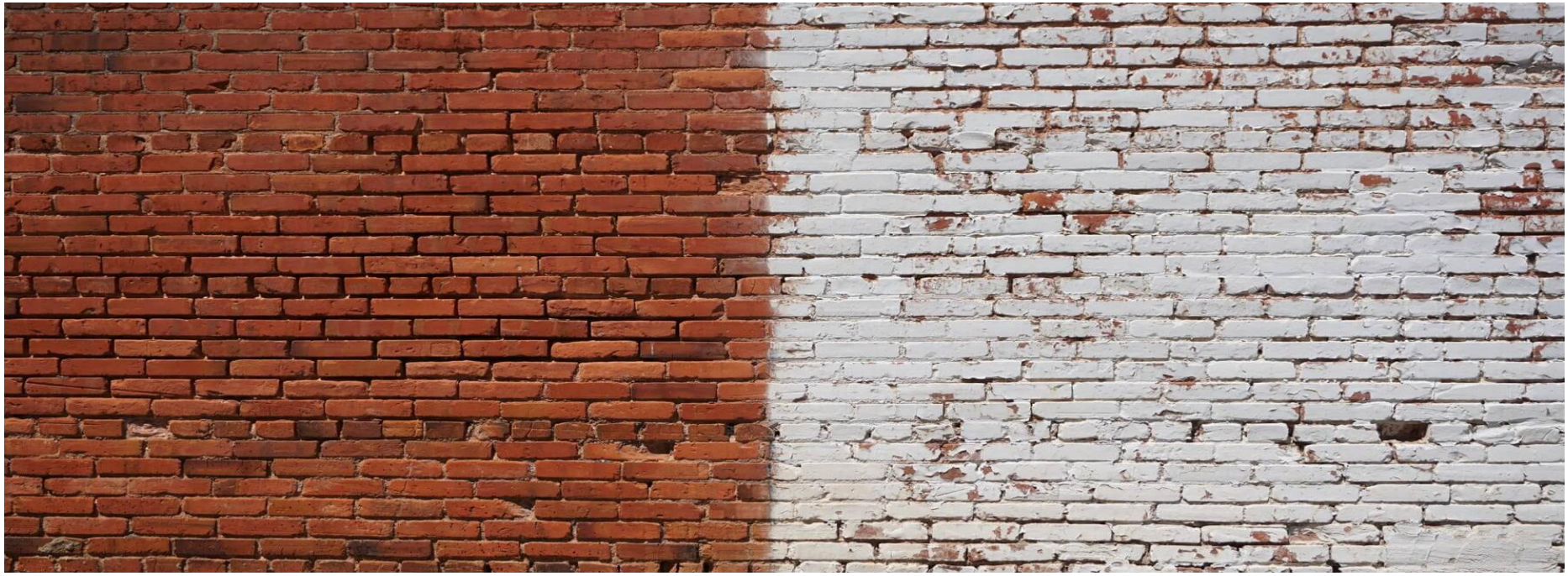
یا جاری اللصیق

به نام همسایه دیوار به دیوار- خدای مهربان



الهی نام تو ما را جواز، مهر تو ما را جهاز،
شناخت تو ما را امان، لطف تو ما را عیان.
نگاه دار تا پریشان نشویم و در راه آر تا
سرگردان نشویم.

خواجه عبدالله انصاری

یا جاری اللصیق

دکتر مهدی زاهدی
فوق تخصص مداخلات قلب و عروق
کارشناس ارشد آموزش پزشکی
عضو هیات علمی دانشگاه علوم پزشکی گلستان

