Other People's Lives

Applying The Results Of Large Clinical Trials And Practice Guidelines To Individual Patient Care

John Coyle, M.D.
March 19, 2009

JACC Vol. 52, No. 8, 2008
August 19, 2008:000–00

Table 1. Applying Classification of Recommendations and Level of Evidence

SIZE OF TREATMENT EFFECT →

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *Risk ≥ Benefit* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

Cardiology

Cardiology Research/Clinical Trials

Rob Califf, MD, cardiologist

- Professor of Medicine
- Vice Chancellor for Clinical Research, Duke University Medical Center
- Director, Duke Translational Medicine Institute

Califf is internationally recognized as a leader in understanding clinical trials, drug development and regulation and the financial, ethical and the complex medical issues they involve. He has extensive interview experience with multiple print and broadcast outlets and is one of the 10 most cited experts in the field of medicine, according to the Institute for Scientific Information, often appearing in the New York Times, Wall Street Journal, USA Today and Forbes, among others.

Cardiology

Cardiology Research/Clinical Trials

Rob Califf, MD, cardiologist

- Professor of Medicine
- Vice Chancellor for Clinical Research, Duke University Medical Center
- Director, Duke Translational Medicine Institute

Califf is internationally recognized as a leader in understanding clinical trials, drug development and regulation and the financial, ethical and the complex medical issues they involve. He has extensive interview experience with multiple print and broadcast outlets and is one of the 10 most cited experts in the field of medicine, according to the Institute for Scientific Information, often appearing in the New York Times, Wall Street Journal, USA Today and Forbes, among others.

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Pierluigi Tricoci, MD, MHS, PhD
Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.

Data Extraction The number of recommendations and the distribution of classes of recommendation (I, II, and III) and levels of evidence (A, B, and C) were determined. The subset of guidelines that were current as of September 2008 was evaluated to describe changes in recommendations between the first and current versions as well as patterns in levels of evidence used in the current versions.

Results Among guidelines with at least 1 revision or update by September 2008, the number of recommendations increased from 1330 to 1973 (+48%) from the first to the current version, with the largest increase observed in use of class II recommendations. Considering the 16 current guidelines reporting levels of evidence, only 314 recommendations of 2711 total are classified as level of evidence A (median, 11%), whereas 1246 (median, 48%) are level of evidence C. Level of evidence significantly varies across categories of guidelines (disease, intervention, or diagnostic) and across individual guidelines. Recommendations with level of evidence A are mostly concentrated in class I, but only 245 of 1305 class I recommendations have level of evidence A (median, 19%).

Conclusions Recommendations issued in current ACC/AHA clinical practice guidelines are largely developed from lower levels of evidence or expert opinion. The proportion of recommendations for which there is no conclusive evidence is also growing. These findings highlight the need to improve the process of writing guidelines and to expand the evidence base from which clinical practice guidelines are derived.

JAMA. 2009;301(8):831-841 www.jama.com

CLINICAL PRACTICE GUIDELINES are systematically developed statements to assist practitioners with decisions about appropriate health care for specific patients' circumstances.[1] Guidelines are often assumed to be the epitome of evidence-based medicine. Yet, guideline recommendations imply not only an evaluation of the evidence but also a value judgment based on personal or organizational preferences regarding the various risks and benefits of a medical intervention for a population.[2]

For more than 20 years, the American College of Cardiology (ACC) and the American Heart Association (AHA) have released clinical practice guidelines to provide recommendations on care of patients with cardiovascular disease. The ACC/AHA guidelines currently use a grading schema based on level of evidence and class of recommendation (available at http://www.acc.org and http://www.aha.org). The level

Reassessment of Clinical Practice Guidelines

Go Gently Into That Good Night

Terrence M. Shaneyfelt, MD, MPH

Robert M. Centor, MD

In 1990, the Institute of Medicine proposed guideline development to reduce inappropriate health care variation by assisting patient and practitioner decisions.[1] Unfortunately, too many current guidelines have become marketing and opinion-based pieces, delivering directive rather than assistive statements.

