



**Study assessInG the morbidity-mortality
beNefits of the I_f inhibitor ivabradine
in patients with coronarY artery disease
without heart failure**

Conflict of interest

Kim Fox receives honoraria, fees, travel expenses from Servier

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Study organisation

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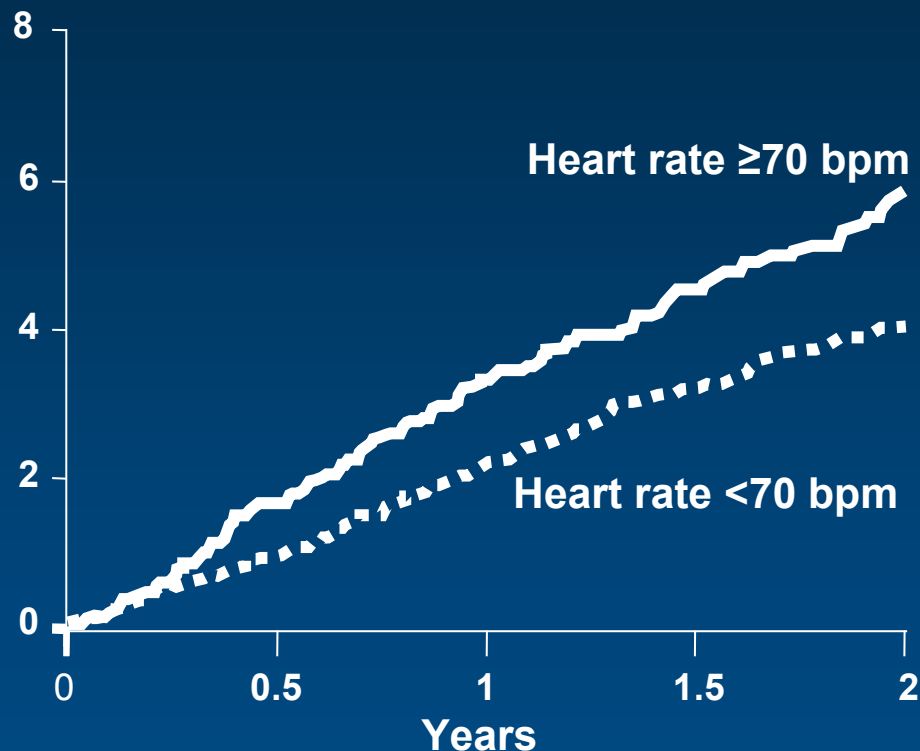
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Effect of ivabradine on hospitalization for fatal/nonfatal MI in patients with stable CAD and LVSD

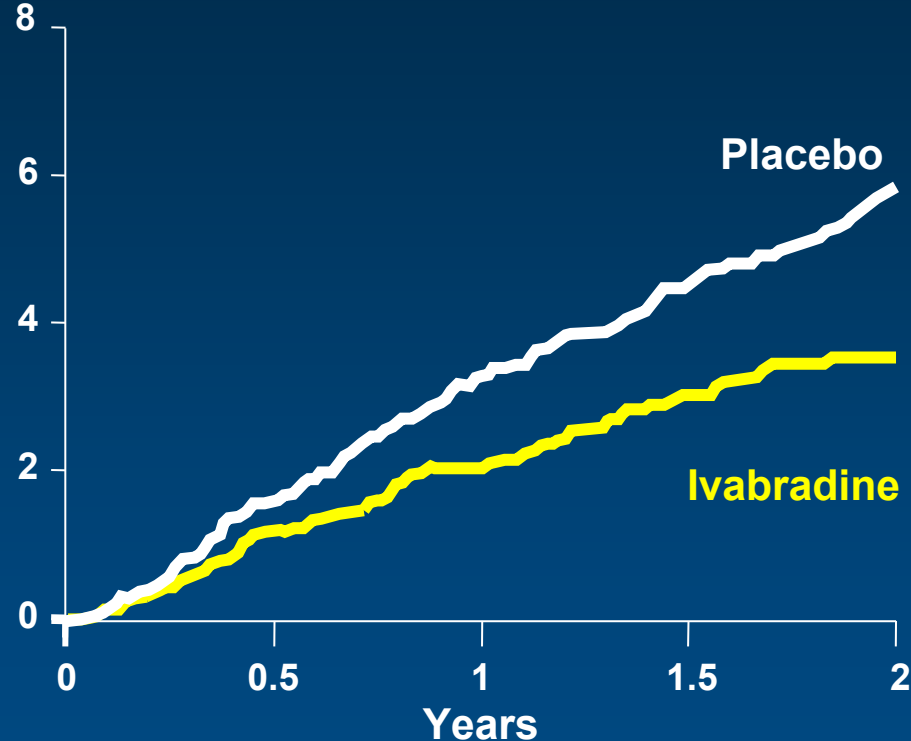
HR (95% CI), 1.46 (1.11–1.91)
P=0.0066

Event rate (%)



