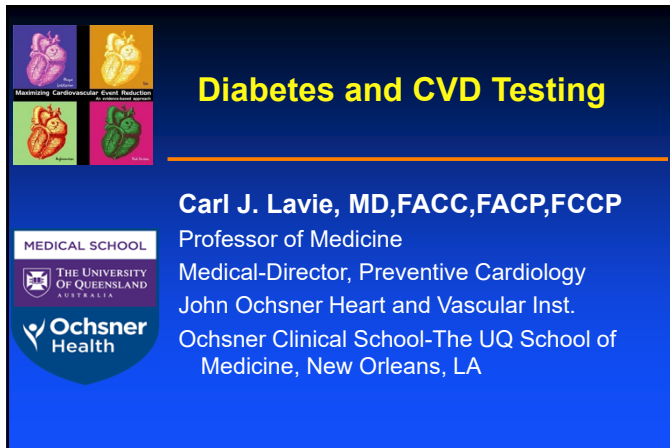




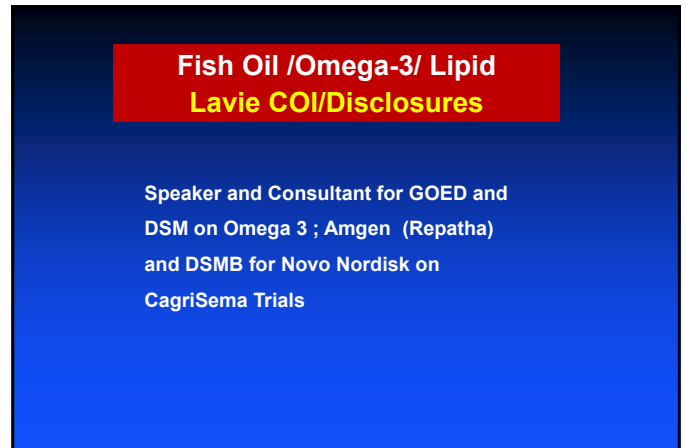
Diabetes and CVD Testing

Maximizing Cardiovascular Event Reduction

Carl J. Lavie, MD, FACC, FACP, FCCP
 Professor of Medicine
 Medical-Director, Preventive Cardiology
 John Ochsner Heart and Vascular Inst.
 Ochsner Clinical School-The UQ School of Medicine, New Orleans, LA

MEDICAL SCHOOL
 THE UNIVERSITY OF QUEENSLAND AUSTRALIA
 Ochsner Health

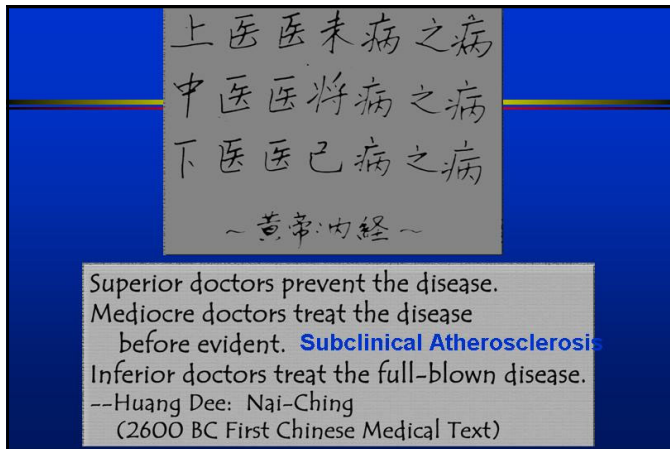
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**Fish Oil /Omega-3/ Lipid
 Lavie COI/Disclosures**

Speaker and Consultant for GOED and DSM on Omega 3 ; Amgen (Repatha) and DSMB for Novo Nordisk on CagriSema Trials

