Baptist Health

Current Landscape of Cardiometabolic Clinical Trials: Lp(a), MASH, Diabetes, Obesity

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Disclosures

- Consultant: Esperion Therapeutics, Novartis, Amgen, Medtronic
- Speaker: Esperion Therapeutics

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Objectives

1. Define the significance of clinical trials in advancing treatment for cardio-metabolic diseases including metabolic dysfunction-associated liver disease, diabetes, obesity and lipoprotein(a)
2. Describe the efficacy and safety profiles of emerging therapies based on current clinical trial data
3. Discuss key components of designing robust cardio-metabolic clinical trials, including patient engagement, patient diversity, endpoints, and the role of the Cardiovascular Nurse

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TERMINOLOGY TIMELINE

- NASH (nonalcoholic steatohepatitis)/NAFLD (nonalcoholic fatty liver disease): excluded other causes of liver disease, including alcohol-related liver disease; underdiagnosis; clinical trial exclusions
- MAFLD (Metabolic dysfunction–associated fatty liver disease)
- MASLD (metabolic dysfunction–associated steatotic liver disease)/MASH

  -presence of hepatic steatosis (5% of hepatocytes) with cardiometabolic risk factors **and** assess for other causes (medications, excessive alcohol, viral hepatitis, etc.)

Rinella ME, et al. Journal of Hepatology, December 2023. vol. 79; 1542–1556
Abushamat LA, et al. Clinical Gastroenterology and Hepatology. 2024;22:1565-1574

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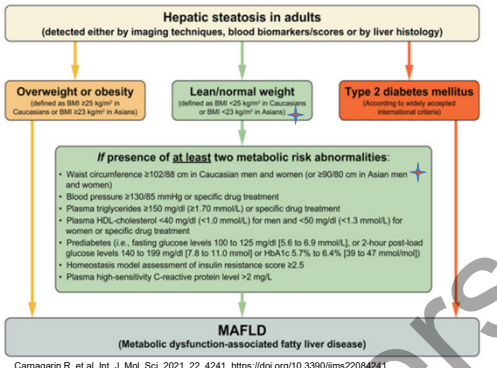
MAFLD/MASLD: Diagnosis



Carnagarin R, et al. Int. J. Mol. Sci. 2021, 22, 4241. https://doi.org/10.3390/ijms22084241

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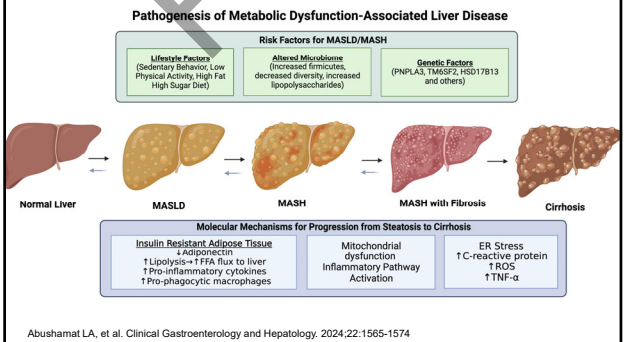
MASLD Spectrum/Progression



Abushamat LA, et al. Clinical Gastroenterology and Hepatology. 2024;22:1565-1574

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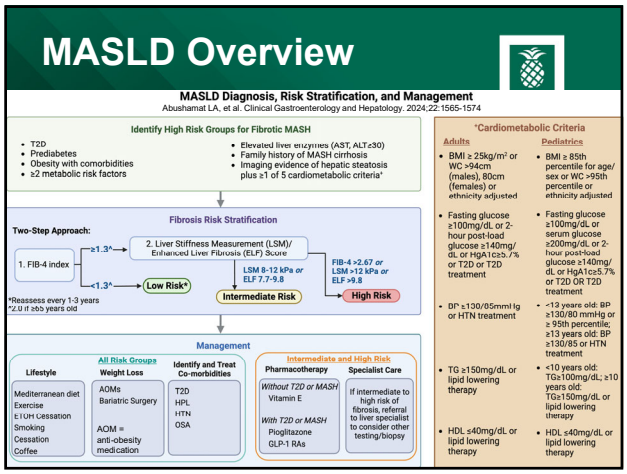
MASLD Overview



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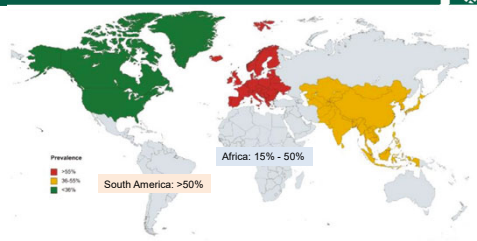
Global Prevalence

