AACE 25th Annual Scientific and Clinical Congress
Pre Congress CME

Cardiovascular Medicine for the Endocrinologist

Incorporating Metabolism into the Endocrinologist’s Practice

Yehuda Handelsman, MD, FACP, FACE, FNLA
Orlando, Wednesday, May 26, 2016

Yehuda Handelsman, MD, FACP, FACE, FNLA
Medical Director & Principal investigator
Metabolic Institute of America

IP- President
American College of Endocrinology

Program Chair & Director
14 World Congress on Insulin Resistance Diabetes & CVD
December 1-3, 2016, Los Angeles, CA

Solo practice
Endocrinology, Diabetes & Metabolism
Tarzana, California
Handelsman Disclosures

Research grant- Amgen, AZ, BMS, BI, Grifolis, Hamni, Intarcia, GSK, Lexicon, Merck, Novo Nordisk, Sanofi, Takeda.

Consultant - Amarin, Amgen, BMS, BI, diaDeux, Eisai, GSK, Janssen, LipoScience, Merck, Novo-Nordisk, Sanofi, Takeda, Vivus

Speaker’s Bureau- Amarin, Amgen, AZ, BI-Lilly, Janssen, Novo-Nordisk, Regeneron, Sanofi, Vivus

IP-President - American College of Endocrinology

Associate Editor: Journal of Diabetes

Dr. Handelsman & his immediate family do not have ownership interest & or stocks of any Pharmaceutical or device company.

Endocrinology Diabetes Metabolism

Obesity
Metabolic Syndrome/Insulin Resistance
Pre-Diabetes
Diabetes
Lipids
HTN
Hormones: Thyroid, Growth Hormone, Cortisol, Incretins
Leptin, Osteocalcin, PTH, prolactin, Oxytocin

The Endocrinologist is- The Doctor of Prevention
A Specialist in The Comprehensive approach to Cardio-Vascular Risk Reduction
The *Endocardiologist* –
The Endocrinologist as Preventive Cardiologist

**Objectives:**

Be aware of the advantage- for patients & endocrinologist- in providing comprehensive care, addressing Obesity, Metabolic Syndrome/IR Hyperglycemia, HTN, Dyslipidemia and Coagulation in the prevention and management Atherosclerosis Cardiovascular Disease


Be Educated of available procedures: C/T & EBCT calcium scoring, Multislice CT scan I.V. angiogram, MR Coronaries (as become available), advanced lipid testing, Dietary-Nutrition-education support, weight loss management & Bariatric Surgery

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**John**

**a Case History**

<table>
<thead>
<tr>
<th>Initial Visit</th>
<th>2007</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>41 y/o man referred for high BP - 157/92 mm Hg</td>
<td>46 y/o with acute MI • RCA stent • LAD 50% • LCX 30% • EF 45%</td>
<td>52 y/o CAD &amp; DM (HbA1c 8%)</td>
</tr>
<tr>
<td>Nonsmoker Sedentary</td>
<td>Adm. glucose = 340 mg/dL D/C glucose = 116 mg/dL Lipids not measured</td>
<td>Stress echo: significant for ischemia Cath: 3VD, EF 35%</td>
</tr>
<tr>
<td>BMI: 32 kg/m²</td>
<td>TC: 203 mg/dL HDL-C: 31 mg/dL TG: 230 mg/dL FG: 112 mg/dL +FH of DM</td>
<td>CABG x 3</td>
</tr>
</tbody>
</table>
Persons at target levels for HbA1c, BP, and LDL-C have substantially 60% lower risks for CVD and CHD.

