Assessment of Coronary Microvascular Disease in both Clinical and Experimental Settings

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Coronary Microvascular Dysfunction

- Coronary microvascular dysfunction in the absence of obstructive coronary artery disease and concurrent myocardial diseases or PCI.

- Coronary microvascular dysfunction in the presence of obstructive coronary artery and in the absence of concurrent myocardial diseases or PCI.

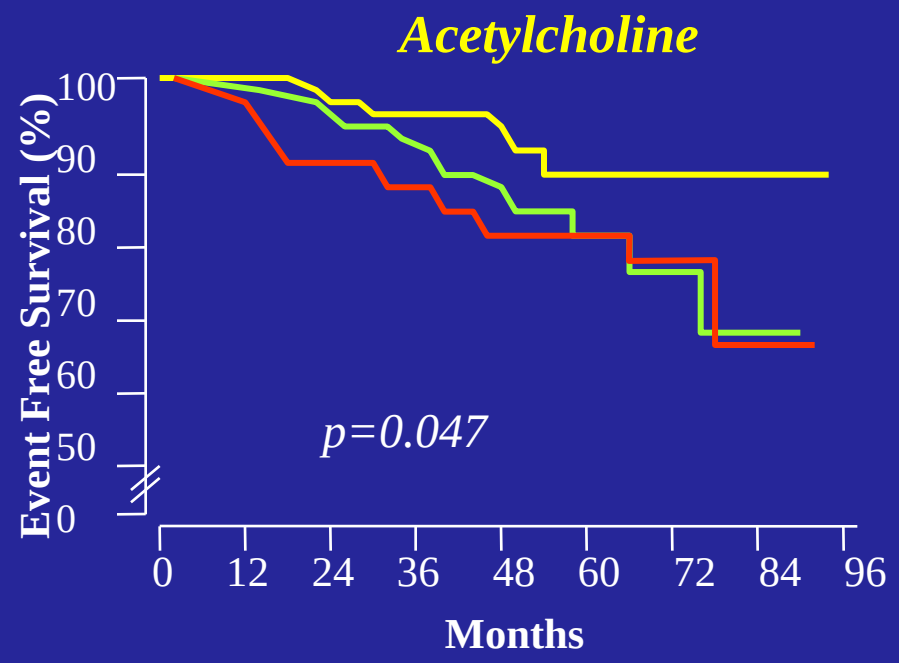
How can vascular dysfunction be tested?

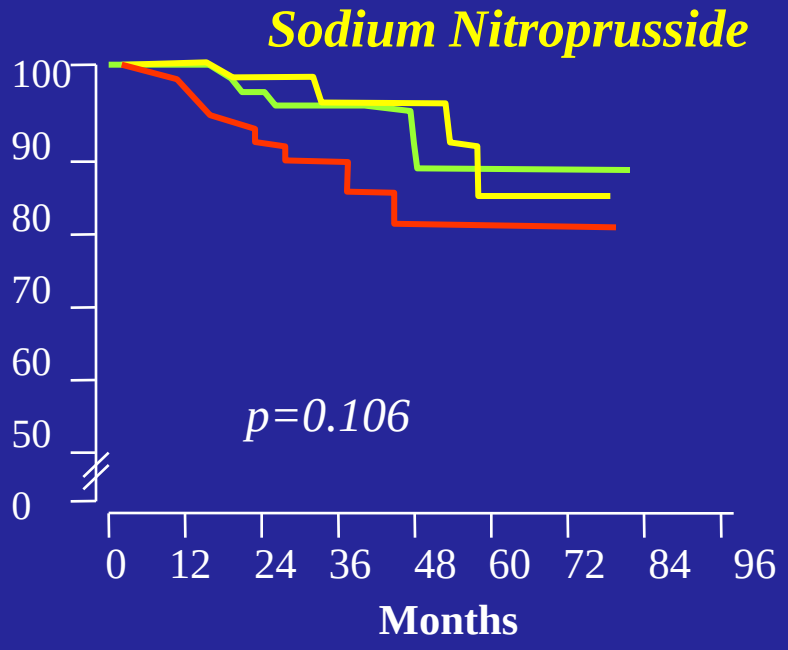
- Bugiardini et al. J Am Coll Cardiol 1993 Abnormal Tl-201 perfusion
- Yoshio et al. J Am Coll Cardiol 1993 Abnormal LV function radionuclide
- Reis SE (WISE) J Am Coll Cardiol 1999 Abnormal coronary flow velocity (intracoronary adenosine/doppler)
- Buchtal (WISE) N Engl J Med 2000 Abnormal Phosphocreatine/ATP ratio (MRI spectroscopy)
- Buffon et al. Am J Physiol 2001 Abnormal lipid hydroperoxide and conjugated dienes production
- Panting et al. N Engl J Med 2002 Abnormal subendocardial perfusion by MRI
- Doyle (WISE) J Cardiovasc Magn Reson. 2003 Abnormal myocardial flow reserve by MRI

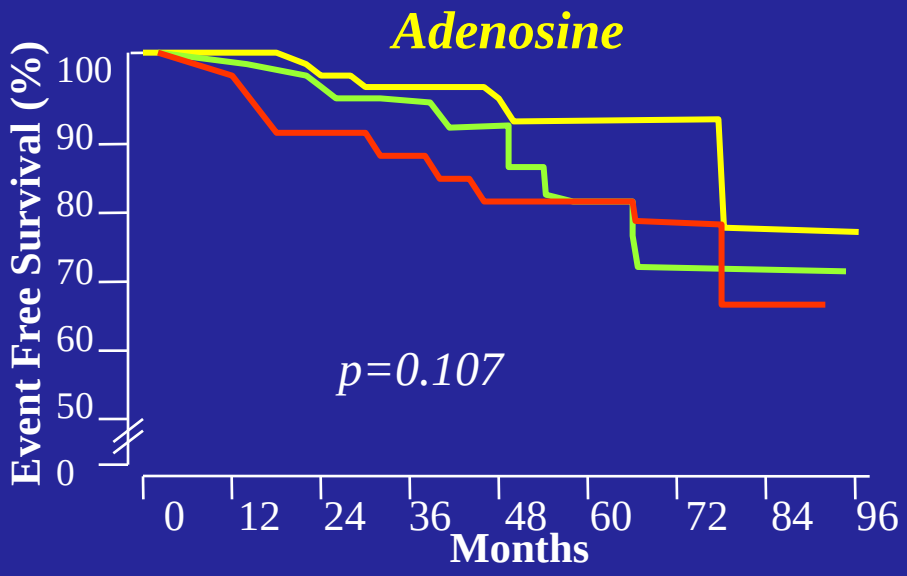
Assessing the Causes of Reduced Coronary Flow Reserve

- There are a number of likely causes for impairment of coronary flow reserve in patients with non-obstructive coronary angiograms.
- Impaired coronary flow reserve does not necessarily mean endothelial vascular dysfunction, because the abnormality could reside in the endothelium-independent response.
- Dysfunction of the endothelium-dependent vasodilatation is strictly related to early atherogenetic process.

Relationship Between Microvascular Coronary Vasomotor Function and Acute Cardiovascular Events

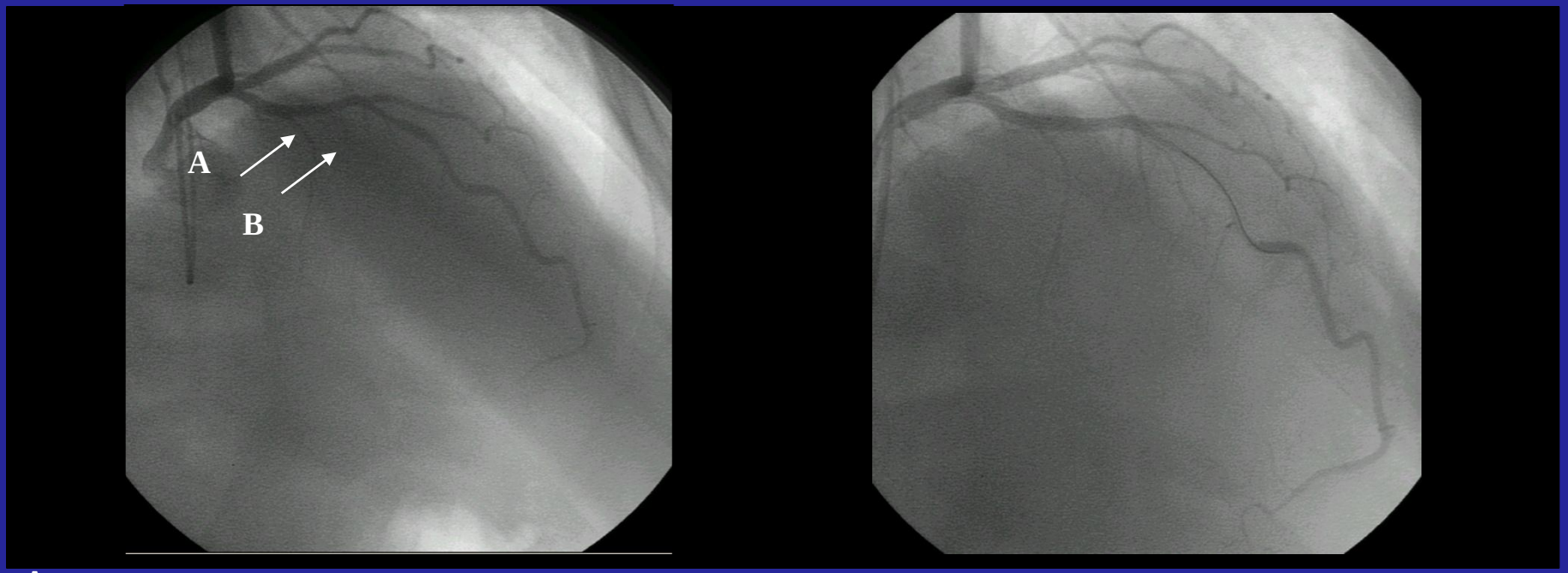






tertile with greatest fall in CVR
tertile with intermediate fall in CVR
tertile with least fall in CVR

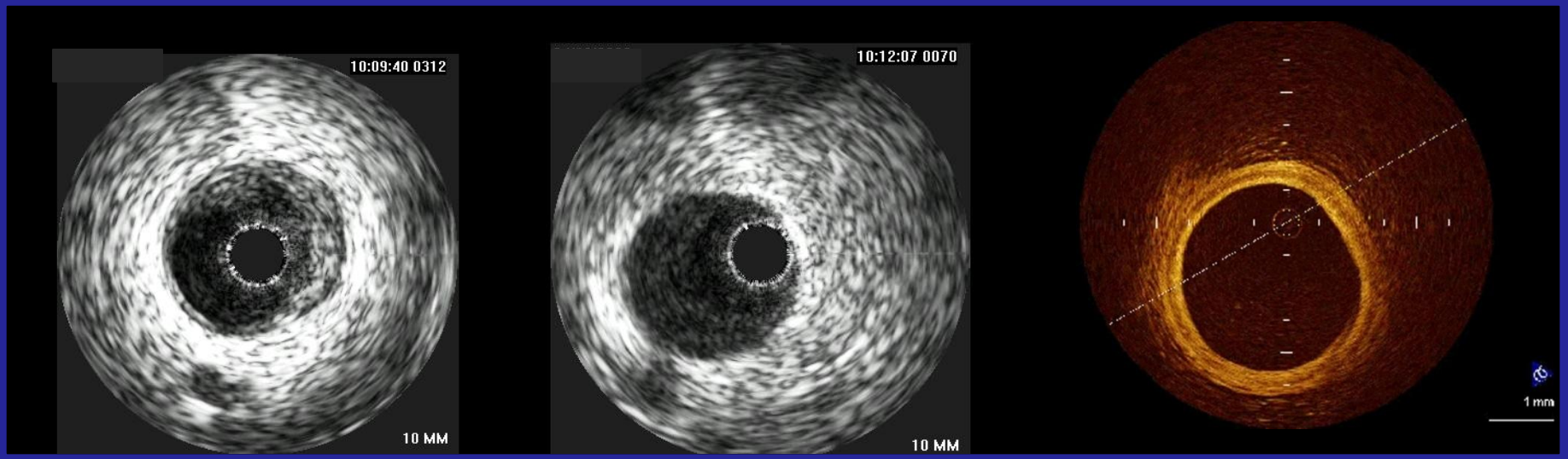
Halcox JP. Circulation 2002;106:653



A

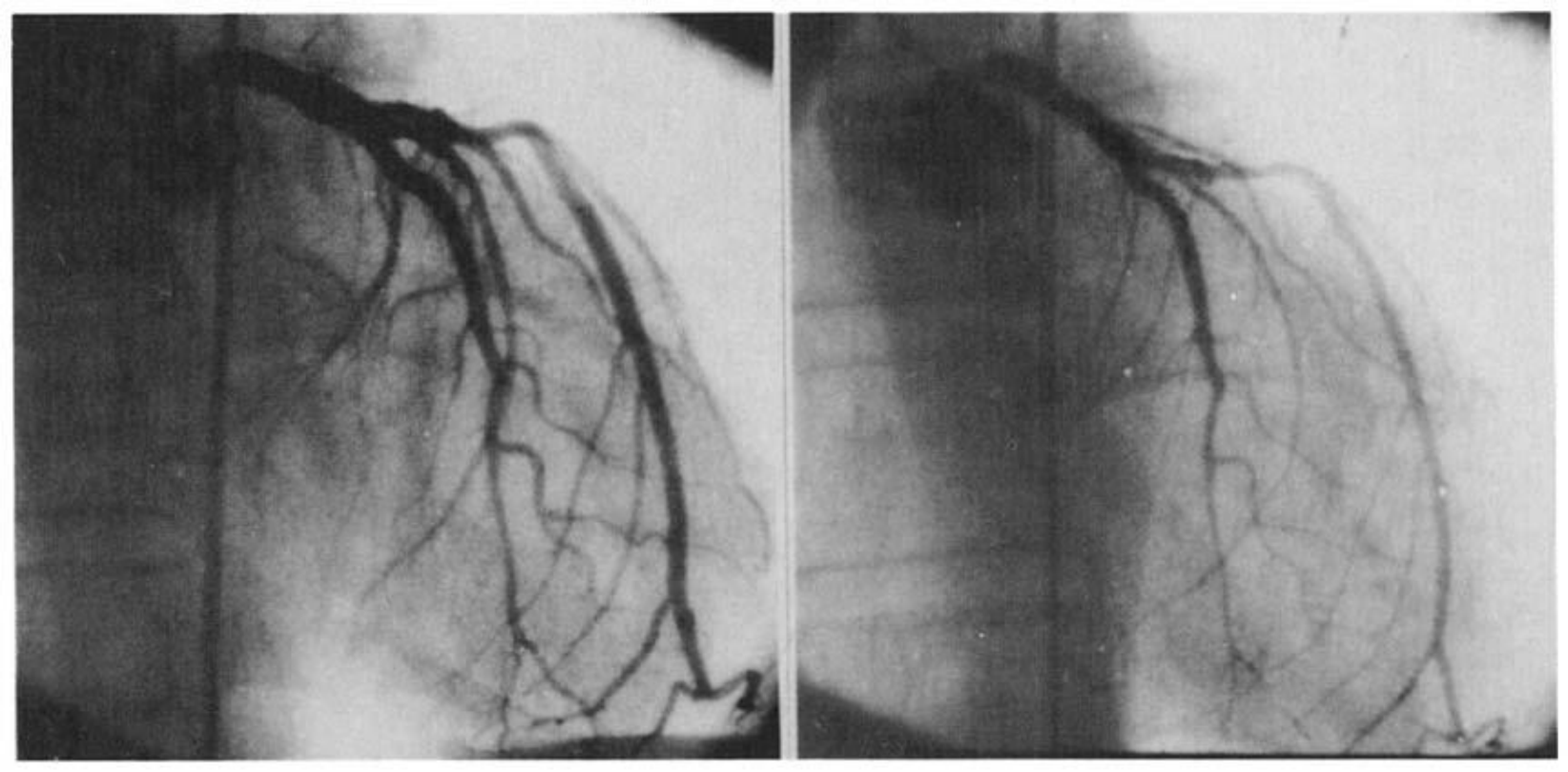
B 1

B 2



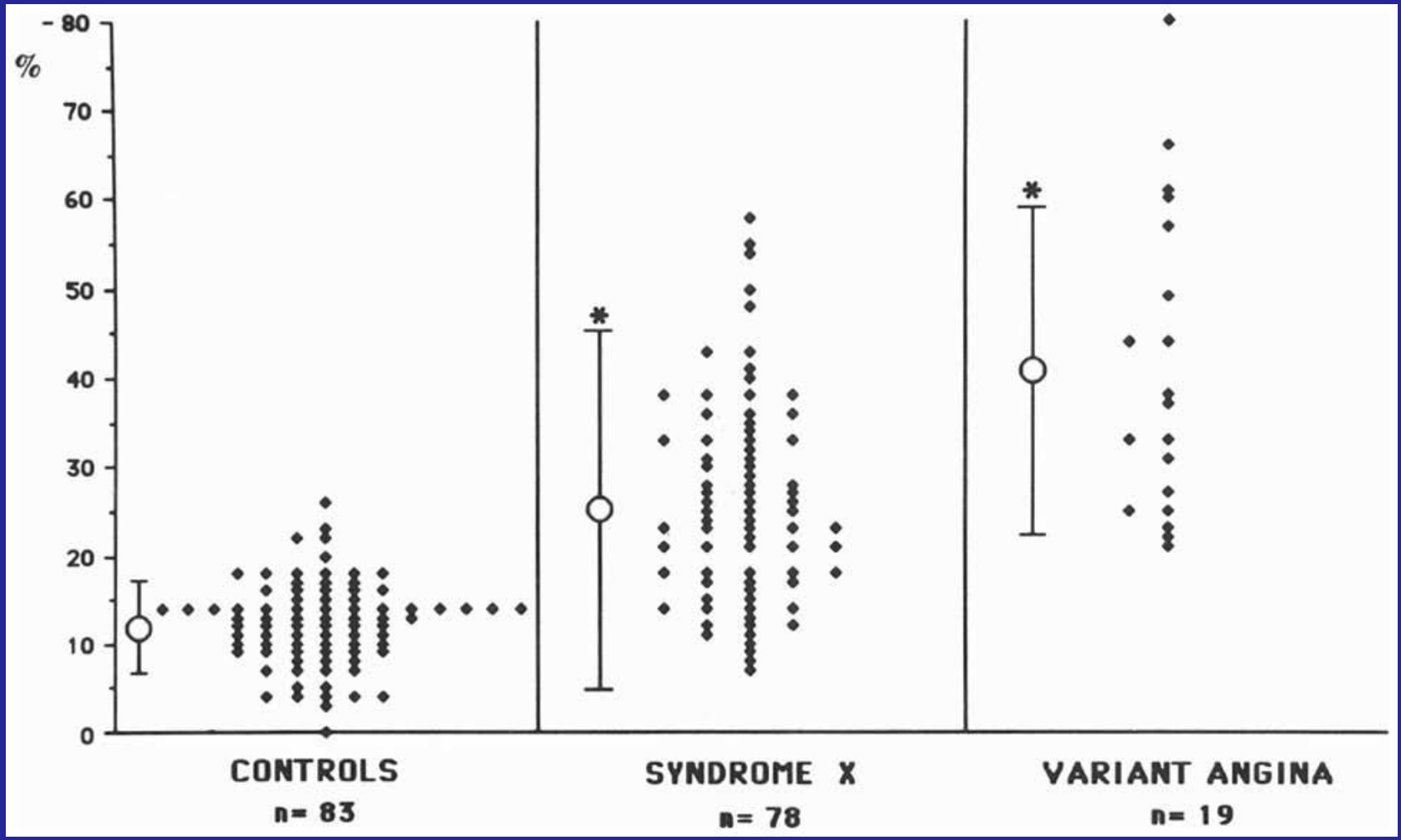
Manfrini O. et al. International Journal of Cardiology. 2103

VASOTONIC ANGINA AND NORMAL CORONARY ARTERIES



Bugiardini R. et al.JACC 1993;2 :417-25

VASOTONIC ANGINA AND NORMAL CORONARY ARTERIES



Bugiardini R. et al.JACC 1993;2 :417-25

VASOTONIC ANGINA AND NORMAL CORONARY ARTERIES

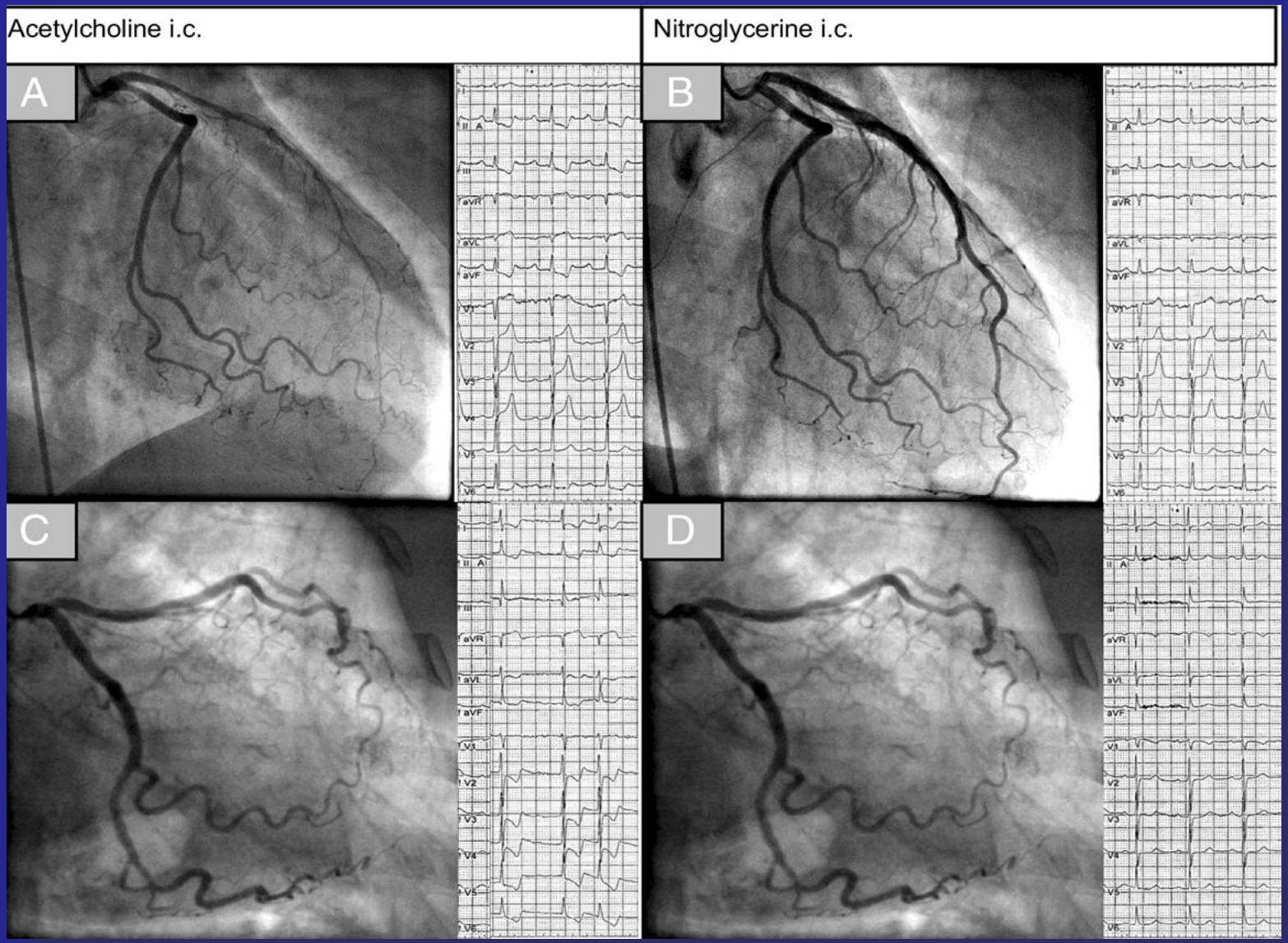
Pt No	Before Nitroglycerin				After Nitroglycerin			
	Baseline		Hyperventilation		Baseline		Hyperventilation	
	GCVBF	ACR	GCVBF	ACR	GCVBF	ACR	GCVBF	ACR
Syndrome X								
1	210	0.39	145	0.46	198	0.40	150	0.51
2	195	0.49	143	0.67	188	0.53	141	0.68
3	84	1.07	67	1.26	80	0.97	69	1.1
4	140	0.70	107	0.88	131	0.58	96	0.91
Mean	157*	0.66†	115*	0.82†	149*	0.62†	114*	0.80‡
± SD	57	0.30	37	0.34	55	0.25	38	0.26
Variant Angina								
1	104	1.37	90	1.92	76	1.05	65	1.21
2	55	1.80	46	2.28	40	2.35	29	3.10
3	58	1.89	40	2.34	51	2.13	42	2.61
4	89	1.02	62	1.43	75	1.20	55	1.61
Mean	77*	1.52§	60*	1.99§	61†	1.68	48†	2.13‡
± SD	24	0.40	22	0.42	18	0.65	16	0.87

