New Approaches to Cardiovascular Risk Management

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Current and Future Approaches to Cardiovascular Risk Management

- Examine why focusing solely on LDL Cholesterol is not enough
- Incorporate New Agents to lower LDL cholesterol into a Treatment Paradigm
- Be able to recommend Optimal Dietary Regimens for patients with Diabetes and Cardiovascular Risk factors
- Evaluation of HTN and Rx goals
- The effect of DM control on CV Risk
Evolution of the Lipid Hypothesis

- Post-mortem exams
- Framingham starts
- Epidemiological studies (WHO, LRC-CPPT, HHS)
- First generation clinical studies (FATS, PLAC 1, REGRESS)
- Atherosclerosis studies (WOSCOPS, CARE, 4S, LIPID, AFCAPS/TEXCAPS)
- Second generation clinical studies

Why LDL-Cholesterol is Not Enough

• Also need to focus on Plaque Stabilization
• Residual Risk Even in Intensely Treated Patients
• Lipoprotein species other than LDL are involved in atherogenesis (ie, VLDL, IDL, HDL)
• LDL-Concentration is not the same as LDL Particle No.
Plaque Rupture- not Stenosis-causes most Acute Myocardial Infarctions

Stable Plaque:
- Lumen stenotic but plaque stable
- Thick fibrous cap

Unstable Plaque:
- Lumen not stenotic but inflamed
- Thin fibrous cap ruptured, leading to thrombus formation
Most MI's Arise From Smaller Stenoses

Case Study: 64 y/o male JG

- Caucasian male, 64 years old; DM x 12 years
- Blood pressure, 132/78 mm Hg (on ACE inhibitor)
- FPG, 114 mg/dL, A1C 6.4 (On Metformin 2 g/d)
- Waist circumference, 89 cm (35 in); BMI-26
- Nonsmoker; on Simvastin 40 mg/Ezetimibe 10 mg qD
- Dyslipidemia
  - TC, 115 mg/dL
  - LDL-C, 71 mg/dL
  - HDL-C, 36 mg/dL
  - Triglycerides, 44 mg/dL
  - Normal TMET 4/13
How Many Feel Most of Their Patient’s Lipids are Under Control?

• If control means LDL <100 or 70, is that enough? (Problem of residual risk)

• Are my patients’ LDL levels truly “at goal” using Friedewald?

• Is my patient heading for an event despite an LDL <70?
Residual CVD Risk in Patients Treated With Intensive Statin Therapy

Statistically significant, but clinically inadequate, CVD reduction

Patients Experiencing Major CVD Events, %

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>LDL-C,* mg/dL</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT-TIMI 22²</td>
<td>4162</td>
<td>95</td>
<td>26.3</td>
<td>22.4</td>
</tr>
<tr>
<td>IDEAL³</td>
<td>8888</td>
<td>104</td>
<td>13.7</td>
<td>12.0</td>
</tr>
<tr>
<td>TNT⁴</td>
<td>10 001</td>
<td>101</td>
<td>10.9</td>
<td>8.7</td>
</tr>
</tbody>
</table>

*Mean or median LDL-C after treatment

Residual Cardiovascular Risk in Major Statin Trials

Lipoprotein species other than LDL-C are involved in atherogenesis (i.e., VLDL, IDL, HDL)
Friedewald Equation Conclusions

• In the era of lower LDL’s for high risk patients the Friedewald equation is too inaccurate for clinical use

• Direct measurement of LDL is needed if:
  – LDL-C < 100 mg/dL
  – Trigs > 200 mg/dL
  – Non-fasting specimen or partial fasting
  – Drugs or disease states that cause elevated triglycerides
Lipids in Diabetic and Nondiabetic Subjects

NHANES III
N = 2844

Serum Concentration, mg/dL

<table>
<thead>
<tr>
<th></th>
<th>Total-C</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>216</td>
<td>131</td>
<td>41</td>
<td>245</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>215</td>
<td>137</td>
<td>51</td>
<td>143</td>
</tr>
</tbody>
</table>

Same LDL-C Levels, Different Cardiovascular Risk

Fewer Particles

- LDL= 130 mg/dL
- More Apo B
- Cholesterol Ester

Correlates with:
- TC 198 mg/dL
- LDL-C 130 mg/dL
- TG 90 mg/dL
- HDL-C 50 mg/dL
- Non-HDL-C 148 mg/dL

More Particles

- More Apo B

Correlates with:
- TC 210 mg/dL
- LDL-C 130 mg/dL
- TG 250 mg/dL
- HDL-C 30 mg/dL
- Non-HDL-C 180 mg/dL

