Stable Angina
Emerging Pharmacotherapy

Waleed EL-Awady
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Zagazig University

- **A 70-year-old farmer with a 1 yr history of stable angina.**
- **He has decreased his work activity to avoid chest discomfort, for which he uses NG (0.4 mg sublingually) approximately 3 times per day.**
- **HR : 59 B/m ,**
- **BP is 130/70 mm Hg.**

- **He had UA 12 yrs earlier, and a DES was implanted in LAD; no other obstructive coronary artery disease was noted at that time.**
- **His medications include**

ASA, LAN, Valsartan (160 mg daily) for HTN, and atorvastatin (40 mg daily).

- **How should this case be evaluated and managed?**

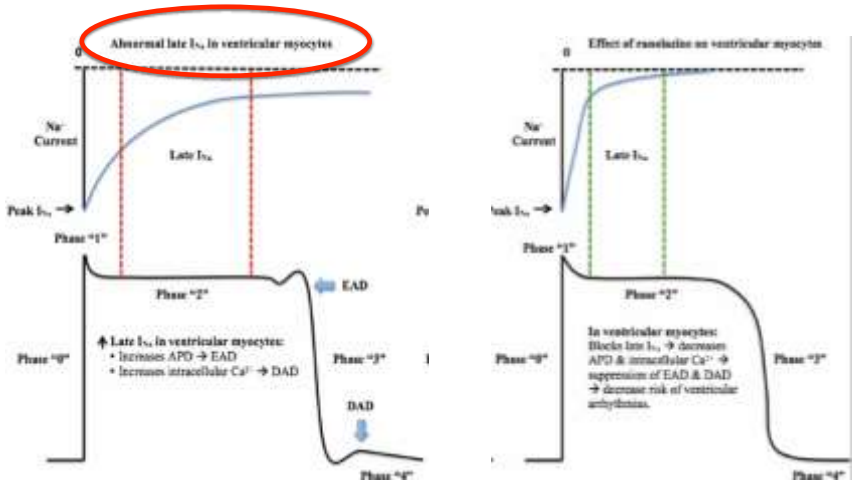
All standard antianginal therapies have a physiological effect (i.e., they affect HR or BP)

Three emerging therapies have a physiological effect and four that have a direct effect on myocardial metabolism.

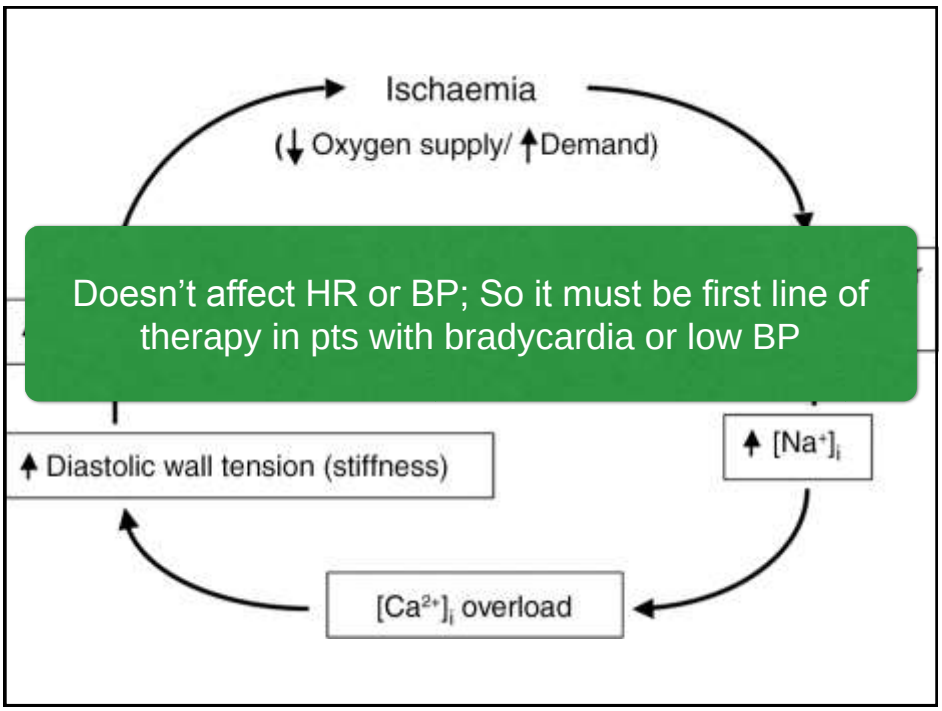
	Common side-effects	Contraindications	Potential drug-drug interactions
Physiological treatments			
Ivabradine	Visual disturbances, headache, dizziness, bradycardia, atrial fibrillation, atrioventricular block	Low heart rate or heart rhythm disorder, severe hepatic disease; not to be prescribed with verapamil and diltiazem; caution for use in patients with atrial fibrillation	QTc extending drugs, macrolide antibiotics, anti-HIV drugs, antifungal drugs
Nicorandil	Headache, facial flushing, dizziness and weakness, nausea, hypotension; oral, anal, or gastrointestinal ulceration	Cardiogenic shock, heart failure, low blood pressure (<100 mm/Hg systolic)	Phosphodiesterase type 5 inhibitors (eg, sildenafil or similar drugs)
Molsidomine	Headache, hypotension	None reported	None reported
Metabolic treatments			
Ranolazine	Dizziness, constipation, nausea	Liver cirrhosis, long QT	Cytochrome P450 3A4 substrates (digoxin, simvastatin, and ciclosporin); QTc extending drugs
Trimetazadine	Gastric discomfort, nausea, headache, movement disorders	Allergy, Parkinson's disease, tremors, movement disorders, severe renal impairment	None reported
Perhexiline	Dizziness, nausea, vomiting, lethargy, tremors	Slow hydroxylators of cytochrome P450, abnormal liver function, neuropathy	Cytochrome P450 substrates
Allopurinol	Rash, gastric discomfort	Hypersensitivity, renal failure	Mercaptopurine, azathioprine

