Ranolazine: New Treatment Paradigm for Myocardial Dysfunction, Arrhythmias, and Myocardial Ischemia

Peter H. Stone, M.D.
Cardiovascular Division
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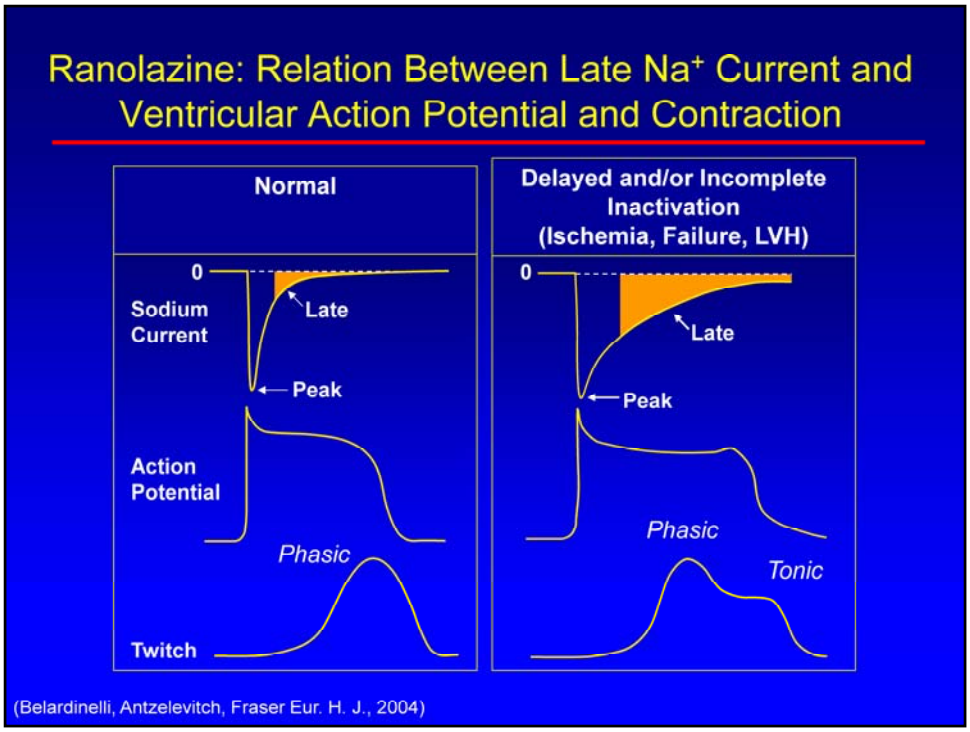

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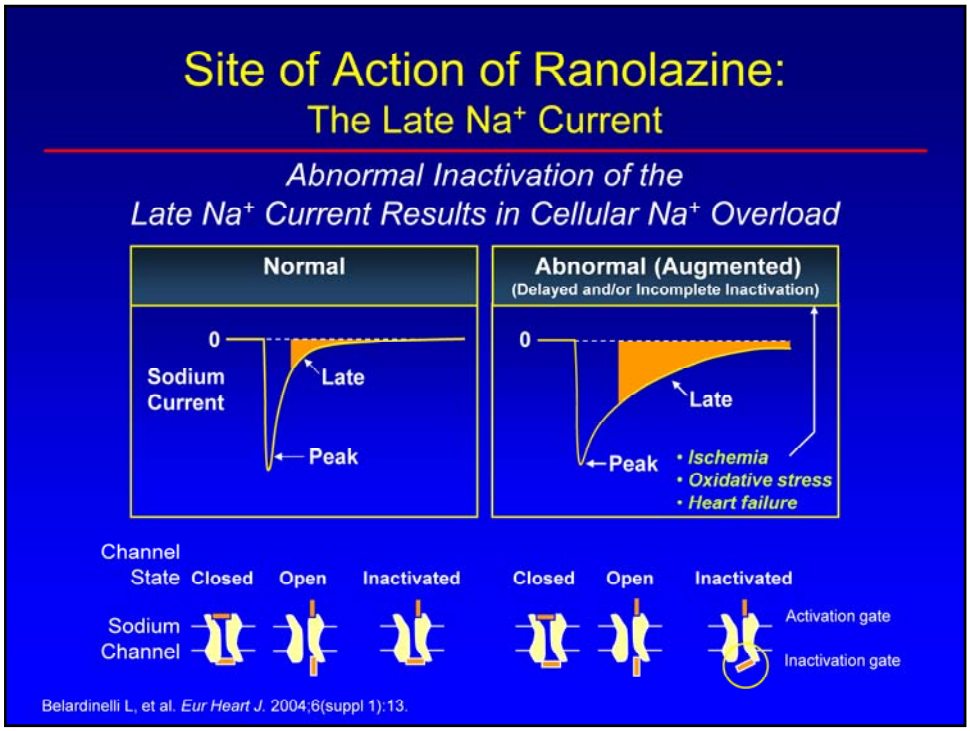

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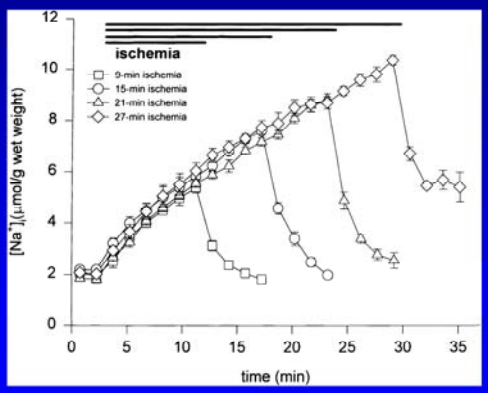
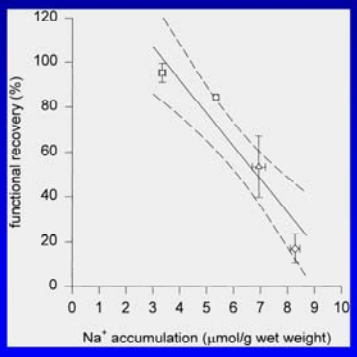
Ischemia-induced Increase in $[Na^+]_i$ and Post-ischemia Recovery of LV Function in Rat Isolated Hearts

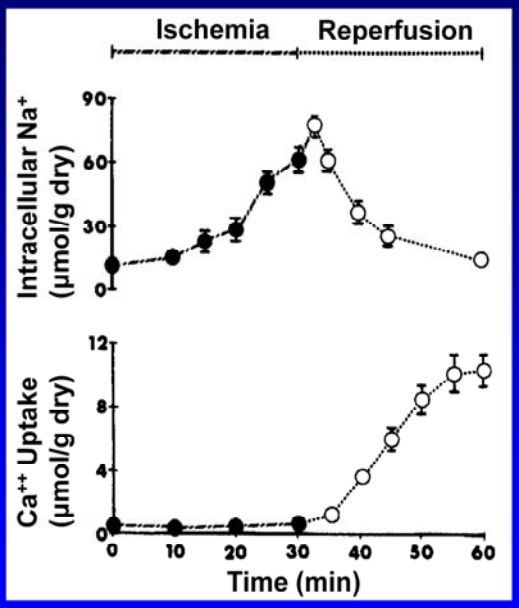




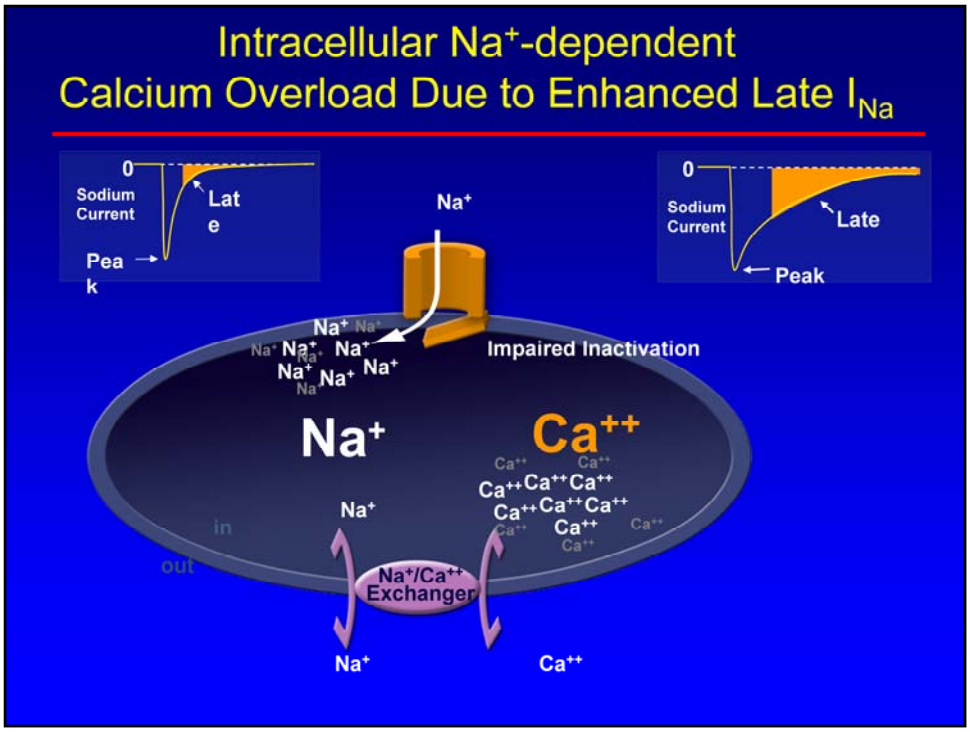
^{23}Na NMR Spectroscopy

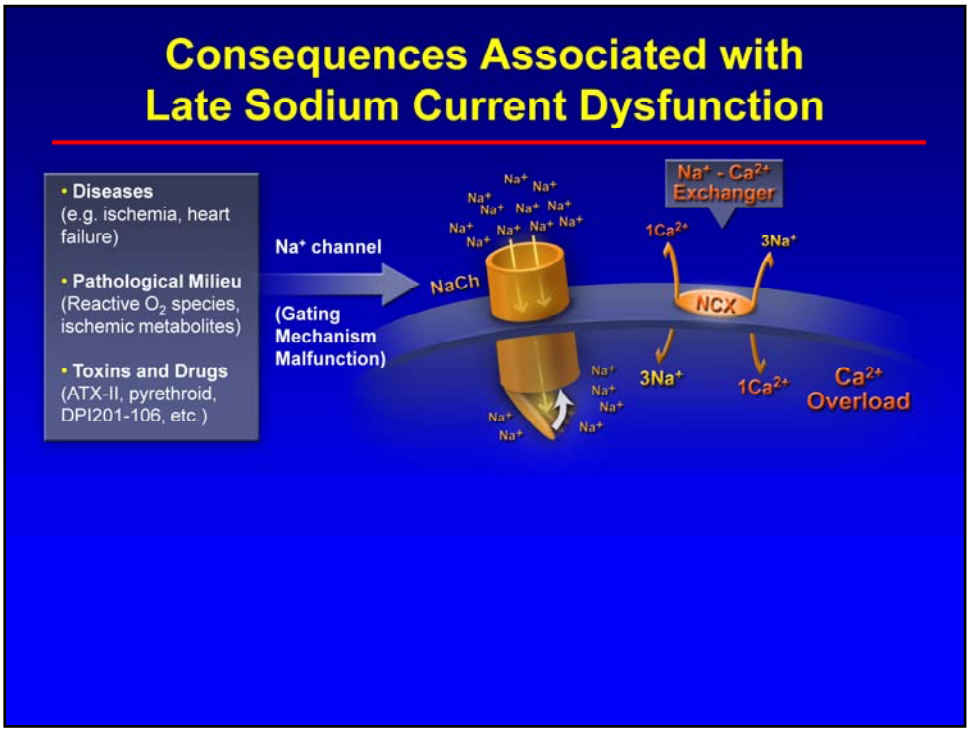
(Imahashi K, et al., Circ Res. 1999;84:1401)

Time Course of Changes in Intracellular [Na^+] and Uptake of Ca^{++} During Ischemia and Reperfusion.



