

Disclosures

Dr Scirica has received honoraria for educational presentations (modest) from CV Therapeutics

The study was supported through a research grant (major) from CV Therapeutics.

**The Effect of Ranolazine on the
Incidence of Arrhythmias in Patients
with Non-ST-Segment Elevation Acute
Coronary Syndrome:**

Results from the MERLIN-TIMI 36 Trial

**September 5th, 2007
Vienna**



Ranolazine in Ischemic Heart Disease



Background

- **New antianginal agent**
 - Anti-ischemic action without clinically significant effect on HR or BP
- **Novel mechanism of action**
 - Inhibition of late I_{Na} (Late phase of sodium current)
- **Approved for treatment of chronic angina**
 - ↑ exercise time, ↓ angina in selected pts
- **Persistent concern b/c prolongation of QT**
 - 2-6 msec with approved doses
 - Theoretical risk of ventricular tachycardia

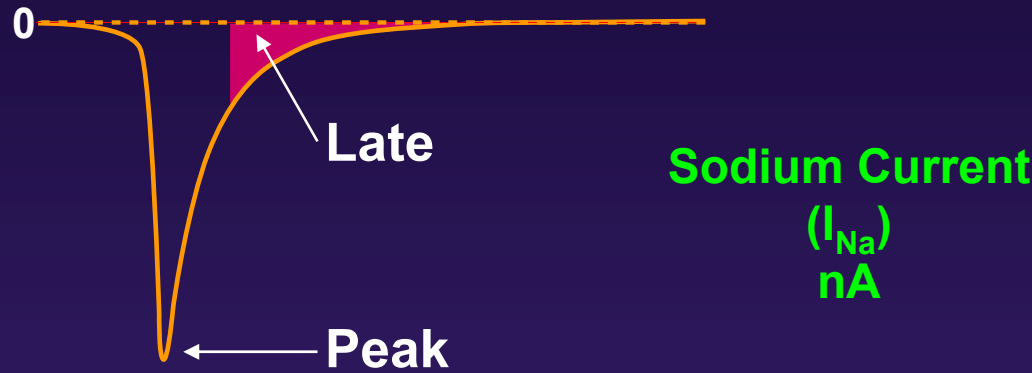


Relation Between Peak and Late I_{Na} and Ventricular Action Potential

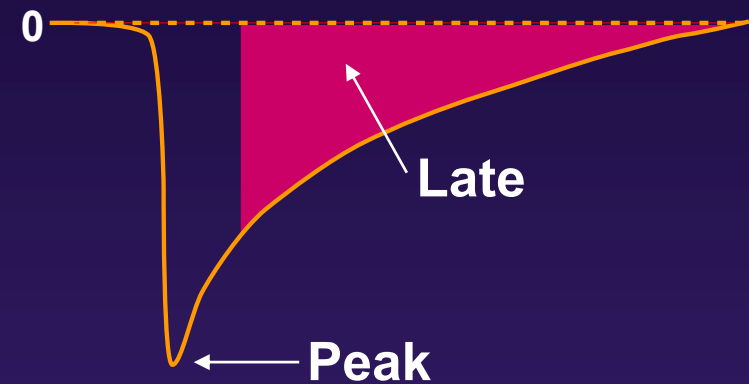


Background

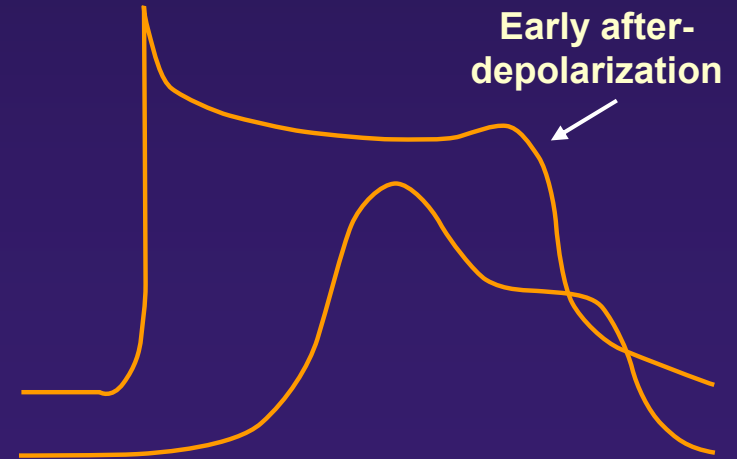
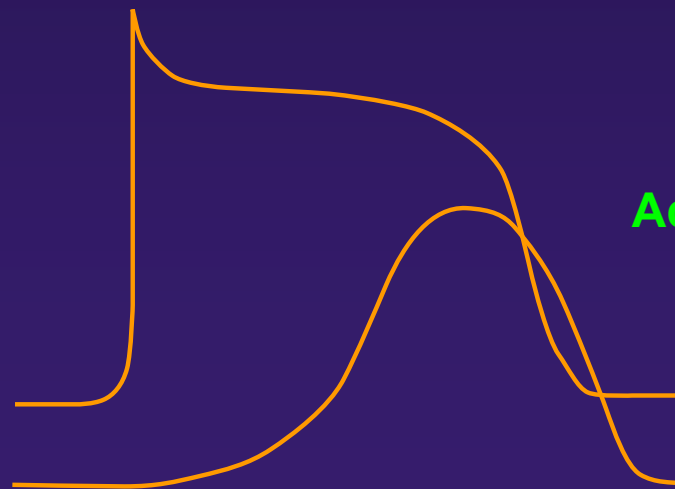
Normal Late I_{Na}



Augmented Late I_{Na} (delayed or incomplete inactivation)



