Management of Cardiovascular Toxicity

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Diplomate NLA

1. Understand some of the impacts on cardiovascular health related to obesity

2. Understand how different eating plans influence different CV comorbid conditions

3. Understand new exercise guidelines
Disclosures

• Speaker’s Bureau
  – Sanofi
  – Regeneron
  – Amgen

• Consultant
  – Akcea
Adipose tissue is an active organ that can become dysfunctional.
CV Consequences of Obesity

- Atherosclerosis
- Heart failure
  - Systolic and diastolic
- LVH
- Prolonged QTc
- Afib
- Not to mention indirect actors like
  - Dyslipidemia
  - Hypertension
  - Diabetes
  - OSA
  - Pulmonary htn
Proposed Mechanism for Atherosclerosis

Hindawi, Journal of Diabetes Research, Volume 2018, Article ID 3407306,
Proposed Mechanism for Heart Failure

**Figure 2: The pathomechanism of heart failure in obesity.**

- **Haemodynamic changes**
  - Cardiac output ↑
  - Blood volume ↑
  - SVR ↓

- **Myocardial fat accumulation**
- **Inflammatory cytokines**
- **Dyslipidaemia**

- **Comorbidities**
  - Diabetes mellitus
  - Sleep apnoea syndrome
  - Alveolar hypoventilation

- **Obesity**

- **Hypertension**

- **Left ventricular hypertrophy**
- **Left ventricular dilatation**

- **Obesity**

- **Myocardial fibrosis**

- **Coronary atherosclerosis**

- **Diastolic dysfunction**

- **Systolic dysfunction**

- **Pulmonary hypertension**
- **Right ventricular failure**

- **Heart failure**
Proposed Mechanism for A fib

![Diagram of proposed mechanism for atrial fibrillation in obesity]

**Figure 3:** The pathomechanism of atrial fibrillation in obesity.
# Metabolic Syndrome and Link to CVD

## Table 1. Definitions of metabolic syndrome

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Absolutely required</td>
<td>None</td>
<td>Insulin resistance* (IGT, IFG, T2D or other evidence of IR)</td>
<td>Hyperinsulinemia† (plasma insulin &gt;75th percentile)</td>
<td>Central obesity (waist circumference†): ≥94 cm (M), ≥80 cm (F)</td>
</tr>
<tr>
<td>Criteria</td>
<td>Any three of the five criteria below</td>
<td>Insulin resistance or diabetes, plus two of the five criteria below</td>
<td>Hyperinsulinemia, plus two of the four criteria below</td>
<td>Obesidad, plus two of the four criteria below</td>
</tr>
<tr>
<td>Obesity</td>
<td>Waist circumference: &gt;40 inches (M), &gt;35 inches (F)</td>
<td>Waist/hip ratio: &gt;0.90 (M), &gt;0.85 (F); or BMI &gt;30 kg/m²</td>
<td>Waist circumference: ≥94 cm (M), ≥80 cm (F)</td>
<td>Central obesity already required</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Fasting glucose ≥100 mg/dl or Rx</td>
<td>Insulin resistance already required</td>
<td>Insulin resistance already required</td>
<td>Fasting glucose ≥100 mg/dl</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>TG ≥150 mg/dl or Rx</td>
<td>TG ≥150 mg/dl or HDL-C: &lt;35 mg/dl (M), &lt;39 mg/dl (F)</td>
<td>TG ≥177 mg/dl or HDL-C &lt;39 mg/dl</td>
<td>TG ≥150 mg/dl or Rx</td>
</tr>
<tr>
<td>Dyslipidemia (second, separate criteria)</td>
<td>HDL cholesterol: &lt;40 mg/dl (M), &lt;50 mg/dl (F); or Rx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>&gt;130 mmHg systolic or &gt;85 mmHg diastolic or Rx</td>
<td>≥140/90 mmHg</td>
<td>≥140/90 mmHg or Rx</td>
<td>&gt;130 mmHg systolic or &gt;85 mmHg diastolic or Rx</td>
</tr>
</tbody>
</table>

*IGT, impaired glucose tolerance; IFG, impaired fasting glucose; T2D, type 2 diabetes; IR, insulin resistance; other evidence includes euglycemic clamp studies.