(Tani and Neely, Circ. Res. 1989;65:1045)


Intracellular Na+-dependent
Calcium Overload Due to Enhanced Late INa
0
Sodium Current
Late
Peak
Na+
Impaired Inactivation
Na+
Ca++
in
out
Na+/Ca++ Exchanger
Na+
Ca++



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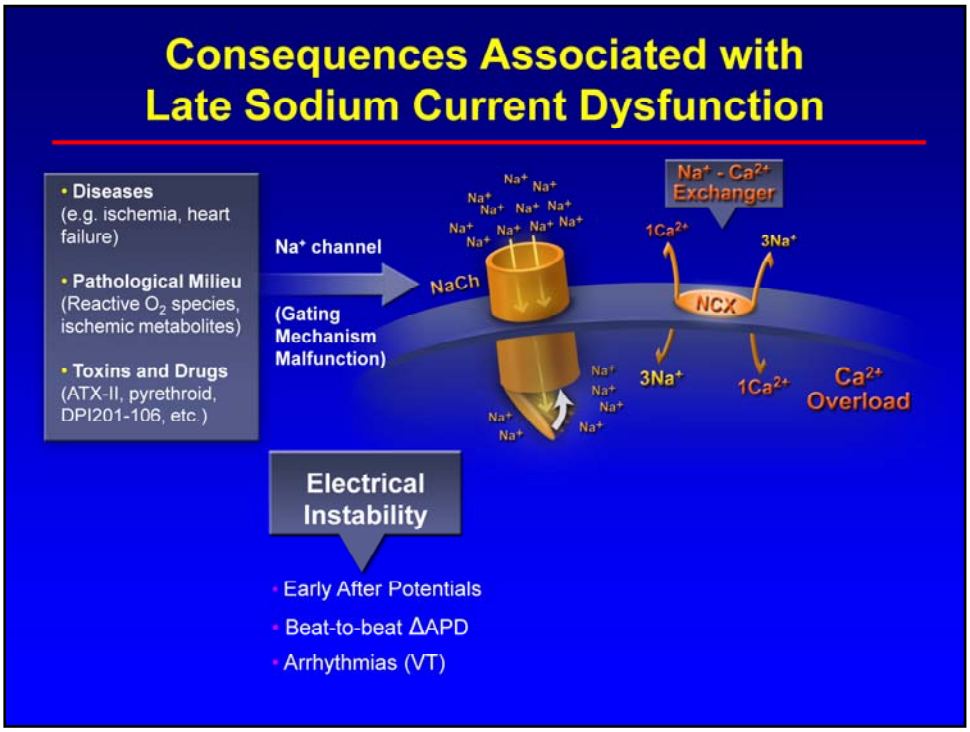

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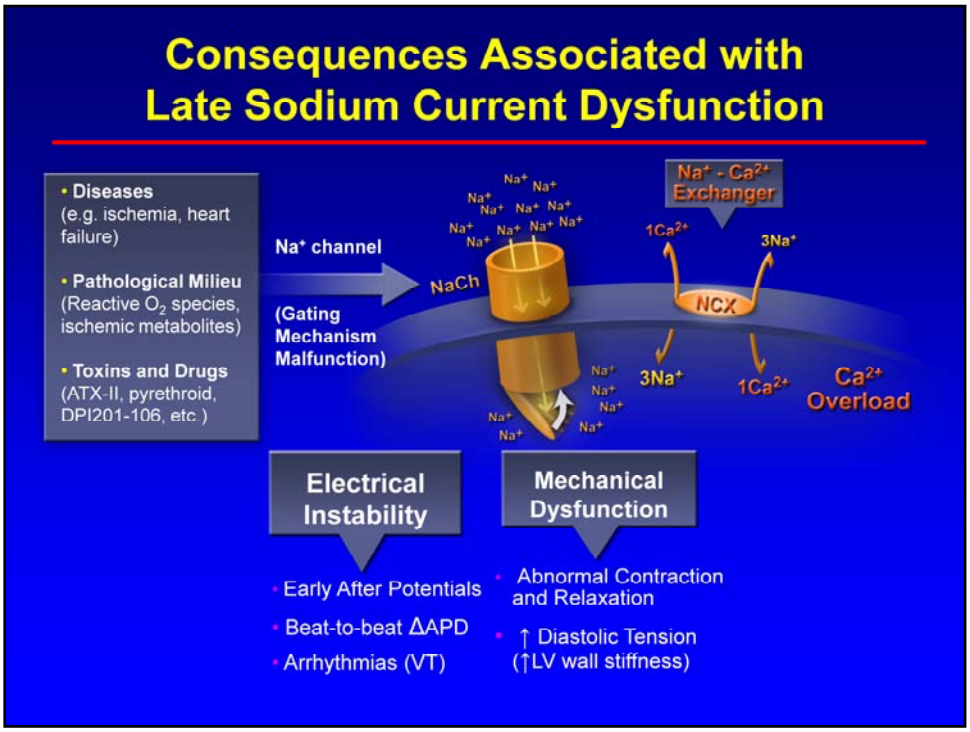

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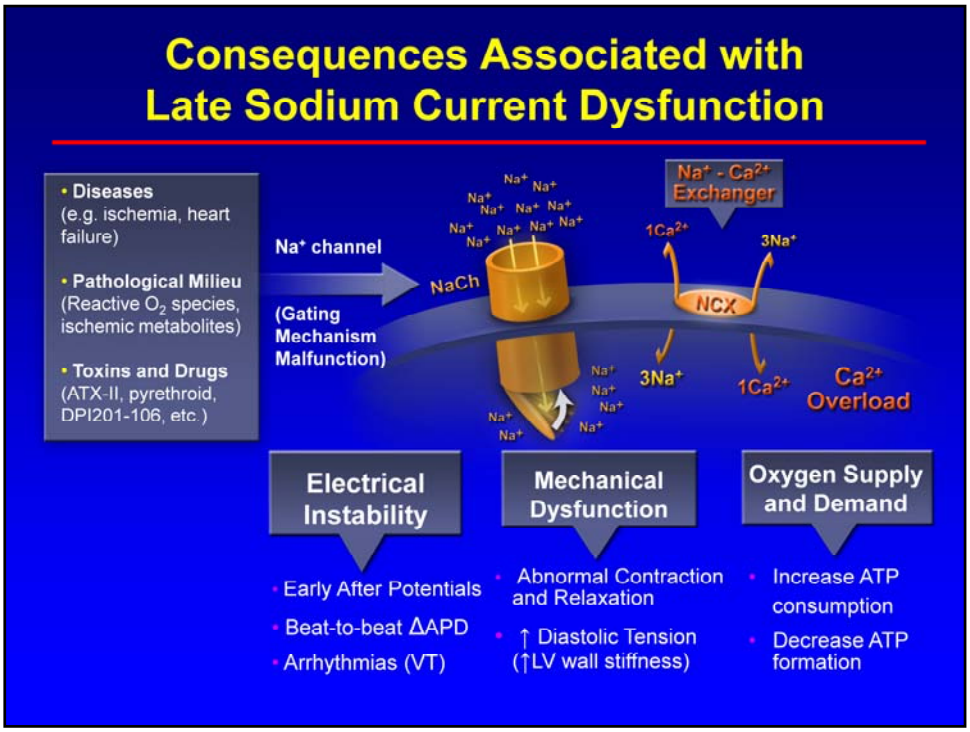

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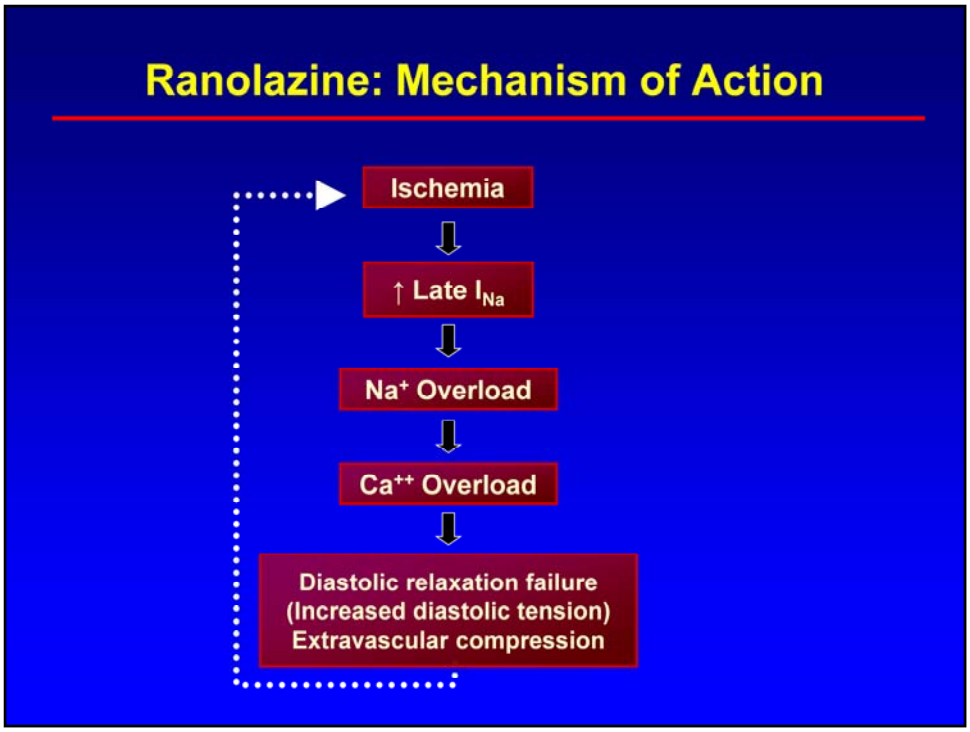

Ischemia is associated with disruptions in cellular sodium and calcium homeostasis.

