Cardiopatia ischemica a coronarie indenni : terapia medica ottimale

B.Castiglioni

Cardiologia Interventistica – UOC Cardiologia 2

Dipartimento Cardiovascolare

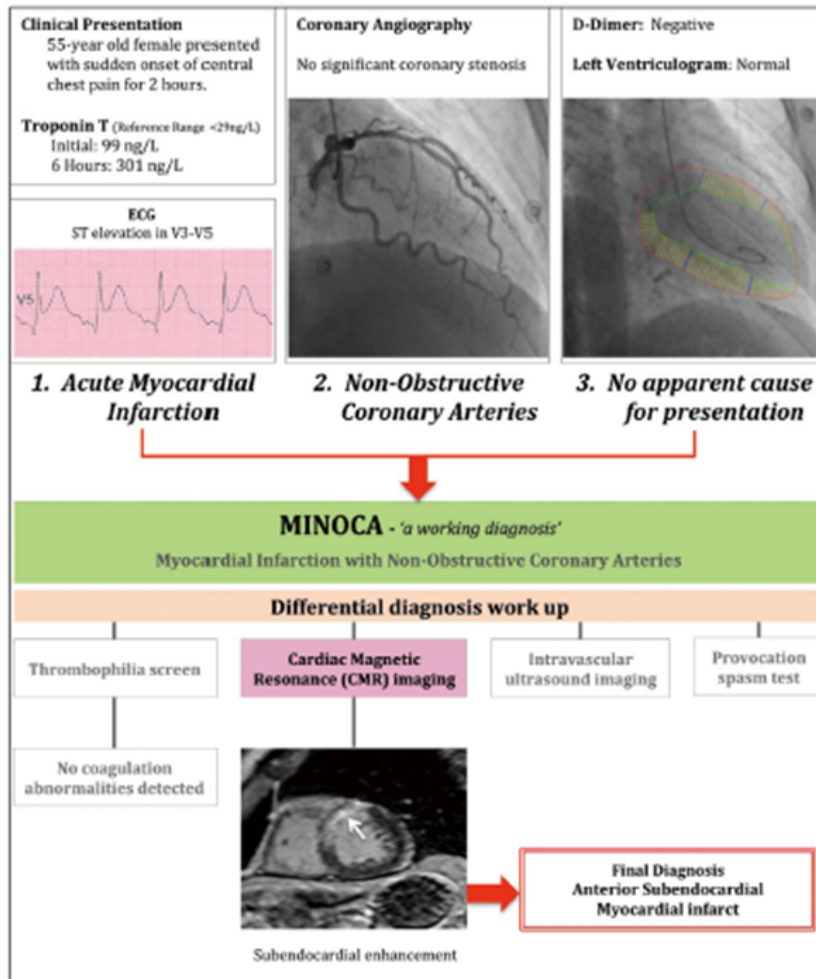Ospedale di Circolo – Fondazione Macchi
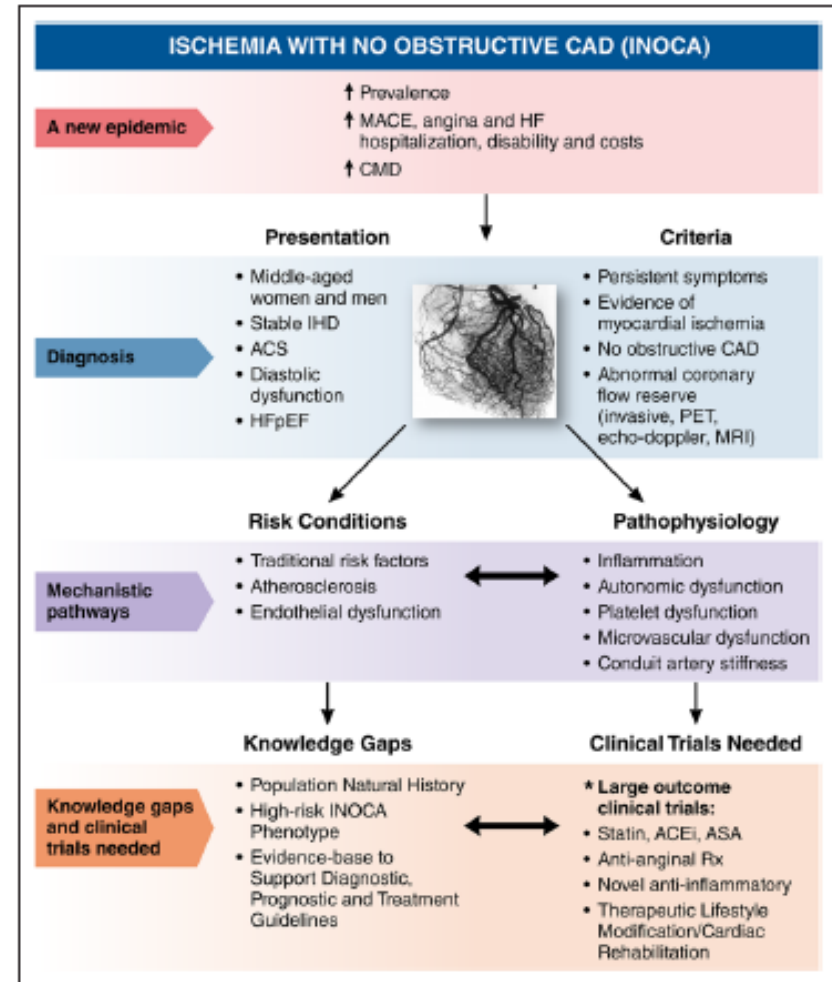
ASST Sette Laghi - Varese

Figure 1. Myocardial Infarction with non-obstructive coronary arteries (MINOCA): a case study of a 55-year-old woman with an acute anterior ST-elevation MI presentation. See text for descriptive details.

MINOCA

Circulation. 2017;135:1075–1092. DOI: 10.1161/CIRCULATIONAHA.116.024534

INOCA

INOCA - ISCHEMIC HEART DISEASE NO OBSTRUCTED CORONARY ARTERIES

The American College of Cardiology-National Cardiovascular Data Registry and National Heart, Lung and Blood Institute–sponsored WISE (Women's Ischemic Syndrome Evaluation) databases suggest that at least **3 to 4 million women and men with signs/symptoms suggestive of myocardial ischemia have no obstructive CAD**

In a European consecutive registry of patients undergoing clinically indicated coronary angiography, **the prevalence of nonobstrucive CAD was 65% among women and 32% in man**

Such individuals incur **healthcare costs and disabilities** similar to those incurred by many with obstructive CAD, in part because of angina and heart failure (HF) hospitalizations and repeat testing.
These cost burdens related **to hospitalizations and repeat angiography** are confirmed by a European consecutive-patient registry.

Circulation. 2017;135:1075–1092.

INOCA

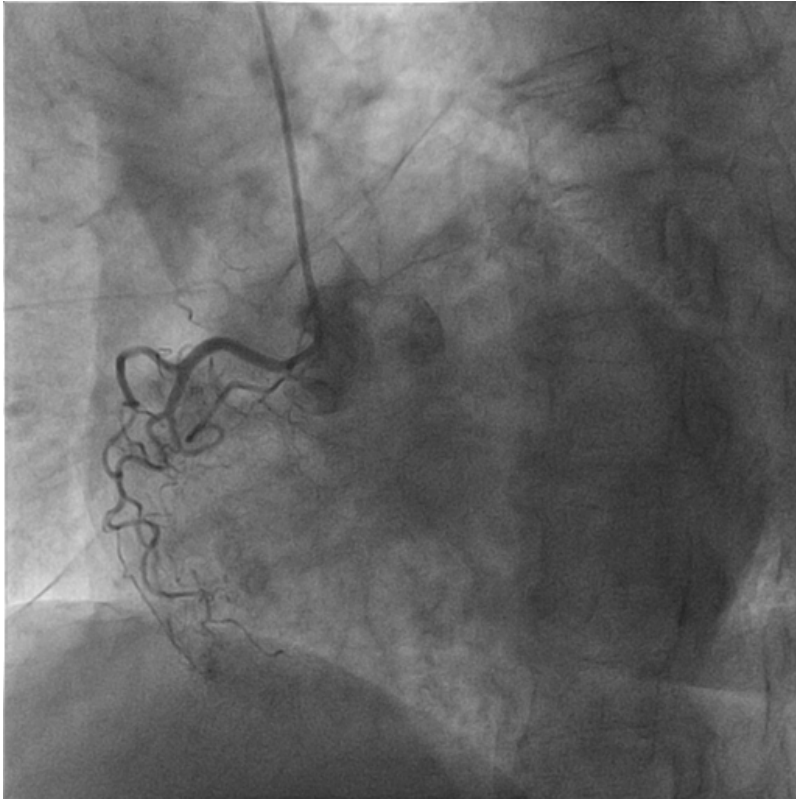Prevalence of Non Obstructive Coronary Artery Disease in Patients with Suspected Angina

