Treatment of Chronic Coronary Atherosclerosis

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The E. Wolfson Medical Center

CME course, Cesaria 2010
OUTLINE

- Pathophysiology
  - Atherosclerosis
  - Ischemia

- Primary prevention – who should be treated

- Therapy
  - Lifestyle
  - Pharmacology
  - Revascularization
Atherosclerosis Timeline

- Foam Cells
- Fatty Streak
- Intermediate Lesion
- Atheroma
- Fibrous Plaque
- Complicated Lesion/Rupture

Endothelial Dysfunction

- From First Decade
- From Third Decade
- From Fourth Decade

Adapted from Pepine CJ. *Am J Cardiol.* 1998;82(suppl 104).
The Glagov Concept
Atherosclerosis progression and luminal narrowing

Similar luminal area despite marked variation in the volume of atheroma due to compensatory enlargement of the artery

Glagov S et al NEJM 316:1371, 1987,
Oxygen Supply
myocardium vs other tissues

- O\textsubscript{2} Delivery
  - Coronary Blood Flow
  - Hemoglobin
  - Arterial O\textsubscript{2} saturation
- Myocardial (A-V) O\textsubscript{2} Difference

- In resting condition coronary sinus blood is desaturated thus oxygen supply to the myocardium during conditions of increased demand is dependent on coronary blood flow.
Impact of diameter stenosis on resting and maximal coronary flow (flow reserve)

- Normalized resting flow
- Normalized flow reserve
Mechanism of stress induced perfusion mismatch

Limited coronary flow reserve (CFR) in the territory supplied by the stenotic artery causing perfusion mismatch.
Fractional Flow Reserve in Clinical Practice

**REST**

**HYPEREMIA**

Crossing the lesion

Distal to the lesion

FFR = 58/112 = 0.52
Consequences of Acute Coronary Ischemia

- Typically causes ECG changes, myocardial dysfunction (diastolic and systolic) and symptoms of chest pain.
- Causes prolonged dysfunction (stunning, occasional repetitive)
- Magnitude of effect modified by adaptive mechanisms (smart heart)
  - Hibernation (adaptation of mechanical function to flow limitation)
  - Preconditioning (protection from future ischemia by past ischemic episodes)
Unusual Presentations of Chronic Angina – Current Understanding

- Diurnal variation of angina
  - Coronary tone, preconditioning
- Angina disappears during walking
  - Coronary tone, preconditioning
- Prolonged fatigue after exertion
  - Myocardial stunning
- CHF symptoms without previous MI
  - Hibernation (repetitive stunning)
OUTLINE

- Pathophysiology
  - Atherosclerosis
  - Ischemia
- Primary prevention – who should be treated
- Therapy
  - Lifestyle
  - Pharmacology
  - Revascularization
בן 55IAS ye 'in:y, uN sIpoR meSHUKHShi hEt MAhLa tLeb
LDL=125mg/dl

leHMa MoMLeL laHetHUL tiSipol bSSetShi?

1. Kay
2. Le

lYi BRIMAT hesiKoN (ShenKBeSha ul PI GorMi hesiKoN)

3. BEncR hMIzra heMTeMiM ShI LDL

4. lYi BRIMAT MeBHoN MeAMShI / MiFiN (AIKo) TeKhes

5. Le

6. lYi BRIMAT meYizBeT BClLi DI-M – BeDIkEt HeDMi

leHMa BRIMAT CRP

shI TeRShT
Assessing CHD Risk in Men - Framingham

### Step 1: Age

<table>
<thead>
<tr>
<th>Years</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td>20-34</td>
<td>-9</td>
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<tr>
<td>35-39</td>
<td>-4</td>
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<tr>
<td>40-44</td>
<td>0</td>
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<tr>
<td>45-49</td>
<td>3</td>
</tr>
<tr>
<td>50-54</td>
<td>6</td>
</tr>
<tr>
<td>55-59</td>
<td>8</td>
</tr>
<tr>
<td>60-64</td>
<td>10</td>
</tr>
<tr>
<td>65-69</td>
<td>11</td>
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<tr>
<td>70-74</td>
<td>12</td>
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<tr>
<td>75-79</td>
<td>13</td>
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### Step 2: Total Cholesterol

<table>
<thead>
<tr>
<th>TC at (mg/dL)</th>
<th>Points at Age 20-39</th>
<th>Points at Age 40-49</th>
<th>Points at Age 50-59</th>
<th>Points at Age 60-69</th>
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<tbody>
<tr>
<td>&lt;160</td>
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<td>0</td>
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<tr>
<td>160-199</td>
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<td>3</td>
<td>2</td>
<td>1</td>
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<tr>
<td>200-239</td>
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<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>240-279</td>
<td>9</td>
<td>6</td>
<td>4</td>
<td>2</td>
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### Step 3: HDL-Cholesterol