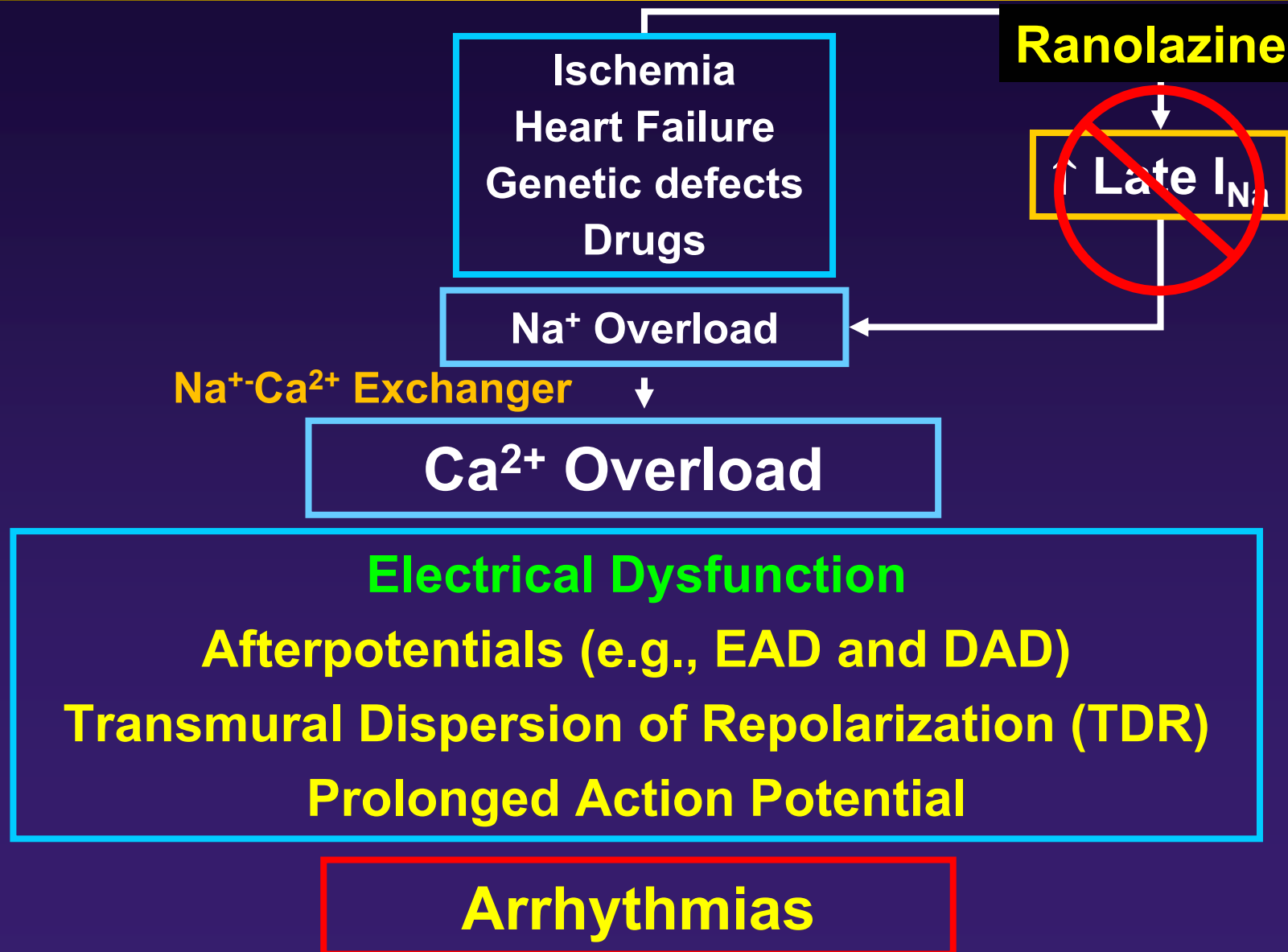
Action Potential
mV



Twitch

Twitch

Consequences of Increased