Chronic iscemic heart disease
What is new in treatment

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Alp Aydınalp

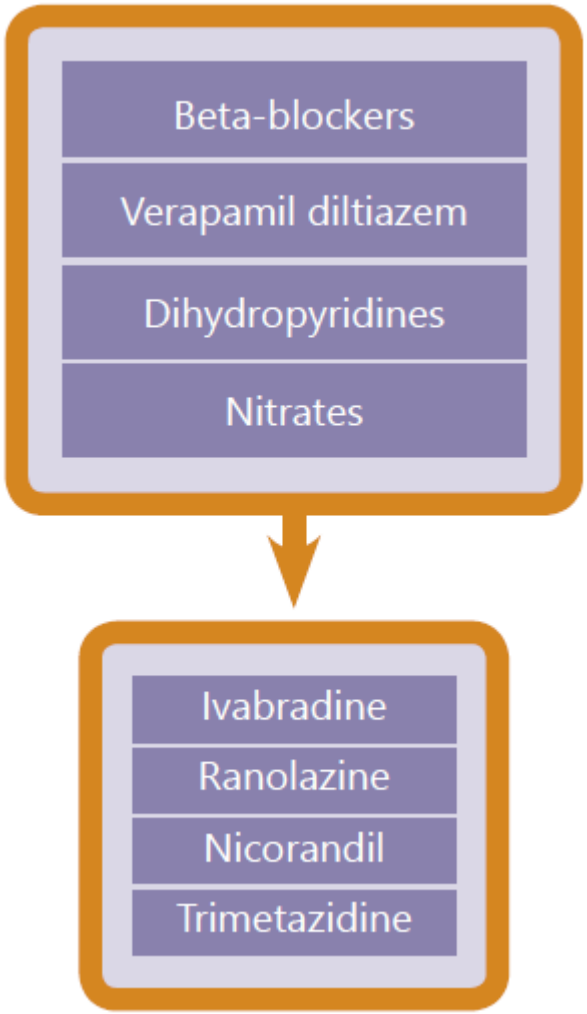
Many of these patients are not candidates for revascularization

- Unsuitable anatomy, such as diffuse coronary disease.
- One or several prior PCIs or CABGs, which may limit further benefit or preclude further revascularization.
- Lack of vascular conduits for CABG.
- Severely impaired left ventricular function in patients with previous CABG or PCI
- Concurrent diseases that increase perioperative or postoperative morbidity or mortality (eg, cerebrovascular disease, advanced complications of diabetes, chronic kidney disease)
- Age, often in combination with other factors.

Newer therapies

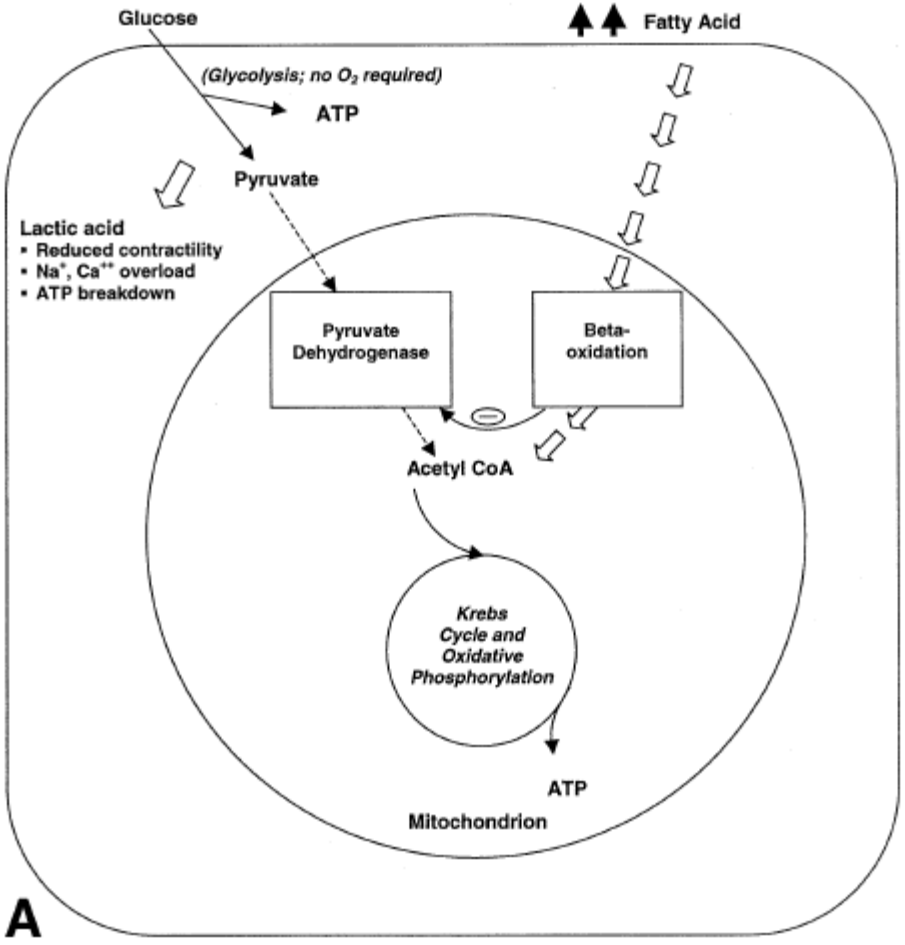
- Medical Therapies
- Mechanical Therapies

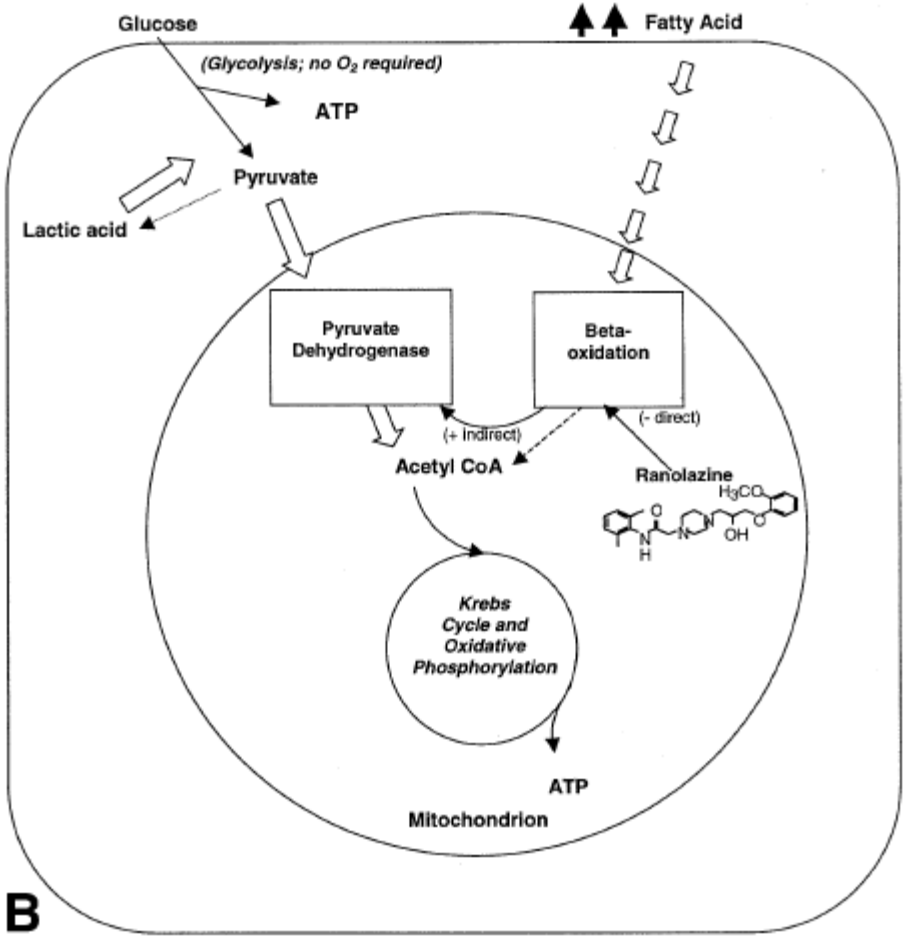
Medical Therapies



Inhibition of fatty acid oxidation

- Switching from fatty acid oxidation to glucose oxidation increases cardiac metabolic efficiency
- Three such agents are ranolazine, trimetazidine, and perhexiline
- Although the heart uses both glucose and fatty acids as fuel, during periods of stress the heart uses more fatty acids, which is less oxygen efficient


Glucose
Fatty Acid
(Glycolysis; no O_2 required)
ATP
Pyruvate
Lactic acid
• Reduced contractility
• Na^+, Ca^{++} overload
• ATP breakdown
Pyruvate Dehydrogenase
Beta-oxidation
Acetyl CoA
Krebs Cycle and Oxidative Phosphorylation
ATP
Mitochondrion
A



However, ranolazine is discussed separately because inhibition of fatty acid oxidation may not be its primary mode of action.

Ranolazine

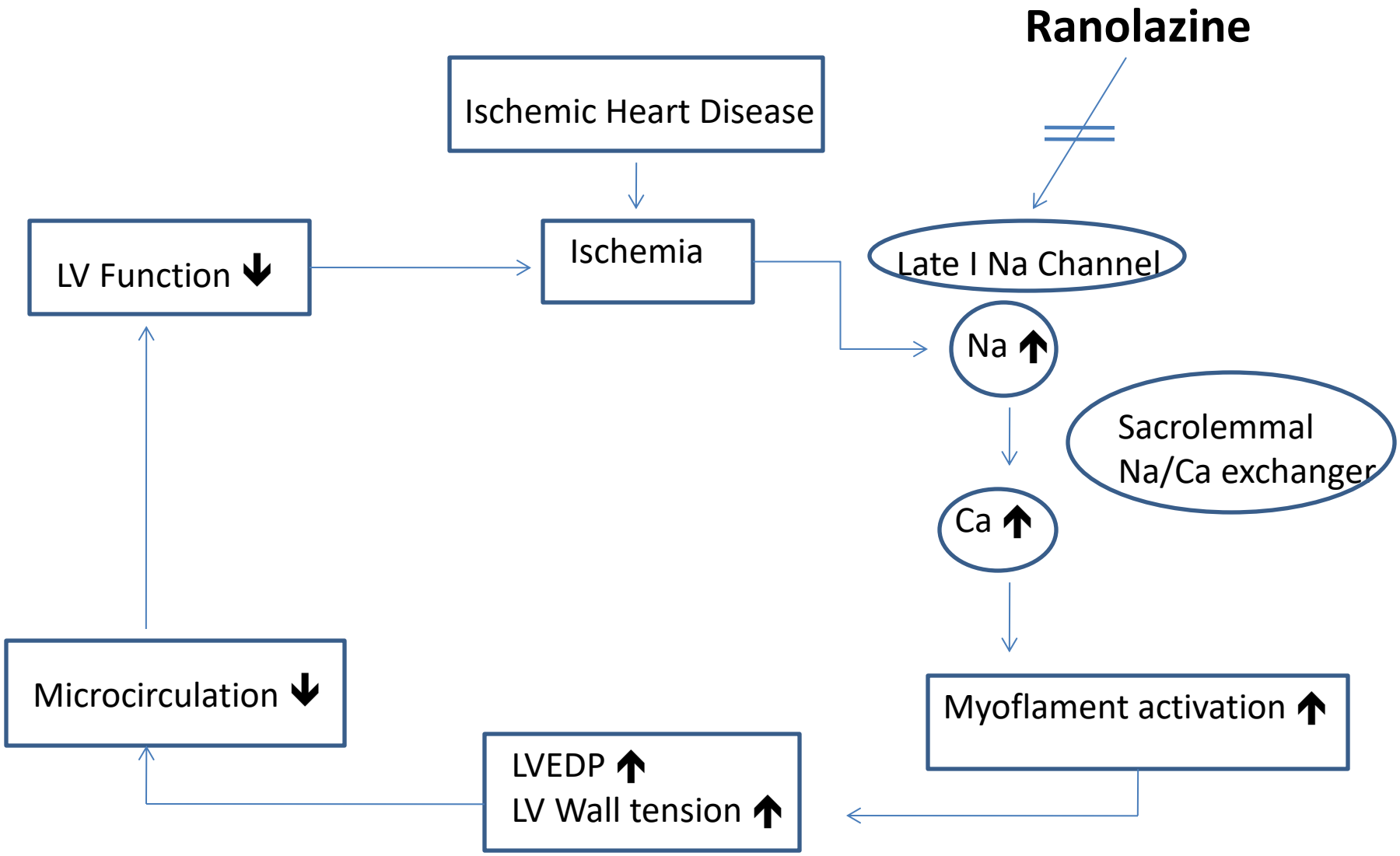
- Ranolazine was approved by the United States Food and Drug Administration (FDA) in 2006 for management of chronic stable angina.
- Although initially thought to act by partial inhibition of fatty acid oxidation, it was later realized that ranolazine had that effect only at serum levels not achieved with the usual dosing.
- A more important mechanism for ranolazine may be the prevention of both calcium overload and the subsequent increase in diastolic tension due to inhibition of late inward sodium channel .
- Since this sodium channel frequently fails to inactivate in a number of important myocardial disease states such as ischemia and hypertrophy, excess entry of sodium ions leads to activation of the sodium/calcium exchanger, thereby raising calcium concentration .

