Silent Myocardial Ischemia

September 27, 2013

3rd Dubrovnik Cardiology Highlights


Milwaukee Calatrava Art Museum

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Medical College of Wisconsin

- Clinical Entity of Silent Myocardial Ischemia – Magnitude of the Problem
- Mechanism of Cardiac Pain and of Silent Ischemia
- Prognostic importance of Silent Myocardial Ischemia

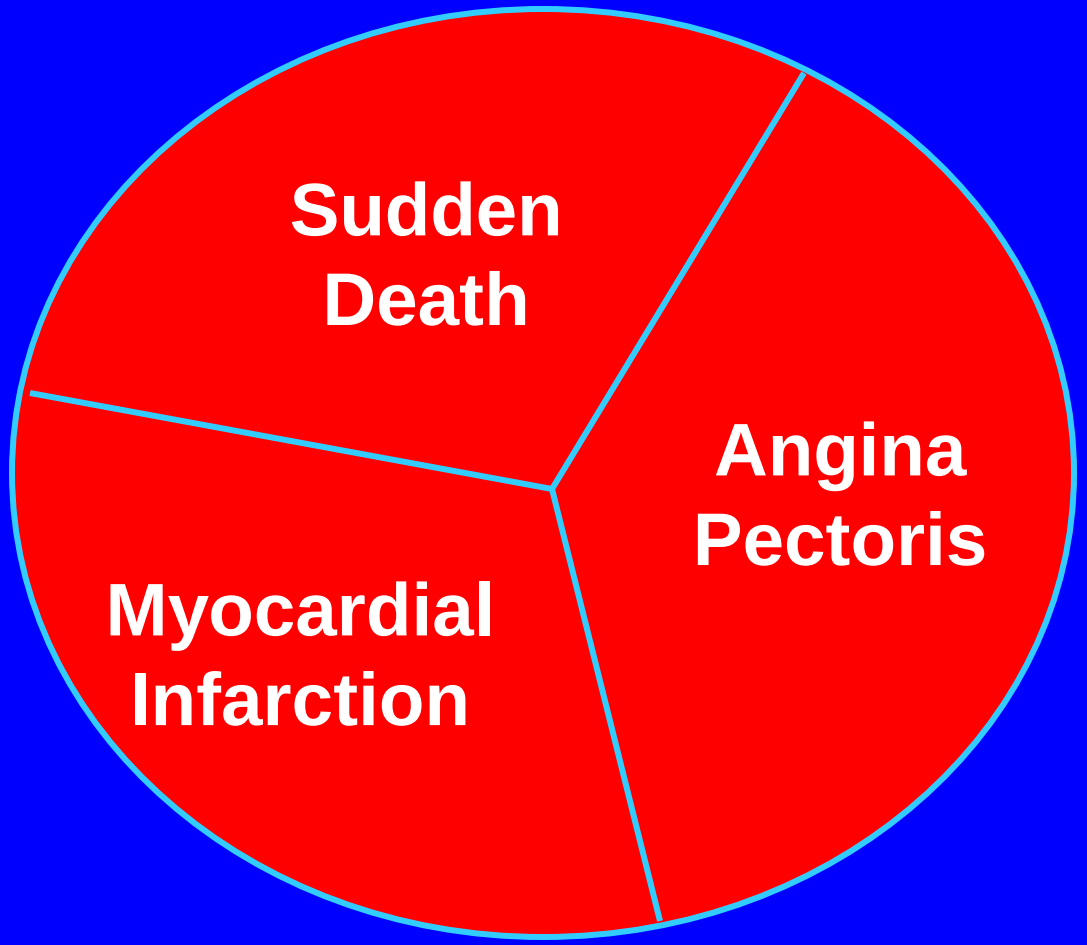
- Disclosures: Grant funding from NIH

Paradox

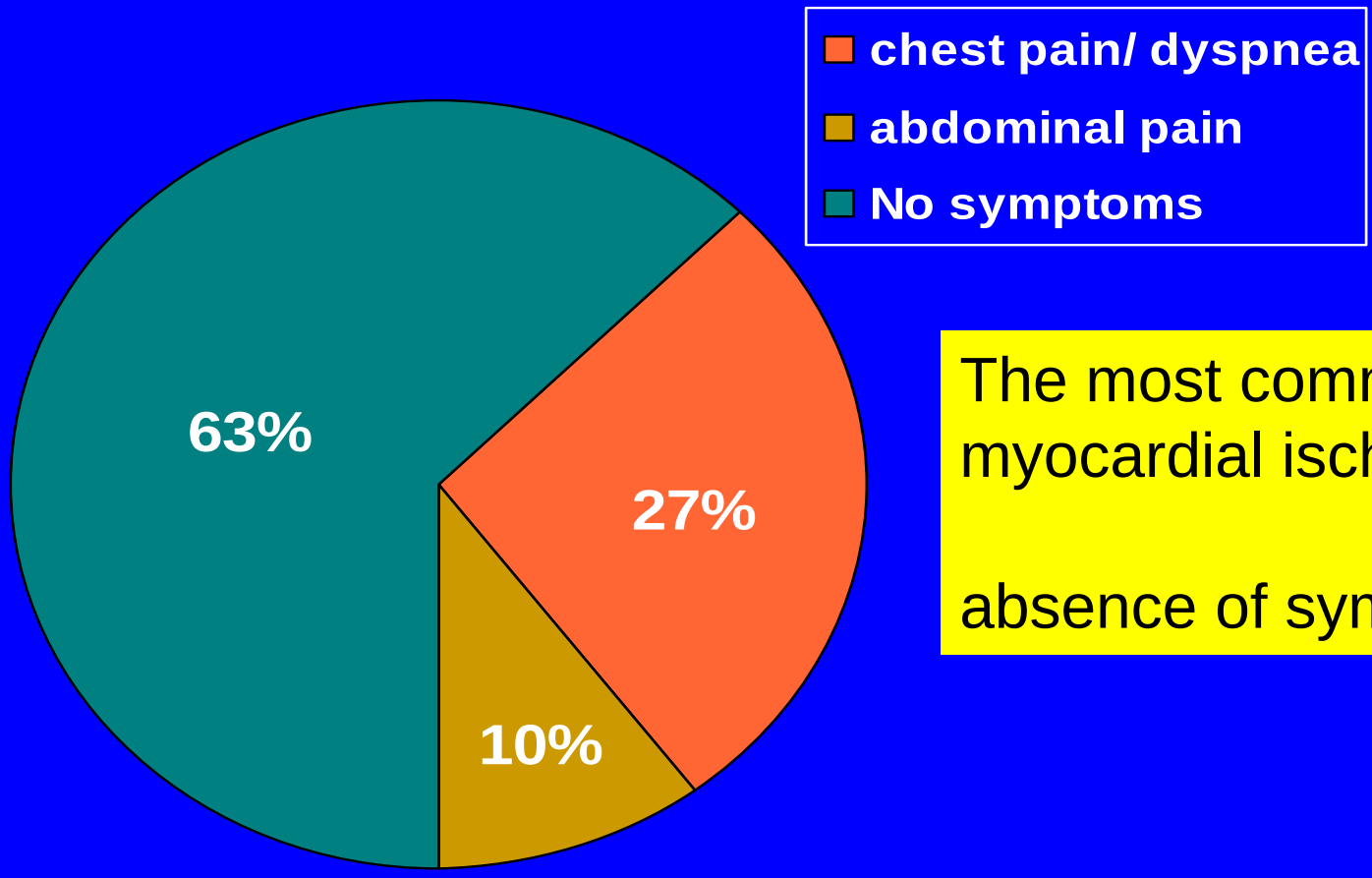
- Coronary disease is the #1 cause of death world-wide.
- We have reduced the death rate from CAD dramatically over the last 50 years (>50% reduction)

Why is it still the #1killer?

Presenting Diagnoses of Patients With Coronary Artery Disease



Symptoms among 48 patients with witnessed sudden cardiac arrest



The most common symptom of myocardial ischemia:

absence of symptoms

-Farb et. al., *Circ.* 1995

Silent Myocardial Ischemia

"Objective evidence for myocardial ischemia without angina or anginal equivalents in a patient with coronary artery disease or coronary spasm."

- Carl Pepine

- Not the same silent coronary disease

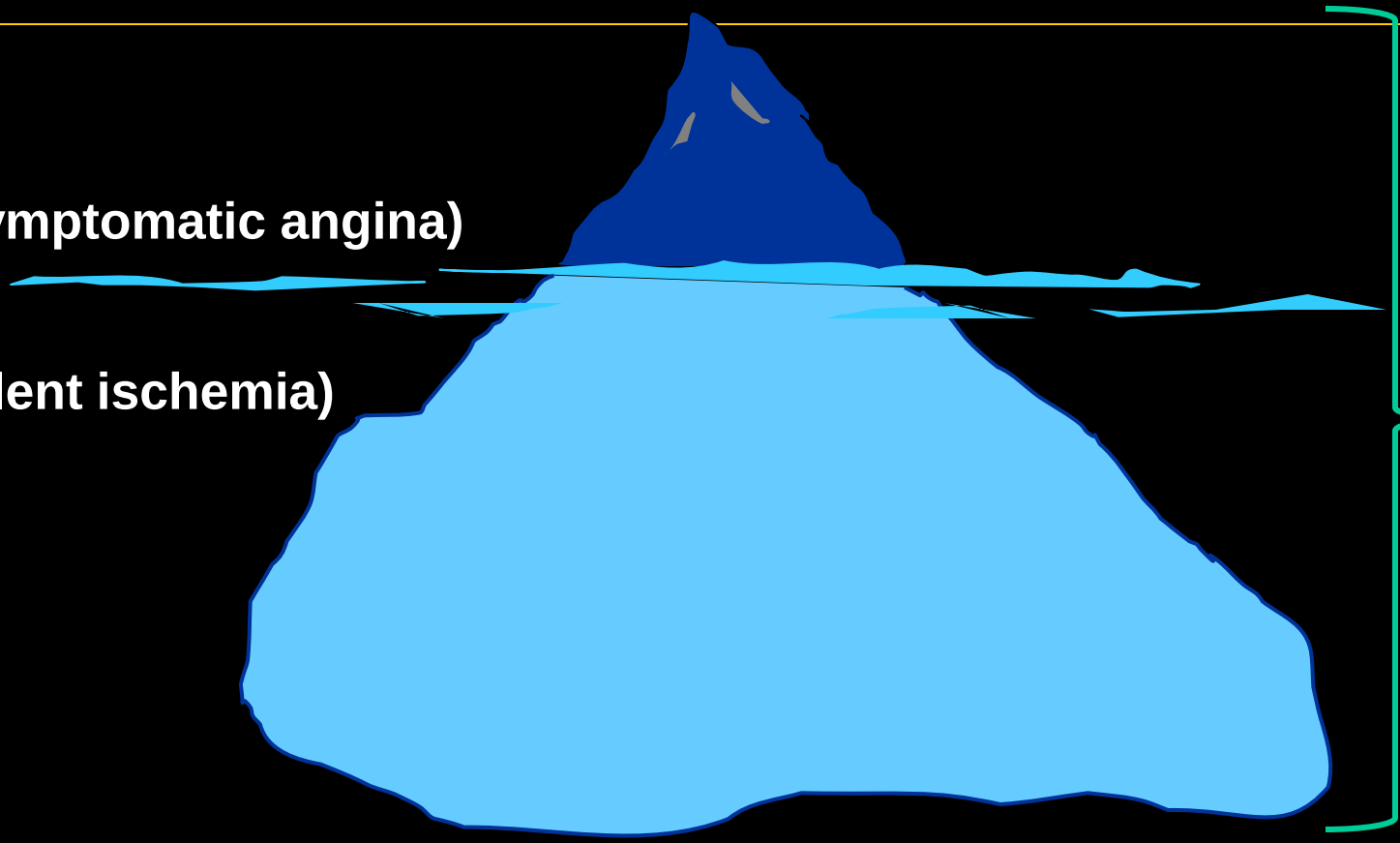
Incidence of Silent Myocardial Ischemia

General Population	2 – 4 %
Stable Angina	40 – 50 %
After Myocardial Infarction	50 %
Sudden Death	100 %
Unstable Angina	90 %
Diabetes	50%
After PTCA	22%

How much of the ischemia is silent?

- Arenja, AJM 2013

Symptomatic Angina: The Tip of the Ischemic Iceberg



1,934 episodes of ST depression, only 470 episodes with angina

Deanfield JE et al: *Lancet* 1983

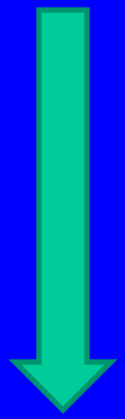
Diagnosing Silent Ischemia

Causes of ST depression

1. Myocardial ischemia
2. LVH
3. Electrolyte imbalance
4. Drugs (digitalis)
5. Normal variant
6. Autonomic imbalance
7. Cerebrovascular disease
8. Hyperventilation
9. Position changes
10. Mitral valve prolapse
11. Emotional stress

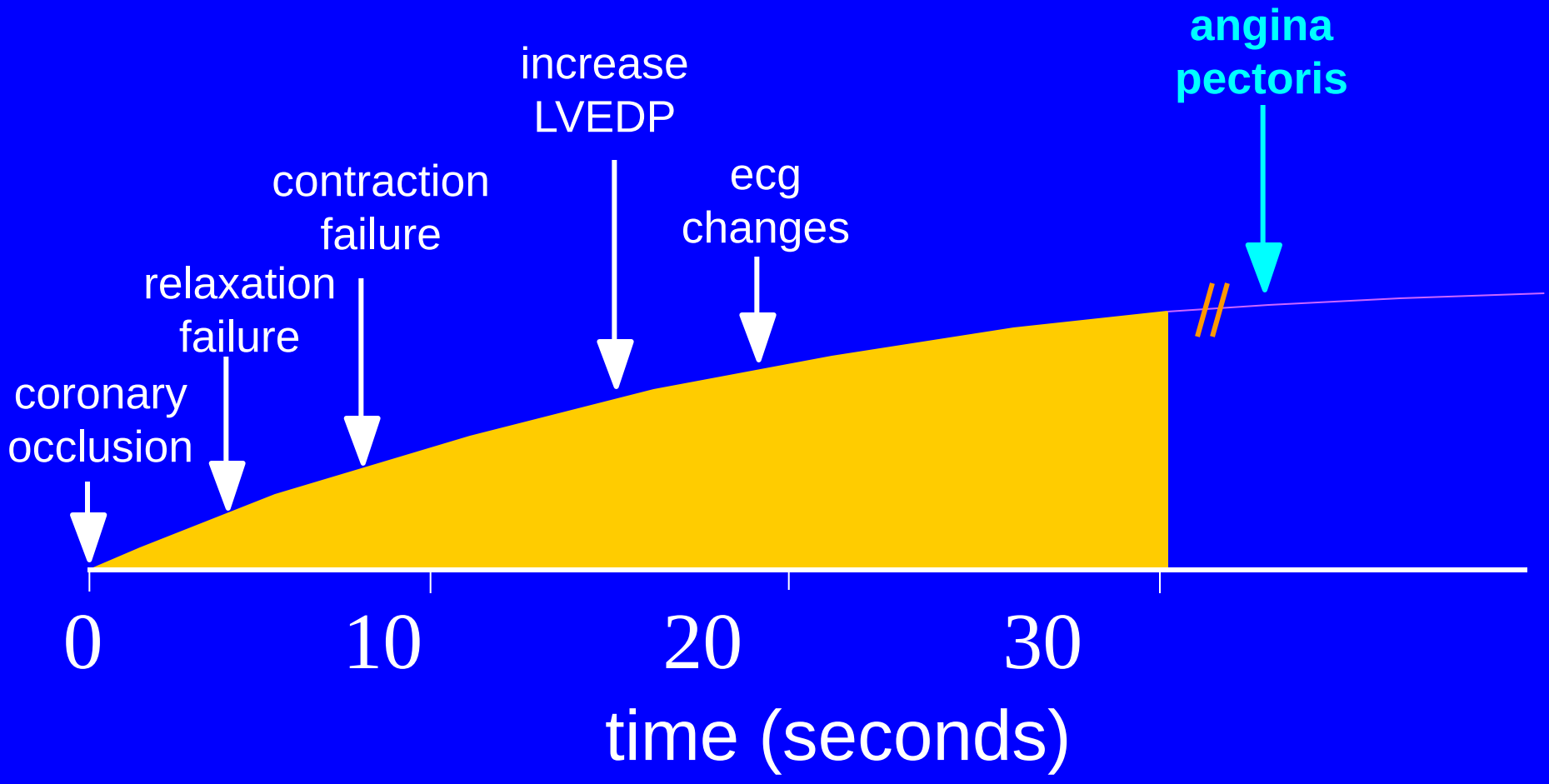
Criteria for SMI on 48 hour Holter:

