# ECOCARDIOCHIRURGIA 2016

**Milano 21-23 marzo 2016**


ECOCARDIOCHIRURGIA.it

# La terapia medica della cardiopatia ischemica stabile.

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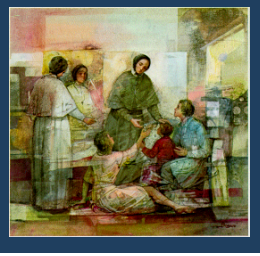
**Ospedale Valduce – Como (IT)**

H. Valduce 1879



# DIMENSIONI DEL PROBLEMA

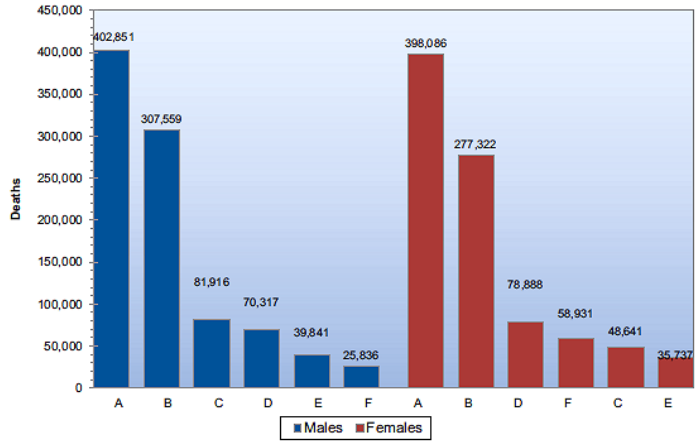



**Chart 13-9.** Cardiovascular disease and other major causes of death for all males and females (United States: 2013). A indicates cardiovascular disease (*International Classification of Diseases, 10th Revision* codes I00–I99); B, cancer (C00–C97); C, accidents (V01–X59 and Y85–Y86); D, chronic lower respiratory disease (J40–J47); E, diabetes mellitus (E10–E14); and F, Alzheimer disease (G30). Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.



**AHA Statistical Update**

**Heart Disease and Stroke Statistics—2016 Update**
**A Report From the American Heart Association**

American Heart Association®



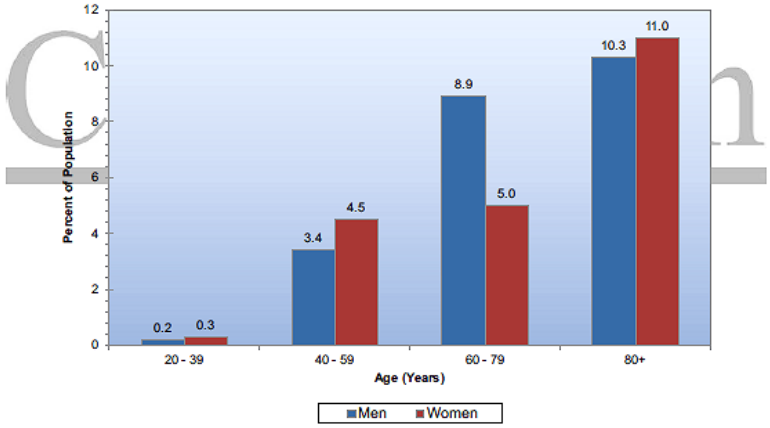
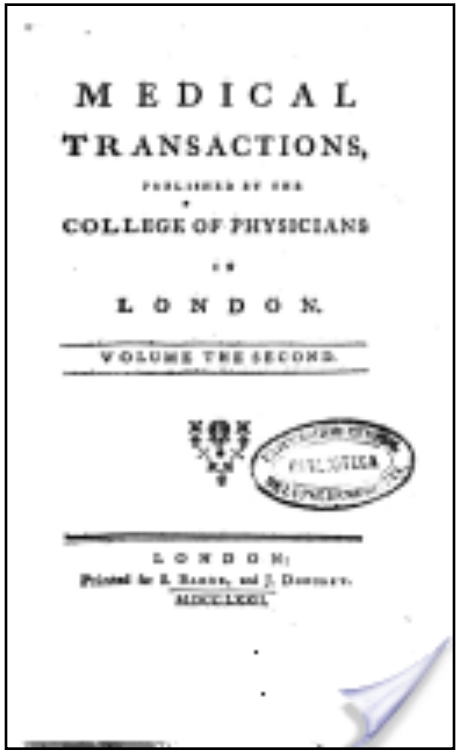



**Chart 19-9.** Prevalence of angina pectoris by age and sex (National Health and Nutrition Examination Survey: 2009–2012). Angina pectoris includes people who either answered "yes" to the question of ever having angina or angina pectoris or were diagnosed with Rose Angina. Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

# ANGINA PECTORIS


MEDICAL
TRANSACTIONS,
PUBLISHED BY THE
COLLEGE OF PHYSICIANS
IN
LONDON.
VOLUME THE SECOND.
LONDON:

"But there is a disorder… marked with strong and peculiar symptoms …. may make it not improperly be called angina pectoris. Those who are afflicted with it are seized while they are walking (more especially if it be uphill, and soon after eating), with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or to continue; but the moment they stand still, all this uneasiness vanishes" c.1768

Heberden. Medical Transactions, Royal College of Physicians- London 1772;2:59-67.

# ESC GUIDELINES

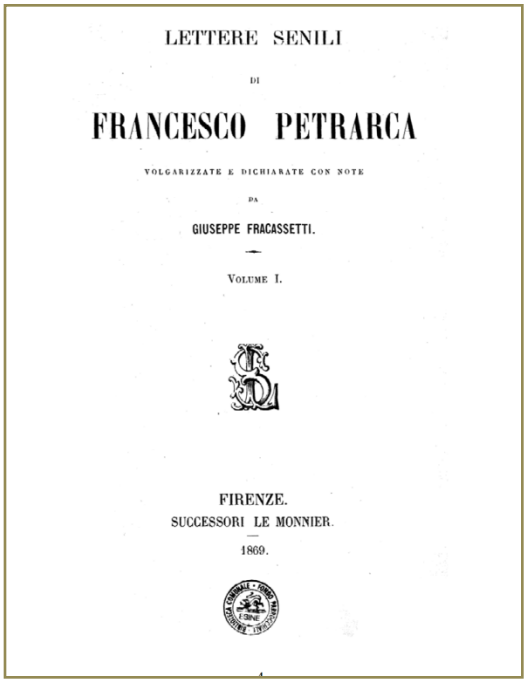
**Table I** Classes of recommendations

| Classes of recommendations | Definition | Suggested wording to use |
|---|---|---|
| Class I | Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. | Is recommended/is indicated |
| Class II | Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure. | |
| *Class IIa* | *Weight of evidence/opinion is in favour of usefulness/efficacy.* | Should be considered |
| *Class IIb* | *Usefulness/efficacy is less well established by evidence/opinion.* | May be considered |
| Class III | Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. | Is not recommended |

**Table 2** Levels of evidence

| | |
|---|---|
| Level of evidence A | Data derived from multiple randomized clinical trials or meta-analyses. |
| Level of evidence B | Data derived from a single randomized clinical trial or large non-randomized studies. |
| Level of evidence C | Consensus of opinion of the experts and/or small studies, retrospective studies, registries. |

# STUDI RANDOMIZZATI NELLA STORIA DELLA MEDICINA



LETTERE SENILI

DI

FRANCESCO PETRARCA

VOLGARIZZATE E DICHIARATE CON NOTE

DA

GIUSEPPE FRACASSETTI.

VOLUME I.

FIRENZE.
SUCCESSORI LE MONNIER.

1869.

LIBRO QUINTO

LETTERA III

A GIOVANNI BOCCACCIO

*Meum tibi consilium*

**Io penso adunque, e francamente dico e sostengo che, se cento o mille uomini, tutti d'una età, di una tempra, di un costume cadessero a un tratto in una medesima malattia, e una metà di loro si desse in cura a medici, quali son questi de' tempi nostri, l'altra metà si lasciasse in balìa della natura e della propria discrezione, io non mi lascio punto aver dubbio che il numero de' morti sarebbe maggiore fra i primi, e maggiore fra i secondi quello dei risanati.**

# DEFINIZIONI

**Stable coronary artery disease is generally characterized by episodes of reversible myocardial demand/supply mismatch, related to ischaemia or hypoxia, which are usually inducible by exercise, emotion or other stress and reproducible—but, which may also be occurring spontaneously.**

**Table 5 Classification of angina severity according to the Canadian Cardiovascular Society**

| | |
|---|---|
| Class I | Ordinary activity does not cause angina such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation. |
| Class II | Slight limitation of ordinary activity. Angina on walking or climbing stairs rapidly, walking or stair climbing after meals, or in cold, wind or under emotional stress, or only during the first few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions. |
| Class III | Marked limitation of ordinary physical activity. Angina on walking one to two blocks[a] on the level or one flight of stairs in normal conditions and at a normal pace. |
| Class IV | Inability to carry on any physical activity without discomfort' – angina syndrome may be present at rest'. |

[a]Equivalent to 100–200 m.

**Table 4 Traditional clinical classification of chest pain**

| | |
|---|---|
| Typical angina (definite) | Meets all three of the following characteristics:<br>• substernal chest discomfort of characteristic quality and duration;<br>• provoked by exertion or emotional stress;<br>• relieved by rest and/or nitrates within minutes. |
| Atypical angina (probable) | Meets two of these characteristics. |
| Non-anginal chest pain | Lacks or meets only one or none of the characteristics. |

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**

**The Task Force on the management of stable coronary artery disease of the European Society of Cardiology**

# DEFINIZIONI

The various clinical presentations of SCAD are associated with different underlying mechanisms that mainly include:

1. plaque-related obstruction of epicardial arteries
2. focal or diffuse spasm of normal or plaque-diseased arteries
3. microvascular dysfunction
4. left ventricular dysfunction caused by prior acute myocardial necrosis and/or hibernation (ischaemic cardiomyopathy)

These mechanisms may act singly or in combination

**Table 3** **Main features of stable coronary artery disease**

| |
|---|
| **Pathogenesis** |
| Stable anatomical atherosclerotic and/or functional alterations of epicardial vessels and/or microcirculation |
| **Natural history** |
| Stable symptomatic or asymptomatic phases which may be interrupted by ACS |
| **Mechanisms of myocardial ischaemia** |
| Fixed or dynamic stenoses of epicardial coronary arteries; |
| Microvascular dysfunction; |
| Focal or diffuse epicardial coronary spasm; |
| The above mechanisms may overlap in the same patient and change over time. |
| **Clinical presentations** |
| Effort induced angina caused by:<br>• epicardial stenoses;<br>• microvascular dysfunction;<br>• vasoconstriction at the site of dynamic stenosis;<br>• combination of the above. |
| Rest angina caused by:<br>• Vasospasm (focal or diffuse)<br>• epicardial focal;<br>• epicardial diffuse;<br>• microvascular;<br>• combination of the above. |
| Asymptomatic:<br>• because of lack of ischaemia and/or of LV dysfunction;<br>• despite ischaemia and/or LV dysfunction. |
| Ischaemic cardiomyopathy |

ACS = acute coronary syndrome; LV = left ventricular; SCAD = stable coronary artery disease.

