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MorBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction

A step further in the management of stable coronary patients with ivabradine

RATIONALE

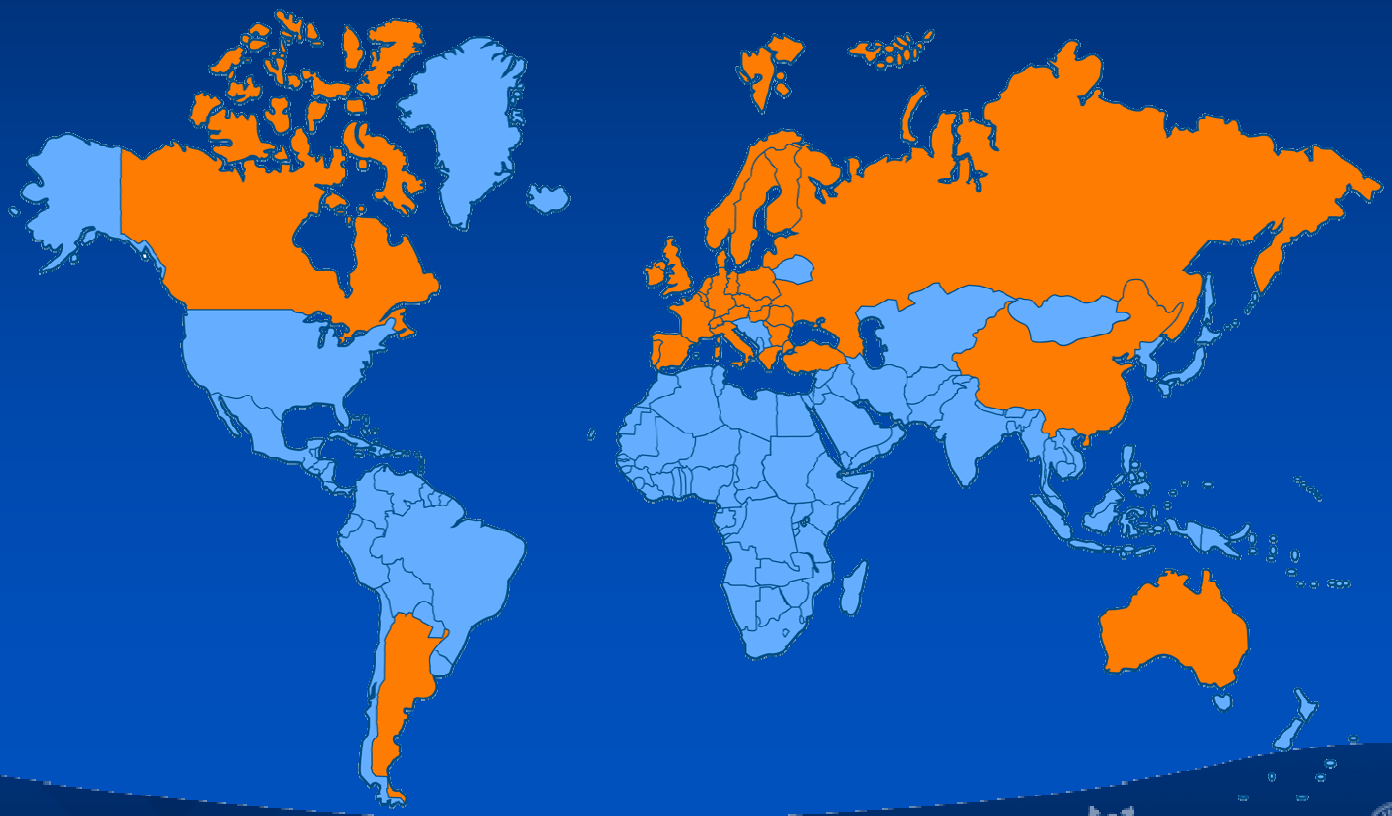
- In CAD patients, high heart rate is associated with higher mortality[1]
- CAD patients with associated LVD are at higher risk of mortality[2]
- Heart rate reduction could reduce mortality in CAD patients[3]
- Ivabradine is a pure heart rate reducing agent with proven antianginal and anti-ischemic efficacy [4,5,6]

1- Diaz A,et al. *Eur Heart J.* 2005;26:867-874. **2-** Emond M. *Circulation.* 1994;90:2645–2657. **3-** Cucherat MI. *Eur Heart J.* 2007;28:3012-3019. **4-** Borer JS et al. *Circulation*. 2003;107:817-823. **5-** Tardif JC,et al. *Eur Heart J.* 2009;30:540-548 **6-** Tardif JC et al. *Eur Heart J*. 2005;26:2529-2536.