The Coronary Artery Surgery Study (CASS)   Women's Ischemia Syndrome Evaluation (WISE) Study
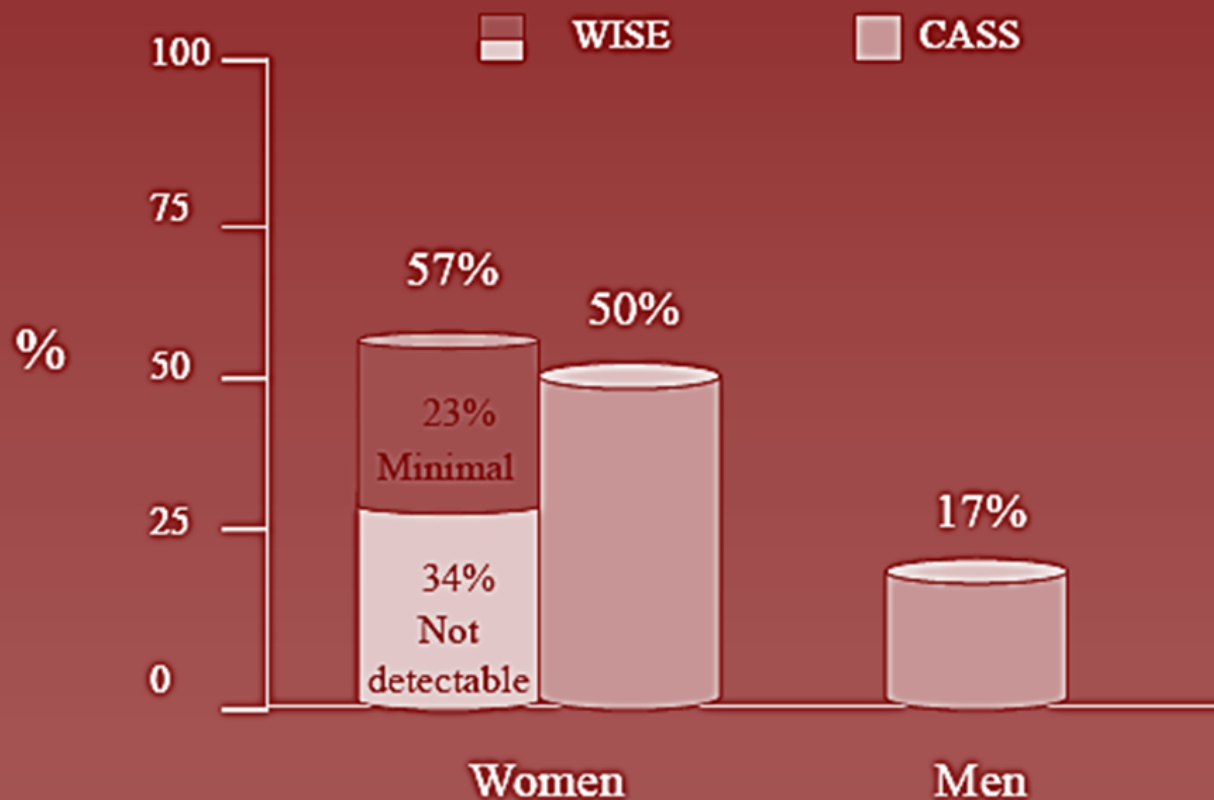
Chaitman BR et al *Circulation 1981;64:360-367*
Sharaf BL et al *Am J Cardiol 2001;87:937-41*

LP , aa 62 , sesso femminile

Ipertensione arteriosa

Angina da sforzo

Test da sforzo positivo per ECG ed angor

Scintigrafia positiva in sede apicale

Table 2. Proposed Definitions

Angina without obstructive CAD

    Typical exercise-induced angina

    Documented stress-induced myocardial ischemia

    Absence of obstructive atherosclerotic CAD*

Cardiac syndrome X (reported here only for historical reasons)

    Typical exercise-induced angina

    Documented stress-induced myocardial ischemia

    Absence of obstructive atherosclerotic CAD*

    Absence of organic nonatherosclerotic causes of epicardial CAD†

    Absence of vasospastic angina (no epicardial vasospasm at ergonovine or acetylcholine test)

Microvascular angina

    Typical exercise-induced angina

    Documented stress-induced myocardial ischemia

    Absence of obstructive atherosclerotic CAD*

    Absence of organic nonatherosclerotic causes of epicardial CAD†

    Absence of vasospastic angina (no epicardial vasospasm at ergonovine or acetylcholine test)

    Active demonstration of coronary microcirculation dysfunction (positive acetylcholine and/or adenosine test results)

True cardiac syndrome X

    Typical exercise-induced angina

    Documented stress-induced myocardial ischemia

    Absence of obstructive atherosclerotic CAD*

    Absence of organic nonatherosclerotic causes of epicardial CAD†

    Absence of vasospastic angina (no epicardial vasospasm at ergonovine or acetylcholine tests)

    No demonstration of coronary microcirculation dysfunction (negative acetylcholine and adenosine test results)

Table 1. Organic Nonatherosclerotic Causes of Epicardial Coronary Artery Disease

	Mechanism Involved
Coronary aneurysms	Slowdown of coronary blood flow and thromboembolic phenomena
Myocardial bridging	Phasic ab extrinseco constriction of coronary arteries during the systolic phase of the cardiac cycle
Coronary anomalies	Extrinsic compression of an epicardial vessel (e.g., anomalous left main artery running between the aorta and the pulmonary trunk during exercise)

Radico et al. jacc : cardiovascular interventions, 2014

One proposed mechanism contributing to INOCA is **coronary microvascular dysfunction (CMD),** defined as epicardial, microvascular endothelial, or nonendothelial dysfunction that limits myocardial perfusion, most often detected as reduced coronary flow reserve (CFR).

CMD may occur in the absence of obstructive CAD and myocardial diseases, in myocardial diseases, or in obstructive CAD or may be iatrogenic.

Coronary vasomotor dysfunction, even without flow-limiting stenosis, identifies patients at risk for cardiac death (WISE : MACE 27% in CFR <2.23 vs MACE 9.3% in CFR >2.32

Table 4.   Definitions of Coronary Microvascular and Macrovascular Dysfunction

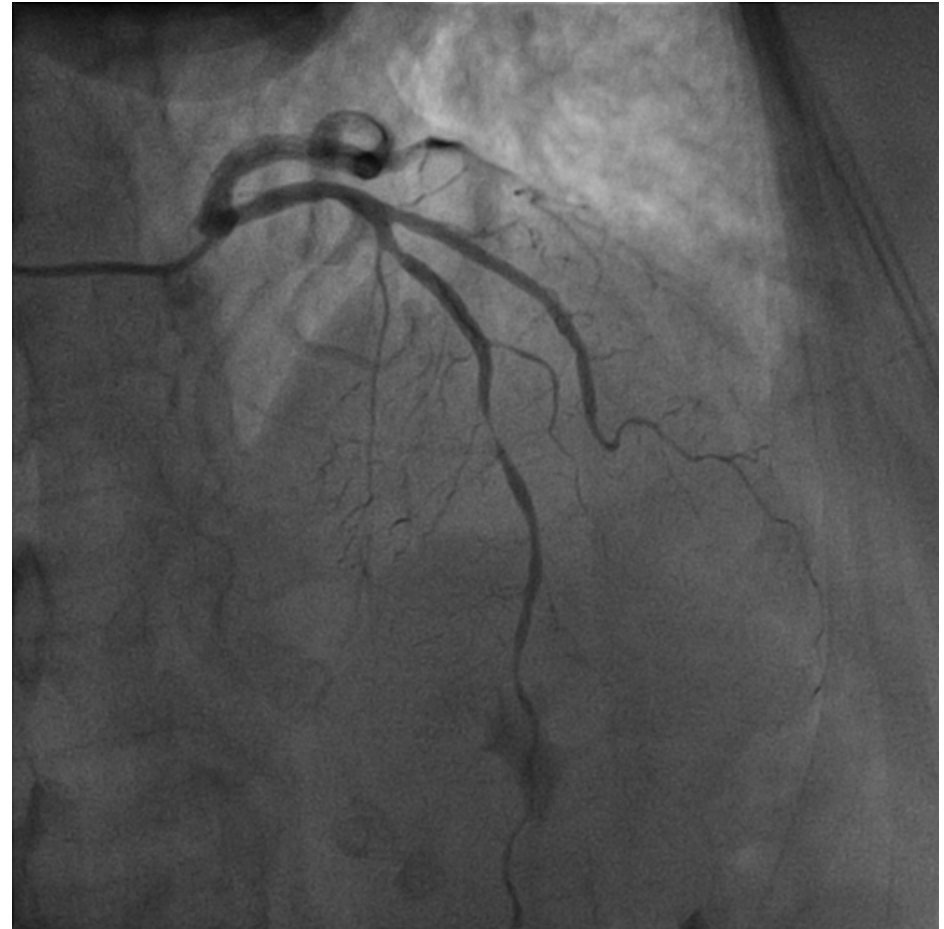| CMD Pathways	Microvascular Dysfunction	Macrovascular Dysfunction
Non–endothelium dependent	CFR in response to adenosine <2.5	Change in coronary artery diameter in response to nitroglycerin <20%
Endothelium dependent	Change in CBF in response to acetylcholine <50%	Change in coronary artery diameter in response to acetylcholine ≤0%
Coronary spasm	Chest pain+ECG changes Change in coronary artery diameter in response to acetylcholine <90%	

Circulation. 2017
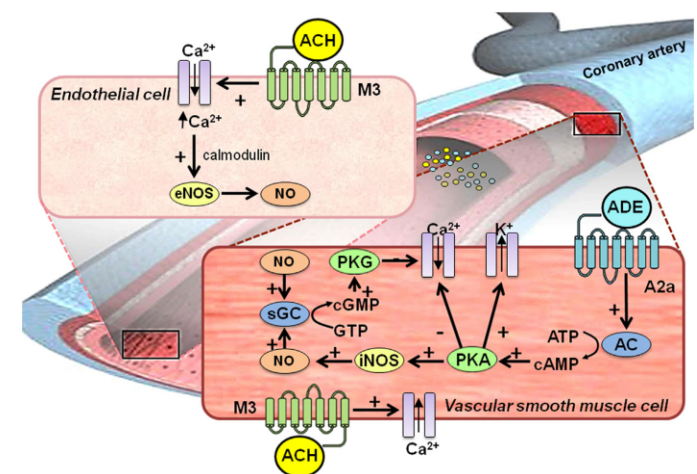
LP , aa 62 , sesso femminile

