



MERLIN *TIMI 36*

METABOLIC **E**FFICIENCY WITH **R**ANOLAZINE
FOR **L**ESS **I**SCHEMIA IN **N**STE ACS



Ranolazine in Ischemic Heart Disease

- Anti-anginal & anti-ischemic effects without clinically significant effect on HR or BP
- **Approved for treatment of chronic angina**
 - ↑ exercise time, ↓ angina in selected pts
- **Novel mechanism of action**
 - Inhibition of late I_{Na} → ↓ Ca^{2+} overload → ↓ adverse energetic, mechanical, electrical consequences
- **Experimental evidence**
 - ↑ LV performance during ischemia
 - ↑ recovery of LV function, ↓ infarct size

Ranolazine in Ischemic Heart Disease

- Ranolazine associated with an \uparrow in QTc (average ~5 msec)
- However, experimental data suggest suppression of pro-arrhythmic markers
- *Indication in chronic angina:* “Because ranolazine prolongs the QT interval, it should be reserved for patients who have not achieved an adequate response with other anti-anginal drugs.”

 **Need for additional safety information**

Objectives

MERLIN-TIMI 36 *Three major aims*

1) ACUTE EFFICACY → 2) CHRONIC EFFICACY

Acute Coronary Syndrome
↓ *major CV events?*

Chronic Management
↓ *recurrent ischemia?*

3) SAFETY

N = 6560

UA/NSTEMI
(Moderate-High Risk)

Standard Therapy

RANDOMIZE (1:1)
Double-blind

Ranolazine
IV to PO

Placebo
Matched IV/PO

Holter

Long-term Follow-up
(Median 348 Days)

Major Inclusion Criteria

- 1) Hospitalized with NSTEMI ACS
- 2) Ischemic sx at rest within 48h
- 3) At least 1 indicator of moderate-high risk
 - ↑ cTn (MI limit) or CK-MB (ULN) **or**
 - ST-depression ≥ 0.1 mV **or**
 - Diabetes Mellitus (insulin or oral rx) **or**
 - TIMI Risk Score for UA/NSTEMI ≥ 3

Major Exclusion Criteria

- Must be enrolled prior to revascularization (if planned)
- Pulmonary edema requiring intubation, sustained SBP < 90 mmHg or shock
- Use of drugs known to ↑ QT
- Clinically significant hepatic disease or end-stage renal disease

Endpoints

Primary Endpoint *composite of*

- Cardiovascular death
- New or recurrent MI
- Recurrent ischemia

Major Secondary Endpoints

- CVD, MI, severe recurrent ischemia
- CVD, MI, severe recurrent ischemia, positive Holter (30 day endpoint)

All elements of 1° endpoint adjudicated by blinded CEC

Ischemia Endpoint Definition

Recurrent Ischemia *defined by*

1. Rest pain with ischemic ECG Δ , or
2. Prompting revascularization, or
3. Rehospitalization for UA, or
4. Worsening angina/ischemia (\uparrow CCS Class) requiring intensification of rx

Severe RI

CCS = Canadian Cardiovascular Society

Major Safety Endpoints

- **Death from any cause**
- **Symptomatic documented arrhythmia**
- **Clinically significant arrhythmias during Holter monitoring**