Late I_{Na}

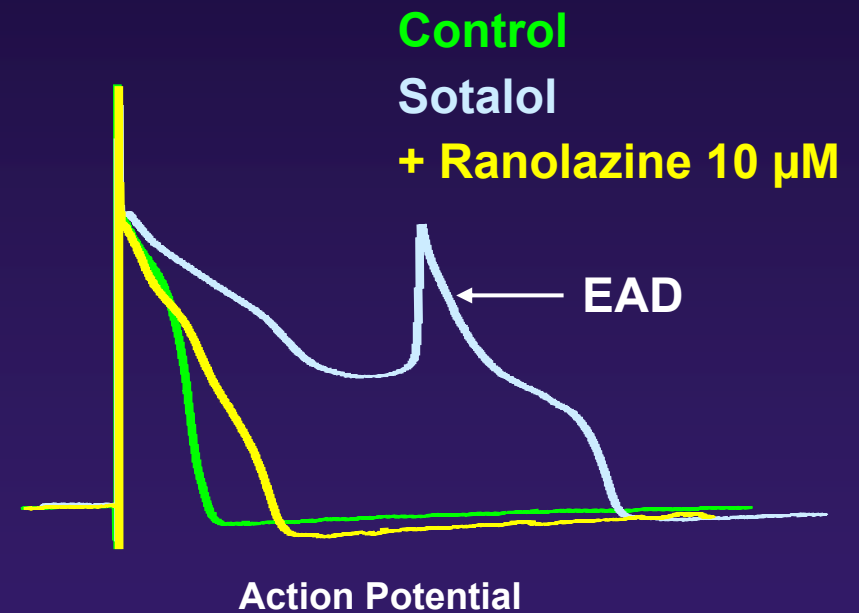
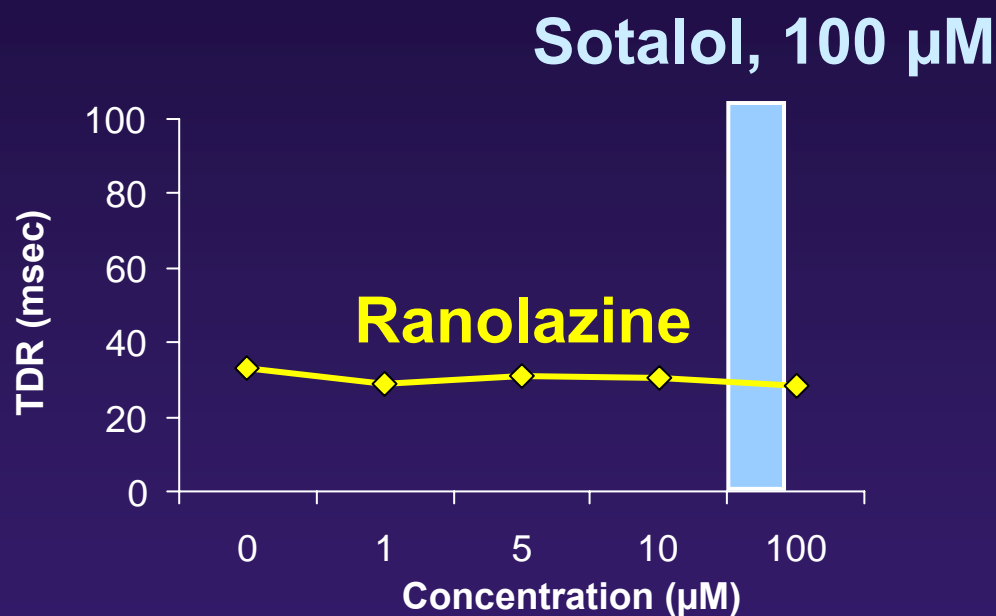


