63° CONGRESSO NAZIONALE SIGG

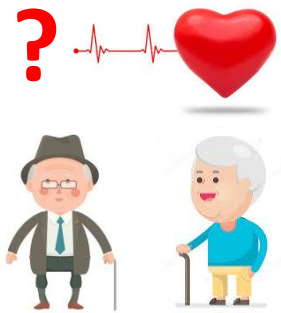
GLI ANZIANI: LE RADICI DA PRESERVARE

ROMA 28 novembre 01 dicembre 2018 Auditorium della Tecnica, Roma

Meet the expert: La cardiopatia ischemica cronica nell'anziano

La terapia alla luce delle linee guida: oltre i beta-bloccanti e gli ace-inibitori

Giorgio Basile
Ricercatore Geriatria Università di Messina



Cardiopatia ischemica cronica:

- ❖ **Angina** — **Stabile**
  Microvascolare
  Vasospasmo
- ❖ **Pregresso infarto miocardico**
- ❖ **Pregressa rivascolarizzazione**
- ❖ **Evidenza strumentale di ischemia miocardica**

Epidemiology and prognosis of chronic stable angina (CSA)

- In Western countries an estimated 30.000-40.000/1.000.000 of the population have CSA
- the prevalence increase with age:

- women 45-64 ys: 5-7%
- women 65-84 ys: 10-12%
- men 45-64 ys: 4-7%
- men 65-84 ys: 14-15%

- ≈ 4.1 million deaths from CAD occur in Europe each year, with 82% > 65 ys, 46% in those aged > 75 ys; the annual death rate is 1.2-2.4%

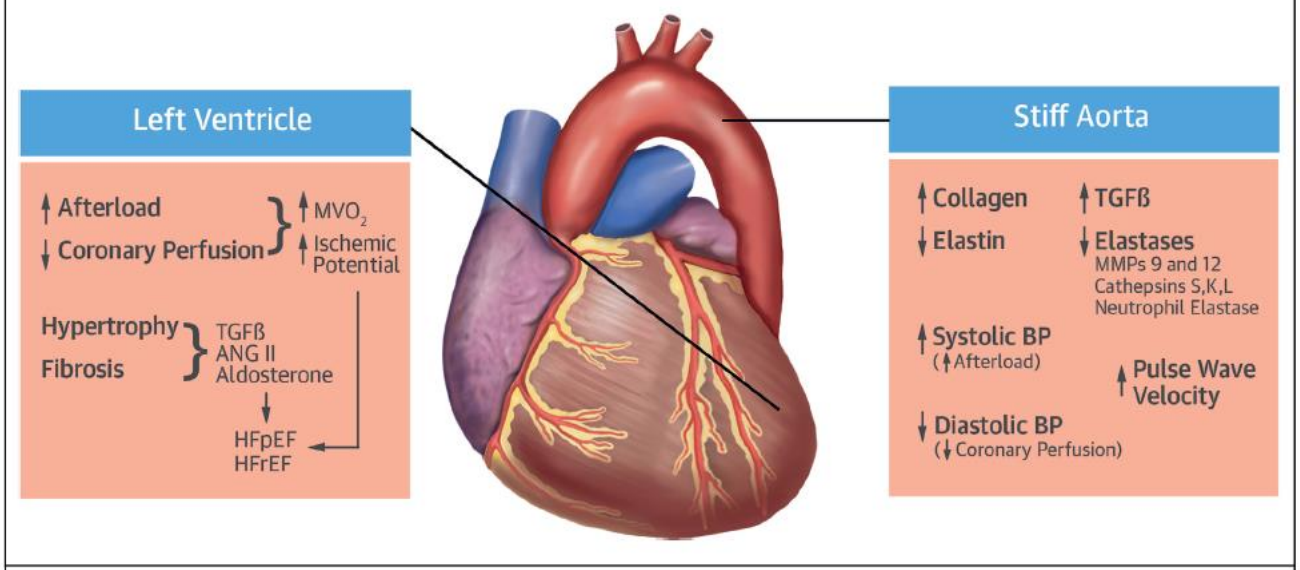
Management of Chronic Stable Angina in Older Adults

- ❑ Aging
- ❑ Coronary Artery Disease
- ❑ Other possible causes of angina
- ❑ Comorbidity
- ❑ Polipharmacy
- ❑ Frailty
- ❑ Life expectancy

The Aging Cardiovascular System

Understanding It at the Cellular and Clinical Levels

FIGURE 1 Pathophysiology of Aortic-LV Dynamics in the Aging CV System



Ang II = angiotensin II; BP = blood pressure; CV = cardiovascular; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; MMP = matrix metalloproteinase; MVo_2 = myocardial oxygen consumption; TGF = transforming growth factor.

Heart

The ageing heart: the systemic and coronary circulation

Shane Nanayakkara, Thomas H Marwick and David M Kaye

Table 1 Cardiac changes with ageing

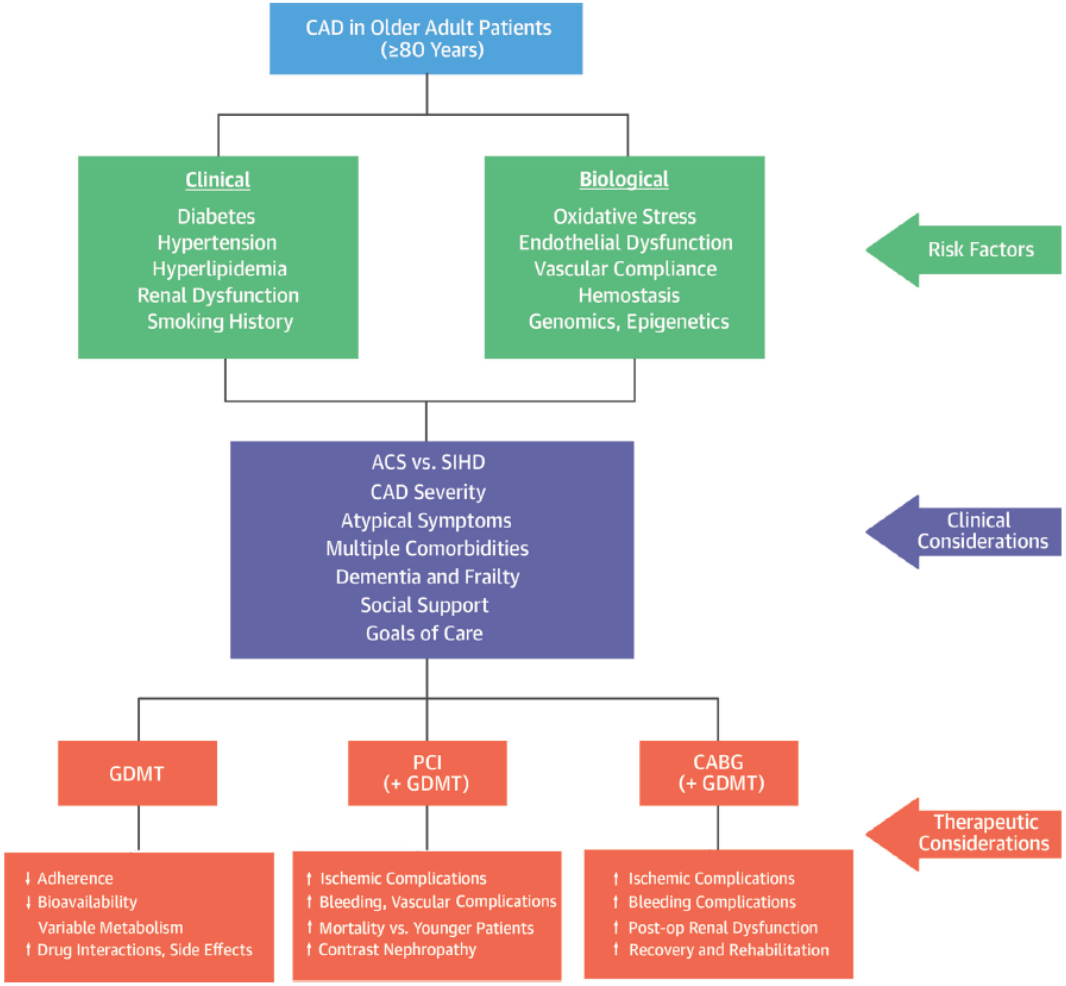
Peripheral vasculature	Coronary arteries	Atria	Ventricle	Conducting system
Increased arterial stiffness	Increased atherosclerosis	Increased left atrial fibrosis	Increased left ventricular mass	Increased prevalence of atrial fibrillation
Progressive aortic dilatation	Increased prevalence of subclinical plaque rupture	Increased left atrial volume	Reduced left ventricular cavity size	Progressive degenerative fibrosis leading to bradycardia
Increased wave reflection	Increased coronary calcification		Increased left ventricular stiffness	
Increased vasoconstriction and impaired vasodilatation	Reduced vasodilatory capacity		Impaired passive filling	
	Reduced ability to form collateral circulation		Increased left ventricular fibrosis	
	Impaired microvascular function			

Heart 2018 104: 370-376

JACC STATE-OF-THE-ART REVIEW

Coronary Artery Disease in Patients ≥80 Years of Age

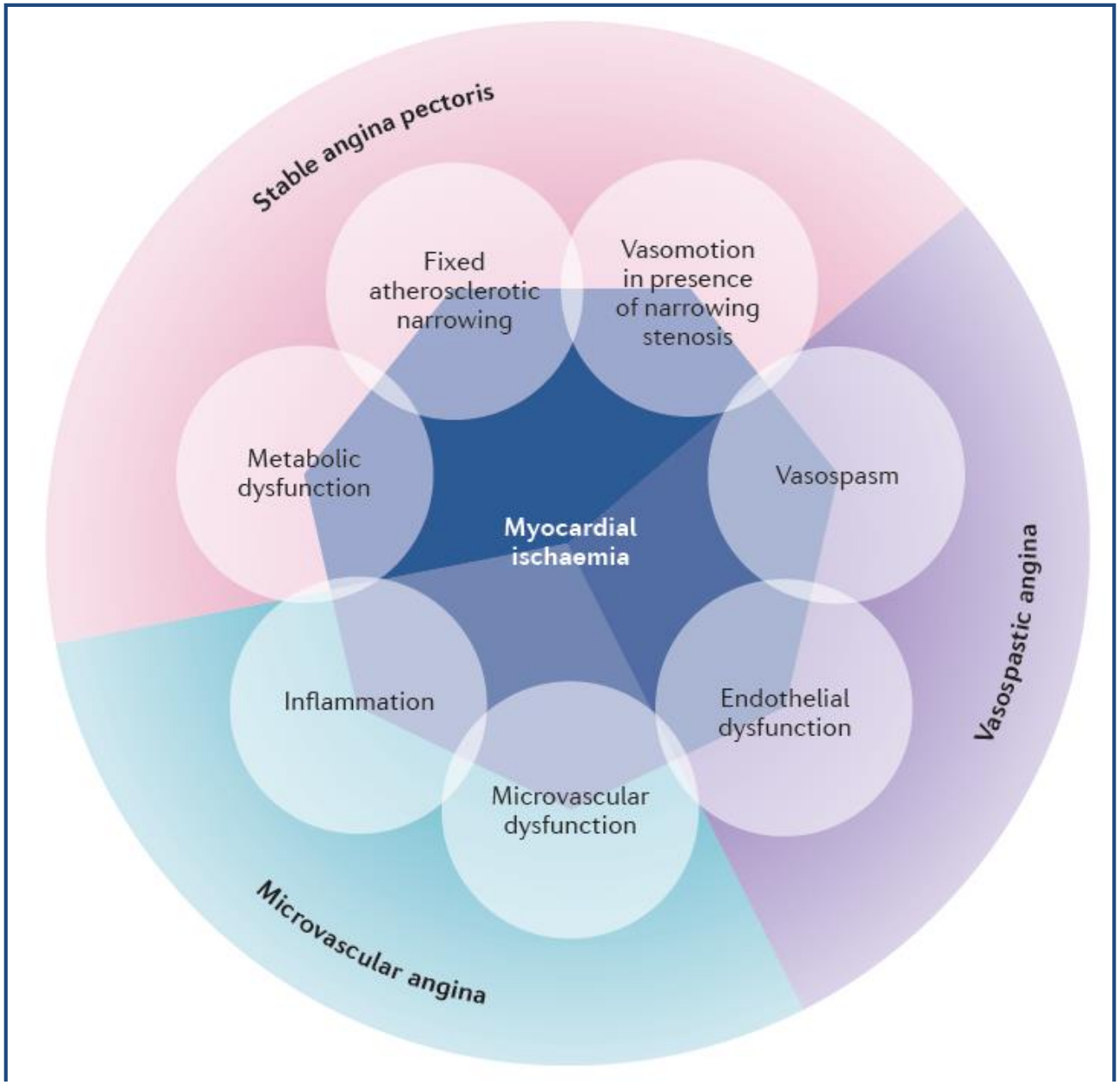
CENTRAL ILLUSTRATION Risk Factors, Clinical Influences, and Treatment Considerations in Older Patients With Coronary Artery Disease



Madhavan, M.V. et al. J Am Coll Cardiol. 2018;71(18):2015-40.

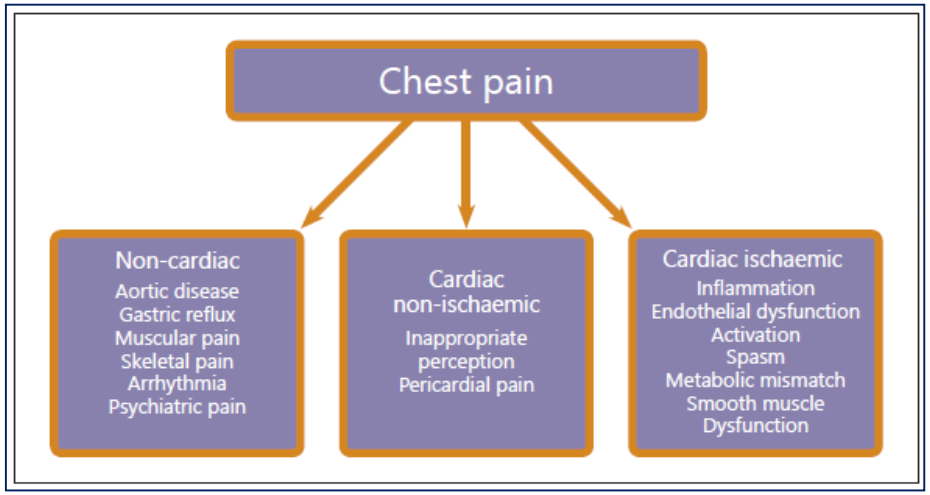
Providers need to consider the unique risk factors, clinical influences, and treatment issues that contribute to the poor prognosis in older compared with younger individuals with cardiovascular disease. ACS = acute coronary syndrome; CABG = coronary artery bypass; CAD = coronary artery disease; GDMT = guideline-directed medical therapy; PCI = percutaneous coronary intervention; SIHD = stable ischemic heart disease; STEMI = ST-segment elevation myocardial infarction.

Different manifestations of myocardial ischaemia.



Treatment of Angina: Where Are We?

Cristina Balla Rita Pavasini Roberto Ferrari



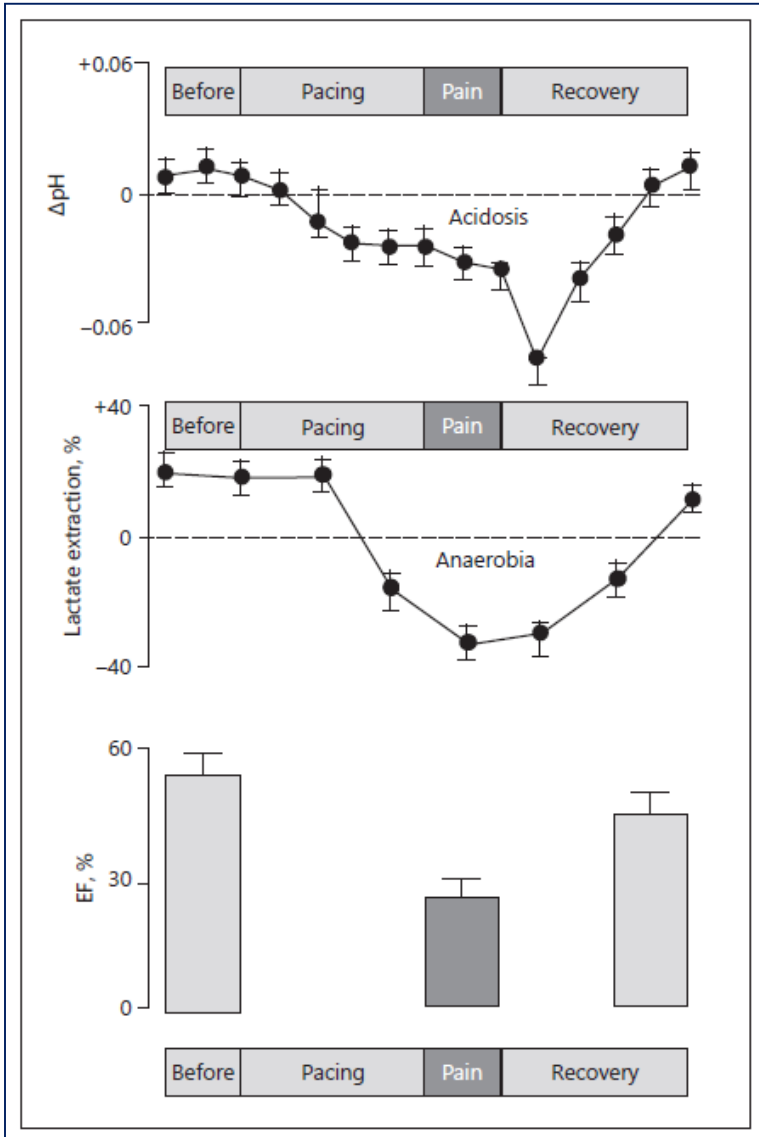


Fig. 3. Metabolic changes during the early phases of ischemia in a patient with CAD subjected to atrial pacing. ΔpH, continuous pH measured in the coronary sinus by a Ph electrode; lactate extraction, concentration of arterial lactate – coronary sinus concentration normalized for the arterial level; EF, ejection fraction.

Cardiology 2018;140:52–67

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

2013 ESC guidelines on the management of stable coronary artery disease

Table 13 Clinical pre-test probabilities[a] in patients with stable chest pain symptoms[108]

	Typical angina		Atypical angina		Non-anginal pain	
Age	Men	Women	Men	Women	Men	Women
30–39	59	28	29	10	18	5
40–49	69	37	38	14	25	8
50–59	77	47	49	20	34	12
60–69	84	58	59	28	44	17
70–79	89	68	69	37	54	24
>80	93	76	78	47	65	32

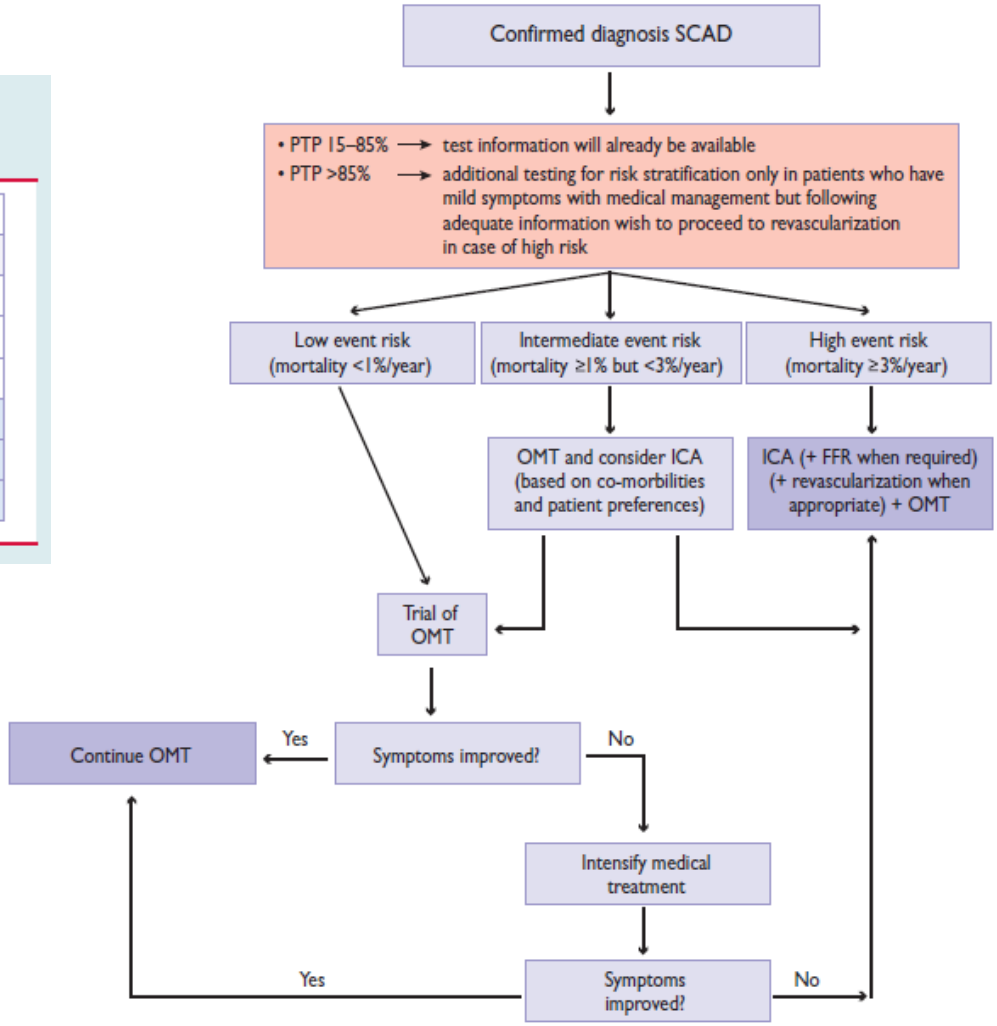


Figure 3 Management based on risk determination for prognosis in patients with chest pain and suspected SCAD (for choice of test see Fig. 2, for definitions of event risk see Table 17). ICA = invasive coronary angiography; OMT = optimal medical therapy; PTP = pre-test probability; SCAD = stable coronary artery disease.

