Chronic Ischemic Heart Disease

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The E. Wolfson Medical Center

Fellows course, November 2008
OUTLINE

- Pathophysiology
  - Atherosclerosis
  - Ischemia

- Therapy
  - Lifestyle
  - Pharmacology
  - Revascularization
OUTLINE

- Pathophysiology
  - Atherosclerosis
  - Ischemia

- Therapy
  - Lifestyle
  - Pharmacology
  - Revascularization
Atherosclerosis Timeline

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,
Myocardial Ischemia

- Oxygen demand
- Oxygen supply
## Components of myocardial oxygen consumption

<table>
<thead>
<tr>
<th>Component</th>
<th>Basal</th>
<th>Volume work</th>
<th>Effect of 50% increase on oxygen consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>20%</td>
<td></td>
<td>Wall stress</td>
</tr>
<tr>
<td>Electrical</td>
<td>1%</td>
<td></td>
<td>Heart rate</td>
</tr>
<tr>
<td>Contractility</td>
<td>45%</td>
<td></td>
<td>Volume work</td>
</tr>
<tr>
<td>Pressure work</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Effect of 50% increase on oxygen consumption

<table>
<thead>
<tr>
<th>Component</th>
<th>Basal</th>
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<tbody>
<tr>
<td>Wall stress</td>
<td>25%</td>
<td></td>
<td>Wall stress</td>
</tr>
<tr>
<td>Contractility</td>
<td>45%</td>
<td></td>
<td>Heart rate</td>
</tr>
<tr>
<td>Pressure work</td>
<td>50%</td>
<td></td>
<td>Volume work</td>
</tr>
</tbody>
</table>

Increase in heart rate and pressure work are the main determinants of oxygen consumption thus: Double product = HR X SBP is a good clinical estimate for myocardial oxygen demand.
Oxygen Supply
myocardium vs other tissues

- O$_2$ Delivery
  - Coronary Blood Flow
  - Hemoglobin
  - Arterial O$_2$ saturation

- Myocardial (A-V) O$_2$ 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

Percent lesion diameter
Mechanism of stress induced perfusion mismatch

Limited coronary flow reserve (CFR) in the territory supplied by the stenotic artery causing perfusion mismatch
Relation between pressure gradient and flow for increasing % stenosis

Resting flow

Resting flow

\[ \text{ΔP across stenosis} \]

\[ \text{Degree of Stenosis} \]

\[ \text{Flow (Q)} \]
Fractional Flow Reserve in Clinical Practice

- REST
- Crossing the lesion
- Distal to the lesion
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)
- Magnitude of effect modified by adaptive mechanisms (smart heart)
  - Hybernation (adaptation of mechanical function to flow limitation)
  - Preconditioning (protection from future ischemia by past ischemic episodes)
LV pressure during ischemia
Myocardial Stunning

Can also be triggered by an episode of ischemia due to an increase in demand (e.g. post exercise)
Hibernating Myocardium (PET)

Perfusion

[^13N]-ammonia scan demonstrates a large anterolateral perfusion defect

Metabolism

[^18F]-fluorodeoxyglucose image demonstrates preserved anterolateral metabolic activity
שאלה 1: חולה עם מחלה כלילית מתנגד לבצע מבחן מאמץ בטענה שמנסיון בעבר גורם לו המבחן לחולשה וקוצר נשימה למשך יממה. מה ההסבר המתקבל ביותר על הדעת המבחן לحلولוoka קוצר נשימה למשר ימא? – מה הסבר המתקבל ביוור על העדעה?

1. אין סיבה אורגנית
2. התקף לב בעקבות המאמץ
3. איסכמיה חריפה מתמשכת
4. Stunning
5. preconditioning העדר

1. התוכן הבועקבות המאמץ
2. איסכמיה חריפה מתמשכת
3. Stunning
4. preconditioning העדר
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 (repeated stunning?)
OUTLINE

- Pathophysiology
  - Atherosclerosis
  - Ischemia

- Therapy
  - Lifestyle
  - Pharmacology
  - Revascularization
Aims of Treatment

- Improve prognosis
  - Prevention of death and myocardial infarction

- Improve quality of life
  - Prevent / minimize symptomatic ischemic events
Modes of Treatment
General and Specific for CAD

- Life style modification
- Pharmacological therapy
- Non-pharmacological
  - Revascularization
    - Surgical, PCI
  - Others
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
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
Therapy with Statins

Relation between atherosclerosis progression and clinical outcome
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

CHD in only 1 of 85 carriers!