Worldwide study

0 917 participants with documented coronary artery disease and left ventricular dysfunction

781 sites in 33 countries across 4 continents



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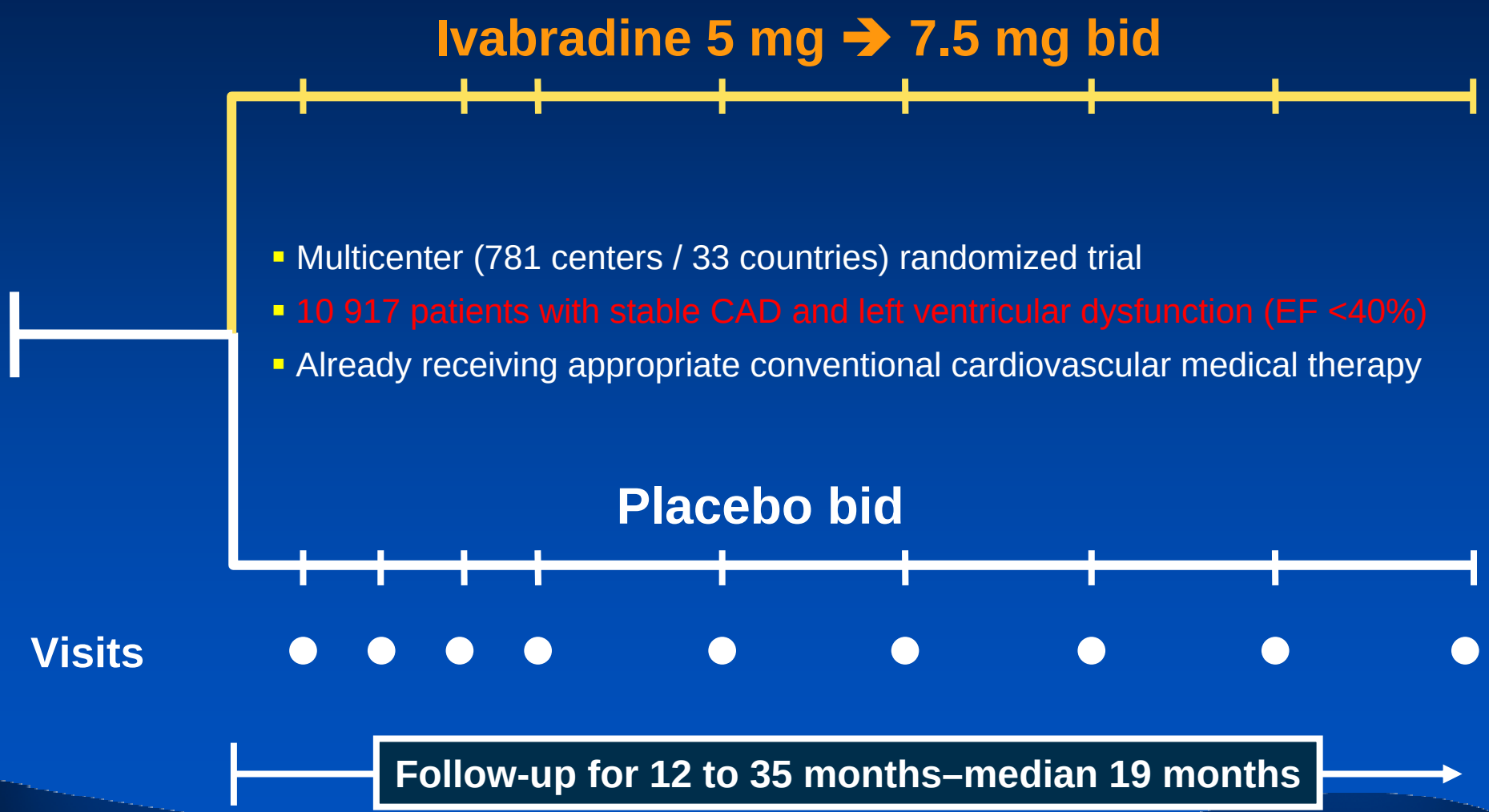
Design of the study



Fox K et al. *Lancet.* 2008;372:807-816.

