

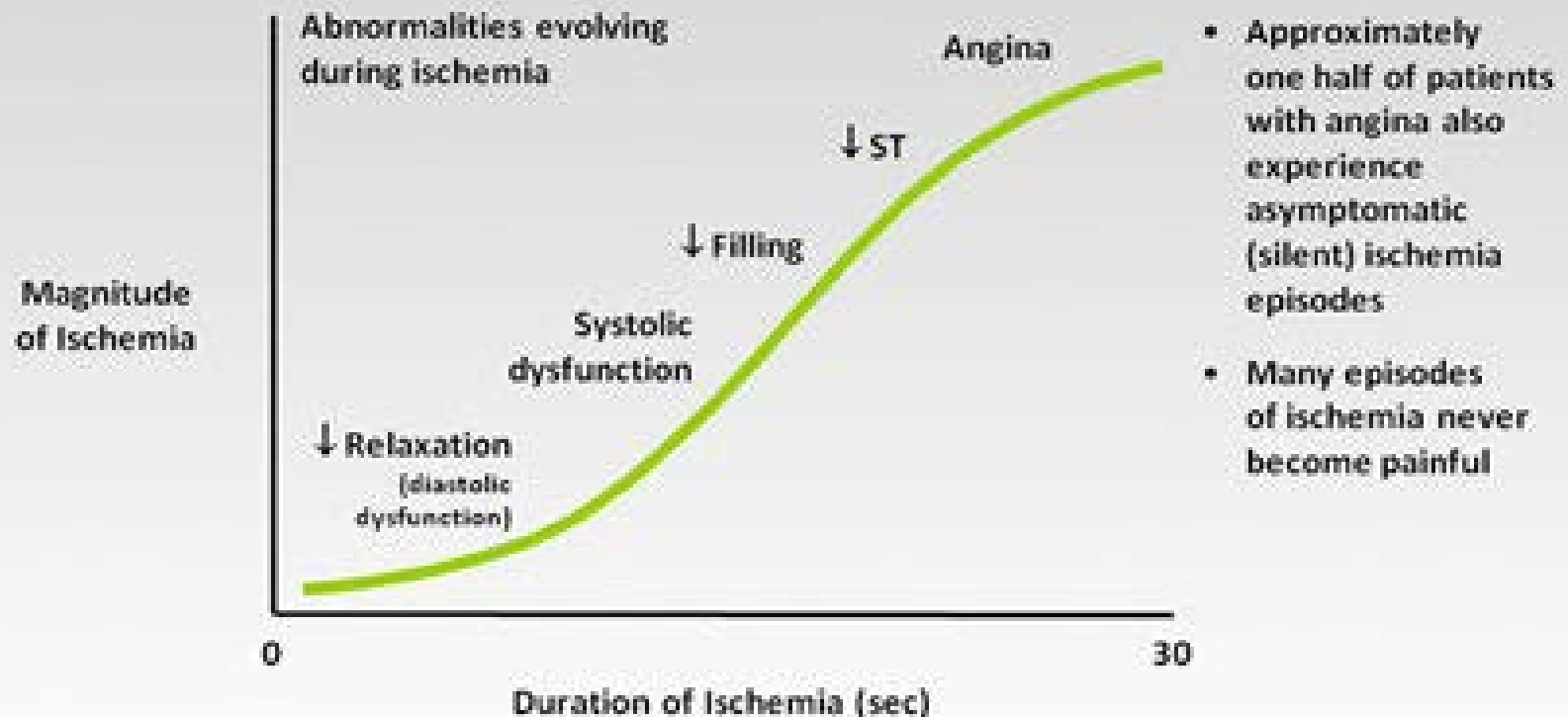
# Ranolazine, ischemic cardiomyopathy and new potential indications

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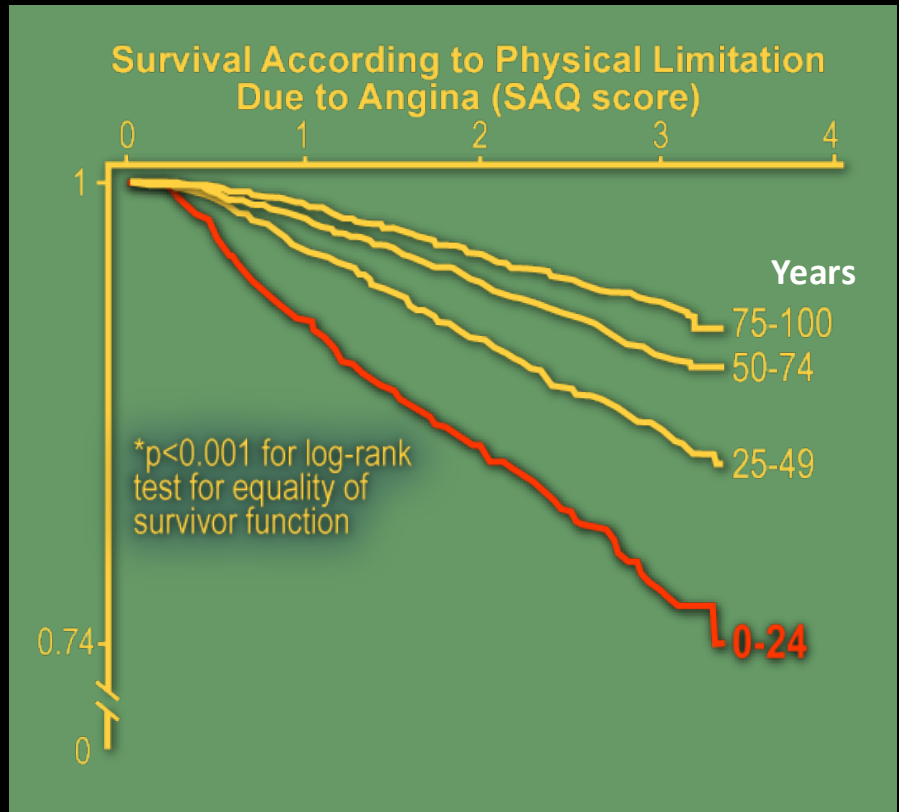
# Symptoms Occur at End of Ischemic Cascade



Adapted from Cohn PF, et al. *Circulation*. 2003;108:1263-1277.

# Angina Symptoms Predict Total Mortality in Patients with CAD

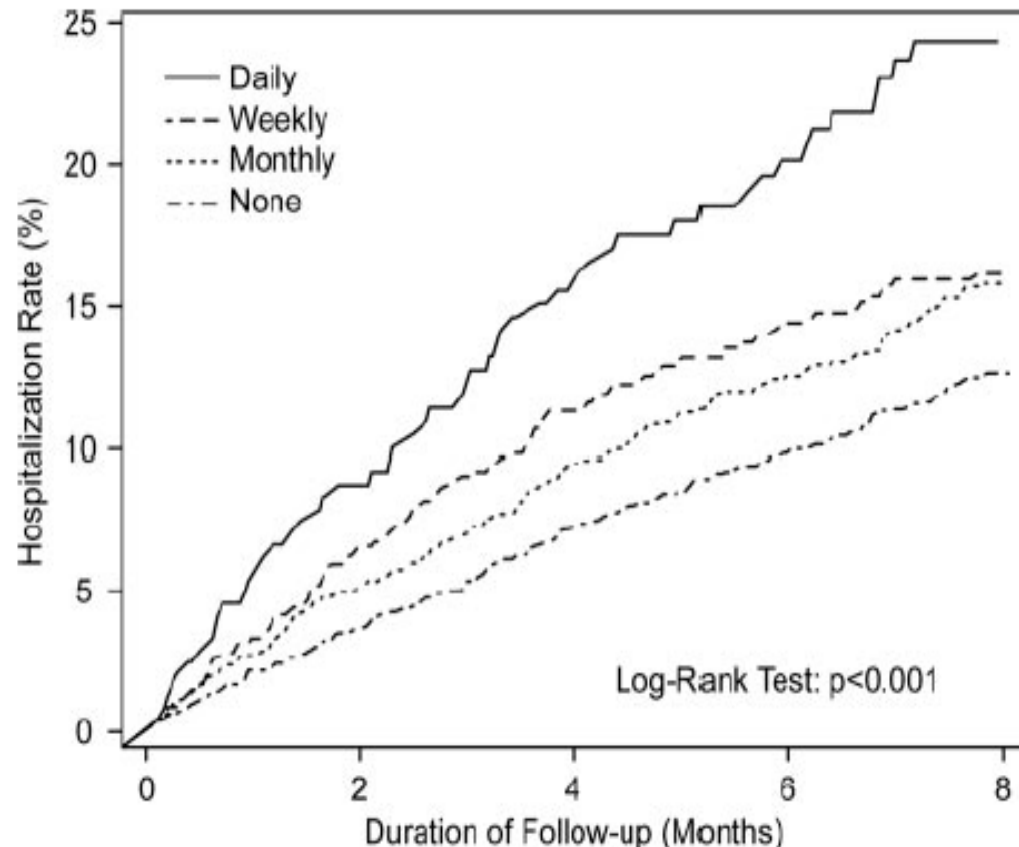
- Prospective study 8900 VA patients with CAD
  - Primary endpoint all-cause mortality
  - Seattle Angina Questionnaire (SAQ)
  - Over 2 years mean follow up
- Results
  - Avg age 67 years
  - 98% male
  - ~66% white
  - ~25% diabetic
  - 896 deaths



Greater physical limitation due to angina  
“strongly associated with higher mortality”

Mozaffarian D, et al. *Am Heart J*. 2003.