"p < 0.03 tp < 0.02 . 1p < 0.04 . §p < 0 .001

ACR = anterior coronary resistance (mm Hg/ml/min)
GCVBF = great cardiac vein blood flow (ml/min)

Bugiardini R et al.JACC 1993;2 :417-25

Acetylcholine Testing in Stable Angina



epicardial spasm

microvascular spasm

Ong P. et al. ACOVA. J Am Coll Cardiol 2012

Clinical Characteristics of Patients with Stabile Angina and Unobstructed Coronary Arteries (<20%) during Ach test

Table 3. Clinical Characteristics of Patients With Stable Angina, Unobstructed Coronary Arteries (<20% Narrowings) and ACH Test

	All Patients With Unobstructed Coronary Arteries (<20% Narrowings) and ACH Test (n = 124)	Epicardial Spasm (n = 36 [28%])	Microvascular Spasm (n = 42 [34%])	ACH Test Uneventful (n = 47 [38%])	p Value *
Age, yrs	63 ± 10	65 ± 11	64 ± 11	62 ± 9	0.32
Male	37 (30%)	8 (23%)	7 (17%)	22 (47%)	<0.01
Exertional chest pain	32 (26%)	14 (40%)	11 (26%)	7 (15%)	0.04
Exertional dyspnea with occasional chest pain at rest	25 (20%)	3 (9%)	10 (24%)	12 (26%)	0.13
Exertional chest pain with occasional symptoms at rest	67 (54%)	18 (51%)	21 (50%)	28 (60%)	0.64
Noninvasive test for ischemia performed	102 (82%)	28 (80%)	35 (83%)	39 (83%)	0.91
Ischemic ECG changes during noninvasive test for ischemia	45 (36%)	9 (26%)	21 (50%)	15 (32%)	0.06
Risk factors					
Hypertension	86 (69%)	21 (60%)	32 (76%)	33 (70%)	0.30
Diabetes mellitus	25 (20%)	5 (14%)	8 (19%)	12 (26%)	0.48
Hypertension and diabetes mellitus	20 (16%)	4 (11%)	7 (17%)	9 (19%)	0.65
Hypercholesterolemia	69 (56%)	17 (49%)	24 (57%)	28 (60%)	0.60
Smokers	16 (16%)	4 (11%)	3 (7%)	11 (23%)	0.09
Positive family history for CVD	55 (44%)	20 (57%)	28 (67%)	7 (15%)	<0.01

Values are n (%) or mean ± SD. ACH = acetylcholine; other abbreviations as in Table 1.

Ong P. et al. ACOVA. J Am Coll Cardiol 2012

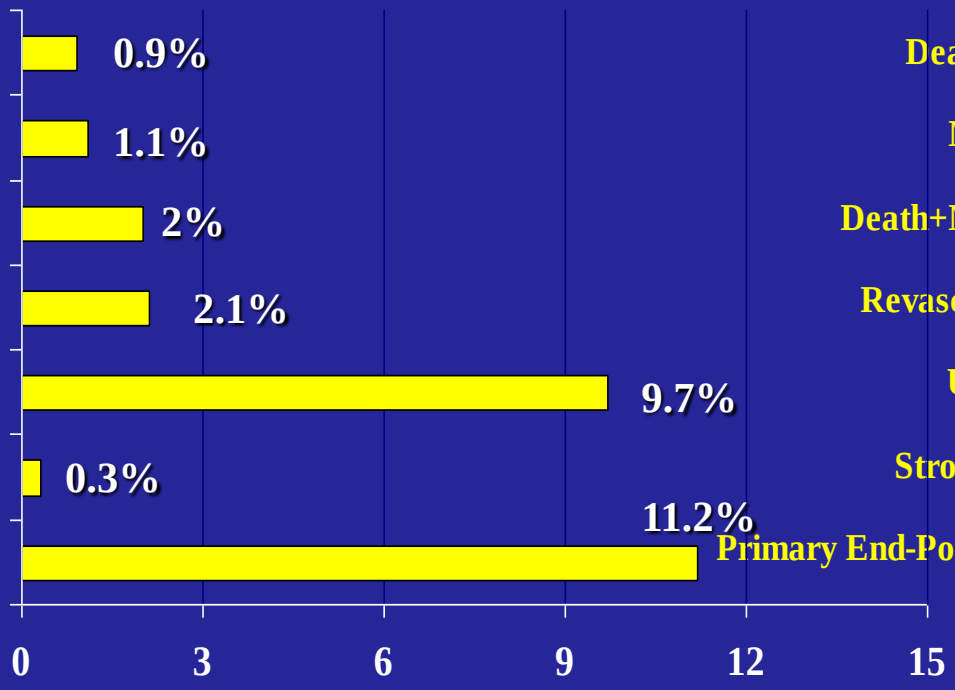
What's the CV risk associated with microvascular dysfunction despite NCA?

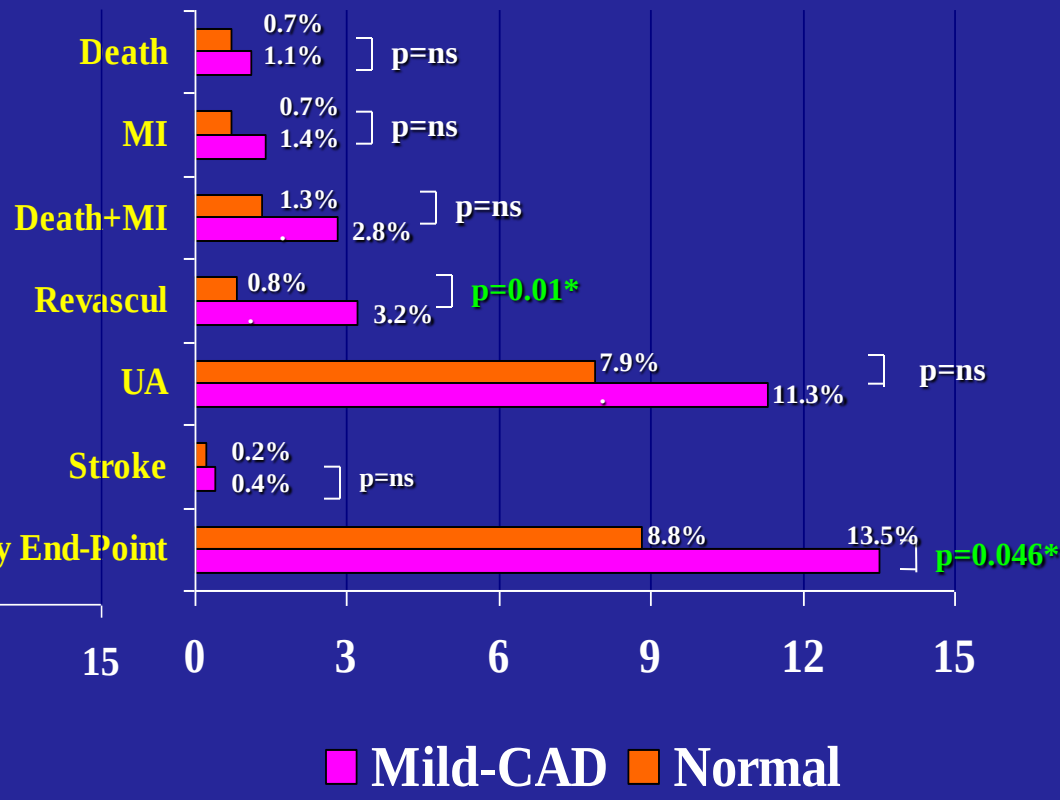
This question is relevant because patients' symptoms and prognosis may be improved with drugs.

Prognosis of Mild-CAD and Normal Angiography

Event Rates 1 year follow–up (910 patients)

TIMI 11B - OPUS-TIMI 16 - PROVE-IT TIMI 22





Bugiardini R .et al Arch Intern Med. 2006;166:1391-5

Six-month clinical outcomes in patients with mild disease

GRACE (Global Registry of Acute Coronary Events)

	Normal or mild disease		
	Men (n = 857)	Women (n = 703)	p Value
	No (%)	No (%)	Normal/ mild disease
Death	15 (2)	14 (2)	0.85
Myocardial infarction	15 (2)	6 (1)	0.18
Stroke	5 (1)	6 (1)	0.56
Rehospitalisation	113 (15)	80 (12)	0.24
Combined end point*	132 (17)	92 (14)	0.19

Day S et al. Heart 2009;95:20-26

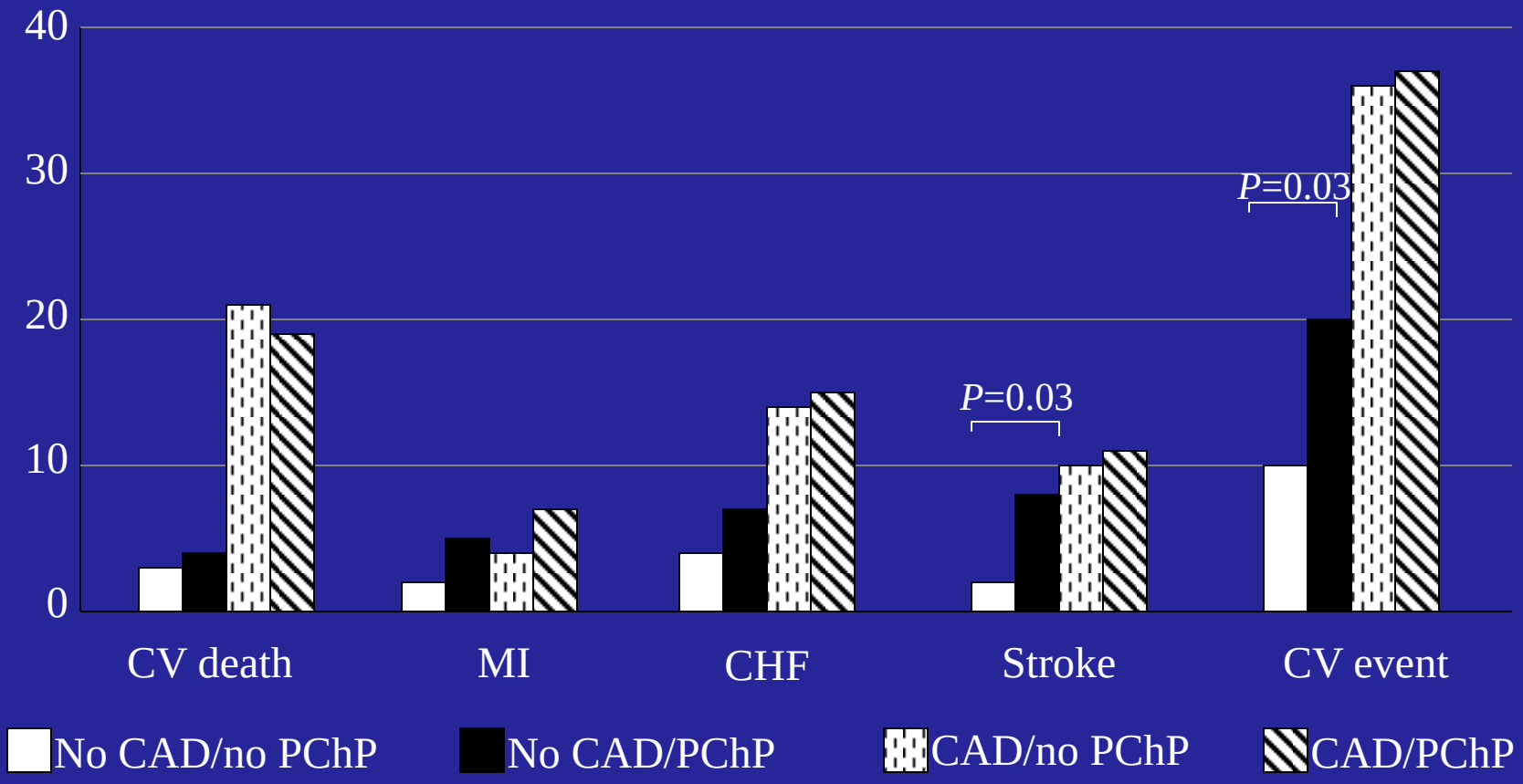
Sex differences in mortality following acute coronary syndromes

Risk of 30-Day Mortality for Women Compared With Men Following ACS in the Cohort With Angiographic Data (n=35128)

	WOMEN		MEN	
All ACS	354 / 9375	(3.8)	625 / 25653	(2.4)
Non-Obstructive Disease	10 / 1367	(0.7)	10 / 2126	(0.5)
Single-Vessel Disease	70 / 3551	(2.0)	100 / 9648	(1.0)
2-Vessel Disease	102 / 2320	(4.4)	159 / 7137	(2.2)
3-Vessel Disease	172 / 2137	(8.8)	356 / 6742	(5.3)

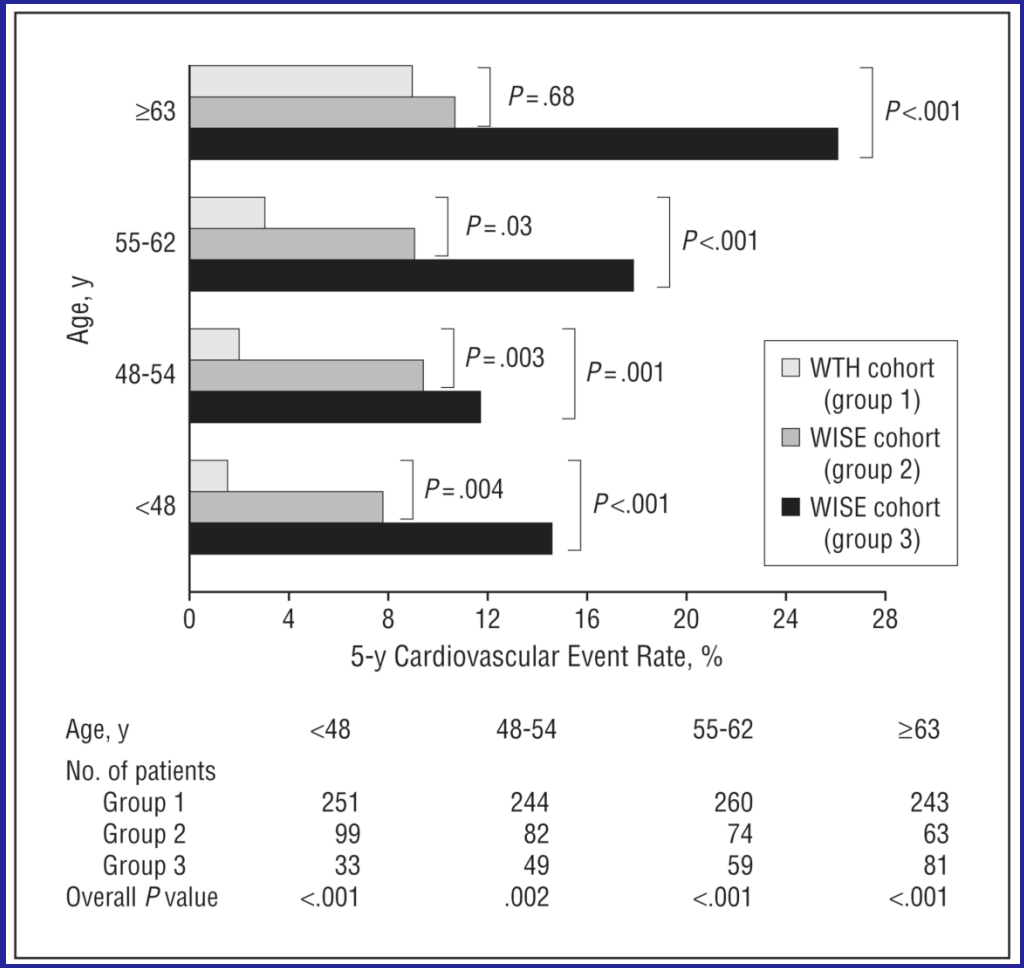
Berger JS et al.; JAMA. 2009;302(8):874-882

Six-year Cardiovascular Event Rates by Coronary Artery Disease (CAD) and Persistent Chest Pain (PChP)



Johonson BD et al. Eur Heart J. 2006;27:1408-15

Five-year primary composite event rate stratified by age and severity of coronary disease

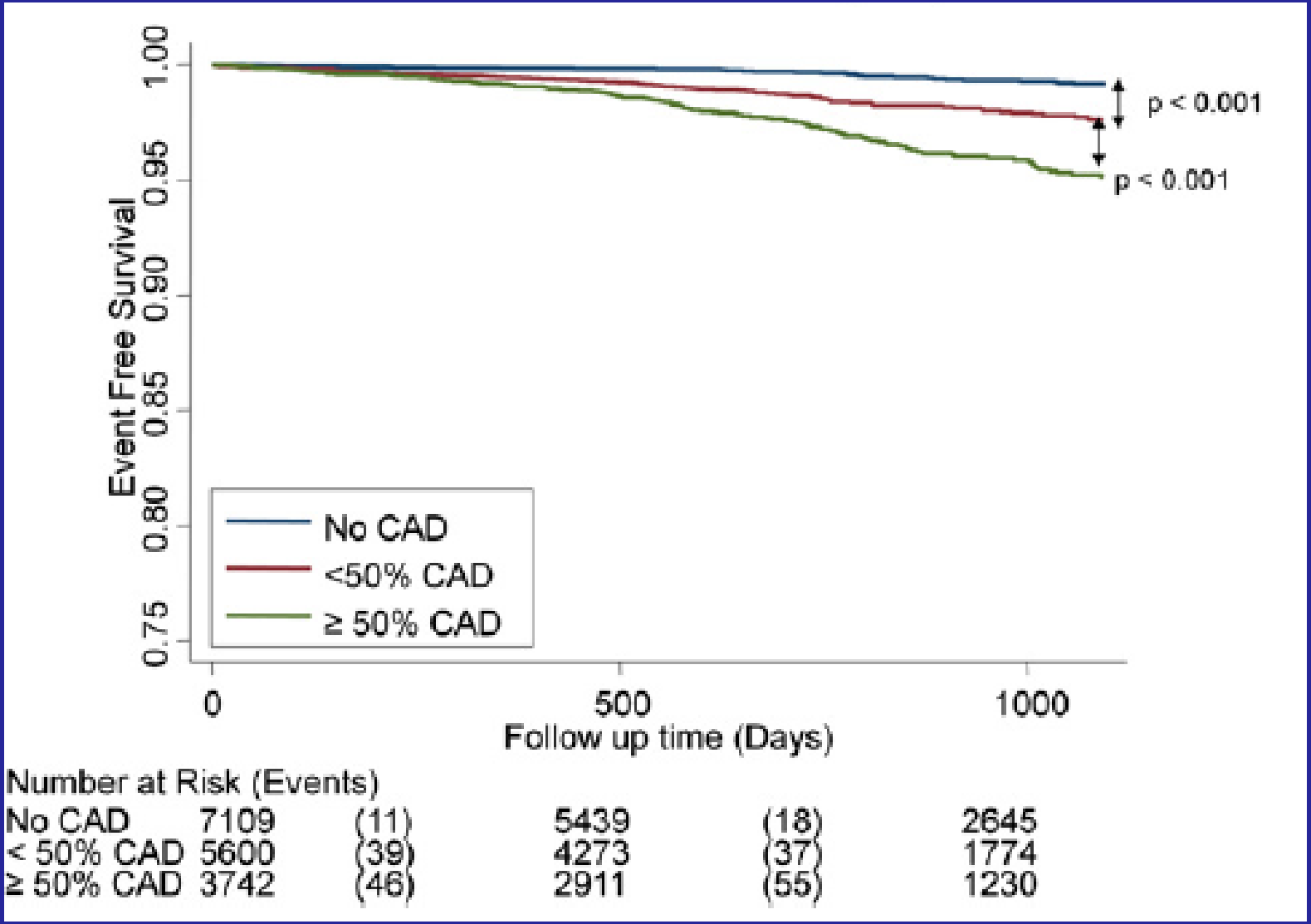


Age, y	<48	48-54	55-62	≥63
No. of patients				
Group 1	251	244	260	243
Group 2	99	82	74	63
Group 3	33	49	59	81
Overall *P* value	<.001	.002	<.001	<.001