Ranolazine

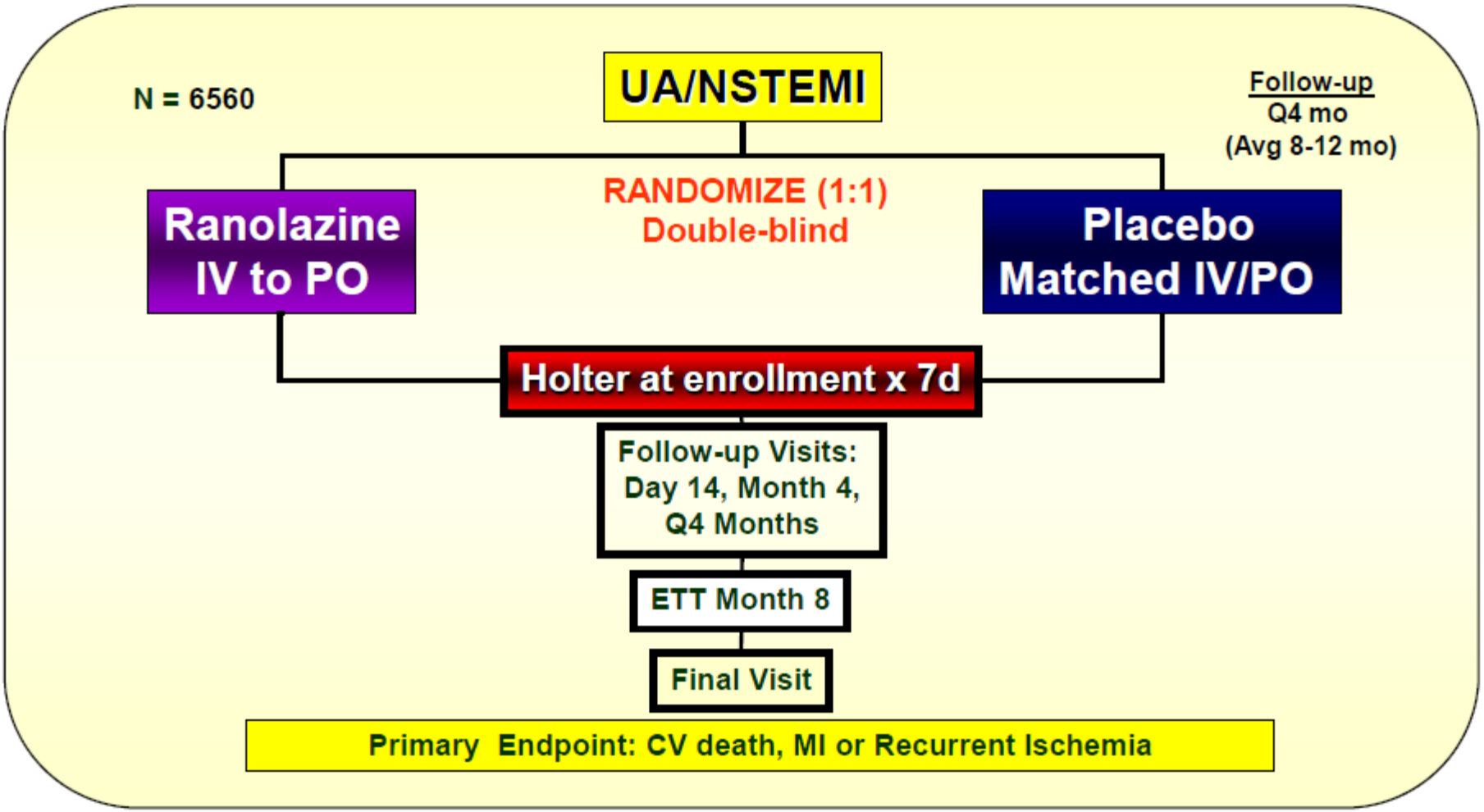
- Given the normal rapid inaction of the late inward sodium channel in normal myocytes, the drug does not exert a significant effect on the normal myocardium at usual dosages.

- This potentially increases its therapeutic window.

- The initial dose of ranolazine is 500 mg twice daily. For patients who remain symptomatic, 1000 mg twice daily may be used.


Ranolazine
Ischemic Heart Disease
LV Function ↓
Ischemia
Late I Na Channel
Na ↑
Sacrolemmal
Na/Ca exchanger
Ca ↑
Microcirculation ↓
Myoflament activation ↑
LVEDP ↑
LV Wall tension ↑

Ranolazine- ACS



Ranolazine- ACS

MERLIN TIMI 36

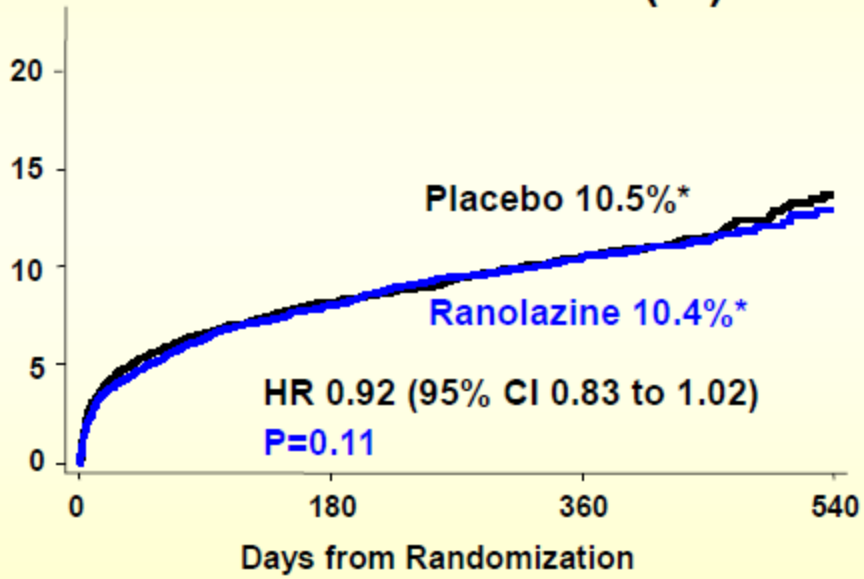
MERLIN – TIMI 36 *Primary Results*

Primary Endpoint - CV Death, MI, or Recurrent Ischemia

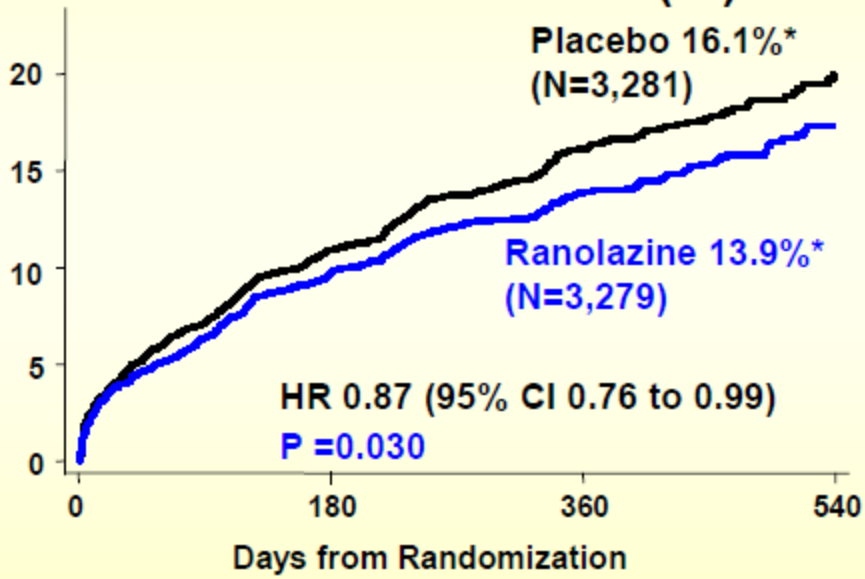
21.8% for Ranolazine vs. 23.5% for Placebo

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

Ranolazine-Stable angina- MARISA

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 43, No. 8, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2003.11.045

Coronary Artery Disease

Anti-Ischemic Effects and Long-Term Survival During Ranolazine Monotherapy in Patients With Chronic Severe Angina

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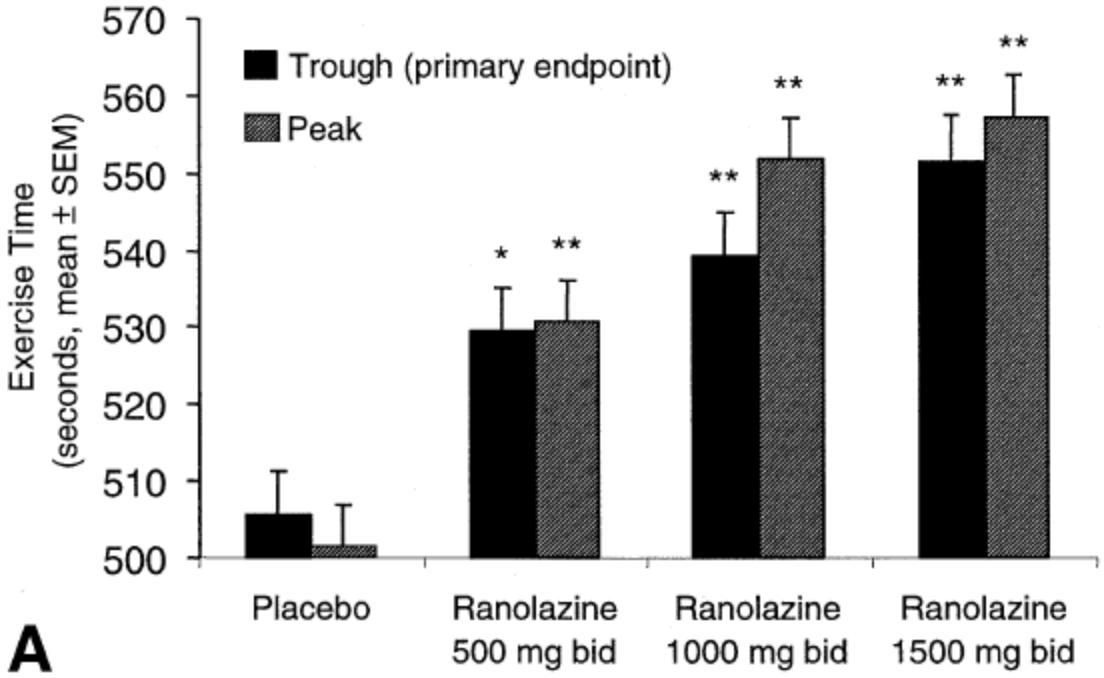
Peter Hanley, MD, FACC,§ Jaroslav Meluzin, MD, PHD,‖ Jerzy Kuch, MD, PHD,¶
Carl J. Pepine, MD, FACC,# Whedy Wang, PHD,† Jeanenne J. Nelson, PHD,** David A. Hebert, PHD,**
Andrew A. Wolff, MD, FACC,† for the MARISA Investigators

St. Louis, Missouri; Palo Alto, California; Kingston, Canada; Warsaw, Poland; Gainesville, Florida; and Research Triang

*In the MARISA trial, ranolazine monotherapy resulted in a dose-dependent increase in pain-free exercise duration and time to angina in 191 patients

*1000 mg twice daily dose being more effective than a lower dose.



Ranolazine-Stable angina- CARISA

Effects of ranolazine on exercise tolerance and angina frequency in patients with severe chronic angina receiving maximally-tolerated background therapy: analysis from the Combination Assessment of Ranolazine In Stable Angina (CARISA) randomized trial

José López Sendón, Stella Lee, Mei L Cheng and Ori Ben-Yehuda (for the CARISA study investigators)

European Journal of Preventive Cardiology
19(5) 952–959

DOI: 10.1177/2047487312450133
ejpc.sagepub.com
SAGE

Received 22 November 2011; accepted 9 May 2012

After 12 weeks of therapy, both doses of ranolazine significantly increased symptom-limited exercise duration, time to onset of angina, and (at peak ranolazine blood level) time to ST segment depression, and reduced angina frequency by 0.8 and 1.2 episodes per week, compared to placebo.

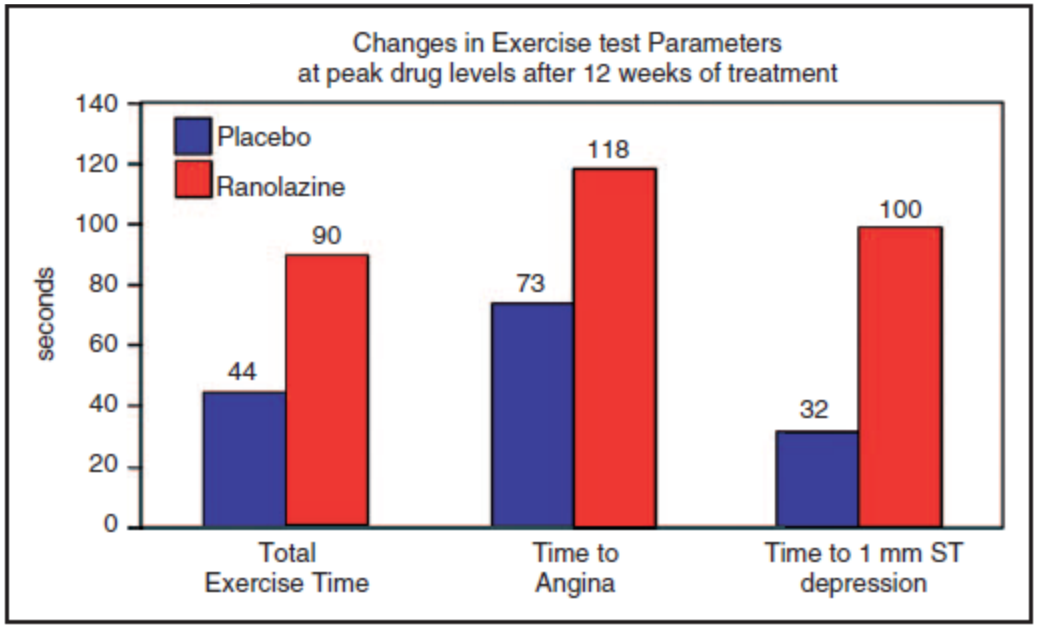


Figure 1. Changes from baseline in total exercise duration (in sec), time to angina onset, and time to 1 mm ST segment depression at peak drug levels after 12 weeks of treatment with placebo or ranolazine (750 or 1000 mg) twice daily.

Ranolazine-Stable angina-ERICA

Journal of the American College of Cardiology
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 48, No. 3, 2006
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.05.044

EXPEDITED REVIEWS

Antianginal Efficacy of Ranolazine When Added to Treatment With Amlodipine

The ERICA (Efficacy of Ranolazine in Chronic Angina) Trial

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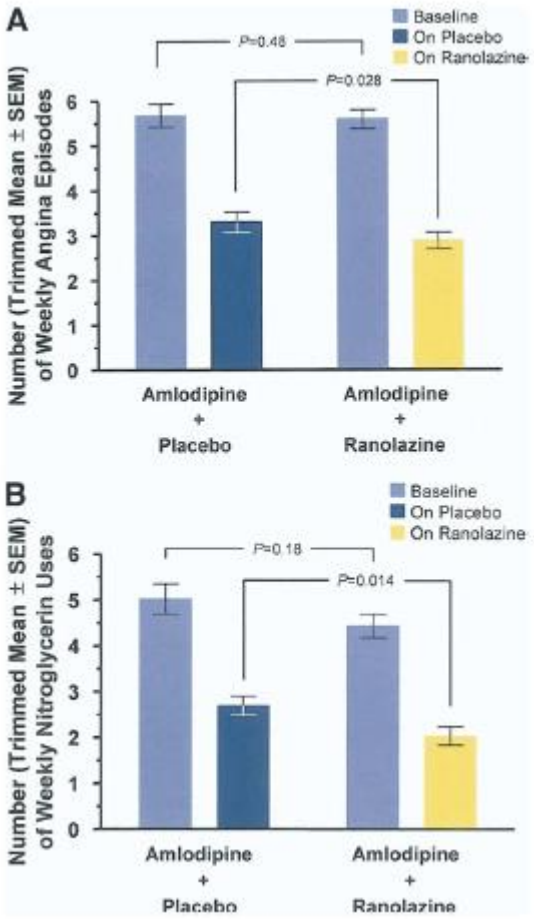
Boston, Massachusetts; Moscow, Russia; and Palo Alto, California

●In the ERICA trial, 565 stable patients with more than three anginal attacks per week were randomly assigned to either ranolazine (1000 mg/day) or placebo [9].