Ranolazine

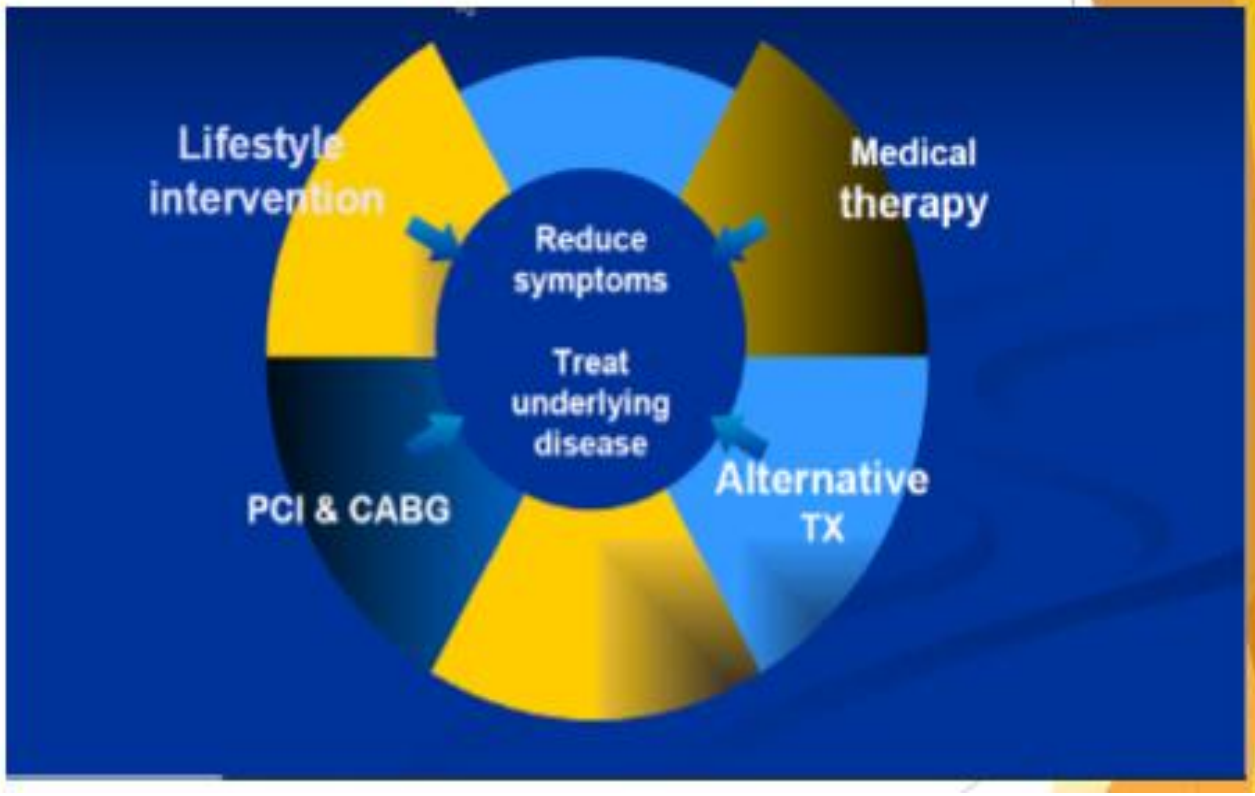
The prevalence of chronic IHD

IHD is progressively increasing for the following reasons:

- (a) the aging of population;
- (b) the reduction in mortality during acute coronary syndrome, with consequent increase of progression to stability;
- (c) the increase of some risk factors such as obesity and diabetes

Management of chronic ischemic heart disease into internal medicine and geriatric departments in Italy, Accepted: 17 September 2019

Stable CAD
Multiple treatment options



Anti ischemic drugs

- **First line:**
  - Nitrates
  - Beta blockers
  - Calcium channel blockers

Conventional Medical therapy

1. ↓ Myocardial Oxygen demand

- ↓ in **HR** (Beta blockers and NDHP Calcium Channel Blockers)
- ↓ in **Myocardial Contractility** (BBs and CCBs)

2. ↑ Oxygen supply

- Long Acting Nitrates
- Calcium Channel Blockers

Conventional medical therapy Gaps

1. Proportion of Patients **continue to experience myocardial angina** despite **optimal conventional medical therapy**

2. Many patients have relative **intolerances to maximum doses** of traditional antianginal agents (b-blockers, CCBs and nitrates) such as **elderly**

3. β-blockers and many CCBs have similar **depressive hemodynamic and electrophysiologic effects**

