Ranolazine: An Update

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Outline

- **Ranolazine in stable angina**
  - **Rationale**
  - **Mechanism**
  - **Prescribing information**
  - **Clinical trials**
- **RIVER-PCI study**
- **Additional drug effects**

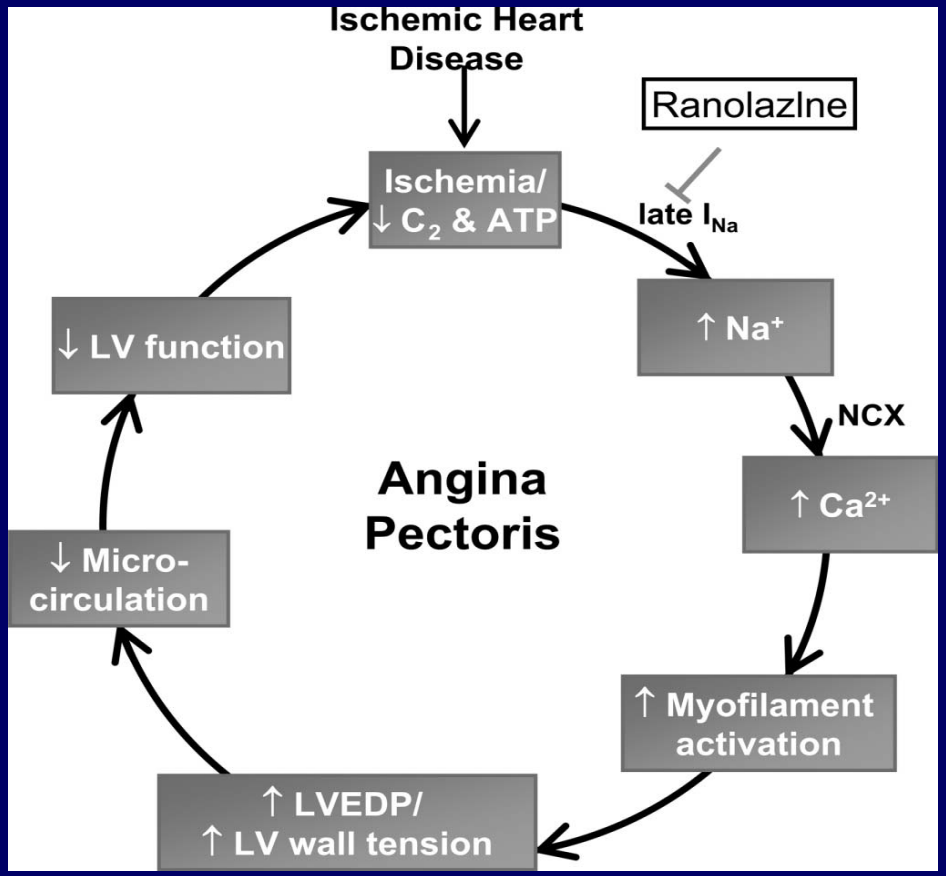
Stable Angina

- **Stable angina estimated prevalence**
  - **9 million people in the US or 3.9% of the population.**
- **Management**
  - **Symptoms relief**
  - **Reducing cardiovascular morbidity and mortality**
- **Guidelines emphasize a stepwise approach to symptomatic treatment**
  - **Patients without high risk non-invasive or anatomic findings**
  - **Implementation of maximal anti-ischemic medical therapy before embarking on a revascularization strategy**
    - **Two classes of therapies to reduce angina symptoms**

Ranolazine Mechanism of Action

- **Ranolazine is indicated for the treatment of chronic angina in combination with beta-blockers, nitrates, CCB**
- **Anti-ischemic and antianginal effects not dependent on reductions in heart rate or blood pressure**
- **Ranolazine at therapeutic levels can inhibit the cardiac late sodium current (I_{Na}) and the delayed rectifier K current (I_{Kr})**
- **Two distinct hypotheses regarding the MOA of ranolazine have been proposed: inhibition of (I_{Na}) Inhibition and of partial fatty acid oxidation (pFOX)**