•All patients were taking 10 mg of amlodipine per day and were allowed to be on long-acting nitrates but not beta blockers; the patients had 5.63 episodes of angina per week at baseline.

•Ranolazine significantly improved the primary end point of anginal episodes per week compared to placebo (2.88 versus 3.31).



Ranolazine-Stable angina-TERISA

Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 20, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.02.011

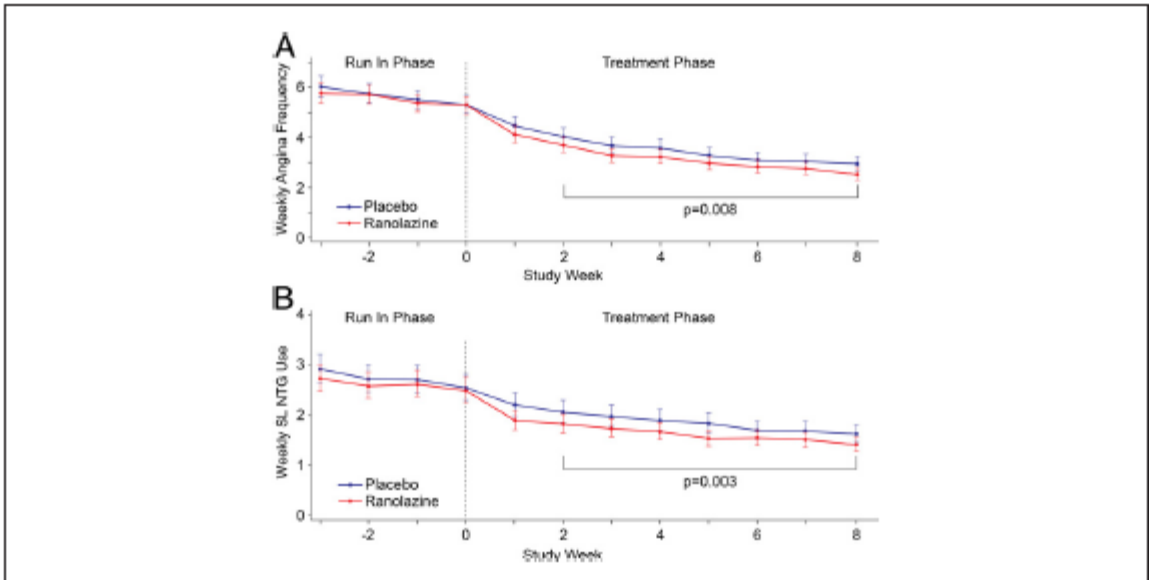
CLINICAL RESEARCH — Late-Breaking Clinical Trials

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



*In the TERISA trial, 949 patients with diabetes and stable angina treated with one to two antianginal drugs were randomly assigned to ranolazine or placebo for eight weeks .

•Weekly angina frequency was lower with ranolazine (3.8 versus 4.3 episodes; p = 0.008) as was weekly sublingual nitroglycerin use (1.7 versus 2.1 doses; p = 0.003).

• Although statistically significant and in agreement with findings in other ranolazine studies, the absolute effects of ranolazine in this study are modest.

Ranolazine-Incomplete Revasc-RIVER-PCI

Ranolazine in patients with incomplete revascularisation after percutaneous coronary intervention (RIVER-PCI): a multicentre, randomised, double-blind, placebo-controlled trial

Lancet 2016; 387: 136–45
Published Online
October 13, 2015
http://dx.doi.org/10.1016/
S0140-6736(15)00459-6

Giora Weisz, Philippe Généreux, Andres Iniguez, Aleksander Zurakowski, Michael Shechter, Karen P Alexander, Ovidiu Dressler, Anna Osmukhina, Stefan James, E Magnus Ohman, Ori Ben-Yehuda, Ramin Farzaneh-Far, Gregg W Stone, for the RIVER-PCI

The issue of whether ranolazine might improve outcomes in such patients was evaluated in the RIVER-PCI trial, which randomly assigned 2651 patients to ranolazine or placebo after incomplete revascularization with PCI .

There was no difference in the rate of the primary efficacy end point (time to first occurrence of ischemia-driven revascularization or ischemia-driven hospitalization without revascularization) between the two groups (26 versus 28 percent; hazard ratio 0.95, 95% CI 0.82-1.10) after a median follow-up of 643 days.

	Ranolazine group (n=1317)	Placebo group (n=1287)	HR (95% CI)	p value
Primary efficacy endpoint	345 (26%)	364 (28%)	0·95 (0·82–1·10)	0·48
Ischaemia-driven revascularisation	201 (15%)	200 (16%)	1·01 (0·83–1·23)	0·91
Ischaemia-driven hospitalisation*	201 (15%)	230 (18%)	0·87 (0·72–1·05)	0·14
Secondary efficacy endpoints				
Sudden cardiac death	7 (<1%)	11 (1%)	0·67 (0·24–1·69)	0·40
Cardiovascular death	21 (2%)	20 (2%)	1·07 (0·58–1·99)	0·82
Myocardial infarction	111 (8%)	116 (9%)	0·97 (0·75–1·26)	0·81
Q wave	7 (<1%)	7 (<1%)	1·05 (0·36–3·07)	0·93
Non-Q-wave	104 (8%)	109 (8%)	0·96 (0·74–1·27)	0·81
Spontaneous	101 (8%)	103 (8%)	0·99 (0·76–1·31)	0·97
Periprocedural	11 (1%)	15 (1%)	0·72 (0·32–1·56)	0·41
Safety events†				
Major adverse cardiovascular events	142 (11%)	144 (11%)	1·00 (0·79–1·26)	0·99
All-cause mortality	42 (3%)	36 (3%)	1·17 (0·75–1·83)	0·49
Stroke	22 (2%)	20 (2%)	1·10 (0·60–2·04)	0·75
Transient ischaemic attack	13 (1%)	3 (<1%)	4·36 (1·40–19·02)	0·02
Heart failure hospitalisation	38 (3%)	25 (2%)	1·55 (0·94–2·60)	0·09
Ischaemia-related	18 (1%)	19 (2%)	0·95 (0·49–1·81)	0·87
Non-ischaemia-related	22 (2%)	13 (1%)	1·72 (0·88–3·51)	0·12

Data are n (%), unless otherwise indicated. HR=hazard ratio. *Without revascularisation. †n=1322 in the ranolazine group, n=1297 in the placebo group (safety analysis set).

Table 3: **Efficacy and safety endpoints**

Ranolazine-USAP-MERIL TIMI 36

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 53, No. 17, 2009
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2009.01.037

Efficacy of Ranolazine in Patients With Chronic Angina

Observations From the Randomized, Double-Blind, Placebo-Controlled MERLIN–TIMI (Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Segment Elevation Acute Coronary Syndromes) 36 Trial

Sean R. Wilson, MD,* Benjamin M. Scirica, MD, MPH,*† Eugene Braunwald, MD,*†
Sabina A. Murphy, MPH,* Ewa Karwatowska-Prokopczuk, MD, PHD,‡ Jacqueline L. Buros, BA,*
Bernard R. Chaitman, MD,§ David A. Morrow, MD, MPH*†
Boston, Massachusetts; Palo Alto, California; and St. Louis, Missouri

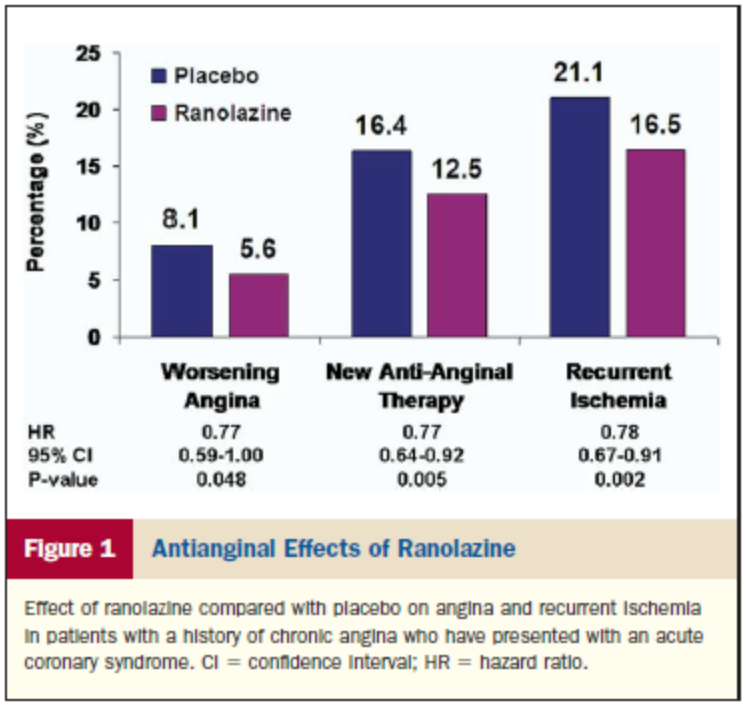


Figure 1 Antianginal Effects of Ranolazine

Effect of ranolazine compared with placebo on angina and recurrent ischemia in patients with a history of chronic angina who have presented with an acute coronary syndrome. CI = confidence interval; HR = hazard ratio.

In the subset of 3565 patients who had prior chronic angina, ranolazine significantly reduced the primary end point of cardiovascular death, MI, and recurrent ischemia due entirely to a significant reduction in recurrent ischemia (hazard ratio [HR] 0.78, 95% CI 0.67-0.91) [13].

There was also an almost significant trend toward a lower rate of worsening angina (HR 0.77, 95% CI 0.55-1.00) and a significant improvement in exercise duration on a treadmill (514 versus 482 seconds).

Table 3 Performance on ETT at 8 Months (s, mean ± SEM)

	Ranolazine (n = 1,190)	Placebo (n = 1,173)	p Value
Total duration	514 ± 7	482 ± 7	0.002
Time to 1-mm ST-segment depression	509 ± 7	479 ± 7	0.003
Time to onset of angina	508 ± 7	477 ± 7	0.002

ETT = exercise tolerance test.

Ranolazine-Women-MERIL TIMI 36

Clinical Features and Outcomes of Women With Unstable Ischemic Heart Disease

Observations From Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36)

Jessica L. Mega, MD, MPH; Judith S. Hochman, MD;
Benjamin M. Scirica, MD, MPH; Sabina A. Murphy, MPH; Sarah Sloan, MA, MS;
Carolyn H. McCabe, BS; Piera Merlini, MD; David A. Morrow, MD, MPH

(*Circulation*. 2010;121:1809-1817.)

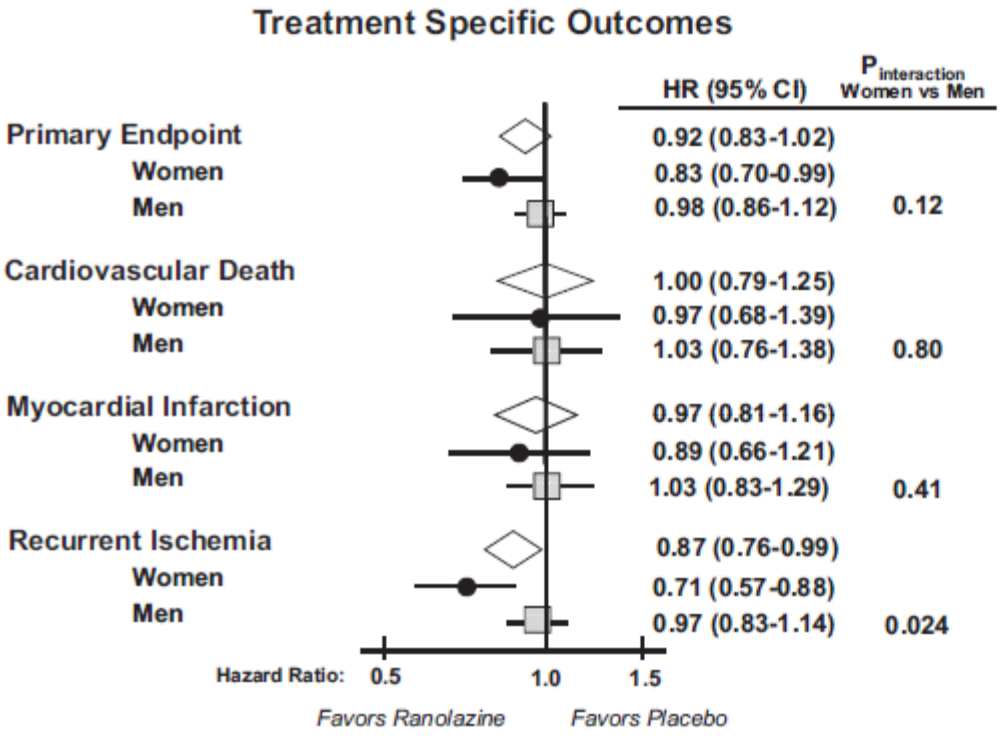


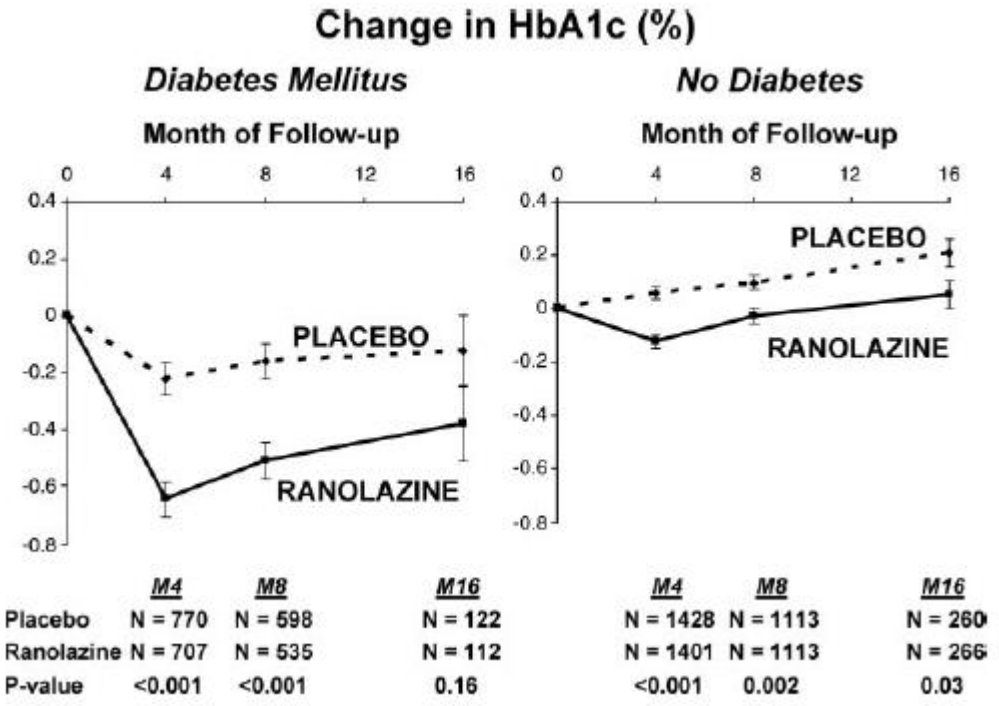
Figure 4. Treatment specific outcomes associated with ranolazine vs placebo in women and men. Outcomes are reported for the overall population (diamonds), women (circles), and men (squares).

