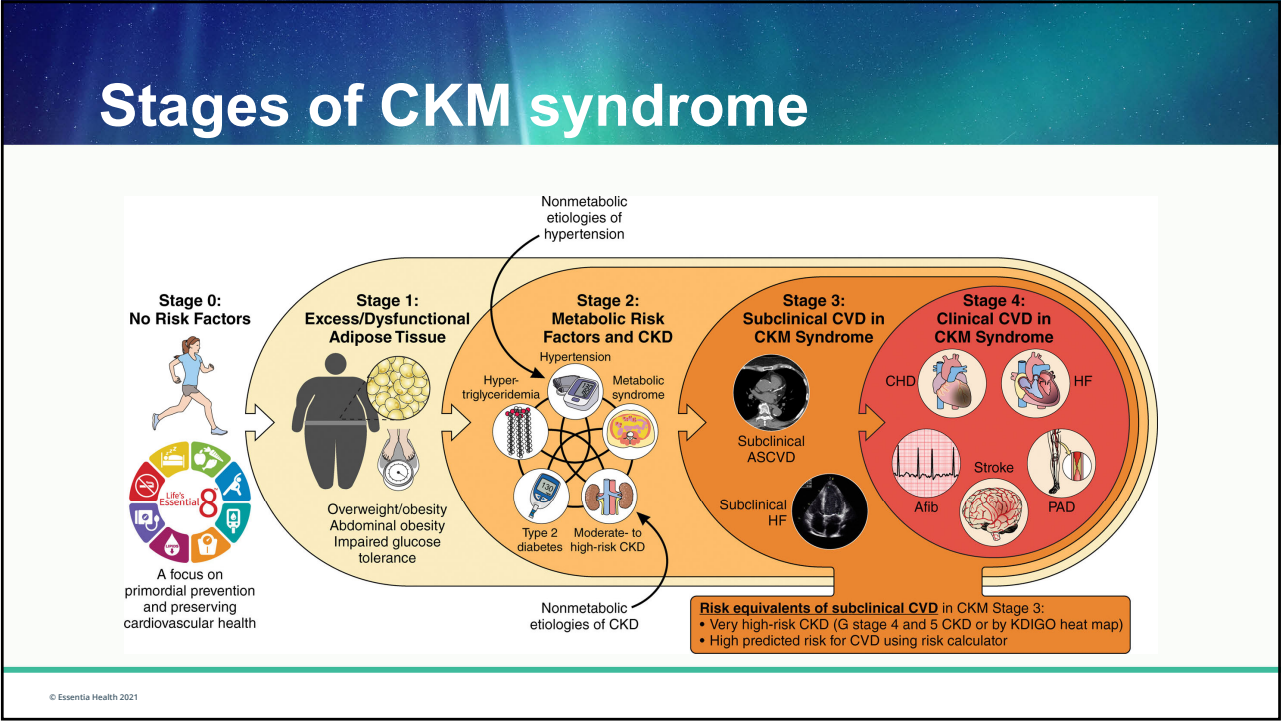
- A health disorder attributed to the connections among **obesity, diabetes, chronic kidney disease (CKD)** and leading to **multiorgan dysfunction** and high rate of adverse cardiovascular disease outcomes

- ✓ Define it
- ✓ Stage and Screen for it
- ✓ Use risk assessment (AHA PREVENT) tools
- ✓ Assess social determinants of health
- ✓ Prevent and Manage

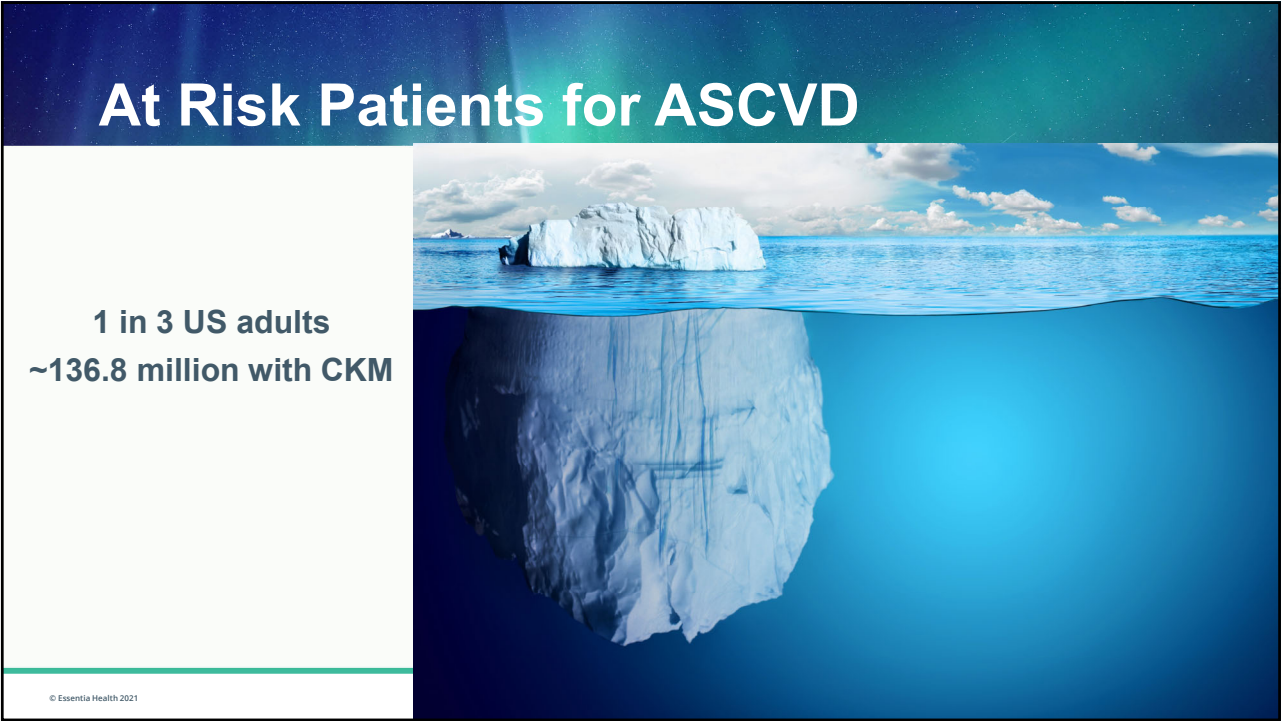
© Essentia Health 2021

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

12



13



14

Goal 1. Lifestyle modifications for all

AHA Life's Essential 8

The diagram illustrates the AHA Life's Essential 8 framework, centered around a large red '8' with 'Life's Essential' written in red. The '8' is divided into two horizontal sections by a dashed blue line. The top section, labeled '4 Health Behaviors', includes: 'Get healthy sleep' (yellow icon of a person sleeping), 'Eat heart healthy diet' (green icon of an apple and fish), 'Be active (30-60 min/day)' (blue icon of a person running), and 'Quit tobacco/vaping' (red icon of a cigarette with a slash). The bottom section, labeled '4 Health Factors', includes: 'Normal blood pressure' (purple icon of a blood pressure cuff), 'Normal cholesterol' (purple icon of a lipid drop with 'LIPIDS' and a downward arrow), 'Normal weight' (orange icon of a scale), and 'Normal blood glucose' (teal icon of a glucose meter). The text 'Life's Essential 8' is written in the center of the diagram.