# DEFINIZIONI

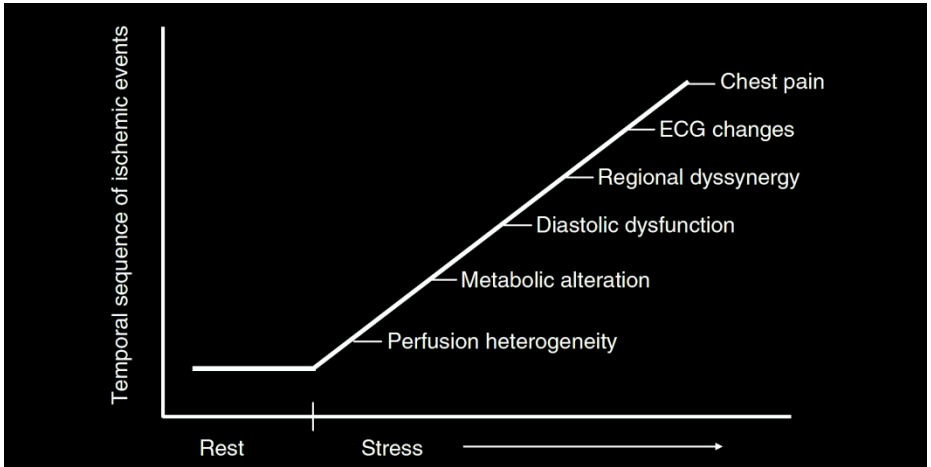
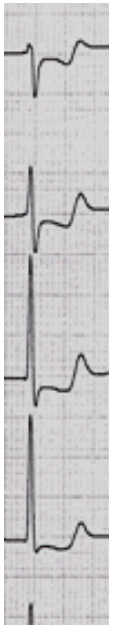



**Fig. 3.1** The classical ischemic cascade, triggered by coronary vasospasm and/or epicardial stenosis. The various markers are usually ranked according to a well-defined time sequence

# DIAGNOSI

## PROBABILITA' PRE-TEST

- Patients in whom anginal pain may be possible but who have a very low probability of significant CAD **< 15%** should have other cardiac causes of chest pain excluded and their CV risk factors adjusted based on risk score assessment. No specific non-invasive stress testing should be performed.
- Patients with an intermediate PTP of **15–85%** should undergo further non-invasive testing.
- In patients with a clinical PTP **> 85%**, the diagnosis of CAD should be made clinically and further testing will not improve accuracy. Further testing may, however, be indicated for stratification of risk of events, especially if no satisfactory control of symptoms is possible with initial medical therapy

# DIAGNOSI

**Table 12 Characteristics of tests commonly used to diagnose the presence of coronary artery disease**

| | Diagnosis of CAD | |
|---|---|---|
| | Sensitivity (%) | Specificity (%) |
| Exercise ECG [a, 91, 94, 95] | 45–50 | 85–90 |
| Exercise stress echocardiography[96] | 80–85 | 80–88 |
| Exercise stress SPECT[96-99] | 73–92 | 63–87 |
| Dobutamine stress echocardiography[96] | 79–83 | 82–86 |
| Dobutamine stress MRI[b,100] | 79–88 | 81–91 |
| Vasodilator stress echocardiography[96] | 72–79 | 92–95 |
| Vasodilator stress SPECT[96, 99] | 90–91 | 75–84 |
| Vasodilator stress MRI[b,98, 100-102] | 67–94 | 61–85 |
| Coronary CTA[c,103-105] | 95–99 | 64–83 |
| Vasodilator stress PET[97, 99, 106] | 81–97 | 74–91 |

CAD = coronary artery disease; CTA = computed tomography angiography; ECG = electrocardiogram; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single photon emission computed tomography.
[a] Results without/with minimal referral bias.
[b] Results obtained in populations with medium-to-high prevalence of disease without compensation for referral bias.
[c] Results obtained in populations with low-to-medium prevalence of 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 |

ECG = electrocardiogram; PTP = pre-test probability; SCAD = stable coronary artery disease.
[a] Probabilities of obstructive coronary disease shown reflect the estimates for patients aged 35, 45, 55, 65, 75 and 85 years.
- Groups in white boxes have a PTP <15% and hence can be managed without further testing.
- Groups in blue boxes have a PTP of 15–65%. They could have an exercise ECG if feasible as the initial test. However, if local expertise and availability permit a non-invasive imaging based test for ischaemia this would be preferable given the superior diagnostic capabilities of such tests. In young patients radiation issues should be considered.
- Groups in light red boxes have PTPs between 66–85% and hence should have a non-invasive imaging functional test for making a diagnosis of SCAD.
- In groups in dark red boxes the PTP is >85% and one can assume that SCAD is present. They need risk stratification only.

# DIAGNOSI


**Sex Differences in Presentation and Outcome Among Patients With Type 2 Diabetes and Coronary Artery Disease Treated With Contemporary Medical Therapy With or Without Prompt Revascularization**

Tamis Holland, J Am Coll Cardiol 2013

| Characteristics | Women (n = 702) | Men (n = 1,666) | p Value |
|---|---|---|---|
| Angina | 66.5% | 58.2% | <0.01 |
| Stable CCS I–II | 63.7% | 73.1% | <0.01 |
| Stable CCS III–IV | 17.8% | 12.5% | |
| Unstable | 18.5% | 14.4% | |
| Angina equivalents | 72.6% | 60.1% | <0.01 |

# CARATTERISTICHE DEL DOLORE ATIPICO IN PAZIENTI RICOVERATI PER SCA


**Acute Coronary Syndromes Without Chest Pain, An Underdiagnosed and Undertreated High-Risk Group***

**Insights From The Global Registry of Acute Coronary Events**

*Brieger D CHEST 2004*

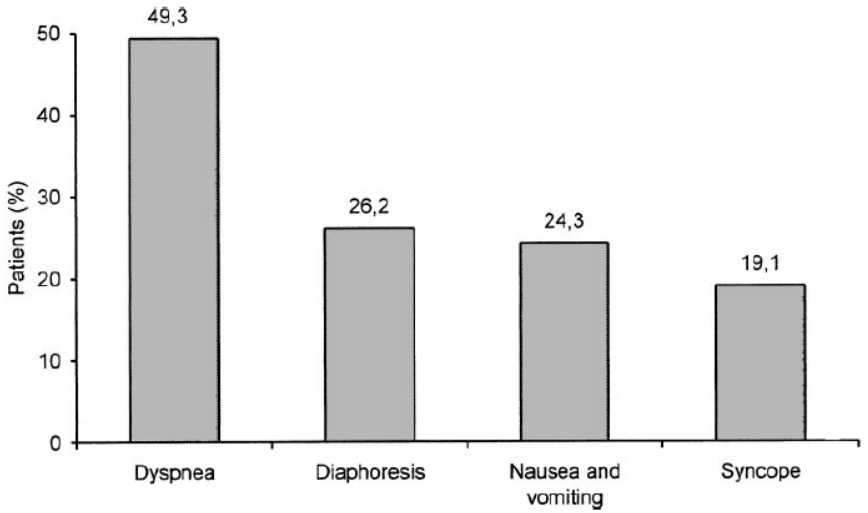
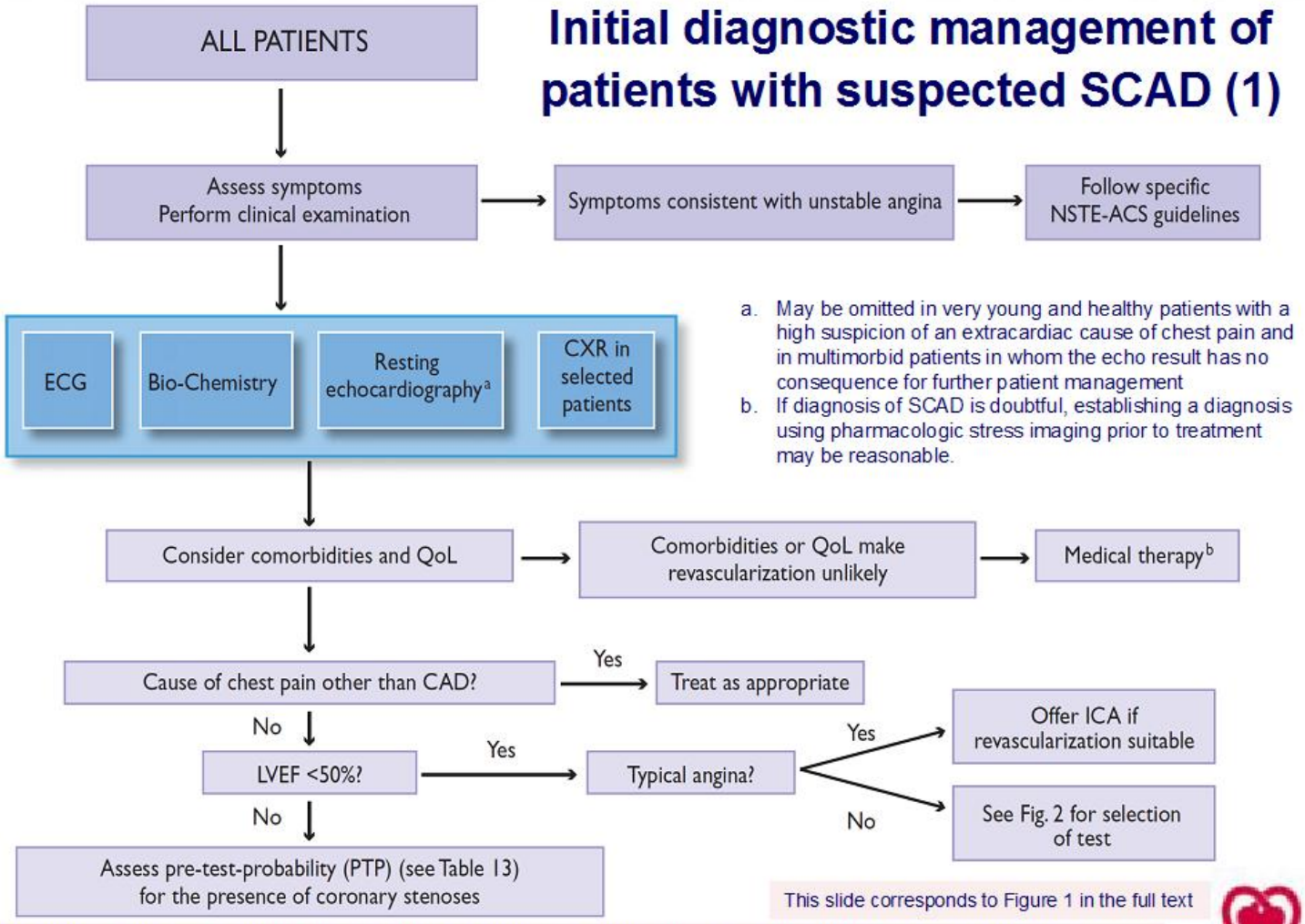



FIGURE 1. Dominant presenting symptoms in patients without chest pain (total exceeds 100% as patients may have presented with more than one dominant symptom).