Ranolazine-Diyabetes-MERIL TIMI 36

Evaluation of the Glycometabolic Effects of Ranolazine in Patients With and Without Diabetes Mellitus in the MERLIN-TIMI 36 Randomized Controlled Trial

David A. Morrow, MD, MPH; Benjamin M. Scirica, MD, MPH; Bernard R. Chaitman, MD; Darren K. McGuire, MD; Sabina A. Murphy, MPH; Ewa Karwatowska-Prokopczuk, MD, PhD; Carolyn H. McCabe, BS; Eugene Braunwald, MD; for the MERLIN-TIMI 36 Investigators

(*Circulation*. 2009;119:2032-2039.)



	M4	M8	M16	M4	M8	M16
Placebo	N = 770	N = 598	N = 122	N = 1428	N = 1113	N = 260
Ranolazine	N = 707	N = 535	N = 112	N = 1401	N = 1113	N = 266
P-value	<0.001	<0.001	0.16	<0.001	0.002	0.03

Glycometabolic effect — Treatment with ranolazine in the MERLIN-TIMI-36 trial population resulted in a statistically significant 0.3 percent absolute reduction in HbA1c levels that was even more pronounced in patients with diabetes mellitus.

There may also have been a reduction in progression to overt clinical diabetes as defined by increase in fasting blood sugar above 110 mg/dL (6.1 mmol/liter)

The mechanism of this effect is unclear.

Ranolazine- Adverse Effects

- Since ranolazine produces a dose-dependent increase in the QT interval, the United States Food and Drug Administration recommended that it should be reserved for patients who have not had an adequate response with other antianginal drugs.

- Ranolazine is contraindicated in patients with preexisting QT interval prolongation or hepatic disease, and in patients taking other drugs that prolong the QT interval or that are potent or moderately potent inhibitors of CYP3A4, such as diltiazem and verapamil.

- Ranolazine also inhibits pathways involved in the metabolism of digoxin and simvastatin, and dose reduction may be required.

Ranolazine- QT interval

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 49, No. 10, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2006.10.067

CLINICAL RESEARCH — Pharmacologic Studies

Long-Term Safety of a Novel Antianginal Agent in Patients With Severe Chronic Stable Angina

The Ranolazine Open Label Experience (ROLE)

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Jacksonville, Florida

Table 6 Cumulative Mortality to Date

Cause of Death	Number of Deaths (%)
Any cause (total deaths)	68 (100.0)
CV deaths	54 (79.4)
Acute MI	23 (33.8)
MI, cardiogenic shock, acute coronary syndrome	3 (4.4)
Sudden death	15 (22.0)
Ventricular tachyarrhythmia	4 (5.9)
CHF, low-output syndrome, cardiac insufficiency	3 (4.4)
Cerebrovascular event	2 (2.9)
Pulmonary embolism	2 (2.9)
Cardiac arrest	1 (1.5)
Hemopericardium	1 (1.5)
Non-CV deaths (cancer, infection, respiratory failure, bowel obstruction, accident, trauma unknown)	14 (20.6)

CV = cardiovascular; other abbreviations as in Table 1.

However, the effect is generally less than with other drugs (mean QTc prolongation 2.4 ms in a review of 746 patients treated for almost three years) [and torsade de pointes has not yet been described .

Most drugs that cause torsade de pointes show reverse use dependence, which is defined as the inverse correlation between the heart rate and QT interval.

The apparent lack of reverse use dependence with ranolazine may protect against the development of torsade de pointes .

Table 5 Electrocardiographic Findings at Baseline and Average Values on Treatment

Interval	Number of Patients Assessed	Milliseconds (Mean ± SE)	
		Baseline	On Treatment
PR	739	167.1 ± 1.0	167.2 ± 0.9
QRS	745	94.6 ± 0.5	93.5 ± 0.4
QTc (Fridericia correction)	739	419.9 ± 0.8	422.3 ± 0.7

Ranolazine-Arythmia-MERIL TIMI 36

Effect of Ranolazine, an Antianginal Agent With Novel Electrophysiological Properties, on the Incidence of Arrhythmias in Patients With Non–ST-Segment–Elevation Acute Coronary Syndrome

Results From the Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) Randomized Controlled Trial

Benjamin M. Scirica, MD, MPH; David A. Morrow, MD, MPH; Hanoch Hod, MD; Sabina A. Murphy, MPH; Luiz Belardinelli, MD; Chester M. Hedgepeth, MD, PhD; Peter Molhoek, MD; Freek W.A. Verheugt, MD; Bernard J. Gersh, MBChB, DPhil; Carolyn H. McCabe, BS; Eugene Braunwald, MD

(*Circulation*. 2007;116:1647-1652.)

Table 2. Rate of Tachyarrhythmias Detected on cECG Monitoring After Non–ST-Segment Elevation MI

	Ranolazine, n (%)	Placebo, n (%)	RR (95% CI)	*P*
Ventricular arrhythmias				
VT ≥3 beats ≥100 bpm	1646 (52.1)	1933 (60.6)	0.86 (0.82, 0.90)	<0.001
VT ≥4 beats ≥100 bpm	662 (20.9)	941 (29.5)	0.71 (0.6, 0.78)	<0.001
VT ≥8 beats (lasting <30 s)	166 (5.3)	265 (8.3)	0.63 (0.52, 0.76)	<0.001
Polymorphic VT ≥8 beats	38 (1.2)	46 (1.4)	0.83 (0.54, 1.28)	0.40
Sustained VT (≥30 s)	14 (0.44)	14 (0.44)	1.01 (0.48, 2.13)	0.98
Monomorphic	4 (0.13)	7 (0.22)	0.59 (0.17, 2.06)	0.37
Polymorphic	10 (0.32)	7 (0.22)	1.41 (0.52, 3.78)	0.46
Supraventricular arrhythmias				
New-onset atrial fibrillation	55 (1.7)	75 (2.4)	0.74 (0.52, 1.05)	0.08
Other SVT ≥120 bpm lasting at least 4 beats	1413 (44.7)	1752 (55.0)	0.81 (0.77, 0.85)	<0.001

VT indicates ventricular tachycardia; SVT, supraventricular tachycardia.

In the MERLIN-TIMI 36 trial, treatment with ranolazine was associated with a

3 percent lower frequency of ventricular tachycardia (VT),

a 10.3 percent lower incidence of supraventricular tachycardia, and

a 0.7 percent reduction in the onset of new atrial fibrillation .

Antiarrhythmic effect — Ranolazine has not been evaluated as a primary anti-arrhythmic agent, although it has exhibited a favorable anti-arrhythmic profile in the MERLIN-TIMI 36 Trial (see above).

Ranolazine- Summary

- In patients with a history of chronic stable angina, including those who are stable after an acute coronary syndrome, ranolazine is effective at reducing anginal symptoms and improving exercise capacity, when added to standard antianginal therapy.

- It may also be an effective anti-arrhythmic agent

- A potential advantage is in contrast to nitrates, they may be safe in patients taking sildenafil or other phosphodiesterase type 5 inhibitor for erectile dysfunction

Ranolazine-AHA -2012 guideline

- Ranolazine can be a substitute for beta blockers for relief of anginal symptoms if initial treatment with beta blockers leads to unacceptable side effects or is ineffective or is contraindicated.

- Ranolazine can be combined with beta blockers for relief of symptoms if initial monotherapy with beta blockers is unsuccessful

Trimetazidine- Stable angina

Combination treatment in stable effort angina using trimetazidine and metoprolol

Results of a randomized, double-blind, multicentre study (TRIMPOL II)

H. Szwed[1], Z. Sadowski[1], W. Elikowski[2], A. Koronkiewicz[3], A. Mamcarz[4], W. Orszulak[5], E. Skibińska[6], K. Szymczak[7], J. Świątek[8] and M. Winter[9]

European Heart Journal (2001) **22**, 2267–2274
doi:10.1053/euhj.2001.2896, available online at http://www.idealibrary.com on IDEAL®

Table 3 Exercise test results (mean ± SD) in the TMZ (n=168) and PL (n=179) groups

	W0	W12	*P* value (TMZ vs PL) at W12	(W12–W0)	*P* value (W12 vs W0)	*P* value (ΔTMZ vs ΔPL) W12–W0
Time to 1 mm STD (s)			<0·01			<0·01
PL	357 ± 116	381 ± 148		24	<0·01	
TMZ	341 ± 114	427 ± 134		86	<0·01	
Exercise test duration (s)			<0·05			<0·01
PL	432 ± 111	458 ± 134		26	<0·01	
TMZ	420 ± 108	485 ± 122		65	<0·01	
Total work done (metabolic equivalents)			<0·05			<0·01
PL	8·65 ± 2·02	8·99 ± 2·50		0·34	<0·01	
TMZ	8·43 ± 1·90	9·65 ± 2·22		1·22	<0·01	
Maximum STD (mm)			<0·01			<0·01
PL	1·74 ± 0·63	1·71 ± 0·72		− 0·03	ns	
TMZ	1·67 ± 0·46	1·42 ± 0·71		− 0·25	<0·01	
Time to onset of angina (s)			<0·01			<0·01
PL	383 ± 117	423 ± 150		40	<0·01	
TMZ	372 ± 116	465 ± 124		93	<0·01	
Mean weekly number of angina attacks			<0·01			<0·01
PL	4·2 ± 4·3	3·3 ± 4·2		− 0·9	<0·01	
TMZ	4·0 ± 3·2	2·1 ± 2·4		− 1·9	<0·01	
Mean weekly nitrate consumption			<0·05			<0·01
PL	3·1 ± 3·3	2·3 ± 3·9		− 0·5	<0·01	
TMZ	2·8 ± 2·5	1·5 ± 1·9		− 1·3	<0·01	
Anginal pain intensity (Borg's scale)			ns			<0·05
PL	2·10 ± 1·39	1·25 ± 1·35		− 0·85	<0·01	
TMZ	2·22 ± 1·42	1·07 ± 1·40		− 1·15	<0·01	
Rate–pressure product			ns			ns
PL	19 001 ± 4010	19 377 ± 4245		376	ns	
TMZ	19 318 ± 4901	20 116 ± 5092		798	ns	

STD=ST segment depression; ΔTMZ = $(W_{12}–W_0)$ in TMZ group; ΔPL = $(W_{12}–W_0)$ in PL group.

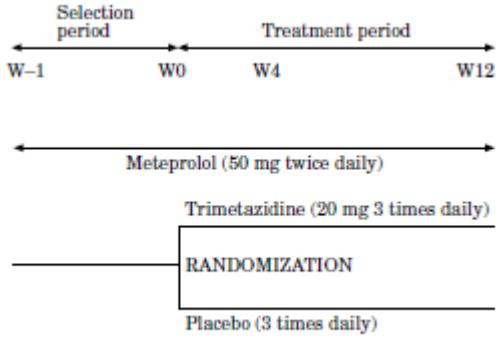


Figure 1 **Study design. W-1=visit at week -1 etc.**

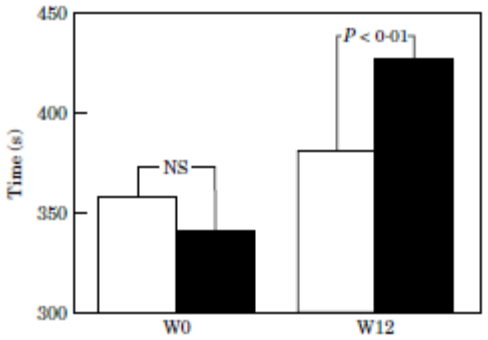


Figure 3 **Time to 1 mm ST segment depression. □=PL; ■=TMZ.**

Perhexiline- Stable angina

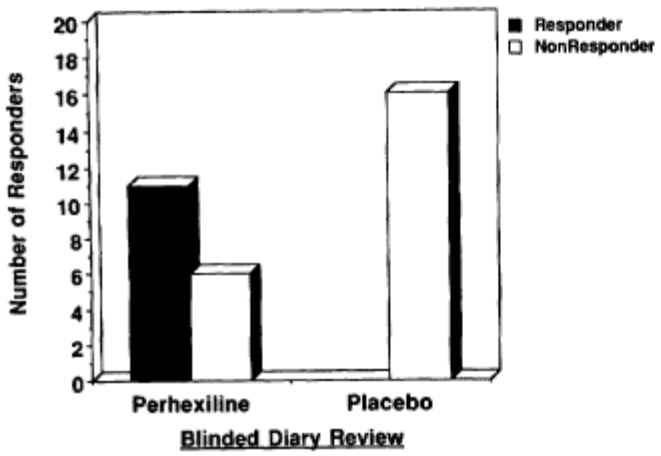
Efficacy and Safety of Perhexiline Maleate in Refractory Angina

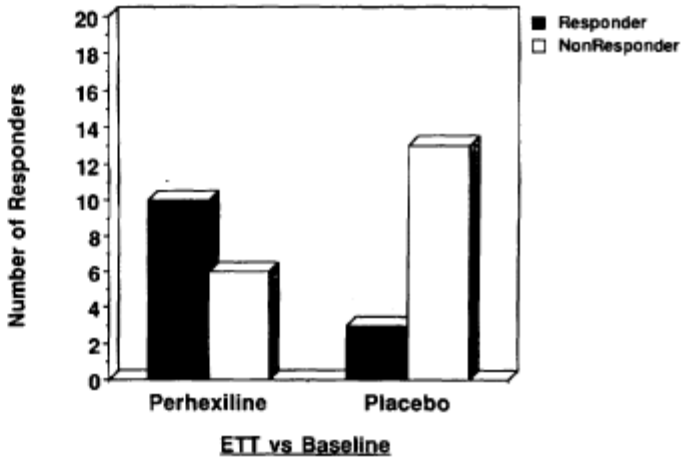
A Double-Blind Placebo-Controlled Clinical Trial of a Novel Antianginal Agent

Patricia L. Cole, MD, Andrew D. Beamer, MD, Noreen McGowan, RN, Catherine O. Cantillon, RN, Kathleen Benfell, RPh, Ralph A. Kelly, MD, L. Howard Hartley, MD, Thomas W. Smith, MD, and Elliott M. Antman, MD