Table 32 Indications for revascularization of stable coronary artery disease patients on optimal medical therapy (adapted from ESC/EACTS 2010 Guidelines)[172]

Indication [a]	To improve prognosis:		To improve symptoms persistent on OMT:		
	Class [d]	Level [e]	Class [d]	Level [e]	Ref. [f]
A Heart Team approach to revascularization is recommended in patients with unprotected left main, 2–3 vessel disease, diabetes or comorbidities.	I	C	I	C	172, 426–428
Left main >50% diameter stenosis[b].	I	A	I	A	172
Any proximal LAD >50% diameter stenosis[b].	I	A	I	A	172
2–3 vessel disease with impaired LV function / CHF.	I	B	IIa	B	172
Single remaining vessel (>50% diameter stenosis[b]).	I	C	I	A	172
Proven large area of ischaemia (>10% LV[c])	I	B	I	B	172
Any significant stenosis with limiting symptoms or symptoms non responsive/intolerant to OMT.	NA	NA	I	A	172
Dyspnoea/cardiac heart failure with >10% ischaemia/viability[c] supplied by stenosis >50%.	IIb	B[429, 430]	IIa	B	172
No limiting symptoms with OMT in vessel other than left main or proximal LAD or single remaining vessel or vessel subtending area of ischaemia <10% of myocardium or with FFR ≥0.80.	III	A	III	C	23, 25, 172, 400

References attached to these recommendations can be found in Table 8 of the original ESC guidelines for myocardial revascularization.[172]
CCS = Canadian Cardiovascular Society; CHF: congestive heart failure; FFR = fractional fow reserve; LAD = left anterior descending; LV = left ventricle; NA: not available; OMT = optimal medical treatment; SCAD = stable coronary artery disease.

Table W3 Decision making according to severity of symptoms/ischaemia

Severe: Angina CCS III–IV or ischaemia >10% ➡ catheterization laboratory.
Moderate-to-severe: Angina CCS II or ischaemia 5–10% ➡ OMT[a] only or catheterization laboratory.
Mild-to-moderate: Angina CCS I or ischaemia <5% ➡ OMT[a] first and defer catheterization laboratory.

[a]If symptoms and/or ischaemia are markedly reduced/eliminated by OMT, then OMT may be continued; if not, catheterization should follow. CCS = Canadian Cardiovascular Society; OMT = optimal medical therapy.

REVIEW ARTICLE

LESS IS MORE

Initial Coronary Stent Implantation With Medical Therapy vs Medical Therapy Alone for Stable Coronary Artery Disease

Meta-analysis of Randomized Controlled Trials

Kathleen Stergiopoulos, MD, PhD; David L. Brown, MD

Background: Prior meta-analyses have yielded conflicting results regarding the outcomes of treatment of stable coronary artery disease (CAD) with initial percutaneous coronary intervention (PCI) vs medical therapy. However, most of the studies in prior systematic reviews used balloon angioplasty as well as medical therapies that do not reflect current interventional or medical practices. We therefore performed a meta-analysis of all randomized clinical trials comparing initial coronary stent implantation with medical therapy to determine the effect on death, nonfatal myocardial infarction (MI), unplanned revascularization, and persistent angina.

Methods: Prospective randomized trials were identified by searches of the MEDLINE database from 1970 to September 2011. Trials in which stents were used in less than 50% of PCI procedures were excluded. Data were extracted from each study, and summary odds ratios (ORs) were obtained using a random effects model.

Results: Eight trials enrolling 7229 patients were identified. Three trials enrolled stable patients after MI, whereas 5 studies enrolled patients with stable angina and/or ischemia on stress testing. Mean weighted follow-up was 4.3 years. The respective event rates for death with stent implantation and medical therapy were 8.9% and 9.1% (OR, 0.98; 95% CI, 0.84-1.16); for nonfatal MI, 8.9% and 8.1% (OR, 1.12; 95% CI, 0.93-1.34); for unplanned revascularization, 21.4% and 30.7% (OR, 0.78; 95% CI, 0.57-1.06); and for persistent angina, 29% and 33% (OR, 0.80; 95% CI, 0.60-1.05).

Conclusion: Initial stent implantation for stable CAD shows no evidence of benefit compared with initial medical therapy for prevention of death, nonfatal MI, unplanned revascularization, or angina.

Arch Intern Med. 2012;172(4):312-319

JAMA
Internal Medicine

Original Investigation

Percutaneous Coronary Intervention Outcomes in Patients With Stable Obstructive Coronary Artery Disease and Myocardial Ischemia

A Collaborative Meta-analysis of Contemporary Randomized Clinical Trials

IMPORTANCE Myocardial ischemia in patients with stable coronary artery disease (CAD) has been repeatedly associated with impaired survival. However, it is unclear if revascularization with percutaneous coronary intervention (PCI) to relieve ischemia improves outcomes compared with medical therapy (MT).

OBJECTIVE The objective of this study was to compare the effect of PCI and MT with MT alone exclusively in patients with stable CAD and objectively documented myocardial ischemia on clinical outcomes.

DATA SOURCES MEDLINE, Cochrane, and PubMed databases from 1970 to November 2012. Unpublished data were obtained from investigators.

STUDY SELECTION Randomized clinical trials of PCI and MT vs MT alone for stable coronary artery disease in which stents and statins were used in more than 50% of patients.

DATA EXTRACTION For studies in which myocardial ischemia diagnosed by stress testing or fractional flow reserve was required for enrollment, descriptive and quantitative data were extracted from
requirement fo
determined by
from any cause
Summary odds
assessed using

RESULTS In 5 trials enrolling 5286 patients, myocardial ischemia was diagnosed in 4064 patients by exercise stress testing, nuclear or echocardiographic stress imaging, or fractional flow reserve. Follow-up ranged from 231 days to 5 years (median, 5 years). The respective event rates for PCI with MT vs MT alone for death were 6.5% and 7.3% (OR, 0.90 [95% CI, 0.71-1.16]); for nonfatal MI, 9.2% and 7.6% (OR, 1.24 [95% CI, 0.99-1.56]); for unplanned revascularization, 18.3% and 28.4% (OR, 0.64 [95% CI, 0.35-1.17]); and for angina, 20.3% and 23.3% (OR, 0.91 [95% CI, 0.57-1.44]).

CONCLUSIONS AND RELEVANCE In patients with stable CAD and objectively documented myocardial ischemia, PCI with MT was not associated with a reduction in death, nonfatal MI, unplanned revascularization, or angina compared with MT alone.

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JAMA Intern Med. 2014;174(2):232-240.

Coronary Artery Disease in Patients ≥80 Years of Age

TABLE 4 Utilization of Guideline-Directed Medical Therapy on Outcomes in Older Adult Patients

First Author (Ref. #)	Year	n	Presentation	Intervention	Outcomes
Skolnick et al. (84)	2007	51,827 (5,557 patients age ≥90 yrs and 46,270 patients age 75-89 yrs)	NSTEACS	Antiplatelet agents, anticoagulants, β-blockers, ACE inhibitor/ARBs, statins, catheterization/revascularization	Patients ≥90 yrs of age more frequently had contraindications to acute medical therapies, and thus were significantly less likely to receive such therapies or interventions. When GDMT was administered, both age groups had reductions in in-hospital mortality, but an increase in hemorrhagic events.
Teo et al. (112)	2009	2,285 (904 patients age ≥65 yrs)	Stable CAD	BP, cholesterol, lifestyle modification, and angina treatment targets in patients randomized to GDMT vs. GDMT/PCI	There was no significant difference in achieved treatment targets between groups receiving GDMT and GDMT/PCI in older cohort.
Gale et al. (81)	2012	616,011 (72,721 patients age ≥85 yrs)	ACS	Antiplatelet agents, β-blockers, ACE inhibitor/ARBs, statins, revascularization	All patients (including older individuals) experienced improvements in in-hospital mortality between 2003 and 2010. Older patients were less likely than younger individuals to receive GDMT, but this difference narrowed over time.
Bucholz et al. (85)	2016	147,429 (mean age 76.6 yrs)	ACS	Aspirin, β-blockers, revascularization (and timing parameters)	Guideline-based therapy was associated with improved early and late survival.
Schoenenberger et al. (82)	2016	13,662 patients age ≥70 yrs	ACS	Antiplatelet agents, anticoagulants, β-blockers, ACE inhibitor/ARB, revascularization	Improvements in adherence to GDMT were associated with reduced in-hospital mortality between 2001-2012.

BP = blood pressure; GDMT = guideline-directed medical therapy; NSTEACS = non-ST-segment elevation acute coronary syndrome; other abbreviations as in Table 3.

Patterns and Intensity of Medical Therapy in Patients Undergoing Percutaneous Coronary Intervention

Borden W, JAMA 2011

William B. Borden, MD
Rita F. Redberg, MD, MSc
Alvin I. Mushlin, MD, ScM
David Dai, PhD
Lisa A. Kaltenbach, MS
John A. Spertus, MD, MPH

Context The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study, which provided optimal medical therapy (OMT) to all patients and demonstrated no incremental advantage of percutaneous coronary intervention (PCI) on outcomes other than angina-related quality of life in stable coronary artery disease (CAD), suggests that a trial of OMT is warranted before PCI. It is unknown to what degree OMT is applied before PCI in routine practice or whether its use increased after the COURAGE trial.

Objective To examine the use of OMT in patients with stable angina undergoing PCI before and after the publication of the COURAGE trial.

Design, Setting, and Participants An observational study of patients with stable CAD undergoing PCI in the National Cardiovascular Data Registry between September 1, 2005, and June 30, 2009. Analysis compared use of OMT, both before PCI and at the time of discharge, before and after the publication of the COURAGE trial. Optimal medical therapy was defined as either being prescribed or having a documented contraindication to all medicines (antiplatelet agent, β-blocker, and statin).

Main Outcome Measures Rates of OMT before PCI and at discharge (following PCI) between the 2 study periods.

…less than half were receiving OMT before PCI …

ALTHOUGH PERCUTANEOUS coronary intervention (PCI) may improve outcomes for patients with acute coronary syndrome, optimal medical therapy (OMT) results in similar rates of cardiovascular events when compared with PCI in patients with stable coronary artery disease (CAD).[1,2] In fact, a meta-analysis of 11 trials[2] concluded that th
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ation (COURAGE) study.[3] In the COURAGE trial, patients with stable CAD underwent diagnostic coronary angiography to define their coronary anatomy and received aggressive secondary prevention therapy,[4] with half

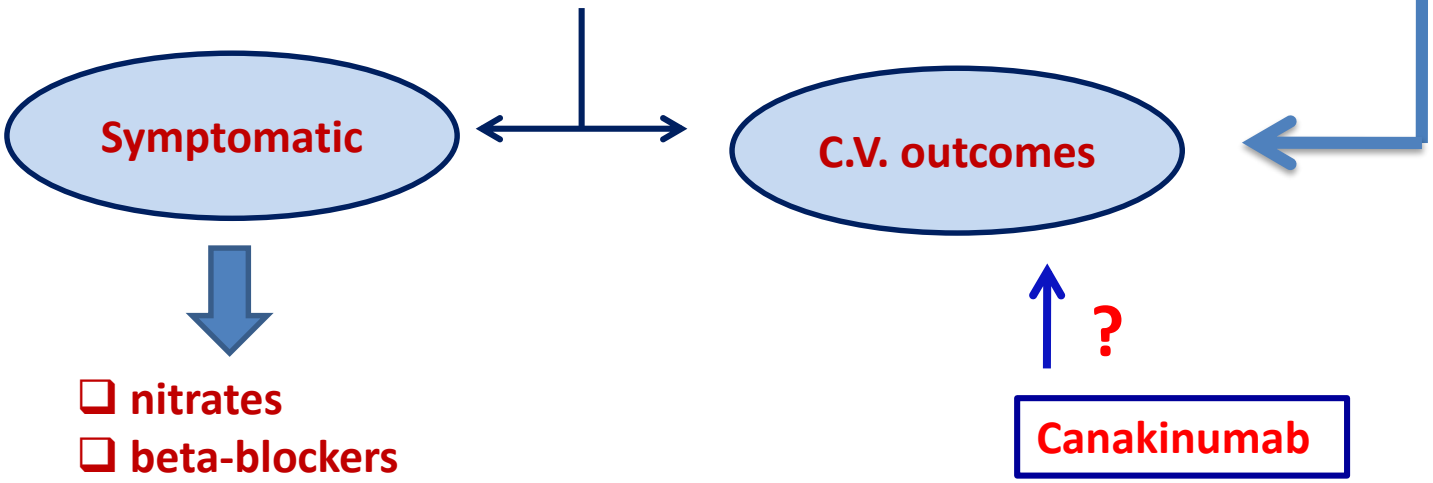
(95% CI, 65.8%-66.1%), respectively (P<.001).

Conclusion Among patients with stable CAD undergoing PCI, less than half were receiving OMT before PCI and approximately two-thirds were receiving OMT at discharge following PCI, with relatively little change in these practice patterns after publication of the COURAGE trial.

JAMA. 2011;305(18):1882-1889 www.jama.com

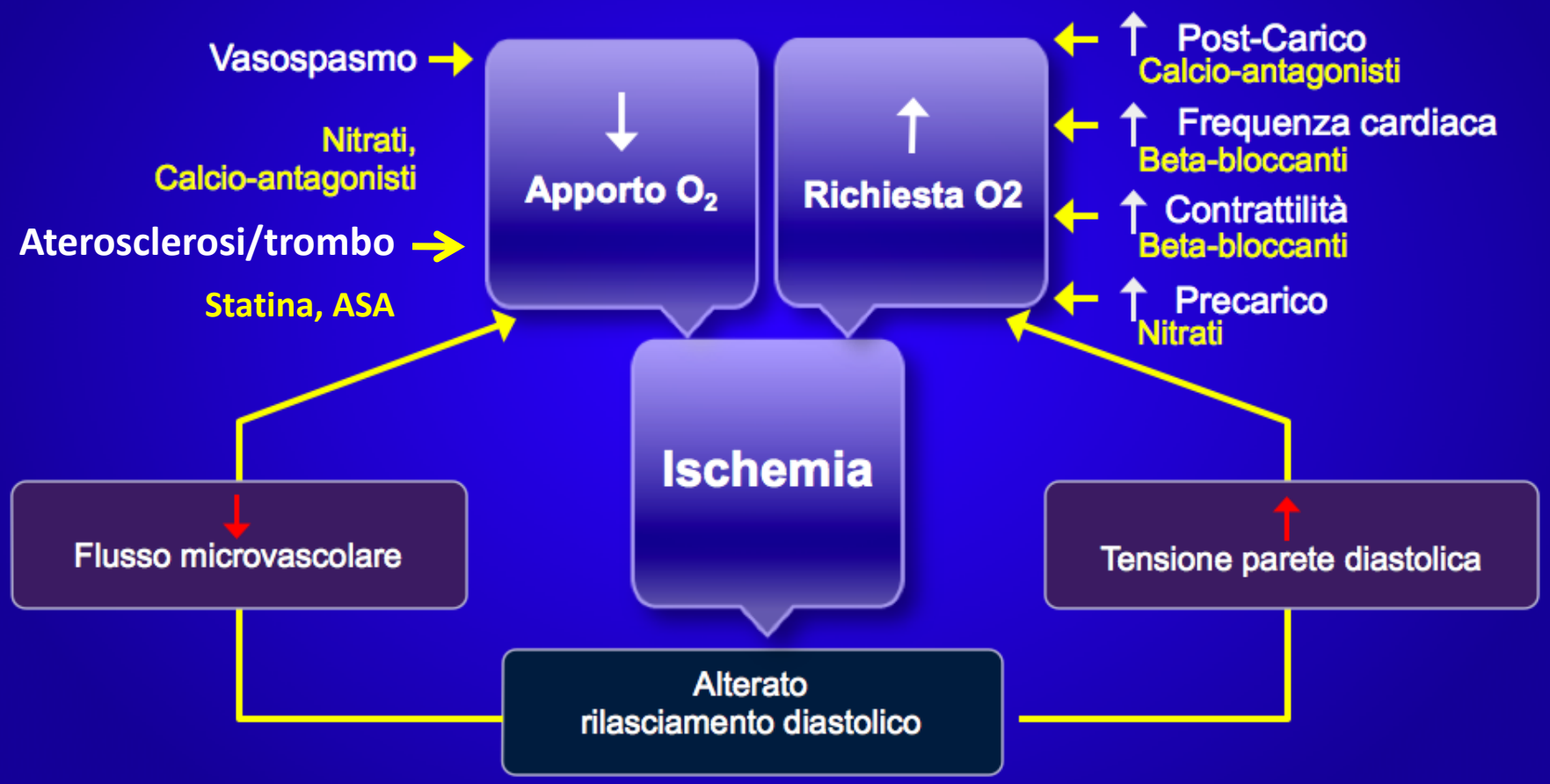
Management of Chronic Stable Angina

- ✓ Lifestyle modifications
- ✓ Control of Cardiovascular Risk Factors
- ✓ Non invasive treatment/Pharmacological therapy



- ❑ nitrates
- ❑ beta-blockers
- ❑ CCB
- ❑ trimetazidine
- ❑ Ivabradine
- ❑ ranolazine

I convenzionali farmaci antianginosi *(beta-bloccanti, calcio-antagonisti, nitrati)* agiscono attraverso la riduzione del doppio prodotto



Bonadei I, et al. Recent Pat Cardiovasc Drug Discov 2011; 6(3):215-21 - Grafico elaborato da: Stone, Cardiol Clin 26 (2008) 603-614 - Malattie del Cuore, Braunwald 7 ^ edizione cap. 50 (pagg. 1297,1299,1300,1303); cap. 44, pag 1103

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

2013 ESC guidelines on the management of stable coronary artery disease

Table 27 Major side-effects, contra-indications, drug–drug interactions (DDI) and precautions of anti-ischaemic drugs. (List is not exhaustive: refer to summary of products characteristics for details.)

