Treatment of Refractory Angina

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The Picture of Advanced Coronary Artery Disease

- A 62 year old man
- Multiple risk factors
- Extensive past CV history
  - PCI 1985
  - CABG 1996 (all SVG)
  - Multiple PCI 1990-95
  - Repeat CABG 1996
  - Recurrent angina – positive stress test 2006
  - Recent cath – normal EF and diffuse CAD
- On excellent medical therapy
  - ASA, Clopidogrel, Statin, Ranolazine, Nitrate, Metoprolol, ARB, and Amlodipine
  - Insulin, anti-depressant

What would you try next in this patient?

A. Increasing medical therapy to maximal tolerated doses
B. Spinal cord stimulation
C. TMR
D. EECP

Disclosures

- Consultant, Honoraria
  - The Medicines Company, Terumo Medical, Astra Zeneca, Eli Lilly/Daiichi-Sankyo, ZOLL
- Research funding
  - Ikaria, sanofi-aventis
- Off-label uses
  - May be discussed in this presentation
- Thanks to Magnus Ohman MD for slides
Refractory angina

- Scope of the problem
- Therapeutic options
  - Challenges
  - Medical therapy
  - Devices
    - Revascularization
    - Spinal cord stimulation
    - EECP
    - TMR
- Future directions

Burden of Chronic Angina in the United States

- Chronic angina occurs in 6.5 million adults in the United States
  - 400,000 new cases diagnosed per year
  - Chronic angina is the initial sign of ischemic heart disease in 50% of patients
  - The symptoms of chronic angina can be debilitating in many patients
  - The prevalence of chronic angina in the US poses a significant burden to the health care system

ESC Joint Study Group on the Treatment of Refractory Angina: Most Common Reasons Why Further Revascularization is not Possible

- Unsuitable coronary anatomy
- Multiple previous CABG or valve surgery
- Lack of surgical conduits
- Extra-cardiac co-morbid illnesses – CKD, COPD, etc
- Advanced age – often in combination with co-morbid illnesses

Angina Symptoms Occur at End of Ischemic Cascade

Abnormalities evolving during ischemia

- Approximately ½ of patients with angina also experience episodes of asymptomatic (silent) ischemia
- Many episodes of ischemia never become painful

Advanced Heart Disease and Refractory Ischemia

- Refractory angina – ESC definition
  - A chronic condition (>3 months) characterized by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty and coronary by-pass surgery. The presence of reversible myocardial ischemia should be clinically established to be the cause of the symptoms
- Advanced heart disease – practical definition
  - Symptomatic patients with multi-vessel CAD who are not candidates for revascularization with either PCI or CABG
Duke Databank Experience with Advanced CAD (3-vessel, L Main, EF<40%, and Severe Angina) Followed for an Average 2.2 Years

- Highly symptomatic
  - 79% CCS angina class III-IV
  - 27% trouble with any activity
- Poor social economic status
  - 36% income <$10,000
  - 43% retired
- High morbidity and mortality during flu
  - 38% mortality
  - 88% re-hospitalization
  - $74,128 in total healthcare costs

Prevalence of Medical Therapy at the Time of Catheterization by Year (Among Patients with Angina and Severe CAD)

<table>
<thead>
<tr>
<th>Year</th>
<th>1995</th>
<th>1997</th>
<th>1999</th>
<th>2001</th>
<th>2003</th>
<th>2005</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Treated Medically at the Time of Catheterization</td>
<td>36</td>
<td>36</td>
<td>34</td>
<td>32</td>
<td>36</td>
<td>30</td>
<td>32</td>
</tr>
</tbody>
</table>

Average: 32% treated medically at the time of catheterization

Refractory angina

- Therapeutic options
  - Challenges
  - Medical therapy
  - Devices
    - Revascularization
    - Spinal cord stimulation
    - EECP
    - TMR

Angina treatment: Objectives

- Prevent MI and death
- Improve quantity of life
- Reduce ischemia and relieve anginal symptoms
- Improve quality of life

Challenges in Evidence Based Medicine

- Challenges unique to refractory angina
  - Few clinical trials of anti-anginal therapies
  - Representation of patients with refractory angina is low in clinical trials
  - Small studies of device therapies
  - Often observational and retrospective rather than prospective and randomized

Refractory angina

- Symptom severity
- Therapeutic options
  - Medical therapy
- Therapeutic options

Management of Angina

- Combination medical therapy— if tolerated
  - Ranolazine
  - Nitrate – oral/topical
  - Beta-Blockers
  - Calcium Channel Blockers
- Once a day dosing may not suffice
  - Check HR and/or BP response with 24-hour recording
- Use life-style modifications
  - Pre-treat with SL NTG for exertion
  - Enroll in cardiac rehab
- Treat hypertension
  - Target BP < 140/80 mmHg