Cardiovascular Disease Events are the Result of Years of Development---given the genetics and environment.
Normal Arterial Wall

Atherosclerosis and Plaque Formation (2)
Atherosclerosis and Plaque Formation (4)

Aortic Atherosclerotic Lesions: Mild, Severe, and Advanced

HDL = high-density lipoprotein


Horizontal images from Braunwald Atlas of Heart Diseases.
Diane

- 59 yrs old woman comes for second Opinion
  - Type 2 diabetes for 5 yrs
  - Denies history of cardiovascular disease
  - ROS: Fatigue, lately sleep disturbance, joint pain
  - Social: office manager, Diet- Variable; exercise- none. Married, 2 adult children. Fx Hx- DM, CKD
  - SMBG: 95–140 mg, mostly pre breakfast
  - Current medications:
    - Metformin 1000mg BID, Atorvastatin 40mg daily

Diane: Physical findings of note: BMI 32.5; Blood Pressure 138/87; H. R.- 84; Neck- acantosis nigricans

Lab Test Results

- TSH - 1.8, FT4- 1.2
- BUN- 22, Cr - 1.3
- Urinary albumin - 100 mcg/min
- ALT - 47
- A1C - 7.4%
- Lipid : TC 189 LDL 112, HDL 42, TG 175
- ECG c/w LVH
Age-adjusted Percentage of U.S. Adults with Obesity or Diagnosed Diabetes

<table>
<thead>
<tr>
<th>Year</th>
<th>Obesity (BMI ≥30 kg/m²)</th>
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<tbody>
<tr>
<td>1994</td>
<td>No Data, &lt;14.0%, 14.0-17.9%, 18.0-21.9%, 22.0-25.9%, ≥26.0%</td>
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<tr>
<td>2000</td>
<td>No Data, &lt;4.5%, 4.5-5.9%, 6.0-7.4%, 7.5-8.9%, ≥9.0%</td>
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<tr>
<td>2009</td>
<td>No Data, &lt;4.5%, 4.5-5.9%, 6.0-7.4%, 7.5-8.9%, ≥9.0%</td>
</tr>
</tbody>
</table>


Technology Progress and the Obesity Epidemic
Overweight and Obesity Increase the Risk of Cardiovascular Disease Mortality

Data are from 1 million men and women (average age, 57 years) followed for 16 years who never smoked and had no history of disease at enrollment.


Multi-Hormonal Control of Body Weight: Role Of Fat-, Gut-, and Islet-Derived Signals

Increased Rates of MI in Type 2 Diabetes
Seven Year Incidence of Fatal/Nonfatal MI


MI=myocardial infarction

Risk of CVD Is Elevated Prior to Diagnosis of Type 2 DM

Insulin Resistance Syndrome & Cardiac Risk Factors

Clinical Syndromes associated with Insulin resistance/Hyperinsulinemia

- Pediatrics
- Non Alcoholic Fatty Liver Disease (NAFLD/NASH)
- Polycystic Ovarian Syndrome (PCOS)
- Skin
- Brain
- Certain cancers
- Sleep/breathing Disorders
- Coagulation
- Dyslipidemia
- Essential Hypertension
- Chronic Kidney Disease
- Cardiovascular Disease
- Congestive Heart Failure
- Type 2 Diabetes mellitus
Clinical Manifestations of Insulin Resistance

- Insulin resistance
- Glucotoxicity
- Lipotoxicity
- ↓ Adiponectin

Atherosclerosis

- Type 2 diabetes and glycemic disorders
- Dyslipidemia
  - Low HDL
  - Small, dense LDL
  - Hypertriglyceridemia
- Hypertension
- Endothelial dysfunction/inflammation (hsCRP)
- Impaired thrombolysis
  - ↑ PAI-1

Factors Secreted by Adipose Tissue

- Adiponectin
- Resistin
- Adipsin
- Estrogen
- ANG-II
- Angiotensin
- Bone morphogenic protein
- TNF-α
- Interleukins (IL-6, IL-8)
- IGF-1
- IGFBP
- Leptin
- TNF-α
- Fatty acids
  - Lysophospholipid
  - Lactate
  - Adenosine
  - Prostaglandins
  - Glutamine
- FSH
- EGF
- TGF-β
- FGF
- CRP
- Retinol
- PAI-1
- ASP
- Leptin
- ADMA
Metabolic Syndrome

Diagnostic Criteria: 3 out of 5
- Central Obesity
- IFG
- High TG
- Low HDL-C
- HTN