†Urinary albumin excretion of ≥20 μg/min or albumin-to-creatinine ratio of ≥30 mg/g.

‡Reliable only in patients without T2D.

§Criteria for central obesity (waist circumference) are specific for each population; values given are for European men and women. Rx, pharmacologic treatment.

Huang PL. Dis Model Mech. 2009; 2(5-6): 231-237
Metabolic Syndrome’s Effects on the Heart

- 1.58X Increase in All-Cause Mortality
- 2.35X increase in CVD
- 2.4X increase in CV death
- 1.99X increase in MI
- 2.27X increase in stroke

Salvatore M, et al, JACC vol56 no14, 2010
Vicious Cycle of Insulin Resistance

Increased Insulin Levels → Central Weight Gain → Insulin Resistance → Increased Insulin Levels
Carbohydrate-Insulin Model
Excessive anabolic drive in adipose tissue

Hunger
↓
↑Energy intake
↓Energy expenditure

Dietary carbohydrate
Insulin secretion
↓
↑Fat storage (anabolic adipose)

↓Circulating metabolic fuels (glucose, lipids)

Resting energy expenditure
↑
Muscular efficiency

Fatigue, physical inactivity

Ludwig D, JAMA int med 2018; 178(8):1098-1103
Impact of Nutritional Ketosis on Energy Metabolism

- When glucose ↓, ketones become energy for CNS (at ~4 mmol/L)
- Adaptation to ketosis takes ~2+ weeks

CPT-I = Carnitine palmitoyltransferase-I

Kirkpatrick CF et al JCL 2019 (in press)
Effects of CHO-restricted Diets on Energy Balance and Body Weight

- RCTs – substitution of fat for CHO results in ↑ energy expenditure
  - ? mechanisms
  - ? changes in catecholamines and thyroid hormone levels
- RCTs – ↓ appetite and hunger reported
  - ? mechanisms
  - ? protein content, changes in gut hormones
- Other
  - Diuretic effects (ketosis and ↓ insulin)
  - ↑ adipose tissue lipolysis
  - ↑ fat oxidation
  - ↑ metabolic costs (gluconeogenesis)
  - Thermic effect of protein

Kirkpatrick CF et al JCL 2019 (in press)
<table>
<thead>
<tr>
<th>Statement</th>
<th>Evidence Level</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A low-CHO diet (50-130 g CHO/day) or very-low-CHO/KD (~20-49 g CHO/day) is a reasonable option for some patients for a limited period of time (2-6 months) to induce weight loss.</td>
<td>IIa</td>
<td>B-R</td>
</tr>
<tr>
<td>Because low-CHO diets or very-low-CHO/KDs are difficult to maintain long-term, a more moderate CHO intake (&gt;130-225 g/day) is reasonable for longer-term (&gt;6 months) weight loss and maintenance.</td>
<td>IIa</td>
<td>B-R</td>
</tr>
</tbody>
</table>

Kirkpatrick CF et al JCL 2019 (in press)
## Key Recommendations for Cardiometabolic Risk Factors*

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>To achieve an <strong>improvement in a patient’s cardiometabolic risk factor profile</strong>, a weight reduction diet that achieves a <strong>clinically significant weight loss (5-10% of body weight)</strong> is recommended.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>As part of low-CHO and very-low-CHO diets, it <strong>is reasonable</strong> for a patient to <strong>choose unsaturated fatty acids over SFAs</strong>.</td>
<td>Ila</td>
<td>B-R</td>
</tr>
<tr>
<td>In patients with overweight or obesity with or without T2D and with elevated TG levels, a <strong>low-CHO diet is reasonable for lowering TG levels (and VLDL-C)</strong> compared to a HCLF diet.</td>
<td>Ila</td>
<td>B-R</td>
</tr>
<tr>
<td>Because <strong>substantial variation in lipid responses</strong> has been observed in patients choosing to follow low-CHO and very-low-CHO diets, <strong>baseline and follow-up lipid profiles are reasonable</strong>.</td>
<td>Ila</td>
<td>B-R</td>
</tr>
</tbody>
</table>

