What Did You Know And When (And How) Did You Know It?

The Evolution Of A Treatment Standard For Non-ST Elevation MI

John Coyle, M.D.
October 21, 2009

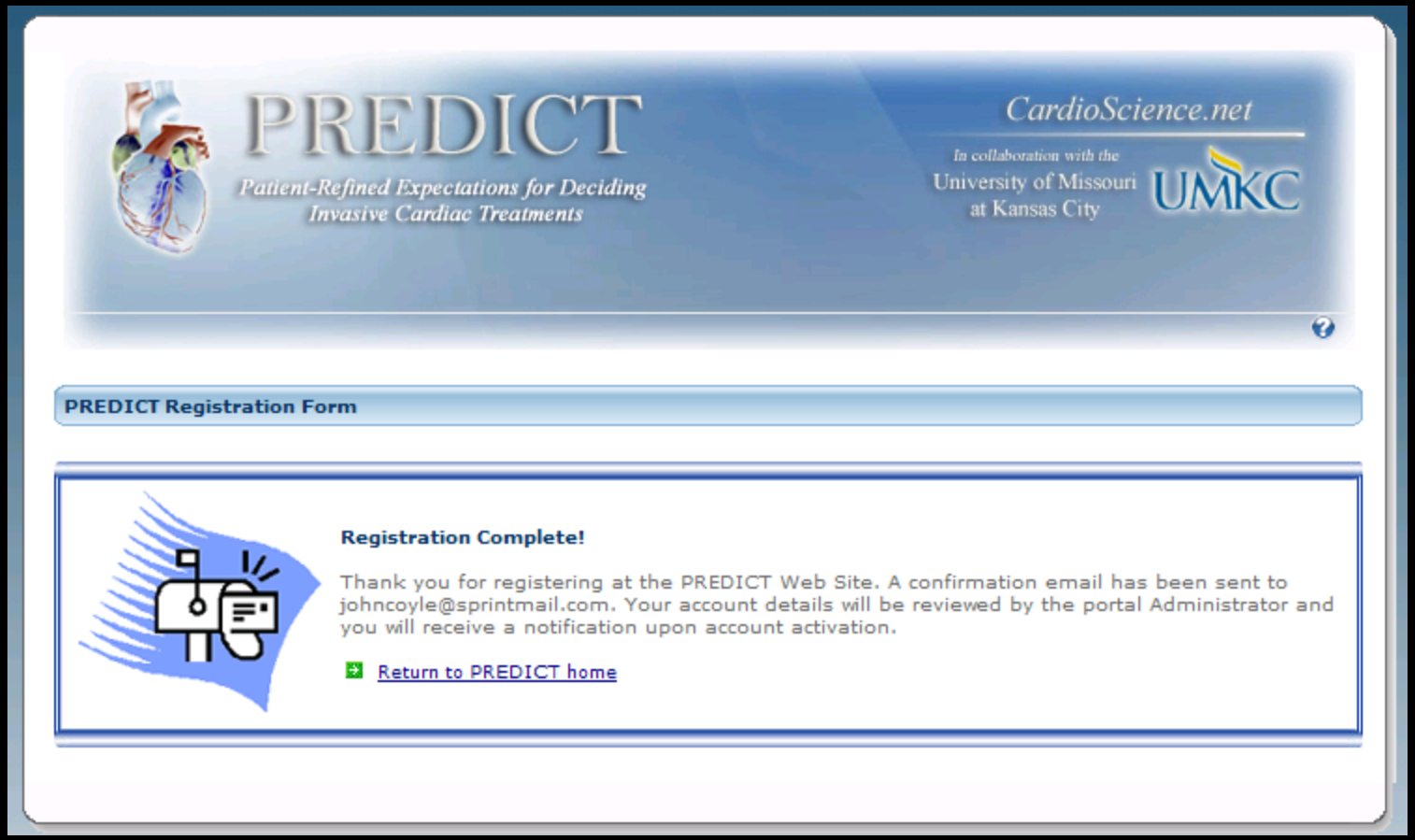
Elective Coronary Angioplasty:

Percentage of patients who believed the following to be true

Patient beliefs	%	
Procedure was an emergency	33	
Procedure would help prevent MI	71	p<0.0001
Procedure would extend life	66	p<0.0001
Procedure saved their life	42	
Procedure improved stress test abnormality	42	
Procedure decreased angina symptoms	31	

Offered only PCI = 68%, or medication 18% or CABG 13%.
Change in alternatives offered after COURAGE = 0%.

Lee J. American Heart Association 2008 Scientific Sessions; November 12, 2008; New Orleans, LA.



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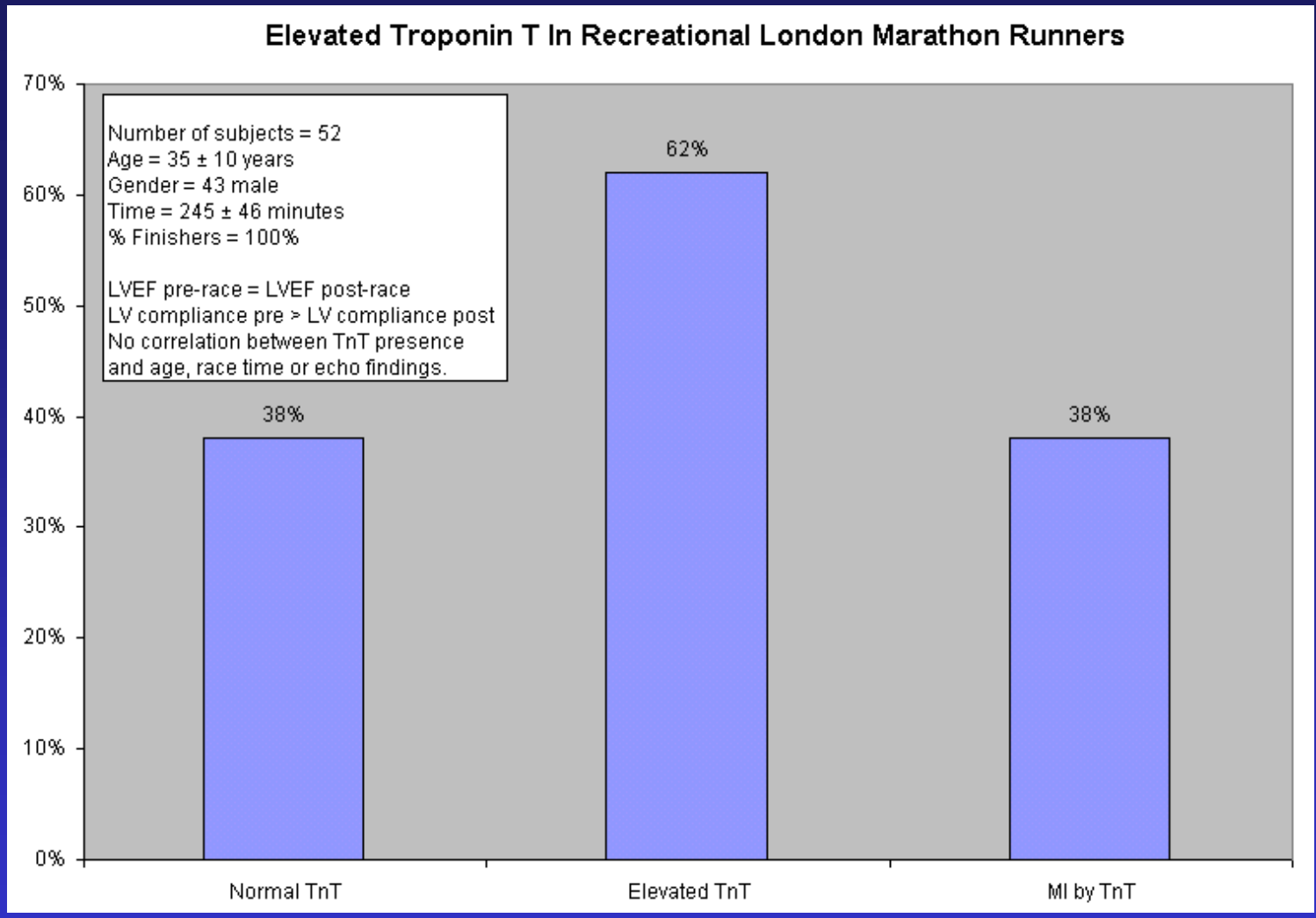
Nonthrombotic Causes and Presumed Mechanism for Elevated Cardiac Troponin Level

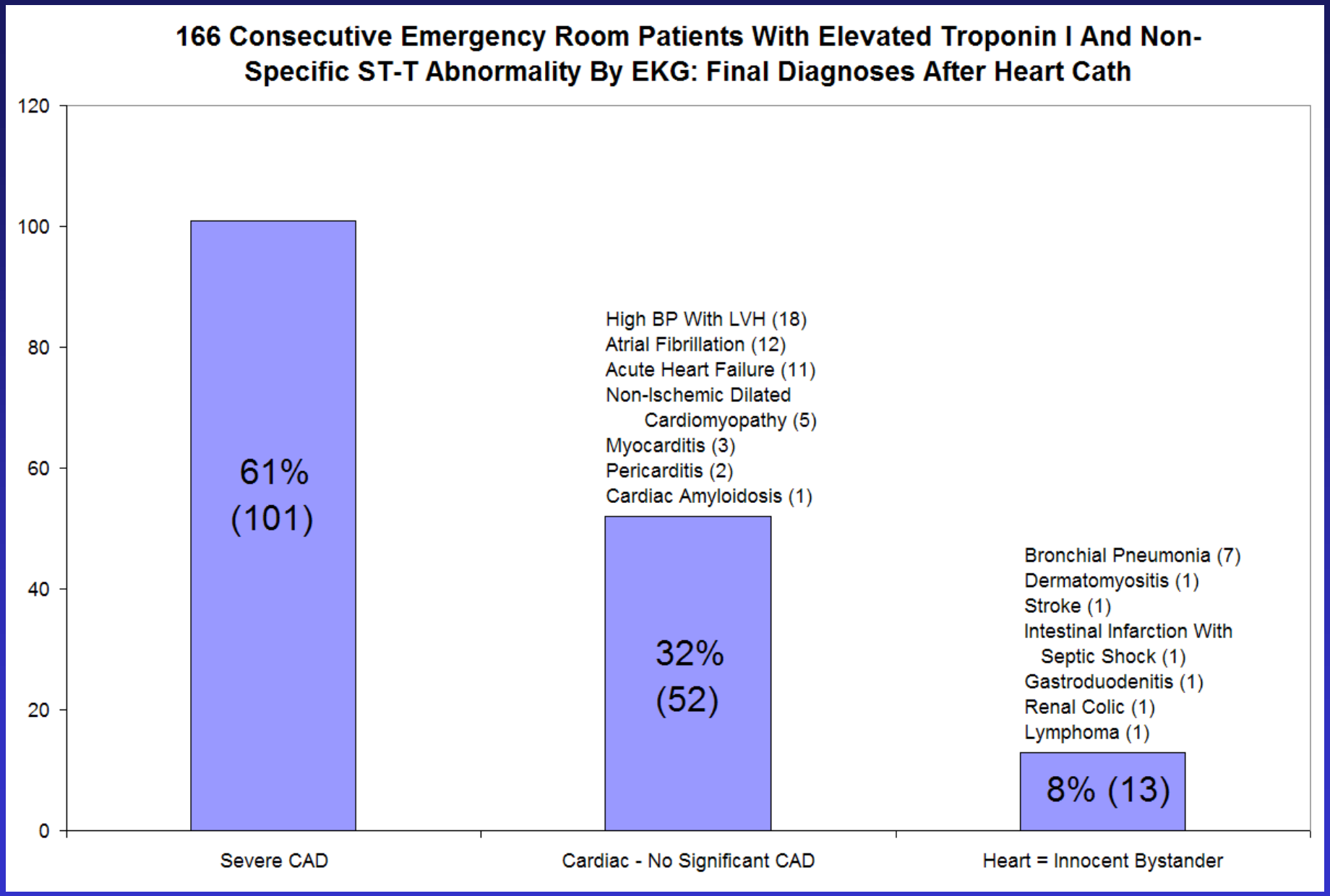
Diagnosis	Mechanism
Demand Ischemia	
Sepsis/systemic inflammatory response syndrome	Myocardial depression/supply–demand mismatch
Hypotension	Decreased perfusion pressure
Hypovolemia	Decreased filling pressure/output
Supraventricular tachycardia/ atrial fibrillation	Supply–demand mismatch
Left ventricular hypertrophy	Subendocardial ischemia
Myocardial Ischemia	
Coronary vasospasm	Prolonged ischemia with myonecrosis
Intracranial hemorrhage or stroke	Imbalance of autonomic nervous system
Ingestion of sympathomimetic agents	Direct adrenergic effects
Direct myocardial damage	
Cardiac contusion	Traumatic
Direct current cardioversion	Traumatic
Cardiac infiltrative disorders	Myocyte compression
Chemotherapy	Cardiac toxicity
Myocarditis	Inflammatory
Pericarditis	Inflammatory
Cardiac transplantation	Inflammatory/immune-mediated
Myocardial strain	
Congestive heart failure	Myocardial wall stretch
Pulmonary embolism	Right ventricular stretch
Pulmonary hypertension or emphysema	Right ventricular stretch
Strenuous exercise	Ventricular stretch
Chronic renal insufficiency	Unknown

Jeremias A, et al. Ann Int Med 142:786, 2005.



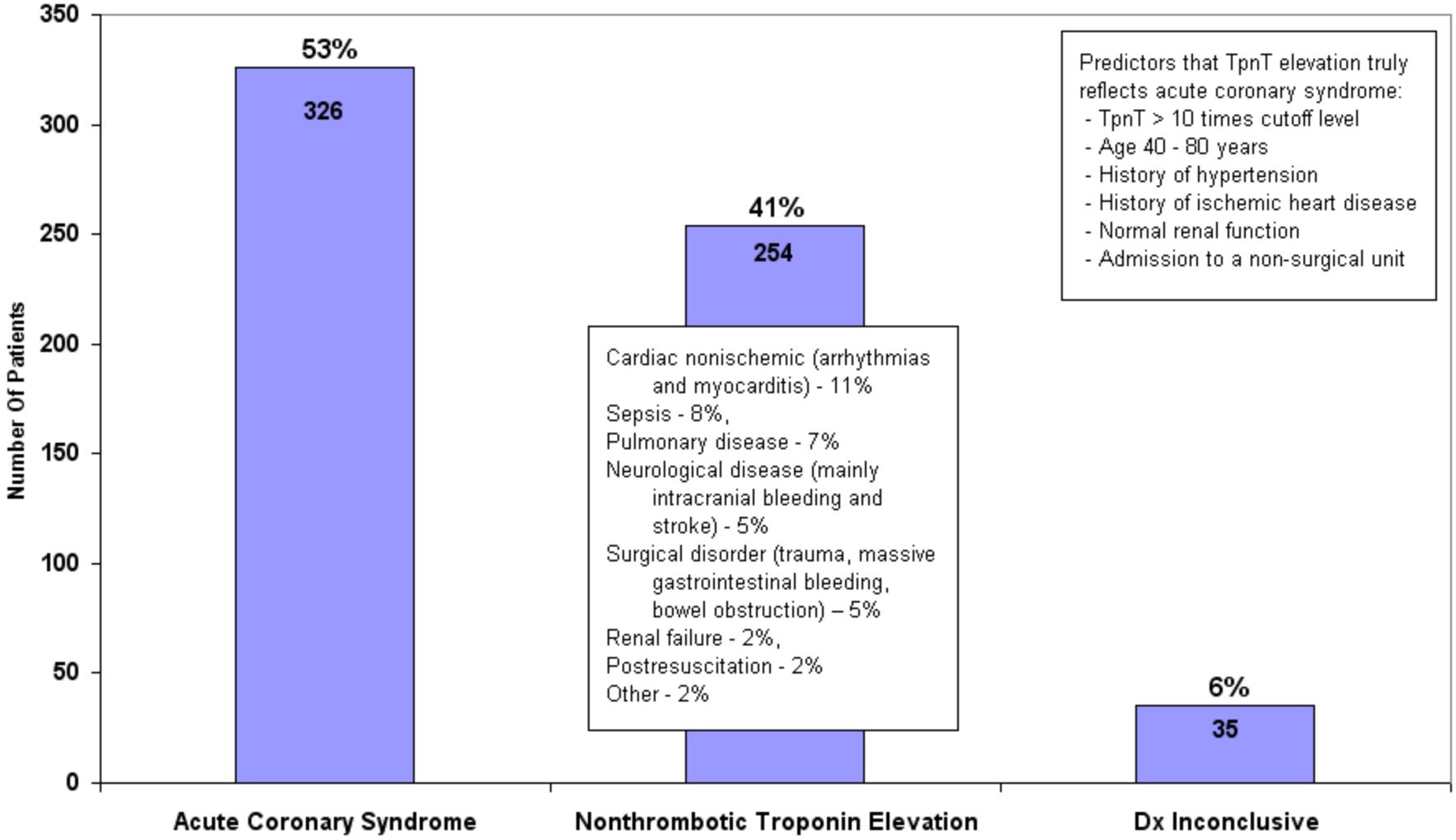
Whyte G et al. Impact of marathon running on cardiac structure and function in recreational runners. Clinical Science (2005) 108: 73–80.

"Detectable increases in biomarkers of cardiac injury are indicative of injury to the myocardium, but elevations are not synonymous with an ischemic mechanism of injury. Therefore, increases do not now and did not in the past mandate a diagnosis of myocardial infarction." Jaffe AS et al. Circulation 102 (2000):1216-1220.



Bucciarelli-Ducci C et al. Coronary Artery Disease 15:499-504, 2004.

Troponin T Elevation In Hospitalized Patients: Final Diagnostic Assignment In All 615 Consecutive Patients With Elevated Troponin T. (January 2003 - October 2003)



Alcalai R, et al. Arch IM 167:276, 2007. Hadassah-Hebrew University Medical Center, Jerusalem.