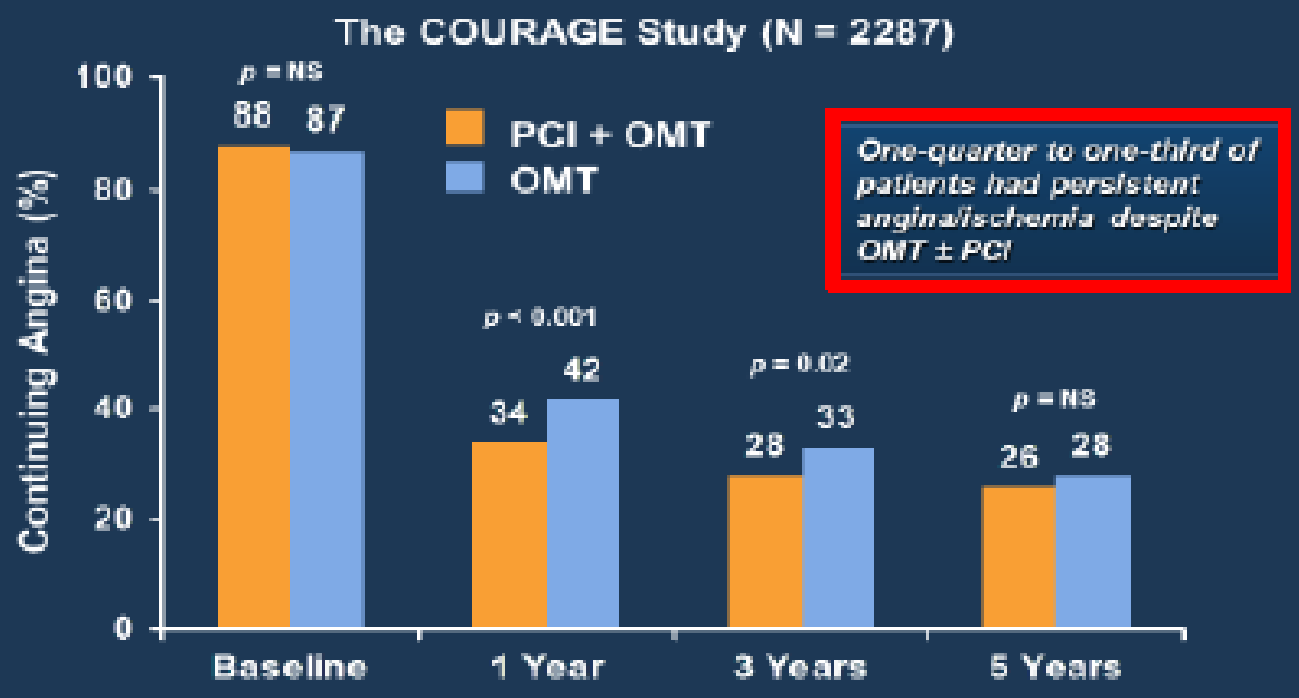
Revascularization for Stable CAD Gaps

1. **One year after PCI or CABG, %25 to 30% of patients still have ongoing angina**

2. **Unsuitable for revascularization procedures:**
   - **Unsuitable anatomy**, such as diffuse coronary disease.
   - One or several **prior PCIs or CABGs**
   - **Lack of vascular** conduits for CABG.
   - Severely **impaired left ventricular function** in patients with previous CABG or PCI.
   - **Concurrent diseases** that increase perioperative or postoperative morbidity or mortality (eg, cerebrovascular disease, advanced complications of diabetes, chronic kidney disease).
   - Age, often in combination with other factors.

Ranolaze 500
Ranolazine

Symptoms of Angina Persist Despite OMT ± PCI



Ranexa was approved after the COURAGE trial was initiated, and therefore was not part of the trial.
PCI = percutaneous coronary intervention; OMT = optimal medical therapy; CAD = coronary artery disease.
Boden WE, et al. *N Engl J Med.* 2007;356:1503-1516.