- **group1(white)- asymptomatic women**
- **group 2(gray)- symptomatic women with normal coronary arteries -0%stenosis**
- **group 3(black)- nonobstructive coronary artery disease – stenosis in any coronary artery- 1%–49%**

Martha Gulati, MD, MS et al.; Arch Intern Med. 2009 May 11; 169(9): 843–850

Survival from Death or MI among 16,451 patients according to severity of CAD on CCTA



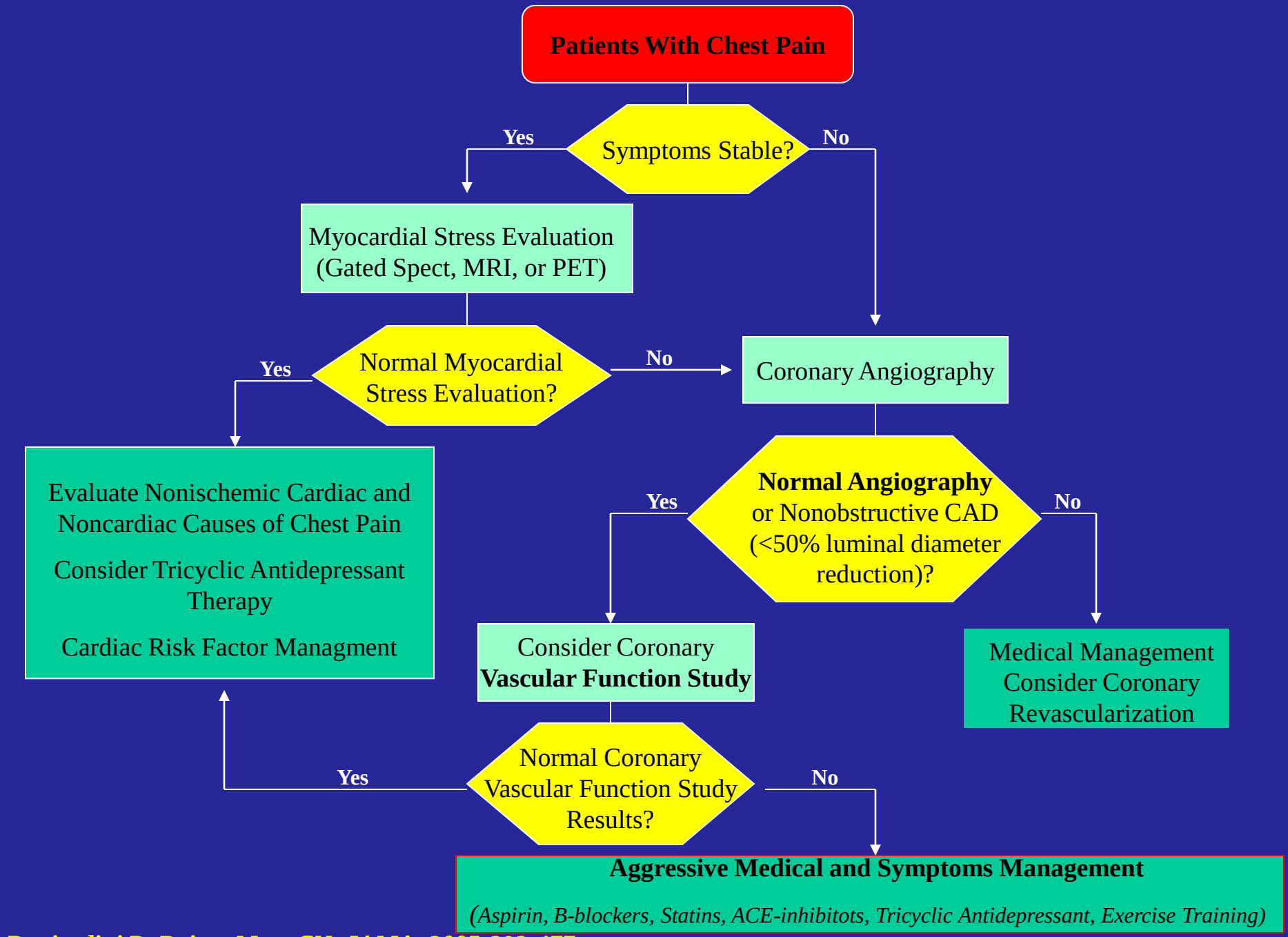
Hulten el al. CONFIRM Study. Am J Cardiol 2013

What is the best method of risk stratification in people with microvascular dyfunction?

There are a variety of questions that are relevant to clinical decision-making, the most important being

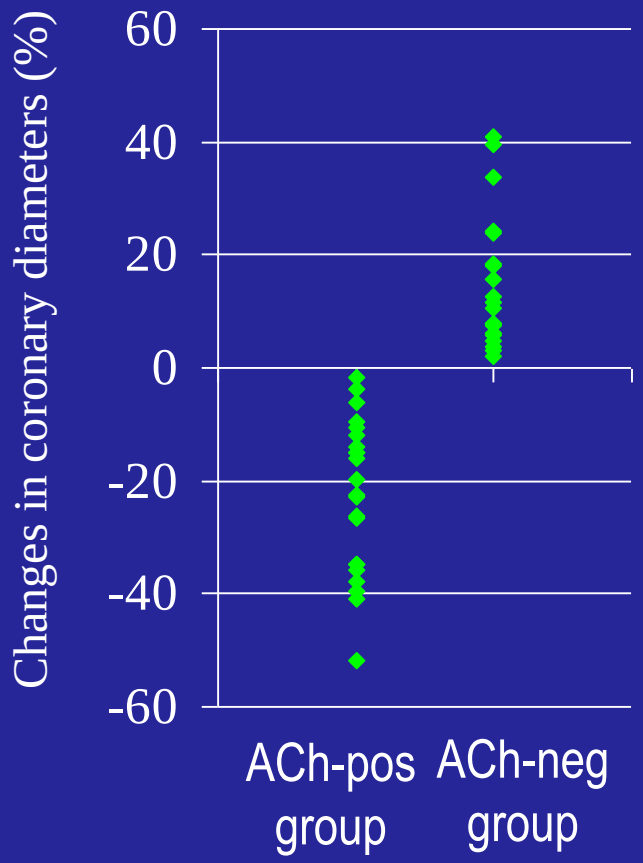
-Is vascular dysfunction a prognostic marker?

Bugiardini R, Bairey Merz CN. JAMA. 2005;293:477.

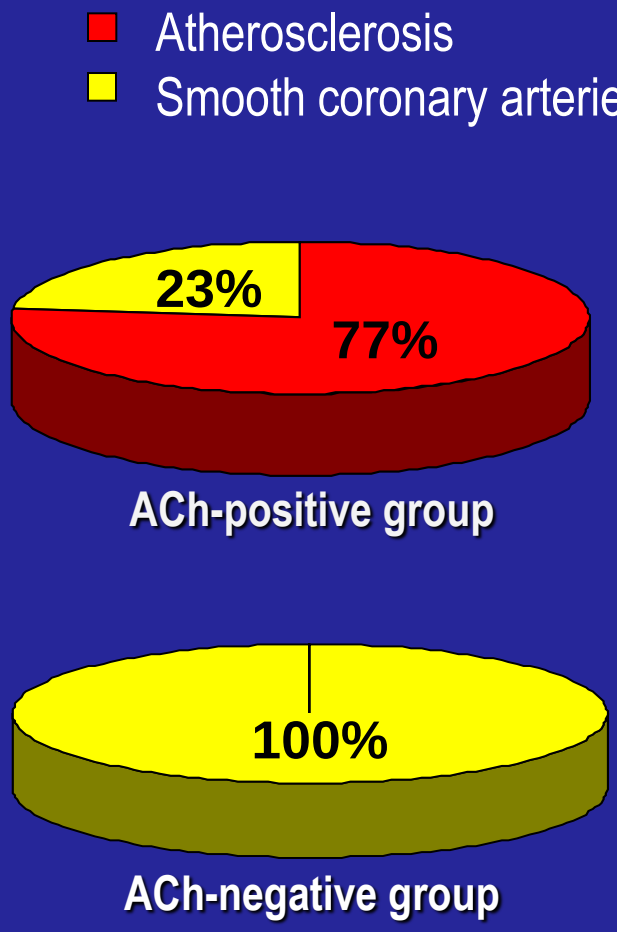


Bugiardini R, Bairey Merz CN. JAMA. 2005;293:477.

Endothelial function predicts future development of coronary artery disease in women with chest pain and normal coronary angiogram

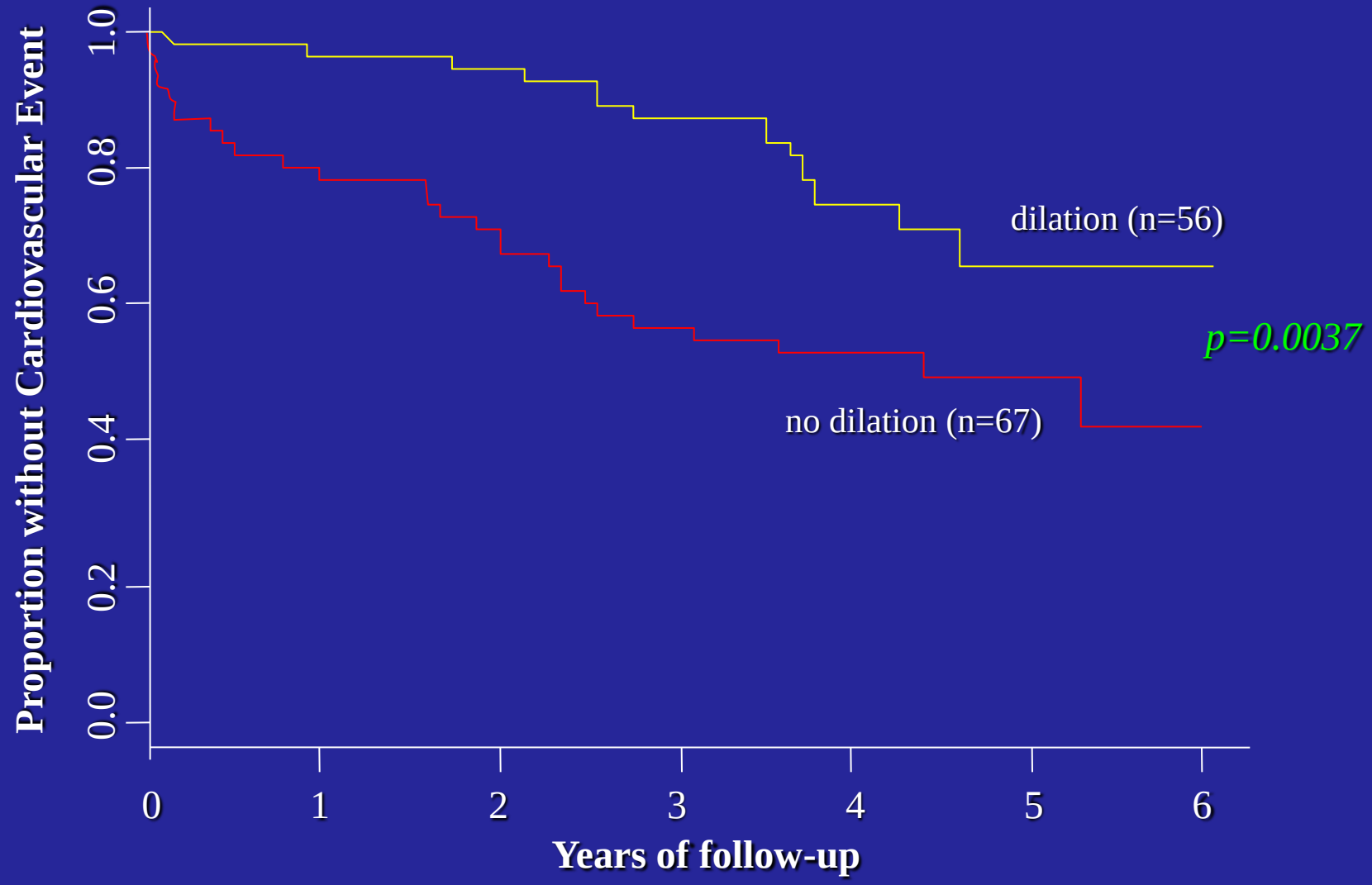


ANGIOGRAMS AT 10 YEARS FOLLOW-UP



Bugiardini R et al. Circulation 2004; 109:2518-2523

Relation between epicardial coronary cross-sectional area response to acetylcholine and risk of cardiovascular event



Von Mering GO et al Circulation 2004;109:722-725

Baseline Characteristics According to Presence or Absence of a Primary End Point in Patients With Nonobstructive Coronary Artery Disease in the PROVE IT-TIMI 22, OPUS-TIMI 16, and TIMI 11B Trials

Characteristic	Patients With Primary End Point (n = 75)*	Patients Without a Primary End Point* (n = 626)	*P* Value
Male	38.7	47.9	.13
Age, mean (SD), y	58.2 (11.1)	57.1 (11.8)	.42
White race	84.0	84.7	.88
History of diabetes	14.7	14.5	.98
History of hypertension	53.3	45.1	.17
Current smoker	26.7	30.9	.45
Prior myocardial infarction	8.0	9.0	.79
History of PAD	4.0	2.7	.46
Drug for management of qualifying event			
Aspirin	94.2	96.9	.24
β-Blocker	69.6	63.9	.36
ACE-I	26.1	26.3	.97
Index event			.04
NSTE-MI	18.2	30.1	
UA	81.8	69.9	
TIMI risk score†			.003
0-2	50.0	67.0	
≥3	50.0	33.0	
Elevated cardiac markers	29.7	41.0	.06
ST-deviation	68.0	57.8	.09

Bugiardini, R. et al. Arch Intern Med 2006;166:1391-1395.

Remarks

- Because the event rate of patients with nonobstructive CAD in ACS is very high, physicians should classify virtually every patient admitted with a clinical diagnosis of ACS to a disease category, even if the angiographic evaluation is absolutely negative.
- We fear that the potential perplexity that this message might cause among primary care physicians is considerable, which implies futher investigations in the attemt to define “internationally recognized” methods of risk stratification.
- There is interest in further information on the role of the microcirculation as specific medical intervention might be of help in “stabilizing” potentially high risk patients.

From: **Unanswered Questions for Management of Acute Coronary Syndrome: Risk Stratification of Patients With Minimal Disease or Normal Findings on Coronary Angiography**

Arch Intern Med. 2006;166(13):1391-1395. doi:10.1001/archinte.166.13.1391

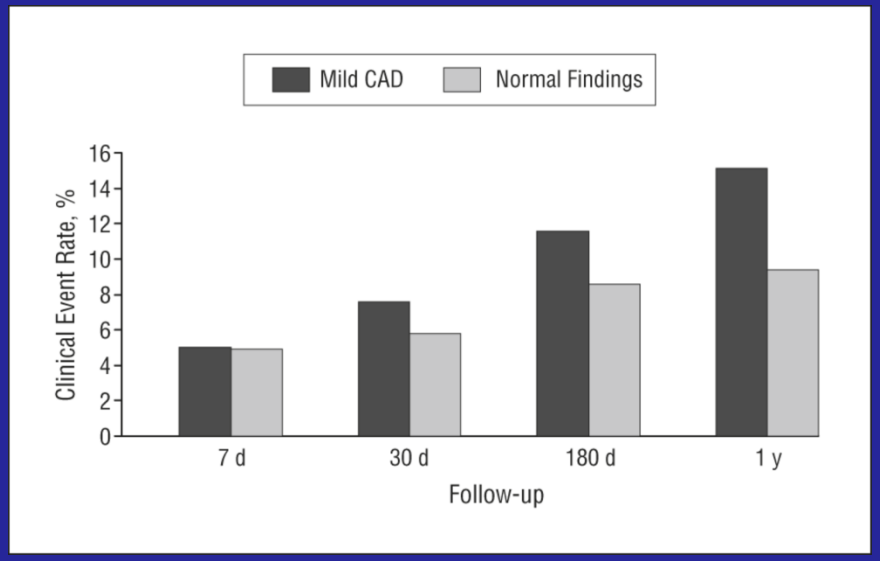
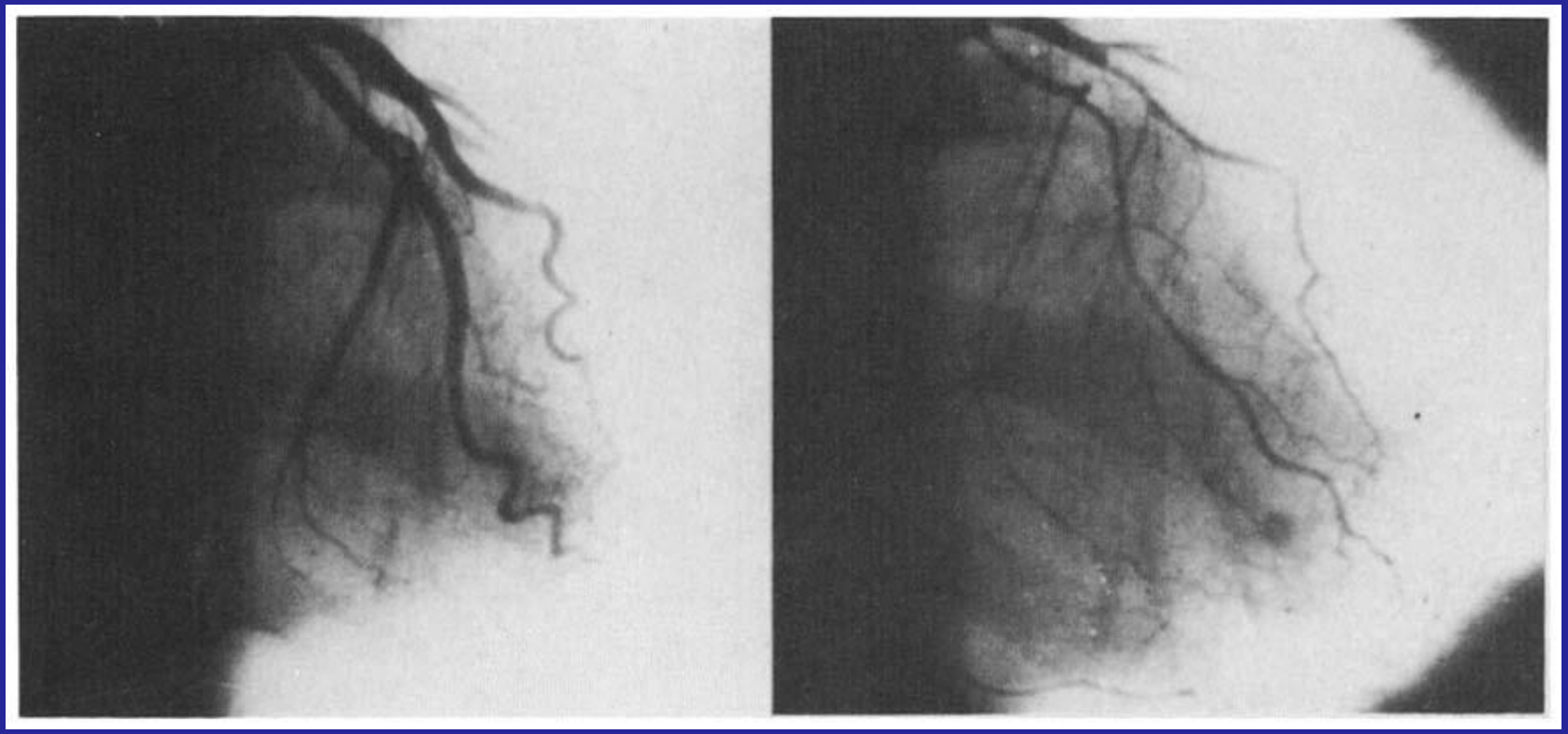


Figure Legend:

Primary end-point event rate for 710 patents with non–ST-segment elevation acute coronary syndromes despite mild coronary artery disease (CAD) or normal findings on angiography at 7, 30, and 180 days, and at 1-year follow-up.