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

15

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

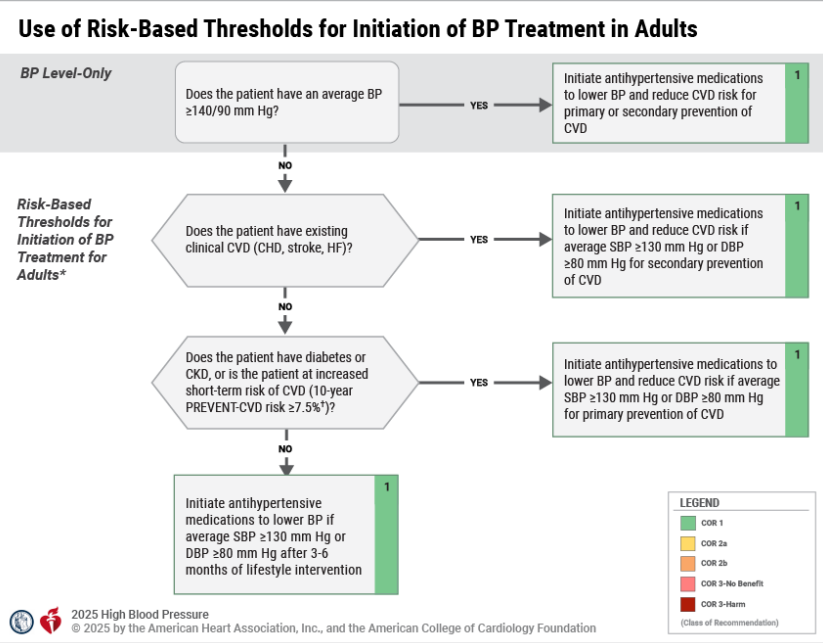
The infographic shows the 2025 AHA/ACC Hypertension guidelines. It starts with 'Lifestyle Before Medication For Patients at Low Risk With Stage 1 High Blood Pressure'. It defines 'Low 10-year CVD risk' as defined by Pooled Cohort Equations < 2.5% and 'Average BP' as 130-139/80-89 mm Hg. A circular diagram shows 'LIFESTYLE' (3-6 Months) and 'MEDICATION' (3-6 Months) leading to 'After 3 to 6 months of lifestyle intervention, initiate medication to lower BP if not at goal'. The infographic is credited to Gaddam et al. JACC 2024;133(15):1558-1564.

16



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

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



BP Level-Only

Does the patient have an average BP $\geq 140/90$ mm Hg?

YES → Initiate antihypertensive medications to lower BP and reduce CVD risk for primary or secondary prevention of CVD **1**

NO →

Risk-Based Thresholds for Initiation of BP Treatment for Adults*

Does the patient have existing clinical CVD (CHD, stroke, HF)?

YES → Initiate antihypertensive medications to lower BP and reduce CVD risk if average SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg for secondary prevention of CVD **1**

NO →

Does the patient have diabetes or CKD, or is the patient at increased short-term risk of CVD (10-year PREVENT-CVD risk $\geq 7.5\%$)?

YES → Initiate antihypertensive medications to lower BP and reduce CVD risk if average SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg for primary prevention of CVD **1**

NO → Initiate antihypertensive medications to lower BP if average SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg after 3-6 months of lifestyle intervention **1**

LEGEND

- COB 1
- COB 2a
- COB 2b
- COB 3-No Benefit
- COB 3-Harm

(Class of Recommendation)

2025 High Blood Pressure
© 2025 by the American Heart Association, Inc., and the American College of Cardiology Foundation

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 $\geq 7.5\%$ using PREVENT.

17

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.

Modified with permission from Whelton et al.
Copyright 2018 American College of Cardiology Foundation and American Heart Association, Inc.

18



American Heart Association

Screening for Features Suggesting Secondary Hypertension

Modified with permission from Whelton et al. Copyright 2018 American College of Cardiology Foundation and American Heart Association, Inc.

Screening for Features Suggesting Secondary Hypertension

Does the patient have any of the following conditions associated with secondary HTN?

- Drug-resistant/induced HTN
- Abrupt onset of HTN
- Onset of HTN at <30 y
- Exacerbation of previously controlled HTN
- Disproportionate TOD for degree of HTN
- Accelerated/malignant HTN
- Onset of diastolic HTN in older adults (age ≥65 y)

- Unprovoked or excessive hypokalemia
- Insomnia or daytime sleepiness
- Concomitant adrenal nodule
- History of early-onset stroke
- Family history of primary aldosteronism

NO → Screening not indicated

YES → Screen for primary aldosteronism and other secondary forms of HTN (1)

Positive screening test? → NO → Enhance medication therapy


YES → Refer to clinician with specific secondary HTN expertise (2b)

LEGEND

- 1 Class I
- 2a Class IIa
- 2b Class IIb
- 3 Class III
- 4 Class IV

(Class of Recommendation)

© 2025 High Blood Pressure
© 2025 by the American Heart Association, Inc., and the American College of Cardiology Foundation



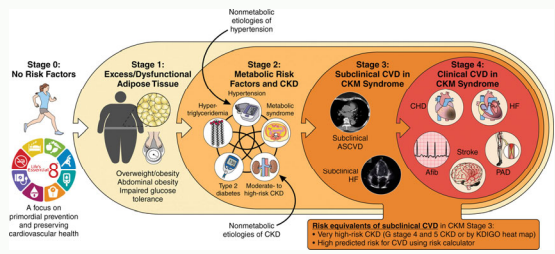
AMERICAN COLLEGE OF CARDIOLOGY

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).

19

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



The diagram illustrates the progression of Kidney Kidney Metabolic (CKM) stages from Stage 0 to Stage 4. Stage 0 is characterized by no risk factors. Stage 1 involves excess/dysfunctional adipose tissue, with risk factors like overweight/obesity, abdominal obesity, and impaired glucose tolerance. Stage 2 includes metabolic risk factors and CKD, with risk factors like hypertriglyceridemia, metabolic syndrome, and type 2 diabetes. Stage 3 is subclinical CVD in CKM syndrome, with risk factors like subclinical ASCVD and subclinical HF. Stage 4 is clinical CVD in CKM syndrome, with risk factors like CHD, stroke, PAD, and HF. The diagram also shows nonmetabolic etiologies of hypertension and CKD, and a focus on primordial prevention and preserving cardiovascular health.