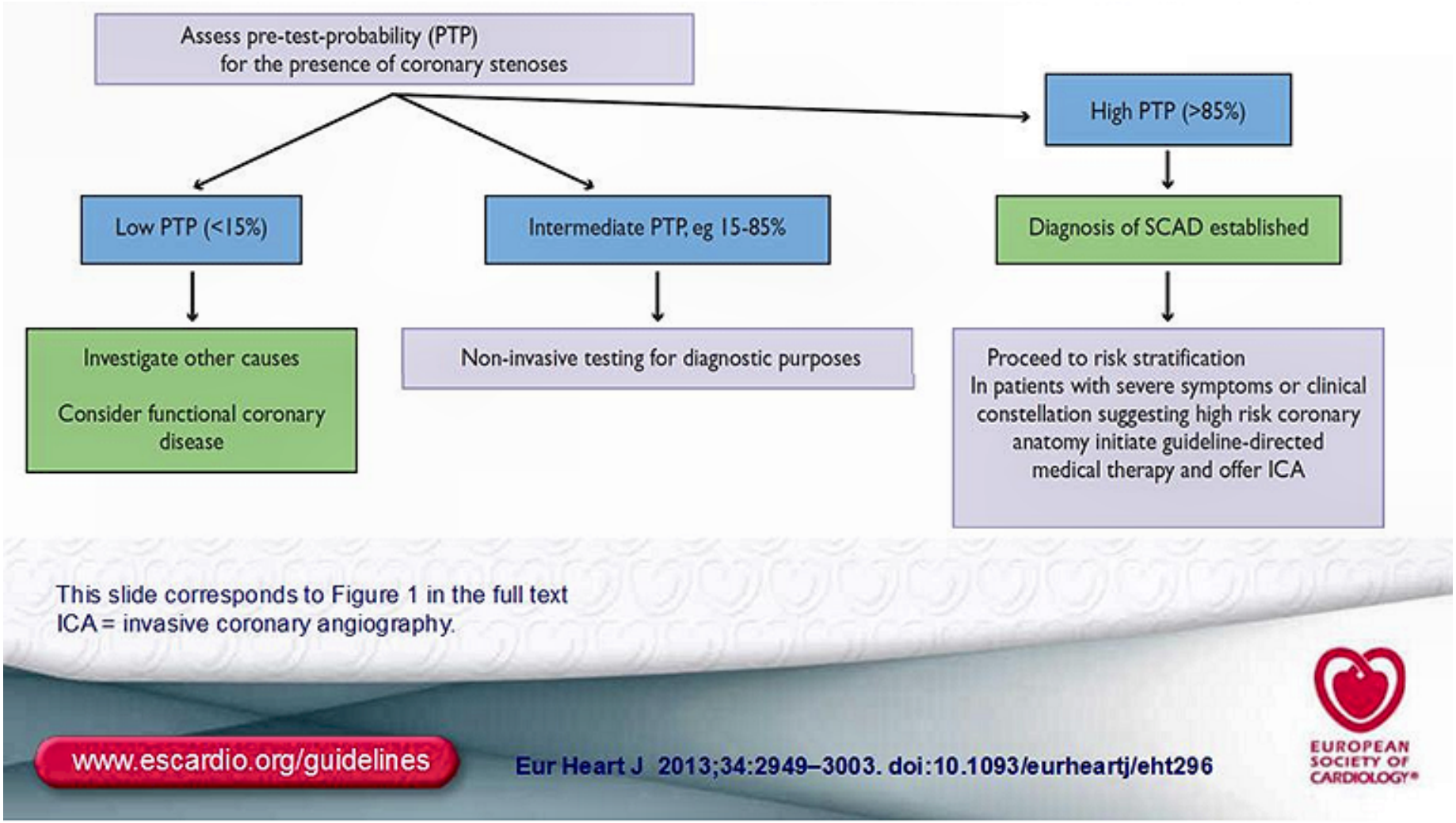
**Su 1,763 pazienti:**

- **Dispnea 49%,**
- **Sudorazione 26%**
- **Nausea/vomito 24%**
- **Presincope/sincope 19%**

# GESTIONE DIAGNOSTICA INIZIALE



# GESTIONE DIAGNOSTICA INIZIALE




# RISCHIO DI IM/MORTE CV

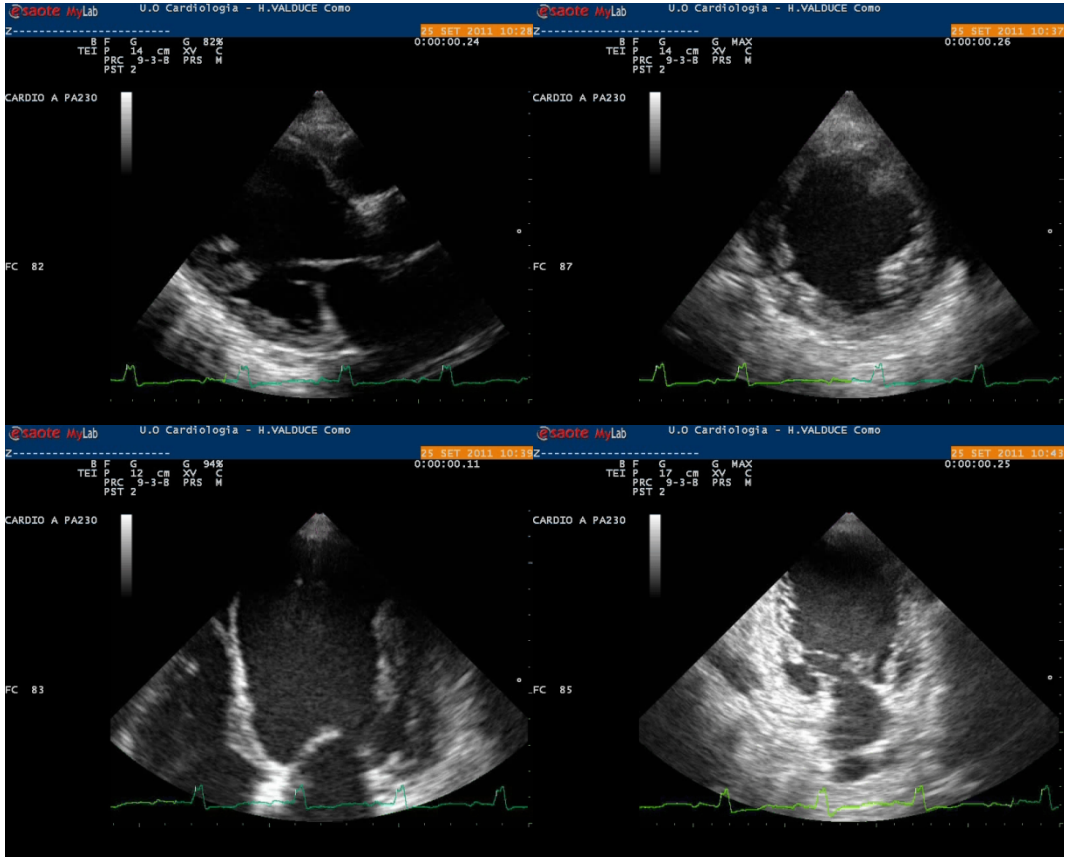
- The process of risk stratification serves to identify patients at high event risk who will benefit from revascularization beyond the amelioration of symptoms.
- Patients with an annual mortality >3% are defined as high event risk patients. Low event risk patients are those with an annual mortality < 1% per year. The intermediate event risk group has an annual mortality of ≥1% but ≤3% per year

# RISCHIO DI IM/MORTE CV

- Event risk stratification generally follows a pyramidal structure, with all patients having event risk stratification by **clinical evaluation** as the most basic requirement, proceeding to assessment of **ventricular function** by resting echocardiography and, in the majority, to noninvasive assessment of **ischaemia/coronary anatomy**.
- An **ICA** for risk stratification will only be required in a selected subgroup of patients.


# LV FUNCTION

- The strongest predictor of long-term survival is LV function
- A patient with an LVEF<50% is already at high risk for CV death (annual mortality > 3%), even without accounting for additional event risk factors




| Recommendation | Class | Level |
|---|---|---|
| Resting echocardiography is recommended to quantify LV function in all patients with suspected SCAD. | I | C |

# NONINVASIVE ASSESSMENT OF ISCHEMIA/CORONARY ANATOMY

**Table 17 Definitions of risk for various test modalities[a]**

| | | |
|---|---|---|
| Exercise stress ECG[b] | High risk<br>Intermediate risk<br>Low risk | CV mortality >3%/year.<br>CV mortality between 1 and 3%/year.<br>CV mortality <1%/year. |
| Ischaemia imaging | High risk<br><br><br>Intermediate risk<br>Low risk | Area of ischaemia >10% (>10% for SPECT; limited quantitative data for CMR – probably ≥2/16 segments with new perfusion defects or ≥3 dobutamine-induced dysfunctional segments; ≥ 3 segments of LV by stress echo).<br>Area of ischaemia between 1 to 10% or any ischaemia less than high risk by CMR or stress echo.<br>No ischaemia. |
| Coronary CTA[c] | High risk<br><br>Intermediate rick<br>Low risk | Significant lesions of high risk category (three-vessel disease with proximal stenoses, LM, and proximal anterior descending CAD).<br>Significant lesion(s) in large and proximal coronary artery(ies) but not high risk category.<br>Normal coronary artery or plaques only. |

CAD = coronary artery disease; CMR = cardiac magnetic resonance; CTA = computed tomography angiography; CV = cardiovascular; ECG = electrocardiogram; ICA = invasive coronary angiography; LM = left main; PTP = pre-test probability; SPECT = single photon emission computed tomography.

[a] For detailed explanation on rationale for risk stratification scheme see web addenda.

[b] From nomogram (see web addenda, Figure W1) or http://www.cardiology.org/tools/medcalc/duke/

[c] See Fig 2 consider possible overestimation of presence of significant multivessel disease by coronary CTA in patients with high intermediate PTP (≥50%) and/or severe diffuse or focal coronary calcifications and consider performing additional stress testing in patients without severe symptoms before ICA.

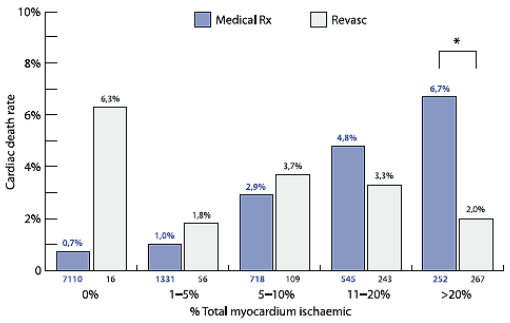



**Figure W2** Relationship between cardiac mortality and extent of myocardial ischaemia, depending on type of therapy.[45] Numbers below columns indicate numbers of patients in each group. *$P < 0.02$. Medical Rx = medical therapy; Revasc = revascularization.

# ICA

- The simplest and most widely used prognostic index is the classification of disease into one-vessel, two vessel, three-vessel, or LM stem CAD
- Patients with severe stenosis of the LM coronary artery have a poor prognosis when treated medically. The presence of severe proximal LAD disease also significantly reduces the survival rate

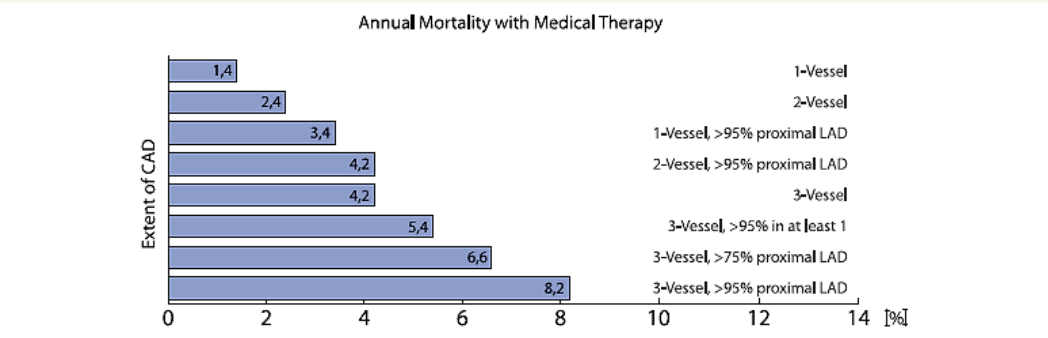



**Figure W3** Cardiac death rates in patients on medical therapy with different extents of angiographically defined coronary artery disease. LAD = left anterior descending.[46]