<table>
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<tr>
<th>HDL-C (mg/dL)</th>
<th>Points</th>
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<td>≥60</td>
<td>-1</td>
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<tr>
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<tr>
<td>40-49</td>
<td>1</td>
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<tr>
<td>&lt;40</td>
<td>2</td>
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### Step 4: Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Systolic BP (mm Hg)</th>
<th>Points if Untreated</th>
<th>Points if Treated</th>
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<tbody>
<tr>
<td>&lt;120</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>120-129</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>130-139</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>140-159</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>≥160</td>
<td>2</td>
<td>3</td>
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### Step 5: Smoking Status

<table>
<thead>
<tr>
<th>Age (points)</th>
<th>Points at Age 20-39</th>
<th>Points at Age 40-49</th>
<th>Points at Age 50-59</th>
<th>Points at Age 60-69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmoker</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Smoker</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

### Step 6: Adding Up the Points

<table>
<thead>
<tr>
<th>Points Total</th>
<th>10-Year Risk</th>
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<tr>
<td>&lt;0</td>
<td>&lt;1%</td>
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<tr>
<td>1</td>
<td>1%</td>
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<tr>
<td>2</td>
<td>1%</td>
</tr>
<tr>
<td>3</td>
<td>1%</td>
</tr>
<tr>
<td>4</td>
<td>1%</td>
</tr>
<tr>
<td>5</td>
<td>2%</td>
</tr>
<tr>
<td>6</td>
<td>2%</td>
</tr>
<tr>
<td>7</td>
<td>3%</td>
</tr>
<tr>
<td>8</td>
<td>4%</td>
</tr>
<tr>
<td>9</td>
<td>5%</td>
</tr>
<tr>
<td>10</td>
<td>6%</td>
</tr>
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</table>

### Step 7: CHD Risk

<table>
<thead>
<tr>
<th>Risk</th>
<th>Point Total</th>
<th>10-Year Risk</th>
<th>Point Total</th>
<th>10-Year Risk</th>
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<tbody>
<tr>
<td>&lt;0</td>
<td>11</td>
<td>8%</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>16%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>20%</td>
<td></td>
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<tr>
<td>4</td>
<td>16</td>
<td>25%</td>
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<tr>
<td>5</td>
<td>17</td>
<td>28%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>30%</td>
<td></td>
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<tr>
<td>7</td>
<td>19</td>
<td>33%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>35%</td>
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<td></td>
</tr>
<tr>
<td>9</td>
<td>21</td>
<td>38%</td>
<td></td>
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</tr>
<tr>
<td>10</td>
<td>22</td>
<td>40%</td>
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</tbody>
</table>

Note: Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA.

Risk subgroups

- **LOW RISK** designated as <0.6% CHD risk per year (<6% in 10 years)
- **INTERMEDIATE RISK** designated as a CHD risk of 0.6%-2.0% per year (6-20% over 10 years)
- **HIGH RISK** designated as a CHD risk of >2% per year (20% in 10 years) (CHD risk equivalent), including those with CVD, diabetes, and PAD

Target LDL and need for statin is determined by level of risk
How Good Is NCEP III At Predicting MI in young?

222 patients with 1st acute MI, no prior CAD
men <55 y/o (75%), women <65 (25%), no DM

- High Risk: 12%
- Intermediate Risk: 18%
- Low Risk: 70%

High Risk Would qualify for statin

Akosah Et al, JACC 2003:41 1475-9
First Presentation is Frequently Sudden Death
might be preventable with early therapy

Myocardial infarction (MI) or death as initial presentation of CAD

- Men: 62%
- Women: 46%

What should be done?
Who should be started on statin RX

- Everyone > 50 years old
- Only those at high risk for event

- Risk predictors:
  - Calcium Score (CAC)
  - Carotid Intima–Media Thickness (CIMT)
  - C Reactive Protein (CRP)
How Is the Coronary Artery Calcium (CAC) Score Calculated?

- Peak density and area in each location, in each coronary artery, are measured.

CAC score = total of area and density of each calcified lesion

<table>
<thead>
<tr>
<th>Hn x-factor (Agatston Scoring)</th>
<th>130-199</th>
<th>200-299</th>
<th>300-399</th>
<th>&gt;400</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Images courtesy of Alan B. Zelinger, MD.
Coronary Artery Calcium (CAC) Score Can Predict Risk-Unadjusted All-Cause Mortality

What is Carotid Intima–Media Thickness (CIMT)?

Normal and Diseased Arterial Histology

[Diagram of carotid artery bifurcation showing flow divider, internal carotid, external carotid, common carotid, and skin surface.]
What is Carotid Intima–Media Thickness (CIMT)?