© Essentia Health 2021

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

20

10 of 33

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)^a
GFR (G)^b
Albuminuria (A)^c

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

21

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

Calcium shown in a heart scan

Blood vessel with calcium and plaque

Calcium

Plaque

WHAT THE TEST RESULTS MEAN

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

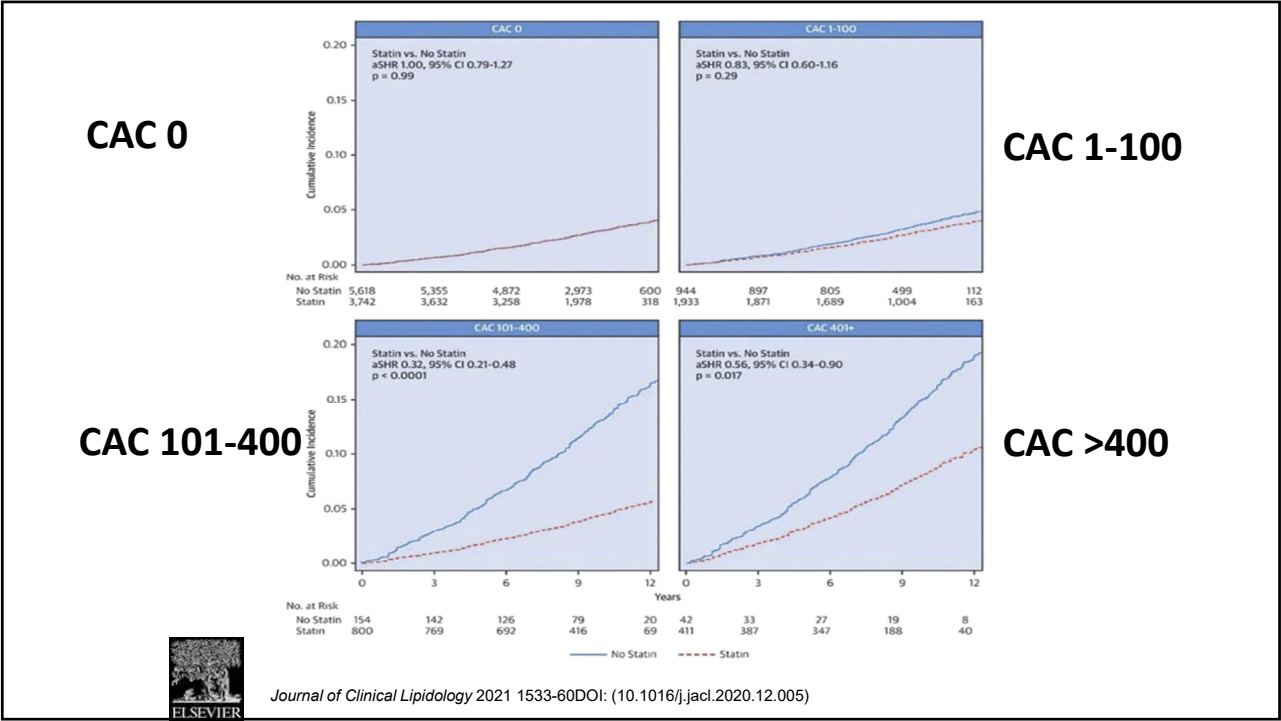
Amount of calcium:	None	Mild	Moderate	Severe
	0	1-99	100-299	300 or more
Chance of heart disease, heart attack or stroke is:	Low			High

TALK WITH YOUR TEAM

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

22

11 of 33



23

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])
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

© Essentia Health 2021

PREVENT Online Calculator - Professional Heart Daily | American Heart Association

24

12 of 33

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

Fibrosis-4 (FIB-4) Index for Liver Fibrosis

Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy.

When to Use

Pearls/Pitfalls

Why Use

Age

Use with caution in patients <35 or >65 years old, as the score has been shown to be less reliable in these patients

AST
Aspartate aminotransferase

ALT
Alanine aminotransferase

Platelet count

Result:

Please fill out required fields.

» Next Steps

Dr. Richard Sterling

Age specific use of FIB-4 Score

Suspected NAFLD

Age, years

≤35

36-64

≥65

Use existing thresholds

Use new thresholds

<1.3

1.3-2.67

>2.67

<2.0

2.0-2.67

>2.67

Alternative fibrosis assessment

Advanced fibrosis* excluded

Further investigation

Advanced fibrosis* likely

Ref: McPherson et al. AJG 2016.

25

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)‡

				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 (mL/min per 1.73 m³) Description and range	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.

26

13 of 33

Assess for risk enhancing factors for CKM syndrome

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

© Essentia Health 2021

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)

27

Assess for risk enhancing factors for CKM syndrome

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

© Essentia Health 2021

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

28

CKM pediatric and adolescence screening (<21 years)

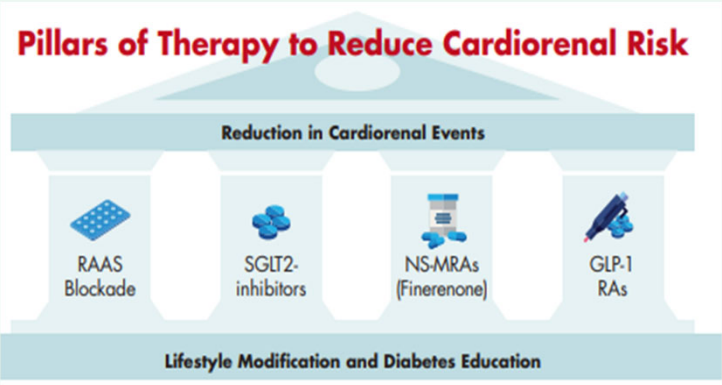
Ref: Ndumele et al.
Circulation
2023;148(20):1606-
1635.

- **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)

29

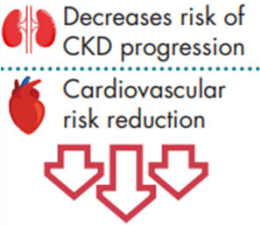
Goal 3. Management of diabetes-related kidney disease

Pillars of Therapy to Reduce Cardiorenal Risk



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

Why Manage?

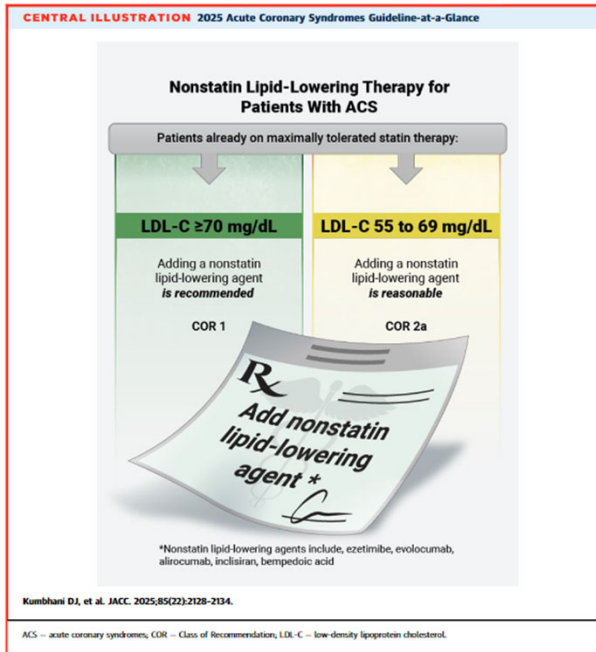


30

Ref: [Infographics](#) | [American Diabetes Association](#)

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)