Current use of the term *guideline* has strayed far from the original intent of the Institute of Medicine. Most current articles called "guidelines" are actually expert consensus reports. It is not surprising, then, that the article by Tricoci et al[2] in this issue of *JAMA* demonstrates that revisions of the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines have shifted to more class II recommendations (conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment) and that 48% of the time, these recommendations are based on the lowest level of evidence (level C: expert opinion, case studies, or standards of care). This trend is especially disconcerting given the quantity of cardiovascular scientific literature published during the last decade.

The overreliance on expert opinion in guidelines is problematic. All guideline committees begin with implicit biases and values, which affects the recommendations they make.[3] However, bias may occur subconsciously and, therefore, go unrecognized. Converting data into recommendations requires subjective judgments; the value structure of the panel members molds those judgments.[4] Guideline consumers could adjust for these biases if guideline panels made their values and goals explicit, but usually they remain opaque.[5]

The most widely recognized bias is financial. Guidelines often have become marketing tools for device and pharmaceutical manufacturers. While the ACC and AHA receive no industry funding for guideline development, they do receive industry support to disseminate guideline products such as pocket guides. Financial ties between guideline panel members and industry are common. "Experts" on guideline panels are more likely to receive industry funding for research, consulting fees, and speakers' honoraria. In 1 study of 44 guidelines, 87% of the guideline authors had some form of industry tie.[6]

Other biases are also important. The specialty composition of a guideline panel likely influences guideline development. Specialty societies can use guidelines to enlarge that specialty's area of expertise in a competitive medical marketplace. Federal guideline committees may focus on limiting costs; committees influenced by industry are more likely to shape recommendations to accord with industry needs.

Guidelines have other limitations. Guidelines are often too narrowly focused on single diseases and are not patient focused. Patients seldom have single diseases, and few if any guidelines help clinicians in managing complexity.[7] Paradoxically, guidelines are also often too comprehensive, covering every possible intervention that could be appropriate for a patient with that single disease. Tricoci et al[2] found that in ACC/AHA guidelines with at least 1 revision, the number of recommendations increased 48% from the first guideline to the most recent version. If there is a main message in such guidelines, it is likely to be lost in the minutiae. Guidelines are not patient-specific enough to be useful and rarely allow for individualization of care. Most guidelines have a one-size-fits-all mentality and do not build flexibility or contextualization into the recommendations.[5,7] There are simply too many guidelines, often on the same topic. For instance, clinicians really do not need 10 different adult pharyngitis guidelines.[8] Moreover, guidelines are often out of date. The evidence base used to create guidelines changes quickly. Most guidelines become outdated after 5 years, and most guideline developers lack formal procedures for updating their guidelines.[9,10] The ACC/AHA guidelines are periodically updated, with updates taking a mean of 4.6 to 8.2 years until publication.[2]

As a result, many clinicians do not use guidelines. An even greater concern, however, is that some of these consensus statements are being turned into performance measures and other tools to critique the quality of physician care. This potential problem could be minimized if performance measures were derived from high-quality guidelines based on the highest level of evidence and applied to patients with a

Author Affiliations: Veterans Affairs Medical Center (Dr Shaneyfelt) and Department of Medicine, University of Alabama School of Medicine (Drs Shaneyfelt and Centor), Birmingham; Huntsville Regional Medical Campus, Huntsville, Alabama

Reassessment of Clinical Practice Guidelines

Go Gently Into That Good Night

Terrence M. Shaneyfelt, MD, MPH

Robert M. Centor, MD

In 1990, the Institute of Medicine proposed guideline development to reduce inappropriate health care variation by assisting patient and practitioner decisions.[1] Unfortunately, too many current guidelines have become marketing and opinion-based pieces, delivering directive rather than assistive statements.

Current use of the term *guideline* has strayed far from the original intent of the Institute of Medicine. Most current articles called "guidelines" are actually expert consensus reports. It is not surprising, then, that the article by Tricoci et al[2] in this issue of *JAMA* demonstrates that revisions of the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines have shifted to more class II recommendations (conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment) and that 48% of the time, these recommendations are based on the lowest level of evidence (level C: expert opinion, case studies, or standards of care). This trend is especially disconcerting given the quantity of cardiovascular scientific literature published during the last decade.