88% risk reduction

Meta-analysis of Statin Trials

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

- **LDL-C Reduction**
- **Risk Reduction**

**Statins**
- Meta-analysis
  - 28
- PCSK9 (whites)
  - Variant
    - 15
  - Nonsense
    - 28
- PCSK9 (blacks)
  - 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
Role of LDL reduction
Correlation between Clinical Outcome and IVUS Data

- PROVE-IT
  - Clinical Outcome
- REVERSAL
  - IVUS data
Patient population
- Patients with ACS

4162 patients

Primary endpoint:
- Death, MI, Documented UA requiring hospitalization, revascularization (> 30 days after randomization), or Stroke

Atorvastatin 80 mg

Pravastatin 40 mg

30 months
Patient population
- Patients with CHD

657 patients

Primary endpoint:
- Change in coronary plaque volume by IVUS

Atorvastatin 80 mg

Pravastatin 40 mg

Brachial reactivity

18 months
Changes from (Post-ACS) Baseline in Median LDL-C

Note: Changes in LDL-C may differ from prior trials:
- 25% of patients on statins prior to ACS event
- ACS response lowers LDL-C from true baseline

<table>
<thead>
<tr>
<th>Time</th>
<th>Median LDL-C (Q1, Q3)</th>
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<tbody>
<tr>
<td>Final</td>
<td>95 (79, 113)</td>
</tr>
<tr>
<td>16 Mos.</td>
<td>62 (50, 79)</td>
</tr>
<tr>
<td>8 Mos.</td>
<td></td>
</tr>
<tr>
<td>4 Mos.</td>
<td></td>
</tr>
<tr>
<td>30 Days</td>
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<tr>
<td>Rand.</td>
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<tr>
<td>&lt;24h</td>
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</table>

LDL-C (mg/dL)

- Pravastatin 40mg: 21% ↓
- Atorvastatin 80mg: 49% ↓

P<0.001
All-Cause Death or Major CV Events in All Randomized Subjects

- Pravastatin 40mg (26.3%)
- Atorvastatin 80mg (22.4%)

16% RR (P = 0.005)
REVERSAL: IVUS Determination of Atheroma Area

Precise Planimetry of EEM and Lumen Borders allows calculation of Atheroma Cross-sectional Area

Images courtesy of Cleveland Clinic Intravascular Ultrasound Core Laboratory

EEM = External Elastic Membrane
REVERSAL Trial – IVUS analysis

Change in total atheroma volume (TAV)
- p=0.02 for change between atorvastatin vs pravastatin

Change in percent obstruction volume
- p=0.0002 for change between atorvastatin vs pravastatin

AHA 2003, Orlando, FL
REVERSAL: Continuous Relationship Between % Reduction in LDL-C and Change in Atheroma Volume: Both Treatment Groups (n=502)

REVERSAL and PROVE-IT
Duality of IVUS and Clinical outcomes

- Significant reduction and lower achieved level of LDL-cholesterol leads to:
  - Attenuation of coronary atherosclerosis progression (regression)
  - Reduction of cardiovascular morbidity and mortality
75% of patients achieving an LDL <70 mg/dL.
ASTEROID: Aggressive statin therapy can induce regression of atherosclerosis

Ref: Nissen S et al. JAMA 2006; 295: e-publication ahead of print
PROVE-IT - Distribution of four-month LDL level
Atorvastatin subgroup

PROVE-IT: Primary End Point By 4-Month *(LDL Level (Multivariable Adjustment

Hazard Ratio

>80-100
>60-80
>40-60
<40

0.80 (0.59, 1.07)
0.67 (0.50, 0.92)
0.61 (0.40, 0.91)

*Age, gender, DM, prior MI, baseline LDL.
Treating to New Targets (TNT) trial: Rationale

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


22% risk reduction

Major CV events (%)