Drug class	Side effects [a]	Contraindications	DDI	Precautions
Short-acting and long-acting nitrates[329]	• Headache • Flushing • Hypotension • Syncope and postural hypotension • Reflex tachycardia • Methaemoglobinaemia	• Hypertrophic obstructive cardiomyopathy	• PDE5 inhibitors (sildenafil or similar agents) • α-adrenergic blockers • CCBs	-
ß-blockers[291, 293, 302,b]	• Fatigue, depression[304] • Bradycardia • Heart block • Bronchospasm • Peripheral vasoconstriction • Postural hypotension • Impotence • Hypoglycaemia/mask hypoglycaemia signs	• Low heart rate or heart conduction disorder • Cardiogenic shock • Asthma • COPD caution; may use cardioselective ß-blockers if fully treated by inhaled steroids and long-acting ß-agonists[330] • Severe peripheral vascular disease • Decompensated heart failure • Vasospastic angina	• Heart-rate lowering CCB • Sinus-node or AV conduction depressors	• Diabetics • COPD[330]
CCBs: heart-rate lowering[303, 304]	• Bradycardia • Heart conduction defect • Low ejection fraction • Constipation • Gingival hyperplasia	• Low heart rate or heart rhythm disorder • Sick sinus syndrome • Congestive heart failure • Low BP	• Cardiodepressant (ß-blockers, flecainide) • CYP3A4 substrates	-
CCBs: Dihydropyridines[27, 305, 331]	• Headache • Ankle swelling • Fatigue • Flushing • Reflex tachycardia	• Cardiogenic shock • Severe aortic stenosis • Obstructive cardiomyopathy	• CYP3A4 substrates	-

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

2013 ESC guidelines on the management of stable coronary artery disease

Drug class	Side effects [a]	Contraindications	DDI	Precautions
Ivabradine[307]	• Visual disturbances • Headache, dizziness • Bradycardia • Atrial fibrillation • Heart block	• Low heart rate or heart rhythm disorder • Allergy • Severe hepatic disease	• QTc prolonging drugs • Macrolide antibiotics • Anti-HIV • Anti-fungal	• Age >75 years • Severe renal failure
Nicorandil[177]	• Headache • Flushing • Dizziness, weakness • Nausea • Hypotension • Oral, anal, gastrointestinal ulceration	• Cardiogenic shock • Heart failure • Low blood pressure	• PDE5 inhibitors (Sildenafil or similar agents)	-
Trimetazidine[315, 316]	• Gastric discomfort • Nausea • Headache • Movement disorders	• Allergy • Parkinson disease • Tremors and movement disorders • Severe renal impairment	• None reported	• Moderate renal impairment • Elderly
Ranolazine[317,218, 318]	• Dizziness • Constipation • Nausea • QT prolongation	• Liver cirrhosis	• CYP450 substrates (digoxin, simvastatin, cyclosporine) • QTc prolonging drugs	-

Table 28 Pharmacological treatments in stable coronary artery disease patients

Indication	Class [a]	Level [b]
General considerations		
Optimal medical treatment indicates at least one drug for angina/ischaemia relief plus drugs for event prevention.	I	C
It is recommended to educate patients about the disease, risk factors and treatment strategy.	I	C
It is indicated to review the patient's response soon after starting therapy.	I	C
Angina/ischaemia[d] relief		
Short-acting nitrates are recommended.	I	B
First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms.	I	A
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
According to comorbidities/tolerance it is indicated to use second-line therapies as first-line treatment in selected patients.	I	C
In asymptomatic patients with large areas of ischaemia (>10%) ß-blockers should be considered.	IIa	C
In patients with vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.	IIa	B
Event prevention		
Low-dose aspirin daily is recommended in all SCAD patients.	I	A
Clopidogrel is indicated as an alternative in case of aspirin intolerance.	I	B
Statins are recommended in all SCAD patients.	I	A
It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g. heart failure, hypertension or diabetes).	I	A

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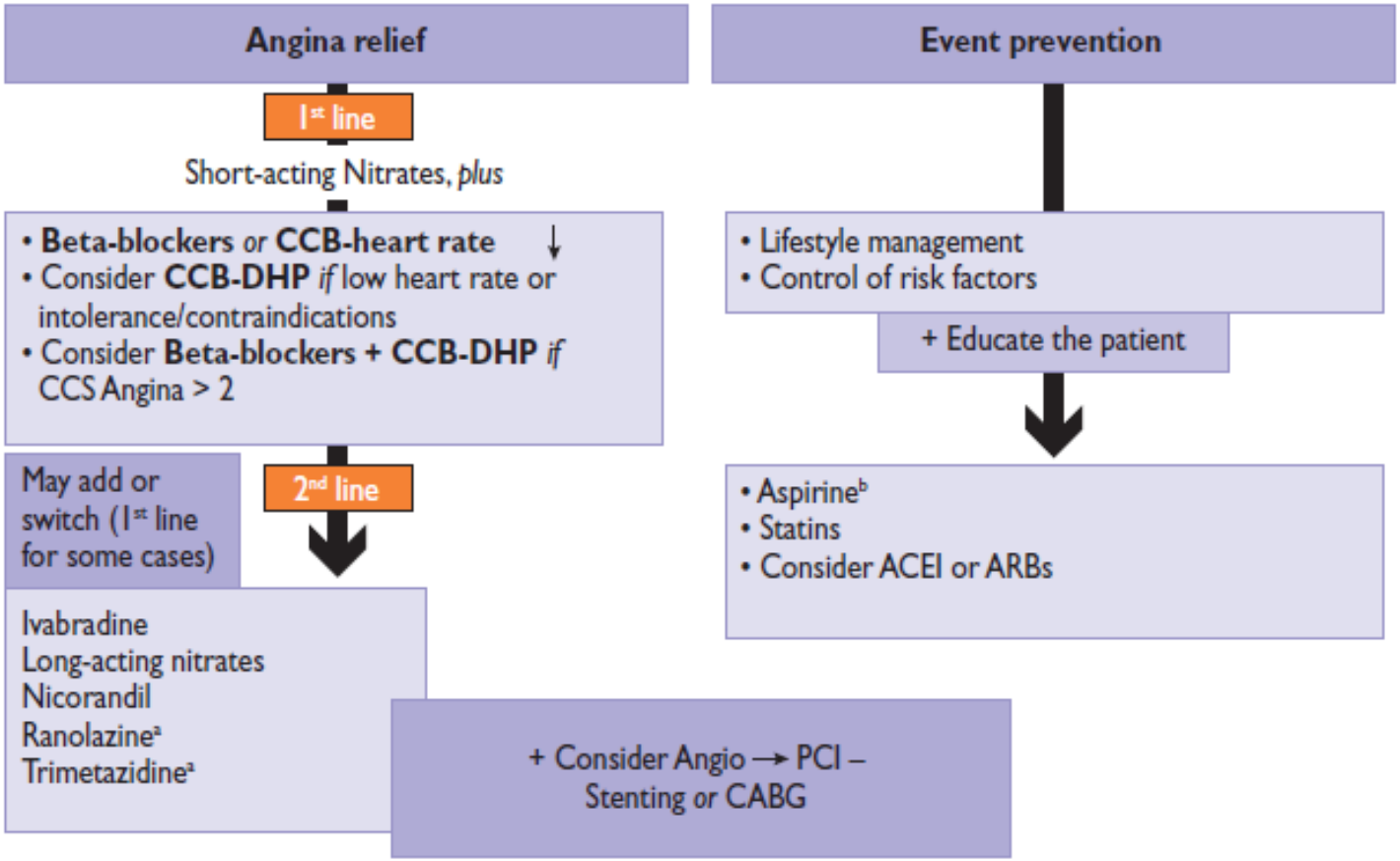
2013 ESC guidelines on the management of stable coronary artery disease

Medical management of patients with SCAD



2013 ESC guidelines on the management of stable coronary artery disease

Eur Heart J , August 30, 2013

Medical management of patient with stable CAD

Angina relief

1st line

Short-acting Nitrates, *plus*

- **Beta-blockers** *or* **CCB-he**
- Consider **CCB-DHP** *if* low intolerance/contraindication
- Consider **Beta-blockers +** CCS Angina > 2

May add or switch (1st line for some cases)

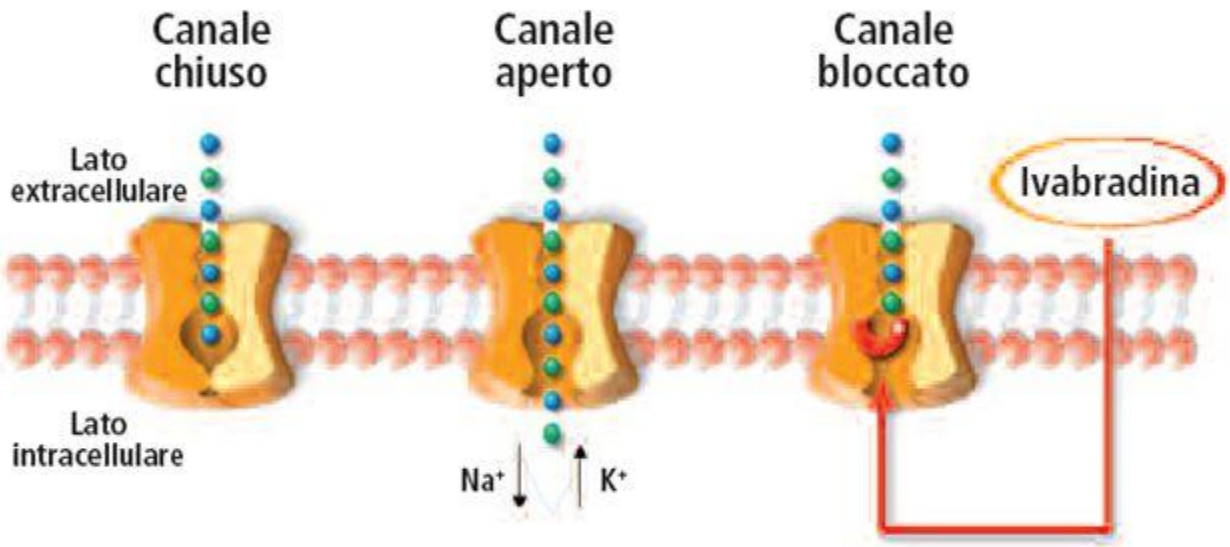
2nd line

Ivabradine
Long-acting nitrates
Nicorandil
Ranolazine[a]
Trimetazidine[a]

Ivabradine
Long-acting nitrates
Nicorandil
Ranolazine[a]
Trimetazidine[a]

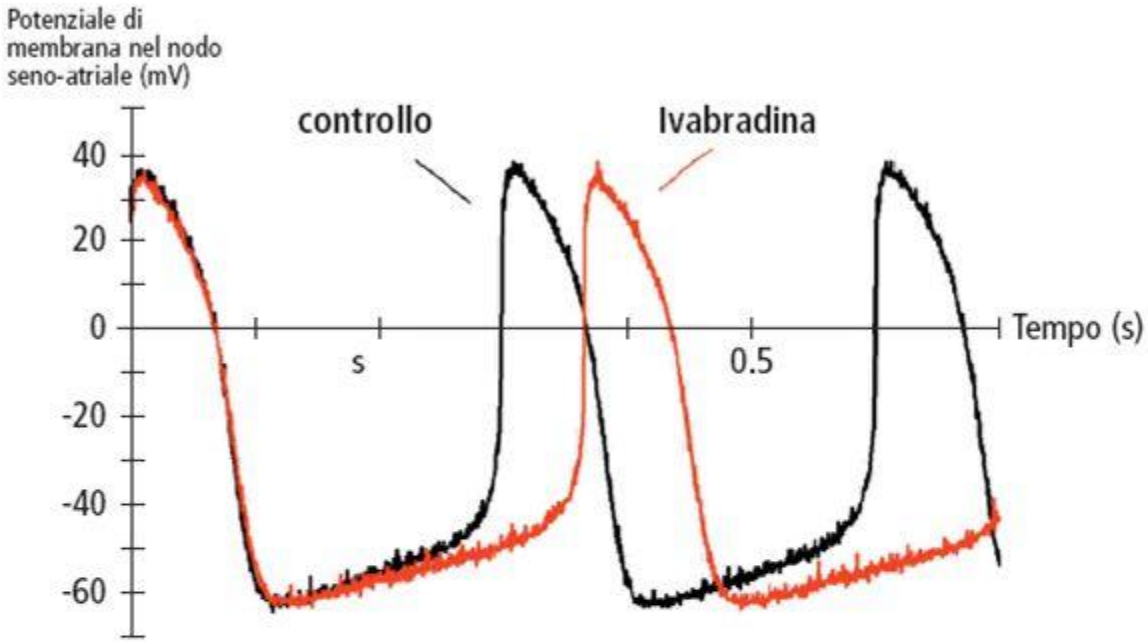
IVABRADINA

Ivabradina è un inibitore specifico e selettivo della "corrente pace-maker" (I_f)



La corrente I_f è stata battezzata **f** per **funny** (buffa) perché è l'unica corrente ionica nel nodo SA che si attiva in fase di iperpolarizzazione, ha la proprietà di generare un ritmo spontaneo di depolarizzazione e controllare la frequenza cardiaca, costituendo quindi il "pacemaker" naturale del cuore.

IVABRADINA



Ivabradina penetra direttamente *all'interno del canale If*, *blocca esclusivamente questa corrente* e *allunga l'intervallo di tempo tra due potenziali d'azione*.
Poiché l'apertura dei canali If è "frequenza dipendente", il farmaco è efficace solo a frequenze cardiache elevate, evitando così il rischio di bradicardizzazioni eccessive.

L'azione di ivabradina permette di ridurre la frequenza cardiaca ed il consumo di ossigeno senza agire a livello periferico sulla muscolatura liscia vascolare (come i calcio-antagonisti) e senza alterare la contrattilità miocardica né la circolazione coronarica (come i beta-bloccanti)

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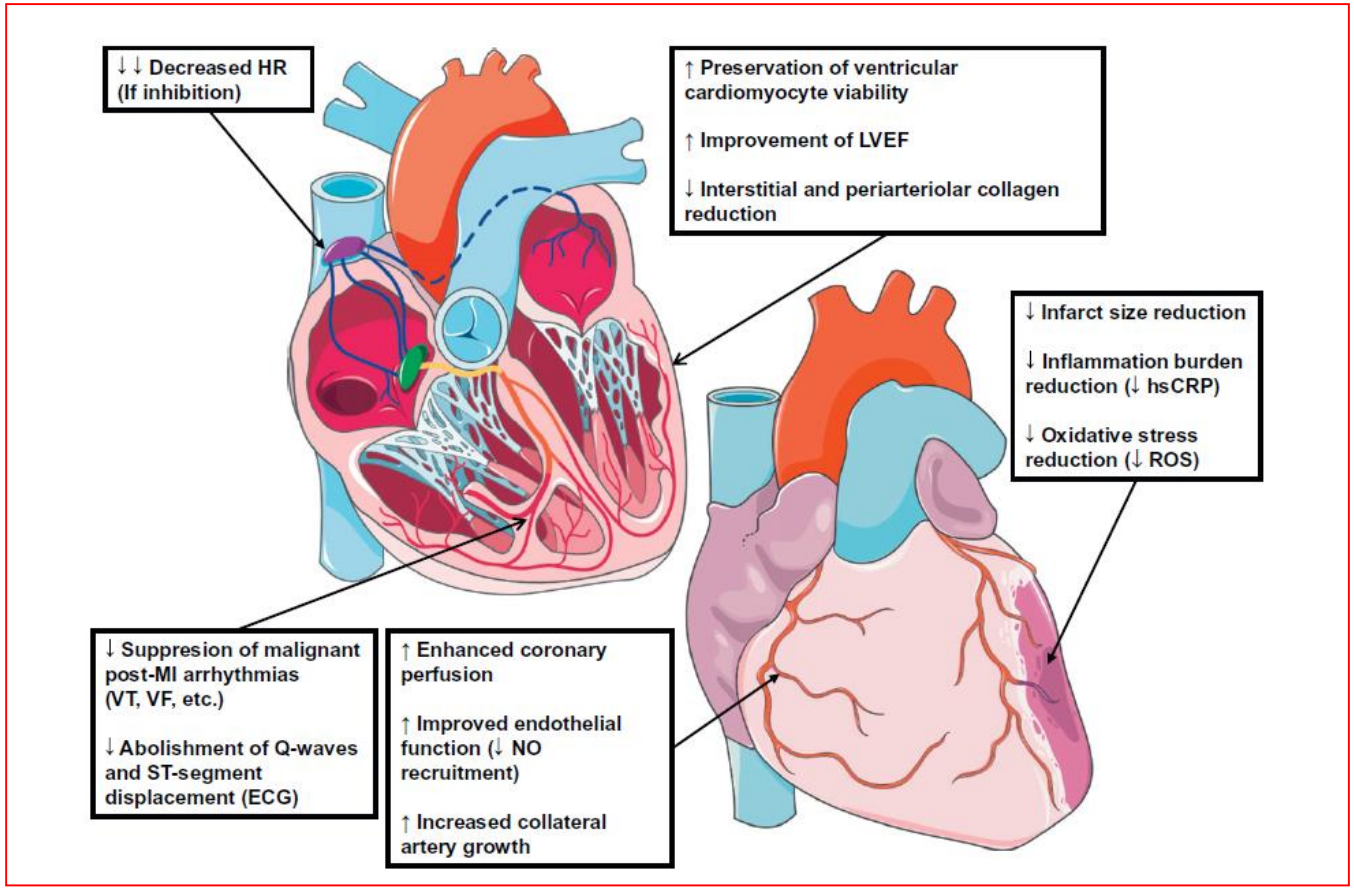
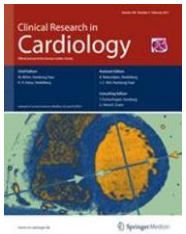
Ivabradine in acute coronary syndromes: Protection beyond heart rate lowering☆

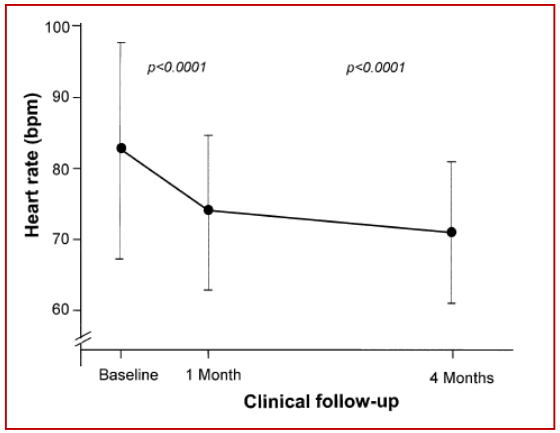


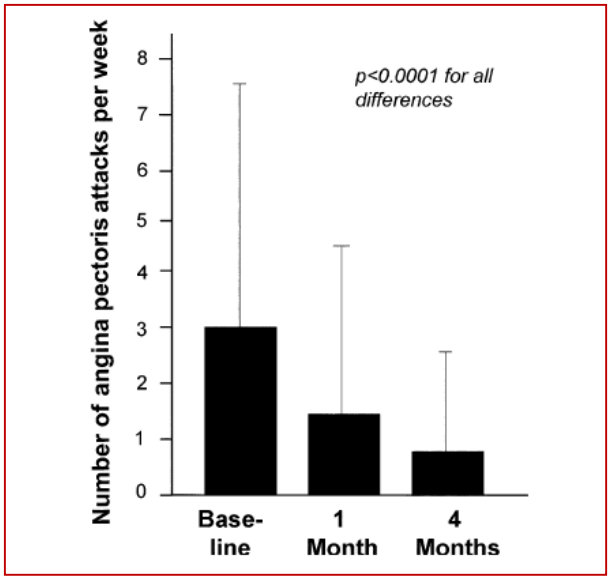


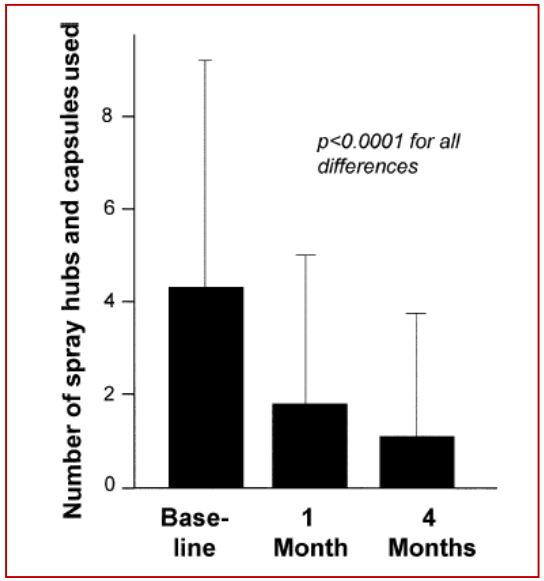
Clin Res Cardiol (2011) 100:121–128
DOI 10.1007/s00392-010-0220-0

ORIGINAL PAPER

Ivabradine for the treatment of stable angina pectoris in octogenarians







Conclusions The results demonstrate that ivabradine efficiently reduces HR, number of angina attacks, and nitrate consumption in octogenarian patients. The treatment was safe and well tolerated without relevant bradycardia.

European Heart Journal
doi:10.1093/eurheartj/ehp358

FASTTRACK
ESC CLINICAL TRIAL UPDATE

Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial

Kim Fox[1]*, Ian Ford[2], P. Gabriel Steg[3], Michal Tendera[4], Michele Robertson[2], and Roberto Ferrari[5] on behalf of the BEAUTIFUL investigators

[1]Royal Brompton Hospital, Sydney Street, London, UK; [2]Robertson Centre for Biostatistics, University of Glasgow, Glasgow, UK; [3]INSERM U-698, Hôpital Bichat-Claude Bernard, AP-HP, University Paris 7, Paris, France; [4]Medical University of Silesia, Katowice, Poland; and [5]Chair of Cardiology, University of Ferrara, S. Maugeri Foundation, Ferrara, Italy

Received 18 June 2009; revised 11 August 2009; accepted 12 August 2009

Aims BEAUTIFUL found no impact of ivabradine on outcomes in patients with stable coronary artery disease (CAD) and left ventricular systolic dysfunction (LVSD). We performed a *post hoc* analysis of the effect of ivabradine in BEAUTIFUL patients whose limiting symptom at baseline was angina, particularly in terms of coronary outcomes.

Methods and results Of the BEAUTIFUL population, 13.8% had limiting angina at baseline (734 ivabradine, 773 placebo); of these, 712 patients had heart rate ≥70 b.p.m. Median duration of follow-up was 18 months. Ivabradine was associated with a 24% reduction in the primary endpoint (cardiovascular mortality or hospitalization for fatal and non-fatal myocardial infarction [MI] or heart failure) (HR, 0.76; 95% CI, 0.58–1.00) and a 42% reduction in hospitalization for MI (HR, 0.58, 95% CI, 0.37–0.92). In patients with heart rate ≥70 b.p.m., there was a 73% reduction in hospitalization for MI (HR, 0.27, 95% CI, 0.11–0.66) and a 59% reduction in coronary revascularization (HR, 0.41, 95% CI, 0.17–0.99). Ivabradine was safe and well tolerated.

Conclusion Our analyses raises the possibility that ivabradine may be helpful to reduce major cardiovascular events in patients with stable CAD and LVSD who present with limiting angina. However, a large-scale clinical trial is ongoing, which will formally test this hypothesis.

Summary of observed cardiovascular risk reduction in angina patients

New results in angina patients

Predefined end point (n=1507)	Hazard ratio	Risk reduction
Primary composite end point	0.76	24%
All-cause mortality	0.87	13%
CV death	0.88	12%
Hospitalization for HF	0.84	16%
Hospitalization for MI	0.58	42%
Coronary revascularization	0.70	30%

Fox K, Ford I, et al; BEAUTIFUL Investigators. Effect of ivabradine on cardiovascular outcomes in patients with stable coronary artery diseaseand left-ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. Eur heart Jour On line.