# INTEGRAZIONE DEI DATI

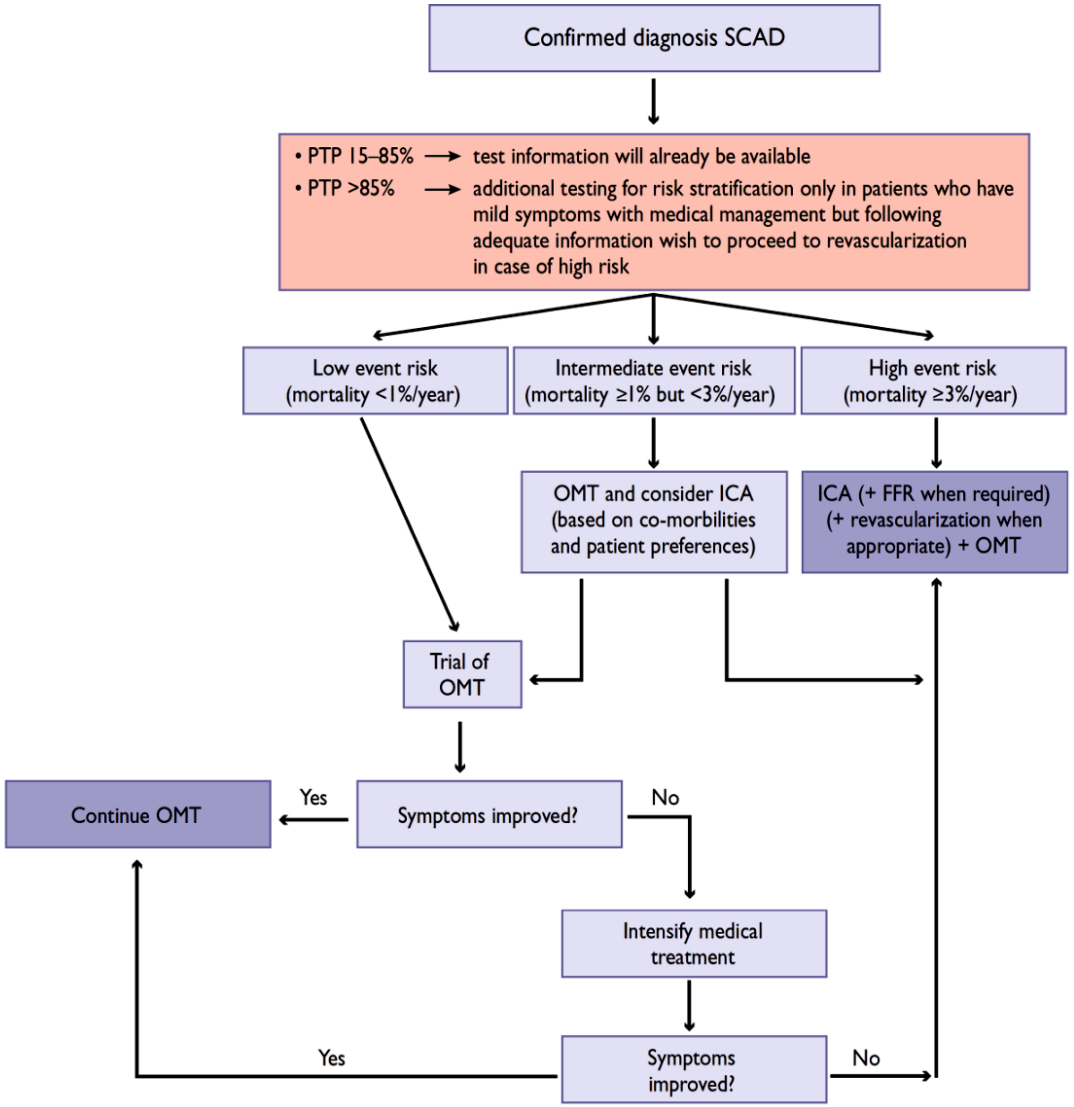



**Figure 3** Management based on risk determination for prognosis in patients with chest pain and suspected SCAD (for choice of test see Fig. 2, for definitions of event risk see Table 17). ICA = invasive coronary angiography; OMT = optimal medical therapy; PTP = pre-test probability; SCAD = stable coronary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

# TERAPIA

## FINALITA’

- Migliorare i sintomi
- Migliorare la mortalita’

## APPROCCI

- Modificazione degli stili di vita
- OMT
- OMT + rivascolarizzazione

# STILI DI VITA

- **Quitting smoking** is potentially the most effective of all preventive measures, being associated with a reduction in mortality of 36% after MI
- **Diet**
- Regular **physical activity** is associated with a decrease in CV morbidity and mortality in patients with established CAD
- **Weight reduction** in overweight and obese people is recommended in order to achieve favourable effects on BP, dyslipidaemia and glucose metabolism
- **Dyslipidemia , hypertension and diabetes** should be managed according to lipid guidelines with pharmacological and lifestyle intervention

# STILI DI VITA

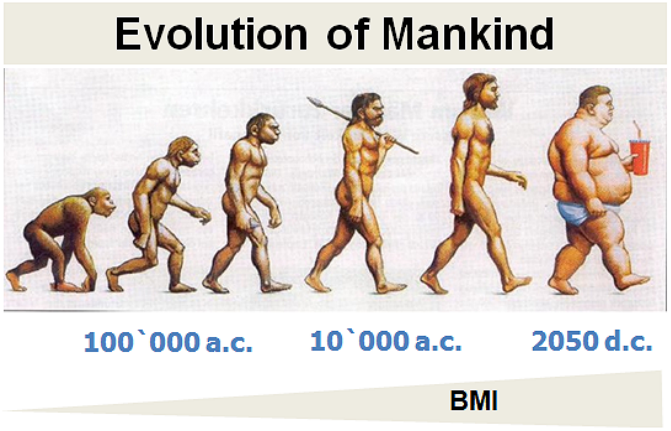
**Table 26** **Blood pressure thresholds for definition of hypertension with different types of blood pressure measurement (adapted from Umpierrez *et al.* 2012 [273]).**

| | SBP (mmHg) | D BP (mmHg) |
|---|---|---|
| Office BP | 140 | 90 |
| Home BP | 135 | 85 |
| Ambulatory BP | | |
| 24-h | 130 | 80 |
| Daytime (or awake) | 135 | 85 |
| Nighttime (or asleep) | 120 | 70 |

BP= blood pressure; DPB= diastolic blood pressure; SBP= systolic blood pressure.

**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.



# PCI VS EXERCISE IN NONACUTE CAD

## Percutaneous Coronary Angioplasty Compared With Exercise Training in Patients With Stable Coronary Artery Disease

### A Randomized Trial

Rainer Hambrecht, MD; Claudia Walther, MD; Sven Möbius-Winkler, MD; Stephan Gielen, MD; Axel Linke, MD; Katrin Conradi, MD; Sandra Erbs, MD; Regine Kluge, MD; Kai Kendziorra, MD; Osama Sabri, MD; Peter Sick, MD; Gerhard Schuler, MD

***Background***—Regular exercise in patients with stable coronary artery disease has been shown to improve myocardial perfusion and to retard disease progression. We therefore conducted a randomized study to compare the effects of exercise training versus standard percutaneous coronary intervention (PCI) with stenting on clinical symptoms, angina-free exercise capacity, myocardial perfusion, cost-effectiveness, and frequency of a combined clinical end point (death of cardiac cause, stroke, CABG, angioplasty, acute myocardial infarction, and worsening angina with objective evidence resulting in hospitalization).

***Methods and Results***—A total of 101 male patients aged ≤70 years were recruited after routine coronary angiography and randomized to 12 months of exercise training (20 minutes of bicycle ergometry per day) or to PCI. Cost efficiency was calculated as the average expense (in US dollars) needed to improve the Canadian Cardiovascular Society class by 1 class. Exercise training was associated with a higher event-free survival (88% versus 70% in the PCI group, $P=0.023$) and increased maximal oxygen uptake (+16%, from 22.7±0.7 to 26.2±0.8 mL $O_2$/kg, $P<0.001$ versus baseline, $P<0.001$ versus PCI group after 12 months). To gain 1 Canadian Cardiovascular Society class, $6956 was spent in the PCI group versus $3429 in the training group ($P<0.001$).

***Conclusions***—Compared with PCI, a 12-month program of regular physical exercise in selected patients with stable coronary artery disease resulted in superior event-free survival and exercise capacity at lower costs, notably owing to reduced rehospitalizations and repeat revascularizations. (***Circulation***. **2004;109:1371-1378.**)

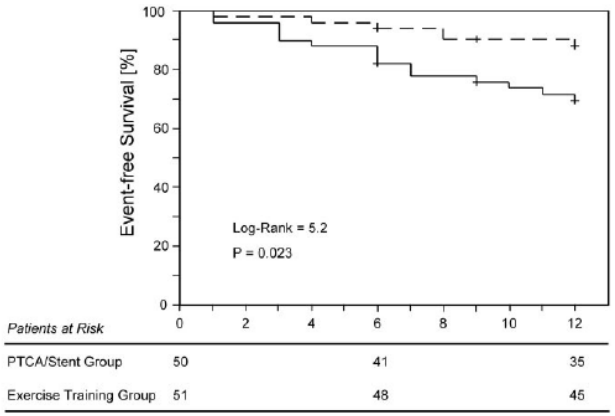
**Key Words:** coronary disease ■ exercise ■ angina ■ angioplasty ■ cost-benefit analysis

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association
Learn and Live

**Percutaneous Coronary Angioplasty Compared With Exercise Training in Patients With Stable Coronary Artery Disease: A Randomized Trial**
Rainer Hambrecht, Claudia Walther, Sven Möbius-Winkler, Stephan Gielen, Axel Linke, Katrin Conradi, Sandra Erbs, Regine Kluge, Kai Kendziorra, Osama Sabri, Peter Sick and Gerhard Schuler
*Circulation* 2004;109:1371-1378; originally published online Mar 8, 2004;
DOI: 10.1161/01.CIR.0000121360.31954.1F
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 75514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

2004

# THE REAL WORLD


**EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries**

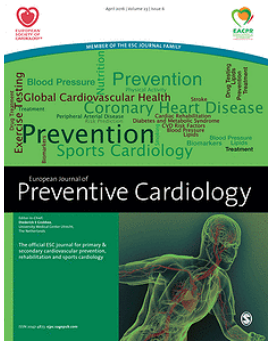


**Table 28** **Pharmacological treatments in stable coronary artery disease patients**

| Indication | Class [a] | Level [b] | Ref. [c] |
|---|---|---|---|
| **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 | 3, 329 |
| First-line treatment is indicated with ß-blockers and/or calcium channel blockers to control heart rate and symptoms. | I | A | 3, 331 |
| 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 | 177, 307, 3, 199, 284, 286, 308, 319-321, 328 |
| For second-line treatment, trimetazidine may be considered. | IIb | B | 313, 315 |
| 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 | 3, 365 |
| **Event prevention** | | | |
| Low-dose aspirin daily is recommended in all SCAD patients. | I | A | 333, 334, 366 |
| Clopidogrel is indicated as an alternative in case of aspirin intolerance. | I | B | 335 |
| Statins are recommended in all SCAD patients. | I | A | 62 |
| It is recommended to use ACE inhibitors (or ARBs) if presence of other conditions (e.g. heart failure, hypertension or diabetes). | I | A | 348, 349, 351, 352 |

ACE = angiotensin converting enzyme; SCAD = stable coronary artery disease.
[a] Class of recommendation.
[b] Level of evidence.
[c] Reference(s) supporting levels of evidence.
[d] No demonstration of benefit on prognosis

# OMT

# OMT

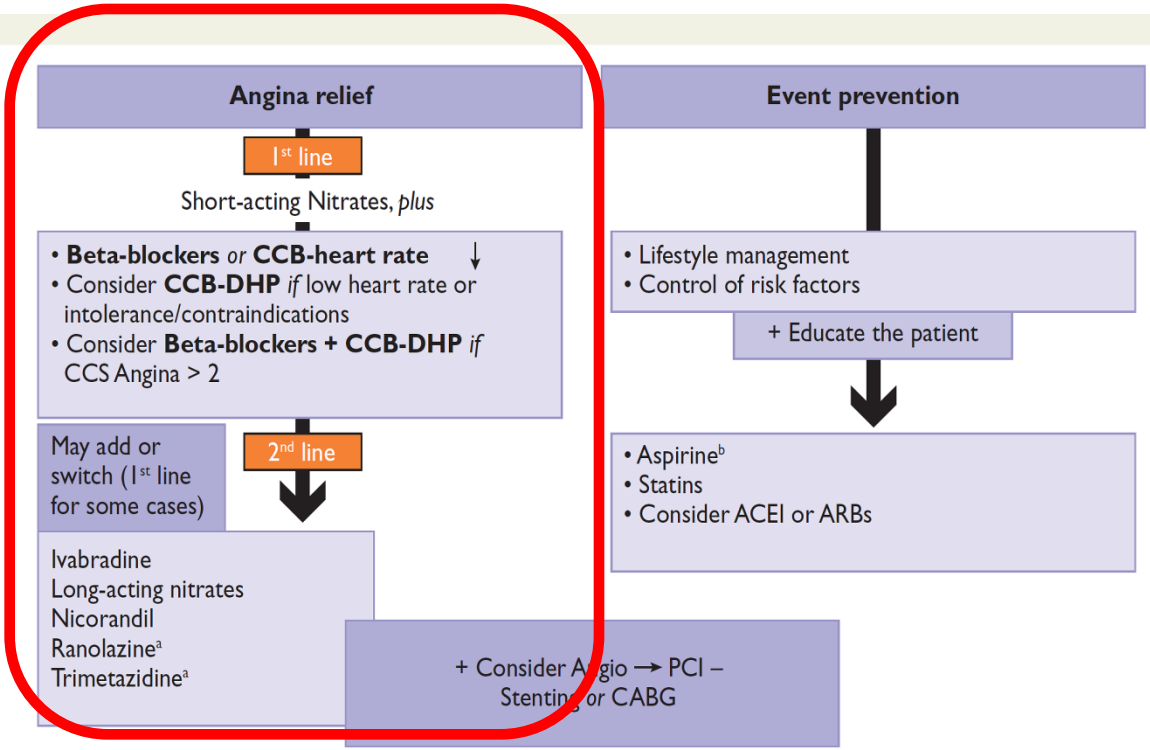



**Figure 4** Medical management of patients with stable coronary artery disease. ACEI = angiotensin converting enzyme inhibitor; CABG = coronary artery bypass graft; CCB = calcium channel blockers; CCS = Canadian Cardiovascular Society; DHP = dihydropyridine; PCI = percutaneous coronary intervention.