# Hospitalization by residual angina

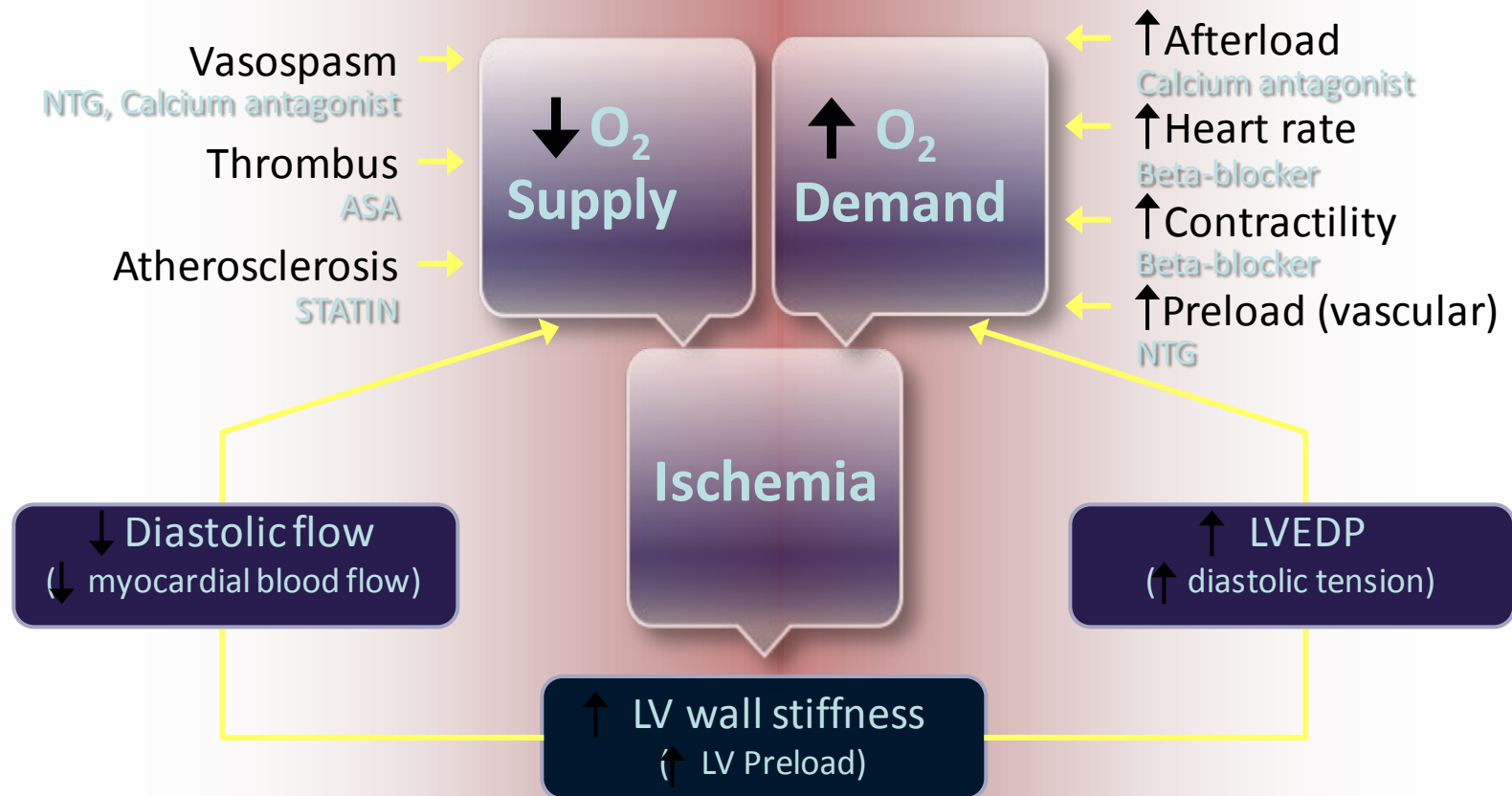


**Figure 1.** Kaplan-Meier curve of time to cardiovascular hospitalization by angina frequency group.

# Chronic Ischemic Heart Disease In “Minorities” Jeopardizes Quality Of Life....

**...OF THE CARDIOLOGIST.**

# Supply and Demand Mismatch and Therapeutic Targets



Adapted from *Braunwald's Heart Disease* 7<sup>th</sup> Edition 2006;  
Brunton, et al. *Goodman & Gilman's Pharmacological Basis of Therapeutics*, 11<sup>th</sup> Edition 2006.

# Antianginal Drugs

— O<sub>2</sub> Supply —||————— O<sub>2</sub> Demand —————|

| Drug class           | Coronary blood flow | Heart rate | Arterial pressure | Venous return | Myocardial contractility |
|----------------------|---------------------|------------|-------------------|---------------|--------------------------|
| β-blockers           | —                   | ↓          | ↓                 | —             | ↓                        |
| DHP CCBs             | ↑                   | ↑*         | ↓                 | —             | ↓                        |
| Non-DHP CCBs         | ↑                   | ↓          | ↓                 | —             | ↓                        |
| Long-acting nitrates | ↑                   | ↑/—        | ↓                 | ↓             | —                        |

CCB = calcium channel blocker, DHP = dihydropyridine \*Except amlodipine

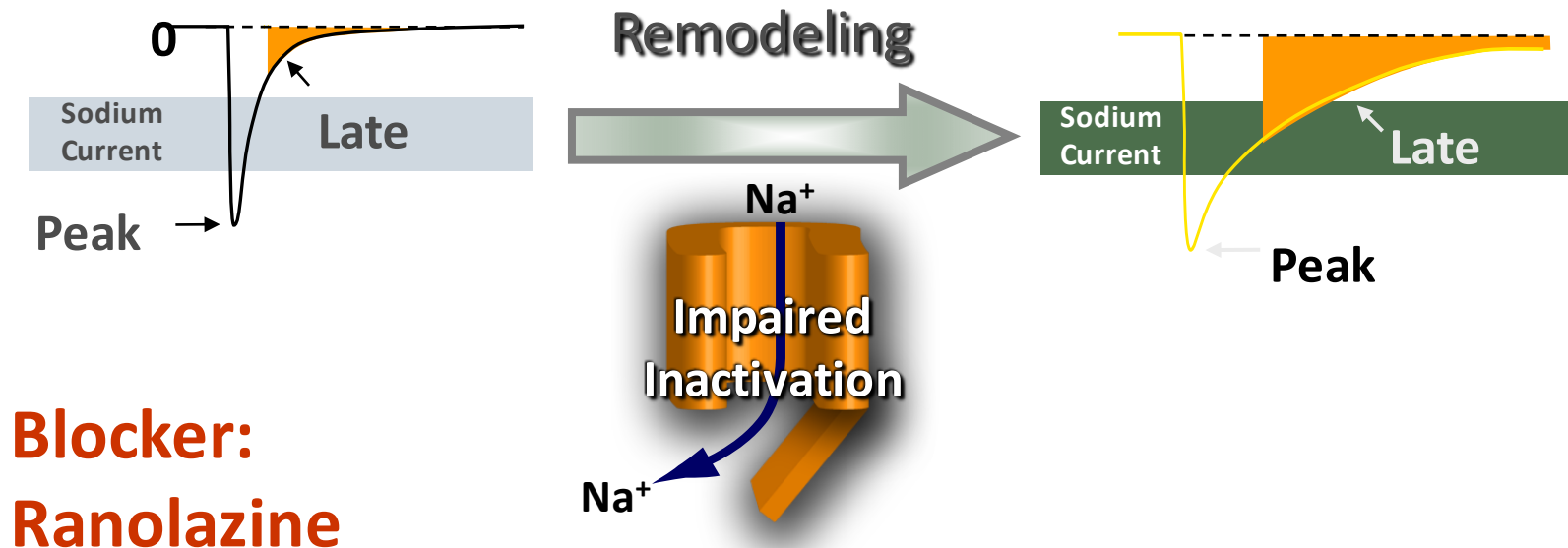
Boden WE et al. *Clin Cardiol.* 2001;24:73-9.

Gibbons RJ et al. ACC/AHA 2002 Chronic Angina Guidelines.

Kerins DM et al. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 10<sup>th</sup> ed.

