Ασθενής με σταθερή στηθάγχη μετά από οξύ στεφανιαίο σύνδρομο: Σύγχρονη αντιμετώπιση με γνώμονα την ποιότητα ζωής και την προσήλωση του ασθενούς στη θεραπεία

Periklis Davlouros
Invasive Cardiology & Congenital Heart Disease
Associate Professor of Cardiology
Patras University Hospital
CONFLICTS OF INTEREST

This presentation is supported by Menarini
Principal Questions...

- What proportion of patients continue to experience angina after hospital discharge for an ACS?
- What is the impact in their quality of life?
Subsequent Questions…

- Guideline recommended therapies following an ACS…
  - Especially for **persistent angina**
  - Potential impact on **QoL**
  - Patient **compliance**
Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective

Tomas Jernberg, Pål Hasvold, Martin Henriksson, Hans Hjelm, Marcus Thuresson, Magnus Janzon

- **108 315 pts @ primary MI (2006-2011)**
  - 97 254 (89.8%) alive 1 week after discharge

- **CV death, Non-fatal MI, Non-fatal stroke**
  - **18.3%** during the first **365 days**

- **Pts without a combined endpoint during 1st 365 ds**
  - D/MI/S **20.0%** in the following **36 months**
CV Risk Following ACS remains High

- Need for disease modifying treatments
  - Antiplatelets
  - Statins
  - B-blockers
  - ACEI/ARBs
  - Eplerinone
2013 ESC guidelines on the management of stable coronary artery disease

**Angina relief**

1st line
- Short-acting Nitrates, plus
- **Beta-blockers or CCB-heart rate ↓**
- Consider CCB-DHP if low heart rate or intolerance/contraindications
- Consider Beta-blockers + CCB-DHP if CCS Angina > 2

2nd line
- May add or switch (1st line for some cases)
  - Ivabradine
  - Long-acting nitrates
  - Nicorandil
  - Ranolazine
  - Trimetazidine

**Event prevention**

- Lifestyle management
- Control of risk factors
- Educate the patient
- Aspirine
- Statins
- Consider ACEI or ARBs

+ Consider Angio → PCI – Stenting or CABG
### 2013 ESC guidelines on the management of stable coronary artery disease

<table>
<thead>
<tr>
<th>Angina/ischaemia relief</th>
<th>Class</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting nitrates are recommended.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>First-line treatment is indicated with β-blockers and/or calcium channel blockers to control heart rate and symptoms.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil or ranolazine, according to heart rate, blood pressure and tolerance.</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>For second-line treatment, trimetazidine may be considered.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>According to comorbidities/tolerance it is indicated to use second-line therapies as first-line treatment in selected patients.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>In asymptomatic patients with large areas of ischaemia (&gt;10%) β-blockers should be considered.</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.</td>
<td>Ila</td>
<td>B</td>
</tr>
</tbody>
</table>
CLASS IIa

2. Ranolazine can be useful when prescribed as a substitute for beta blockers for relief of symptoms in patients with SIHD if initial treatment with beta blockers leads to unacceptable side effects or is ineffective or if initial treatment with beta blockers is contraindicated (846). (Level of Evidence: B)

3. Ranolazine in combination with beta blockers can be useful when prescribed for relief of symptoms when initial treatment with beta blockers is not successful in patients with SIHD (847,848). (Level of Evidence: A)
Electro-Mechanical consequences of Ischemia…

Monophasic Action Potential (Cardiac Muscle Cell)

+ 10mV

Phase 0, Na$^+$ enters the cell
Depolarization

- 90 mV

Resting Potential

Depolarization → Repolarization

Phase 2, Ca$^{2+}$ enters the cell,
Initiation of contraction

Phase 3, K$^+$ exits the cell
Repolarization

$I_{Na^+L}$

Failure to Inactivate
Electro-Mechanical consequences of Ischemia...

Diagram showing the normal and delayed or incomplete inactivation of sodium current and action potential in ischemia-related conditions.
Electro-Mechanical consequences of Ischemia…

[Graph showing normal and delayed or incomplete inactivation of sodium current, action potential, and twitch responses.]
Diastolic relaxation failure increases oxygen consumption and reduces oxygen supply.