HR (95% CI), 0.64 (0.49–0.84)
P=0.001

Event rate (%)



Overall placebo population (n=5438)

Patients with heart rate ≥ 70 bpm (n= 5392)

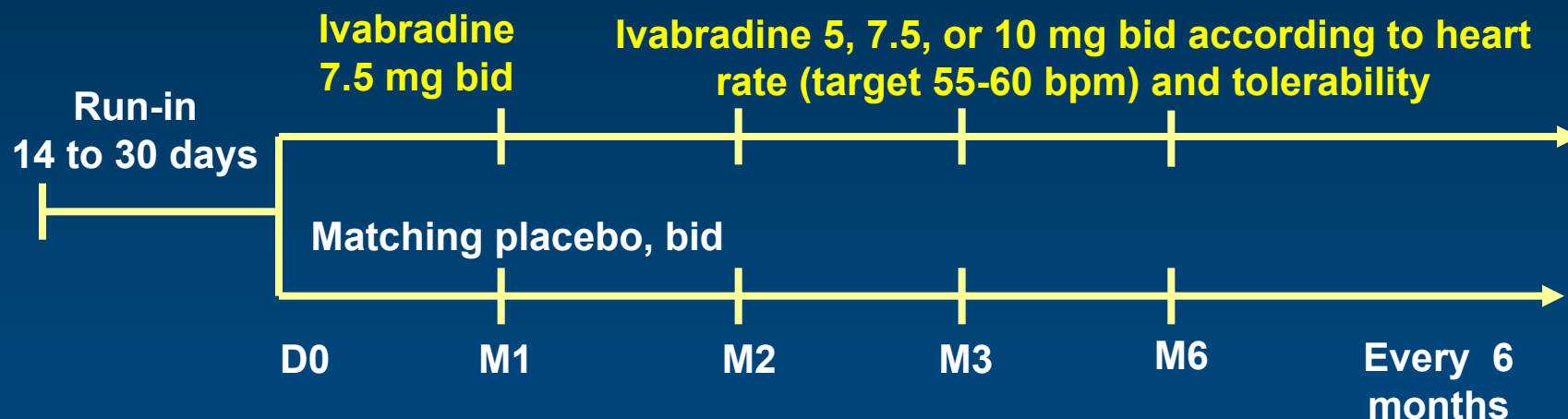
Study design

Study outcomes

- Events: 2.8% PY placebo, N=19 102
- Median follow-up: 27.8 months
- 51 countries - 1139 centres

Population

- ≥ 55 years, stable CAD
- With at least one other CV risk factor (including angina CCS class $\geq II$)
- Without clinical heart failure (LVEF $>40\%$)
- HR ≥ 70 bpm



Primary composite end point: cardiovascular death or nonfatal myocardial infarction

- *Primary analysis: ivabradine versus placebo on primary end point*
- *Prespecified analysis: in patients with angina CCS class $\geq II$ on primary end point*

Patients and follow-up

19 102 patients randomized

Ivabradine (n=9550)

235 had incomplete follow-up
✓ 231 withdrew consent
✓ 3 lost to follow-up
✓ 1 medical reason

9550 analyzed

✓ 6037 with angina
✓ 3513 with no angina

Placebo (n=9552)

