Advanced Treatment Choices for Ischemic Heart Disease in 2018

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Presenter Disclosure Information

- No financial relationships to disclose
Coronary Heart Disease: The Scope of the Problem

- CHD is the leading cause of death in the United States
- 16.5 million people in the U.S. have CHD
  - 9.1 million men (7%) and 7.4 million women (5%)
  - By age 60, 20% of men and 6% of women have CHD
- 790,000 people have CHD events / year
  - 580,000 are first events
  - 210,000 are recurrent events
  - 168,000 are silent events
- 360,000 CHD deaths (1 in every 7 deaths)
- 3.4 million people in the U.S. have chronic stable angina.

AHA Heart Disease & Stroke Statistics:2017 Update
http://circ.ahajournals.org/content/early/2017/01/25/CIR.00000000000000485
Goals of Treatments for Chronic CAD

• Reduce acute coronary events (MI, cardiac death)
  – Pacify the platelets
  – Treat the plaques
    • Stabilize the plaques
    • Slow the atherosclerotic process
• Relieve the symptoms of angina
Anti-platelet Therapy

- Aspirin remains the mainstay
Anti-platelet Therapy: Aspirin for Secondary Prevention

Meta-analysis from the Antithrombotic Trialists' Collaboration

AT Collaboration. BMJ 2002;324:71-86

Non-fatal MI ↓28%
Mortality ↓11%
Anti-platelet Therapy: Aspirin for “Primary and a half” Prevention

AT Collaboration. BMJ 2002;324:71-86
Aspirin Therapy and Clinical Outcomes in Non-Obstructive CAD (<50%) by Cardiac CTA

Adjusted HR = 0.649 (95% CI 0.492–0.857)
P = 0.0023 (Cox regression)
P = 0.0431 (log-rank)

Aspirin Therapy and Clinical Outcomes in Non-Obstructive CAD (<50%) by Cardiac CTA

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 years (n = 5,108)</td>
<td>0.887</td>
<td>0.336 – 1.446</td>
<td>0.3326</td>
</tr>
<tr>
<td>≥ 65 years (n = 3,264)</td>
<td>0.665</td>
<td>0.450 – 0.980</td>
<td>0.0053</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 5,888)</td>
<td>0.678</td>
<td>0.478 – 0.962</td>
<td>0.0263</td>
</tr>
<tr>
<td>Female (n = 2,486)</td>
<td>0.591</td>
<td>0.372 – 0.941</td>
<td>0.0266</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 7,190)</td>
<td>0.883</td>
<td>0.332 – 1.039</td>
<td>0.0673</td>
</tr>
<tr>
<td>Yes (n = 1,272)</td>
<td>0.632</td>
<td>0.457 – 0.874</td>
<td>0.0055</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (n = 5,779)</td>
<td>0.829</td>
<td>0.506 – 1.352</td>
<td>0.4522</td>
</tr>
<tr>
<td>Yes (n = 2,593)</td>
<td>0.593</td>
<td>0.417 – 0.842</td>
<td>0.0035</td>
</tr>
<tr>
<td><strong>CACS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 (n = 5,755)</td>
<td>0.828</td>
<td>0.549 – 1.247</td>
<td>0.3661</td>
</tr>
<tr>
<td>≥ 100 (n = 1,733)</td>
<td>0.556</td>
<td>0.345 – 0.896</td>
<td>0.0159</td>
</tr>
<tr>
<td><strong>LDL-C (100 mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100 mg/dL (n = 2,007)</td>
<td>0.633</td>
<td>0.361 – 1.112</td>
<td>0.1117</td>
</tr>
<tr>
<td>≥ 100 mg/dL (n = 5,008)</td>
<td>0.583</td>
<td>0.356 – 0.988</td>
<td>0.0450</td>
</tr>
<tr>
<td><strong>LDL-C (130 mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 130 mg/dL (n = 4,793)</td>
<td>0.733</td>
<td>0.478 – 1.125</td>
<td>0.1566</td>
</tr>
<tr>
<td>≥ 130 mg/dL (n = 2,222)</td>
<td>0.371</td>
<td>0.150 – 0.922</td>
<td>0.0328</td>
</tr>
<tr>
<td><strong>hsCRP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 mg/L (n = 4,458)</td>
<td>0.747</td>
<td>0.426 – 1.309</td>
<td>0.3082</td>
</tr>
<tr>
<td>≥ 2 mg/L (n = 2,400)</td>
<td>0.577</td>
<td>0.406 – 0.821</td>
<td>0.0022</td>
</tr>
<tr>
<td><strong>GFR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60 mL/min/1.73m² (n = 943)</td>
<td>0.465</td>
<td>0.290 – 0.746</td>
<td>0.0015</td>
</tr>
<tr>
<td>≥ 60 mL/min/1.73m² (n = 6,890)</td>
<td>0.746</td>
<td>0.520 – 1.071</td>
<td>0.1118</td>
</tr>
<tr>
<td><strong>Total (n = 6,372)</strong></td>
<td>0.649</td>
<td>0.492 – 0.857</td>
<td>0.0023</td>
</tr>
</tbody>
</table>