Survival In 615 Consecutive Hospitalized Patients With Elevated Troponin T According To Diagnosis

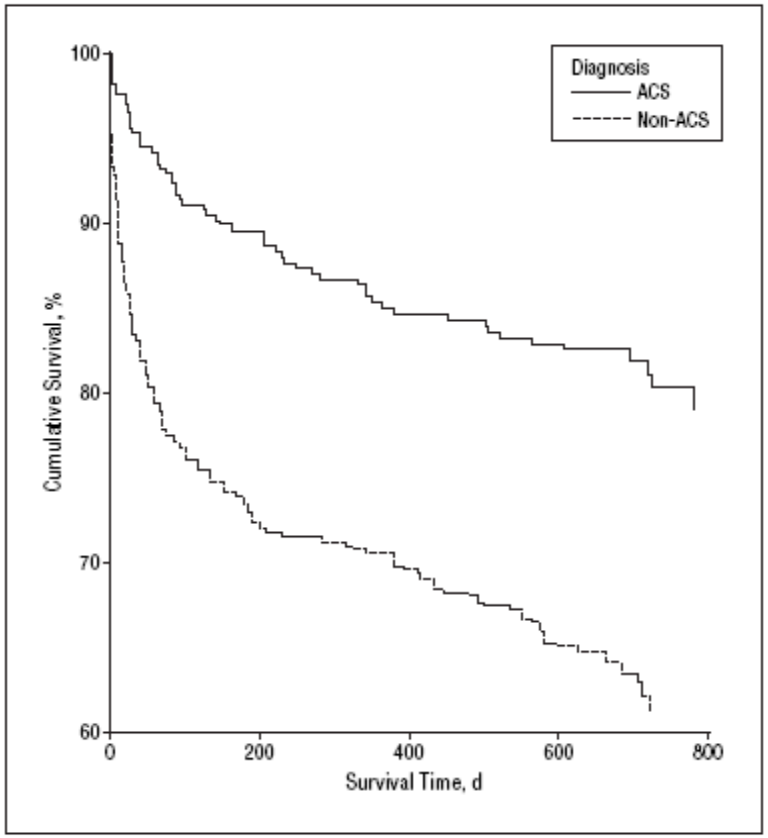


Figure 1. Survival curves according to principal diagnosis during hospitalization after adjustment for age, sex, diabetes, plasma creatinine levels, and left ventricular function. ACS indicates acute coronary syndrome.

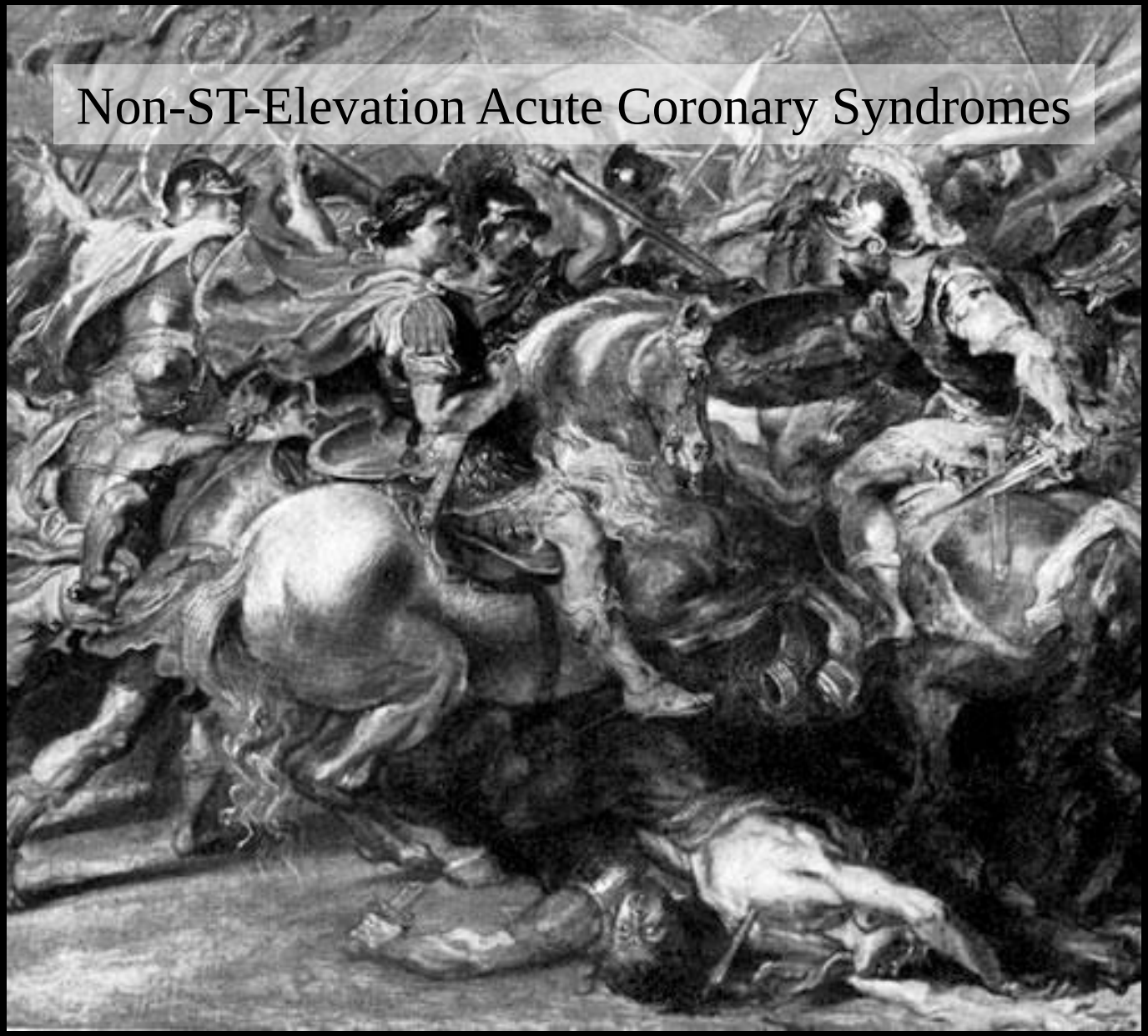
The findings suggest that "troponin level probably should serve as an indicator of a critical state of a noncardiac condition," they write. Often in their study "the troponin test was performed as a 'screening' test for a patient with deteriorating health, and as such it is only a marker of multiorgan failure and poor prognosis. We think this attitude should be discouraged because it may lead to inappropriate treatment and interventions."

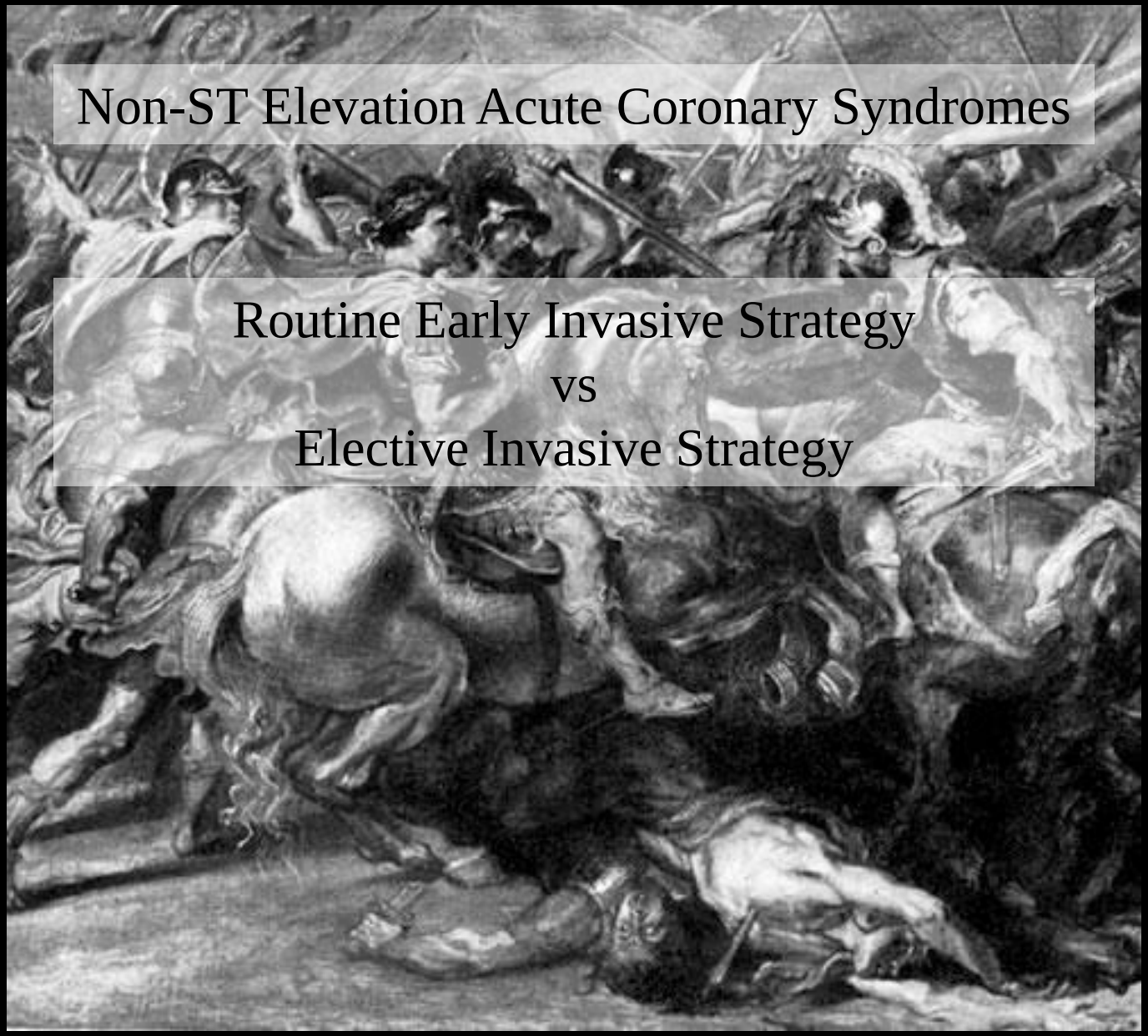
"Our results strengthen the fact that even in a diagnostic test with a known excellent sensitivity and specificity, to ignore the pretest probability, namely the clinical evaluation, results in a high rate of misdiagnosis."

Dr. James De Lemos (Southwestern Medical Center), who was not involved in the study, observed that treatment guidelines that call for antithrombotics and other ACS-appropriate interventions when troponins are elevated can be misinterpreted—they are supposed to apply only to patients who also have a clinical presentation that indicates ACS. It's that group in whom the test is most useful, "not in broad groups of sick patients, because we don't know yet what to do with those tests.“

Alcalai R, et al. Arch IM 167:276, 2007. Hadassah-Hebrew University Medical Center, Jerusalem.

Non-ST-Elevation Acute Coronary Syndromes





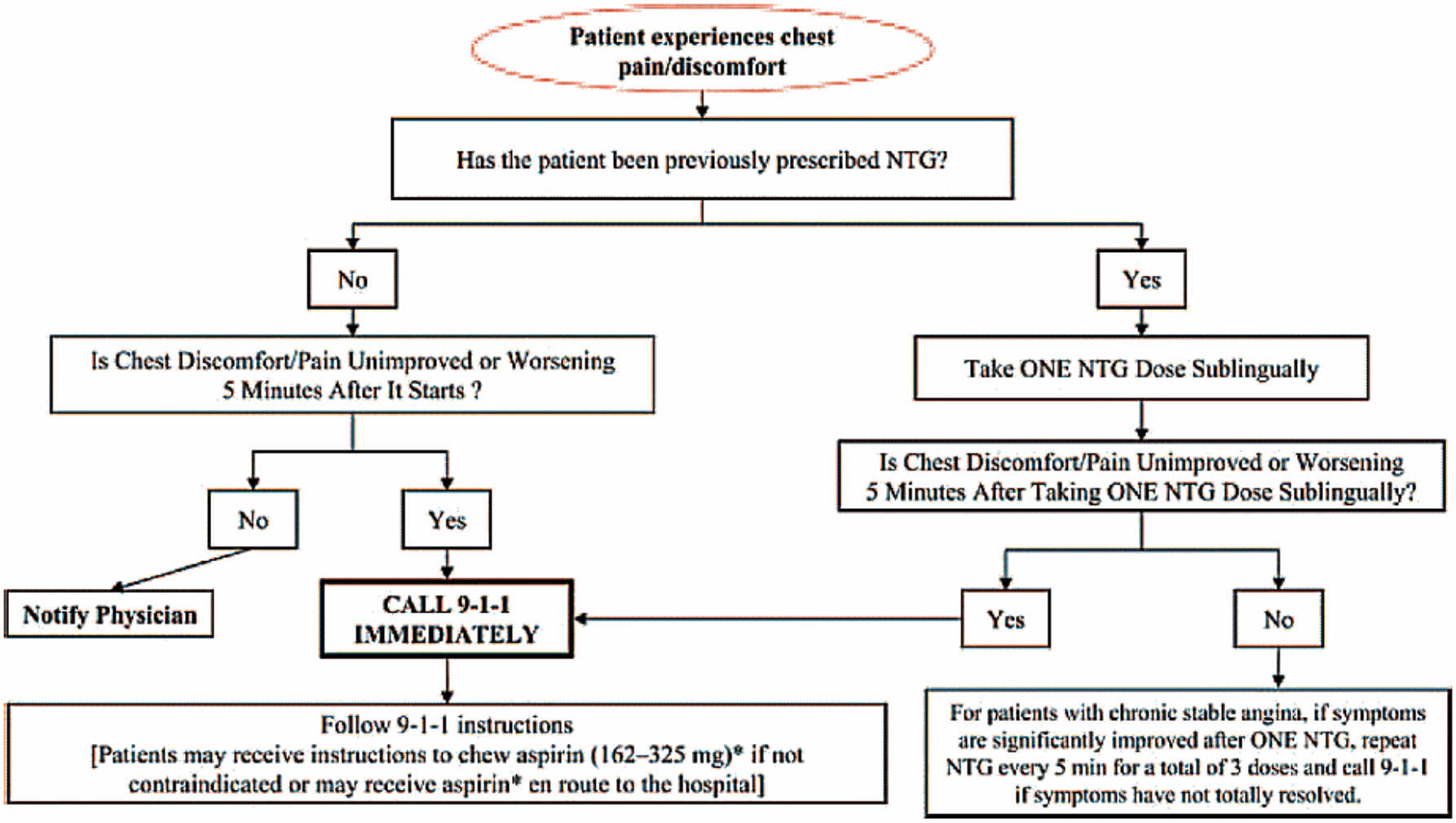
Non-ST Elevation Acute Coronary Syndromes

Routine Early Invasive Strategy
vs
Elective Invasive Strategy

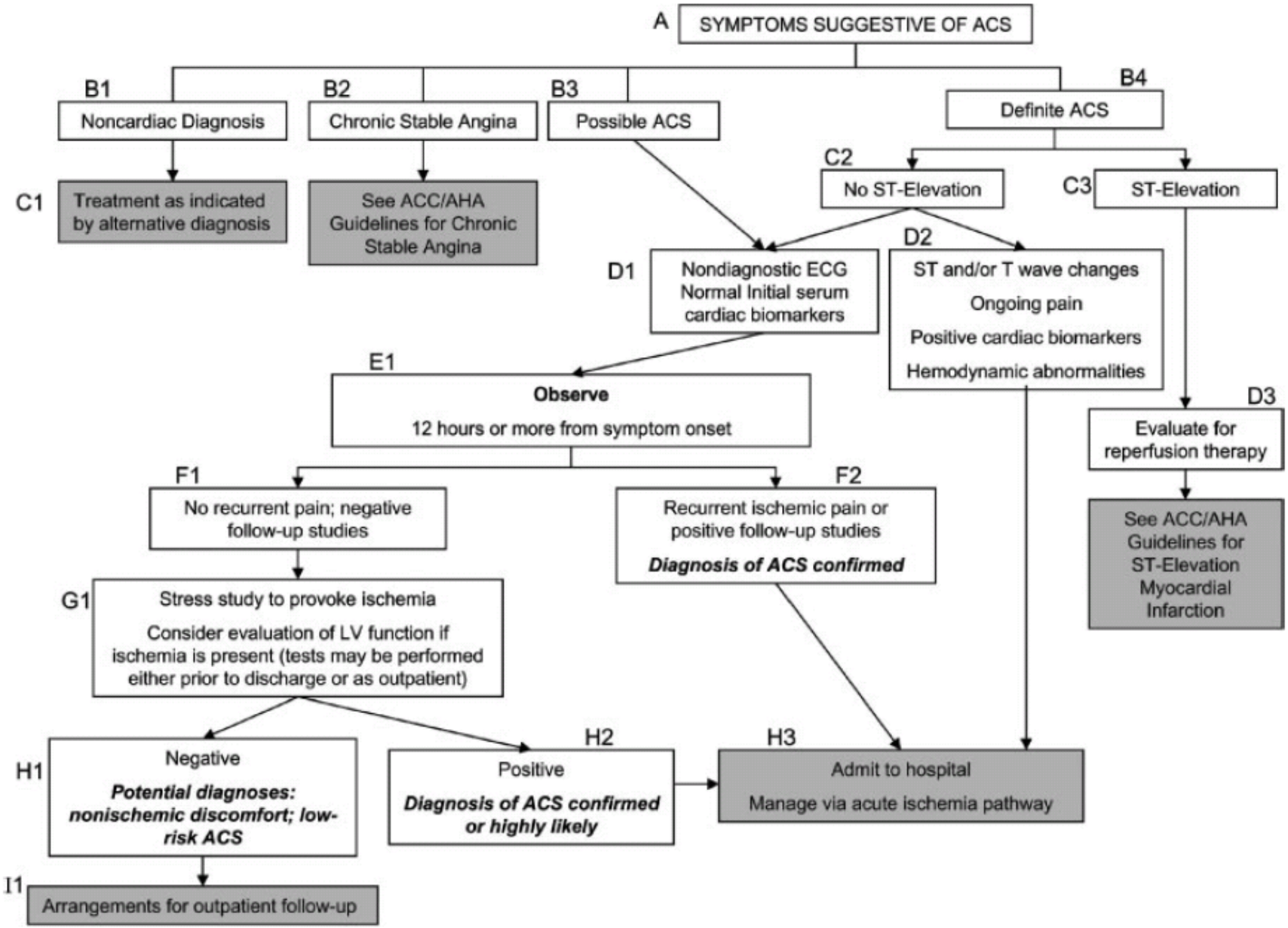

Non-ST Elevation Acute Coronary Syndromes
Routine Early Invasive Strategy
vs
Elective Invasive Strategy
18+ Years Of Cordial Dialogue

ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction

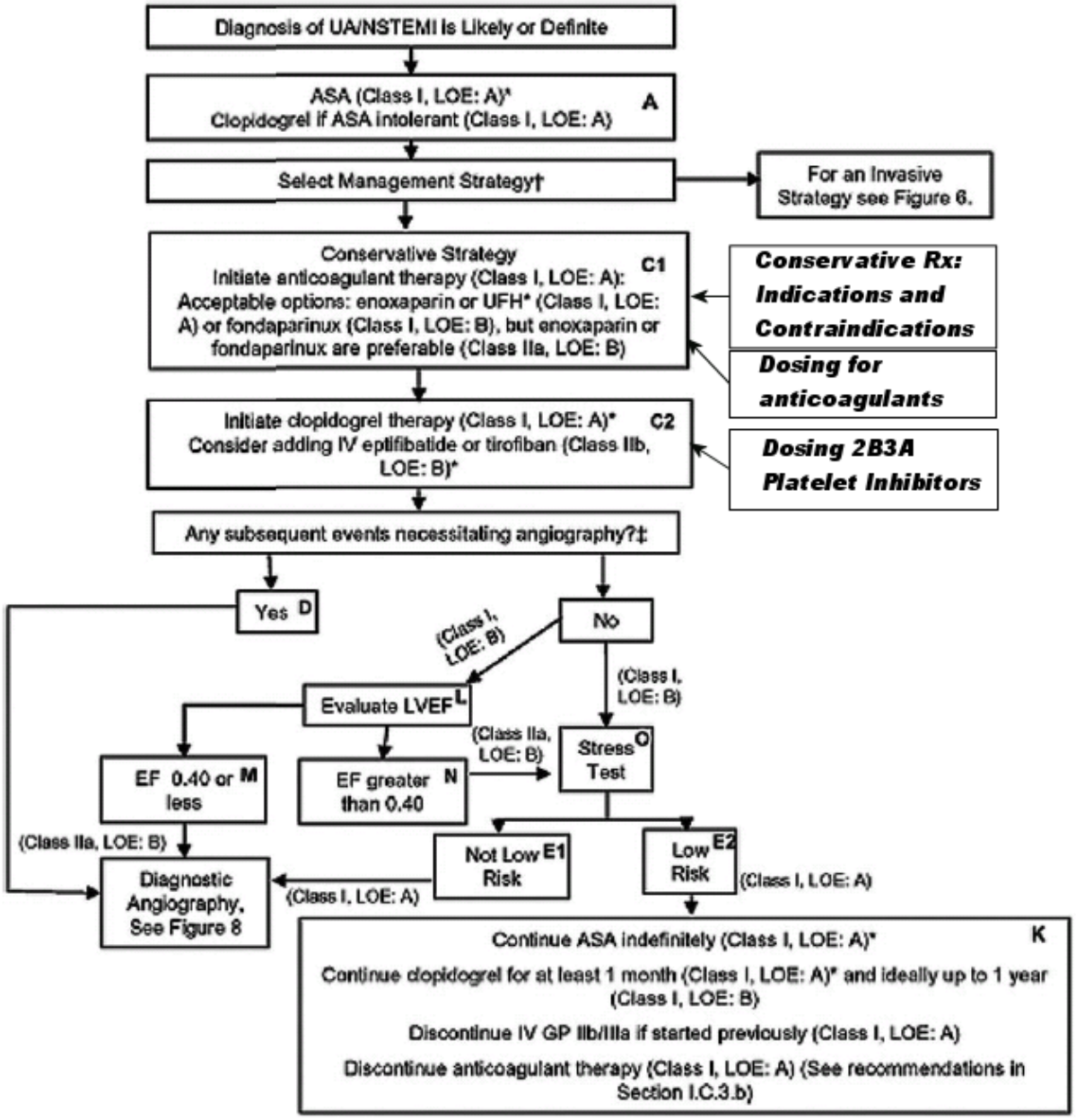
Initial Response To Patient Complaint Of Chest Pain/Discomfort



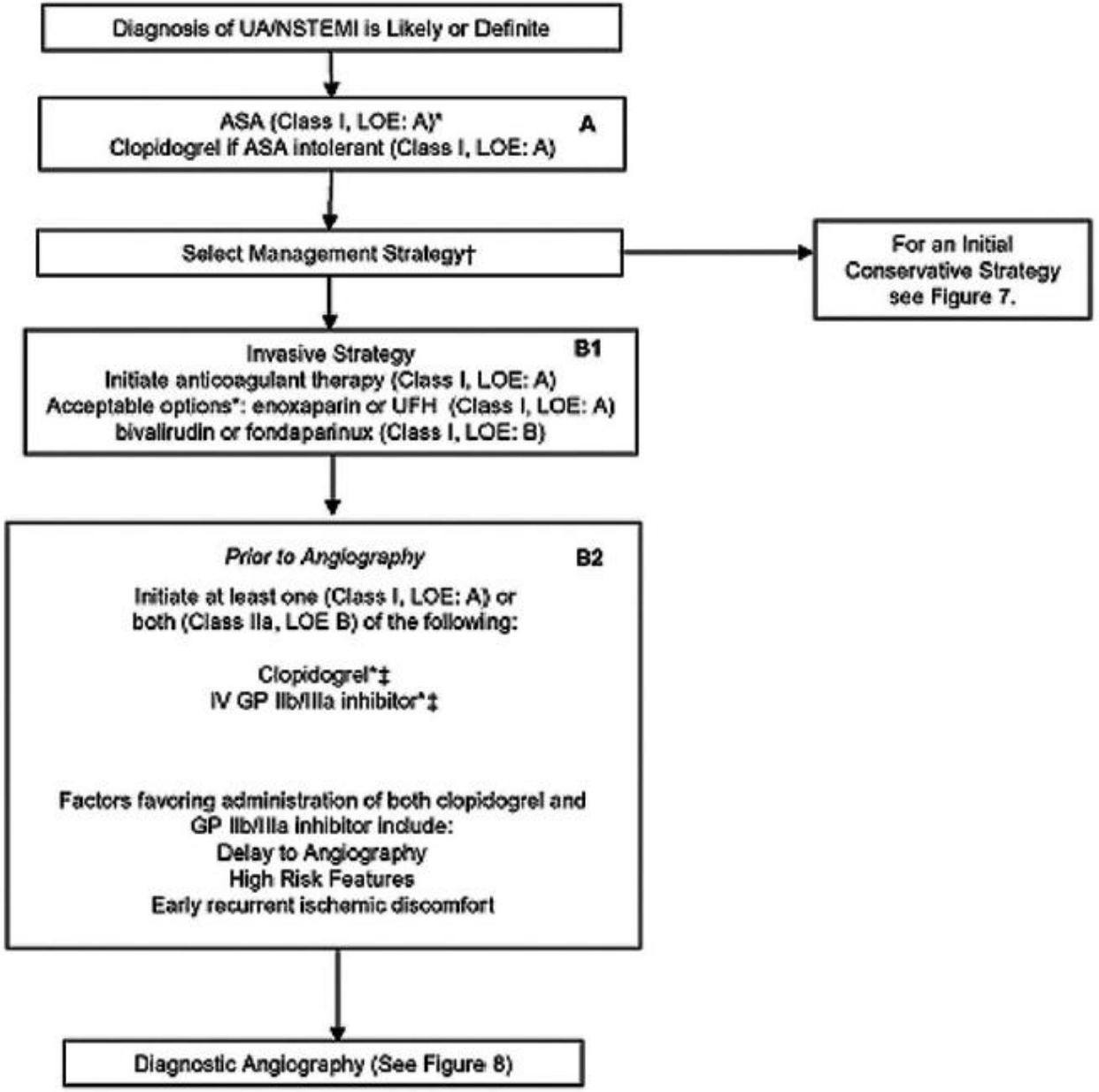
Initial Evaluation Of Chest Pain/Discomfort



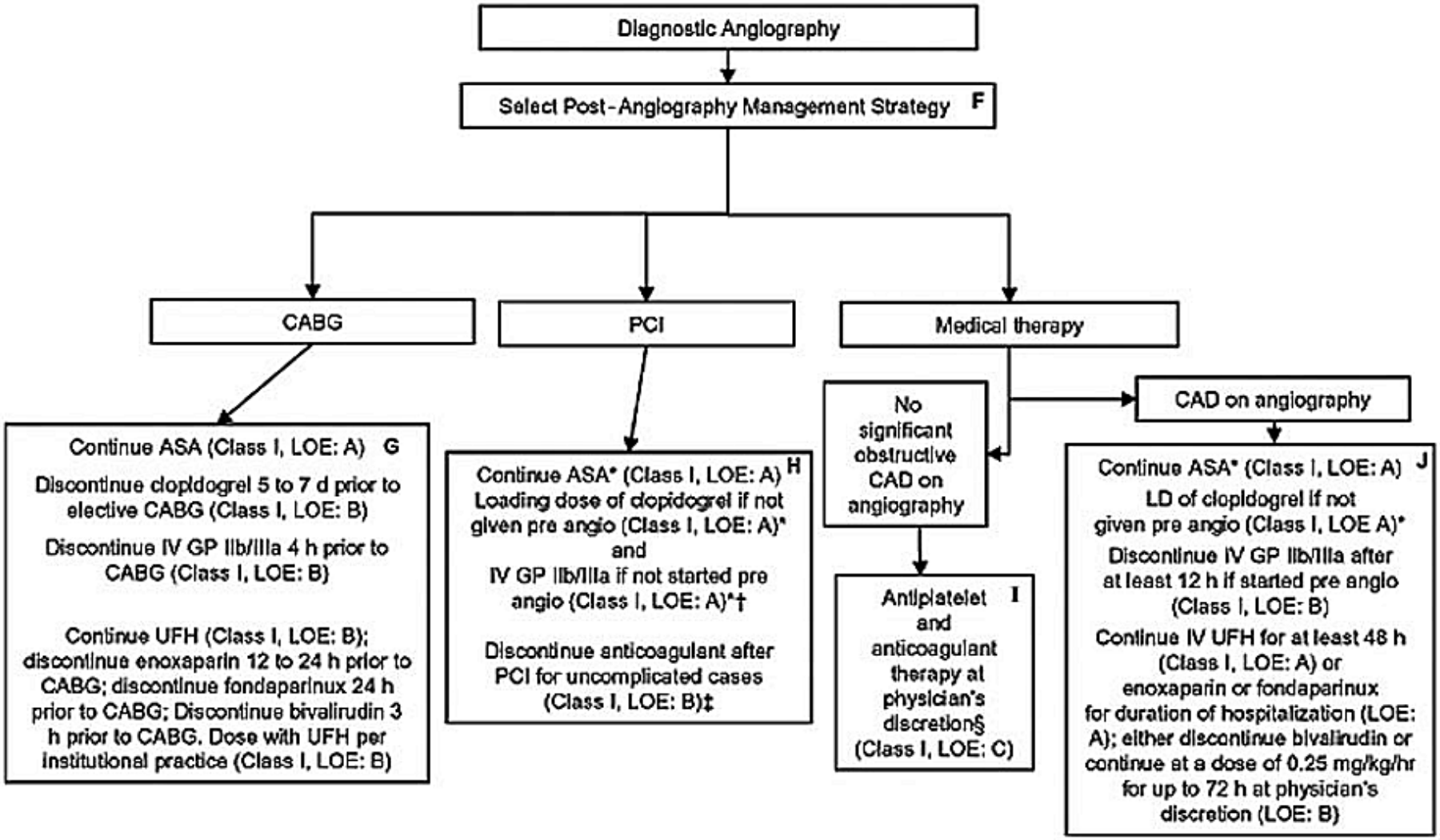
Conservative Management Pathway In Unstable Angina/ NSTEMI



Invasive Management Pathway In Unstable Angina/ NSTEMI (Step 1)



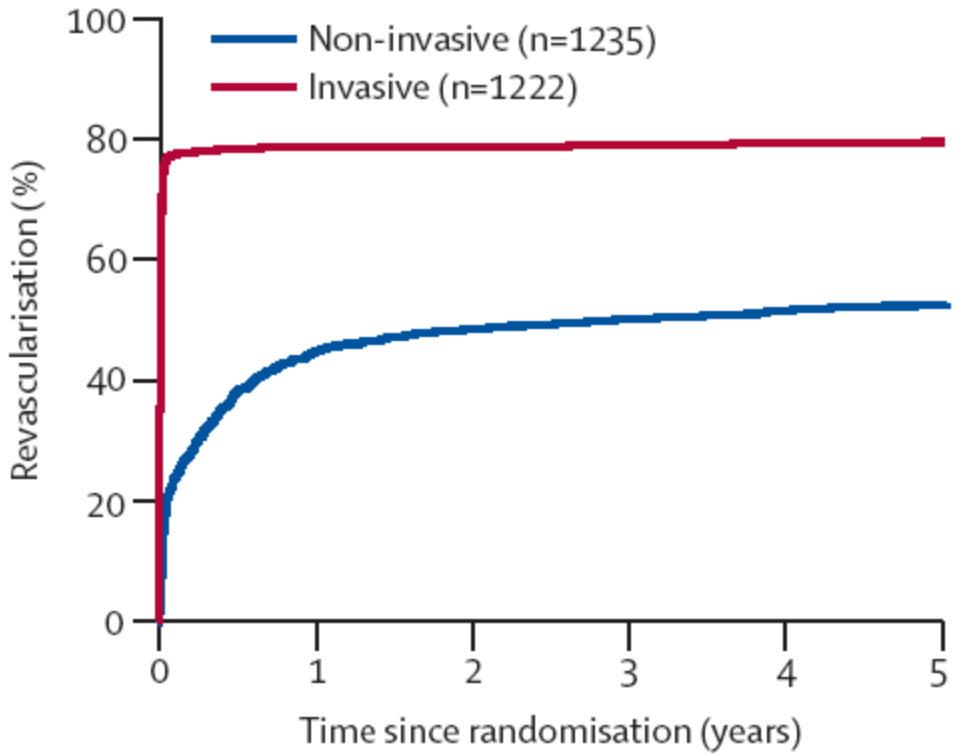
Invasive Management Pathway In Unstable Angina/ NSTEMI (Step 2)



Clinical Trials Evaluating Early Invasive Versus Selective Invasive Treatment Of Non-ST-Elevation MI

Studies Favoring Routine Early Invasive Strategy	Studies Favoring/Allowing Selective Invasive Strategy
TACTICS-TIMI 18	VANQUISH
RITA 3 Enrollment: 1997-2001 Size: 1810 pts Follow-up: 5 years	TIMI IIIB
FRISC II Enrollment: 1996-1998 Size: 2457 pts Follow-up: 5 years	ICTUS Enrollment: 2001-2003 Size: 1200 pts Follow-up: 4 years

FRISC-II: Date of First Revascularization



Numbers at risk

Invasive	1222	1095	1065	940	910	876
Non-invasive	1235	1061	1017	887	854	832

Figure 2: **Timing of first revascularisation procedure**

ICTUS: Invasive vs. Selectively Invasive Strategy In Patients With Unstable Angina/Non-ST Elevation MI (NEJM 353:1085,2005)

Eligible patients had to have all three of the following:

(1) symptoms of ischemia that were increasing or occurred at rest, with the last episode occurring no more than 24 hours before randomization;
(2) an elevated cardiac troponin T level (=0.03 µ g per liter); and
(3) either ischemic changes as assessed by electrocardiography (defined as ST-segment depression or transient ST-segment elevation exceeding 0.05 mV, or T-wave inversion of =0.2 mV in two contiguous leads) **or a documented history of coronary artery disease** as evidenced by previous myocardial infarction, findings on previous coronary angiography, or a positive exercise test.