200 had incomplete follow-up
✓ 199 withdrew consent
✓ 1 lost to follow-up

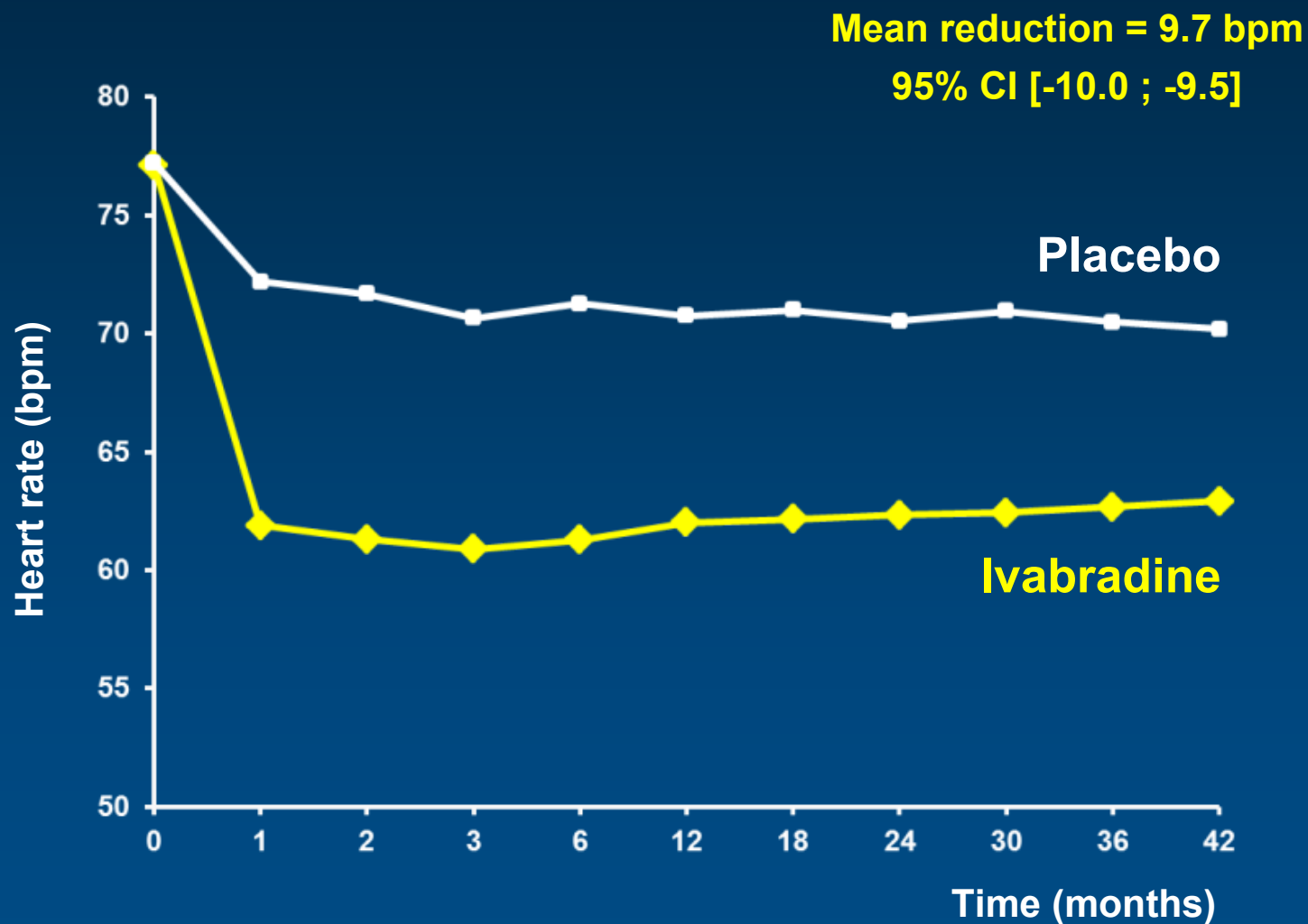
9552 analyzed

✓ 6012 with angina
✓ 3540 with no angina

	Ivabradine n=9550	Placebo n=9552
Age, years	65	65
Male, %	73	72
Resting heart rate, bpm	77	77
LV ejection fraction, %	56	56
Previous MI, %	73	73
Previous coronary revasc, %	68	68
Dyslipidemia, %	72	72
Diabetes mellitus, %	43	43
Peripheral artery disease, %	21	21
Current smoker, %	24	24
Hypertension, %	87	86

	Ivabradine n=9550	Placebo n=9552
Antiplatelet or anticoagulants, %	98	98
Statins, %	92	92
ACE inhibitors or ARB, %	82	81
Beta-blockers, %	83	83
Dihydropyridine CCB, %	27	27
Diltiazem or verapamil, %	5	4
Organic nitrates, %	41	39