Long-Term Medication Use with CAD
Duke Cardiovascular Database: 1995-2002

- Therapeutic options
- Medical therapy

Six Medical Therapies Proven to Reduce Death

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Indication</th>
<th># pts</th>
<th>Reduction in deaths</th>
<th>Relative Absolute C/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>MI</td>
<td>18,773</td>
<td>23%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Fibrinolytics</td>
<td>MI</td>
<td>58,000</td>
<td>18%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>MI</td>
<td>28,970</td>
<td>13%</td>
<td>1.3%</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>MI</td>
<td>101,000</td>
<td>6.5%</td>
<td>6%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>2nd prev</td>
<td>54,360</td>
<td>15%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>2nd prev</td>
<td>20,312</td>
<td>21%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Statins</td>
<td>2nd prev</td>
<td>17,617</td>
<td>23%</td>
<td>2.7%</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>2nd prev</td>
<td>9,297</td>
<td>17%</td>
<td>1.9%</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>CHF</td>
<td>7,105</td>
<td>23%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>CHF</td>
<td>12,385</td>
<td>26%</td>
<td>4%</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>CHF</td>
<td>1,663</td>
<td>30%</td>
<td>11%</td>
</tr>
</tbody>
</table>
**CHARM Placebo group (n=3774): Predictors of Death**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>Chi-square (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10y)</td>
<td>1.78 (1.0-2.6)</td>
<td>132 (0.001)</td>
</tr>
<tr>
<td>EF (per 5%)</td>
<td>0.86 (0.84-0.9)</td>
<td>57 (0.001)</td>
</tr>
<tr>
<td>NYHA class</td>
<td>1.66 (1.4-1.9)</td>
<td>40 (0.001)</td>
</tr>
<tr>
<td>Heart rate (per 10 bpm)</td>
<td>1.22 (1.1-1.3)</td>
<td>29 (0.001)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.96 (0.94-0.97)</td>
<td>26 (0.001)</td>
</tr>
<tr>
<td>Atherosclerosis (&gt; v. &lt;50%)</td>
<td>0.54 (0.43-0.70)</td>
<td>24 (0.001)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.72 (1.42-2)</td>
<td>21 (0.001)</td>
</tr>
<tr>
<td># medications</td>
<td>1.18 (1.0-1.5)</td>
<td>12 (0.001)</td>
</tr>
<tr>
<td>Diastolic BP (per 10)</td>
<td>0.90 (0.82-0.99)</td>
<td>7 (0.007)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.75 (0.63-0.90)</td>
<td>9 (0.002)</td>
</tr>
<tr>
<td># comorbidities</td>
<td>1.05 (1.0-1.1)</td>
<td>2 (0.188)</td>
</tr>
</tbody>
</table>

Granger B et al. Lancet 2005

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**TERISA: Study Design**

- **Run-in Phase**: Single-blind placebo (4 weeks)
- **Treatment Phase**: Randomized double-blind parallel group phase (8 weeks): ranolazine (target dose 1000 mg bid vs. matching placebo)

**Study Endpoints**

- **Primary**: Average weekly number of angina episodes from weeks 2-8 of treatment
- **Key Secondary**: Average weekly number of SL NTG doses from weeks 2-8 of treatment

**Baseline Characteristics by Study Group**

<table>
<thead>
<tr>
<th>Antisanginal medications</th>
<th>Ranolazine (n=462)</th>
<th>Placebo (n=465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>on 1 (%)</td>
<td>56.1</td>
<td>55.7</td>
</tr>
<tr>
<td>on 2 (%)</td>
<td>43.9</td>
<td>44.3</td>
</tr>
<tr>
<td>Beta blockers (%)</td>
<td>90.5</td>
<td>89.9</td>
</tr>
<tr>
<td>Calcium channel blockers (%)</td>
<td>26.8</td>
<td>30.8</td>
</tr>
<tr>
<td>Long acting nitrates (%)</td>
<td>34.8</td>
<td>32.5</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>82.5</td>
<td>82.4</td>
</tr>
<tr>
<td>Antiplatelet agents (%)</td>
<td>89.8</td>
<td>86.5</td>
</tr>
<tr>
<td>ACE-I/ARBs (%)</td>
<td>88.1</td>
<td>87.5</td>
</tr>
<tr>
<td>Diary compliance - median % (IQR)</td>
<td>98 (95-98)</td>
<td>98 (95-98)</td>
</tr>
</tbody>
</table>

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**Weekly Angina Frequency by Study Group**

- **Run In Phase**
- **Treatment Phase**

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**Enrollment and Randomization**

- Assessed for Eligibility (n=1185)
  - Excluded (n=236)
  - Not meeting inclusion criteria (n=43)
  - Failed run-in (n=193)
- Randomized (n=949), 105 centers
- Discontinuation of Treatment (n=11)
- Randomized to Ranolazine (n=473)
- Randomized to Placebo (n=476)
- Analyzed (n=462)
- Analyzed (n=465)
Refractory angina