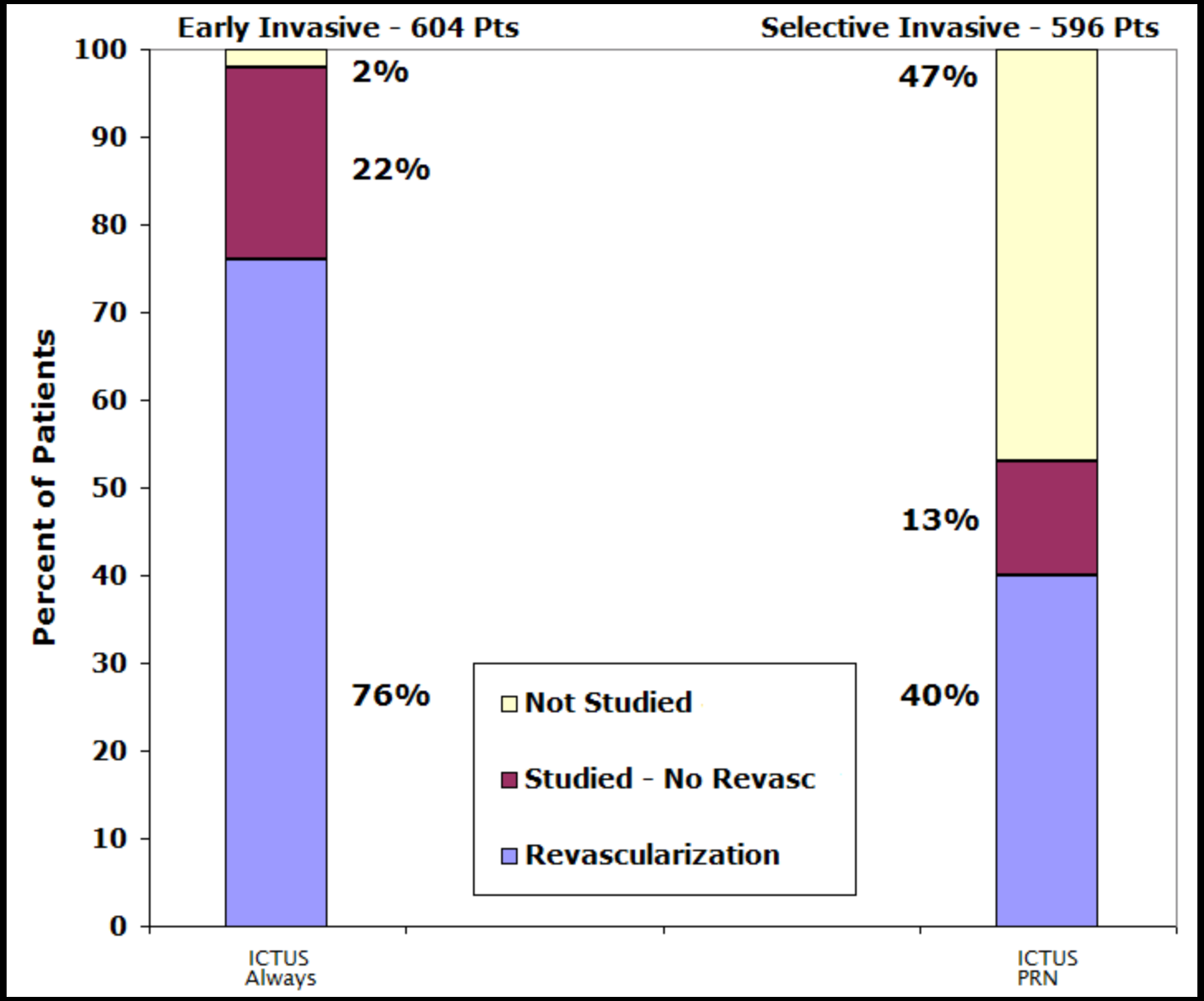
Exclusion criteria:
(1) age younger than 18 years or older than 80 years,
(2) myocardial infarction with ST-segment elevation in the past 48 hours,
(3) an indication for primary percutaneous coronary intervention or fibrinolytic therapy,
(4) hemodynamic instability or overt congestive heart failure,
(5) the use of oral anticoagulant drugs in the past 7 days,
(6) fibrinolytic treatment within the past 96 hours,
(7) percutaneous coronary intervention within the past 14 days,
(8) a contraindication to treatment with percutaneous coronary intervention or glycoprotein IIb/IIIa inhibitors,
(9) recent trauma or risk of bleeding,
(10) hypertension despite treatment (i.e., systolic pressure >180 mm Hg or diastolic pressure >100 mm Hg),
(11) weight greater than 120 kg, or
(12) inability to give informed consent.

Protocol:
(1) Patients receive 300 mg of **aspirin** at the time of randomization, followed by at least 75 mg daily indefinitely.
(2) Enoxaparin (1 mg per kilogram of body weight, to a maximum of 80 mg) twice daily subcutaneously for at least 48 hours. Patients already started on unfraction ated heparin were switched to enoxaparin immediately after randomization.
(3) Early use of **clopidogrel** (300 mg immediately, followed by 75 mg daily) in combination with aspirin.
(4) All interventional procedures during the initial hospital phase were performed with the use of **abciximab**, given as a bolus dose of 0.25 mg per kilogram, followed by an infusion of 0.125 μ g per kilogram per minute for 12 hours, and started 10 to 60 minutes before the first balloon inflation. Abciximab was also available for use in patients who subsequently underwent percutaneous revascularization.
(5) The protocol recommended intensive lipid-lowering therapy, preferably **80 mg of atorvastatin daily** or the equivalent, started as soon as possible after randomization and continued indefinitely.

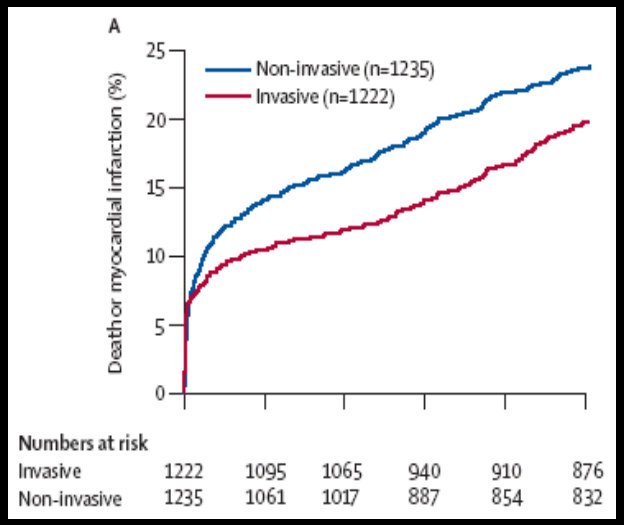
Patients assigned to the early invasive strategy were scheduled to undergo angiography within 24 to 48 hours after randomization and percutaneous coronary intervention when appropriate on the basis of the coronary anatomy. Coronary-artery bypass grafting was recommended in patients with extensive three-vessel disease or severe left main-stem disease and was to be performed as soon as possible during the initial hospitalization period.

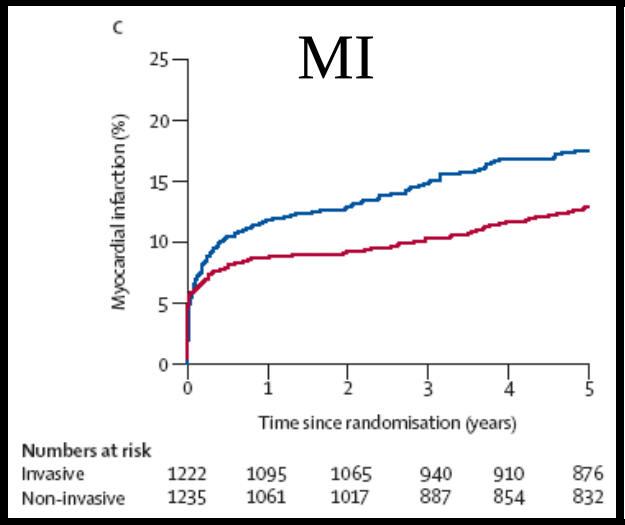
Patients assigned to the selectively invasive strategy were treated medically. These patients were scheduled to undergo angiography and subsequent revascularization only if they had refractory angina despite optimal medical treatment, hemodynamic or rhythmic instability, or clinically significant ischemia on the predischarge exercise test. Coronary angiography and revascularization after the initial hospital phase were performed if severe anginal symptoms (i.e., Canadian Cardiovascular Society [CCS] class lll or lV) persisted despite optimal antianginal medication or if ischemia was documented on subsequent testing. Follow-up outpatient visits occurred at 1, 6, and 12 months after randomization.

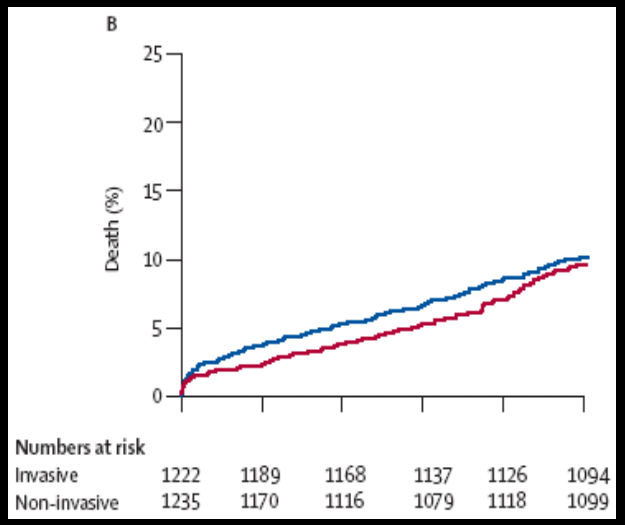
ICTUS: Revascularization During Initial Hospitalization