Atorvastatin 10 mg
Atorvastatin 80 mg

HR = 0.78 (0.69–0.89)
P < 0.001

Major CV Events Across Quintiles of Achieved LDL

LaRosa JC. AHA. 2005
**Event Rates**

<table>
<thead>
<tr>
<th>Odds Reduction</th>
<th>High Dose</th>
<th>Std Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>-17%</td>
<td>147/2099 (7.0)</td>
<td>172/2063 (8.3)</td>
</tr>
<tr>
<td>-15%</td>
<td>205/2265 (9.1)</td>
<td>235/2232 (10.5)</td>
</tr>
<tr>
<td>-21%</td>
<td>334/4995 (6.7)</td>
<td>418/5006 (8.3)</td>
</tr>
<tr>
<td>-12%</td>
<td>411/4439 (9.3)</td>
<td>463/4449 (10.4)</td>
</tr>
<tr>
<td>-16%</td>
<td>1097/13798 (8.0)</td>
<td>1288/13750 (9.4)</td>
</tr>
</tbody>
</table>

**Meta-Analysis of Intensive Statin Therapy**

**Coronary Death or MI**

Cannon CP, et al.
This relationship is consistent with a large body of epidemiologic data and data available from clinical trials of LDL-C–lowering therapy.

These data suggest that for every 30-mg/dL change in LDL-C, the relative risk for CHD is changed in proportion by about 30%.

The relative risk is set at 1.0 for LDL-C = 40 mg/dL.

Prediction of LDL-C target in 5 years

- An LDL-C of 50 mg/dL in a high-risk population
- An LDL-C of 75 mg/dL in a lower-risk population

Christopher Cannon

Valentin Fuster
Role of RAAS Modulation in CAD
Implications from recent clinical trials
Benefit of ACE inhibition in CAD

Post-MI, HF, LVEF <40%

High risk

EUROPA
HOPE
SOLVD (prev)
SAVe
AIRE
TRACE
SOLVD

All CAD patients

EUROPA: EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease

Objective: Assess effects of the ACEI perindopril on CV risk in a broad-spectrum population with stable CAD and without HF

Design: N = 12,218, age ≥18 years, with CAD/without HF at randomization

Treatment: Perindopril 8 mg or placebo

Follow-up: 4.2 years

Primary outcome: CV death, nonfatal MI, cardiac arrest

EUROPA: Primary outcome

CV death, MI, cardiac arrest

**EUROPA Investigators. Lancet. 2003;362:782-8.**

**Fox KM. Br J Cardiol. 2004;11:195-204.**

**Primary outcome (%)**

- **Placebo** – 9.9%
- **Perindopril - 8.0% 8 mg**

**Time (years)**

- **RRR 20% (95% CI: 9%–29%)**
  - **P = 0.0003**

**CV death, MI, cardiac arrest**

- 0%
- 1%
- 2%
- 3%
- 4%
- 5%
- 6%
- 7%
- 8%
- 9%
- 10%
- 11%
- 12%
- 13%
- 14%

**P < 0.05**

**P = 0.35**
EUROPA: Effect of ACEI on fatal/nonfatal MI and HF hospitalizations

**Fatal and nonfatal MI**

- **RRR 24%**
- **AR 5.2% vs 6.8%**
- **P < 0.001**

**HF hospitalization**

- **RRR 39%**
- **AR 1.0% vs 1.7%**
- **P = 0.002**

**AR = absolute risk (perindopril vs placebo)**

PEACE: Prevention of Events with Angiotensin Converting Enzyme inhibition

Objective: Assess effect of ACEI in patients with stable CAD and normal/slightly reduced LV function

Design: N = 8290 randomized

Treatment: Trandolapril 4 mg or placebo

Follow-up: 4.8 years

Primary outcome: CV death, nonfatal MI, CABG, PCI

PEACE: Primary outcome

CV death, MI, CABG/PCI; N = 8290

Patients with event (%)

Time (years)