# Mechanisms of action potential prolongation : late $I_{Na}$

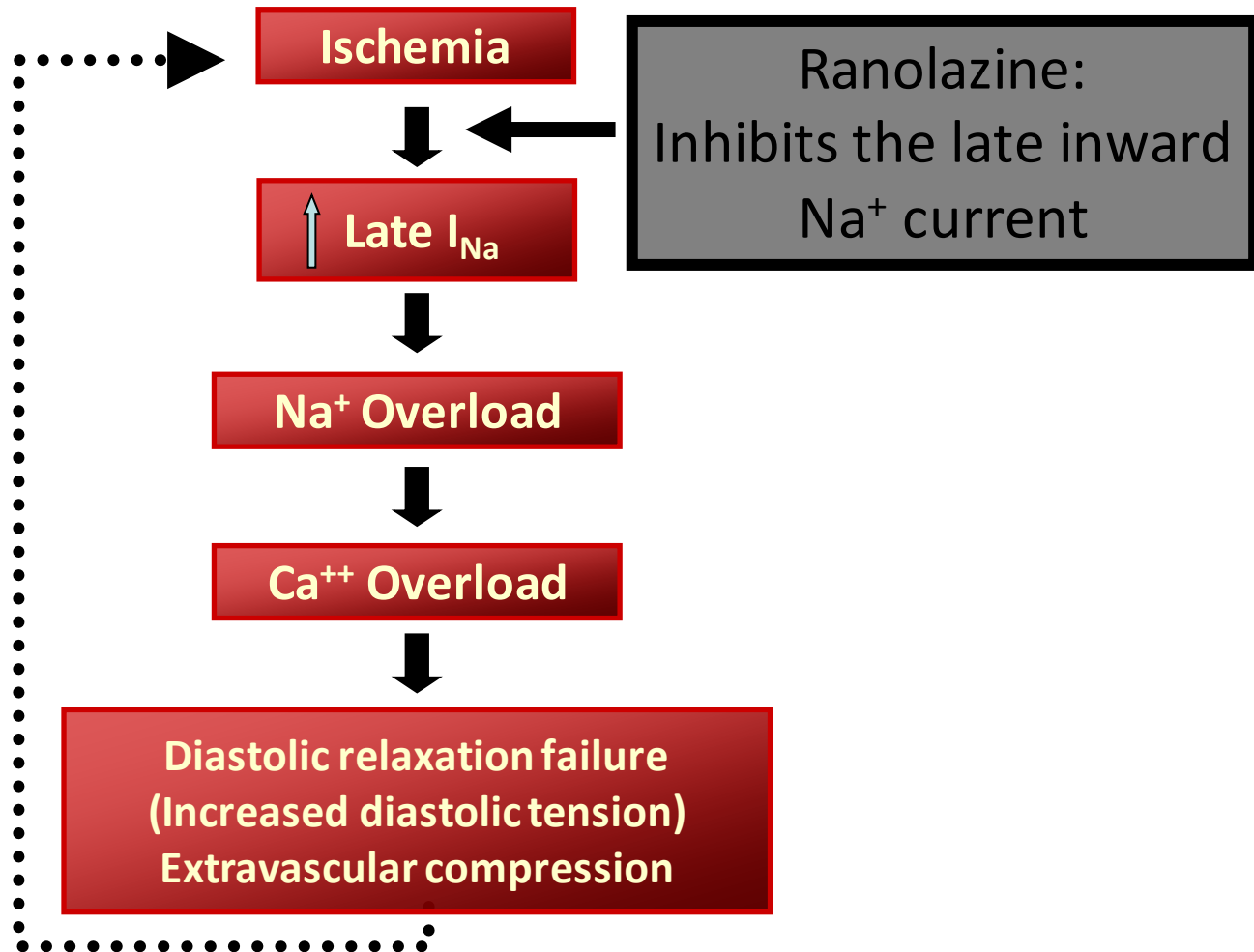
However, late  $I_{Na}$  is increased in myocytes exposed to hypoxia,<sup>10</sup> ischaemic metabolites,<sup>11,12</sup> and reactive oxygen species,<sup>13</sup> and it is increased in post-ischaemic 'remodelled' ventricular myocytes.<sup>14</sup>



Adapted from Belardinelli L et al. *Eur Heart J Suppl.* 2006;(8 suppl A):A10-13.

Belardinelli L et al. *Eur Heart J Suppl.* 2004;6(suppl 1):13-7.

# Ranolazine: Mechanism of Action

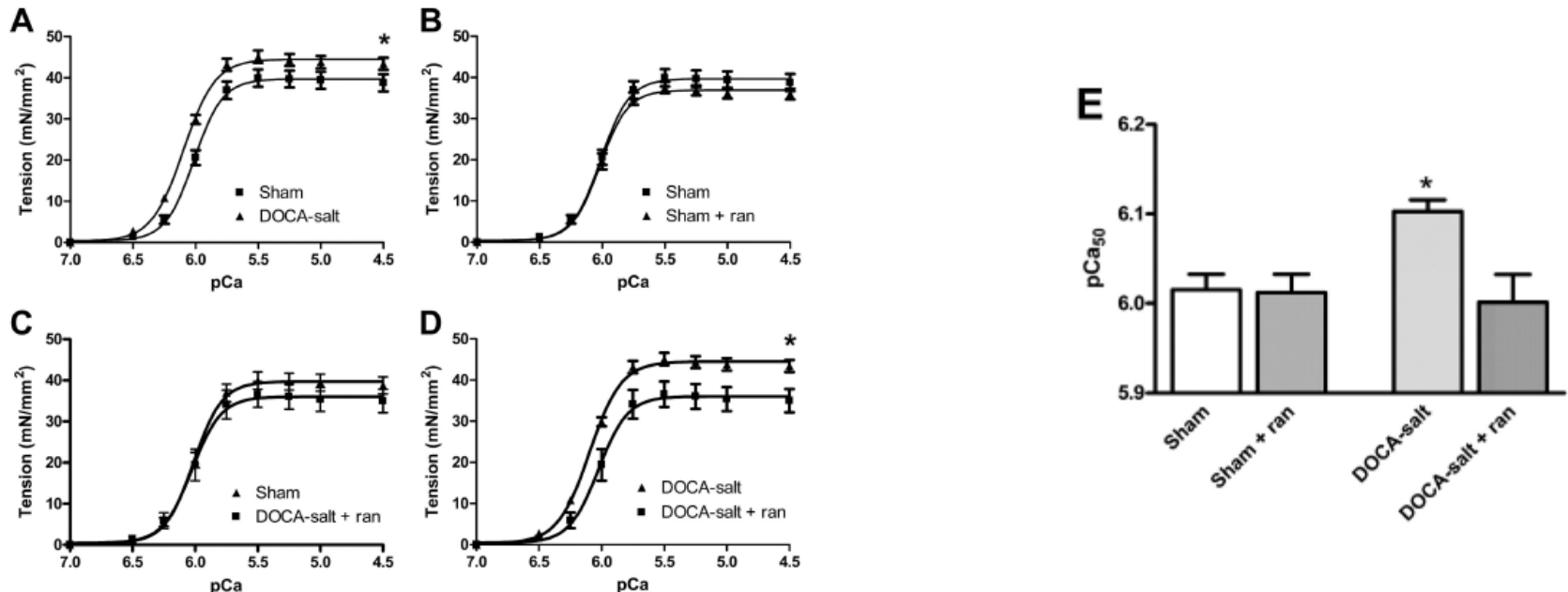


# Ranolazine Improves Cardiac Diastolic Dysfunction Through Modulation of Myofilament Calcium Sensitivity

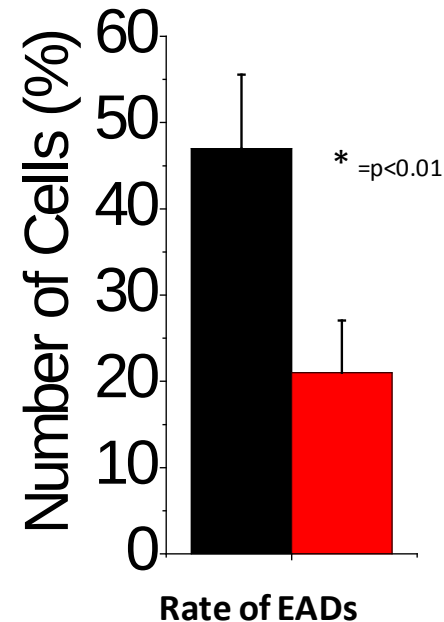
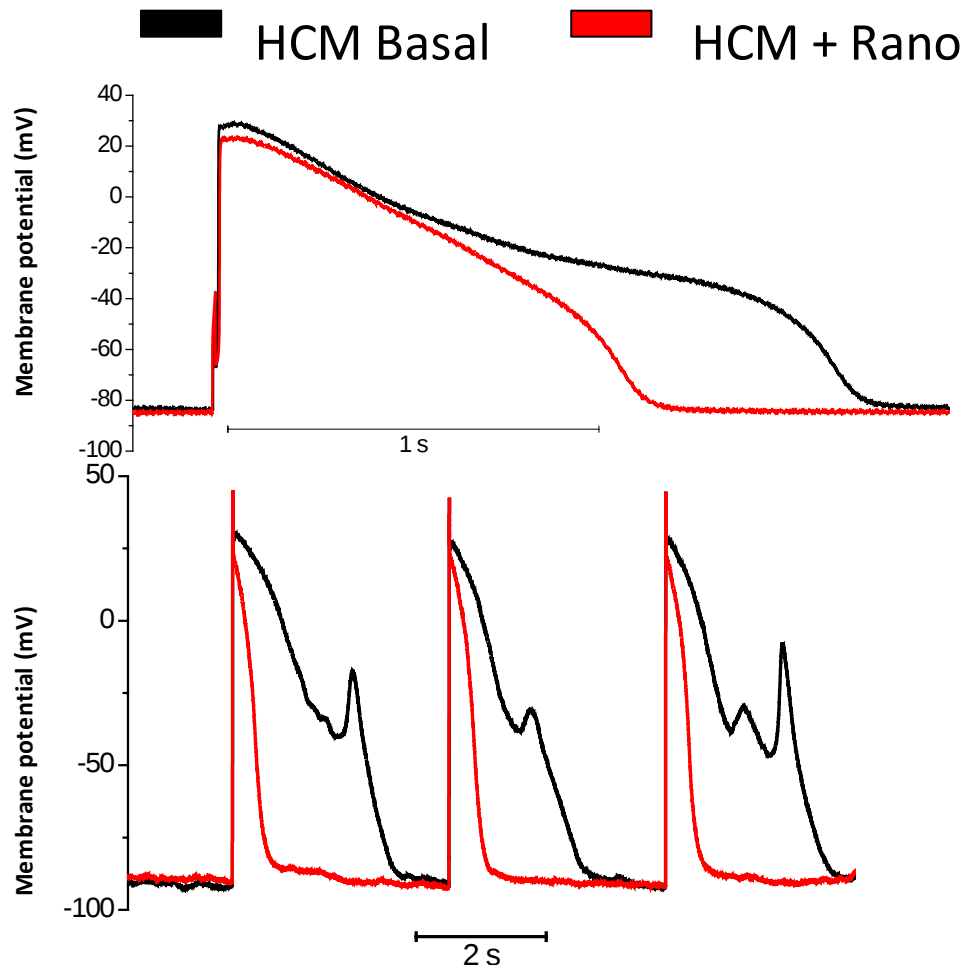
Joshua D. Lovelock,\* Michelle M. Monasky,\* Euy-Myoung Jeong,\* Harvey A. Lardin, Hong Liu, Bindiya G. Patel, Domenico M. Taglieri, Lianzhi Gu, Praveen Kumar, Narayan Pokhrel, Dewan Zeng, Luiz Belardinelli, Dan Sorescu, R. John Solaro, Samuel C. Dudley, Jr