Mean CIMT 1.174 mm
Carotid Disease as a Marker of Cardiovascular Risk: MI or Stroke


<table>
<thead>
<tr>
<th>Years</th>
<th>Cumulative Event-Free Rate (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>N=4476</td>
</tr>
<tr>
<td>1</td>
<td>1st Quintile IMT</td>
</tr>
<tr>
<td>2</td>
<td>2nd Quintile IMT</td>
</tr>
<tr>
<td>3</td>
<td>3rd Quintile IMT</td>
</tr>
<tr>
<td>4</td>
<td>4th Quintile IMT</td>
</tr>
<tr>
<td>5</td>
<td>5th Quintile IMT</td>
</tr>
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</table>

N=4476
CVD Risk in the Women’s Health Study According to Quintiles of CRP

Ridker PM et al. N Engl J Med 2002;347:1557-1565. Copyright 2002 Massachusetts Medical Society. All rights reserved.
Predictive utility of a screening test

- When making decisions about the predictive utility of new tests, the focus is not on relative risks.
- Rather, the best measure of the additional utility of a new test is to be found in comparing the areas under receiver operating characteristic curves (AUC).
ROC Curve, its AUC and Corresponding Odds Ratio

MESA Study – 6,814 Patients: 3.5 year follow-up

Risk of Coronary Events Associated with Increasing CAC after Adjustment for Standard Risk Factors

Fully adjusted – Detrano et al– NEJM 2008
The 1st S.H.A.P.E. Guideline
Towards the National Screening for Heart Attack Prevention and Education (SHAPE) Program

Apparantly Healthy Population Men>45y Women>55y

Step 1

Very Low Risk

Exit

Exit

All >75y receive unconditional treatment

Coronary Calcium Score (CCS)

Carotid IMT (CIMT) & Carotid Plaque

Atherosclerosis Test

Step 2

Negative Test

- CCS =0
- CIMT<50th percentile

No Risk Factors

+ Risk Factors

Positive Test

- CCS ≥1
- CIMT ≥50th percentile or Carotid Plaque

Step 3

Lower Risk

<160 mg/dl

5-10 years

Follow Existing Guidelines

Angiography

Myocardial Ischemia Test

Moderate Risk

<130 mg/dl

<100 Optional

Individualized

High Risk

<130 mg/dl

<100 mg/dl

<70 Optional

Individualized

Moderately High Risk

<100-399 or ≥75th%

CIMT ≥1mm or ≥75th%

<50% Stenotic Plaque

≥50% Stenotic Plaque

Very High Risk

≥100 & >90th%

CIMT ≥400

≥50% Stenotic Plaque

ABI<0.9

CRP>4mg/Optional

1: No history of angina, heart attack, stroke, or peripheral arterial disease.
2: Population over age 75y are considered high risk and recommended to receive therapy without risk assessment.
3: Must have all of the following Cho<200 mg/dl + blood pressure ≤120/80 mmHg + no diabetes + no smoking + no family history + no metabolic syndrome.
4: Pending standard practice guidelines
5: One or more risk factor: high cholesterol, high blood pressure, diabetes, smoking, family history, metabolic syndrome.
6: For stroke prevention, follow existing guidelines.
Most Myocardial Infarctions Are Caused by Low-Grade Stenoses:

Coronary stenosis severity prior to MI

- >70% Stenosis: 14%
- 50%-70% Stenosis: 18%
- <50% Stenosis: 68%


Failure rate of primary and secondary prevention is high even with statin therapy
Prediction and Prevention: The Vulnerable Plaque

➢ Project Goal: Prevent heart attacks

➢ 700,000 new and 500,000 recurrent Myocardial Infarctions (MI) annually
➢ Vulnerable plaque causes most heart attacks

Current standard of primary & Secondary prevention

Preventing MI

Currently in development. Not available for sale.
Detection of Vulnerable Plaque
Catheter Base and Non-invasive techniques

 prediction should be reliable enough to justify invasive therapy (stent)
 otherwise, patients with any plaques, should be on statins
Soft Plaque (CTA): A marker of vulnerability?

LAD: with narrowing

RCA: with minimal narrowing
OUTLINE

- Pathophysiology
  - Atherosclerosis
  - Ischemia
- Primary prevention – who should be treated
- Therapy
  - Lifestyle
  - Pharmacology
  - Revascularization
Aims of Treatment

- Improve prognosis
  - Prevention of death and myocardial infarction

- Improve quality of life
  - Prevent / minimize symptomatic ischemic events
Aims and Modes of Treatment
From the Guidelines

- **Improve prognosis**
  - “Lifestyle changes and drug treatment play vital roles in modifying the atherosclerotic disease process and ‘stabilising’ coronary plaques ***”
  - “In certain circumstances, such as in patients with severe lesions in coronary arteries supplying a large area of jeopardised myocardium, **revascularization** offers additional opportunities to improve prognosis by improving existing perfusion or providing alternative routes of perfusion”

ESC guidelines on the management of stable AP - 2006
Aims and Modes of Treatment
From the Guidelines

- Improve quality of life
  - “Lifestyle changes, drugs, and revascularization all have a role to play in minimising or eradicating symptoms of angina, although not necessarily all in the same patient”

ESC guidelines on the management of stable AP - 2006
From 1980 to 2000, the age-adjusted mortality rate from CAD fell (per 100,000 population):

- Men: from 542.9 to 266.8 (51%)
- Women: from 263.3 to 134.4 (49%)

A previously validated model was used to estimate the roles of specific cardiac treatments and changes in risk factors in this decline.