Placebo

Trandolapril 4 mg

4% Risk reduction
HR 0.96 (0.88–1.06)
P = 0.43

ACEI trials in CAD patients without HF: Key baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>EUROPA</th>
<th>HOPE</th>
<th>PEACE</th>
<th>QUIET</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>12,218</td>
<td>9297</td>
<td>8290</td>
<td>1750</td>
</tr>
<tr>
<td>Follow-up (yrs)</td>
<td>4.2</td>
<td>4.5</td>
<td>4.8</td>
<td>2.3</td>
</tr>
<tr>
<td>ACEI/dose (mg)</td>
<td>P-8</td>
<td>R-10</td>
<td>T-4</td>
<td>Q-20</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>60</td>
<td>66</td>
<td>64</td>
<td>58</td>
</tr>
<tr>
<td>Men (%)</td>
<td>85</td>
<td>73</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>CAD/Cor rev (%)</td>
<td>100/55</td>
<td>80/44</td>
<td>100/72</td>
<td>100/100</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>12</td>
<td>39</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>27</td>
<td>47</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>65</td>
<td>53</td>
<td>55</td>
<td>49</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>NA</td>
<td>NA</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>PVD (%)</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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)
- \( P = 0.6 \)


HOPE, EUROPA, PEACE, QUIET: Differences in baseline CV risk

Annualized event rate in placebo group (%/yr)

<table>
<thead>
<tr>
<th>Event</th>
<th>HOPE</th>
<th>EUROPA</th>
<th>PEACE</th>
<th>QUIET</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>1.8</td>
<td>1.0</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>2.7</td>
<td>1.5</td>
<td>1.1</td>
<td>2.0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Event rate (%)</th>
<th>ACEI</th>
<th>Placebo</th>
<th>Favors ACEI</th>
<th>Favors placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>7.5</td>
<td>8.9</td>
<td>0.86</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>6.4</td>
<td>7.7</td>
<td>0.86</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>2.1</td>
<td>2.7</td>
<td>0.77</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td>15.5</td>
<td>16.3</td>
<td>0.93</td>
<td>0.025</td>
<td></td>
</tr>
</tbody>
</table>

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
שאלה 2: טיפול ב- ARB (Concatchet לסטרול)
במעכבי ACE (оказ שביעיל במחקר):

1. VALIANT
2. ONTARGET
3. CHARM
4. כל הנ"ל
5. אם אחדenzhen
Because of an extraordinary effort by investigators in 40 countries, it was possible to complete recruitment for the ONTARGET study in May 2003, seven months ahead of the scheduled timeline. The ONTARGET trial currently recruited 25,621 patients.

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>
<thead>
<tr>
<th></th>
<th>Ramipril</th>
<th>Telmisartan</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic</strong></td>
<td>-6.0</td>
<td>-6.9</td>
<td>-8.4</td>
</tr>
<tr>
<td><strong>Diastolic</strong></td>
<td>-4.6</td>
<td>-5.2</td>
<td>-6.0</td>
</tr>
</tbody>
</table>
Time to Primary Outcome

![Graph showing cumulative hazard ratio for different treatments over years of follow-up.]

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Telmisartan</th>
<th>Ramipril</th>
<th>Telmisartan plus ramipril</th>
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<tbody>
<tr>
<td></td>
<td>8542</td>
<td>8177</td>
<td>7778</td>
</tr>
<tr>
<td></td>
<td>8576</td>
<td>8214</td>
<td>7832</td>
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<td></td>
<td>8502</td>
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<td>1703</td>
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<td>7375</td>
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<td></td>
<td></td>
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<td>1718</td>
</tr>
</tbody>
</table>

NEJM 2008: 358; 1547-1559
Telmisartan vs. Placebo in ACE intolerant patients

**TRANSCEND**

Time to Primary Outcome

- Telmisartan
- Placebo

Cumulative Incidence Rates

No. at Risk
- T: 2954, 2807, 2699, 2577, 2278, 1091
- PI: 2972, 2839, 2713, 2575, 2253, 1069

Years of Follow-up

- HR: 0.92 (0.81-1.05)
- p-value = 0.2158

ESC: SEP 2008
Implications

• 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???
שאלה 3: טיפולי בדיהידרופירידין (אמולודיפין):

1. קשר בין נמוך יותר של תעוקת חזה (ברחובים עם מחלה
ACE כלילית ייזבה) בחולים שנמשכים בתרופות החמצות
2. לא נופל ממעכבי ACE ביטוי פעולותיה של תקשורת כלילית
(בבדיקות IVUS)
3. בשילוב עם ACE/ARB
4. עדיף על טיפולי דיוורני becutin
5. תחלואה וموت כלי בברחובים
6. כל ה
7.建档 מהני
8._playing מחינל
9. 의미
Avoiding Cardiovascular Events through COMbination Therapy in Patients Living with Systolic Hypertension