Associated Conditions
- HyperCoagulability ↑ PAI-1
- ↑ Small, dense LDL-C
- Endothelial Dysfunction
- Vasculopathy
- ↑ Sympathetic nervous system activity
- ↑ Inflammation: CRP, WBC

Insulin Resistance

Obstructive
- Caused by relaxation of muscles supporting palate
- Risk factors
  - Obesity
  - Hypertension
  - Male gender
  - Neck circumference >44 cm
  - Narrowed airway
  - Age
  - Family history
  - Alcohol, sedative use
  - Smoking

Central
- Caused by neural signaling failure between brain and muscles surrounding lungs
- Risk factors
  - CHF
  - Atrial fibrillation
  - Cerebrovascular disease
  - Brain tumor

Can be found at: http://www.medscape.com(px/urlinfo

Prevalence of Sleep Apnea in T2DM

Sleep AHEAD Study Obese Patients With T2DM (N=305)

OSA, obstructive sleep apnea.

PAI-1 Levels and Glucose Tolerance

Reproduced with permission from Lippincott, Williams and Wilkins.
Increased Coronary Artery Calcification in PCOS

ECAC = Epidemiology of Coronary Artery Calcification Study

Christian RC, JCEM, 2003

Long-term Complications of Diabetes
Consequences of Sustained Hyperglycemia

Diabetic Retinopathy
Leading cause of blindness in working age adults

Diabetic Nephropathy
Leading cause of end-stage renal disease

Cardiovascular Disease
2-fold to 4-fold increase in cardiovascular events and mortality

Diabetic Neuropathy
Leading cause of nontraumatic lower extremity amputations

Diabetes Retinopathy
Stroke

Microvascular Complications of Diabetes

Nephropathy  Retinopathy  Neuropathy

Prevalence of Diabetes Macrovascular and Microvascular Complications

- In NHANES, "chronic kidney disease" refers to people with microalbuminuria (albumin:creatinine ratio >30 µg/mg).
- In the NHANES analysis, "foot problems" includes foot/toe amputations, foot lesions, and numbness in the feet.
- "Eye damage" includes a positive response by NHANES participants to the question, "Have you been told diabetes has affected your eyes/had retinopathy?" Retinopathy is damage to the eye's retina. In NHANES, people without diagnosed diabetes were not asked this question, therefore, prevalence information for nondiabetics is not available.

Every Single Day in the United States….

- 4,100 new cases of diabetes are diagnosed
- 230 people have a diabetes-related amputation
- 120 people with diabetes progress to end-stage renal disease
- 66 people with diabetes become blind

Causes of Death in Diabetic Autonomic Neuropathy

- Sudden unexplained
- Cardiac arrhythmia
- Silent myocardial infarction
  - More likely to die of heart attack
  - Greater incidence of cardiac failure
- Aspiration pneumonia
- Ulcers, amputations, gangrene
- Chronic renal failure

Accessed April 13, 2009
Risk Factors for Diabetic Microvascular Complications (DMC)

<table>
<thead>
<tr>
<th>Modifiable</th>
<th>Diabetic Peripheral Neuropathy</th>
<th>Diabetic Retinopathy</th>
<th>Diabetic Nephropathy</th>
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<tbody>
<tr>
<td>• Hyperglycemia</td>
<td>• Hyperlipidemia</td>
<td>• Hyperglycemia</td>
<td></td>
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<tr>
<td>• Hyperlipidemia</td>
<td>• Smoking</td>
<td>• Hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>• Smoking</td>
<td>• Alcohol intake</td>
<td>• Weight</td>
<td></td>
</tr>
<tr>
<td>• Alcohol intake</td>
<td>• Hypertension</td>
<td>• Hypertension</td>
<td></td>
</tr>
<tr>
<td>• Hypertension</td>
<td></td>
<td>• Weight</td>
<td></td>
</tr>
</tbody>
</table>

Algorithm for Managing Microvascular Complications of Type 2 Diabetes

**Screening/prevention**

- **Retinopathy**
  - Annual exam
  - Dilated exam
  - Retinal vessels
  - Cataract
  - Intraocular pressure