Basale

Post acetilcolina

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Radico et al. jacc : cardiovascular interventions, 2014
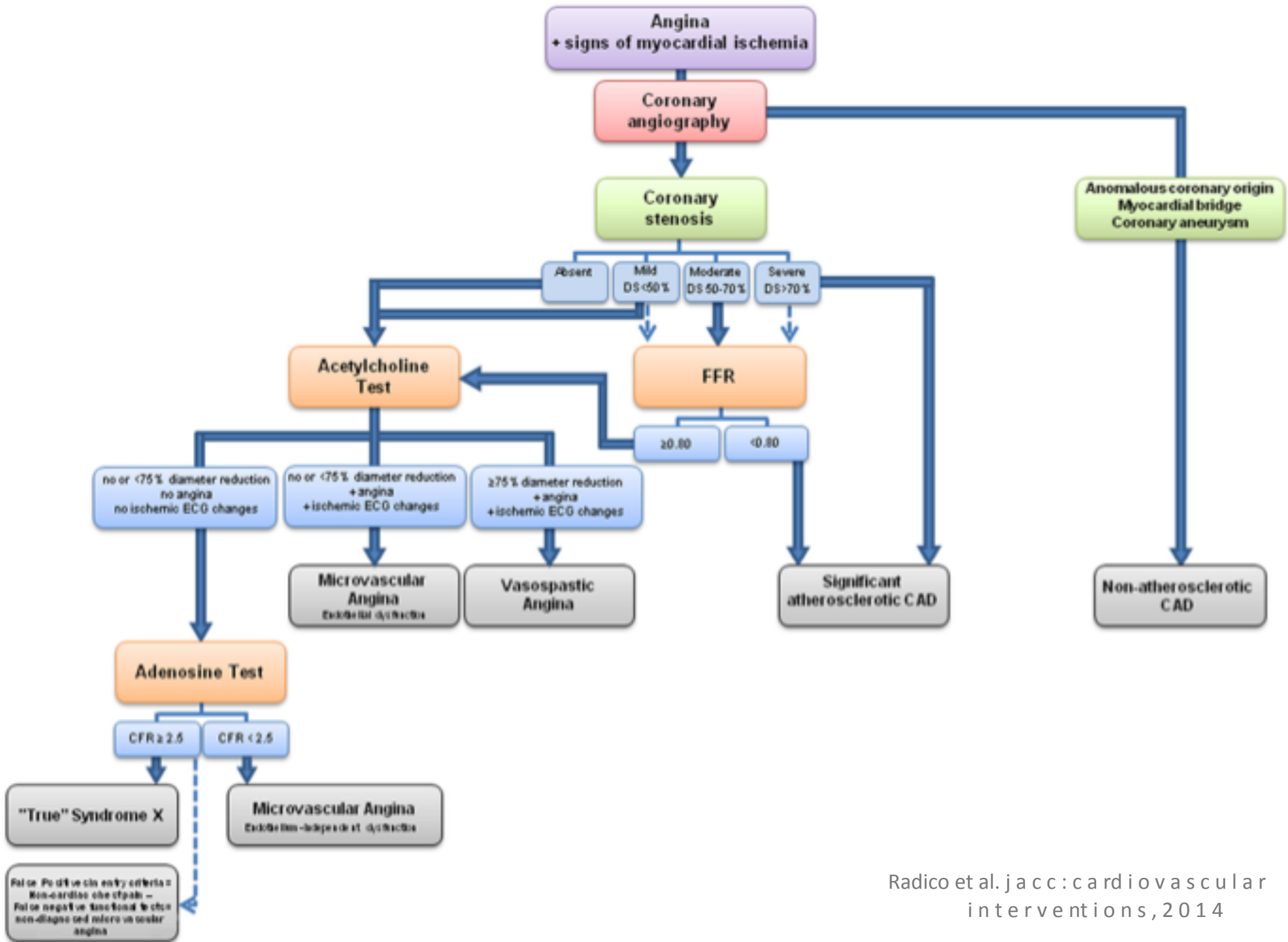
q   Conditions associated with increased risk for CMD appear similar to those for obstructive CAD and include traditional atherosclerosis risk factors

§   Eta'
§   Ipertensione arteriosa
§   Diabete mellito
§   Dislipidemia

q   Evidence **linking microvascular and inflammatory responses** to risk factors indicates that oxidative stress, reduced nitric oxide bioavailability, and endothelial activation are common early features of coronary microvascular responses to atherosclerosis risk factors.

q   Abnormal cardiac adrenergic nerve function (interaction between autonomic nervous system and endothelium)

Circulation. 2017
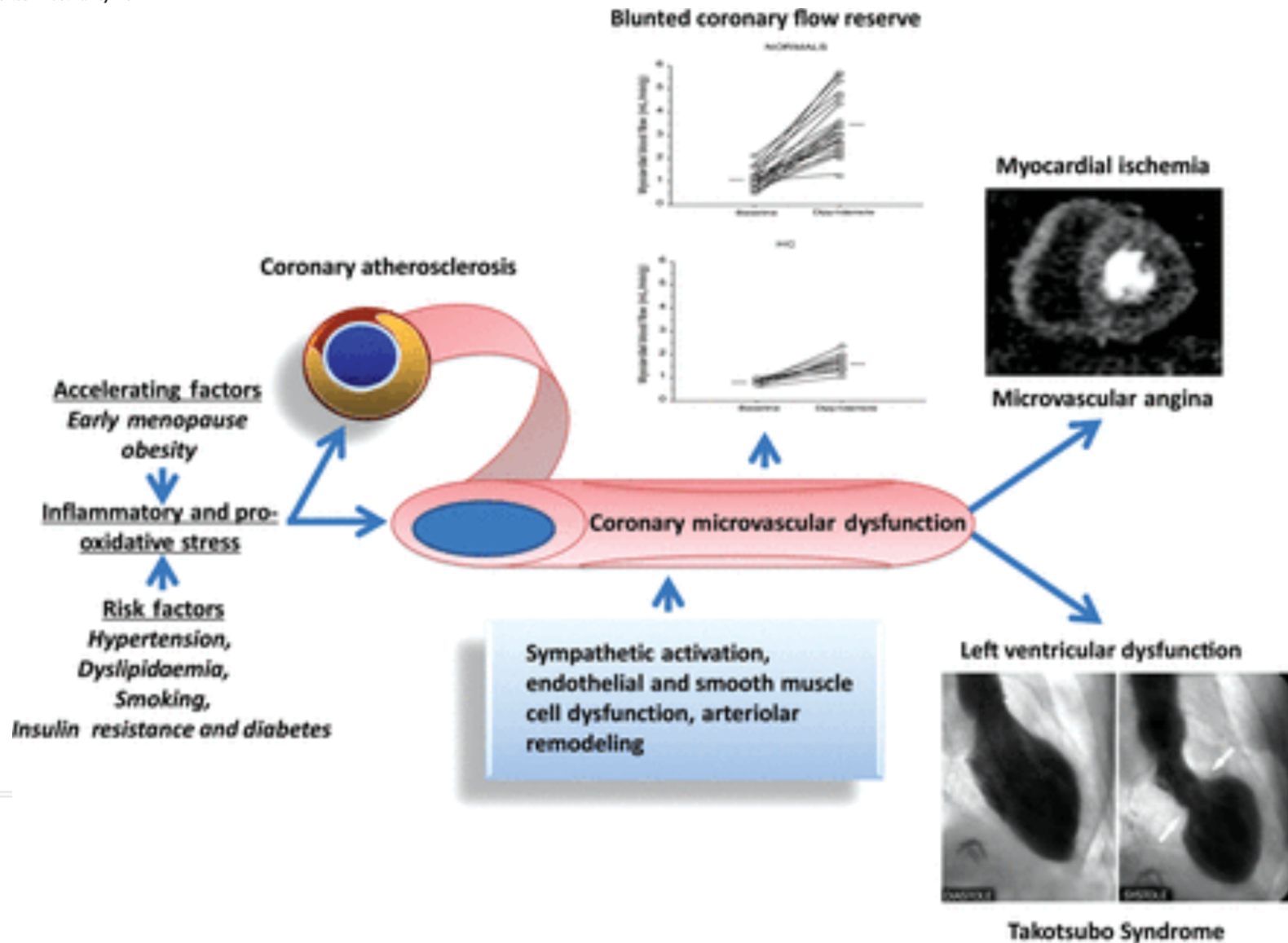
From: Coronary microvascular dysfunction: an update
Eur Heart J. 2013;35(17):1101-1111

37 674 patients :   8391 patients NO CAD - 8384 patients (22.3%) nonobstructive CAD and 20 899 patients (55.4%) had obstructive CAD