FRISC-II: 5-Year Outcomes

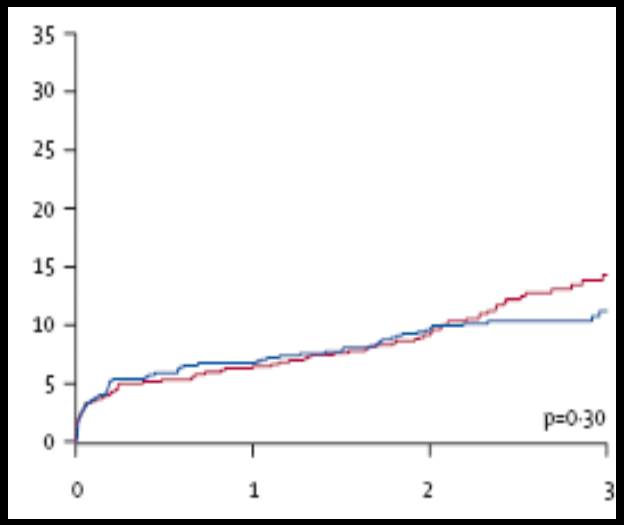


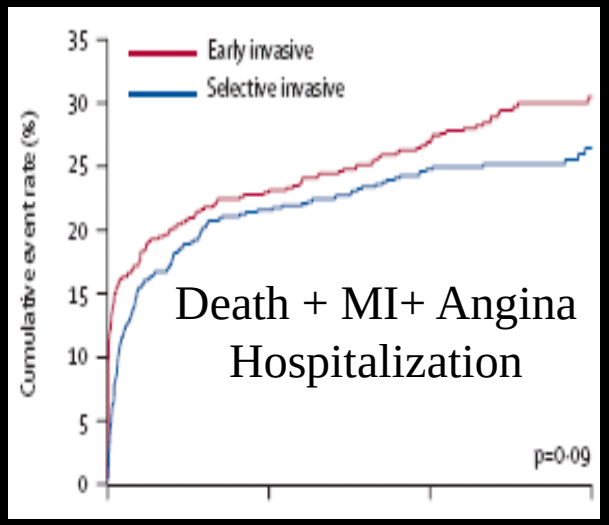


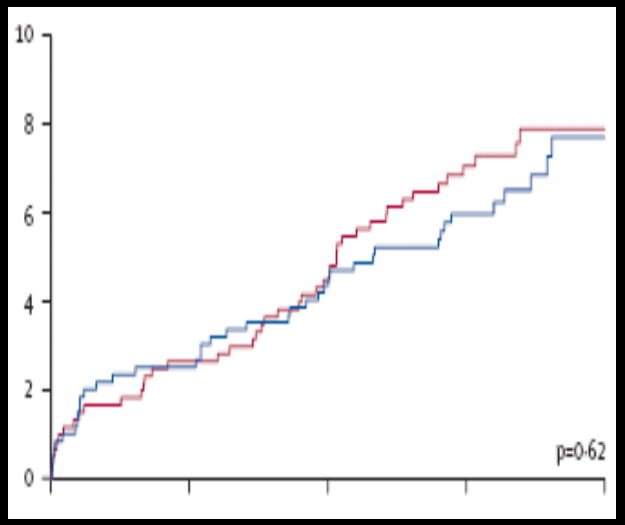


Death + MI

Death

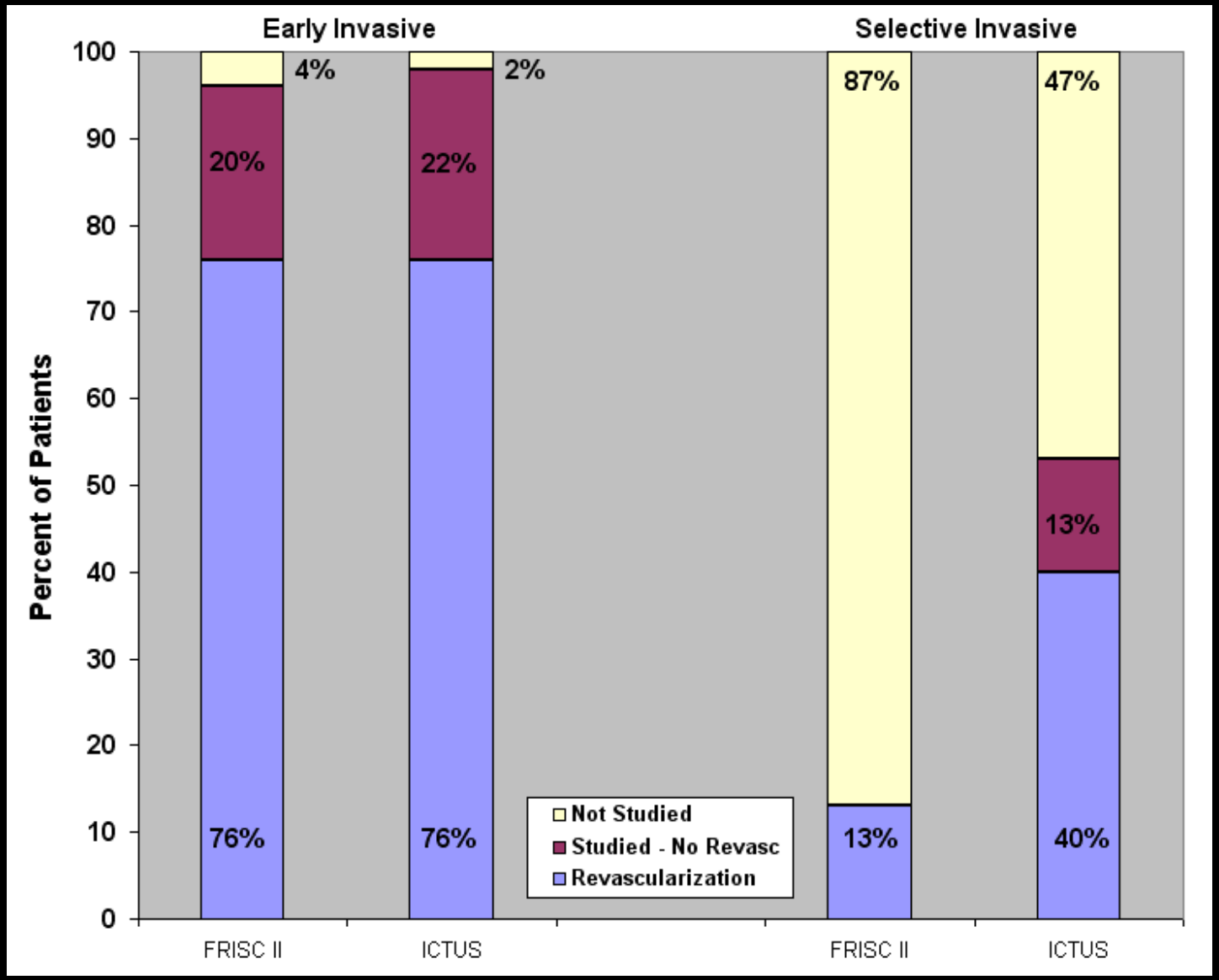




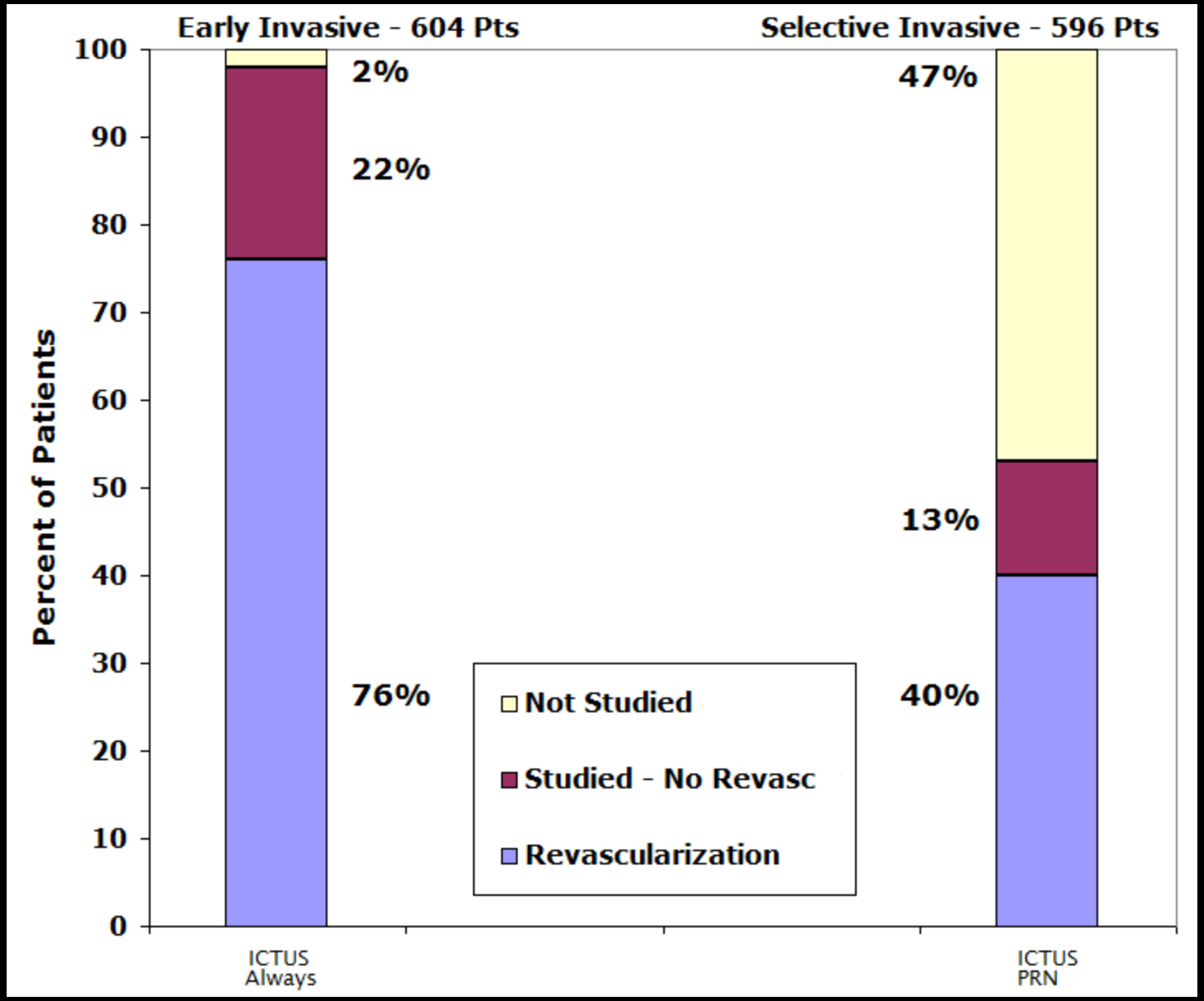


ICTUS: 3 and 4-Year Outcomes

FRISC II and ICTUS: Revascularization During Initial Hospitalization



ICTUS: Revascularization During Initial Hospitalization



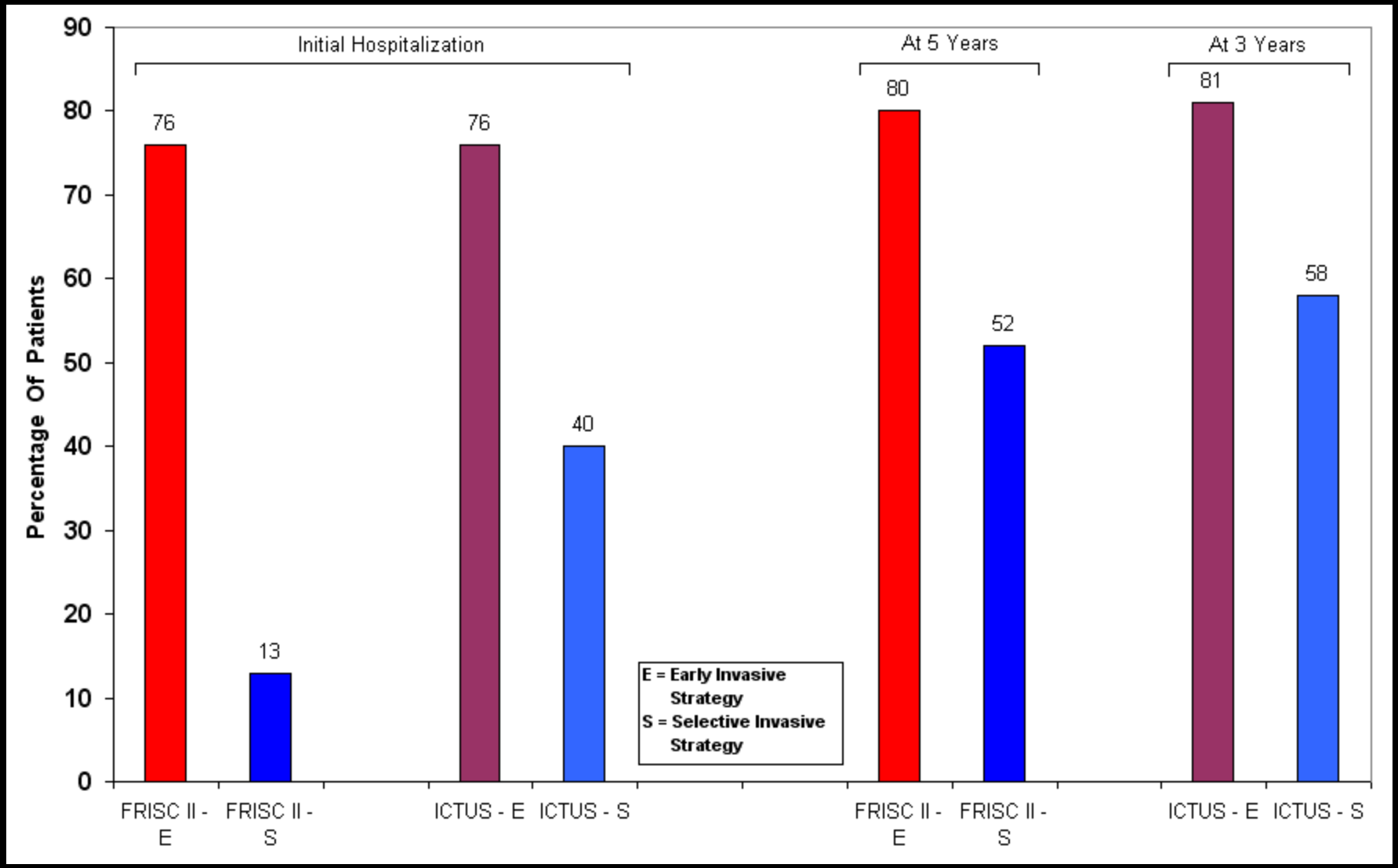
ICTUS: Randomization

	Early invasive (n=604)	Selective invasive (n=596)
Age (years)	62 (55–71)	62 (54–71)
Men	446 (74%)	434 (73%)
Diabetes mellitus	86 (14%)	80 (13%)
History of myocardial infarction	153 (25%)	125 (21%)
Previous aspirin use	235 (39%)	221 (37%)
ST-segment deviation ≥0·1mV*	284 (49%)	290 (51%)
C-reactive protein (mg/L)†	3·5 (1·7–9·6)	4·3 (1·9–11·4)
Creatinine clearance (mL/min/1·73 m²)	85 (68–103)	85 (70–103)
Troponin T (μg/L)	0·29 (0·12–0·78)	0·29 (0·13–0·69)
Low risk (FRISC score 1–2)	163 (27%)	173 (29%)
Medium risk (FRISC score 3–4)	368 (61%)	346 (58%)
High risk (FRISC score 5–7)	73 (12%)	77 (13%)

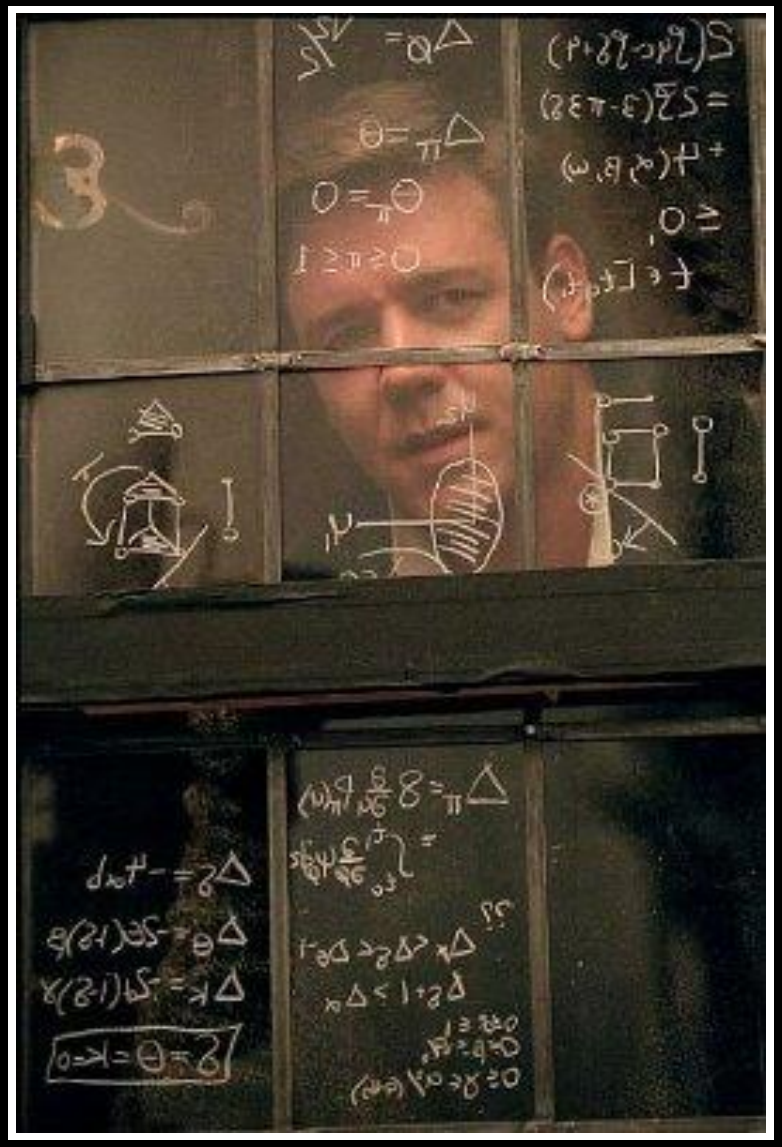
Data are number (%) or median (25th–75th percentile). *Measured on electrocardiogram at admission in 578 patients in the early invasive group and 571 in the selective invasive group; †Samples for C-reactive protein were available in 579 patients in the early invasive group and 565 patients in the selective invasive group.

Table 1: Baseline characteristics

FRISC II and ICTUS: Early and Late Revascularization



Addition Of Choice And Game Theory



Nash Equilibrium

In Game Theory, a set of strategies, one for each player, such that no player has an incentive to unilaterally change his action. Players are in equilibrium if a change in strategies by any one of them would lead that player to earn less than if he remained with his current strategy.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Braess Paradox

In a network in which all the moving entities rationally seek the most efficient route, adding extra capacity can actually reduce the network's overall efficiency. Drivers seeking the shortest route to a given destination eventually reach what is known as the Nash equilibrium, in which no single driver can do any better by changing his or her strategy unilaterally. The problem is that the Nash equilibrium is less efficient than the equilibrium reached when drivers act unselfishly—that is, when they coordinate their movements to benefit the entire group.

In Some Situations, The Following May Be True:

When You Take The Meeting,
You Take The Deal

The Alchemy Of Experience

RITA 3 : Evaluation Over Time

2002 In patients presenting with unstable coronary artery disease, an interventional strategy is preferable to a conservative strategy, mainly because of the halving of refractory or severe angina, and with no increased risk of death or myocardial infarction.
2006 In patients with non-ST-elevation acute coronary syndrome, a routine invasive strategy leads to long term reduction in risk of death or non-fatal myocardial infarction, and *this benefit is mainly in high-risk patients*.The findings provide support for national and international guidelines in the *need for more robust risk stratification in acute coronary syndrome*.

FRISC II : Evaluation Over Time

2000. The 1-year results of this trial definitely indicate the need for a mind change in the treatment of unstable coronary-artery disease. These results show that an invasive strategy, including an initial period of stabilisation and protection by platelet inhibitory and anticoagulant medication, lowers mortality, the risk of myocardial infarction, recurrence of angina and ischaemia, and the need for readmission. Although associated with a certain periprocedural risk, a revascularisation procedure rapidly transforms unstable coronary-artery disease into a stable condition with a low event rate over the forthcoming year.

2006. These findings lend support to the current recommendation of an early invasive approach in *moderate to high risk* non-ST-elevation acute coronary syndrome. The results also emphasize the need for *further development of risk stratification* and of adjuvant medical treatments, to improve the tailoring of treatment and outcome of early revascularisation in clinical practice.

ICTUS: 3-Year Outcome vs FRISC II Score

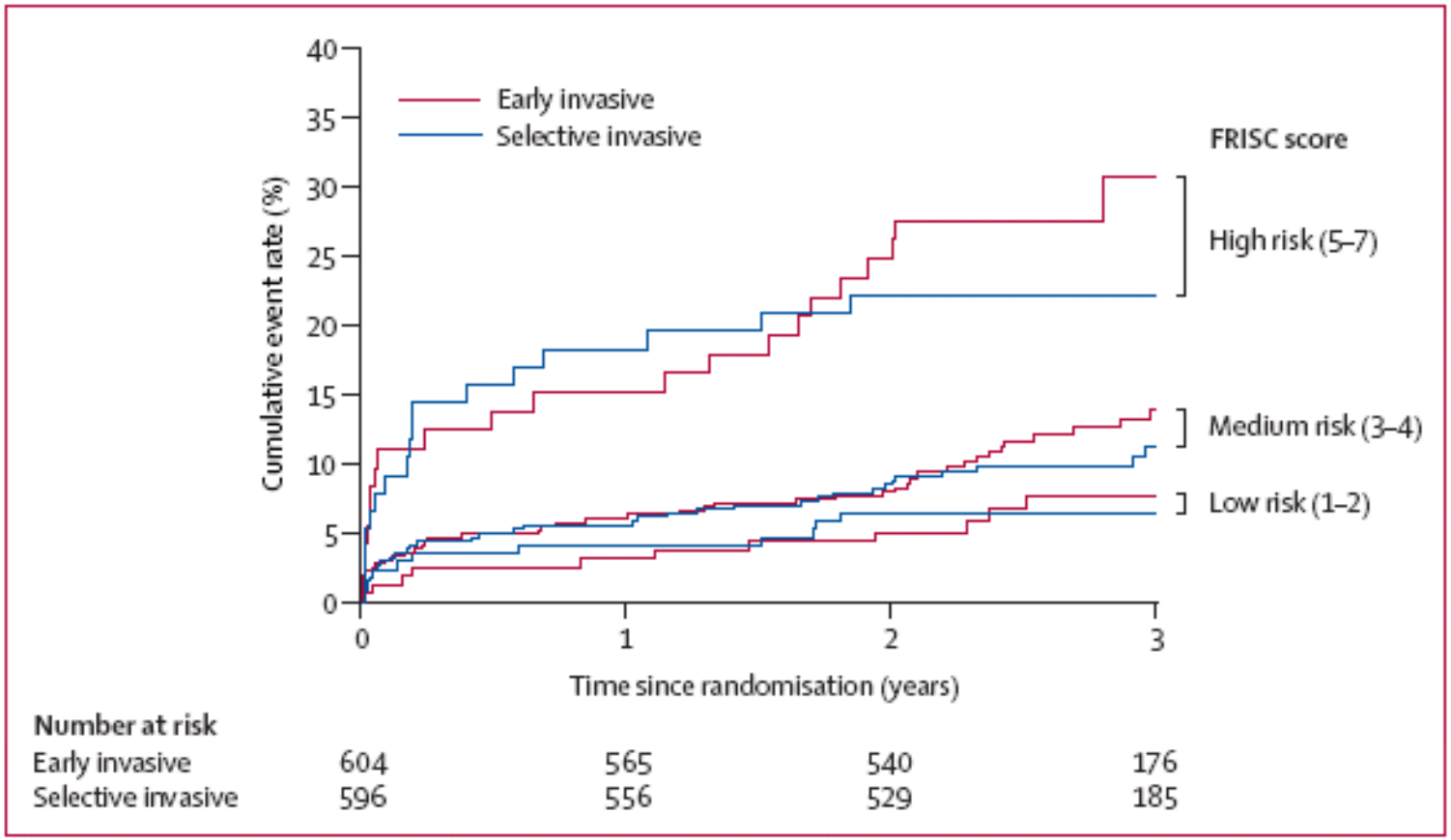


Figure 4: **Cumulative risk of death or spontaneous myocardial infarction by treatment strategy and FRISC score**
p=0·64 for interaction between FRISC score (three groups) and treatment strategy.

The FRISC II score is the sum of the following factors present at admission: age older than 65 years, male sex, diabetes mellitus, previous myocardial infarction, ST segment depression on admission, raised troponin concentration (≥0·03 μg/L),and raised concentration of C-reactive protein (≥10 mg/L).

ICTUS : Evaluation Over Time

2005. We could not demonstrate that, given optimized medical therapy, an early invasive strategy was superior to a selectively invasive strategy in patients with acute coronary syndromes without ST-segment elevation and with an elevated cardiac troponin T level.

2007 Long-term follow-up of the ICTUS trial suggests that an early invasive strategy might not be better than a more selective invasive strategy in patients with NSTE-ACS and an elevated cardiac troponin, and implementation of either strategy might be acceptable in these patients.

Conclusions

1. Science is a method for discovering truth by the progressive refinement of models.
2. The ACC/AHA Guidelines program has for its goal the systematic incorporation of the most reliable scientific data and (when ideal data is not available) learned consensus for the purpose of optimizing patient care.
3. One should follow the ACC/AHA Guidelines.
4. If the ICTUS and FRISC II trials present reliable data, it is possible that routine Early Invasive treatment for NSTEMI (as opposed to Selective Invasive treatment) results in a systematic inefficiency of about 25%. If this analysis is correct, annual savings of billions of dollars could be achieved by employing a Selective Invasive strategy routinely, without any worsening of patient outcomes.

Conclusions (continued)

5. Unfortunately, an ideal set of indicators for selection of patients who require Invasive Therapy in NSTEMI (probably about 60% of all NSTEMI patients over a period of 5 years after onset of symptoms) is not available.

6. As technology for treatment of NSTEMI continues to evolve, it is essential that well-designed trials be carried out to assess the efficacy of various strategies. Unfortunately, need for these trials has not been universally embraced.

7. A full understanding of the factors that lead to most effective health care will probably require utilization of concepts from a variety of disciplines, including behavioral economics.