Atherogenic Dyslipidemia

Treating Beyond LDL-C to Reduce Residual CVD Risk
(Small, Dense LDL, and the Concept of Particle No.)
LDL Particle Number Distribution in T2DM Subjects

Percent of Subjects

LDL-C 71-99 mg/dL (n=1,484)

LDL-C ≤ 70 mg/dL (n=871)

AHA Scientific Sessions, 2005
Patients stabilized post-ACS ≤ 10 days
LDL-C ≤ 125 mg/dL (or ≤ 100 mg/dL if prior statin)

Double-blind

ASA + Standard Medical Therapy

Simvastatin 40 mg*

Ezetimibe/ Simvastatin 10/40 mg*

Follow-up visit day 30, every 4 months

Duration: Minimum 2.5 year follow-up (5250 events)

Primary Endpoint: CV death, MI, Hospitalization for UA, Revascularization (> 30 days after randomization), or Stroke

*uptitrated to 80 mg if LDL-C > 79 mg/dL

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT)

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL-C</th>
<th>hs-CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td>69.9</td>
<td>145.1</td>
<td>137.1</td>
<td>48.1</td>
<td>3.8</td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Δ in mg/dL:
- LDL-C: -16.7, -19.3, -16.7, +0.6, -0.5

Number at risk:
- Simva: 9009, 8921, 8306, 7843, 7289, 6939, 6607, 6192, 5684, 5267, 4395, 3387, 2569, 1068
- Ez/Simva: 8990, 8899, 8230, 7701, 7264, 6864, 6583, 6256, 5734, 5354, 4508, 3484, 2608, 1078

IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE IT)

Primary Endpoint - ITT

Event Rate (%)

<table>
<thead>
<tr>
<th>Time Since Randomization (years)</th>
<th>EZ/Simva – 32.7% 2572 events</th>
<th>Simva – 34.7% 2742 events</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td></td>
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<td>3</td>
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<td>4</td>
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<td>5</td>
<td></td>
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<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR 0.936  CI (0.887, 0.988)
p = 0.016

NNT = 50

7-year event rates

American Association of Clinical Endocrinologists and American College of Endocrinology

Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease

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<table>
<thead>
<tr>
<th>Risk category</th>
<th>Risk factors(^a)/10-year risk(^b)</th>
<th>Treatment goals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LDL-C (mg/dL)</td>
</tr>
<tr>
<td>Extreme Risk</td>
<td>– Progressive ASCVD including unstable angina in patients after achieving an LDL-C &lt;70 mg/dL</td>
<td>&lt;55</td>
</tr>
<tr>
<td></td>
<td>– Established clinical cardiovascular disease in patients with DM, CKD 3/4, or HeFH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– History of premature ASCVD (&lt;55 male, &lt;65 female)</td>
<td></td>
</tr>
<tr>
<td>Very High Risk</td>
<td>– Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk &gt;20%</td>
<td>&lt;70</td>
</tr>
<tr>
<td></td>
<td>– Diabetes or CKD 3/4 with 1 or more risk factor(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– HeFH</td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>– ≥2 risk factors and 10-year risk 10%-20%</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>– Diabetes or CKD 3/4 with no other risk factors</td>
<td></td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>≤2 risk factors and 10-year risk &lt;10%</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Low Risk</td>
<td>0 risk factors</td>
<td>&lt;130</td>
</tr>
</tbody>
</table>
The 10-year risk of a coronary event (high, intermediate, or low) sample tools

- Framingham Risk Assessment Tool

- Multi-Ethnic Study of Atherosclerosis (MESA) 10-year ASCVD Risk w Coronary Artery Calcification Calculator
  (https://www.mesanhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx)

- Reynolds Risk Score, which includes hsCRP and family history of premature ASCVD
  (http://www.reynoldsriskscore.org)

- United Kingdom Prospective Diabetes Study (UKPDS) risk engine to calculate ASCVD risk in individuals with T2DM
  (https://www.dtu.ox.ac.uk/riskengine)
Multi-Ethnic Study of Atherosclerosis

- **MESA investigated the correlates of subclinical CVD**: The study enrolled 6,814 patients between July 2000 and September 2002; at baseline, all patients were free of clinical CVD.

- **10-year outcomes showed that CAC is an independent risk factor for CVD**: CAC predicts CVD risk in patients with or without traditional risk factors and in patients with family history of premature CHD.