Mean heart rate reduction

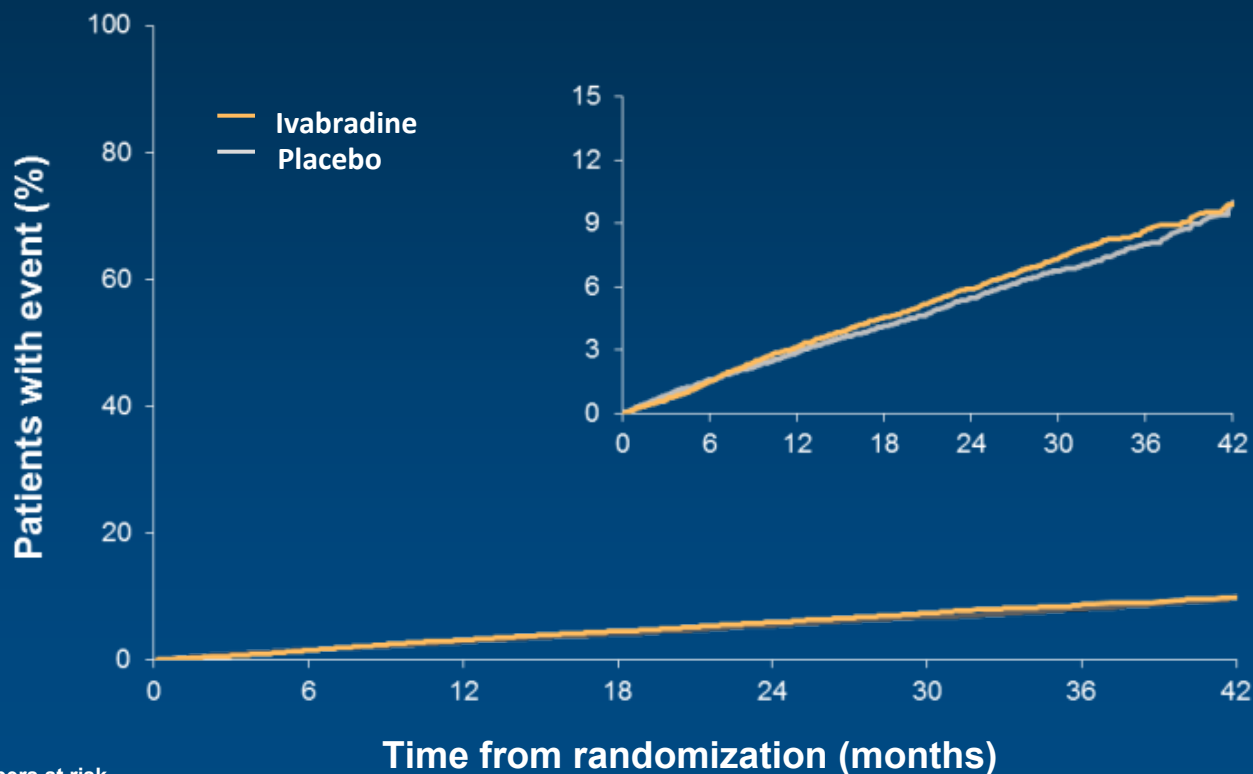


Primary composite end point

Ivabradine n=654 (3.03% PY)

Placebo n=611 (2.82% PY)

HR = 1.08 [95% CI 0.96-1.20] $P=0.20$



Numbers at risk

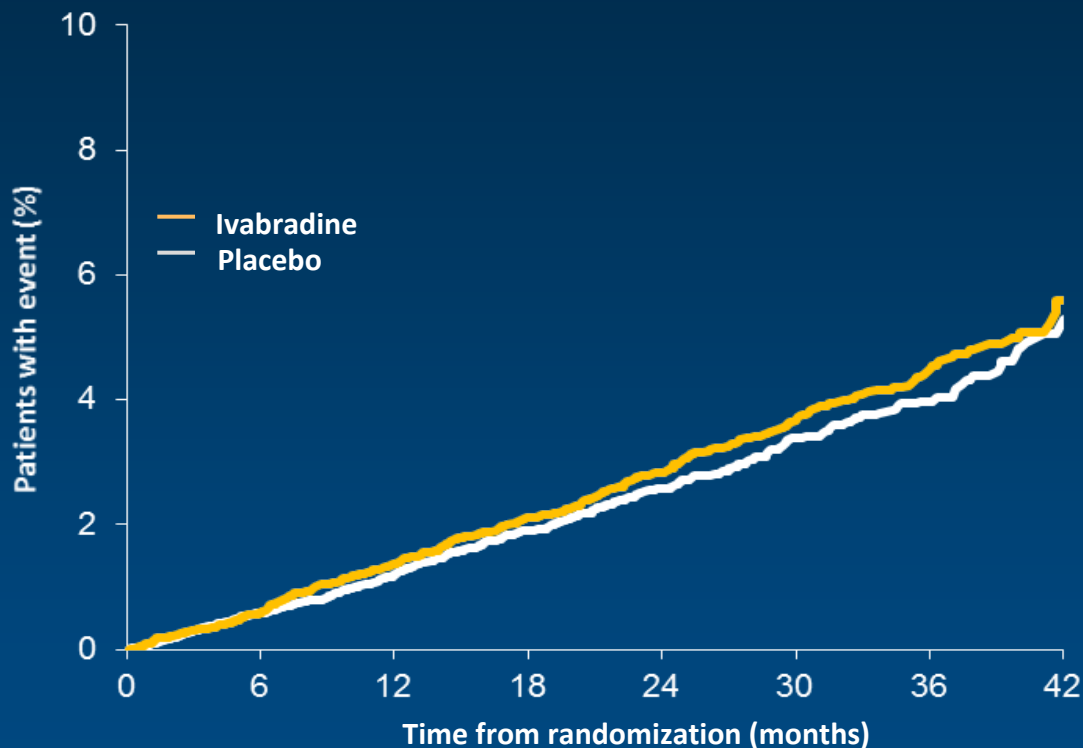
Ivabradine	9550	9297	9077	8611	5570	3776	1832	349
Placebo	9552	9311	9130	8656	5649	3749	1836	365

