Πρακτικές οδηγίες για την διαχείριση ασθενών με Σταθερή Στεφανιαία Νόσο και συννοσηρότητες. Το παράδειγμα της Ρανολαζίνης

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Καθηγητής Καρδιολογίας
Πανεπιστημίου Πατρών
Επεμβατική Καρδιολογία-Συγγενείς Καρδιοπάθειες

Sodium Current

Late $I_{Na}$

Peak $I_{Na}$
This presentation is supported by Menarini Hellas
CAD Treatment

- Treatment recommendation based on…
  - Clinical presentation
  - Severity and magnitude of ischemia
  - Extent and distribution of coronary anatomic disease
  - LV function
  - Presence of other medical conditions
  - Evidence of the effectiveness of each strategy
Medical therapy of ischaemia

Treatement strategies

↓ O₂ supply
Vasospasm
NTG, Ca channel blocker

Thrombus
ASA

Atherosclerosis
Statin

↑ O₂ demand

Afterload
Ca channel blocker

Heart rate
β blocker

Contractility
β blocker

Preload (vascular)
NTG

Ischaemia

↓ Diastolic flow
↓ myocardial blood flow

↑ LVEDP
↑ diastolic tension

↑ LV wall stiffness
↑ LV preload

Late Iₙ Na
Ranolazine
Electro-Mechanical consequences of Ischemia…

Monophasic Action Potential (Cardiac Muscle Cell)

+ 10 mV

Phase 0, Na⁺ enters the cell
Depolarization

- 90 mV

Depolarization

Repolarization

Resting Potential

Phase 2, Ca²⁺ enters the cell,
Initiation of contraction

Phase 3, K⁺ exits the cell
Repolarization

Failure to Inactivate

\( I_{Na^+_L} \)
Electro-Mechanical consequences of Ischemia…

Normal

Delayed and/or Incomplete Inactivation (Ischemia, Failure, LVH)

Sodium Current

Action Potential

Peak

Late

0

Patras University Hospital
Electro-Mechanical consequences of Ischemia…

![Graph showing normal and abnormal action potential and twitch responses to ischemia](image)
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 O$_2$ 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)
Ischemia Begets Ischemia...

Ranolazine (RANEXA) inhibits the late inward Na current, in a Concentration, Voltage & Frequency Dependent Manner...

↑ LV Diastolic Tension

↑ Na⁺ᵢ

Ca²⁺ᵢ Overload

Ranolazine: Dose dependent increase in Exercise Duration

A

B

Plasma Ranolazine Concentration (ng base/mL, mean ± SE)

Exercise Duration (seconds, LS mean ± SE)

0 500 1000 1500 2000 2500 3000 3500 4000 4500

510 530 550 570

Placebo  Ranolazine 500 mg bid  Ranolazine 1000 mg bid  Ranolazine 1500 mg bid

Trough (primary endpoint)  Peak

*  **  **  **

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Relationship Between Changes in ST-Segment Depression and Exercise Time Adjusted for RPP

![Graph showing the relationship between ST-segment depression and exercise time for different treatments. The graph compares Placebo, Ran 500, Ran 1000, and Ran 1500 treatments.](image)

*Stone, P. H. et al. J Am Coll Cardiol 2010;56:934-942*
Effect of ranolazine on myocardial perfusion detected by SPECT

Myocardial perfusion

Open-label, non-randomised pilot study. Twenty patients with known or a high probability of CAD and reversible perfusion defects on exercise treadmill (SPECT). Four weeks ranolazine treatment (up to 1,000 mg twice daily) was added to baseline conventional anti-anginal therapy.

Representative Example of Improvement in Myocardial Perfusion by Single-Photon Emission Computed Tomography

Ranolazine treatment:
- Increased exercise time vs. baseline (425 ± 105 s vs. 393 ± 116 s, \( p=0.017 \))
- Improved angina in 75% patients (n=15) after treatment
- Improved perfusion pattern and severity in 70% patients (n=14)

PDS: perfusion defect size detected by SPECT; LV, left ventricular myocardium

Note: in the European Union ranolazine is indicated as add-on therapy for patients with stable angina, at a maximum dose of 750 mg bid.