The overreliance on expert opinion in guidelines is problematic. All guideline committees begin with implicit biases and values, which affects the recommendations they make.[3] However, bias may occur subconsciously and, therefore, go unrecognized. Converting data into recommendations requires subjective judgments; the value structure of the panel members molds those judgments.[4] Guideline consumers could adjust for these biases if guideline panels made their values and goals explicit, but usually they remain opaque.[5]

The most widely recognized bias is financial. Guidelines often have become marketing tools for device and pharmaceutical manufacturers. While the ACC and AHA receive no industry funding for guideline development, they do receive industry support to disseminate guideline products such as pocket guides. Financial ties between guideline panel members and industry are common. "Experts" on guideline panels are more likely to receive industry funding for research, consulting fees, and speakers' honoraria. In 1 study of 44 guidelines, 87% of the guideline authors had some form of industry tie.[6]

Other biases are also important. The specialty composition of a guideline panel likely influences guideline development. Specialty societies can use guidelines to enlarge that specialty's area of expertise in a competitive medical marketplace. Federal guideline committees may focus on limiting costs; committees influenced by industry are more likely to shape recommendations to accord with industry needs.

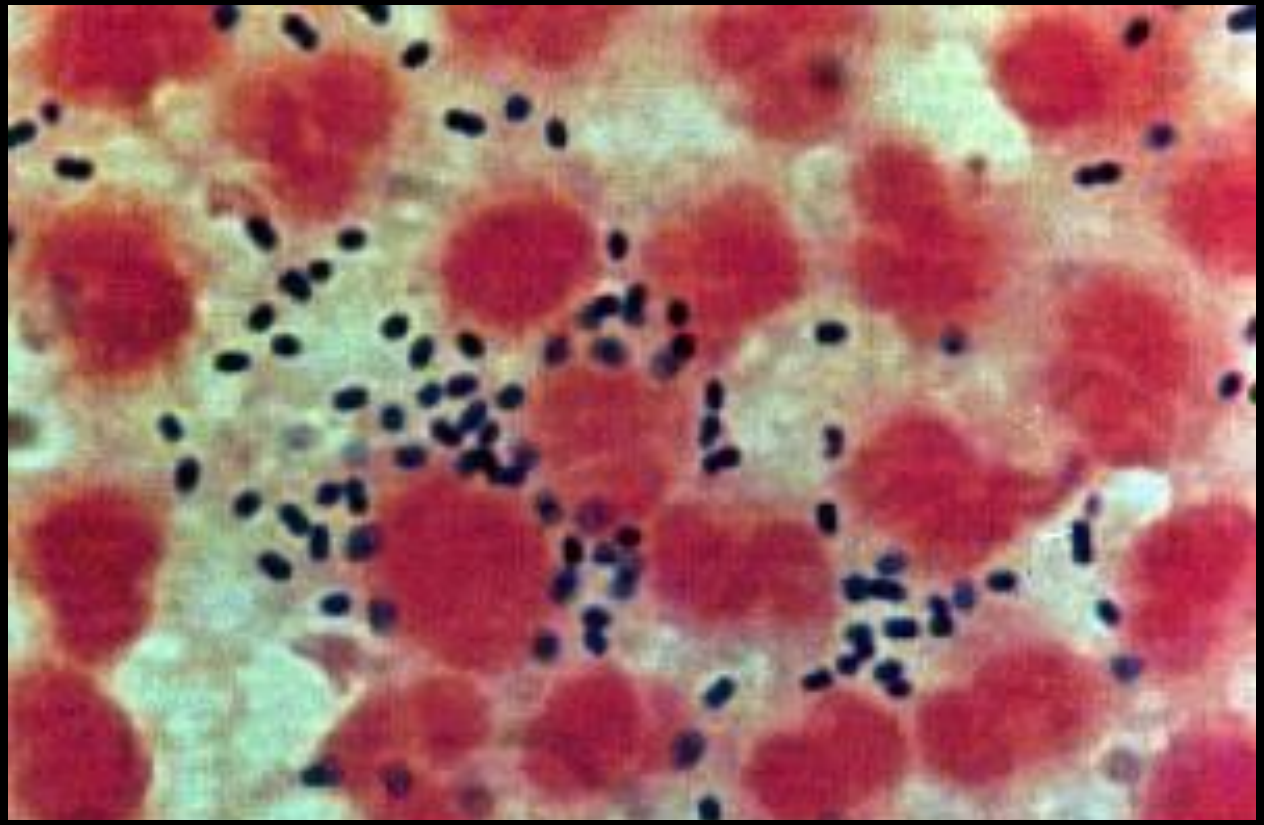
Guidelines have other limitations. Guidelines are often too narrowly focused on single diseases and are not patient focused. Patients seldom have single diseases, and few if any guidelines help clinicians in managing complexity.[7] Paradoxically, guidelines are also often too comprehensive, covering every possible intervention that could be appropriate for a patient with that single disease. Tricoci et al[2] found that in ACC/AHA guidelines with at least 1 revision, the number of recommendations increased 48% from the first guideline to the most recent version. If there is a main message in such guidelines, it is likely to be lost in the minutiae. Guidelines are not patient-specific enough to be useful and rarely allow for individualization of care. Most guidelines have a one-size-fits-all mentality and do not build flexibility or contextualization into the recommendations.[5,7] There are simply too many guidelines, often on the same topic. For instance, clinicians really do not need 10 different adult pharyngitis guidelines.[8] Moreover, guidelines are often out of date. The evidence base used to create guidelines changes quickly. Most guidelines become outdated after 5 years, and most guideline developers lack formal procedures for updating their guidelines.[9,10] The ACC/AHA guidelines are periodically updated, with updates taking a mean of 4.6 to 8.2 years until publication.[2]