Ranolazine

Ranolazine



Ranolazine blocks late I Na , causing decrease in APD and intracellular Ca 2 + with suppression of EAD and DAD and resulting in decrease risk of ventricular arrhythmias.



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CLINICAL RESEARCH Late-Breaking Clinical Trials

Evaluation of Ranolazine in Patients With Type 2 Diabetes Mellitus and Chronic Stable Angina

Results From the TERISA Randomized Clinical Trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina)

Mikhail Kosiborod, MD,*† Suzanne V. Arnold, MD, MHA,*† John A. Spertus, MD, MPH,*† Darren K. McGuire, MD, MHSC,‡ Yan Li, PHD,* Patrick Yue, MD,§ Ori Ben-Yehuda, MD,§ Amos Katz, MD,‖ Philip G. Jones, MS,* Ann Olmsted, PHD,§ Luiz Belardinelli, MD,§ Bernard R. Chaitman, MD¶

Kansas City and St. Louis, Missouri; Dallas, Texas; Foster City, California; and Ashkelon, Israel

CLINICAL RESEARCH Late-Breaking Clinical Trials

Evaluation of Ranolazine in Patients With Type 2 Diabetes Mellitus and Chronic Stable Angina

Results From the TERISA Randomized Clinical Trial (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina)

Examine the efficacy of Ranolazine Vs placebo on weekly angina frequency and SL NG use in Pts

- T2DM
- CAD
- Chronic stable angina

who remain symptomatic despite treatment with up to 2 antianginal agents.

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TERISA; Study Endpoint

- Primary : Average weekly number of angina from weeks 2 to 8 of treatment
- Key Secondary: Average weekly number of SL NTG doses from weeks 2-8 of treatment

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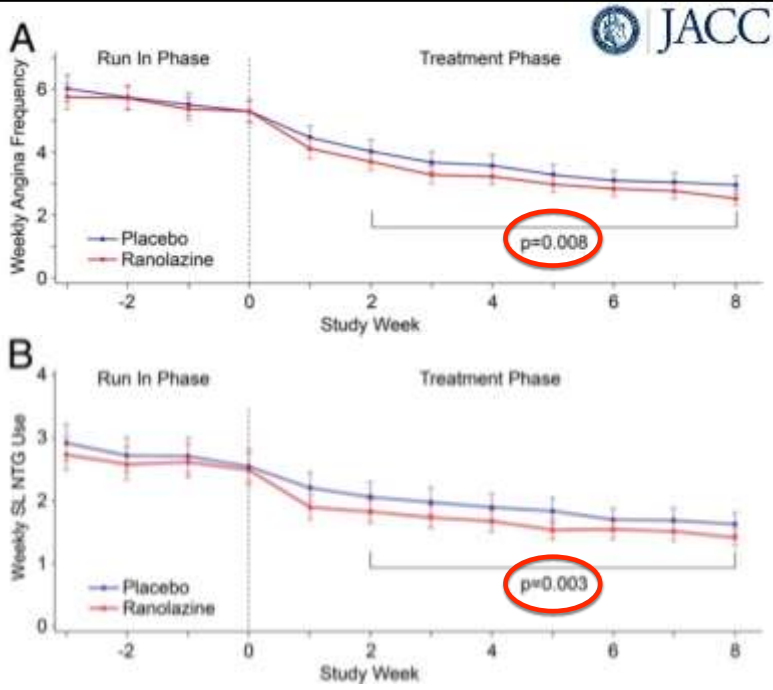