Scheme for the pathophysiology of myocardial ischemia and the role of late INa inhibition with ranolazine



Sarcolemmal Na/Ca exchanger

Maier, LS J Cardiovasc Pharmacol 2009

Effects of Calcium Overload in Ischemia

- **Increased intracellular calcium may result in sustained myocardial contraction, which leads to**
  - **Increased oxygen demand**
  - **Decreased microvascular blood flow**
  - **Reduced oxygen supply**
- **Scientific literature suggests that this leads to worsening of ischemia, exacerbating the cycle of ischemia**

Meissner A et al. Am J Physiol Heart Cir Physiol. 1995; 268: H100-H111

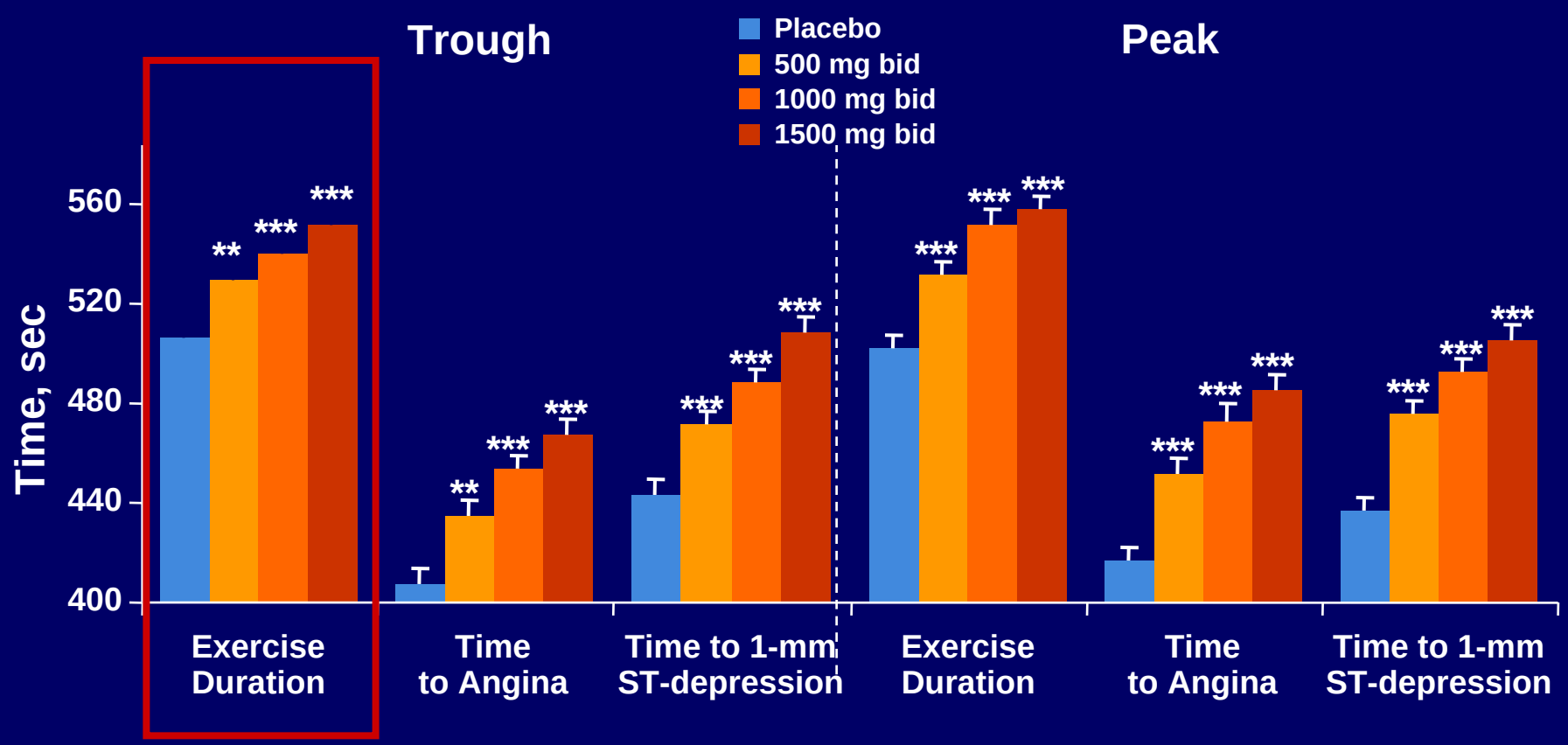
Ranolazine

- **Dosing**
  - 500 mg twice a day, titrate to 1000 mg twice a day
- **Steady State**
  - Within 3 days of twice-daily dosing
- **Metabolism**
  - Metabolized in the liver and intestine
  - Primary metabolism by CYP3A, and < 20% by CYP2D6
- **Precautions**
  - QT prolonging drugs, personal/FH