*Circ Res.* 2012;110:841-850

In conclusion, the present study demonstrates that ranolazine treatment improves diastolic function through modulation of myofilament activity.

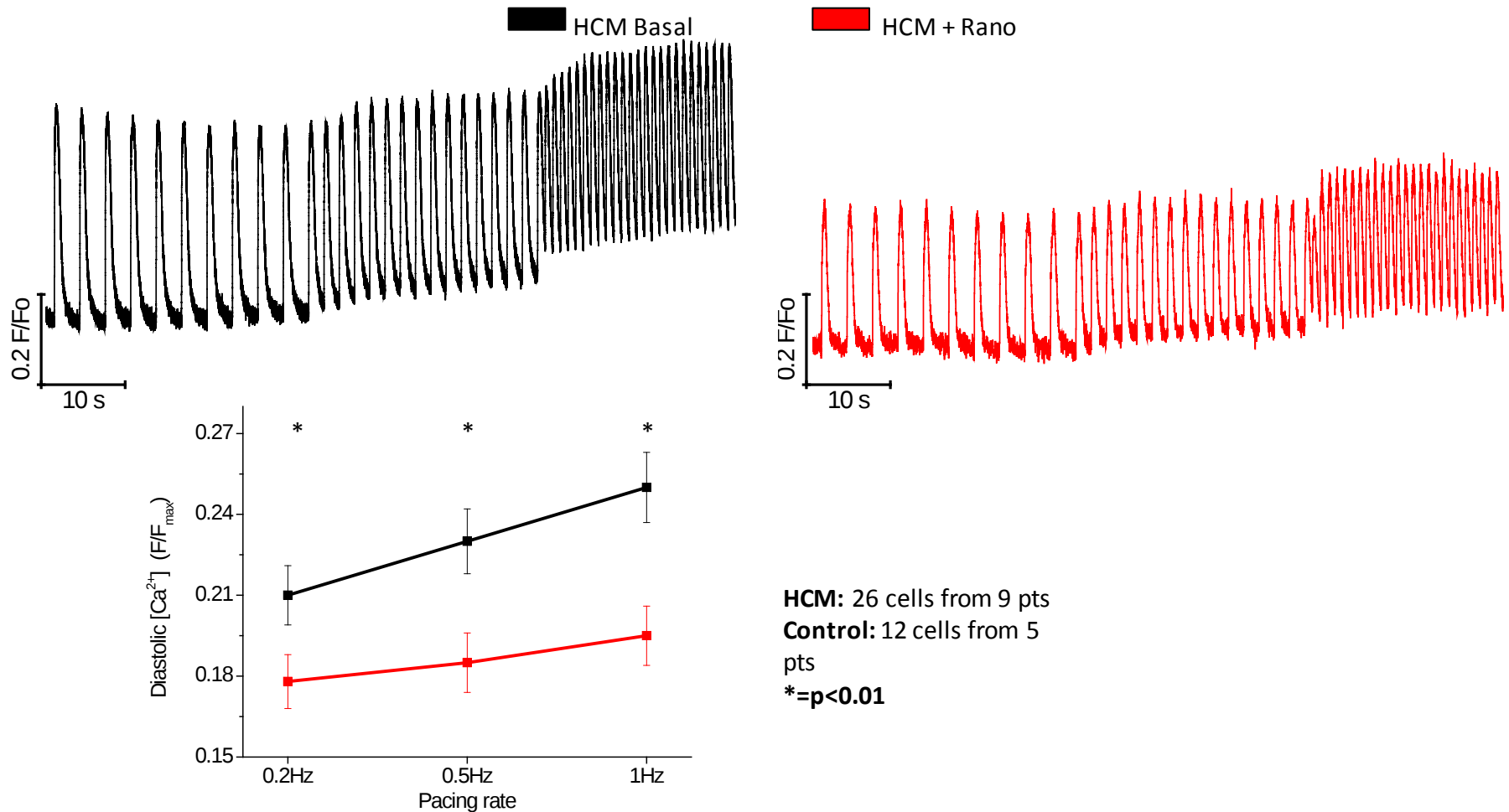


# Ranolazine reduces the rate of EADs in HCM cardiomyocytes



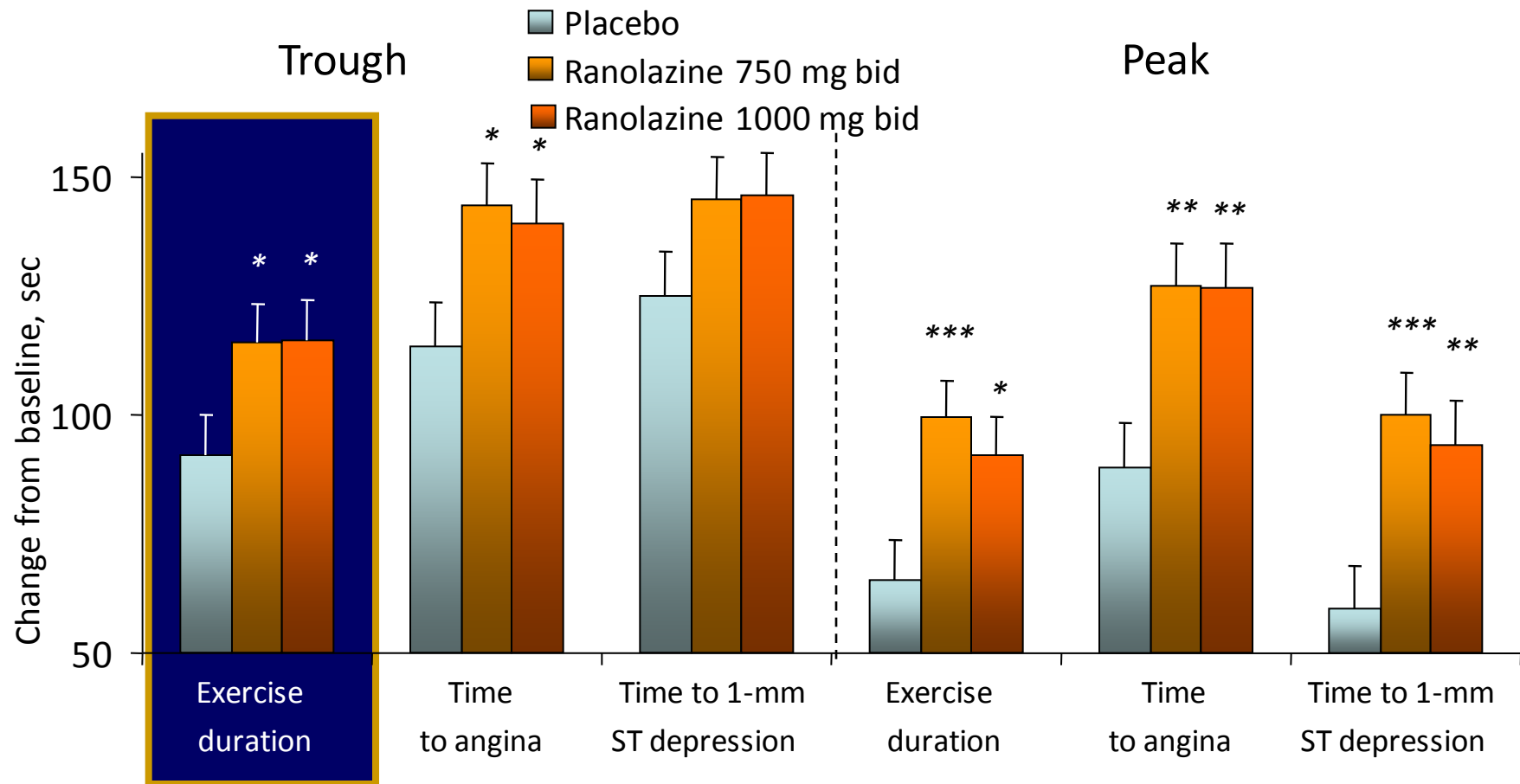
Coppini et al submitted

# Ranolazine reduces diastolic Ca<sup>2+</sup>



# CLINICAL STUDIES

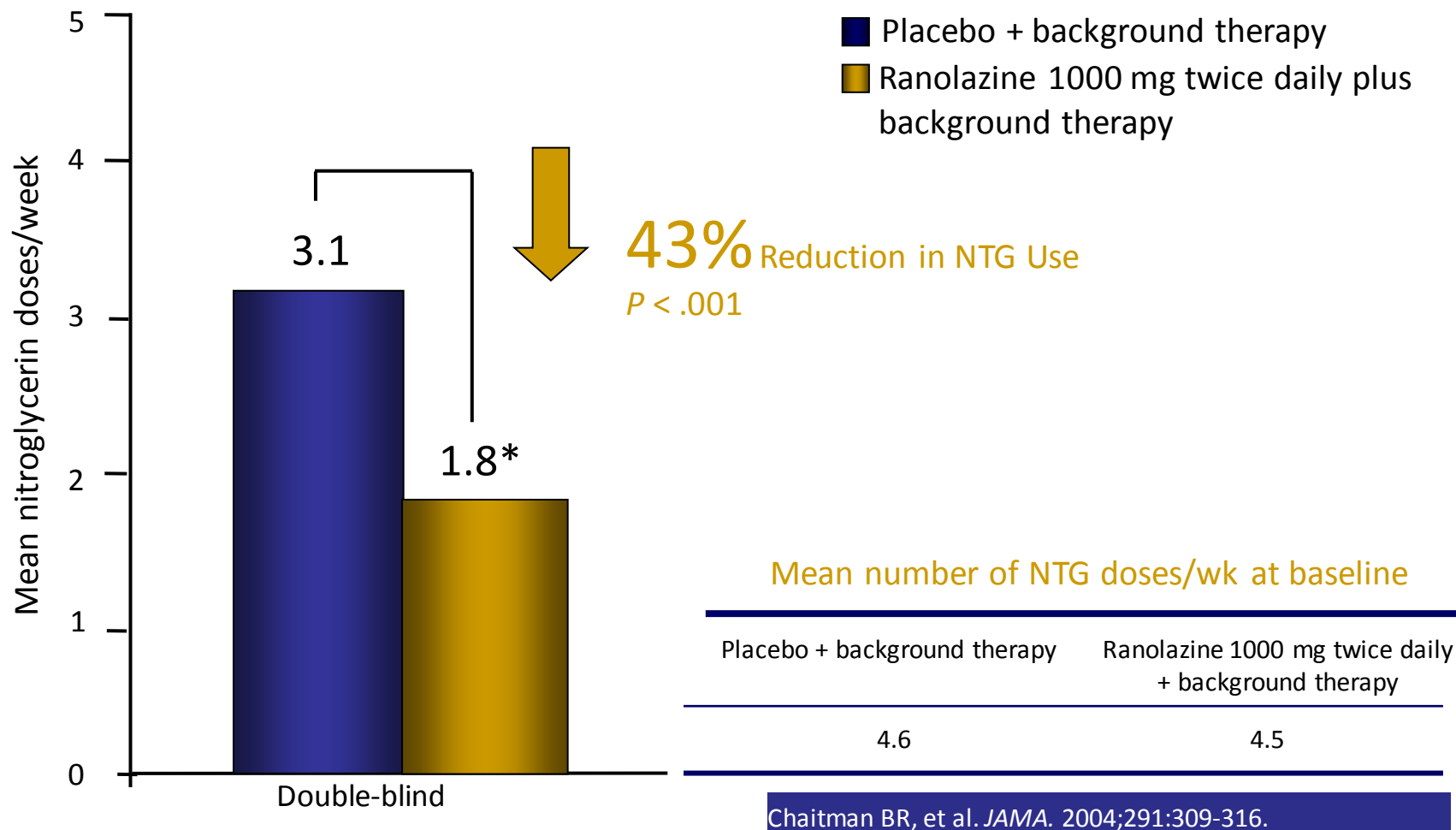
# CARISA: Is Ranolazine effective on top of atenolol/amlodipine?



N = 791, ITT/LOCF; LS mean  $\pm$  SE. \* $P < .05$ ; \*\* $P \leq .01$ ; \*\*\* $P \leq .001$  vs placebo

Chaitman BR, et al. *JAMA*. 2004;291:309-316.

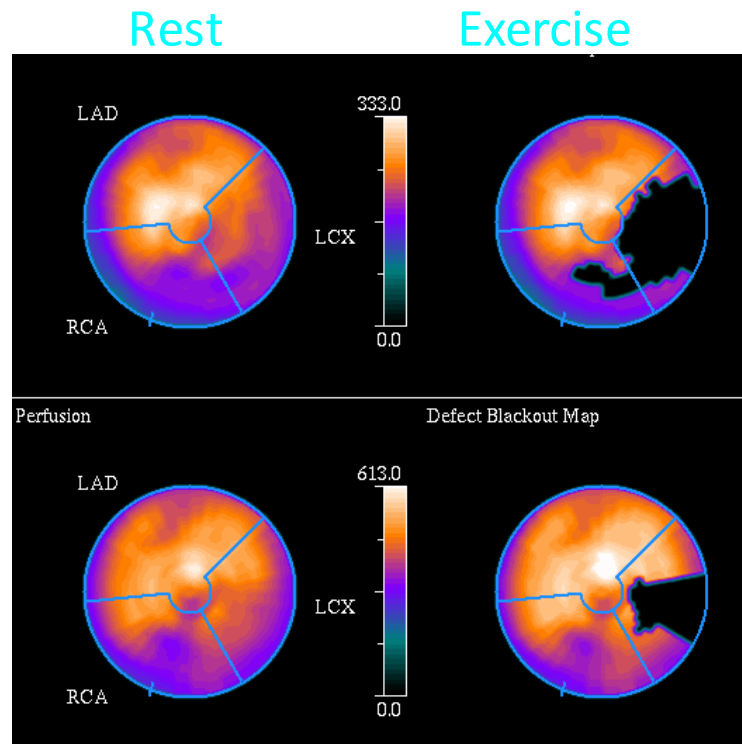
# CARISA: Ranolazine Reduces Weekly Nitroglycerin Use vs Placebo



# Effects of Ranolazine on Stress MPI

Baseline  
Peak HR = 142 bpm

After RAN (3-4 wks)  