[a]Data for diabetics.

[b]if intolerance, consider clopidogrel

# FARMACI ANTIANGINOSI

| | $O_2$ Supply | | $O_2$ Demand | | |
|---|---|---|---|---|---|
| Drug class | Coronary blood flow | Heart rate | Arterial pressure | Venous return | Myocardial contractility |
| β-blockers | — | ↓ | ↓ | — | ↓ |
| DHP CCBs | ↑ | ↑* | ↓ | — | ↓ |
| Non-DHP CCBs | ↑ | ↓ | ↓ | — | ↓ |
| Long-acting nitrates | ↑ | ↑/— | ↓ | ↓ | — |

CCB = calcium channel blocker, DHP = dihydropyridine *Except amlodipine

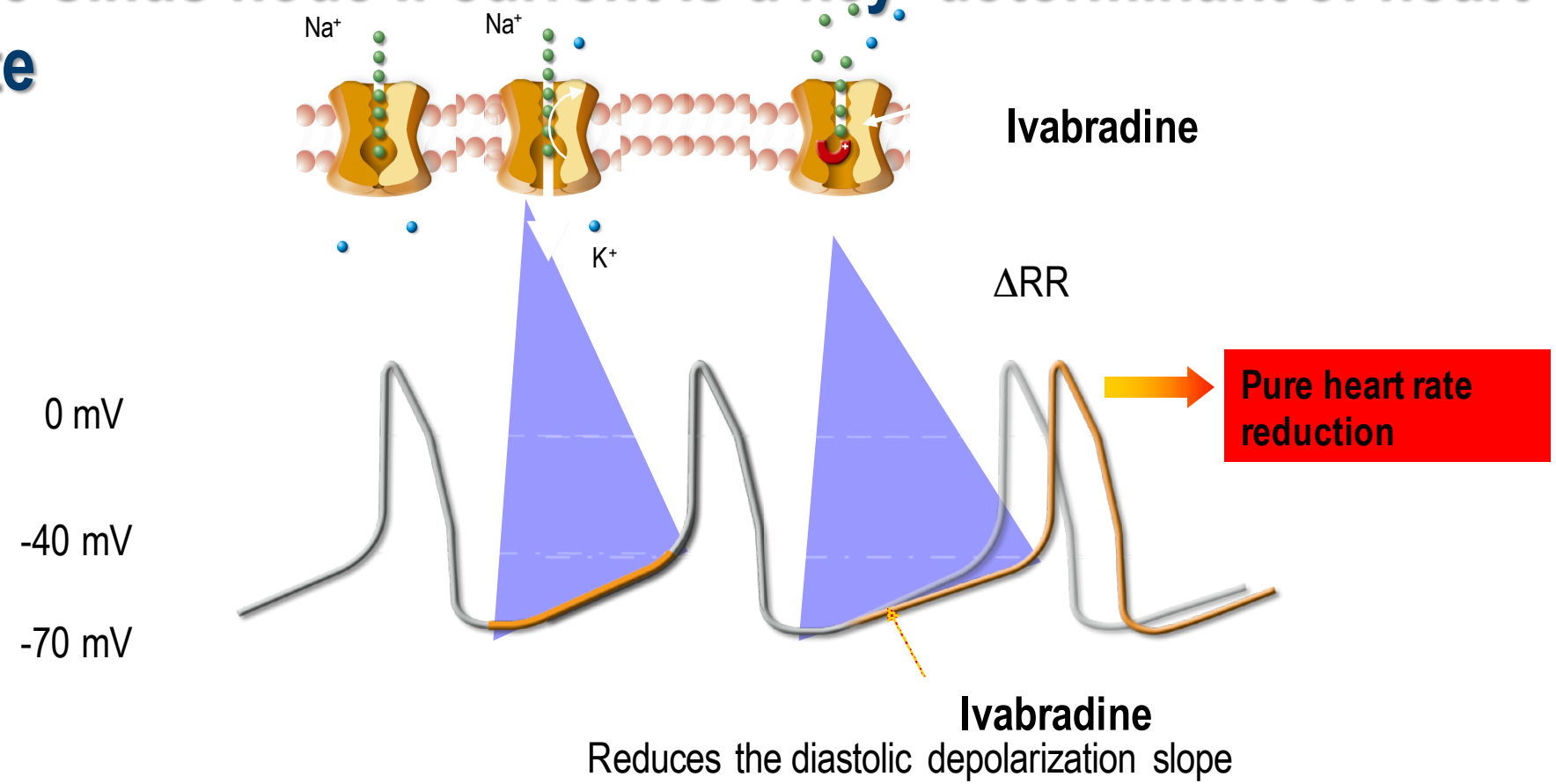
Boden WE et al. Clin Cardiol. 2001;24:73-9
Gibbons RJ et al. ACC/AHA 2002 Chronic Angina Guidelines
Kerins DM et al. The Pharmacological Basis of Therapeutics. 10th ed

# FARMACI ANTIANGINOSI
# TERAPIE DI COMBINAZIONE

| Study | Combinations | Findings |
|---|---|---|
| **TIBET - Fox KM**<br>*Eur Heart J* 1996;17:96-103 | Atenolol<br>Nifedipine SR<br>Combination<br>608 patients | **No additive benefit of combined therapy** |
| **IMAGE - Savonitto S**<br>*J Am Coll Cardiol* 1996;27:311-316 | Metoprolol<br>Nifedipine SR<br>Combination<br>249 patients | **No additive benefit of combined therapy** |
| **CESAR - Knight C and Fox KM**<br>*Am J Cardiol* 1998;81:133-136 | Amlodipine + Atenolol vs<br>Diltiazem + Atenolol | **No additive benefit of combined therapy** |
| **Meta-analysis (22 studies)**<br>**Klein W, Jackson G, and Tavazzi L**<br>*Coron Artery Dis* 2002; 13:427-436 | β-Blocker<br>Calcium antagonist<br>Combination | **No additive benefit of combined therapy after 6 hours** |

# FARMACI INNOVATIVI: IVABRADINA

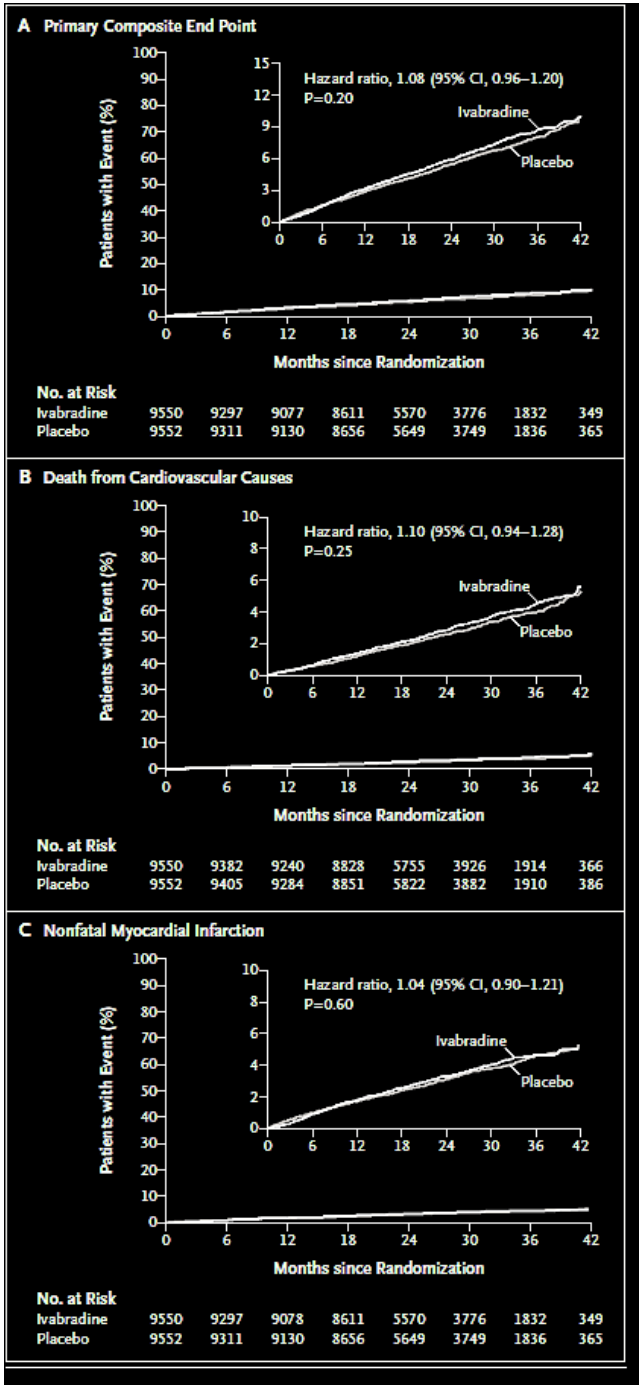
## The sinus node If current is a key determinant of heart rate




Adapted from: Thollon C, et al. Br J Pharmacol. 1994;112:37-42
DiFrancesco A, et al. Drugs. 2004;64:1757-1765

# IVABRADINA

- è un efficace anti-ischemico
- è sicura ed efficace nelle cardiopatie con disfunzione sistolica e FC ≥ 60
- non è inferiore al beta bloccante ed ha benefici additivi se aggiunta al beta bloccante
- può essere aggiunta ad altri farmaci antianginosi (non verapamile o diltiazem).
- non associare a potenti Inibitori CYP 3°A4 (Antifungini azolici, Antibiotici macrolidi, Inibitori delle proteasi HIV, nefazodone