Baseline Characteristics

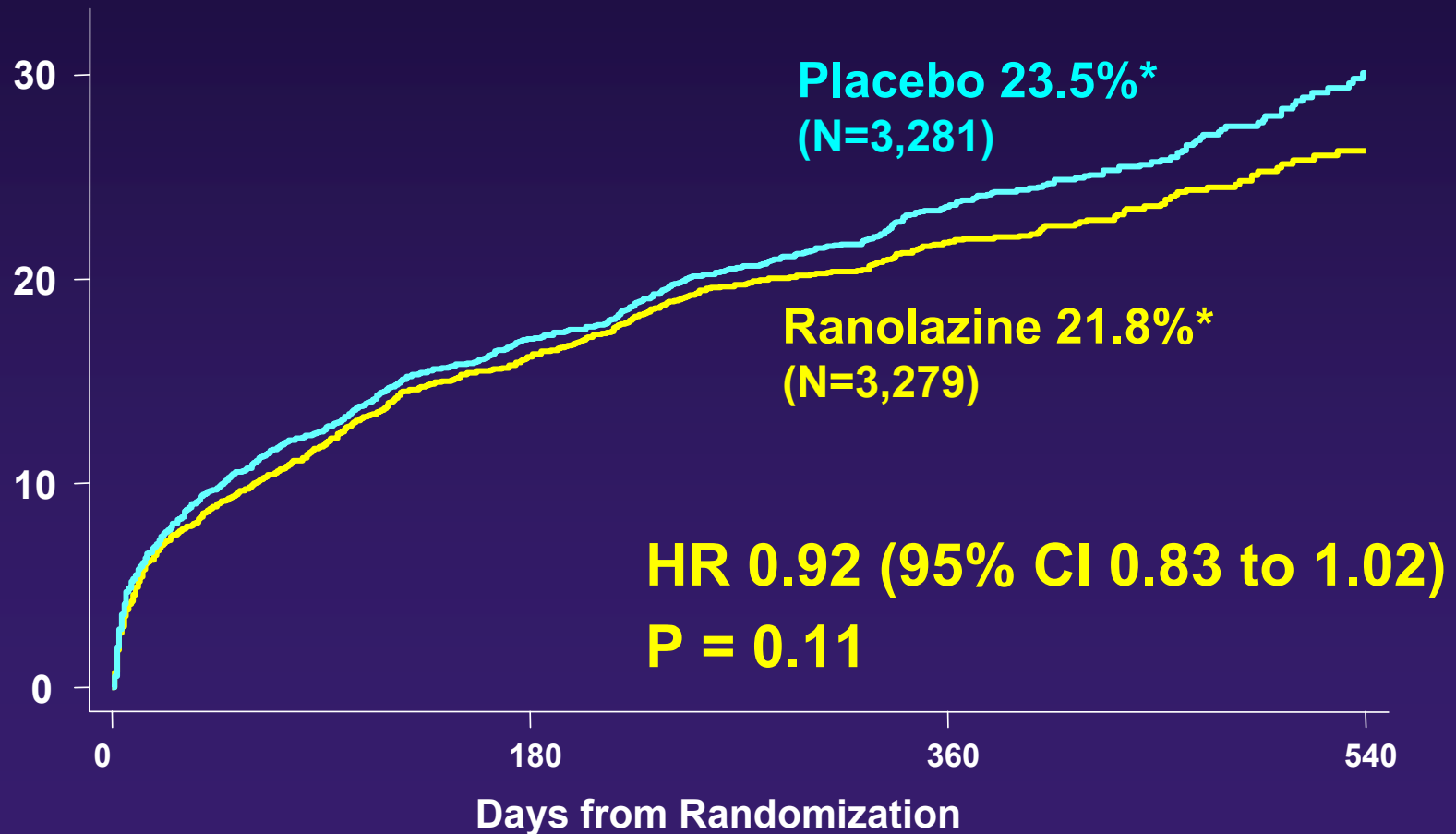
Enrollment October 2004 to May 2006. 9 lost to F/U	PLACEBO (N=3,281)	RANOLAZINE (N=3,279)
Age (yrs, median)	64	64
Female (%)	36	34
Diabetes (%)	34	34
Prior MI	33	34
Prior CHF	17	16
<i>Presentation</i>		
Sx to rando (median, hrs)	23	24
NSTEMI (%)	51	51
ST↓ ≥ 1mm (%)	35	35
TRS ≥ 4 (%)	46	45