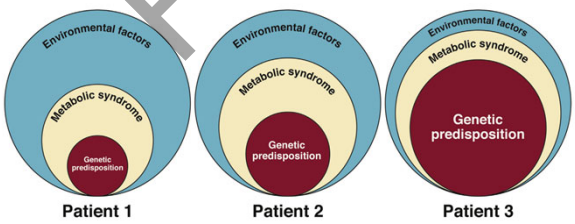


- **Overall: 38.8%** (32.9-44.9); **North America: 36.9%** (30.1- 41.6)
- Europe: 55.3% (36.2-73); Asia: 37.31% (29.8-43.2)
- **Lean: 5.37%** (4.7-6.6); **Nonobese: 29.8%** (26.1-33.7)
- **Expected >60% prevalence in the US by 2030**

Chan KE, et al. The Journal of Clinical Endocrinology & Metabolism, 2022, 107, 2691–2700;
Teng MLB, et al. Clinical and Molecular Hepatology 2023;29(Suppl):S32-S42

8

MAFLD: Heterogeneous Disease



- Prevalence of fatty liver: Hispanic ethnicity>White>Black
- Fibrosis risk did not differ according to race/ethnicity
- Rising prevalence among Asian populations
- Globally – higher among males

Eslam M, Sanyal AJ, George J. Gastroenterology 2020;158:1999–2014

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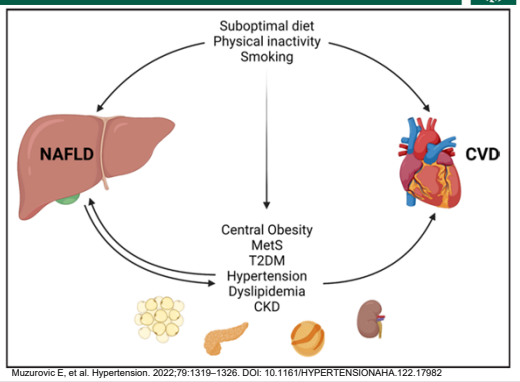
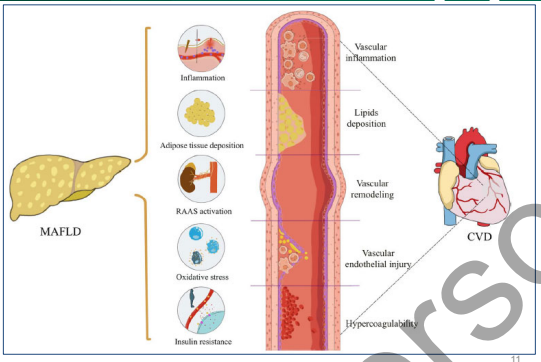
Cardiometabolic Risk Factors for NAFLD and CVD



Muzurovic E, et al. Hypertension. 2022;79:1319–1326. DOI: 10.1161/HYPERTENSIONAHA.122.17982

10

Mechanisms of MAFLD and Incident CVD



Zhou X-D, Cai J , Targher G *et al and* CHESS-MAFLD consortium. *Cardiovascular Diabetology (2022) 21:270*

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Trial Design is Critical: CVD Mortality – NAFLD vs MAFLD

Study	Patients (n)	Outcomes
Muthiah et al.[46] (2022) NHANES III – Type 2 diabetes patients	Total/MAFLD/NAFLD=4,982/4,982/excluded Both MAFLD and NAFLD=2,950 MAFLD only=2,032 NAFLD only=Excluded	1. MAFLD-only had increased cardiovascular mortality compared to MAFLD+NAFLD (HR 1.26, 95% CI 1.05–1.52).
Niriella et al.[31] 2021 Community-based cohort study with 7-year follow-up	Total/MAFLD/NAFLD=2,985/990/940 Both MAFLD and NAFLD=902 MAFLD only=88 NAFLD only=38	1. MAFLD had increased overall cardiovascular non-fatal and fatal events when compared to NAFLD (RR 4.2, 95% CI 1.5–11.5 vs. *RR* 3.7, 95% CI 1.3–10.3, *P*<0.006). 2. MAFLD-only had significantly higher rates of cardiovascular non-fatal and fatal events when compared to NAFLD only (RR 7.2, 95% CI 2.4–21.5 vs. RR 1.9, 95% CI 0.25–14.8).
Nguyen et al.[47] (2021) NHANES III	Total/MAFLD/NAFLD=2,997/2,742/2,494 Both MAFLD and NAFLD=2,240 MAFLD only=503 NAFLD only=254	1. On unadjusted modelling, MAFLD-only had higher increased cardiovascular disease mortality vs. NAFLD+MAFLD (HR 9.4, 95% CI 2.6–34.6, *P*=0.001 vs. HR 7.0, 95% CI 2.1–23.1, *P*=0.002). On adjusted modelling, neither MAFLD-only or NAFLD+MAFLD had statistically significant associations with cardiovascular mortality, but MAFLD-only had a trend towards significance (HR 6.7, 95% CI 0.9–47.1, *P*=0.06).
Lee et al.[32] (2021) Nationwide Korean health screening database	Total/MAFLD/NAFLD=3,628,540/2,680,217/3,573,644 Both MAFLD and NAFLD=2,625,321 MAFLD only=948,323 NAFLD only=54,896	1. NAFLD+MAFLD had higher increased cardiovascular events when compared to MAFLD-only and NAFLD-only (HR 1.56, 95%CI 1.54–1.58 vs. HR 1.43, 95% CI 1.41–1.45 vs. HR 1.09, 95% CI 1.03–1.15).
Guerreiro et al.[33] (2021) Database of Brazilian patients undergoing liver biopsy at university hospital	Total/MAFLD/NAFLD=171/154/109 Both MAFLD and NAFLD MAFLD only NAFLD only	1. Non-significant higher prevalence of high-risk cardiovascular scores was observed in MAFLD group compared to NAFLD group (36.4% vs. 25.7%, *P*=0.209).

MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Surveys; HR, hazard ratio; 95% CI, 95% confidence interval; RR, risk ratio.

There is a stronger association with MAFLD, compared to NAFLD on CVD morbidity and mortality. MAFLD diagnosis helps to identify patients for additional cardiovascular risk assessment and intervention

Gofton C, et al. Clin Mol Hepatol 2023;29(Suppl):S17-S31

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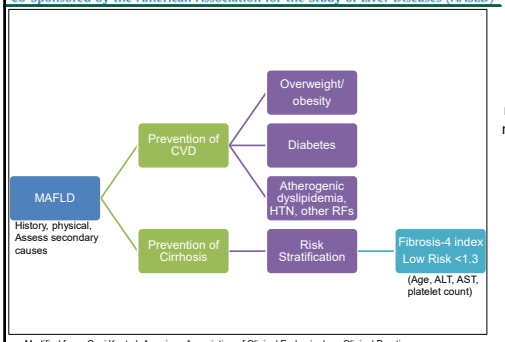
American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings

Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)



Risk of CVD morbidity and mortality, CKD, cancer with MAFLD

Modified from: Cusi K, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD)Endocrine Practice 28 (2022) 528e562

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TREATMENT: MASLD

"The mainstay of treatment…is lifestyle modification, with a focus on sustainably reducing adiposity, improving insulin sensitivity, and reducing cardiometabolic risk factors associated with the metabolic syndrome."

Duell PB, et al. Arterioscler Thromb Vasc Biol. 2022;42:e168–e185. DOI: 10.1161/ATV.0000000000000153

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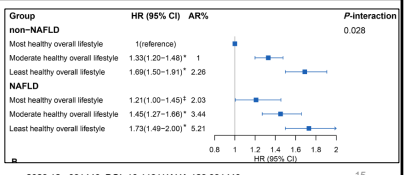
Lifestyle, NAFLD, and Cardiovascular Outcomes

- UK Biobank, n=134,616 with NAFLD; 40-69 yrs old; 61.9% women
- Lifestyle scores (diet, physical activity, sleep habits)
- Outcomes: MACE (first MI, cerebral infarction, or CVD death) and all-cause death
- Healthier overall lifestyle associated with lower risk of MACE (with and without NAFLD)

Characteristics	Total (N=134616)	Non-NAFLD (N=104742)	NAFLD (N=29874)	P value
Age, y	55.78 (8.28)	55.62 (8.36)	56.34 (7.95)	<0.001
Sex, female (%)	83366 (61.93)	70059 (66.89)	13308 (44.55)	<0.001
Race (%)				
White	124516 (92.52)	96673 (92.30)	27843 (93.24)	<0.001
Asian	3467 (2.58)	2812 (2.68)	667 (2.23)	
Black	2535 (1.88)	1952 (1.87)	583 (1.95)	
Mixed	1366 (1.01)	1093 (1.03)	272 (0.91)	
Chinese and other ethnic group	2732 (2.03)	2222 (2.12)	499 (1.67)	
TDI	-1.36 (3.02)	-1.47 (2.96)	-0.97 (3.18)	<0.001
BMI (kg/m²)	27.53 (4.92)	25.77 (3.29)	33.71 (4.69)	<0.001



Wu W, Ma W, Yuan S, et al. J Am Heart Assoc. 2023;12:e031440. DOI: 10.1161/JAHA.123.031440

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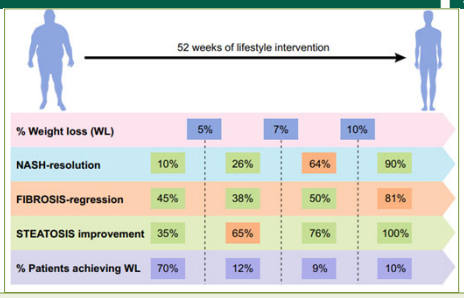
Treatment: Weight Loss



Probability of reaching NASH resolution, fibrosis regression and steatosis improvement with lifestyle intervention by percentage weight loss