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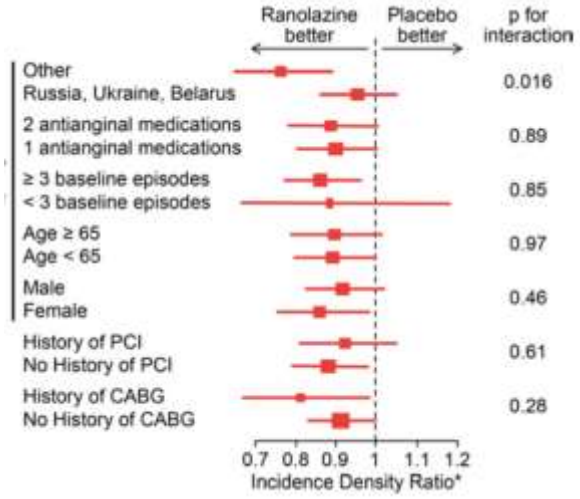
Subgroup Analyses of the Primary End Point of Weekly Angina Frequency



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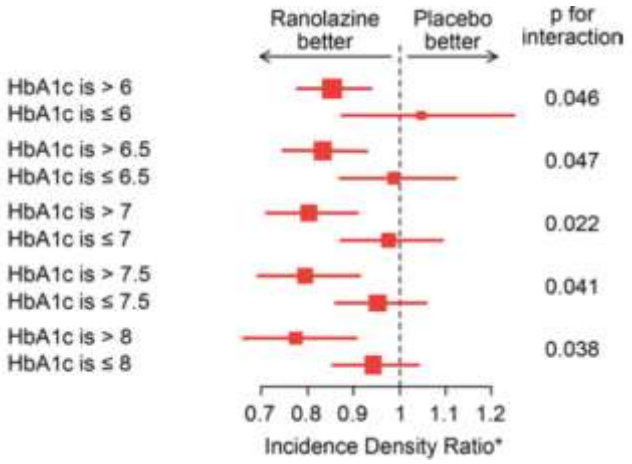
Exploratory Analysis-HBA1C



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Safety Endpoints

Safety endpoints*	n = 470	n = 474	
Serious adverse events			
Serious adverse event	16 (3.4)	20 (4.2)	0.51
Death	3 (0.6)	2 (0.4)	0.69
Nonfatal myocardial infarction	1 (0.2)	3 (0.6)	0.62
Stroke/transient ischemic attack	1 (0.2)	4 (0.8)	0.37
Unstable angina or coronary revascularization	6 (1.3)	7 (1.5)	0.79
Notable nonserious adverse events			
Dizziness	17 (3.6)	6 (1.3)	0.019
Nausea	17 (3.6)	2 (0.4)	<0.001
Headache	7 (1.5)	9 (1.9)	0.63
Constipation	8 (1.7)	2 (0.4)	0.063
Hypoglycemia	3 (0.6)	0 (0.0)	0.12
Any adverse event	126 (26.8)	105 (22.2)	0.096

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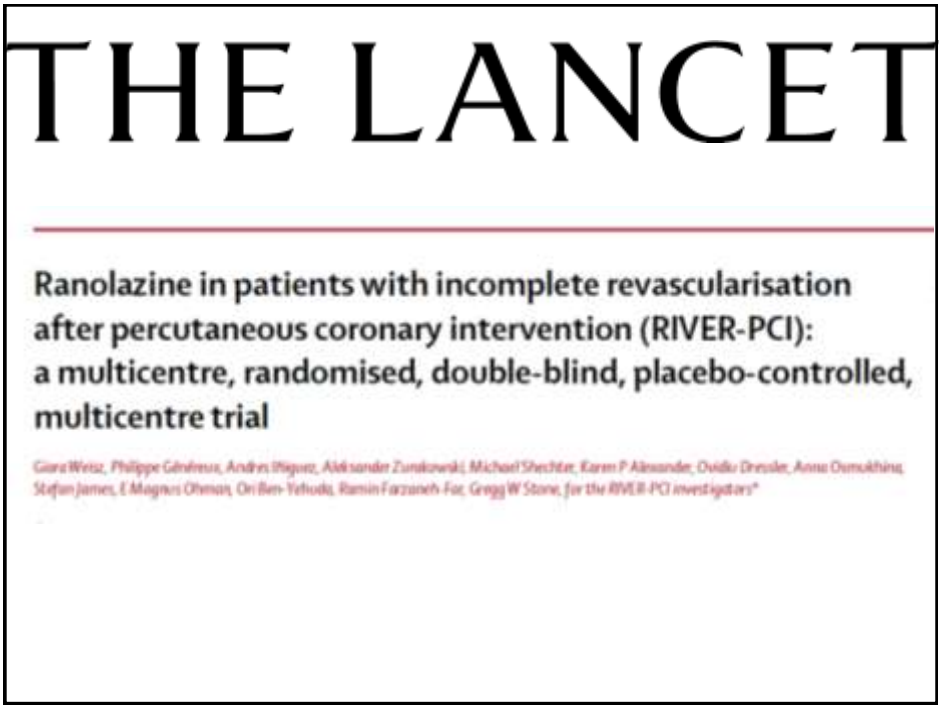
TERISA; Conclusion