Ranolazine for Angina with Non-obstructive CAD in Women

(A) And (B): Placebo first-pass subendocardial anterolateral and inferolateral hypoperfusion at the mid-ventricular level. After treatment with ranolazine, (C) and (D) significant improvement in the areas of hypoperfusion (arrows).
Lack of Effect of Ranolazine on HR and BP in Pts with Chronic Angina

A. Heart Rate

B. Arterial Blood Pressure

Ranolazine Concentration (µM)
Therapeutic Levels = 2 to 8 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, Anna Paola Cirillo, Gennaro Cice, Luigi Fini, Luca del Guercio, Bruno Trimarco, 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>

p = 0.000

**Weekly nitroglycerin consumption**

<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>-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
2013 ESC guidelines on the management of stable coronary artery disease

<table>
<thead>
<tr>
<th>Angina/ischaemia IV relief</th>
<th></th>
<th></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>IIa</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>IIa</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>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>
2013 ESC guidelines on the management of stable coronary artery disease

ALL PATIENTS

Assess symptoms
Perform clinical examination

Symptoms consistent with unstable angina

Follow specific NSTE-ACS guidelines

ECG  Bio-Chemistry  Resting echocardiography\(^a\)  CXR in selected patients

Consider comorbidities and QoL

Comorbidities or QoL make revascularization unlikely

Medical therapy\(^b\)
Ranolazine: Excellent safety profile...

<table>
<thead>
<tr>
<th>Table 8. Co-morbidities relevant to treatment of myocardial ischaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta blockers</strong></td>
</tr>
<tr>
<td>General recommendation in guidelines</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>AV block</td>
</tr>
<tr>
<td>Bradycardia</td>
</tr>
<tr>
<td>COPD/asthma</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
</tbody>
</table>
Stable angina pectoris: which drugs or combinations to use in which patients

Heart Rate

>60 bpm
- BP
  - SBP ≥120
    - BB or Non-DHP CCB*
      - DHP
        - LA nitrates
          - Nicorandil
          - Trimetazidine
  - SBP <120
    - Ranolazine
      - Ivabradine**

≤60 bpm
- BP
  - SBP ≥120
    - DHP
      - LA nitrates
        - Nicorandil
        - Trimetazidine
  - SBP <120
    - Ranolazine
      - Trimetazidine

* normal ejection fraction; ** heart rate > 70 bpm

First-line
Second-line
Third-line
Nitrate Tolerance & PDE-5 Inhibitors interaction

NITRATE MECHANISMS
Opie 2004

- Isosorbide dinitrate
- Isosorbide mononitrate
- Mononitrate R-ONO₂
- Nitroglycerin

Physiologic dilators

Cytoplasm

- A-II
- Peroxynitrate
- NO⁻
- Nitrosothiols
- SH

Liver

Vasodilation

EXCESS NITRATES
• Deplete SH
• Peroxynitrate

Nitrate tolerance

SERIOUS NITRATE INTERACTION
Opie 2004

- Penile nerves
- GTP
- Excess NO⁻
- Cyclic GMP
- NITRATES
- PDE 5 INHIBITORS
  - sildenafil
  - tadalafil
  - vardenafil

VASODILATION

- BP↓, Syncope
- Erection

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Diabetes in Cardiology Cohorts  30-50%
DM: The Role of Cardiologists...

## Prevalence Rates of CV Comorbidities in Persons With T2DM: Results of a Systematic Literature Review

<table>
<thead>
<tr>
<th>Sex</th>
<th>CV Outcome</th>
<th>Studies</th>
<th>N</th>
<th>Rate (%)</th>
<th>95% Confidence Interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both</td>
<td>Stroke</td>
<td>39</td>
<td>3,901,505</td>
<td>7.6</td>
<td>6.6, 8.6</td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td>13</td>
<td>3,518,833</td>
<td>10.0</td>
<td>7.5, 12.5</td>
</tr>
<tr>
<td></td>
<td>Angina pectoris</td>
<td>4</td>
<td>354,743</td>
<td>14.6</td>
<td>12.0, 17.3</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
<td>14</td>
<td>601,154</td>
<td>14.9</td>
<td>13.0, 16.7</td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis</td>
<td>4</td>
<td>1153</td>
<td>29.1</td>
<td>21.7, 36.4</td>
</tr>
<tr>
<td></td>
<td>Coronary artery disease</td>
<td>42</td>
<td>3,833,200</td>
<td>21.2</td>
<td>20.3, 22.2</td>
</tr>
<tr>
<td></td>
<td>CVD (any)</td>
<td>53</td>
<td>4,289,140</td>
<td>32.2</td>
<td>30.0, 34.4</td>
</tr>
</tbody>
</table>

Globally, more than 30% of persons with T2DM have some form of CV disorder. CVD is a major cause of mortality in patients with T2DM.