Death rate ratio (95% CI)
Anti-platelet Therapy: Clopidogrel (Plavix)

- Currently used most often in combination with aspirin following stent implantation
  - 1 month for bare metal stents
  - ≥ 12 months for drug-eluting stents
- Used with aspirin for 3-9 months following acute coronary syndromes:
  - CURE trial showed a 23% ↓ in MI (6.7% to 5.3%)
  - Event curves continue to separate even at 12 months, so the benefits might continue
  - Some have therefore prescribed combination therapy indefinitely for high-risk patients

Aspirin + Clopidogrel vs Aspirin Alone for Preventing Cardiovascular Events Among Patients at High Risk

JAMA Clinical Evidence Synopsis in 2018 summarizing a Cochrane review of 15 clinical trials

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of RCTs</th>
<th>No. of Participants</th>
<th>Estimated Absolute Risk per 1000 Participants (95% CI) for Aspirin Plus Clopidogrel</th>
<th>Estimated Absolute Risk per 1000 Participants for Aspirin Alone</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac mortality</td>
<td>7</td>
<td>31,903</td>
<td>37 (33-41)</td>
<td>37</td>
<td>0.98 (0.88-1.10)</td>
<td>.77</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>9</td>
<td>32,908</td>
<td>56 (46-66)</td>
<td>53</td>
<td>1.05 (0.87-1.25)</td>
<td>.62</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6</td>
<td>16,175</td>
<td>45 (40-52)</td>
<td>58</td>
<td>0.78 (0.69-0.90)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>5</td>
<td>40,06</td>
<td>63 (51-78)</td>
<td>86</td>
<td>0.73 (0.59-0.91)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>10</td>
<td>33,300</td>
<td>30 (26-34)</td>
<td>21</td>
<td>1.44 (1.25-1.64)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Abbreviation: RCT, randomized clinical trial.

The risk of having a cardiovascular event in the aspirin plus clopidogrel group is based on the assumed risk of having a cardiovascular event in the aspirin alone group and the relative risk of having a cardiovascular event in the aspirin plus clopidogrel group.

a The 95% CIs are not included because this column contains the reference values.

JAMA. Published online July 26, 2018.
https://jamanetwork.com/journals/jama/fullarticle/2695067
The Benefits of Statin Therapy Are Clear: 4S (Simvastatin Survival) Study

1 Death from coronary disease and non-fatal heart attacks.
2 Finished the study without suffering any coronary events or other atherosclerotic events such as stroke.

Lancet 1994; 344:1383-89
Meta-analysis of high-dose vs. standard-dose statin therapy: Achieved LDL of 70 vs. 100

Risk of Coronary Death or MI

LDL Goals Over the Prior Decade: Lower is Better

ATP III Updated Guidelines in 2004 (ATP III-R): Target LDL ≤ 70

HPS = Heart Protection Study; CARE = Cholesterol and Recurrent Events Trial; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease; 4S = Scandinavian Simvastatin Survival Study.
New ACC/AHA Guidelines -- Part 3: Panel Member Addresses Controversies Surrounding New Cholesterol Guideline

On Nov. 12, 2013, the American Heart Association (AHA) and the American College of Cardiology (ACC) released four new sets of clinical practice guidelines to assist primary care clinicians in identifying adults who may be at high risk for developing atherosclerotic cardiovascular disease (ASCVD) and who may benefit from lifestyle changes or drug therapy for prevention.¹

MPR offers a four-part series summarizing the new guidelines and discussing how they differ from earlier recommendations.
2013 ACC/AHA Cholesterol Guidelines

- **High-intensity statin therapy**
  - Goal = lowering LDL-C by ≥ 50%
  - Atorvastatin 40-80 mg, rosuvastatin 20-40 mg daily
- **Moderate-intensity statin therapy**
  - In those ≥ 75 years of age, or those who don’t tolerate or are at risk from high-dose statins
  - Goal = lowering LDL-C by 30-50%
  - Atorvastatin 10-20 mg, rosuvastatin 5-10 mg daily

http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a.full.pdf+html
2018: Meta-regression of achieved LDL-C and rate of major vascular events