- **CAC was the strongest predictor of CVD in low-risk patients.**

- **The MESA risk score uses traditional risk factors and CAC to predict 10-year CHD risk**: The incorporation of CAC into this risk score has improved risk prediction.

Abbreviations: CAC, coronary artery calcification; CHD, coronary heart disease; CVD, cardiovascular disease; MESA, Multi-Ethnic Study of Atherosclerosis.

MESA: CHD Event Rates With Increasing CAC Score and Based on Risk Factor Burden

- **Hard events = MI, resuscitated cardiac arrest, CHD death**
- Abbreviations: CAC, coronary artery calcification; CHD, coronary heart disease; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction
MESA: Cumulative CHD Incidence Across Coronary Artery Calcium Categories
STATIN THERAPY
If TG > 500 mg/dL, fibrates, Rx-grade omega-3 fatty acids, niacin

If statin-intolerant

Try alternate statin, lower statin dose or frequency, or add nonstatin LDL-C-lowering therapies
Repeat lipid panel; assess adequacy, tolerance of therapy
Intensify therapies to attain goals according to risk levels

<table>
<thead>
<tr>
<th>RISK LEVELS</th>
<th>HIGH</th>
<th>DM but no other major risk and/or age &lt;40</th>
<th>VERY HIGH</th>
<th>DM + major ASCVD risk(s) (HTN, Fam Hx, low HDL-C, smoking) or ASCVD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>&lt;100</td>
<td>&lt;100</td>
<td>&lt;70</td>
<td></td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>&lt;130</td>
<td>&lt;100</td>
<td>&lt;150</td>
<td></td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>&lt;150</td>
<td>&lt;150</td>
<td>&lt;150</td>
<td></td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>&lt;3.5</td>
<td>&lt;3.0</td>
<td>&lt;3.0</td>
<td></td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>&lt;90</td>
<td>&lt;80</td>
<td>&lt;80</td>
<td></td>
</tr>
<tr>
<td>LDL-P (nmol/L)</td>
<td>&lt;1200</td>
<td>&lt;1000</td>
<td>&lt;1000</td>
<td></td>
</tr>
</tbody>
</table>

IF NOT AT DESIRABLE LEVELS: Intensify lifestyle therapy (weight loss, physical activity, dietary changes) and glycemic control; consider additional therapy

TO LOWER LDL-C: Intensify statin, add ezetimibe, PCSK9i, colesevelam, or niacin
TO LOWER Non-HDL-C, TG: Intensify statin and/or add Rx-grade OM3 fatty acid, fibrate, and/or niacin
TO LOWER Apo B, LDL-P: Intensify statin and/or add ezetimibe, PCSK9i, colesevelam, and/or niacin
TO LOWER LDL-C in FH:** Statin + PCSK9i
NEW LIPID AGENTS

- Mipomersin (Kynmaro)
- Lomitapide (Juxtapid)
- PCSK9 inhibitors
  - Alirocumab (Praluent) Sanofi/Regeneron-75-150 mg q 2 weeks
  - Evolocumab (Repatha) Amgen-140 mg/mL q2 weeks or 420 mg/mL monthly HoFH
**Mipomersen**: Crosses the Hepatocyte and Nuclear Membrane to Target the mRNA for Apo B

Mechanism of Action of Lomitapide

Lomitapide binds and inhibits Microsomal Triglyceride Transport Protein (MTP), thereby preventing the assembly of apo B containing lipoproteins in the enterocytes and hepatocytes.

This inhibits the synthesis of chylomicrons and VLDL-C.

PCSK9 (Proprotein convertase subtilisin/kexin type 9)
Targets LDL-R for Lysosomal Degradation

Blockade of PCSK9 Lowers LDL Levels by Increasing LDL Receptors on cell surface

Chan JC, et al. PNAS 2009;106:9820-9825
Change in LDL-C from Baseline to Week 24
According to HeFH status (ITT)

HeFH population
- Placebo: 
  - n=271
  - LS mean (SE) % change in calculated LDL-C from baseline to Week 24: -56.3±1.9%
- Alirocumab: 
  - n=145
  - LS mean difference vs. placebo: -63.2%
  - Interaction p-value: 0.6038

Non-HeFH population
- Placebo: 
  - n=1259
  - LS mean (SE) % change in calculated LDL-C from baseline to Week 24: -62.1±0.8%
- Alirocumab: 
  - n=635
  - LS mean difference vs. placebo: -61.5%

Change from Baseline to Week 24
Fasting Triglycerides, HDL-C, and Apo A1 (ITT)