MI a 1 anno
0.11%NO CAD
2.47% 3V oLM

CAD non ostruttiva rischio di MI da 2 a 4.5 volte superiore a NO CAD

Mortalita' a 1 anno
1.38%NO CAD
4.30% % 3V oLM
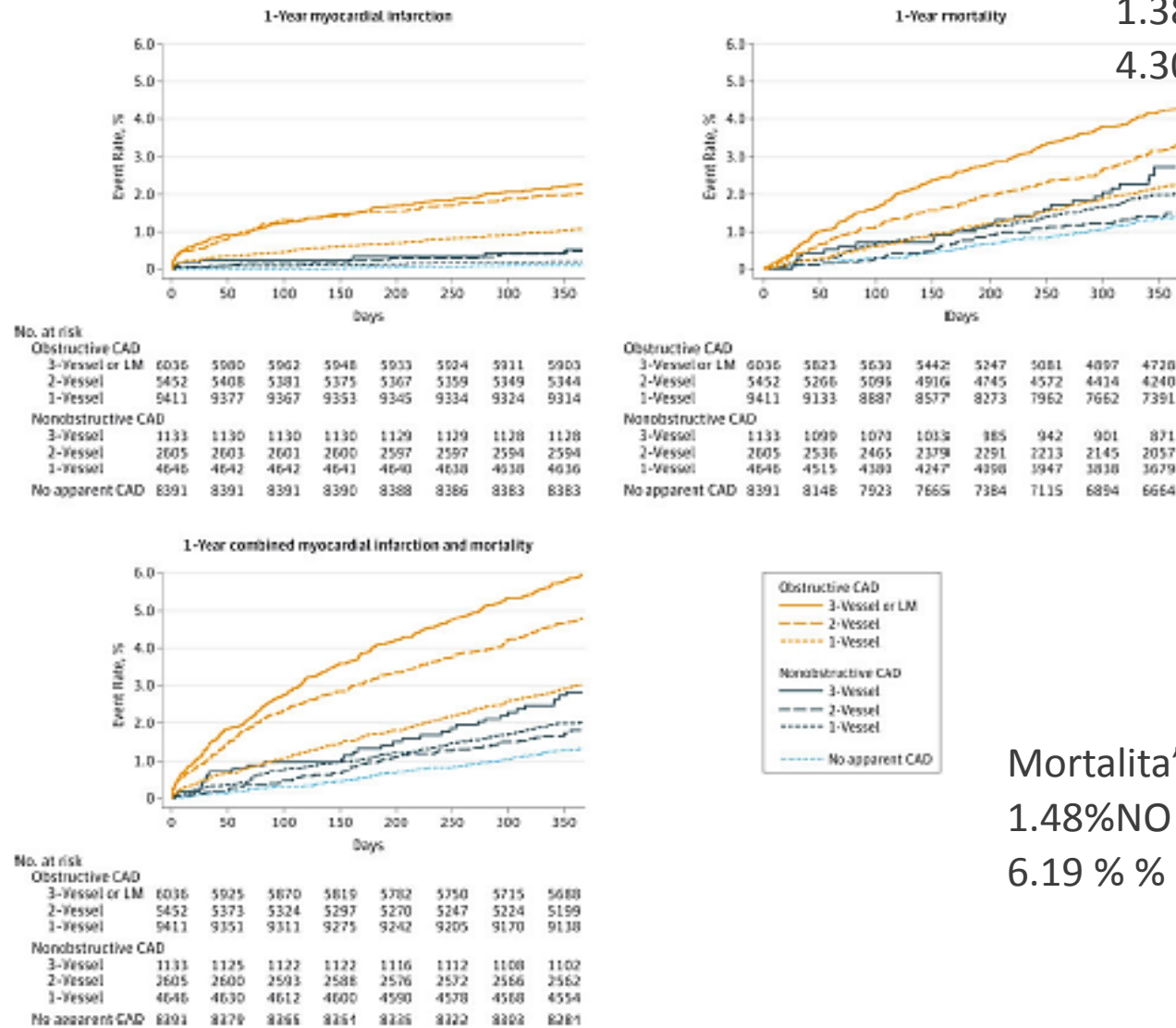
Mortalita' +MI a 1 anno
1.48%NO CAD
6.19 % % 3V oLM

Figure 1. Time-to-Event Plots for 1-Year Myocardial Infarction, Mortality, and Combined Myocardial Infarction and Mortality,by CAD Extent
CAD indicates coronary artery disease; LM, left main.

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Maddox et al. Page 15

1-Year myocardial infarction

	No. of Events	No. of Patients	HR (95% CI)
Obstructive CAD			
3-Vessel or left main	137	6036	19.5 (9.9-38.2)
2-Vessel	110	5452	16.5 (8.1-33.7)
1-Vessel	101	9411	9.0 (4.2-19.0)
Nonobstructive CAD			
3-Vessel	6	1133	4.5 (1.6-12.5)
2-Vessel	13	2605	4.6 (2.0-10.5)
1-Vessel	10	4646	2.0 (0.8-5.1)
No apparent CAD	8	8391	1 [Reference]

HR (95% CI): 0.5 1.0 5.0 50.0

1-Year mortality

	No. of Events	No. of Patients	HR (95% CI)
Obstructive CAD			
3-Vessel or left main	239	6036	3.4 (2.6-4.4)
2-Vessel	164	5452	2.8 (2.1-3.7)
1-Vessel	192	9411	1.9 (1.4-2.6)
Nonobstructive CAD			
3-Vessel	27	1133	1.6 (1.1-2.5)
2-Vessel	35	2605	1.0 (0.7-1.5)
1-Vessel	85	4646	1.4 (1.0-2.0)
No apparent CAD	103	8391	1 [Reference]

HR (95% CI): 0.5 1.0 2.0 6.0

1-Year combined myocardial infarction and mortality

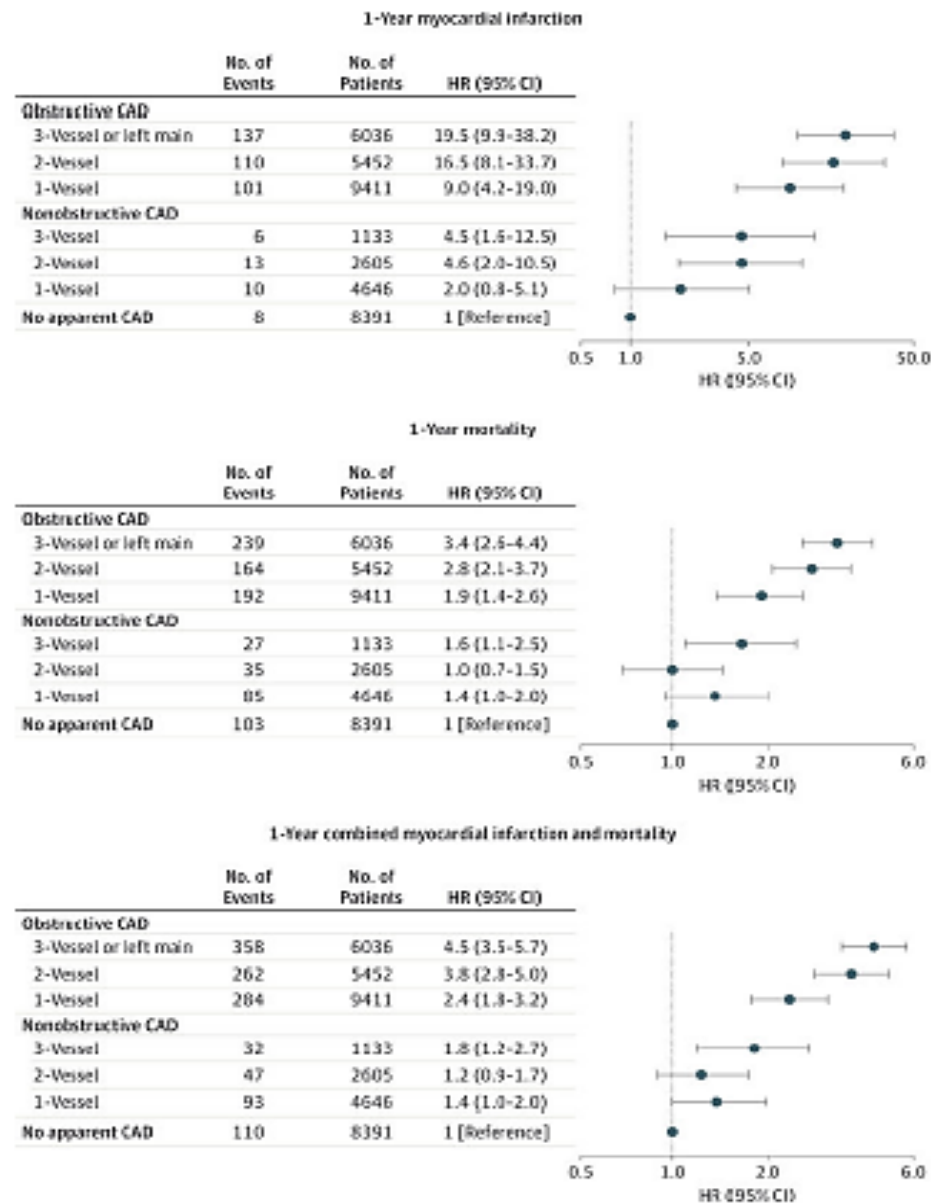|	No. of Events	No. of Patients	HR (95% CI)
Obstructive CAD			
3-Vessel or left main	358	6036	4.5 (3.5-5.7)
2-Vessel	262	5452	3.8 (2.8-5.0)
1-Vessel	284	9411	2.4 (1.8-3.2)
Nonobstructive CAD			
3-Vessel	32	1133	1.8 (1.2-2.7)
2-Vessel	47	2605	1.2 (0.8-1.7)
1-Vessel	93	4646	1.4 (1.0-2.0)
No apparent CAD	110	8391	1 [Reference]