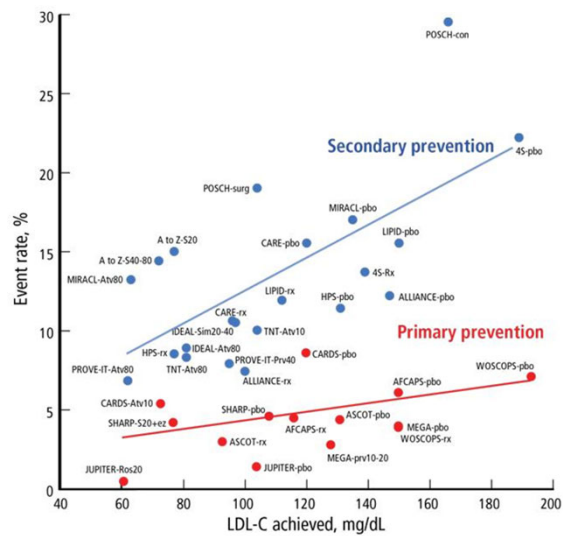


**LDL goal
as low as
possible
(<55 if
known
ASCVD/
ACS)**

31

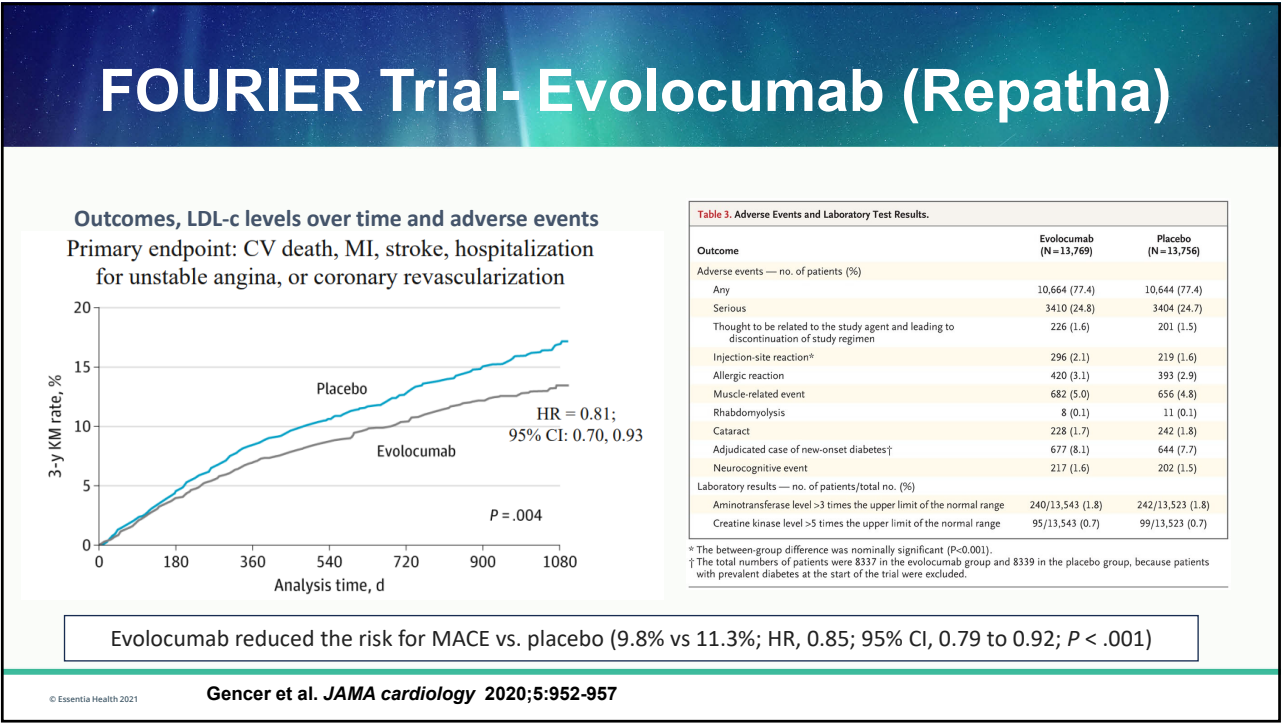
**CV benefit
with lower
LDL**

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.