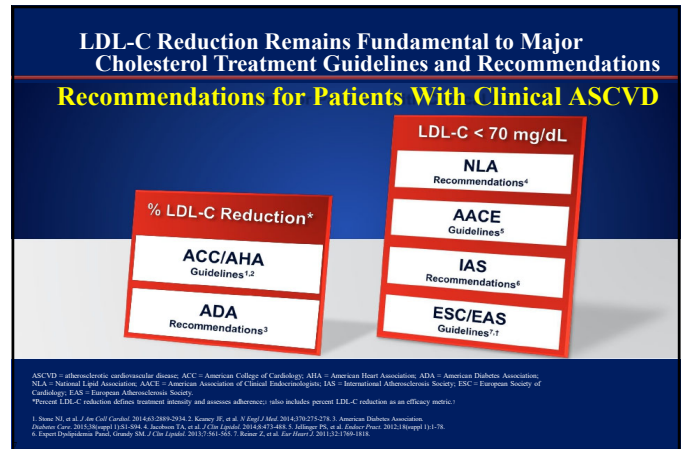
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上医医未病之病
 中医医将病之病
 下医医已病之病
 ~ 黄帝内经 ~

Superior doctors prevent the disease.
 Mediocre doctors treat the disease before evident. **Subclinical Atherosclerosis**
 Inferior doctors treat the full-blown disease.
 --Huang Dee: Nai-Ching
 (2600 BC First Chinese Medical Text)

3



LDL-C Reduction Remains Fundamental to Major Cholesterol Treatment Guidelines and Recommendations

Recommendations for Patients With Clinical ASCVD

LDL-C < 70 mg/dL

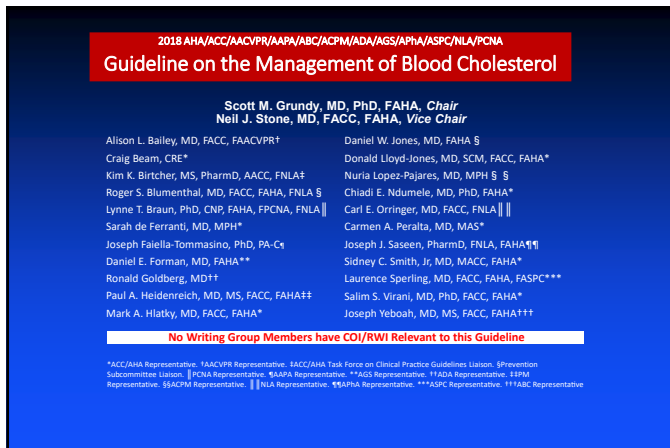
% LDL-C Reduction*

ACC/AHA Guidelines^{1,2}
 ADA Recommendations³

NLA Recommendations⁴
 AACE Guidelines⁵
 IAS Recommendations⁶
 ESC/EAS Guidelines^{7,8}

ASCVD = atherosclerotic cardiovascular disease; ACC = American College of Cardiology; AHA = American Heart Association; ADA = American Diabetes Association; NLA = National Lipid Association; AACE = American Association of Clinical Endocrinologists; IAS = International Atherosclerosis Society; ESC = European Society of Cardiology; EAS = European Atherosclerosis Society.
 *Percent LDL-C reduction defines treatment intensity and assesses adherence; value includes percent LDL-C reduction as an efficacy metric.
 1. Stone NJ, et al. *J Am Coll Cardiol*. 2014;63:2888-2914. 2. Kewey JE, et al. *N Engl J Med*. 2013;370:2725-2735. 3. American Diabetes Association. *Diabetes Care*. 2013;36(suppl 1):S84-S94. 4. Jacobson TA, et al. *J Clin Lipidol*. 2014;8:473-489. 5. Sirtoga PS, et al. *Endocr Pract*. 2012;18(suppl 1):1-78. 6. Expert Opinion. *Thromb Haemostasis*. 2013;113(suppl 2):S1-S15. 7. Kaste J, et al. *Eur Heart J*. 2013;34:1730-1744.