Sequence Variations in PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley Jr., Ph.D. and Helen H. Hobbs, M.D.

*proprotein convertase subtilisin/kexin type 9 serine protease gene

Background: PCSK9 mutation and its effect on LDL-C level


- PCSK9 is responsible for degradation of LDL receptors in liver cells
- Various genetic variations are present in blacks (2%) and whites (3.2%)
  - Subjects have increased LDL receptor density (statin like effect)
  - Associated with a 20-40 percent reduction in mean LDL cholesterol

- Clinical significance was determined in 15792 participants of ARIC: a prospective study of atherosclerosis in the community
- Data represents 15 years of follow-up
Distribution of Plasma LDL-C and Incidence of CHD among 3363 Black Participants in the Study
Carriers and noncarriers of PCSK9 nonsense mutation

Plasma LDL-C 28% lower in carriers

15 years follow-up

CHD in only 1 of 85 carriers!

88% risk reduction

Relation Between Reduction of LDL-C and Cardiovascular Risk Reduction
Statins as compared to PCSK9 mutation

Statins Meta-analysis
- LDL-C Reduction: 28
- Risk Reduction: 31

PCSK9 (whites) Variant
- LDL-C Reduction: 15
- Risk Reduction: 50

PCSK9 (blacks) Nonsense
- LDL-C Reduction: 28
- Risk Reduction: 88
Atherosclerosis Progression
Implication for therapy

- Atherosclerosis is a slowly progressive disease
  - Disease starts at childhood but becomes clinically evident decades later
- It takes years until the maximal benefit of therapy is evident
  - 5 years (F/U time in many statin trials) are not enough to obtain the full benefit from therapy
ASTEROID: Aggressive statin therapy can induce regression of atherosclerosis

Ref: Nissen S et al. JAMA 2006; 295: e-publication ahead of print
Treating to New Targets (TNT) trial: Rationale

Screening

Percent with CHD event

LDL-C, mg/dl

Modified from Kastelein JJP. Atherosclerosis. 1999;143(suppl 1):S17-S21
**TNT: Treatment effects on primary outcome**


The diagram shows the impact of Atorvastatin on major cardiovascular (CV) events over a 6-year period.

- **Atorvastatin 10 mg**
- **Atorvastatin 80 mg**

**Graph Details:**
- **Y-axis:** Major CV events (%)
- **X-axis:** Years
- **HR = 0.78 (0.69–0.89)**
- **P < 0.001**

The graph illustrates a 22% risk reduction for Atorvastatin 10 mg compared to the placebo, with a hazard ratio (HR) of 0.78, indicating a statistically significant reduction in major CV events.
Major CV Events Across Quintiles of Achieved LDL

LaRosa JC. AHA. 2005

*P-value for trend across LDL-C
JUPITER Trial: LDL and event* reduction

LDL decrease 50 percent at 12 months

HR 0.56, 95% CI 0.46-0.69
P < 0.00001

Ridker et al NEJM 2008

*Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death
Role of RAAS Modulation in CAD
Implications from recent clinical trials
Benefit of ACE inhibition in CAD

- SOLVD
- SAVE
- AIRE
- TRACE
- HOPE
- EUROPA
- PEACE
- Post-MI, HF, LVEF <40%
- High risk

All CAD patients

ACEI trials in CAD without HF: Primary outcomes

**EUROPA**
CV death/MI/cardiac arrest
- Placebo
- Perindopril 8 mg
- 20% Risk reduction
- HR 0.80 (0.71–0.91)
- P = 0.0003

**HOPE**
CV death/MI/stroke
- Placebo
- Ramipril 10 mg
- 22% Risk reduction
- HR 0.78 (0.70–0.86)
- P < 0.001

**PEACE**
CV death/MI/CABG/PCI
- Placebo
- Trandolapril 4 mg
- 4% Risk reduction
- HR 0.96 (0.88–1.06)
- P = 0.43

**QUIET**
All CV events
- Placebo
- Quinapril 20 mg
- 4% Risk increase
- HR 1.04 (0.89–1.22)
- P = 0.6

### EUROPA, HOPE, PEACE, QUIET: Totality of trial evidence

<table>
<thead>
<tr>
<th>Event type</th>
<th>ACEI</th>
<th>Placebo</th>
<th>Favors ACEI</th>
<th>Favors placebo</th>
<th>P</th>
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<td>All-cause death</td>
<td>7.5</td>
<td>8.9</td>
<td>0.86</td>
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<tr>
<td>MI</td>
<td>6.4</td>
<td>7.7</td>
<td>0.86</td>
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<td>0.0004</td>
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<td>2.7</td>
<td>0.77</td>
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<td>0.0004</td>
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<td>Revascularization</td>
<td>15.5</td>
<td>16.3</td>
<td>0.93</td>
<td></td>
<td>0.025</td>
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</table>

