Updates in Metabolic Syndrome Literature: A Case Approach

Marc Cornier, M.D.
Division of Endocrinology, Metabolism and Diabetes
Anschutz Health and Wellness Center
University of Colorado School of Medicine
marc.cornier@ucdenver.edu

Introduction

• Review of literature from 2015 to present
• Concentrated on clinical studies/trials
• Categories:
  – Metabolic Syndrome, Obesity, Lipids, Diabetes, HTN and CVD
  – “Major” clinical journals
• Should any of these new findings help guide changes to our guidelines?

Case 1:

Patient is a 63 yo woman with a history of T2DM for the past 7 years. Her A1c is currently 8.1% on metformin. She has no known complications and is up to date with screenings.
She is also on an ACEI for hypertension and a moderate-intensity statin for hypercholesterolemia.

Will better glycemic control reduce her risk for atherosclerotic cardiovascular disease (ASCVD)?
Empagliflozin and CVD Outcomes

Question: Does empagliflozin in addition to standard care, reduce CVD morbidity and mortality in patients with T2DM?

Design: Double blind placebo-controlled RCT of empagliflozin 10 mg or 25 mg or placebo once daily

Patients: 7,020 adults with T2DM at high risk for CVD

1° Outcome: Death from CVD causes, nonfatal myocardial infarction, or nonfatal stroke, as analyzed in the pooled empagliflozin group versus the placebo group.

2° Outcome: Primary outcome plus hospitalization for unstable angina.

Empagliflozin and CVD Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Empagliflozin (N=4687)</th>
<th>Placebo (N=2333)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° Endpoint</td>
<td>490 (10.5%)</td>
<td>282 (12.1%)</td>
<td>0.86 (0.74-0.99)</td>
</tr>
<tr>
<td>Noninferiority</td>
<td></td>
<td></td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Superiority</td>
<td></td>
<td></td>
<td>P=0.04</td>
</tr>
<tr>
<td>2° Endpoint</td>
<td>599 (12.8%)</td>
<td>333 (14.3%)</td>
<td>0.89 (0.78-1.01)</td>
</tr>
<tr>
<td>Noninferiority</td>
<td></td>
<td></td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Superiority</td>
<td></td>
<td></td>
<td>P=0.08</td>
</tr>
<tr>
<td>3° Endpoint</td>
<td>All cause Mortality</td>
<td>209 (5.7%)</td>
<td>195 (8.3%)</td>
</tr>
<tr>
<td>CVD Mortality</td>
<td>172 (3.7%)</td>
<td>137 (5.9%)</td>
<td>0.62 (0.49-0.77)</td>
</tr>
</tbody>
</table>

LEADER Trial “Top-Line” Results

- Patients: 9,340 adults with T2DM with h/o of CVD (81%) or high risk for CVD (19%), A1c 8.7%
- RCT of Liraglutide vs placebo + standard of care
- Preliminary Results:
  - Showed “non-inferiority”
  - Statistically significant reduction in primary outcome:
    - CVD death, non-fatal MI or non-fatal stroke
Pioglitazone after Stroke/TIA

Question: Does insulin sensitization with pioglitazone benefit patients with cerebrovascular disease?

Design: Double blind placebo-controlled RCT of pioglitazone 45 mg or placebo once daily

Patients: 3,876 adults with recent ischemic stroke or TIA and insulin resistance but not diabetes

1° Outcome: fatal or nonfatal stroke or myocardial infarction.
2° Outcomes: stroke; acute coronary syndrome; the composite of stroke, myocardial infarction, or heart failure resulting in hospitalization or death; death from any cause; diabetes; and cognitive decline from baseline

Pioglitazone after Stroke/TIA

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Pioglitazone (N=1939)</th>
<th>Placebo (N=1937)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° Endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke or MI</td>
<td>175 (9.0%)</td>
<td>228 (11.8%)</td>
<td>0.76 (0.62-0.93)</td>
<td>0.007</td>
</tr>
<tr>
<td>2° Endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>127 (6.5%)</td>
<td>154 (8.0%)</td>
<td>0.82 (0.61-1.10)</td>
<td>0.19</td>
</tr>
<tr>
<td>ACS</td>
<td>96 (5.0%)</td>
<td>128 (6.6%)</td>
<td>075 (0.52-1.07)</td>
<td>0.11</td>
</tr>
<tr>
<td>Diabetes</td>
<td>73 (3.8%)</td>
<td>149 (7.7%)</td>
<td>0.48 (0.33-0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>136 (7.0%)</td>
<td>146 (7.5%)</td>
<td>0.92 (0.73-1.17)</td>
<td>0.52</td>
</tr>
</tbody>
</table>
Summary and Implications