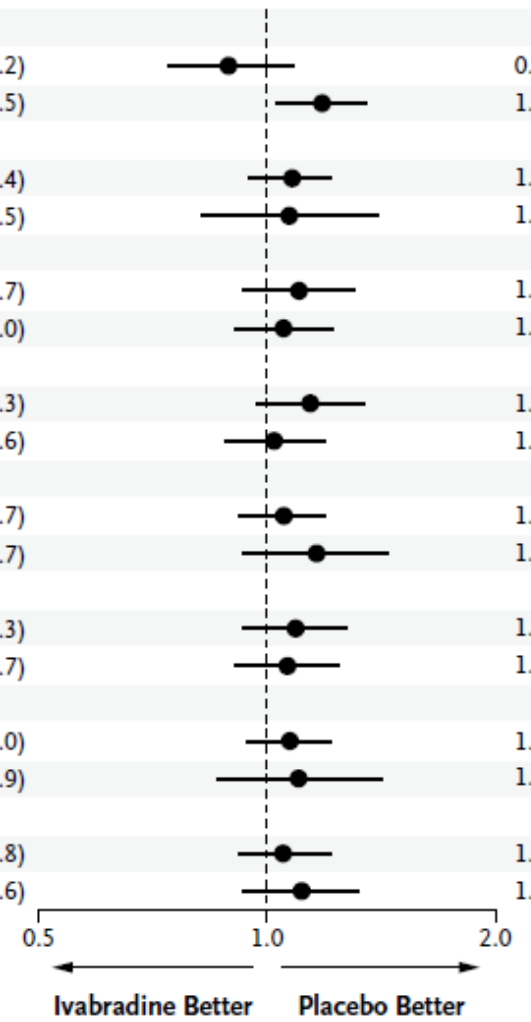
The NEW ENGLAND JOURNAL of MEDICINE

Fox K, September 2014

Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure

SIGNIFY

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	15,878	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)	



2013 ESC guidelines on the management of stable coronary artery disease

Eur Heart J , August 30, 2013

Medical management of patient with stable CAD

Angina relief

1st line

Short-acting Nitrates, *plus*

- **Beta-blockers** *or* **CCB-he**
- Consider **CCB-DHP** *if* low intolerance/contraindication
- Consider **Beta-blockers +** CCS Angina > 2

May add or switch (1st line for some cases)

2nd line

Ivabradine
Long-acting nitrates
Nicorandil
Ranolazine[a]
Trimetazidine[a]

Ivabradine

Long-acting nitrates

Nicorandil

Ranolazine[a]

Trimetazidine[a]

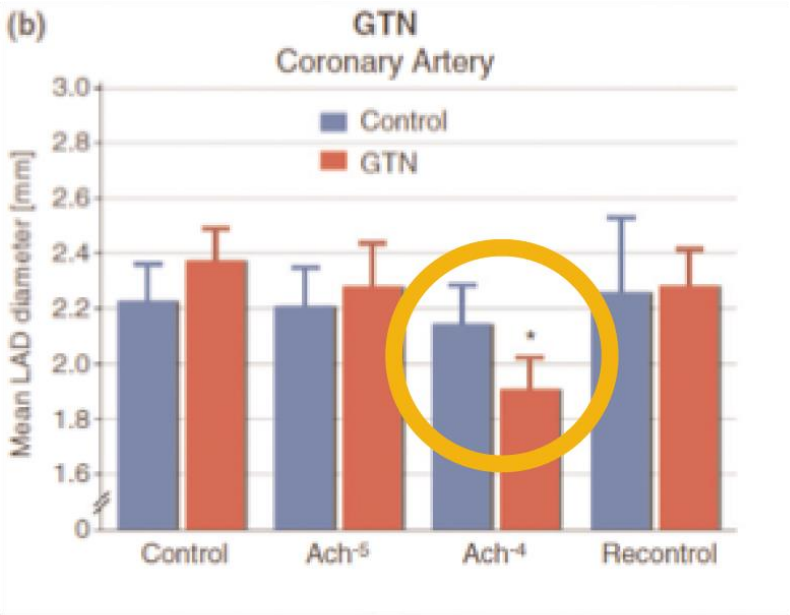
Long-acting nitrates for angina prophylaxis

Long-acting nitrates for angina prophylaxis. Long-acting nitrates are not continuously effective if regularly taken over a prolonged period without a nitrate-free or nitrate-low interval of about 8–10 hours (tolerance). Worsening of endothelial dysfunction is a potential complication of long-acting nitrates, hence the common practice of the routine use of long-acting nitrates as first line therapy for patients with effort angina needs re-evaluation.[283]

Current Opinion in Pharmacology
2013; 13:251-259

Nitrate therapy and nitrate tolerance in patients with coronary artery disease

Thomas Münzel and Tommaso Gori



Prolonged exposure to organic nitrates induces tolerance, sympathetic activation, and endothelial dysfunction in patients with cardiovascular disease

Nitrate-induced endothelial disfunction, human studies

Isosorbide-5-mononitrate and endothelial function: a wolf in sheep's clothing

Rassaf, Eur Heart J 2013

Taken together, the seminal findings reported by Oelze *et al*. and emerging data from preclinical studies using PKC, NADPH oxidase inhibitors, and inorganic nitrates may lead to a rethink and re-evaluation of our current therapeutic strategies in using various types of NO donors and oxidative stress-modulating substances in patients with vascular dysfunction and diseases.

2013 ESC guidelines on the management of stable coronary artery disease

Eur Heart J , August 30, 2013

Medical management of patient with stable CAD

Angina relief

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Ivabradine

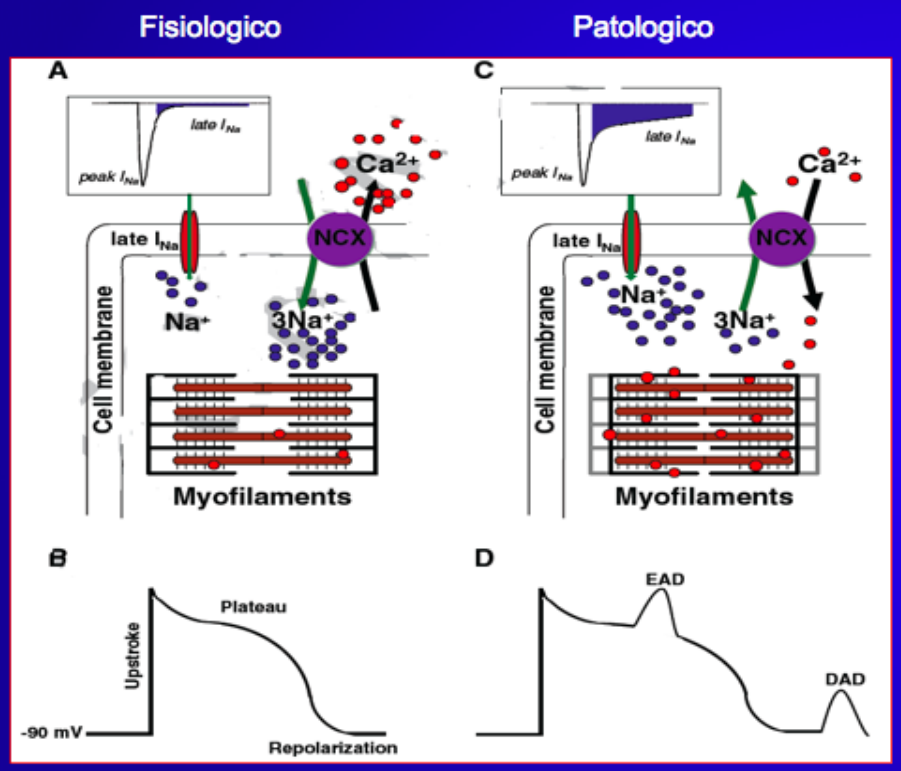
Long-acting nitrates

Nicorandil

Ranolazine[a]

Trimetazidine[a]

Ranolazina: meccanismo d'azione



Ischemia

↑ corrente tardiva di sodio

sovraccarico di sodio

sovraccarico di calcio

Mancato rilassamento diastolico (aumento della tensione diastolica) Compressione extravascolare

Ranolazina: inibisce la corrente tardiva del sodio

L'inibizione della corrente tardiva del sodio è in grado di ridurre il sovraccarico di calcio sodio-indotto ed i suoi effetti dannosi sulla funzione miocardica

Sossalla, Pharmacology & Therapeutics 133 (2012) 311-323 - Belardinelli L. Heart 2006;92(Suppl. IV):iv6-iv14 - Belardinelli L. Eur Heart J Supplements 2004;6(Suppl. 1):13-7

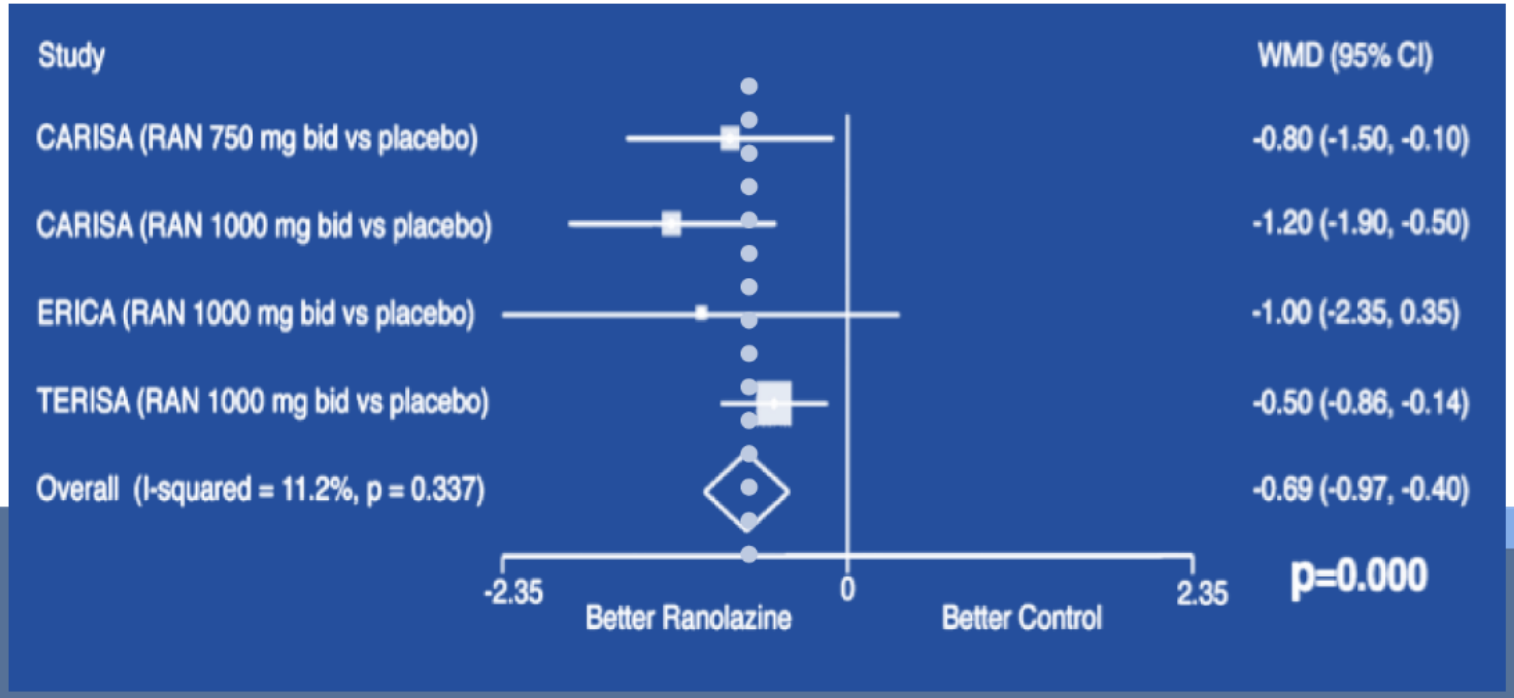
Effects of ranolazine in symptomatic patients with stable coronary artery disease. A systematic review and meta analysis

Savarese, Int. J Cardiol 2013

Gianluigi Savarese[a], Giuseppe Rosano[b], Carmen D'Amore[a], Francesca Musella[a], Giuseppe Luca Della Ratta[a], Angela Maria Pellegrino[a], Tiziana Formisano[a], Alice Vitagliano[a], Annapaola Cirillo[a], Gennaro Cice[c], Luigi Fimiani[a], Luca del Guercio[d], Bruno Trimarco[a], Pasquale Perrone-Filardi[a]*

[a] Department of Advanced Biomedical Science, Federico II University, Naples, Italy / [b] Clinical and Experimental Research Center, IRCCS San Raffaele, Rome, Italy
[c] Division of Cardiology , Second University of Naples, Naples, Italy / [d] Department of vascular and Endovascular Surgery, Federico II University, Naples, Italy

Mean difference estimate of weekly angina onset in Ranolazine versus control study groups



Original Paper

Safety and Efficacy of Extended-Release Ranolazine in Patients Aged 70 Years or Older With Chronic Stable Angina Pectoris

Michael W. Rich, MD;[1] Michael Crager, PhD;[2] Charles R. McKay, MD[3]

Table II. Average Weekly Rate of Angina and Nitroglycerin Consumption Over 6 Weeks[a]

	Younger Than 70 Years		70 Years or Older	
	Placebo (N=409)	Ranolazine 1000 mg bid (N=403)	Placebo (N=130)	Ranolazine 1000 mg bid (N=135)
Average Weekly Rate of Angina				
Mean (SE)	4.16±0.46	3.11±0.23	3.21±0.41	2.08±0.23
Mean (SE) excluding outliers[b]	3.61±0.20	3.11±0.23	3.21±0.41	2.08±0.23
25th percentile	1.20	0.70	0.70	0.40
Median	2.33	1.83	1.94	1.37
75th percentile	4.61	3.43	3.73	2.80
P value[c]	<.001		.065	
Average Weekly Rate of Nitroglycerin Consumption				
Mean (SE)	3.63±0.43	2.47±0.30	2.45±0.35	1.51±0.21
Mean (SE) excluding outliers[d]	3.15±0.26	2.18±0.22	2.45±0.35	1.51±0.21
25th percentile	0.30	0.20	0.20	0.00
Median	1.49	0.91	0.98	0.64
75th percentile	3.70	2.20	2.70	1.80
P value[c]	<.001		.077	

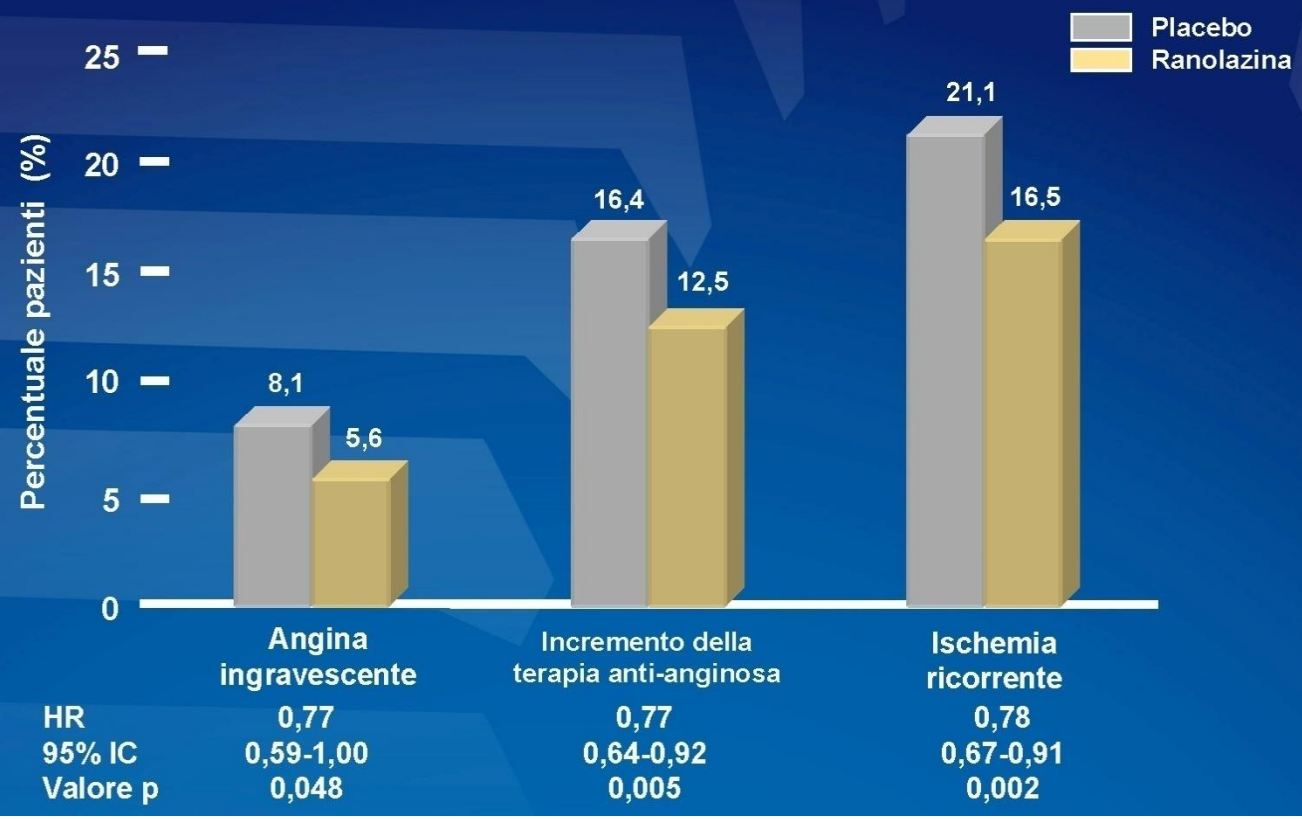
[a]Data from the Combination Assessment of Ranolazine in Stable Angina (CARISA) and Efficacy of Ranolazine in Chronic Angina (ERICA) trials combined. [b]Two outlying values of 70 and 160 attacks per week were excluded. Both occurred in the placebo group in patients younger than 70 years. [c]Cochran-Mantel-Haenszel mean scores test with rank-based scores, stratifying by background therapy. [d]Four outlying values of 60, 62, 91, and 112 per week were excluded. Two each occurred in the ranolazine and placebo groups in patients younger than 70 years.

Table III. Adverse Events, Selected Serious Adverse Events, and Early Discontinuations Due to Adverse Events for All Dosed Patients in CARISA and ERICA

	Younger Than 70 Years			70 Years or Older		
Adverse Events[a]	Placebo (N=420)	Ranolazine (N=604)	*P* Value[b]	Placebo (N=132)	Ranolazine (N=231)	*P* Value[b]
Any adverse event	131 (31.2)	194 (32.1)	.79	43 (32.6)	102 (44.2)	.034
Any cardiac adverse event	37 (8.8)	38 (6.3)	.14	2 (1.5)	2 (0.9)	.62
Constipation	7 (1.7)	33 (5.5)	.002	2 (1.5)	30 (13.0)	<.001
Nausea	4 (1.0)	21 (3.5)	.012	1 (0.8)	12 (5.2)	.037
Dyspepsia	3 (0.7)	6 (1.0)	.74	1 (0.8)	5 (2.2)	.42
Dizziness	9 (2.1)	26 (4.3)	.079	3 (2.3)	15 (6.5)	.083
Headache	10 (2.4)	14 (2.3)	1.00	1 (0.8)	8 (3.5)	.16
Peripheral edema	7 (1.7)	11 (1.8)	1.00	4 (3.0)	9 (3.9)	.78
Asthenia	2 (0.5)	6 (1.0)	.48	1 (0.8)	9 (3.9)	.10
Serious adverse events						
Any serious adverse event	17 (4.0)	30 (5.0)	.55	4 (3.0)	14 (6.1)	.31
Myocardial infarction	2 (0.5)	5 (0.8)	–	0	1 (0.4)	–
Syncope	0	2 (0.3)	–	0	1 (0.4)	–
TIA/CVA	0	2 (0.3)	–	0	1 (0.4)	–
Early discontinuations	15 (3.6)	27 (4.5)	.52	5 (3.8)	23 (10.0)	.040
Most frequent classes of adverse events causing termination						
Gastrointestinal disorders	0	5 (0.8)	.08	2 (1.5)	9 (3.9)	.34
Nervous system disorders	0	8 (1.3)	.024	1 (0.8)	10 (4.3)	.063
Cardiac disorders	8 (1.9)	9 (1.5)	.17	3 (2.3)	5 (2.2)	.28

Data are presented as No. (%). [a]Incidence >2% on ranolazine in either subgroup. [b]Fisher exact test. Abbreviations: CARISA, Combination Assessment of Ranolazine in Stable Angina; CVA, cerebrovascular accident; ERICA, Efficacy of Ranolazine in Chronic Angina; TIA, transient ischemic attack.