- Ranolazine was more effective than placebo in reducing angina frequency and SL NTG use in pts with type 2 DM, CAD and chronic angina
- The therapeutic effectiveness of Ranolazine was more pronounced in
  - In those with higher baseline HbA1c
- Future studies are needed to explore potential dual effects of ranolazine on angina and glucose control in patients with T2DM



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RIVER-PCI; Background

- Incomplete revascularization (ICR) is common, present in 17-85% of patients following PCI
- ICR has been strongly associated with increased rates of repeat hospitalization, repeat revascularization, and mortality

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RIVER-PCI; Primary Objective

To evaluate the efficacy of

Ranolazine Vs placebo

as part of standard medical therapy in:

chronic angina and incomplete revascularization post-PCI

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RIVER-PCI; Primary Endpoint

Time to first Ischemia-Driven

-Revascularization or
-Hospitalization without revascularization

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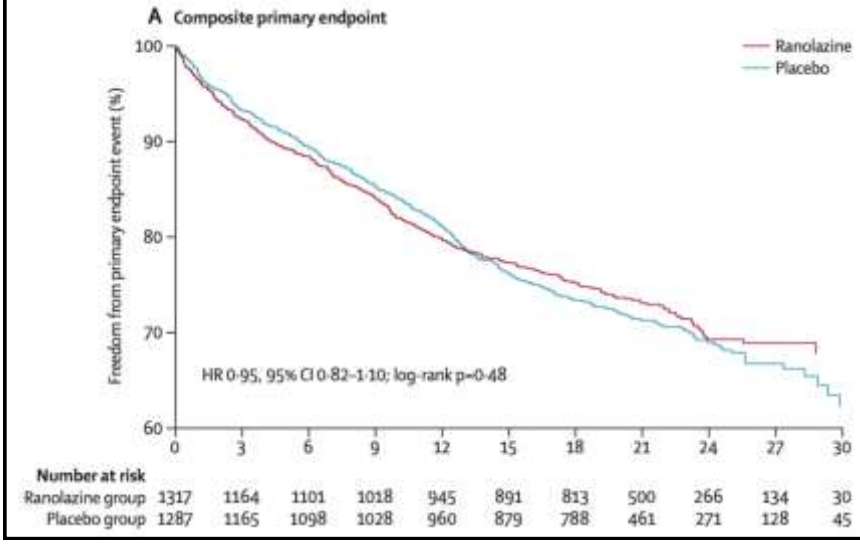
RIVER-PCI; Primary Endpoint



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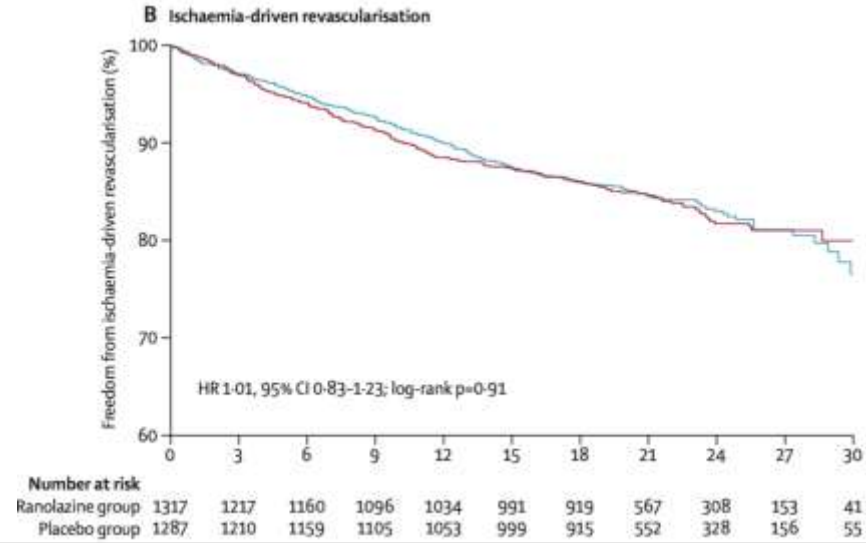
RIVER-PCI; Primary Endpoint



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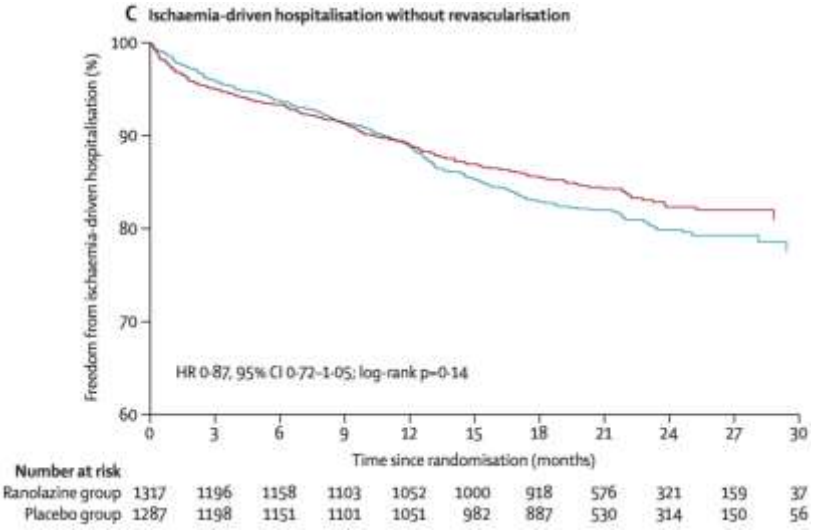
RIVER-PCI; Primary Endpoint