4



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

Scott M. Grundy, MD, PhD, FAHA, **Chair**
 Neil J. Stone, MD, FACC, FAHA, **Vice Chair**

Alison L. Bailey, MD, FACC, FAACVPR†
 Craig Beam, CRE*
 Kim K. Birtcher, MS, PharmD, AACC, FNLA‡
 Roger S. Blumenthal, MD, FACC, FAHA, FNLA §
 Lynne T. Braun, PhD, CNP, FAHA, FPCNA, FNLA||
 Sarah de Ferranti, MD, MPH*
 Joseph Faiella-Tommasino, PhD, PA-C†
 Daniel E. Forman, MD, FAHA**
 Ronald Goldberg, MD††
 Paul A. Heidenreich, MD, MS, FACC, FAHA‡‡
 Mark A. Hlatky, MD, FACC, FAHA*

Daniel W. Jones, MD, FAHA §
 Donald Lloyd-Jones, MD, SCM, FACC, FAHA*
 Nuria Lopez-Pajares, MD, MPH § §
 Chiadi E. Ndumele, MD, PhD, FAHA*
 Carl E. Orringer, MD, FACC, FNLA||
 Carmen A. Peralta, MD, MAS*
 Joseph J. Saseen, PharmD, FNLA, FAHA¶¶
 Sidney C. Smith, Jr, MD, MACC, FAHA*
 Laurence Sperling, MD, FACC, FAHA, FASPC***
 Salim S. Virani, MD, PhD, FACC, FAHA*
 Joseph Yeboah, MD, MS, FACC, FAHA†††

No Writing Group Members have COI/RWI Relevant to this Guideline

*ACC/AHA Representative. †AACVPR Representative. ‡ACC/AHA Task Force on Clinical Practice Guidelines Liaison. §Prevention Subcommittee Liaison. ¶PCNA Representative. ††AAPA Representative. **AGS Representative. †††ADA Representative. ††††EPPM Representative. †††††ACPM Representative. ††††††NLA Representative. †††††††APHA Representative. ††††††††ASPC Representative. †††††††††NAC Representative.

5



2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

A Report of the American College of Cardiology Solution Set Oversight Committee
 Endorsed by the National Lipid Association

Writing Committee

Donald M. Lloyd-Jones, MD, FACC, Chair
 Pamela R. Morris, MD, FACC, Vice Chair
 Patricia M. Hecht, MD, FACC
 Kim R. Johnston, PharmD, MS, FACC
 Andrew M. Gotro, MD

Section Set Oversight Committee

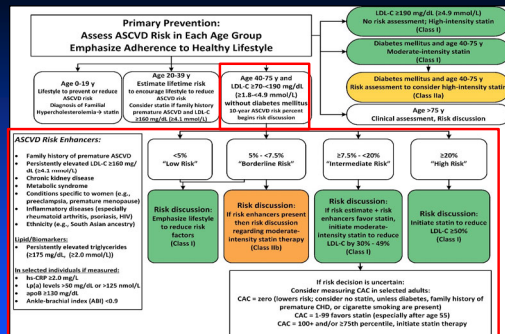
Nicole M. Brown, MD, FACC, Chair
 Jon W. Sargaret, MD, FACC
 Hylton Buckner, MD, PhD, FACC
 John P. Evans, MD, FACC
 Chayakorn Krittasing, MD

Ronnie M. Harshbarger, DPhil, PA-C, USA, CDE, AACC
 Margo R. Mittleman, PhD, ACP, CDE, AACC
 Gail R. Ostergren, MD, FACC
 Richard P. Taylor, MD, PhD
 Andrew Arora-Waring, MD, FACC
 John F. Winkles, MD, MS

Hilary J. Kraybill, MD, PhD, FACC
 Christopher S. Pappas, MD, FACC
 David A. Clark-McIntyre, MD, PhD
 David R. Weisberger, MD, PhD, FACC
 Megan Coughlin, MD, MPH, FACC - Ex Officio

This document was approved by the American College of Cardiology Clinical Policy Approval Committee in August 2022.
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Questions on Primary Prevention in Diabetes Mellitus

Primary Prevention

- What about DM at age 39 and 76
- Should HSCR and/or CAC impact intensity of statins in DM
- Should clinicians worry about statins worsening blood glucose in DM
- Should clinicians worry about higher intensity statins worsening glucose more than low intensity statins