Early Type 2 Diabetes Mellitus: A Cardiovascular Disease

United Kingdom Prospective Diabetes Study (n = 3867)
Mean f/u = 10 years

10-year risk, %

Blindness  ESRD  Amputation  Net Micro- vasc  CVA  CAD  Macro-vasc

Ranolazine Significantly Reduced HbA1c in Pts With DM and CAD

Change from baseline in HbA1c levels over time in diabetic pts treated with ranolazine in the double-blind and open-label phase

MERLIN-TIMI 36: Effect of Ranolazine on HbA₁c in Patients with Diabetes

**A. Worsening Hyperglycemia¹**

- Placebo:
  - 20.6%
- Ranolazine:
  - 14.2%

P < 0.001, RR 0.63

**B. Failure to Achieve HbA₁c < 7%²**

- Placebo:
  - 51%
- Ranolazine:
  - 41%

P <0.001, RR 0.80

1. KM Cumulative Incidence of ≥1% increase in HbA₁c at 12 months
2. At 4 months
Effects of ranolazine in symptomatic patients with stable coronary artery disease.
A systematic review and meta-analysis

Gianluigi Savarese a, Giuseppe Rosano b, Carmen D’Amore a, Francesca Musella a, Giuseppe Luca Della Ratta a, Angela Maria Pellegrino a, Tiziana Formisano a, Alice Vitagliano a, Anna Paola Cirillo a, Gennaro Cice c, Luigi Fimiani a, Luca del Guercio d, Bruno Trimarco a, Pasquale Perrone-Filardi a,b,1

Glycemic control

CARISA (RAN 750 mg bid vs placebo)
-0.50 (-0.89, -0.11)

CARISA (RAN 1000 mg bid vs placebo)
-0.70 (-1.09, -0.31)

MERLIN-TIMI36 (RAN 1000 mg bid vs placebo)
-0.20 (-0.38, -0.02)

Overall (I-squared = 68.2%, p = 0.043)
-0.43 (-0.75, -0.11)

p=0.009

Better Ranolazine

Better Control
Effect of concurrent antidiabetes drug treatment on pts treated with ranolazine reaching an A1C goal of ≤7%.

Ranolazine acts on top of optimal antiDM TX…
Efficacy and Safety of Ranolazine in Diabetic Patients: A Systematic Review and Meta-analysis

A. HbA1c

Ranolazine reduced A1C by 0.49% vs. Placebo

B. FSG
## Antihyperglycemic and Metabolic Effects of Ranolazine in Patients With Diabetes Mellitus

<table>
<thead>
<tr>
<th>Medication/Class</th>
<th>Decrease in HbA1c%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.5%</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1-2%</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.5-1.5%</td>
</tr>
<tr>
<td>Glinides</td>
<td>0.5-1.5%</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>0.5-1%</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>0.5-1%</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>0.5-0.8%</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>0.5-0.6%</td>
</tr>
<tr>
<td>Bile-acid sequestrants</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
Efficacy and Safety of Ranolazine in Diabetic Patients: A Systematic Review and Meta-analysis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ranolazine</th>
<th>placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Eckel 2015</td>
<td>4</td>
<td>232</td>
<td>2.2%</td>
</tr>
<tr>
<td>Kipnes 2013</td>
<td>4</td>
<td>39</td>
<td>8.8%</td>
</tr>
<tr>
<td>MERLIN-TIMI 36</td>
<td>29</td>
<td>770</td>
<td>60.3%</td>
</tr>
<tr>
<td>Pettus+glimepiride 2016</td>
<td>13</td>
<td>215</td>
<td>26.7%</td>
</tr>
<tr>
<td>TERISA</td>
<td>3</td>
<td>462</td>
<td>2.1%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1718</td>
<td>1661</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>53</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.01; Chi^2 = 4.15, df = 4 (P = 0.39); I^2 = 4%

Test for overall effect: Z = 0.73 (P = 0.47)

A. Hypoglycemia

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ranolazine</th>
<th>placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td>Pettus+glimepiride 2016</td>
<td>4</td>
<td>215</td>
<td>14.2%</td>
</tr>
<tr>
<td>Kipnes 2013</td>
<td>1</td>
<td>39</td>
<td>6.1%</td>
</tr>
<tr>
<td>Eckel 2015</td>
<td>19</td>
<td>232</td>
<td>79.7%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>486</td>
<td>489</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>24</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.68, df = 2 (P = 0.43); I^2 = 0%

Test for overall effect: Z = 0.93 (P = 0.35)

B. Persistent hyperglycemia
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
Figure 3. Mean number of anginal attack and weekly consumption of sublingual nitroglycerin with ranolazine in the TERISA.\textsuperscript{53} $p < 0.01$ for both comparisons.
These data suggest that ranolazine is particularly beneficial in patients with stable angina who have suboptimally controlled T2DM.