HR (95% CI): 0.5 1.0 2.0 6.0

Figure 2. Adjusted Cox Model Results for 1-Year Myocardial Infarction, Mortality, and Combined Myocardial Infarction and Mortality by CAD Extent, Relative to No Apparent CAD CAD indicates coronary artery disease; HR, hazard ratio.
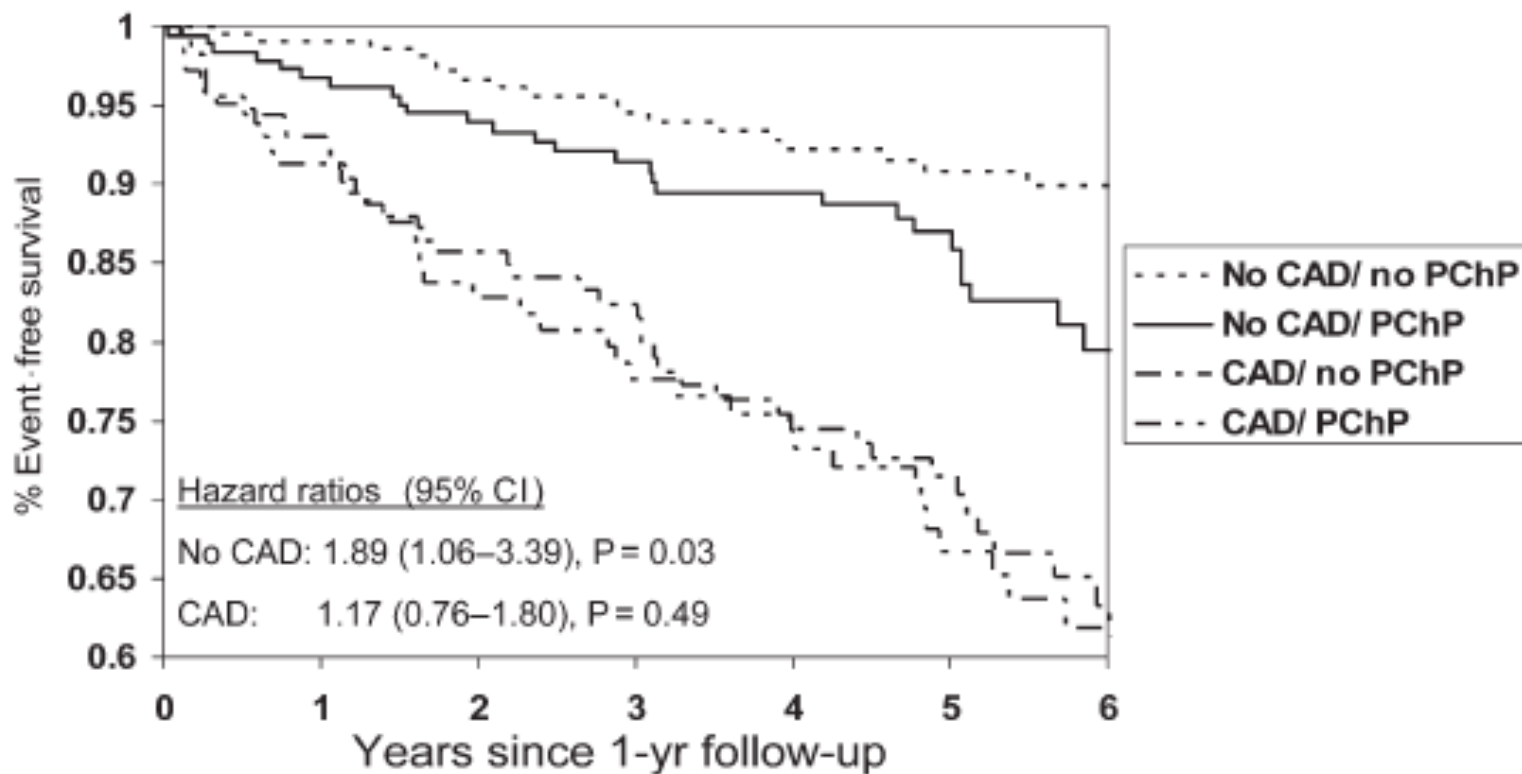
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Figure 3 Event-free survival from CV events by CAD and PChP. CV events defined as CV death, MI, CHF, or stroke.

B. Delia Johnson et Al European Heart Journal (2006) 27, 1408–1415

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Potential Therapies for CMD

Pharmacologic	Non-Pharmacologic
• Nitrates	• Exercise
• Statins	• Cognitive behavioral therapy
• ACE-I	• Transcendental meditation
• ACE-I + Aldosterone blockade	• Transcutaneous electrical nerve stimulation
• Calcium antagonists	
• Low-dose tricyclic antidepressants	**CONTROLLO FATTORI DI RISCHIO CARDIOVASCOLARE**
• Estrogens	
• PDE-5 inhibitors	
• Exercise	
• L-arginine	
• Ranolazine	
• Ivabradine	
• Ranolazine + Ivabradine	
• Metformin	
• Rho-kinase inhibitors	
• Endothelin receptor blockers	*Circulation.* 2017;135:1075–1092, mod .

Terapia antiaggregante ?

Table 6. Treatment of Subjects With Angina, Evidence of Myocardial Ischemia, and No Obstructive Coronary Artery Disease

CMD
Abnormal endothelial function
ACE-Is
Statins
L-arginine supplementation
Aerobic exercise
Enhanced external counterpulsation
Abnormal nonendothelial function
β-Blockers/α-blockers
Nitrates
Antianginal
Ranolazine
Ivabradine
Xanthine derivatives
Abnormal smooth muscle function (Prinzmetal angina)
Calcium channel blockers
Nitrates
Abnormal cardiac nociception
Low-dose tricyclic medication
Spinal cord stimulation
Cognitive behavioral therapy

ACE-I indicates angiotensin converting enzyme inhibitor; and CMD, coronary microvascular dysfunction.

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Circulation. 2017;135:1075–1092.

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STATINA + ACE INIBITORE

Pizzi et al   Therapy of Cardiac Syndrome X   55

TABLE 2. Seattle Angina Questionnaire Domain Score at Baseline and After 6 Months of Treatment

	Atorvastatin+ Ramipril	Placebo	P
Physical limitation			<0.001
Baseline	50.8±9.9	52.7±13.9	
6 mo	84.5±12.6	60.1±12.6	
Angina stability			<0.001
Baseline	52.4±10.1	54.4±13.6	
6 mo	84.2±10.5	62.6±13.2	
Angina frequency			<0.001
Baseline	50.2±7.6	50.8±12.7	
6 mo	82.1±13.8	62.4±10.5	
Quality of life			<0.001
Baseline	50.7±6.6	52.7±10.9	
6 mo	86.5±11.7	61.9±9.4	
Treatment satisfaction			0.002
Baseline	51.2±9.3	52.5±11.8	
6 mo	83.2±13.3	69.5±10.9	
Summary score			<0.001
Baseline	51.3±6.4	52.6±11.9	
6 mo	84.2±9.8	63.3±8.6	

Probability values are reported for comparison by 2-way ANOVA, comparing differences attributable to treatment.

TABLE 3. Exercise Stress Test and Flow-Mediated Dilation of Brachial Artery at Baseline and After 6 Months of Treatment

	Atorvastatin+ Ramipril	Placebo	P
Peak exercise			
Time, s			0.045
Baseline	450.0±82.2	481.2±79.2	
6 mo	555.6±84.6	488.4±79.2	
Rate-pressure product			0.9
Baseline	24.56±2.1	25.2±2.5	
6 mo	24.47±1.8	25.3±2.5	
ST depression, mV			0.003
Baseline	0.21±0.6	0.22±0.8	
6 mo	0.12±0.3	0.21±0.8	
Flow-mediated dilation of brachial artery			
Flow mediated dilation, %			0.001
Baseline	2.2±1.3	2.1±1.3	
6 mo	4.2±1.7	2.3±1.2	
Brachial artery diameter, mm			0.9
Baseline	4.1±0.7	4.0±0.8	
6 mo	4.2±0.8	4.1±0.8	
Nitroglycerin, %			0.6
Baseline	11.2±3.6	11.1±3.3	
6 mo	12.0±3.3	11.3±3.3	

Circulation , 2004

BC 2017

Maseri, Am J Cardiol , 1999

G. Siitsch et al. /International Journal of Cardiology , 1995

FIGURE 1. Design of the study.