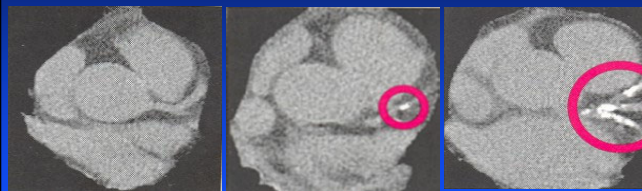
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Selected Examples of Candidates for CAC Measurement Who Might Benefit From Knowing Their CAC Score Is Zero

- Patients reluctant to initiate statin who wish to understand their risk & potential for benefit more precisely
- Patients concerned about need to reinstitute statin after discontinuation for ? statin-associated symptoms
- Men, 55-80 y/o; women, 60-80 y/o with low burden of risk factors who question whether they would benefit Rx
- 40-55 y/o with 10-yr risk of ASCVD 5% - 7.4% with risk-enhancing factors

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Heart Scans from 3 Individuals Classified at Same CHD Risk According to ASCVD Risk



Normal coronaries with little or no plaque build-up.

Coronaries with beginning calcification and early plaque build-up.

Coronaries with extensive calcification and plaque build-up.

10

Normal Distribution of CAC scores in Asymptomatic Men

	Age Groups						
	40-44	45-49	50-54	55-59	60-64	65-69	≥ 70
Median	0	2	16	47	121	205	295
75 th Percentile	11	29	94	222	453	672	794
90 th Percentile	56	142	321	671	1026	1333	1571

Nasir K, Raggi P, Rumberg JA et al, *Am J Cardiol.* 2004 ;93:1146-9.

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Normal Distribution of CAC scores in Asymptomatic Women

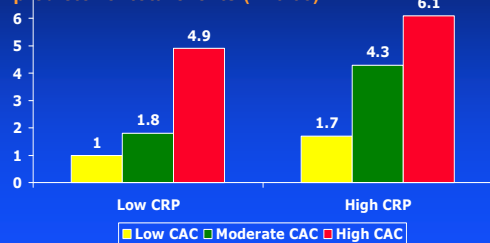
	Age Groups						
	40-44	45-49	50-54	55-59	60-64	65-69	≥ 70
Median	0	0	0	0	2	15	36
75 th Percentile	0	1	3	20	59	122	195
90 th Percentile	9	17	48	155	202	527	645

Nasir K, Raggi P, Rumberg JA et al, *Am J Cardiol.* 2004 ;93:1146-9.

12

Relative Risk of Hard CHD Events Associated Across CRP and CAC Levels.

CAC a potent predictor of cardiac events ($P=0.0005$), whereas CRP was only a modest predictor of total events ($P=0.03$).



Park R, Detrano R, Xiang M et al *Circulation*. 2002; 106: 2073–

Limitations of Statins

- Muscle Side Effects-consider Coenzyme Q 10 and check and treat low D
- Many patients do not obtain all lipid goals despite intensive doses
- Considerable Residual Risk
- Concern about other Adverse Effects- Liver, Diabetes, Memory, etc
- Most effective in patients with higher CHD risk

Statins in Diabetes Mellitus

- Patients with DM need statins more than most other patients in primary prevention
- Statins increase blood sugar and increase prevalence of DM
- Higher dose/intensity statins worsen blood sugar mores so than do lower doses/intensity
- Patients who develop DM on statins have the same protection against CHD/stroke as do patients who do not develop DM
- Pitavastatin has least effects on glucose
- DM patients may need coQ10 and D

Need for CAC in Diabetes Mellitus

- Patients with DM who do not want to take lipid meds;
- Patients with DM who have side effects on statins
- Patients with DM who may need more intensive statins or other agents
- To decide on need for baby ASA in older patients with DM
- To decide on stress testing in patients with DM

Need for HSCRP in Patients with Diabetes Mellitus

- Patients with DM who do not want to take lipid meds;
- Patients with DM who have side effects on statins
- Patients with DM who may need more intensive statins or other agents
- To decide on need for baby ASA in older patients with DM
- To help motivate patients for lifestyle interventions to lower CHD risks