Peak HR = 142 bpm



25%

Reversible  
Perfusion  
Defect Size

10%

| MPI Variables (n=21)              | Baseline    | After RAN   | p Value |
|-----------------------------------|-------------|-------------|---------|
| Summed difference score           | $7.2 \pm 5$ | $4.7 \pm 4$ | 0.006   |
| Total perfusion defect size (PDS) | $24 \pm 16$ | $17 \pm 15$ | 0.003   |
| Ischaemia PDS                     | $16 \pm 11$ | $8 \pm 5$   | 0.005   |

Venkataraman J. A C C : C ardiovascular I maging, V O L . 2 , N O . 1 1 , 2 0 0 9

# EU-Therapeutic indications

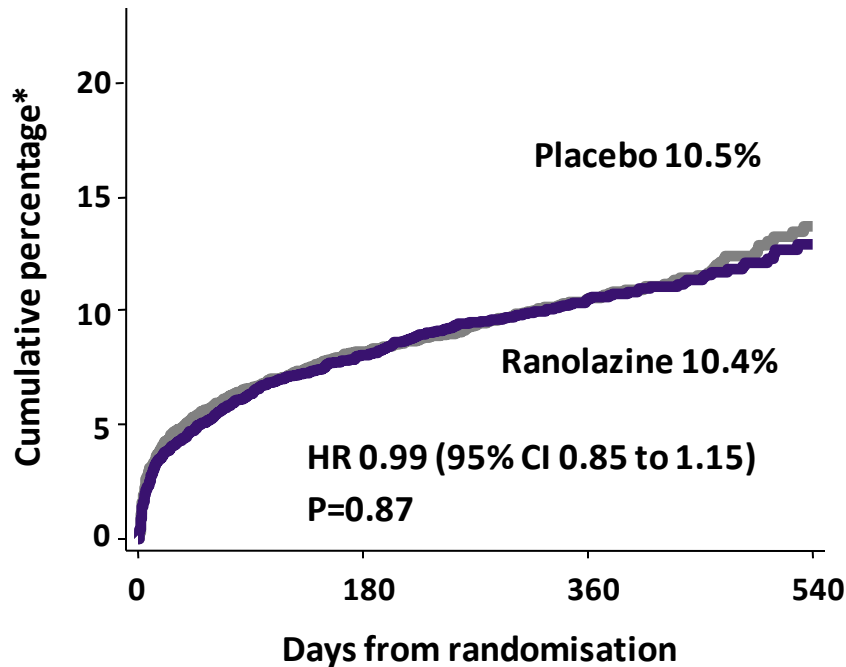
Ranolazine is indicated as **add-on therapy** for the symptomatic treatment of patients with **stable angina pectoris** who are **inadequately controlled** or **intolerant to first-line antianginal therapies** (such as **beta-blockers** and/or **calcium antagonists**).