Cardiovascular death

Ivabradine n=329 (1.49% PY)

Placebo n=301 (1.36% PY)

HR = 1.10 [95% CI 0.94-1.28] $P=0.25$



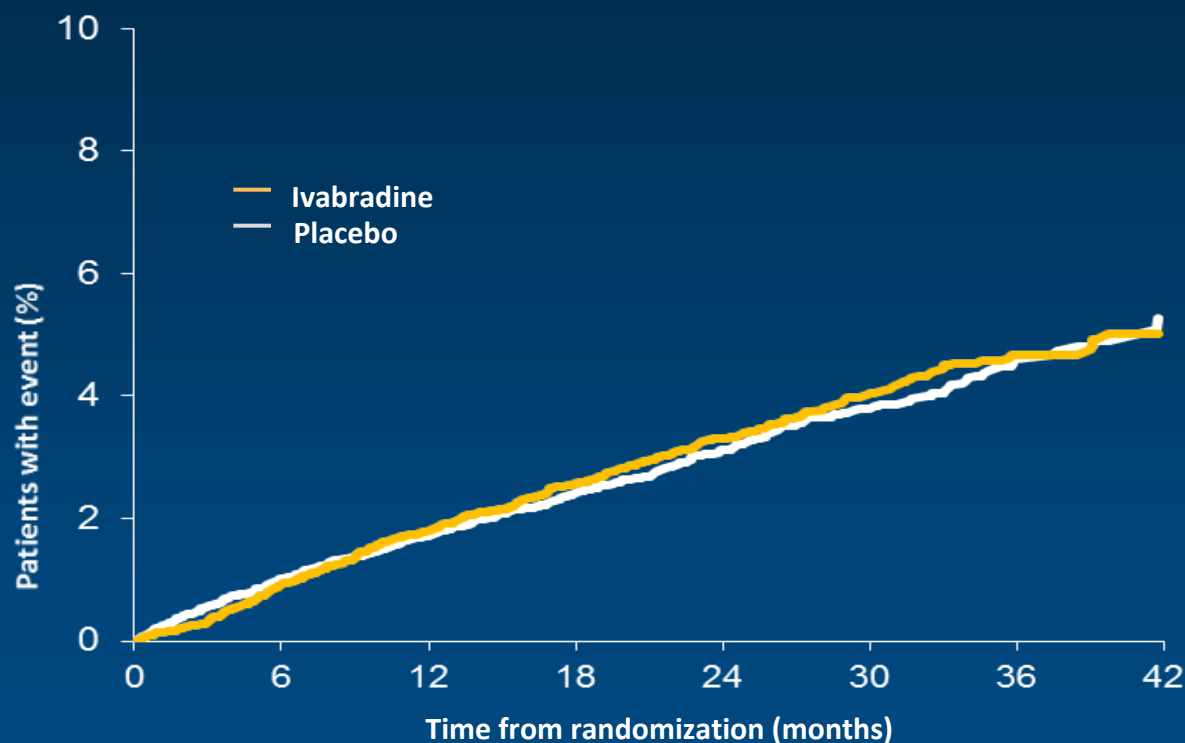
Numbers at risk

Ivabradine	9550	9382	9240	8828	5755	3926	1914	366
Placebo	9552	9405	9284	8851	5822	3882	1910	386

Nonfatal myocardial infarction

Ivabradine n=351 (1.63% PY) Placebo n=339 (1.56% PY)

HR = 1.04 [95% CI 0.90-1.21] $P=0.60$



Numbers at risk

Ivabradine	9550	9297	9078	8611	5570	3776	1832	349
Placebo	9552	9311	9130	8656	5649	3749	1836	365

