NAFLD and Cardiovascular Disease

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About the Presenter

Laurence S. Sperling, MD

DISCLOSURES

No potential conflicts related to this presentation

• Not a liver specialist
• Comments do not directly represent organizational viewpoints
Interplay between NAFLD and CVD

- Brief Case
- Spectrum of Cardiometabolic Risk
- NAFLD & CVD
Interplay between NAFLD and CVD

• Brief Case
• Spectrum of Cardiometabolic Risk
• NAFLD & CVD
Case (for Concern)

- 57 yo F post-IMI, CABG
- Hx HTN, former Tob use; no EtoH
- BMI 27, fbg 114
- TC 191; HDL 32; TG 175; LDL 124
- Non-HDL 159; SGOT 45; SGPT 48
- Told “statin intolerant” given mildly elevated transaminases after statin Rx
Interplay between NAFLD and CVD

• Brief Case
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• NAFLD & CVD
PREVALENCE OF METABOLIC SYNDROME

• NHANES III - metabolic syndrome
  – 24% of men; 23.4% of women
  – 42% of individuals > age 60

• Underscores need to control obesity epidemic/improve physical activity

The CardioMetabolic Health Alliance

Working Toward a New Care Model for the Metabolic Syndrome

FIGURE 2 Stages in the Evolution of MetS and Recommended Therapy by Stage

MetS. A greater emphasis on assessing nutritional quality and levels of physical activity, with a focus on filling the gap between public health approaches and implementation in clinical practice, will be needed. Care models will continue to incorporate ACOs, but uncertainty exists as to how the ACA will affect MetS care in the future. It is foreseen that health care will transition to a greater degree from the clinic to the community, improving access to care, and that there will be a broadening of stakeholders to include public health, community, and industry sectors. Screening and performance metrics will enhance implementation of new care models in the future. Finally, the TT affirmed a call to action to encourage ongoing partnerships, funding, and initiatives to improve the lives of people with or at risk for MetS.
Lifetime Risk of Diabetes from Birth According to Sex and Race/Ethnicity, USA

Narayan et al., *JAMA*, 2003
The “Ticking Clock”: From “No Symptoms” to Overt Disease

Health Status/QOL

Time (years)

Normotensive

Insulin Resistance/ the Metabolic Syndrome

Hypertension/DM

Atherosclerosis

Death

QOL, quality of life.
Adipose tissue

$\uparrow$ IL-6  $\downarrow$ Adiponectin

$\uparrow$ Leptin  $\uparrow$ TNF$\alpha$

$\uparrow$ Adipsin (Complement D)

$\uparrow$ Plasminogen activator inhibitor-1 (PAI-1)

$\uparrow$ Lipoprotein lipase

$\uparrow$ Angiotensinogen

$\uparrow$ Insulin

$\uparrow$ FFA

$\uparrow$ Resistin

$\uparrow$ Leptin

$\uparrow$ Lactate

Inflammation

Hypertension

Atherogenic dyslipidemia

Insulin Resistance

Thrombosis

Adverse Effects of Cardiometabolic Syndrome


Predicting ASCVD Risk?


- Arterial imaging/function
- Biomarkers
- Metabolic syndrome
- Family history
- Pooled 10 yr ASCVD Risk Equation
SES and CV Outcomes: Challenges & Interventions


Low SES
- Poor access to care and healthy foods
- Psychosocial factors
- Behavioral factors
- Environmental factors

Traditional CVD Risk Factors
- Hypertension
- Dyslipidemia
- Diabetes
- Smoking
- Obesity
- Poor diet
- Physical inactivity

Interventions
- Behavioral counseling (physical activity, smoking, alcohol)
- Community-based programs
- Health education
- Local and federal health policy

Interventions
- Guideline-based care
- Lifestyle modification
- Task shifting
Social Determinants of Health: Geomapping- “Hot spots”

- Health varies at a very LOCAL level

- National Health Index
  - Profile of Diabetes
Identifying those at increased risk.......
AHA/ACC Special Report

Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease

Donald M. Lloyd-Jones, MD, ScM, FACC, FAHA; Lynne T. Braun, PhD, CNP, FAHA; Chiadi E. Nduele, MD, PD, FAHA; Sidney C. Smith, Jr, MD, MACC, FAHA; Laurence S. Sperling, MD, FACC, FAHA; Salim S. Virani, MD, PhD, FACC, FAHA; Roger S. Blumenthal, MD, FACC, FAHA