Fasting Triglycerides
- Alirocumab: -17.3% (P<0.001)
- Placebo: -20.8%

HDL-C
- Alirocumab: 4.6% (P<0.001)
- Placebo: -0.6%

Apo A1
- Alirocumab: 4.0% (P<0.001)
- Placebo: 1.2%

These are secondary endpoints in ITT analysis population. *Analyzed with the use of multiple imputation, followed by robust regression. A combined estimate for adjusted mean (±SE) is shown.
GAUSS-2 and ODYSSEY ALTERNATIVE
PCSK9 Inhibitors Well Tolerated by Statin-intolerant Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Drug</th>
<th>Patients Completing Treatment, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAUSS-2[a]</td>
<td>307</td>
<td>Evolocumab</td>
<td>96</td>
</tr>
<tr>
<td>ODYSSEY ALTERNATIVE[b]</td>
<td>314</td>
<td>Alirocumab</td>
<td>95</td>
</tr>
</tbody>
</table>

## CV Events in Long-Term PCSK9 Inhibitor Trials

<table>
<thead>
<tr>
<th></th>
<th>ODYSEY LONG TERM</th>
<th>OSLER-1 and OSLER-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Alirocumab</td>
</tr>
<tr>
<td>Event rate, %</td>
<td>3.3 (26/788)</td>
<td>1.7 (27/1550)</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.52 (0.31-0.90)</td>
<td></td>
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</tbody>
</table>

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Anthony C. Keech, M.D., Narimon Honarpour, M.D., Ph.D., Stephen D. Wiviott, M.D., Sabina A. Murphy, M.P.H., Julia F. Kuder, M.A., Huei Wang, Ph.D., Thomas Liu, Ph.D., Scott M. Wasserman, M.D., Peter S. Sever, Ph.D., F.R.C.P., and Terje R. Pedersen, M.D., for the FOURIER Steering Committee and Investigators*

ABSTRACT

BACKGROUND
Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9) and lowers low-density lipoprotein (LDL) cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain.

METHODS
We conducted a randomized, double-blind, placebo-controlled trial involving 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 years.

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (M.S.S., R.P.G., S.D.W., S.A.M., J.F.K.); Sydney Medical School, National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney (A.C.K.); Amgen, Thousand Oaks, CA (N.H., H.W., T.L., S.M.W.); International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London (P.S.S.); and Oslo University Hospital, Ullevål and Medical Faculty, University of Oslo, Oslo (T.R.P). Address reprint requests to Dr. Sabatine at the TIMI Study Group, Division of Cardiovascular Medi-
Fourier Trial Population Overview

- 40-85 y/o
- Hx of ASCVD
- LDL > 70 or non-HDL > 100
- On Statin Rx of Atorvastatin 20 mg/d or higher, with or without Ezetimibe
- LDL baseline 92 mg/dL and at 48 weeks 30 mg/dL
- Adverse effects on cognition, glucose metabolism and other parameters similar to placebo
FOURIER Evolocumab Study

LDL-C Levels Over time

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; LDL-C, low-density lipoprotein cholesterol.

FOURIER Evolocumab Study Endpoints

Cumulative event rates for the primary efficacy endpoint
(Composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)

Cumulative rates for the key secondary efficacy endpoint (Composite of cardiovascular death, MI, or stroke)

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; MI, myocardial infarction.

FOURIER Primary and Secondary Endpoints

- At 26 months, extremely tight lipid control with evolocumab led to a 15% decrease in risk for the primary composite endpoint and 20% decrease in risk for a secondary composite endpoint
  - The primary endpoint included MI, cardiovascular death, stroke, coronary revascularization, or hospitalization for unstable angina
  - The secondary endpoint included cardiovascular death, MI, or stroke
- Beyond the second year of follow-up, the risk reduction increased to 20% for the primary endpoint and to 25% for the secondary endpoint
- For singular endpoints at 26 months, very tight lipid control reduced the risk of MI by 27%, stroke by 21%, and coronary revascularization by 22%

Abbreviations: FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk trial; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

PCSK9 Inhibitors

- > 10,000 patients have been treated in phase 2 and phase 3 trials with marked LDL-C reduction
- 2 PCSK9 inhibitors, Alirocumab (Praluent) and Evolocumab (Repatha), have been approved, and more are on the way
- Not only do they work well with statins, their effect on cholesterol lowering is additive
- Low Side effect profile
- Large outcome trials like Fourier are underway with other agents
- Drug acquisition costs are relatively expensive, compared to traditional therapies
The Future?
THE HUMAN MICROBIOME
Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk

W.H. Wilson Tang, M.D., Zeneng Wang, Ph.D., Bruce S. Levison, Ph.D., Robert A. Koeth, B.S., Earl B. Britt, M.D., Xiaoming Fu, M.S., Yuping Wu, Ph.D., and Stanley L. Hazen, M.D., Ph.D.
Gut Microbiota participates in Atherosclerosis in the presence of specific dietary exposures

“Standard American Diet” = SAD

ARTICLE

gut flora metabolism of phosphatidylcholine promotes cardiovascular disease

eggs, milk, liver, red meat, poultry, shell fish and fish, are believed to be the major dietary sources for choline, and hence TMAO production^{14}.

TMAO is formed from dietary Carnitine and Choline in Omnivores
Red Meat Consumption and Mortality: Results from 2 Prospective Cohort Studies, *Archives of Internal Medicine*. 2012; 172(7):555-563

1 serving per day (3 oz) increase in red meat corresponds to:

- 13% increase in total mortality (unprocessed red meat)
- 20% increase in total mortality (processed red meat)

**Health Professionals Follow-up Study**
(n=37,698) men, 40-75 yo 1986-2008

**Nurses Health Study**
(n=83,644) women, 35-55 yo 1980-2008
LIFESTYLE THERAPY
RISK STRATIFICATION FOR DIABETES COMPLICATIONS

INTENSITY STRATIFIED BY BURDEN OF OBESITY AND RELATED COMPLICATIONS

**Nutrition**
- Maintain optimal weight
- Calorie restriction
- Plant-based diet; high polyunsaturated and monounsaturated fatty acids
- Avoid trans fatty acids; limit saturated fatty acids

**Physical Activity**
- 150 min/week moderate exertion (eg. walking, stair climbing)
- Strength training
- Increase as tolerated

**Sleep**
- About 7 hours per night

**Behavioral Support**
- Community engagement
- Screen for mood disorders

**Smoking Cessation**
- No tobacco products

**Structured counseling**
**Meal replacement**

**Structured program**

**Medical evaluation/clearance**
**Medical supervision**

**Screen for obstructive sleep apnea**

**Refer to mental healthcare professional**
**Behavioral therapy**

**Structured programs**

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FIGURE 1
Restoration of myocardial perfusion

Positron emission tomography performed on a patient with coronary artery disease shows an area of myocardium with insufficient blood flow (top). Following only 3 weeks of plant-based nutritional intervention, normal blood flow was restored (bottom).

FIGURE 2
Reversal of coronary artery disease

Coronary angiography reveals a diseased distal left anterior descending artery (A). Following 32 months of a plant-based nutritional intervention without cholesterol-lowering medication, the artery regained its normal configuration (B).
What is a Plant-Based Diet?

• Beware of Junk Food - white bread, potato chips and diet cola are technically plant based.

• Whole food, non-processed is the goal; this will be high in fiber and promote a healthy microbiome.

• Complex Carbohydrates are desirable and not to be avoided. Resistant Starch remains intact through cooking and digestion - i.e., beans, potatoes, split peas, slightly green bananas, barley and brown rice.

Concentrate on what is included instead of what isn’t.
Refined (Simple) vs. Whole (Complex) Carbs

• *Whole grains* are derived from the seeds of grasses and include rice, oats, rye, wheat, wild rice, quinoa, barley, buckwheat, bulgur, corn, millet, amaranth, and sorghum. (They have zero cholesterol and are low in fat.)

• *Refined grains*-the bran and germ have been removed, leaving only the endosperm. These end products are stripped of vitamins, minerals, and fiber.
Hepatic fructose metabolism.

1. ↑ Uric Acid & ↓ NO
2. Causes De Novo Lipogenesis
3. ↑ Hepatic Steatosis
4. ↑ Muscle & Liver IR
5. Antagonizes Leptin & Satiety

What We Really Have is a FIBER Deficiency

• **Soluble fiber**-can be dissolved in water, and can be found in oats, barley, beans, peas, apples, citrus fruits, carrots and seaweed. Soluble fiber lowers cholesterol and glucose.

• **Insoluble fiber**-improves digestion, constipation, increases satiety, and removes toxins. Foods include vegetables like asparagus, celery, wheat bran, whole grains, and nuts.
How much Protein do we Need?