**Safety Outcomes in Trials of Therapy to Achieve Very Low LDL-C Levels**

<table>
<thead>
<tr>
<th>Safety Outcome</th>
<th>Patients With Event, No.</th>
<th>Meta-analysis Data</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experimental Arm</td>
<td>Control Arm</td>
<td>Risk Ratio (95% CI)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>12,809</td>
<td>12,836</td>
<td>1.00 (0.98-1.02)</td>
</tr>
<tr>
<td>Myalgias or myopathy</td>
<td>116</td>
<td>135</td>
<td>0.85 (0.66-1.08)</td>
</tr>
<tr>
<td>Aminotransferase elevation</td>
<td>488</td>
<td>510</td>
<td>0.96 (0.85-1.08)</td>
</tr>
<tr>
<td>New-onset diabetes</td>
<td>1272</td>
<td>1320</td>
<td>0.97 (0.90-1.05)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>132</td>
<td>118</td>
<td>1.11 (0.87-1.43)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1,747</td>
<td>1,715</td>
<td>1.02 (0.96-1.09)</td>
</tr>
</tbody>
</table>

ACE Inhibitors for Risk Reduction

- HOPE (Heart Outcomes Prevention Evaluation) Study in 2000
  - 9300 high-risk patients (vascular disease or DM + one other CV risk factor and no LV dysfunction or CHF)
  - Randomized to ramipril 10 mg qd vs. placebo for 5 years
  - Ramipril group had lower rates of
    - MI ↓ 20%
    - CV mortality ↓ 26%, All-cause mortality ↓ 16%

## ACE Inhibitors for Risk Reduction: A Combined Analysis of Multiple Trials

Percent reduction in odds of CV death, non-fatal MI, or stroke

<table>
<thead>
<tr>
<th>Trials</th>
<th>Number of patients</th>
<th>Annual rates in placebo groups</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEACE</td>
<td>8290</td>
<td>2.13</td>
<td>7 (-8 to 19)</td>
<td>0.328</td>
</tr>
<tr>
<td>HOPE total</td>
<td>9297</td>
<td>3.95</td>
<td>25 (16 to 32)</td>
<td>0.0001</td>
</tr>
<tr>
<td>HOPE lower risk</td>
<td>3083</td>
<td>2.17</td>
<td>18 (-4 to 35)</td>
<td></td>
</tr>
<tr>
<td>HOPE medium risk</td>
<td>3100</td>
<td>3.58</td>
<td>20 (3 to 33)</td>
<td></td>
</tr>
<tr>
<td>HOPE high risk</td>
<td>3114</td>
<td>5.98</td>
<td>24 (12 to 34)</td>
<td></td>
</tr>
<tr>
<td>EUROPA total</td>
<td>12218</td>
<td>2.60</td>
<td>19 (8 to 28)</td>
<td>0.0007</td>
</tr>
<tr>
<td>EUROPA lower risk</td>
<td>3976</td>
<td>1.40</td>
<td>19 (-5 to 38)</td>
<td></td>
</tr>
<tr>
<td>EUROPA medium risk</td>
<td>3975</td>
<td>2.41</td>
<td>28 (11 to 41)</td>
<td></td>
</tr>
<tr>
<td>EUROPA high risk</td>
<td>3975</td>
<td>4.00</td>
<td>10 (-4 to 22)</td>
<td></td>
</tr>
<tr>
<td>AIRE</td>
<td>1986</td>
<td>22.6</td>
<td>24 (7 to 38)</td>
<td>0.0068</td>
</tr>
<tr>
<td>TRACE</td>
<td>1749</td>
<td>17.0</td>
<td>25 (9 to 33)</td>
<td>0.0028</td>
</tr>
<tr>
<td>SOLVD-P</td>
<td>4228</td>
<td>7.4</td>
<td>15 (2 to 27)</td>
<td>0.0252</td>
</tr>
<tr>
<td>SOLVD-T</td>
<td>2569</td>
<td>13.1</td>
<td>23 (10 to 33)</td>
<td>0.0009</td>
</tr>
<tr>
<td>SAVE</td>
<td>2231</td>
<td>9.8</td>
<td>20 (4 to 33)</td>
<td>0.0168</td>
</tr>
</tbody>
</table>

Do ARBs Confer Similar Benefit?: ONTARGET Study

Kaplan–Meier curves for the primary outcome = CV death, MI, stroke, or hospitalization for CHF

Telmisartan not inferior to ramipril
Combination therapy no better

Other Potential Therapeutic Strategies: Treating Elevated Homocysteine

- Vitamin treatments can lower homocysteine
  - Folic acid, vitamin B12, vitamin B6
- We had been treating for years, presumptively, while awaiting evidence of improved CV outcomes
- 3 large randomized trials in 2006 and 2010 showed no reduction in MI or stroke
  - HOPE 2 Study
  - The Norwegian Vitamin Trial (NORVIT)
  - SEARCH trial

Armitage JM et al. JAMA 2010; 303:2486-2494.
Other Potential Therapeutic Strategies: Antioxidant Vitamins