VASOTONIC ANGINA AND NORMAL CORONARY ARTERIES



Bugiardini R et al.JACC 1993;2 :417-25

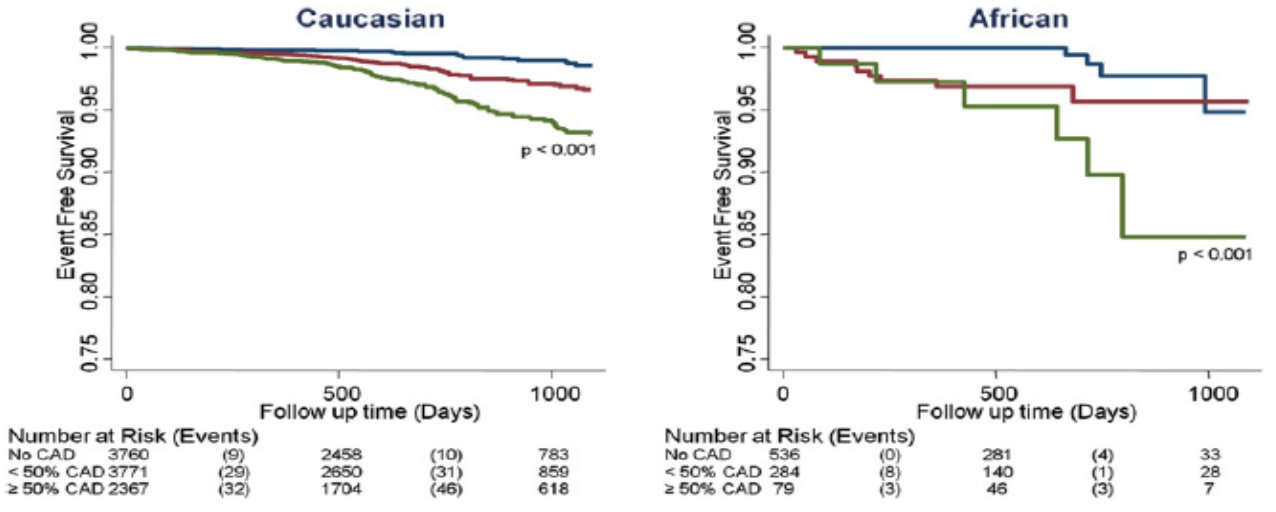
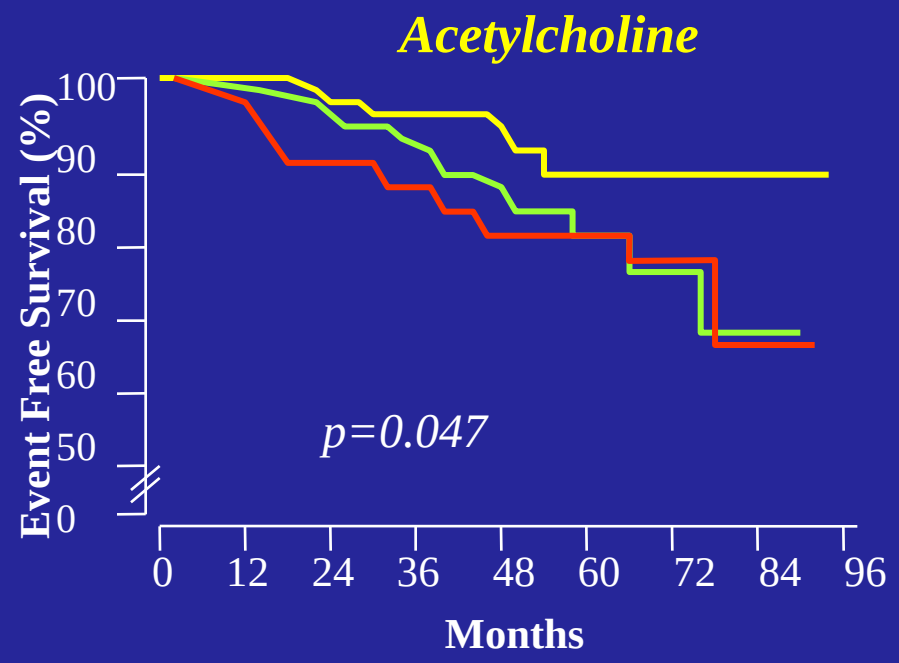
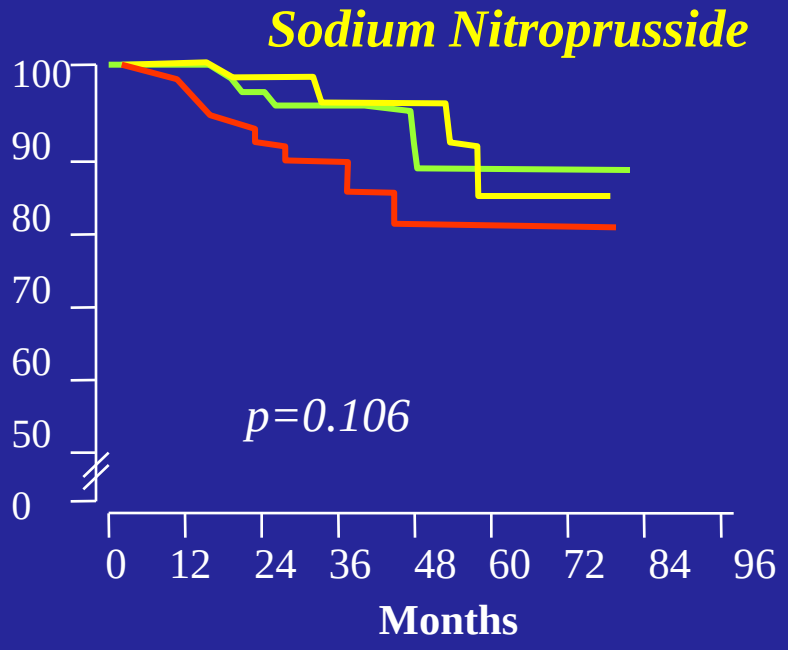


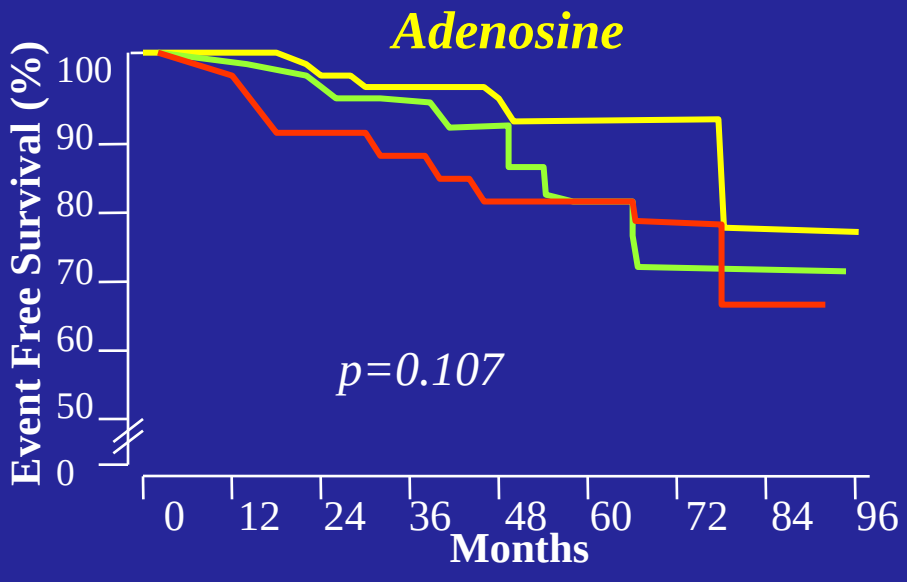
Figure 4. Survival from death or MI according to severity of CAD on CCTA, stratified by ethnicity.

Hulten el al. CONFIRM Study. Am J Cardiol 2013 (In press)

Relationship Between Microvascular Coronary Vasomotor Function and Acute Cardiovascular Events







tertile with greatest fall in CVR
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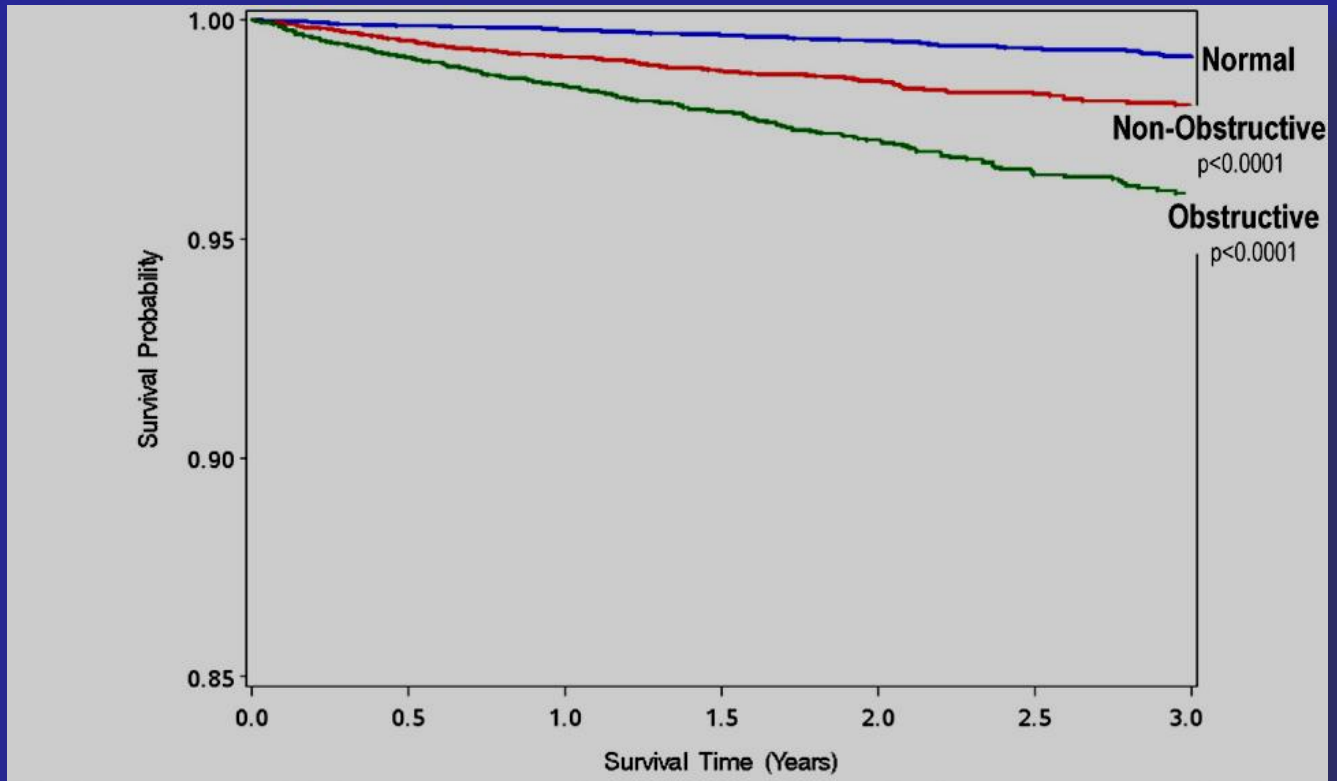
Halcox JP. Circulation 2002;106:653

Unadjusted All-Cause 3-Year Kaplan-Meier Survival by the Maximal Per-Patient Presence of Normal, Non-Obstructive and Obstructive CAD

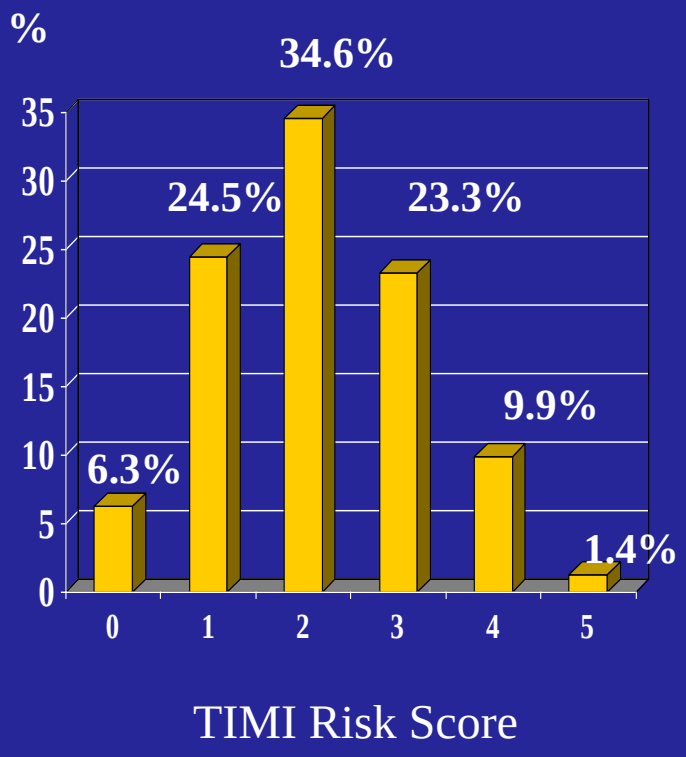


At Risk	Year 0	Year 1	Year 2	Year 3
Normal	10146	9357	5800	2907
Non-Obstructive (1-49%)	8114	7437	4081	1930
Obstructive (≥50%)	5594	5135	3153	1430

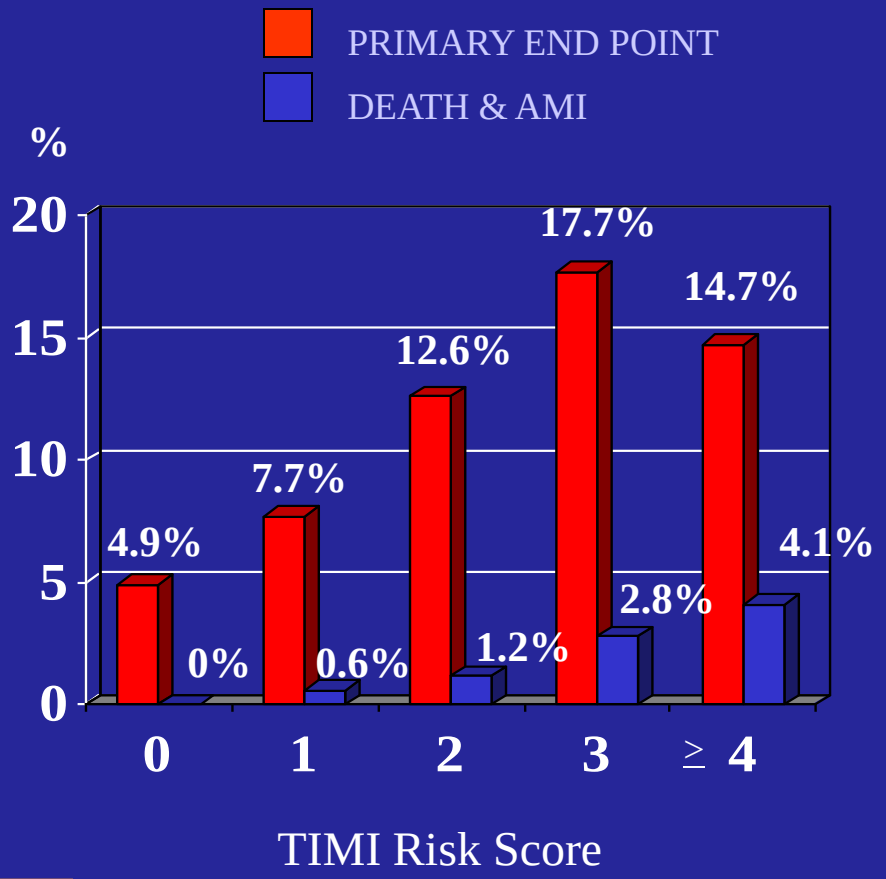
James K. Min et al., JACC; 2011,Vol 58, No.8, 849-60
CONFIRM study

Prognostic Value of TIMI Risk Score in Non-obstructive CAD at 1-year Follow-up

Distribution of TIMI Risk Score



EVENT RATES



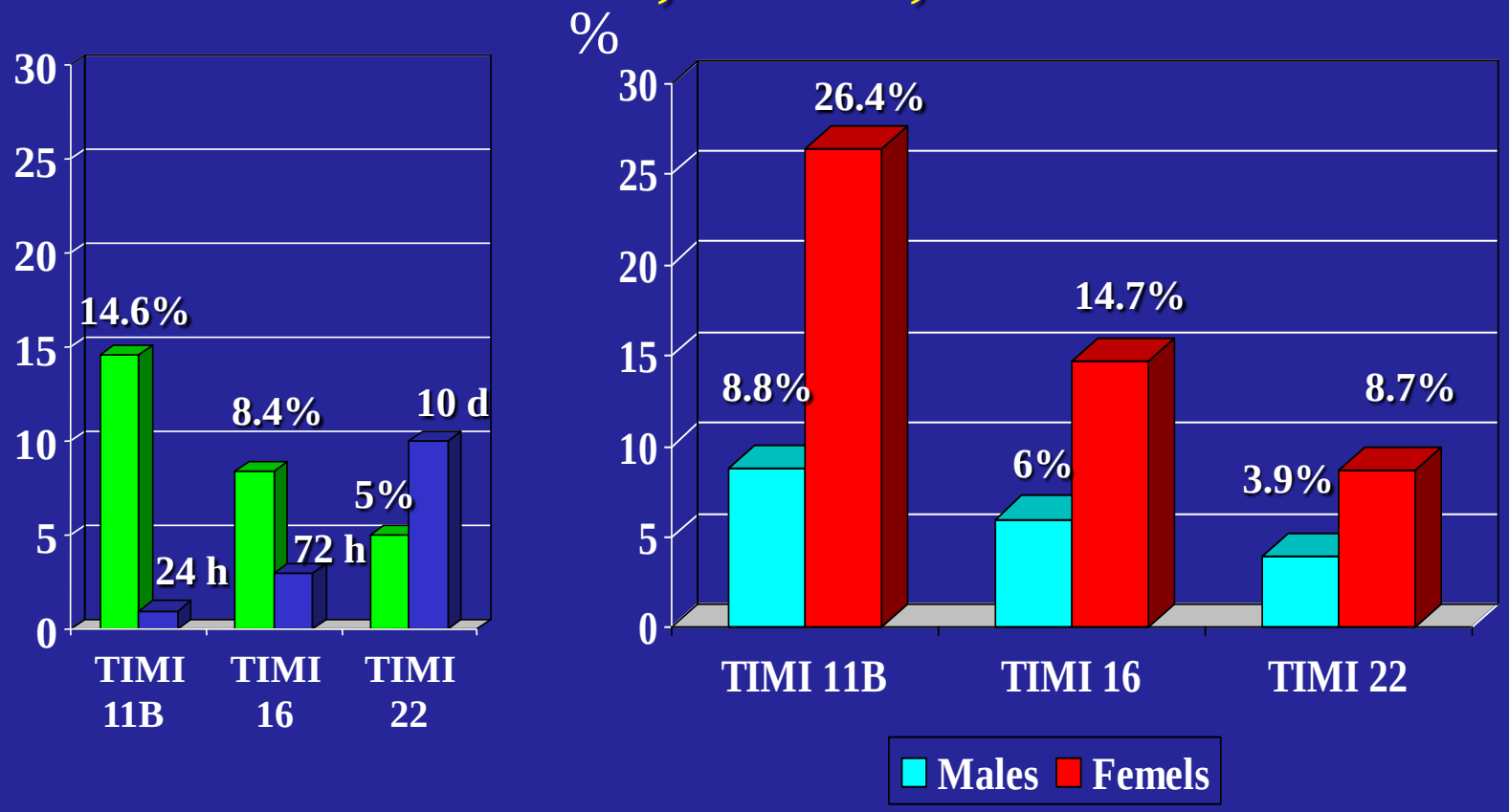
Age <65y, at least 3 risk factors, ST-deviation, aspirin in last 7 days, elevated markers, severe angina symptoms, prior significant stenosis.

Microcirculation, Syndrome X, and Non Obstructive CAD Revisited

- This syndrome was first reported by Likoff et al. (N Eng J Med 1967;276:1063-6) in a group of 15 women with angina, ischemic electrocardiographic responses to exercise and a normal coronary arteriogram.
- Inappropriate constriction of pre-arteriolar vessels of the coronary microvasculature was suggested to be a possible underlying mechanism of disease as proposed by Maseri et al (J Am Coll Cardiol1991;17:499-506).
- Most older studies found that men and women with Syndrome X are not at increased risk of dying early or having a heart attack (Kaski JC et al JAm Coll Cardiol. 1995;25:807-814)
- However, the prognosis of Syndrome X and nonobstructive coronary artery disease was suggested to be far less benign than generally assumed according to more recent studies, the first being “Angina with "normal" coronary arteries: a changing philosophy” (Bugiardini **R**, Bairey Merz CN JAMA. 2005;293:477-84).

Frequency of Non-obstructive CAD in ACS

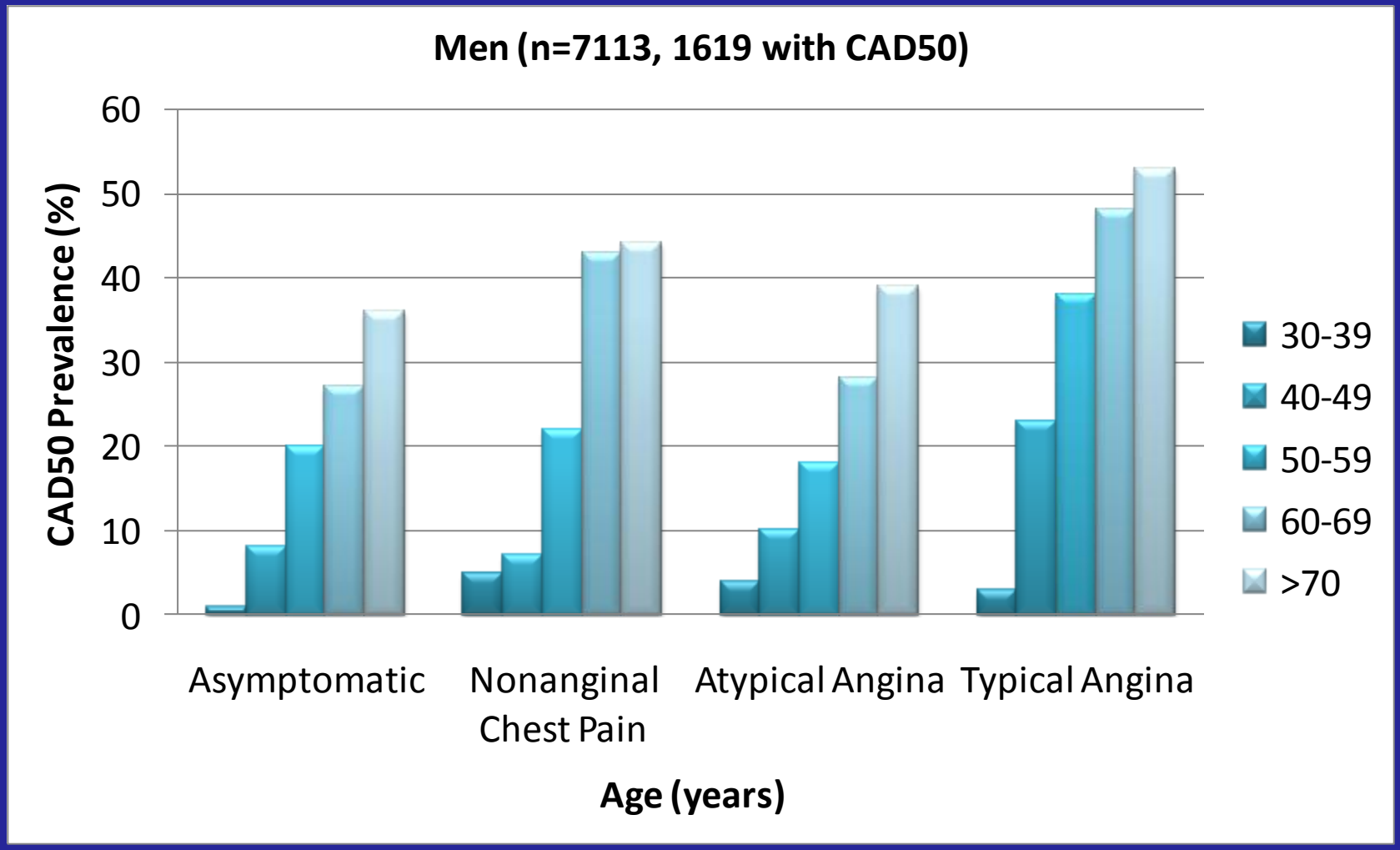
TIMI 11B, TIMI 16, TIMI 22



Bugiardini R et al *Arch Intern Med. 2006;166:1391-5*

CONFIRM Study:

Prevalence of angiographically confirmed 50% stenotic coronary artery disease (CAD50) stratified by age decade