*Ranolazine European SmPC*

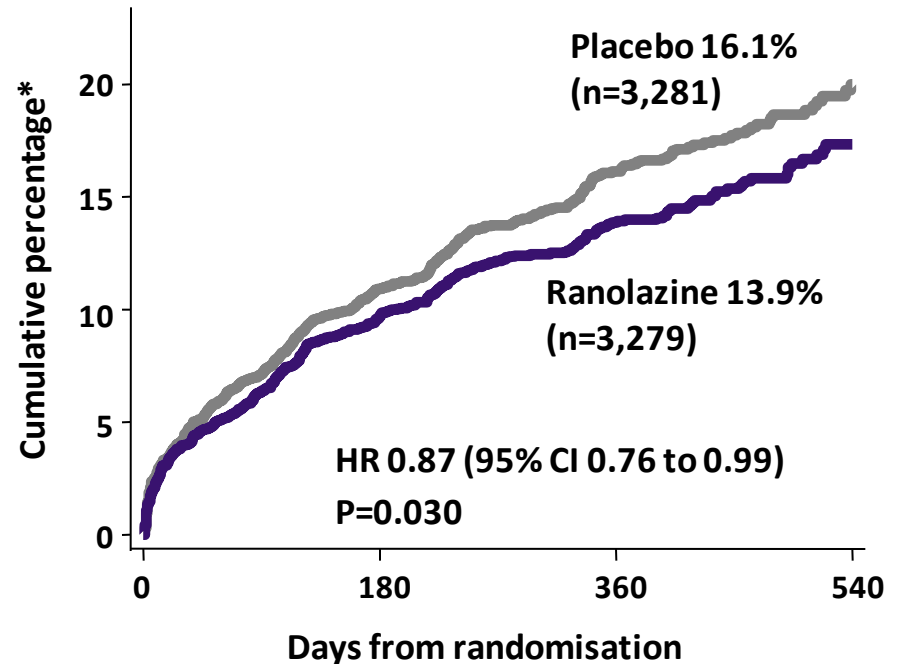
# MERLIN: components of the primary efficacy end-point

■ Placebo ■ Ranolazine

## CV death or MI



## Recurrent ischaemia

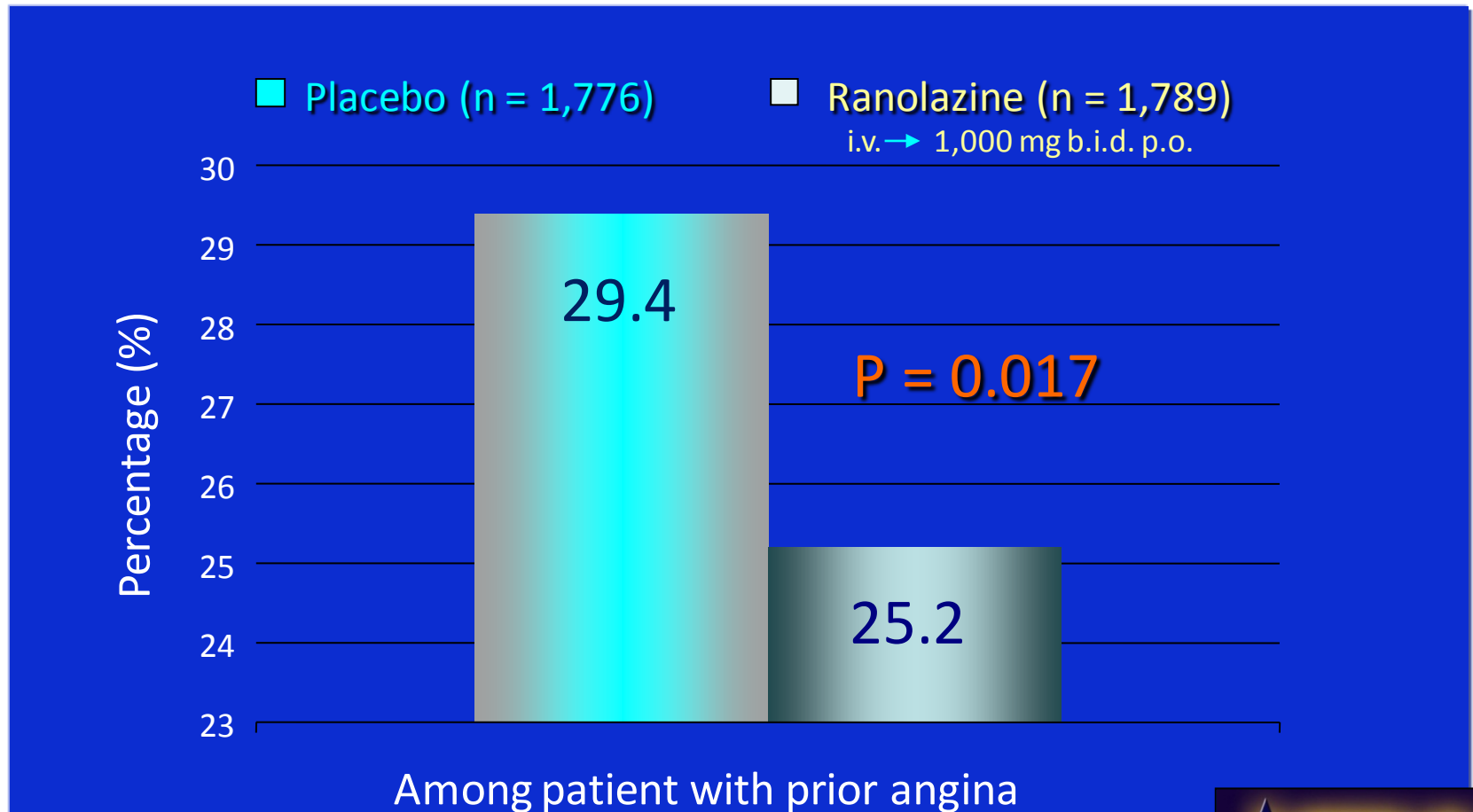


Morrow D, et al. JAMA 2007;297:1775-83

\*Kaplan-Meier cumulative incidence at 12 months

# RESULTS - Primary End Point

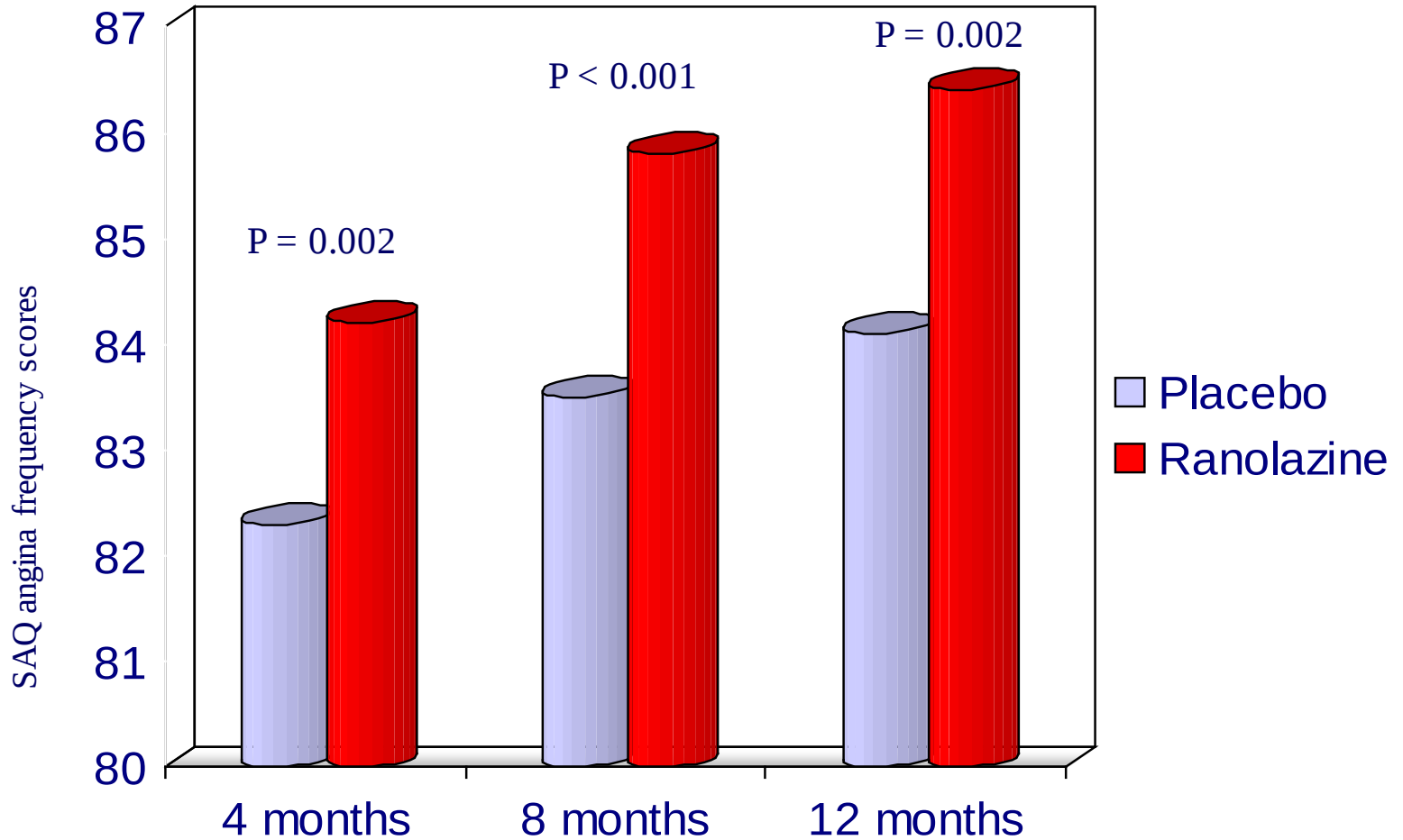
(CV death, MI or Recurrent Ischemia)