An enhanced late sodium current is likely to contribute to the sodium overload observed in ischemia. Late phase sodium channels have been shown to remain open longer in ischemic conditions. Sodium overload may result from decreased efflux and increased influx during ischemia, with greater intracellular accumulation of sodium as the duration of ischemia increases.

This is followed by an increase in intracellular Calcium through the Na/Ca exchanger on the myocyte wall.

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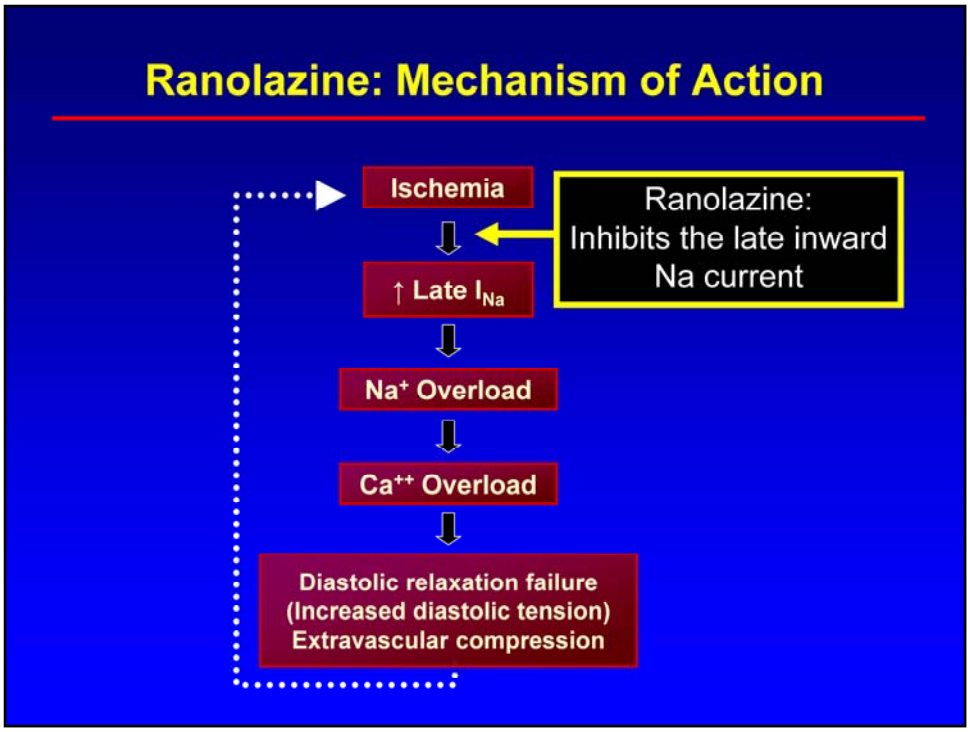

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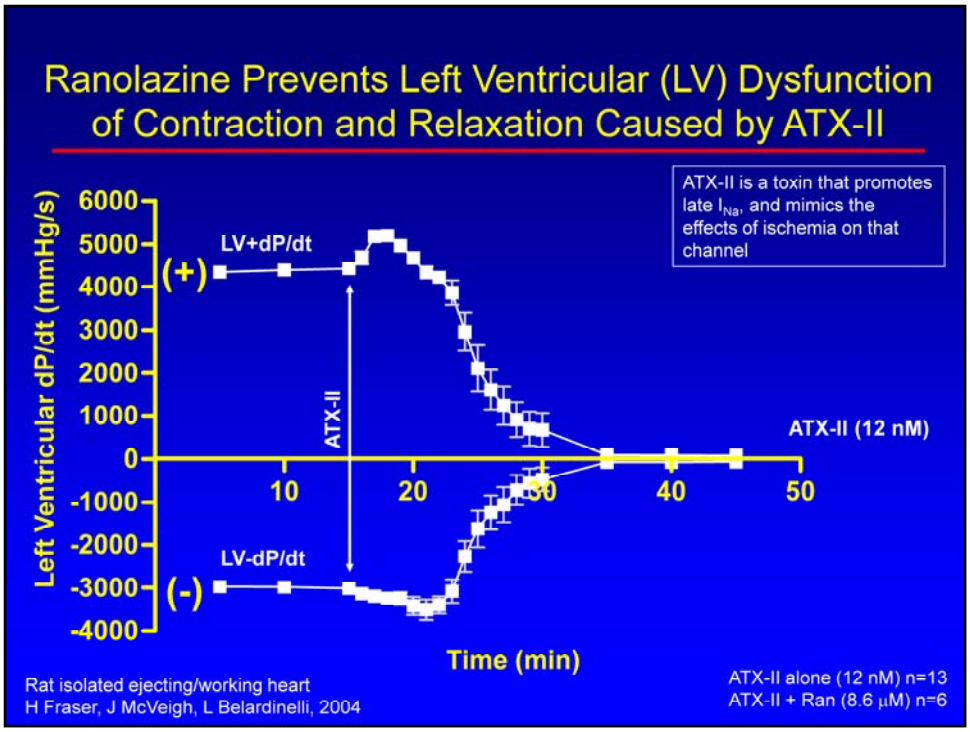
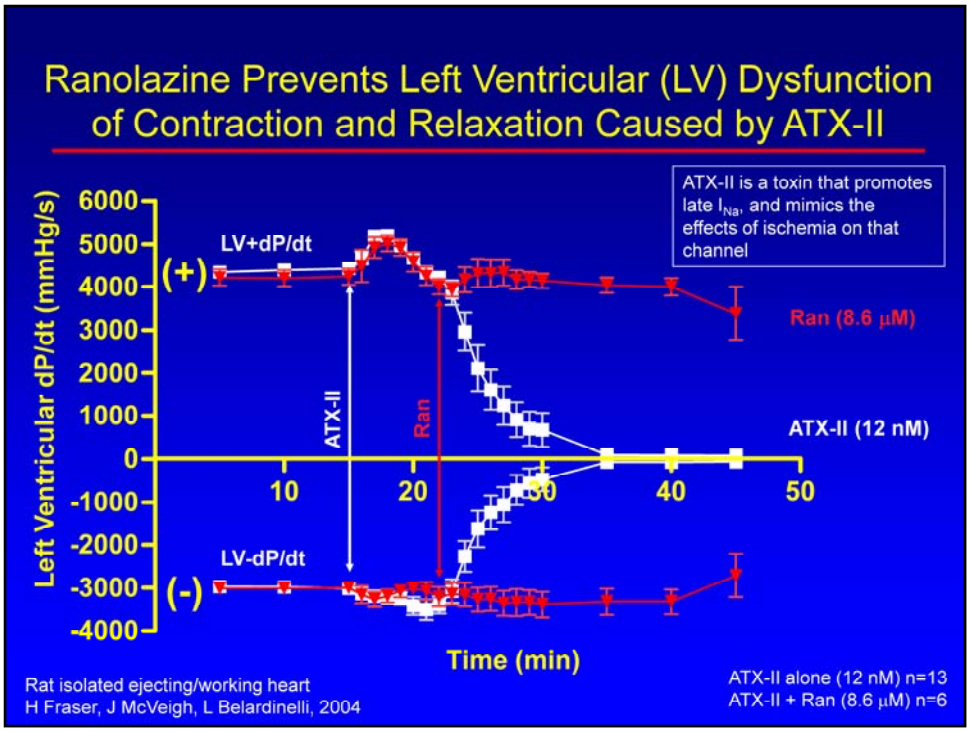

Ranolazine Prevents Left Ventricular (LV) Dysfunction of Contraction and Relaxation Caused by ATX-II
ATX-II is a toxin that promotes late I_{Na}, and mimics the effects of ischemia on that channel
Left Ventricular dP/dt (mmHg/s)
6000
5000
4000
3000
2000
1000
0
-1000
-2000
-3000
-4000
(+)
(-)
LV+dP/dt
LV-dP/dt
ATX-II
ATX-II (12 nM)
10
20
30
40
50
Time (min)
Rat isolated ejecting/working heart
H Fraser, J McVeigh, L Belardinelli, 2004
ATX-II alone (12 nM) n=13
ATX-II + Ran (8.6 μM) n=6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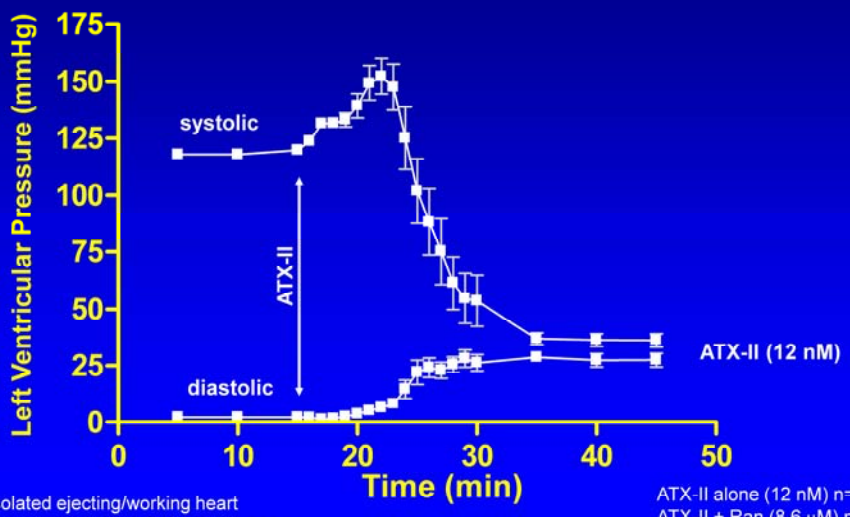

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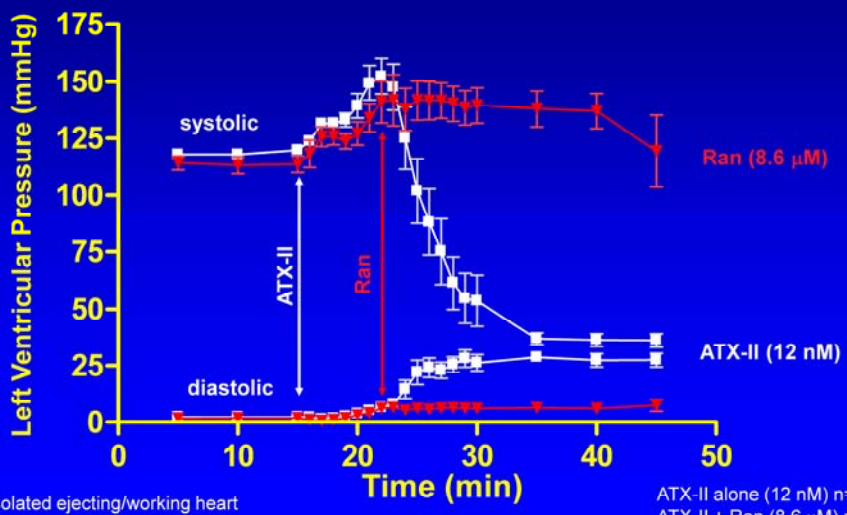