  - Moderate CYP3A Inhibitors (dose limit)
  - diltiazem, verapamil, erythromycin, fluconazole, and grapefruit juice
- **Contraindications**
  - Strong CYP3A Inhibitors/inducers
  - ketoconazole, clarithromycin, antiretrovirals/ rifampin, anticonvulsants, St. John's wort
  - Liver cirrhosis/Dialysis
- **Side Effects**
  - dizziness, nausea, asthenia, and constipation

Randomized Clinical Trials in Stable Angina

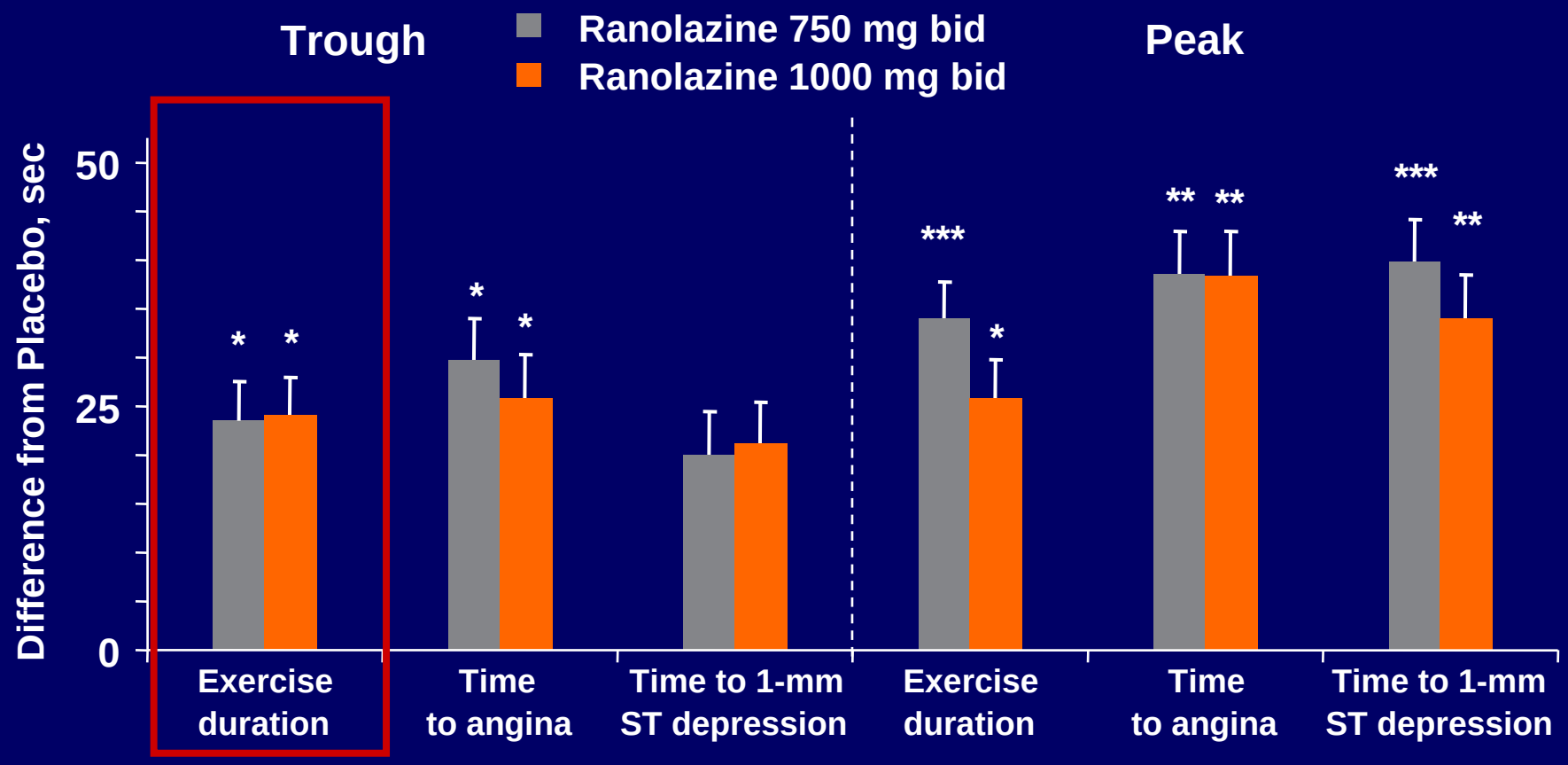
- **MARISA (Monotherapy Assessment of Ranolazine in SA)**
  - **Improved exercise duration, time to angina, time to ST depression**
- **CARISA (Combination ARISA): Efficacy was demonstrated when used in combination with one of three standard therapies for angina**
  - **Above plus reduction in angina frequency**
- **ERICA (Efficacy of Ranolazine in Chronic Angina) Demonstrated efficacy in patients with refractory angina symptoms while on maximum dose of amlodipine**
  - **Reduction in angina frequency and NTG use**