Wilson S.R. et al.: J Am Coll Cardiol 2009; 53 (17): 1510-1516

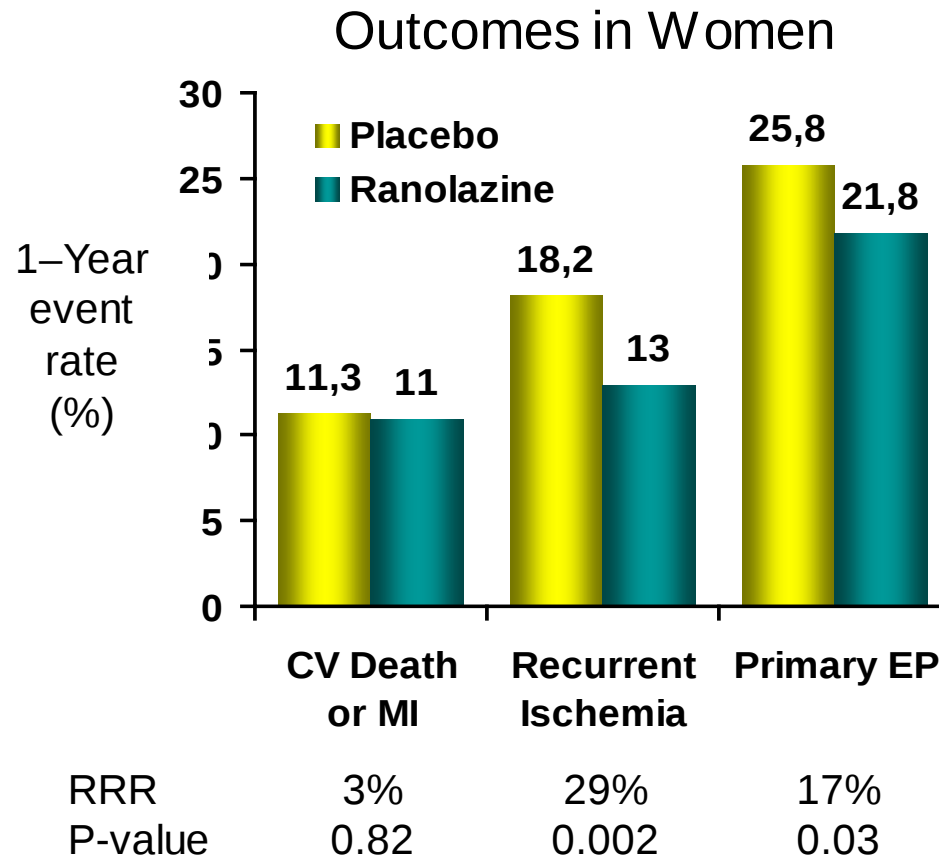


# Higher SAQ angina frequency scores MERLIN-TIMI 36 study



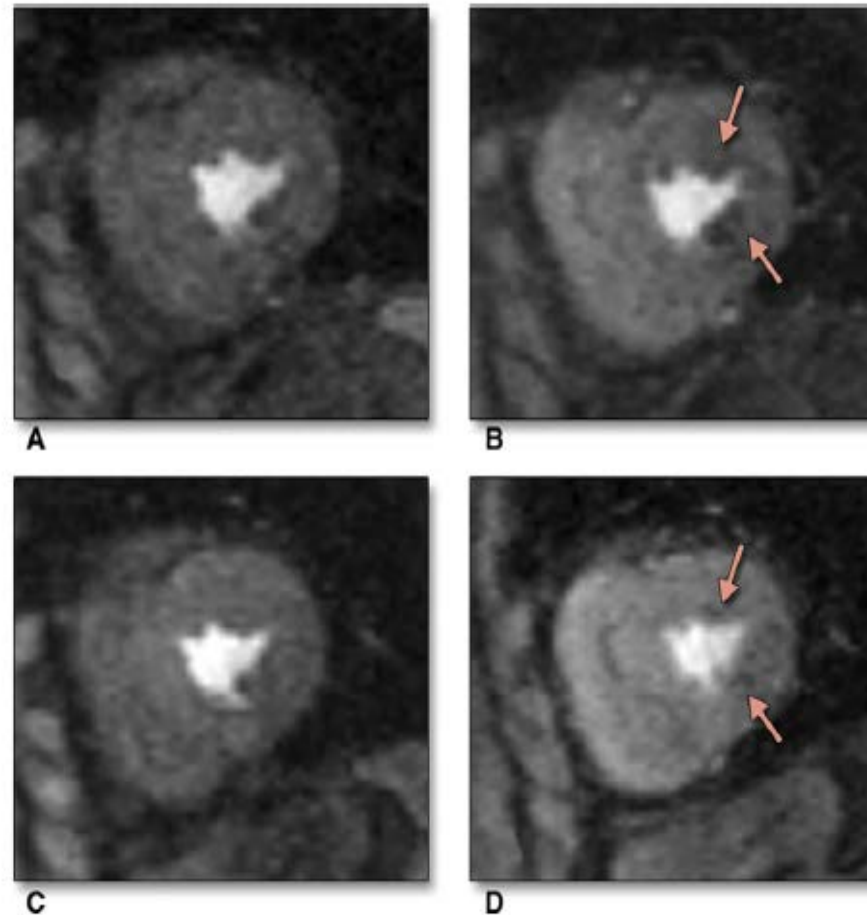
Arnold S.V. et al.; Circulation 2008; 1: 107-115

# Ranolazine is particularly effective in women



Mega JL et al. *Circulation* 2011.

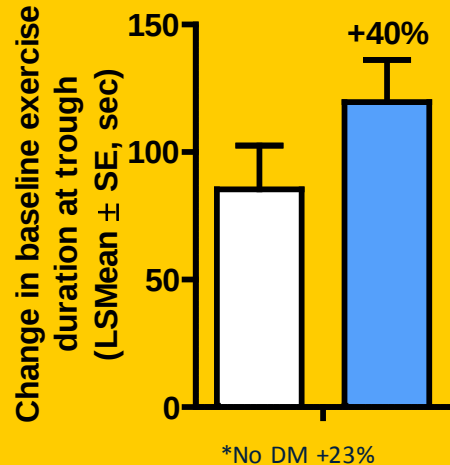
# Ranolazine Improves Angina in Women With Evidence of Myocardial Ischemia But No Obstructive Coronary Artery Disease



[Mehta PK](#), (J Am Coll Cardiol Img 2011;4:514–22)

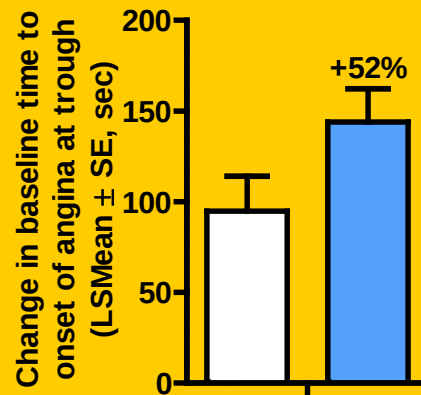
# Ranolazine in diabetics with chronic stable angina

Exercise duration



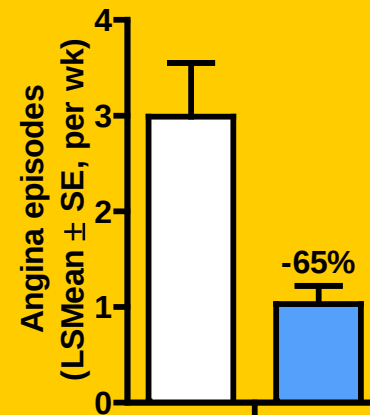
\*No DM +23%

Time to angina onset



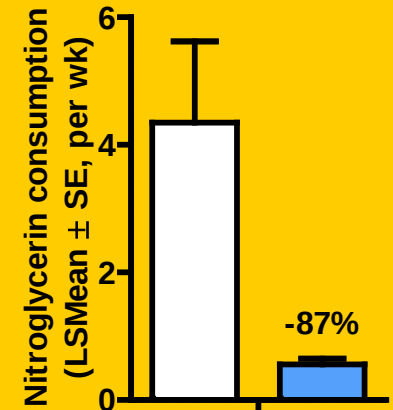
\*No DM +16%

Angina episodes



\*No DM -27%

Nitroglycerin use



\*No DM -25%

Placebo (n=57)