Hannah JR WN and Harrison SA. Clinics in Liver Disease. May 2016; 339-350. https://doi.org/10.1016/j.cld.2015.10.008
Duell PB, et al. Arterioscler Thromb Vasc Biol. 2022;42:e168–e185. DOI: 10.1161/ATV.0000000000000153
Romero-Gomez M, et al. Journal of Hepatology 2017 vol. 67 | 829–846
Stahl EP, et al. JACC. 2019; ;73:948–63

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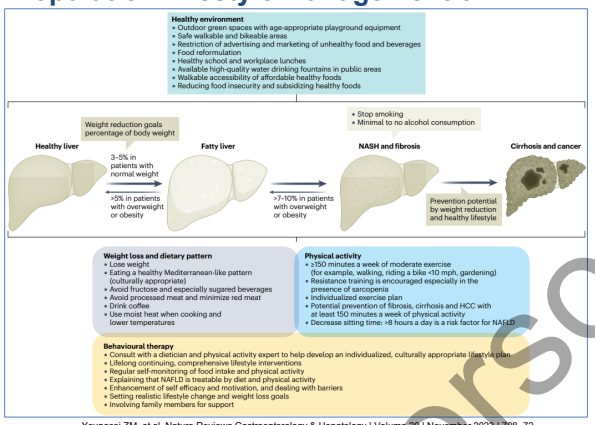
Population Lifestyle Management of MAFLD



Younossi ZM, et al. Nature Reviews Gastroenterology & Hepatology | Volume 20 | November 2023 | 708–72

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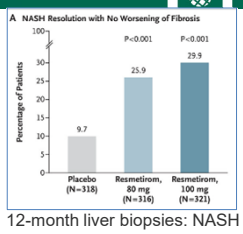
Resmetirom: FDA approved

- Noncirrhotic non-alcoholic steatohepatitis with moderate to advanced fibrosis, to be used with diet and exercise
- Accelerated approval pathway
- Phase 3 RCT (n=966)
- >50% women, 88% White, 22% Hispanic or Latino ethnicity
- Randomized to:
  - placebo (n=321),
  - resmetirom 80 mg (n=322), or resmetirom 100 mg (n=323)



- 12-month liver biopsies: NASH resolution or improvement in liver scarring
- Most common AE: Diarrhea/nausea, greatest in 100mg dose
- Caution: CYP450 Interactions
- Not for decompensated cirrhosis

https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-patients-liver-scarring-due-fatty-liver-disease
Harrison SA, et al. N Engl J Med 2024;390:497-509. DOI: 10.1056/NEJMoa2309000

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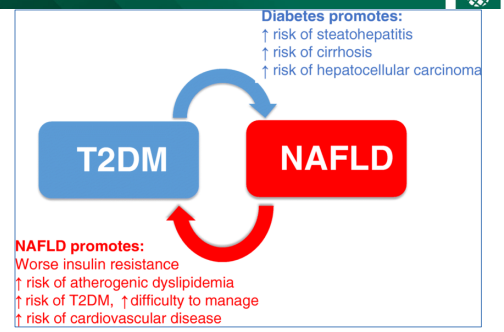
T2DM and NAFLD (MASLD)



Prevalence of MAFLD much higher with T2DM (>60%)

Jeeyavudeen S, et al. World J Gastroenterol 2023; 29(1): 126-143;
Budd J, Cusi, et al. Curr Diab Rep 20, 59 (2020). https://doi.org/10.1007/s11892-020-01349-1

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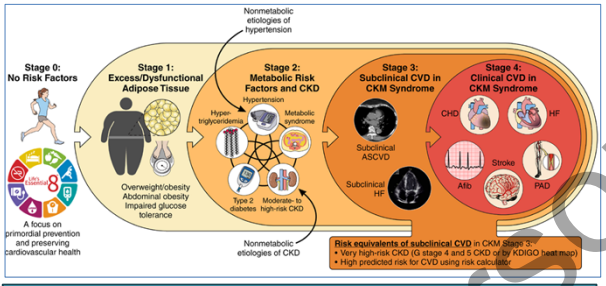
AHA PRESIDENTIAL ADVISORY

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



"Screening for advanced liver fibrosis related to MASLD every 1–2 y for individuals with diabetes, prediabetes, or ≥2 metabolic risk factors using the FIB-4 index"

Ndumele CE, et al. Circulation. 2023;148:1606–1635. DOI: 10.1161/CIR.0000000000001184

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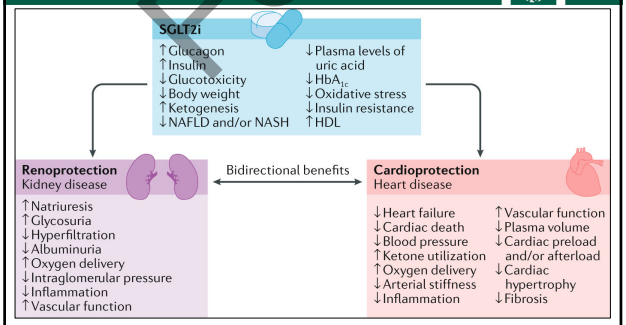
SGLT2 Inhibitors