Hepatotoxicity and peripheral neuropathy their incidence can be dramatically reduced by maintaining plasma drug concentrations between 150 and 600 ng/mL

Australia and New Zeland





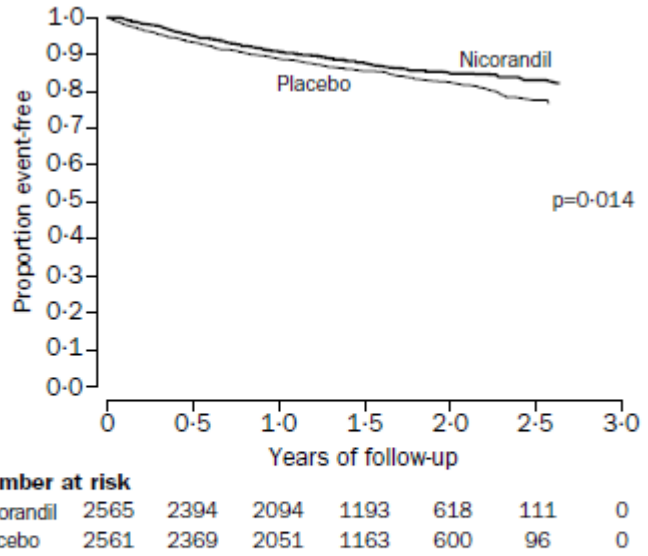
Nicorandil-Stabil angina

Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial

Lancet 2002; **359:** 1269–75

	Nicorandil (n=2565)	Placebo (n=2561)
β-blockers	1453 (57%)	1422 (56%)
ACE inhibitors	739 (29%)	759 (30%)
All receptor antagonists	69 (3%)	75 (3%)
Diuretics	788 (31%)	760 (30%)
Calcium-channel blockers	1411 (55%)	1397 (55%)
Nitrates	2219 (87%)	2234 (87%)
Aspirin/antiplatelets	2278 (89%)	2236 (87%)
Anticoagulants	107 (4%)	120 (5%)
Other antihypertensives	8 (0%)	4 (0%)
Other antiarrhythmic	124 (5%)	105 (5%)
Antidiabetics		
Insulin	77 (3%)	96 (4%)
Oral hypoglycaemics	51 (2%)	58 (2%)
Cholesterol modifiers		
Statins	1449 (56%)	1486 (58%)
Others	65 (3%)	69 (3%)

ACE=angiotensin-converting enzyme. AII=angiotensin II.



Number at risk

Nicorandil	2565	2394	2094	1193	618	111	0
Placebo	2561	2369	2051	1163	600	96	0

Figure 2: **Kaplan-Meier estimates of primary endpoint: coronary heart disease death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain**

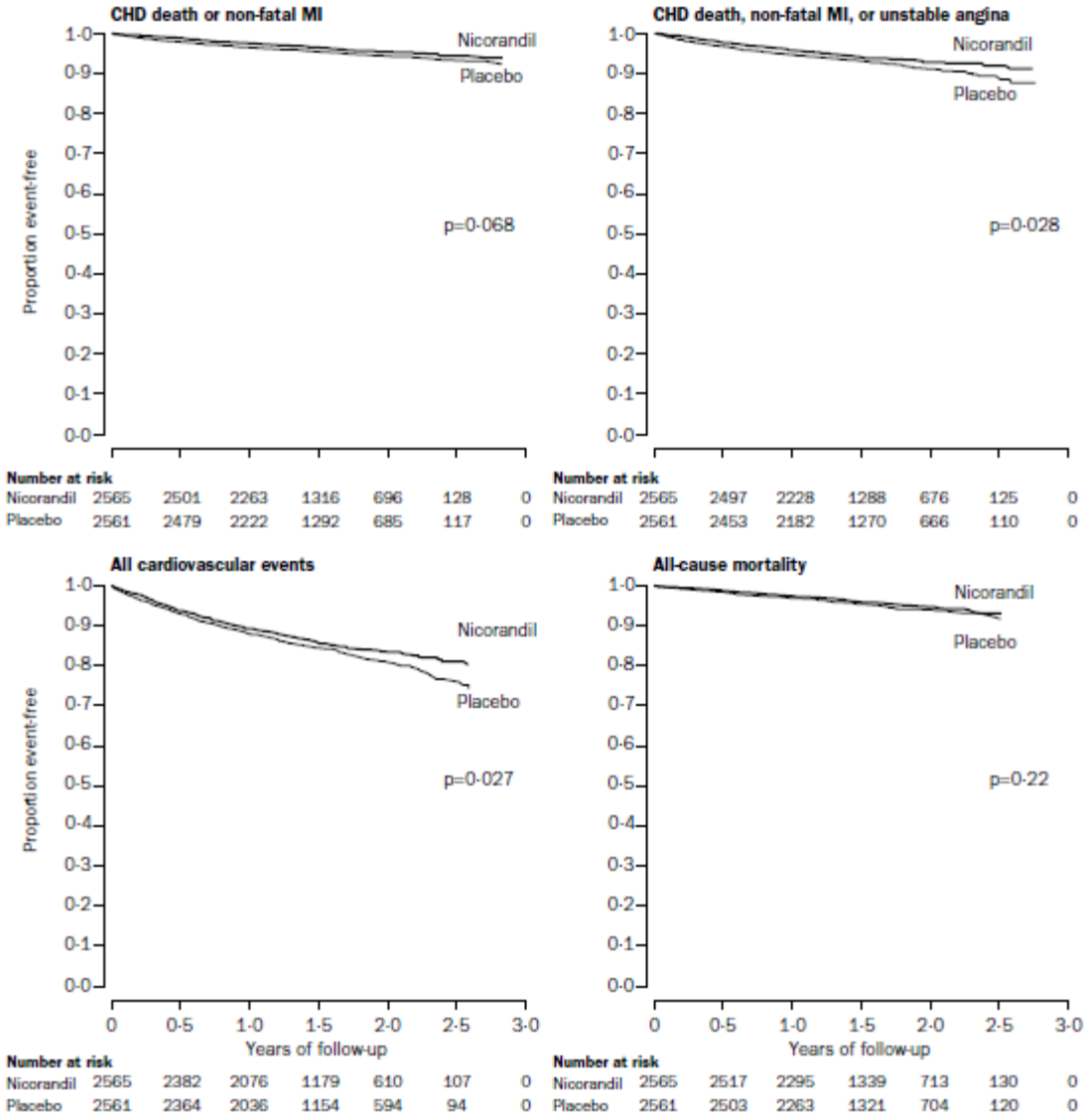


Figure 3: **Kaplan-Meier estimates for secondary endpoint and additional composite endpoints**
CHD=coronary heart disease. MI=myocardial infarction.

Allopurinol-Stable angina

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

www.thelancet.com Vol 375 June 19, 2010

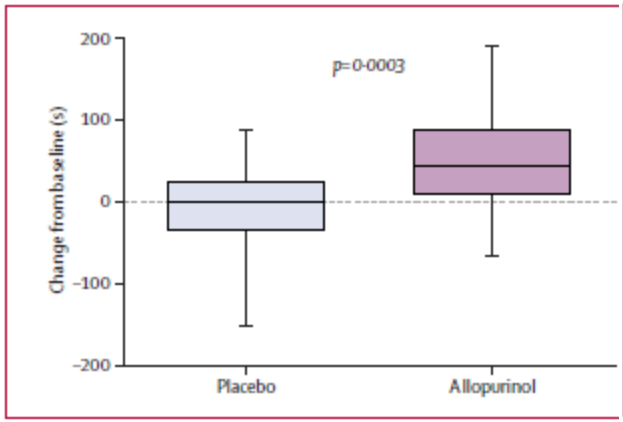


Figure 2: **Change in total exercise time from baseline**
Data are median (IQR).

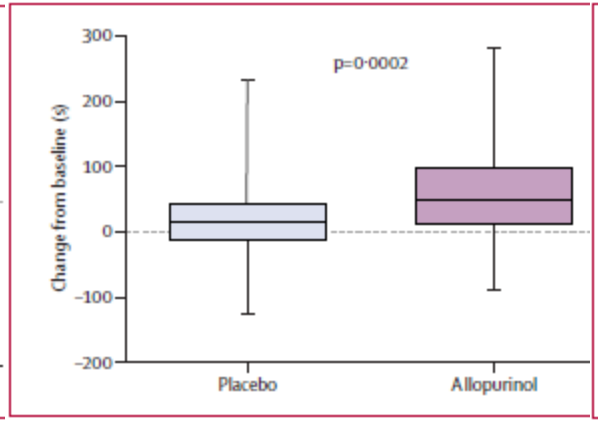


Figure 3: **Change in time to ST depression from baseline**
Data are median (IQR).

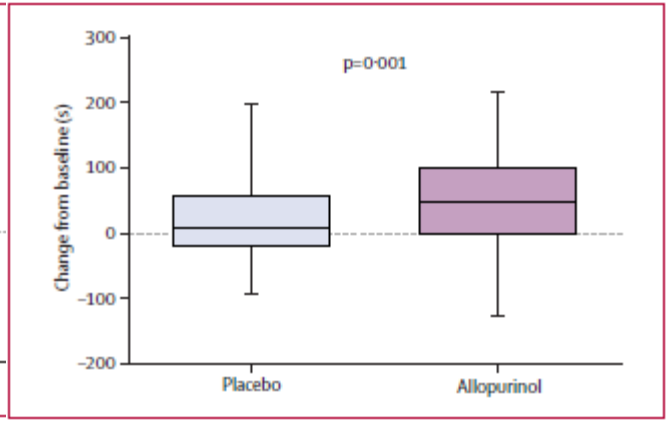


Figure 4: **Change in time to chest pain symptoms from baseline**
Data are median (IQR).

	Baseline	Placebo	Allopurinol	Point estimate* (95% CI)	Mann-Whitney p value*
Total exercise time (s)	301 (251–447)	307 (232–430)	393 (280–519)	58 (45–77)	0·0003
Time to ST depression (s)	232 (182–380)	249 (200–375)	298 (211–408)	43 (31–58)	0·0002
Time to symptoms (s)	234 (189–382)	272 (200–380)	304 (222–421)	38 (17–55)	0·001

Data are median (IQR), unless otherwise indicated. *For difference between allopurinol and placebo.

***Table 3:* Effect of allopurinol on total exercise time, time to ST depression, and time to symptoms**

Allopurinol-Stable angina

Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 58, No. 8, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.12.052

Coronary Artery Disease

Mechanistic Insights Into the Therapeutic Use of High-Dose Allopurinol in Angina Pectoris

Narasimharajapura S. Rajendra, MD, Sheila Ireland, RGN, RM, Jacob George, MD, Jill J. F. Belch, MD, Chim C. Lang, MD, Allan D. Struthers, MD

Dundee, United Kingdom

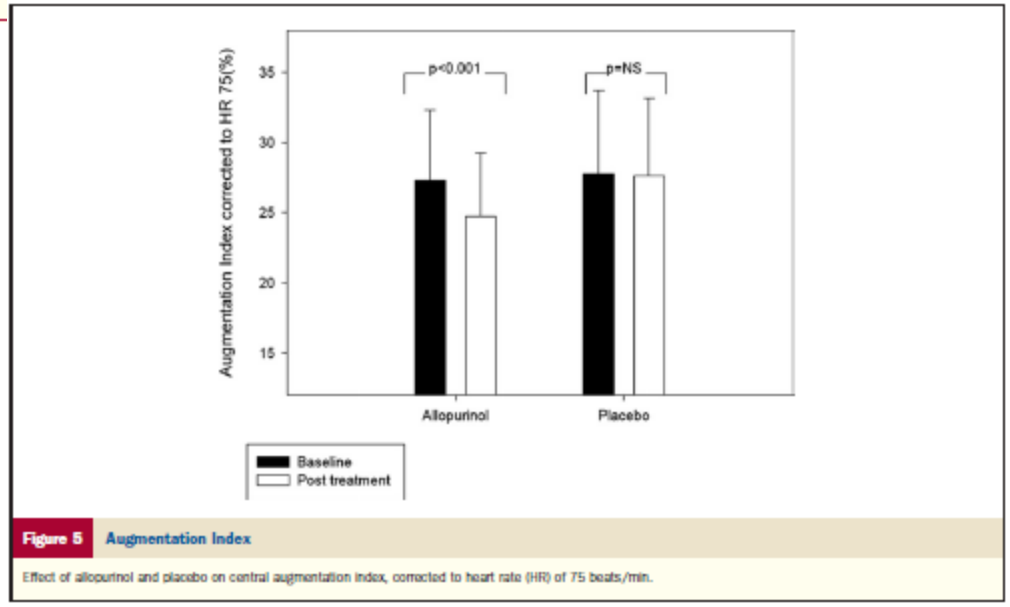


Figure 5 Augmentation Index

Effect of allopurinol and placebo on central augmentation index, corrected to heart rate (HR) of 75 beats/min.

Ivabradine- Stable angina

The NEW ENGLAND JOURNAL of MEDICINE

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

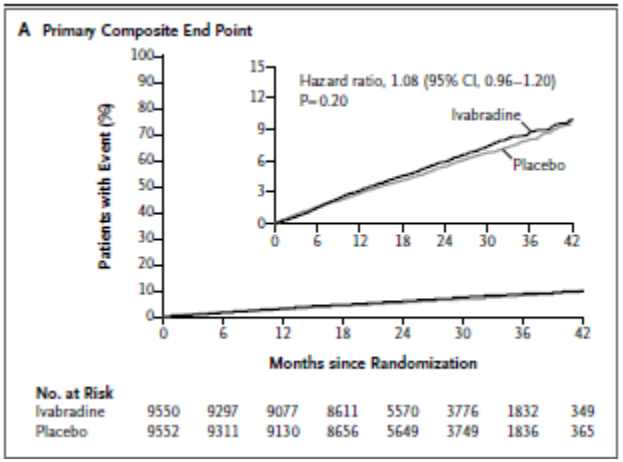
Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure

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*

Table 3. Adverse Events during the Study.*

Event	Ivabradine (N=9539)	Placebo (N=9544)	P Value
	no. of patients with event (%)		
Any adverse event	6990 (73.3)	6382 (66.9)	<0.001
Selected adverse events†			
Bradycardia	1718 (18.0)	223 (2.3)	<0.001
Symptomatic	757 (7.9)	110 (1.2)	<0.001
Asymptomatic	1047 (11.0)	126 (1.3)	<0.001
Phosphenes	512 (5.4)	52 (0.5)	<0.001
Blurred vision	117 (1.2)	37 (0.4)	<0.001
Atrioventricular block			
Second degree	44 (0.5)	31 (0.3)	0.13
Third degree	20 (0.2)	19 (0.2)	0.87
Atrial fibrillation	508 (5.3)	362 (3.8)	<0.001
QT-interval prolongation‡	171 (1.8)	65 (0.7)	<0.001
Supraventricular tachyarrhythmia	137 (1.4)	113 (1.2)	0.13
Immune disorder	22 (0.2)	28 (0.3)	0.40
Severe ventricular arrhythmia	79 (0.8)	66 (0.7)	0.28

* The incidence of adverse events is provided for all the patients who had at least one dose of study drug. Patients may have had more than one type of adverse event (including symptomatic and asymptomatic bradycardia).
† Selected adverse events were those listed in the risk-management plan for ivabradine.
‡ Data include prolongation of the corrected QT interval and uncorrected QT interval as assessed by means of electrocardiography.