TABLE I Study Results

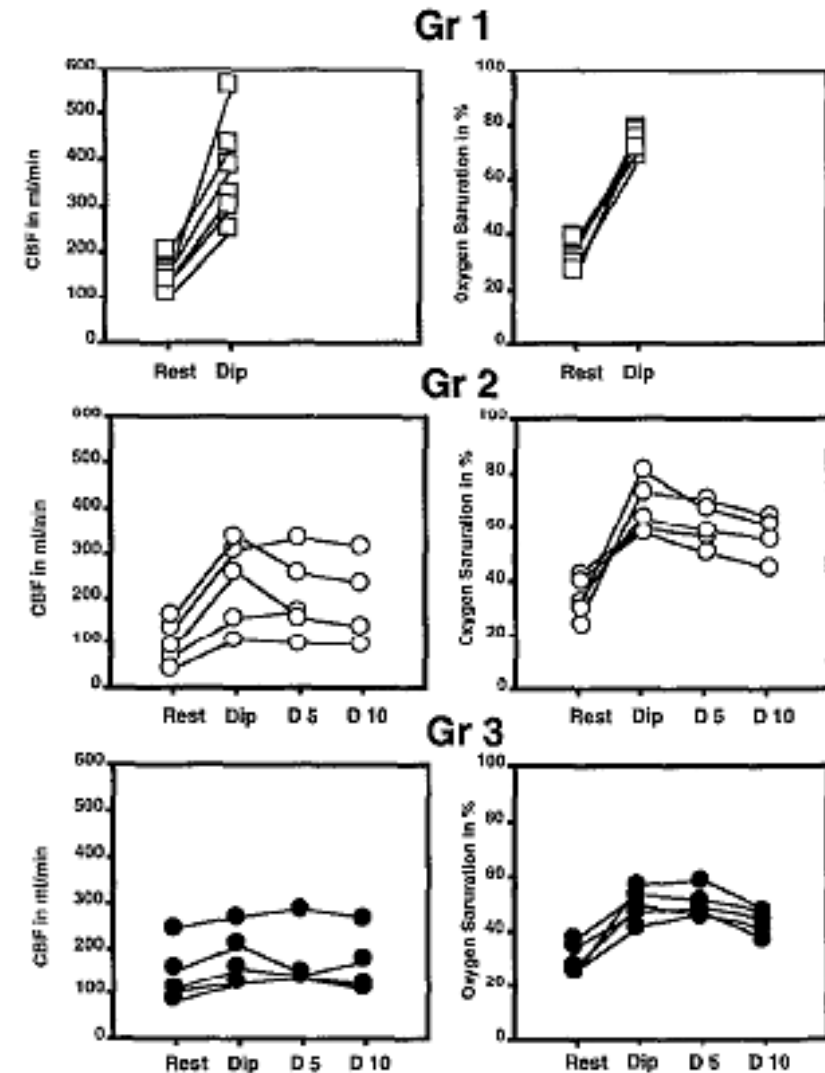|	Baseline	ISMN	Amlodipine	Atenolol
No. anginal episodes/ 4 wks/patient	24 ± 18	24 ± 22	22 ± 22	15 ± 13*
Duration of chest pain episodes (min)	12 ± 6	11 ± 7	16 ± 17	14 ± 13
Severity of chest pain (scale 1–5)	2.5 ± 0.9	2.3 ± 1.2	2.7 ± 1.0	2.5 ± 1.2
Sublingual nitrate consumption	5.8 ± 8	10.1 ± 18	6.6 ± 14	5.0 ± 10
Quality of life (scale 0 – 100 mm)	22 ± 17	30 ± 27	51 ± 25*	59 ± 29*

*p <0.05 versus baseline.

Fig. 2. Plots of coronary blood flow (CBF) and coronary sinus oxygen saturation in the 3 study groups at rest, after dipyridamole (Dip; groups 1–3; Gr) and 5 and 10 min after diltiazem (D 5 and 10 respectively; Gr 2 and 3).

Effect of Oral L-arginine on Blood Pressure and Symptoms and Endothelial Function in Patients With Systemic Hypertension, Positive Exercise Tests, and Normal Coronary Arteries. Margonato et Al , Am J Cardiol 2004
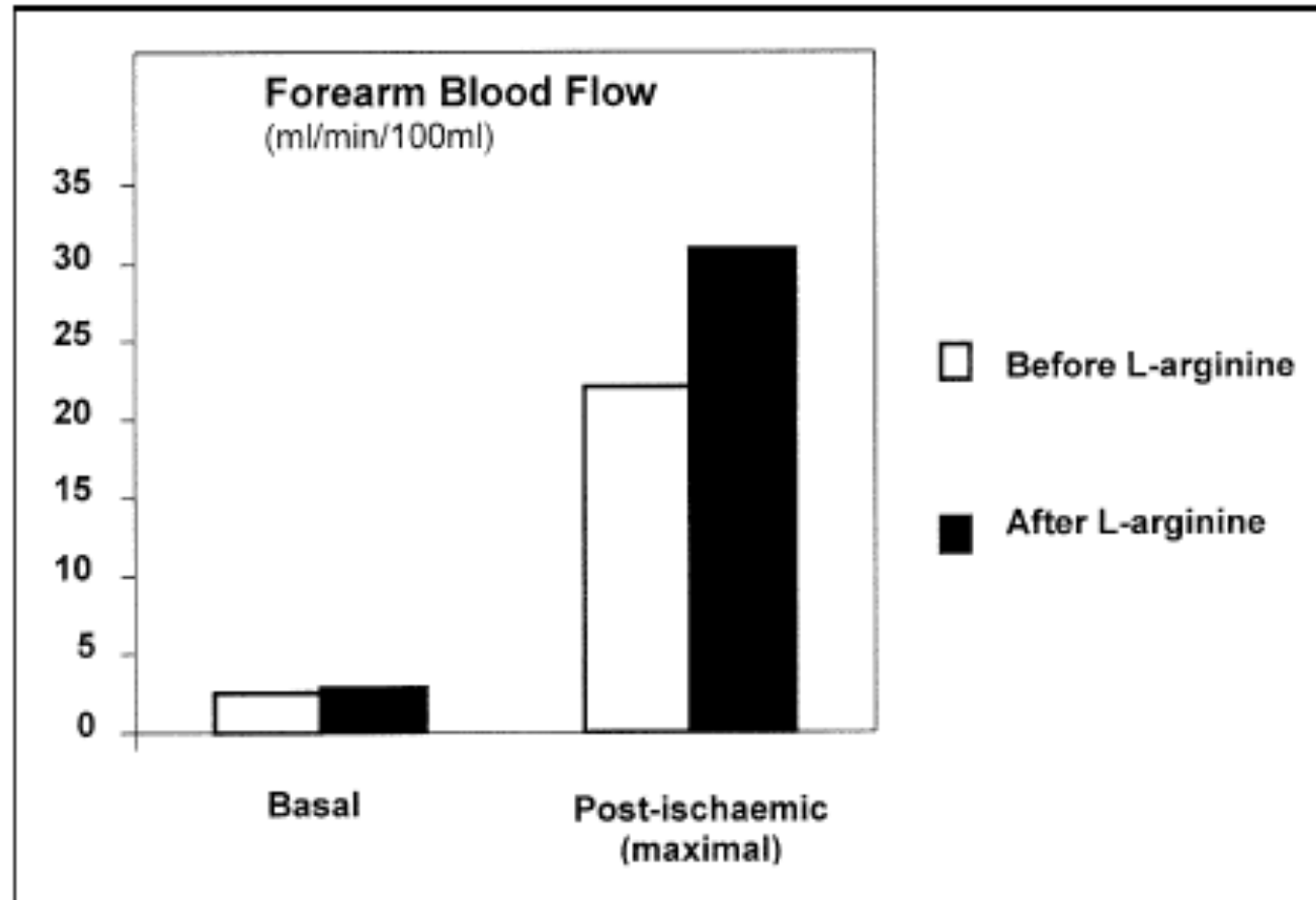

Forearm Blood Flow
(ml/min/100ml)

☐ Before L-arginine

■ After L-arginine

Basal

Post-ischaemic
(maximal)

FIGURE 1. Resting and maximal FBF after ischemia (p <0.01).

RANOLAZINE Improves Angina in Women With Evidence of Myocardial Ischemia But No Obstructive Coronary Artery Disease . Puja K. Mehta, J Am Coll Cardiol Img 2011;4:514 –22

20 pazienti

Table 2. SAQ Scores on Ranolazine Versus Placebo

	Ranolazine	Placebo	Treatment Effect (p Value)
Physical functioning	91.7 (79.2, 97.9)	83.3 (66.6, 97.2)	**0.046**
Angina stability	75.0 (50.0, 100.0)	50.0 (25.0, 75.0)	**0.008**
Angina frequency	80.0 (50.0, 100.0)	75.0 (60.0, 87.5)	0.197
Treatment satisfaction	87.5 (75.0, 100.0)	93.8 (75.0, 100.0)	0.058
Quality of life	75.0 (60.4, 83.3)	66.7 (58.3, 75.0)	**0.021**

Values are median (minimum, maximum). A higher SAQ score is better in each domain. The **bold** type indicates statistically significant p Values.
SAQ = Seattle Angina Questionnaire.

Table 3. Visual and Quantitative CMR Defects on Ranolazine versus Placebo

	Ranolazine	Placebo	Treatment Effect (p Value)
Percentage of ischemic myocardium	11.7 (8.0, 19.3)	16.0 (8.6, 22.7)	0.64
Summed difference score	10.2 (3.5, 15.2)	14.8 (5.5, 19.5)	0.82
MPRI			
Global	2.1 (2.2, 2.4)	1.9 (1.7, 2.5)	0.66
Mid-ventricular	2.4 (2.0, 2.8)	2.1 (1.7, 2.5)	0.074
Subendocardial (whole)	2.0 (1.7, 2.2)	1.8 (1.5, 2.3)	0.66
Subendocardial (mid-ventricular)	2.1 (1.7, 2.5)	1.9 (1.5, 2.3)	1.0
Subepicardial (whole)	2.3 (2.1, 2.6)	2.0 (1.8, 2.5)	0.18
Subepicardial (mid-ventricular)	2.6 (2.2, 3.0)	2.2 (1.9, 2.5)	0.18

Values are median (minimum, maximum). For summed difference score, lower is better.
MPRI = myocardial perfusion reserve index (higher is better perfusion reserve).