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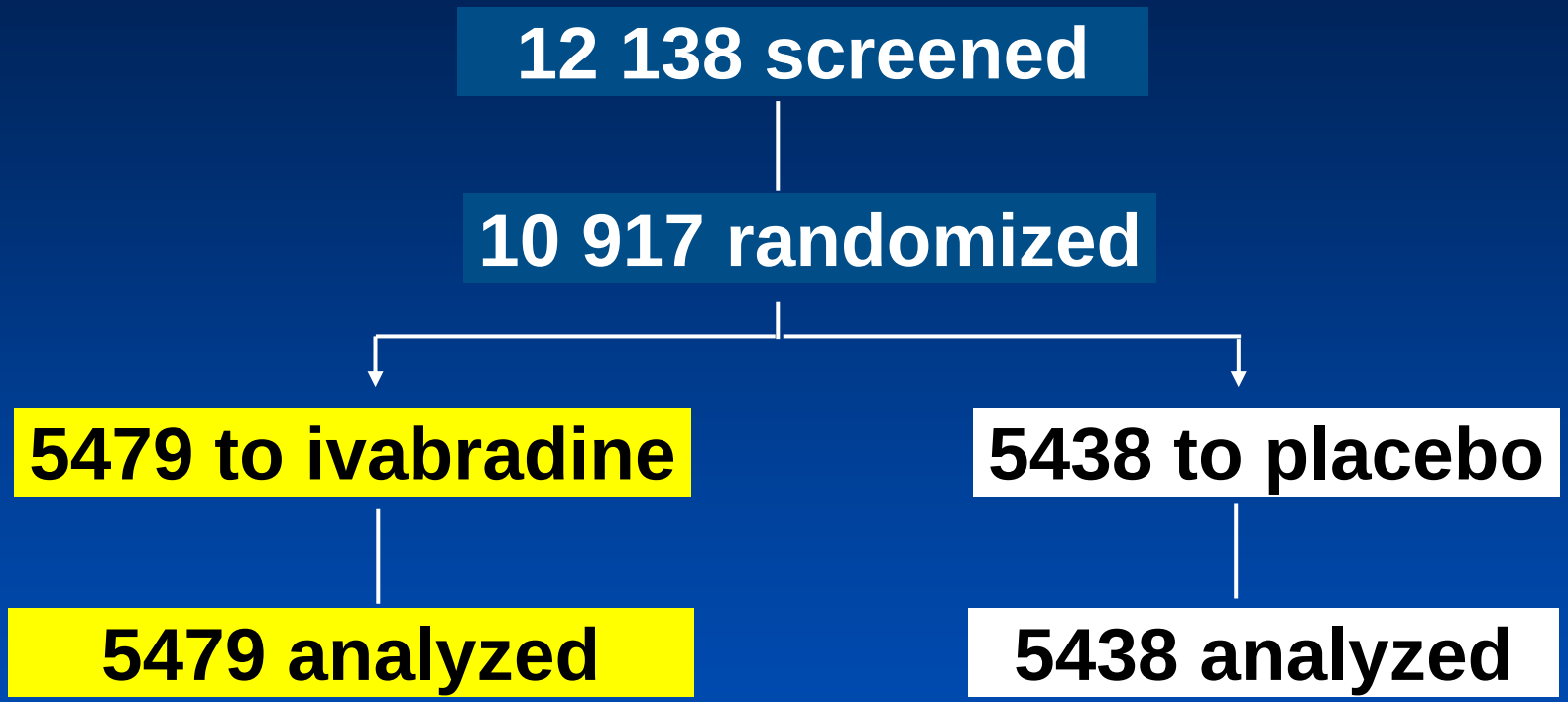
Patients and follow-up



Median study duration: 19 months
Maximum: 35 months

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Baseline characteristics

	Placebo	Ivabradine	All
Time since CAD diagnosis (years)	8.2 (7.1)	8.1 (7.0)	8.2 (7.0)
Previous MI (%)	89	88	88
Time since last MI (years)	6.2 (6.0)	5.9 (5.7)	6.0 (5.9)
History of diabetes (%)	37	37	37
History of hypertension (%)	71	71	71
Previous coronary revascularization (%)	52	51	52