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RIVER-PCI; Conclusion

Ranolazine did not reduce the composite rate of ischemia-driven revascularization or hospitalization in pts with chronic angina and incomplete revascularization post-PCI

No differences in the secondary endpoints of SCD , CV death or MI

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RIVER-PCI; Limitation

- Anti-anginal medication use (other than ranolazine) was left to local standards, and most patients were on one or two additional anti-ischemia agents
- There was high rate of study drug discontinuation and the median duration of ranolazine use was shorter, which may have biased the results toward the null

Use of Anti-Ischemic Medications (cont.)

Ranolazine can be useful when prescribed as a substitute for BB for relief of symptoms in pts with SIHD if initial treatment with BB leads to unacceptable side effects or is ineffective or if initial treatment with BB is contraindicated.

Ranolazine in combination with BB can be useful when prescribed for relief of symptoms when initial treatment with BB is not successful in patients with SIHD.

Ivabradine

Selective HR–lowering (physiological) agent that inhibits the If current in the pacemaker cells in SA node.

Approved in HF to prevent hospitalization in pts who have an increased HR despite adequate BB therapy.

It has also been reported to be effective in improving TED in pts with chronic angina who are not receiving background therapy.

Ivabradine

	Background treatment	N	Study type	Dose; frequency	Total exercise duration	Self-reported angina frequency
Ivabradine						
Borer et al (2003)[19]	None	360	Dose escalation	2·5 mg, 5 mg, 10 mg; all bid	Increased 10 mg only	No reduction
Tardif et al (2005)[20]	None	939	Non-inferiority	7·5 mg, 10 mg; all bid	Non-inferior to atenolol	Similar to atenolol
Ruzyllo et al (2007)[21]	None	1195	Non-inferiority	7·5 mg, 10 mg; all bid	Non-inferior to amlodipine	Similar to amlodipine
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Nicorandil						
Hayata et al (1986)[23]	None	11	Superiority	20 mg; once per day	Increased; similar to NTG	Not reported
Meany et al (1989)[24]	None	46	Dose titration	10 mg, 20 mg; all bid	Increased	Not reported
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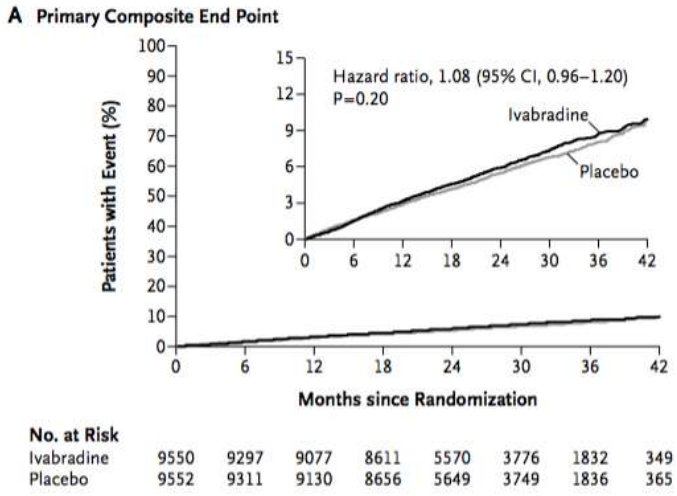
Doring (1992)[26]	LAN	129	Superiority	10 mg tid; 20 mg bid	Increased; superior to LAN	Similar to LAN
Rajaratnam et al (1999)[27]	None	24	Superiority	10 mg, 20 mg; all bid	Increased	Not reported

The NEW ENGLAND JOURNAL of MEDICINE

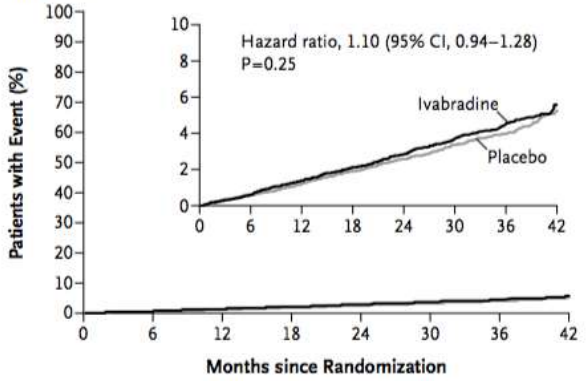
ESTABLISHED IN 1812 SEPTEMBER 18, 2014 VOL. 371 NO. 12

Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure

Kim Fox, M.D., Ian Ford, Ph.D., Philippe Gabriel Steg, M.D., Jean-Claude Tardif, M.D., Michal Tendera, M.D., and Roberto Ferrari, M.D., for the SIGNIFY Investigators*

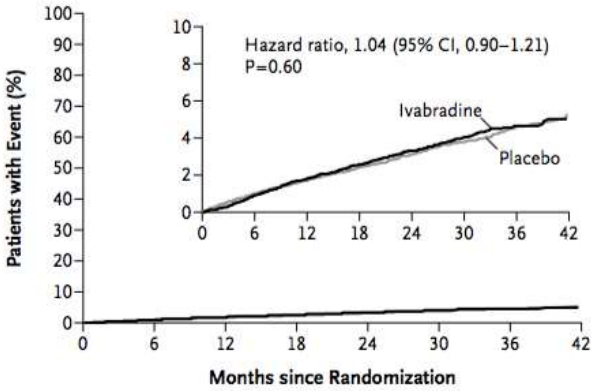


B Death from Cardiovascular Causes

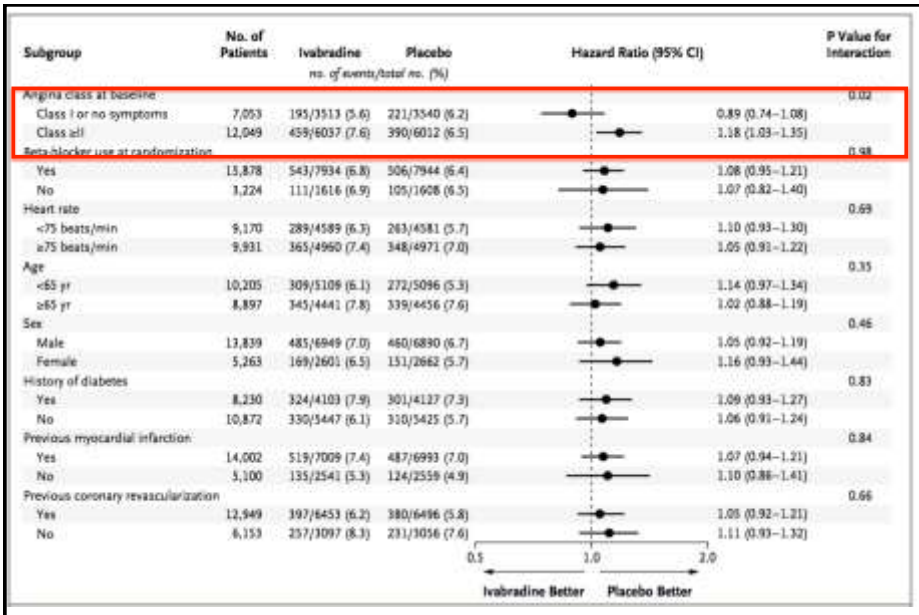


No. at Risk								
Ivabradine	9550	9382	9240	8828	5755	3926	1914	366
Placebo	9552	9405	9284	8851	5822	3882	1910	386

C Nonfatal Myocardial Infarction



No. at Risk								
Ivabradine	9550	9297	9078	8611	5570	3776	1832	349
Placebo	9552	9311	9130	8656	5649	3749	1836	365



Subgroup	No. of Patients	Ivabradine	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
		no. of events/total no. (%)			
Angina class at baseline					0.02
Class I or no symptoms	7,053	195/3513 (5.6)	221/3540 (6.2)	0.89 (0.74–1.08)	
Class ≥II	12,049	459/6037 (7.6)	390/6012 (6.5)	1.18 (1.03–1.35)	
Beta-blocker use at randomization					0.98
Yes	13,878	543/7934 (6.8)	506/7944 (6.4)	1.08 (0.95–1.21)	
No	3,224	111/1616 (6.9)	105/1608 (6.5)	1.07 (0.82–1.40)	
Heart rate					0.69
<75 beats/min	9,170	289/4589 (6.3)	263/4581 (5.7)	1.10 (0.93–1.30)	
≥75 beats/min	9,931	365/4960 (7.4)	348/4971 (7.0)	1.05 (0.91–1.22)	
Age					0.35
<65 yr	10,205	309/5109 (6.1)	272/5096 (5.3)	1.14 (0.97–1.34)	
≥65 yr	8,897	345/4441 (7.8)	339/4456 (7.6)	1.02 (0.88–1.19)	
Sex					0.46
Male	13,839	485/6949 (7.0)	460/6890 (6.7)	1.05 (0.92–1.19)	
Female	5,263	169/2601 (6.5)	151/2662 (5.7)	1.16 (0.93–1.44)	
History of diabetes					0.83
Yes	8,230	324/4103 (7.9)	301/4127 (7.3)	1.09 (0.93–1.27)	
No	10,872	330/5447 (6.1)	310/5425 (5.7)	1.06 (0.91–1.24)	
Previous myocardial infarction					0.84
Yes	14,002	519/7009 (7.4)	487/6993 (7.0)	1.07 (0.94–1.21)	
No	5,100	135/2541 (5.3)	124/2559 (4.9)	1.10 (0.86–1.41)	
Previous coronary revascularization					0.66
Yes	12,949	397/6453 (6.2)	380/6496 (5.8)	1.05 (0.92–1.21)	
No	6,153	257/3097 (8.3)	231/3056 (7.6)	1.11 (0.93–1.32)	