Anti ischemic drugs

First line:

- Nitrates
- Beta blockers
- Calcium channel blockers

Second line:

- **Ranolazine**
- Ivabradine
- Nicorandil
- Trimetazidine

Ranolazine: Label Approval

- On 27 Jan 2006, FDA approval for use in patients with chronic angina who continue to be symptomatic on β-Blockers, CCBs or Nitrates.
- The only second line drug approved by FDA
- Dosage form: 500 mg extended release tablets
- Dose administration: 500 mg BID as a starting dose and increase to 1000 mg BID based on clinical symptoms as maximum dose.

Ranolazine

- May be used with βblockers, nitrates, CCBs, anti-platelet therapy, lipid-lowering therapy, ACE inhibitors, and ARBs.

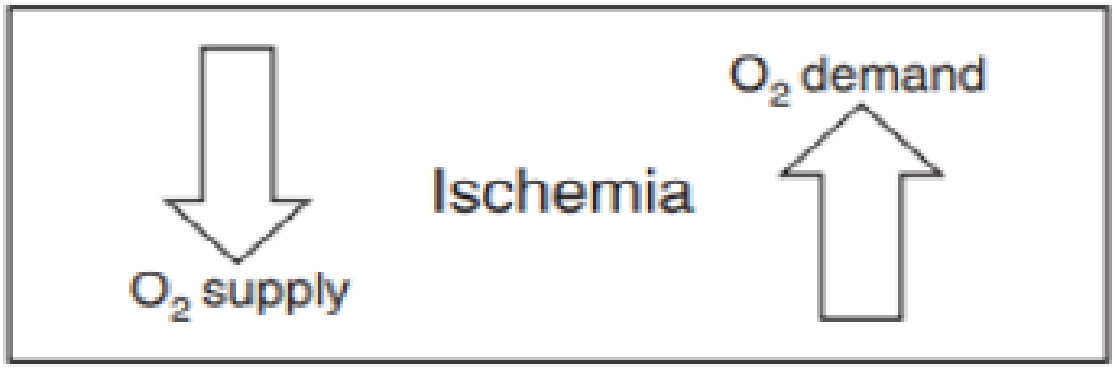
- Combining **ivabradine, ranolazine and nicorandil is not recommended** because of the unknown safety profile

Mechanism of action

Two distinct hypothesis have been proposed which **differ from MOA of traditional antianginals:**

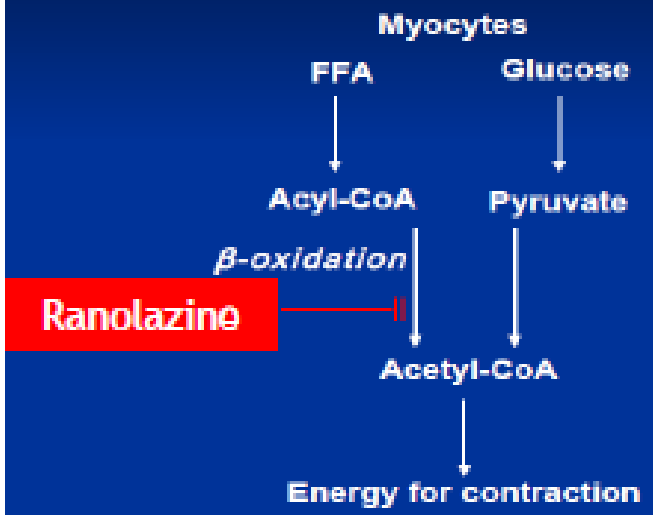
1. Partial inhibition of fatty acid oxidation(pFOX)

2. Inhibition of late sodium inward current (late INa)



First mechanism

Metabolic modulation (pFOX):