Odds ratio

ACE inhibitors: ESC guidelines on the management of stable AP - 2006

Class I

- ACE-inhibitor therapy in patients with coincident indications for ACE-inhibition, such as hypertension, heart failure, LV dysfunction, prior MI with LV dysfunction, or diabetes
  - level of evidence A

Class IIa

- ACE-inhibitor therapy in all patients with angina and proven coronary disease
  - level of evidence B
Role of ARB’s: The ONTARGET Program


*Planned. Actual=25,620; †Planned. Actual=5926.

The ONTARGET Trial

Inclusion Criteria

- Age $\geq$ 55 years
- At high risk of developing a CVD event, with a history of
  - Coronary artery disease
  - Peripheral arterial occlusive disease (PAOD)
  - Cerebrovascular event
  - Diabetes mellitus with end organ disease
- Intolerant to ACE inhibitors (TRANSCEND)

Criteria similar to HOPE trial

## Change in BP (mmHg)

<table>
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<th>Ramipril</th>
<th>Telmisartan</th>
<th>Combination</th>
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<tr>
<td>Systolic</td>
<td>-6.0</td>
<td>-6.9</td>
<td>-8.4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>-4.6</td>
<td>-5.2</td>
<td>-6.0</td>
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</table>
Telmisartan vs. Placebo in ACE intolerant patients

**Transcend**

Time to Primary Outcome

- Telmisartan
- Placebo

Cumulative Incidence Rates

HR: 0.92 (0.81-1.05)

p-value = 0.2158

No. at Risk
- Telmisartan (T): 2954, 2807, 2699, 2577, 2278, 1091
- Placebo (P): 2972, 2839, 2713, 2575, 2253, 1069

ESC: SEP 2008
• Telmisartan is as effective as ramipril, with a slightly better tolerability.
• Combination therapy is not superior to ramipril, and has increased side effects.
• Telmisartan is not better than placebo in ACE intolerant patients

How can Telmisartan be as effective as Ramipril (HOPE population) and at the same time not be better than placebo???
Antiplatelet Therapy
Antiplatelet therapy – beyond aspirin

- Aspirin is a weak antiplatelet agent
- Role of aspirin in treatment in patients with ACS and in stable CAD is proven beyond doubt
- Addition of clopidogrel to aspirin is helpful to improve outcome in ACS
- Is there benefit to combination therapy (aspirin and clopidogrel) in stable CAD?
Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA)
Study Design

Patients age ≥ 45 years at high risk of atherothrombotic events
(n=15603)

1-month visit 3-month visit Visits every 6 months

Low dose ASA 75–162 mg/day

Double-blind treatment up to 1040 primary efficacy events*

Low dose ASA 75–162 mg/day

Clopidogrel 75 mg/day (n=7802)

Placebo 1 tablet/day (n=7801)

Final visit (Fixed study end date)

* MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death; event-driven trial

Inclusion criteria

Must include:
- Signed Written Informed Consent
- Patients aged ≥45 years
- At least one of four criteria

1. Documented cerebrovascular disease
2. Documented coronary disease
3. Documented symptomatic PAD
4. 2 major or 1 major and 2 minor or 3 minor risk factors

Major Risk Factors:
- Type I or Type II diabetes
- Diabetic nephropathy
- Ankle Brachial Index <0.9
- Asymptomatic carotid stenosis > 70%
- Presence of at least one carotid plaque

Minor Risk Factors:
- SBP ≥150 mm Hg (despite therapy)
- Hypercholesterolemia
- Current smoking >15 cigarettes/day
- Male ≥65 years or female ≥70 years
First Occurrence of MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death

*All patients received ASA 75-162mg/day

Median follow-up was 28 months

# Primary Efficacy Results (MI/Stroke/CV Death)* by Category of Inclusion Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented AT</td>
<td>12,153</td>
<td>0.88 (0.77, 0.998)</td>
<td>0.046</td>
</tr>
<tr>
<td>Coronary</td>
<td>5,835</td>
<td>0.86 (0.71, 1.05)</td>
<td>0.13</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>4,320</td>
<td>0.84 (0.69, 1.03)</td>
<td>0.09</td>
</tr>
<tr>
<td>PAD</td>
<td>2,838</td>
<td>0.87 (0.67, 1.13)</td>
<td>0.29</td>
</tr>
<tr>
<td>Multiple RF</td>
<td>3,284</td>
<td>1.20 (0.91, 1.59)</td>
<td>0.20</td>
</tr>
<tr>
<td>Overall Population</td>
<td>15,603</td>
<td>0.93 (0.83, 1.05)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