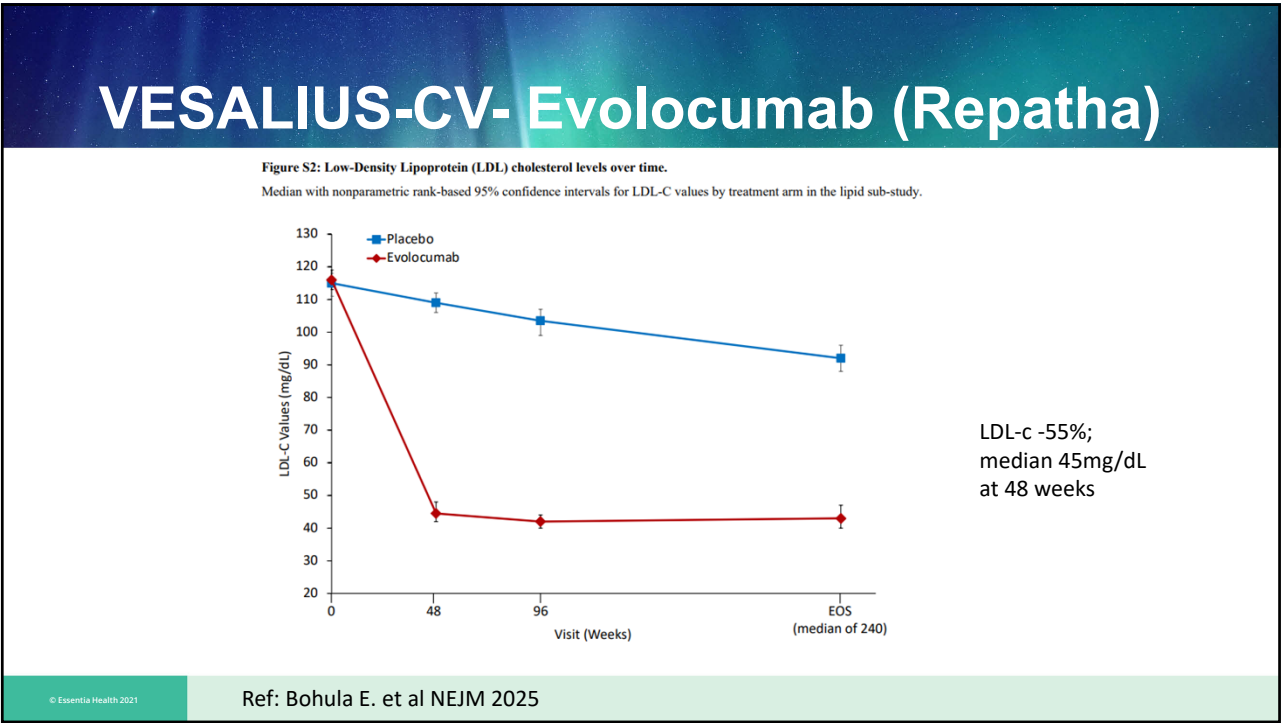


Marc S. Sabatine CCJM 2016;83:181-186

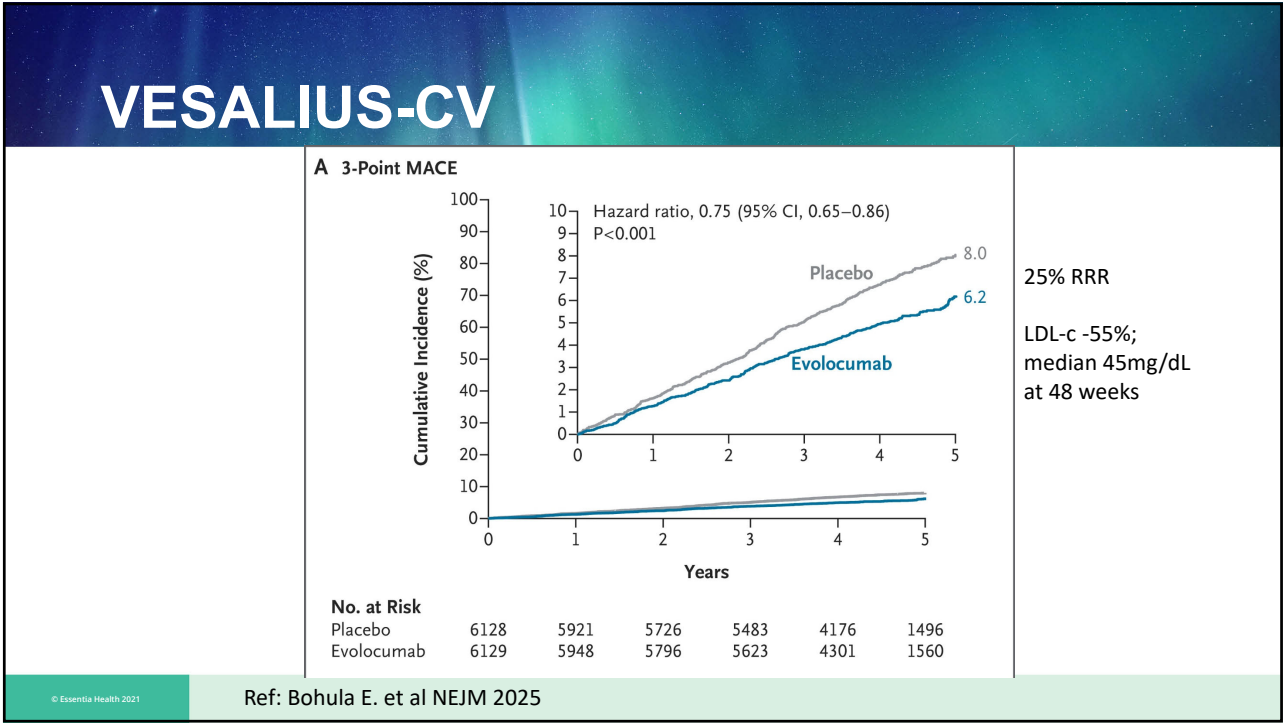
32



33



34



35

Goal 4. Optimize lipid lowering therapy

	Bempedoic acid (nexletol)	Ezetimibe (zetia)	CETPI Obicetrapib	PCSK9i Enlicitide	PCSK9i Iaroprostat	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

© Essentia Health 2021

36

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%
Statin	Atorvastatin (40 mg‡) 80 mg Rosuvastatin 20 mg (40 mg§)	Atorvastatin 10 mg (20 mg) Rosuvastatin (5 mg) 10 mg Simvastatin 20–40 mg§ Pravastatin 40 mg (80 mg) Lovastatin 40 mg (80 mg) Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1–4 mg	Simvastatin 10 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

37

Approach to lipid lowering therapy

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

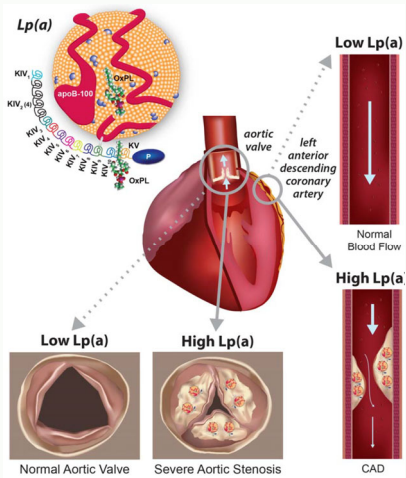
Nurmohamed, N.S. et al. J Am Coll Cardiol. 2021;77(12):1564–75.

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)
- Evincumab (Evkeeza) infusion monthly for HeFH (LDL-independent)
- Consider trials

38

Check lipoprotein(a) once



An estimated
20% to 30%
of people
worldwide have
high levels
of plasma
lipoprotein(a)

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

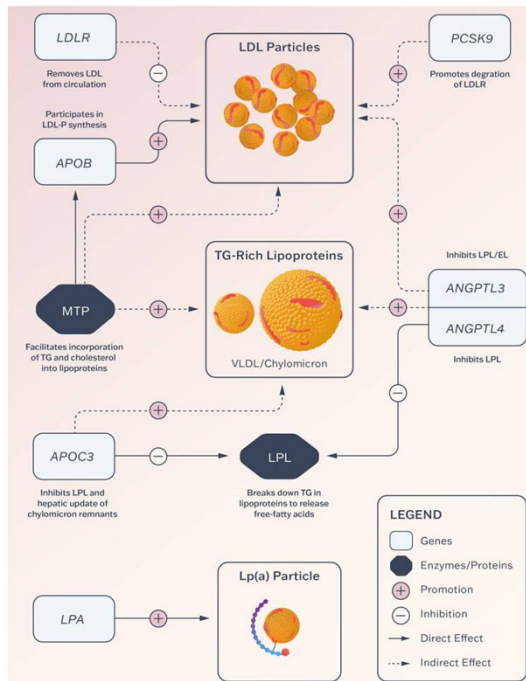
Ref: Journal Of Lipid Research Cover March 2016

Ref: [Lp\(a\): A Toolkit for Health Care Professionals \(heart.org\)](https://www.heart.org)

39

Targetable genes in lipoprotein disorders

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



40

Targetable genes in lipoprotein disorders

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

© Essentia Health 2021

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	Lipisen	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.

41

Targetable genes in lipoprotein disorders

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

© Essentia Health 2021

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, angiotensin-like 3; ANGPTL4, angiotensin-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.

42

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**

Group	Low Risk - Lp(a) ≤50 mg/dL	Intermediate Risk - Lp(a) ≤50 mg/dL	High Risk - Lp(a) ≤50 mg/dL	Low Risk - Lp(a) >50 mg/dL	Intermediate Risk - Lp(a) >50 mg/dL	High Risk - Lp(a) >50 mg/dL	
0	2353	1724	1237	333	2300	2221	2148
1000	541	451	1128	333	525	429	495
2000	504	395	971	271	504	395	416
3000	495	366	843	224	495	366	416

© Essentia Health 2021

Bhatia et al. Atherosclerosis 2023

43

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

Lp(a) Group	Evolocumab (%)	Placebo (%)	ARR (%)	NNT	HR	95% CI
≤120nmol/L	6.74	8.15	1.41	71	0.89	0.79-1.01
>120 nmol/L	7.50	9.91	2.41	41	0.75	0.64-0.88

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

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

44

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%

B Mechanisms of action of investigative therapies to lower Lp(a) levels

Injectable RNA-based therapies: Antisense oligonucleotides and small interfering RNA (siRNA) prevent translation of LPA messenger RNA (mRNA)

Oral small molecule inhibitor therapy: Muvalaplin binds to apo(a) to prevent formation of Lp(a)