Concomitant Treatment

Hospitalization and/or discharge	PLACEBO (N=3,281)	RANOLAZINE (N=3,279)
Aspirin (%)	96	96
Heparin (UFH/LMWH) (%)	90	91
Thienopyridine (%)	65	64
Beta-blocker (%)	90	89
Statin (%)	82	83
ACEI/ARB (%)	79	78
Oral nitrates (%)	31	29
Early Invasive (%)	41	41
Coronary angio (%)	59	59

Primary Endpoint

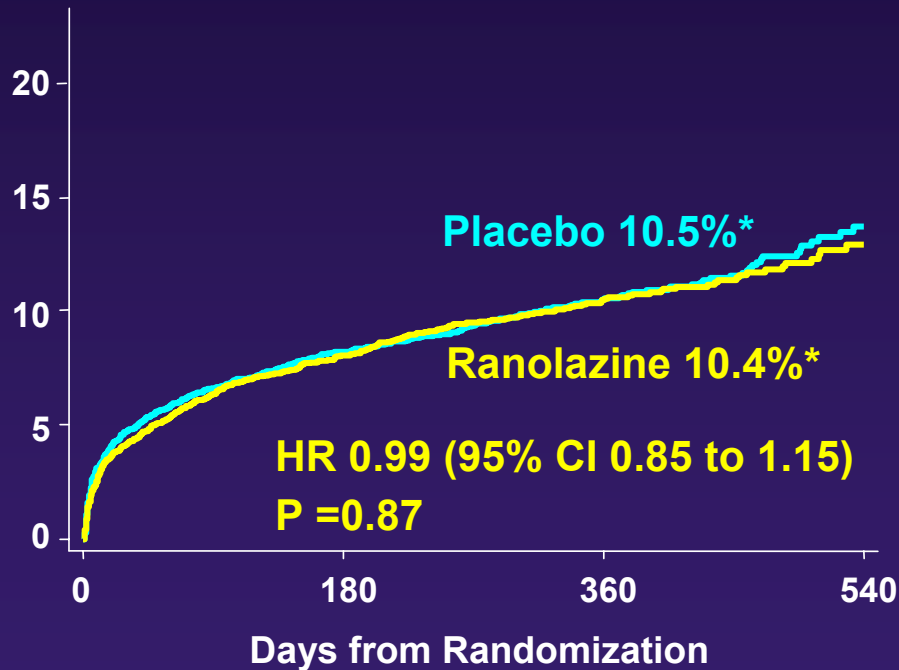
CV Death, MI, or Recurrent Ischemia (%)



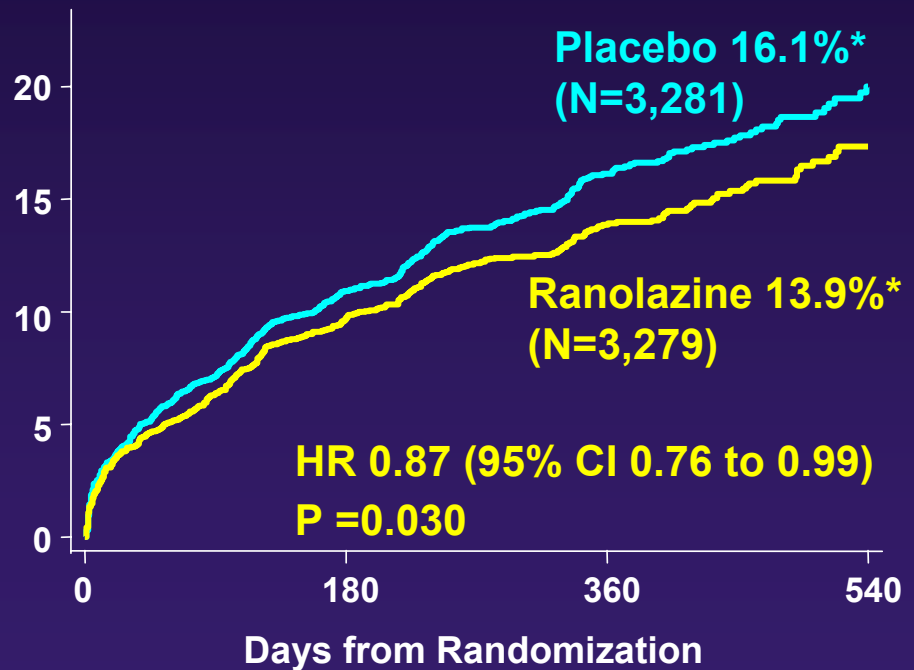
*KM cumulative incidence (%) at 12 months