Increased myocardial tension during diastole:

- Increases myocardial $\text{O}_2$ consumption
- Compresses intramural small vessels
  - Reduces myocardial blood flow
- Worsens ischemia and angina
Consequences associated with dysfunction of late sodium current

- **Diseases** (e.g., ischemia, heart failure)
- **Pathological milieu** (reactive O₂ species, ischemic metabolites)
- **Toxins and drugs** (e.g., ATX-II, etc.)

**Mechanical dysfunction**
- Abnormal contraction and relaxation
- ↑ diastolic tension (↑ LV wall stiffness)

**Oxygen supply and demand**
- Increase ATP consumption
- Decrease ATP formation

**Electrical instability**
- Early after potentials
- Beat-to-beat ΔAPD
- Arrhythmias (VT)
Ranolazine (RANEXA) inhibits the late inward Na current, in a Concentration, Voltage & Frequency Dependent Manner...


Ischemia

\[ \text{Ca}^{2+}_{i} \text{Overload} \]

\[ \text{LV Diastolic Tension} \]

\[ \text{Na}^{+}_{i} \]
Lack of Effect of Ranolazine on HR and BP in Pts with Chronic Angina

A. Heart Rate

Ranolazine Concentration (µM)
Therapeutic Levels = 2 to 8 µM

B. Arterial Blood Pressure

Ranolazine Concentration (µM)
Effects of ranolazine in symptomatic patients with stable coronary artery disease. A systematic review and meta-analysis

Gianluigi Savarese, Giuseppe Rosano, Carmen D’Amore, Francesca Musella, Giuseppe Luca Della Ratta, Angela Maria Pellegrino, Tiziana Formisano, Alice Vitagliano, Annaapaola Cirillo, Gennaro Cice, Luigi Fini, Luca del Guercio, Bruno Trimmer, Pasquale Perrone-Filardi

**Weekly angina frequency**

<table>
<thead>
<tr>
<th>Study</th>
<th>WMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARISA (RAN 750 mg bid vs placebo)</td>
<td>-0.80 (-1.50, -0.10)</td>
</tr>
<tr>
<td>CARISA (RAN 1000 mg bid vs placebo)</td>
<td>-1.20 (-1.90, -0.50)</td>
</tr>
<tr>
<td>ERICA (RAN 1000 mg bid vs placebo)</td>
<td>-1.00 (-2.35, 0.35)</td>
</tr>
<tr>
<td>TERISA (RAN 1000 mg bid vs placebo)</td>
<td>-0.50 (-0.86, -0.14)</td>
</tr>
<tr>
<td>Overall (I-squared = 11.2%, p = 0.337)</td>
<td>-0.69 (-0.97, -0.40)</td>
</tr>
</tbody>
</table>

**Weekly nitroglycerin consumption**

<table>
<thead>
<tr>
<th>Study</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CARISA (RAN 750 mg bid vs placebo)</td>
<td>-1.00 (-1.91, -0.09)</td>
</tr>
<tr>
<td>CARISA (RAN 1000 mg bid vs placebo)</td>
<td>-1.30 (-2.22, -0.38)</td>
</tr>
<tr>
<td>ERICA (RAN 1000 mg bid vs placebo)</td>
<td>-0.90 (-2.19, 0.39)</td>
</tr>
<tr>
<td>TERISA (RAN 1000 mg bid vs placebo)</td>
<td>-0.40 (-0.68, -0.12)</td>
</tr>
<tr>
<td>Overall (I-squared = 37.7%, p = 0.186)</td>
<td>-0.53 (-0.79, -0.28)</td>
</tr>
</tbody>
</table>

p=0.000

Patras University Hospital
Evaluation of Ranolazine in Patients with Type 2 Diabetes Mellitus and Chronic Stable Angina