MARISA



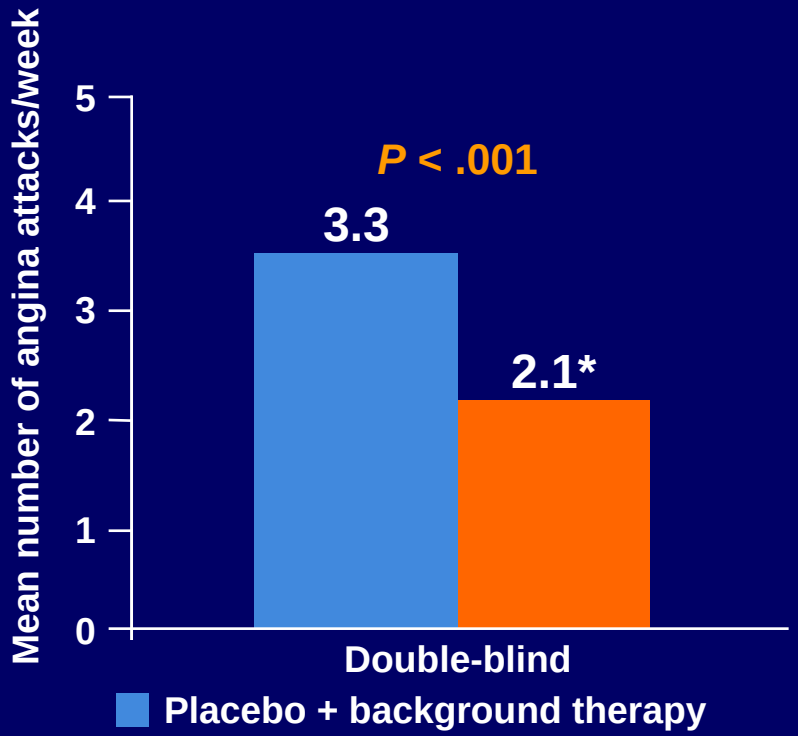
The red box denotes the primary study endpoint
N = 175, All/Near Completers population; LS means ± SE.
***P* < .01 vs placebo; ****P* < 0.001 vs. placebo
Chaitman BR. *Circulation*. 2006;113:2462-2472.