- **>1 mm flat ST depression**
- **>30 seconds duration**
- **Reversible changes**



98% specific for SMI

Time Course of Events During Myocardial Ischemia



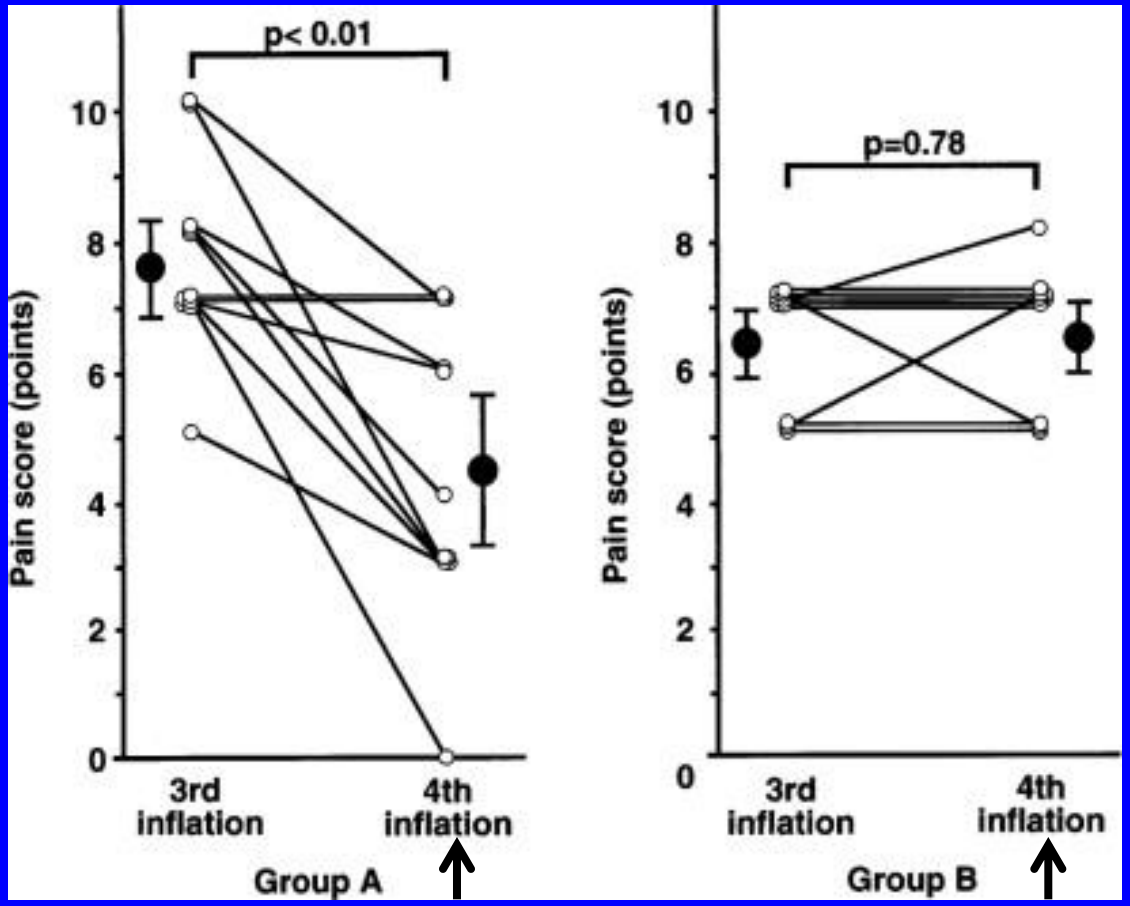
What Is the Cause of Angina Pectoris?

- Inflammation → Myocarditis?
- Mechanical Stimuli → PVCs?
- Chemical agents
- Combination

Chemical Agents Implicated as Mediator of Angina Pectoris

- bradykinin
- acetylcholine
- substance P
- serotonin
- histamine
- prostaglandin E_2
- adenosine
- lactic acid
- H^+
- K^+

Role of Adenosine



aminophylline saline

- Single blind study of 21 male patients undergoing PTCA
- Aminophylline was given to ½ of subjects (group A), saline to group B

Myocardial release of adenosine may be the mechanism of Angina Pectoris

Inhibiting adenosine receptors with aminophylline (4th inflation Group A) reduced the amount of ischemic pain despite a comparable degree of ST-segment depression.

- Hashino, JACC 1996

Mechanism of Silent Myocardial Ischemia

(theories)

1. Magnitude of ischemia stimulus
   - severity
   - duration

Severity of Ischemia

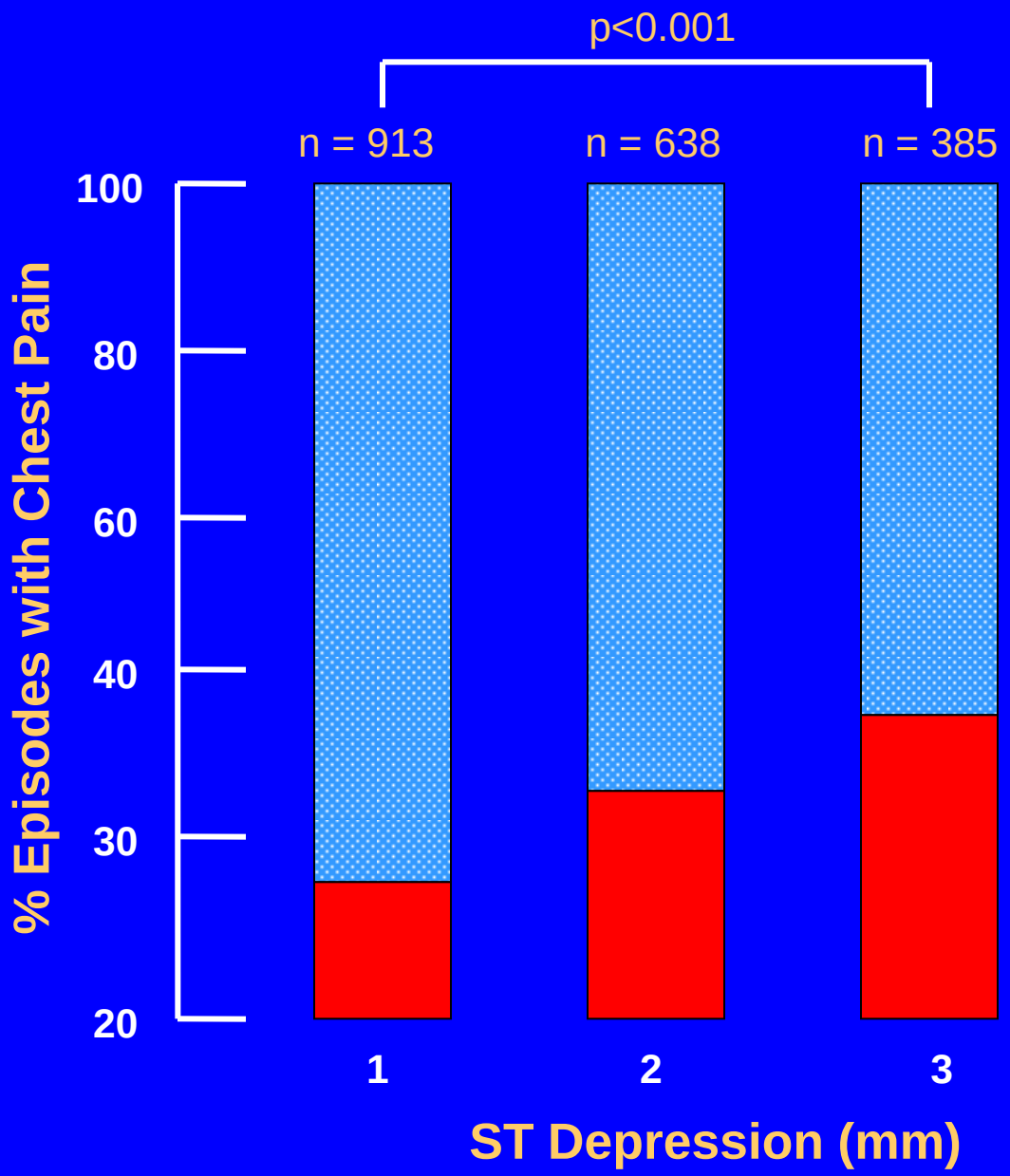


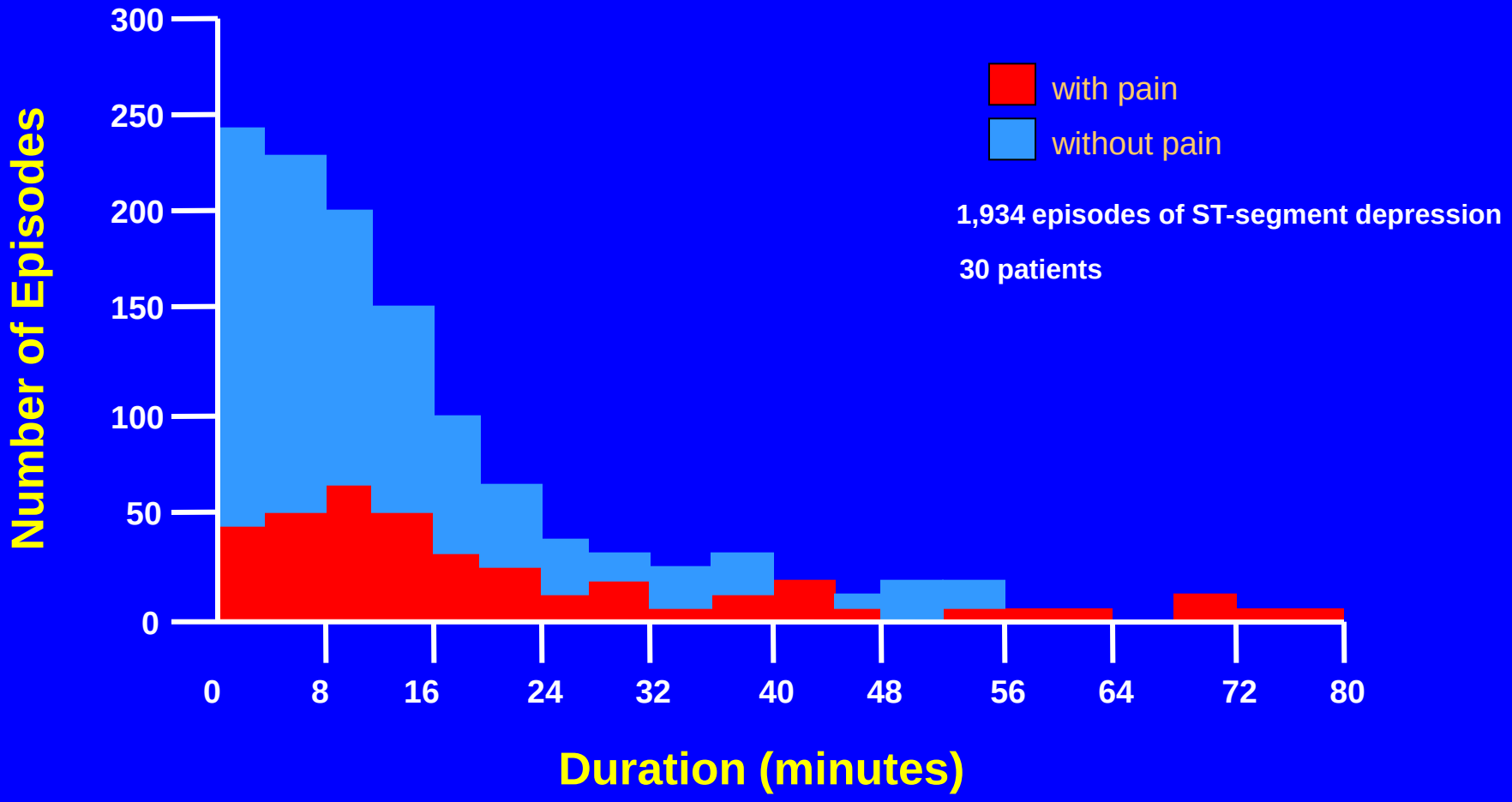
Figure 1. Relationship between the severity of ST-segment depression and the presence of angina in 1,934 episodes of ST-segment depression detected by Holter monitoring in patients with chronic stable angina and coronary disease.

Painful episodes

Silent episodes

Deanfield JE et al: *Lancet* 1983

Duration of Ischemia



- Cecchi JACC 1983

Proportion of MI unrecognized during 30-year Framingham follow-up

(5,127 men and women)

Age (years)	30 to 44	45 to 54	55 to 64	65 to 74	75 to 84	85 to 95
Men	29%	18%	25%	29%	42%	33%
Women	---	41%	31%	35%	36%	46%

Average for men – 28%

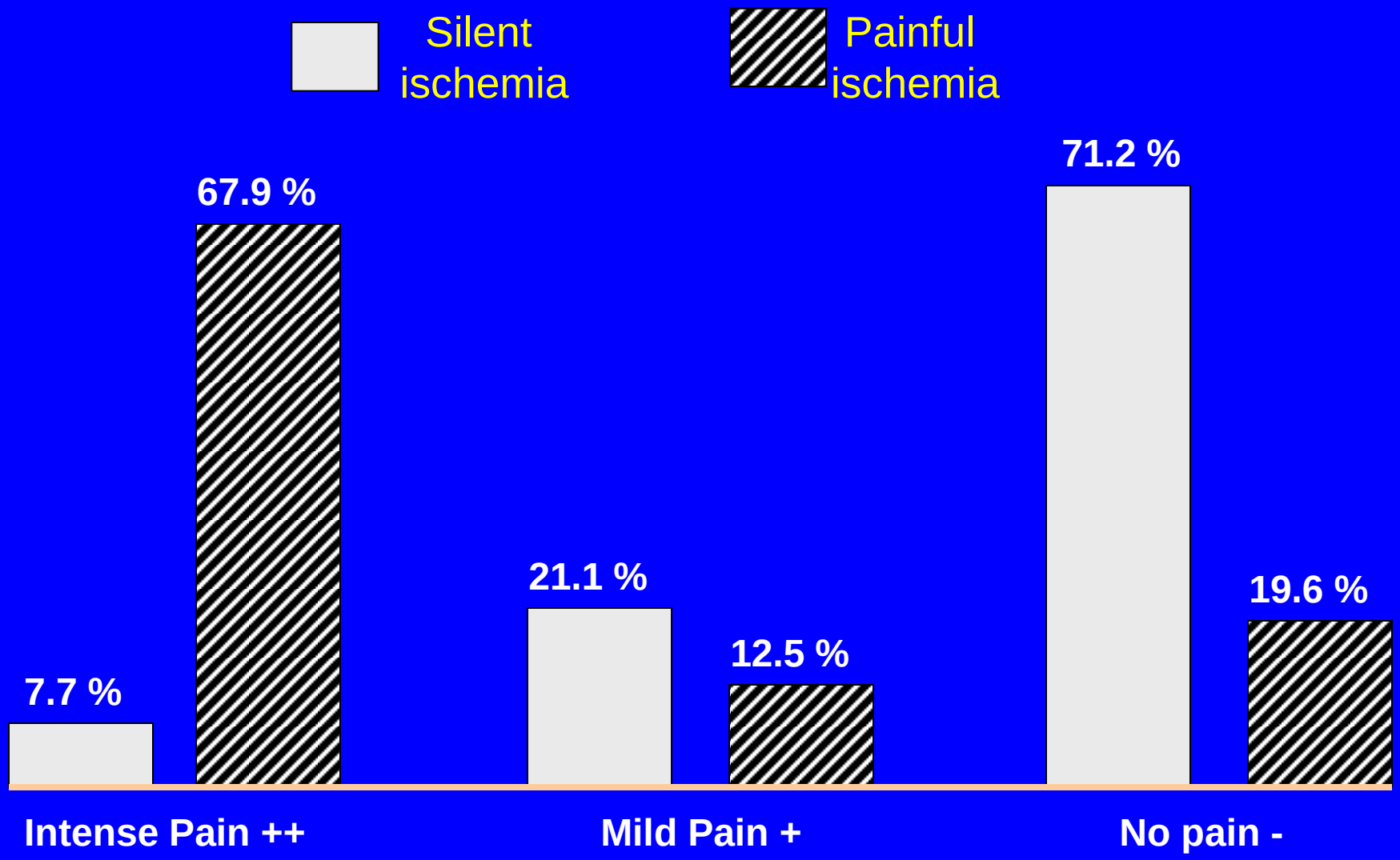
Average for women – 35%

Mechanism of Silent Myocardial Ischemia

(theories)

1. Magnitude of ischemia stimulus
   - severity
   - duration
2. Change in perception of ischemic stimulus
   - increased pain threshold

Reaction of patients to maximal intensity of the test current (500 mA) in the pulpal test. The difference in dental pain reaction between symptomatic and asymptomatic patients was statistically significant ($p < 0.0005$).