**Exploratory Analysis – HbA1c**

- **HbA1c ≤ 7.5**
  - Ranolazine better
  - Placebo better
  - p for interaction = 0.038

- **HbA1c >8**
  - Ranolazine better
  - Placebo better

- **HbA1c ≤ 8**
  - Ranolazine better
  - Placebo better

**Incidences Density Ratio**

- 0.7
- 0.8
- 0.9
- 1
- 1.1
- 1.2
SAQ Angina Frequency - Subgroups

Mean Treatment Difference - Repeated Measure Adjusted for Baseline

Mean Difference (95% CI)

Ranolazine – Placebo

<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>
SAQ Angina Frequency – Diabetes and Baseline Angina
Ranolazine – Placebo (Adjusted for Baseline Score)

Interaction
P=0.02

LS Mean Difference (95% CI)
Ranolazine-Placebo

Study Visit (Months)
Effect of Ranolazine on Glucose Stimulated Insulin Secretion (GSIS) in Pancreatic Islets

Mouse Islets

Rat Islets

Human Islets

Preliminary studies in isolated rat and human pancreatic islets suggest ranolazine may promote glucose-stimulated insulin secretion...
Selective Nav.1.3 blockers ↓ Glucagon secretion

Inhibits glucagon secretion, increases β-cell function

Promotes pancreatic glucagon secretion and preserves pancreatic function.

Human Islets (A-F)
Diabetic Cardiomyopathy: Dual Benefit of Ranolazine

* Hypothesis: Glucose increases pCaMKII, which increases late INa

* Nishio et al JACC 52 (2012) 1103–1111
* Luo and Anderson et al JCI, 2013
* Mourouzis et al Unpublished data 2013
EFFECTS OF RANOLAZINE ON LV DIASTOLIC FUNCTION


ISOVOLUMIC RELAXATION (msec)  MITRAL E-WAVE VEL. (cm/s)

p < 0.05
Results of this proof-of-concept study revealed that ranolazine improved measures of hemodynamics but that there was no improvement in relaxation parameters.
Effect of Ranolazine on Left Ventricular Dyssynchrony in Patients With CAD

**Baseline Systolic Dyssynchrony (Phase SD = 40.1°, BW = 117°)**

**Baseline Diastolic Dyssynchrony (Phase SD = 63.5°, BW = 189°)**

**Post-Ranolazine Systolic Dyssynchrony (Phase SD = 18.0°, BW = 56°)**

**Post-Ranolazine Diastolic Dyssynchrony (Phase SD = 26.1°, BW = 65°)**
SUPRAVENTRICULAR TACHYARRHYTHMIAS IN THE MERLIN-TIMI 36 TRIAL

A. Supraventricular Tachycardia

Placebo: 1752 (53.5%)
Ranolazine: 1413 (43.2%)

$\Delta=339$, RR 0.81, p<0.001

B. New-Onset Atrial Fibrillation

Placebo: 75 (2.3%)
Ranolazine: 55 (1.7%)

$\Delta=20$, RR 0.74, p=0.08

Patras University Hospital

Ranolazine vs Amiodarone for AF Prophylaxis After CABG

- Retrospective cohort study
- 393 pts undergoing CABG
- Amiodarone (400 mg preoperative followed by 200 mg twice daily for 10-14 days) - N=211 (53.7%)
- Ranolazine (1500 mg preoperative followed by 1000 mg twice daily for 10-14 days) - N=182 (46.3%)
- Mean age 65 ± 10 years, 72% men

Ranolazine associated independently with a reduction of post-op AF

\[ P = 0.035 \]
Comparison of Effectiveness of *Ranolazine* Plus *Amiodarone* Versus *Amiodarone* Alone for Conversion of Recent-Onset Atrial Fibrillation