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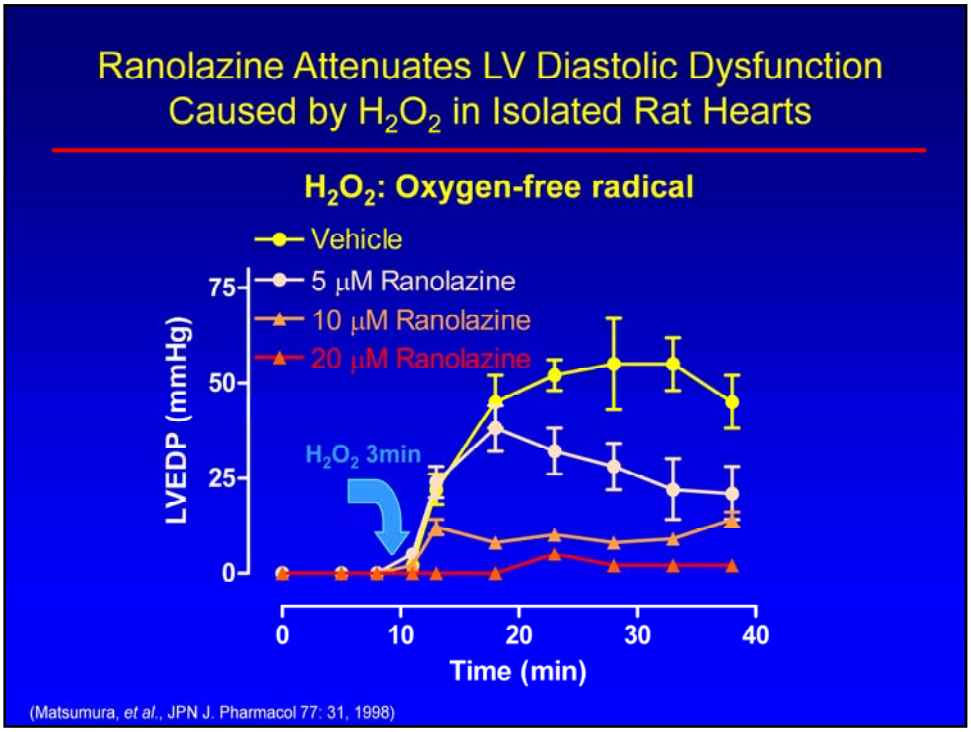
Role(s) of Oxygen Free Radicals in Pathophysiological Processes

Ischemia/Reperfusion Injury
"Stunned Myocardium"
Development and Progression of HF

Increased O_2 free radicals in the myocardium

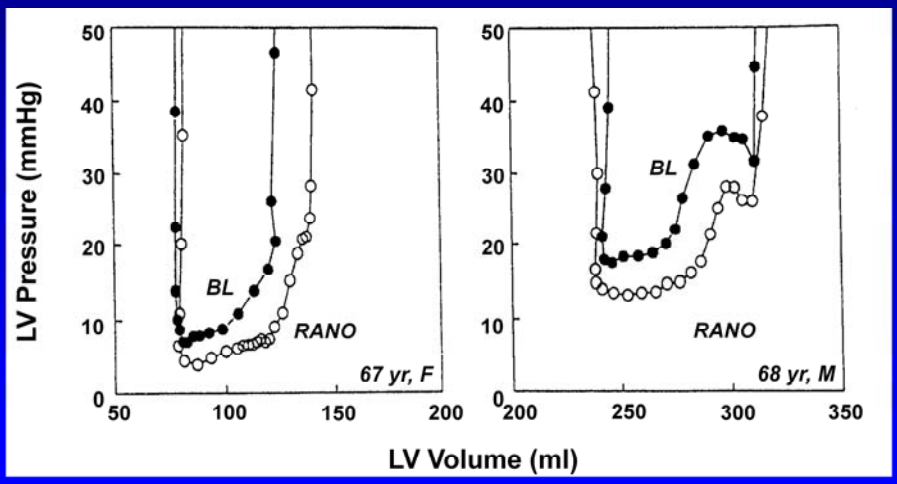
- increase late I_{Na}
- cause Ca^{2+} influx via reverse mode of NCX
- induce severe diastolic dysfunction



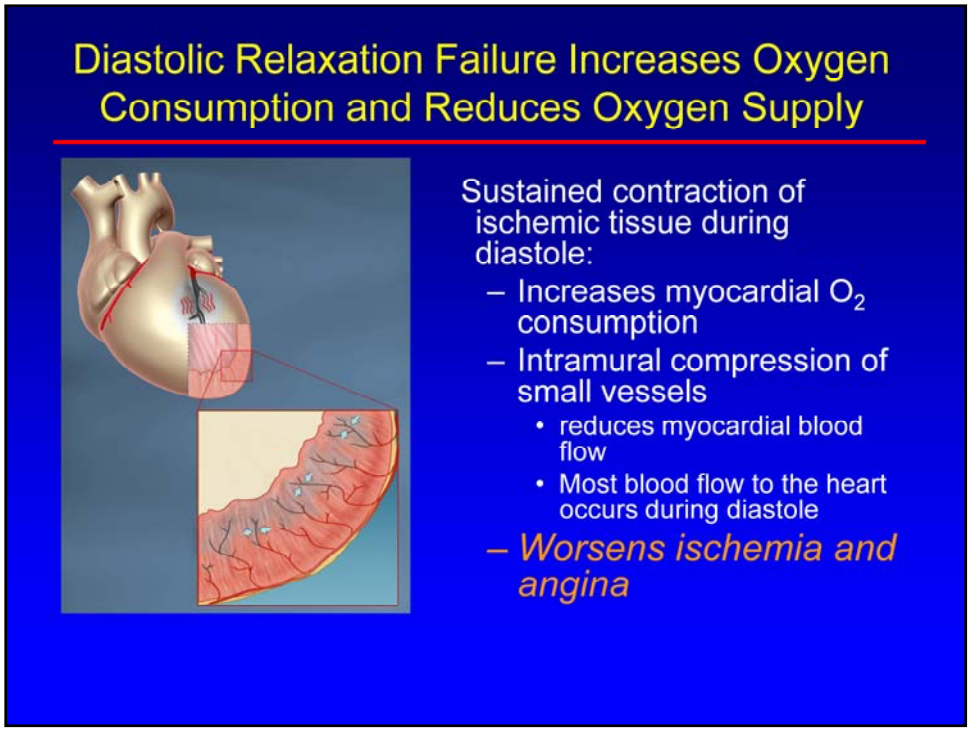
Matsumura, *et al*., JPN J. Pharmacol 77: 31, 1998

Maruyama, *et al*., J Pharm. Pharmacol 52: 709, 2000

Ranolazine Improves LV Diastolic Compliance in Patients with Ischemic Heart Disease



(Hayashida W, et al. Cardiovasc Drugs Ther 1994;8:741)



Cellular calcium overload causes impaired contractility and, more significantly, impaired relaxation.

Sustained contraction of the ischemic cardiomyocyte during diastole, or diastolic relaxation failure, consumes energy.

This increases the demand for oxygen and worsens ischemia and angina.

Sustained contraction of the ischemic cardiomyocyte during diastole, or diastolic relaxation failure, also causes compression of the intramural vessels that supply the myocardium with blood and oxygen.

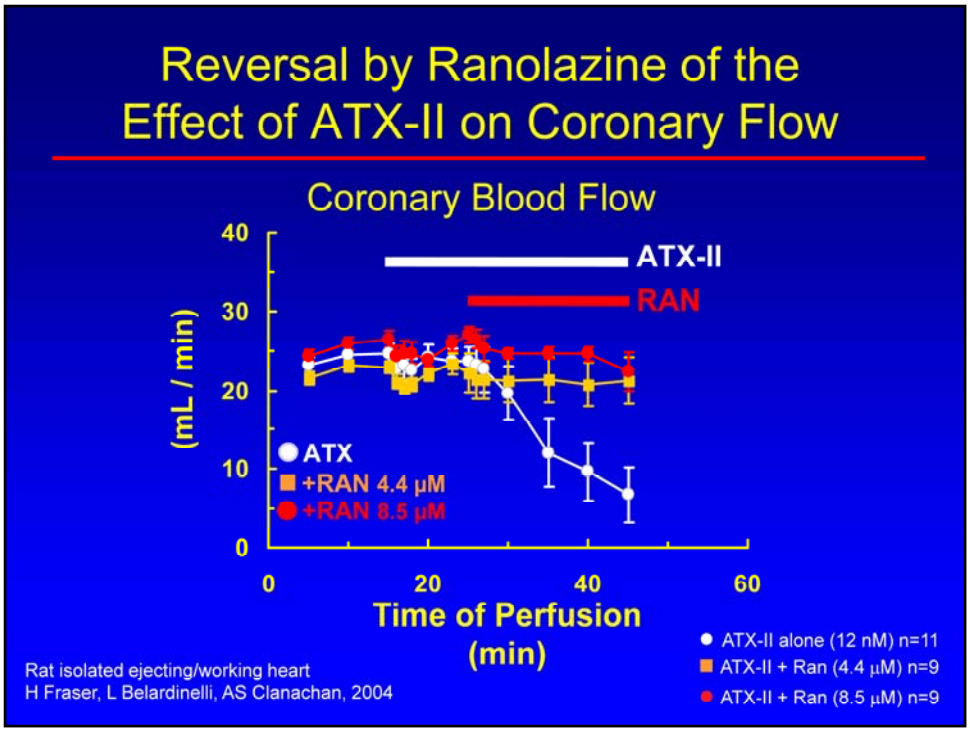
This significantly reduces myocardial blood flow and oxygen supply, since most blood flow to the heart occurs during diastole.

As a consequence, ischemia and angina become worse.

Meyer M, Keweloh B, Guth K, Holmes J, Pieske B, Lehnart S, Just H, Hasenfuss G. Frequency-dependence of myocardial energetics in failing human myocardium as quantified by a new method for the measurement of oxygen consumption in muscle strip preparations. *J Mol Cell Cardiol.* 1998;30:1459-1470.