*Results from the TERISA Randomized Clinical Trial*


*On behalf of the TERISA Investigators*
Weekly Angina Frequency by Study Group

Run In Phase

Treatment Phase

Weekly Angina Frequency

-2 0 2 4 6 8
Study Week

Placebo
Ranolazine

p=0.008

Patras University Hospital
These data suggest that ranolazine is particularly beneficial in patients with stable angina who have suboptimally controlled T2DM.
SAQ Angina Frequency - Subgroups

Mean Treatment Difference - Repeated Measure Adjusted for Baseline

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.0 (-0.2, 2.2)</td>
</tr>
<tr>
<td>Age &lt;75 years</td>
<td>1.1 (-0.1, 2.4)</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>-0.2 (-3.6, 3.3)</td>
</tr>
<tr>
<td>Men</td>
<td>1.2 (-0.1, 2.5)</td>
</tr>
<tr>
<td>Women</td>
<td>-0.2 (-2.9, 2.4)</td>
</tr>
<tr>
<td>Non-ACS PCI indication</td>
<td>1.2 (-0.3, 2.7)</td>
</tr>
<tr>
<td>ACS PCI indication</td>
<td>0.6 (-1.2, 2.5)</td>
</tr>
<tr>
<td>No diabetes</td>
<td>0.2 (-1.2, 1.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.7 (0.5, 4.9)</td>
</tr>
<tr>
<td>Angina Monthly/None (SAQ &gt;60)</td>
<td>0.1 (-1.1, 1.4)</td>
</tr>
<tr>
<td>Angina Weekly/Daily (SAQ ≤60)</td>
<td>2.3 (0.0, 4.6)</td>
</tr>
</tbody>
</table>
Table 3. Cumulative Rate of the Composite Primary End Point and Its Components within One Year after Randomization.‡

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Early Invasive Strategy (N=604)</th>
<th>Selectively Invasive Strategy (N=596)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.  rate (%)†</td>
<td>no.  rate (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>15  2.5</td>
<td>15  2.5</td>
<td>0.99 (0.49–2.00)</td>
<td>0.97</td>
</tr>
<tr>
<td>Myocardial infarction‡</td>
<td>90  15.0</td>
<td>59  10.0</td>
<td>1.50 (1.10–2.04)</td>
<td>0.005</td>
</tr>
<tr>
<td>Peak CK-MB ≥1 to &lt;3×ULN</td>
<td>43  7.2</td>
<td>27  4.6</td>
<td>1.57 (0.98–2.51)</td>
<td>0.05</td>
</tr>
<tr>
<td>Peak CK-MB ≥3 to &lt;5×ULN</td>
<td>15  2.5</td>
<td>7  1.2</td>
<td>2.09 (0.86–5.10)</td>
<td>0.09</td>
</tr>
<tr>
<td>Peak CK-MB ≥5 to &lt;10×ULN</td>
<td>14  2.3</td>
<td>13  2.2</td>
<td>1.06 (0.50–2.23)</td>
<td>0.86</td>
</tr>
<tr>
<td>Peak CK-MB ≥10×ULN</td>
<td>11  1.8</td>
<td>6  1.0</td>
<td>1.79 (0.67–4.80)</td>
<td>0.23</td>
</tr>
<tr>
<td>No CK-MB, new Q waves</td>
<td>7  1.2</td>
<td>6  1.0</td>
<td>1.15 (0.39–3.37)</td>
<td>0.80</td>
</tr>
<tr>
<td>Spontaneous</td>
<td>22  3.7</td>
<td>27  4.6</td>
<td>0.80 (0.46–1.34)</td>
<td>0.45</td>
</tr>
<tr>
<td>Related to percutaneous coronary intervention or coronary-artery bypass grafting</td>
<td>68  11.3</td>
<td>32  5.4</td>
<td>2.09 (1.39–3.14)</td>
<td>0.001</td>
</tr>
<tr>
<td>FRISC II definition‡</td>
<td>73  12.1</td>
<td>46  7.8</td>
<td>1.56 (1.10–2.22)</td>
<td>0.008</td>
</tr>
<tr>
<td>TACTICS–TIMI 18 definition¶</td>
<td>51  8.5</td>
<td>35  5.9</td>
<td>1.43 (0.95–2.17)</td>
<td>0.07</td>
</tr>
<tr>
<td>Rehospitalization for anginal symptoms</td>
<td>44  7.4</td>
<td>64  10.9</td>
<td>0.68 (0.47–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Primary composite end point</td>
<td>137  22.7</td>
<td>126  21.2</td>
<td>1.07 (0.87–1.33)</td>
<td>0.33</td>
</tr>
<tr>
<td>FRISC II definition‡</td>
<td>122  20.2</td>
<td>115  19.3</td>
<td>1.05 (0.83–1.32)</td>
<td>0.52</td>
</tr>
<tr>
<td>TACTICS–TIMI 18 definition¶</td>
<td>102  16.9</td>
<td>105  17.6</td>
<td>0.96 (0.75–1.23)</td>
<td>0.87</td>
</tr>
</tbody>
</table>
At 1 year, 14% of pts who received invasive therapies experienced angina (CCS classification) vs. 13% of pts who received conservative therapies...
Angina at 1 yr post-MI: Frequency…

Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) multicenter cohort study

- 1 in 5 pts experience angina 1 yr post-MI…
  - Among those, 1 in 5 had angina daily or weekly…
## Angina at 1 yr post-MI: Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Less likely to have angina</th>
<th>More likely to have angina</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger age (10-y decrease)</td>
<td></td>
<td></td>
<td>1.19 (1.09-1.30)</td>
</tr>
<tr>
<td>Effect of nonwhite race for females</td>
<td></td>
<td></td>
<td>0.88 (0.68-1.15)</td>
</tr>
<tr>
<td>Effect of nonwhite race for males</td>
<td></td>
<td></td>
<td>1.50 (1.16-1.96)</td>
</tr>
<tr>
<td>Baseline angina</td>
<td></td>
<td></td>
<td>1.78 (1.54-2.06)</td>
</tr>
<tr>
<td>History of CABG surgery</td>
<td></td>
<td></td>
<td>1.92 (1.51-2.44)</td>
</tr>
<tr>
<td>Recurrent rest angina during MI hospitalization</td>
<td></td>
<td></td>
<td>1.54 (1.22-1.93)</td>
</tr>
<tr>
<td>Smoking cessation after hospitalization</td>
<td></td>
<td></td>
<td>1.11 (0.87-1.40)</td>
</tr>
<tr>
<td>Persistent smoking after hospitalization</td>
<td></td>
<td></td>
<td>1.23 (1.02-1.48)</td>
</tr>
<tr>
<td>Outpatient revascularization</td>
<td></td>
<td></td>
<td>1.37 (1.09-1.73)</td>
</tr>
<tr>
<td>New depressive symptoms</td>
<td></td>
<td></td>
<td>1.96 (1.34-2.87)</td>
</tr>
<tr>
<td>Persistent depressive symptoms</td>
<td></td>
<td></td>
<td>1.88 (1.29-2.75)</td>
</tr>
<tr>
<td>Transient depressive symptoms</td>
<td></td>
<td></td>
<td>1.77 (1.49-2.11)</td>
</tr>
</tbody>
</table>
Angina at 1 yr post-MI: Risk Factors

Angina associated with a variety of adverse cardiac outcomes, including poor functional status, diminished health-related QoL, recurrent MI, and mortality...
Change in Angina Symptom Status After Acute Myocardial Infarction and Its Association With Readmission Risk: An Analysis of the Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status (TRIUMPH) Registry

- Prior to MI
  - No Angina: 1622 patients
  - Angina: 1293 patients

- MI
  - 60% change
  - Angina free: 1278 patients (78%)
  - Resolved Angina: 788 patients
  - New Angina: 344 patients (21%)
  - Persistent Angina: 505 patients
Angina 30 days after MI, whether persistent or newly developed, led to higher rates of readmission…
OBJECTIVES
Efficacy: Composite of CV Death, MI or RI
Safety: Clinically Significant Arrhythmia