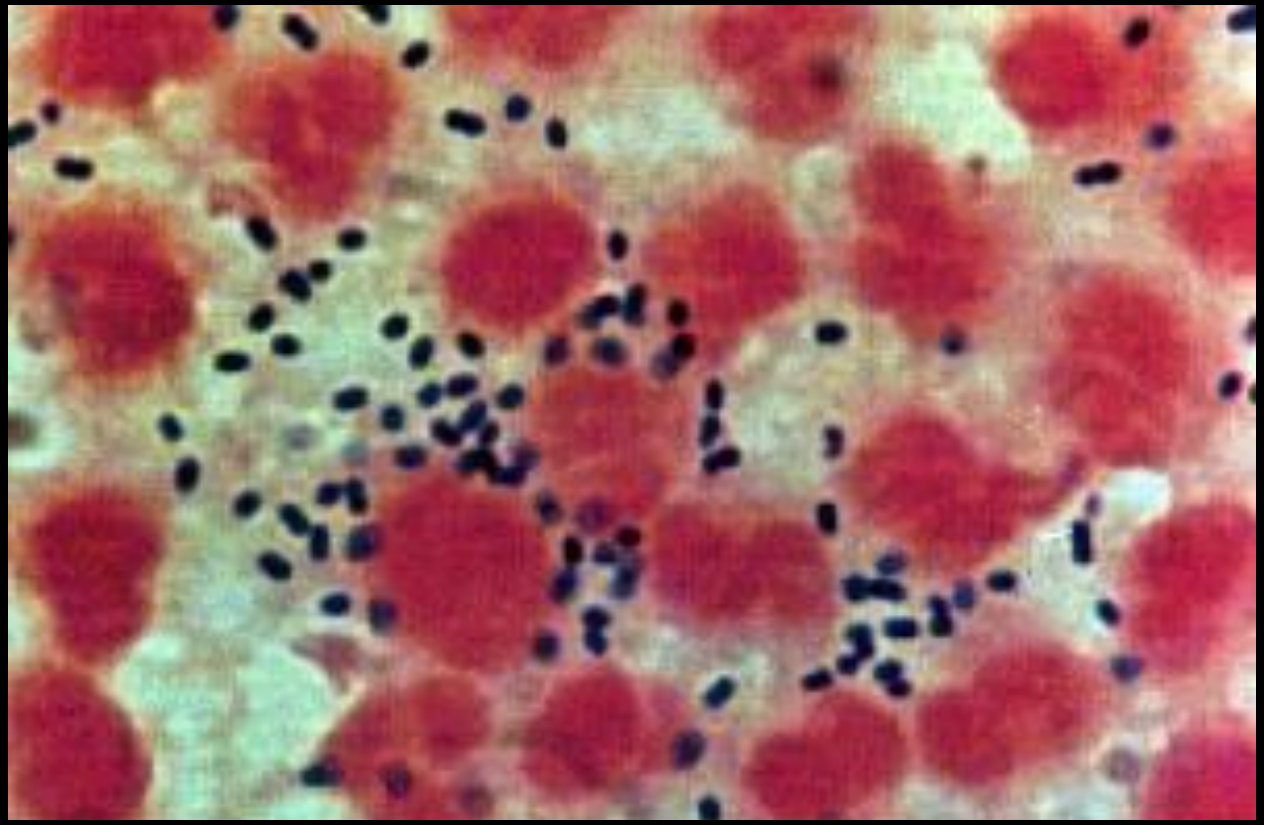
As a result, many clinicians do not use guidelines. An even greater concern, however, is that some of these consensus statements are being turned into performance measures and other tools to critique the quality of physician care. This potential problem could be minimized if performance measures were derived from high-quality guidelines based on the highest level of evidence and applied to patients with a