• Does better glycemic control reduce "macrovascular" disease (ASCVD) in diabetes?
  – Yes:
    • DCCT/EDIC (T1DM)
    • UKPDS 10-YEAR
    • PROactive
    • EMPA REG
    • LEADER
  – No:
    • ACCORD
    • ADVANCE
    • VADT

• How about in prediabetes or insulin resistance? Do diabetes treatments reduce CVD?
  – Yes:
    • STOP NIDDM (acarbose)
    • IRIS Trial (pioglitazone)
  – No data:
    • Metformin
    • Others
Risk Factor Control in T2DM

- 2,018 adults with DM without CVD, from the:
  - Atherosclerosis Risk in Communities (ARIC) Study
  - Multi-Ethnic Study of Atherosclerosis (MESA)
  - Jackson Heart Study (JHS).
- Followed for CHD and CVD events over a mean 11-years.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP at target (&lt;130/80 mmHg)</td>
<td>41.8%</td>
</tr>
<tr>
<td>LDL-C at target (&lt;100 mg/dL)</td>
<td>32.1%</td>
</tr>
<tr>
<td>HbA1c at target (&lt;7%)</td>
<td>41.9%</td>
</tr>
<tr>
<td>None (BP, LDL-C, HbA1c) at target</td>
<td>25.2%</td>
</tr>
<tr>
<td>Any one (BP, LDL-C, HbA1c) at target</td>
<td>41.1%</td>
</tr>
<tr>
<td>Any two (BP, LDL-C, HbA1c) at target</td>
<td>26.5%</td>
</tr>
<tr>
<td>All three (BP, LDL-C, HbA1c) at target</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

• Followed for CHD and CVD events over a mean 11-years.
Summary and Implications

• We are still not doing a good job with CVD risk reduction in patients with T2DM
• Risk factor control is associated with significant reductions in new CVD
• Better glycemic control does appear to reduce CVD risk in certain populations and/or with certain glucose lowering therapies
• Unclear if specific to mechanisms of action, class effects or to specific agents
• Better glycemic control is clearly associated with reduced microvascular outcomes

Case 2:

• Patient is a 66 yo man with the metabolic syndrome.
• He is overweight with a BMI of 28 and elevated waist circumference.
• He has untreated mildly elevated BP – 144/88.
• His labs are significant for:
  – Total-C 200, LDL-C 130, HDL 45, TG 125, A1c 5.7
Will he benefit from more aggressive CVD risk reduction? Should we start him on a statin or BP lowering therapy? Are other markers of risk useful?

HOPE-3 Trial:
Heart Outcomes Prevention Evaluation
HOPE-3: Cholesterol Lowering in Intermediate-Risk Persons without CVD

Question: Are LDL and BP lowering effective in primary prevention of CVD in moderate risk individuals?

Design: 2x2 design - multicenter placebo-controlled RCT of rosuvastatin 10 mg vs placebo and candesartan/HCTZ 16/12.5 mg vs placebo, followed for 5.6 years

Patients: 12,705 adults (men > 55, women > 60-65) with at least one CVD risk factor (46% women, mean age 66)

1° Outcomes:
1) Composite of death from CVD, nonfatal MI, or nonfatal stroke
2) First co-primary outcome + revascularization, heart failure and resuscitated cardiac arrest

HOPE-3: Baseline Characteristics

Cardiovascular risk factors
- Elevated waist-hip ratio: 87%
- Recent or current smoking: 27%
- Low HDL-C: 39%
- IFG or IGT: 13%
- Early diabetes mellitus: 6%
- Family hx of premature CHD: 29%
- Early renal dysfunction: 3%
- Hypertension: 38%
- Presence of 2 risk factors: 47%
- Presence of ≥3 risk factors: 24%
- Systolic Blood pressure: 138 mmHg
- Body-mass index: 27 kg/m²

Cholesterol
- Total: 202 mg/dL
- LDL: 128 mg/dL
- HDL: 45 mg/dL
- Triglycerides: 127 mg/dL
- Fasting plasma glucose: 95 mg/dL
- hsCRP: 2.0 mg/L

NEJM Epub April 2, 2016

Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease


NEJM Epub April 2, 2016
HOPE-3: Cholesterol Lowering in Intermediate-Risk Persons without CVD


NEJM Epub Apr 2, 2016.

Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease

NEJM Epub Apr 2, 2016.
• LDL lowering with Rosuvastatin 10 mg resulted in:
  – Significant reduction in primary outcomes
  – Significant reduction in MI, Stroke, revascularization, and hospitalizations for CVD
  – No increase in new-onset diabetes or cancers
  – Slight increase in muscle symptoms (5.8% vs 4.7%)
• BP lowering with candesartan/HCTZ 16/12.5 mg does not improve outcomes except in those with baseline SBP>143.4 mmHg
• BP and LDL lowering in combination further improve outcomes beyond that seen with LDL lowering alone
Long-Term Safety and Efficacy of Lowering Low-Density Lipoprotein Cholesterol With Statin Therapy
20-Year Follow-Up of West of Scotland Coronary Prevention Study
Ian Fred, PhD; Heather Murray, MSc; Colin McCowan, PhD; Chris J. Packard, DSc.
Summary and Implications

- Conclusions about primary prevention of CVD:
  - Lipid lowering +/- BP lowering in primary prevention of moderate risk adults is reduced clinical events and is cost effective.
  - Statin treatment for 5 years was associated with a legacy benefit, with improved survival and a substantial reduction in cardiovascular disease outcomes over a 20-year period without signals for significant harm.
- These studies support the wider adoption of primary prevention strategies in moderate risk individuals.

Coronary Artery Calcium Score and Mortality

**Question:** How well do CAC scores predict long-term mortality in persons without symptoms of CAD?

**Design:** Observational cohort with median follow-up of 14.6 years.

**Patients:** 9715 patients without symptoms of CAD

**Outcomes:** Time to all-cause mortality
Question: Are "negative" CVD risk markers important for many medical decisions?

Design: Comparison of 13 negative risk markers:
- CAC score of 0, CIMT <25%, no carotid plaque,
- normal brachial flow-mediated dilation, normal ABI,
- hsCRP <2, homocysteine <10 μmol/L, pro-BNP <100,
- no microalbuminuria, no family history of CHD, no
- Metabolic Syndrome, and healthy lifestyle

Patients: 6814 participants from the MESA study
Outcomes: all and hard CHD and CVD events over the 10-year follow-up.
**Summary and Implications**

- Elevated CAC score is associated with increased mortality.
- CAC scores can improve reclassification of risk.
- Among all negative risk markers, CAC score of 0 was the strongest, with an adjusted mean DLR of 0.41 for CHD and 0.54 for CVD.
  - In comparison, hsCRP <2 mg/L and normal ABI had DLRs >0.80.
  - Among “clinical” features, absence of any family history of CHD was the strongest with DLRs 0.76 for CHD and 0.81 for CVD.
- CAC score, whether low or high, can be helpful in making clinical decisions about CVD risk reduction.

**Case 3:**

- Patient is a 46 yo woman with the T2DM. She is mildly obese and sedentary. She has gained more weight since changing jobs to a “desk” job. She reports being too busy with her family obligations to go to the gym but knows she should be more active.
- She is on metformin and has an A1c of 7.1%

Is her ‘inactivity’ a risk for weight gain? Will reducing her inactivity help her improve her metabolic health?
Low Physical Activity and Energy Balance

A. N = 421

B. Graph showing relationship between physical activity and energy intake.

12-mo f/u

Diabetes Care. Epub Apr 13, 2016.
Interrupting Sitting in T2DM

Question: Does interrupting prolonged sitting with brief bout of activity improve cardiometabolic risk in T2DM?

Design: randomized crossover trial of 8-hr conditions: 1) uninterrupted sitting (SIT), 2) sitting + 3-min bouts of walking (LW), and 3) sitting + 3-min bouts of resistance activities (SRA)

Patients: 24 inactive overweight/obese adults with T2DM

Outcomes: glucose, insulin and triglyceride responses


Interrupting Sitting in T2DM

Summary and Implications

• Low levels of physical activity are associated with:
  – Higher BMI, BW, fat mass
  – Reduced number of steps
  – Reduced total and activity energy expenditure
  – Higher energy intake
  – Higher disinhibition and cravings

• Threshold for achieving energy balance was at an activity level corresponding to ~7100 steps/day

• Breaking up sedentary behavior results in significant improvements in insulin sensitivity in insulin resistant individuals with T2DM
Case 4:

- Patient is a 42 yo woman who is seeking help with weight loss. She's heard a lot about low carb diets being the best diets for weight loss. She wants to know if this true and if this is a good idea for her.

Are all calories created equally?
Or does cutting carbs really do result in greater metabolic benefit and weight loss?

Carb vs Fat Restriction

Question: Do the metabolic and endocrine adaptations to carbohydrate restriction result in augmented body fat loss compared to an equal calorie reduction of dietary fat?