Morrow DA et al. JAMA 2007; 297: 1775-83
MERLIN - TIMI 36 Trial

Cardiovascular Death, MI, or Recurrent Ischemia, %

No. at Risk
Placebo Ranolazine
3279 2450 1223 269

Patras University Hospital

Morrow DA et al. JAMA 2007; 297: 1775-83
MERLIN - TIMI 36 Trial

Recurrent Ischemia

Cumulative Percentage

Days After Randomization

HR, 0.87 (95% CI, 0.76-0.99)
Log-Rank $P = 0.03$

8% RRR

13% RRR
Ranolazine, more effective in the acute phase of ACS when \( \uparrow \) HR…

### Events by heart rate at onset (bpm)

<table>
<thead>
<tr>
<th>Heart Rate</th>
<th>Hazard Ratio</th>
<th>Ischemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>0.87</td>
<td>18.3 16.0 0.02</td>
</tr>
<tr>
<td>&gt; 90</td>
<td>0.84</td>
<td>11.8 10.0 0.027</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>0.82</td>
<td>5.5 4.6 0.083</td>
</tr>
<tr>
<td>&gt; 110</td>
<td>0.61</td>
<td>2.5 1.6 0.007</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>0.50</td>
<td>1.2 0.6 0.013</td>
</tr>
</tbody>
</table>
At 4 mos after ACS

- No angina 50.2% pts
- Monthly angina 29.5%
- Weekly angina 15.6%
- Daily angina 4.7%
Economic Impact of Angina After an Acute Coronary Syndrome
Insights From the MERLIN-TIMI 36 Trial

Suzanne V. Arnold, David A. Morrow, Yang Lei, David J. Cohen, Elizabeth M. Mahoney, Eugene Braunwald, Paul S. Chan

Table 1. Baseline and Clinical Characteristics Stratified by Frequency of Angina at 4 Months After Hospitalization

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>None (n=2739)</th>
<th>Monthly (n=1608)</th>
<th>Weekly (n=854)</th>
<th>Daily (n=259)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North</td>
<td>15.7</td>
<td>15.0</td>
<td>12.3</td>
<td>8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>America, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td>41.2</td>
<td>25.4</td>
<td>22.1</td>
<td>18.1</td>
<td></td>
</tr>
<tr>
<td>Eastern</td>
<td>27.5</td>
<td>33.4</td>
<td>27.5</td>
<td>17.0</td>
<td></td>
</tr>
<tr>
<td>Europe, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Russia, %</td>
<td>4.7</td>
<td>13.9</td>
<td>27.0</td>
<td>43.2</td>
<td></td>
</tr>
<tr>
<td>East/Africa, %</td>
<td>11.0</td>
<td>12.3</td>
<td>11.0</td>
<td>13.5</td>
<td></td>
</tr>
</tbody>
</table>
Kaplan-Meier curve of time to **cardiovascular hospitalization** by angina frequency group.
Cumulative **costs** of cardiovascular hospitalizations by angina frequency group...
29.3% reported angina within the first 6 wks

MI pts treated with PCI at 233 US hospitals from 2010 to 2012
Of patients with angina

- 2.7% had daily angina
- 18.0% had weekly angina
- 79.3% had < once/wk but at least once a month...
<table>
<thead>
<tr>
<th>Candidate variable</th>
<th>Decreased likelihood of 6-week angina</th>
<th>Increased likelihood of 6-week angina</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 5 year decrease)</td>
<td></td>
<td></td>
<td>1.18 (1.16-1.21)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td></td>
<td></td>
<td>1.41 (1.28-1.55)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Black vs. white</td>
<td></td>
<td></td>
<td>1.25 (1.06-1.47)</td>
<td></td>
</tr>
<tr>
<td>Other vs. white</td>
<td></td>
<td></td>
<td>0.98 (0.74-1.29)</td>
<td></td>
</tr>
<tr>
<td>Insurance</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Government vs. private</td>
<td></td>
<td></td>
<td>1.24 (1.11-1.38)</td>
<td></td>
</tr>
<tr>
<td>None vs. private</td>
<td></td>
<td></td>
<td>1.34 (0.18-1.52)</td>
<td></td>
</tr>
<tr>
<td>Prior PCI or CABG</td>
<td></td>
<td></td>
<td>1.29 (1.19-1.41)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>College vs. HS</td>
<td></td>
<td></td>
<td>1.03 (0.93-1.13)</td>
<td></td>
</tr>
<tr>
<td>Less than HS vs. HS</td>
<td></td>
<td></td>
<td>1.26 (1.10-1.44)</td>
<td></td>
</tr>
<tr>
<td>Not employed</td>
<td></td>
<td></td>
<td>1.23 (1.10-1.36)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Patients with vs. without AP at 6 weeks