Kenneth Jamerson¹, George L. Bakris², Bjorn Dahlof³, Bertram Pitt¹, Eric J. Velazquez⁴, and Michael A. Weber⁵
for the ACCOMPLISH Investigators

University of Michigan Health System, Ann Arbor, MI¹; University of Chicago-Pritzker School of Medicine, Chicago, IL²; Sahlgrenska University Hospital, Gothenburg, Sweden³; Duke University School of Medicine, Durham, NC⁴; SUNY Downstate Medical College, Brooklyn, NY⁵
ACCOMPLISH: Design

*Beta blockers; alpha blockers; clonidine; (loop diuretics).

Jamerson KA et al. Am J Hypertens. 2003;16(part2)193A
Systolic Blood Pressure Over Time

**ACEI / HCTZ**
N=5733

**CCB / ACEI**
N=5713

- **Mean values are taken at 30 months F/U visit**

<table>
<thead>
<tr>
<th>Month</th>
<th>ACEI / HCTZ</th>
<th>CCB / ACEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>130mmHg</td>
<td>129.3 mmHg</td>
</tr>
<tr>
<td></td>
<td>Difference of 0.7 mmHg p&lt;0.05*</td>
<td>129.3 mmHg</td>
</tr>
<tr>
<td></td>
<td>DBP: 71.1</td>
<td>DBP: 72.8</td>
</tr>
<tr>
<td></td>
<td>N=5733</td>
<td>N=5713</td>
</tr>
</tbody>
</table>

*Mean values are taken at 30 months F/U visit*
HR (95% CI): 0.80 (0.72, 0.90)

20% Risk Reduction

ACEI / HCTZ

CCB / ACEI

p = 0.0002

INTERIM RESULTS Mar 08
Antiplatelet Therapy
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?
One-Year Cardiovascular Event Rates in a Global Contemporary Registry of >68,000 Outpatients with Atherothrombosis: the REDuction of Atherothrombosis for Continued Health (REACH) Registry Results

Ph.G Steg*, DL. Bhatt, PWF.Wilson, EM.Ohman, J. Röther, CS. Liau, AT. Hirsch, JL. Mas, S. Goto, on behalf of the REACH Registry Investigators

*AP-HP, Hôpital Bichat-Claude Bernard, Paris, France

Presented at the ACC – Atlanta 2006
Inclusion criteria

Must include

Signed
Written
Informed Consent

Patients aged >45 years

1 At least of four criteria

- Documented cerebrovascular disease
  Ischemic stroke or transient ischemic attack
- Documented coronary disease
  Angina, MI, angioplasty/stent/bypass
- Documented historical or current intermittent claudication associated with ABI <0.9

At least 3 atherothrombotic risk factors

- Male ≥65 years or female ≥70 years
- Current smoking >15 cigarettes/day
- Type I or Type II diabetes
- Hypercholesterolemia
- Diabetic nephropathy
- Hypertension
- Ankle Brachial Index (ABI) <0.9 in either leg at rest
- Asymptomatic carotid stenosis ≥70%
- Presence of at least one carotid plaque

1 At least one of four criteria

3 atherothrombotic risk factors

1 At least one of four criteria

3 atherothrombotic risk factors
1-year results

Unless otherwise specified, event rates have been adjusted for age, hypertension, diabetes, smoking and cholesterol
CV death / MI / stroke

Constant slope is a marker of stability – chronic phase
<table>
<thead>
<tr>
<th>Event Description</th>
<th>Total (N=63,129)</th>
<th>Symptomatic (N=51,685)</th>
<th>Multiple RF only (N=11,444)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>1.5</td>
<td>1.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1.2</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>1.6</td>
<td>1.8</td>
<td>0.8</td>
</tr>
<tr>
<td>CV death/MI/ stroke</td>
<td>3.5</td>
<td>3.9</td>
<td>1.7</td>
</tr>
<tr>
<td>CV death/MI/ stroke/hospitalization for atherothrombotic events*</td>
<td>12.9</td>
<td>14.5</td>
<td>5.4</td>
</tr>
</tbody>
</table>

*TIA, unstable angina, other ischemic arterial event including worsening of peripheral arterial disease

RF=risk factor
1-year cardiovascular event rates as function of number of symptomatic disease locations*