Mechanism of Silent Myocardial Ischemia

(theories)

1. Magnitude of ischemia stimulus
   - severity
   - duration
2. Change in perception of ischemic stimulus
   - increased pain threshold
   - increased circulating endorphin levels

Mechanism of Silent Myocardial Ischemia

(theories)

1. Magnitude of ischemia stimulus
   - severity
   - duration
2. Change in perception of ischemic stimulus
   - increased pain threshold
   - increased circulating endorphin levels
3. Neural dysfunction
   - diabetes
   - post-MI; post-transplant
   - afferent neural cardiac stunning

Clinical Importance of SMI

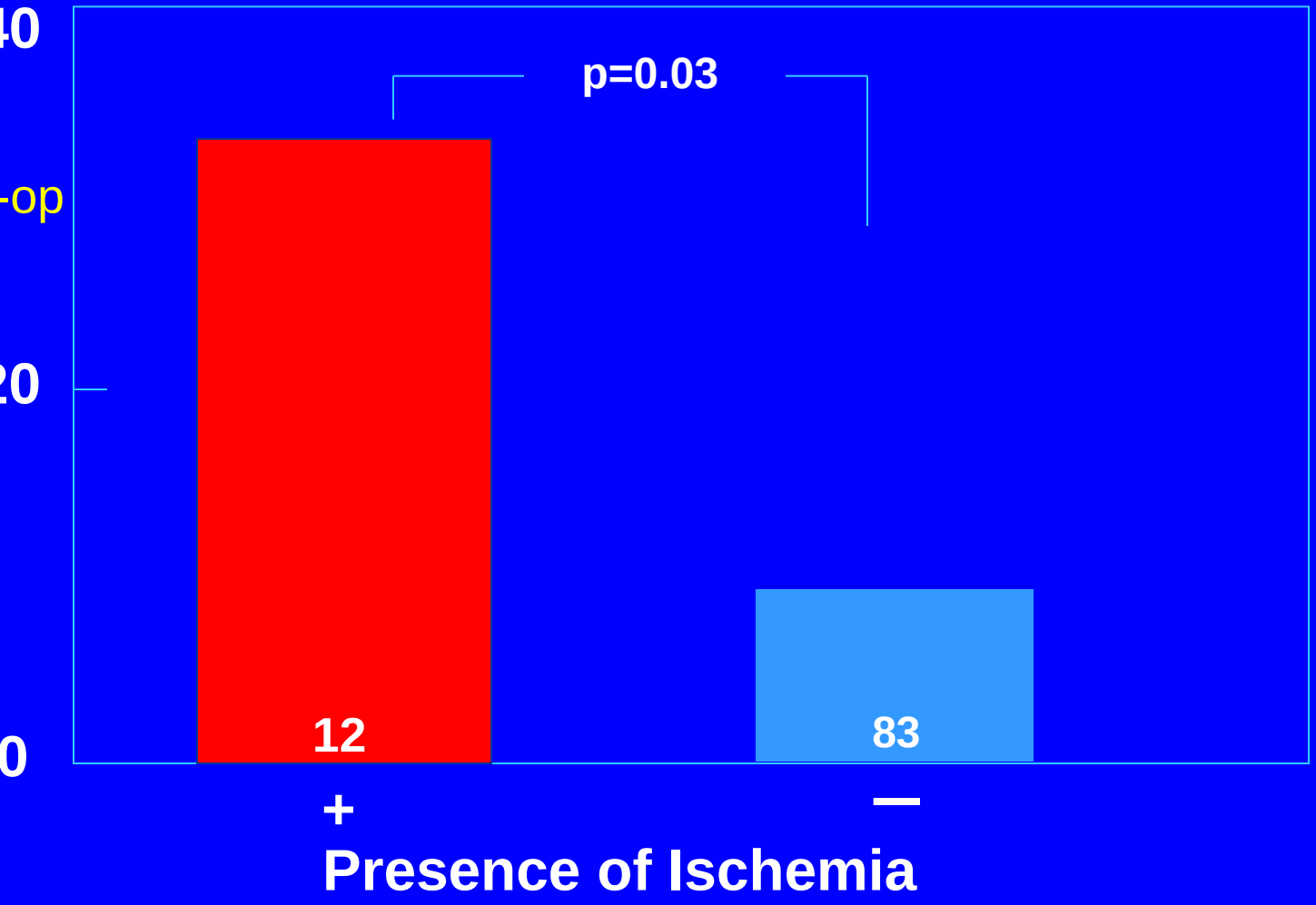
- Prognostic Importance
- Therapeutic Implications

- "SMI is associated with as poor a prognosis as clinical myocardial infarction"

Valenci, Arch Card Disease, 2011

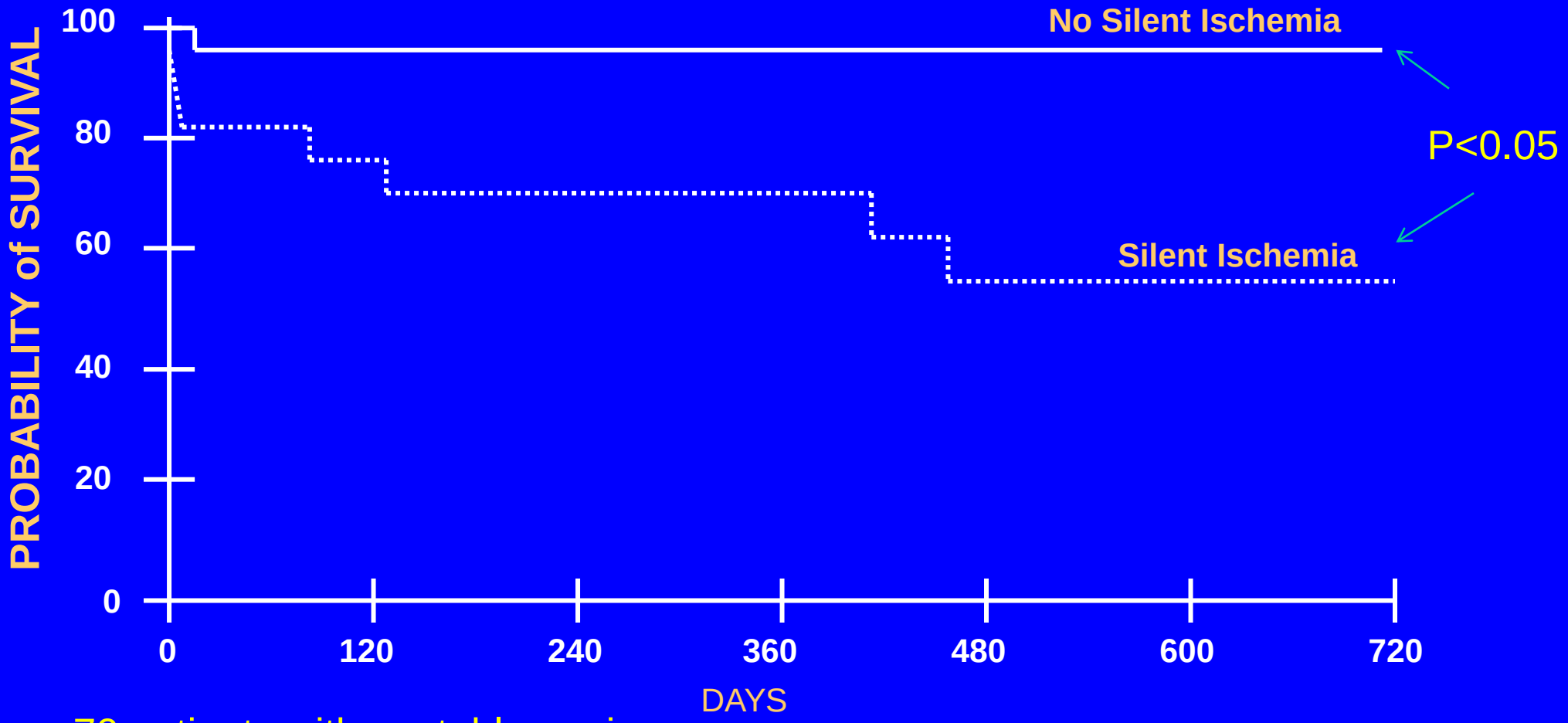
Prognosis of Preoperative Silent Myocardial Ischemia

- 95 patients for CABG
- Holter monitoring pre-op



- Janosi et al. Cardiology 1991

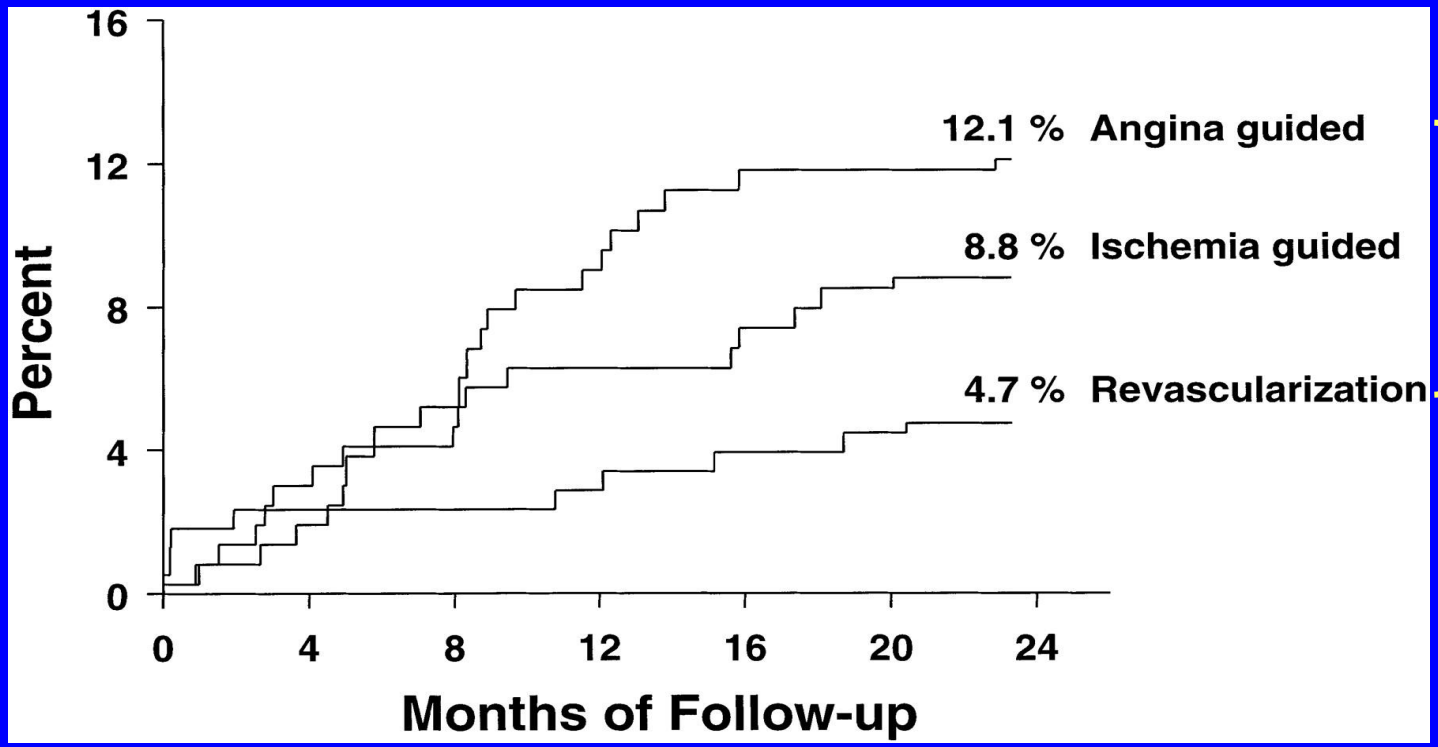
Silent Myocardial Ischemia



- 70 patients with unstable angina
- All treated medically to reduce angina
- 37 with SMI, 33 without
- f/u for 5 years

- Gottlieb, et al. NEJM1986

ACIP (Asymptomatic Cardiac Ischemia Pilot Study)
-Mortality or Myocardial Infarction -



27% reduction (p=NS)

61% reduction

P<0.01 revascularization vs angina guided

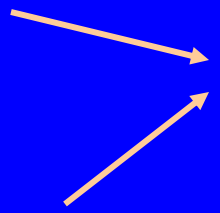
- 558 patients with non-invasive evidence of ischemia
- 2 year follow up of 3 therapeutic approaches

ACIP: Revascularization improved outcomes in this higher risk group. Treating ischemia (silent or painful) was important.

Davies, R. F. et al. Circulation 1997;95:2037-2043

Clinical Trials
(Silent Ischemia)

- ASIST (Atenolol Silent Ischemia Study). — trend toward reduced complications on atenolol
- TIBET (Total Ischemic Burden European Trial) — trend toward better prognosis on combined Rx (nifed. + atenolol)
- ACIP (Asymptomatic Cardiac Ischemia Pilot Study)
- TIBBS (Total Ischemic Burden Bisprolol Study)



reducing ischemia reduces adverse outcomes (MI, death, readmission, intervention)

ISCHEMIA trial (in progress): 8000 patients – should help tell if a medical strategy based on SMI reduces MACE

What we do know (2013):

Silent ischemia is more prevalent than angina in patients with CAD

SMI is easy to diagnose

SMI portends a worse prognosis

Treatment with traditional anti-anginal Rx reduces SMI

It is important to treat ischemia (silent and/or painful)

Treatment with PCI is superior to medical Rx

What we don't know (2013):

Is aggressive Tx of SMI to reduce "hard" endpoints (death, MI) beneficial and cost effective? In which patients should we use it?

Management Tips

HOLTER:

- use in high risk patients to search for SMI
  e.g. post-MI, “treated” unstable angina, DM
- to optimize prognosis, follow ischemia, not symptoms
- may require multiple tests to optimize Tx
- do not use to search for SMI in low risk patients

Therapeutic goals: TREAT ISCHEMIA, not pain; reduce heart rate; use combination drug regimens.