Diseases desperate grown

By desperate appliance are reliev'd,

Or not at all

Claudius in "Hamlet"

Diseases desperate grown

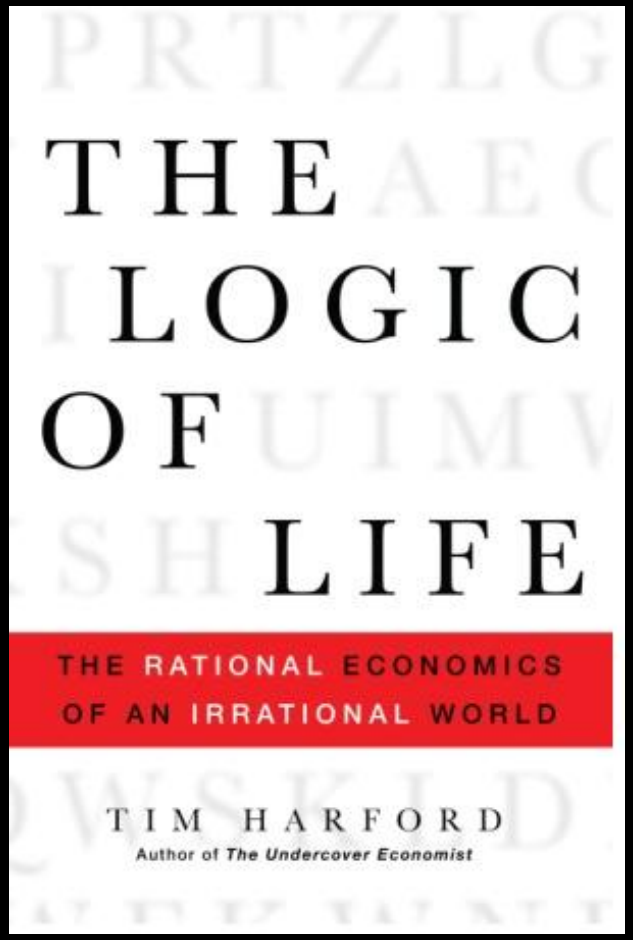
By desperate appliance are
reliev'd,

~~Or not at all~~ About 60% of the time

Claudius in "Hamlet"

The rest is silence.

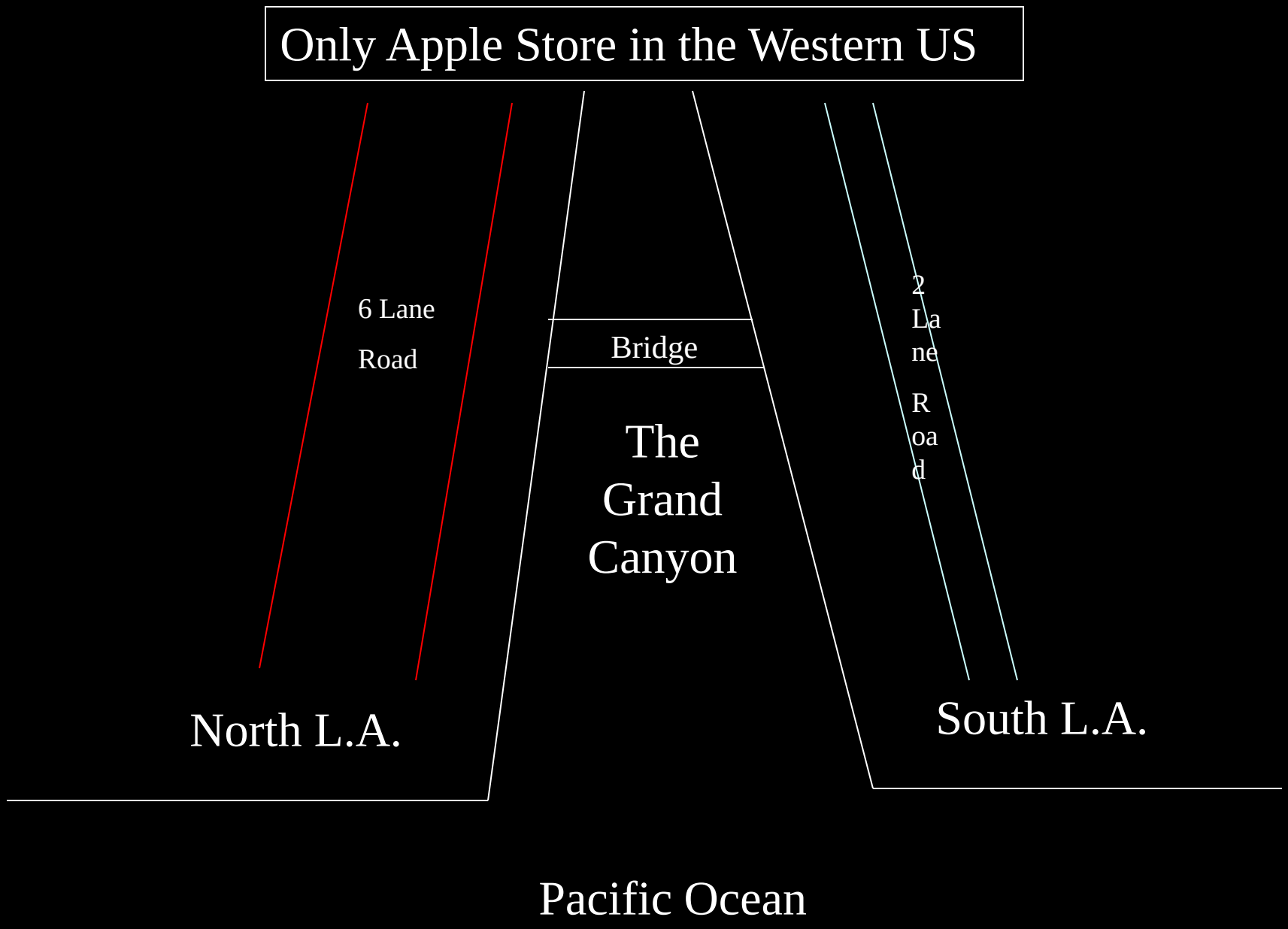

THANK YOU



Chris Ferguson

Ferguson at the 2007 World Series of Poker


Only Apple Store in the Western US
6 Lane Road
2 Lane Road
The Grand Canyon
North L.A.
South L.A.
Pacific Ocean


Only Apple Store in the Western US
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Road
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South L.A.
Pacific Ocean


Only Apple Store in the Western US
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Pacific Ocean

Califf's Principles

Principle 1. Treatment Effects Are Modest

"The benefit of most cardiovascular therapies is much smaller than was anticipated before the first large-scale outcome trials. Relative risk reductions of 25% are rarely exceeded…for post–myocardial infarction (MI) patients. *This means that the patient's outcome is determined more by the natural history of the disease than by the treatments we deliver*, and that *multiple combined treatments* will be needed in most cases to achieve the best possible outcome.

…

A practitioner's individual experience is simply not adequate to recognize treatment effects of the size usually seen in therapies to prevent future events in a chronic disease. In fact, a practitioner's personal experience has a reasonable probability of misleading him or her about what to expect when the next patient is treated. Within any large clinical trial, multiple practitioners will experience outcomes that differ from the overall results of the trial."

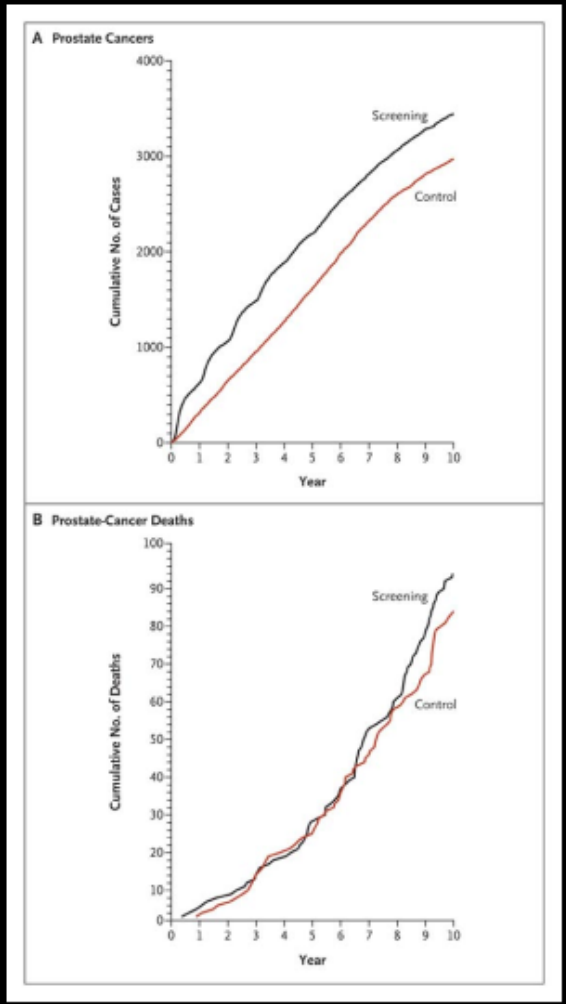
Califf RM , DeMets DL. *Circulation* 2002;106;1015-1021.

Nowadays most people die of a sort of creeping common sense…

But What About Elective Coronary Artery Angioplasty?

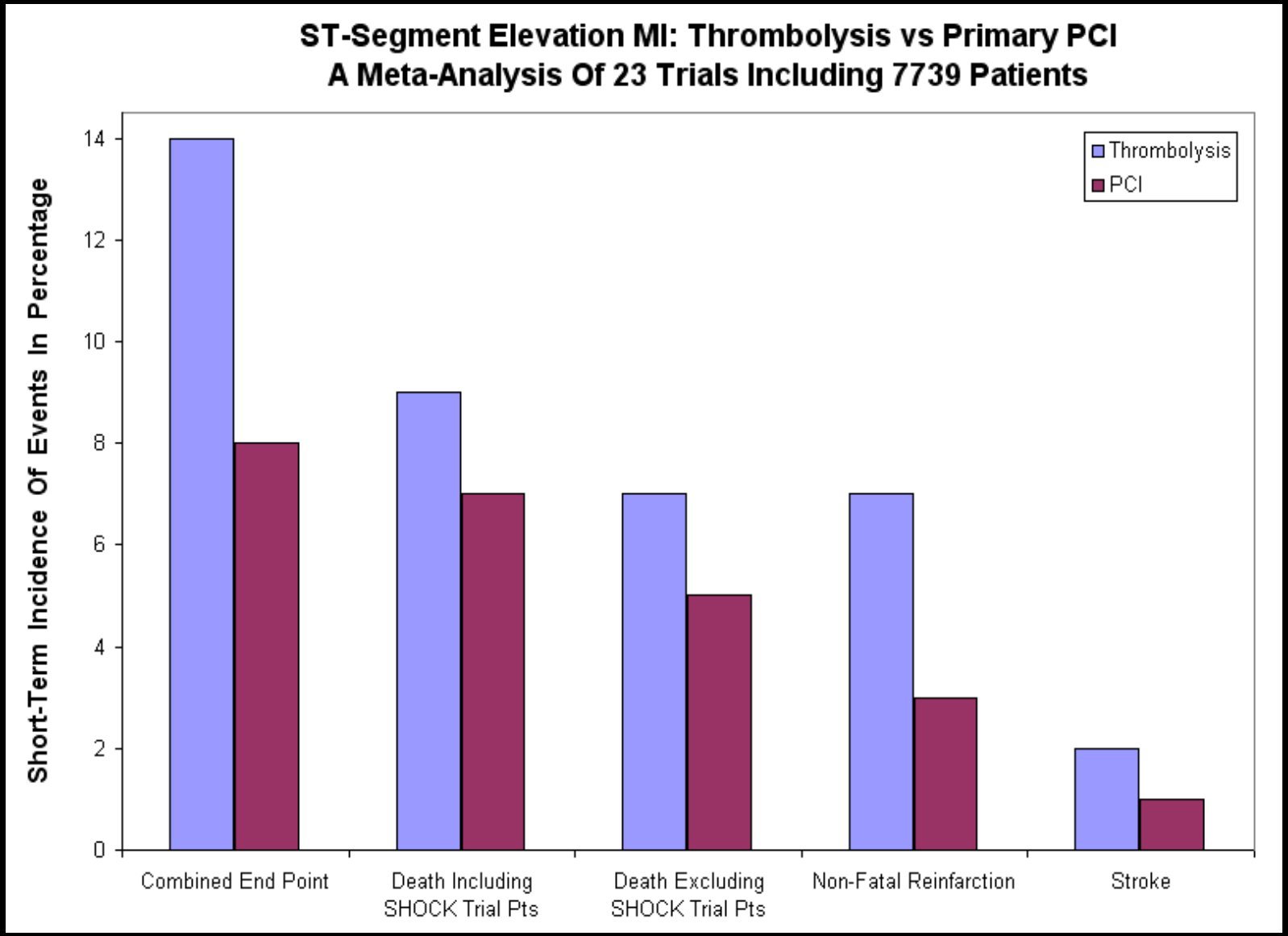
1. 2004. "Current evidence would suggest that outside the setting of an acute myocardial infarction, the principal, if not the only, benefit of PCI is to reduce angina and improve quality of life. Randomized trials of PCI versus medical therapy in patients with chronic stable angina suggest that routine revascularization has no effect on the risk of death or myocardial infarction and that its benefits are restricted to reducing angina and improving exercise tolerance." (Krumholz HM. Circulation 2004;110:3746-3748.)
2. 2007. “As an initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy.” COURAGE – 2287 patients. (Boden WE. NEJM 2007;356:1503–16.)
3. 2009. To no one's surprise except all the patients who are convinced that their cardiologists saved their lives, elective PCI over the last 20 years has had no discernible effect on mortality or MI when compared to medical therapy, according to a new network meta-analysis by Thomas Trikalinos of 25,388 pts in 61 trials . (Lancet 373:911, Mar 14, 2009.)

Number of Diagnoses of All Prostate Cancers (Panel A) and Number of Prostate-Cancer Deaths (Panel B)



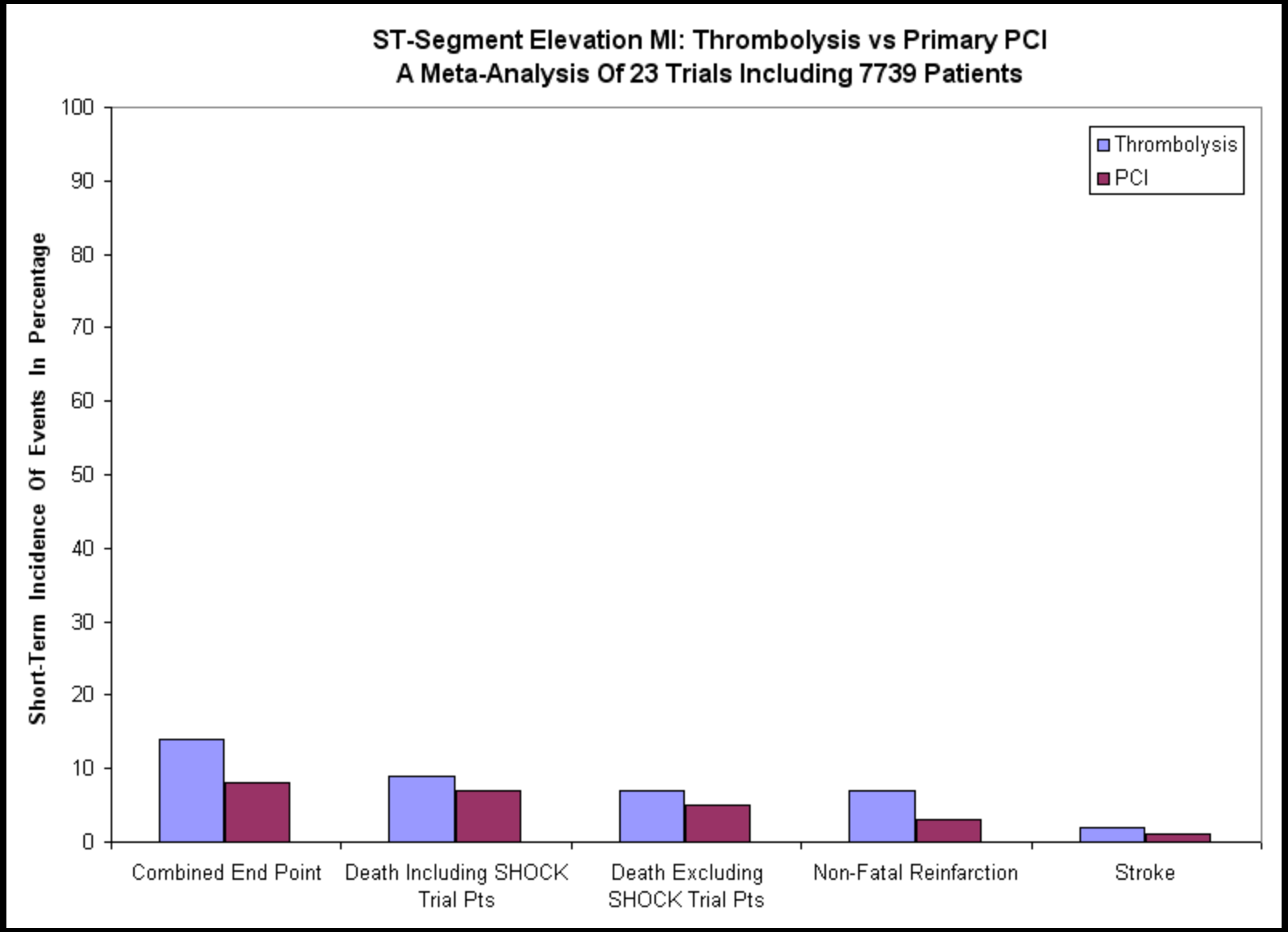
Andriole G et al. N Engl J Med 2009;10.1056/NEJMoa0810696

But What About Coronary Artery Angioplasty in Acute MI?



Grines et al. Lancet 2003; 361: 13-20

But What About Coronary Artery Angioplasty in Acute MI?