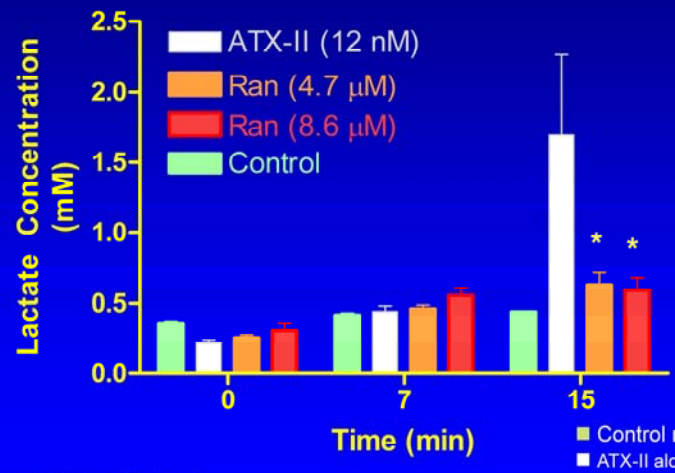
Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med*. 2004;350:1953-1999.

Reversal by Ranolazine of the Effect of ATX-II on Coronary Flow



Rat isolated ejecting/working heart
H Fraser, L Belardinelli, AS Clanachan, 2004

Ranolazine Reduces Lactate Production Caused by ATX-II



Control n=1-3
ATX-II alone (12 nM) n=4-9
ATX-II + Ran (4.7 μM) n=12
ATX-II + Ran (8.6 μM) n=3-6

Rat isolated ejecting/working heart
H Fraser, J McVeigh, L Belardinelli, 2004

Ranolazine Improves Myocardial Blood Flow During Reperfusion

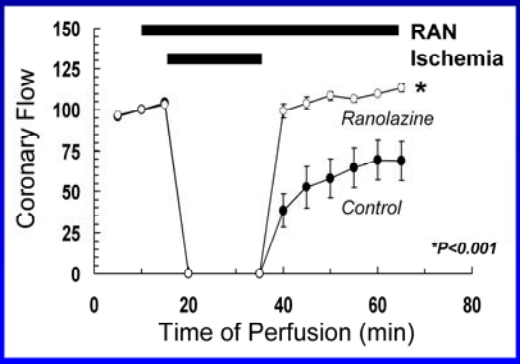
Isolated Perfused Rabbit Heart

Coronary Flow

Baseline

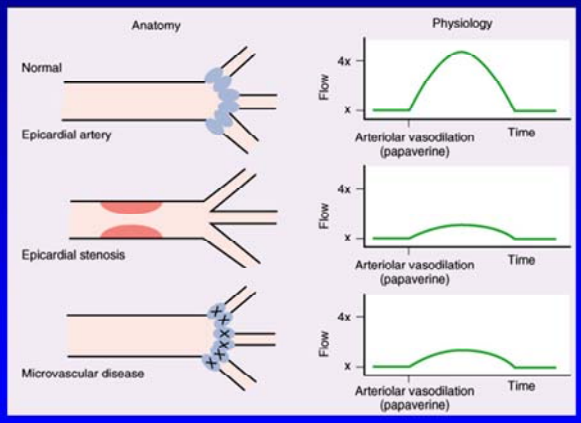
Untreated: 24±1.3 ml/min

Ranolazine: 20±1.2 ml/min



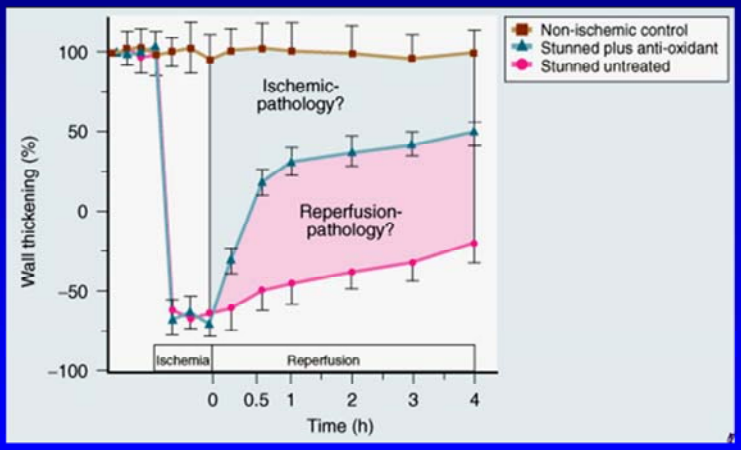
(Clanachan AS et al. Eur H J. 2005)

Nature and Location of Limitations to Coronary Blood Flow

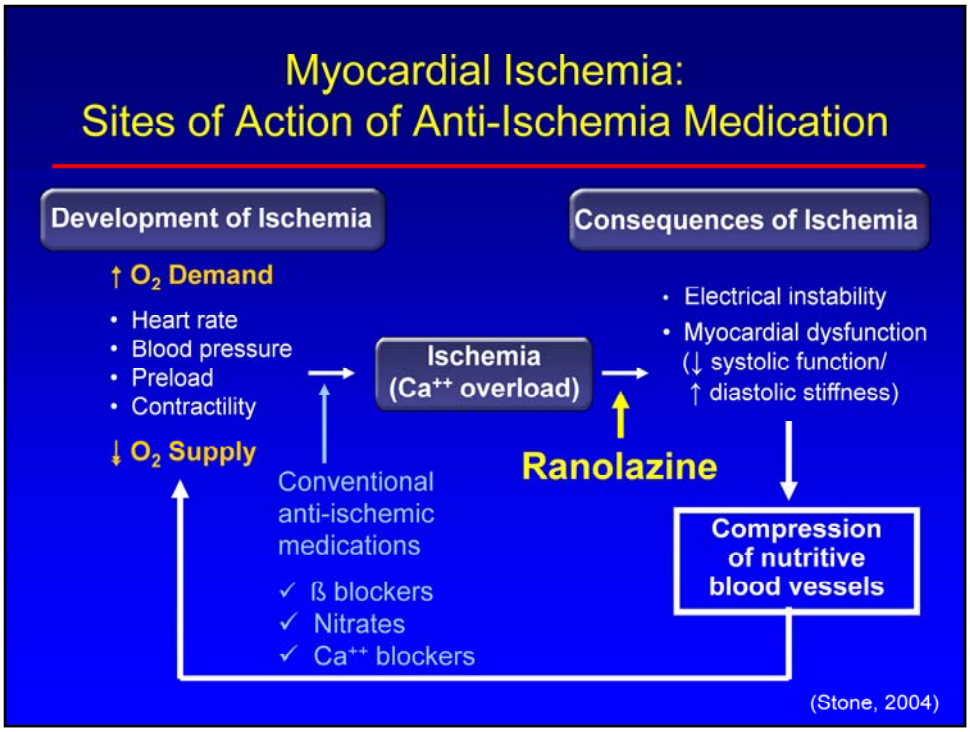


(Kern in Braunwald. Heart Disease. 2005)

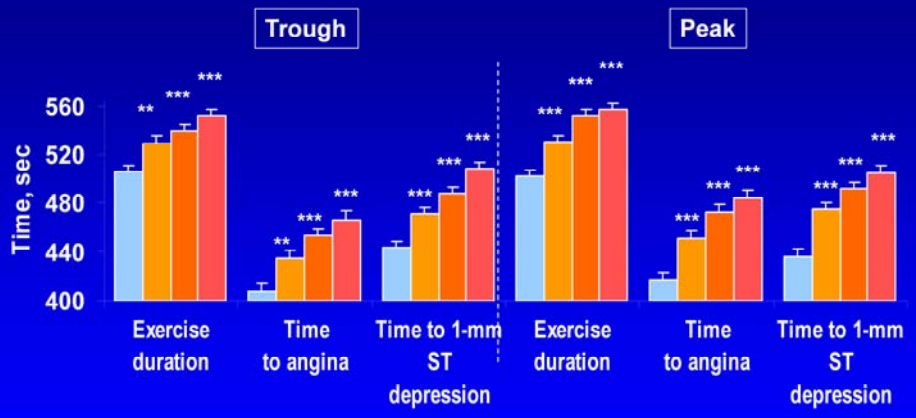
Myocardial Injury Results Both From Ischemia Injury and Reperfusion Injury



(Kloner, et al. Circulation 1998;97:1848)


Myocardial Ischemia:
Sites of Action of Anti-Ischemia Medication
Development of Ischemia
Consequences of Ischemia
↑ O2 Demand
• Heart rate
• Blood pressure
• Preload
• Contractility
↓ O2 Supply
Ischemia
(Ca++ overload)
• Electrical instability
• Myocardial dysfunction
(↓ systolic function/
↑ diastolic stiffness)
Ranolazine
Conventional
anti-ischemic
medications
✓ ß blockers
✓ Nitrates
✓ Ca++ blockers
Compression
of nutritive
blood vessels
(Stone, 2004)

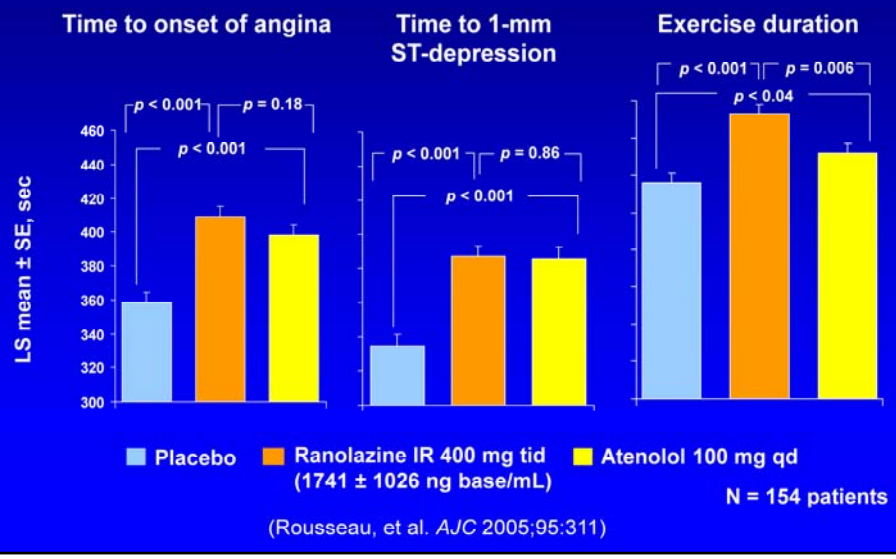
Monotherapy With Ranolazine Increases Exercise Performance at Trough and Peak: MARISA