PCI, CABG – same indictions for SMI, as with painful ischemia

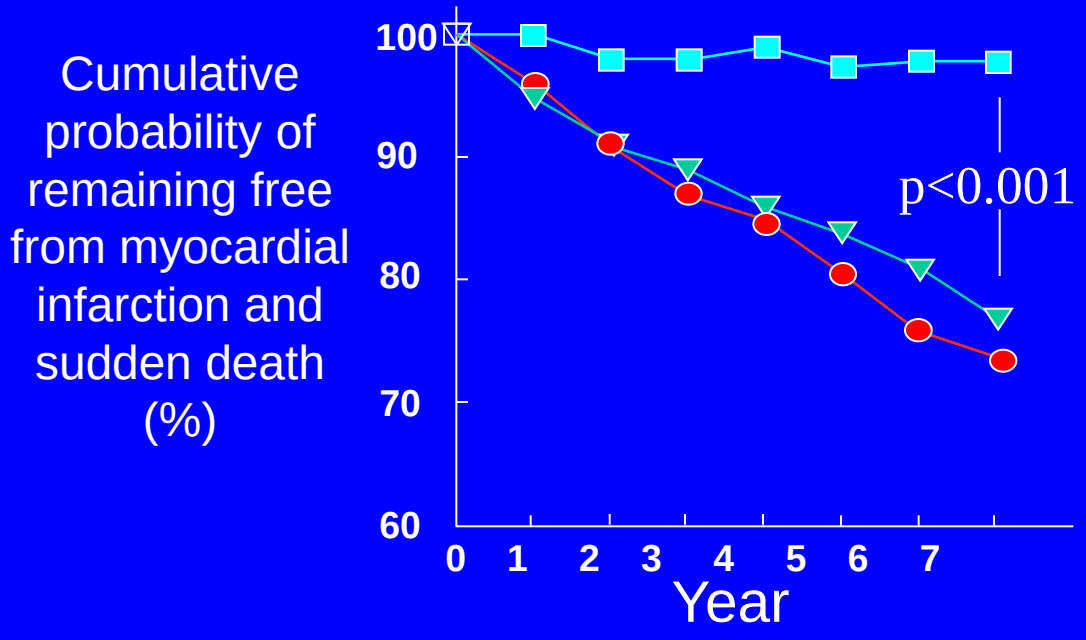

“The End”

Characteristics that must be explained by a hypothesis for the mechanism of SMI:

- occurs in the same patient during some but not all episodes of ischemia.
- is not directly correlated to the severity, location, or the duration of the ischemic episode.
- is more common in unstable than in stable anginal patterns.

Neural Stunning Hypothesis: Temporary (5-15 min) ischemia stuns the pain fibers for an extended (hours) period of time during which additional ischemia is silent

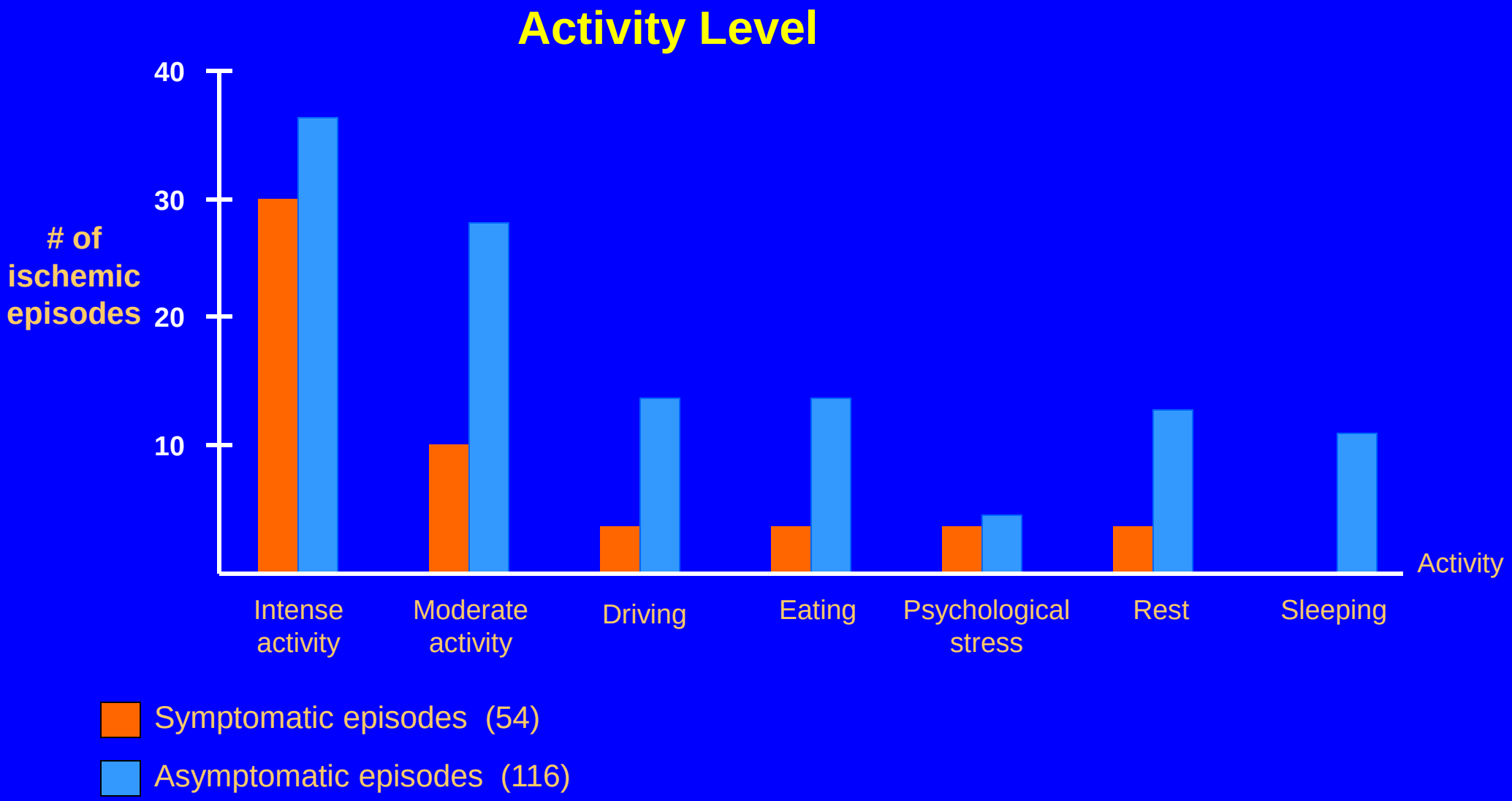
Risk of Cardiac Events in Patients with Silent Ischemia (CASS)



- Control; n=1019
- Group 1 (SI on GXT); n=424
- Group 2 (PI on GXT); n=456

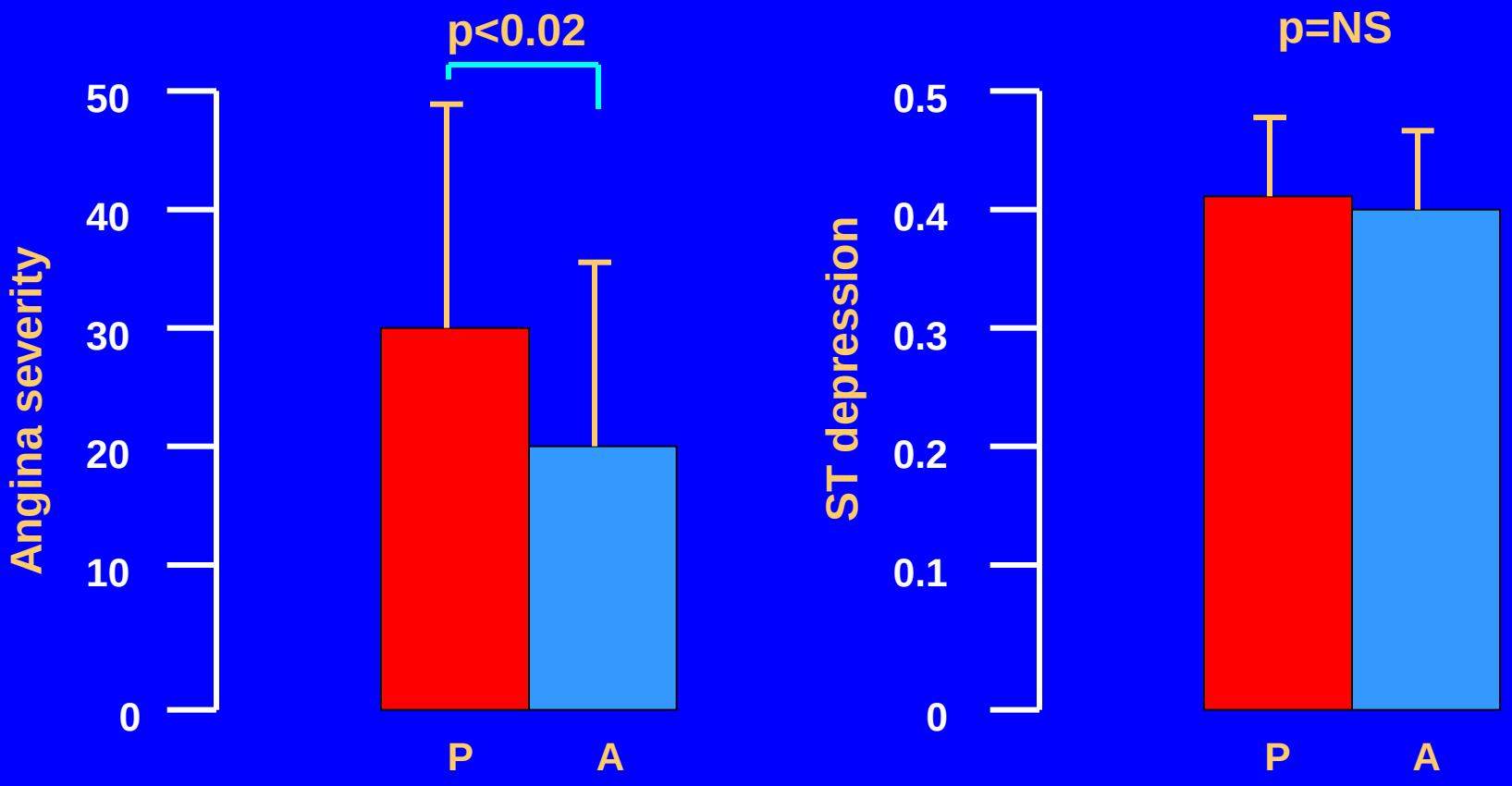
- Weiner, et al. 1988

Clinical Characteristics of SMI



Cohn PF: *Am J Cardiol* 1985: 56: 28D-34D

Role of Adenosine

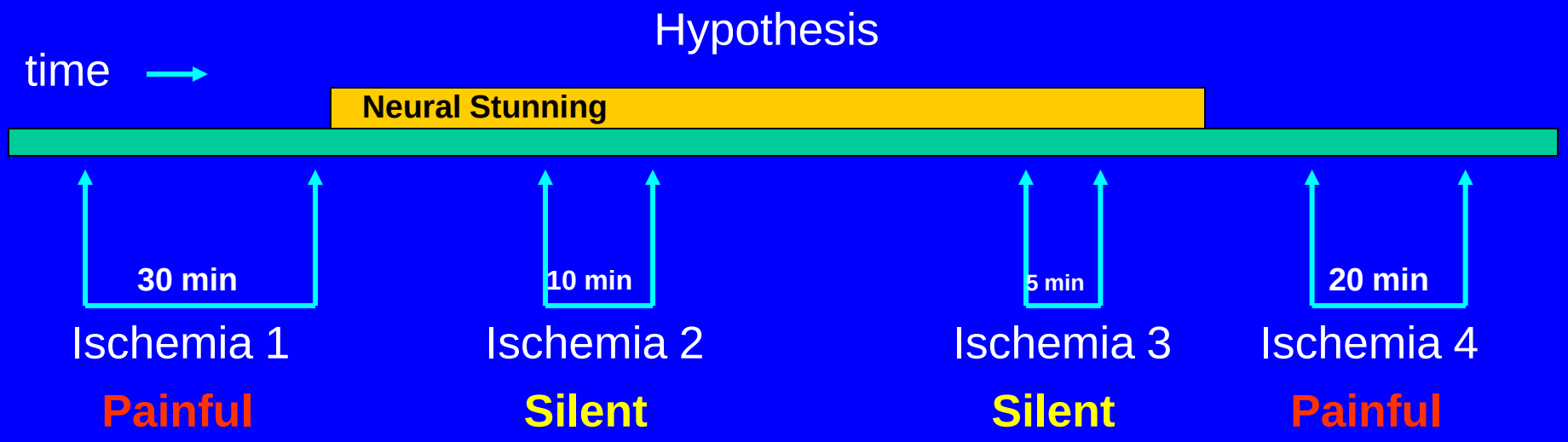


Bar graphs of effect of aminophylline on exercise-induced chest pain. The severity of chest pain at its onset was less after aminophylline (A) (7 mg/kg) than placebo (P), despite a comparable degree of ST-segment depression.

Mechanism of Silent Myocardial Ischemia

(theories)

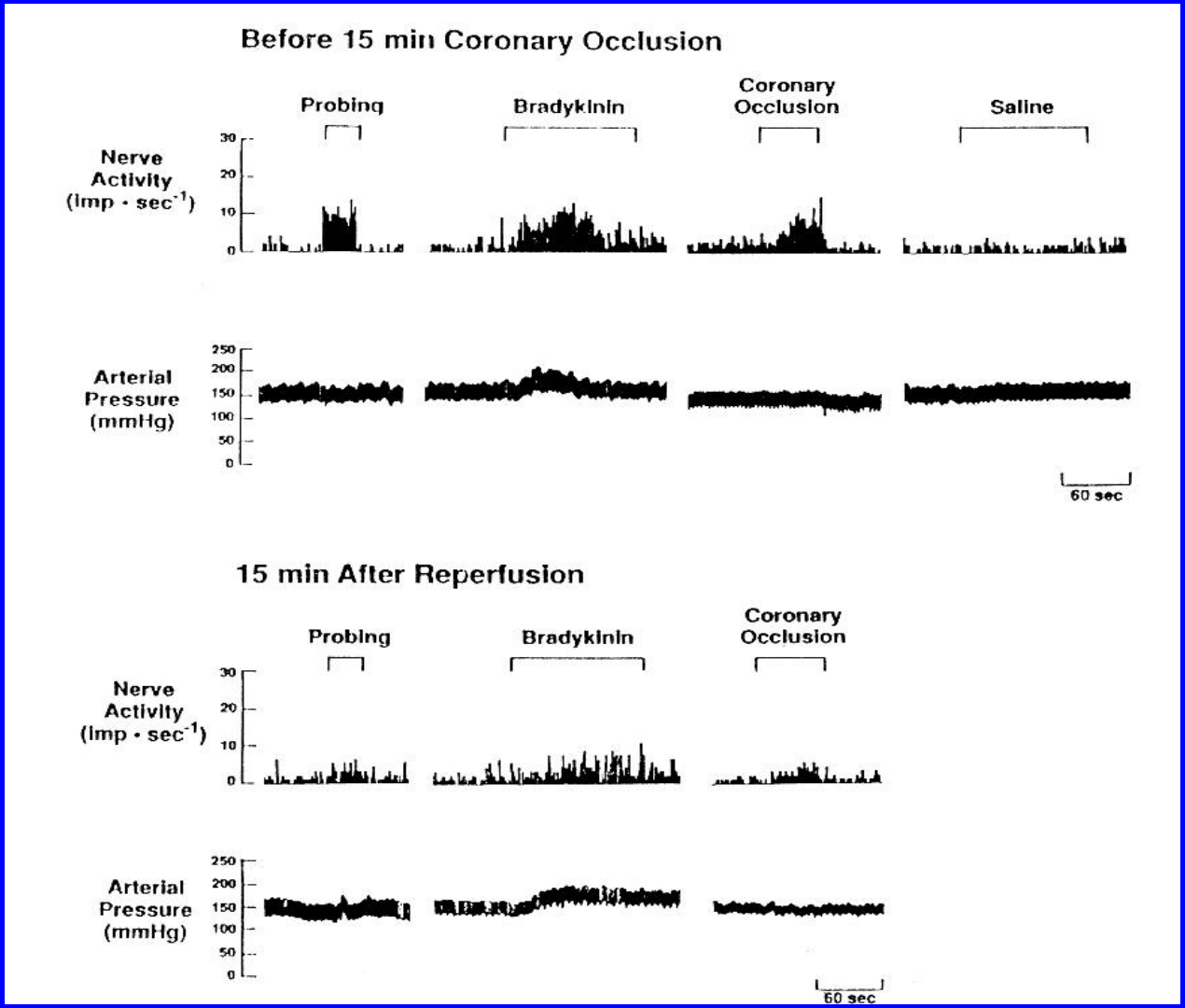
4. Temporary alteration in nerve conduction (Neural stunning hypothesis)