Effects of Ranolazine in Experimental Models on Pro-Arrhythmic Substrate and Triggers



Background

No ↑ in Transmural Dispersion of Repolarization (TDR) ↓ Early Afterdepolarization (EAD)



However, the potential anti-arrhythmic actions of ranolazine have yet to be evaluated in humans

N = 6560

UA/NSTEMI
(Moderate-High Risk)

Standard Therapy

RANDOMIZE (1:1)
Double-blind

Ranolazine
IV to PO

Placebo
Matched IV/PO

Holter
Continuous
7-day recording

Long-term Follow-up
(Median 348 Days)

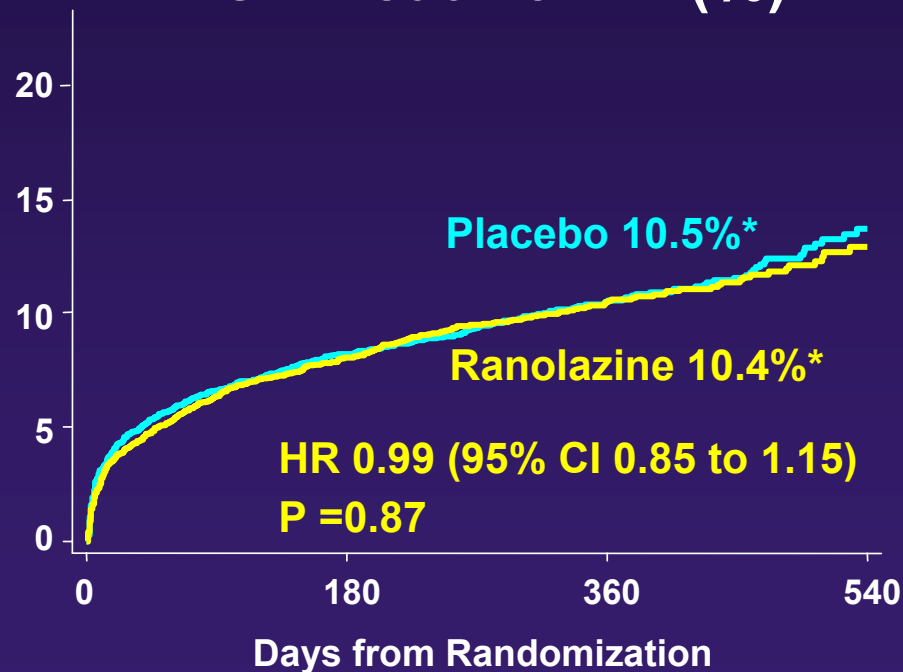
Primary Endpoint

Primary Endpoint - CV Death, MI, or Recurrent Ischemia

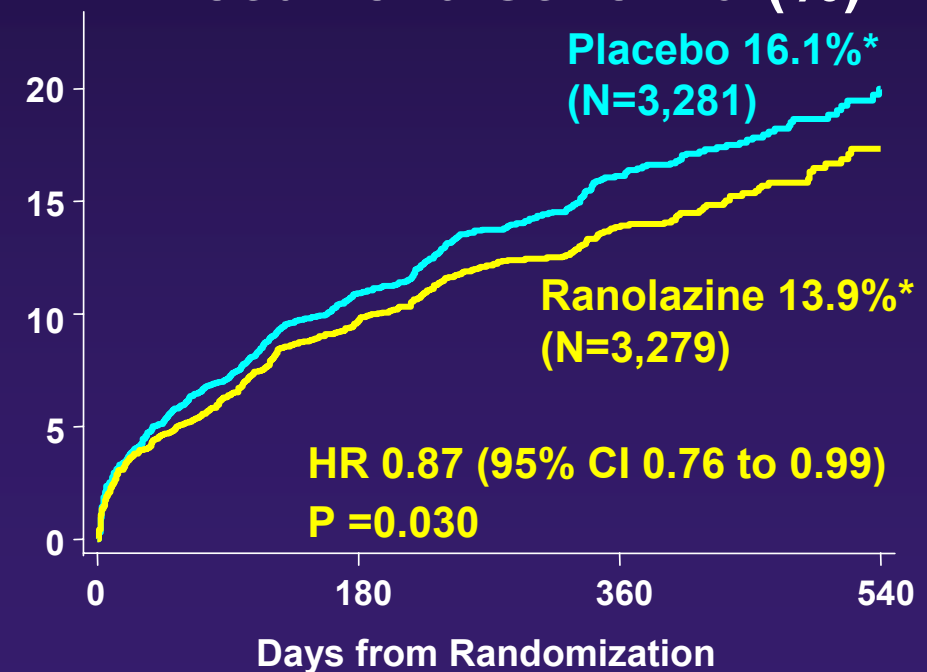
21.8% for Ranolazine vs. 23.5% for Placebo