Values in parentheses are standard deviations

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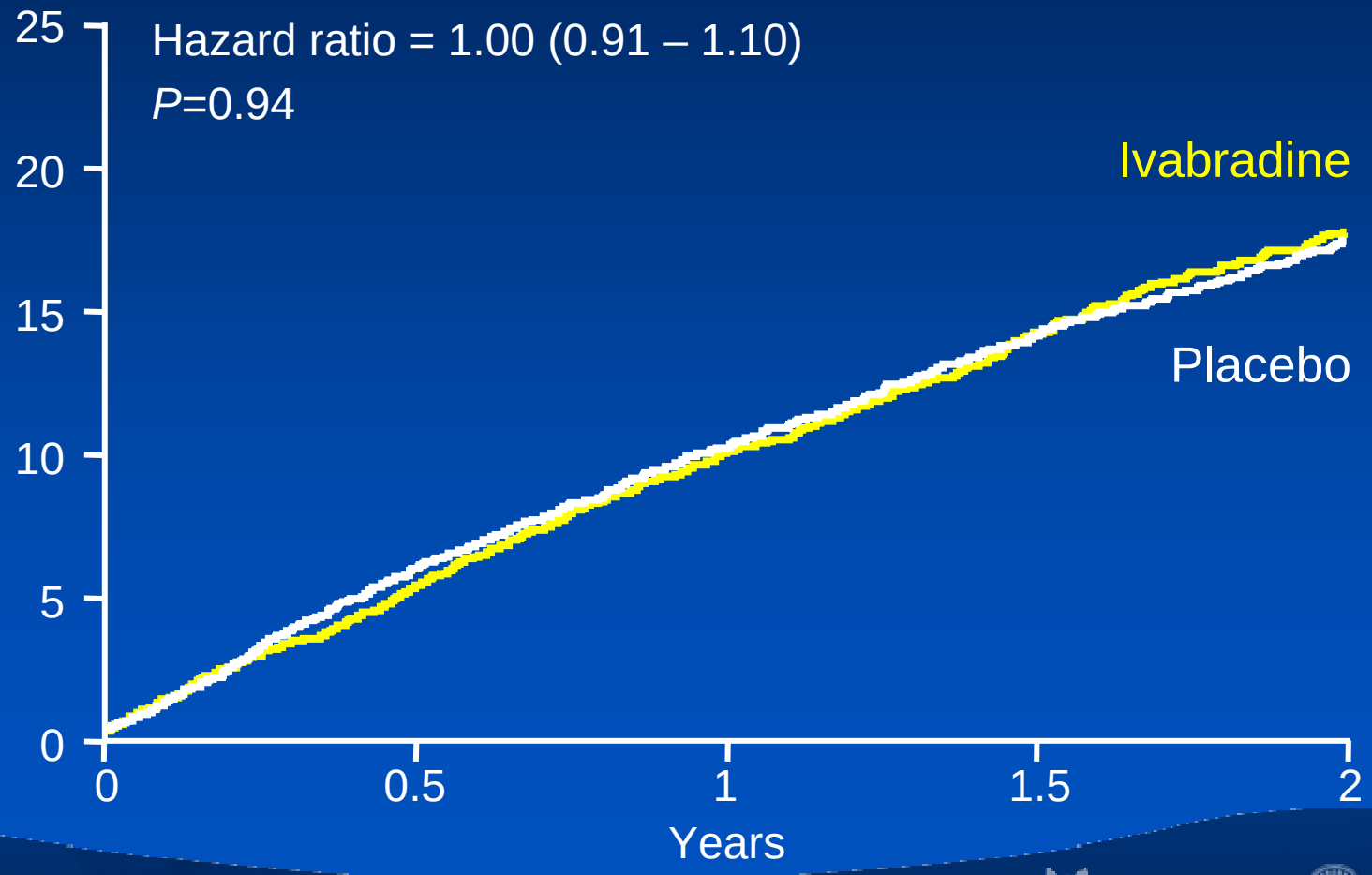
Results

BEAUTIFUL Effect of ivabradine on primary endpoint (Overall population)

% with primary composite end point of CV death, hospitalization for acute MI, or for new-onset or worsening heart failure



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Ivabradine reduces all coronary events in coronary patients with HR ≥70 bpm

Predefined end point	Hazard ratio	Risk reduction	*P* value
Fatal MI	0.69	31%	0.114
Fatal and nonfatal MI	0.64	36%	0.001
Fatal and nonfatal MI or unstable angina	0.78	22%	0.023
Fatal and nonfatal MI, unstable angina, or revascularization	0.77	23%	0.009
Coronary revascularization	0.70	30%	0.016