Hypothesis

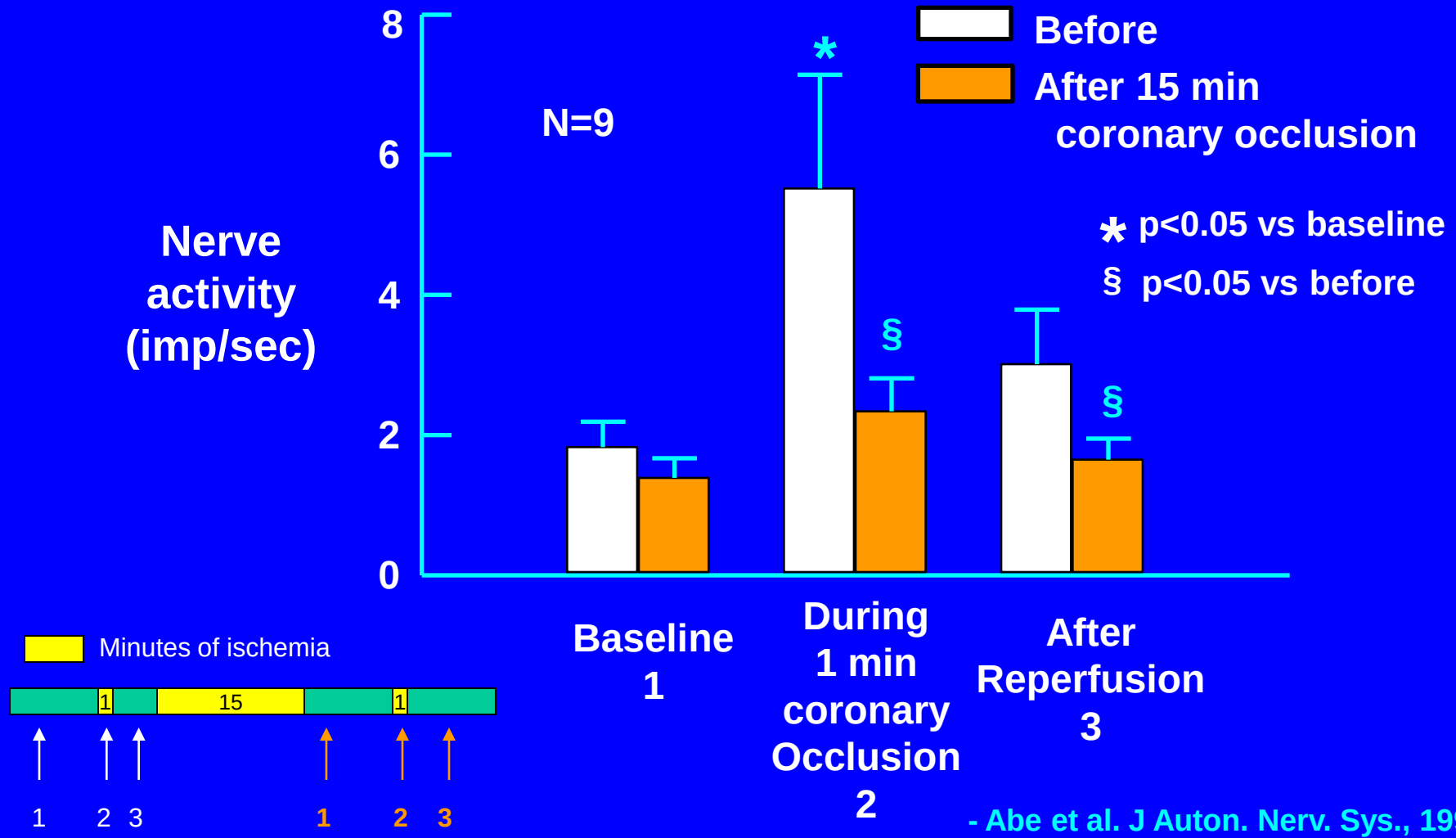
Silent myocardial ischemia results from neural stunning of cardiac afferent sympathetic sensory fibers

Evidence of Afferent Neural Stunning



- Abe et al. J Auton. Nerv. Sys., 1998

Effect of 15 min Coronary Occlusion on Ischemia-sensitivity of afferent cardiac nerves



- Abe et al. J Auton. Nerv. Sys., 1998

Summary and Conclusion

- Cardiac sensation occurs by activation of sympathetic afferent C fibers in the heart.
- Brief periods of ischemia impair cardiac sympathetic function for up to several hours causing neural stunning.

- **Most characteristics of SMI can be explained by the "neural stunning hypothesis"**

ACIP (Asymptomatic Cardiac Ischemia Pilot Study)
- Mortality -

- 558 clinically stable patients with positive stress test and positive Holter, and CAD by cath

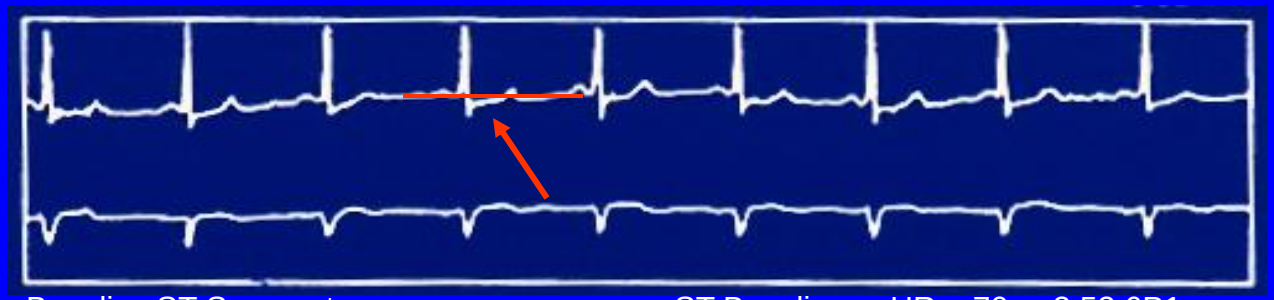
-randomized to:
  - angina-guided Tx
  - ischemia-guided Tx (Holter)
  - revascularization

- Two year follow-up

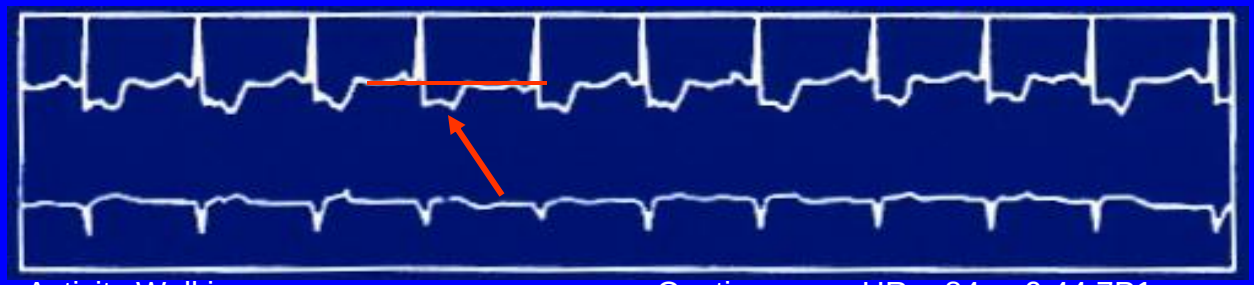
- Endpoints: Cardiac death, MI, UA, CABG, treatment failure

Davies, R. F. et al. Circulation 1997;95:2037-2043

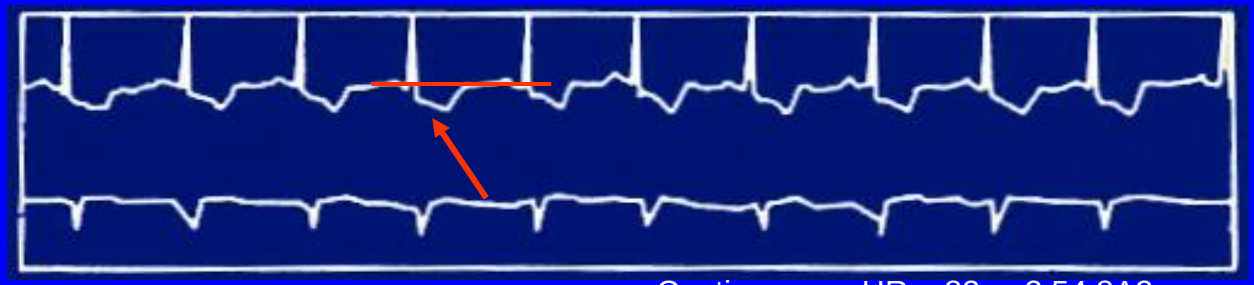
Example of Silent Ischemia



Baseline ST Segment ST Baseline HR = 70 3:53.6P1



Activity Walking Continuous HR = 84 9:44.7P1
Duration of ST-Segment Depression: 12 min.



Continuous HR = 83 2:54.8A2
Activity: Sleep
Duration of ST-Segment Depression: 53 min.

Electrocardiographic strips of representative ambulatory ST-segment depression. HR = heart rate.

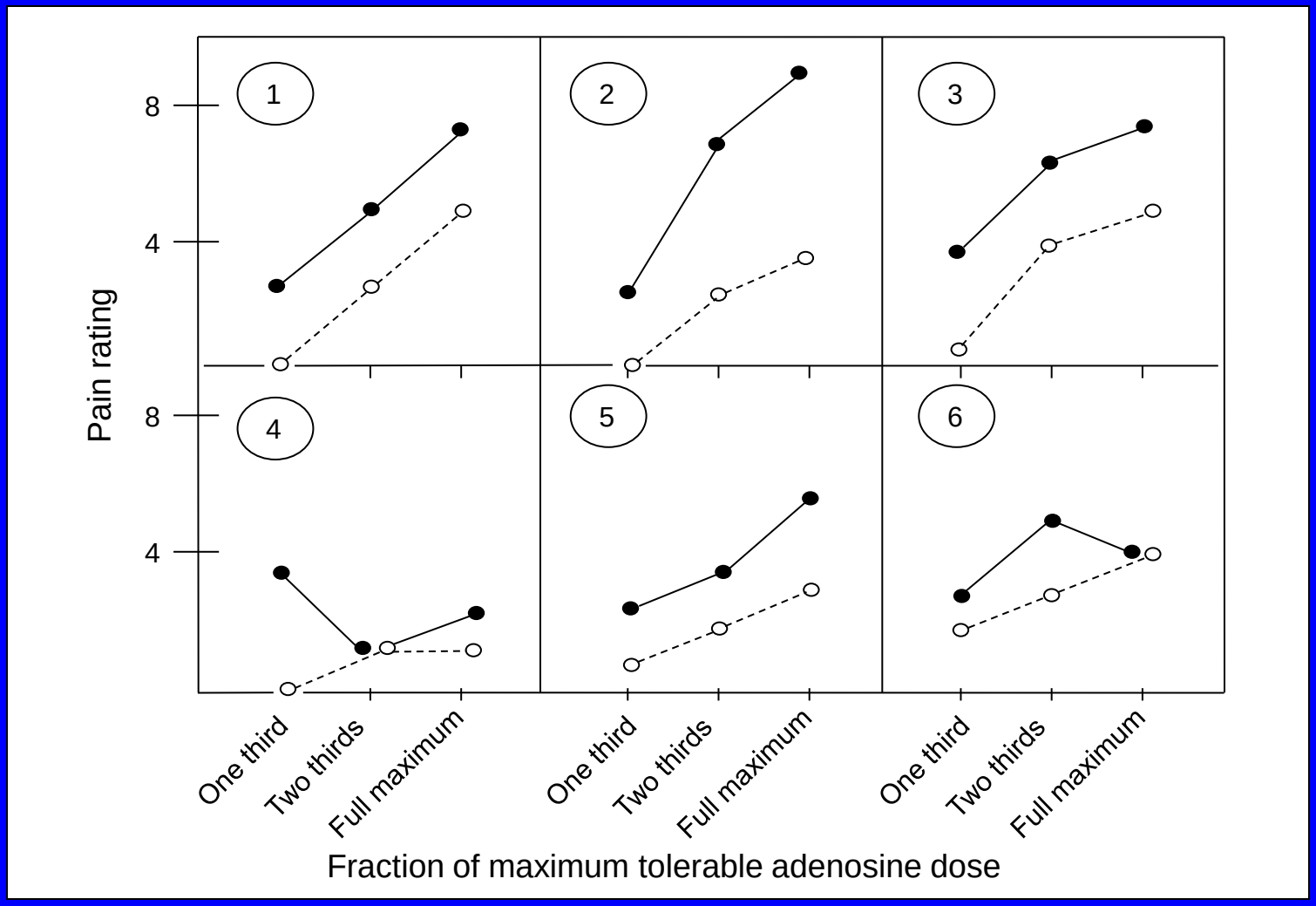
19 survivors of Sudden Cardiac Death

Silent Myocardial Ischemia

19/19
Silent Ischemia on Holter

- Sharma 1981

Role of Adenosine



Rating of central chest pain according to Borg scale (0-9) after three intravenous doses of adenosine in subjects 1 to 6 before (●——●) and after (○– – –○) aminophylline. Adenosine given as rapid bolus injection of one third, two thirds, and full maximum tolerable dose.