Author Affiliations: Veterans Affairs Medical Center (Dr Shaneyfelt) and Department of Medicine, University of Alabama School of Medicine (Drs Shaneyfelt and Centor), Birmingham; Huntsville Regional Medical Campus, Huntsville, Alabama

QUIET! →

JAMA 2009;301:868





“Captain of the men of death.” - Osler

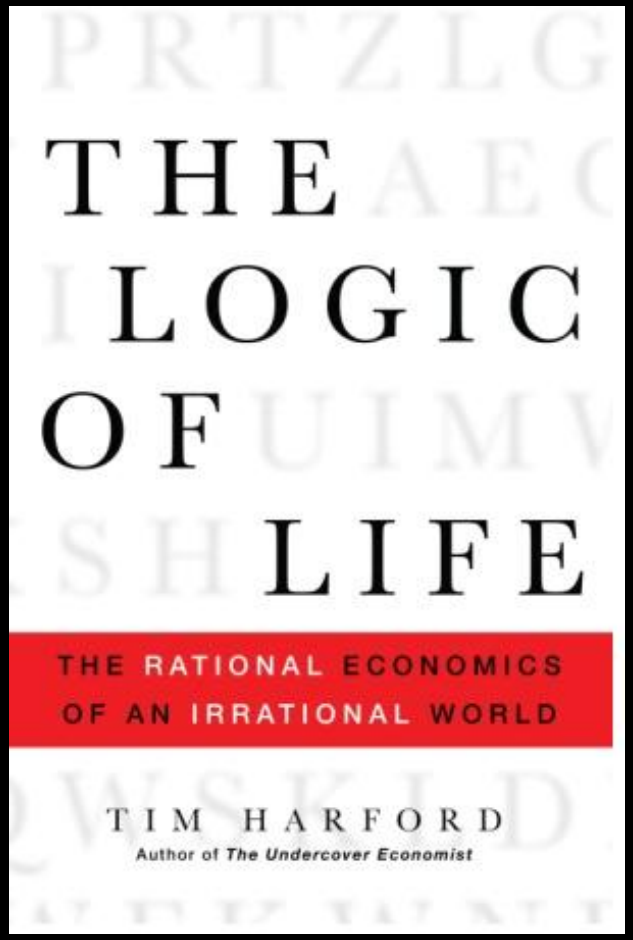
Califf's Principles

Principle 1. Treatment Effects Are Modest

Therapy	Indication	# pts	Reduction in Deaths Relative	Absolute
Aspirin	MI	18,773	23%	2.4%
Fibrinolytics	MI	58,000	18%	1.8%
Beta blocker	MI	28,970	13%	1.3%
ACE inhibitor	MI	101,000	6.5%	0.6%
Aspirin	2nd prev	54,360	15%	1.2%
Beta blocker	2nd prev	20,312	21%	2.1%
Statins	2nd prev	17,617	23%	2.7%
ACE inhibitor	2nd prev	9,297	17%	1.9%
ACE inhibitor	CHF	7,105	23%	6.1%
Beta blocker	CHF	12,385	26%	4.0%
Spironolactone	CHF	1,663	30%	11%