© Essentia Health 2021

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

45

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

Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease

O'Donoghue ML et al. DOI: 10.1056/NEJMoa2211023

Trial Week	Placebo	10 mg, Every 12 wk	75 mg, Every 12 wk	225 mg, Every 12 wk	225 mg, Every 24 wk
Baseline	0	0	0	0	0
Day 2	0	-10	-10	-10	-10
Week 4	0	-60	-70	-90	-90
Week 8	0	-65	-75	-95	-95
Week 12	0	-60	-70	-90	-90
Week 16	0	-65	-75	-95	-95
Week 20	0	-60	-70	-90	-90
Week 24	0	-65	-75	-95	-95
Week 28	0	-60	-70	-90	-90
Week 32	0	-65	-75	-95	-95
Week 36	0	-60	-70	-90	-90
Week 40	0	-65	-75	-95	-95
Week 44	0	-60	-70	-90	-90
Week 48	0	-65	-75	-95	-95

© Essentia Health 2021

46

Future Therapies

CRISPR Cas9 mRNA targeting LPA

Intravenous delivery to the liver

CRISPR/Cas9-based editing of *LPA*

Reduced plasma Lp(a) levels

CTX320 consists of Cas9 mRNA and guide RNA (sgRNA) targeting *LPA* encapsulated in lipid nanoparticles (LNPs)

Transient expression of Cas9 and sgRNA in hepatocytes to reduce apo(a) expression permanently

Reduced risk: ASCVD, Aortic Valve Calcification, MACE

CRISPR CTX320

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

© Essentia Health 2021

Ref: [PowerPoint Presentation](#)

47

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

Olezarsen (Antisense Oligonucleotide)

GalNAc₃ binds to APOC3 mRNA

↓ RNase H-mediated degradation

↓ ApoC-III protein levels

↑ LPL activity & triglyceride clearance

↓ Plasma triglycerides and pancreatitis risk

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

© Essentia Health 2021


48

24 of 33

Goal 5. Weight loss strategies

- Goal 10-15% body weight reduction

Behavioral Changes: Diet and Exercise




5%-10% weight loss

Exercise and caloric restriction with additive weight loss effect

Weight loss difficult to sustain, with significant regain over time

Limited data in HF, but successful weight loss associated with improved functional status and reduced symptom burden in HFpEF

Anti-Obesity Medications



10%-20% weight loss

Weight regain with cessation of anti-obesity medications

Semaglutide:


- Significant improvement in functional status and symptom burden in HFpEF
- Reduced rates of MACE and HF hospitalization in HF*

Tirzepatide - additional benefit:

- Reduced risk for CV death or HF events in HFpEF (low event rates prevent conclusive assessment)

*Secondary analysis

Metabolic and Bariatric Surgery



10%-30% weight loss

Weight loss often sustained over years

No randomized data in HF

Observational data suggests that MBS:

- Reduces risk of incident HF
- Decreases rates of HF hospitalization and inpatient mortality

Individuals with HF, especially HFREF, may have higher rates of complications with surgery

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.

49

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

Pre-initiation

- Confirm HF stability with volume and arrhythmia assessment
- Provide education
- Store in refrigerator to maintain stability
- Inject under skin of abdomen, thigh, upper arm
- Inject one day of the week (same day each week), any time of day

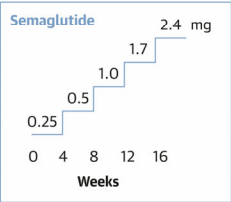
During dose escalation

- Titration every 4 wk
- Monitor for GI adverse effects which may affect volume status and kidney function
- Stop and report abdominal pain (possible pancreatitis or gallbladder disease)
- Stop and report swelling of face, lips, tongue, or throat, rash, or itching (possible hypersensitivity reaction)

Long-term follow-up

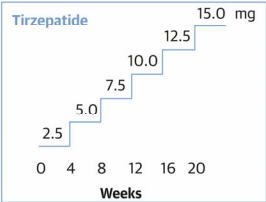
- Ongoing volume assessment every 3-6 mo
- Monitor control of diabetes
- If <5% weight loss, consider alternative treatment strategy
- Stop if pregnant
- Report lump in the neck, hoarseness, or dysphagia (possible thyroid tumors)
- Report symptoms of hypoglycemia (if diabetes) or change in vision (if diabetes-related retinopathy)

Semaglutide



Weeks	Dose (mg)
0	0.25
4	0.5
8	1.0
12	1.7
16	2.4

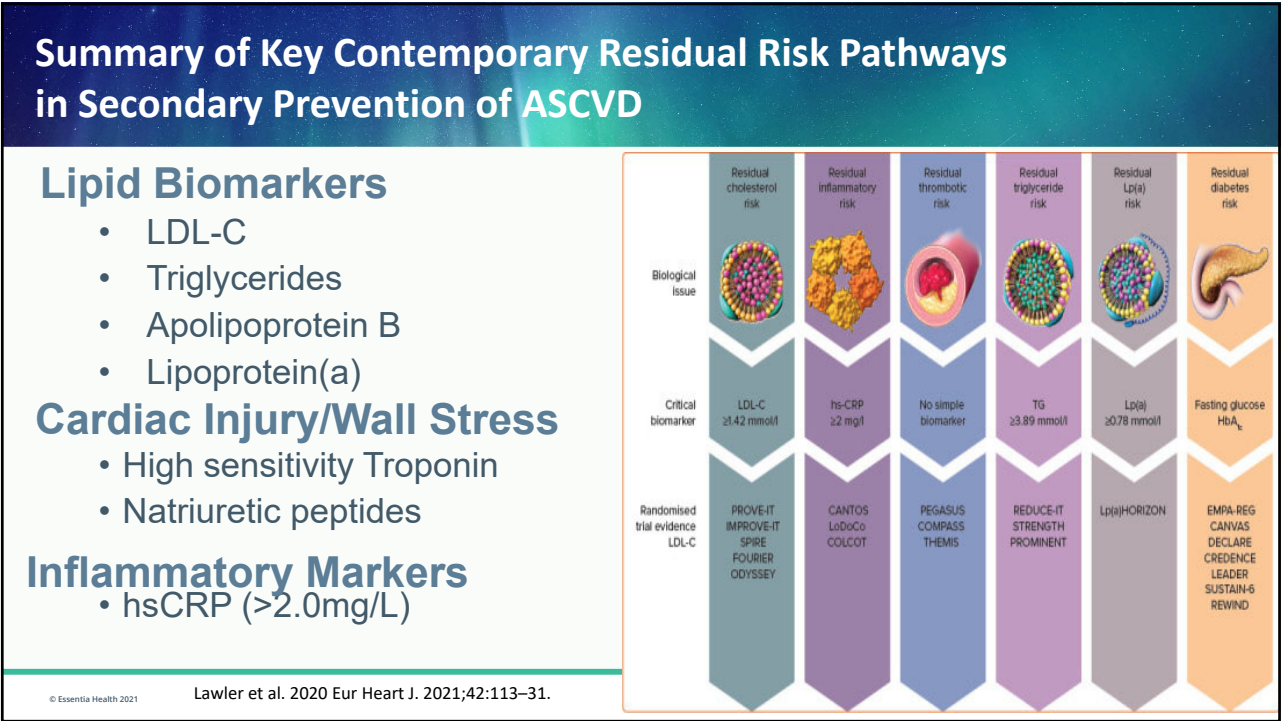
Tirzepatide



Weeks	Dose (mg)
0	2.5
4	5.0
8	7.5
12	10.0
16	12.5
20	15.0

50

25 of 33



51

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

How do we address all of these CKM issues?