# IVABRADINA

The NEW ENGLAND JOURNAL of MEDICINE

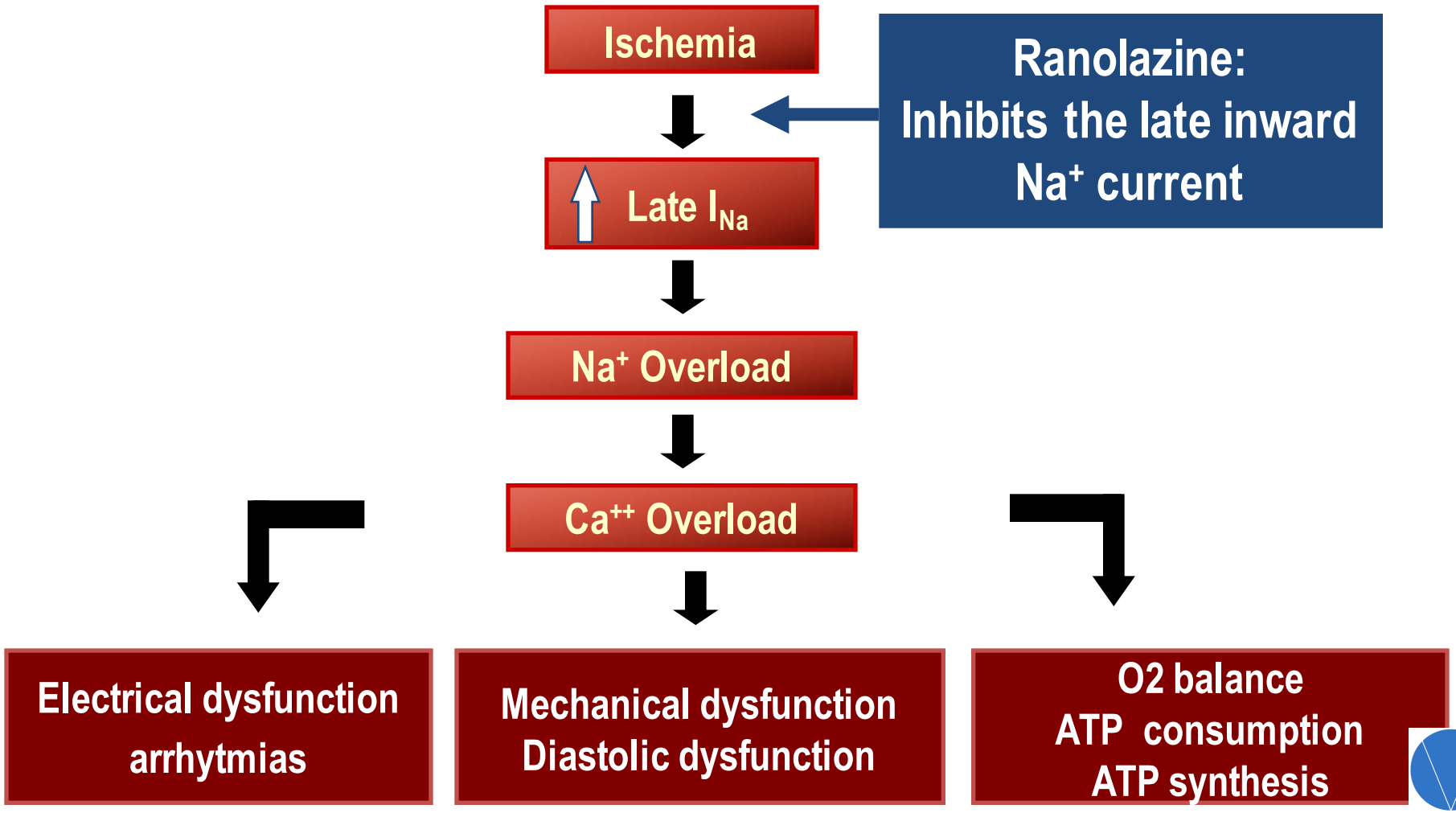
ESTABLISHED IN 1812 SEPTEMBER 18, 2014 VOL. 371 NO. 12

## 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*

SIGNIFY

# FARMACI INNOVATIVI: RANOLAZINA



# RANOLAZINA

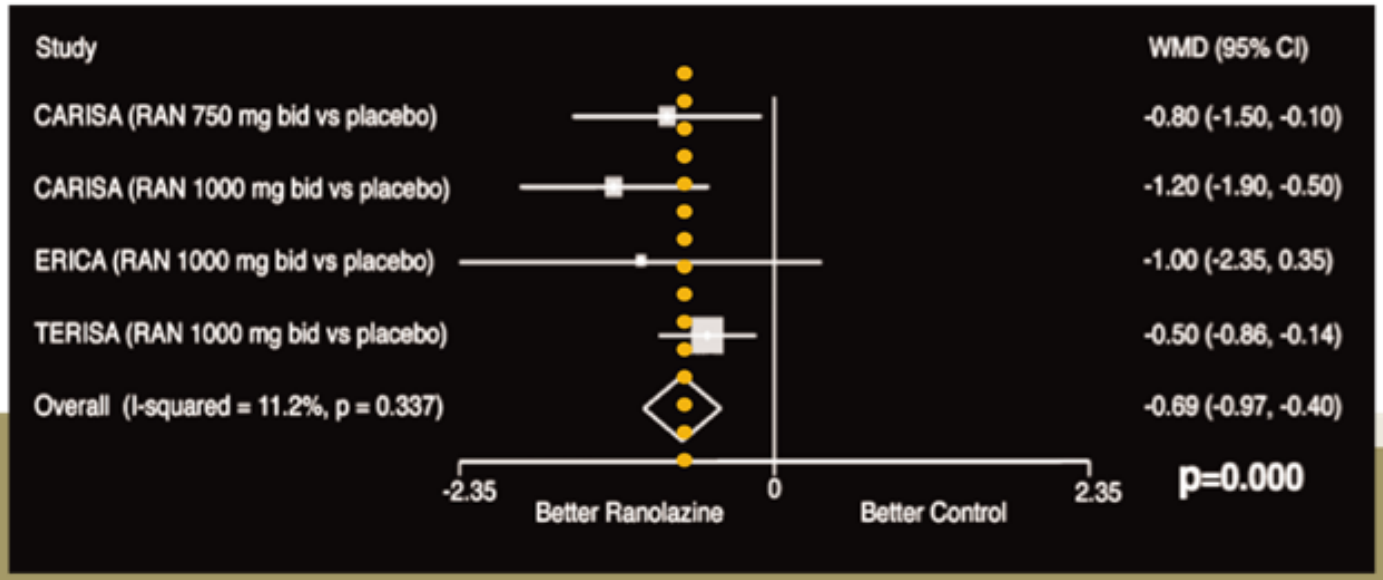

**Effects of ranolazine in symptomatic patients with stable coronary artery disease. A systematic review and meta analysis**

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



# RANOLAZINA

**Health Services and Outcomes Research**

## Effects of Ranolazine on Angina and Quality of Life After Percutaneous Coronary Intervention With Incomplete Revascularization

### Results From the Ranolazine for Incomplete Vessel Revascularization (RIVER-PCI) Trial

Karen P. Alexander, MD; Giora Weisz, MD; Kristi Prather, MPH; Stefan James, MD; Daniel B. Mark, MD; Kevin J. Anstrom, PhD; Linda Davidson-Ray, MA; Adam Witkowski, MD, PhD; Angel J. Mulkay, MD; Anna Osmukhina, PhD; Ramin Farzaneh-Far, MD; Ori Ben-Yehuda, MD; Gregg W. Stone, MD; E. Magnus Ohman, MD

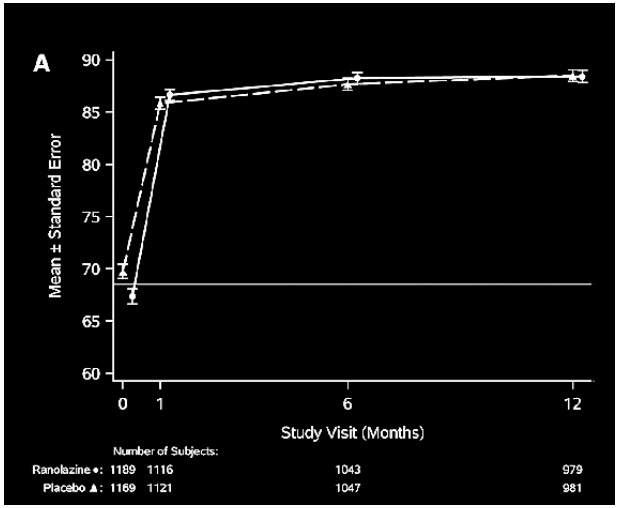
***Background***—Angina often persists or returns in populations following percutaneous coronary intervention (PCI). We hypothesized that ranolazine would be effective in reducing angina and improving quality of life (QOL) in incomplete revascularization (ICR) post-PCI patients.

***Methods and Results***—In RIVER-PCI, 2604 patients with a history of chronic angina who had ICR post-PCI were randomized 1:1 to oral ranolazine versus placebo; QOL analyses included 2389 randomized subjects. Angina and QOL questionnaires were collected at baseline and months 1, 6, and 12. Ranolazine patients were more likely than placebo to discontinue study drug by month 6 (20.4% versus 14.1%, $P<0.001$) and 12 (27.2% versus 21.3%, $P<0.001$). Following qualifying index PCI, the primary QOL outcome (Seattle Angina Questionnaire [SAQ] angina frequency score) improved markedly, but similarly, in the ranolazine and placebo groups, respectively, from baseline (67.3±24.5 versus 69.7±24.0, $P=0.01$) to month 1 (86.6±18.1 versus 85.8±18.5, $P=0.27$) and month 12 (88.4±17.8 versus 88.5±17.8, $P=0.94$). SAQ angina frequency repeated measures did not differ in adjusted analysis between groups post baseline (mean difference 1.0; 95% CI -0.2, 2.2; $P=0.11$). Improvement in SAQ angina frequency was observed with ranolazine at month 6 among diabetics (mean difference 3.3; 95% CI 0.6, 6.1; $P=0.02$) and those with more angina (baseline SAQ angina frequency ≤60; mean difference 3.4; 95% CI 0.6, 6.2; $P=0.02$), but was not maintained at month 12.

***Conclusions***—Despite ICR following PCI, there was no incremental benefit in angina or QOL measures by adding ranolazine in this angiographically-identified population. These measures markedly improved within 1 month of PCI and persisted up to 1 year in both treatment arms.

***Clinical Trial Registration***—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01442038.

(***Circulation***. **2016;133:39-47. DOI: 10.1161/CIRCULATIONAHA.115.019768.**)