Victor Y. et al.; *Circulation. 2011;124:2423-2432*

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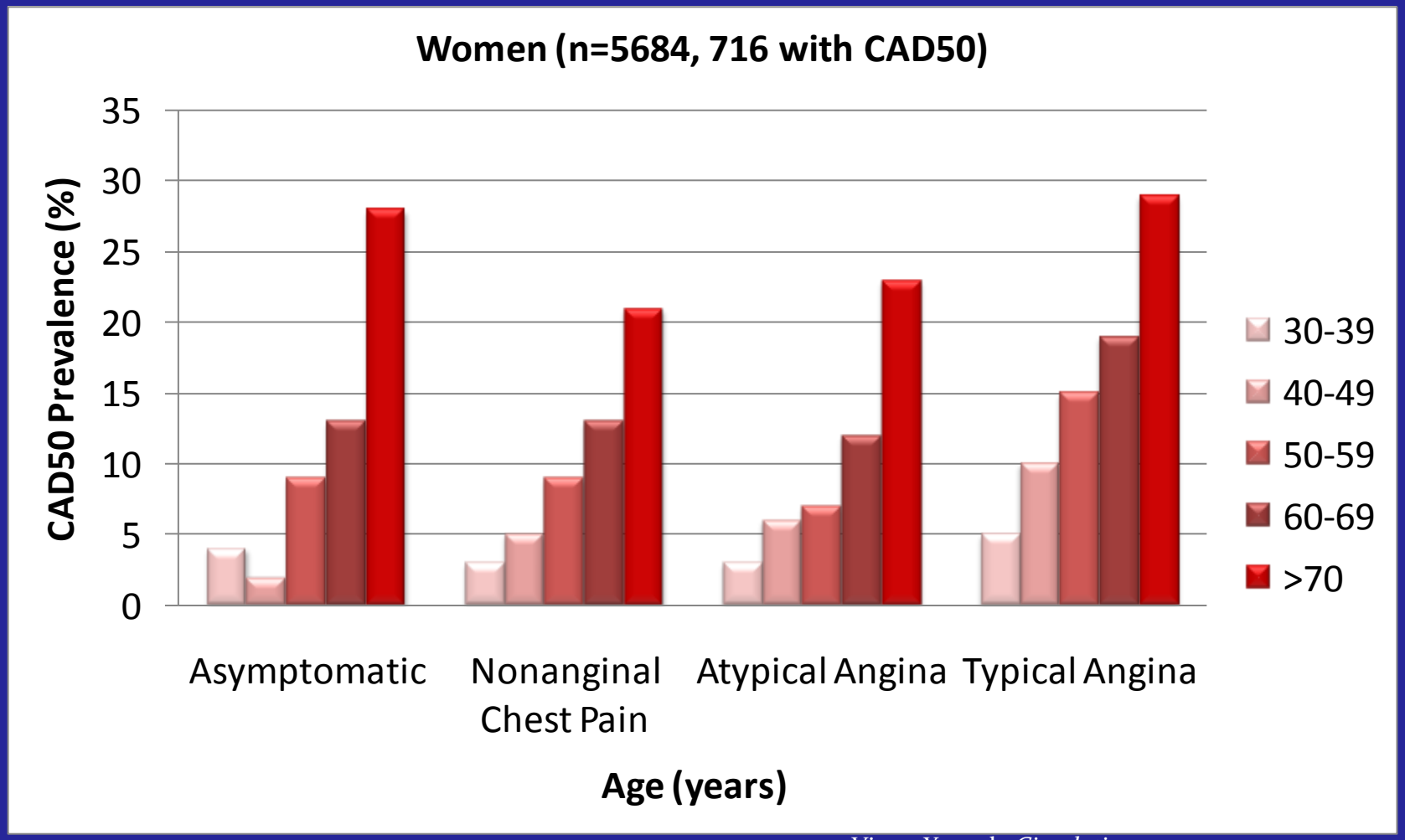
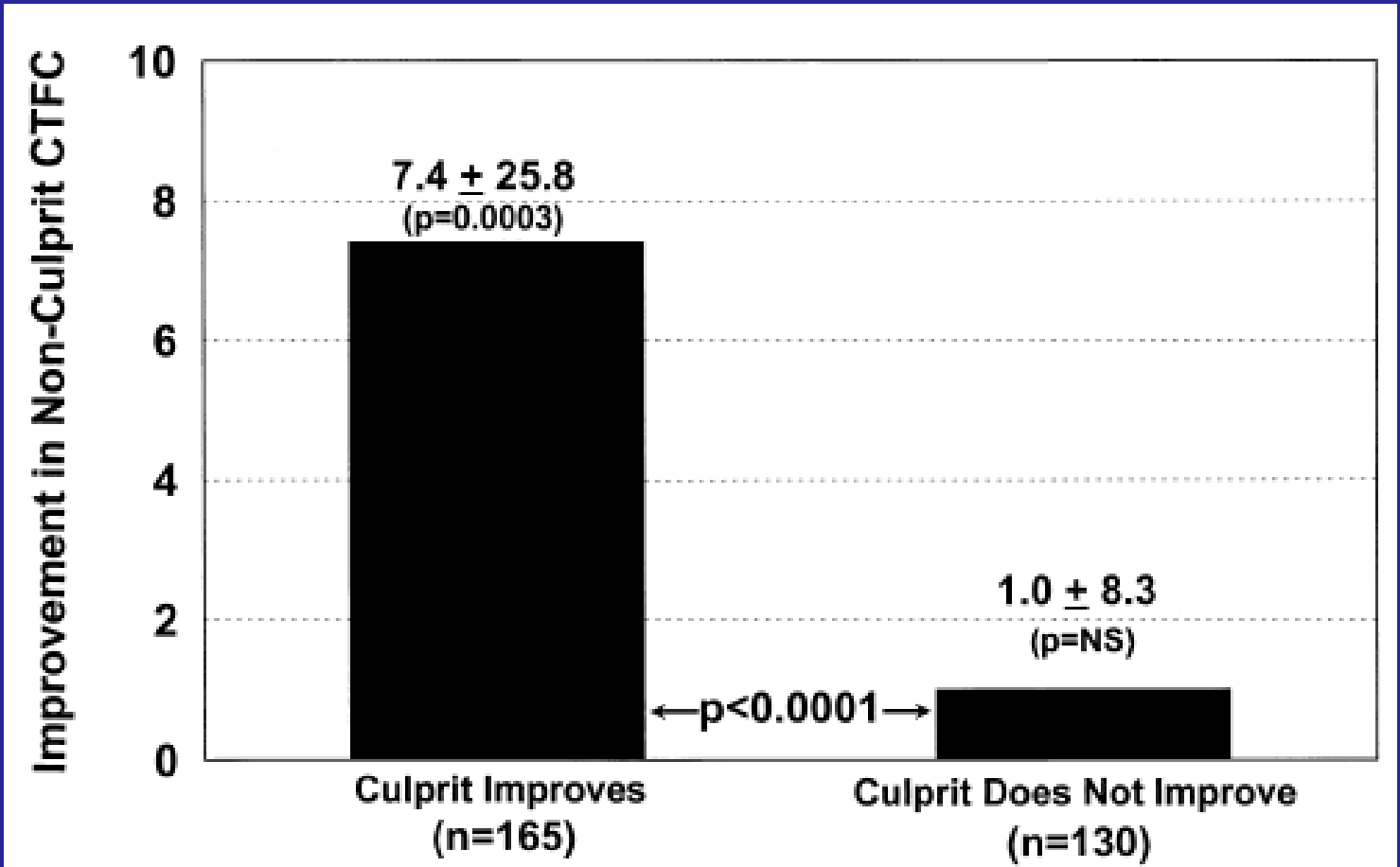


Victor Y. et al.; *Circulation. 2011;124:2423-2432*

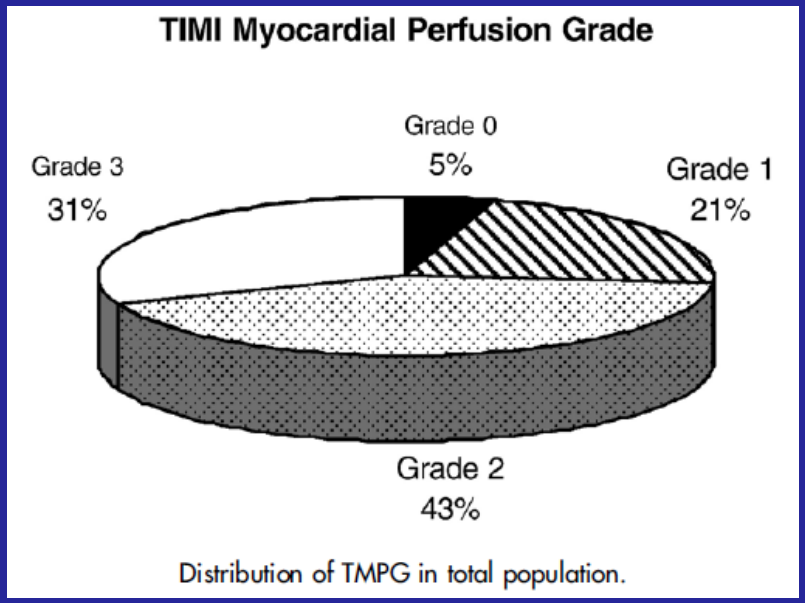
Impaired coronary blood flow in nonculprit arteries in the setting of acut myocardial infarction

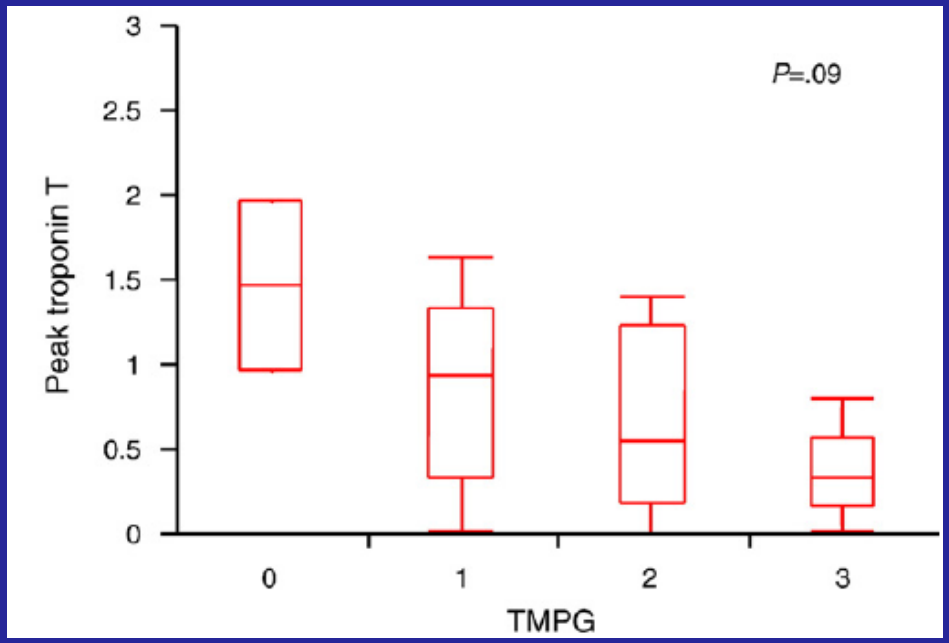


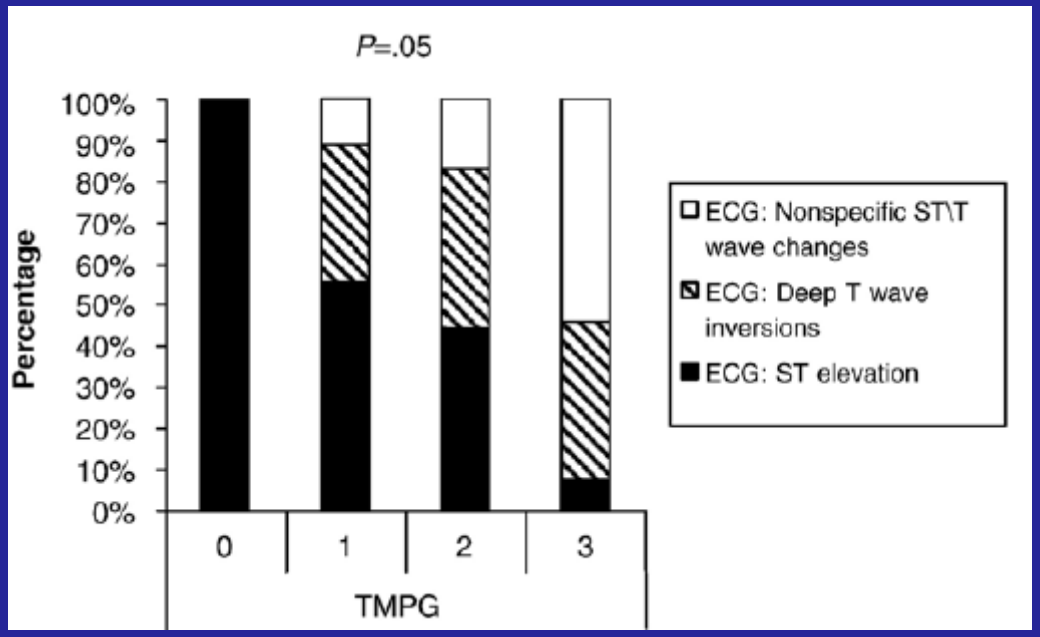
Relationship between improved nonculprit artery flow and improved culprit artery flow between 60 and 90 min after thrombolytic administration. When flow improved in the culprit artery, flow in the associated nonculprit artery improved by 7.4 frames (p = 0.0003), but when flow in the culprit artery did not improve, there was no significant improvement in nonculprit artery flow (1.0 frame, p = NS

Gibson MC et al. J Am Coll Cardiol 1999; 34:974-982

Myocardial perfusion in apical ballooning syndrome: Correlate of myocardial injury







TMPG= TIMI myocardial perfusion grade
TMPG 0- minimal or no myocardial perfusion;
TMPG 1-dye stains the myocardium and the stain persists on the next injection;
TMPG 2-dye enters the myocardium but washes out slowly so that dye is strongly persistent at the end of the injection;
TMPG 3-normal entrance and exit of dye in the myocardium.

Elesber a et al. Am Heart J 2006; 152:469

Chest Pain and Normal Coronary Angiograms
Diagnosis of Vascular Dysfunction

This is really were the controversy is.

Consistent with the notion that women are protected against CHD, they present with

-Less coronary narrowing

-Preserved LV function

But, often, they have

-Reduced Coronary Flow Reserve

A variety of questions are relevant to clinical decision-making

-How can vascular dysfunction be tested?

-Is vascular dysfunction a prognostic marker?

How can vascular dysfunction be tested?

- Bugiardini et al. J Am Coll Cardiol 1993 Abnormal Tl-201 perfusion
- Yoshio et al. J Am Coll Cardiol 1993 Abnormal LV function radionuclide
- Reis SE (WISE) J Am Coll Cardiol 1999 Abnormal coronary flow velocity (intracoronary adenosine/doppler)
- Buchtal (WISE) N Engl J Med 2000 Abnormal Phosphocreatine/ATP ratio (MRI spectroscopy)
- Buffon et al. Am J Physiol 2001 Abnormal lipid hydroperoxide and conjugated dienes production
- Panting et al. N Engl J Med 2002 Abnormal subendocardial perfusion by MRI
- Doyle (WISE) J Cardiovasc Magn Reson. 2003 Abnormal myocardial flow reserve by MRI

Assessing the Causes of Reduced Coronary Flow Reserve

- There are a number of likely causes for impairment of coronary flow reserve in patients with non-obstructive coronary angiograms.
- Impaired coronary flow reserve does not necessarily mean endothelial vascular dysfunction, because the abnormality could reside in the endothelium-independent response.
- Dysfunction of the endothelium-dependent vasodilatation is strictly related to early atherogenetic process.

Women with non-obstructive coronary artery disease and normal angiograms: remarks

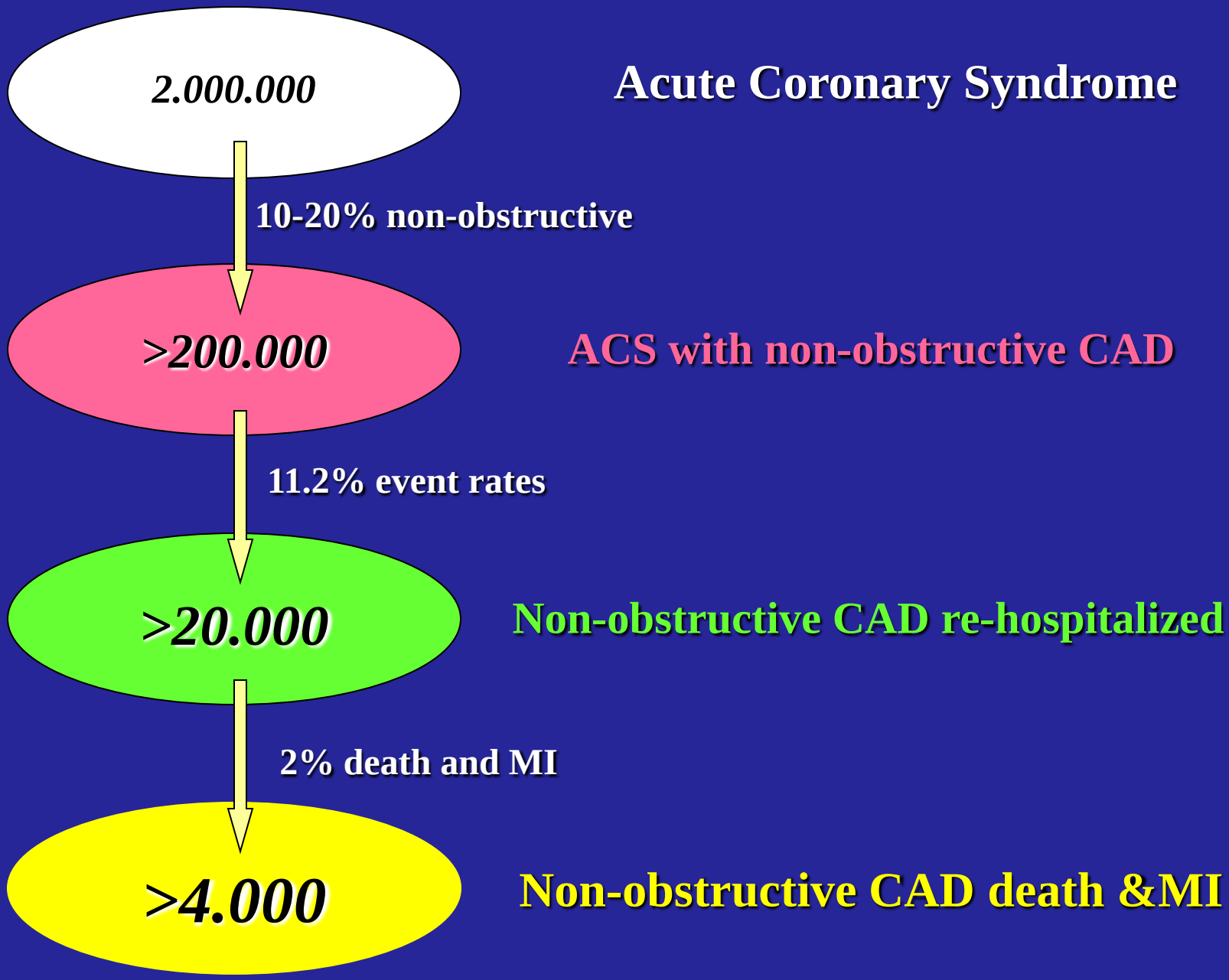
(1) Women with rather stable symptoms or suspected angina have a prognosis that is not as benign as previously thought.

(2) Assessment of severe endothelial dysfunction may identify groups who will develop atherosclerosis and subsequent events (up to 14% at 4 year follow-up).

(3) Women with acute coronary syndrome have a relatively poor prognosis at 1-year follow-up, with 2% rate of MI and death and 11.2% of recurrence of UA.

(4) The TIMI Risk Score could be used in clinical practice to predict the likelihood of non-obstructive CAD patients to develop future coronary events. Up to 30% of patients have a score $\geq$ 3-4, and have 2.8-4% of death and myocardial infarction annually.

(5) Aggressive medical treatment is warrant in non-obstructive coronary artery disease and normal angiograms especially in women with ACS.


2.000.000
Acute Coronary Syndrome
10-20% non-obstructive
>200.000
ACS with non-obstructive CAD
11.2% event rates
>20.000
Non-obstructive CAD re-hospitalized
2% death and MI
>4.000
Non-obstructive CAD death &MI

Non-obstructive CAD in ACS Trials: Misperception and Gender Bias.

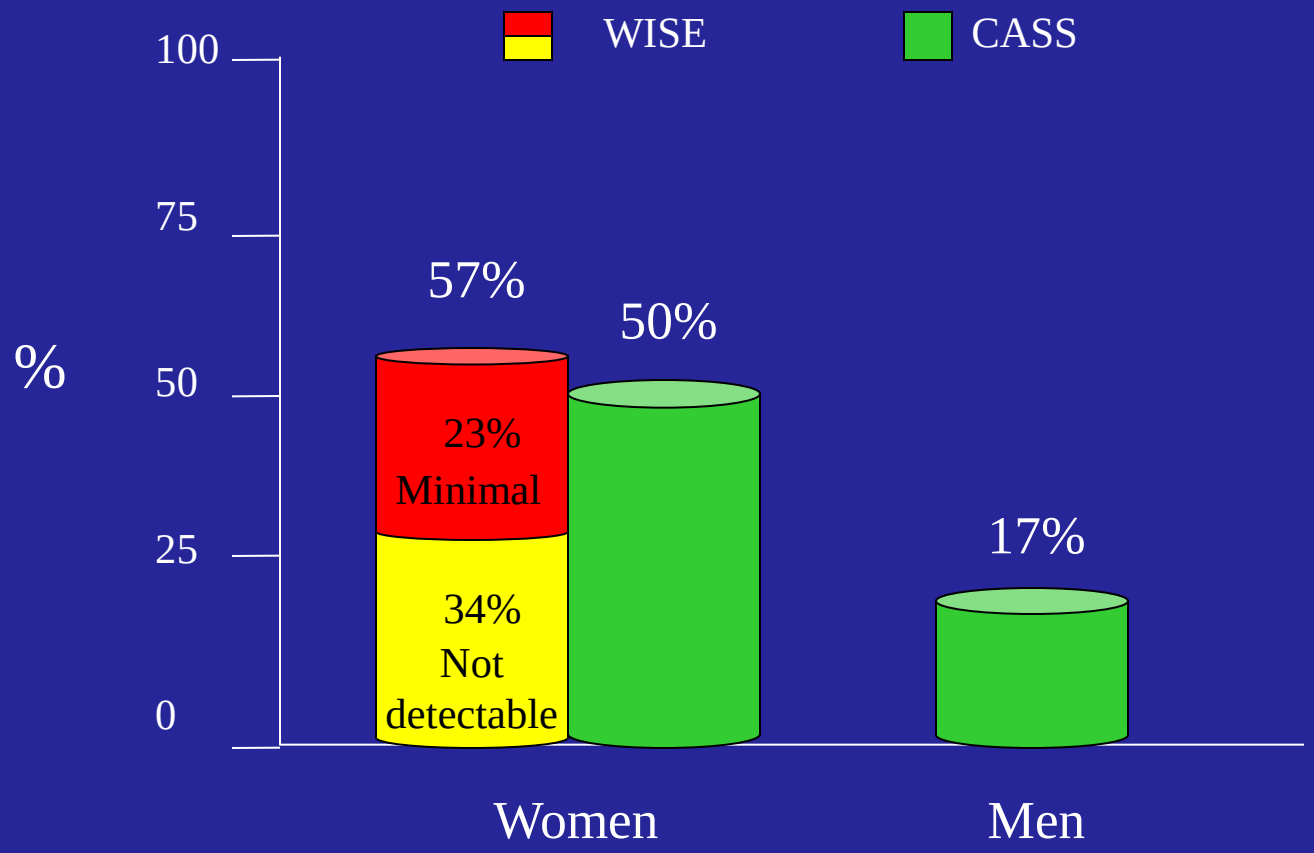
Many patients had been catheterized before the entry into the study in OPUS-TIMI 16 and PROVE IT-TIMI 22 and were not enrolled if they had non-obstructive coronary disease.