Ranolazina, nei pazienti con angina cronica dello studio MERLIN-TIMI 36, ha ridotto in maniera significativa l'angina ingravescente, l'incremento della terapia anti-anginosa e l'ischemia ricorrente



Wilson SR et al, JACC 2009; 53: 1510-6

Qualità della vita nei pazienti con angina cronica dello Studio MERLIN-TIMI 36:

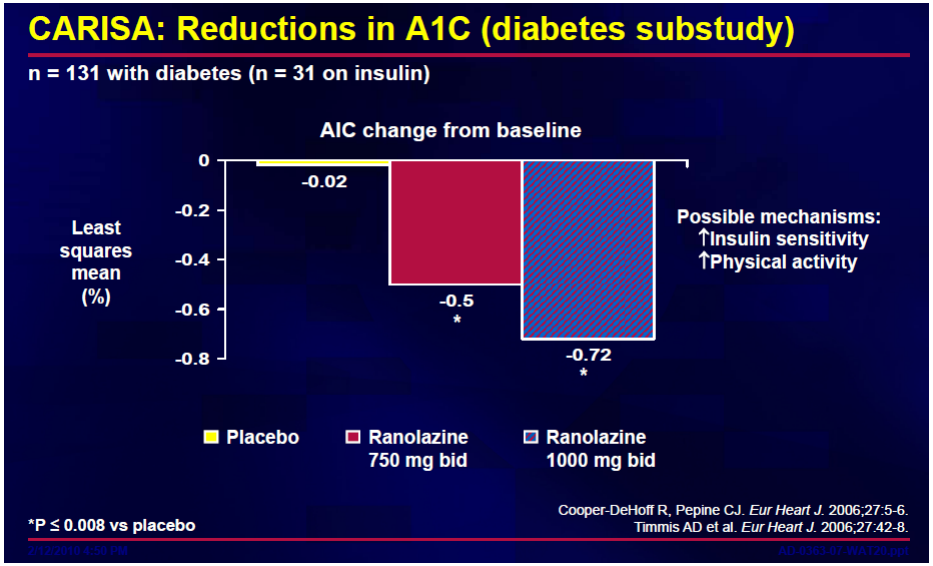
Effetto benefico significativo e prolungato del trattamento con Ranolaxina vs placebo

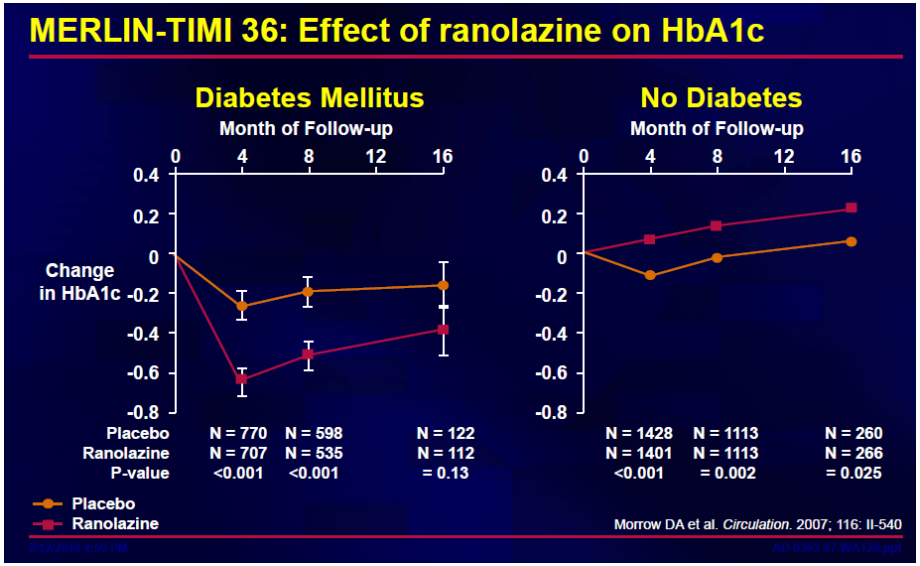
Effetto del trattamento con Ranolazina vs placebo a 12 mesi

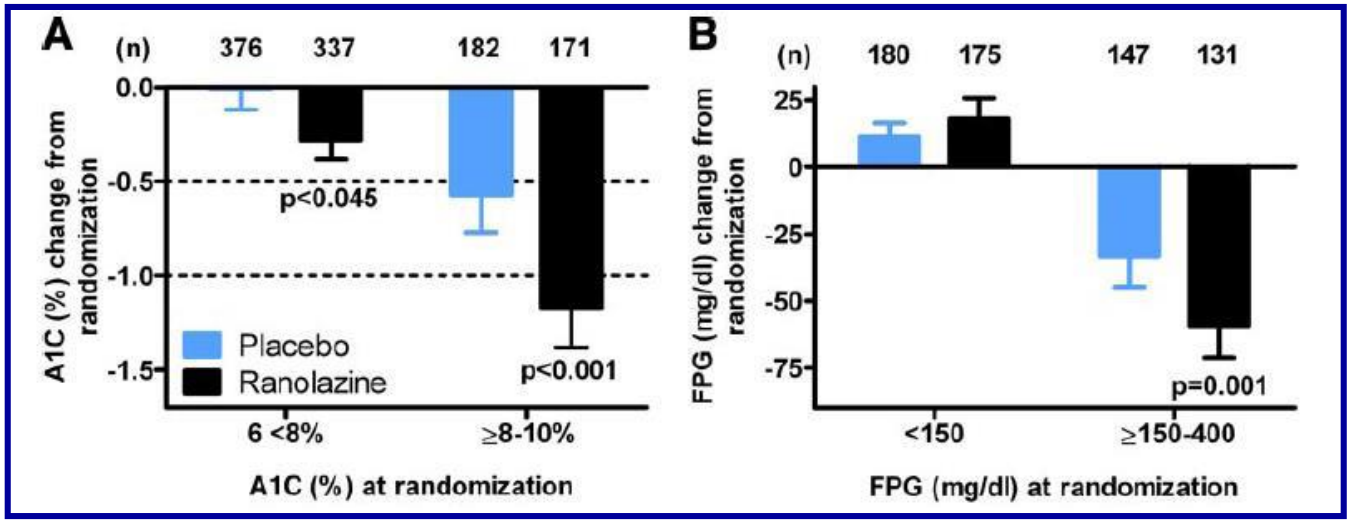
Parametro di outcome	Anamnesi positiva per precedente angina		Anamnesi negativa per precedente angina		P per l'interazione
	effetto medio del trattamento (IC 95%)	P	effetto medio del trattamento (IC 95%)	%	
Frequenza dell'angina (SAQ)	3.43 (1.81, 5.0)	**<0,001**	0.33 (-1.50, 2.16)	0,724	0,003
Limitazioni fisiche (SAQ)	1.79 (-0.07, 3.64)	**0,059**	-1.15 (-3.21, 0.91)	0,274	0,191
Percezione malattia (SAQ)	2.66 (1.19, 4.13)	**<0,001**	0.72 (-0.85, 2.29)	0,369	0,022
Soddisfazione per trattamento (SAQ)	1.46 (0.46, 2.46)	**0,004**	-0.01 (-1.09, 1.07)	0,990	0,022
Componente fisica del SF-12	0.80 (0.04, 1.57)	**0,040**	0.35 (-0.45, 1.16)	0,387	0,326
Componente mentale del SF-12	0.91 (0.17, 1.64)	**0,016**	-0.24 (-1.02, 0.54)	0,551	0,012
Score Dispnea	-0.12 (-0.22, -0.03)	**0,013**	0.03 (-0.08, 0.14)	0,612	0,171
EuroQoL-5D	0.015 (0.003, 0.026)	**0,011**	0.004 (-0.008, 0.017)	0,497	0,144

Arnold SV et al. Circulation 2008; 1:107-115

RANOLAZINA E METABOLISMO GLUCIDICO







Chislom JW et al, Diabetes Care 2010

Blockade of Na^+ Channels in Pancreatic α-Cells Has Antidiabetic Effects

Diabetes 2014;63:3545–3556 | DOI: 10.2337/db13-1562

Clinical Implications

The HbA_{1c}-lowering effect of ranolazine has been previously demonstrated in three clinical studies, but the mechanism of this effect remained unclear. The current study shows that NaCh blockers inhibit glucagon release from pancreatic islets and also have antidiabetic effects due to the direct inhibition of I_{Na} in α-cells. Overall, these data suggest that a major factor contributing to increased glucagon levels may lie at the α-cell level (i.e., hypersecretion of glucagon), which can be corrected by the blockade of $Na_v1.3$ channels. Although the role of NaChs in the pathophysiology of human diabetes requires further investigation, the findings from the current study suggest that the inhibition of α-cell I_{Na} could become an attractive drug target for combination therapy with other classes of antidiabetic agents.

EUROPEAN SOCIETY OF CARDIOLOGY®

2013 ESC guidelines on the management of stable coronary artery disease

Eur Heart J , August 30, 2013

Medical management of patient with stable CAD

Angina relief

1st line

Short-acting Nitrates *plus*

- **Beta-blockers** *or* **CCB-he**
- Consider **CCB-DHP** *if* low intolerance/contraindication
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Nicorandil
Ranolazine[a]
Trimetazidine[a]

Ivabradine

Long-acting nitrates

Nicorandil

Ranolazine[a]

Trimetazidine[a]

Trimetazidine in the Prevention of Tissue Ischemic Conditions

Angiology
1-8

DOI: 10.1177/0003319718780551
journals.sagepub.com/home/ang
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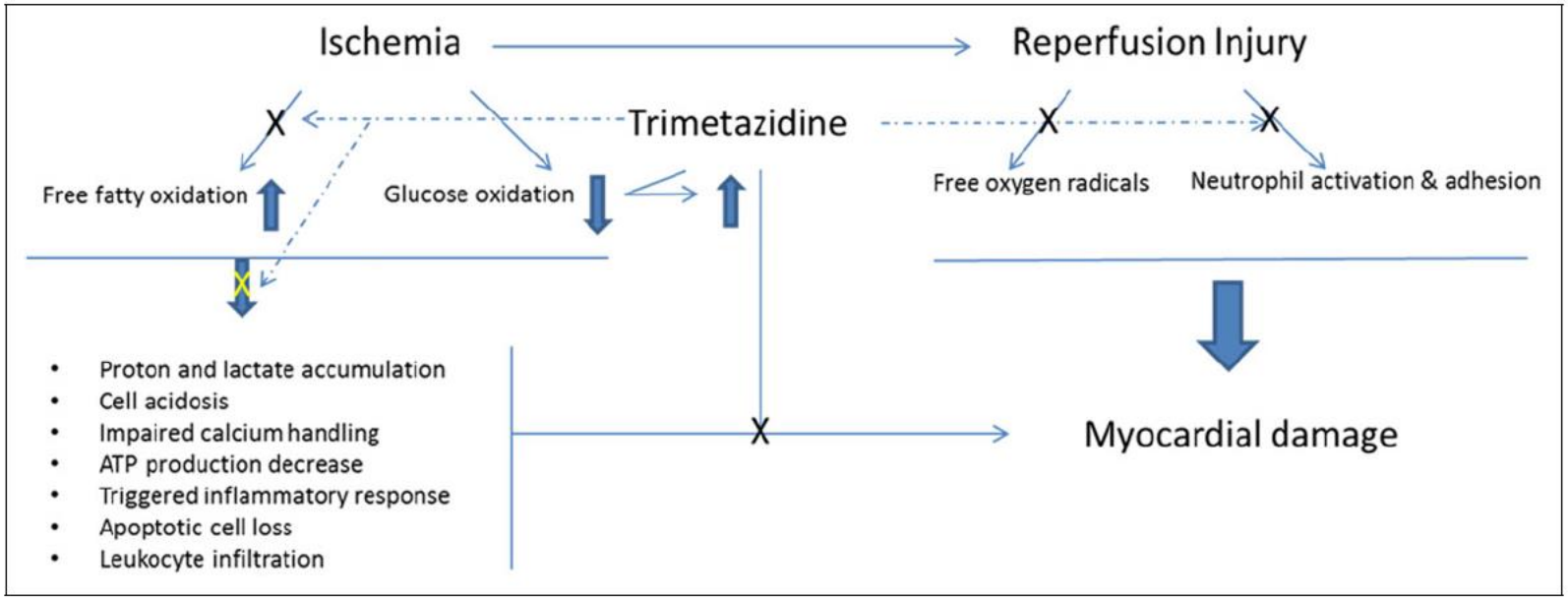


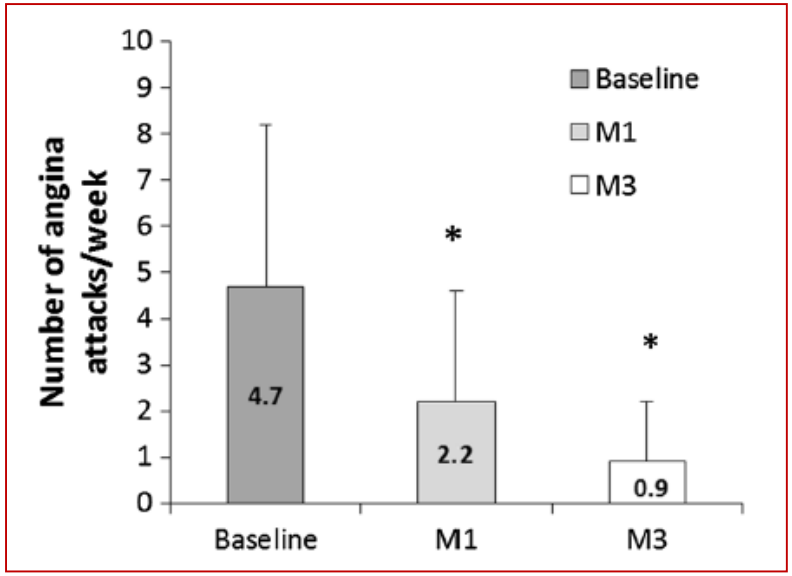
Adv Ther (2018) 35:1368–1377
https://doi.org/10.1007/s12325-018-0756-3

ORIGINAL RESEARCH

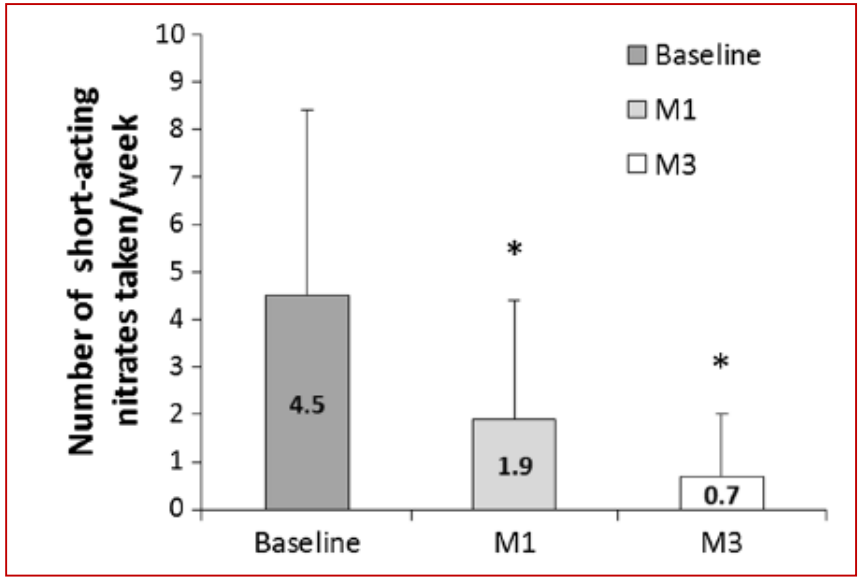
Anti-Anginal Effectiveness and Tolerability of Trimetazidine Modified Release 80 Mg Once Daily in Stable Angina Patients in Real-World Practice

Table 1 Demographics and baseline characteristics of the study population (n = 3066 patients)

	N = 3066 patients
Males, n (%)	1470 (47.9%)
Age, years ± SD	62.8 ± 7.3
Age > 65 years, n (%)	1398 (45.6%)



Changes in mean weekly angina attacks



Changes in number of short-acting nitrates taken per week

CONSENSUS
STATEMENT

OPEN

EXPERT CONSENSUS DOCUMENT

A 'diamond' approach to personalized treatment of angina

Roberto Ferrari[1,2], Paolo G. Camici[3], Filippo Crea[4], Nicolas Danchin[5], Kim Fox[6], Aldo P. Maggioni[7], Athanasios J. Manolis[8], Mario Marzilli[9,10], Giuseppe M. C. Rosano[11,12] and José L. Lopez-Sendon[13]

Abstract | In clinical guidelines, drugs for symptomatic angina are classified as being first choice (β-blockers, calcium-channel blockers, short-acting nitrates) or second choice (ivabradine, nicorandil, ranolazine, trimetazidine), with the recommendation to reserve second-choice medications for patients who have contraindications to first-choice agents, do not tolerate them, or remain symptomatic. No direct comparisons between first-choice and second-choice treatments have demonstrated the superiority of one group of drugs over the other. Meta-analyses show that all antianginal drugs have similar efficacy in reducing symptoms, but provide no evidence for improvement in survival. The newer, second-choice drugs have more evidence-based clinical data that are more contemporary than is available for traditional first-choice drugs. Considering some drugs, but not others, to be first choice is, therefore, difficult. Moreover, double or triple therapy is often needed to control angina. Patients with angina can have several comorbidities, and symptoms can result from various underlying pathophysiologies. Some agents, in addition to having antianginal effects, have properties that could be useful depending on the comorbidities present and the mechanisms of angina, but the guidelines do not provide recommendations on the optimal combinations of drugs. In this Consensus Statement, we propose an individualized approach to angina treatment, which takes into consideration the patient, their comorbidities, and the underlying mechanism of disease.

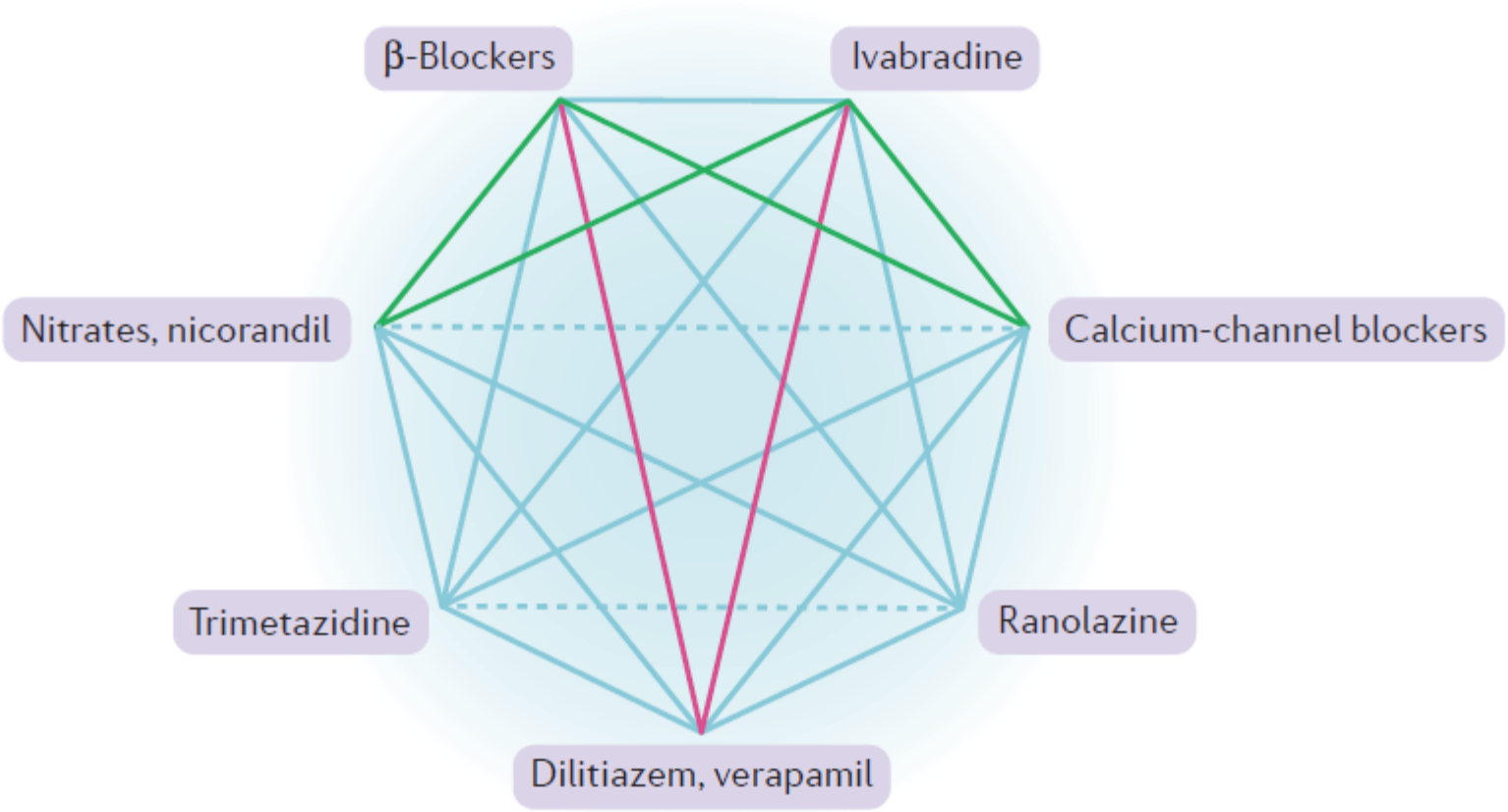


Figure 1 | **Possible combinations of different classes of antianginal drugs.** The schematic shows useful combinations (green lines), combinations that are not recommended (red lines), possible combinations (blue solid lines), and drugs with similar actions (blue dashed lines).

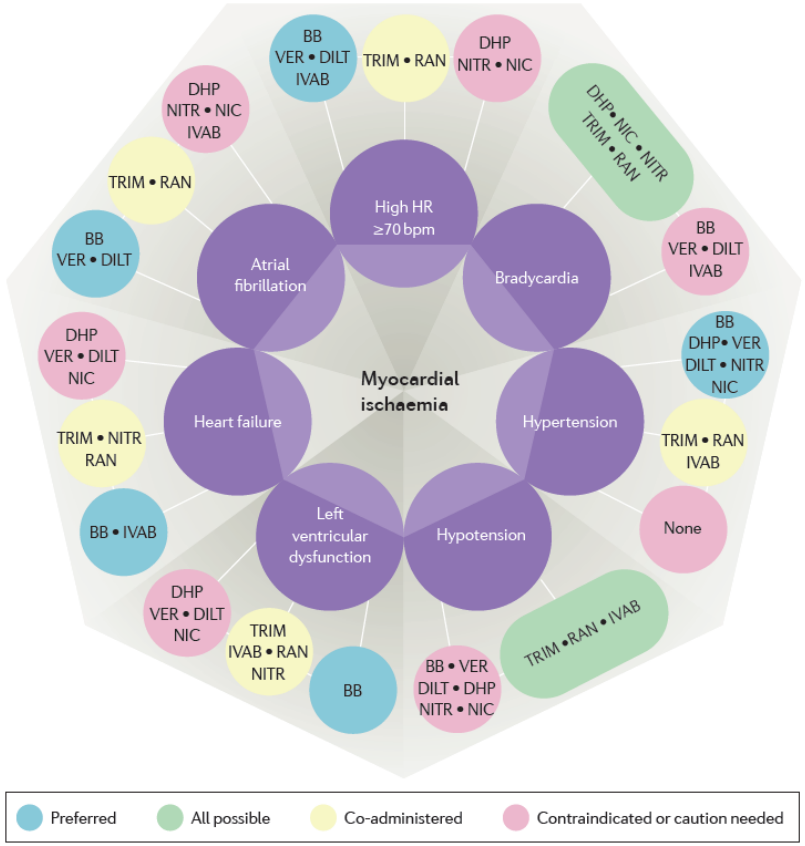


Figure 4 | **Possible combinations of classes of antianginal drugs according to different comorbidities.** BB, β-blockers; DHP, dihydropyridine calcium-channel blockers; DILT, diltiazem; HR, heart rate; IVAB, ivabradine; NIC, nicorandil; NITR, nitrates; RAN, ranolazine; TRIM, trimetazidine; VER, verapamil.