the rates of death and nonfatal MI were higher among pts who received ivabradine than among those who received placebo (7.6% vs. 6.5%, P = 0.02).

Although no clear explanation was provided for these findings, ivabradine should not be used to treat angina in the absence of heart failure

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Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure

0.96 to 1.20; P=0.20), nor were there significant differences in the incidences of death from cardiovascular causes and nonfatal myocardial infarction. Ivabradine was associated with an increase in the incidence of the primary end point among patients with activity-limiting angina but not among those without activity-limiting angina (P=0.02 for interaction). The incidence of bradycardia was higher with ivabradine than with placebo (18.0% vs. 2.3%, P<0.001).

CONCLUSIONS

Among patients who had stable coronary artery disease without clinical heart failure, the addition of ivabradine to standard background therapy to reduce the heart rate did not improve outcomes. (Funded by Servier; SIGNIFY Current Controlled Trials number, ISRCTN61576291.)

Allopurinol

Xanthine oxidase inhibitor used to prevent gout

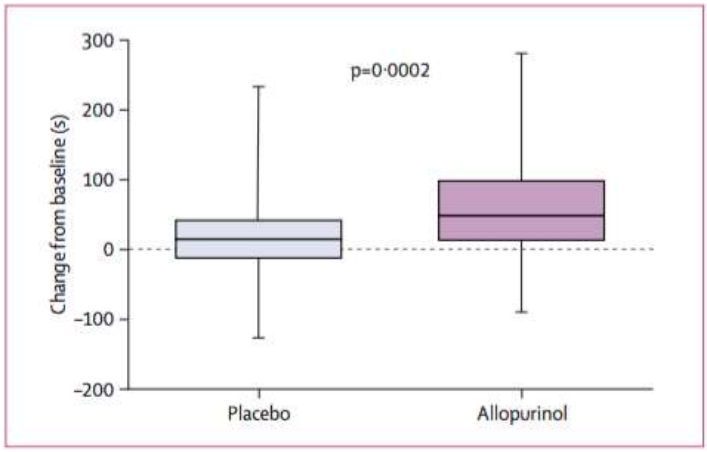
Proposed as an antianginal metabolic agent.

Potential mechanisms include:

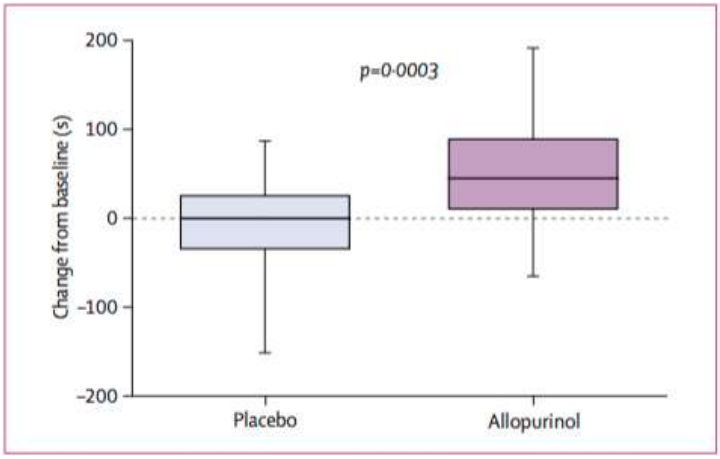
-Decreased myocardial O_2 Demand

-Improved vascular endothelial function

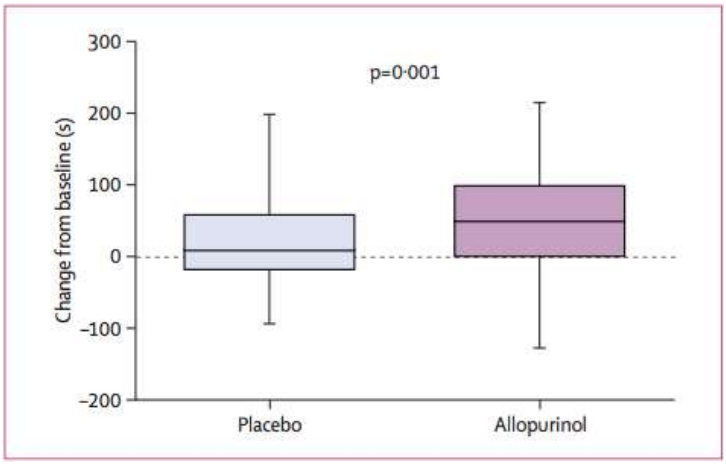
Change in total exercise time from baseline