Incidence of selected adverse events (n=19 083)

	Ivabradine (n=9539) % (n)	Placebo (n=9544) % (n)
Symptomatic bradycardia	7.9 (757)	1.2 (110)
Asymptomatic bradycardia	11.0 (1047)	1.3 (126)
Atrial fibrillation	5.3 (508)	3.8 (362)
Phosphenes	5.4 (512)	0.5 (52)

Incidence of selected adverse events (n=19 083)

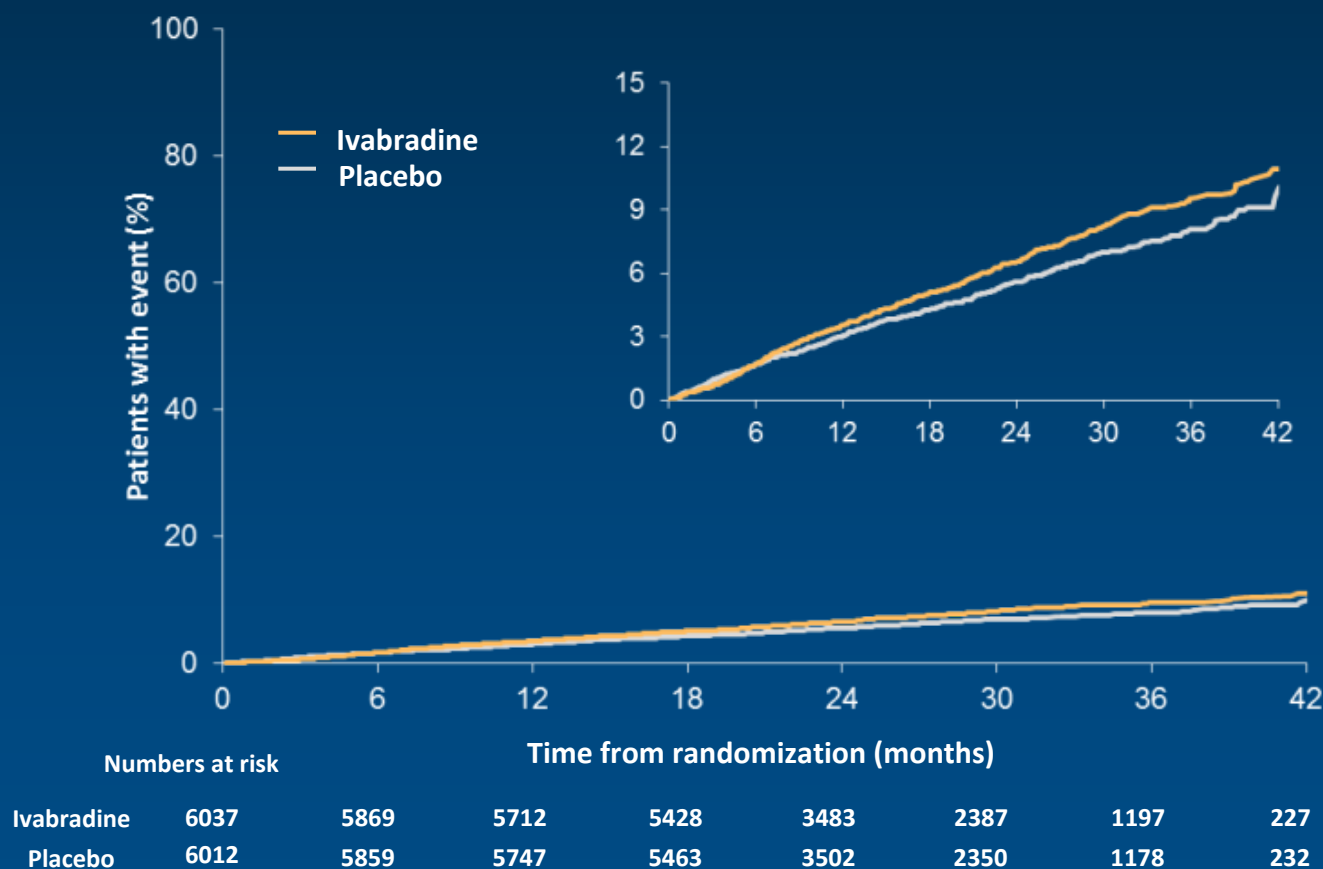
	Ivabradine (n=9539) % (n)	Placebo (n=9544) % (n)
Ventricular tachycardia	0.6 (54)	0.4 (41)
Ventricular fibrillation	0.3 (27)	0.3 (26)
Torsades de pointes	0 (1)	0 (3)