- There is no evidence of improved outcomes
  - **Simvastatin and niacin trial**: 800 IU vitamin E, 1000 mg vitamin C, 25 mg beta carotene, 100 mcg selenium; No benefit from vitamins alone, but when given with statin therapy there was a blunting of the outcomes improvement of statin therapy
  - **Heart Protection Study**: 600 mg vitamin E, 250 mg vitamin C, and 20 mg beta-carotene daily: Neutral effect on mortality and vascular events in 5 years
  - **SECURE trial**: Vitamin E had no effect on progression of atherosclerosis in carotid arteries by ultrasound

Other Potential Therapeutic Strategies: Multivitamins

- 18 trials, 2 million subjects
- No benefit in incidence of CHD, CHD mortality, or overall cardiovascular mortality

## Alpha Omega Trial: Primary and secondary outcomes in EPA-DHA alone vs. placebo/ALA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>EPA-DHA (n=2404), %</th>
<th>Placebo or ALA-only (n=2433), %</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major CV events*</td>
<td>14.0</td>
<td>13.8</td>
<td>1.01 (0.87–1.17)</td>
</tr>
<tr>
<td>Incident CV disease</td>
<td>7.0</td>
<td>7.6</td>
<td>0.92 (0.75–1.13)</td>
</tr>
<tr>
<td>Death from CV disease</td>
<td>3.3</td>
<td>3.4</td>
<td>0.98 (0.72–1.33)</td>
</tr>
<tr>
<td>Death from CHD</td>
<td>2.8</td>
<td>2.9</td>
<td>0.95 (0.68–1.32)</td>
</tr>
<tr>
<td>Ventricular arrhythmia-related events</td>
<td>2.8</td>
<td>3.0</td>
<td>0.90 (0.65–1.26)</td>
</tr>
<tr>
<td>Any death</td>
<td>7.7</td>
<td>7.6</td>
<td>1.01 (0.82–1.24)</td>
</tr>
</tbody>
</table>

*Primary end point; EPA=eicosapentaenoic acid; DHA=docosahexaenoic acid; ALA=alpha-linolenic acid

### Meta-analysis in 2018: Association of Omega-3 Fatty Acids With Major Vascular Events

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events (%)</th>
<th>Rate Ratios (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Control</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>1121 (2.9)</td>
<td>1155 (3.0)</td>
</tr>
<tr>
<td>Coronary heart disease death</td>
<td>1301 (3.3)</td>
<td>1394 (3.6)</td>
</tr>
<tr>
<td>Any</td>
<td>3085 (7.9)</td>
<td>3188 (8.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>574 (1.9)</td>
<td>554 (1.8)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>117 (0.4)</td>
<td>109 (0.4)</td>
</tr>
<tr>
<td>Unclassified/Other</td>
<td>142 (0.4)</td>
<td>135 (0.3)</td>
</tr>
<tr>
<td>Any</td>
<td>870 (2.2)</td>
<td>843 (2.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary</td>
<td>3044 (9.3)</td>
<td>3044 (9.3)</td>
</tr>
<tr>
<td>Noncoronary</td>
<td>305 (2.7)</td>
<td>330 (2.9)</td>
</tr>
<tr>
<td>Any</td>
<td>3290 (10.0)</td>
<td>3313 (10.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>3230 (15.2)</td>
<td>6071 (15.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10 randomized clinical trials, 77,917 participants

Control Other Risk Factors

- Smoking cessation
- Control hypertension
- Control of hyperglycemia in diabetics
  - United Kingdom Prospective Diabetes Study: For each 1% reduction in mean HbA1c there was a 14% RR for nonfatal MI (p < 0.0001)
- Avoid saturated fats
  - Avoid trans-fats
  - Increase intake of polyunsaturates
- Weight loss

Benefits of Exercise ≈ Other “Interventions”

- Reduces atherosclerosis
  - Patients with angiographically proven CAD randomized to regular exercise or usual care
  - After 1 year, underwent repeat coronary angiography
  - Least exercise: atherosclerosis progressed
  - Most exercise: atherosclerosis modestly regressed (p < 0.005)

- Reduces CV events and mortality
  - ↓ mortality post-MI by 20-25%
  - Even with only moderate levels of exercise

Relative Risk of Cardiovascular Disease vs. Pace (Adjusted for Age and Walking Time)

Manson J et al. NEJM 2002;347:716

- Rarely or never: 1
- < 2 MPH Casual: 1.07
- 2-3 MPH Average: 0.73
- 3-4 MPH Brisk: 0.57
- >4 MPH Very brisk: 0.4

P for trend = 0.002
“Prescribe” Exercise

- Moderate intensity aerobic exercise for a total of $\geq 30$ min at least 5 days per week
  - Episodes of exercise should be at least 10 min long
- Moderate resistance (strength) training at least twice per week