Woman were more often excluded.

There is not awareness that atherosclerosis poses a serious health risk even in its mild form, especially in women

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



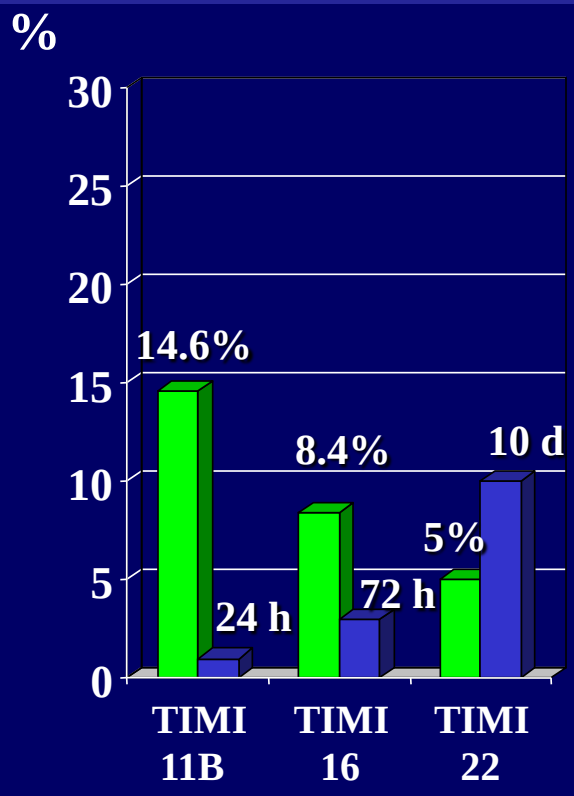
Chaitman BR et al *Circulation 1981;64:360-367*

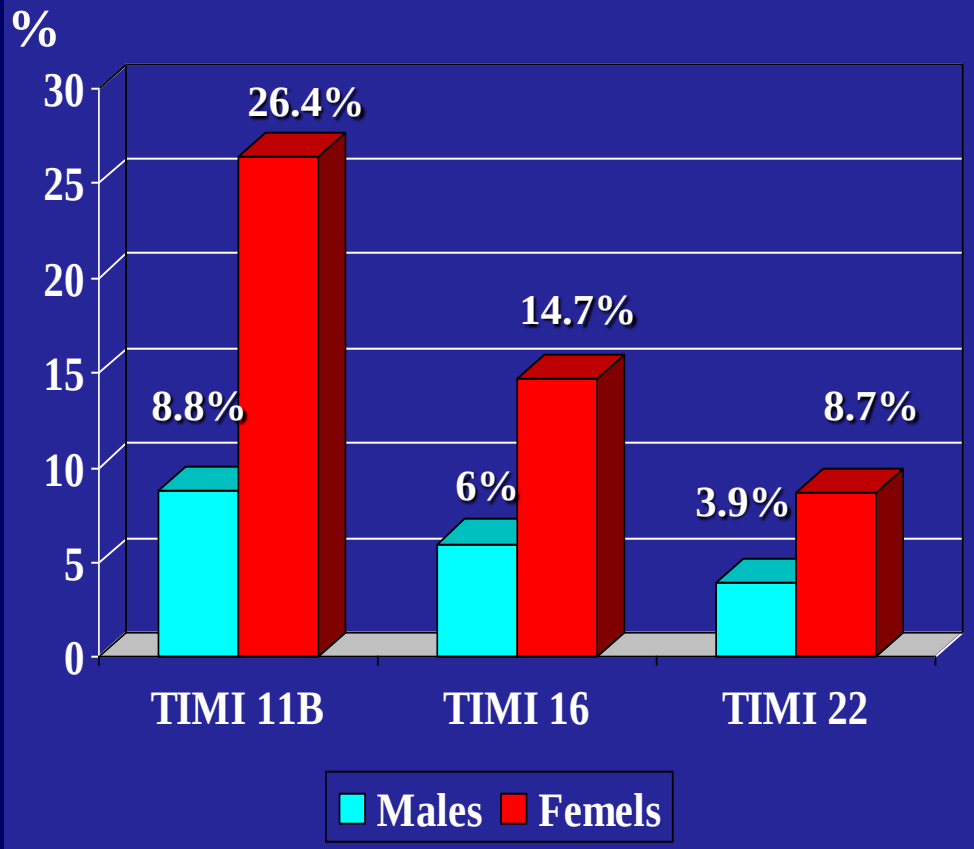
Sharaf BL et al *Am J Cardiol 2001;87:937-41*

Prevalence of Non-obstructive CAD in ACS Trials

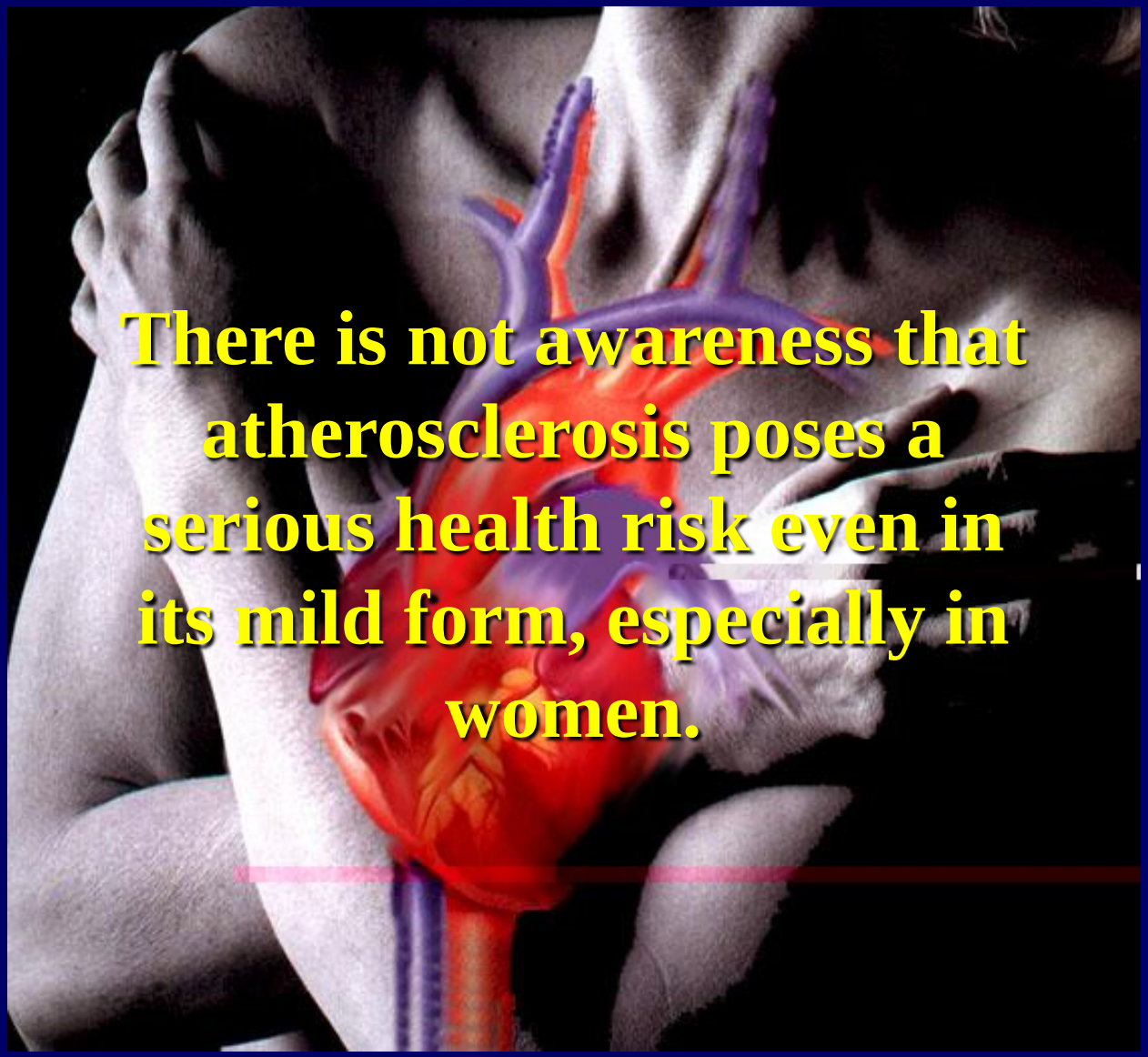
- Many patients had been catheterized before the entry into the study in OPUS-TIMI 16 and PROVE IT-TIMI 22 and were not enrolled if they had non-obstructive coronary disease.
- Women were more often excluded.
- There is not awareness that atherosclerosis poses a serious health risk even in its mild form, especially in women.

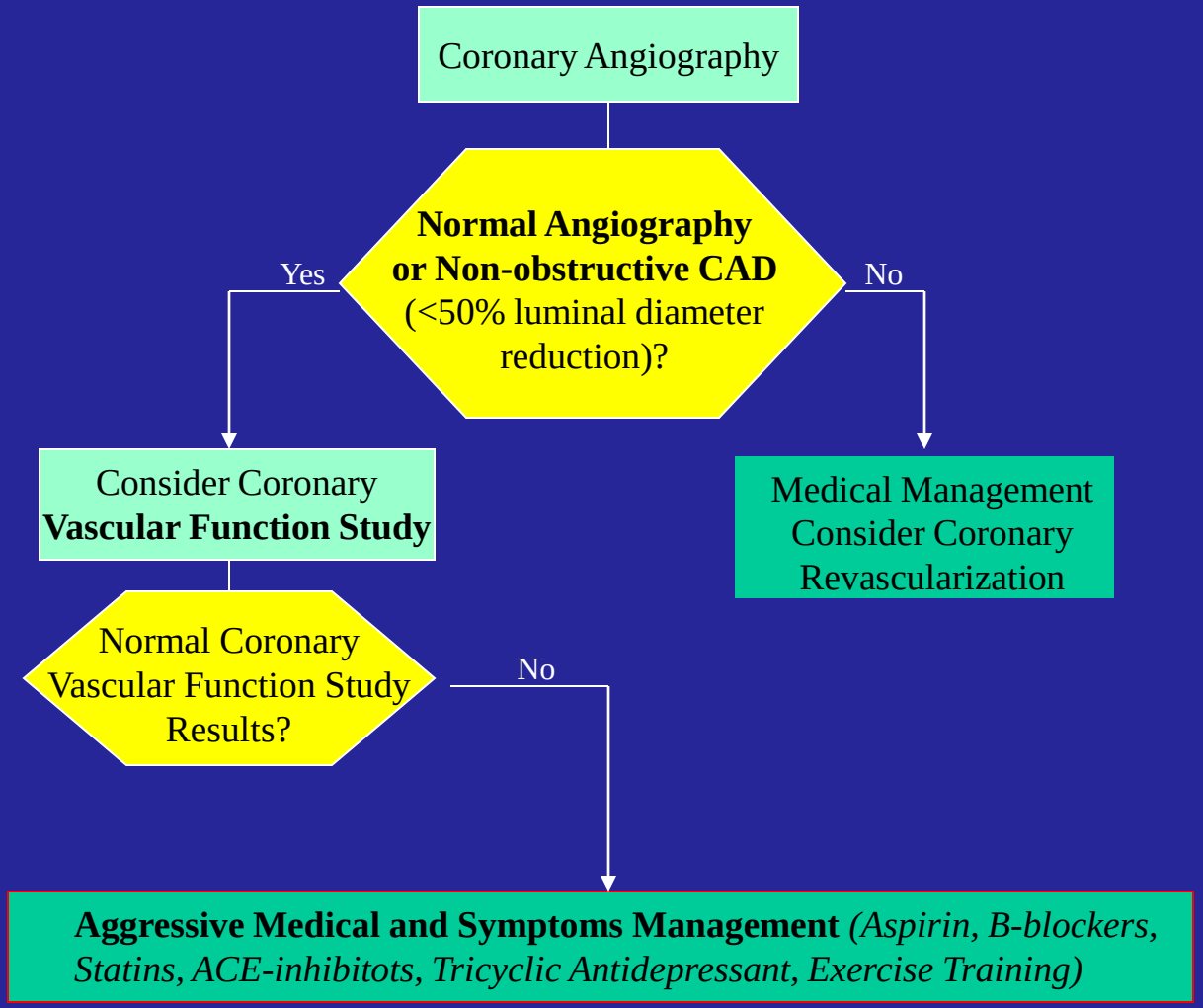
FREQUENCY of NON-OBSTRUCTIVE CAD
in TIMI 11B, TIMI 16, TIMI 22





TIMI investigators, 2005


There is not awareness that atherosclerosis poses a serious health risk even in its mild form, especially in women.



Modified from Bugiardini R, Bairey Merz CN. JAMA. 2005;293:477

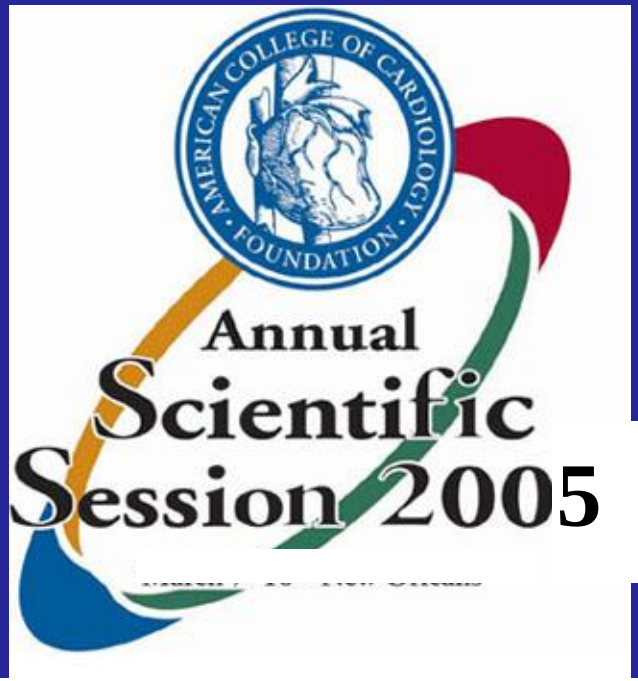
Myocardial Flow Reserve Index: An NHLBI WISE Study

	Full population n=184	I_{MFRI} n=55	A_{MFRI} n=129
Risk factors			
Former cigarette smoker	31%	33%	30%
Current cigarette smoker	20%	24%	18%
Family history of CAD	65%	69%	63%
History of hypertension	67%	75%	63%
History of diabetes	26%	35%	22%
Hystory of dyslipidemia	60%	62%	59%
Extent of coronary disease (≥ 70% stenosis)			
O Vessel disease	86%	78%	89%
1 Vessel disease	12%	20%	9%*
2 Vessel disease	2%	2%	2%
3 Vessel disease	0%	0%	0%

A_{MFRI}: ≥ 2 out of 12 myocardial regions had an MFRI ≥ 1.5

p <0.05 between A_{MFRI} and I_{MFRI}

Doyle M. et al. *J Cardiovasc Magn Reson. 2003;5:475-485*



Chest Pain and a Normal Coronary Angiogram

Raffaele Bugiardini

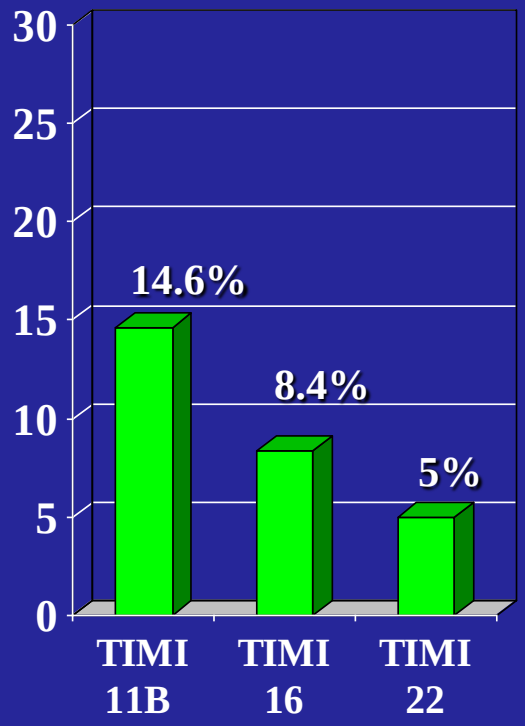
Dipartimento di Medicina Interna, Cardioangiologia, Epatologia

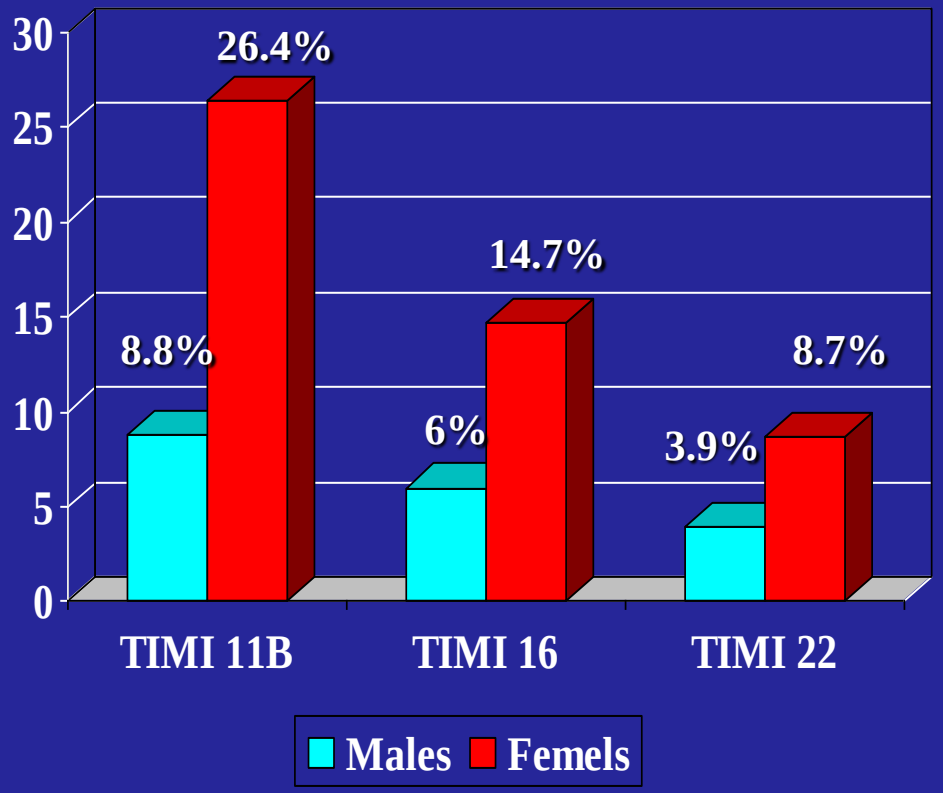
University of Bologna - Italy

Research on normal or near normal angiography

- Since 1984, more women than men die each year from heart disease.
- Women often do not have obstructive CAD, so they experience myocardial ischemia by a pathophysiologic mechanism different from that of the majority of men with obstructive CAD.
- The assumption is that part of the failure to translate in women what is generally known to be of therapeutic benefit into clinical practice could reflect a lack of information on prognosis and treatment of non-obstructive CAD and normal angiography in the usual clinical settings.