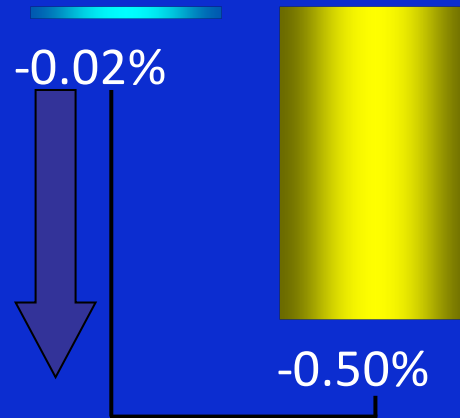
Ranolazine (1000 mg)(n=64)

T2DM- Type 2 diabetes mellitus  
SE- Standard error  
Ranolazine  $\downarrow$  HbA1c by 0.7%

# Ranolazine Significantly Reduced HbA1c in Patients With Diabetes and CAD

Absolute Reduction in HbA1c From Baseline to Week 12\*

Mean Change From Baseline in HbA1c (%)



0.48% reduction\*

$p = 0.008$

Placebo (n = 37)      Ranolazine 750 mg b.i.d. (n = 47)

\*At baseline, mean HbA1c was 7.9% in patients receiving ranolazine and 7.5% in patients receiving placebo.



NEW INDICATIONS

# Comparison of Effectiveness and Safety of Ranolazine Versus Amiodarone for Preventing Atrial Fibrillation After Coronary Artery Bypass Grafting

Ronald H. Miles, MD<sup>a</sup>, Rod Passman, MD, MSCE<sup>b</sup>, and David K. Murdock, MD, MS<sup>a,\*</sup>

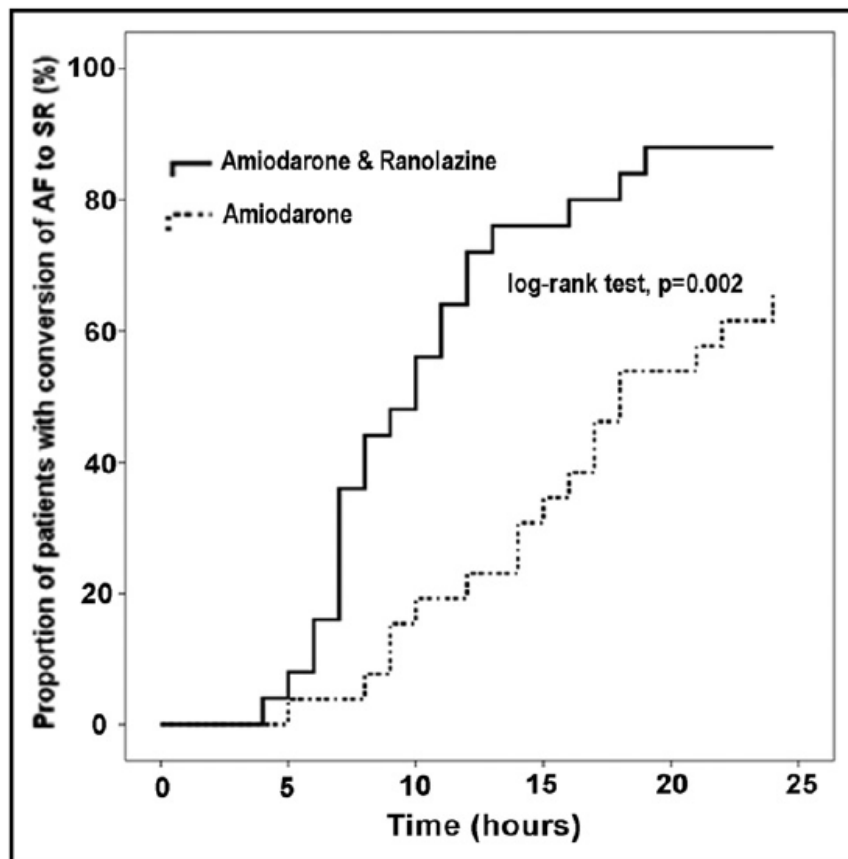
| Characteristic                      | Amiodarone | Ranolazine | p Value |
|-------------------------------------|------------|------------|---------|
| Postoperative atrial fibrillation   | 26.5%      | 17.5%      | 0.035   |
| Heart block                         | 0%         | 0%         | 1.0     |
| Stroke or transient ischemic attack | 0%         | 0.5%       | 0.87    |
| Renal failure with dialysis         | 1.1%       | 0.9%       | 0.88    |
| Prolonged ventilation               | 6.0%       | 3.8%       | 0.28    |
| 30-Day readmission                  | 10.4%      | 10.4%      | 1.0     |
| 30-Day Mortality                    | 1.09%      | 0.94%      | 0.88    |

**Comparison of Effectiveness of Ranolazine Plus Amiodarone  
Versus Amiodarone Alone for Conversion of Recent-Onset  
Atrial Fibrillation**

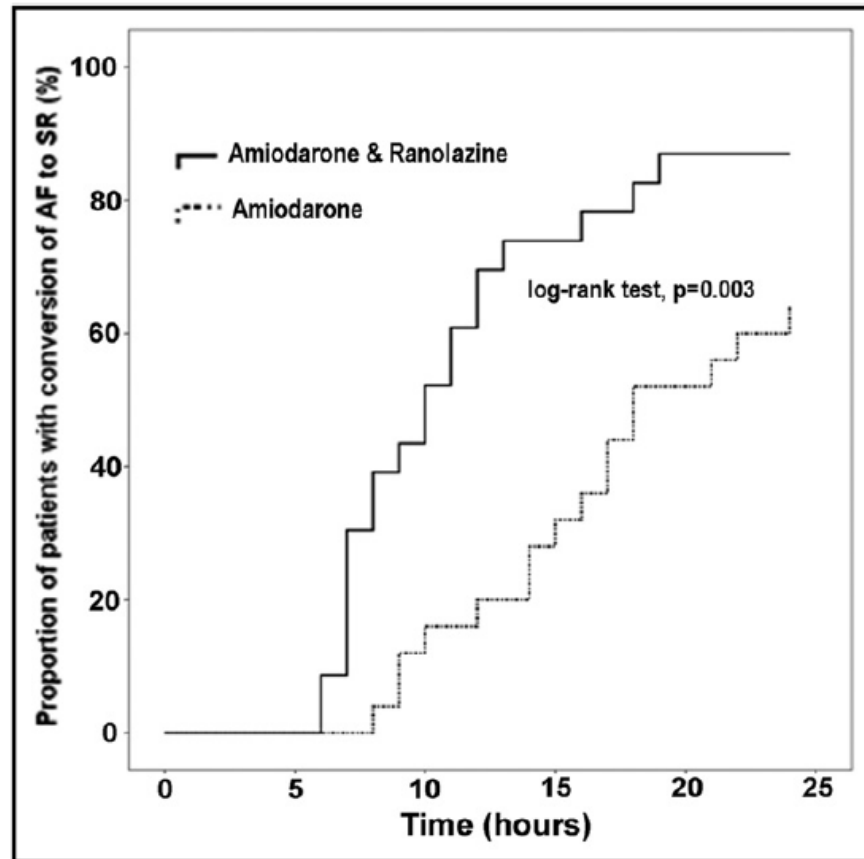
Nikolaos Fragakis, MD<sup>a,†</sup>, Konstantinos C. Koskinas, MD<sup>a,\*†</sup>, Demosthenes G. Katritsis, MD<sup>b</sup>,  
Efsthathios D. Pagourelas, MD<sup>a</sup>, Theodoros Zografos, MD<sup>b</sup>, and Paraschos Geleris, MD<sup>a</sup>

Am J Cardiol 2012;110:673–677

There were no proarrhythmic events in either group. In conclusion, addition of ranolazine to standard amiodarone therapy is equally safe and appears to be more effective compared to amiodarone alone for conversion of recent-onset AF.



>0 h <24 h



>6 h <24 h

# Conclusions I

- Inhibition of late sodium current effectively reduces the deleterious consequences of ischemia
- Ranolazine on top of first line antiischemic drugs reduces ischemic symptoms in chronic stable angina
- It is particularly valuable in patients with bradycardia, hypotension or left ventricular dysfunction
- Ranolazine may have an extended role in chronic stable angina in women and in patients with diabetes, atrial fibrillation and diastolic dysfunction.

## Conclusions I I

- Inhibition of late sodium current may help to control arrhythmias, which are due to ischemia
- Ranolazine may be beneficial in atrial fibrillation prevention and DC cardioversion (+Amiodarone)
- It may also help to restore SR in DC cardioversion resistant patients (2 g orally 3-4 hours before)
- Ranolazine may be beneficial in patients with Hypertrophic Cardiomyopathy