No significant differences in

- MI type (STEMI vs. NSTEMI)
- Location of culprit lesion
- LVEF
- **Prevalence of multivessel disease**
Extent of PCI similar between groups

Pts @ AP Not significantly more likely to have incomplete revascularization…
Study Design

Patients with History of Chronic Angina AND Incomplete Revascularization After PCI
N=2600

1:1 Randomization
Strata: ACS vs. non-ACS, DM vs. non-DM

Ranolazine
1000 mg BID

Placebo
245 sites
15 countries

Primary Endpoint
Ischemia-driven revascularization or Ischemia-driven hospitalization

Event driven
Minimum 1 Year Follow-up

Primary Endpoint

Ischemia-driven revascularization or ischemia-driven hospitalization

HR [95%CI] = 0.95 [0.82, 1.10]

p-value = 0.48

No. at risk
Ranolazine 1317 1164 1101 1018 945 891 813 500 266 134 30
Placebo 1287 1165 1098 1028 960 879 788 461 271 128 45

Weisz G et al. Lancet 2015
RIVER-PCI: Interpretation

- **RIVER-PCI**: Ischemia driven revasc/hosp **27%**

- Pts with angina and ICR are at risk of having subsequent ischemia driven revasc/rehosp despite medical Tx…
RIVER-PCI: An alternative interpretation

- **RIVER-PCI**: Ischemia driven revascularization/hospitalization 27%

- **Medical Tx** is unlikely to be sufficient for many of these pts and/or **complete revascularization** is necessary in most pts with ongoing angina…
RIVER-PCI: Ischemia driven revasc/hosp 27%

Clinical practice:
- Revasc often in response to findings other than angina...
- Revasc pursued **without attempting titration of anti-ischemic medical therapy**...
- Tendency may be enhanced among a population with documented ICR in the year following PCI...
Pts with angina experience a substantial improvement in anginal status post-PCI even when revascularization is incomplete…
Pts @ AP in 6 wks: 3190

2891 answered SAQ questions at 6 mos…

- 44.5%: Reported AP at 6 ms
  - 4.4% daily angina
  - 20.8% weekly angina
  - 74.7% monthly angina
At **12 mos**, (2715 pts with 6-wk angina)

- **38.9%** continued to have angina
  - 4.5% had daily angina
  - 22.0% had weekly angina
  - **73.6%** had monthly angina

- **Pts without AP at 6 wks**: 11.0% angina at 12 mos
  - 14.8% daily/weekly, 85.2% monthly
Rates of guideline-directed secondary prevention medication use at discharge similar between groups.

*Calcium channel blockers, long-acting nitrates, and ranolazine* were infrequently prescribed at discharge: 6.6%, 4.9%, and 0.6%, respectively.
Temporal Patterns of Anti-Anginal Medication Use Over Follow-Up

- Of patients with 6-wk angina
- **92.0%** reported taking **β-blockers** at any time in the year following their MI
- **23.3%** were prescribed any **non–β-blocker (NBAM)** antianginal medication at any time over 12-month follow-up...
Temporal patterns of antianginal medication use. CCB indicates calcium channel blocker; Ran, ranolazine.
Temporal Patterns of Anti-Anginal Medication Use Over Follow-Up

- 1056 pts @ persistent angina through 1 yr
  - 68.8% never prescribed any NBAM
- Pts @ daily/weekly angina at 12-mo
  - 61.3% never prescribed NBAM
Temporal Patterns of Anti-Anginal Medication Use Over Follow-Up