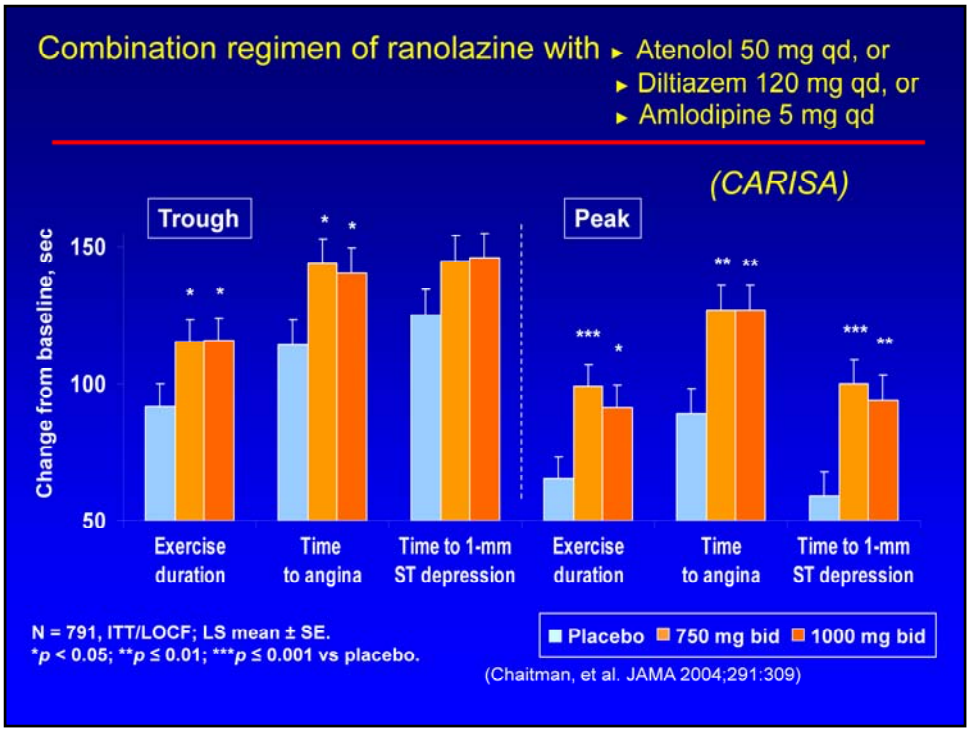
N = 175, All/Near Completers population;
LS means ± SE.
**$p < 0.01$ vs placebo; ***$p < 0.001$ vs. placebo

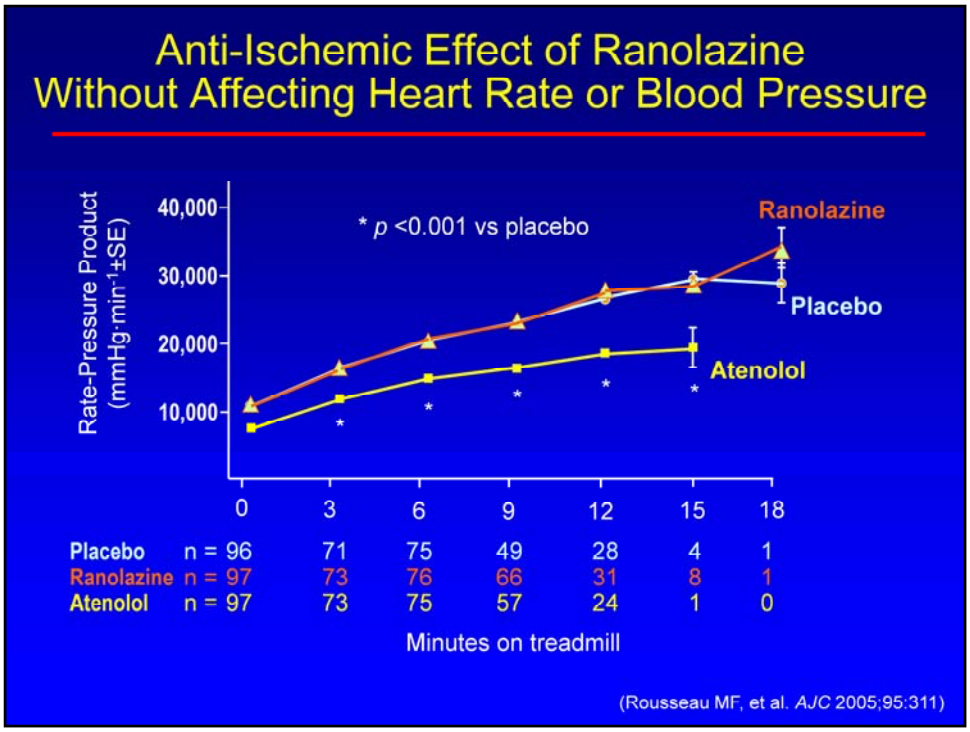
(Chaitman, et al JACC 2004;43:1375)

Ranolazine is at Least as Effective as Atenolol 100 mg Daily



(Rousseau, et al. *AJC* 2005;95:311)


Combination regimen of ranolazine with
▸ Atenolol 50 mg qd, or
▸ Diltiazem 120 mg qd, or
▸ Amlodipine 5 mg qd
(CARISA)
Trough
Peak
Change from baseline, sec
150
100
50
Exercise duration
Time to angina
Time to 1-mm ST depression
Exercise duration
Time to angina
Time to 1-mm ST depression
N = 791, ITT/LOCF; LS mean ± SE.
*p < 0.05; **p ≤ 0.01; ***p ≤ 0.001 vs placebo.
Placebo
750 mg bid
1000 mg bid
(Chaitman, et al. JAMA 2004;291:309)



Values are least square means ± SE from a mixed-model repeated measures analysis of variance.

Ranolazine: Adverse Events

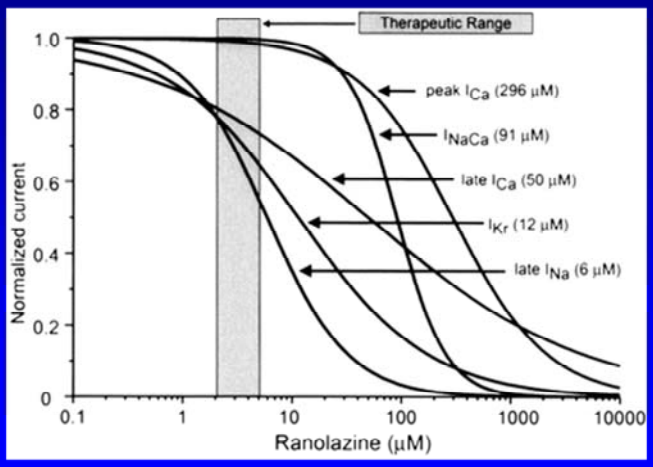
	Placebo (n=552)	Ranolazine (n=835)
Constipation (%)	2	8
Nausea (%)	1	4
Dizziness (%)	2	5
Headache (%)	2	3
Pts discontinuing Rx (%)	3	6

Ranolazine prolongs the QTc an average of about 6 msec.

(No episode of torsades de pointes has been observed.)

Drug-induced torsade de pointes: major electrophysiologic events

Electrophysiologic Effects of Ranolazine



(Antzelevitch, et al. Circulation 2004;110:904)

Ion Current Effects—I_{Kr} and Late I_{Na}

Ion current	Effect on action potential	Effect on ECG	Ranolazine potency IC_{50}
I_{Kr} inhibition	Lengthens	↑ QT	12 μM
Late I_{Na} inhibition	Shortens	↓ QT	≥ 5 μM

Average therapeutic concentration range
850 to 2500 ng/mL (~2 to 6 μM)

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Late I_{Na} effect mitigates I_{Kr} effect

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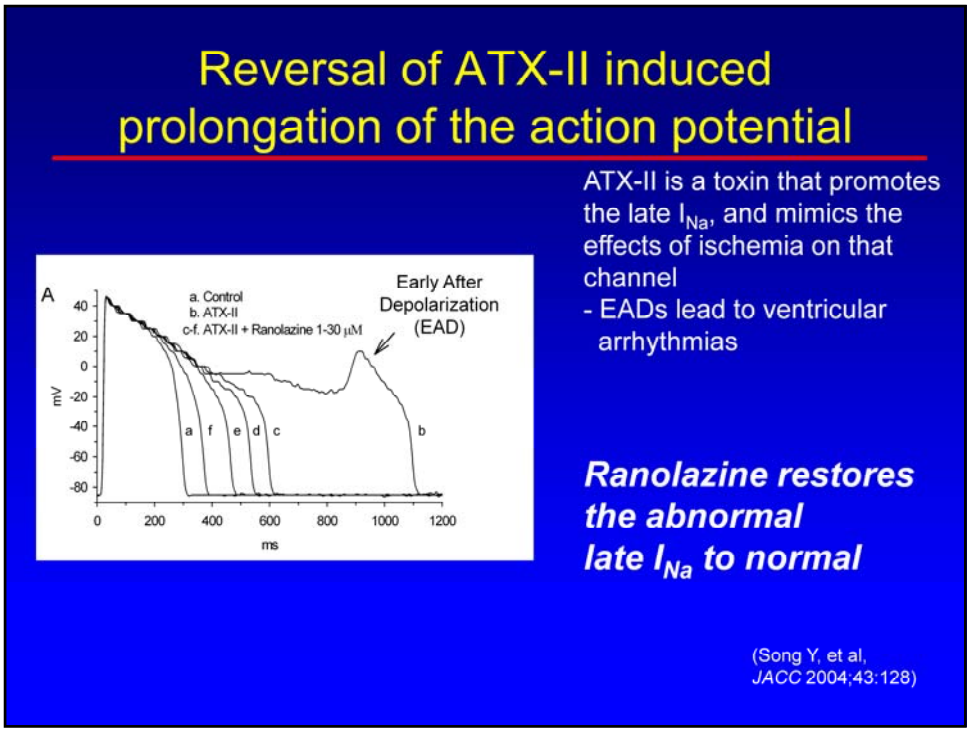
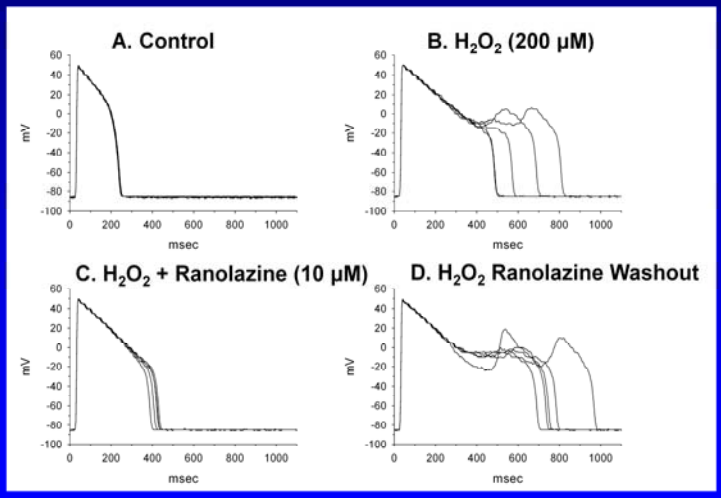


Song et al., PACE 2003, 26(4, Part II):993

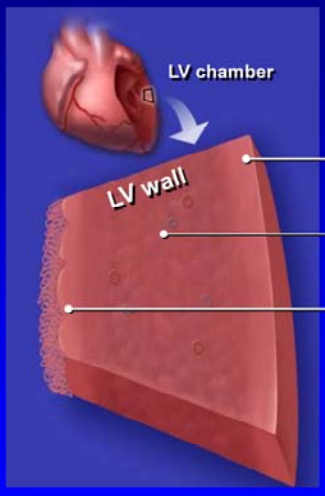
The effect of RAN to inhibit EAD activity and to abbreviate the AP is also nicely demosntrated in this sudy by Song et al

Suppression by Ranolazine of H_2O_2-induced EADs in a Guinea Pig Ventricular Myocyte



(Song Y, et al.; ACC, 2006)

Transmural Differences of Ventricular Repolarization—A Mechanism for Arrhythmias



	APD, msec
	Normal
Epicardium	230
Mid-myocardium	289
Endocardium	271

Shimizu et al. *JCE*. 1999;10:154-164.