All p values <0.001

*Pts with ≥3 risk factors but no symptoms are counted as 0, even in the presence of asymptomatic carotid plaque or reduced ABI

**TIA, unstable angina, other ischemic arterial event including worsening of peripheral arterial disease

CV death
Non-fatal MI
Non-fatal stroke
CV death / MI / stroke

Percent

0 1 2 3

0.6 0.7 0.8 1.5

1.4 1.2 1.5 1.5

2.4 1.9 2.9 3.4

3.8 1.5 3.7 5.7

7.1
CV death/MI/stroke vs bleeding*: symptomatic vs RF only (unadjusted)

<table>
<thead>
<tr>
<th></th>
<th>RF only</th>
<th>Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death/MI/stroke</td>
<td>1.69</td>
<td>3.89</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.51</td>
<td>0.87</td>
</tr>
</tbody>
</table>

*: requiring hospitalization or transfusion
Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA)
Study Design

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

**Clopidogrel 75 mg/day**
(n=7802)

**Placebo 1 tablet/day**
(n=7801)

- Low dose ASA 75–162 mg/day
- Double-blind treatment up to 1040 primary efficacy events*
- Visits every 6 months
- Final visit (Fixed study end date)

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

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

Inclusion criteria

**Must include**
- Signed Written Informed Consent
- Patients aged >45 years

**At least one of four criteria**
- Documented cerebrovascular disease
- Documented coronary disease
- Documented symptomatic PAD
- 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
Overall Population: Primary Efficacy Outcome (MI, Stroke, or CV Death)†

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</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>
</tbody>
</table>

Overall Population 15,603 0.93 (0.83, 1.05) 0.22

* 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>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 Death64 (3.9)</td>
<td>36 (2.2)</td>
<td>1.74 (1.16, 2.62)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction40 (2.4)</td>
<td>33 (2.0)</td>
<td>1.19 (0.75, 1.89)</td>
<td>0.45</td>
<td></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.
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
OUTLINE

- Pathophysiology
  - Atherosclerosis
  - Ischemia

- Therapy
  - Lifestyle
  - Pharmacology
  - Revascularization
COURAGE

Clinical Outcomes Utilizing Revascularization and Aggressive Guideline-Driven Drug Evaluation
Stable CAD: PCI vs Conservative Medical Management

Meta-analysis of 11 randomized trials; N = 2,950

<table>
<thead>
<tr>
<th>Event</th>
<th>Favors PCI</th>
<th>Favors Medical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td>P 0.68</td>
</tr>
<tr>
<td>Cardiac death or MI</td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td>CABG</td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>PCI</td>
<td></td>
<td>0.34</td>
</tr>
</tbody>
</table>

Risk ratio (95% CI)

Hypothesis

PCI + Optimal Medical Therapy
will be Superior to
Optimal Medical Therapy Alone
Inclusion/Exclusion Criteria

**Inclusion**
- Men and Women
- 1, 2, or 3 vessel disease
  (> 70% visual stenosis of proximal coronary segment)
- Anatomy suitable for PCI
- CCS Class I-III angina
- Objective evidence of ischemia at baseline, ECG or imaging
- ACC/AHA Class I or II indication for PCI