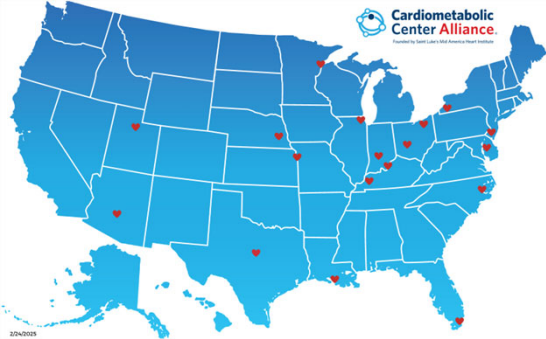
Essentia Health

© Essentia Health 2021

52

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.



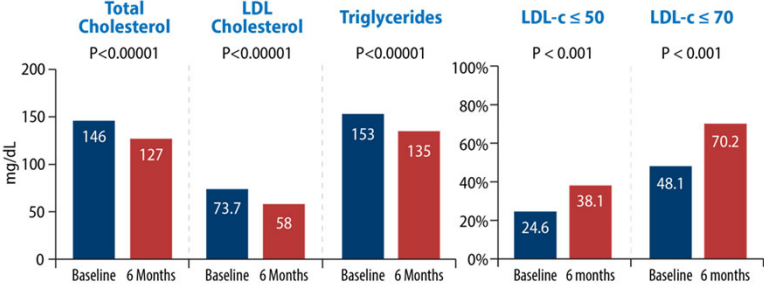
© Essentia Health 2021

[Home - Cardiometabolic Center Alliance \(cardiometabolicalliance.org\)](https://cardiometabolicalliance.org)

53

Cardiometabolic clinic- lipid for DM2

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

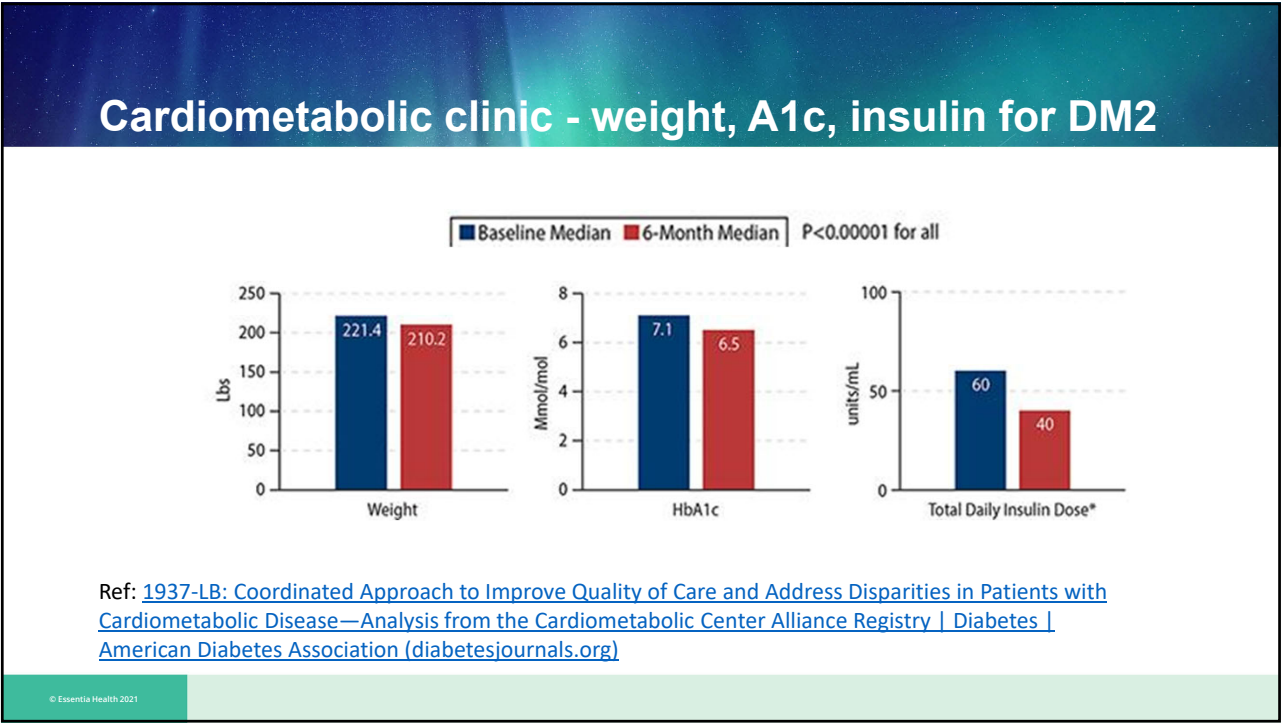


Measure	Baseline	6 Months	P-value
Total Cholesterol (mg/dL)	146	127	P < 0.00001
LDL Cholesterol (mg/dL)	73.7	58	P < 0.00001
Triglycerides (mg/dL)	153	135	P < 0.00001
LDL-c ≤ 50 (%)	24.6	38.1	P < 0.001
LDL-c ≤ 70 (%)	48.1	70.2	P < 0.001

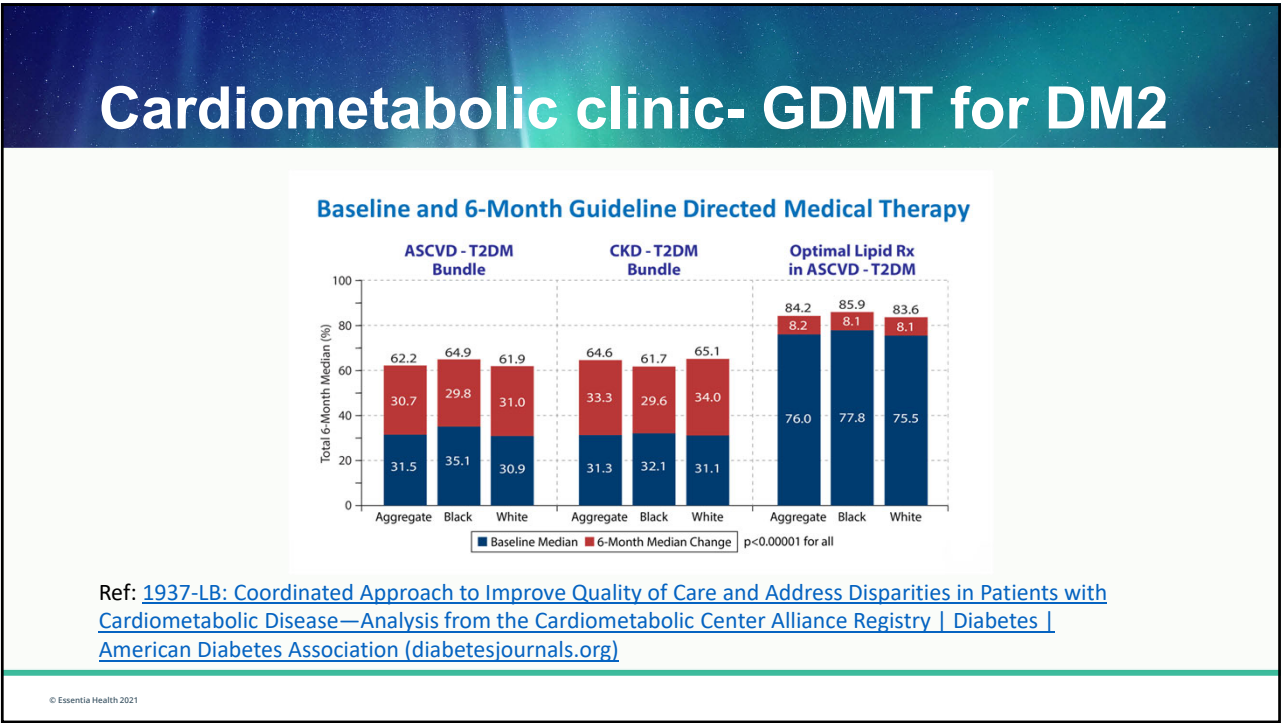
Ref: [1937-LB: Coordinated Approach to Improve Quality of Care and Address Disparities in Patients with Cardiometabolic Disease—Analysis from the Cardiometabolic Center Alliance Registry | Diabetes | American Diabetes Association \(diabetesjournals.org\)](#)