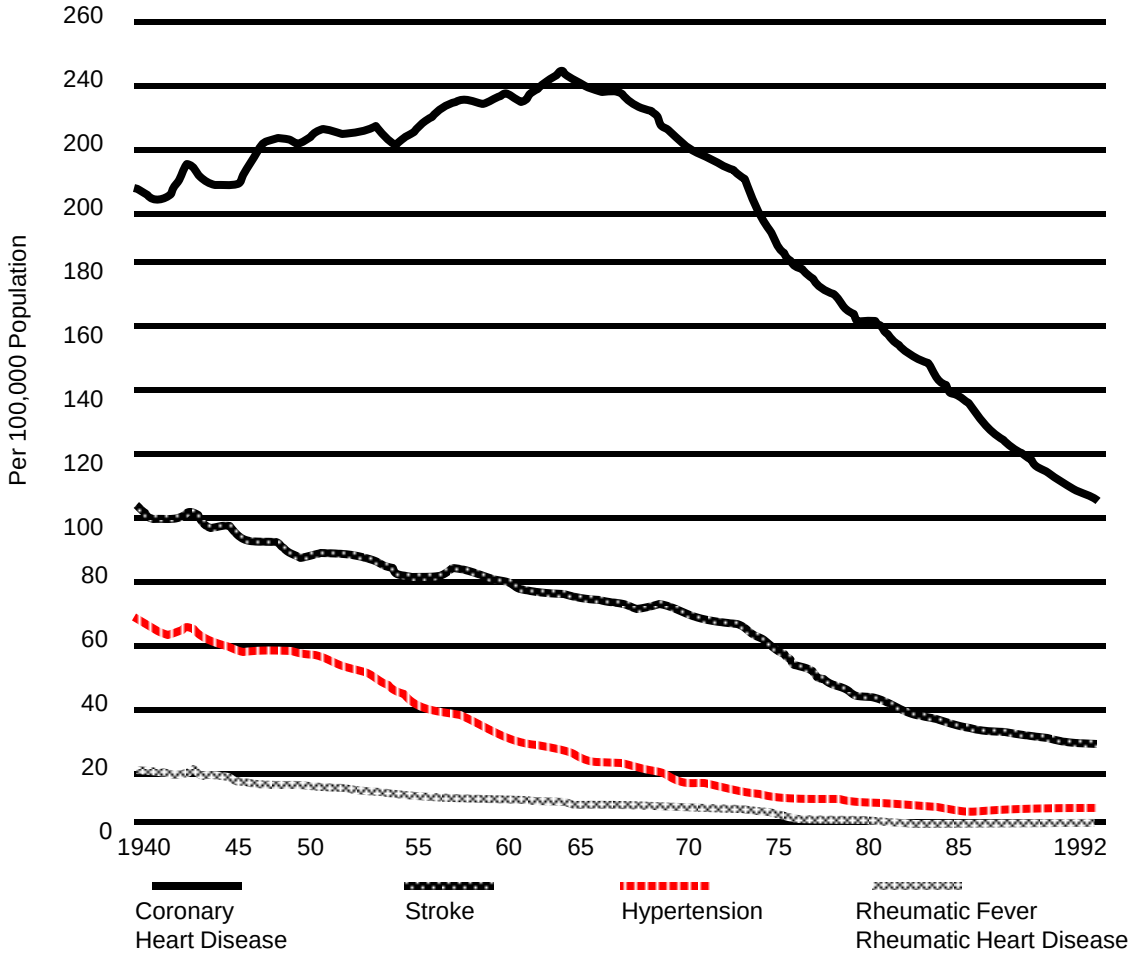
American Heart Association℠

Fighting Heart Disease and Stroke

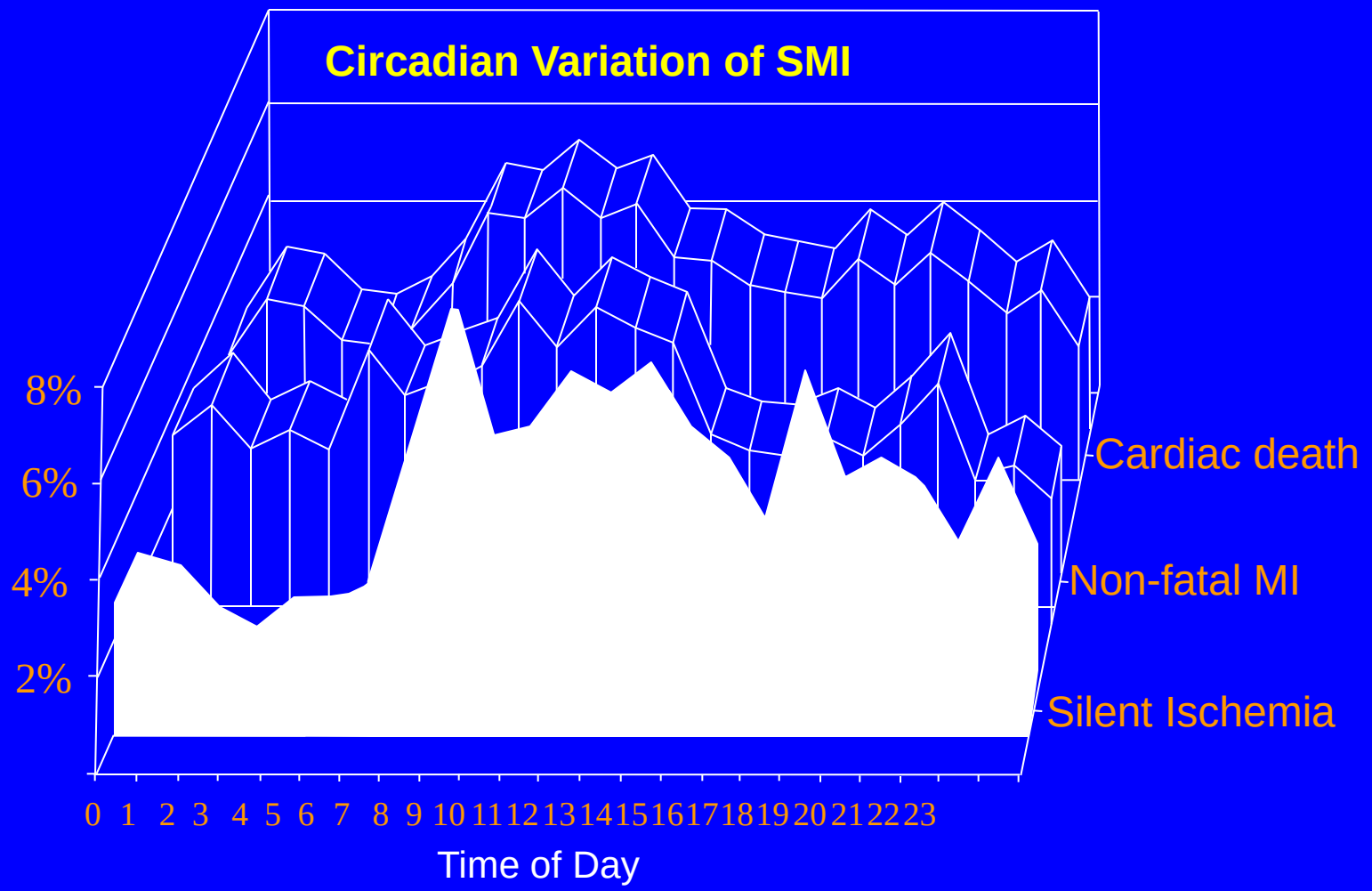
Heart and Stroke Facts: 1996 Statistical Supplement

Age-Adjusted Death Rates for Major Cardiovascular Diseases

United States: 1940 - 92



Age-adjusted to 1940 U.S. population and to the 6th Revision ICDA. Source: National Center for Health Statistics and the American Heart Association.



Three-dimensional representations of circadian distribution of silent ischemia in 150 patients off therapy, of nonfatal myocardial infarction, and of out-of-hospital cardiac death[20] showing similar distributions and plotted as the percentage of total events during each hour of the day.

- Fox and Mulcahy, Circulation 82:II-159, 1990

TIBET (Total Ischemic Burden European Trial)

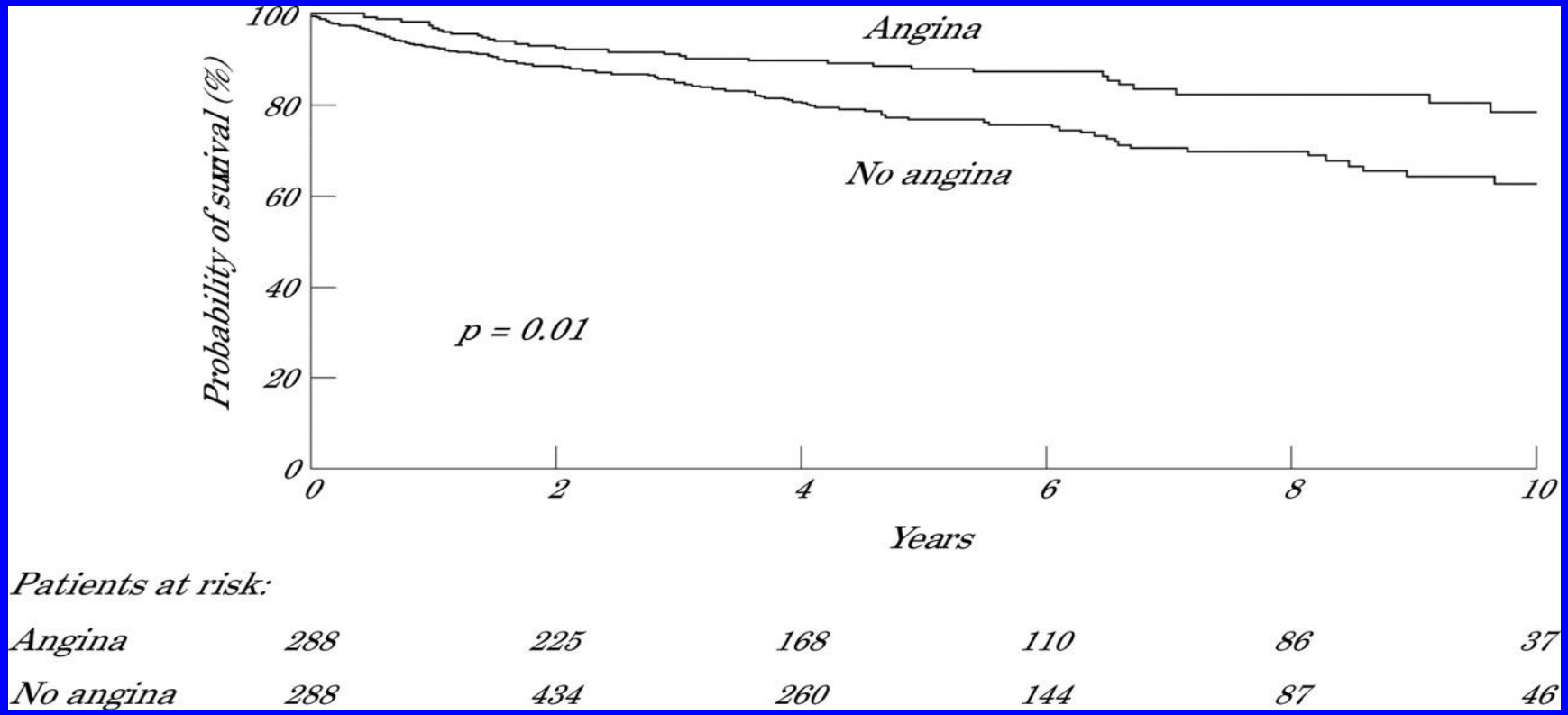
		Off treatment Event on Holter	
		Yes	No
Hard Endpoint	Yes	33	30
	No	265	299
			(P=0·42)
		Yes	No
Hard+Soft Endpoint	Yes	58	51
	No	240	278
			(P=0·19)

- 682 patients with chronic stable angina; ST depression on stress testing
- 50% with SMI on 24 hour Holter
- randomized to:
  - nifedipine
  - beta blocker
  - both
- Two year follow-up
- Endpoints: Cardiac death, MI, UA, CABG, treatment failure

In this low risk population,
- presence of SMI did not affect cardiac prognosis
- combination drug therapy tended to reduce hard endpoints

- Dargie, et al. Eur. H. J. 1996

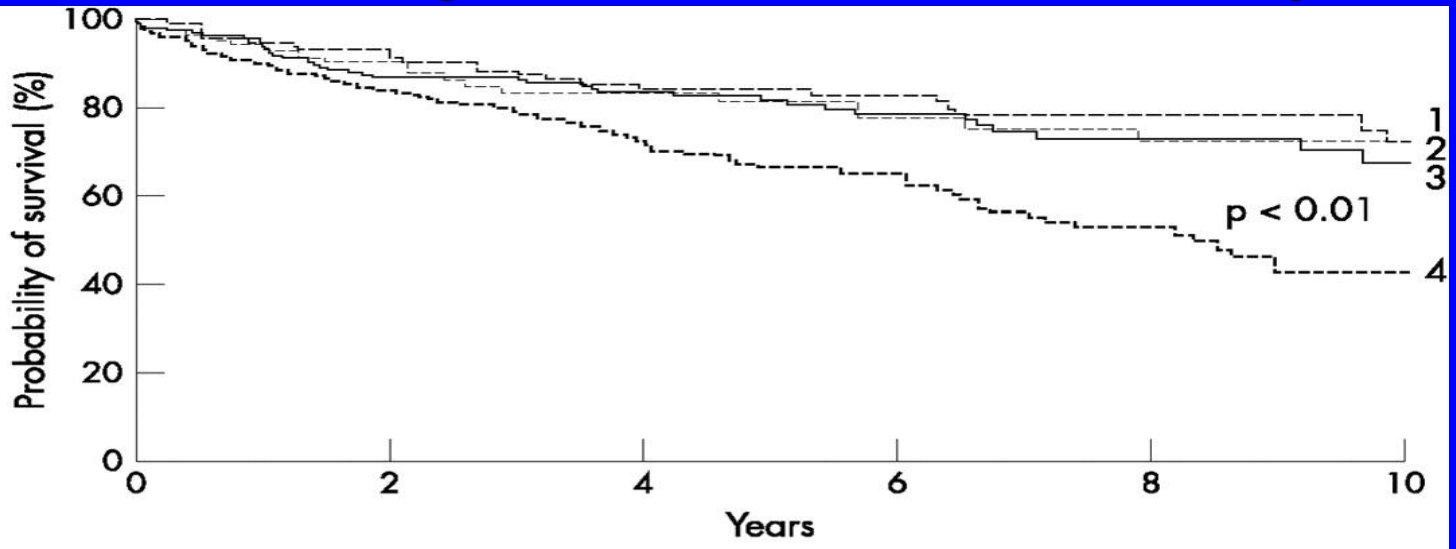
Prognosis in Silent Myocardial Ischemia (Dobutamine Stress Echo)



- 949 consecutive patients with ischemia on DSE
- 69% with SMI

Biagini, E et al. Heart 2005;91:737-742

Prognosis in Silent Myocardial Ischemia (DSE stratified by # vessels with CAD)



Patients at risk:						
1: No angina, SVD	134	100	76	55	35	22
2: Angina, SVD	68	59	48	36	24	13
3: Angina, MVD	220	155	109	61	42	18
4: No angina, MVD	509	317	164	72	35	15

- 949 consecutive patients with ischemia on DSE
- 69% with SMI

SMI might be prognostically *worse* than painful ischemia

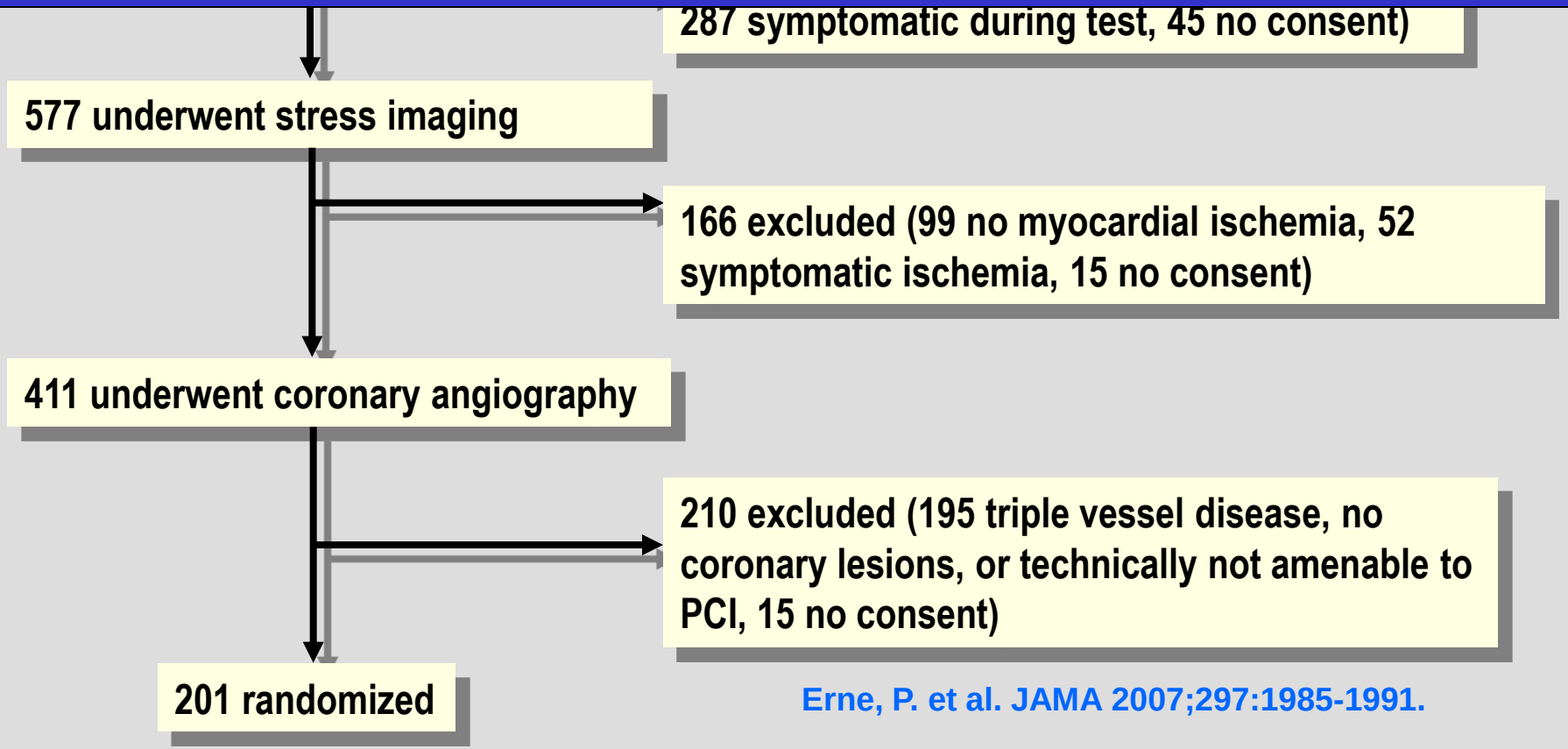
Biagini, E et al. Heart 2005;91:737-742

The Swiss Interventional Study on Silent Ischemia Type II (SWISSI II)

SUMMARY

1. Positive exercise test for ischemia
2. Positive imaging test for ischemia
3. Angiographic CAD
4. Long-term follow-up (to 15 years)

Therefore: High risk group with CAD, long follow-up



Erne, P. et al. JAMA 2007;297:1985-1991.