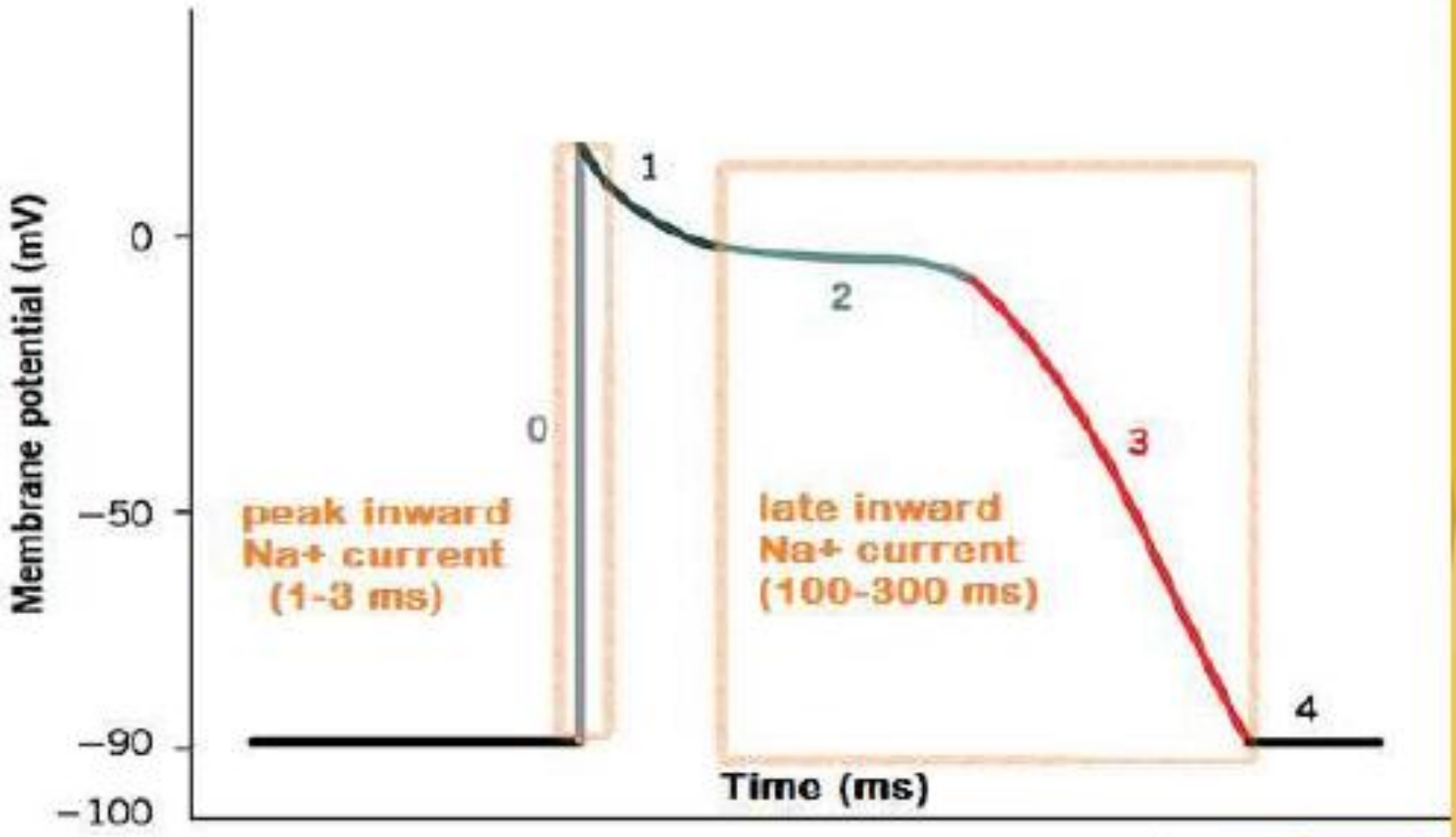


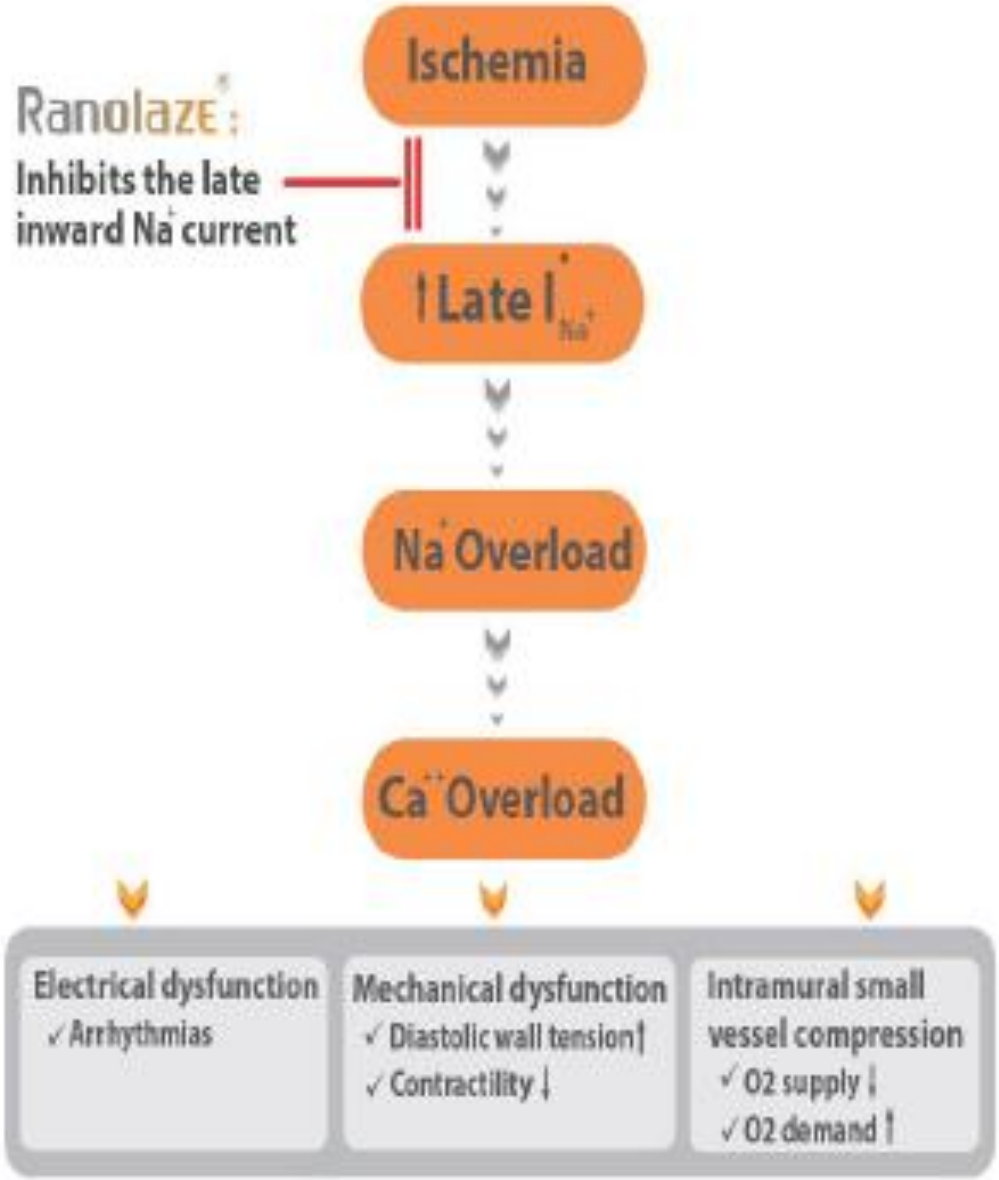
- O2 requirement of glucose pathway is lower than FFA pathway
- During ischemia, oxidized FFA levels rise, blunting the glucose pathway

pFOX = partial fatty acid oxidation
FFA = free fatty acid

MacInnes A et al. *Circ Res.* 2003;93:e26-32.
Lopaschuk GD et al. *Circ Res.* 2003;93:e33-7.
Stanley WC. *J Cardiovasc Pharmacol Ther.* 2004;9(suppl 1):S31-45.