FDA Indications: Type 2 DM, Heart failure, Chronic kidney disease

Jeeyavudeen S, et al. *World J Gastroenterol* 2023; 29(1): 126-143

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JAMA Internal Medicine | Original Investigation

Comparing Effectiveness and Safety of SGLT2 Inhibitors vs DPP-4 Inhibitors in Patients With Type 2 Diabetes and Varying Baseline HbA_{1c} Levels

- New-user; n=144,614 US commercially insured adults
- Primary outcome: Composite MI, stroke, all-cause death and hospitalization for heart failure
- Safety outcomes: Hypovolemia, fractures, falls, genital infections, diabetic ketoacidosis, acute kidney injury, and lower-limb amputation.

SGLT2i	DPP-4i
canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin	alogliptin, saxagliptin, linagliptin, or sitagliptin

D'Andrea ED, et al. JAMAInternMed.2023;183(3):242-254.doi:10.1001/jamainternmed.2022.6664

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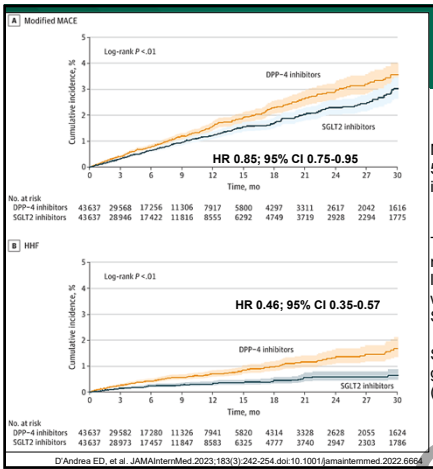

D'Andrea ED, et al. JAMAInternMed.2023;183(3):242-254.doi:10.1001/jamainternmed.2022.6664

Mean age: 62 (12.4) years, 54% male; with T2D initiating treatment

The risk of hypovolemia, nonvertebral fractures, falls, lower-limb amputations were similar between SGLT2i vs DPP-4i

SGLT2i – increased risk of genital infections (HR 2.17; 1.98-2.36)

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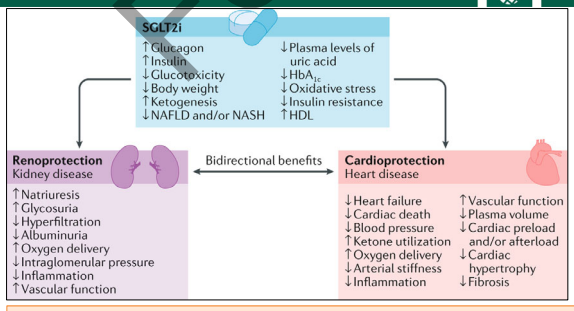
SGLT2 Inhibitors



SGLT2i emerging data: lower AST, ALT, reduction in FIB-4 score compared to placebo

Jeeyavudeen S, et al. *World J Gastroenterol* 2023; 29(1): 126-143

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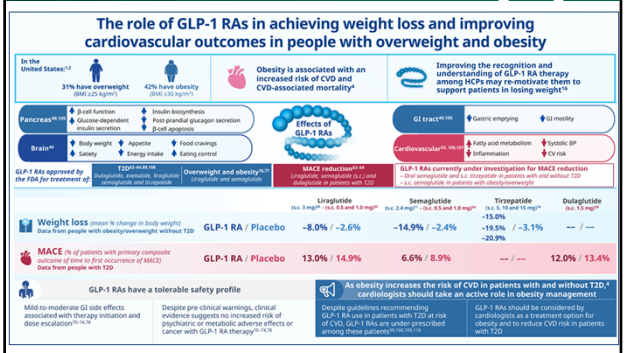
GLP-1 RAs Overweight, Obesity and CVD Risk Reduction



Michos ED, et al. J Am Heart Assoc. 2023;12:e029282. DOI: 10.1161/JAHA.122.029282

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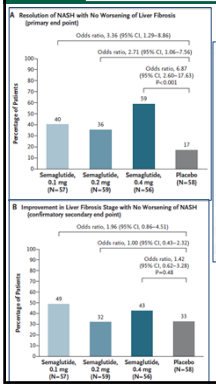
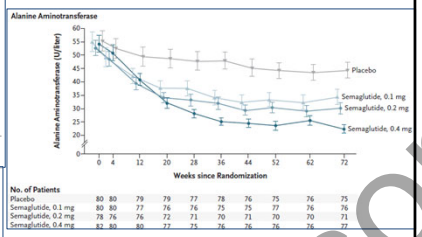
A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis

P.N. Newsome, K. Buchholtz, K. Cusi, M. Linder, T. Okanoue, V. Ratziu, A.J. Sanyal, A.-S. Sejling, and S.A. Harrison, for the NN9931-4296 Investigators*



n=320; Mean age: 52.4 (10.8) years; 55% female



Side effects: nausea, diarrhea, emesis, constipation, decreased appetite, GERD, Gallbladder disorders, tachycardia

Newsom PN, et al. N Engl J Med 2021;384:1113-24
DOI: 10.1056/NEJMoa2028395

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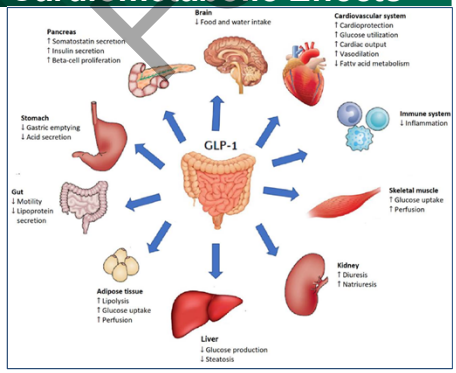
GLP1-RA Cardiometabolic Effects



Khan MS, et al. Circulation. 2020;142:1205–1218. DOI: 10.1161/CIRCULATIONAHA.120.045888

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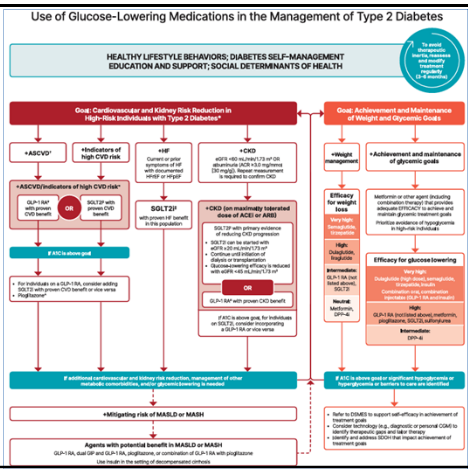
Putting It All Together!


Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes
HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT; SOCIAL DETERMINANTS OF HEALTH
To avoid therapeutic inertia, reassess and modify treatment regularly (3–6 months)
Goal: Cardiovascular and Kidney Risk Reduction in High-Risk Individuals with Type 2 Diabetes*
Goal: Achievement and Maintenance of Weight and Glycemic Goals
+ASCVD
+Indicators of high CVD risk
+HF
+CKD
+Weight management
+Achievement and maintenance of glycemic goals
+ASCVD/indicators of high CVD risk
OR
SGLT2i
+CKD (on maximally tolerated dose of ACEi or ARB)
If A1C is above goal
Efficacy for weight loss
Efficacy for glucose lowering
+Mitigating risk of MASLD or MASH
Agents with potential benefit in MASLD or MASH

ADA Professional Practice Committee. Diabetes Care 2025;48(Suppl. 1):S181–S206 | https://doi.org/10.2337/dc25-S009

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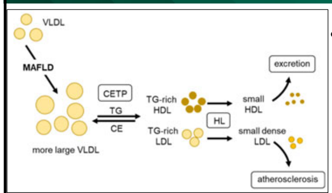
Dyslipidemia and Cardiometabolic Disease



MAFLD-associated dyslipidemia:
Elevated triglyceride synthesis in the liver, small LDL particles and low HDL-C levels;
Mixed data on Lp(a)

- Statins: first line for primary/secondary CVD prevention; cardiometabolic improvement
  - Safe with baseline elevated LFTs up to 3x ULN
  - Reduction in steatosis grade

Newman CB, Preiss D, et al., Arterioscler Thromb Vasc Biol. 2019;39:e38–e81.
Ofpnjqxpf J1jyfq3Uw; Lfxywtjsyjwtq37578 6=-7.?69=26:83itn?653:6694ul37578 67;5:93
R fwys F1jyfq3HzwwFymjwtxhqjwWju37577 Ozq@79-<.?:882:9;3itn?653655<4x66==825772 5657=293
Sanjay KV, et al. Curr Res Pharmacol Drug Discov. 2021 Sep 4;2:100051. doi: 10.1016/j.crphar.2021.100051.

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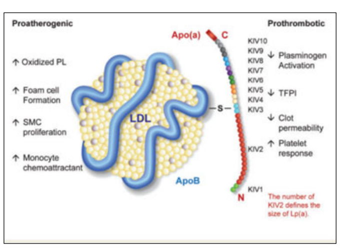
Lipoprotein(a)

- LDL-like particle with apolipoprotein(a) [Apo(a)] bound to apolipoprotein B-100 (ApoB)
- Apo(a): 10 different kringle IV (KIV)
- Apo(a) varies in size by the LPA gene, determines the number of kringle IV type 2 (KIV-2) repeats
- Lp(a) level is predominantly genetically determined


Proatherogenic
Prothrombotic
Oxidized PL
Foam cell Formation
SMC proliferation
Monocyte chemoattractant
Apo(a)
C
LDL
ApoB
S
N
KIV10
KIV9
KIV8
KIV7
KIV6
KIV5
KIV4
KIV3
KIV2
KIV1
Plasminogen Activation
TFPI
Clot permeability
Platelet response
The number of KIV2 defines the size of Lp(a).