* First Occurrence of MI (fatal or not), Stroke (fatal or not), or CV Death
RF= Risk Factors, AT= Atherothrombosis
Bhatt DL. Oral presentation at ACC 2006.
## Multiple Risk Factor Population: Secondary Efficacy Results

<table>
<thead>
<tr>
<th>Endpoint* – N (%)</th>
<th>Clopidogrel (n=1659)</th>
<th>Placebo + ASA (n=1625)</th>
<th>+ ASA RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Secondary Endpoint†</td>
<td>224 (13.5)</td>
<td>216 (13.3)</td>
<td>1.01 (0.84, 1.22)</td>
<td>0.88</td>
</tr>
<tr>
<td>All Cause Death</td>
<td>89 (5.4)</td>
<td>62 (3.8)</td>
<td>1.41 (1.02, 1.95)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td>64 (3.9)</td>
<td>36 (2.2)</td>
<td>1.74 (1.16, 2.62)</td>
<td>0.01</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>40 (2.4)</td>
<td>33 (2.0)</td>
<td>1.19 (0.75, 1.89)</td>
<td>0.45</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>27 (1.6)</td>
<td>29 (1.8)</td>
<td>0.91 (0.54, 1.54)</td>
<td>0.73</td>
</tr>
<tr>
<td>Stroke</td>
<td>35 (2.1)</td>
<td>36 (2.2)</td>
<td>0.95 (0.60, 1.52)</td>
<td>0.84</td>
</tr>
<tr>
<td>Hospitalization‡</td>
<td>140 (8.4)</td>
<td>147 (9.0)</td>
<td>0.93 (0.74, 1.18)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

*Intention to treat analysis
†First occurrence of MI (fatal or not), stroke (fatal or not), cardiovascular death (including hemorrhagic death), or hospitalization‡
‡For UA, TIA, or revascularization

Bhatt DL. Oral presentation at ACC 2006.
CHARISMA – post hoc subgroup analysis cardiovascular death, MI, or stroke

Patients with prior MI

Validity of subgroup analysis in a negative trial?

Patients with CAD
Without prior MI
CHARISMA – time dependence of daily hazard

Ischemic event

Bleeding
Recommendations for pharmacological therapy to improve prognosis

Class I

- **Aspirin** 75 mg daily in all patients without specific contraindications (ie active GI bleeding, aspirin allergy or previous aspirin intolerance) *(level of evidence A)*

- **Statin** therapy for all patients with coronary disease *(level of evidence A)*

- **ACE-inhibitor** therapy in patients with coincident indications for ACE-inhibition, such as hypertension, heart failure, LV dysfunction, prior MI with LV dysfunction, or diabetes *(level of evidence A)*

- **Oral beta blocker** therapy in patients post-MI or with heart failure *(level of evidence A)*

ESC guidelines on the management of stable AP - 2006
Recommendations for pharmacological therapy to improve prognosis

Class IIa

- **ACE-inhibitor** therapy in all patients with angina and proven coronary disease *(level of evidence B)*

- **Clopidogrel** as an alternative antiplatelet agent in patients with stable angina who cannot take aspirin eg **Aspirin allergic** *(level of evidence B)*

- **High-dose statin** therapy in high risk (>2% annual CV mortality) patients with proven coronary disease *(level of evidence B)*

Class IIb

- **Fibrate** therapy in patients with low HDL and high triglycerides who have diabetes or the metabolic syndrome *(level of evidence B)*

ESC guidelines on the management of stable AP - 2006
pharmacological therapy to improve symptoms and/or reduce ischaemia

- Beta Blockers
- Nitrates
  - Short, long acting
- Ca Channel Blockers
  - Dihydropyridines, Non-dihydropyridines
- Others
  - K channel opener - Nicorandil
  - Sinus node inhibitor – Ivabradine
  - Metabolic modifiers – Trimetazidine, Ranolazine
OUTLINE

- Pathophysiology
  - Atherosclerosis
  - Ischemia
- Primary prevention – who should be treated
- Therapy
  - Lifestyle
  - Pharmacology
  - Revascularization
COURAGE

Clinical Outcomes Utilizing Revascularization and Aggressive Guideline-Driven Drug Evaluation
Hypothesis

PCI + Optimal Medical Therapy will be Superior to Optimal Medical Therapy Alone
Optimal Medical Therapy