Second mechanism




Ischemia
Ranolaze:
Inhibits the late inward Na+ current
↑ Late I_{Na^+}
Na^+ Overload
Ca^{++} Overload
Electrical dysfunction
✓ Arrhythmias
Mechanical dysfunction
✓ Diastolic wall tension↑
✓ Contractility ↓
Intramural small vessel compression
✓ O2 supply ↓
✓ O2 demand ↑

Ranolazine

- Ranolazine is a well-tolerated medication that **selectively inhibits the late sodium current**

- Hence prevents sodium dependent **calcium accumulation**

- **Has anti-ischemic and metabolic properties:**
  - ↓ diastolic stiffness,
  - ↓ frequency of anginal attacks,
  - ↑ exercise tolerance,
  - ↑ time to ST changes on treadmill tests,
  - improves diastolic flow

Ranolaze 50
Ranolazine

Pharmacokinetics

- **The half-life** at steady state is 7 hours.
- **Peak plasma** concentration is obtained 2 to 6 hours after administration
- **Age, sex, and congestive heart failure do not influence pharmacokinetics**
- **Protein binding:** ~62%
- **maximum recommended dose:** 1,000 mg twice daily

Pharmacokinetics

- **Pregnancy Considerations: category C**
  - Adverse events have been observed in animal reproduction studies,
- **Breast-Feeding Considerations**
  - It is not known if ranolazine is excreted into breast milk, Risk benefit assessment
- **Dietary Considerations**
  - Limit the use of grapefruit juice; the ranolazine dose should not exceed 500 mg twice daily when taken with grapefruit juice or grapefruit-containing products

Contraindication

- **Taking strong inhibitors of CYP3A4**
  - Antifungals (ketoconazole and other azole class),
  - Antibiotics (macrolides: Clarithromycin),
  - HIV protease inhibitors (ritonavir, lopinavir),
- **Taking inducers of CYP3A4**
  - **(Rifampin, Phenytoin, Carbamazepine,...)**
- **Liver cirrhosis**
- **creatinine clearance of ≤30 mL/min, dialysis**

Dose adjustment

- No need to dose adjustment based on **age**, **renal** and **hepatic** impairment, and **CHF**

- **Limit RANOLAZE to 500 mg BD with:**
  - diltiazem,
  - verapamil,
  - erythromycin,
  - fluconazole

Side effects

- Dizziness (may be dose-related)
- Tinnitus
- Abdominal pain
- Peripheral edema
- Dyspnea
- Headache
- Constipation
- Nausea
- Palpitation
- QT prolongation (it is recommended that an ECG be performed 1 to 2 weeks after initiation)

Monitoring Parameters

- Baseline and follow up ECG (1 to 2 weeks after initiation) to evaluate QT interval

- Monitor renal function periodically in patients with moderate to severe renal impairment:

  - (Particularly for increases in serum creatinine accompanied by increased BUN; consider monitoring blood pressure in patients with renal dysfunction; correct and maintain serum potassium in normal limits)

Advantages of Ranolazine compared to other antianginal drugs

- Not affect heart rate or blood pressure

- Reduces HbA1c modestly

- in contrast to nitrates, they may be safe in patients taking sildenafil or other **phosphodiesterase type 5 inhibitor** for erectile dysfunction