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Witztum, J. L., & Ginsberg, H. N. (2016, March). J Lipid Res, 57(3), 336-339
Gencer B, et al. European Heart Journal, Volume 38, Issue 20, 21 May 2017, Pages 1553–1560

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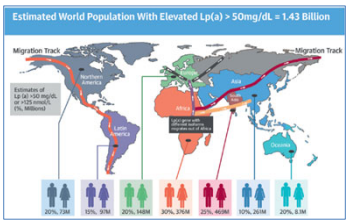
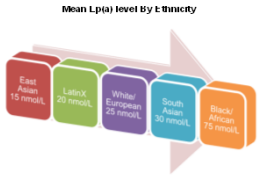
Global Variation of Elevated Lp(a)





- Global 10%-30% high Lp(a) >50 mg/dL (>100 nmol/L)

Mehta, A., et al. (2022). Lipoprotein (a) and ethnicities. Atherosclerosis, 349, 42-52
Patel, N., Mittal, N., Choubdar, P.A. et al. Lipoprotein(a)—When to Screen and How to Treat. Curr Cardiovasc Risk Rep 16, 111–120 (2022).

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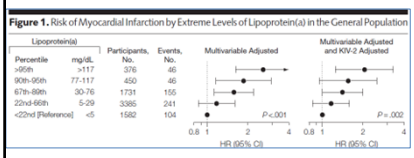
Genetically Elevated Lipoprotein(a) and Increased Risk of Myocardial Infarction

Table 1. Basic Characteristics of Participants (White Individuals of Danish Descent) in the 3 Studies

	CCHS	CGPS	CIHDS
Total, No.	8637	29 388	2461
Women, No. (%)	5302 (61)	15 260 (52)	566 (23)
Age, mean (SD), y	55 (17)	59 (13)	60 (10)
Diabetes mellitus, No. (%)	311 (4)	1346 (5)	242 (10)

Abbreviations: CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; CIHDS, Copenhagen Ischemic Heart Disease Study.

- Causal association between elevated Lp(a) and increased risk of MI, ASCVD



- Elevated Lp(a) HR: 1.22 (1.09- 1.37) per doubling of Lp(a)

Adjusted: age, sex, T chol, TG, BMI, HTN, DM, smoking, use of lipid-lowering therapy; kringle IV type 2 genotype, HRT menopause

Kamstrup, P. R., et al. 2009. Jama, 301(22), 2331-2339.

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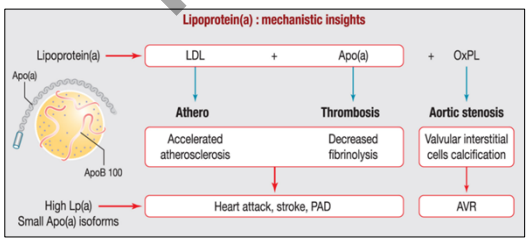
Pathophysiology: Lp(a) and Oxidized Phospholipids on Arterial and Aortic Disease



Durlach, V., et al. (2021). Archives of cardiovascular diseases, 114(12), 828–847

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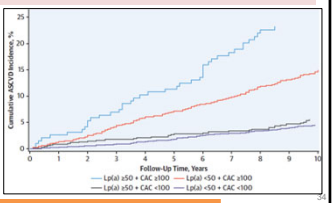
Independent Association of Lipoprotein(a) and Coronary Artery Calcification With Atherosclerotic Cardiovascular Risk

- MESA: n=4,512; Dallas Heart Study: n=2,078
- Elevated Lp(a): highest race-specific quintile
- CAC score categories: 0, 1-99, ≥100

Elevated Lp(a) and CAC score were independently associated with incident ASCVD

TABLE 4 Joint Association of Elevated Lp(a) and CAC Score With Incident ASCVD Among MESA Participants

	HR (95% CI)	*P* Value
Lp(a) quintile 5 and CAC ≥100	4.71 (3.01-7.40)	<0.01
Lp(a) quintiles 1-4 and CAC ≥100	2.99 (2.06-4.33)	<0.01
Lp(a) quintile 5 and CAC 1-99	2.35 (1.36-4.08)	<0.01
Lp(a) quintiles 1-4 and CAC 1-99	2.17 (1.49-3.16)	<0.01
Lp(a) quintile 5 and CAC = 0	1.31 (0.73-2.35)	0.36
Lp(a) quintiles 1-4 and CAC = 0	Referent	



Even with a calcium score of zero:
An elevated Lp(a) is associated with an increased risk of CVD

Mehta, A. et al. 2022. Journal of the American College of Cardiology, 79(8), 757-768

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When Should We Screen for Lp(a)?
(Recommended Units: nmol/L)

Guidelines Vary	
FH of premature ASCVD (<55 years old men, <65 years old women)	A personal history of premature ASCVD
Familial Hypercholesterolemia (LDL-C ≥190 mg/dL)	For cascade screening of family members with severe hypercholesterolemia and/or elevated Lp(a)
To aid discussion about whether to prescribe a statin in those aged 40-75 years with borderline (5.0%-7.4%) 10-year ASCVD risk	To identify those at risk for progressive valvular aortic stenosis

"Lp(a) should be measured at least once in adults to identify those with high cardiovascular risk."