HR 0.92 (95% CI 0.83 to 1.02), P = 0.11

CV Death or MI (%)



Recurrent Ischemia (%)



*KM Cumulative Incidence (%) at 12 months

Morrow DA et al, JAMA 2007;297(16):1775-83

Methods

- **7-day Continuous ECG (Holter) monitoring**
 - Started at randomization (mean duration 6.3 d)
 - Customized monitors and analysis software (DelMar Reynolds / Spacelabs)
 - Evaluated in TIMI Core Laboratory blinded to treatment and clinical outcome
- **Sudden Cardiac Death through entire clinical follow-up (mean 12 months)**
 - Adjudicated by blinded Clinical Events Committee

Arrhythmia Endpoints Analysis

- **Clinically Significant Arrhythmia**

- VT ≥ 3 beats
- SVT ≥ 120 bpm lasting ≥ 4 beats
- New onset a-fib
- Bradycardia < 45 bpm, CHB, or a vent. pause ≥ 2.5 s

- **Further Classification**

- Ventricular Tachycardia
 - Non-sustained VT ≥ 8 beats
 - Sustained VT (lasting > 30 seconds)
 - Mono or Poly-morphic
- Ventricular Pauses ≥ 3 s

Baseline Characteristics

Results

Holter Cohort 6,351 pts (97% of entire trial)	RANOLAZINE (n=3,162)	PLACEBO (n=3,189)
Age (yrs, median)	64	64
Female (%)	34	36
Prior MI (%)	34	34
Prior heart failure (%)	17	17
Prior vent arrhythmia (%)	3.8	3.9
EF <40% (%)	14	13
NSTEMI on admission (%)	51	51
Beta-blocker (%)	89	90