- While ivabradine improves angina in patients with CCS class II angina or higher taking optimal medical therapy, we are concerned about an increase in the risk of cardiovascular death and nonfatal myocardial infarction.

Fasudil-Stable angina

Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 41, No. 1, 2003
ISSN 0735-1097/03/$30.00
PII S0735-1097(02)02632-3

Rho-Kinase Inhibition With Intracoronary Fasudil Prevents Myocardial Ischemia in Patients With Coronary Microvascular Spasm

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Fukuoka, Japan

Journal of the American College of Cardiology
© 2005 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 46, No. 10, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.07.047

CLINICAL RESEARCH **Clinical Trial**

Efficacy and Safety of Fasudil in Patients With Stable Angina

A Double-Blind, Placebo-Controlled, Phase 2 Trial

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Melbourne, Florida; St. Louis, Missouri; Montville, New Jersey; New Orleans, Louisiana; Oklahoma City, Oklahoma; Santa Ana, California; Madison, Wisconsin; and Auburn, Maine

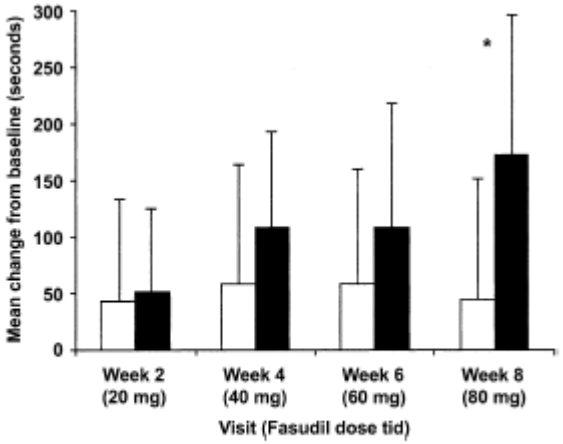

Figure 4. Changes in mean time to ≥1 mm ST-segment depression from baseline for fasudil- **(solid bars)** and placebo-treated **(open bars)** patients. *p = 0.001. tid = three times daily.

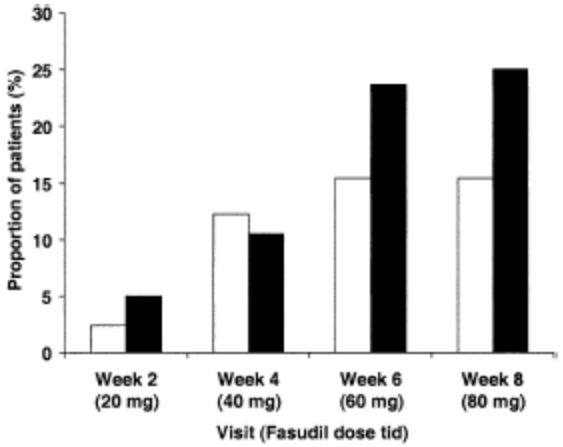

Figure 5. Improvements in angina by ≥1 Canadian Cardiovascular Society angina class in patients treated with fasudil **(solid bars)** and placebo **(open bars)**. tid = three times daily.

Testosterone-Stable angina

Low-Dose Transdermal Testosterone Therapy Improves Angina Threshold in Men With Chronic Stable Angina

A Randomized, Double-Blind, Placebo-Controlled Study

Katherine M. English, MBChB, MRCP; Richard P. Steeds, MBBS, MRCP;
T. Hugh Jones, MD, MRCP; Michael J. Diver, PhD; Kevin S. Channer, MD, FRCP

(*Circulation*. 2000;102:1906-1911.)

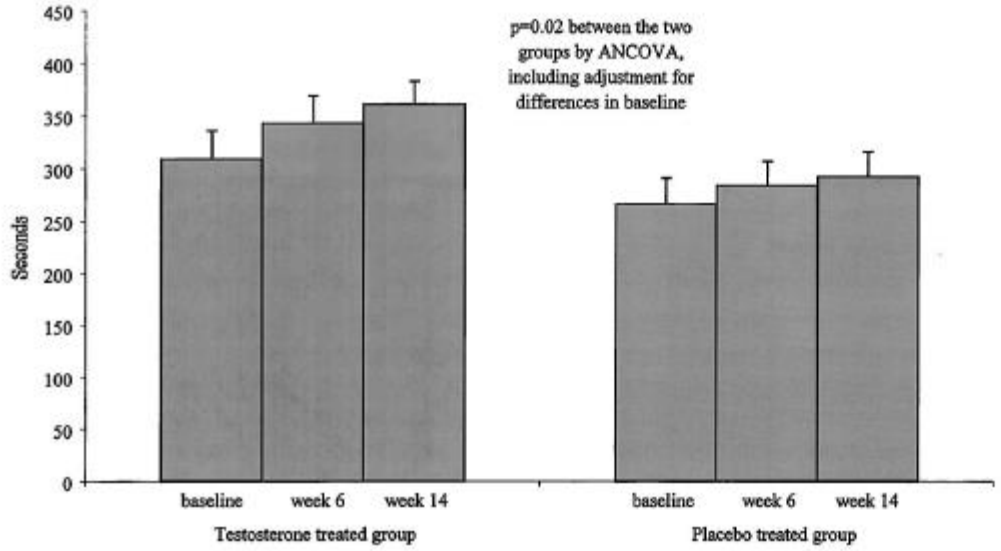

Figure 1. Time to 1-mm ST-segment depression in testosterone-treated and placebo groups at baseline and at weeks 6 and 12.

Statins- Stable angina

The New England Journal of Medicine

AGGRESSIVE LIPID-LOWERING THERAPY COMPARED WITH ANGIOPLASTY IN STABLE CORONARY ARTERY DISEASE

BERTRAM PITT, M.D., DAVID WATERS, M.D., WILLIAM VIRGIL BROWN, M.D., AD J. VAN BOVEN, M.D., PH.D., LEONARD SCHWARTZ, M.D., LAWRENCE M. TITLE, M.D., DANIEL EISENBERG, M.D., LINDA SHURZINSKE, M.S., AND LISA S. MCCORMICK, PHARM.D., FOR THE ATORVASTATIN VERSUS REVASCULARIZATION TREATMENT INVESTIGATORS*

(N Engl J Med 1999;341:70-6.)

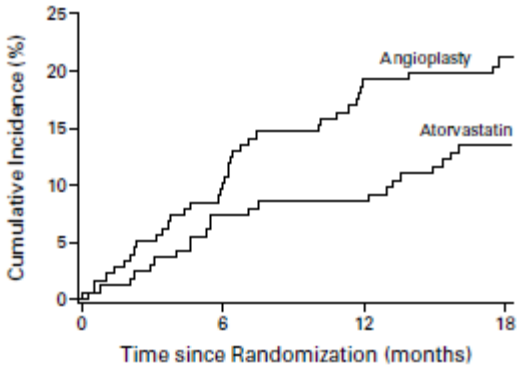

Figure 2. Cumulative Incidence of First Ischemic Events.
The time to an ischemic event was significantly longer in the atorvastatin group (P= 0.03), and the risk reduction was 36 percent (95 percent confidence interval, 5 to 67 percent).

Statins- Stable angina

Potent anti-ischaemic effects of statins in chronic stable angina: incremental benefit beyond lipid lowering?

John E. Deanfield[1]*, Phillipe Sellier[2], Erik Thaulow[3], Jan Bultas[4], Carla Yunis, Harry Shi[5], Jan Buch[5], and Bruce Beckerman[5]

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Received 22 June 2009; revised 3 March 2010; accepted 23 March 2010; online publish-ahead-of-print 21 May 2010

European Heart Journal (2010) **31**, 2650–2659
doi:10.1093/eurheartj/ehq133

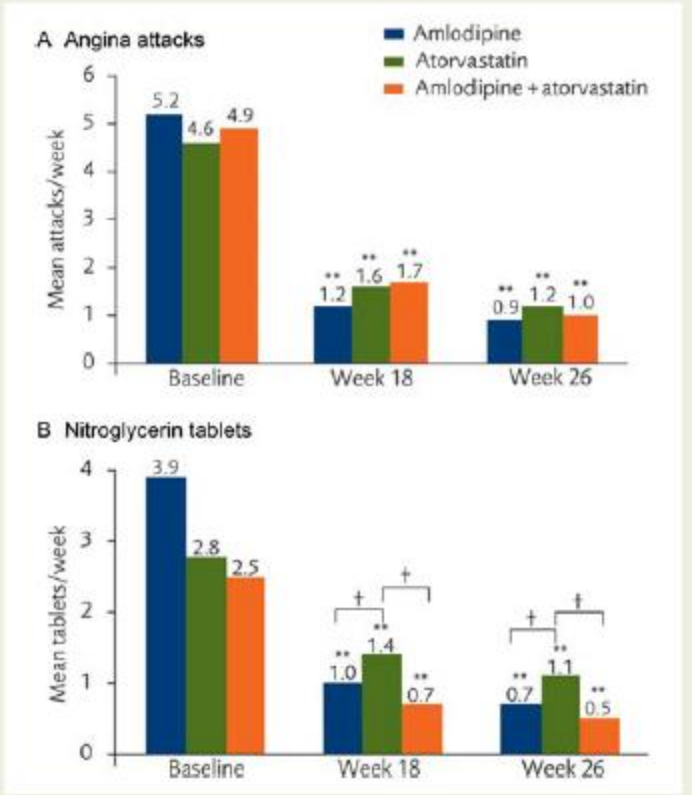

Figure 5 (*A*) Mean angina attacks/week and (*B*) mean number of nitroglycerin tablets/week, based on patients' diaries. $^{**}P < 0.001$ vs. baseline; $^{\dagger}P < 0.05$ change from baseline between groups.

Stable Angina

- Steam cell ?

- Therapeutic angiogenesis ?
  - Fibroblast growth factors (FGFs)
  - Vascular endothelial growth factors (VEGFs)
  - Platelet-derived growth factor (PDGF)

Mechanical Therapies- Stable Angina

- Enhanced external counterpulsation
- Spinal cord stimulation
- Transmyocardial laser revascularization
- Coronary sinus reducing device
- Apheresis

Enhanced external counterpulsation Stable Angina

- External counterpulsation (ECP), also referred to as enhanced external counterpulsation (EECP), is a technique that increases arterial blood pressure and retrograde aortic blood flow during diastole (diastolic augmentation).

- Cuffs are wrapped around the patient's calves, thighs, and pelvis and, using compressed air, sequential pressure (up to 300 mmHg) is applied in early diastole to propel blood back to the heart.

EECP-Stable angina

Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 33, No. 7, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(99)00140-0

CLINICAL STUDIES **Myocardial Ischemia**

The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP): Effect of EECP on Exercise-Induced Myocardial Ischemia and Anginal Episodes

Rohit R. Arora, MD,* Tony M. Chou, MD,† Diwakar Jain, MD,‡ Bruce Fleishman, MD,§ Lawrence Crawford, MD,‖ Thomas McKiernan, MD,¶ Richard W. Nesto, MD#

New York, New York; San Francisco, California; New Haven, Connecticut; Columbus, Ohio; Pittsburgh, Pennsylvania; Maywood, Illinois; Boston, Massachusetts

Table 2. Exercise Treadmill Test

	Inactive CP				Active CP				Between-Group p Value
	n	Pre-CP	Post-CP	p Value	n	Pre-CP	Post-CP	p Value	
Exercise duration (s)	58	432 ± 22	464 ± 22	< 0.03	57	426 ± 20	470 ± 20	< 0.001	< 0.31
Time to ≥1-mm ST-segment depression (s)	56	326 ± 21	330 ± 20	< 0.74	56	337 ± 18	379 ± 18	< 0.002	= 0.01

Duration in seconds, mean ± SEM.
Pre-CP: baseline, before counterpulsation; Post-CP: follow-up, postcounterpulsation. p values are computed based on adjusted change in duration from baseline to follow-up.

Table 3. Angina Counts

			Improvement			Worsening				p Value
		Median	50+%	25%–49%	0%–24%	1%–25%	26%–50%	51%–100%	100+%	
Intention to treat										
Inactive CP	66	0%	21	3	28	2	2	4	6	
Active CP	71	−20%	32	1	33	0	0	2	3	< 0.05
≥34 sessions										
Inactive CP	59	0%	19	2	24	0	2	5	7	
Active CP	57	−50%	29	1	23	0	0	0	4	< 0.02

Categories of change are expressed in percent versus baseline. Daily average of self-reported episodes of angina pectoris are computed over three 24-h periods. p values are calculated for between-group differences using a Cochran-Mantel-Haenszel chi-square test for ordered categories stratified by treatment center.

EECP-Stable angina

Two-Year Clinical Outcomes After Enhanced External Counterpulsation (EECP) Therapy in Patients With Refractory Angina Pectoris and Left Ventricular Dysfunction (Report from the International EECP Patient Registry)

Ozlem Soran, MD, MPH[a,*,†], Elizabeth D. Kennard, PhD[b], Abdallah Georges Kfoury, MD[c], and Sheryl F. Kelsey, PhD[b], for the IEPR Investigators

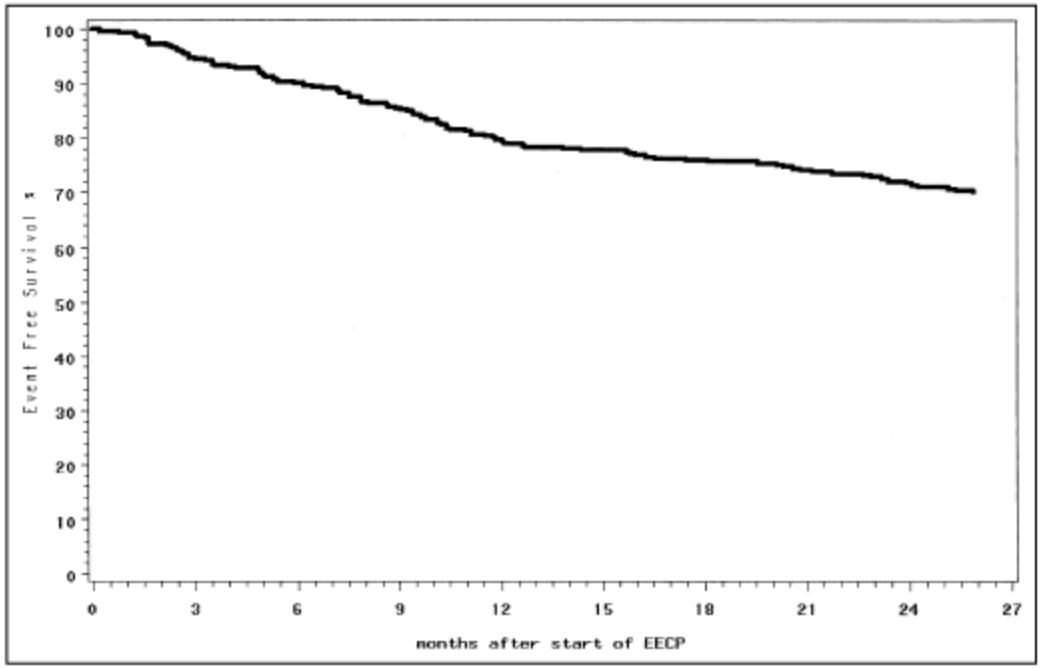


Figure 3. Event-free survival rate. Events were death, coronary artery bypass grafting, myocardial infarction, and percutaneous coronary intervention.