- Among pts with continued angina over the entirety of follow-up…

- *Factor most strongly associated with use of NBAM at any time during 1-yr FU was prescription of a NBAM at the time of discharge after the index event (OR 29.7, 95% CI, 16.7–52.9)…*
However…

Only 15% pts were prescribed NBAM at the time of discharge

(These pts comprised 45% of pts prescribed these medications at any time over the course of FU)
Temporal Patterns of Anti-Anginal Medication Use Over Follow-Up

Factors associated with non-β-blocker antianginal medication among patients with continued angina over the entirety of follow-up. C-index for the multivariable model=0.81.
11.9% pts with 6-wk angina underwent symptom-driven, unplanned PCI or CABG in the 12 mos following index Mis...

At the time of revasc

- 86.6% were taking β-blockers
- 25.9% were taking NBAM
  - 19.2% ONE
  - 6.0% TWO
  - 0.8% THREE
Notably, less than one third of pts who returned for symptom-driven unplanned coronary revascularization were treated with a NBAM before their procedure...
MERLIN TIMI-36*
PRE-SPECIFIED EXPLORATORY ANALYSIS

PATRAS UNIVERSITY HOSPITAL

MERLIN N = 6560 pts (UA/NSTEMI)
442 sites (17 countries)

Patients with History of Chronic Angina

N = 3565 (54%)

Placebo
1776

Ranolazine
1789

Wilson S et al. J Am Coll Cardiol. 53:1510–6, 2009

The addition of ranolazine to standard treatment for ACS was not effective in reducing major cardiovascular events.
The recurrent ischemia was significantly lower in patients treated with ranolazine than placebo (p=0.03)

## OBSERVATIONS IN PTS WITH HISTORY OF ANGINA

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ranolazine</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=1776</strong></td>
<td><strong>N = 1789</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>29.4</td>
<td>25.2</td>
<td>0.86</td>
<td>p = 0.017</td>
</tr>
<tr>
<td>CV death or MI</td>
<td>12.5</td>
<td>11.9</td>
<td>0.97</td>
<td>p = 0.71</td>
</tr>
<tr>
<td><strong>Recurrent ischemia</strong></td>
<td>21.1</td>
<td>16.5</td>
<td>0.78</td>
<td>p = 0.002</td>
</tr>
</tbody>
</table>

- **Severe recurrent ischemia** **:**
  - 14.4
  - 11.9
  - 0.81
  - p = 0.026

- **Prompting revascularization**
  - 6.4
  - 4.5
  - 0.66
  - p = 0.006

- **Worsening angina** **:**
  - 8.2
  - 5.6
  - 0.77
  - p = 0.048

---

*KM Cumulative Incidence at 12 months; ** Ischemia with ECG changes, prompting rehospitalization, or revascularization; ***†≥ 1 CCS Class and requiring intensification of anti-anginal Rx
Clinical Perspective

- Strategies to increase provider awareness of angina burden coupled with symptom-driven management, including prescription of anti-anginal medications, should be explored.

Fanaroff et al. JAHA 2017
Ranolazine: A pleiotropic drug with excellent safety profile.

<table>
<thead>
<tr>
<th>Co-morbidities relevant to treatment of myocardial ischaemia</th>
<th>Beta blockers</th>
<th>Calcium channel blockers</th>
<th>Nitrates</th>
<th>Ivabradine</th>
<th>Ranolazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>General recommendation in guidelines</td>
<td>1st line</td>
<td>2nd line</td>
<td>2nd line</td>
<td>2nd line HR &gt;60 bpm</td>
<td>2nd line</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Improves outcomes</td>
<td>Contraindicated</td>
<td>Safe</td>
<td>Improves outcomes</td>
<td>May be used</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Indicated</td>
<td>Indicated</td>
<td>Safe</td>
<td>No effect</td>
<td>May be used</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Limited</td>
<td>Limited</td>
<td>Limited</td>
<td>May be used</td>
<td>May be used</td>
</tr>
<tr>
<td>AV block</td>
<td>Contraindicated</td>
<td>Diltiazem and verapamil contraindicated</td>
<td>May be used</td>
<td>May be used</td>
<td>May be used</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Limited</td>
<td>Limited</td>
<td>Limited</td>
<td>Limited</td>
<td>May be used</td>
</tr>
<tr>
<td>COPD/asthma</td>
<td>Limited</td>
<td>May be used</td>
<td>May be used</td>
<td>May be used</td>
<td>May be used</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Difficult control</td>
<td>May be used</td>
<td>May be used</td>
<td>May be used</td>
<td>May be used</td>
</tr>
</tbody>
</table>
Καλό καρναβάλι...
Female pt, 78 yrs, HTN, DM, scheduled bowel surgery (Ca)