Grines et al. Lancet 2003; 361: 13-20

Califf's Principles

Principle 2: Qualitative Interactions Are Uncommon, but Quantitative Interactions Are Usual

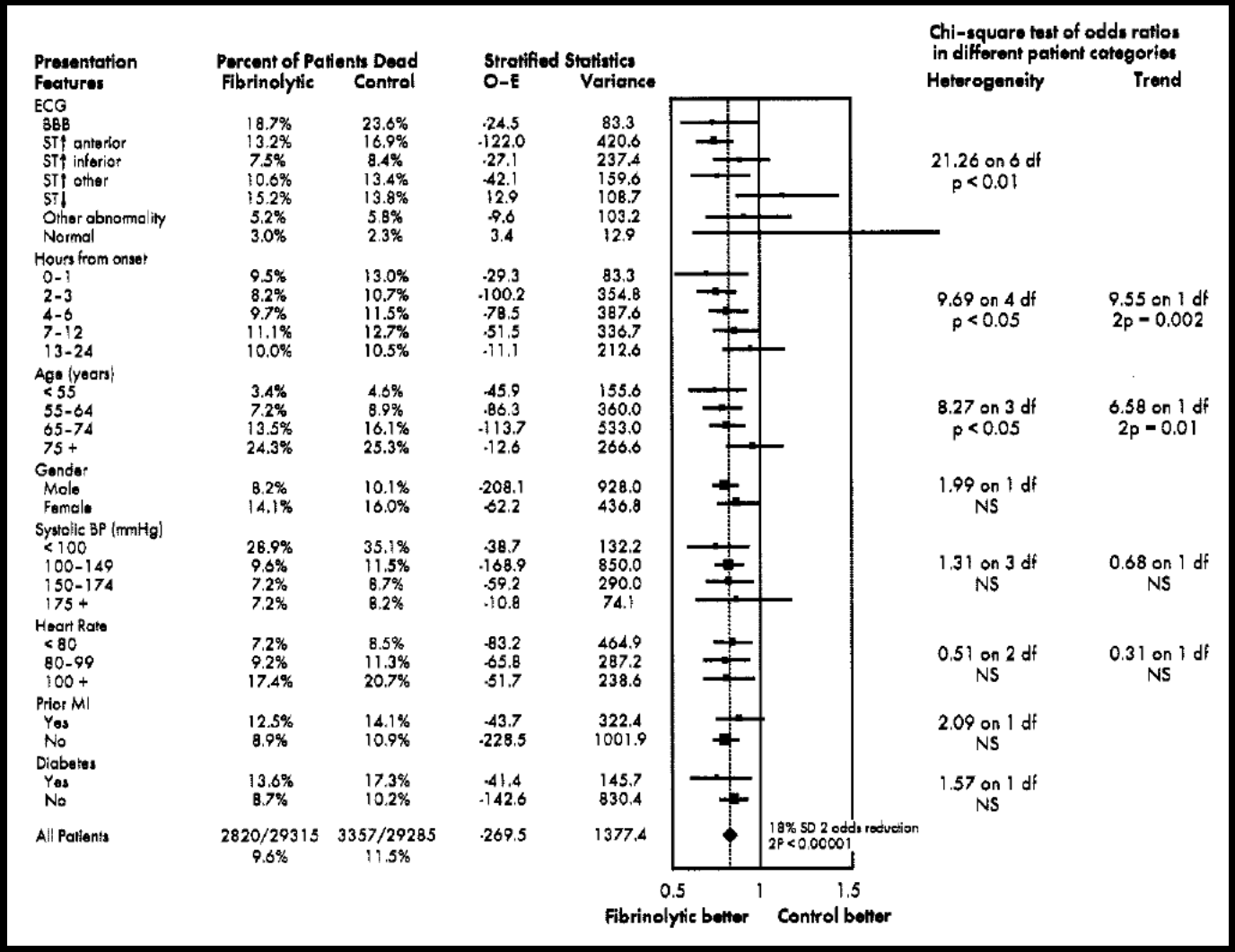


Figure 2. Overview of treatment effect of fibrinolytic therapy in myocardial infarction. This figure demonstrates several key points: the treatment effects are modest; the only qualitative interaction is a reversal of the treatment benefit seen in all other subgroups in patients with ST-segment depression; and there are many quantitative interactions, with the greatest absolute benefit seen in the highest-risk patients.

Adapted with permission from Elsevier Science: the Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients.

Lancet. 1994;343:311–322.

Next Up:

Close Examination of One Randomized, Prospective, Partly Double-Blind Trial
and
Two Large Registries

ACC/AHA 2008: Device-Based Therapies of Cardiac Rhythm Abnormalities

Source: ACC/AHA 2008 Pocket Guide

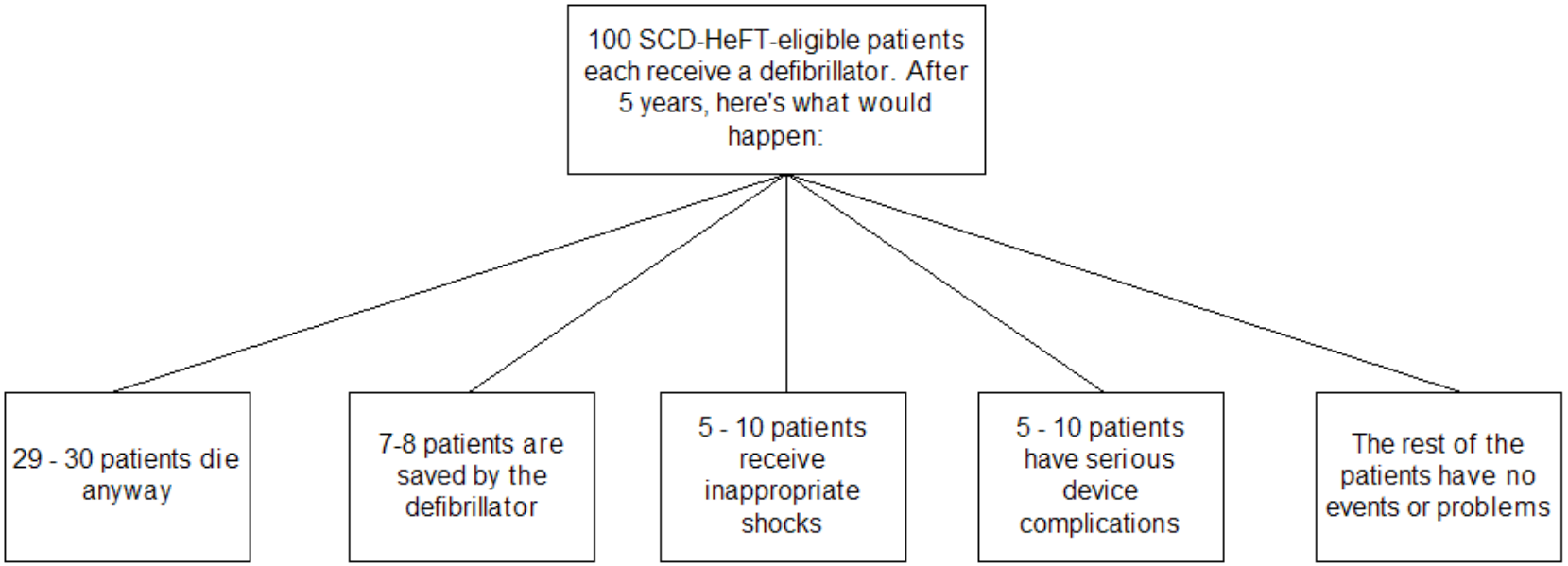
1. Recommendations for Permanent Pacing in Sinus Node Dysfunction
2. Recommendations for Acquired Atrioventricular Block in Adults
3. Recommendations for Permanent Pacing in Chronic Bifascicular Block
4. Recommendations for Permanent Pacing After the Acute Phase of Myocardial Infarction
5. Recommendations for Permanent Pacing in Hypersensitive Carotid Sinus Syndrome and Neurocardiogenic Syncope
6. Recommendations for Pacing After Cardiac Transplantation
7. Recommendations for Permanent Pacemakers That Automatically Detect and Pace to Terminate Tachycardias
8. Recommendations for Pacing to Prevent Tachycardia
9. Recommendation for Pacing to Prevent Atrial Fibrillation
10. Recommendations for Cardiac Resynchronization Therapy in Patients With Severe Systolic Heart Failure
11. Recommendations for Pacing in Patients With Hypertrophic Cardiomyopathy
12. Recommendations for Permanent Pacing in Children, Adolescents, and Patients With Congenital Heart Disease
13. Recommendations for Implantable Cardioverter-Defibrillators
14. Recommendations for Implantable Cardioverter-Defibrillators in Pediatric Patients and Patients With Congenital Heart Disease

Teaching Points From SCD-HeFT: Benefits Of Prophylactic Cardioverter-Defibrillator Implant In CHF Patients

Lecturer: Lynn W. Stevenson, M.D., Professor of Medicine (Harvard) and Director of the Cardiomyopathy and Heart Failure Service at the Brigham and Women's Hospital, Boston. Source: ACCEL interview, May 2006. (Also, see NEJM 2005;352:225-37)

The study group: Nearly 2500 patients with NYHA Class II - III Heart Failure and LV EF <35%, average age = 60 y.o.

Results: Cardioverter-Defibrillator implant reduced annual mortality by 1.5%/year. Amiodarone therapy = Placebo.



When this information is presented to CHF patients, 1/3 want an ICD, 1/3 don't want an ICD, 1/3 want to think it over.

It is critically important to remember that these numbers only apply to SCD-HeFT -eligible patients. SCD-HeFT patients are expected to have an average survival of 7 years. In fact, most patients in the CHF population are significantly older than the SCD-HeFT patients and are in significantly worse health, with multiple co-morbidities and a shorter life expectancy. ICD implant is a wonderful therapeutic option for some patients, but for many its benefits are quite limited.

Table 1: Characteristics of patients at their first hospital admission because of heart failure

Characteristic	No. (%) of patients* *n = 14 374*
Age, yr	
Mean (SD)	77.1 (12.0)
< 55	712 (5.0)
55–64	1 212 (8.4)
65–74	2 880 (20.0)
75–84	5 472 (38.1)
≥ 85	4 098 (28.5)
Sex	
Male	7 833 (54.5)
Female	6 541 (45.5)
Prior hospital admission	
For any reason	11 482 (79.9)
Because of cardiovascular event other than heart failure	7 211 (50.2)
Comorbidity	
Myocardial infarction	2 550 (17.7)
Ischemic heart disease	6 773 (47.1)
Cerebrovascular disease	1 644 (11.4)
Atrial fibrillation or flutter	5 232 (36.4)
Ventricular tachycardia, ventricular fibrillation or cardiac arrest	328 (2.3)
Hypertension	10 183 (70.8)
Diabetes mellitus	5 150 (35.8)
Cancer	1 273 (8.9)
Chronic kidney disease	
No dialysis	2 975 (20.7)
Dialysis	289 (2.0)
Chronic pulmonary disease	3 421 (23.8)
Rheumatoid arthritis	215 (1.5)
Dementia	886 (6.2)
Treatment	
Defibrillator implantation	65 (0.5)
Any pacemaker implantation	1 061 (7.4)

Note: SD = standard deviation.
*Unless stated otherwise.

Table 2: Change in selected characteristics of the study population after each hospital admission because of heart failure

Characteristic	Hospital admission; no. (%) of patients* First *n = 14 374*	Second *n = 4 303*	Third *n = 1 681*	Fourth *n = 713*
Age, yr, mean (SD)	77.1 (12.0)	78.9 (11.2)	79.4 (11.1)	79.8 (10.6)
Sex, male	7 833 (54.5)	2 320 (53.9)	877 (52.2)	352 (49.4)
Myocardial infarction	2 550 (17.7)	984 (22.9)	478 (28.4)	215 (30.2)
Ischemic heart disease	6 773 (47.1)	2 124 (49.4)	1 012 (60.2)	460 (64.5)
Cerebrovascular disease	1 644 (11.4)	544 (12.6)	240 (14.3)	110 (15.4)
Atrial fibrillation or flutter	5 232 (36.4)	1 792 (41.6)	801 (47.7)	388 (54.4)
Ventricular tachycardia, ventricular fibrillation or cardiac arrest	328 (2.3)	130 (3.0)	67 (4.0)	38 (5.3)
Chronic kidney disease				
No dialysis	2 975 (20.7)	1 266 (29.4)	693 (41.2)	353 (49.5)
Dialysis	289 (2.0)	97 (2.3)	42 (2.5)	21 (2.9)
Chronic pulmonary disease	3 421 (23.8)	1 212 (28.2)	624 (37.1)	333 (46.7)
Dementia	886 (6.2)	208 (4.8)	107 (6.4)	50 (7.0)
Defibrillator implantation	65 (0.5)	30 (0.7)	19 (1.1)	11 (1.5)
Any pacemaker implantation	1 061 (7.4)	472 (11.0)	247 (14.7)	117 (16.4)

Note: SD = standard deviation.
*Unless stated otherwise.

Table 3: Causes and sites of death among patients admitted to hospital with heart failure

Site; cause of death	No. (%) of deaths *n = 8967*
In hospital	
Noncardiac death	3400 (37.9)
Cardiac death	2355 (26.3)
Out of hospital	
Noncardiac death	1986 (22.1)
Cardiac death*	1226 (13.7)
Residential nursing home	543 (6.1)
Home, independent living	525 (5.9)
Home, with home or daycare support	148 (1.7)
Hospice	10 (0.1)

*Defined as death occurring out of acute care hospital with the underlying cause of death reported as cardiac disease.

Stevenson, LW, et al.

CMAJ
2009;180(6):611-6

Maximum Potential Survival Benefit From Defibrillator Implant In CHF Patients

Hospital admission	Median survival (95% CI), yr		
	Hypothetical	Observed	Difference
First (*n* =14 374)	2.96 (2.84 to 3.08)	2.33 (2.25 to 2.40)	0.63 (0.49 to 0.77)
Second (*n* = 4303)	1.71 (1.57 to 1.85)	1.34 (1.23 to 1.44)	0.37 (0.20 to 0.55)
Third (*n* = 1681)	1.27 (1.12 to 1.42)	0.99 (0.89 to 1.09)	0.28 (0.10 to 0.46)
Fourth (*n* = 713)	0.91 (0.72 to 1.10)	0.71 (0.55 to 0.87)	0.20 (–0.04 to 0.45)

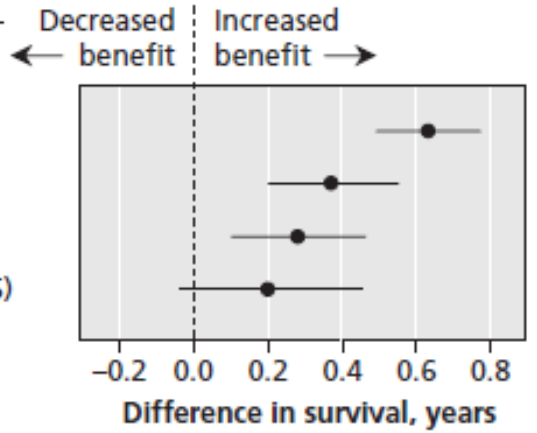


Figure 1: The maximum potential benefit of preventing sudden death with the use of implantable defibrillators among patients admitted to hospital because of heart failure. The values shown represent the difference between the observed survival after each hospital admission and the hypothetical survival whereby all out-of-hospital cardiac deaths were assumed to be preventable.

Stevenson, LW, et al. ***CMAJ*** **2009;180(6):611-6**

Maximum Potential Survival Benefit From Defibrillator Implant In CHF Patients

Table 4: Hypothetical* 2-year survival rates in subgroups defined by age, chronic kidney disease, cancer and dementia†

Subgroup	Hospital admission; hypothetical 2-year survival rate, % (95% CI)			
	First	Second	Third	Fourth
Age < 65 yr				
Without chronic kidney disease (*n* = 1491)	84 (82–86)	70 (65–76)	62 (52–73)	51 (33–70)
With chronic kidney disease (*n* = 433)	66 (61–70)	50 (41–58)	48 (37–59)	32 (16–47)
Age 65–80 yr				
Without chronic kidney disease or dementia (*n* = 3927)	69 (68–71)	58 (55–62)	49 (43–55)	41 (31–51)
With chronic kidney disease or dementia (*n* = 1474)	50 (48–53)	41 (37–45)	34 (29–40)	30 (22–38)
Age 80–90 yr				
Without chronic kidney disease, dementia or cancer (*n* = 3812)	53 (52–55)	43 (40–46)	36 (31–41)	31 (23–40)
With chronic kidney disease, dementia or cancer (*n* = 2095)	35 (33–37)	29 (25–32)	28 (23–33)	31 (24–38)
Age > 90 yr (*n* = 1142)	34 (31–37)	31 (26–36)	31 (22–41)	24 (10–38)

Note: CI = confidence interval.
*Survival rate based on the assumption that all out-of-hospital cardiac deaths could have been prevented.
†Subgroups are defined according to characteristics that are strong predictors of sudden death or overall death among patients with heart failure.

Stevenson, LW, et al. *CMAJ* 2009;180(6):611-6

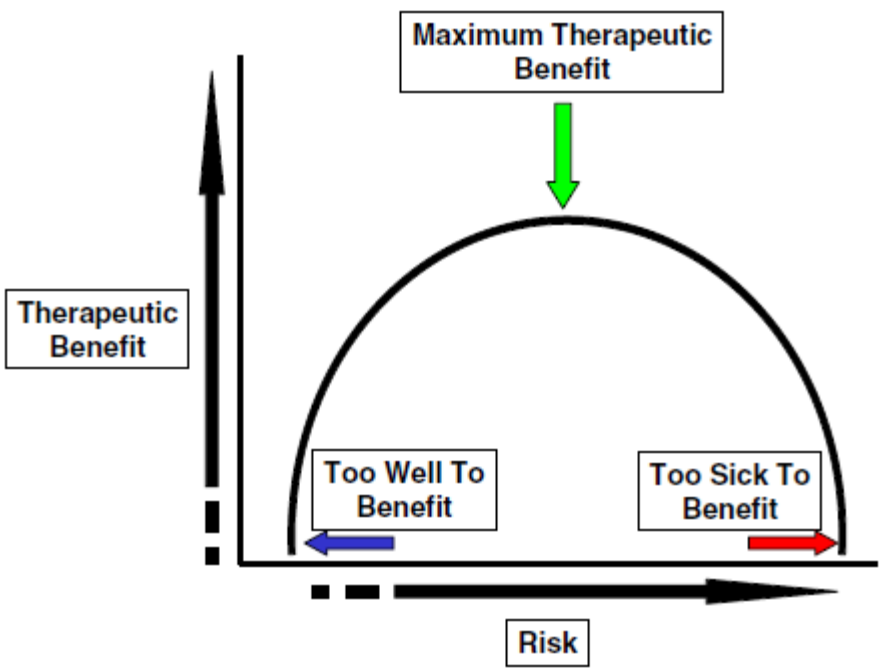


Figure 1 The Goldilocks Effect

When considering treatment for many diseases there will be some patients who are too well to benefit and will thrive without treatment and others who are too sick who will die despite intensive management. In between, there will be a group that obtains the maximum benefit from treatment. This may be likened to the story of Goldilocks, who found that 1 bowl of porridge was too hot, 1 was too cold, but another was just right. In more scientific terms, it might be called the risk–benefit parabola or optimal treatment window.