© Essentia Health 2021

54



55



56

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		Notes
Glycemic Management	Labs & Testing	Result	Date	Standard Goal ¹	
	HbA1c			< 7%	
	Time in Range			> 70% TIR	
Cardiovascular Risk	Time Below Range			< 4% time <70 mg/dL < 1% time <54 mg/dL	
	LDL-C			□ < 55 mg/dL □ < 70 mg/dL	
	BP			< 130/80 mmHg	
Kidney Risk	BNP/NTproBNP			Screen for HR/prevent worsening	
	LP(a)			Screen for high risk	
Liver Risk	eGFR			Screen for/prevent decline in eGFR	
	UACR			Screen/reduce ≥30% (if uACR ≥300)	
Weight Management	Fib-4			Screen for liver disease	
	Weight			If indicated, reduction of □ 5% □ 10%	
	BMI			< 25 kg/m ²	
	Waist Circumference			women < 35 in men < 40 in	

© Essentia Health 2021

57

Optimized GDMT for cardio-metabolic disease

© Essentia Health 2021

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 ARB⁵ 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 surgery¹²	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

58


Optimized GDMT for cardio-metabolic disease

© Essentia Health 2021

Therapeutic Agents to Reduce Cardiovascular Risk ¹						
ASCVD or high risk ²		Heart Failure			CKD	NASH or NAFLD ³
<u>Cardiorenal risk reduction</u>	Ensure benefits outweigh increased risk of bleeding	<u>Cardiorenal risk reduction</u> , minimize signs and symptoms of congestion/volume overload, & improve LVEF			<u>Cardiorenal risk reduction</u> , minimize/prevent decline in eGFR, & if urinary albumin ≥300, reduce ≥30%	<u>Cardiorenal risk reduction</u>
<u>GLP-1ra</u> <u>SGLT2i</u> Consider: TZD ⁶⁻⁷	<u>Anti-thrombotic Agent(s)</u>	HFrEF (c) <u>SGLT2i</u> <u>ARNi</u> ⁸ <u>SMRA</u> ¹⁰ BB Diuretic ⁹	HFmrEF <u>SGLT2i</u> Diuretic ⁹ — Consider: <u>ARNi</u> ⁸ <u>MRA</u> ¹⁰ BB	HFpEF <u>SGLT2i</u> Diuretic ⁹ — Consider: <u>ARB</u> / <u>ARNi</u> ⁸ <u>MRA</u> ¹⁰	<u>SGLT2i</u> ¹¹ <u>ACE-i or ARB</u> <u>NSMRA</u>	<u>GLP-1ra</u> TZD ⁷
		ICD CRT				
<u>ESC/EASD '19</u> <u>ADA '23</u>		<u>AHA/ACC/HFSA '22</u> <u>ESC/EASD '19</u> <u>ADA '23</u>			<u>KDIGO '22</u> <u>ADA '23</u>	<u>AGA '21</u> ¹³ <u>AACE '22</u> <u>ADA '23</u>
Therapy Optimized?						
No to one or both						


59

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

© Essentia Health 2021

[CKM Health Groundbreakers | American Heart Association](#)

60

30 of 33

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

© Essentia Health 2021

61

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

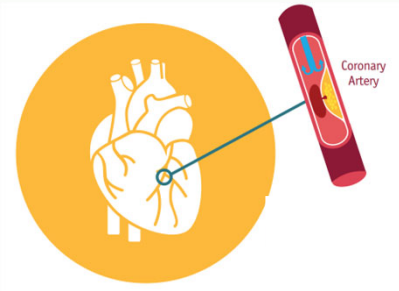
- Hypercholesterolemia, high triglycerides
 - Labs: repeat fasting lipid panel, lipoprotein(a), apolipoprotein B (on treatment goal same as LDL)
 - LDL goal <55 given ACS, DM.
 - High-intensity statin, ezetimibe, and PCSK9i (evolocumab/ alirocumab/ inclisiran)
 - After LDL at goal, get TG to goal <150
 - Start icosapent ethyl (vascepa 2g BID) if TG >150
 - Consider TG-lowering therapy if >500
- Obesity (BMI 35 kg/m²)
 - 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

© Essentia Health 2021

62

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



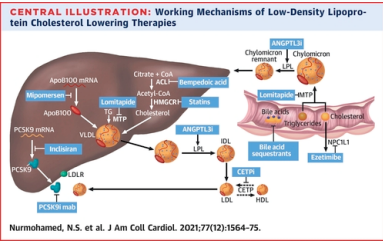
© Essentia Health 2021

[Home - Cardiometabolic Center Alliance \(cardiometabolicalliance.org\)](https://cardiometabolicalliance.org)

63

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 \downarrow LDL-C $\geq 50\%$ and LDL-C < 70 mg/dL



© Essentia Health 2021

Ref: [Familial Hypercholesterolemia | CDC](#)

64

Summary

Stage CKM syndrome

The diagram illustrates the progression of Stage CKM syndrome through five stages:

- Stage 0: No Risk Factors** - A focus on primordial prevention and preserving cardiovascular health.
- Stage 1: Excess/Dysfunctional Adipose Tissue** - Includes overweight/obesity, abdominal obesity, and impaired glucose tolerance.
- Stage 2: Metabolic Risk Factors and CKD** - Includes hypertension, hypertriglyceridemia, metabolic syndrome, type 2 diabetes, and moderate-to-high-risk CKD. It also notes nonmetabolic etiologies of CKD.
- Stage 3: Subclinical CVD in CKM Syndrome** - Includes subclinical ASCVD and subclinical HF.
- Stage 4: Clinical CVD in CKM Syndrome** - Includes CHD, HF, stroke, PAD, and Atrial Fibrillation (Afib).

Risk equivalents of subclinical CVD in CKM Stage 3:

- Very high-risk CKD (G stage 4 and 5 CKD or by KDIGO heat map)
- High predicted risk for CVD using risk calculator

© Essentia Health 2021

- 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.

65

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 2021

66