Figure 1. Overview of treatment effects in acute MI, secondary prevention, and heart failure. The major point of this figure is that the treatment effects are modest, with relative risk reductions (RRRs) of 10% to 25%. These small but important reductions require a quantitative, systematic approach to realize the potential for a substantial impact on the public health.

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



Chris Ferguson

Ferguson at the 2007 World Series of Poker

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.)

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%.

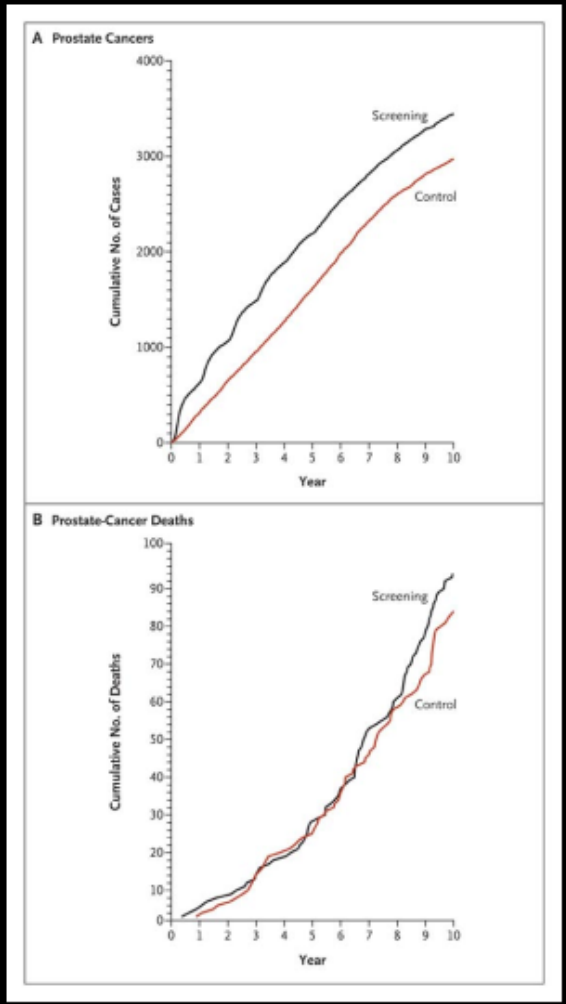
Lee J. American Heart Association 2008 Scientific Sessions; November 12, 2008; New Orleans, LA.

Patient Choice of Therapy in Localized Prostate Cancer

- "The ***perceptions of treatment efficacy related to cancer control far outweigh available supporting evidence***, and the majority of patients appear to select a prostate cancer treatment based primarily on its perceived ability to control the tumor. There may be several reasons for the misperception regarding the impact of treatment on cancer control. One factor may be the ubiquity of terminology such as "the war on cancer," and the health care system's emphasis on battling or combating the tumor. Men also may be influenced by high-profile success stories of patients. Importantly, the physicians many men rely on may intentionally or unintentionally be providing falsely optimistic information regarding the impact of therapy on cancer eradication and cancer-specific survival.
- "The literature suggests that ***side effects are not emphasized (and in some cases not even mentioned) by physicians***, and when information is presented it is done so in a way that is confusing or misinterpreted by patients. Because of this problem, patients may often ignore or discount the information they do receive. A recent review of decision aids and other sources of information available to patients by Fagerlin et al. has shown that most materials 1) contain biases toward active treatment, 2) minimize the role of watchful waiting, and 3) underestimate the likelihood and impact of side effects."
- "***The role of the physician recommendation*** has received considerable attention in prostate cancer decision making due to the widely recognized preferences held by each physician specialty. As might be expected, opinions regarding the optimal treatment for localized prostate cancer vary among urologists, radiation oncologists, oncologists, and general practitioners. Urologists nearly universally indicate that surgery is the optimal treatment strategy, and radiation oncologists similarly indicate that radiation therapy is optimal. "