- **Nephropathy**
  - Annual microalbumin
    - Screen urine albumin
    - Repeat to confirm
    - Measure serum creatinine at least annually and calculate estimated GFR

- **Neuropathy**
  - Comprehensive foot exam
    - Inspection
    - Vascular (pulses, ABI)
    - Vibratory perception
    - Monofilament sensation

**Treatment priorities**

- Glucose control
- Hypertension
- ACE inhibitor
- Glucose control
- Hypertension
- ACE inhibitor or ARB
- Glucose control
- Foot care/foot wear

Challenges in the Treatment of Patients With Type 2 Diabetes

- Goals for CV risk especially LDL-C, A1C & HTN have become more stringent, complicated and difficult to achieve.\(^1\)
- Add-on therapy is an increasing part of an intensive approach to therapy.\(^2\)
- CV risks — elevated A1C and LDL-C as well as HTN — represent commonly associated conditions that increase overall cardiovascular risk and the treatment imperative.\(^3\)

- **Global Control**— addressing A1C, LDL-C, HTN & coagulopathy, matters

LDL-C = low-density lipoprotein cholesterol;
A1C = glycosylated hemoglobin.


Individualized Comprehensive Goals For Diabetes

**A1C Goals**

≤6.5% for most; provided safely

<6.5% (5%) As close to health (normal) for new, relatively young, healthy; provided safely

≥7% (7.5/8.5 % - glucose?) Less stringent for “less healthy” — multiple co-morbidities, labile, short life expectancy

**Blood Pressure:** 130/80 - General; 120/80 with CKD or stroke risk; >140/90 - Hypotension/dizzy Risk

**Lipids:** < 100 – General risk; < 70 – High risk
Diane: Obesity

BMI: 32.5

Treatment: None
Consider: Lifestyle & Intervention (?)

Weight Change and Mortality in Diabetes

Intentional loss resulted in a relative risk reduction† of:
- 22% ↓ all-cause death
- 24% ↓ death from CVD + diabetes

*Mortality rates are directly age-standardized to the age distribution of the cohort and expressed per 1000 person-years.
†Adjusted for age, sex, initial BMI.

Consider Long term management with Pharmaceutical Intervention

Effects of Phentermine/Topiramate ER in Advanced T2DM

Poorly Controlled Type 2 Diabetes

**Weight**

- Placebo (n=55)
- Phen/TPN 15/92 mg (n=75)

**Glucose Control**

- Baseline Mean A1C (%)
  - Placebo (n=55): 8.6
  - Phen/TPN 15/92 mg (n=75): 8.8

- LS Mean ΔA1C (%)
  - Placebo (n=55): -1.13
  - Phen/TPN 15/92 mg (n=75): -1.61

- Change in diabetes medications (score)
  - Placebo (n=55): 30
  - Phen/TPN 15/92 mg (n=75): -16

*P=0.038 vs placebo.
† Net score reflecting change in medication number and change in dose level of diabetes medications.

Effect of Lorcaserin in Type 2 Diabetes
BLOOM-DM Study

Weight

Baseline Mean ΔA1C (%)

-1.5

Patients Increasing Use of Antidiabetic Agents (%)

Baseline

Placebo (n=248)
Lorcaserin 10 mg BID (n=251)
Lorcaserin 10 mg QD (n=95)

Glucose Control

Baseline Mean A1C (%)

8.0
8.1
8.1

Diane : Lipid Control

TC : 189
LDL : 112
HDL : 42
TG : 175

Med: Atorvastatin 40mg
Consider: Combination Medication: Ezetimibe, PCSK9i, Omega 3 Fish oil, Fibrates