American Heart Association and American College of Sports Medicine 2007 guidelines
Treating the Symptoms of Angina
Anti-ischemic Medications: Mechanism of Action

- Decrease myocardial oxygen demand in the face of limited blood flow
  - Reduce heart rate
  - Reduce contractility
  - Reduce wall tension: afterload (SBP), preload
- Increase oxygen delivery
  - Vasodilation in the setting of increased vasomotor tone or vasospasm
  - Increase duration of diastole.
Anti-ischemic Medications: Beta Blockers

- Mainstay of therapy of angina in CAD
- ↓ heart rate, ↓ BP, and ↓ contractility
- Reduce late mortality and non-fatal recurrent infarction post-MI by 25%
- Please note: Despite a widely held belief, there is NO reduction in MI or mortality among those with CAD but without a prior MI

Anti-ischemic Medications: Nitrates

- ↓ Preload by venodilation, ↓ BP, ↑ collateral circulation
- Minimize any component of increased vasomotor tone or spasm
- Relieve symptoms of exertional angina
- Particularly useful in patients with LV dysfunction
- Sublingual: PRN or prophylactically
Anti-ischemic Medications: Calcium Channel Blockers

- Nifedipine or amlodipine
  - For those with hypertension, vasospasm
  - Long-acting preparations are safest
- Diltiazem or verapamil
  - For those with higher heart rates or who cannot tolerate beta blockers
Anti-ischemic Medications: Combination Therapy

- When one alone does not provide symptomatic relief, two or three agents are more efficacious.
- Nitrates and beta-blockers are especially complementary.
Persistent Angina

• Of the 3.4 million Americans with chronic stable angina, 5-15% may have symptoms refractory to triple therapy

• Revascularization is an option
  – But some patients are poor candidates for revascularization
  – Some have persistent angina despite revascularization

• Is there any other pharmacologic option for anti-anginal therapy?
An Additional Pharmacologic Option: Ranolazine (Ranexa)

- Newer antianginal agent: Approved by FDA in 2006
- Mechanism of action is uncertain:
  - Does not decrease heart rate or blood pressure
- Has anti-ischemic efficacy when used alone
  - Efficacy similar to atenolol
- Effective in combination with other anti-anginal medications
  - Because it does not decrease HR or BP it can be added even when HR or BP limits standard therapy
- Dosage = 500 mg or 1000 mg twice daily.

Ranolazine: Precautions

- **Side effects:**
  - Dizziness, nausea, constipation, vasovagal syncope
- **May slightly prolong QTc (avg. 2-5 ms):**
  - But trial data showed no evidence of proarrhythmia or sudden death
- **Metabolized by liver (cytochrome P3A), excreted in urine:**
  - Avoid use in sig. liver dysfunction, reduce dose in renal failure
  - Limit dose to 500 mg for those on digoxin, diltiazem, verapamil, erythromycin, fluconazole, TCAs, grapefruit
  - Do not use with strong CYP3A inhibitors: ketoconazole, clarithromycin, etc.
  - Long list of drug interactions, so read prescribing info each time

CV Therapeutics package insert
Coronary Artery Revascularization
Percutaneous Coronary Intervention (PCI)

- **Balloon angioplasty (PTCA → POBA)**
  - Initial success rate = 90-95%
  - Restenosis rate = 30-35%
- **Intracoronary stents**
  - Clinical restenosis rate decreased to 17%
  - Made angioplasty safer for high risk lesions (e.g., proximal LAD).
Bare-metal Stents: The Risk of Restenosis
Drug-Eluting Stents (DES)

- Stents are coated with polymers impregnated with drugs to arrest the cell cycle and thus prevent neointimal proliferation after stent placement.
Drug-Eluting Stents: Intermediate Outcomes

Restenosis (> 50%) at 9 months

- Bare Stent: 35%
- Sirolimus Coated: 3%

P < 0.001

Major Adverse Cardiac Events at 9 months

- Bare Stent: 21%
- Sirolimus Coated: 9%

P < 0.001

The SIRIUS Study: 1058 patients at 53 US centers
Large Trial Data of DES vs. BMS: Survival Free of MI and Reintervention

Drug-Eluting Stents: Is there a downside to arresting cell growth?
Endothelialization in Drug-Eluting Stents vs. Bare Metal Stents

Drug-Eluting Stents: The Risk of Thrombosis
Drug-Eluting Stents: Require Dual Antiplatelet Therapy (DAPT) for ≥ 12 Months

Aspirin plus clopidogrel or other thienopyridine (P2Y12 inhibitor), i.e., ticagrelor or prasugrel)
Large Trial Data of DES vs. BMS: Survival Free of MI

SMART-DATE: Randomized open-labelled trial of 6 vs 12-months of DAPT following PCI