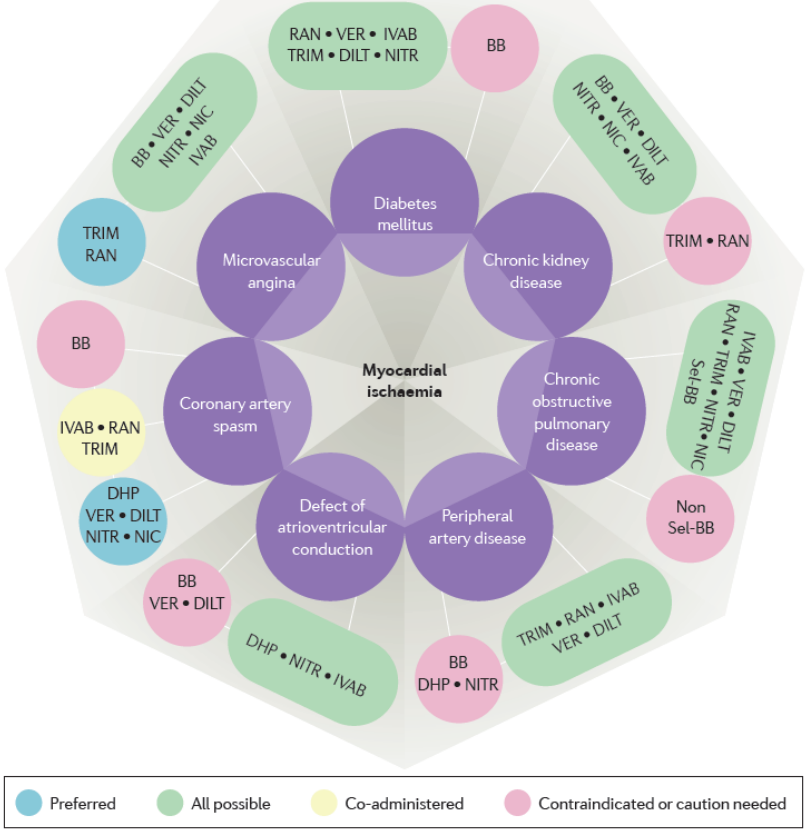
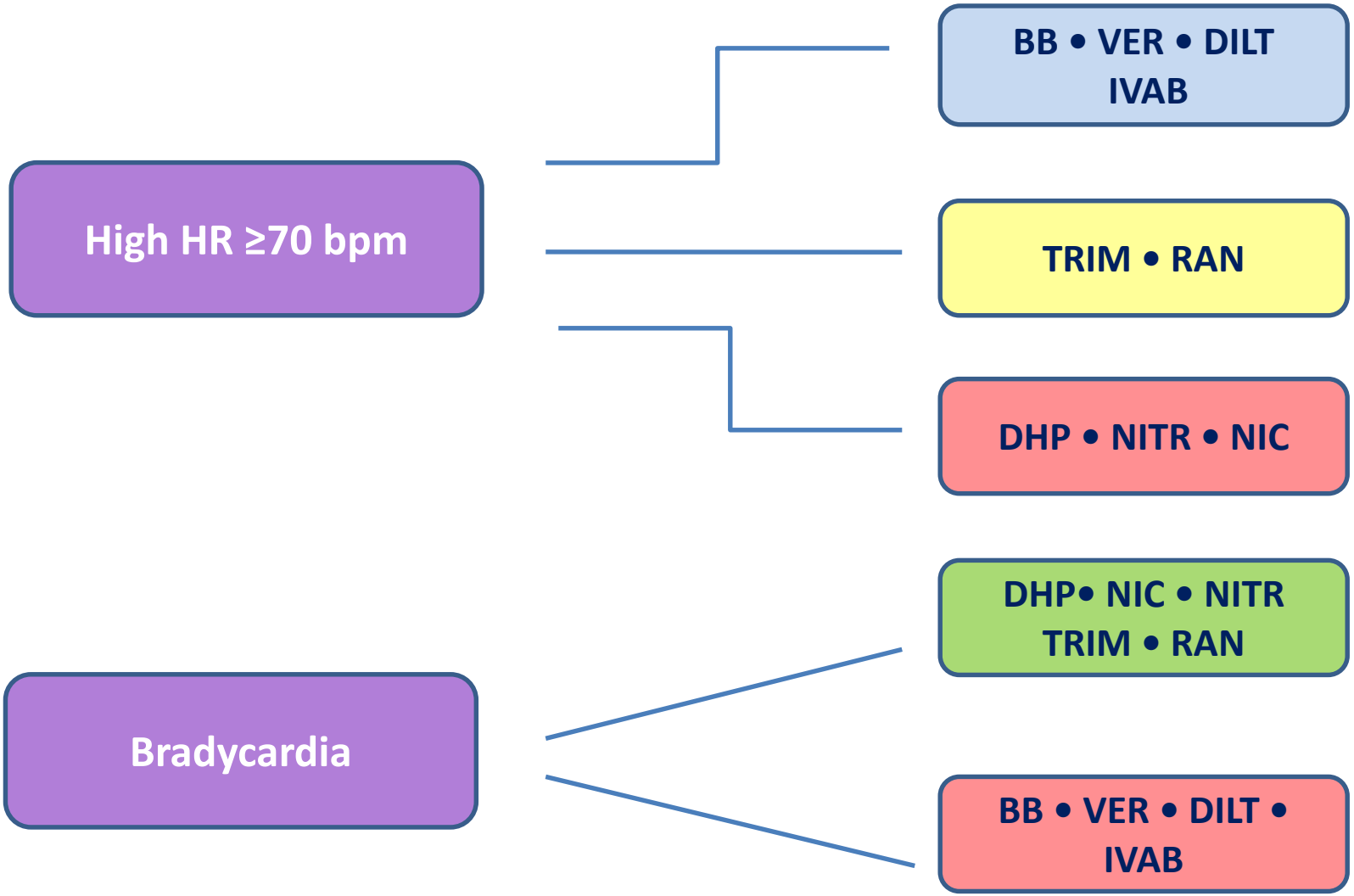


Figure 5 | **Possible combinations of classes of antianginal drugs according to different comorbidities.** BB, β-blockers; DHP, dihydropyridine calcium-channel blockers; DILT, diltiazem; IVAB, ivabradine; NIC, nicorandil; NITR, nitrates; Non Sel-BB, nonselective β-blockers; RAN, ranolazine; Sel-BB, β_1-selective blockers; TRIM, trimetazidine; VER, verapamil.

Possible combinations of classes of antianginal drugs according to different comorbidities

(Nat Rev Cardiol 2018; 15, 121)



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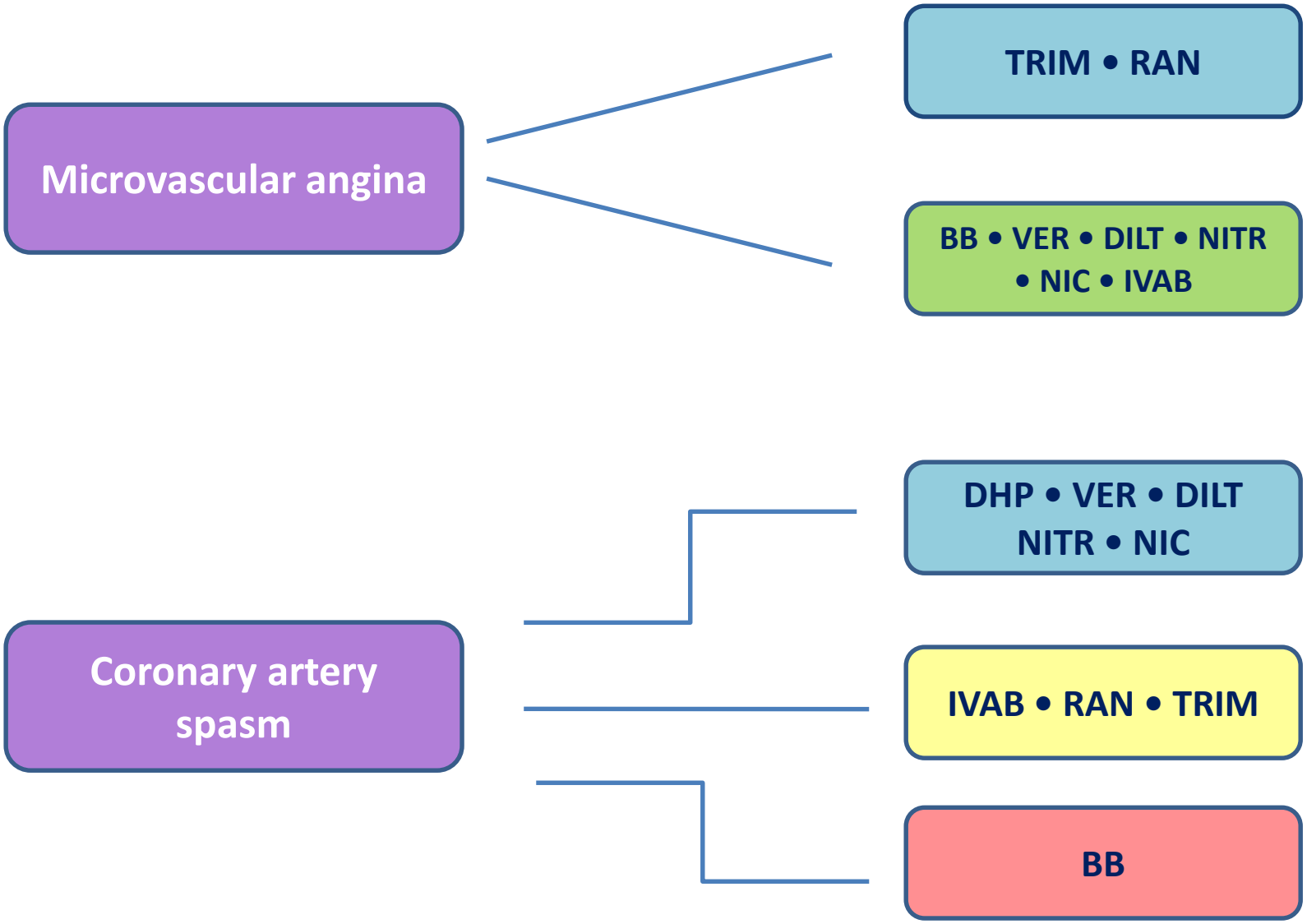

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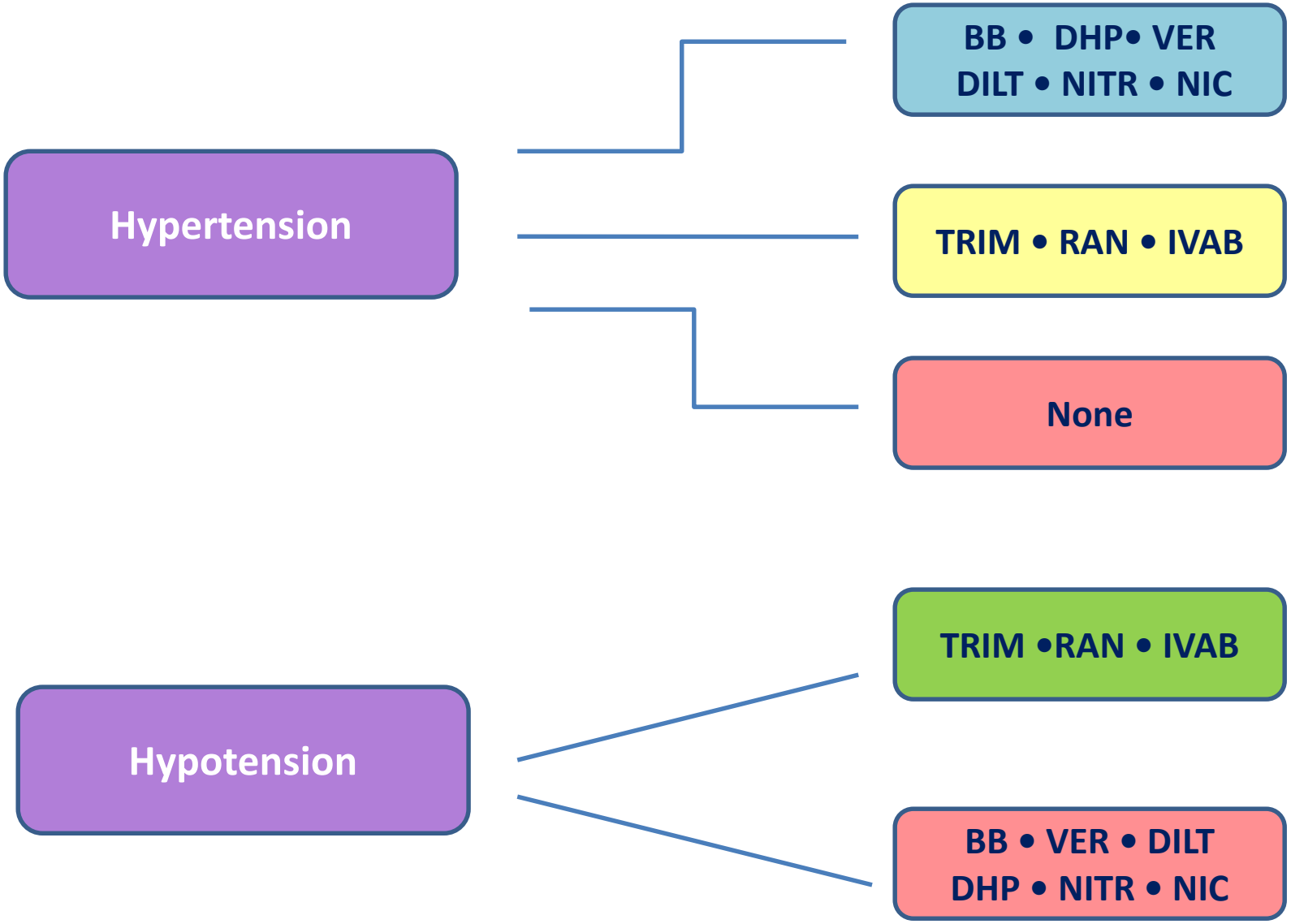

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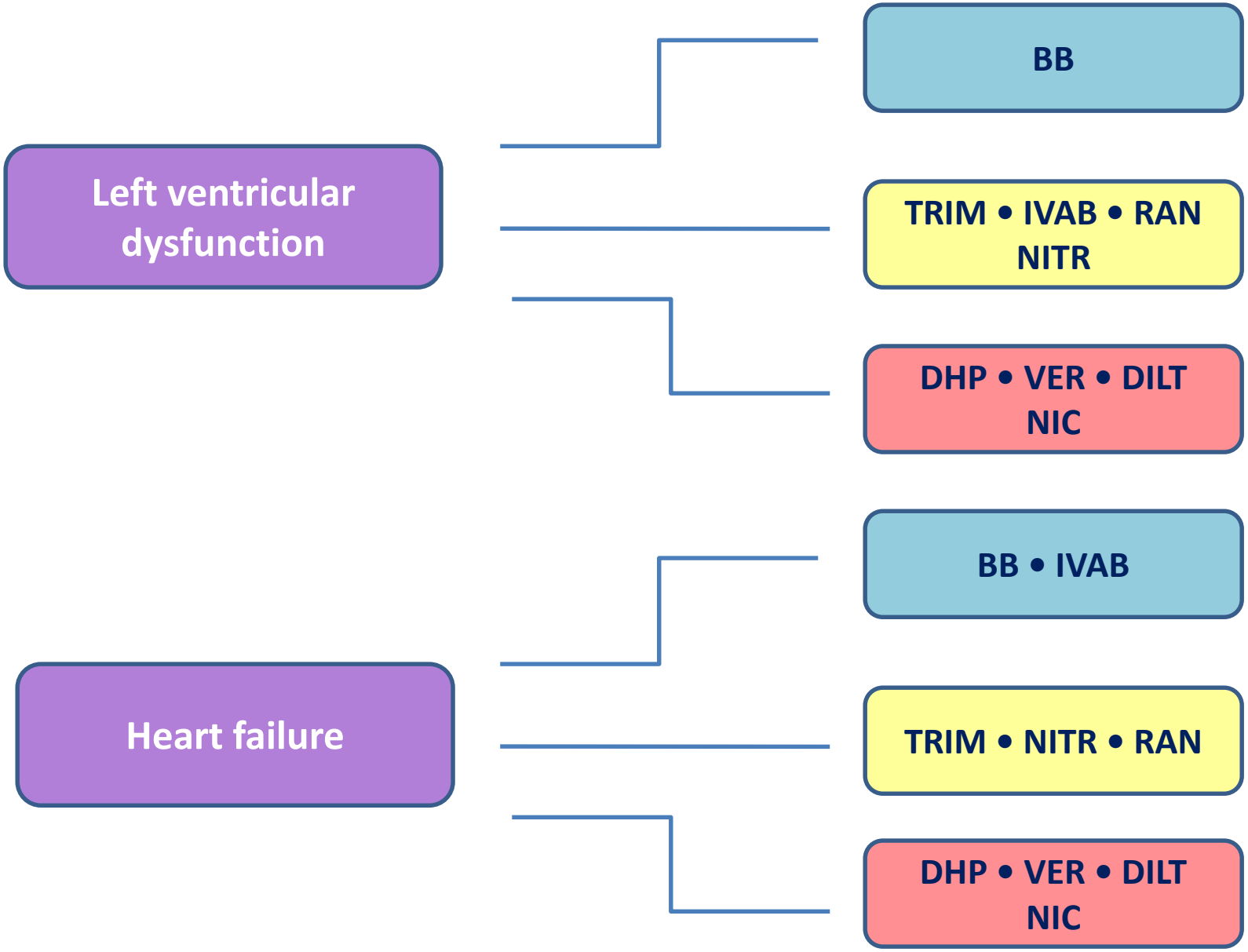

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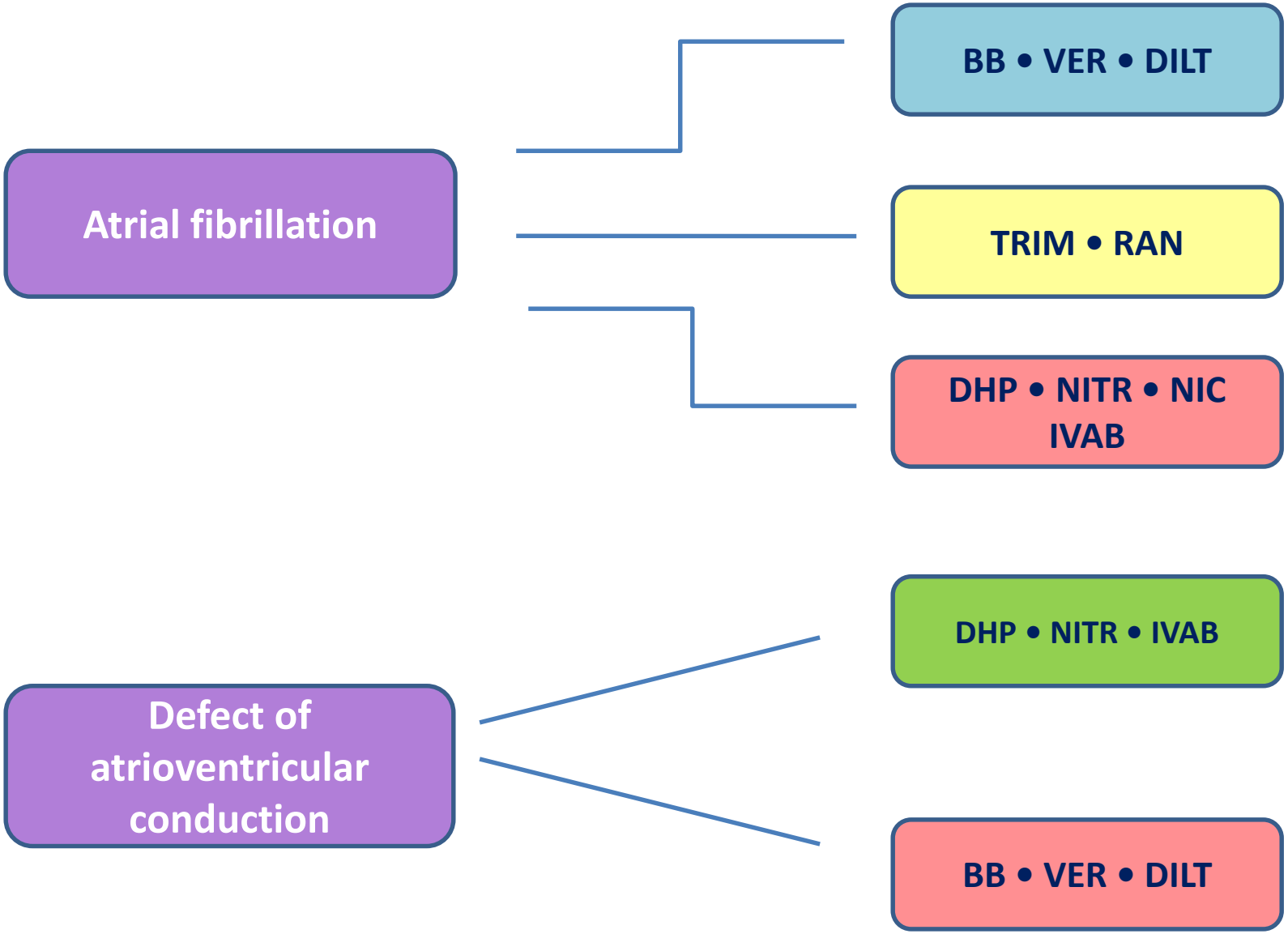