*P<0.001 vs placebo, †P=0.087 vs placebo.
‡Mean A1C from 95 patients in lorcaserin 10 mg QD group.
BLOOM-DM, Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus.
Outcomes in Fibrate Trials: Diabetic or Metabolic Syndrome Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Control</th>
<th>Drug</th>
<th>RRR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHS*</td>
<td>292</td>
<td>13.0%</td>
<td>3.9%</td>
<td>71%</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>FIELD†</td>
<td>7664</td>
<td>10.8%</td>
<td>8.9%</td>
<td>19%</td>
<td>.004</td>
</tr>
<tr>
<td><strong>Secondary Prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIP‡</td>
<td>1470</td>
<td>18.4%</td>
<td>14.1%</td>
<td>25%</td>
<td>.03</td>
</tr>
<tr>
<td>VA-HIT§</td>
<td>769</td>
<td>29.4%</td>
<td>21.2%</td>
<td>32%</td>
<td>.004</td>
</tr>
</tbody>
</table>

RRR, relative risk reduction

* Patients with TG >204 mg/dL and an LDL/HDL >5 (may or may not have had DM or the MS)
† Patients with diabetes and no prior CVD
‡ Patients with the metabolic syndrome
§ Patients with diabetes


ARBITER 2:
HDL-C↑18% (p=0.002); TG ↓10% (p=0.03); No change in LDL

Baseline Carotid IMT

Δ Carotid IMT After 1 Year

*Within-group comparisons.

Diane: Blood Pressure Control

BP: 138/87

Urinary albumin: 100 mcg/min

Med: None

Consider: ACE or ARB

UKPDS: Blood Pressure Control in Type 2 DM

Effect of Intensive BP Lowering on Risk of Micro- & Macrovascular Complications

Benefits of 144/82 vs 154/87

Mean Systolic Blood-Pressure Levels at Each Study Visit

Primary and Secondary Outcomes

Table 3. Primary and Secondary Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Therapy (N = 2363)</th>
<th>Standard Therapy (N = 2371)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome&lt;sup&gt;*&lt;/sup&gt;</td>
<td>208</td>
<td>237</td>
<td>2.09</td>
<td>0.88</td>
</tr>
<tr>
<td>Prespecified secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>126</td>
<td>146</td>
<td>1.28</td>
<td>0.87</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>36</td>
<td>62</td>
<td>0.53</td>
<td>0.59</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>34</td>
<td>55</td>
<td>0.47</td>
<td>0.63</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>150</td>
<td>144</td>
<td>1.19</td>
<td>1.07</td>
</tr>
<tr>
<td>From cardiovascular cause</td>
<td>60</td>
<td>58</td>
<td>0.49</td>
<td>1.06</td>
</tr>
<tr>
<td>Primary outcome plus revascularization or nonfatal heart failure</td>
<td>521</td>
<td>551</td>
<td>5.31</td>
<td>0.95</td>
</tr>
<tr>
<td>Major coronary disease event†</td>
<td>253</td>
<td>270</td>
<td>2.41</td>
<td>0.94</td>
</tr>
<tr>
<td>Fatal or nonfatal heart failure</td>
<td>83</td>
<td>90</td>
<td>0.78</td>
<td>0.94</td>
</tr>
</tbody>
</table>

<sup>*</sup> The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

† Major coronary disease events, as defined in the protocol, included fatal coronary events, nonfatal myocardial infarction, and unstable angina.
Diane: Glycemic Control

A1C: 7.4%

Med: Metformin 1000 BID
Consider: Combination Med

Epidemiologic Relationships Between A1c and All-cause Mortality in the ACCORD Trial
Does A1C achieved predict a risk for all-cause mortality?

**CHD Events**

Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials

Kapil K Roy, Sreenivas Rao Kondapally Sehassai, Shanelle Wijesuriya, Rupa Sivakumaran, Sarah Nethercott, David Preiss, Sebastian Ergas, Naveed Sattar

Lancet 2009; 373: 1765–72

<table>
<thead>
<tr>
<th>Intensive treatment/standard treatment</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
<th>Odds ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Participants</td>
<td>Events</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>LRPDS</td>
<td>3071/1549</td>
<td>466/233</td>
<td>8.6%</td>
</tr>
<tr>
<td>PROactive-3</td>
<td>2505/1253</td>
<td>164/202</td>
<td>20.2%</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>5571/3569</td>
<td>310/337</td>
<td>36.5%</td>
</tr>
<tr>
<td>VADT</td>
<td>892/899</td>
<td>77/90</td>
<td>9.0%</td>
</tr>
<tr>
<td>ACCORD</td>
<td>3118/3122</td>
<td>205/248</td>
<td>25.7%</td>
</tr>
<tr>
<td>Overall</td>
<td>17267/15773</td>
<td>1192/1136</td>
<td>100%</td>
</tr>
</tbody>
</table>