• The average American diet contains @ 120 grams of protein
• RDA for adults-0.8 gram/kg/day
• Multiple studies correlate meat consumption with DM, Inflammation, Obesity, CVD, Dyslipidemia, HTN, CKD, Cancer
- MUFA (monounsaturated fatty acids)-found in olives, peanuts, avocados, pecans, almonds, their oils, and canola oil.
- PUFA (polyunsaturated fatty acids)-make up omega-3 and omega-6. Found in walnuts, flaxseeds, hempseeds, vegetable oils (especially canola, soybean, and flaxseed), fish, and marine oils.
- SFA (saturated fatty acids)-found primarily in animal products. They raise cholesterol and promote heart disease.
- TFA (trans fatty acids)-if you see hydrogenated or partly hydrogenated-stay away!
Sprint Trial
Systolic Blood Pressure Intervention Trial

Background: Optimal target for SBP lowering uncertain

Randomized 9300: SBP 120 vs. 140 mm Hg

Stopped at 3.3 years; planned average 5 year f/u

“Landmark NIH study…Milestone…Major Advance…SPRINT shows intensive blood pressure management may save lives”
Systolic BP over Course of the Trial

Ave SBP

Std: 134.6 mm Hg

Intensive: 121.5 mm Hg

MD's chose Rx
SPRINT: MAIN RESULTS

Primary Outcome
Death from any Cause

MI, ACS, Stroke, CHF, CV death

25%  243 vs 319
NNT 61

27%  155 vs 210
NNT 90

ANY DEATH
Hypertension Caveats

- Use ACE i first d/t cost; @ 10% intolerant d/t cough
- In DM, Beta blockers can mask hypoglycemia and worsen glucose intolerance
- Don’t be surprised if it takes 2-4 agents for control
- Salt restriction is helpful!
- Consider screening for Secondary HTN-ie renin/aldo ratio, Cushing’s, Pheo, etc.
Rule Out Endocrine Causes

- Onset before age 25
- Not controlled on 3 drugs, including diuretic
- Palpitations, Headache, Sweats (1/300)
- Abdominal bruit, central obesity, striae
- Adrenal Nodule; hypokalemia
Evaluation for Endocrine Causes

- Renal Vascular Hypertension
  Clinical Suspicion (Duplex US)
- Pheochromocytoma
  History
- Cushing’s Syndrome
  Exam
- Primary Aldosteronism
  Lab
Other Causes of Secondary HTN

- Obesity
- Aging
- Sleep Apnea
- CKD
- Thyroid or PTH
- Excess Na
- Excess EtOH

- Drugs
  - NSAID’s, OC’s, illicit, supplements
- Improper BP measurement
- White Coat Phenomenon
- Noncompliance
BP Goals for DM patients?

2003
JNC7 <130/80 mm

2013
ADA raised target to
<140/90 mm

2017....
ADA suggests <130/80 if at
High risk and it’s safe
Risk of T2D Complications With Intensive Glucose and BP Control

United Kingdom Prospective Diabetes Study

<table>
<thead>
<tr>
<th>BP: Benefits of 144/82 vs. 154/87 mm Hg</th>
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<tbody>
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<td>Risk Reduction (%)</td>
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<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Any diabetes-related endpoint</td>
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<tr>
<td>Diabetes-related death</td>
</tr>
<tr>
<td>Stroke</td>
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<td>Heart failure</td>
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<td>Vision deterioration</td>
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</tbody>
</table>

-21 P=0.13
-24 P=0.005
-32 P=0.019
-44 P=0.013
-56 P=0.29
-42 P=0.004
-34 P=0.004
-47 P=0.004

<table>
<thead>
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<th>A1C: Benefits of 7.0% vs. 7.9%</th>
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-16 P=0.052
-12 P=0.029
-10 P=0.34
-9 P=0.68
-27 P=0.45
-21 P=0.015
NR

ENDOCRINE
Intensive Glycemic Control Reduces Long-term Macrovascular Risk

UKPDS¹
T2D, newly diagnosed (N=4209)

DCCT²
T1D, 5-6 years duration (N=1441)

15% risk reduction
P=0.01

Randomized treatment

Conventional

Intensive

Years

Proportion With MI

CV Outcome
Cumulative incidence

Randomized treatment

Conventional

Intensive

But it takes a long time!
Steno-2: Effects of Multifactorial Intervention on CV Outcomes

N = 160 with type 2 diabetes and microalbuminuria

53% risk reduction
P = 0.01

*CV death, MI, stroke, revascularization, amputation

New Approaches to Cardiovascular Risk Management

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