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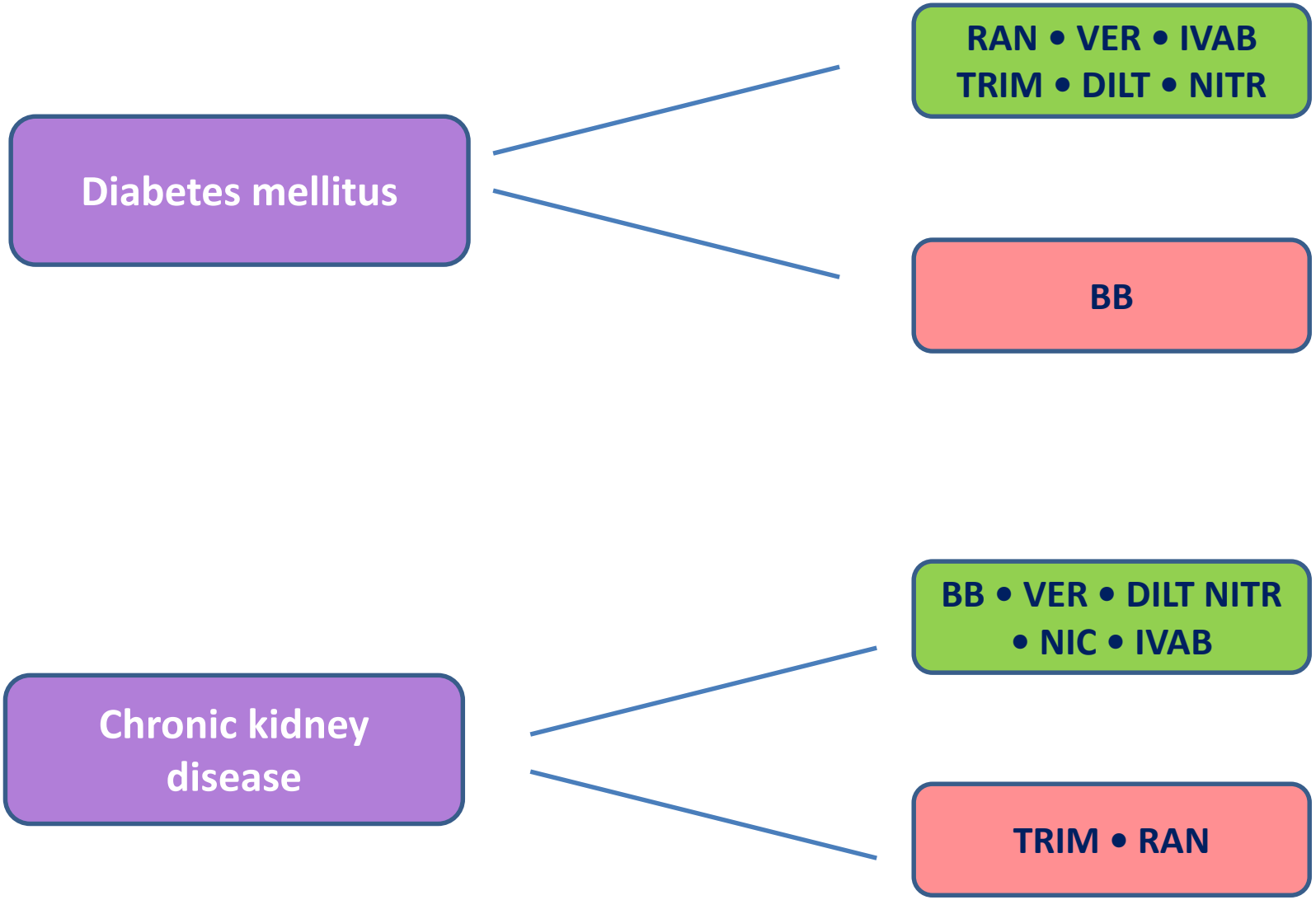

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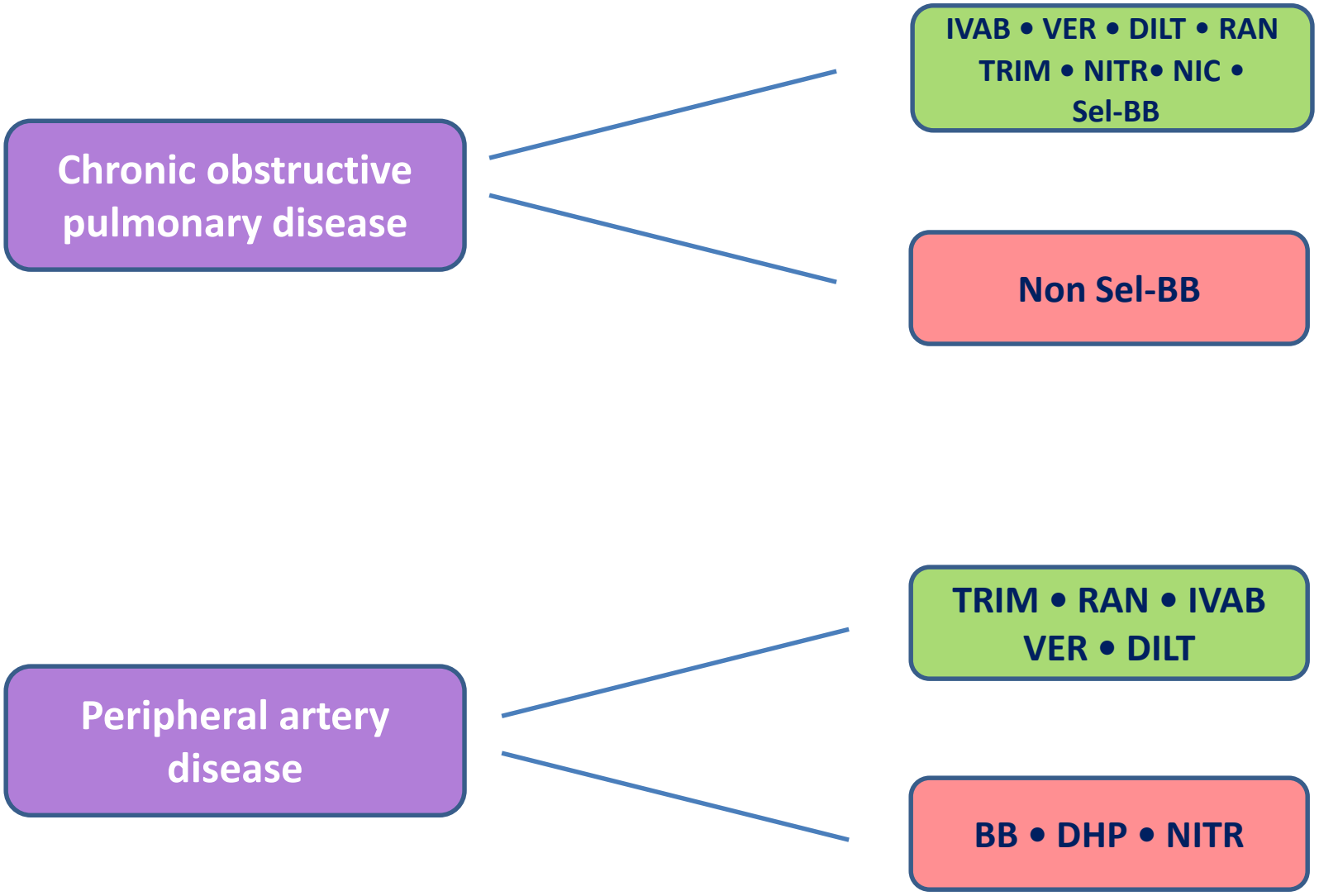

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European Heart Journal (2013) 34, 2949–3003
doi:10.1093/eurheartj/eht296

2013 ESC guidelines on the management of stable coronary artery disease

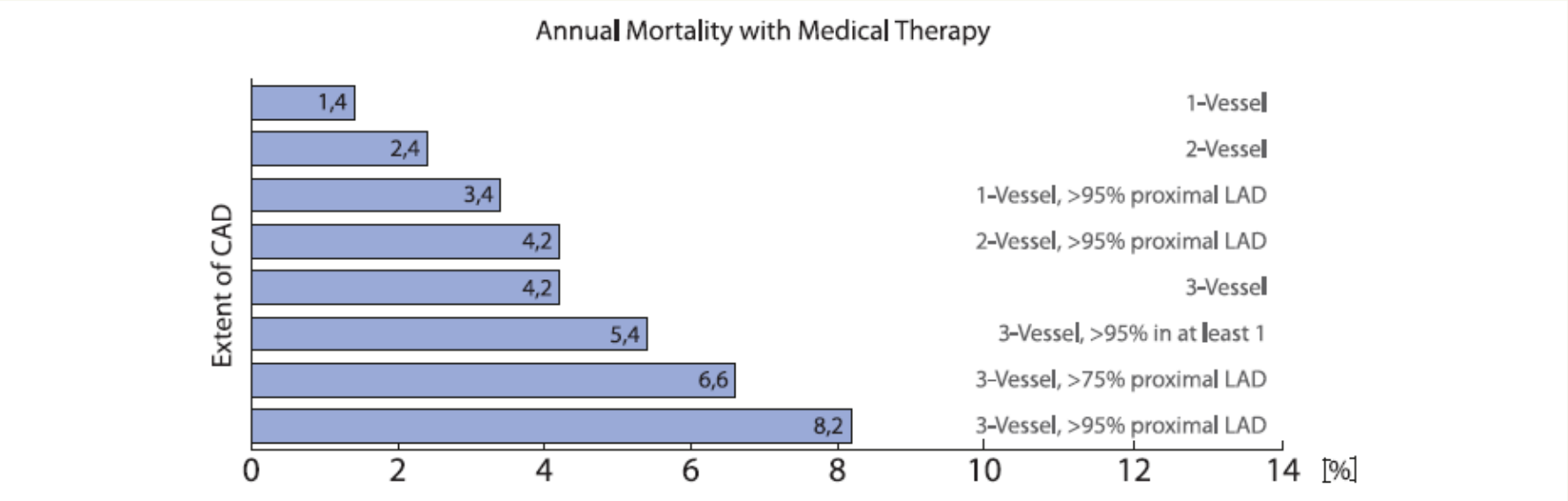


Figure W3 Cardiac death rates in patients on medical therapy with different extents of angiographically defined coronary artery disease. LAD = left anterior descending.[46]

Physical Activity and Mortality in Patients With Stable Coronary Heart Disease

ABSTRACT

BACKGROUND Recommendations for physical activity in patients with stable coronary heart disease (CHD) are based on modest evidence.

OBJECTIVES The authors analyzed the association between self-reported exercise and mortality in patients with stable CHD.

METHODS A total of 15,486 patients from 39 countries with stable CHD who participated in the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) study completed questions at baseline on hours spent each week taking mild, moderate, and vigorous exercise. Associations between the volume of habitual exercise in metabolic equivalents of task hours/week and adverse outcomes during a median follow-up of 3.7 years were evaluated.

RESULTS A graded decrease in mortality occurred with increased habitual exercise that was steeper at lower compared with higher exercise levels. Doubling exercise volume was associated with lower all-cause mortality (unadjusted hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.79 to 0.85; adjusting for covariates, HR: 0.90; 95% CI: 0.87 to 0.93). These associations were similar for cardiovascular mortality (unadjusted HR: 0.83; 95% CI: 0.80 to 0.87; adjusted HR: 0.92; 95% CI: 0.88 to 0.96), but myocardial infarction and stroke were not associated with exercise volume after adjusting for covariates. The association between decrease in mortality and greater physical activity was stronger in the subgroup of patients at higher risk estimated by the ABC-CHD (Age, Biomarkers, Clinical–Coronary Heart Disease) risk score (p for interaction = 0.0007).

CONCLUSIONS In patients with stable CHD, more physical activity was associated with lower mortality. The largest benefits occurred between sedentary patient groups and between those with the highest mortality risk.

(J Am Coll Cardiol 2017;70:1689–700)

TABLE 1 Baseline Characteristics of Study Population by Physical Activity Tertile

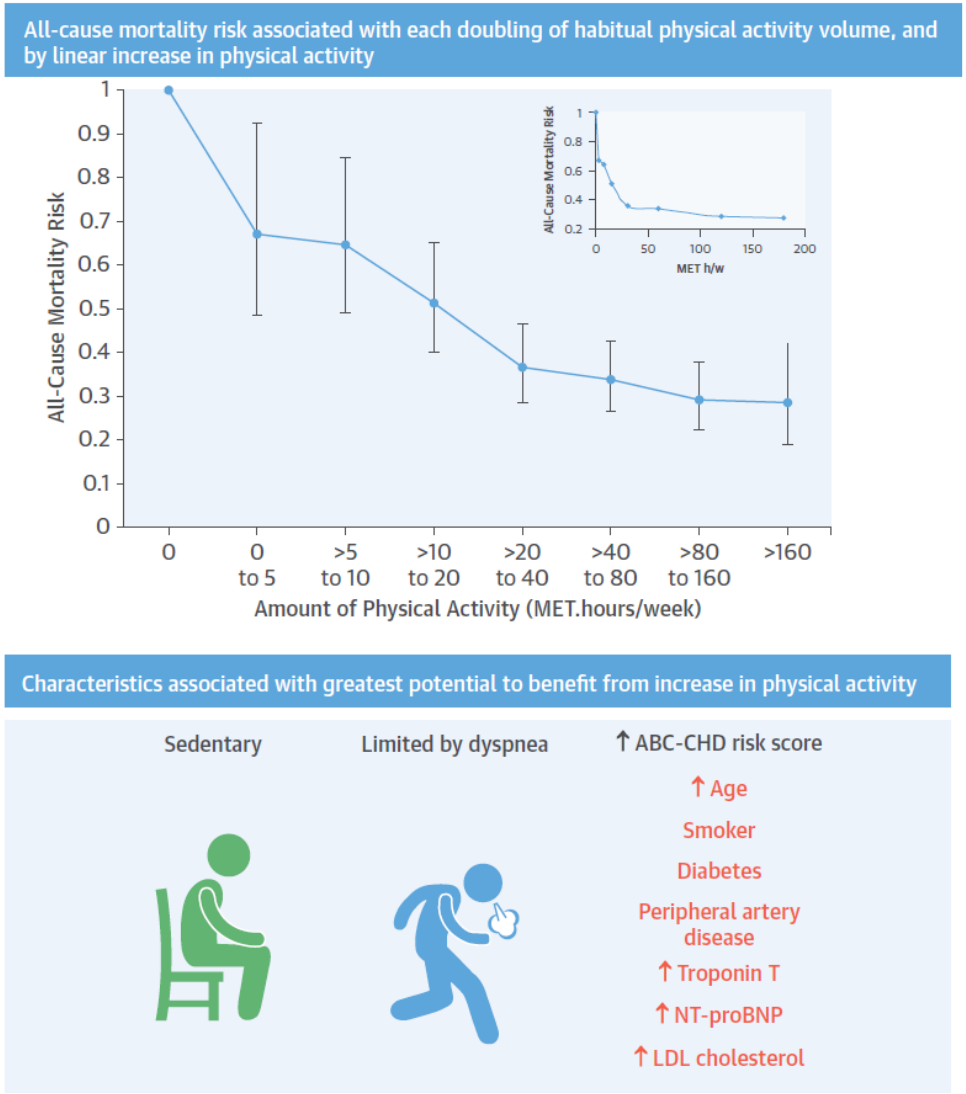
	All Subjects (N = 15,487)	Least Active (n = 5,281)	Intermediate Activity (n = 5,055)	Most Active (n = 5,151)	p Value
Age, yrs	65.0 ± 12.0	65.0 ± 12.0	65.0 ± 11.0	64.0 ± 12.0	<0.0001
Female	2,885 (18.6)	921 (17.4)	989 (19.6)	975 (18.9)	0.0170
Time from qualifying event to randomization, yrs	3.42 ± 6.38	3.22 ± 6.32)	3.49 ± 6.66	3.57 ± 6.25	<0.0001
Follow-up time from randomization, yrs	3.79 ± 0.31	3.75 ± 0.32	3.80 ± 0.31	3.81 ± 0.31	<0.0001
Attended cardiac rehabilitation	5,397 (35.1)	1,608 (30.7)	1,865 (37.2)	1,924 (37.6)	<0.0001
Geographic region					
Asia/Pacific	3,052 (19.7)	1,275 (24.1)	1,054 (20.9)	723 (14.0)	<0.0001
Eastern Europe	3,442 (22.2)	805 (15.2)	1,107 (21.9)	1,530 (29.7)	<0.0001
North America	3,969 (25.6)	1,397 (26.5)	1,323 (26.2)	1,249 (24.2)	<0.0001
South America	1,177 (7.6)	646 (12.2)	320 (6.3)	211 (4.1)	<0.0001
Western Europe	3,847 (24.8)	1,158 (21.9)	1,251 (24.7)	1,438 (27.9)	<0.0001

PHYSICAL ACTIVITY. At baseline, patients underwent a detailed medical history, physical examination, and fasting blood samples, and they were invited to complete a lifestyle questionnaire. Questions related to physical activity (based on the International Physical Activity Questionnaire [20]), were completed by 15,486 subjects (97.8%). Each subject was asked "How many hours during a typical week do you spend doing the following activities for 10 minutes or more? Please estimate to the nearest 1 h for each category: 1) Doing MILD physical activity such as easy walking, yoga, Tai Chi, mild house work? 2) Doing MODERATE physical activity such as fast walking, jogging, aerobics, gardening, bicycling, dancing, swimming or house cleaning? 3) Doing VIGOROUS exercise such as running, lifting heavy objects, playing strenuous sports or strenuous work?" Each level of exercise includes a range of intensities estimated to be <3 metabolic equivalents (METs) for task for mild, 3 to 6 METs for moderate, and >6 METs for vigorous intensity physical activity (21). To estimate the METs h/week, 2 METs were assigned for mild, 4 METs for moderate, and 8 METs for vigorous

Mild physical activity: easy walking, yoga, mild house work
Moderate physical acitivity: fast walking, jogging, gardening, bicycling, dancing, swimming
Vigorous physical activity: running, strenous sports or work

Metabolic equivalents (METs) h/week
2 METs → Mild
4 METs → Moderate
8 METs → Vigorous

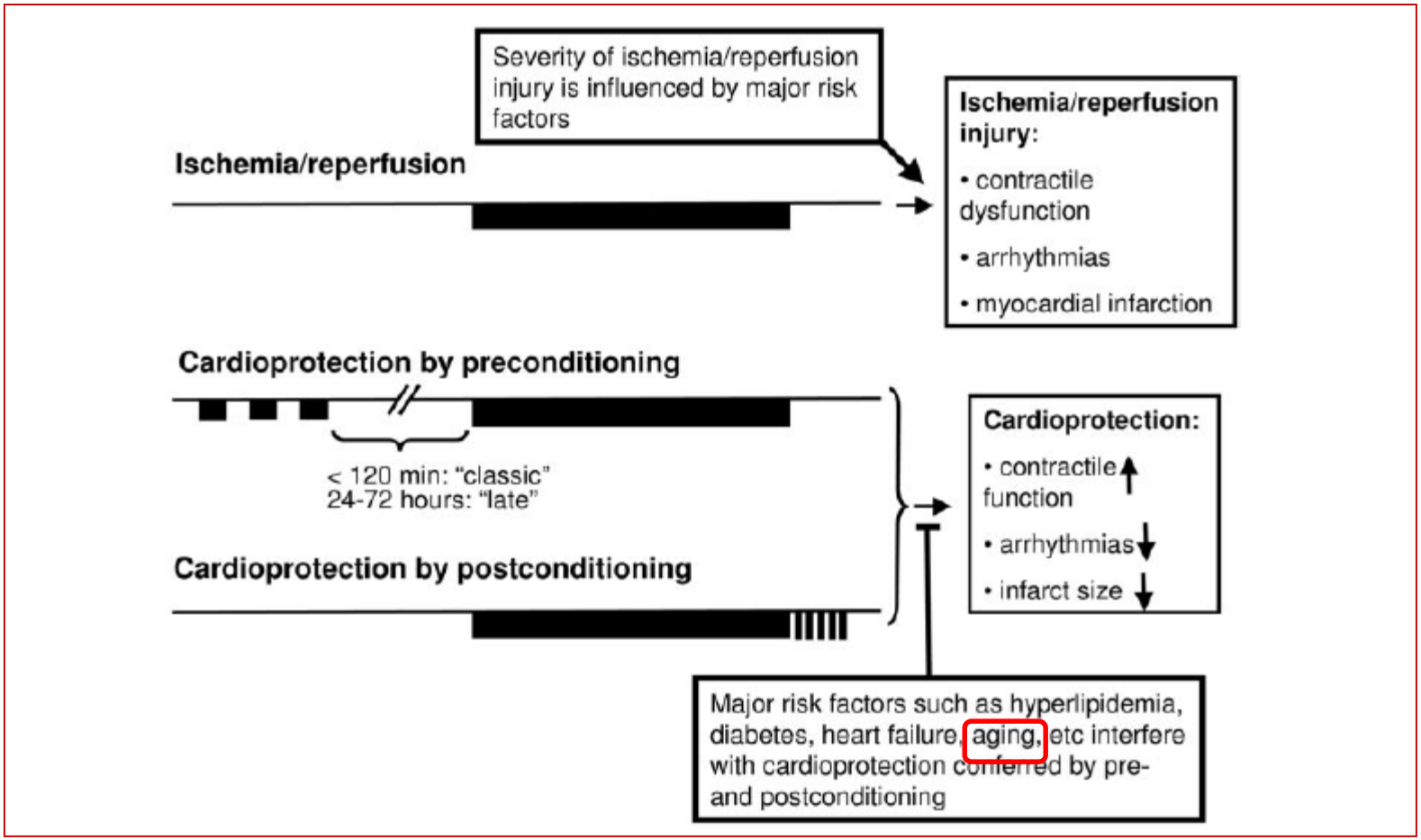
CENTRAL ILLUSTRATION **Habitual Physical Activity and Mortality in Patients With Stable Coronary Artery Disease**



Stewart, R.A.H. et al. J Am Coll Cardiol. 2017;70(14):1689–700.