**Frequenza di angina all'arruolamento, a 1, 6 e 12 mesi**

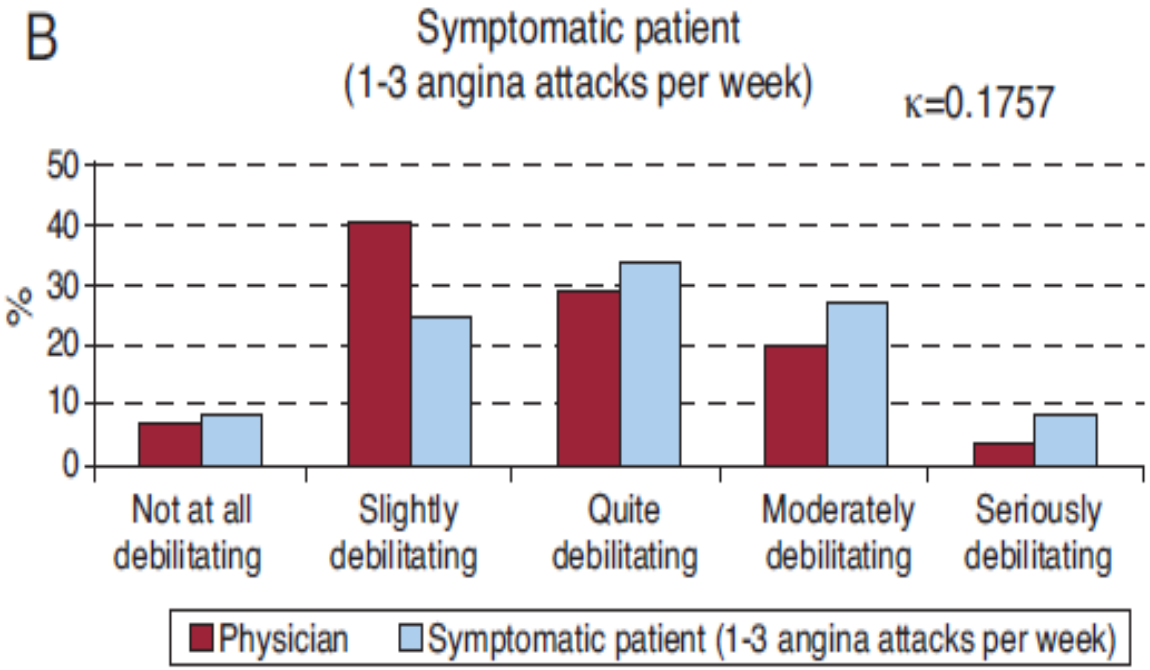
# THE REAL WORLD

## Percezione del medico e del paziente sulla efficacia del trattamento sui sintomi anginosi


Stable Angina in Spain and its Impact on Quality of Life. The AVANCE Registry

Borras X, Rev Esp Cardiol 2012

**2.024 pts with Chronic Ischemic Heart Disease**



# OMT

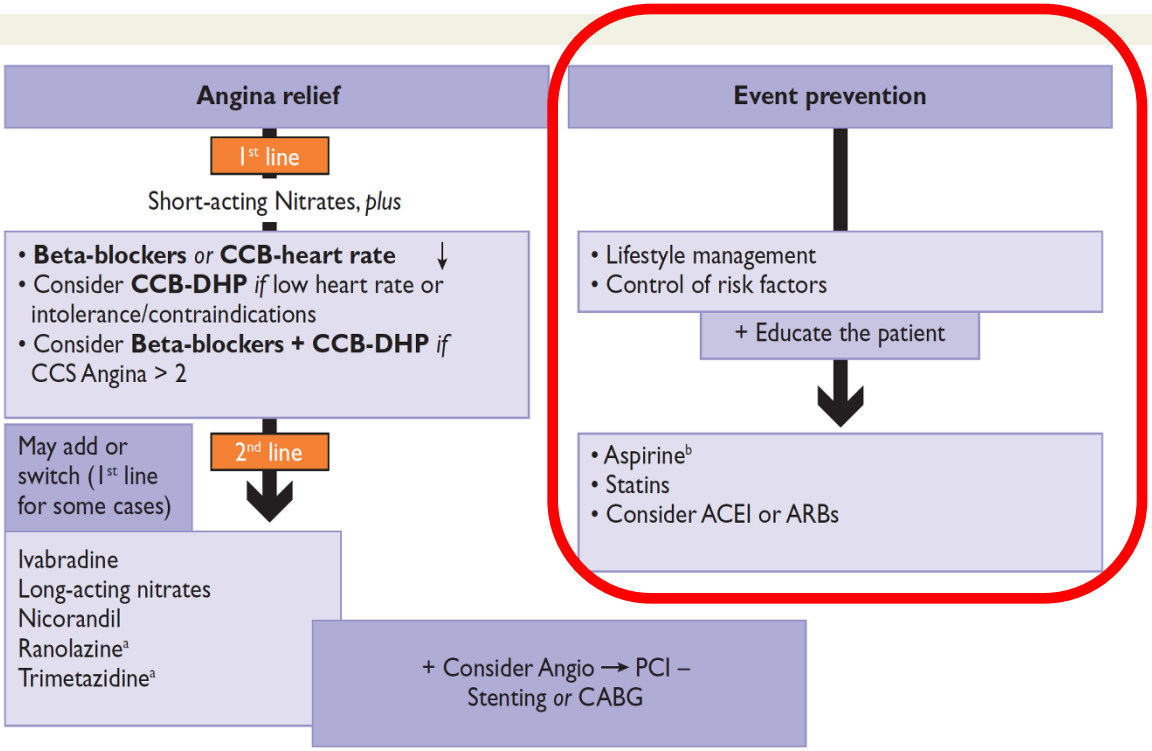



**Figure 4** Medical management of patients with stable coronary artery disease. ACEI = angiotensin converting enzyme inhibitor; CABG = coronary artery bypass graft; CCB = calcium channel blockers; CCS = Canadian Cardiovascular Society; DHP = dihydropyridine; PCI = percutaneous coronary intervention.

[a]Data for diabetics.

[b]if intolerance, consider clopidogrel

# EVENT PREVENTION


**Si può sempre crescere di più**

**Anche nella prevenzione secondaria**

# FARMACI INNOVATIVI: EZETIMIBE

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 18, 2015 VOL. 372 NO. 25

## Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Michael A. Blazing, M.D., Robert P. Giugliano, M.D., Amy McCagg, B.S., Jennifer A. White, M.S., Pierre Theroux, M.D., Harald Darius, M.D., Basil S. Lewis, M.D., Ton Oude Ophuis, M.D., Ph.D., J. Wouter Jukema, M.D., Ph.D., Gaetano M. De Ferrari, M.D., Witold Ruzyllo, M.D., Paul De Lucca, Ph.D., KyungAh Im, Ph.D., Erin A. Bohula, M.D., D.Phil., Craig Reist, Ph.D., Stephen D. Wiviott, M.D., Andrew M. Tershakovec, M.D., M.P.H., Thomas A. Musliner, M.D., Eugene Braunwald, M.D., and Robert M. Califf, M.D., for the IMPROVE-IT Investigators*

**CONCLUSIONS**

When added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol levels and improved cardiovascular outcomes. Moreover, lowering LDL cholesterol to levels below previous targets provided additional benefit. (Funded by Merck; IMPROVE-IT ClinicalTrials.gov number, NCT00202878.)

The NEW ENGLAND JOURNAL of MEDICINE

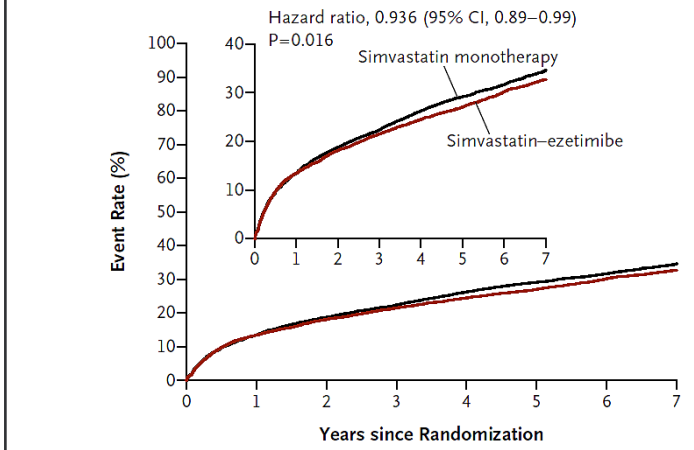
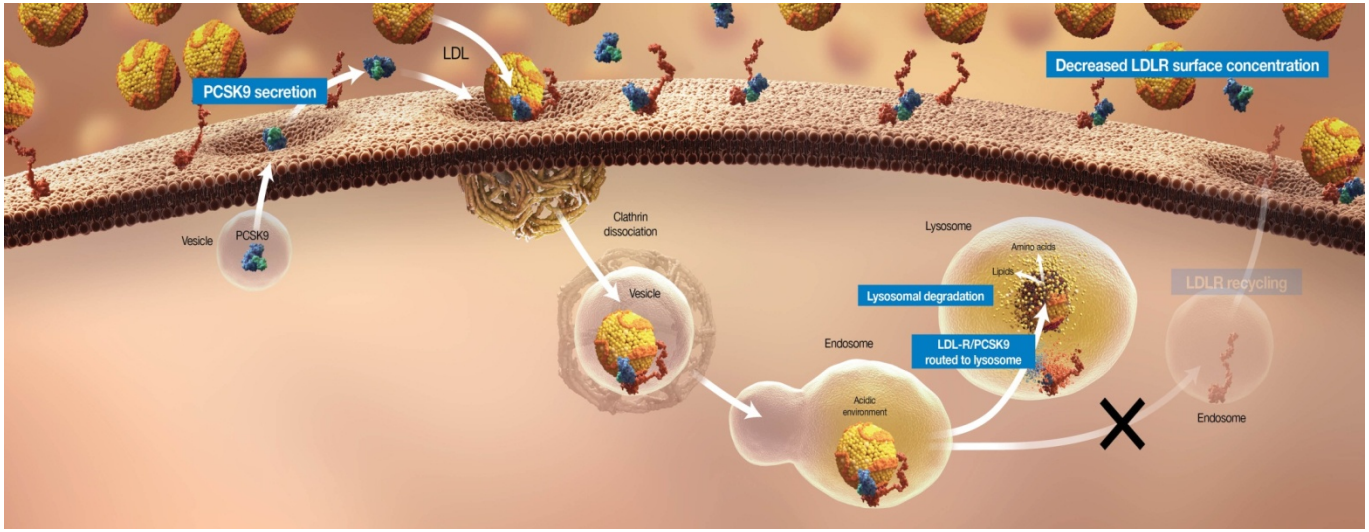
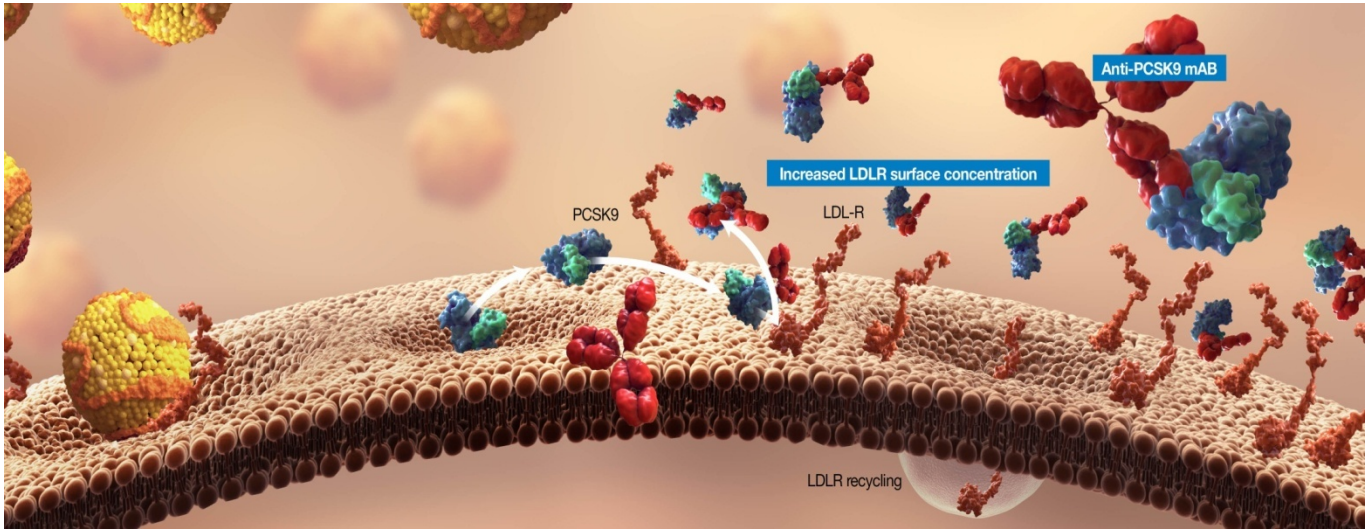



**Figure 1. Kaplan–Meier Curves for the Primary Efficacy End Point.**

Shown are the cumulative event rates for the primary composite end point of death from cardiovascular disease, a major coronary event (nonfatal myocardial infarction, documented unstable angina requiring hospital admission, or coronary revascularization occurring at least 30 days after randomization), or nonfatal stroke in the intention-to-treat population during the overall study period (i.e., beginning from the time of randomization to the day of the first occurrence of a primary end-point event, the day of the last office or phone visit, or the day of death during follow-up). The inset shows the same data on an enlarged y axis.