Primary Arrhythmia Endpoints

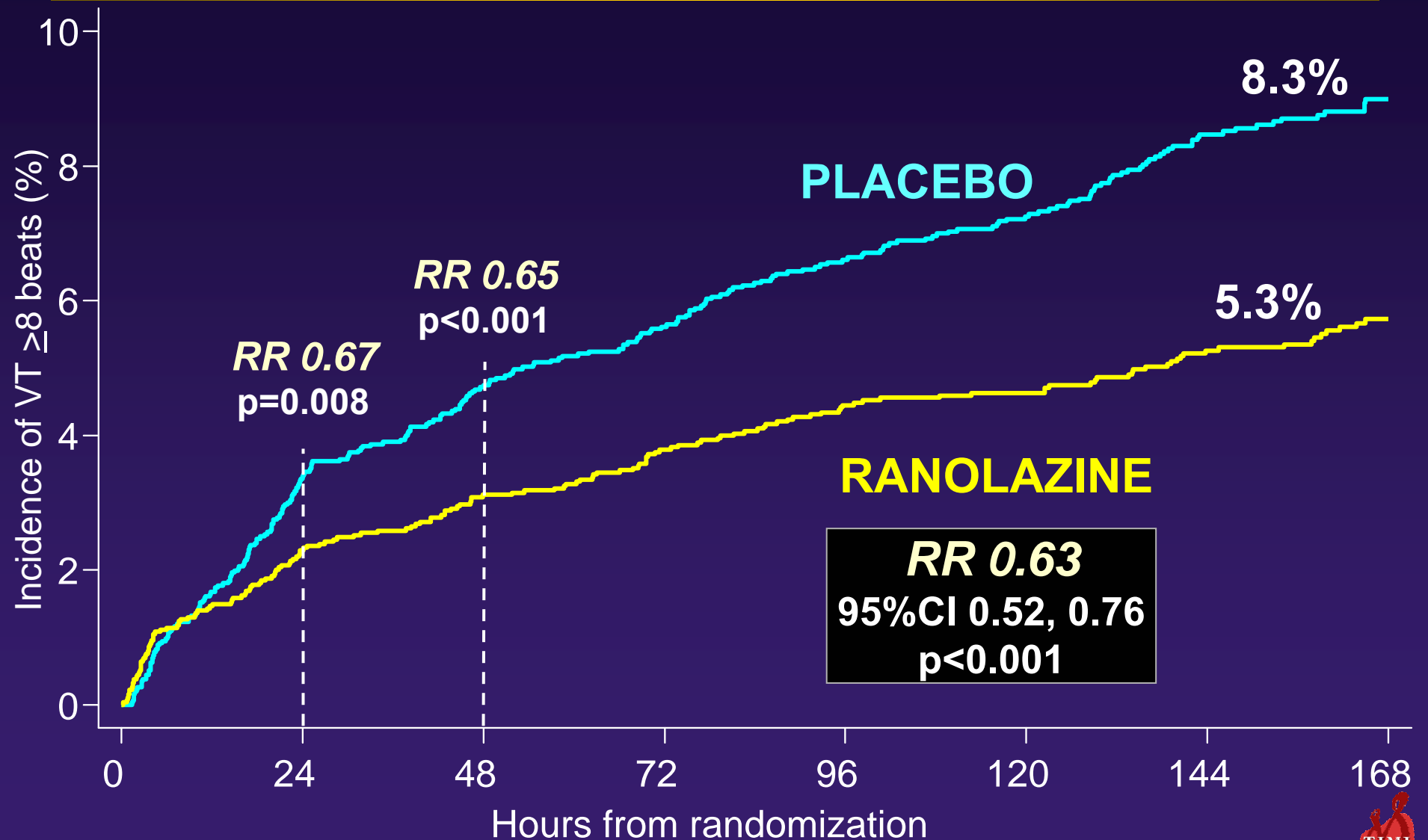
Results

	RANOLAZINE (%)	PLACEBO (%)	P value
Ventricular Events			
VT \geq 3 beats	52.0	60.6	<0.001
Supraventricular Events			
SVT \geq 4 beats	44.7	55.0	<0.001
New-onset atrial fib	1.7	2.4	0.08
Bradycardic Events			
Brady <45 bpm, CHB, or pause \geq 2.5s	39.8	46.6	<0.001
Pause \geq 3 sec	3.1	4.3	0.01