Change in time to ST depression from baseline



Change in time to chest pain from baseline



THE LANCET

Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial

Awsan Noman, Donald S C Ang, Simon Ogston, Chim C Lang, Allan D Struthers

increased it to 307 s (232–430; p=0·0003); the point estimate was 58 s (95% CI 45–77). Allopurinol increased the time to chest pain from a baseline of 234 s (IQR 189–382) to 304 s (222–421), and placebo increased it to 272 s (200–380; p=0·001); the point estimate was 38 s (95% CI 17–55). No adverse effects of treatment were reported.

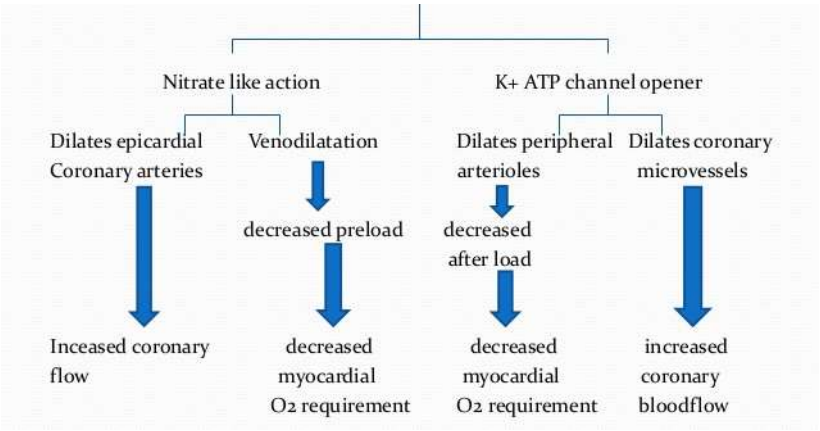
Interpretation Allopurinol seems to be a useful, inexpensive, well tolerated, and safe anti-ischaemic drug for patients with angina.

Funding British Heart Foundation.

Because of limited clinical data

US guidelines do not recommend allopurinol for the treatment of angina, but it is recommended in the European guidelines.

Nicorandil



Nicorandil; 5 Small RCTs

	Background treatment	N	Study type	Dose; frequency	Total exercise duration	Self-reported angina frequency
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Borer et al (2003)[19]	None	360	Dose escalation	2·5 mg, 5 mg, 10 mg; all bid	Increased 10 mg only	No reduction
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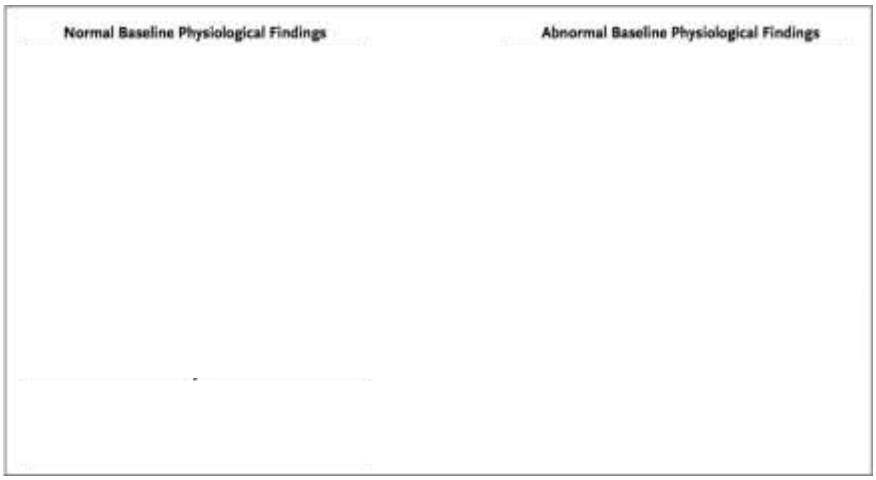
Nicorandil

The Canadian Cardiovascular Society's class distribution was similar in both groups (nicorandil and placebo) and there were no reported reductions in angina.

Nicorandil might be an option for pts who cannot tolerate standard anti-angina drugs, but its use is limited by a paucity of data about its anti-angina effect and a large withdrawal by pts because of headache.



Conclusion

- Many treatments have been used to reduce the effects of ischaemia on the myocardium with a reduction in angina.
- We propose a possible framework for an individualised approach with standard and emerging treatments.
- Studies of the experimental drugs have been few, so knowledge about long-term safety and efficacy is scarce.
- With population Aging in which medical treatment tends to be a mainstay to reduce angina, a greater number of and better therapies than those available are urgently needed.

Thank You