Pharmacologic
- Anti-platelet: aspirin; clopidogrel in accordance with established practice standards
- Statin: simvastatin ± ezetimibe or ER niacin
- ACE Inhibitor or ARB: lisinopril or losartan
- Beta-blocker: long-acting metoprolol
- Calcium channel blocker: amlodipine
- Nitrate: isosorbide 5-mononitrate

Lifestyle
- Smoking cessation
- Exercise program
- Nutrition counseling
- Weight control

Applied to Both Arms by Protocol and Case-Managed
## Risk Factor Goals

<table>
<thead>
<tr>
<th>Variable</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Cessation</td>
</tr>
<tr>
<td>Total Dietary Fat / Saturated Fat</td>
<td>&lt;30% calories / &lt;7% calories</td>
</tr>
<tr>
<td>Dietary Cholesterol</td>
<td>&lt;200 mg/day</td>
</tr>
<tr>
<td><strong>LDL cholesterol (primary goal)</strong></td>
<td>60-85 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol (secondary goal)</td>
<td>&gt;40 mg/dL</td>
</tr>
<tr>
<td>Triglyceride (secondary goal)</td>
<td>&lt;150 mg/dL</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>30-45 min. moderate intensity 5X/week</td>
</tr>
<tr>
<td><strong>Body Weight by Body Mass index</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Initial BMI</strong></td>
<td></td>
</tr>
<tr>
<td>25-27.5</td>
<td>Weight Loss Goal</td>
</tr>
<tr>
<td>&gt;27.5</td>
<td>BMI &lt;25</td>
</tr>
<tr>
<td><strong>Weight Loss Goal</strong></td>
<td>10% relative weight</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td>&lt;130/85 mmHg</td>
</tr>
<tr>
<td>Diabetes</td>
<td>HbAlc &lt;7.0%</td>
</tr>
</tbody>
</table>
## Long-Term Improvement in Treatment Targets (Group Median ± SE Data)

<table>
<thead>
<tr>
<th>Treatment Targets</th>
<th>Baseline</th>
<th>60 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCI +OMT</td>
<td>OMT</td>
</tr>
<tr>
<td>SBP</td>
<td>131 ± 0.77</td>
<td>130 ± 0.66</td>
</tr>
<tr>
<td>DBP</td>
<td>74 ± 0.33</td>
<td>74 ± 0.33</td>
</tr>
<tr>
<td>Total Cholesterol mg/dL</td>
<td>172 ± 1.37</td>
<td>177 ± 1.41</td>
</tr>
<tr>
<td>LDL mg/dL</td>
<td>100 ± 1.17</td>
<td>102 ± 1.22</td>
</tr>
<tr>
<td>HDL mg/dL</td>
<td>39 ± 0.39</td>
<td>39 ± 0.37</td>
</tr>
<tr>
<td>TG mg/dL</td>
<td>143 ± 2.96</td>
<td>149 ± 3.03</td>
</tr>
<tr>
<td>BMI Kg/M²</td>
<td>28.7 ± 0.18</td>
<td>28.9 ± 0.17</td>
</tr>
<tr>
<td>Moderate Activity (5x/week)</td>
<td>25%</td>
<td>25%</td>
</tr>
</tbody>
</table>
Survival Free of Death from Any Cause and Myocardial Infarction

Optimal Medical Therapy (OMT)

PCI + OMT

Hazard ratio: 1.05
95% CI (0.87-1.27)
P = 0.62

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Therapy</td>
<td>1138</td>
<td>1017</td>
<td>959</td>
<td>834</td>
<td>638</td>
<td>408</td>
<td>192</td>
<td>3</td>
</tr>
<tr>
<td>PCI</td>
<td>1149</td>
<td>1013</td>
<td>952</td>
<td>833</td>
<td>637</td>
<td>417</td>
<td>200</td>
<td>3</td>
</tr>
</tbody>
</table>
Hypothesis: Reduction in Ischemia will be greater for patients randomized to PCI+OMT than for those randomized to OMT

Serial Rest/Stress Myocardial Perfusion SPECT (MPS)
To compare patient management strategy for ischemia reduction

- Pre-Rx = Off Meds
- 6-18m = On Meds

*Timing chosen to occur beyond window of in-stent restenosis & delayed to allow effects of medical Rx to be observed

PCI+OMT (n=159)
OMT (n=155)

Repeat MPS* at 6-18 m
Repeat MPS* at 6-18 m

Mean = 374±50 days

Quantification of extent and severity of ischemia by nuclear perfusion study: total perfusion deficit (TPD)

% ischemic myocardium: 
(stress TPD - rest TPD)

- < 5%: minimal (“no ischemia”)
- 5.0% - 9.9%: mild
- ≥ 10%: moderate-to-severe

Significant reduction in ischemia:
- ≥ 5% reduction in ischemic myocardium*

*threshold exceeds test repeatability

Pre-Rx TPD: 28%

12m TPD: 2%
% with ischemia reduction ≥5% myocardium

(n=105 moderate-to-severe pre-Rx ischemia)