Primary composite end point (angina population: CCS class \geq II, n=12 049)

Ivabradine n=459 (3.37% PY)

Placebo n=390 (2.86% PY)

HR = 1.18 [95% CI 1.03-1.35] $P=0.018$



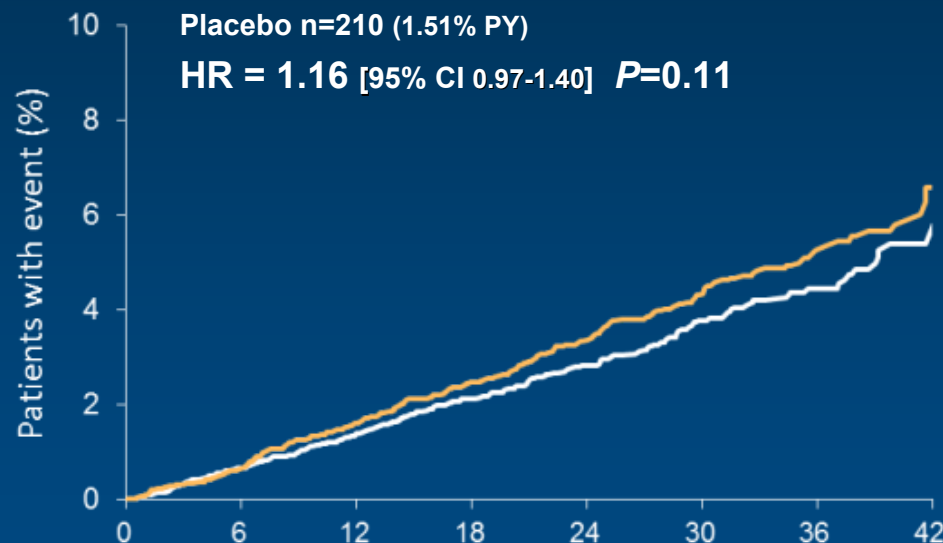
Components of primary composite end point (angina population: CCS class \geq II, n=12 049)

Cardiovascular death

Ivabradine n=245 (1.76% PY)

Placebo n=210 (1.51% PY)

HR = 1.16 [95% CI 0.97-1.40] $P=0.11$



Numbers at risk

Time from randomization (months)

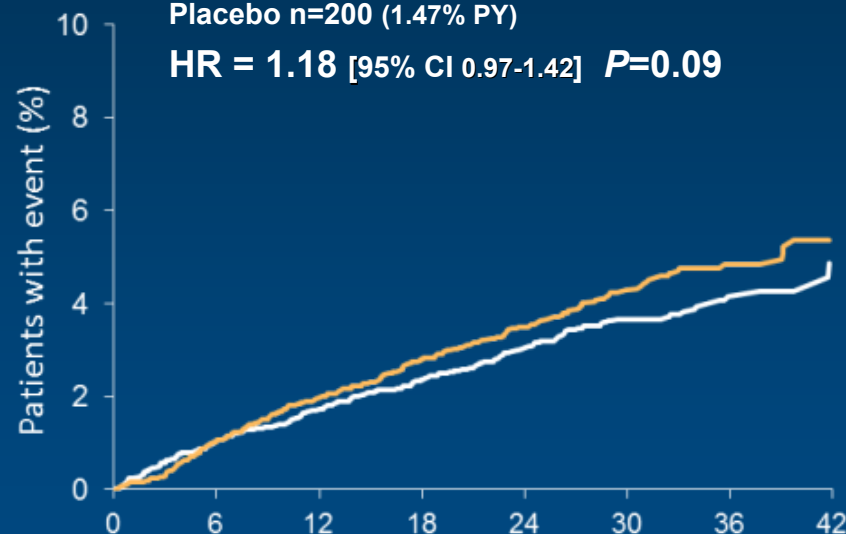
Ivabradine	6037	5930	5823	5574	3604	2483	1249	238
Placebo	6012	5919	5844	5583	3605	2434	1224	247

Nonfatal myocardial infarction

Ivabradine n=235 (1.72% PY)

Placebo n=200 (1.47% PY)