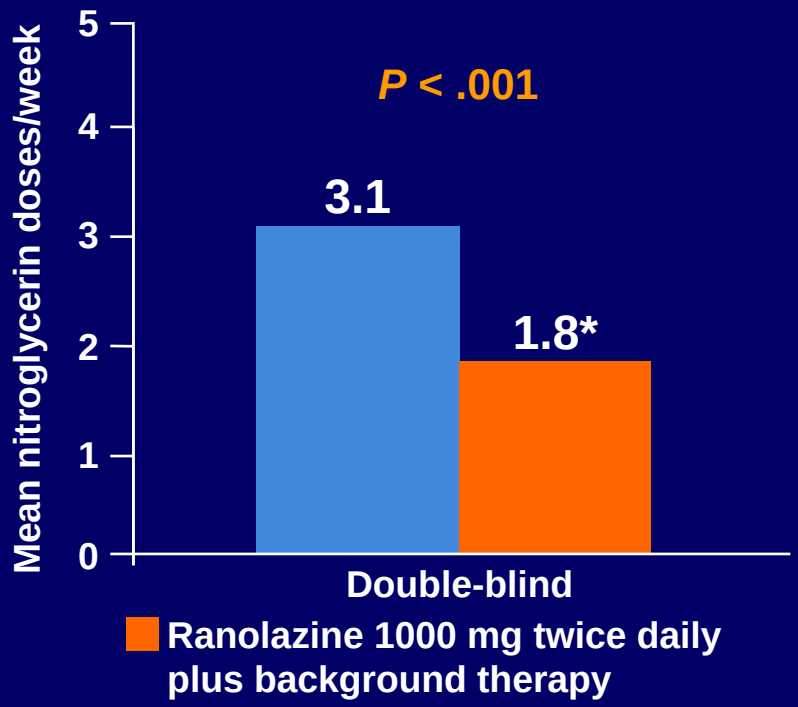
CARISA Efficacy



The red box denotes the primary study endpoint
N = 791, ITT/LOCF; LS mean ± SE. *P < .05; **P ≤ .01; ***P ≤ .001 vs placebo
Chaitman BR, et al. *JAMA*. 2004;291:309-316.

CARISA: Ranolazine Reduces Weekly Angina Frequency and Nitroglycerin Use Versus Placebo