*Kirkpatrick CF et al JCL 2019 (in press)*
• Challenges
  – Difficult long term adherence
    • Weight loss and metabolic effects tend to regress to other diets after 6 months
  – Could lead to LBW reduction if insufficient protein intake
    • Gout
    • Kidney stones
  – Could lead to high Saturated fat intake
    • Increased LDL

Kirkpatrick CF et al JCL 2019 (in press)
The DASH diet (Dietary Approaches to Stop Hypertension) has been shown to help lower blood pressure and prevent heart disease, stroke, diabetes and even some forms of cancer. It focuses on eating more fresh fruits and vegetables.

This is a guide to how much of each food group you should eat every day, based on eating 2,000 calories per day.
Figure 1. Mean Systolic and Diastolic Blood Pressures at Base Line and during Each Intervention Week, According to Diet, for 379 Subjects with Complete Sets of Weekly Blood-Pressure Measurements.

Appel L et al, NEJM 1997 DASH
Many Trials have shown the downstream benefits of DASH diet beyond HTN

- Mitka M. DASH dietary plan could benefit many, but few hypertensive patients follow it. The Journal of the American Medical Association. 2007 Jul 11;2982, p 164-5.
- [No authors listed] One on one. What is the DASH diet? Mayo Clinic women’s healthsource. 2007 Jul;
High Triglycerides

• GISSI-Prevenzione
  – Lancet 1999
• Jelis
  – Lancet 2007
• REDUCE-IT
  – NEJM 2019

• CV benefits of supplementation with marine based omega 3s
## REDUCE-IT results

<table>
<thead>
<tr>
<th>End Point</th>
<th>Icosapent Ethyl (N=4089)</th>
<th>Placebo (N=4090)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite</td>
<td>705 (17.2)</td>
<td>901 (22.0)</td>
<td>0.75 (0.68–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Key secondary composite</td>
<td>459 (11.2)</td>
<td>606 (14.8)</td>
<td>0.74 (0.65–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular death or nonfatal myocardial infarction</td>
<td>392 (9.6)</td>
<td>507 (12.4)</td>
<td>0.75 (0.66–0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>250 (6.1)</td>
<td>355 (8.7)</td>
<td>0.69 (0.58–0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urgent or emergency revascularization</td>
<td>216 (5.3)</td>
<td>321 (7.8)</td>
<td>0.65 (0.55–0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>174 (4.3)</td>
<td>213 (5.2)</td>
<td>0.80 (0.66–0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>108 (2.6)</td>
<td>157 (3.8)</td>
<td>0.68 (0.53–0.87)</td>
<td>0.002</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>98 (2.4)</td>
<td>134 (3.3)</td>
<td>0.72 (0.55–0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Death from any cause, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>549 (13.4)</td>
<td>690 (16.9)</td>
<td>0.77 (0.69–0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>274 (6.7)</td>
<td>310 (7.6)</td>
<td>0.87 (0.74–1.02)</td>
<td>—</td>
</tr>
</tbody>
</table>

### Figure 4. Hierarchical Testing of End Points.

Shown is the prespecified plan for hierarchical testing of end points. The rates of all end points up to death from any cause were significantly lower in the icosapent ethyl group than in the placebo group.
Guidelines (HHS/AHA)

• Move more + Sit Less
• 150 to 300 minutes of moderate intensity exercise/week or 75 to 150 minutes of vigorous intensity exercise/week
• Mix of Aerobic and muscle strengthening exercises that should be spread out throughout the week
Figure 1-3. Relationship Among Moderate-to-Vigorous Physical Activity, Sitting Time, and Risk of All-Cause Mortality in Adults