FREQUENCY of NON-OBSTRUCTIVE CAD
in TIMI 11B, TIMI 16, TIMI 22





TIMI investigators, 2005

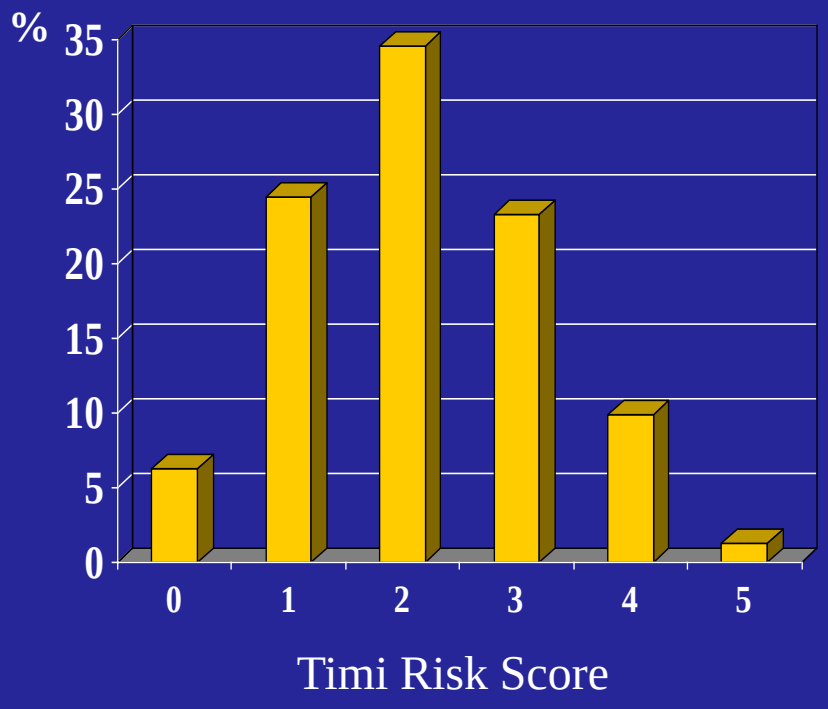
Hazard Ratios for baseline variables of TIMI Risk Score in TIMI 11B, OPUS-TIMI16, and PROVE-IT/TIMI 22 patients with non-obstructive CAD

	HR	95% CI		p
Age >65 y	**0.70**	**0.41**	**1.20**	0.2
At least 3 risk factors	**0.96**	**0.52**	**1.81**	0.9
ST-deviation	**1.24**	**0.75**	**2.04**	0.4
Use of aspirin in last 7 days	**2.61**	**1.52**	**4.48**	**0.001**
Elevated serum markers	**0.83**	**0.48**	**1.40**	0.5
Severe angina symptoms (>2events in last 24h)	**1.56**	**0.95**	**2.58**	0.08

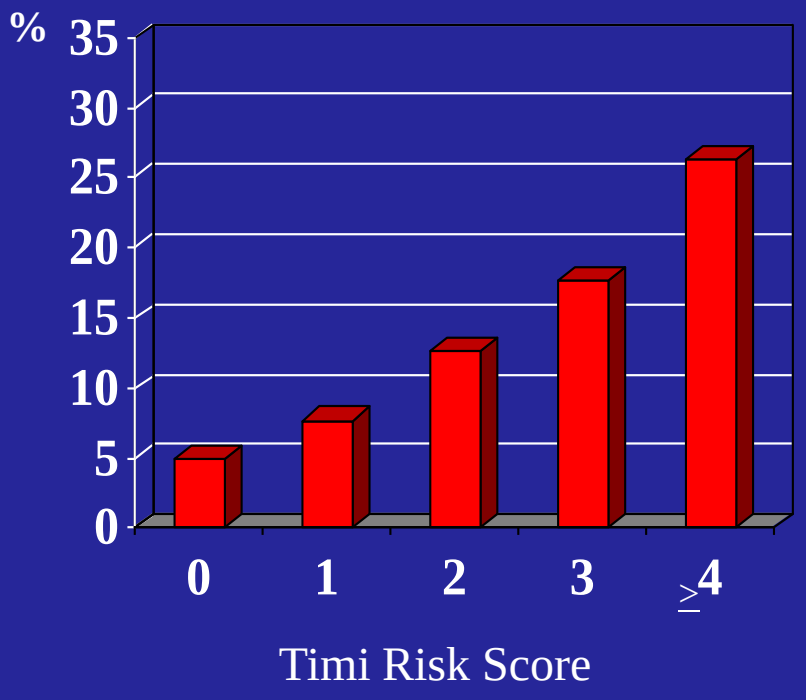
TIMI investigators, 2005

TIMI Risk Score 1-year follow-up

Percent of Patients



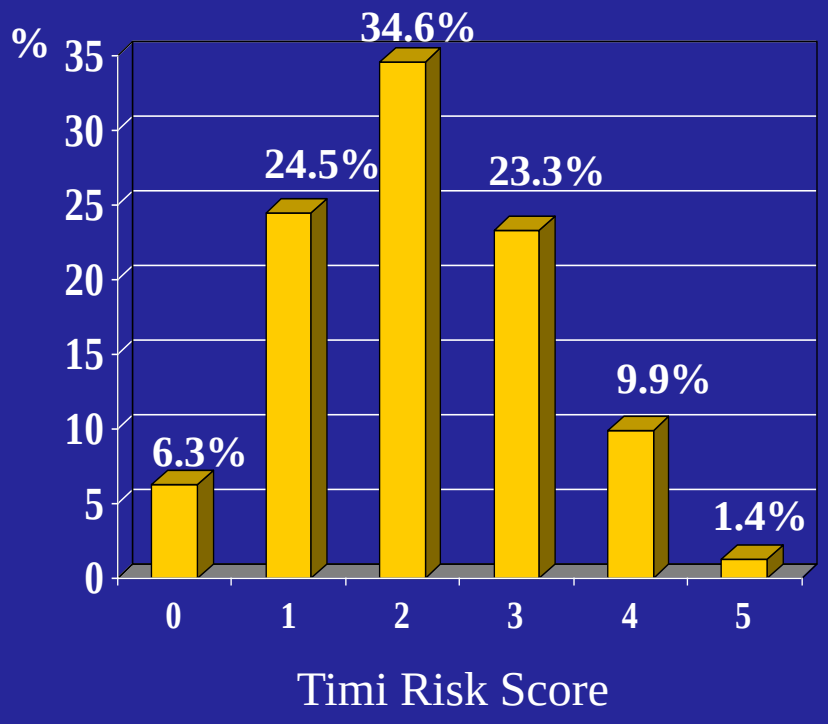
Event Rates



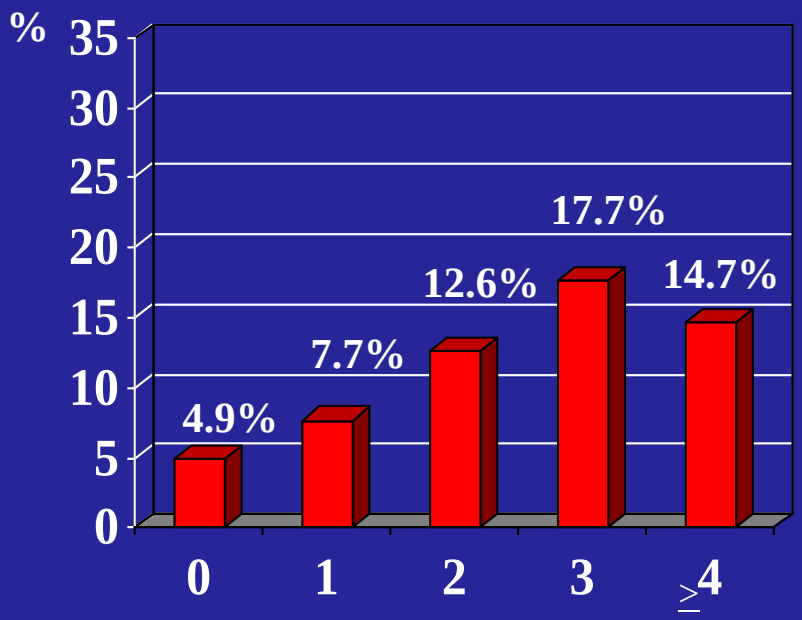
TIMI investigators, 2005

Prognostic Value TIMI Risk Score 1-year follow-up

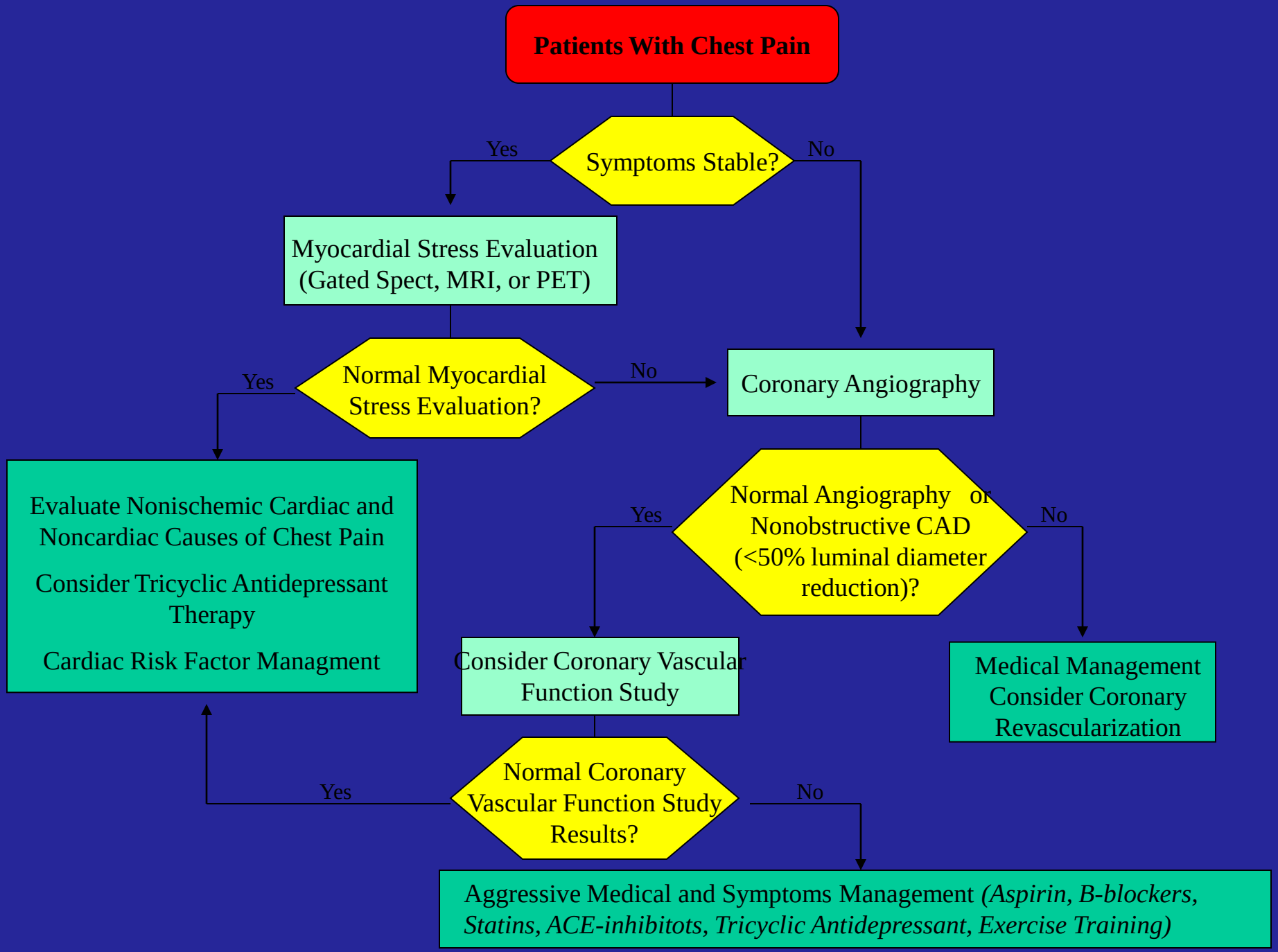
Percent of Patients



Event Rates



TIMI investigators, 2005


Patients With Chest Pain
Symptoms Stable?
Yes
No
Myocardial Stress Evaluation (Gated Spect, MRI, or PET)
Normal Myocardial Stress Evaluation?
Yes
No
Coronary Angiography
Evaluate Nonischemic Cardiac and Noncardiac Causes of Chest Pain
Consider Tricyclic Antidepressant Therapy
Cardiac Risk Factor Managment
Normal Angiography or Nonobstructive CAD (<50% luminal diameter reduction)?
Yes
No
Consider Coronary Vascular Function Study
Medical Management Consider Coronary Revascularization
Normal Coronary Vascular Function Study Results?
Yes
No
Aggressive Medical and Symptoms Management (Aspirin, B-blockers, Statins, ACE-inhibitots, Tricyclic Antidepressant, Exercise Training)

Annual Scientific Session 2004

7-10 March New Orleans

Chest Pain With Normal Coronary Angiograms: Lessons From the WISE Trial

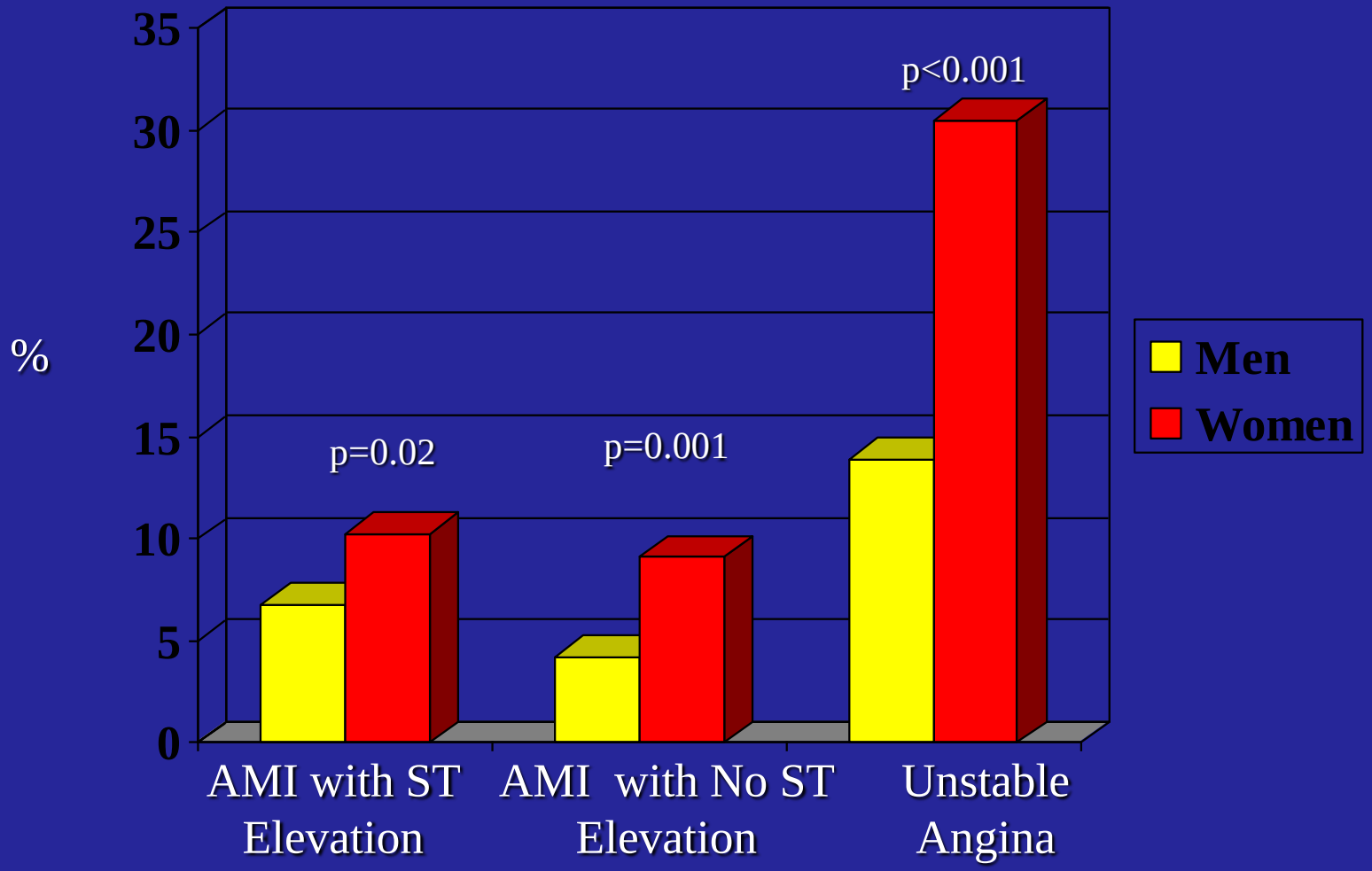
Raffaele Bugiardini, MD, FAHA, FACC

Dipartimento di Medicina Interna, Cardioangiologia, Epatologia
Università Alma Mater Studiorum- Bologna

Italy

Prevalence of Non Obstructive CAD among Women with Acute Coronary Syndrome

GUSTO IIb



Hochman JS *N Engl J Med 1999;341:226-232*

CHEST PAIN CHARACTERISTICS

of Women with Myocardial Ischemia and Normal Angiograms

	Ach-positive*	Ach-negative	
Location favorig ischemic origin, %	**82 %**	**72 %**	**ns**
Duration, min	**17.9 ± 12.3**	**28.9 ± 14**	**<0.01**
Intensity (scale from 1 to 4)	**2.0 ± 0.9**	**2.8 ± 1.1**	**<0.02**
Setting in which occurs,%			
Rest	**36%**	**28%**	**ns**
Exertional/Pycological Stress	**41%**	**40%**	**ns**
Rest and Exertional	**23%**	**32%**	**ns**
Episodes per week, n	**7.9 ± 5.3**	**9.1 ± 5.5**	**ns**
Labeled "typical" by cardiologist, %	**64%**	**52%**	**ns**

* 59% of patients in Ach-positive group developed angiographically visible atherosclerosis at 10 year follow- up

Bugiardini et al. Circulation 2004;109:2518

CARDIOVASCULAR DISEASE IN WOMEN WITH NCA INCREASING ATTENTION

Women with chest pain and normal coronary arteries at angiography were first described 37 years ago.
(Likoff et al NEJM 1967).

Focus of scientific attention only in the past 10 to 15 years.

Recent interest stimulated by studies which, starting in early 1990', reported higher death rate in in specific subsets of women with non obstructive CAD as well as to report differences in vascular function. (Quyyumi AA et al. Circulation. 1992)

Tendency to disregard these women relative to their symptoms was in part due to perception of a more benign course in women.

Clinical Methods for Assessing Endothelium-Dependent Dilation

Coronary Arteries

- Epicardial Artery Diameter Δ with ACh
- CBF Δ with ACh
- Epicardial Artery Diameter Δ with Adenosine

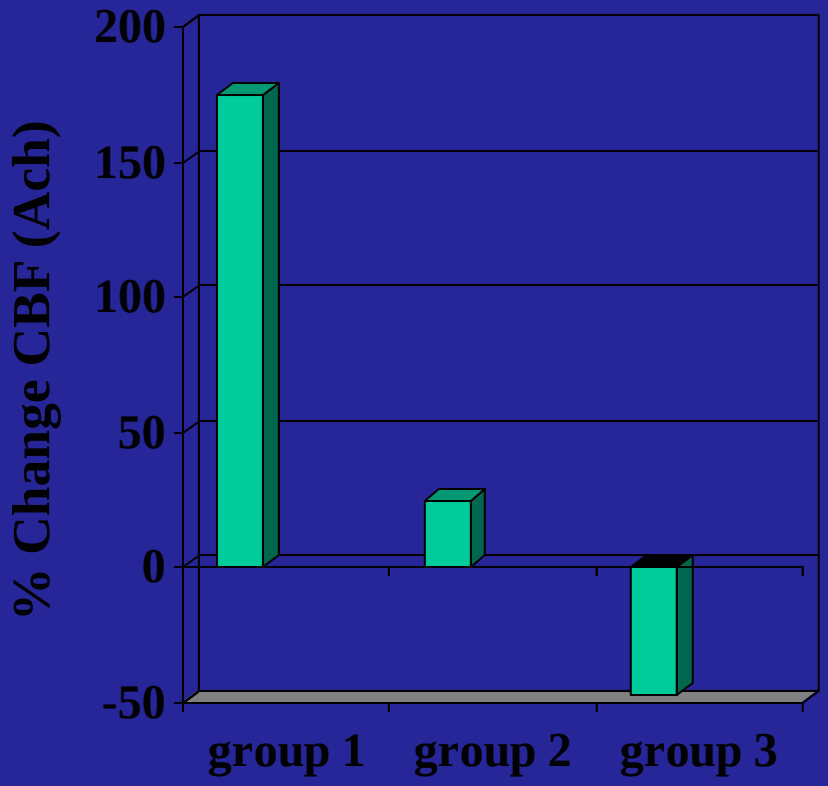
Forearm

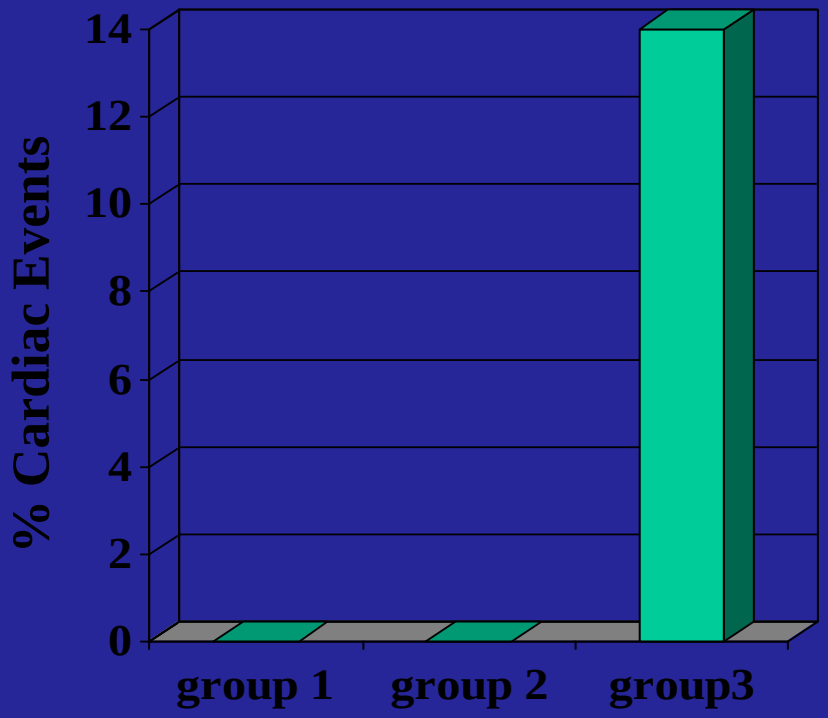
- Brachial Artery Diameter Δ with Arterial Occlusion
- Forearm Blood Flow with ACh

Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr, Lerman A.
Circulation 2000;101:948-954.

- Follow-up (average 28-month) was obtained in 157 patients
- Patients had angiographically coronary artery lesions <40% lumen diameter stenosis without evidence of coronary spasm.
- Exclusion criteria included history of myocardial infarction, percutaneous coronary revascularization, CABG, unstable angina pectoris, history of variant angina
- A normal coronary endothelium-dependent function was defined as an increase in CBF of >50%. in response to acetylcholine (10-4 mol/L).

Long-term Follow-up of Patients with Mild Coronary Artery Disease and Endothelial Dysfunction





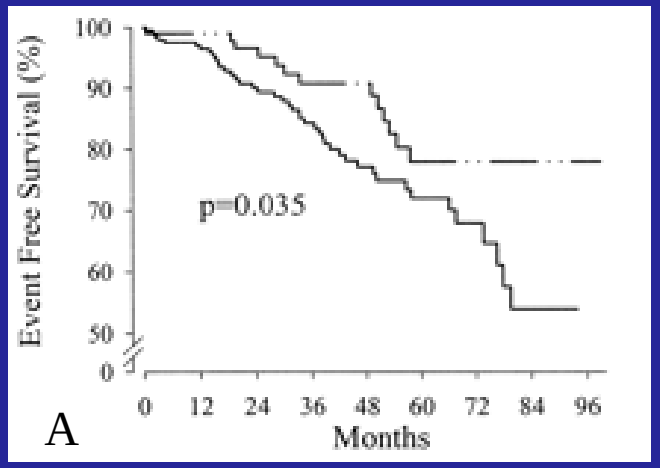
Suwaidi JA et al. Circulation 2000;101:948-954.