HR = 1.18 [95% CI 0.97-1.42] $P=0.09$



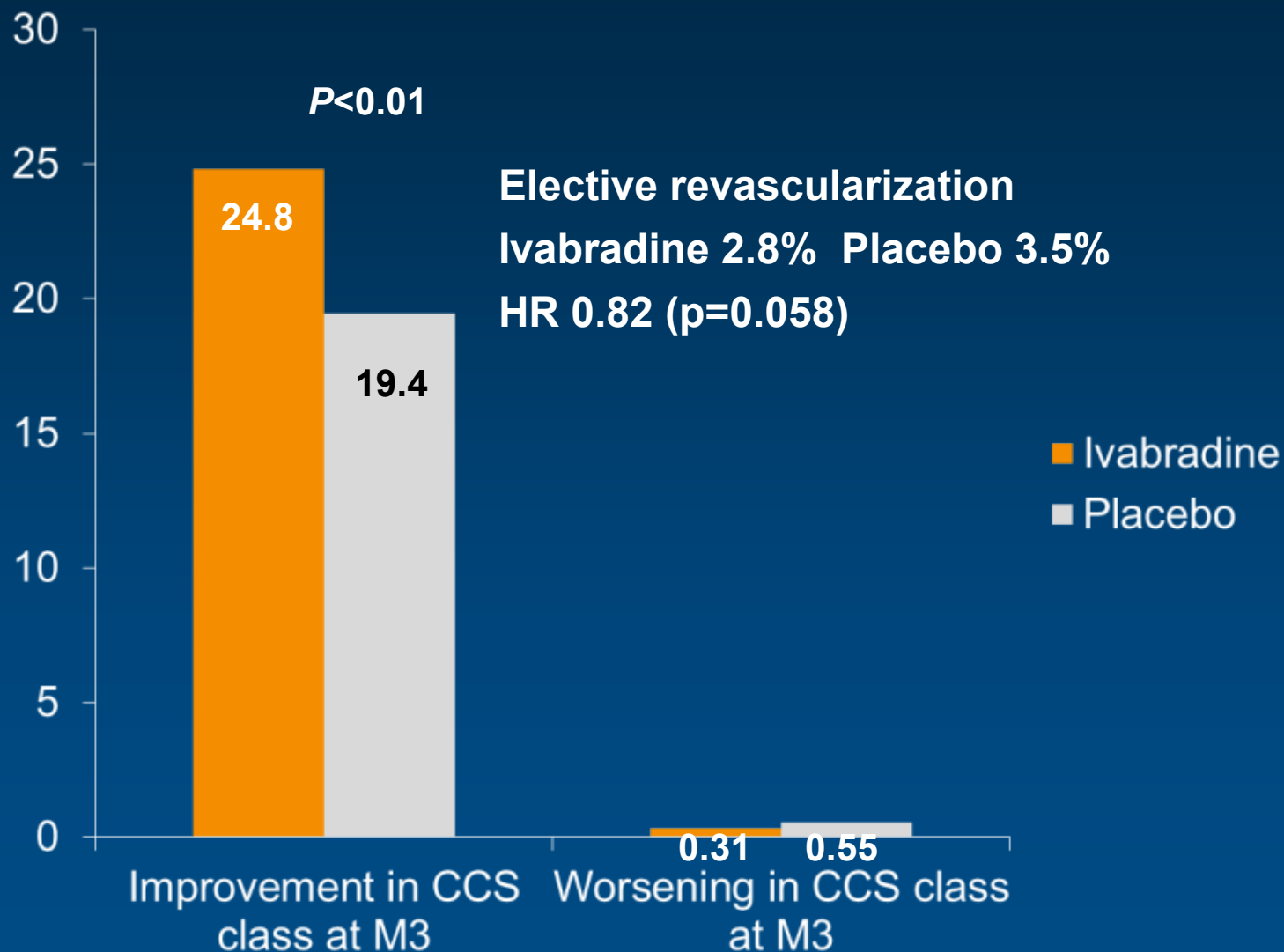
Time from randomization (months)

Ivabradine	6037	5869	5713	5428	3483	2387	1197	227
Placebo	6012	5859	5747	5463	3502	2350	1178	232

— Ivabradine — Placebo

Effect of ivabradine on symptoms (angina population: CCS class \geq II, n=12 049)

Patients (%)



Conclusion

- Lowering heart rate with ivabradine in CAD patients without clinical heart failure does not reduce the risk of CV death or nonfatal MI
- In the subgroup of patients with angina (CCS class \geq II), there appeared to be an increase in CV death or nonfatal MI
- In the same subgroup there appeared to be improvement in symptoms and need for elective coronary revascularization

- o **19 102** patients from **51** countries

- o **1139** centers

- o More than **5400** investigators

- o Study supported by



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ORIGINAL ARTICLE

Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure

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for the SIGNIFY Investigators*