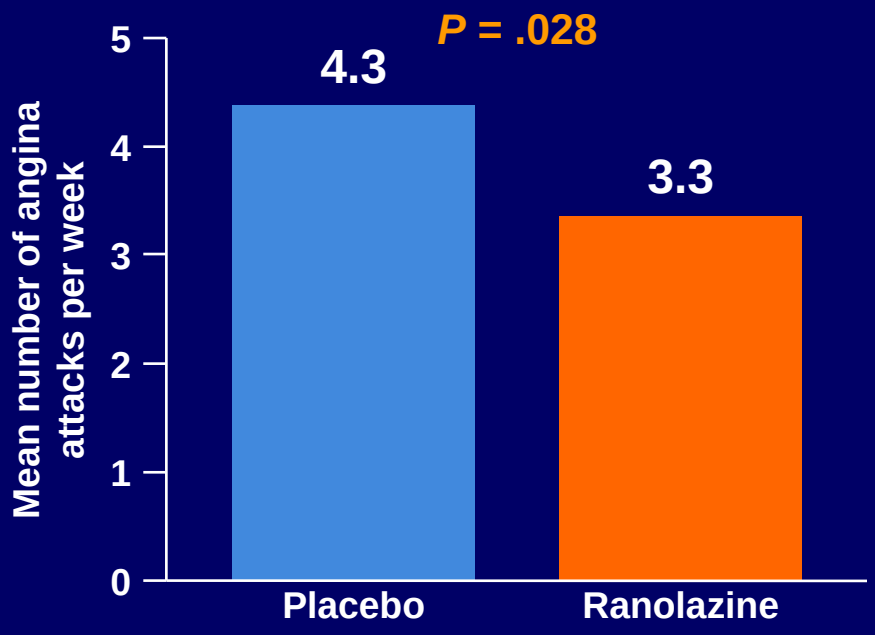




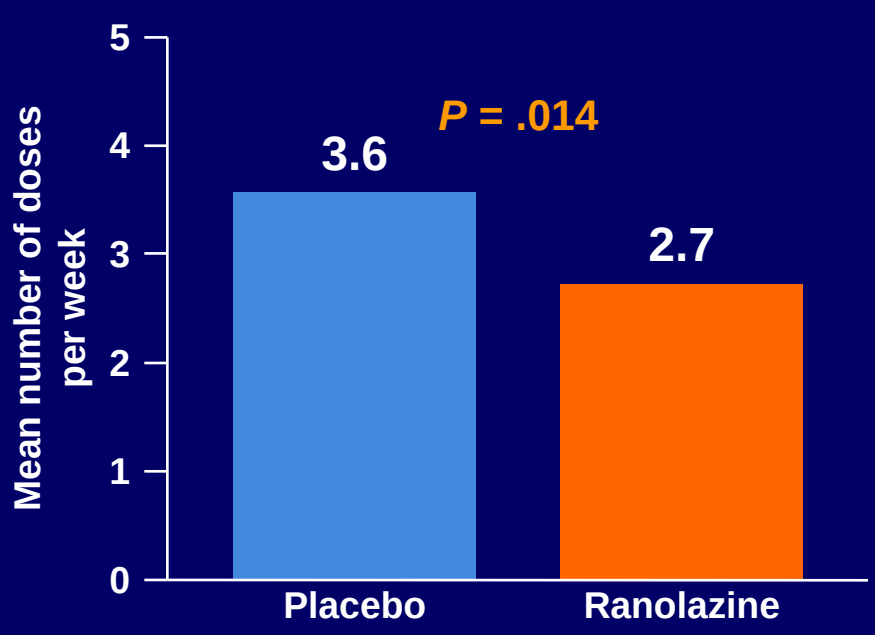
Chaitman BR, et al. *JAMA*. 2004;291:309-316.

ERICA: Efficacy

Average weekly angina attacks over 6-week study period



Average weekly nitroglycerin use over 6-week study period



* Mean reduction in weekly angina attacks was 0.3 for females and 1.3 for males

Modified from Stone P, et al. *J Am Coll Cardiol*. 2006;48(3):566-75.

RIVER-PCI: Ranolazine for Incomplete VEssel Revascularization Post - PCI Study

Objective	**To evaluate the effects of RAN in patients with incomplete revascularization post-PCI**
Design	**Placebo-controlled double blind event driven study**
Patients	**Patients (N~2,600) with a history of angina, clinically indicated PCI and incomplete revascularization defined as at least 50% residual stenosis in 2 mm vessel**
Treatment	**Patients randomized to RAN 1,000 mg BID or placebo within 14 days of PCI**
Endpoints	
Primary	**Time to first occurrence of ischemia-driven revascularization or ischemia-driven hospitalization without revascularization**
Secondary	**Sudden cardiac death; CV death, MI**

Ranolazine- Additional Effects

- **Glycemic control**
  - **Modest effects on glycemic control**
    - **CARISA HA1c decreased 0.5-0.7**
    - **MERLIN HA1c decreased 0.7**
  - **Animal model increases glucose stimulated insulin secretion**
- **Diastolic heart failure**
  - **Attenuates diastolic dysfunction in models of ischemia reperfusion**
- **Antiarrythmic**
  - **Suppresion of early after depolarizations**
  - **MERLIN study significantly lower rate of arrythmia on holter**

Summary

- Ranexa is approved for the treatment of SA
- Reduces frequency of angina and NTG use
- Increases exercise duration
- Know drug interaction
- Current trial of ranolazine in PCI patients with incomplete revascularization
  - RIVER-PCI
- Additional effects include improved gylcemic control, diastolic function and arrythmias