# FARMACI INNOVATIVI: EVOLOCUMAB



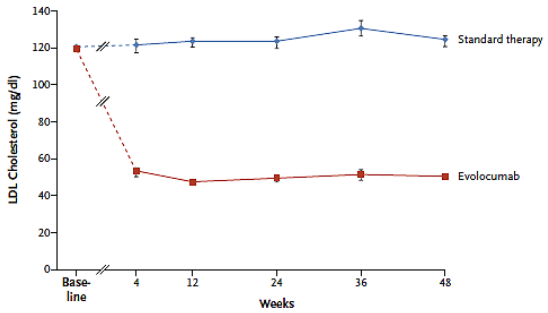



# EVOLOCUMAB

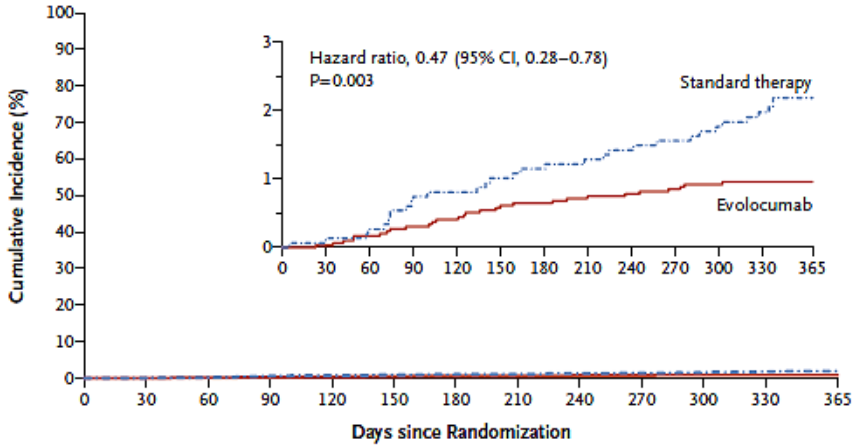
ORIGINAL ARTICLE

## Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Stephen D. Wiviott, M.D., Frederick J. Raal, M.B., B.Ch., M.Med., Ph.D., Dirk J. Blom, M.B., Ch.B., M.Med., Ph.D., Jennifer Robinson, M.D., M.P.H., Christie M. Ballantyne, M.D., Ransi Somaratne, M.D., Jason Legg, Ph.D., Scott M. Wasserman, M.D., Robert Scott, M.D., Michael J. Koren, M.D., and Evan A. Stein, M.D., Ph.D., for the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Standard therapy | 1489 | 394 | 1388 | 1376 | 402 | 1219 |
| Evolocumab | 2976 | 864 | 2871 | 2828 | 841 | 2508 |
| Absolute reduction (mg/dl) | | 60.4 | 73.4 | 70.4 | 72.7 | 70.5 |
| Percentage reduction | | 45.3 | 60.9 | 58.8 | 54.0 | 58.4 |
| P value | | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |




| No. at Risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Standard therapy | 1489 | 1486 | 1481 | 1473 | 1467 | 1463 | 1458 | 1454 | 1447 | 1438 | 1428 | 1361 | 407 |
| Evolocumab | 2976 | 2970 | 2962 | 2949 | 2938 | 2930 | 2920 | 2910 | 2901 | 2885 | 2871 | 2778 | 843 |

**Figure 2. Cumulative Incidence of Cardiovascular Events.**

Included among the cardiovascular events were death, myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure. Cardiovascular events were reported in 29 of 2976 patients in the evolocumab group (Kaplan–Meier 1-year event rate, 0.95%) and in 31 of 1489 patients in the standard-therapy group (Kaplan–Meier 1-year event rate, 2.18%). The inset shows the same data on an expanded y axis. The P value was calculated with the use of a log-rank test.

**CONCLUSIONS**

During approximately 1 year of therapy, the use of evolocumab plus standard therapy, as compared with standard therapy alone, significantly reduced LDL cholesterol levels and reduced the incidence of cardiovascular events in a prespecified but exploratory analysis. (Funded by Amgen; OSLER-1 and OSLER-2 ClinicalTrials.gov numbers, NCT01439880 and NCT01854918.)

N ENGL J MED 372;16 NEJM.ORG APRIL 16, 2015

The NEW ENGLAND JOURNAL of MEDICINE

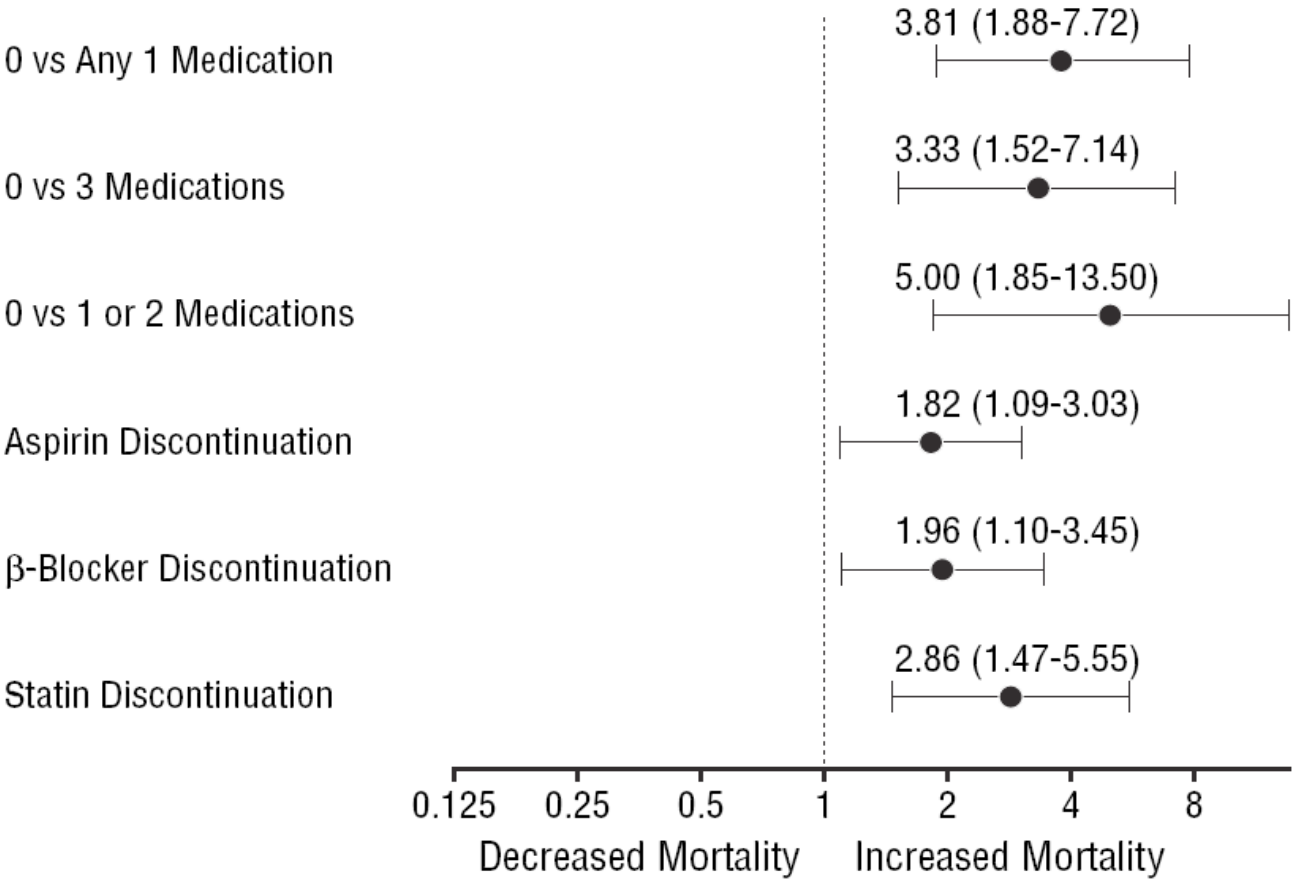
# NEW DRUGS
# OLD PROBLEMS

## Long-term adherence to EB secondary prevention therapies after ACS (Duke Databank n=31750 pts)

| Adherence to pharmacological therapy after 6 months | |
|---|---|
| Aspirin | 76.6% |
| B-blockers | 50.9% |
| Statins | 40.5% |
| ACE-i/ATII | 31.0% |
| CC blockers | 29.4% |

Newby et al, Circulation 2006; 113: 203-12

# DISCONTINUATION OF EB THERAPIES AFTER ACS AND CLINICAL OUTCOME





Ho PM, et al Arch. Int. Med. 2006; 166:1842-1846

# IL TARGET



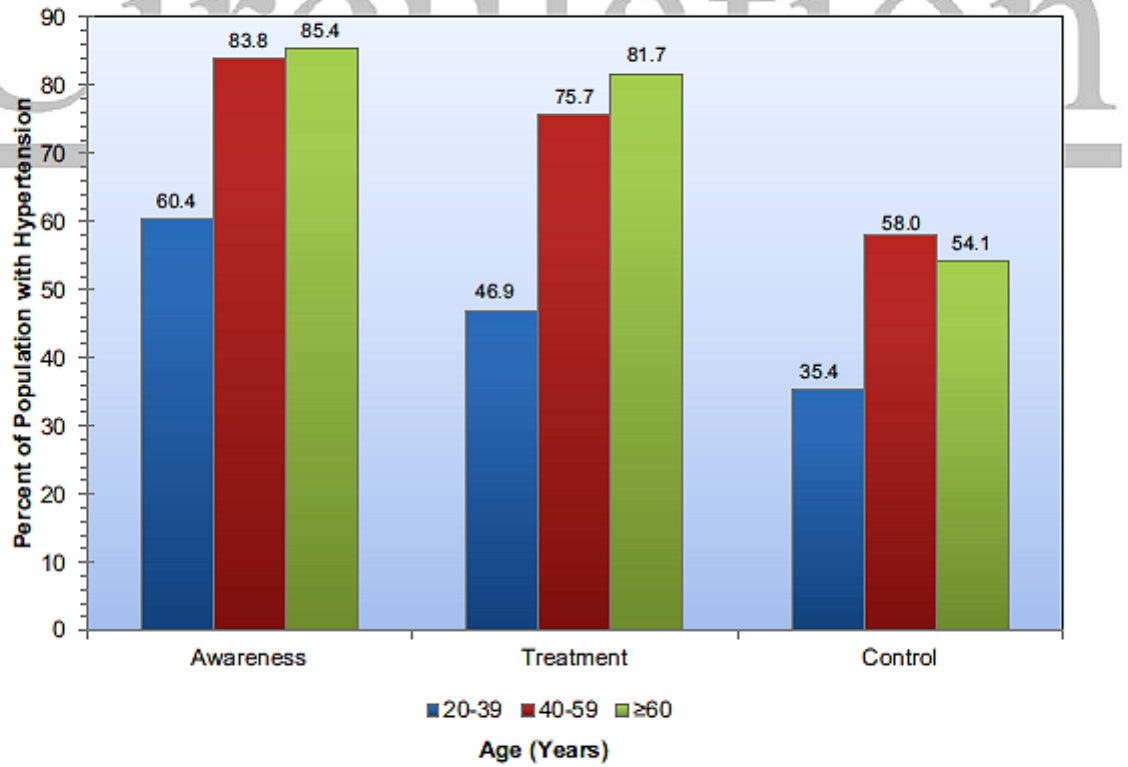



**Chart 9-4.** Extent of awareness, treatment, and control of high blood pressure by age (National Health and Nutrition Examination Survey: 2007–2012). Hypertension is defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or if the subject said "yes" to taking antihypertensive medication. Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute.

**AHA Statistical Update**

**Heart Disease and Stroke Statistics—2016 Update**
**A Report From the American Heart Association**

American Heart Association®

# ADHERENCE TO MEDICATION

***Drugs don't work in patients***

***who don't take them***

The NEW ENGLAND JOURNAL of MEDICINE

Orsterberg L and Blaschke T, *N Engl J Med* 2005;353:487-97

**Sebbene i medici lo curassero, gli estraessero sangue e gli dessero da inghiottire delle medicine, ciò nonostante egli guarì lo stesso**

**Lev Tolstoj**
**Guerra e pace**