National Lipid Association (NLA), 2019; American College of Cardiology (ACC) / American Heart Association (AHA), 2018; European Atherosclerosis Statement, 2022; Canadian Guidelines, 2021; HEART UK Consensus 2019. Kronenberg, F., et al. (2022). Eur Heart J, 43(39), 3925-3946.*

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Emerging Lp(a) Therapies

Emerging Lp(a) Therapeutics

Antisense Oligonucleotides	Small-interfering RNA			Oral Agents
Bind apo(a) mRNA preventing translation and production of Lp(a)	RNA-induced silencing complex (RISC) mediated degradation of apo(a) mRNA, preventing translation of protein and subsequent production			Disrupts noncovalent interaction between apo(a) & apoB100, preventing disulfide bond and Lp(a) formation
Pelacarsen	**Olpasiran**	**SLN360**	**LY3819469**	**Muvalaplin**
Phase 3 completed enrollment	Phase 3 enrolling	Phase 2 completed enrollment	Phase 1 & 2 ongoing	Phase 2 ongoing
In phase 2, mean percent reduction in Lp(a) ranged from 35-80%	In phase 2, mean percent reduction in Lp(a) ranged from 70.5%-100.5%	In phase 1, reduction in Lp(a) in dose dependent manner; well-tolerated	-	In phase 1, placebo adjusted Lp(a) reduction 63-65%

Data expected first half of 2026*

Kaur G, et al. American Journal of Preventive Cardiology 18 (2024) 100641
*https://ir.ionis.com/static-files/66c5e90a-3651-480d-a596-1cf0d1a52991

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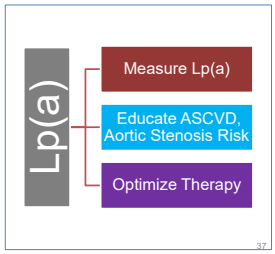
Highlights on Lp(a)

- Prevalent, genetically determined, causal risk factor for ASCVD and calcific aortic stenosis
- Awareness of elevated Lp(a) improves ASCVD risk stratification
- Inform clinical decisions and shared decision-making for ASCVD risk management
- Measure Lp(a) at least once!



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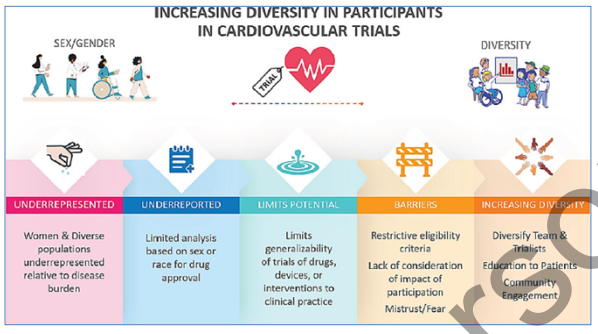
Improving Diversity in Clinical Trials



Michos ED, et al. American Journal of Preventive Cardiology; 8: (2021) 100250

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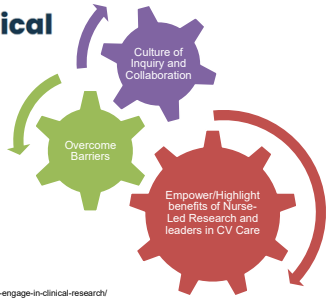
Role of CV Nurse in Clinical Trials

Empowering Cardiovascular Nurses to Engage in Clinical Research

February 18, 2025 | Diana Baptiste



https://pcna.net/empowering-cardiovascular-nurses-to-engage-in-clinical-research/

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Improving Diversity in Clinical Trials

Michos ED, et al. American Journal of Preventive Cardiology; 8: (2021) 100250

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Summary

- Cardiometabolic disorders, including MASLD are highly prevalent; focus is to manage CVD risk factors and co-morbid conditions
- Lifestyle modifications are the foundation for treatment with pharmacologic therapies to optimize cardiometabolic risk factors (DM, obesity, dyslipidemia)
- There are evolving indications and emerging treatments; however, improving diversity in clinical trial enrollment and increasing CV nurse research leaders is critical to understand safety and efficacy in population subgroups

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Baptist Health

THANK YOU

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CARDIOVASCULAR NURSING SYMPOSIUM

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