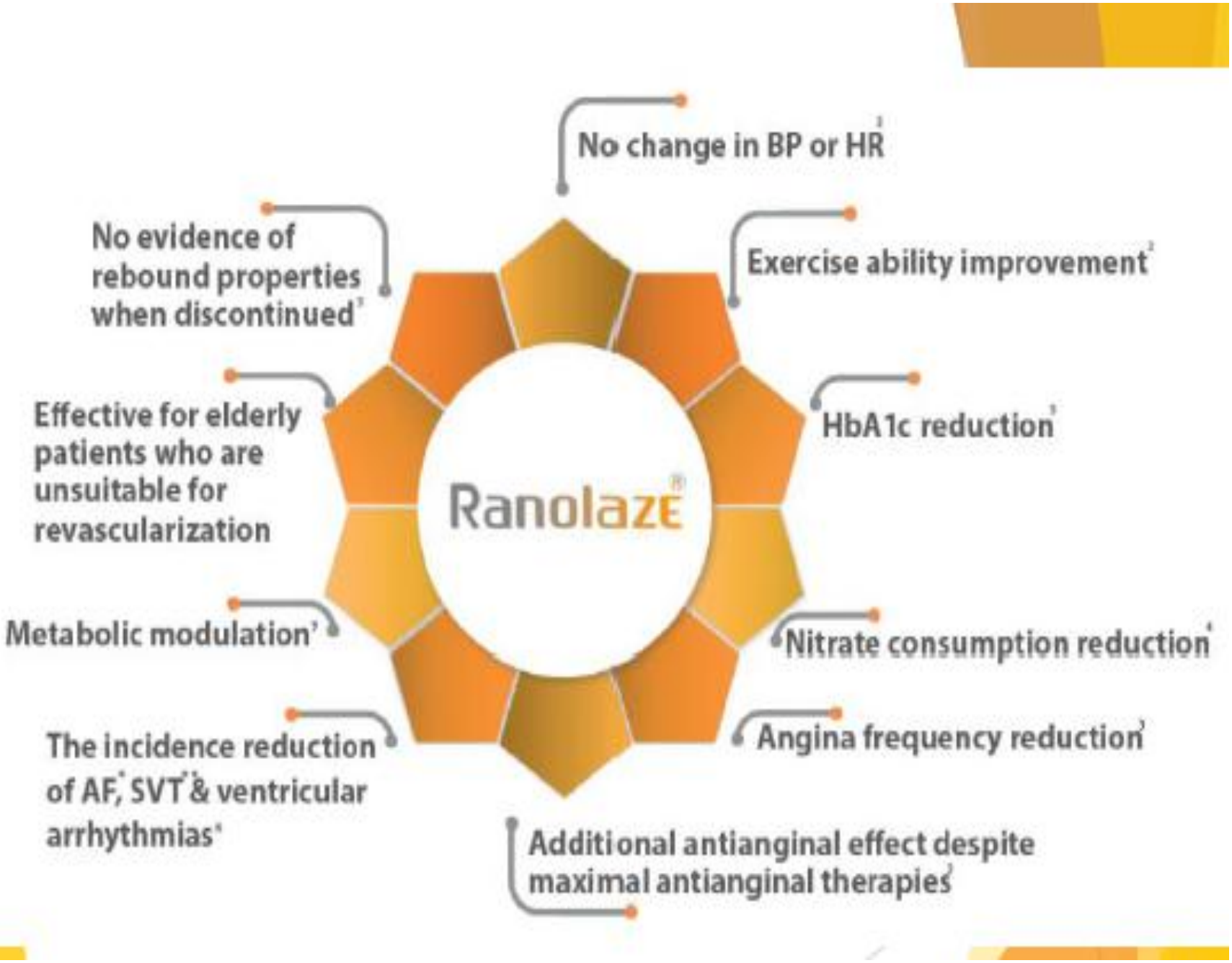
ESC
European Society of Cardiology
European Heart Journal (2019) 00, 1–71
doi:10.1093/eurheartj/ehz425

ESC GUIDELINES

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC)

In subjects with baseline low heart rate and low BP, ranolazine or trimetazidine may be considered as a first-line drug to reduce angina frequency and improve exercise tolerance.	IIb	C


Ranolaze®
No change in BP or HR[1]
Exercise ability improvement[2]
HbA1c reduction[3]
Nitrate consumption reduction[4]
Angina frequency reduction[2]
Additional antianginal effect despite maximal antianginal therapies[2]
The incidence reduction of AF,[5] SVT[2,3] & ventricular arrhythmias[6]
Metabolic modulation[7]
Effective for elderly patients who are unsuitable for revascularization
No evidence of rebound properties when discontinued[7]

زهی عشق زهی عشق که ما راست خدایا
چه نغزست و چه خوبست چه زیباست خدایا
چو سیلیم و چو جوییم همه سوی تو پوییم
که منزلگه هر سیل به دریاست خدایا