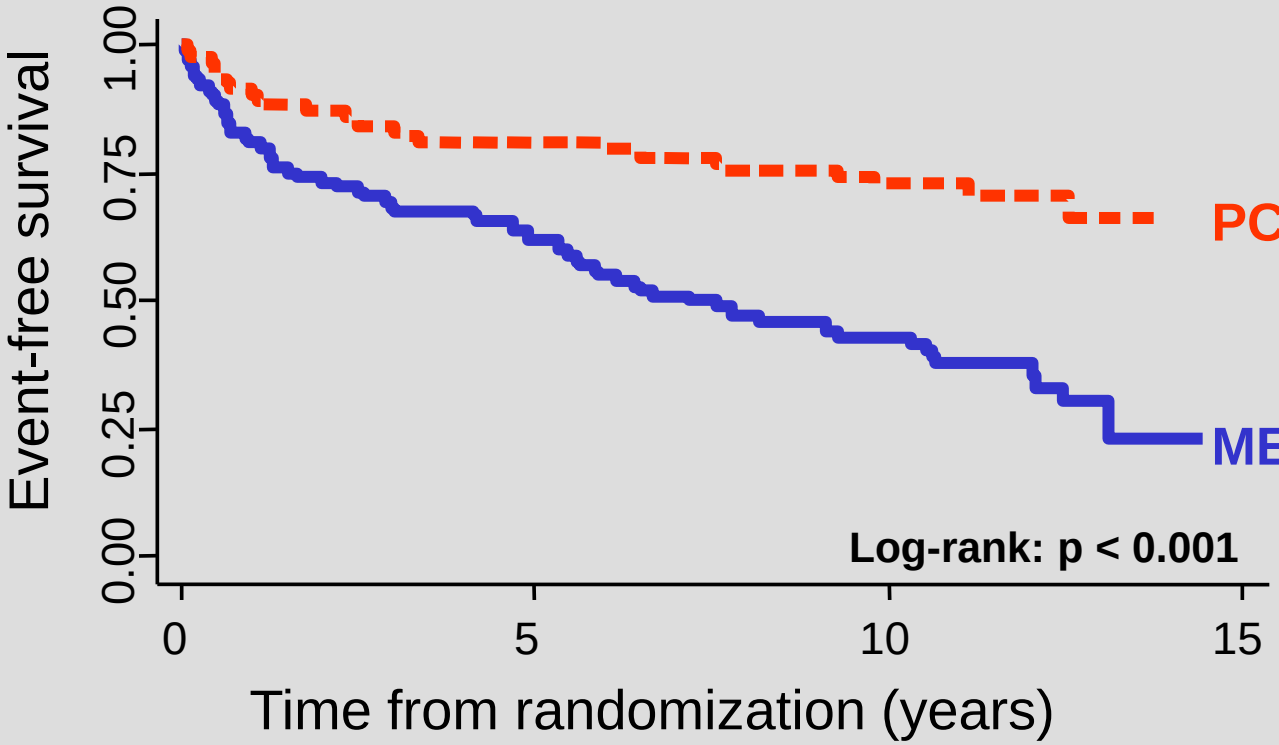
Interventions

Patients were randomized to:

- **PCI group (n = 96)**
  - PCI with the aim of full revascularization (without residual >75% stenoses)
- **MED group (n = 105)**
  - Anti-ischemic therapy: bisoprolol (5-10 mg/d), and/or amlodipine (5-10 mg/d), and/or molsidomine (4-12 mg bid), aiming to eliminate or maximally reduce silent ischemia during bicycle ergometry
- **In both groups:**
  - Risk factor control: counseling (eating habits, smoking, exercise), and/or ACE inhibitor for hypertension (if needed)
  - Acetylsalicylic acid (100 mg/d) and statin

Erne, P. et al. JAMA 2007;297:1985-1991.

Survival Free of MACE: Primary End Point (Cardiac Death, Non-Fatal MI, Revascularization)



Number of events:

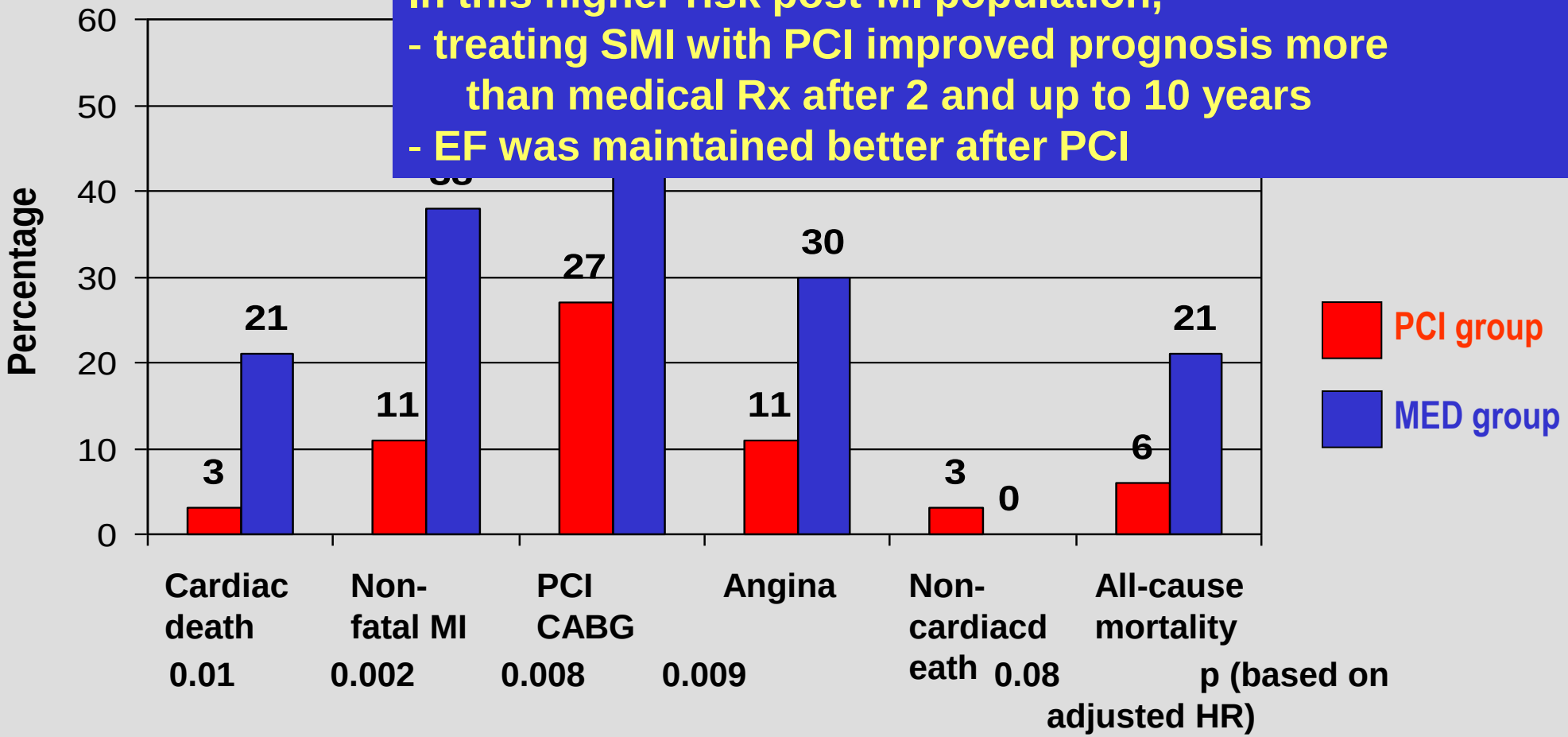
PCI group	27 (28%)
MED group	67 (64%)

Absolute event reduction: 6.3% per year (95% CI, 3.7%-8.9%; P < 0.001)
Adjusted hazard ratio: 0.33 (95% CI, 0.20-0.55; P < 0.001)

Erne, P. et al. JAMA 2007;297:1985-1991.

Secondary End Points (Components of Primary End Point, Angina, All-Cause Mortality)

In this higher risk post-MI population,
- treating SMI with PCI improved prognosis more than medical Rx after 2 and up to 10 years
- EF was maintained better after PCI



Erne, P. et al. JAMA 2007;297:1985-1991.

Test of the Neural Stunning Hypothesis

- Patients with painful and painless ischemia on Holter Monitoring.
- Measure the percentage of painful vs painless episodes of ischemia (>5 minutes duration) which:

  1) follow within 1 hour after an episode of ischemia lasting greater than 15 minutes.

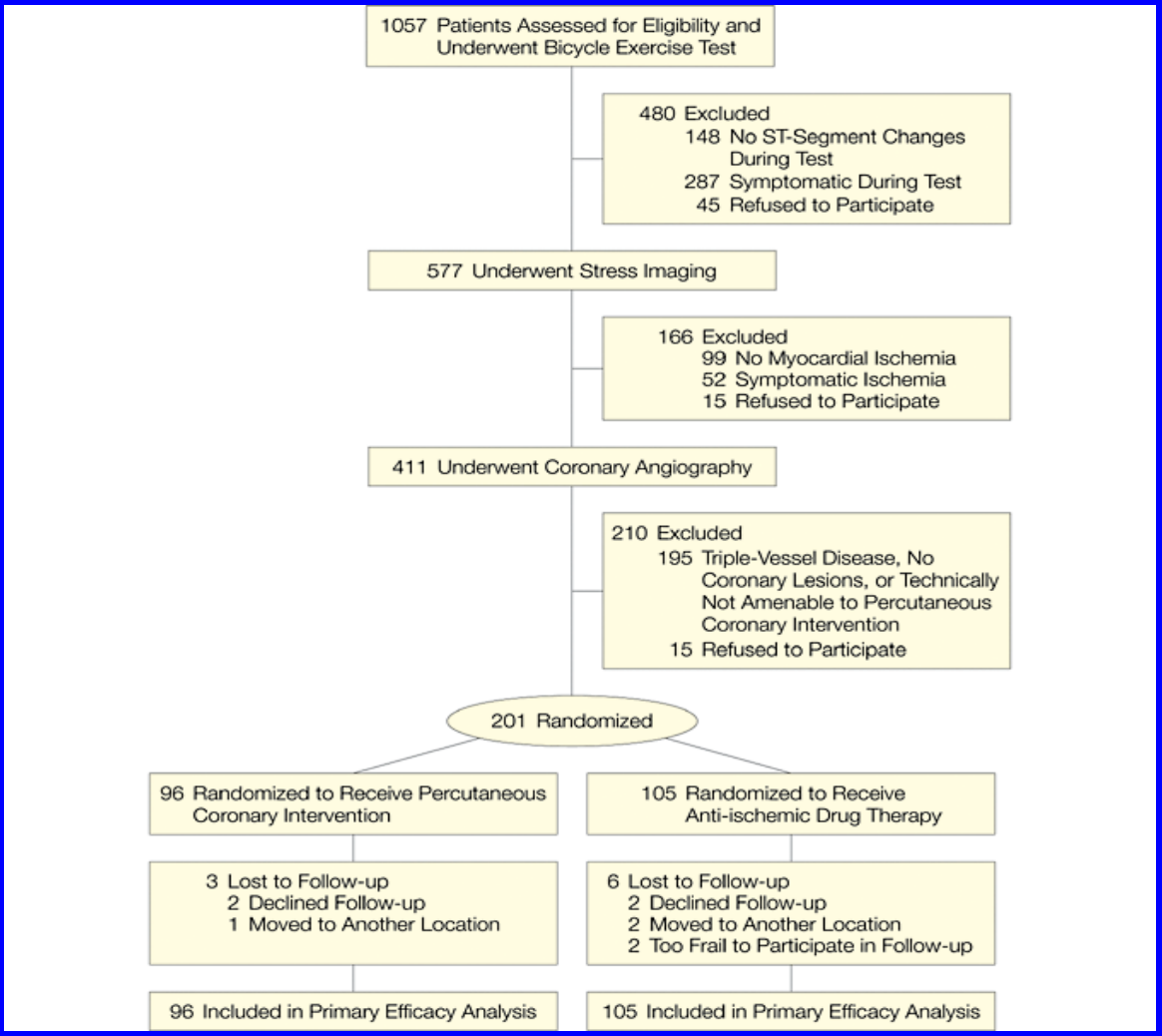
  or

  2) occur more than 5 hours from any episode of ischemia greater than 5 minutes in duration.

Properties of Nerve Growth Factor

- important for development of cardiac sympathetic innervation
- increases the number of sodium channels in neural membrane
- increased levels in myocardial ischemia
- protects against diabetic neuropathy, ischemic retinal ganglion cell damage, oxidant neural toxicity

Trial Profile



Erne, P. et al. JAMA 2007;297:1985-1991.

Event Outcomes

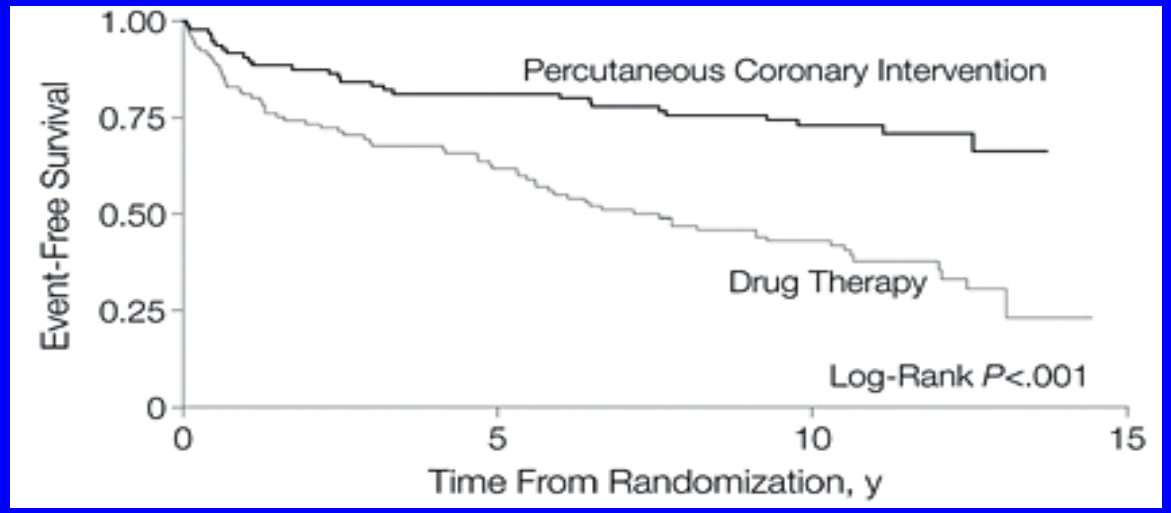
Table 2. Event Outcomes

	Event Rates*		Hazard Ratio (95% CI)		
	PCI (n = 96)	Drug Therapy (n = 105)	Unadjusted	Adjusted†	*P* Value
Primary end point‡					
Cardiac death, nonfatal recurrent MI, symptom-driven revascularization	27/841	67/703	0.35 (0.23-0.55)	0.33 (0.20-0.55)	<.001
Secondary end points§					
Cardiac death	3/1019	22/1048	0.14 (0.04-0.45)	0.19 (0.05-0.67)	.01
Nonfatal recurrent MI	11/938	40/856	0.26 (0.13-0.51)	0.31 (0.15-0.65)	.002
Symptom-driven revascularization	26/846	46/735	0.52 (0.32-0.84)	0.48 (0.28-0.82)	.008
Angina not leading to revascularization	11/973	32/948	0.33 (0.17-0.66)	0.37 (0.18-0.78)	.009
Death from noncardiac causes	3/1019	0/1048			
All-cause mortality	6/1019	22/1048	0.27 (0.11-0.68)	0.42 (0.16-1.11)	.08

Abbreviations: CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention.
*Presented as number of events/number of person-years of observation.
†Adjusted for age, sex, weight, diabetes, dyslipidemia, number of diseased vessels, number of lesions more than 75%, lesions in left circumflex artery, left ventricular ejection fraction, and left ventricular end diastolic pressure.
‡If a patient experienced more than 1 event of the primary end point, only the first event was counted.
§More than 1 type of event (initial and subsequent events) were allowed per patient.