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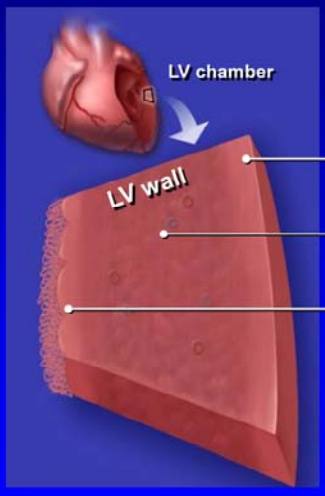

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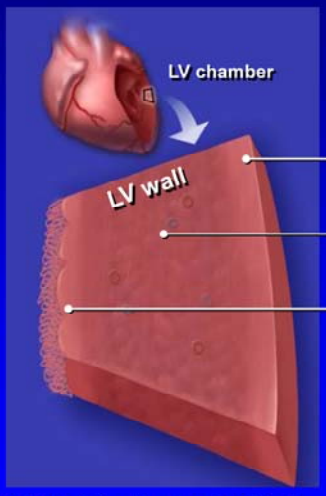
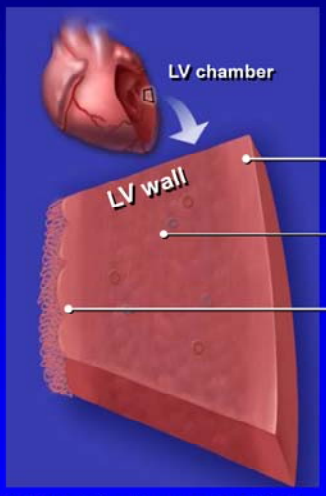


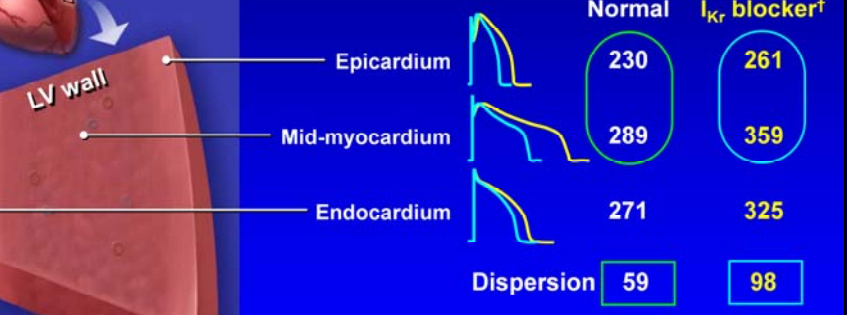
	APD, msec	
	Normal	I_{Kr} blocker†
Epicardium	230	261
Mid-myocardium	289	359
Endocardium	271	325
Dispersion	59	

†d-Sotalol (I_{Kr} blockers) 100 μM.

Shimizu et al. *JCE*. 1999;10:154-164.

Transmural Differences of Ventricular Repolarization—A Mechanism for Arrhythmias





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Dispersion	59	98

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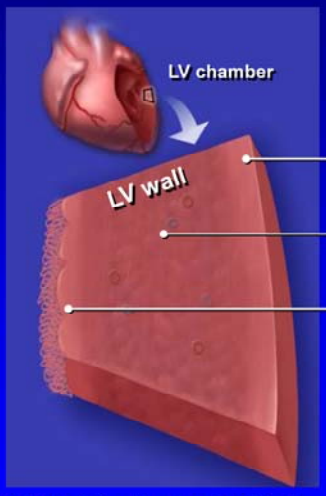
Transmural Differences of Ventricular Repolarization—A Mechanism for Arrhythmias



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Arrhythmias enabled

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Effect of Ranolazine on Transmural Dispersion of Refractory Periods

Canine LV Wedge Preparation

Ranolazine Concentration	QT (msec)	Transmural Dispersion of Repolarization (msec)
Control	277	33
1 µmol/L	284 *	29
5 µmol/L	295 *	31
10 µmol/L	301 *	31
100 µmol/L	307 *	28

* $p<0.05$ vs control

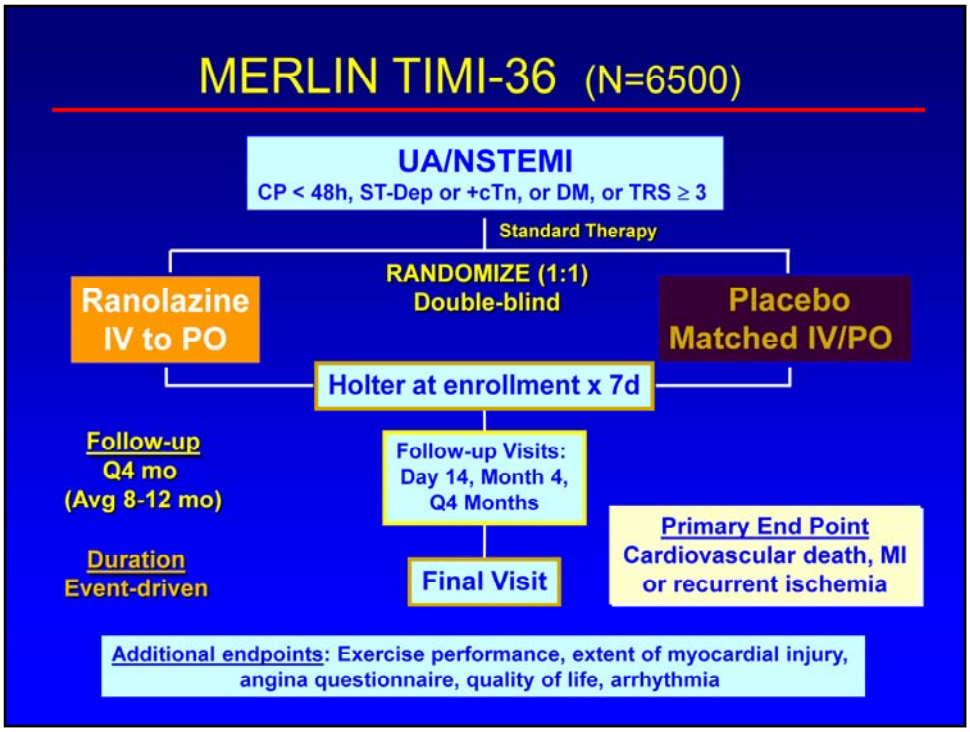
No torsade could be provoked during endo- or epicardial pacing, even in setting of hypokalemia

(Antzelevitch, et al. Circ 2004;110:904)

Association of Increased Transmural Dispersion of Repolarization (TDR) and EADs in Canine LV Myocardium with Occurrence of Torsade de Pointes (TdP) in Humans

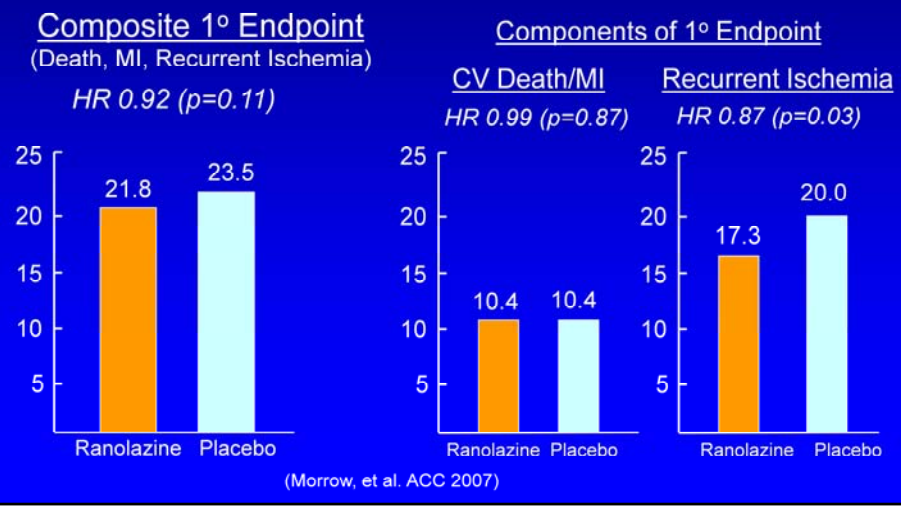
	Effect in canine LV		Effect in Humans	
	EADs	↑ TDR	↑ QT	↑ TdP
Amiodarone	-	-	+	±
Cisapride	+	+	+	+
Erythromycin	+	+	+	+
Quinidine, low concentration	+	+	+	+
Sotalol	+	+	+	+
Mibefradil	+	+	+	+
Ranolazine	-	-	+	-

(Antzelevitch C, et al. *J Cardiovasc Pharmacol Therapeut* 2004;9(Suppl I):S65)


MERLIN TIMI-36 (N=6500)
UA/NSTEMI
CP < 48h, ST-Dep or +cTn, or DM, or TRS ≥ 3
Standard Therapy
RANDOMIZE (1:1)
Double-blind
Ranolazine
IV to PO
Placebo
Matched IV/PO
Holter at enrollment x 7d
Follow-up
Q4 mo
(Avg 8-12 mo)
Follow-up Visits:
Day 14, Month 4,
Q4 Months
Primary End Point
Cardiovascular death, MI
or recurrent ischemia
Duration
Event-driven
Final Visit
Additional endpoints: Exercise performance, extent of myocardial injury,
angina questionnaire, quality of life, arrhythmia