What About Lpa

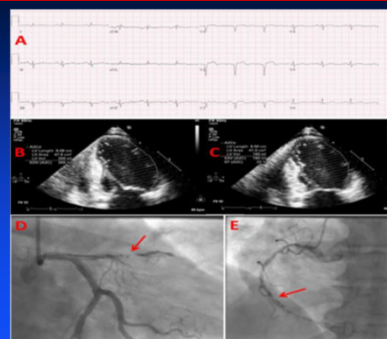
- Very Genetically Determined –Most have very low levels
- Strong independent risk factor for MI and Stroke
- Involved in atherosclerosis , is a pro-oxidant , and competitive inhibitor of fibrinolysis
- Nicotinic Acid , Estrogen and PCSK9 meds lower
- Good meds likely coming under evaluation
- Now get LDL <70, baby ASA, Vit C 1000 once or twice , and Omega 3 maybe at higher dose

Who Needs Lpa Assessment

- Not in Guidelines yet but probably once in all adults
- Patients with DM who are already at increased risk may benefit from having Lpa assessed
- Patients with DM and FH CAD or with FH high Lpa even more so need assessment

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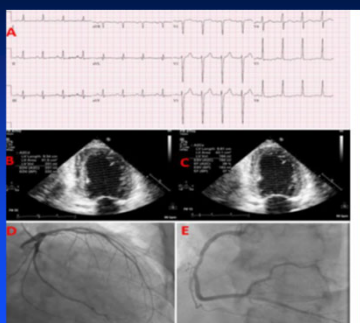
Diabetes, CHD and HF



Oktay AA et al Endotext 2020

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Diabetes, NICM and HF



Oktay AA et al Endotext 2020

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Pathophysiology DM and HF

Pathophysiological Mechanisms	Intermediate Mechanisms	Subclinical Abnormalities	Clinical Manifestation
<ul style="list-style-type: none"> ➢ Insulin resistance ➢ Hyperglycemia ➢ Inflammation ➢ RAAS overactivation ➢ Oxidative stress ➢ Myocardial energy substrate alteration ➢ Epigenetics ➢ AGEs ➢ Autoimmunity* 	<ul style="list-style-type: none"> ➢ Myocardial fibrosis ➢ Cardiomyocyte hypertrophy ➢ Lipotoxicity ➢ Mitochondrial dysfunction ➢ ER Stress ➢ Impaired calcium handling ➢ Endothelial dysfunction ➢ Microvascular dysfunction ➢ Impaired myocardial perfusion ➢ Apoptosis 	<ul style="list-style-type: none"> ➢ LV hypertrophy ➢ LV Systolic dysfunction ➢ LV Diastolic dysfunction ➢ Right ventricular dysfunction ➢ Left atrial enlargement and myopathy 	<ul style="list-style-type: none"> ➢ Asymptomatic CMP ➢ HF with preserved EF ➢ HF with reduced EF

Oktay AA et al Endotext 2020

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Other CVD Testing in Diabetes

- Should BNP be a regular test?
- When should Echocardiography be performed?
- Who should have a stress test?
- In those with stress test, which one should be performed?
- Who should have angiography? Invasive or CTCA?

23

Other CVD Testing in Diabetes BNP Testing?

- Should BNP be a regular test? –Possibly periodically in DM
- In patients with edema not clearly from VI or drug effect (eg amlodipine)
- In patients with dyspnea , probably even if deconditioning, COLD , or IHD is suspected
- Could lead to other testing, diuretic therapy to prevent clinical HF, and other meds (SGLT2Is , GLP1 agonists etc)

24

Other CVD Testing in Diabetes Echo/CFD Testing?

- Should Echo/CFD be routine test in DM?
- Low risk and high clinical information
- However, cost is very high in patients with no clinical symptoms or signs on VHD, AF, or DM
- Therefore selective utilization is required considering “cost effectiveness”

25

Other CVD Testing in Diabetes Echo/CFD Testing?

- Should Echo/CFD be routine test in DM?
- Dyspnea
- Peripheral Edema not clearly VI
- Abnormal ECG
- Elevated BNP
- Heart murmur

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Other CVD Testing in DM Stress Testing?

- Should Stress Testing be routine in DM?
- If so , in what ages and how often?
- Relatively low risk but questionable cost-effectiveness
- If ordered , what test to get?