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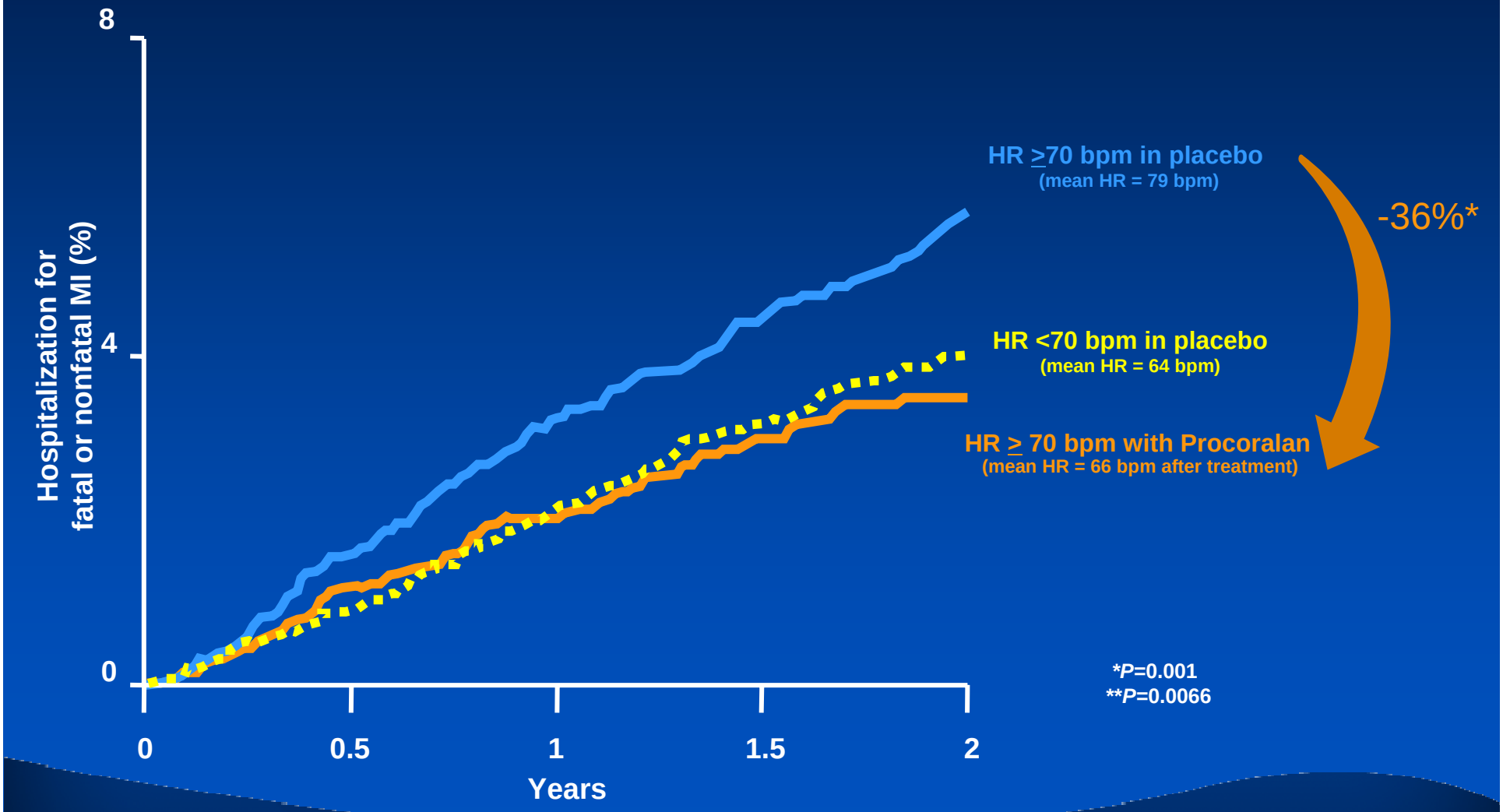
Ivabradine shifts the patients from high risk to low risk



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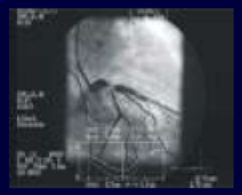

Patient

Protection by ivabradine from ischemia, not heart failure endpoints

[% reduction in endpoints]

	BEAUTIFUL population		Limiting angina	
	all	HR>70min^{-1}	all	HR>70min^{-1}
Primary composite endpoint	0%	9%	24% p=0.05	31% p=0.06
Mortality	-4%	-2%	13%	17%
Hospitalization for HF	1%	3%	16%	4%
Hospitalization for MI	13%	36% p=0.001	42% p=0.021	73% p=0.002
Coronary revascularization	17%	30% p=0.016	30%	59% p=0.04

Mechanism(s) of ivabradine's pleiotropic action

- Anti-oxidant effect
- Reduction of sodium influx, secondary sodium-calcium exchange and ultimate calcium overload

Mechanistic studies required !