Published Online Ahead of Print November 10, 2018 in Circulation and JACC
Refining Risk Estimates for Individual Patients

Estimate Absolute 10-year ASCVD Risk

- **Low Risk**: 0 - <5%
- **Borderline Risk**: 5% - <7.5%
- **Intermediate Risk**: 7.5% - <20%
- **High Risk**: ≥20%

Clinician-patient discussion considering risk-enhancing factors and net benefit of therapy

If uncertainty remains, consider CAC score and revise decision based on results

Lifestyle modification

Lifestyle and drug therapy

American College of Cardiology

American Heart Association
Refining Risk Estimates for Individual Patients

<table>
<thead>
<tr>
<th>Risk-Enhancing Factors for Clinician–Patient Risk Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Family history of premature ASCVD;</strong> (males, age &lt;55 y; females, age &lt;65 y)</td>
</tr>
<tr>
<td>• <strong>Primary hypercholesterolemia</strong> (LDL-C, 160-189 mg/dL [4.1–4.8 mmol/L]; non-HDL-C 190-219 mg/dL [4.9-5.6 mmol/L])*</td>
</tr>
<tr>
<td>• <strong>Metabolic syndrome</strong> (increased waist circumference, elevated triglycerides [&gt;175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [&lt;40 mg/dL in men; &lt;50 in women mg/dL] are factors; tally of 3 makes the diagnosis)</td>
</tr>
<tr>
<td>• <strong>Chronic kidney disease</strong> (eGFR 15-59 mL/min/1.73 m² with or without albuminuria, not treated with dialysis or kidney transplantation)</td>
</tr>
<tr>
<td>• <strong>Chronic inflammatory conditions</strong> such as psoriasis, RA, or HIV/AIDS</td>
</tr>
<tr>
<td>• <strong>History of premature menopause</strong> (before age 40 y) and <strong>history of pregnancy-associated conditions that increase later ASCVD risk</strong> such as pre-eclampsia</td>
</tr>
<tr>
<td>• <strong>High-risk race/ethnicities</strong> (e.g. South Asian ancestry)</td>
</tr>
<tr>
<td>• <strong>Lipid/biomarkers:</strong> Associated with increased ASCVD risk</td>
</tr>
<tr>
<td>- Persistently* elevated, primary hypertriglyceridemia (≥175mg/dL);</td>
</tr>
<tr>
<td>- If measured:</td>
</tr>
<tr>
<td>- <strong>Elevated high-sensitivity C-reactive protein</strong> (≥2.0 mg/L)</td>
</tr>
<tr>
<td>- <strong>Elevated Lp(a)</strong> A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥ 50 mg/dL or ≥125 nmol/L constitutes a risk enhancing factor especially at higher levels of Lp(a)</td>
</tr>
<tr>
<td>- <strong>Elevated apoB</strong> ≥130 mg/dL - A relative indication for its measurement would be triglyceride ≥ 200 mg/dL. A level ≥ 130 mg/dL corresponds to an LDL-C &gt;160 mg/dL and constitutes a risk enhancing factor</td>
</tr>
<tr>
<td>- <strong>ABI (ABI)</strong> &lt;0.9</td>
</tr>
</tbody>
</table>
### Table 2: Compliance Rates for Coronary Artery Disease Performance Measures in 8,132 Patients