27

Other CVD Testing in DM Stress Testing Indications

- Should Stress Testing be routine in DM?
- Chest Pain
- Dyspnea
- Worrisome ECG
- High CAC – above 400 or maybe above 75th or 90th percentile

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Other CVD Testing in DM Stress ECG Indications

- Should Stress Testing be routine in DM?
- Stress ECG is least expensive
- Has lowest sensitivity and specificity for CAD
- Has information on exercise capacity , which is perhaps the greatest predictor of prognosis and survival
- Need a near normal ECG
- Need to be able to perform exercise

29

Other CVD Testing in DM Stress Echo Indications

- Should Stress EchoTesting be routine in DM?
- Stress ECG is least expensive but stress echo also provides higher sensitivity and specificity
- Provides data on LV and valve structure and fx
- Not a good test with systolic LV dysfunction
- Poor specificity in LBBB
- Exercise preferred as get METs, but DSE has similar sensitivity and specificity for CAD

30

Other CVD Testing in DM Stress Nuclear Indications

- Should Stress Nuclear Testing be routine in DM?
- Stress ECG is least expensive but stress echo considerably less expensive
- Similar sensitivity and specificity as Stress Echo and much better than Stress ECG
- Better than Stress echo with TDS Echo images (often in obesity, COPD, Chest wall issues)
- Better than stress echo when LVEF low
- Better with LBBB (Regadenoscan Nuclear not exercise)

31

Other CVD Testing in DM PET Stress Indications

- PET Stress is the “Rolls Royce” of Stress Testing
- By far the most expensive stress test
- Limited as no exercise information –no METs or information on exercise capacity/fitness
- Best in obesity and LV dysfunction
- Best not only to diagnose CAD but to quantitate the amount of myocardium in danger
- Often can provide comfort that medical management may be best in CAD

32

Other CVD Testing in DM Coronary Angiography Indications

- Bad symptoms
- Marked ischemia or high risk features on non-invasive testing
- Uncertainty if there is significant CAD
- Pros and cons and shared decision making
- Some patient and physician biases

33

Other CVD Testing in DM Coronary Angiography Indications

- Invasive vs non-invasive
- Need for revascularization merits invasive
- Invasive is higher risk and more expensive
- CTCA is less expensive, but has dye load and is not accurate with high CAC
- If CTCA leads to invasive, cost even higher and there is an extra dye load

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Other CVD Testing in DM ECG

- No guidelines
- If symptoms or abnormalities on physical exam
- Hypertension
- Consider once at mid age (40, 45, 50 years?)
- Possibly periodically every 5-10 years

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Diabetes Case Study

A 60 yo male of India Descent with HTN on HCTZ presented with DOE and leg edema. The patient also had DM treated with glipizide 5 mg daily and dyslipidemia treated with Atorvastatin 10 mg and had a CAC scan with CAC score of 45.

36



Diabetes Case Study

PE showed a pulse of 88, BP 155/95 and RR 12. O2 sat was 92%. BMI was 31 and WC 39 inches. There was evidence of JVD, crackles at the bases, RRR with 1/6 Systolic murmur, positive hepatjugular Reflux, and 2+ lower extremity edema.

37

DM Case Study

- What testing is needed now?
- a) ECG and CXR
- b) Color Flow Echo
- c) BNP
- d) Stress Nuclear
- e) all of the above
- f) just a,b,c

38



Diabetes Case Study

Laboratory values included cardiomegaly and Interstitial edema on CXR; ECG showed ST abn, IVCD, and LAE; FBS 144; TC 190, TG 225, HDL 32, LDL 113
A1C 7.5
BNP- 1200
CFD-LVEF 33, Global hypo, mod LAE, mod MR and TR, PASP 50

39



Diabetes Case Study

Additional Testing Needed??

40

HF Therapies Indicated

- BB –Carvedilol may have most evidence and least adverse cardiometabolic effects
- RAAS-ACEI, ARB, or ARNI
- AA
- Loop Diuretic
- Digitalis
- ICD, CRT
- SGLT2i

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Other Therapies Indicated

- Diet-Low sweets and carbs; lower salt;
- Higher statin
- Omega-3, maybe pure EPA

42

HF Therapies Indicated

- BB –Carvedilol may have most evidence and least adverse cardiometabolic effects
- RAAS-ACEI, ARB, or ARNI
- AA
- Loop Diuretic
- Digitalis
- ICD, CRT
- Omega-3 ; Co Q 10??