PCI + OMT (n=54) OMT (n=51)

78.0% 52.0%

p=0.007
Rates of Death or MI by Residual Ischemia

COURAGE Trial

P=0.063

P=0.023

P=0.002

0% (n=22) 1%-4.9% (n=160) 5%-9.9% (n=94) ≥10% (n=61)
Fractional Flow Reserve in Clinical Practice

REST

HYPEREMIA

Crossing the lesion

Distal to the lesion

FFR = 58/112 = 0.52
Diameter Stenosis versus FFR

- Diameter stenosis is the main determinant of coronary stenosis

However
- Resistance is also influenced by lesion length and the 3D morphology of the stenosis

- Anatomical assessment is not accurate enough to determine physiological significance
- Coronary angiography provides only the anatomical data
FAME study: **HYPOTHESIS**

**FFR** guided Percutaneous Coronary Intervention (PCI) in *multivessel disease*, is superior to current *angiography* guided PCI
<table>
<thead>
<tr>
<th></th>
<th>ANGIO-group (N=496)</th>
<th>FFR-group (N=509)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td># indicated lesions per patient</td>
<td>2.7±0.9</td>
<td>2.8±1.0</td>
<td>0.34</td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>2.5±0.6</td>
<td>2.5±0.7</td>
<td>0.81</td>
</tr>
<tr>
<td>% stenosis severity</td>
<td>61±17</td>
<td>60±18</td>
<td>0.24</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>1.0±0.4</td>
<td>1.0±0.5</td>
<td>0.35</td>
</tr>
<tr>
<td>50-70% narrowing, No (%)</td>
<td>550 (41)</td>
<td>624 (44)</td>
<td>-</td>
</tr>
<tr>
<td>70-90% narrowing, No (%)</td>
<td>553 (41)</td>
<td>530 (37)</td>
<td>-</td>
</tr>
<tr>
<td>90-99% narrowing, No (%)</td>
<td>207 (15)</td>
<td>202 (14)</td>
<td>-</td>
</tr>
<tr>
<td>Total occlusion, No (%)</td>
<td>40 (3)</td>
<td>58 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Patients with ≥1 total occlusion (%)</td>
<td>7.5</td>
<td>10.6</td>
<td>0.08</td>
</tr>
</tbody>
</table>
# Indicated lesions per patient

<table>
<thead>
<tr>
<th></th>
<th>ANGIO-group (N=496)</th>
<th>FFR-group (N=509)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td># indicated lesions per patient</td>
<td>2.7 ± 0.9</td>
<td>2.8 ± 1.0</td>
<td>0.34</td>
</tr>
</tbody>
</table>

**FFR results**

- Lesions successfully measured, No (%)  
  ANGIO-group: -
  FFR-group: 1329 (98%)

- Lesions with FFR ≤ 0.80, No (%)  
  ANGIO-group: -
  FFR-group: 874 (63%)

- Lesions with FFR > 0.80, No (%)  
  ANGIO-group: -
  FFR-group: 513 (37%)
## FAME study: Procedural Results (1)

<table>
<thead>
<tr>
<th></th>
<th>ANGIO-group (N=496)</th>
<th>FFR-group (N=509)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td># indicated lesions per patient</td>
<td>2.7 ± 0.9</td>
<td>2.8 ± 1.0</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>FFR results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesions successfully measured, No (%)</td>
<td>-</td>
<td>1329 (98%)</td>
<td>-</td>
</tr>
<tr>
<td>Lesions with FFR ≤ 0.80 ,No (%)</td>
<td>-</td>
<td>874 (63%)</td>
<td>-</td>
</tr>
<tr>
<td>Lesions with FFR &gt; 0.80 ,No (%)</td>
<td>-</td>
<td>513 (37%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>stents per patient</strong></td>
<td>2.7 ± 1.2</td>
<td>1.9 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lesions successfully stented (%)</td>
<td>92%</td>
<td>94%</td>
<td>-</td>
</tr>
<tr>
<td>DES, total, No</td>
<td>1359</td>
<td>980</td>
<td>-</td>
</tr>
</tbody>
</table>
FFR-guided

30 days 2.9%
90 days 3.8%
180 days 4.9%
360 days 5.3%

Angio-guided

absolute difference in MACE-free survival

FAME study: Event-free Survival
Impact of revascularization on outcome - controversial

- Anatomic obstruction with documented ischemic physiology
  - Long term outcome is **better** with PCI compared to OMT
    - COURAGE nuclear substudy, FAME

- Anatomic obstruction without documented ischemic physiology
  - Long term outcome is **worse** with PCI compared to OMT
    - DEFER, FAME
תודה רבה