Design: randomized cross-over study of 6-days of 30% energy-restricted diet achieved either through selective reduction of fat (RF) or carbohydrate (RC)

Patients: 19 obese adults
1° Outcome: fat mass loss
2° Outcomes: fat and carbohydrate oxidation

Article

Calorie for Calorie, Dietary Fat Restriction Results in More Body Fat Loss than Carbohydrate Restriction in People with Obesity

In an article published in Cell Metabolism, researchers conducted a randomized cross-over study of 6-days of 30% energy-restricted diet achieved either through selective reduction of fat (RF) or carbohydrate (RC). The study included 19 obese adults and measured outcomes such as fat mass loss and fat and carbohydrate oxidation. The results showed that dietary fat restriction resulted in more body fat loss compared to carbohydrate restriction.
Carb vs Fat Restriction

Baseline
2740 kcal/d
Fat 109 g
Carb 350 g
Protein 115 g

RF
1918 kcal/d
Fat 17 g
Carb 352 g
Protein 105 g

RC
1918 kcal/d
Fat 108 g
Carb 140 g
Protein 101 g
Summary and Implications

- Findings:
  - Carb restriction results in less insulin secretion and increased fat oxidation as compared to fat restriction during reduced calorie intake.
  - Fat restriction did not reduce fat oxidation and as a result led to greater fat loss (463 g vs 245 g, p<0.0001)
  - Reduced total weight with CR likely due to glycogen depletion

- Conclusions:
  - "In contrast to previous claims about a metabolic advantage of carbohydrate restriction for enhancing body fat loss our data and model simulations support the opposite conclusion when comparing the RF and RC diets. Furthermore, we can definitively reject the claim that carbohydrate restriction is required for body fat loss..."

Case 5:

- Patient is a 56 yo man with relatively well controlled diabetes. He enjoys an occasional glass of wine or beer and asks you if this is safe and reasonable considering his diabetes. He has actually read that drinking wine might be good for his heart.

How does wine/alcohol impact metabolic health especially in those with diabetes?
Is it safe for him to consume alcohol on a regular basis?

TGIF!
Question: Does moderate alcohol intake improve cardiometabolic risk in adults with T2DM?

Design: 2-year RCT of 150 ml (~5 oz) of water, white wine or red wine with dinner

Patients: 224 alcohol abstaining adults with T2DM

1° Outcome: lipid and glycemic control profiles

2° Outcomes: genetic testing, BP, liver biomarkers, medication use, symptoms, and quality of life.

*JAMA 2015;313:677-686.

<table>
<thead>
<tr>
<th></th>
<th>Water (N=83)</th>
<th>White Wine (N=68)</th>
<th>Red Wine (N=73)</th>
<th>Effects of Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C (mg/dl)</td>
<td>1.70 (4.0%)</td>
<td>0.66 (1.5%)</td>
<td>3.6 (7.9%)*</td>
<td></td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>10.4 (7.0%)</td>
<td>1.6 (0.6%)*</td>
<td>-1.3 (-9.8%)*</td>
<td></td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>2.1 (2.2%)</td>
<td>2.2 (2.4%)</td>
<td>0.18 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>FBG (mg/dl)</td>
<td>10.3 (6.9%)</td>
<td>-7.1 (-4.6%)*</td>
<td>4.0 (2.7)</td>
<td>√</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>0.34</td>
<td>0.27</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>-0.19</td>
<td>-1.36*</td>
<td>-0.98</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>-4.8 (-3.5%)</td>
<td>1.7 (1.2%)</td>
<td>-4.3 (-3.1%)</td>
<td>√</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>-1.3</td>
<td>-1.5</td>
<td>-1.6</td>
<td></td>
</tr>
<tr>
<td>Number of MetS criteria</td>
<td>-0.01 (-0.03%)</td>
<td>-0.2 (-6.3%)</td>
<td>-0.4 (-13.3%)*</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05

• Adding a glass of wine to dinner was not associated with any safety concerns.
  – No effects on TGs, BP, LFTs, adiposity, hypoglycemia
• Red wine increased HDL-C by 8%.
• White wine reduced fasting glucose.
• Slow ethanol metabolizers had significant benefits in glycemic control (FBG, HOMA-IR, and A1c) with both wines compared with fast ethanol metabolizers.
• Fast metabolizers had greater reductions in BP.
• Sleep quality improved in both wine groups (p=0.04).
• Red wine further reduced the number of components of the metabolic syndrome by 0.34 (p=0.049).
Cheers!

???????