Effect of Ranolazine in Patients with ACS: *the MERLIN Trial*

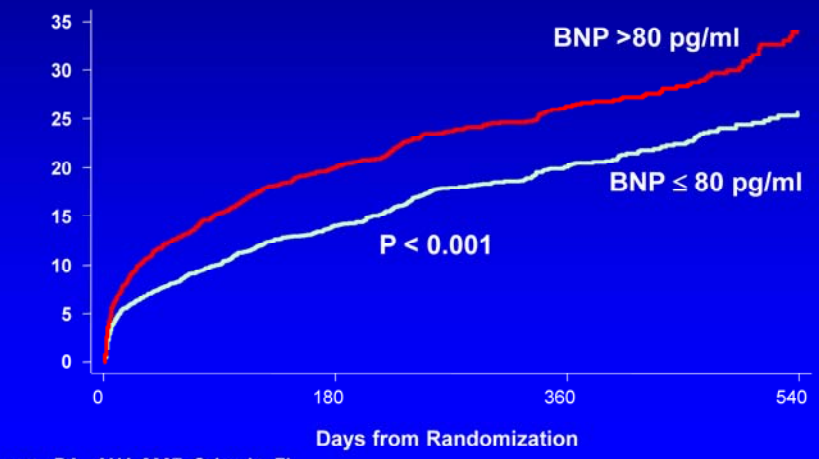
6560 pts with ACS: randomized to IV, then PO ranolazine vs placebo
Followup median 348 days



(Morrow, et al. ACC 2007)

Baseline BNP and Clinical Outcomes

MERLIN TIMI 36

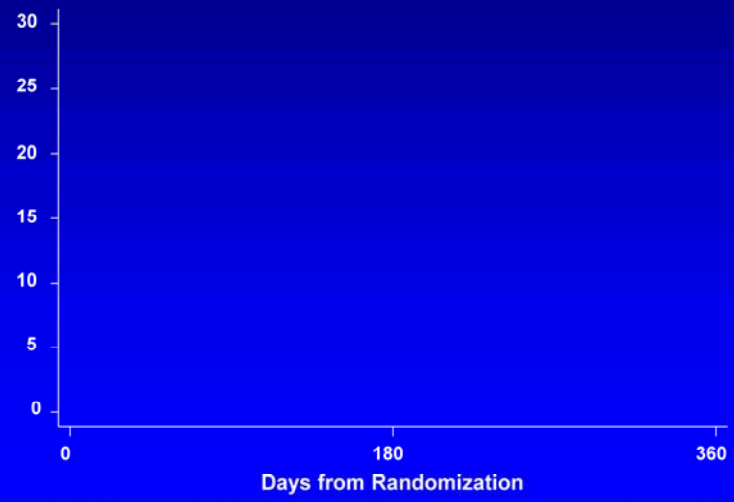


Morrow DA. AHA 2007, Orlando, FL

Baseline BNP and Effect of Ranolazine on Primary Endpoint

MERLIN TIMI 36

CV Death, MI, or Recurrent Ischemia (%)



*KM cumulative incidence (%) at 12 months

Morrow DA. AHA 2007, Orlando, FL

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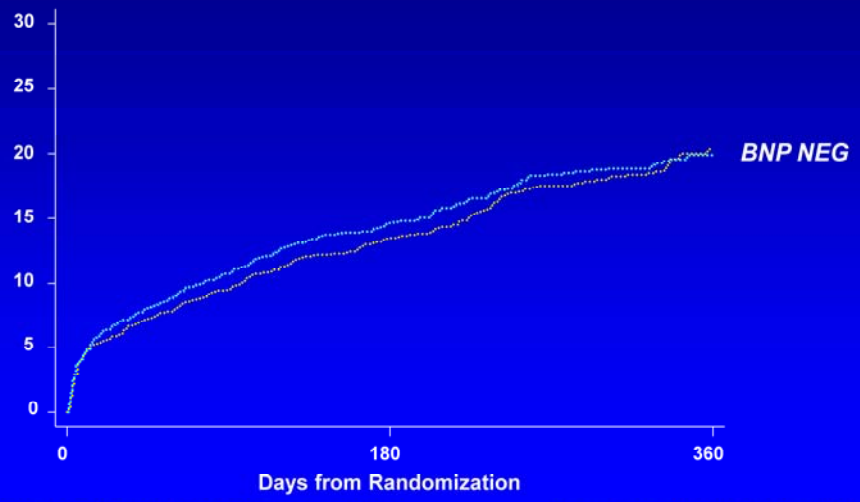

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Morrow DA. AHA 2007, Orlando, FL

Baseline BNP and Effect of Ranolazine on Primary Endpoint

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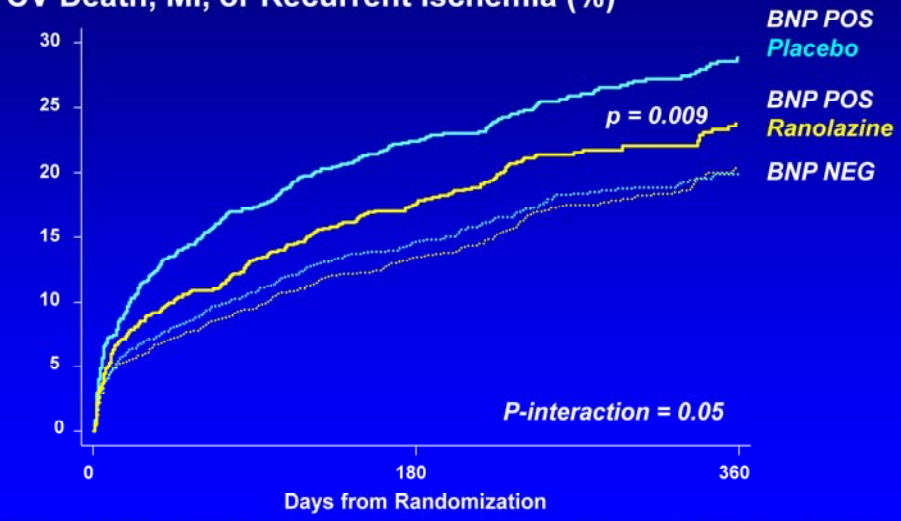
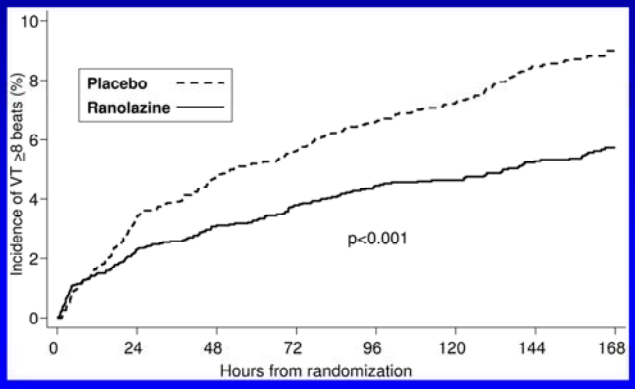


*KM cumulative incidence (%) at 12 months

Morrow DA. AHA 2007, Orlando, FL

K-M Estimated Rates of First Occurrence of Ventricular Tachycardia > 8 Beats

MERLIN Study of 6560 Patients Treated within 48 Hrs of ACS

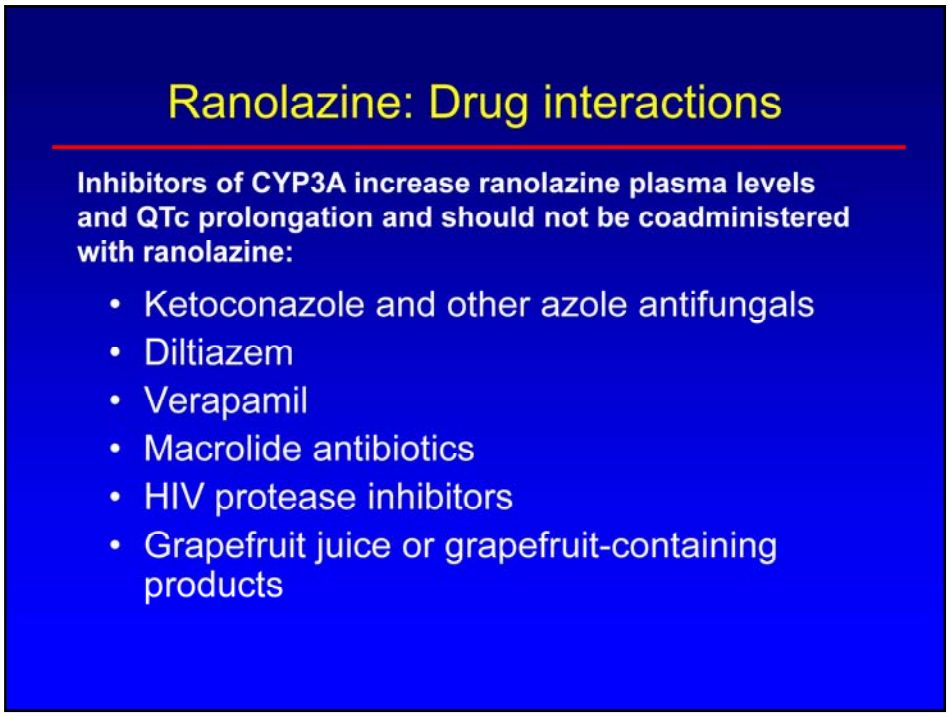


(Scirica, et al. Circulation 2007;116:1647)

Effect of Ranolazine on Tachyarrhythmias

	Ranolazine (n=3162)	Placebo (n=3189)	RR	p
Ventricular Arrhythmias				
VT > 4 beats > 100 bpm (%)	20.9	29.5	0.71	<0.001
VT > 8 beats, < 30 sec (%)	5.3	8.3	0.63	<0.001
Sustained VT (%)	0.4	0.4	1.01	0.98
Supraventricular Arrhythmias				
Atrial Fib (%)	1.7	2.4	0.74	0.08
Other SVT (%)	44.7	55.0	0.81	<0.001

(Scirica, et al. Circulation 2007;116:1647)



Ranolazine: Drug interactions

Ranolazine is primarily metabolized by CYP3A. Potent or moderately potent inhibitors of this enzyme will increase ranolazine plasma levels and QTc. Their concomitant administration should be avoided.

Less potent CYP3A inhibitors such as simvastatin and cimetidine did not increase the exposure to ranolazine in healthy volunteers.

Plasma concentrations are not significantly altered by concomitant digoxin at 0.125 mg qd.

Summary: Ranolazine's Unique Pharmacologic Profile to Improve Myocardial Function, Ischemia, and Arrhythmias

- Prevents Na^{+}-induced Ca^{++} overload in ischemia and heart failure
  - Improves diastolic dysfunction
  - May have a more primary role in improving myocardial function
- Anti-anginal and anti-ischemic efficacy
- Anti-ischemic properties do not depend on changes in:
  - heart rate
  - blood pressure
- Complementary to existing agents that depend on hemodynamic mechanisms
- Safe and well-tolerated
- Prolongs QTc slightly, but stabilizes myocardial repolarization
  - No evidence for torsade de pointes
  - May even have a primary anti-arrhythmic effect