Components of Primary Endpoint

CV Death or MI (%)



Recurrent Ischemia (%)



*KM Cumulative Incidence (%) at 12 months

Additional Efficacy Endpoints*

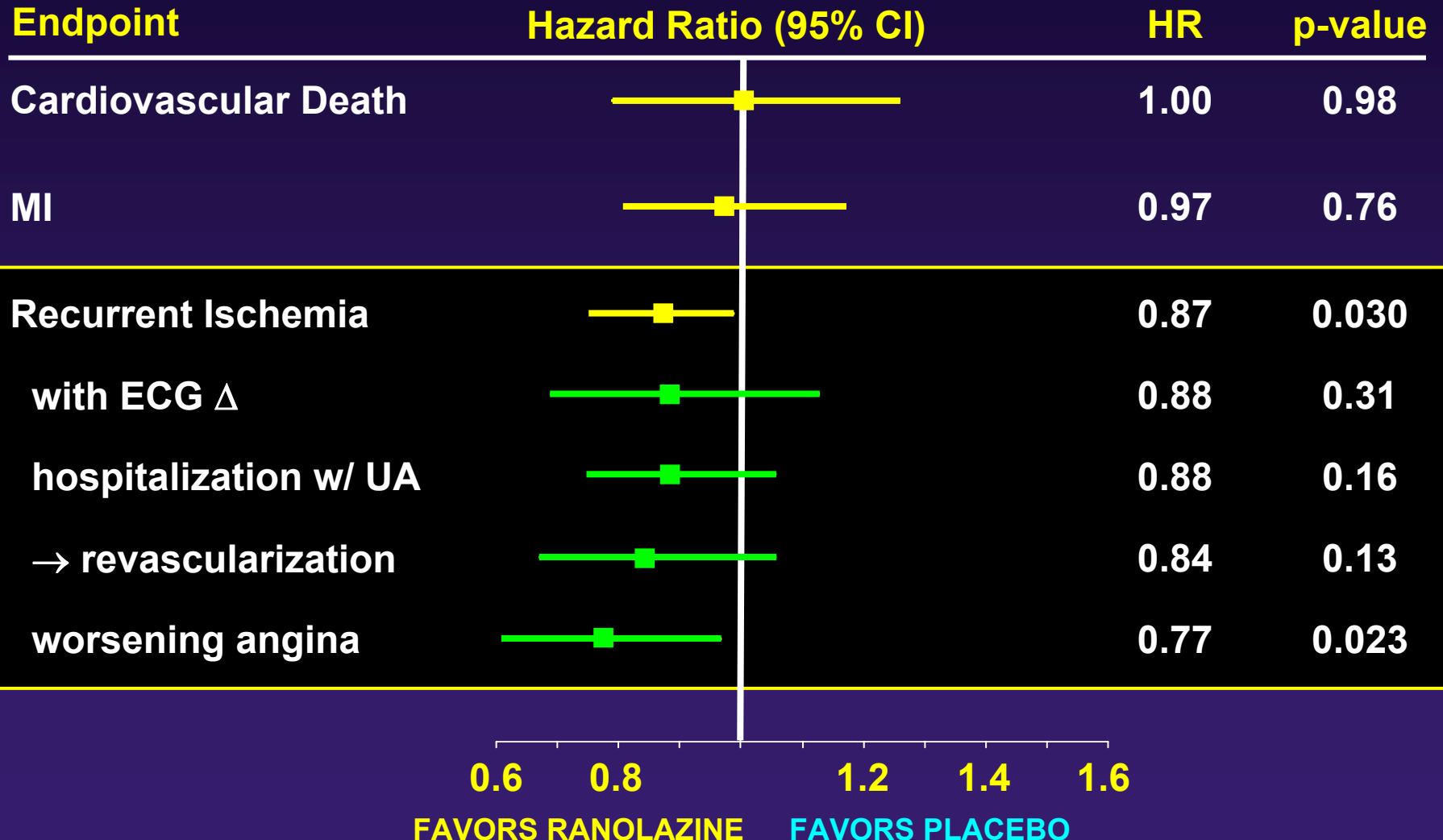
	PLACEBO (N=3,281)	RANOLAZINE (N=3,279)	HR	p-value
CVD, MI, Severe RI	19.2	18.7	0.96	p = 0.50
Failure of therapy[†]	38.3	36.8	0.94	p = 0.16
30-day endpoint**	25.1	23.1	0.92	p = 0.055
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CV Death	4.5	4.4	1.00	p = 0.98
MI	7.6	7.4	0.97	p = 0.76