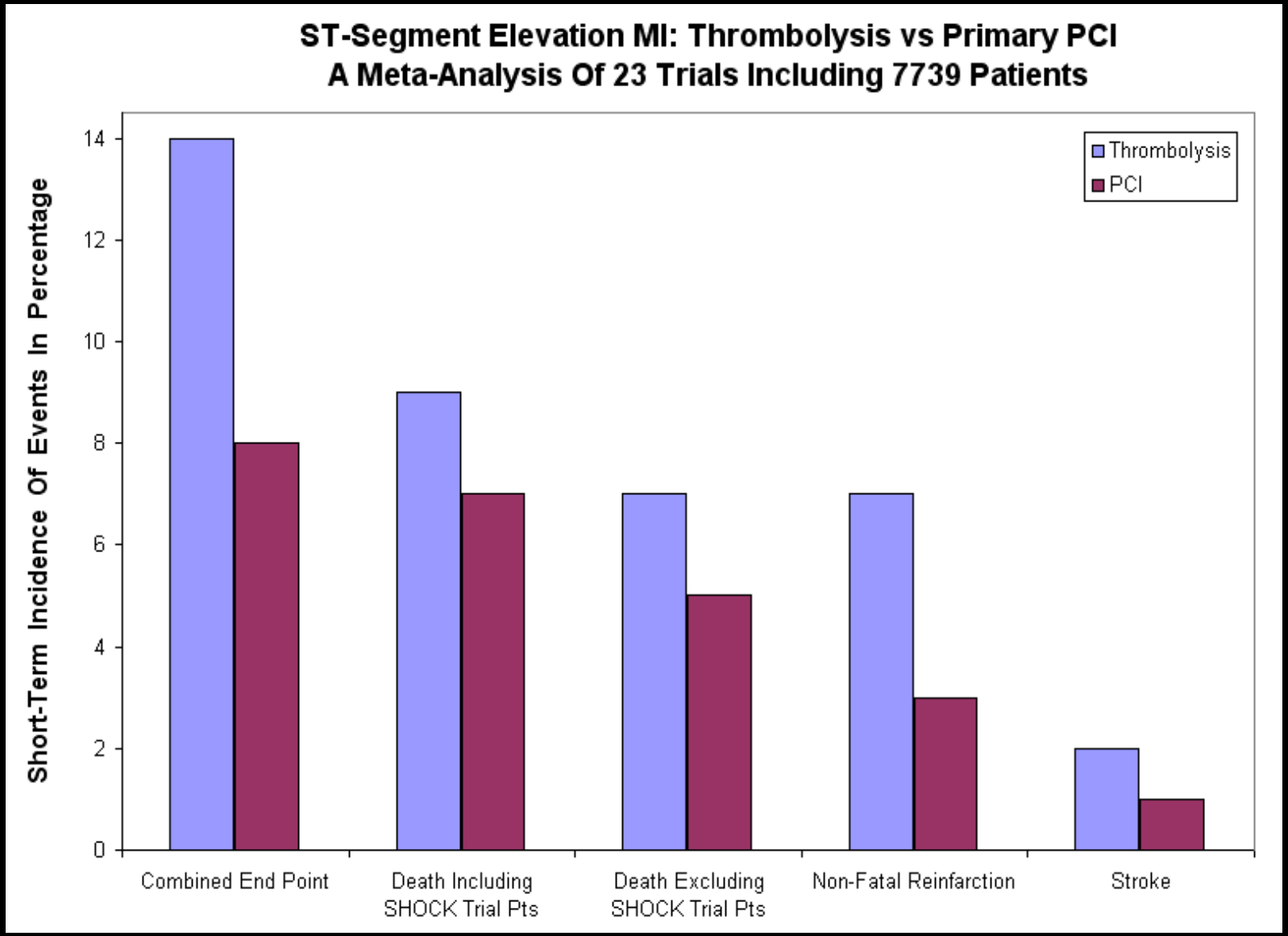
Zeliadt et al. Cancer 2006;106:1865–74

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