43

Lipid Abnormalities Needing Treatment

- LDL Goal < 70 mg/DI
- TGs
- HDL
- Non-HDL

44

Therapies Available for LDL-C

- Statins (40-80 Atorva or 20-40 Rosuva)
- Ezetimide
- Bempedoic Acid
- PCSK9Is
- Inclisiran

45

What About TGs

- Combined EPA/DHA
- Pure EPA
- Fenofibrate
- Weight loss
- Low sugar and Carbs
- Low alcohol

46

What About HDL

- Probably not nicotinic acid
- Exercise, weight loss
- Low dose alcohol??

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What About Sugar

- Weight loss
- Low sweets and carbs
- Exercise
- SGLT2I will help BS, A1C and systolic HF

48

Weight Loss in DM

- What is needed for weight loss?
- a) Nothing there is obesity paradox
- b) Diet and exercise
- c) Bariatric Surgery
- d) GLP1 agonist
- e) b, c and possibly d

49

What About Obesity

- Does mild obesity increase risk of CVD risk factors
- Does mild obesity worsen risk of CVD
- Does mild obesity worsen prognosis following HF
- Would weight loss help patient
- Would exercise help
- GLP1-agonists eg Semaglutide 2.4 mg weekly data coming from SELECT and HFpEF and recent trials with Tirzepatide.

50

What About Low PA and Fitness

- Patient has low level of PA and Fitness
- This is major risk factor for CVD/HF and prognosis in patients with HF events
- Low PA and Fitness play a major role in the "Obesity Paradox" in CVD and HF.

51

What About Low PA and Fitness

- Patient needs Cardiac Rehabilitation if LVEF remains low
- Most in the US do not attend and very few attend in India
- Best to get PA > 150 minutes per week; steps over 10,000/d (recent major paper says 7200-8800/d) and improve fitness

52



Diabetes Case Study 2

A 65 yo Caucasian male with HTN on HCTZ presented with dyslipidemia and side effects/myopathy on Rosuvastatin 20 mg now stopped. Lipids showed TC 280, TG 300, HDL 33, LDL 191. He does not want statin. Pulse 78 BP 128/76, and ECG and BNP normal.

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Therapies Indicated

- Meets criteria for statins
- At least can be on Ezetimide
- At least can be on Omega-3 and dietary treatment

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Diabetes Case Study

Additional Testing Needed??

55

Additional Testing Needed

- CAC- score 880
- Lpa – value 85 (30 ULN)
- HSCR- 4.5
- Vit D – Level 11

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Therapies Indicated

- Baby ASA
- Vit D to get level > 30- initially 50,000 IU weekly
- CoQ 10 200 mg /d
- Increase O3 to 1000-1500 EPA+ DHA
- Possible Vit C 1000 mg BID
- Statin along with the Ezetimide to start a few weeks after the D and CoQ10- goal LDL < 70

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Additional Testing Needed

- Stress Testing
- Stress imaging better but exam, ECG , and BNP all normal
- Stress ECG if cost an issue
- Later repeat lipids (no need for repeat Lpa now) , Vit D and possibly repeat HSCR

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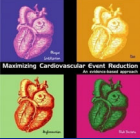
Need for CVD Testing in DM

- There are several potential testing useful in patients with DM besides simple ECG
- Lpa
- HSCR
- BNP
- CAC
- Echo
- Stress Testing
- Angiography
- **Need the best testing , in the correct patient, at the right time**

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Diabetes and CVD Testing

Carl J. Lavie, MD,FACC,FACP,FCCP
Professor of Medicine
Medical-Director, Preventive Cardiology
John Ochsner Heart and Vascular Inst.
Ochsner Clinical School-The UQ School of
Medicine, New Orleans, LA

MEDICAL SCHOOL
THE UNIVERSITY
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