Nikolaos Fragakis, MD[^1], Konstantinos C. Koskinas, MD[^2], [Demosthenes G. Katritsis, MD[^3]], Efstathios D. Pagourelis, MD[^4], Theodoros Zografos, MD[^5], Paraschos Geleris, MD[^6]

[^1]: 3rd Cardiology Department, Hippokrateion Hospital, Aristotle University Medical School, Thessaloniki, Greece
[^2]: Department of Cardiology, Athens Euroclinic, Athens, Greece

![Graph showing comparison of effectiveness of Ranolazine Plus Amiodarone versus Amiodarone alone for conversion of recent-onset atrial fibrillation.](image)

**The American Journal of Cardiology**

Volume 110, Issue 5, 1 September 2012, Pages 673–677
2 g of RZ, administered 3.5–4 hours prior to EC in pts previously resistant to EC, resulted in 76% being able to be restored to sinus rhythm…
Ranolazine supresses AF…

Representative example of surface (lead V1) and intracardiac electrograms (posterolateral left atrium, LA) at 12 min after atrial fibrillation (AF) initiation demonstrating early termination of AF by ranolazine.

Effect of ranolazine on atrial conduction velocity due to peak Na inhibition
Similar to the actions of other potent sodium channel blockers, including flecainide and propafenone
Suggest that ranolazine affects factors that are important not only in maintaining AF but also possibly in initiating AF…
MERLIN: Ranolazine supresses SVT & VT in pts with NSTE/ACS

In more than 6300 pts admitted with NSTE/ACS, treatment with ranolazine resulted in significantly lower incidence of VT, SVT, and significant ventricular pauses.

Kaplan-Meier estimated rates of the first occurrence of an episode of VT lasting at least 8 beats.

Benefit by adding ranolazine in ischemic heart disease patients to a stable class III antiarrhythmic agent for reducing VT burden and reducing ICD shocks.
Rates of guideline-directed secondary prevention medication use at discharge similar between groups

*Calcium channel blockers, long-acting nitrates, and ranolazine (NBAM)* 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…

Fanaroff et al. JAHA 2017
Temporal patterns of antianginal medication use. CCB indicates calcium channel blocker; Ran, ranolazine.
Temporal Patterns of Anti-Anginal Medication Use Over Follow-Up

<table>
<thead>
<tr>
<th>Candidate variable</th>
<th>Decreased likelihood of NBB angina med prescription</th>
<th>Increased likelihood of NBB angina med prescription</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharged on NBB anti-anginal medication</td>
<td></td>
<td></td>
<td>27.7 (15.6-52.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td>2.19 (1.48-3.24)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Number of diseased vessels</td>
<td></td>
<td></td>
<td>1.48 (1.19-1.84)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SAQ angina frequency score (per 10 unit decrease)</td>
<td></td>
<td></td>
<td>1.09 (1.04-1.15)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age (per 5 year increase)</td>
<td></td>
<td></td>
<td>1.11 (1.04-1.20)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td></td>
<td>1.53 (1.13-2.07)</td>
<td>0.006</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td></td>
<td></td>
<td>1.37 (0.97-1.93)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

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.
Temporal Patterns of Anti-Anginal Medication Use Over Follow-Up

- Pts @ post-MI angina
- **NBAMs:** CCBs, long-acting nitrates, and ranolazine as part of antianginal regimens remained stable over the 1-year follow-up
  - ≈10% pts CCBs
  - 10% long-acting nitrates
  - 2% ranolazine
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...
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)
<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Ranolazine</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></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>
<tr>
<td>Severe recurrent ischemia**</td>
<td>14.4</td>
<td>11.9</td>
<td>0.81</td>
<td>p = 0.026</td>
</tr>
<tr>
<td>Prompting revascularization</td>
<td>6.4</td>
<td>4.5</td>
<td>0.66</td>
<td>p = 0.006</td>
</tr>
<tr>
<td>Worsening angina***</td>
<td>8.2</td>
<td>5.6</td>
<td>0.77</td>
<td>p = 0.048</td>
</tr>
</tbody>
</table>

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

OBSERVATIONS IN PTS WITH HISTORY OF ANGINA

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

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

- Bradycardia
- Low BP
- Nitrate tolerance/drug interactions
- Asthma/COPD
- HFrEF
- HFpEF
- DM (especially uncontrolled)
- AF (prophylaxis & cardioversion)
- ICD shocks