*KM Cumulative Incidence (%) at 12 months

[†]CV Death, MI, RI, Holter ischemia, New/worsening HF, Early +ETT

**CV Death, MI, severe RI, Holter ischemia

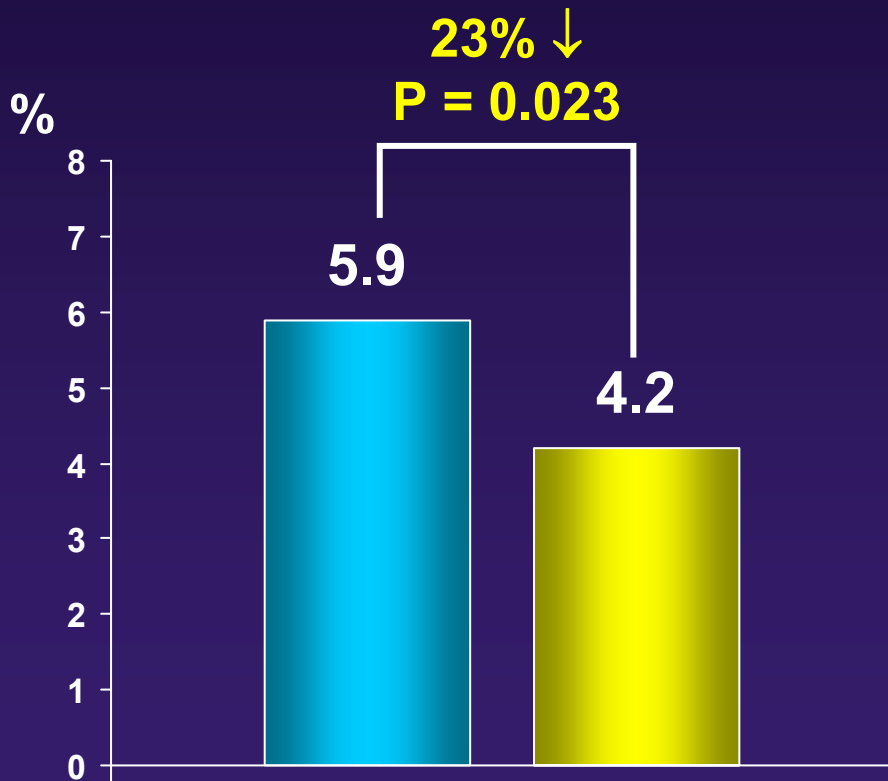
Components of Recurrent Ischemia



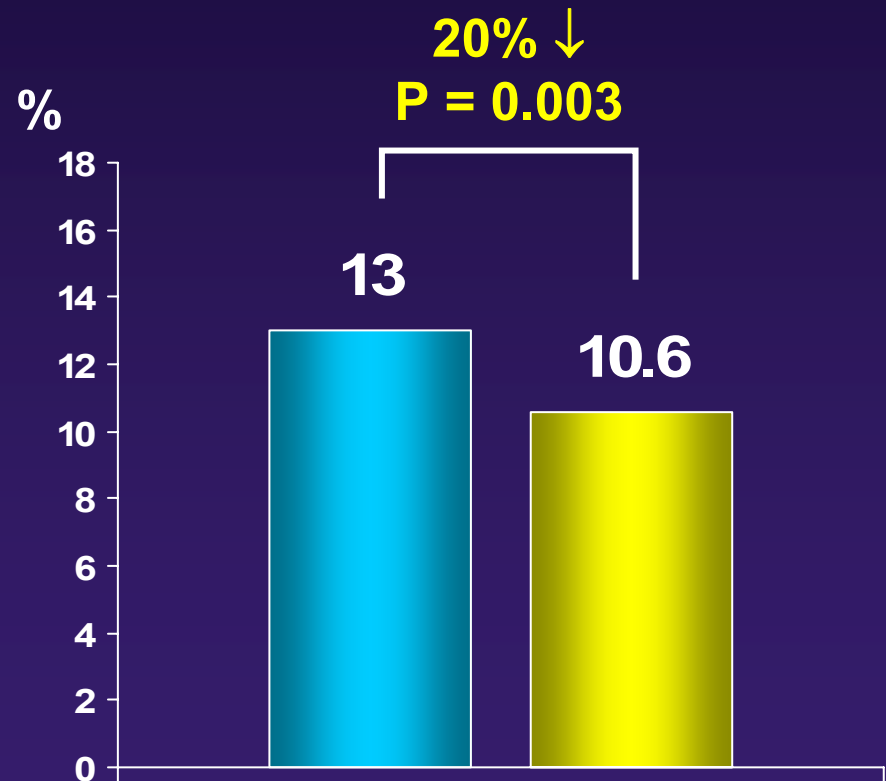
Assessment of Anti-anginal Effects

PLACEBO
(N=3,281)

RANOLAZINE
(N=3,279)