Source: This heat map is adapted from data found in Ekelund U, Steene-Johannessen J, Brown WJ. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonized meta-analysis of data from more than 1 million men and women. Lancet. 2016;388:1302-1310. doi:10.1016/S0140-6736(16)30370-1.
Figure 2-1. Relationship of Moderate-to-Vigorous Physical Activity to All-Cause Mortality

Table 4-1. Examples of Different Aerobic Physical Activities and Intensities, Based on Absolute Intensity

<table>
<thead>
<tr>
<th>Moderate-Intensity Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Walking briskly (2.5 miles per hour or faster)</td>
</tr>
<tr>
<td>- Recreational swimming</td>
</tr>
<tr>
<td>- Bicycling slower than 10 miles per hour on level terrain</td>
</tr>
<tr>
<td>- Tennis (doubles)</td>
</tr>
<tr>
<td>- Active forms of yoga (for example, Vinyasa or power yoga)</td>
</tr>
<tr>
<td>- Ballroom or line dancing</td>
</tr>
<tr>
<td>- General yard work and home repair work</td>
</tr>
<tr>
<td>- Exercise classes like water aerobics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vigorous-Intensity Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Jogging or running</td>
</tr>
<tr>
<td>- Swimming laps</td>
</tr>
<tr>
<td>- Tennis (singles)</td>
</tr>
<tr>
<td>- Vigorous dancing</td>
</tr>
<tr>
<td>- Bicycling faster than 10 miles per hour</td>
</tr>
<tr>
<td>- Jumping rope</td>
</tr>
<tr>
<td>- Heavy yard work (digging or shoveling, with heart rate increases)</td>
</tr>
<tr>
<td>- Hiking uphill or with a heavy backpack</td>
</tr>
<tr>
<td>- High-intensity interval training (HIIT)</td>
</tr>
<tr>
<td>- Exercise classes like vigorous step aerobics or kickboxing</td>
</tr>
</tbody>
</table>
### Adults and Older Adults

- Lower risk of all-cause mortality
- Lower risk of cardiovascular disease mortality
- Lower risk of cardiovascular disease (including heart disease and stroke)
- Lower risk of hypertension
- Lower risk of type 2 diabetes
- Lower risk of adverse blood lipid profile
- Lower risk of cancers of the bladder, breast, colon, endometrium, esophagus, kidney, lung, and stomach
- Improved cognition*
- Reduced risk of dementia (including Alzheimer’s disease)
- Improved quality of life
- Reduced anxiety
- Reduced risk of depression
- Improved sleep
- Slowed or reduced weight gain
- Weight loss, particularly when combined with reduced calorie intake
- Prevention of weight regain following initial weight loss
- Improved bone health
- Improved physical function
- Lower risk of falls (older adults)
- Lower risk of fall-related injuries (older adults)

**Note:** The Advisory Committee rated the evidence of health benefits of physical activity as strong, moderate, limited, or grade not assignable. Only outcomes with strong or moderate evidence of effect are included in this table.

*See Table 2-3 for additional components of cognition and brain health.
Being Active Doesn’t Take Much

Exercise per week

150 minutes of moderate intensity exercise/week

- Non exercising
- Exercising
Effect of Weight Reduction on AFib

- 1415 patients
- Weight loss of >10% resulted in a 6-fold greater probability of remaining arrhythmia free
Exercise and AFib: Yes, it is good for you

- Better cardio-pulmonary fitness leads to less AFib
- Endurance sports athletes trend towards more AFib

Elliott et al. Heart Rhythm 2017; 14, 1713-1720
• Obesity has many direct and indirect effects on cardiovascular health
• A comprehensive approach to weight reduction leads to the sustained lifestyle changes needed to maintain weight and CV benefits
• Focus the interventions in a more personalized fashion based on the clinical manifestations effecting the patient
Where we are headed

Where we can go