Angina CCS II, HR 65 bpm, BP 130/80 mmHg, slightly overweight

ECHO: Anterior wall motion abnormality, LVEF 50%, Low LVEDP, LA 46 mm, MR 1-2+

ASA, Rosuvastatin, Nebivolol, Nitrates, Lisinopril, Metformin...
Ποιό από τα παρακάτω ενδείκνυται:

1. Ενίσχυση αντι-ισχαιμικής αγωγής και να προχωρήσει στο χειρουργείο
2. Λειτουργικός έλεγχος ισχαιμίας
3. Στεφανιογραφία
Ποιό από τα παρακάτω ενδείκνυται;

2. Λειτουργικός έλεγχος ισχαιμίας
Cang: Chronic total occlusion of mLAD
Collaterals from RCA…
Ποιό από τα παρακάτω ενδείκνυται;

1. Προσπάθεια αγγειοπλαστικής της χρονίας ολικής έμφραξης

2. Παραπομπή για χειρουργική αντιμετώπιση

3. Λειτουργική δοκιμασία για εκτίμηση της έκτασης της ισχαιμίας

4. Ενίσχυση της φαρμακευτικής αγωγής

5. Το 3 + 4
Ποιό από τα παρακάτω ενδείκνυται;

5. Το 3 + 4
SPECT

Stress

Rest

Apex

Mid

Base

Patras University Hospital

Ποιό από τα παρακάτω ισχύει;

1. Προσθιοδιαφραγματική ισχαιμία μέσης έκτασης
2. Προσθιοδιαφραγματική ισχαιμία μικρής έκτασης
3. Κατωτεροδιαφραγματική ισχαιμία μέσης έκτασης
4. Κατωτεροδιαφραγματική ισχαιμία μεγάλης έκτασης
5. Artifact κατωτέρου και μέση ισχαιμία προσθίου
Ποιό από τα παρακάτω ισχύει;

1. Προσθιοδιαφραγματική ισχαιμία μέσης έκτασης
Ποιό από τα παρακάτω ενδείκνυται;

1. Προσπάθεια αγγειοπλαστικής της χρονίας ολικής έμφραξης με BMS και χειρουργείο σε 1 μήνα
2. Προσπάθεια αγγειοπλαστικής της χρονίας ολικής έμφραξης με DES και χειρουργείο σε 6 μήνες
3. Παραπομπή για χειρουργική αντιμετώπιση (CABG) και χειρουργείο σε 3-6 μήνες
4. Ενίσχυση της φαρμακευτικής αγωγής και αν είναι ασυμπτωματική να προχωρήσει στο χειρουργείο
Ποιό από τα παρακάτω ενδείκνυται;

4. Ενίσχυση της φαρμακευτικής αγωγής και αν είναι ασυμπτωματική να προχωρήσει στο χειρουργείο.
Παρεμβάσεις

1. Αύξηση δόσης νιτρωδών
2. Προσθήκη Ρανολαζίνης 375 mg x 2

Ηπιες γαστρεντερικές διαταραχές για 3-4 ημέρες που υποχώρησαν

Βελτίωση συμπτωμάτων αλλά στηθάγχη στη μέγιστη κόπωση

Άυξηση ρανολαζίνης σε 500 mg x 2 => Ασυμπτωματική
After optimal anti-ischemic medical therapy