<table>
<thead>
<tr>
<th>Performance Measure</th>
<th>Unit of Assessment</th>
<th>Denominator</th>
<th>Numerator</th>
<th>Compliance Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blocker therapy after myocardial infarction</td>
<td>Patients</td>
<td>1,782</td>
<td>1,540</td>
<td>86.4%</td>
</tr>
<tr>
<td>Blood pressure measurement</td>
<td>Last encounter</td>
<td>7,698</td>
<td>7,235</td>
<td>94.0%</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>Patients</td>
<td>7,944</td>
<td>6,742</td>
<td>84.9%</td>
</tr>
<tr>
<td>Screening for diabetes mellitus</td>
<td>Patients</td>
<td>6,199</td>
<td>822</td>
<td>13.3%</td>
</tr>
<tr>
<td>Smoking query</td>
<td>Patients</td>
<td>8,132</td>
<td>6,812</td>
<td>83.8%</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>Patients</td>
<td>500</td>
<td>356</td>
<td>71.2%</td>
</tr>
<tr>
<td>Symptom and activity assessment</td>
<td>Patients</td>
<td>8,132</td>
<td>6,981</td>
<td>85.8%</td>
</tr>
<tr>
<td>ACE-I or ARB therapy</td>
<td>Patients</td>
<td>4,623</td>
<td>3,349</td>
<td>72.4%</td>
</tr>
<tr>
<td>Annual lipid profile</td>
<td>Patients</td>
<td>8,132</td>
<td>6,044</td>
<td>74.3%</td>
</tr>
<tr>
<td>Drug therapy for lowering LDL cholesterol</td>
<td>Patients</td>
<td>1,607</td>
<td>1,355</td>
<td>84.3%</td>
</tr>
<tr>
<td>Cardiac rehabilitation referral†</td>
<td>Patients</td>
<td>1,108</td>
<td>200</td>
<td>18.1%</td>
</tr>
</tbody>
</table>

2018 ACC ECDP on Novel Therapies for CV Risk Reduction in T2DM & ASCVD
Das SR, Everett BM, Sperling LS. JACC 2018. Nov. 14 2018

- Extension of Paradigm - ASCVD Risk Reduction
- Focus on Rx with Evidence for ASCVD Event Reduction
- CV Clinicians MUST be Champions & actively involved in new approaches to integrated patient-centered comprehensive care
Diabetes Collaborative Registry

Diabetes Real-World Data and Evidence Alliance across Medicine

“... the first clinical registry aimed at tracking and improving the quality of diabetes and cardiometabolic care across the primary and specialty care continuum
Measures & Metrics

- 8 diabetes metrics selected for registry, 6 either ACC/AHA endorsed or Physician Quality Reimbursement System (PQRS) measures

- Topic areas include:
  - A1c Control
  - Medication Rx for CAD & Diabetes comorbidity
  - Nephropathy
  - Smoking Cessation
  - Dietary Intake Counseling
  - Physical Activity Counseling
  - Eye Exam
  - Foot Exam
Roadmap for Prevention of CVD

- Launch in Paris at ESC/ WCC 2019
- Global focus on those living with T2DM
- Emphasis on implementation science

Interplay between NAFLD and CVD

- Brief Case
- Spectrum of Cardiometabolic Risk
- NAFLD & CVD
Nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD) are both manifestations of end-organ damage of the metabolic syndrome. Through multiple pathophysiological mechanisms, CVD and NAFLD are associated with each other. Systemic inflammation, endothelial dysfunction, hepatic insulin resistance, oxidative stress, and altered lipid metabolism are some of the mechanisms by which NAFLD increases the risk of CVD. Patients with NAFLD develop increased atherosclerosis, cardiomyopathy, and arrhythmia, which clinically result in cardiovascular morbidity and mortality. Defining the mechanisms linking these 2 diseases offers the opportunity to further develop targeted therapies. The aim of this comprehensive review is to examine the association between CVD and NAFLD and discuss the overlapping management approaches. (J Am Coll Cardiol 2019;73:948-63) © 2019 by the American College of Cardiology Foundation.
NAFLD & CVD

- NAFLD associated with insulin resistance
- Associated with > 2-fold increased risk of T2DM
- Association of NAFLD & CVD likely independent of cardiometabolic RFs

NAFLD & CV Events: 3 Meta-analyses

- Targher  34K  16 studies  MACE OR 1.64
- Haddad   26K  6 studies   CV events  RR 1.77
- Wu       165K 34 studies  Prevalent CVD 1.81

- Severity of disease associated with increased events
- Association with CVD mortality unclear
- Variability; heterogeneity

NAFLD & Atherosclerosis

- NAFLD independently associated with increased CIMT and CAC
- Increased arterial stiffness and endothelial dysfunction
- Association of NAFLD and high risk plaque by CTA after adjusting for extent and severity of atherosclerosis

Coronary calcification / Evidence of diffuse hepatic fatty infiltration
NAFLD: Altered Serum Lipoproteins

- Liver vital role on lipid metabolism
- Metabolic dyslipidemia
  - Elevated TG & VLDL, low HDL, small dense LDL-C
- Contributes to increased risk for CVD