La frequenza cardiaca come target terapeutico dopo sindrome coronarica acuta e nella cardiopatia ischemica cronica
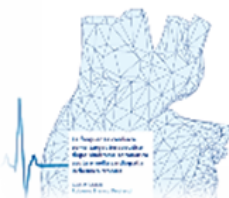
Marco Ambrosetti[1], Giuseppe Scardina[2], Giuseppe Favretto[3], Pier Luigi Temporelli[4], Pompilio Massimo Faggiano[5], Cesare Greco[6], Roberto Franco Pedretti[7]

FREQUENZA CARDIACA E PROGNOSI NELLA CHD: PRESUPPOSTI FISIOPATOLOGICI

La FC ha un ruolo attivo:
1) nella genesi dell'ischemia miocardica
2) nella disfunzione endoteliale
3) nella progressione dell'aterosclerosi e dell'instabilità di placca
4) nel rimodellamento sfavorevole del ventricolo sinistro
5) nell'induzione di aritmie ventricolari

La FC elevata si associa a una ridotta tolleranza allo sforzo (e quindi della qualità di vita), fenomeno mediato principalmente dallo sviluppo di una incompetenza cronotropa.

La frequenza cardiaca come target terapeutico dopo sindrome coronarica acuta e nella cardiopatia ischemica cronica

Marco Ambrosetti[1], Giuseppe Scardina[2], Giuseppe Favretto[3], Pier Luigi Temporelli[4], Pompilio Massimo Faggiano[5], Cesare Greco[6], Roberto Franco Pedretti[7]

B **Algoritmo per il controllo del target di frequenza cardiaca nel paziente con cardiopatia ischemica cronica**
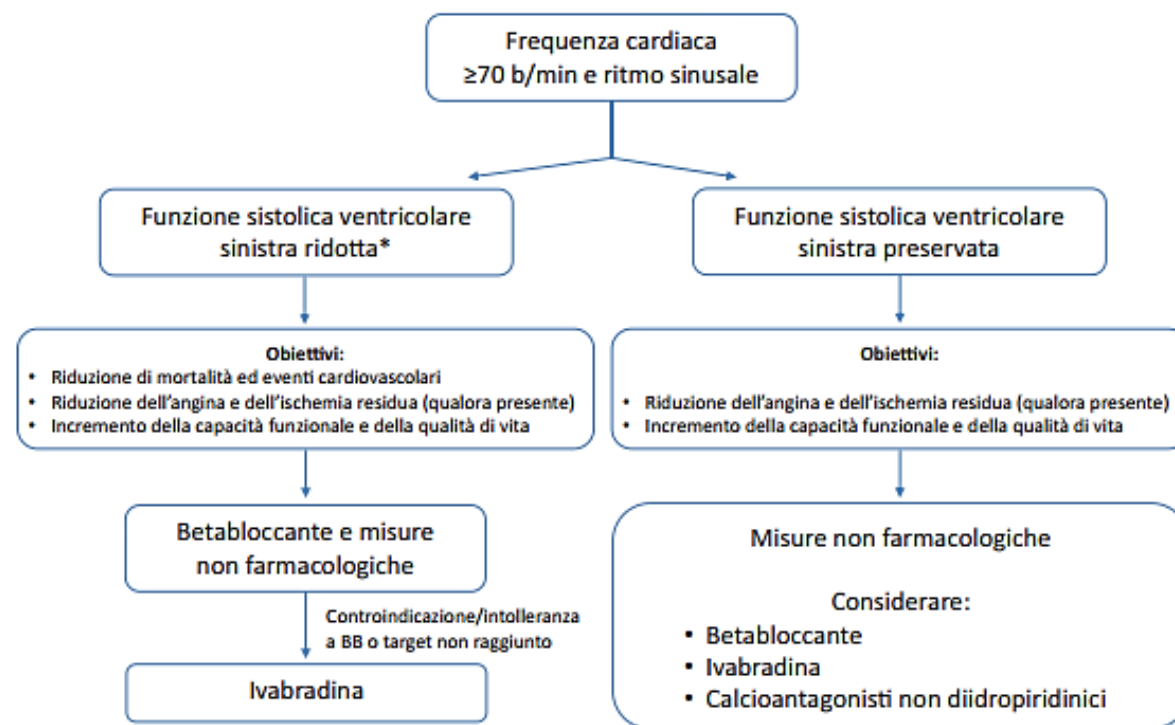
*FEVS <50%, con maggiori evidenze per FEVS <40%

Figura 1. Algoritmo decisionale per l'identificazione e il raggiungimento del target di frequenza cardiaca nel paziente con cardiopatia ischemica. *A*: paziente stabile con recente (<1 anno) sindrome coronarica acuta. *B*: paziente con cardiopatia ischemica cronica. BB, betabloccante.

Coronary Artery Disease/Ivabradine and Ranolazine in Microvascular Angina A. Villano et Al , Am J Cardiol 2013

Table 1
Main clinical characteristics of patients enrolled in the study

| Variable	Ivabradine (n = 16)	Ranolazine (n = 15)	Placebo (n = 15)	p
Age (yrs)	57 ± 12	57 ± 11	60 ± 9	0.72
Male/female	2/14	3/12	4/11	0.61
BMI (kg/m^2)	29 ± 5	27 ± 4	28 ± 4	0.40
Family history of CVD	13 (81%)	12 (80%)	11 (73%)	0.85
Hypertension*	12 (75%)	13 (87%)	10 (67%)	0.43
Hypercholesterolemia[†]	12 (75%)	8 (53%)	9 (60%)	0.44
Active smokers	2 (13%)	2 (13%)	2 (13%)	0.99
Drug therapy				
Beta blockers	12 (75%)	11 (73%)	8 (53%)	0.44
Calcium antagonist	7 (44%)	5 (33%)	9 (60%)	0.33
Nitrates	1 (6%)	1 (7%)	3 (20%)	0.38
Antiaggregants	8 (50%)	7 (47%)	5 (33%)	0.62
ACE inhibitors	7 (44%)	3 (20%)	4 (27%)	0.33
ARBs	3 (19%)	4 (27 %)	5 (33%)	0.65
Statins	7 (44%)	4 (27%)	6 (40 %)	0.59
Diuretics	5 (31%)	6 (40%)	7 (47%)	0.68

Table 2
SAQ and EuroQoL scores at baseline and after 4 weeks of treatment in the 3 groups

	Ivabradine	Ranolazine	Placebo	p	p*
Physical limitation					<0.001
Baseline	65.4 ± 15	69.8 ± 16	68.2 ± 20	0.78	
Follow-up	76.5 ± 16	84.1 ± 12	67.0 ± 21	<0.001[‡]	
Angina stability					<0.001
Baseline	43.8 ± 30	40.0 ± 25	56.7 ± 26	0.23	
Follow-up	56.3 ± 33	90.0 ± 18[†]	55.0 ± 25	<0.001[‡]	
Angina frequency					<0.001
Baseline	64.4 ± 14	61.3 ± 12	72.7 ± 17	0.10	
Follow-up	73.1 ± 18	81.3 ± 17[†]	71.3 ± 18	0.001[‡]	
Treatment satisfaction					<0.001
Baseline	75.8 ± 15	68.8 ± 16	75.8 ± 15	0.36	
Follow-up	84.4 ± 14	90.8 ± 9[†]	74.2 ± 14	<0.001[‡]	
Disease perception					<0.001
Baseline	49.5 ± 23	45.0 ± 17	60.0 ± 22	0.15	
Follow-up	62.5 ± 26	79.4 ± 14[†]	57.2 ± 23	<0.001[‡]	
EuroQoL VAS					<0.001
Baseline	66.6 ± 14	61.3 ± 17	65.7 ± 17	0.62	
Follow-up	72.5 ± 17	79.3 ± 13[†]	64.3 ± 19	<0.001[‡]	