- 2712 patients s/p drug eluting stent for acute coronary syndrome
- Randomized to 6-months vs 12 or more months of DAPT, followed for 18 months

DAPT Study: 12 vs. 30 months of dual antiplatelet therapy after drug eluting stents

- 9961 patients who had completed 12 months of DAPT after a DES
- Randomized to an additional 18 months of DAPT vs. aspirin

Prediction Rule for Benefit and Harm of DAPT Beyond 1 Year After PCI: The “DAPT Score”

<table>
<thead>
<tr>
<th>Clinical Prediction Score</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>≥75</td>
<td>-2</td>
</tr>
<tr>
<td>65–&lt;75</td>
<td>-1</td>
</tr>
<tr>
<td>&lt;65</td>
<td>0</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>MI at presentation</td>
<td>1</td>
</tr>
<tr>
<td>Prior PCI or prior MI</td>
<td>1</td>
</tr>
<tr>
<td>Paclitaxel-eluting stent</td>
<td>1</td>
</tr>
<tr>
<td>Stent diameter &lt;3 mm</td>
<td>1</td>
</tr>
<tr>
<td>CHF or LVEF &lt;30%</td>
<td>2</td>
</tr>
<tr>
<td>Vein graft stent</td>
<td>2</td>
</tr>
</tbody>
</table>

Total score range: -2 to 10

Low risk < 2
High risk ≥ 2

Conclusions About Drug-eluting Stents

- DES are effective in reducing restenosis
- DAPT should be continued for at least 6 and preferably 12 months after DES
  - Continuation of DAPT for longer than 12 months after DES may be reasonable for patients who tolerated DAPT without a bleeding complication and are not at high risk of bleeding
- Impact of DAPT should be considered prior to stent implantation when such therapy may be problematic in the long-term, e.g.:
  - A surgical procedure is anticipated
  - Chronic warfarin therapy is required
  - Peptic ulcer disease / GI bleeding

Mauri L, Smith SC, Jr.. JAMA Cardiol 2016;1:733-734
Traditional Assumptions Regarding Treatment of CAD with Ischemia

• Patients with symptomatic CAD and chronic angina who have significant coronary stenoses “need” revascularization
• PCI will improve prognosis
  – Prevent MI
  – Prevent cardiac death
• PCI will significantly improve symptoms.
Routine stenting of significant coronary stenoses: The COURAGE Trial

- COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
  - 2278 subjects with stable CAD
  - $\geq 70\%$ stenosis in a proximal epicardial coronary artery and objective evidence of myocardial ischemia
  - Mild to moderate angina
  - Anatomy suitable for PCI
- Randomized to PCI + optimal medical therapy vs. optimal medical therapy alone
- 2.5 to 7 year follow-up (mean 4.6 years)
- Primary outcome: Death or non-fatal MI.

Survival Free from Death or Non-Fatal MI

PCI + OMT

Optimal Medical Therapy (OMT)

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

Freedom from Angina During Follow-up

Courage: Extended follow-up to 12 years

Unadjusted hazard ratio for death, PCI plus medical therapy vs. medical therapy alone, 0.98 (95% CI, 0.83–1.15)
P=0.79 by log-rank test

Fractional Flow Reserve vs. Angiography for Multivessel Evaluation 2 (FAME 2) Trial

- Hypothesis: Patients with functionally significant stenoses, as determined by measurement of fractional flow reserve (FFR), PCI plus BMT would be superior to BMT alone.

- 888 patients were randomized to PCI vs. BMT alone
  - With stable CAD for whom PCI was being considered
  - Who had a functionally significant stenosis (FFR ≤ 0.80) in at least one visually stenotic (≥50%) coronary were randomly assigned
  - 332 patients with FFR > 0.80 (non stenotic) were entered into a registry and received BMT

- The primary end point was a composite of death, MI, or urgent revascularization.
  - Study terminated early due to sig. differences in primary endpoint

FAME 2: Incidence of Primary End Point of Death, MI, or Urgent Revascularization

FAME-2: Incidence of MI

PCI vs. medical therapy:
Hazard ratio, 1.05 (95% CI, 0.51–2.19); P=0.89

PCI vs. registry:
Hazard ratio, 1.61 (95% CI, 0.48–5.37); P=0.41

Medical therapy vs. registry:
Hazard ratio, 1.65 (95% CI, 0.50–5.47); P=0.41

FAME-2: Incidence of All-Cause Mortality

FAME-2: Incidence of “Urgent” Revascularization

Meta-analysis of Initial Stenting vs. Medical Management for Stable Coronary Stenoses