NAFLD: Impact on LV Structure and Function

- NAFLD impacts LV remodeling, LV mass, and diastolic function
- NAFLD causes increased body surface area leading to increased LV filling pressures, cardiac output and volume overload

NAFLD: Cardiac Structural & Valvular Changes

- Increased LV wall thickness & mass
- Diastolic dysfunction & higher LV filling pressures
- Independently associated with aortic sclerosis and MAC
- Association with epicardial adipose tissue (EAT)

NAFLD & Cardiac Arrhythmias

• Increased risk for atrial fibrillation, QTc prolongation, ventricular arrhythmias
• Associated with autonomic dysfunction

CENTRAL ILLUSTRATION: Nonalcoholic Fatty Liver Disease Increasing Risk of Cardiovascular Disease: Pathophysiologial Mechanisms

- \( \uparrow \text{ADMA} \)
  - Impaired Redox Status
  - \( \uparrow \text{Homocysteine} \)
  - \( \uparrow \text{Platelet Activation} \)
  - \( \uparrow \text{Systemic Inflammation} \)

- \( \uparrow \text{Plasma Free Fatty Acid Level} \)
  - \( \uparrow \text{Liver Fat Content} \)
  - \( \uparrow \text{Hepatic Lobular Inflammation} \)

- \( \uparrow \text{Hepatic Insulin Resistance} \)
  - Impaired Redox Status
  - \( \uparrow \text{Hepatic Fatty Acid Accumulation} \)

- \( \uparrow \text{Hepatic Glucose Production} \)
  - \( \downarrow \text{Hepatic Insulin Signaling} \)

Endothelial Dysfunction

Systemic Insulin Resistance

Altered Lipid Metabolism

CVD
  - CV Events/Mortality
  - Atherosclerosis
  - Cardiomyopathy
  - Arrhythmias

Oxidative Stress

Plaque Formation/Instability

Systemic Inflammation

- \( \uparrow \text{IL-6} \)
- \( \uparrow \text{M1/M2} \)
- \( \uparrow \text{hsCRP} \)
- \( \uparrow \text{CCL3} \)
- \( \uparrow \text{sICAM-1} \)
- \( \uparrow \text{TNF}_{\alpha} \)
- \( \uparrow \text{IL-1}\beta \)


Stahl EP, Dhindsa DS, Chalasani NP, Sperling LS JACC 2019;73:948-963
NAFLD & ASCVD Prevention

• Importance of comprehensive CV risk assessment
• Identification of NAFLD
• Focus on lifestyle modifications
  – Healthy dietary patterns
  – Physical activity
  – Weight loss
• Limit EtoH

NAFLD & Statins

• Underutilized in patients with liver disease
• Significant hepatic injury extremely rare (1: > 100K)
• Patients with NAFLD and elevated transaminases not at increased risk
• Potential to improve NAFLD?
• Reduction in CV events (GREACE trial)?

2018 Cholesterol Guideline Writing Committee

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Statin Safety and Statin-Associated Side Effects

- Statins modestly increase risk of incident diabetes in susceptible individuals
  - focus on net clinical benefit; Not cause for discontinuation
  - Opportunity to discuss diabetes prevention and focus on risk reduction

- Severe statin-associated hepatotoxicity is rare
  - Thorough evaluation for nonstatin etiologies when transaminase elevation noted
  - Statins not contraindicated in those with increased ASCVD risk with chronic, stable liver disease
### Recommendations for Statin Safety and Statin-Associated Side Effects

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>C-LD</td>
<td>In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful.</td>
</tr>
</tbody>
</table>
Interplay between NAFLD and CVD

• NAFLD & CVD share numerous RFs; both are manifestations of end-organ damage of MetS
• NAFLD may independently increase risk of atherosclerosis, cardiomyopathy, and arrhythmias
• Further investigation is needed regarding pathophysiologic mechanisms, tools for risk assessment, and treatment approaches
• CV Specialists need to have greater awareness of this interplay
Cardiovascular Prevention Center – Founded 1997

- Primary and secondary prevention clinics
- HeartWise Risk Reduction Program
- Optimal Living
- Women’s Heart Program
- Cardio-oncology
- Cardio-inflammatory
- Sports Cardiology
- Subclinical markers of atherosclerosis
- Screenings and Risk Factor management
- LDL apheresis
- Housestaff / fellow training programs
- Clinical and Translational Science Research
Thanks......