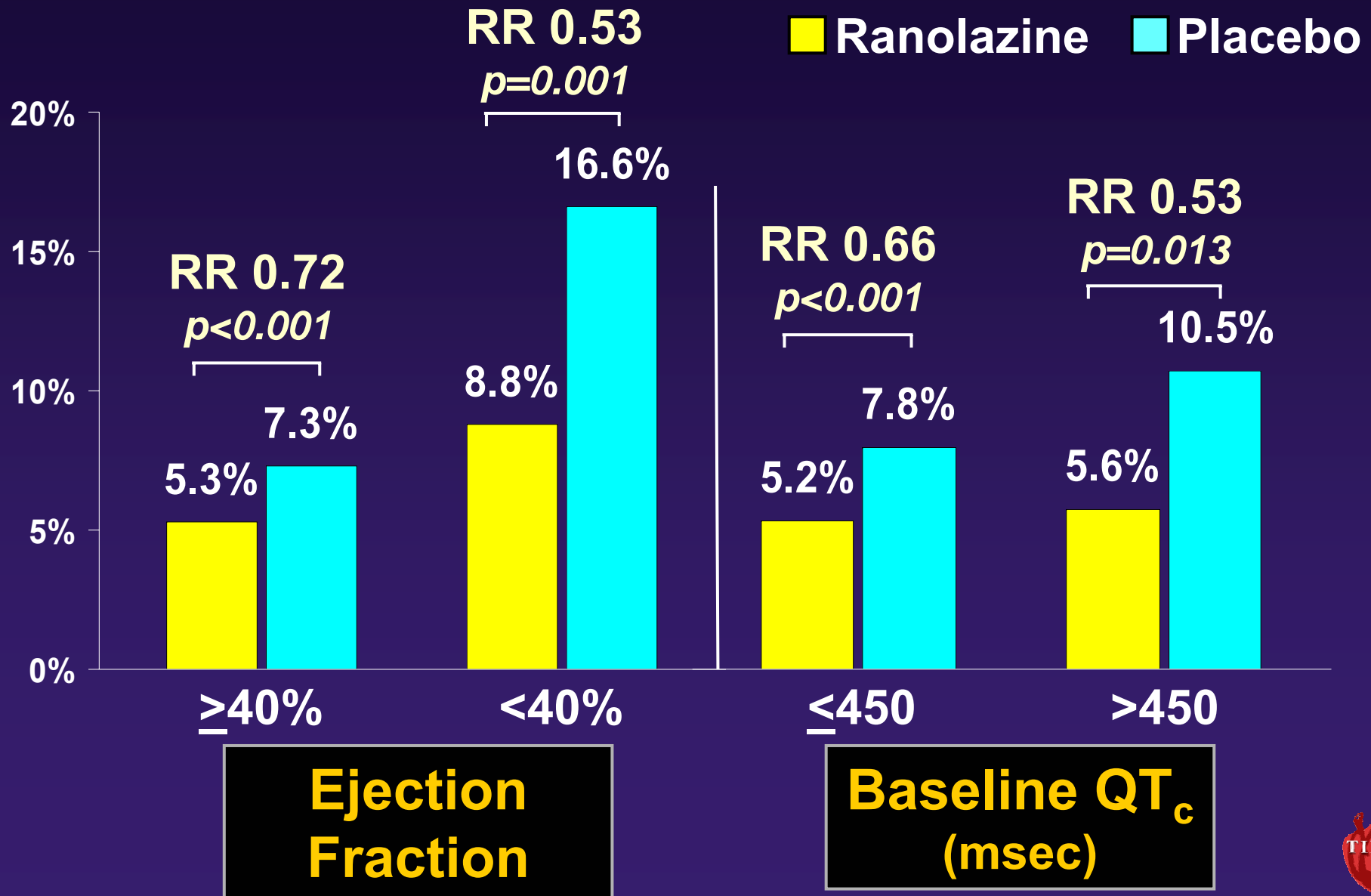
First Occurrence of Ventricular Tachycardia Lasting ≥ 8 Beats

Results



Incidence of VT ≥ 8 Beats in Subgroups

Results



Ventricular Tachycardia Events



Results

	RANOLAZINE (%)	PLACEBO (%)	P value
Polymorphic VT \geq 8 beats	1.2	1.4	0.40
Sustained VT (\geq 30s)	0.44	0.44	0.98
Monomorphic VT	0.13	0.22	0.37
Polymorphic VT	0.32	0.22	0.46



Sudden Cardiac Death Through Follow-up (mean 12 months)



Results

	RANOLAZINE (%)	PLACEBO (%)	P value
Overall	1.7	1.9	0.36
EF \geq40%	1.5	1.5	0.48
EF <40%	2.7	4.9	0.07
QTc \leq450 msec	1.4	1.6	0.86
QTc >450 msec	3.0	3.0	0.27
TRS 0-4	1.2	1.3	0.47
TRS 5-7	3.5	3.9	0.73
No Prior HF	1.2	1.3	0.63
Prior HF	4.1	4.3	0.58

P values for interaction >0.05



Conclusions

- Among patients with ACS, ranolazine, an inhibitor of late I_{Na} , has anti-arrhythmic effects as assessed by Holter monitoring
- In particular, patients treated with ranolazine had fewer episodes of VT \geq 8 beats, SVT, and ventricular pauses \geq 3 seconds
- Consistent effect in several high-risk subgroups

Conclusions (cont.)

- **This is the 1st clinical report of potential anti-arrhythmic actions of ranolazine and supports anti-arrhythmic findings in experimental models**
- **There was no evidence for a significant excess risk of polymorphic ventricular tachycardia or sudden cardiac death**
- **Studies specifically designed to evaluate the potential role of ranolazine as an anti-arrhythmic agent are warranted**