**Death**

<table>
<thead>
<tr>
<th>Source</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hambrecht\textsuperscript{15}</td>
<td>1.02 (0.02-52.43)</td>
<td>.99</td>
</tr>
<tr>
<td>MASS II\textsuperscript{13}</td>
<td>0.76 (0.27-2.16)</td>
<td>.60</td>
</tr>
<tr>
<td>COURAGE\textsuperscript{17}</td>
<td>0.84 (0.61-1.18)</td>
<td>.32</td>
</tr>
<tr>
<td>BARI 2D\textsuperscript{14}</td>
<td>1.06 (0.71-1.58)</td>
<td>.78</td>
</tr>
<tr>
<td>FAME 2\textsuperscript{16}</td>
<td>0.33 (0.03-3.16)</td>
<td>.33</td>
</tr>
<tr>
<td>Overall</td>
<td>0.90 (0.71-1.16)</td>
<td>.42</td>
</tr>
</tbody>
</table>

**Non-fatal MI**

<table>
<thead>
<tr>
<th>Source</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hambrecht\textsuperscript{15}</td>
<td>3.12 (0.12-78.45)</td>
<td>.49</td>
</tr>
<tr>
<td>MASS II\textsuperscript{13}</td>
<td>1.24 (0.40-3.88)</td>
<td>.71</td>
</tr>
<tr>
<td>COURAGE\textsuperscript{17}</td>
<td>1.24 (0.94-1.65)</td>
<td>.13</td>
</tr>
<tr>
<td>BARI 2D\textsuperscript{14}</td>
<td>1.29 (0.82-2.04)</td>
<td>.27</td>
</tr>
<tr>
<td>FAME 2\textsuperscript{16}</td>
<td>1.06 (0.51-2.22)</td>
<td>.88</td>
</tr>
<tr>
<td>Overall</td>
<td>1.24 (0.99-1.55)</td>
<td>.06</td>
</tr>
</tbody>
</table>

**Unplanned revascularization**

<table>
<thead>
<tr>
<th>Source</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hambrecht\textsuperscript{15}</td>
<td>2.60 (0.63-10.71)</td>
<td>.18</td>
</tr>
<tr>
<td>MASS II\textsuperscript{13}</td>
<td>1.84 (0.91-3.73)</td>
<td>.09</td>
</tr>
<tr>
<td>COURAGE\textsuperscript{17}</td>
<td>0.60 (0.48-0.74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BARI 2D\textsuperscript{14}</td>
<td>0.61 (0.46-0.80)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>FAME 2\textsuperscript{16}</td>
<td>0.13 (0.07-0.24)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Overall</td>
<td>0.64 (0.35-1.17)</td>
<td>.14</td>
</tr>
</tbody>
</table>

**Angina during follow-up**

<table>
<thead>
<tr>
<th>Source</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hambrecht\textsuperscript{15}</td>
<td>6.82 (0.79-58.85)</td>
<td>.08</td>
</tr>
<tr>
<td>MASS II\textsuperscript{13}</td>
<td>3.06 (0.83-11.29)</td>
<td>.09</td>
</tr>
<tr>
<td>COURAGE\textsuperscript{17}</td>
<td>0.91 (0.74-1.10)</td>
<td>.33</td>
</tr>
<tr>
<td>BARI 2D\textsuperscript{14}</td>
<td>0.87 (0.59-1.28)</td>
<td>.47</td>
</tr>
<tr>
<td>FAME 2\textsuperscript{16}</td>
<td>0.42 (0.25-0.72)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Overall</td>
<td>0.90 (0.57-1.44)</td>
<td>.67</td>
</tr>
</tbody>
</table>

ORBITA

- Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina
- 230 pts with angina, ischemia, ≥ 1 severe (≥ 70%) stenosis in a single coronary artery
  - All pts underwent 6 weeks of medical optimization with initiation and up titration of antianginal therapy
- Then 200 patients (98% with class II or III angina), were randomized to PCI with DES or a sham procedure
  - Post-procedure, both pts and care providers were blinded to treatment assignment
- At 6-week follow-up, pts in both groups were receiving a mean of 2.9 meds

https://doi.org/10.1016/S0140-6736(17)32714-9
The primary outcome was change in exercise time on a treadmill
  - A difference of at least 30 sec would be significant

Secondary endpoints were:
  - angina severity
  - angina stability and angina frequency
  - physical limitation
  - change in peak oxygen uptake
  - Duke treadmill score
  - change in exercise time to 1 mm ST-segment depression
  - change in wall motion score index on dobut. stress echo

https://doi.org/10.1016/S0140-6736(17)32714-9
PCI did not significantly improve exercise time
   - The incremental increase in avg. exercise time = 16 sec (P=0.20)
PCI did not significantly improve measures on well-validated patient-centered angina questionnaires
PCI did not significantly improve the Duke treadmill score or peak oxygen uptake
PCI did significantly improve the dobutamine stress echo wall-motion index
   - Indicating that PCI reduced ischemic burden (improved perfusion distal to stented lesion).