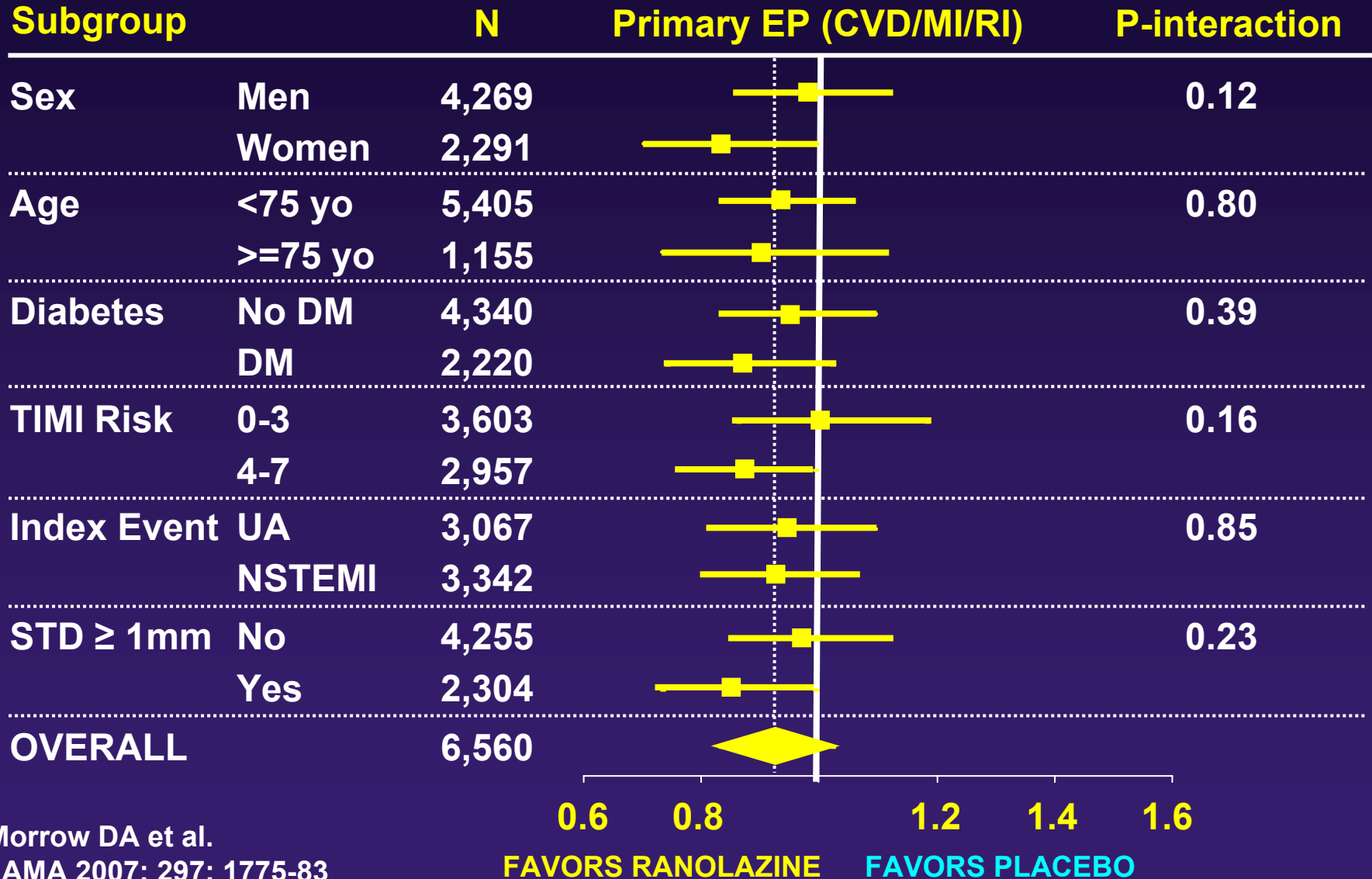


Worsening Angina (%)*



Antianginal Increase (%)*

Efficacy Results in Major Subgroups



Major Safety Endpoints

	PLACEBO (N=3,273*)	RANOLAZINE (N=3,268*)	HR	P-value
Death - any cause (N)	175	172	0.99	p = 0.91
Sudden cardiac death	65	56	0.87	p = 0.43
Symptomatic Documented arrhythmia	102	99	0.97	p = 0.84
Clinically significant arrhythmia[†] on Holter	83.1%	73.7%	0.89	p<0.001

*safety analysis cohort (received at least one dose)

[†] VT ≥ 3 beats, SVT >120bpm, new AF, brady<45 bpm, CHB or pause >2.5s

Tolerability

Adverse events >4%

	PLACEBO (N=3,273)	RANOLAZINE (N=3,268)
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Dizziness (%)	7	13
Nausea	6	9
Constipation	3	9
Asthenia	3	5

Syncope*	2	3	p = 0.011
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*Includes vasovagal syncope

Conclusions

- **An 8% relative ↓ in the primary endpoint w/ ranolazine was not statistically significant**
- **No effect on CV death or MI**
- **Supportive evidence for efficacy as an anti-anginal in broader population than ever studied before**
 - **23% ↓ in worsening angina**
 - **20% ↓ in advancement of anti-anginal rx**

Conclusions (cont.)

- Results reassuring with respect to each of the major safety endpoints
 - *No adverse trend in all-cause mortality or arrhythmia*
- Potential anti-arrhythmic effects of ranolazine (inhibitor of late Na⁺ current) suggested by ↓ in arrhythmias (Holter) warrant additional investigation