Intensive treatment better Standard treatment better

---

**Large Non-Insulin CVOTs in T2DM**

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARMELENA</th>
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<tbody>
<tr>
<td>DPP4-i</td>
<td>saxagliptin</td>
<td>alogliptin</td>
<td>sitagliptin</td>
<td>linagliptin</td>
<td>linagliptin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>8,300</td>
<td>7,400</td>
<td>6,000</td>
<td>8,300</td>
<td></td>
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<tr>
<td>Results</td>
<td>2013</td>
<td>2013</td>
<td>June 2015</td>
<td>2017</td>
<td>2017</td>
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</tbody>
</table>

- NEUTRAL
- POSITIVE

<table>
<thead>
<tr>
<th>Study</th>
<th>LEADER</th>
<th>ELIXA</th>
<th>SUSTAIN 6</th>
<th>EXSCEL</th>
<th>REWIND</th>
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<tbody>
<tr>
<td>GLP1-RA</td>
<td>liraglutide</td>
<td>lixisentide</td>
<td>semaglutide</td>
<td>exenatide LR</td>
<td>dulaglutide</td>
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<td>Comparator</td>
<td>placebo</td>
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<td>N</td>
<td>16,500</td>
<td>19,800</td>
<td>6,000</td>
<td>5,400</td>
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<tr>
<td>Results</td>
<td>2016</td>
<td>2015</td>
<td>2016</td>
<td>2018</td>
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- NEUTRAL
- POSITIVE

<table>
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<tr>
<th>Study</th>
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<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>7,300</td>
<td>4,300</td>
<td>22,200</td>
<td>3,900</td>
</tr>
<tr>
<td>Results</td>
<td>Sept 2015</td>
<td>2017</td>
<td>2019</td>
<td>2020</td>
</tr>
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</table>
CHICAGO: Treatment effect on posterior wall CIMT


Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (10-year CVD risk 5%, i.e. men 50 & women 60 with no additional CVD risk), since the potential adverse effects from bleeding likely offset the potential benefits.
Global Approach: CVD Risk in Diabetes

<table>
<thead>
<tr>
<th>Potential Target</th>
<th>Potential Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP reduction</td>
<td>25-40% (ACEI/ARB/Thiazide)</td>
</tr>
<tr>
<td>LDL-c reduction</td>
<td>20-370% (Statin)</td>
</tr>
<tr>
<td>HDL-c and TG</td>
<td>10-20% (Fibrate, niacin)</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>20-30% (ASA in 2º prevention)</td>
</tr>
<tr>
<td>Glucose lowering</td>
<td>Neutral – up to 10-15%</td>
</tr>
<tr>
<td>Stop Smoking</td>
<td>25-35%</td>
</tr>
</tbody>
</table>

Does it Work?

Steno-2 Study: Reduction in CV and Microvascular Disease

Reductions After 7.8 Years of Intensive vs Conventional Rx

<table>
<thead>
<tr>
<th>Percent</th>
<th>CV Disease</th>
<th>Nephropathy</th>
<th>Retinopathy</th>
<th>Autonomic Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-58</td>
<td>-57</td>
<td>-56</td>
<td>-62</td>
</tr>
</tbody>
</table>

**Steno-2: Effects of Multifactorial Intervention on CV Outcomes**

N = 160 with type 2 diabetes and microalbuminuria

Primary composite outcome* (%)

Follow-up (months)

53% risk reduction

Conventional

Intensive

*CV death, MI, stroke, revascularization, amputation


---

**Steno-2: 13 year mortality**

Cumulative Incidence of Death (%)