Erne, P. et al. JAMA 2007;297:1985-1991.

SWISSI II Trial (Swiss Interventional Study on Silent Ischemia Type II)



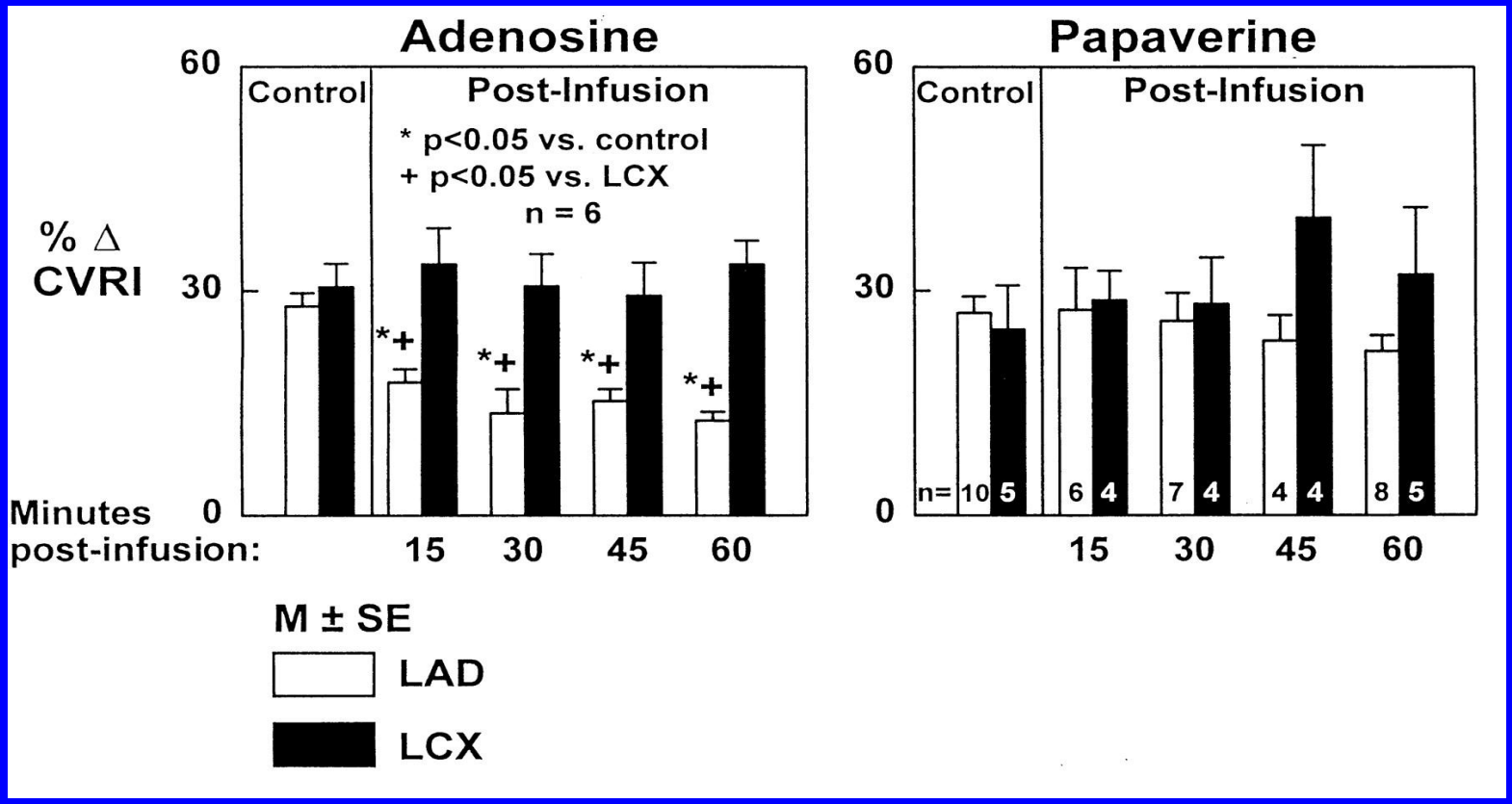
No. at Risk			
Percutaneous Coronary Intervention	96	77	54
Anti-ischemic Drug Therapy	105	64	37

- 201 asymptomatic patients post MI with SMI on imaging, 1-2 v CAD.
- randomized to PCI or drug Tx
- 2.6 year f/u for MACE

In this higher risk post-MI population,
- **treating SMI with PCI improved prognosis more than medical Rx after 2 and up to 10 years**
- **EF was maintained better after PCI**

Erne, P. et al. JAMA 2007;297:1985-1991.

Sympathetic Stunning: Role of Adenosine



Dog model of stellate stimulation before and after 15 minutes of adenosine infusion into the LAD

Pettersen, M. D. et al. Circ Res 1995;76:95-101

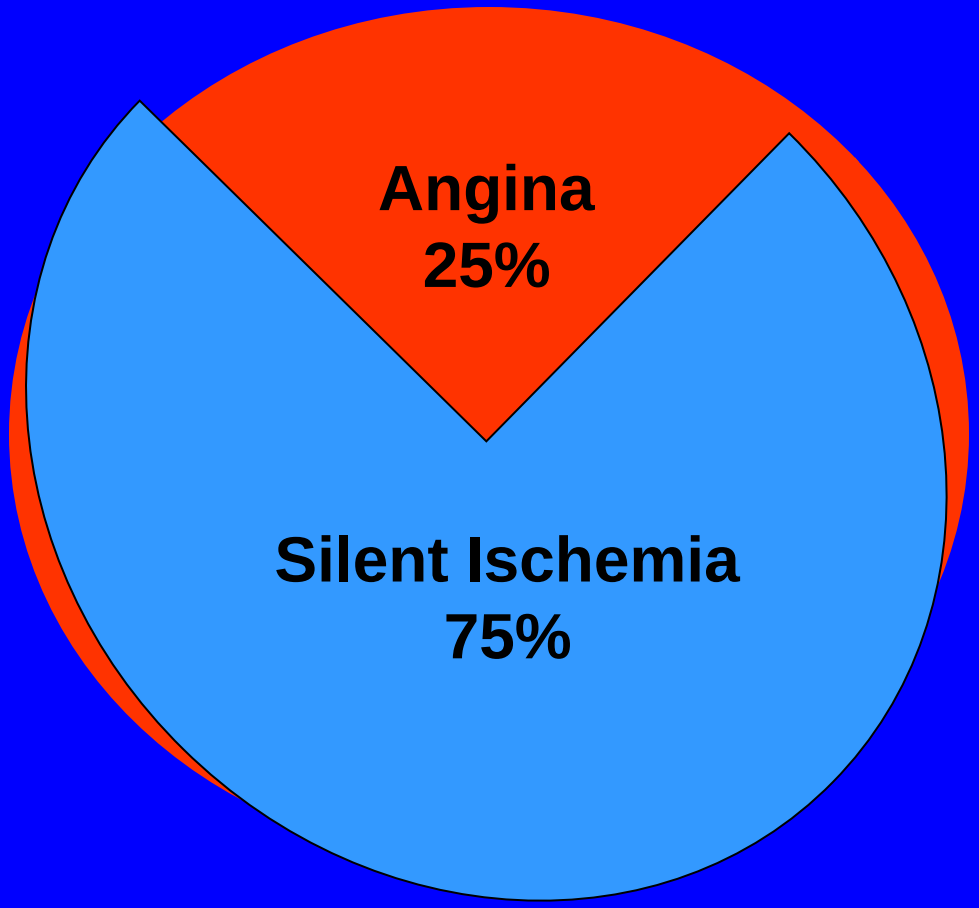
SMI: A growing clinical dilemma: 3 out of 4 ischemic episodes silent

Pepine (1977)

2,826 hrs of Holter monitoring 411 episodes of ST depression, only 101 with angina.

Deanfield (1983)

1,934 episodes of ST depression, only 470 episodes with angina



Alternate Theory of Heart Pain

The cardiac sensory system's ability to evolve and adapt cannot keep pace with the toxic changes in human eating habits (e.g. Big Mac)

The Teleological Paradox of Angina Pectoris

"…it is hard to understand the biological strategy and hence development of a system providing the wild animal with hundreds of fibers exclusively designed for signaling unlikely coronary emergencies."

- Malliani '1986

Sympathetic Stunning: Role of Adenosine Receptors

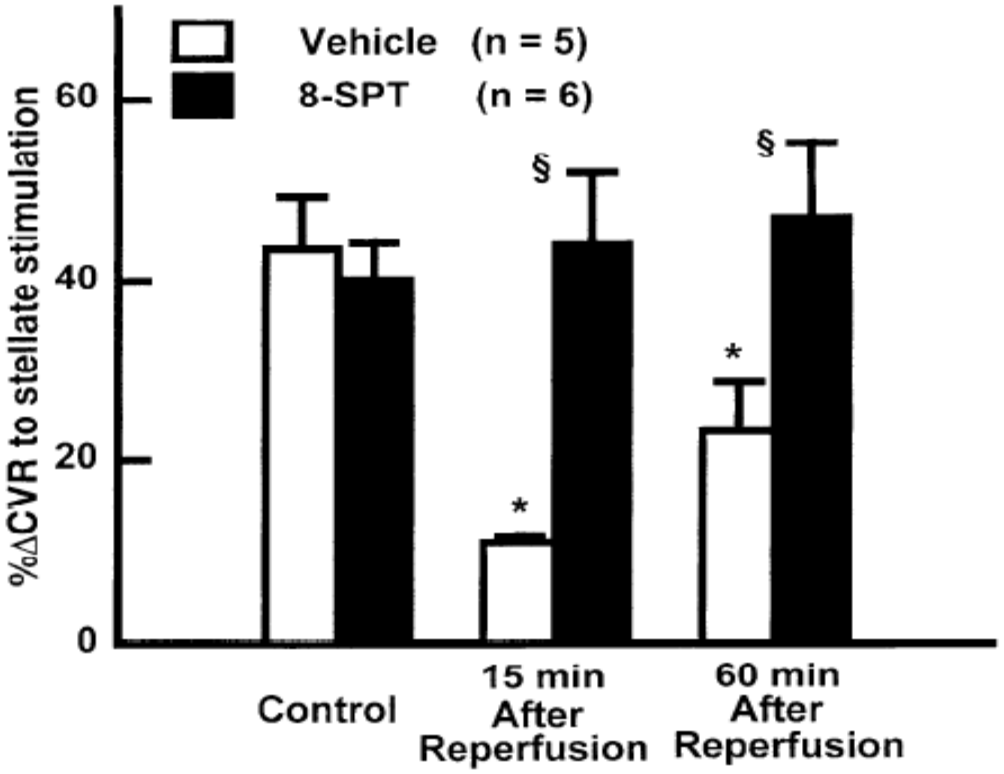
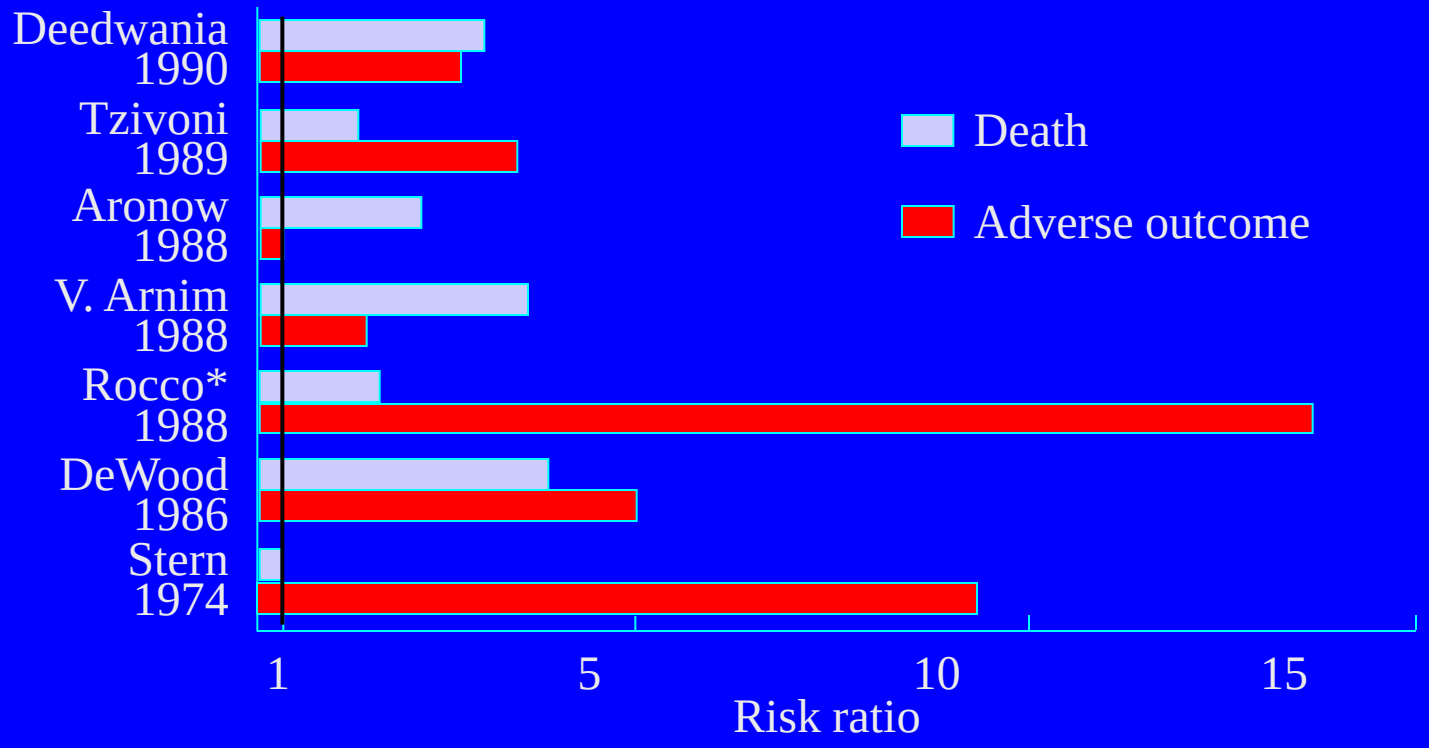


Fig. 3. Effect of 8-SPT on percent change in coronary vascular resistance (%ΔCVR). Values are means ± SE; *n*, no. of dogs. In vehicle group, coronary constriction (LAD bed) to SS was impaired during reperfusion. In contrast, 8-SPT, a nonselective adenosine-receptor antagonist, prevented this attenuation in constriction. Sympathetic coronary constriction in LCX bed was not affected in any protocol (data not shown). Significant difference ($P < 0.05$) from: * control; § vehicle group.

- Abe, et al., AJP, 1997



Bar graphs showing influence of silent ischemia, as detected by ambulatory monitoring, on risk of death ( ) or adverse outcome (eath and/or nonfatal myocardial infarction,) in patients with stable angina or stab e coronary artery disease. Data from seven studies comprising >500 patients, with follow-up ranging from 6 to 36 months. The increased risk for adverse outcome associated with detectable ischemia ranges from about twofold to 14-fold and for death from about twofold to fourfold for adverse outcome. *Antianginal medications discontinued.

- Pepine, et al. Circ 1990