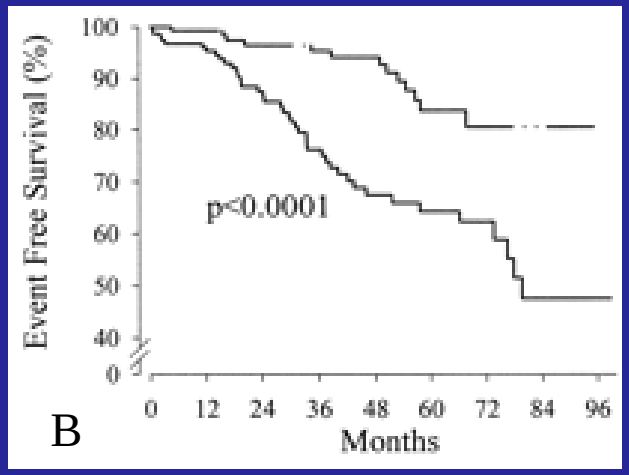
Halcox JP, Schenke WH, Zalos G, et al.
Circulation 2002;106:653-658.

- Follow-up (average 28-month) was obtained in 308 subjects undergoing cardiac catheterization for investigation of chest pain or abnormal noninvasive cardiac investigations
- Subjects who were referred for revascularization after cardiac catheterization were excluded
- Subjects with unstable angina, recent myocardial infarction (<3 months), NYHA class III to IV heart failure, or unrevascularized 3-vessel or left main disease were excluded.
- Coronary endothelium-dependent function was assessed by changes in CBF and vessel diameters in response to acetylcholine (10-6 mol/L).

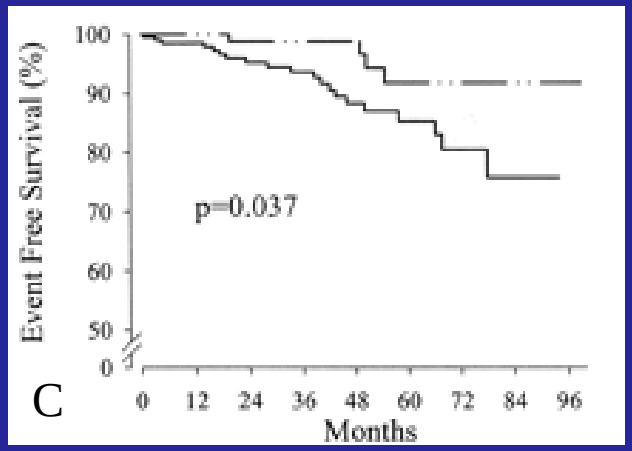
Relationship between endothelium-dependent coronary vascular function and cardiovascular prognosis

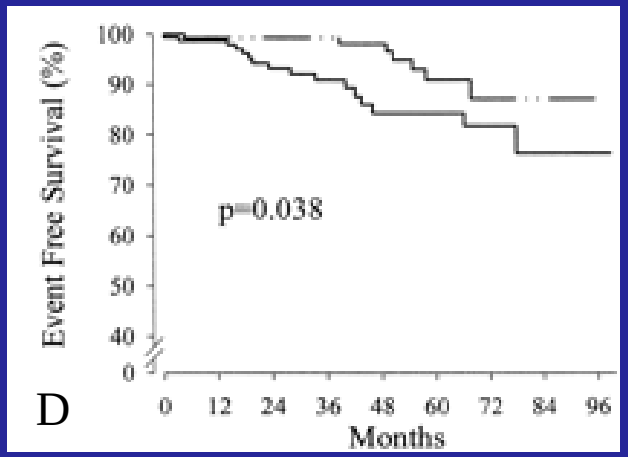
Acute cardiovascular events or coronary revascularization procedure





Sudden cardiac death, myocardial infarction, or stroke





–··– represents tertile with greater fall in CVR (A and C) or epicardial vasodilation (B and D) with Ach

— 2 tertiles with lesser fall in CVR (A and C) or epicardial vasoconstriction (B and D) with Ach

Halcox JPJ et al. Circulation,2002;106:653-658

von Mering GO, Arant CB, Wessel TR, et al. (WISE).

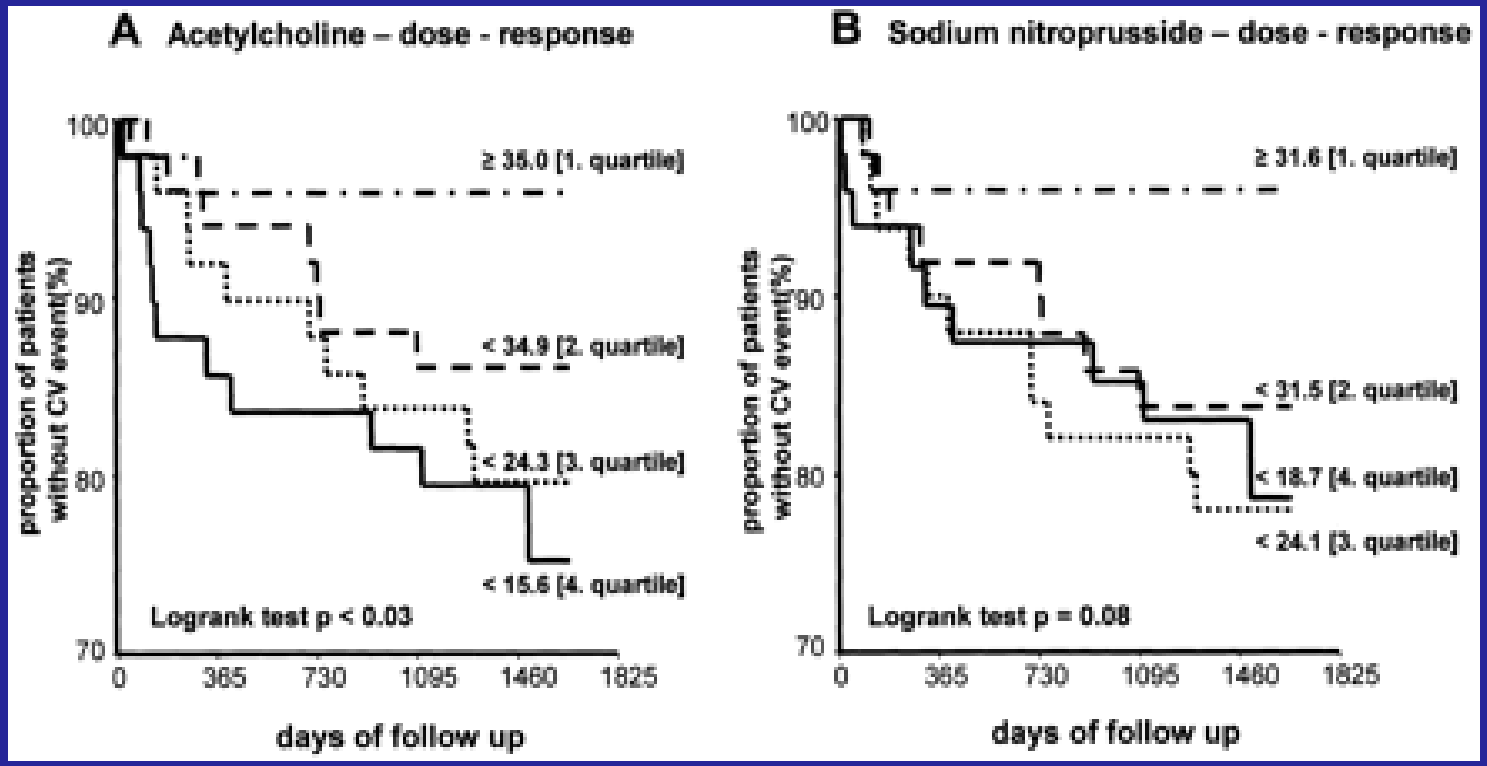
Circulation 2004;109:722-725.

- Follow-up (average 48-month) was obtained in 168 women undergoing cardiac catheterization for investigation of suspected myocardial ischemia.
- coronary reactivity testing was performed in an epicardial coronary artery free of obstructive CAD (<50% diameter).
- Seventy-five percent had no or only mild epicardial coronary artery disease (CAD).
- Coronary endothelium-dependent function was assessed by changes in CBF and vessel diameters in response to acetylcholine (10-6 mol/L).

Fichtlscherer S, Breuer S, Andreas M. Zeiher AM. Circulation. 2004;110:1926-1932.

- Follow-up (average 47-month) was obtained in 198 patients undergoing cardiac catheterization for unstable angina.
- Patients with impaired left ventricular ejection fraction (<45%) as assessed by echocardiography were excluded.
- Forearm blood flow (FBF) responses to acetylcholine (ACH; 10 to 50 µg/min) were measured by venous occlusion plethysmography before hospital discharge within 5 days of an episode of an ACS.

Prognostic value of systemic endothelial dysfunction in patients with acute coronary syndromes



Fichtlscherer S et al. Circulation 2004;110:1926-32

Long-term Prognosis of Non-obstructive Coronary Artery Disease in the Setting of Acute Coronary Syndrome - PROVE IT-TIMI 22

Clinical events through follow-up (Kaplan-Meier rates)

	Obstructive CAD N=3325	Non Obstructive CAD N=178	p-value	Non Obstructive CAD Mild-CAD N=124	Non Obstructive CAD Normal N=54	p-value
Death - %	3.5	0.6	0.1048	0.9	0	0.5235
MI - %	7.4	1.2	0.0040	0.8	2.0	0.5328
Death or MI - %	10.4	1.9	0.0013	1.7	2.0	0.8823
Revascularization - %	19.6	4.9	<0.0001	6.0	2.0	0.2979
Unstable angina -%	4.3	2.4	0.2972	2.5	2.1	0.8464
Stroke - %	0.9	1.8	0.1920	1.7	2.1	0.8678
Primary endpoint* - %	26.8	9.7	<0.0001	10.2	8.3	0.7121

* Death/MI/UA/revascularization/stroke

Bugiardini R et al. in press

METHODS

STUDY POPULATION

42 women (mean age 51.6 ± 8.8)

Inclusion Criteria:

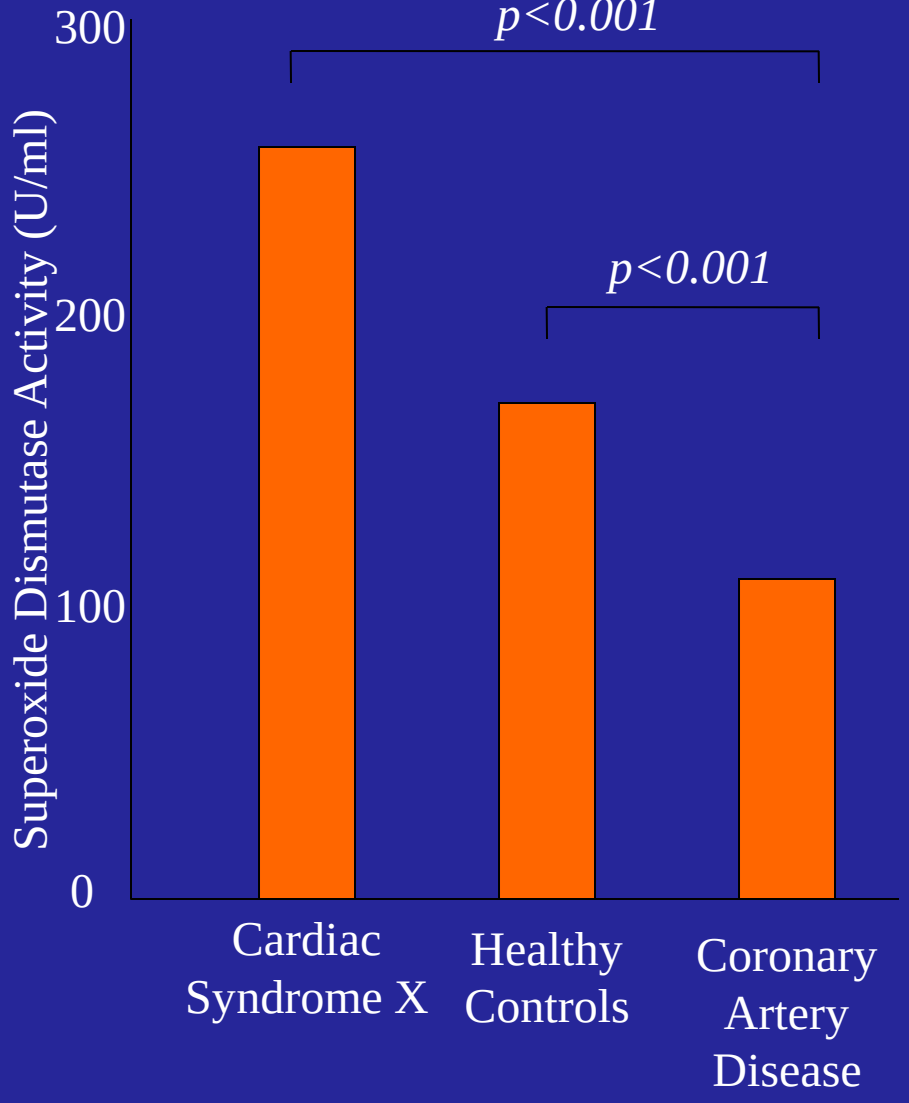
- de novo angina
- ECG ischemia during exercise stress test
- myocardial reversible perfusion defects (SPECT)
- normal angiograms.

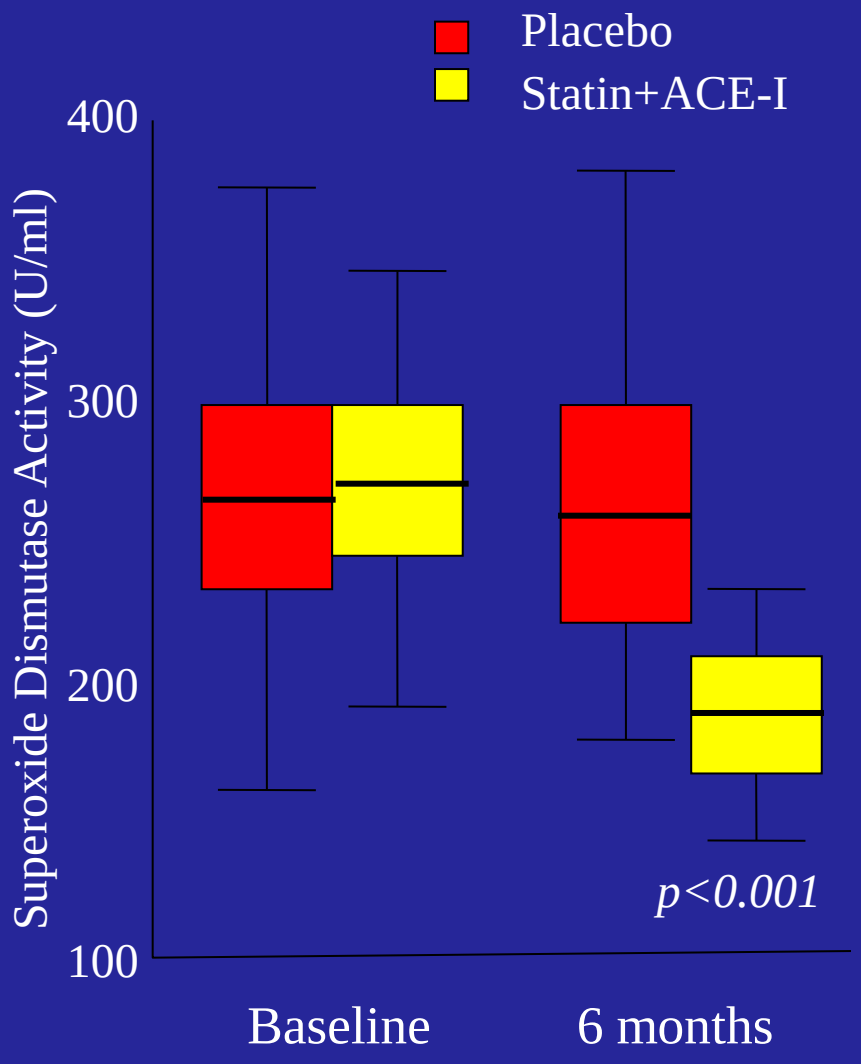
Exclusion Criteria:

- hypercholesterolemia and/or hypertriglyceridemia
- diabetes mellitus
- valvular heart disease
- cardiomyopathy

Bugiardini R et al. Circulation ***2004; 109:2518-2523***

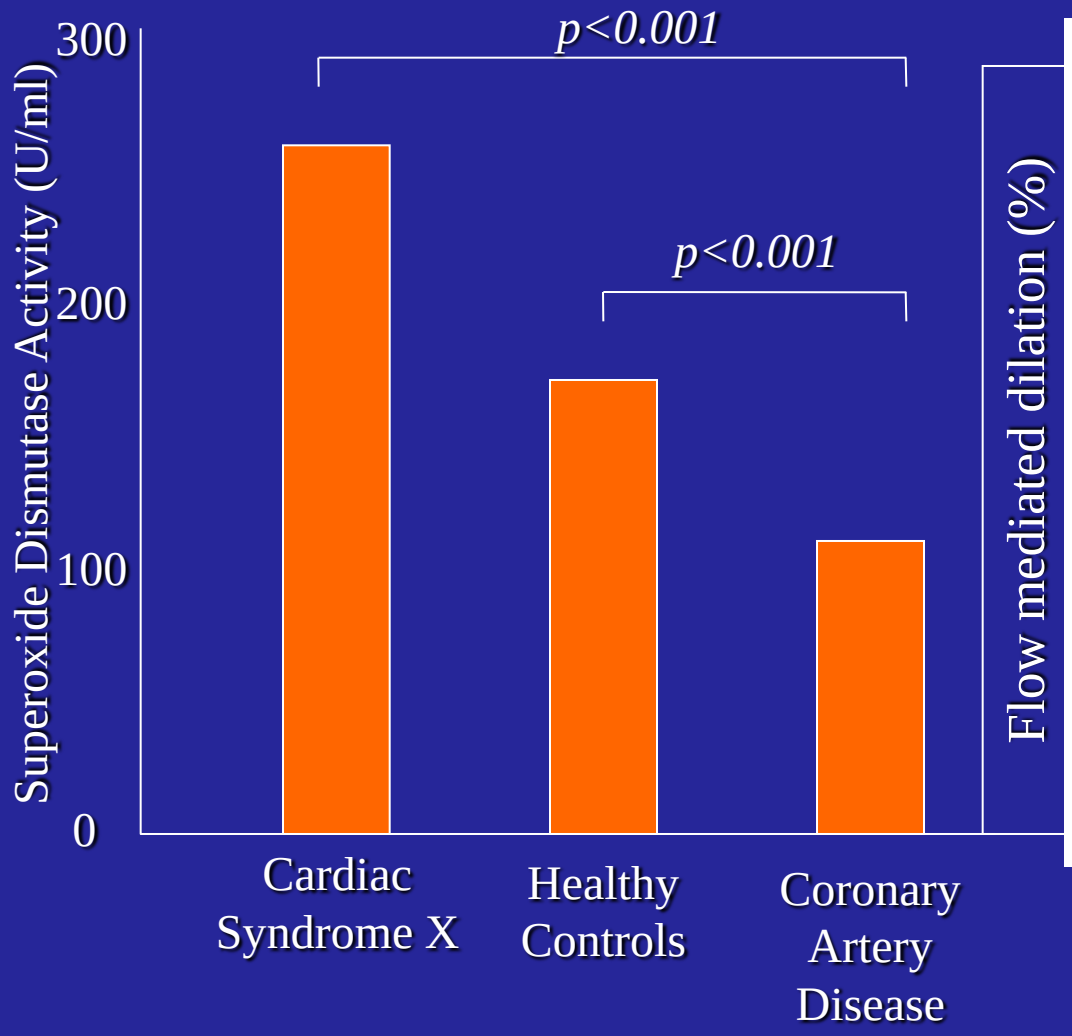
Superoxide Dismutase Activity

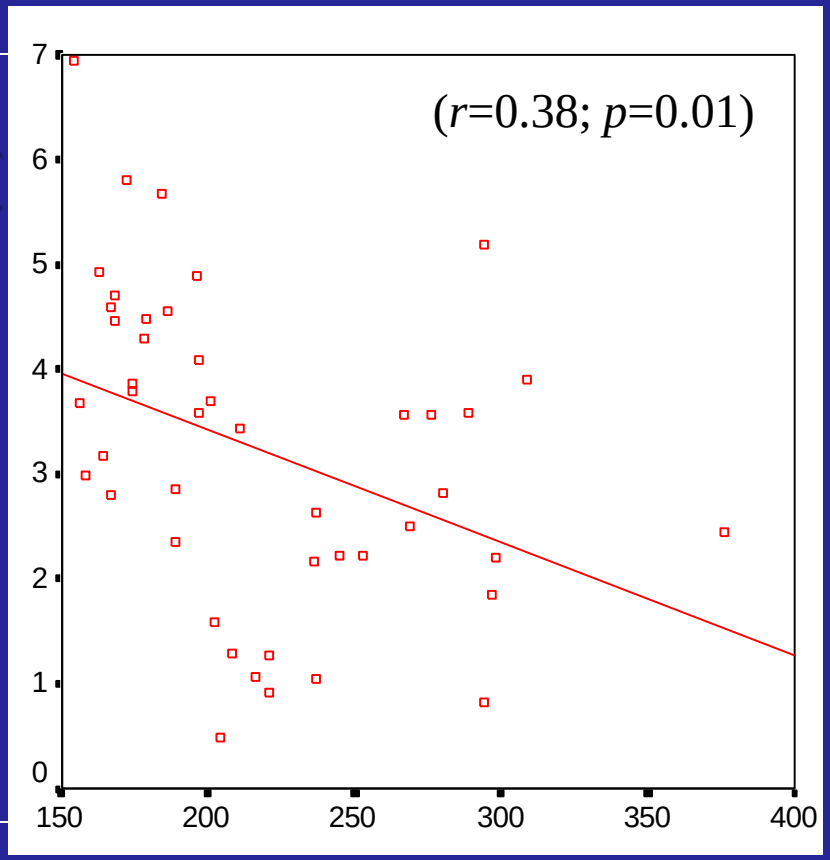




Pizzi C et al. *Circulation 2004;109:53-58*

Superoxide Dismutase Activity





Pizzi C et al. *Circulation 2004;109:53-58*