Years of Follow-up

Conventional therapy

Intensive therapy

P=0.02

50%

6.3%

2.8%

30%

Summary - Diabetes Complications

- The obesity epidemic contributes to diabetes & CVD epidemics
- Target multiple conditions to reduce risk
- Utilize lifestyle modification for prevention & treatment
- Institute intensive treatment for glycemic control
- Benefit of LDL-lowering treatment in diabetic patients
- Benefit of ACE/ARB in HTN in Diabetes
- Consider comprehensive care of all risk factors, with combination medications, to reduce CVD & complication

Noninvasive Tests

Anthropometric Measures
Exercise Stress Tests
Ankle-Brachial Index
Cardiac Computed Tomography
Cardiac Magnetic Resonance
Anthropometric Measures

- BMI (kg/m²)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≤0.95</td>
<td>≤0.80</td>
</tr>
<tr>
<td>Overweight</td>
<td>0.96-1.0</td>
<td>0.81-0.85</td>
</tr>
<tr>
<td>High</td>
<td>&gt;1.0</td>
<td>&gt;0.85</td>
</tr>
</tbody>
</table>

*Measured with nonstretchable tape measure. Waist measured by placing tape around unclothed abdomen at the narrowest point between the costal margin and iliac crest. Hips measured over light clothing at the level of greatest circumference around the buttocks. The figure above shows the proper placement of the tape.

BMI = body mass index.


Stress Testing

- Exercise ECG stress testing
  - Least expensive, but less accurate, particularly in women and asymptomatic people
- Echocardiography
  - Ability to visualize cardiac structures, but imaging is suboptimal in very obese patients with COPD. This has recently been significantly affected by the use of contrast agents, which make analysis of many previously nondiagnostic studies much more accurate
- Nuclear stress testing
  - Most expensive and creates images of very low resolution
  - Direct measurement of perfusion
  - May have added prognostic value in women
Cardiac Stress Tests: Exercise ECG

Predicts risk for CVD events in men without CVD symptoms\(^1,2\)

A. Survival free of CHD in high-risk men according to the presence of ST-segment depression. yellow = absent, white = present.
B. Survival free of CHD in high-risk men according to achievement of THR. yellow = achieved THR; white = failed to achieve THR.
C. Survival free of CHD in high-risk men according to exercise capacity. yellow = median METs or higher; white = less than median METs.\(^1\)

MET = metabolic equivalent of the task.

Exercise ECG (Cont’d)

- Single-vessel disease is less likely to be detected than multivessel disease, and 2-vessel disease less likely than 3-vessel\(^1\)
- Used in conjunction with pretest probability based on risk factors and symptoms
  - According to ACC/AHA guidelines, diagnostic value may be greatest for those with intermediate pretest probability\(^1\)
  - In a Framingham offspring cohort study, prognostic value was greatest for men in the highest-risk group\(^2\)
- Inability to exercise to 10 METs indicates a poorer overall prognosis
- For asymptomatic women, the exercise capacity and heart rate, but not the exercise ECG (ST-segment depression), appear to predict cardiovascular and all-cause mortality\(^3\)

Cardiac Stress Tests: Echo Stress Test

- Less expensive than nuclear stress testing
- Widely available because echo machines are portable
- Gives additional information about the structures within the heart, LV wall thickness, LV function assessed as wall motion
- New echo contrast agents may provide more direct information about perfusion
- Has incremental risk-predicting value above clinical, exercise, and resting echocardiographic variables


Cardiac Stress Tests: Nuclear Stress Test

- Higher sensitivity (but lower specificity) than stress echocardiography
  - Single-vessel disease detection sensitivity of myocardial perfusion is 76% (vs. 67% for stress echo)
  - Gated SPECT enhances specificity

SPECT = single-photon emission computed tomography.
Peripheral Arterial Disease

- Atherosclerosis generally begins in the abdominal aorta and ascends to involve the aortic arch and the coronary arteries, as well as the carotid arteries.
- The location of plaque, either in the coronary arteries or in the carotids, determines the clinical impact (heart attack vs stroke).
- The most widely employed clinical tests for PAD include carotid ultrasound, ABI, and abdominal ultrasound, looking primarily for abdominal aortic aneurysms.
  - ABI is also an effective clinical tool in assessing generalized cardiovascular risk.