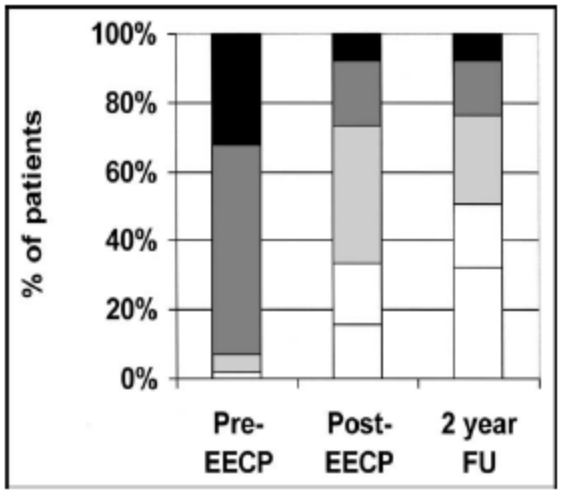


Figure 1. Angina classes 0 *(white bars)*, I *(pale gray bars)*, II *(medium gray bars)*, III *(dark gray bars)*, and IV *(black bars)* before EECP (n = 363), after EECP (n = 358), and at 2-year follow-up (FU; n = 265).

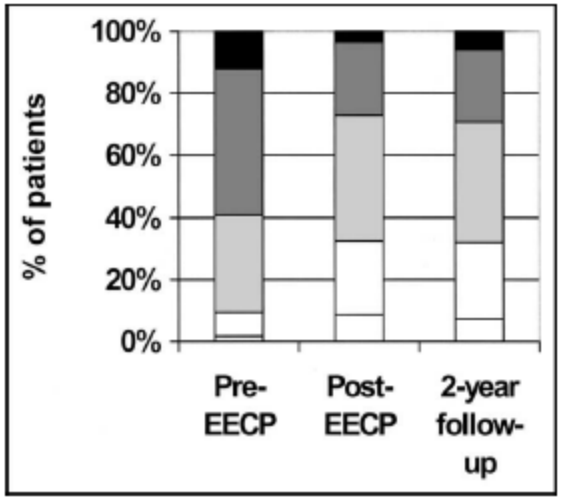
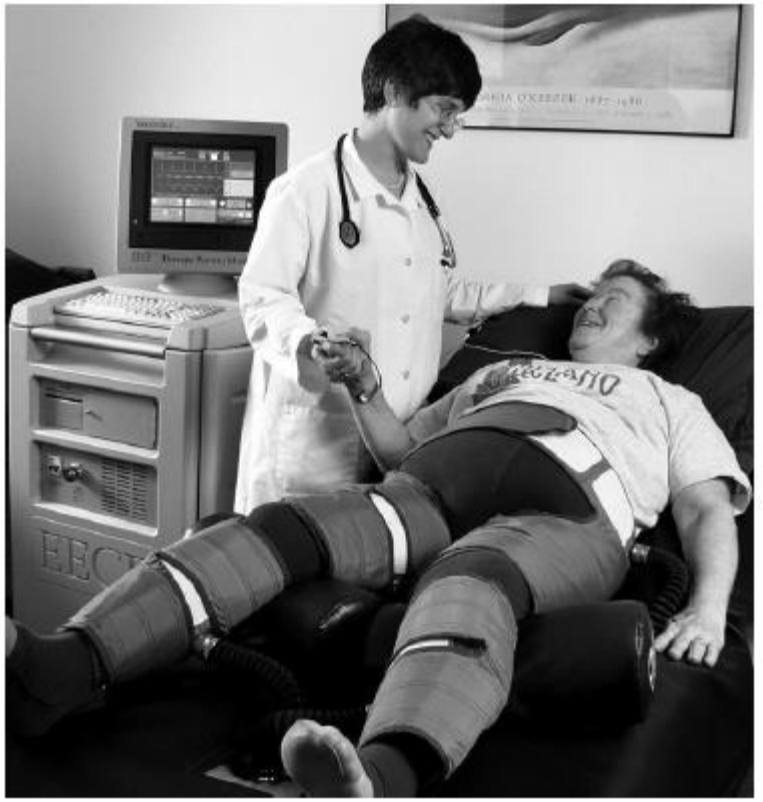


Figure 2. Quality of life rated as poor *(black bars)*, fair *(dark gray bars)*, good *(medium gray bars)*, very good *(pale gray bars)*, and excellent *(white bars)* before and after EECP and at 2-year follow-up.

EECP-Stable angina



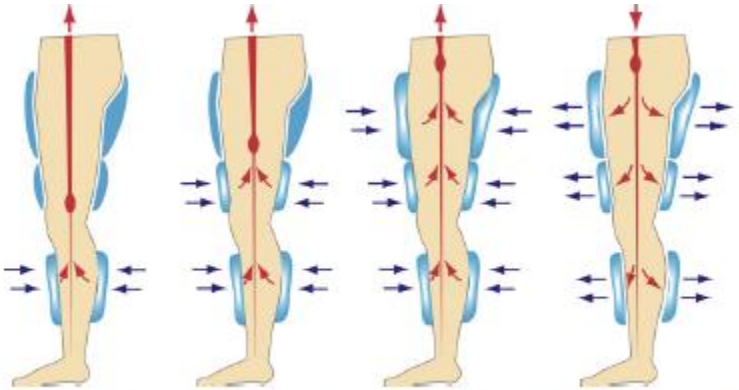
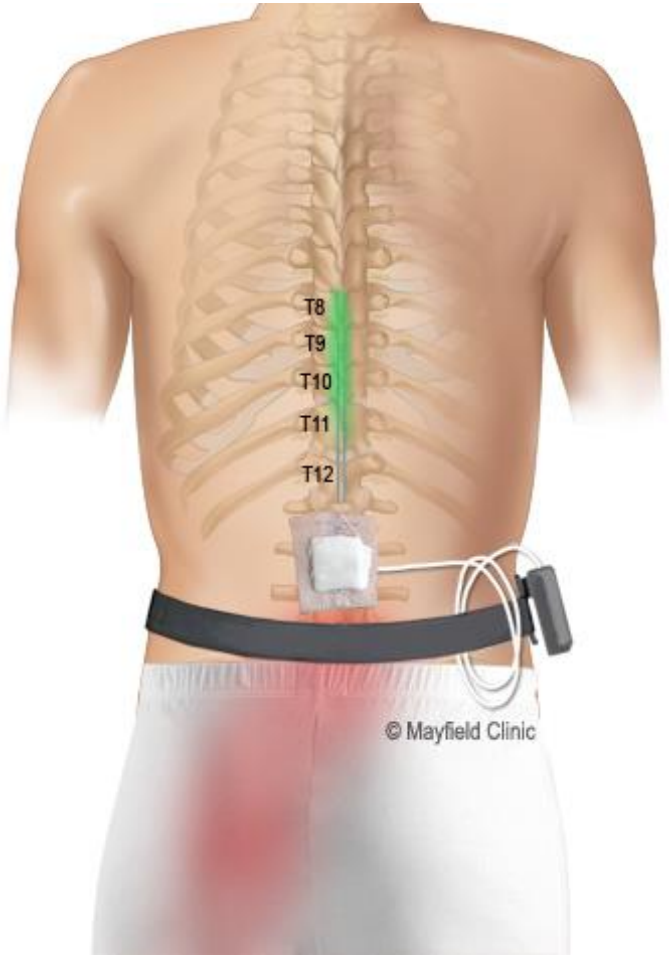


Fig. 2. Schematic of EECP cuffs. The procedure consists of sequential leg compression, distal to proximal, by the EECP cuffs at 50 ms intervals during early diastole followed by simultaneous cuff deflation at the onset of systole.

Spinal cord stimulation- Stable angina



Spinal cord stimulation- Stable angina

- Spinal cord stimulation at the T1 to T2 level is another approach to the management of refractory angina.
- Spinal cord stimulation was originally developed to treat neurogenic pain and then applied to the refractory angina population.
- While the approach is clearly effective in some, objective evidence of its efficacy is not compelling.
- Studies of this therapy tend to be small and open label randomized trials or observational studies

Spinal cord stimulation- Stable angina

Electrical Stimulation Versus Coronary Artery Bypass Surgery in Severe Angina Pectoris: The ESBY Study.
Mannheimer, Clas; MD, PhD; Eliasson, Tore; MD, PhD; Augustinsson, Lars-Erik; MD, PhD; Blomstrand, Christian; MD, PhD; Emanuelsson, Hakan; MD, PhD; Larsson, Sture; MD, PhD; Norrsell, Henrik; Hjalmarsson, Ake; MD, PhD

Circulation. 97(12):1157-1163, March 31, 1998.

			P	
	Preoperative	Follow-up	Comparison of Preoperative vs Postoperative	Comparison of CABG vs SCS
Maximum workload capacity, W				
CABG	86.2 (23.1)	99.0 (28.0)	.002	
SCS	90.6 (29.2)	92.2 (33.7)	NS	.02
ST-segment depression on maximum workload, mm				
CABG	−1.46 (1.36)	−0.68 (1.52)	.0009	
SCS	−2.01 (1.17)	−1.95 (1.18)	NS	.005
ST-segment depression on comparable workload, mm				
CABG	−1.40 (1.39)	−0.46 (1.13)	.0001	
SCS	−1.73 (1.14)	−1.66 (1.24)	NS	.0009
RPP on maximum workload, mm Hg/min×10^3				
CABG	21.6 (5.4)	25.4 (5.6)	<.0001	
SCS	21.4 (5.8)	21.2 (6.9)	NS	.0003
RPP on comparable workload, mm Hg/min×10^3				
CABG	21.3 (5.4)	23.0 (5.4)	.034	
SCS	20.9 (5.7)	20.6 (6.5)	NS	.03

CABG indicates coronary artery bypass graft surgery; SCS, spinal cord stimulation; and RPP, rate-pressure product.
Values are given as mean (1 SD).

Spinal cord stimulation- Stable angina

Electrical Stimulation Versus Coronary Artery Bypass Surgery in Severe Angina Pectoris: The ESBY Study.
Mannheimer, Clas; MD, PhD; Eliasson, Tore; MD, PhD; Augustinsson, Lars-Erik; MD, PhD; Blomstrand, Christian; MD, PhD; Emanuelsson, Hakan; MD, PhD; Larsson, Sture; MD, PhD; Norrsell, Henrik; Hjalmarsson, Ake; MD, PhD

Circulation. 97(12):1157-1163, March 31, 1998.

			P	
	Preoperative	Follow-up	Comparison of Preoperative vs Postoperative	Comparison of CABG vs SCS
Nitrate consumption, doses/week				
CABG	13.7 (12.1)	3.1 (8.7)	<.0001	
SCS	15.2 (18.8)	4.1 (10.5)	<.0001	NS
Anginal attack frequency, attacks/wk				
CABG	16.2 (12.6)	5.2 (10.3)	<.0001	
SCS	14.6 (13.5)	4.4 (7.4)	<.0001	NS
Self-estimated treatment effect, % better or symptom free				
CABG		79.5%		
SCS		83.7%		NS

CABG indicates coronary artery bypass graft surgery; SCS, spinal cord stimulation.
Values are given as mean (1 SD).

Spinal cord stimulation- Stable angina

European Heart Journal (2006) 27, 1048–1053
doi:10.1093/eurheartj/ehi827

Clinical research
Coronary heart disease

An open label, single-centre, randomized trial of spinal cord stimulation vs. percutaneous myocardial laser revascularization in patients with refractory angina pectoris: the SPiRiT trial

Duncan McNab[1], Sadia N. Khan[1], Linda D. Sharples[2,3], Judy Y. Ryan[3], Carol Freeman[3] Noreen Caine[3], Sue Tait[3], Ian Hardy[4], and Peter M. Schofield[1]*

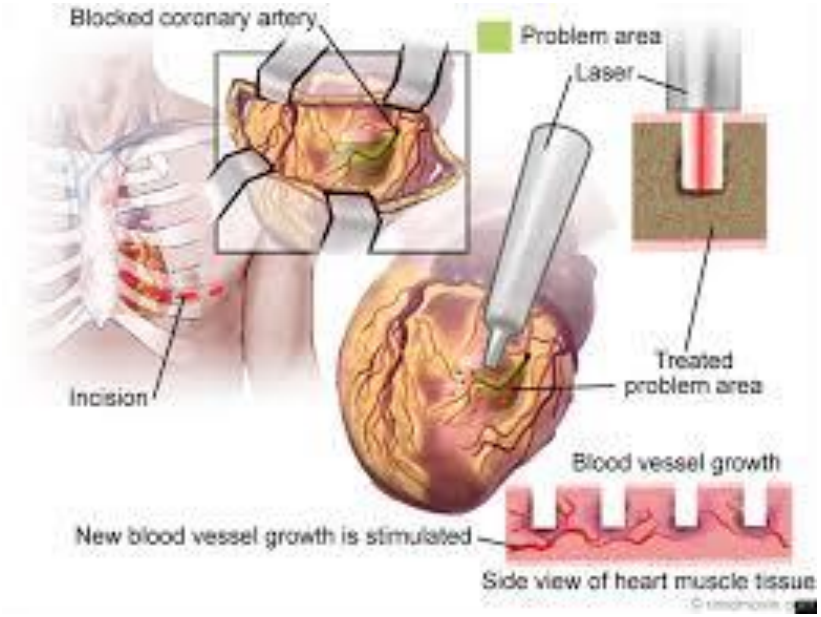
[1]Department of Cardiology, Papworth Hospital NHS Trust, Papworth Everard, Cambridge CB3 8RE, UK; [2]MRC Unit, Cambridge, UK; [3]Department of Research and Development, Papworth Hospital NHS Trust, Cambridge [4]Department of Anaesthetics, Papworth Hospital NHS Trust, Cambridge, UK

Table 4 Comparisons of CCS class between SCS and PMR at 3 and 12 months

	SCS	PMR	*P*-value
CCS class at 3 months	($n = 32$)	($n = 33$)	
1	9 (28%)	4 (12%)	0.049
2	12 (38%)	11 (33%)	
3	8 (25%)	11 (33%)	
4	3 (9%)	7 (21%)	
Change in CCS $\geq$ 2 classes			
No	20 (63%)	28 (85%)	0.077
Yes	12 (37%)	5 (15%)	
CCS class at 12 months	($n = 30$)	($n = 30$)	
1	6 (20%)	3 (10%)	0.093
2	15 (50%)	11 (37%)	
3	4 (13%)	8 (27%)	
4	5 (17%)	8 (27%)	
Change in CCS $\geq$ 2 classes			
No	19 (63%)	24 (80%)	0.166
Yes	11 (37%)	6 (20%)	

[a]On the basis of comparisons which were not adjusted for baseline.