JACC 2009;53:608–11.

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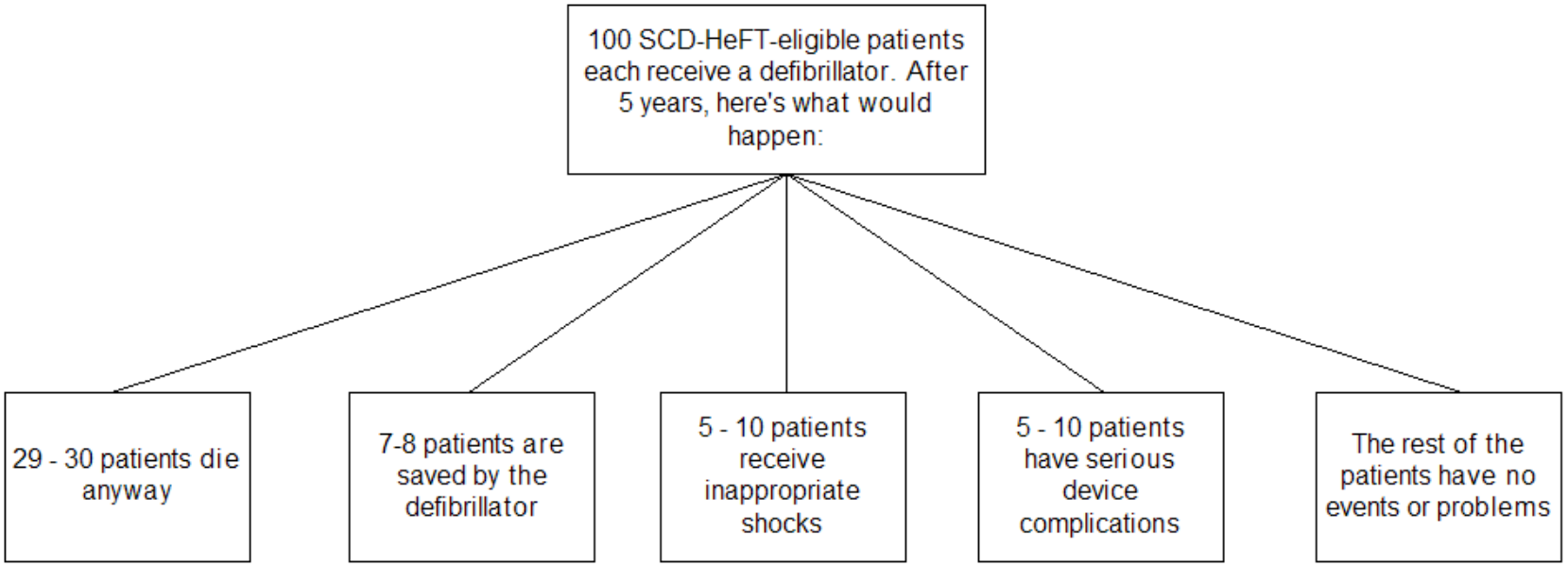

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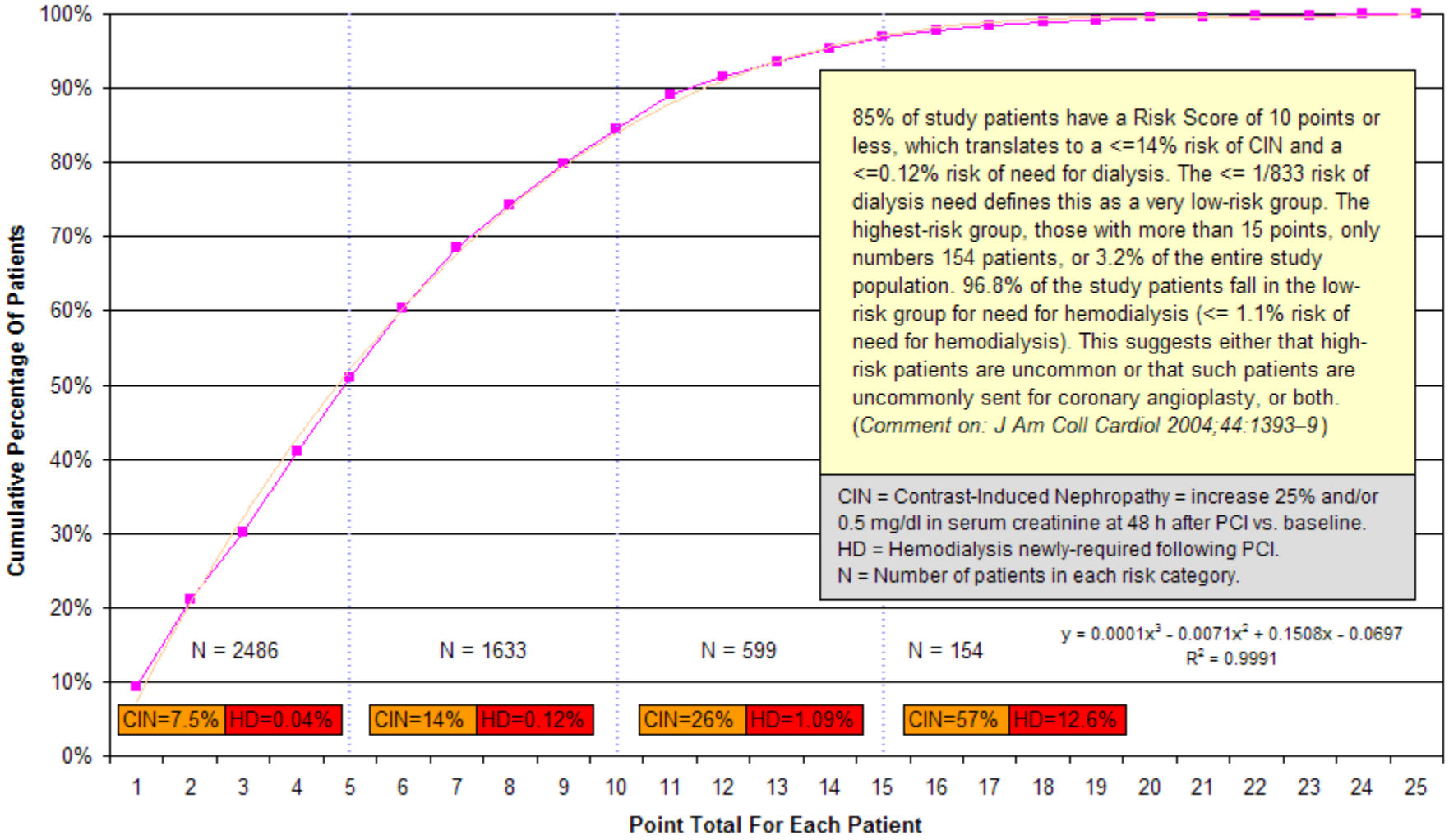
Blue Pill Red Pill

Contrast-Induced Nephropathy Risk Point Distribution In The Columbia 2004 Percutaneous Coronary Intervention (PCI) Study Population: GFR-Based Scheme



Blue Pill Red Pill

Principle 3: Long-Term Effects Deserve Evaluation

Many therapies have different effects in the short term than in the long term. This phenomenon has been recognized for some time with regard to surgical procedures in which the patient accepts an early perioperative risk in return for long-term benefit.

- With coronary artery bypass grafting, the benefit of surgery does not exceed the early hazard until a year after the average procedure.
- In acute myocardial infarction, fibrinolytic therapy increases the risk of death in the first day and then reduces the risk of death after this period of early hazard.
- The diet combination phenfluramine dexpheneramine (fen phen). In small clinical trials performed over short periods of time, the combination caused weight loss. Only longer-term clinical observations raised the issue of valvular insufficiency. Yet, because longer-term randomized clinical trials were not done, the community is unclear about the extent to which the valvular lesions caused irreversible harm.
- In HERS, the administration of hormone replacement therapy to postmenopausal women with an intact uterus and with documented coronary heart disease led to excess thrombotic events in the first year and fewer thrombotic events between the first and fourth years of follow-up.

Califf RM , DeMets DL. *Circulation* 2002;106;1015-1021, 1172-1175.

Califf's Principles

Principle 4: Applying the Results of Clinical Trials Is Beneficial

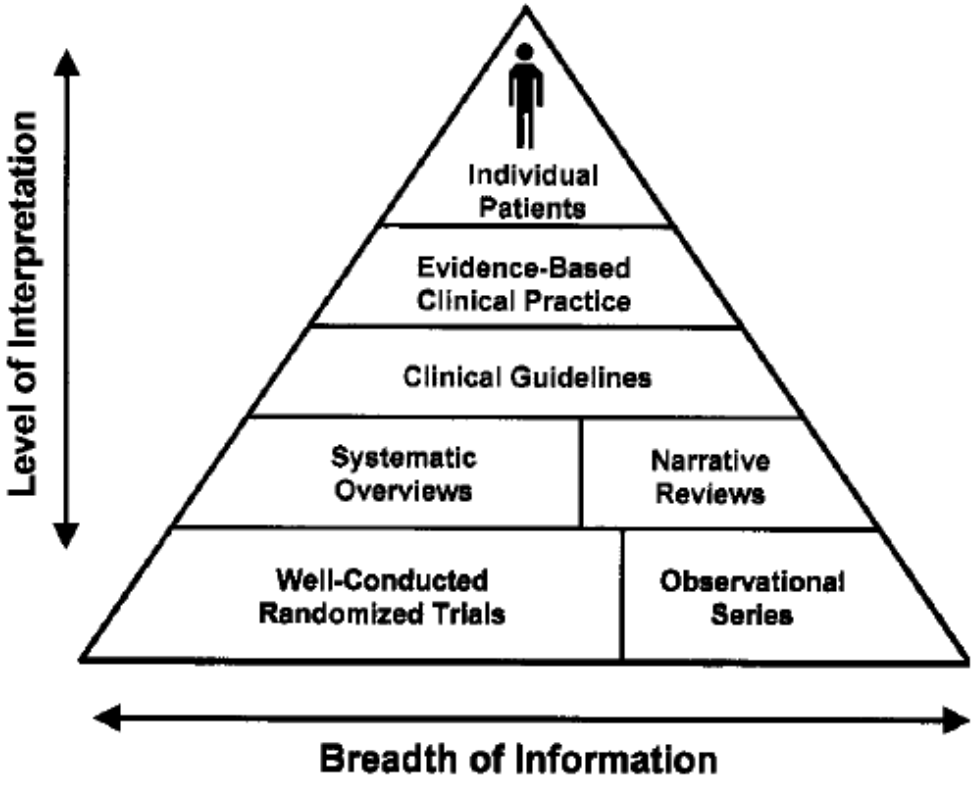


Figure 2. The pyramid of clinical evidence. In a rational, quantitative world, the recommendation for the individual patient would emanate from evidence built along the left-hand side of the pyramid. By integrating clinical trial outcome data into systematic overviews and guidelines, evidence-based clinical practice occurs. To the extent the guidelines lack empirical support with the best methodology, the pyramid is seen as less solid.

Califf RM , DeMets DL. *Circulation* 2002;106;1015-1021, 1172-1175.

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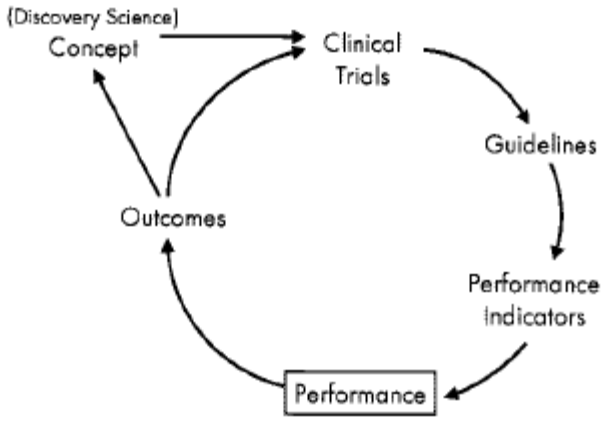


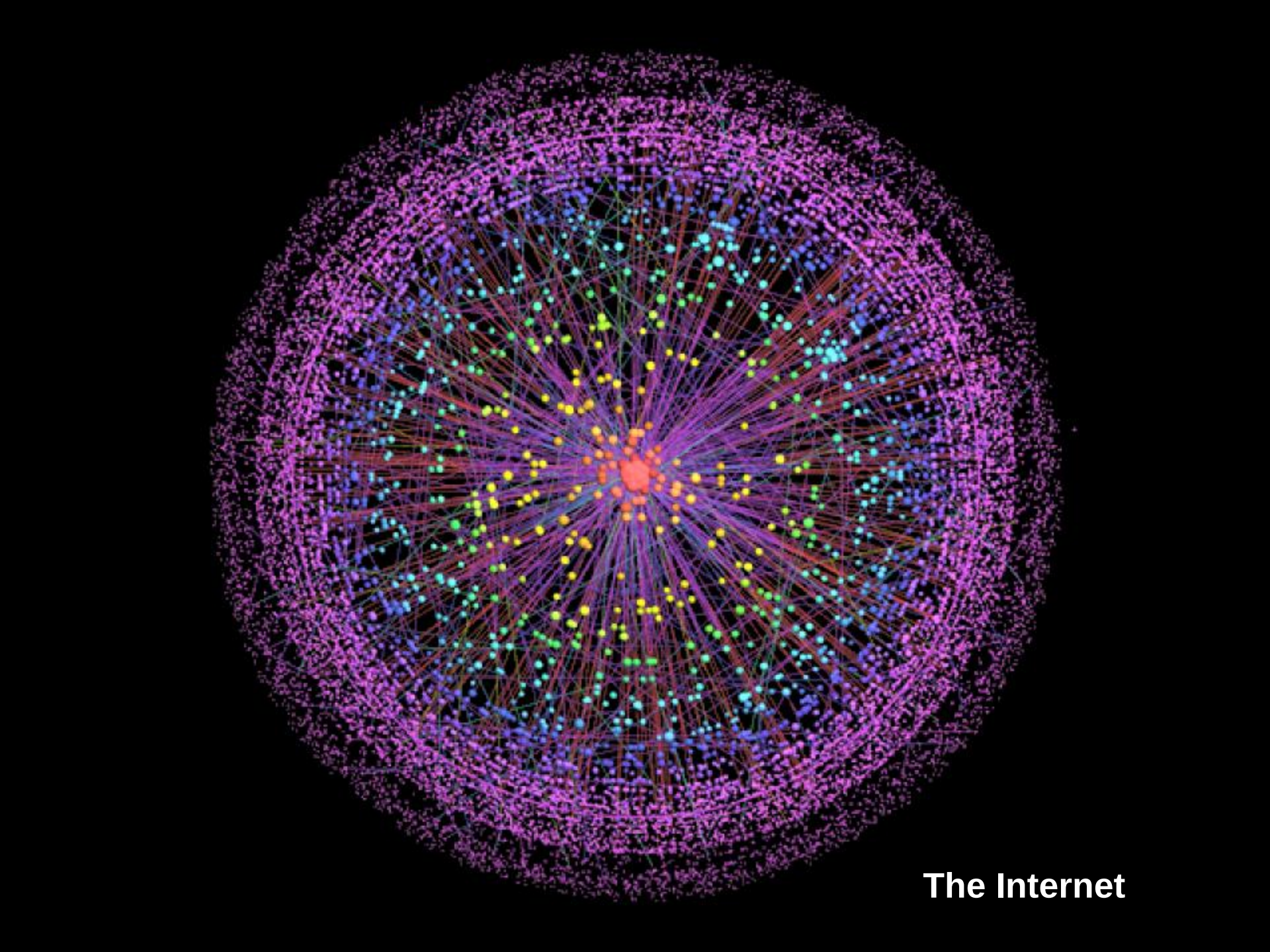
Figure 3. The quantitative cycle of quality can be envisioned as driven by discovery science (both physical and behavioral), which leads to inventions that may lead to medical therapy or technology that can be evaluated in clinical trials. If the clinical trials are adequately designed and performed to produce a definitive result to inform clinical practice, a clinical practice guideline could be devised. Clear clinical practice guidelines can be used to derive performance indicators, which can be used to measure clinical performance (for example, patients with elevated LDL cholesterol should be treated with a statin). Practices with better performance as measured by adherence to performance indicators should have better outcomes, and by measuring outcomes, deviations can stimulate new discoveries and clinical trials. Adapted with permission from Garson A. President's page: The great circle: a target for better patient care. *J Am Coll Cardiol.* 1999;34:294–295.

Califf RM , DeMets DL. *Circulation* 2002;106;1015-1021, 1172-1175.

Principle 5: Participation Is Imperative

Take-Home Messages

1. Medicine is currently in a difficult transitional period in which new technologies and the therapeutic strategies that new technologies engender are increasing exponentially. This is quite unlike anything that has ever happened before.
2. In conjunction with emergence of new technologies and strategies, new structures for social control are also emerging, e.g. guidelines and the working groups that create/enforce guidelines.
3. Guidelines in turn are critically dependent on generation of highly reliable information by large properly-conducted randomized trials and large registries, with newer data feeding back to alter older recommendations.
4. Unfortunately, the entire endeavor of generation/application of clinical guidelines is under constant threat of malfunction due to self-dealing on the part of any/all of the parties involved in the process. (“I already know…”)
5. Even the best trial conclusion or wisest guideline may not apply to an individual patient, who may have idiosyncratic characteristics that make application of the conclusion or guideline recommendation inappropriate.
6. You must know the rules to break the rules. Rules can be rightly broken for cause, but cause must be clearly stated and review should be anticipated.


The Internet