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Coronary Artery Disease/Ivabradine and Ranolazine in Microvascular Angina A. Villano et Al , Am J Cardiol 2013
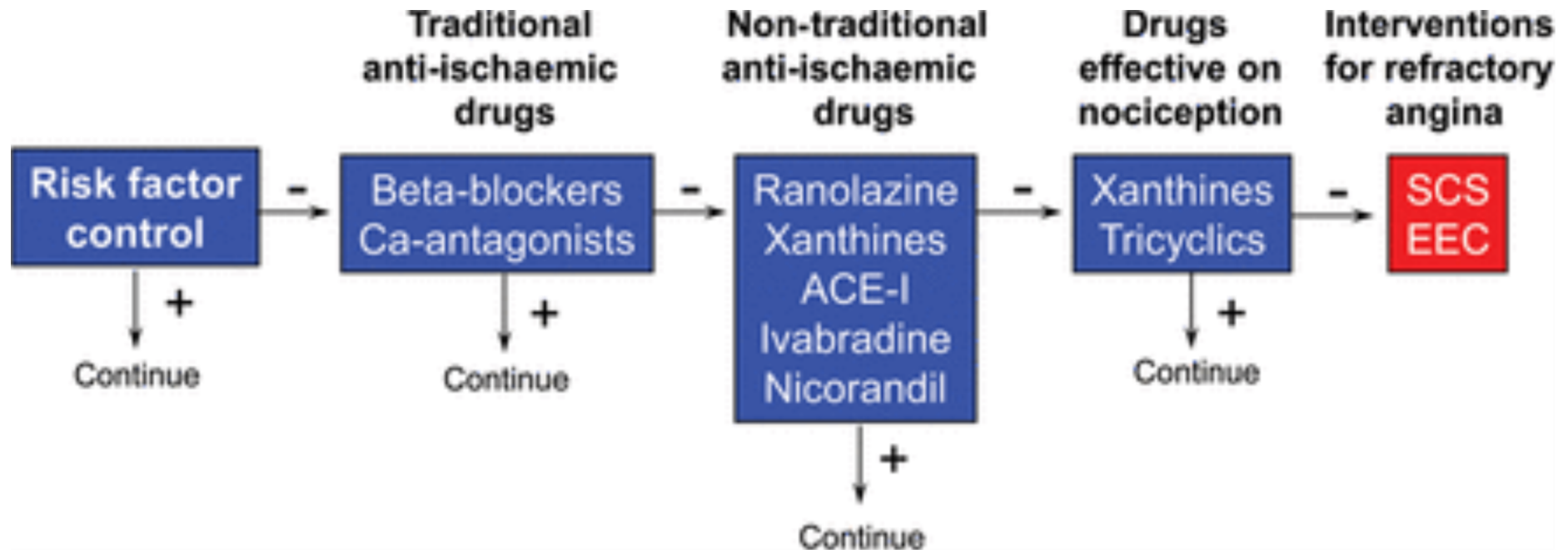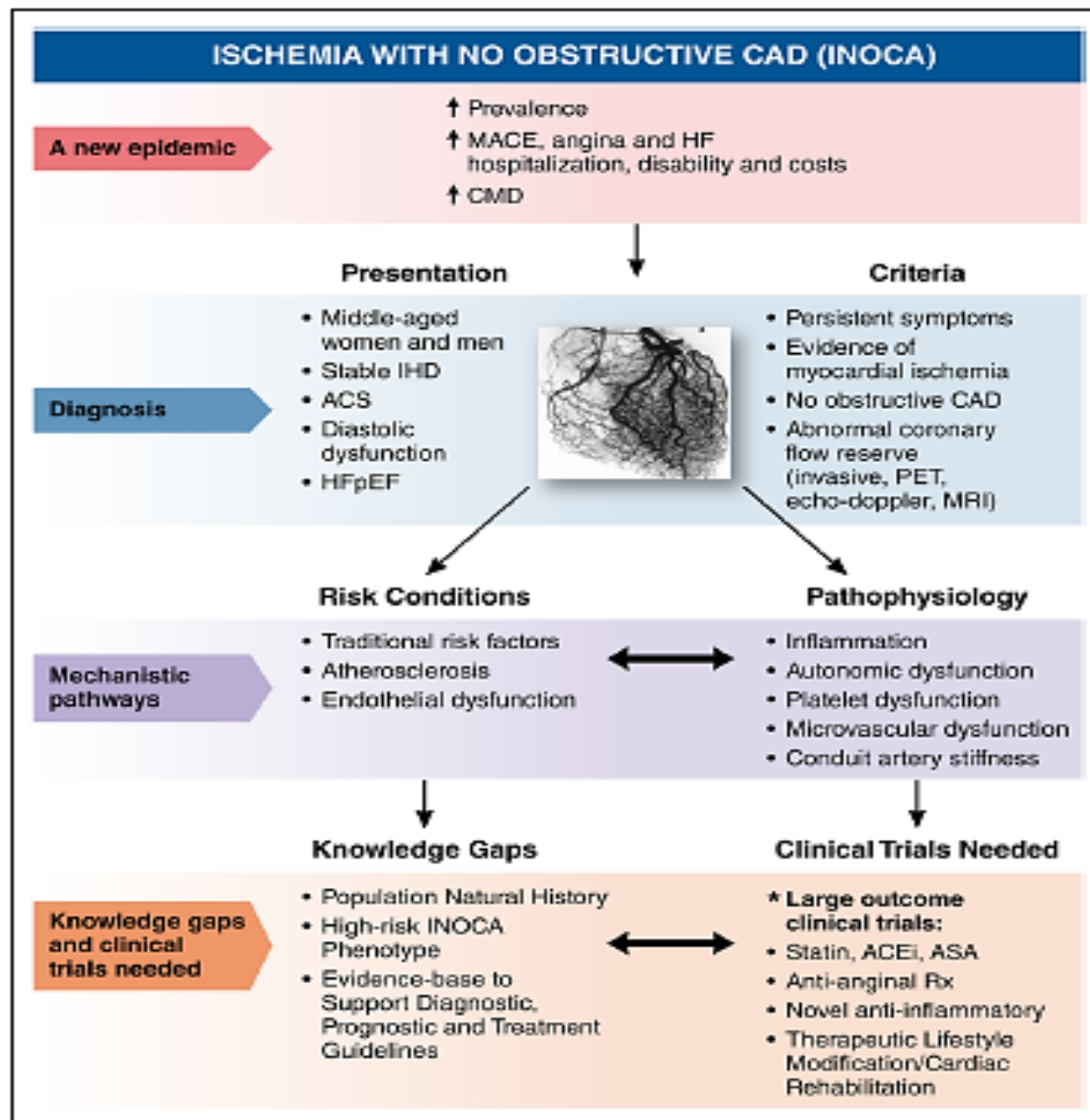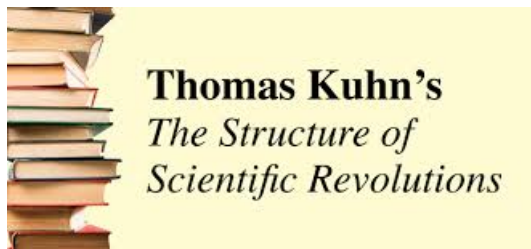
REVIEW
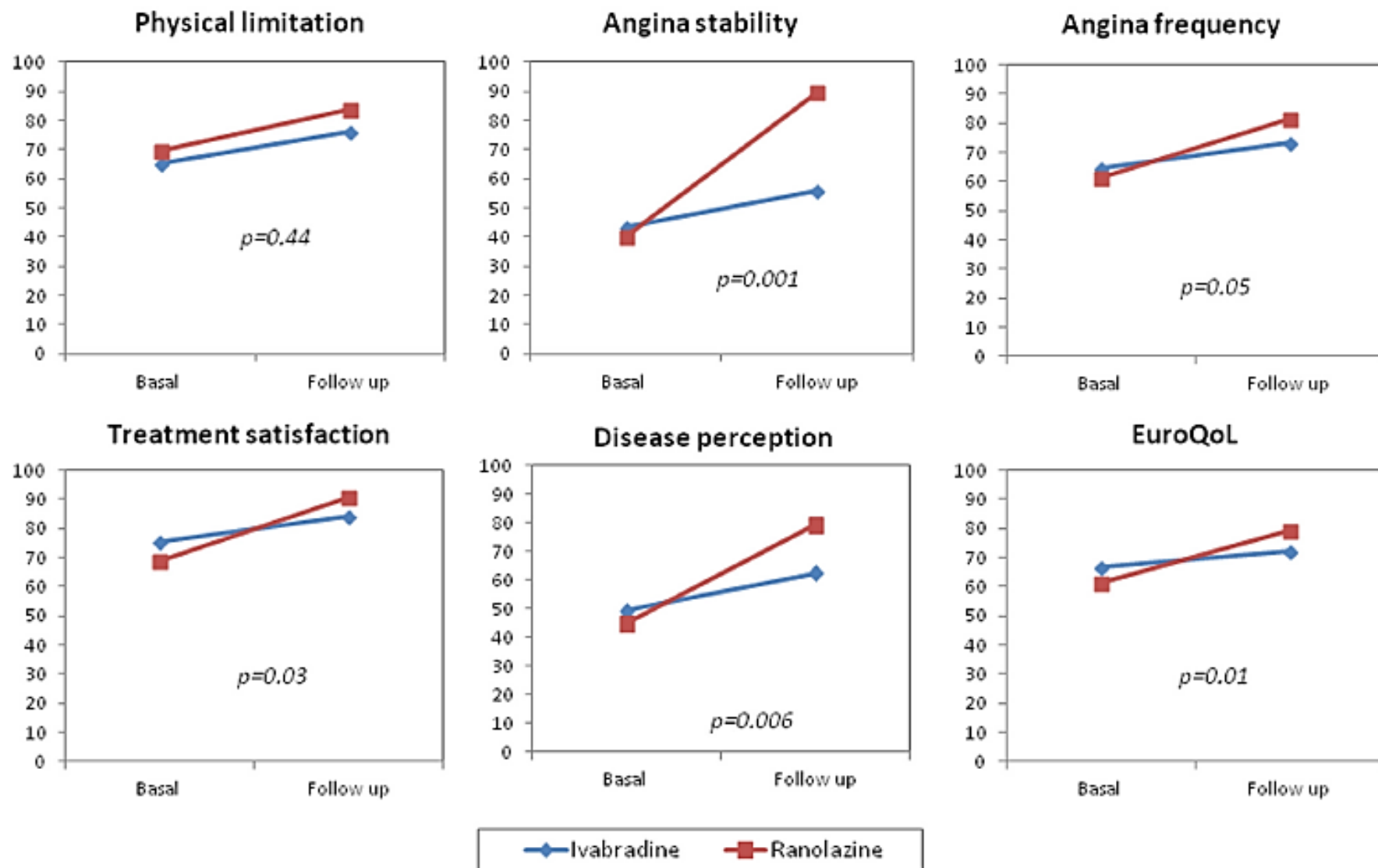
Clinical update

Coronary microvascular dysfunction: an update

Filippo Crea[1]*, Paolo G. Camici[2], and Cathleen Noel Bairey Merz[3]

From: Coronary microvascular dysfunction: an update , Eur Heart J. 2013;35(17):1101-1111

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Thomas Kuhn's
The Structure of Scientific Revolutions

Kuhn's scientific revolution

Adoption of different ways of thinking that promise new, better solutions in the future

Le rivoluzioni scientifiche/2

- La perdita «kuhniana» nel passaggio da un paradigma all'altro (cfr. Gillies-Giorello, fig. 11.1)
- Il criterio del manuale e l'invisibilità delle rivoluzioni
T. Kuhn, La struttura delle rivoluzioni scientifiche (1962), Einaudi, 1969, pp. 167-168.

Radico et al. jacc : cardiovascularinterventions, 2014