All-cause mortality risk associated with each doubling of habitual exercise volume and by linear increase in physical activity **(inset)** in 15,486 patients with stable coronary heart disease. Selected characteristics of patients who had the greatest reduction in mortality associated with increase in physical activity are also illustrated. ABC-CHD = Age, Biomarkers, Clinical Variables-Coronary Heart Disease; LDL = low-density lipoprotein; METs = metabolic equivalents; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Interaction of Cardiovascular Risk Factors with Myocardial Ischemia/Reperfusion Injury, Preconditioning, and Postconditioning



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Myocardial Infarction

High Level of Physical Activity Preserves the Cardioprotective Effect of Preinfarction Angina in Elderly Patients

Pasquale Abete, MD, PHD,* Nicola Ferrara, MD,‡§ Francesco Cacciatore, MD, PHD,*‖ Elio Sagnelli, MD,* Maria Manzi, MD,* Vincenzo Carnovale, MD,* Claudio Calabrese, MD,*‖ Domenico de Santis, MD,* Gianluca Testa, MD,* Giancarlo Longobardi, MD,§ Claudio Napoli, MD, PHD, FACA,†¶ Franco Rengo, MD*§

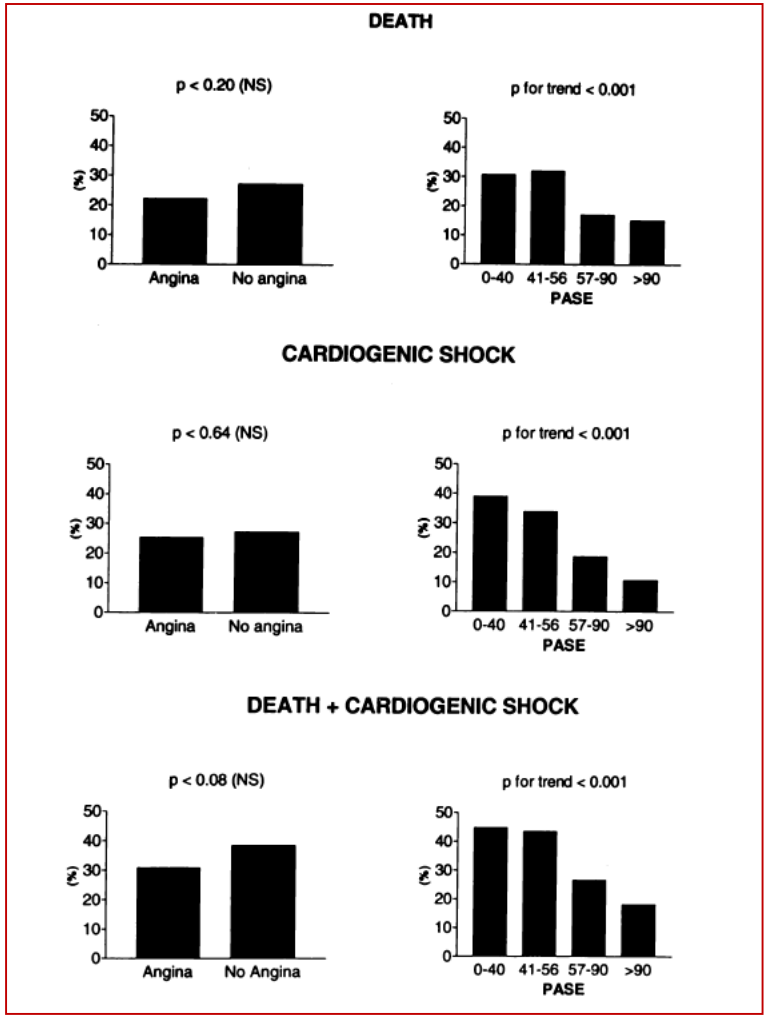
OBJECTIVES The study investigated the effects of physical activity on preinfarction angina, a clinical equivalent of ischemic preconditioning (PC), in adult and elderly patients with acute myocardial infarction (AMI).

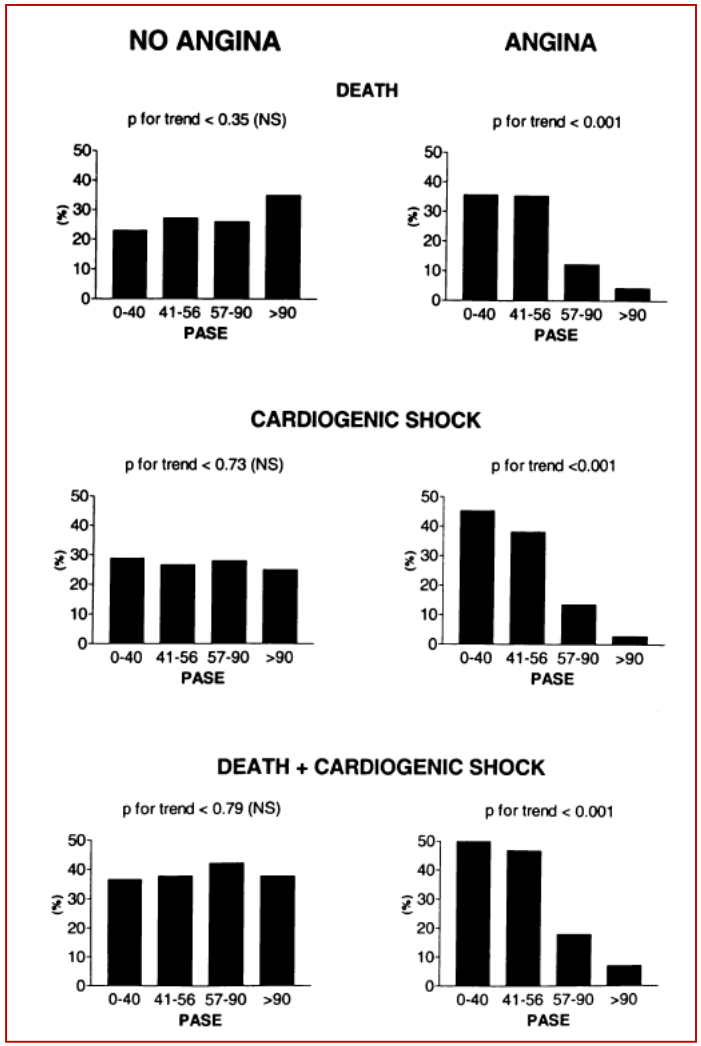
BACKGROUND Preinfarction angina seems to confer protection against in-hospital mortality in adult but not in elderly patients. However, it has been experimentally demonstrated that exercise training restores the protective effect of PC in the aging heart.

METHODS We retrospectively verified whether physical activity preserved the protective effect of preinfarction angina against in-hospital mortality in 557 elderly patients with AMI. Physical activity was quantified according to the Physical Activity Scale for the Elderly (PASE).

RESULTS In-hospital mortality was 22.2% in elderly patients with preinfarction angina and 27.2% in those without ($p = 0.20$). When the PASE score was stratified in quartiles (0 to 40, 41 to 56, 57 to 90, >90), a high score was strongly associated with reduced in-hospital mortality (30.8%, 32.2%, 17.2% and 15.3%, respectively, $p < 0.001$ for trend). Interestingly, a high level of physical activity reduced in-hospital mortality in elderly patients with preinfarction angina (35.7%, 35.4%, 12.3% and 4.23%, respectively, $p < 0.001$ for trend) but not in those without (23.0%, 27.2%, 26.0% and 35.0%, respectively, $p = 0.35$ for trend). Accordingly, the protective role of preinfarction angina on in-hospital mortality was present only in elderly patients showing a high level of physical activity (adjusted odds ratio, 0.09; 95% confidence interval, 0.01 to 0.57; $p < 0.05$).

CONCLUSIONS Physical activity and not preinfarction angina protects against in-hospital mortality in elderly patients with myocardial infarction. Nevertheless, the protective effect of preinfarction angina is preserved in elderly patients with a high level of physical activity. (J Am Coll Cardiol 2001; 38:1357–65) © 2001 by the American College of Cardiology


DEATH
p < 0.20 (NS)
p for trend < 0.001
(%)
Angina
No angina
0-40
41-56
57-90
>90
PASE
CARDIOGENIC SHOCK
p < 0.64 (NS)
p for trend < 0.001
DEATH + CARDIOGENIC SHOCK
p < 0.08 (NS)
p for trend < 0.001
No Angina


NO ANGINA
ANGINA
DEATH
p for trend < 0.35 (NS)
p for trend < 0.001
(%)
0-40
41-56
57-90
>90
PASE
CARDIOGENIC SHOCK
p for trend < 0.73 (NS)
p for trend <0.001
DEATH + CARDIOGENIC SHOCK
p for trend < 0.79 (NS)
p for trend < 0.001

Effect of Sustaining Lifestyle Modifications (Non-smoking, Weight Reduction, Physical Activity and Mediterranean Diet) After Healing of Myocardial Infarction, Percutaneous Intervention or Coronary Bypass (From the REGARDS Study)

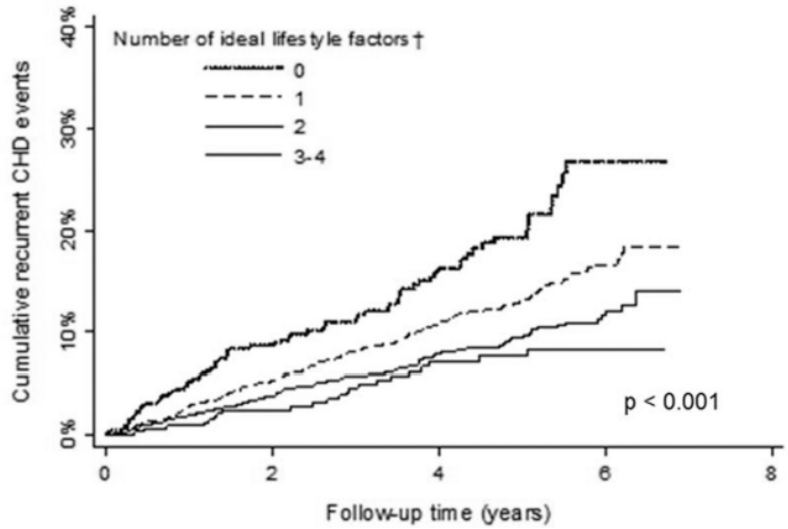


Figure 1.
Crude cumulative incidence for recurrent coronary heart disease associated with number of ideal lifestyle factors.
†Ideal lifestyle factors were defined as not having abdominal obesity, physical activity ≥ 4 times per week, Mediterranean diet score in the highest quartile, and being a non-smoker.

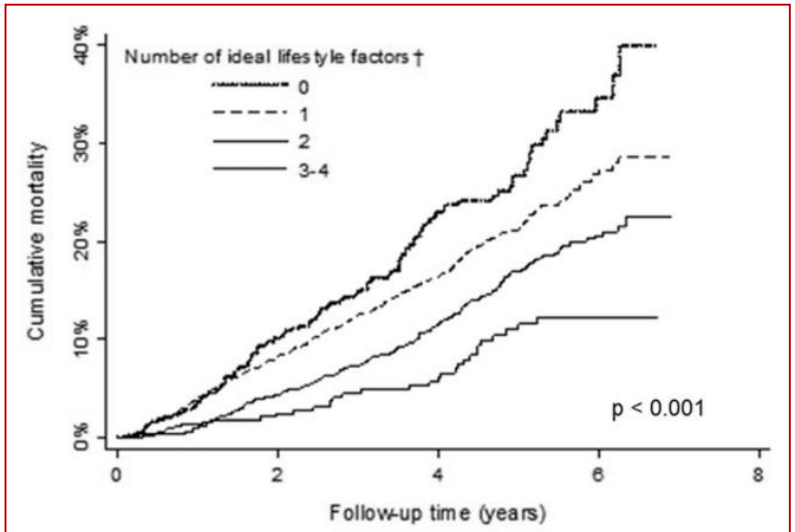


Figure 2.
Crude cumulative incidence for all-cause mortality associated with number of ideal lifestyle factors.
†Ideal lifestyle factors were defined as not having abdominal obesity, physical activity ≥ 4 times per week, Mediterranean diet score in the highest quartile, and being a non-smoker.

Participant characteristic	Number of ideal lifestyle factors‡			
	0 (n = 240)	1 (n = 1,383)	2 (n = 1,452)	3 – 4 (n = 1,100)
Percentage of sample	5.7%	33.1%	34.8%	26.4%
Age (years)	64.8 (0.5)	67.2 (0.3)	69.7 (0.3)	70.4 (0.3)

Am J Cardiol. 2014 June 15; 113(12): 1933–1940.

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

ESC GUIDELINES

2013 ESC guidelines on the management of stable coronary artery disease

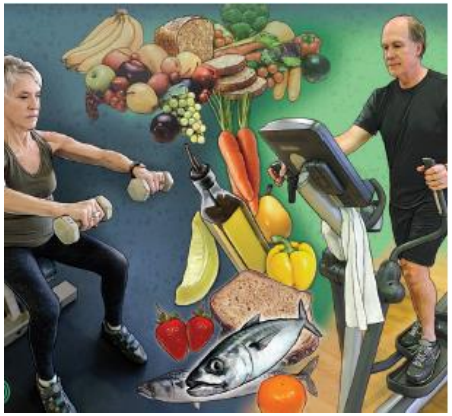


Table 25 Recommended diet intakes

• Saturated fatty acids to account for <10% of total energy intake, through replacement by polyunsaturated fatty acids.
• Trans unsaturated fatty acids <1% of total energy intake.
• <5 g of salt per day.
• 30–45 g of fibre per day, from wholegrain products, fruits and vegetables.
• 200 g of fruit per day (2–3 servings).
• 200 g of vegetables per day (2–3 servings).
• Fish at least twice a week, one being oily fish.
• Consumption of alcoholic beverages should be limited to 2 glasses per day (20 g/day of alcohol) for men and 1 glass per day (10 g/day of alcohol) for non-pregnant women.

Effect of a Mediterranean Type of Diet on the Rate of Cardiovascular Complications in Patients With Coronary Artery Disease

Insights Into the Cardioprotective Effect of Certain Nutriments

MICHEL DE LORGERIL, MD, PATRICIA SALEN, BSc, JEAN-LOUIS MARTIN, PhD,*
NICOLE MAMELLE, PhD,* ISABELLE MONJAUD, BSc, PAUL TOUBOUL, MD,†
JACQUES DELAYE, MD†

Lyon, France

Objectives. We sought to describe the various cardiovascular complications that occurred in the Lyon Diet Heart Study (a secondary prevention trial testing the protective effects of a Mediterranean type of diet), to analyze their relations with the associated drug treatments and to gain insights into the possible mechanisms underlying the beneficial effects of certain nutriments.

Background. Dietary habits are implicated in coronary heart disease, and the traditional Mediterranean diet is thought to be cardioprotective. However, the exact mechanisms of this protection are unknown.

Methods. A total of 605 patients (303 control subjects and 302 study patients) were studied over a mean period of 27 months. Major primary end points (cardiovascular death and nonfatal acute myocardial infarction), secondary end points (including unstable angina, stroke, heart failure and embolisms) and minor end points (stable angina, need for myocardial revascularization, postangioplasty restenosis and thrombophlebitis) were analyzed separately and in combination.

Results. When major primary and secondary end points were combined, there were 59 events in control subjects and 14 events in the study patients, showing a risk reduction of 76% ($p < 0.0001$). When these end points were combined with the minor end points, there were 104 events in control subjects and 68 events in the study patients, giving a risk reduction of 37% ($p < 0.005$). By observational analysis, only aspirin among the medications appeared to be significantly protective (risk ratio after adjustment for prognosis factors 0.45; 95% confidence interval 0.25 to 0.80).

Conclusions. These data show a protective effect of the Mediterranean diet. However, the risk reduction varied depending on the type of end point considered. Our hypothesis is that different pathogenetic mechanisms were responsible for the development of the various complications. It is likely that certain nutriments characteristic of the Mediterranean diet (omega-3 fatty acids, oleic acid, antioxidant vitamins) have specific cardioprotective effects.

(J Am Coll Cardiol 1996;28:1103–8)

The Mediterranean Diet and reduced cardiovascular disease

The Mediterranean diet (MD) may reduce cardiovascular disease (CVD) and mortality, but who actually benefits from its benefits?

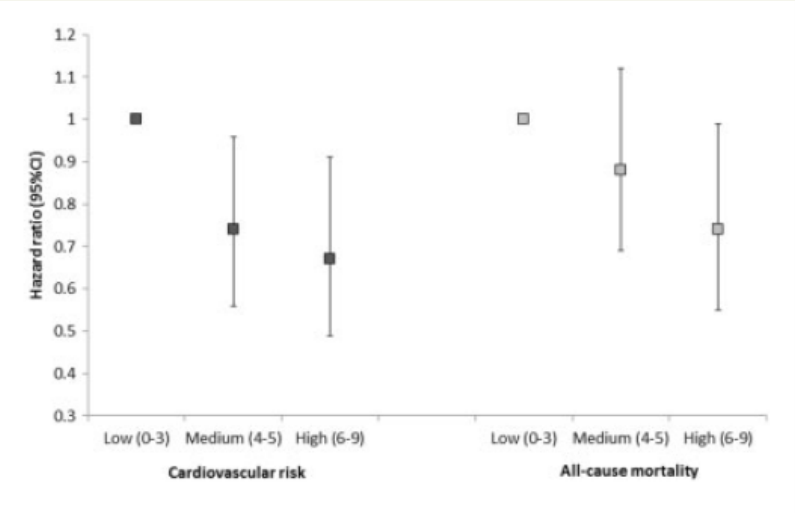


Figure 1 Risk of fatal and non-fatal cardiovascular disease (coronary heart disease/stroke) and all-cause mortality associated with different categories of adherence to the Mediterranean diet in the elderly (age ≥ 65 years) sample of the Moli-sani study ($n = 5162$).

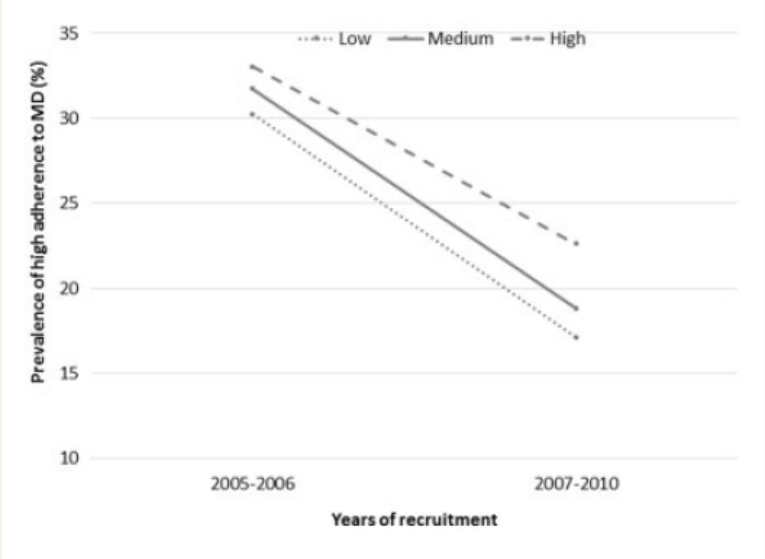


Figure 2 Prevalence of high adherence to the Mediterranean diet over time across different wealth groups in the Moli-sani cohort (based on data published in reference 21).

European Heart Journal, Volume 38, Issue 8, 21 February 2017, Pages 535–536

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Guidelines planned in 2019

- **CVD in Diabetes**
  Chairpersons: Francesco Consentino & Peter Grant
- **Acute Pulmonary Embolism**
  Chairpersons: Stravos Konstantinides and Guy Meyer
- **Supraventricular Tachycardia**
  Chairpersons: Joseph Brugada & Demosthenes Katritsis
- **Chronic Coronary Syndromes** (previously Stable Coronary Artery Disease)
  Chairpersons: William Wijns & Juhani Knuuti
- **Dyslipidaemias**
  Chairpersons: Colin Baigent, François Mach and Alberico Catapano

Grazie per l'attenzione!