Transmyocardial laser revascularization
Stable angina



Laser- Stable angina

Journal of the American College of Cardiology
© 2005 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 46, No. 10, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.06.079

Interventional Cardiology

A Blinded, Randomized, Placebo-Controlled Trial of Percutaneous Laser Myocardial Revascularization to Improve Angina Symptoms in Patients With Severe Coronary Disease

Martin B. Leon, MD, Ran Kornowski, MD, William E. Downey, MD, Giora Weisz, MD, Donald S. Baim, MD, Robert O. Bonow, MD, Robert C. Hendel, MD, David J. Cohen, MD, MSc, Ernest Gervino, DSc, Roger Laham, MD, Nicholas J. Lembo, MD, Jeffrey W. Moses, MD, Richard E. Kuntz, MD, MSc

New York, New York

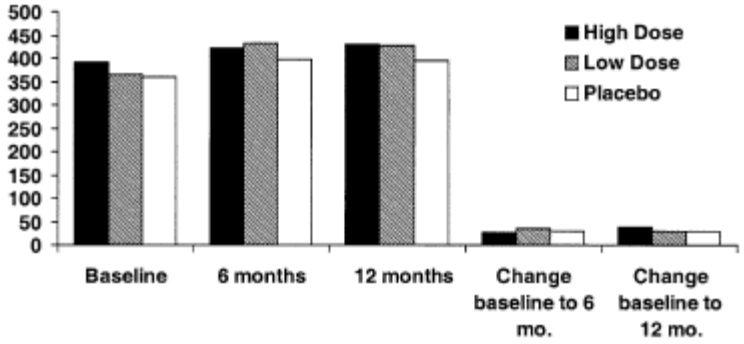


Figure 2. Exercise duration(s) at baseline, at 6 months, and at 12 months of follow-up and the change in exercise duration between baseline and 6 months. The change in exercise duration was maintained at 12 months. All comparisons between groups were not statistically significant.

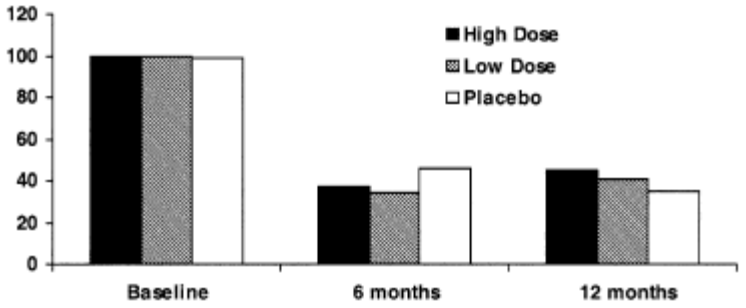
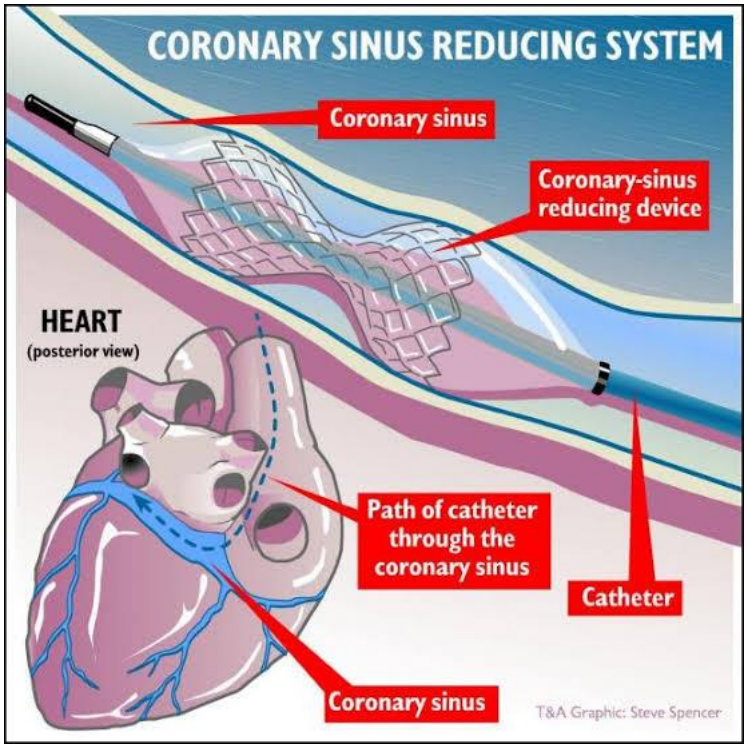


Figure 3. Canadian Cardiovascular Society angina class III or IV at baseline and 6- and 12-month follow-up. All comparisons between groups were not statistically significant.

Coronary Sinus Reducing Device- Stable Angina



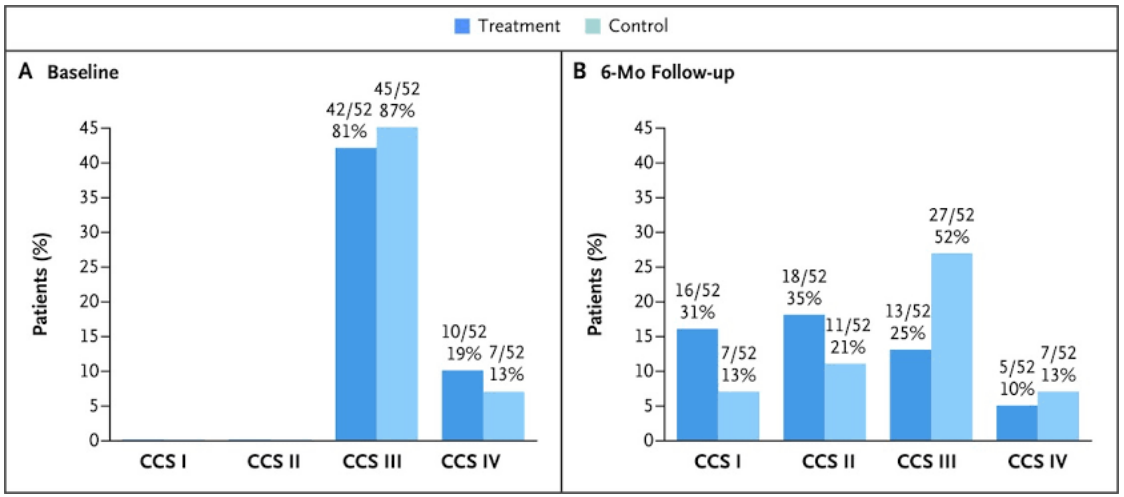
Coronary Sinus Reducing Device-Stable Angina

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of a Device to Narrow the Coronary Sinus in Refractory Angina

Stefan Verheye, M.D., Ph.D., E. Marc Jolicœur, M.D., Miles W. Behan, M.D., Thomas Pettersson, M.D., Paul Sainsbury, M.D., Jonathan Hill, M.D., Mathias Vrolix, M.D., Pierfrancesco Agostoni, M.D., Thomas Engstrom, M.D., Marino Labinaz, M.D., Ranil de Silva, M.D., Marc Schwartz, R.C.I.S., Nathalie Meyten, M.D., Neal G. Uren, M.D., Serge Doucet, M.D., Jean-François Tanguay, M.D., Steven Lindsay, M.D., Timothy D. Henry, M.D., Christopher J. White, M.D., Elazer R. Edelman, M.D., Ph.D., and Shmuel Banai, M.D.



Apheresis-Stable Angina

European Heart Journal (2017) **38**, 1561–1569
doi:10.1093/eurheartj/ehx178

CLINICAL RESEARCH
Coronary artery disease

Apheresis as novel treatment for refractory angina with raised lipoprotein(a): a randomized controlled cross-over trial

Tina Z. Khan[1,2], Li-Yueh Hsu[3], Andrew E. Arai[3], Samantha Rhodes[1], Alison Pottle[1], Ricardo Wage[1], Winston Banya[1], Peter D. Gatehouse[1,2], Shivraman Giri[4], Peter Collins[1,2], Dudley J. Pennell[1,2*†], and Mahmoud Barbir[1,2†]

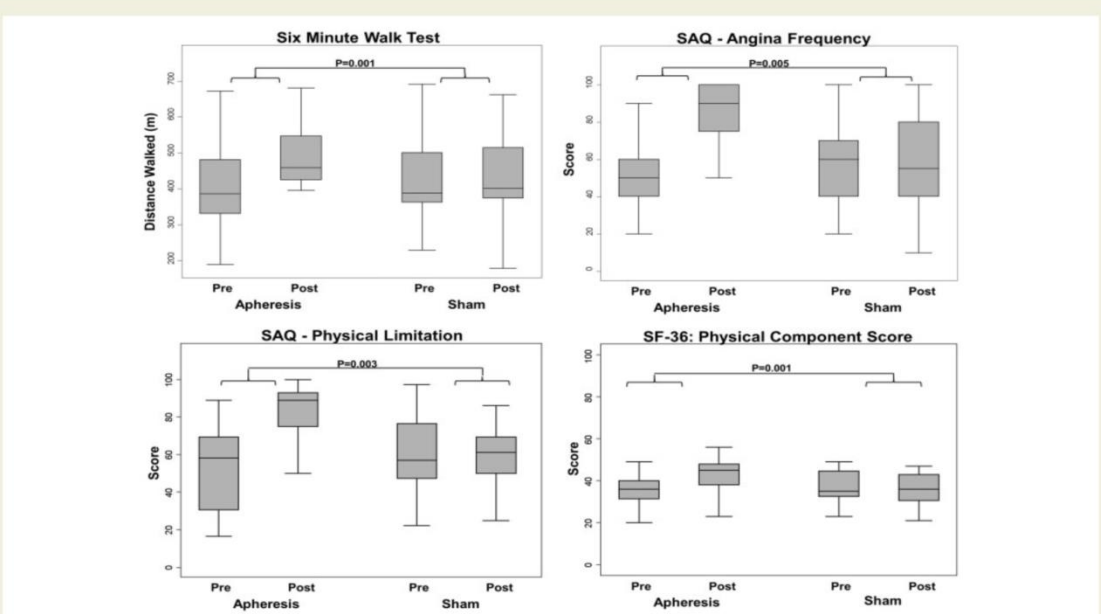


Figure 3 Improvements during apheresis compared with sham. Graphs showing improvements during apheresis compared with sham in: distance walked on 6 min walk test (top left); angina (top right); physical limitation (bottom left); overall physical wellbeing (bottom right).

Indication	Class [a]	Level [b]
For second-line treatment it is recommended to add long-acting nitrates or ivabradine or nicorandil or ranolazine, according to heart rate, blood pressure and tolerance.	IIa	B
For second-line treatment, trimetazidine may be considered.	IIb	B

Table 35 Treatment options in refractory angina

Recommendations	Class [a]	Level [b]	Ref. [c]
EECP should be considered for symptom relief in patients with invalidating angina refractory to optimal medical and revascularization strategies.	IIa	B	509, 510
TENS may be considered to ameliorate symptoms of invalidating angina refractory to optimal medical and revascularization strategies.	IIb	C	-
SCS may be considered to ameliorate symptoms and quality of life in patients with invalidating angina refractory to optimal medical and revascularization strategies.	IIb	B	511
TMR is not indicated in patients with invalidating angina refractory to optimal medical and revascularization strategies.	III	A	514

EECP = enhanced external counterpulsation; TENS = transcutaneous electrical nerve stimulation; TMR = transmyocardial revascularization; SC = spinal cord stimulation.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting levels of evidence.

European Heart Journal (2013) **34**, 2949–3003
doi:10.1093/eurheartj/eht296

ESC

2013 ESC guidelines on the management of stable coronary artery disease

2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease

CLASS IIa

1. Treatment with a long-acting nondihydropyridine calcium channel blocker (verapamil or diltiazem) instead of a beta blocker as initial therapy for relief of symptoms is reasonable in patients with SIHD (420). *(Level of Evidence: B)*
2. Ranolazine can be useful when prescribed as a substitute for beta blockers for relief of symptoms in patients with SIHD if initial treatment with beta blockers leads to unacceptable side effects or is ineffective or if initial treatment with beta blockers is contraindicated (846). *(Level of Evidence: B)*
3. Ranolazine in combination with beta blockers can be useful when prescribed for relief of symptoms when initial treatment with beta blockers is not successful in patients with SIHD (847,848). *(Level of Evidence: A*

CLASS IIb

1. Enhanced external counterpulsation (EECP) may be considered for relief of refractory angina in patients with SIHD (910). *(Level of Evidence: B)*
2. Spinal cord stimulation may be considered for relief of refractory angina in patients with SIHD (911,912). *(Level of Evidence: C)*
3. Transmyocardial revascularization (TMR) may be considered for relief of refractory angina in patients with SIHD (913–915). *(Level of Evidence: B)*

SUMMARY AND RECOMMENDATIONS

- Most patients with stable angina pectoris can have an acceptable frequency (and severity) of angina with conventional medical therapies, such as beta blockers, calcium channel blockers, nitrates, and/or myocardial revascularization with either percutaneous coronary intervention (PCI) or coronary bypass graft surgery (CABG).

- For these patients for whom angina remains problematic, a number of medical and mechanical therapies have been evaluated for the treatment of refractory angina.

- Only ranolazine has demonstrated significant efficacy in large trials.

SUMMARY AND RECOMMENDATIONS

- Ranolazine is effective at reducing anginal symptoms and improving exercise capacity when added to conventional medical therapy. The initial dose is 500 mg twice daily. For patients who remain symptomatic, 1000 mg twice daily may be used.

SUMMARY AND RECOMMENDATIONS

- Other medical therapies such as fatty acid oxidation inhibitors or nicorandil have demonstrated some efficacy in studies.

- Until further supporting evidence is available, I do not recommend their use for the prevention of anginal episodes.

SUMMARY AND RECOMMENDATIONS

- External counterpulsation is the best studied of possible mechanical therapies to improve angina. While approved for use in some countries, it is not widely used.