Ankle-Brachial Index

- Ratio of ankle to arm systolic blood pressure (SBP)
  - ABI ≤0.90 indicates peripheral artery disease\(^1\)\(^-\)\(^3\)
- 1592 randomly selected older adults (55 to 74 years)\(^3\)
  - ABI ≤0.90 at baseline added predictive value for fatal MI
- ABI is useful to refine the assessment of intermediate-risk patients ≥50 years old\(^1\),\(^2\)

“Imaging has at least 3 virtues”

Once subclinical atherosclerosis is detected, intensity of drug therapy could be adjusted for plaque burden


Noninvasive Screening – Carotid Intima-Media Thickness (CIMT)

• CIMT measured by carotid artery ultrasound\(^1\)
  - SHAPE Task Force: Warranted for screening asymptomatic men 45 to 75 years old and women 55 to 75 years old who are not in the category of very low cardiovascular risk

SHAPE = Screening for Heart Attack Prevention and Education.
What is Carotid Intima-media Thickness (CIMT)?

Normal and diseased arterial histology

Which site? CCA, ICA, bulb
CCA most reproducible
ICA/Bulb:
Plaque
Greater magnitude of change
Computer-assisted
1 cm longitudinal measurement
Easy- takes minutes
Accurate- .0x mm
Noninvasive Screening – Coronary Artery Calcium Score (CACS)

Relationship between CACS and the baseline Framingham risk score in the prediction of coronary death or nonfatal MI*

<table>
<thead>
<tr>
<th>CACS</th>
<th>0</th>
<th>1-100</th>
<th>101-300</th>
<th>≥301</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-15</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>16-20</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥21</td>
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</table>

Framingham Risk Score, %

*Hazard ratio by bivariate Cox regression analysis. Risk categories are the estimated 10-year risk for coronary death or MI based on the Framingham risk score. The CACS is measured by coronary computed tomography (CCT).


CT angiographic image showing severe left circumflex coronary artery stenosis and 2 areas of calcification.

Heart with extensive calcification and plaque build-up.
Ultrafast Electron Beam Computed Tomography

- Commonly used for CCT ("heart scan")
- Provides very rapid scanning times, 3-D capability; eliminates motion artifacts
- EBCT-determined CACS accurately predicts CAD death, nonfatal MI, and need for coronary revascularization
- SHAPE Task Force recommends CCT for patients 45 (men) or 55 (women) to 75 years old at any estimated risk level above very low
  - ACCF, however, recommends CCT screening only for high-risk patients

\[3-D = \text{three-dimensional}; \ A0 = \text{ascending aorta}; \ PA = \text{pulmonary artery}; \ LAD = \text{left anterior descending}; \ LA = \text{left atrium.}\]


Multislice Computed Tomography

- Several synonyms: multislice, multidetector, spiral, multirow CT
- Conventional CT using fast multidetector scanners
- Validated alternative to EBCT for coronary calcium detection
- Also used for:
  - Diagnostic CT angiography
    - May be limited by large number of nonevaluable cases and high false-positive rate
  - Image-guided interventional procedures and therapy

Cardiac Magnetic Resonance Imaging

- Noninvasive two- or three-dimensional imaging technique based on proton magnetic properties of tissue structures
- Used to assess atherosclerosis and other cardiac disease (congenital heart disease, pericardial disease)

Three-dimensional magnetic resonance image of coronary artery, postmortem

SAMPLE TESTS REIMBURSEMENT

CXR: 30.22
• EKG 18.40
• Treadmill 140.16
• Cardiac Echo: 252.00
• Carotid US: 230.27 Cash-300
• ABD U/S 135.47
• Arterial LE 216.67
• Thyroid u/s/ 118.93
• Dexe/%Fat 50.00 / Cash 100-200
• Sleeping Test: 238.78
• Aorta US: 116.48

• POTENTIAL OTHER TESTS: Stress Echocardiogram *
Renal Arteries US * Lower Extremities (Duplex) Veins