**Exclusion**
- Uncontrolled unstable angina
- Complicated post-MI course
- Revascularization within 6 months
- Ejection fraction <30%
- Cardiogenic shock/severe heart failure
- History of sustained or symptomatic VT/VF
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>LDL cholesterol (primary goal)</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>Body Weight by Body Mass index</td>
<td>Initial BMI</td>
</tr>
<tr>
<td></td>
<td>25-27.5</td>
</tr>
<tr>
<td></td>
<td>&gt;27.5</td>
</tr>
<tr>
<td></td>
<td>loss</td>
</tr>
<tr>
<td></td>
<td>Weight Loss Goal</td>
</tr>
<tr>
<td></td>
<td>BMI &lt;25</td>
</tr>
<tr>
<td></td>
<td>10% relative weight</td>
</tr>
<tr>
<td>Blood Pressure</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>Months 60</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCI +OMT</td>
<td>OMT</td>
<td>PCI +OMT</td>
<td>OMT</td>
</tr>
<tr>
<td>SBP</td>
<td>0.77 ± 131</td>
<td>0.66 ± 130</td>
<td>0.81 ± 124</td>
<td>0.92 ± 122</td>
</tr>
<tr>
<td>DBP</td>
<td>0.33 ± 74</td>
<td>0.33 ± 74</td>
<td>0.81 ± 70</td>
<td>0.65 ± 70</td>
</tr>
<tr>
<td>Total Cholesterol mg/dL</td>
<td>1.37 ± 172</td>
<td>1.41 ± 177</td>
<td>1.74 ± 143</td>
<td>1.64 ± 140</td>
</tr>
<tr>
<td>LDL mg/dL</td>
<td>1.17 ± 100</td>
<td>1.22 ± 102</td>
<td>1.33 ± 71</td>
<td>1.21 ± 72</td>
</tr>
<tr>
<td>HDL mg/dL</td>
<td>0.39 ± 39</td>
<td>0.37 ± 39</td>
<td>0.67 ± 41</td>
<td>0.75 ± 41</td>
</tr>
<tr>
<td>TG mg/dL</td>
<td>2.96 ± 143</td>
<td>3.03 ± 149</td>
<td>4.13 ± 123</td>
<td>4.70 ± 131</td>
</tr>
<tr>
<td>BMI Kg/M²</td>
<td>0.18 ± 28.7</td>
<td>0.17 ± 28.9</td>
<td>0.34 ± 29.2</td>
<td>0.31 ± 29.5</td>
</tr>
<tr>
<td>(Moderate Activity (5x/week</td>
<td>25%</td>
<td>25%</td>
<td>42%</td>
<td>36%</td>
</tr>
</tbody>
</table>
Survival Free of Death from Any Cause and Myocardial Infarction

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Years</th>
<th>Medical Therapy</th>
<th>PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1138</td>
<td>1017</td>
<td>1149</td>
</tr>
<tr>
<td>1</td>
<td>1017</td>
<td>959</td>
<td>1013</td>
</tr>
<tr>
<td>2</td>
<td>959</td>
<td>834</td>
<td>952</td>
</tr>
<tr>
<td>3</td>
<td>834</td>
<td>638</td>
<td>833</td>
</tr>
<tr>
<td>4</td>
<td>638</td>
<td>408</td>
<td>637</td>
</tr>
<tr>
<td>5</td>
<td>408</td>
<td>192</td>
<td>417</td>
</tr>
<tr>
<td>6</td>
<td>192</td>
<td>30</td>
<td>200</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio: 1.05
95% CI (0.87-1.27)
P = 0.62
### Freedom from Angina by CCS Class During Long-Term Follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PCI + OMT</th>
<th>OMT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina free – no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>1 Yr</td>
<td>66%</td>
<td>58%</td>
</tr>
<tr>
<td>3 Yr</td>
<td>72%</td>
<td>67%</td>
</tr>
<tr>
<td>5 Yr</td>
<td>74%</td>
<td>72%</td>
</tr>
</tbody>
</table>

The comparison between the PCI group and the medical-therapy group was significant at 1 year (P<0.001) and 3 years (P=0.02) but not at baseline or 5 years.
Recommendations for pharmacological therapy to improve symptoms and/or reduce ischaemia

Class I

- Provide **short-acting nitroglycerin** for acute symptom relief and situational prophylaxis, with appropriate instructions on how to use the treatment (level of evidence B)

- Test the effects of a **beta-1 blocker**, and titrate to full dose; consider the need for 24 h protection against ischaemia (level of evidence A)

- In case of beta-blocker intolerance or poor efficacy attempt monotherapy with a **calcium channel blocker** (level of evidence A), **long acting nitrate** (level of evidence C), or **nicorandil** (level of evidence C)

- If the effects of **beta-blocker** monotherapy are insufficient, add a **dihydropyridine calcium channel blocker** (level of evidence B)

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

Class IIa
- In case of beta-blocker intolerance try sinus node inhibitor (level of evidence B)
- If CCB monotherapy or combination therapy (CCB with beta-blocker) is unsuccessful, substitute the CCB with a long-acting nitrate or nicorandil. Be careful to avoid nitrate tolerance (level of evidence C)

Class IIb
- Metabolic agents may be used where available as add on therapy, or as substitution therapy when conventional drugs are not tolerated (level of evidence B)

ESC guidelines on the management of stable AP - 2006