https://doi.org/10.1016/S0140-6736(17)32714-9
Coronary Artery Bypass Surgery (CABG): Long-term Outcomes

• Effectively relieves symptoms of angina
• Reduces mortality in selected groups
  – 3-vessel disease
  – Left main stenosis (or left-main equivalent)
  – Particularly in those with severe symptoms, early positive exercise tests, and/or impaired LV function
Meta-analysis of Randomized Trials of CABG vs. PCI in the Modern Era

- 6 randomized trials
  - 6055 patients with multi-vessel CAD
  - Median follow-up 4.1 years
- Primary outcomes
  - Death
  - Myocardial infarction
  - Repeat revascularization
  - Stroke

Meta-analysis of Randomized Trials of CABG vs. PCI in the Modern Era

Mortality

<table>
<thead>
<tr>
<th>Source</th>
<th>RR (95% CI)</th>
<th>Z Value</th>
<th>P Value</th>
<th>Death/Total</th>
<th>Favors CABG</th>
<th>Favors PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTS10,11</td>
<td>0.97 (0.66-1.43)</td>
<td>-0.16</td>
<td>.87</td>
<td>46/584</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MASS II6</td>
<td>0.67 (0.37-1.23)</td>
<td>-1.29</td>
<td>.20</td>
<td>16/203</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SoS2,15</td>
<td>0.63 (0.41-0.95)</td>
<td>-2.23</td>
<td>.03</td>
<td>34/500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARDia7</td>
<td>1.02 (0.39-2.69)</td>
<td>0.05</td>
<td>.96</td>
<td>8/242</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYNTAX multivessel9,12</td>
<td>0.60 (0.39-0.92)</td>
<td>-2.36</td>
<td>.02</td>
<td>31/547</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FREEDOM16</td>
<td>0.73 (0.56-0.95)</td>
<td>-2.31</td>
<td>.02</td>
<td>86/947</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>0.73 (0.62-0.86)</td>
<td>-3.69</td>
<td>&lt;.001</td>
<td>221/3023</td>
<td>303/3032</td>
<td></td>
</tr>
</tbody>
</table>

Meta-analysis of Randomized Trials of CABG vs. PCI in the Modern Era

Repeat Revascularization

Meta-analysis of Randomized Trials of CABG vs. PCI in the Modern Era

**Stroke**

<table>
<thead>
<tr>
<th>Source</th>
<th>RR (95% CI)</th>
<th>Z Value</th>
<th>P Value</th>
<th>stroke/total CABG</th>
<th>stroke/total PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTS$^{10,11}$</td>
<td>0.92 (0.52-1.65)</td>
<td>-0.27</td>
<td>0.79</td>
<td>21/584</td>
<td>23/590</td>
</tr>
<tr>
<td>MASS II$^6$</td>
<td>1.73 (0.70-4.31)</td>
<td>1.18</td>
<td>0.24</td>
<td>12/203</td>
<td>7/205</td>
</tr>
<tr>
<td>CARDia$^7$</td>
<td>7.17 (0.89-57.87)</td>
<td>1.85</td>
<td>0.06</td>
<td>7/242</td>
<td>1/248</td>
</tr>
<tr>
<td>SYNTAX multivessel$^{9,12}$</td>
<td>1.14 (0.56-2.32)</td>
<td>0.38</td>
<td>0.71</td>
<td>16/547</td>
<td>14/548</td>
</tr>
<tr>
<td>FREEDOM$^{16}$</td>
<td>1.69 (1.01-2.85)</td>
<td>1.98</td>
<td>0.05</td>
<td>37/947</td>
<td>22/953</td>
</tr>
</tbody>
</table>
| Meta-analysis        | 1.36 (0.99-1.86)  | 1.51    | 0.06    | 93/2523           | 67/2544          

Meta-analysis of Randomized Trials of CABG vs. PCI in the Modern Era

Major Adverse Cardiovascular and Cerebrovascular Events (MACCE)

THE GOOD NEWS: Hospital discharges for CHD in the United States from 1970-2010

AHA Heart Disease & Stroke Statistics: 2017 Update
http://circ.ahajournals.org/content/early/2017/01/25/CIR.00000000000000485
THE BAD NEWS: Frequency of Use of Statins and Aspirin in Patients with Previous CABG

Coronary Heart Disease: Reflective Statement

**Key Points:**
- Aspirin, statins, ACEIs/ARBs, and exercise all reduce risk of MI and/or cardiac death in pts with CAD
- Routine PCI in pts with stable angina or ischemia does not reduce risk of MI or cardiac death

**Next Best Steps:**
- Make sure your patients with CAD are on OMT, including aspirin + a mod. or high-dose statin
- Prescribe aerobic exercise
- Maintain DAPT ≥ 12 months in patients s/p DES