- Therapeutic options
- Devices
- Revascularization

Between 1986–2000 and Treated Without Revascularization
Over a 7-Year Mean Follow-up in 29,082 Patients Catheterized for CAD at Duke

Influence of Severity and Location of Stenosis on Cardiac Death
Over a 7-Year Mean Follow-up in 29,082 Patients Catheterized for CAD at Duke Between 1986–2000 and Treated Without Revascularization

Safety and Tolerability

<table>
<thead>
<tr>
<th>Ranolazine</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious Adverse Events</td>
<td>n=470</td>
<td>n=474</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>16 (3.4)</td>
<td>20 (4.2)</td>
</tr>
<tr>
<td>Death</td>
<td>3 (0.6)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>1 (0.2)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Stroke/transient ischemic attack</td>
<td>1 (0.2)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Unstable angina or coronary revascularization</td>
<td>6 (1.3)</td>
<td>7 (1.5)</td>
</tr>
</tbody>
</table>

Weekly SL NTG Doses

| Placebo | Ranolazine | p=0.003 |

<table>
<thead>
<tr>
<th>Study Week</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>SL NTG Doses</td>
<td>Run In Phase</td>
<td>Treatment Phase</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COURAGE Trial
N=2297 pts. With significant CAD and myocardial ischemia

PCI vs. medical therapy in Stable CAD
Effect on mortality; N=17 randomized trials, 7513 pts.
**PCI versus Medicine Meta-Analysis:**
*Reduction in Angina*

6 RCTs: 953 PCI pts and 951 Med pts

- **End point**
  - Angina
  - Death
  - PTCA
  - CABG

- **Risk ratio (95% CI)**
  - Angina: 0.70 (0.50 to 0.98)
  - Death: 1.32 (0.65 to 2.70)
  - PTCA: 1.29 (0.71 to 3.36)
  - CABG: 1.59 (1.09 to 2.32)

*Test of heterogeneity P=0.001*

<table>
<thead>
<tr>
<th></th>
<th>0.04</th>
<th>0.06</th>
<th>0.08</th>
<th>0.10</th>
<th>0.12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favour SCA</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Favour PTCA</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Favour medical treatment</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

**Revascularization Survival Benefit Attribution**
*Duke 1986-2000*

Additional Months of Life per 17 Years by CABG

- CABG better
- PCI better
- *p<0.05*

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Intermed</th>
<th>High</th>
<th>Low</th>
<th>Intermed</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG vs Med</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revasc vs Med</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Survival by residual ischemia**

N=314 patients in COURAGE nuclear substudy

Unadjusted p=0.001
Risk-adjusted p=0.09

Cumulative Event-Free Survival, %

- F/U in years: 1.5, 4.9, 5

**Challenges with revascularization**

- No suitable angiographic targets!

**Refractory angina**

- Therapeutic options
  - Devices
    - Spinal cord stimulation
    - EECP
    - TMR

**Device therapy for angina**

- Spinal Cord Stimulator (SCS)
  - Surgically or percutaneously implanted, C7-T1 level
  - Mechanisms of benefit
    - Reduced nociception
    - Reduction in overall sympathetic tone
    - Potential changes in cerebral blood flow affecting pain perception
    - Potential enhancement of coronary perfusion
  - Class IIb, LOE B in the guidelines
  - Few randomized studies*
  - Risks
    - Lead migration (5-13%), lead breakage (5-9%), infection (3%)
    - Potential masking of AMI

*Eckert S, Horstkottke D. Am J Cardiovasc Drugs 2009*
*Gibbons RJ, et al. Circulation 2003*
**Enhanced External CounterPulsation**

- May release angiogenic growth factors
- Recruit/develop collateral coronary circulation
- May have long-lasting effects in some patients
- Class IIb, LOE B
  - Placebo-controlled randomized trial showing decreased angina, increased exercise time
- Low risk, but requires therapy for several hours over several weeks

*Enhanced External CounterPulsation*

**TransMyocardial Revascularization (TMR)**

*Meta-analysis of 7 RCTs, N=1053 patients*

- Angina relief ≥ 2 classes at 1 year

**TransMyocardial Revascularization (TMR)**

**RIVER PCI Study GS-US-259-0116**

- 2600 patients, event driven outcome study
- Ranolazine 1000 mg BID vs. Placebo (1:1 randomization)
Inclusion criteria and endpoints

- Underwent PCI for any indication within 14 days of randomization
- History of chronic angina with at least 2 episodes which occurred on at least 2 separate days and at least 14 days prior to PCI
- Incomplete revascularization
  - one or more visually estimated ≥ 50% stenoses in one or more coronary arteries with reference vessel diameter ≥ 2.0mm
- Primary: Time to first occurrence of
  - Ischemia-driven revascularization, or
  - Ischemia-driven hospitalization (without revascularization)
- Secondary: Time to first occurrence of
  - Sudden cardiac death
  - Cardiovascular death
  - Myocardial infarction