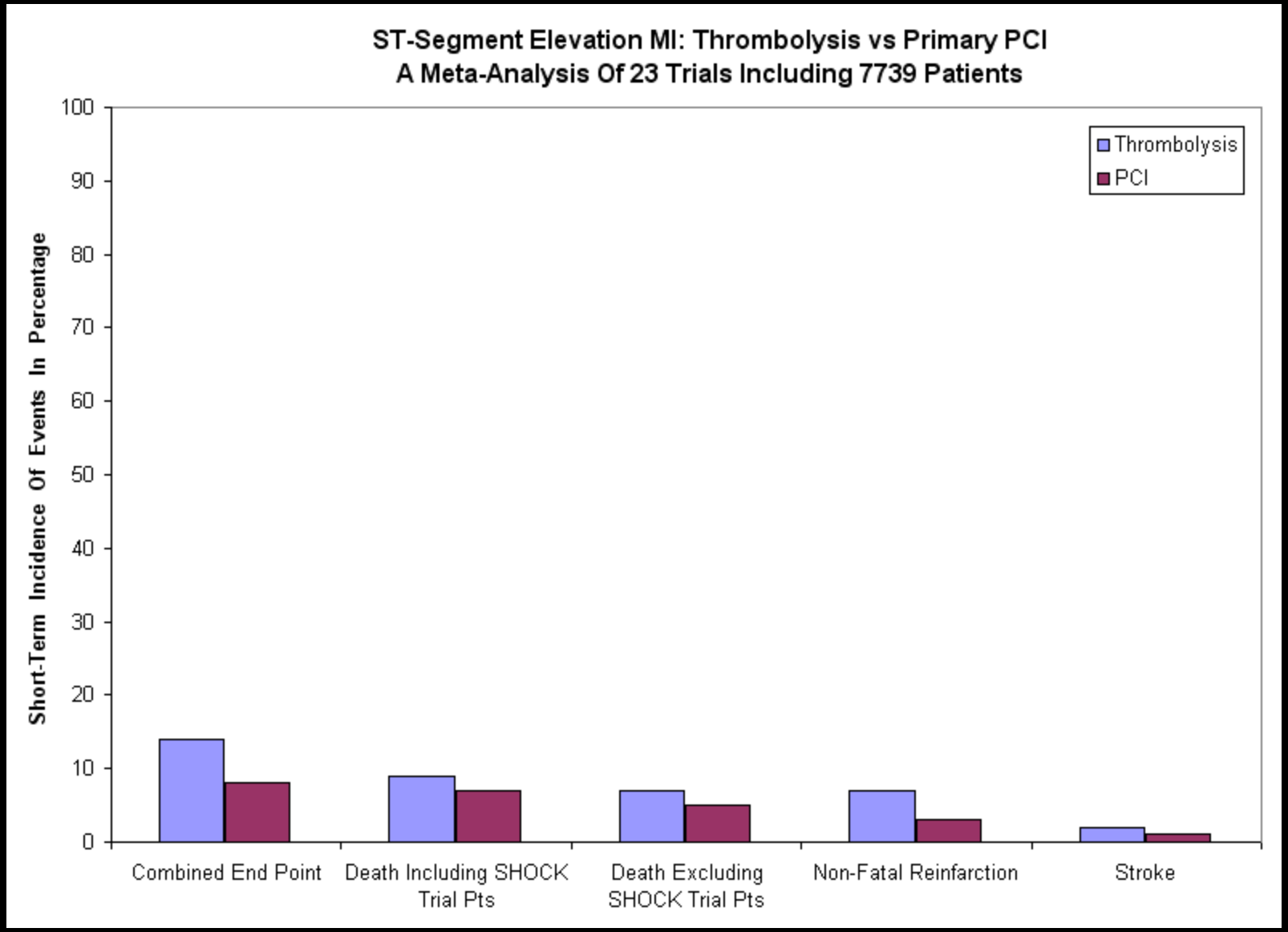
Andriole G et al. N Engl J Med 2009;10.1056/NEJMoa0810696

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

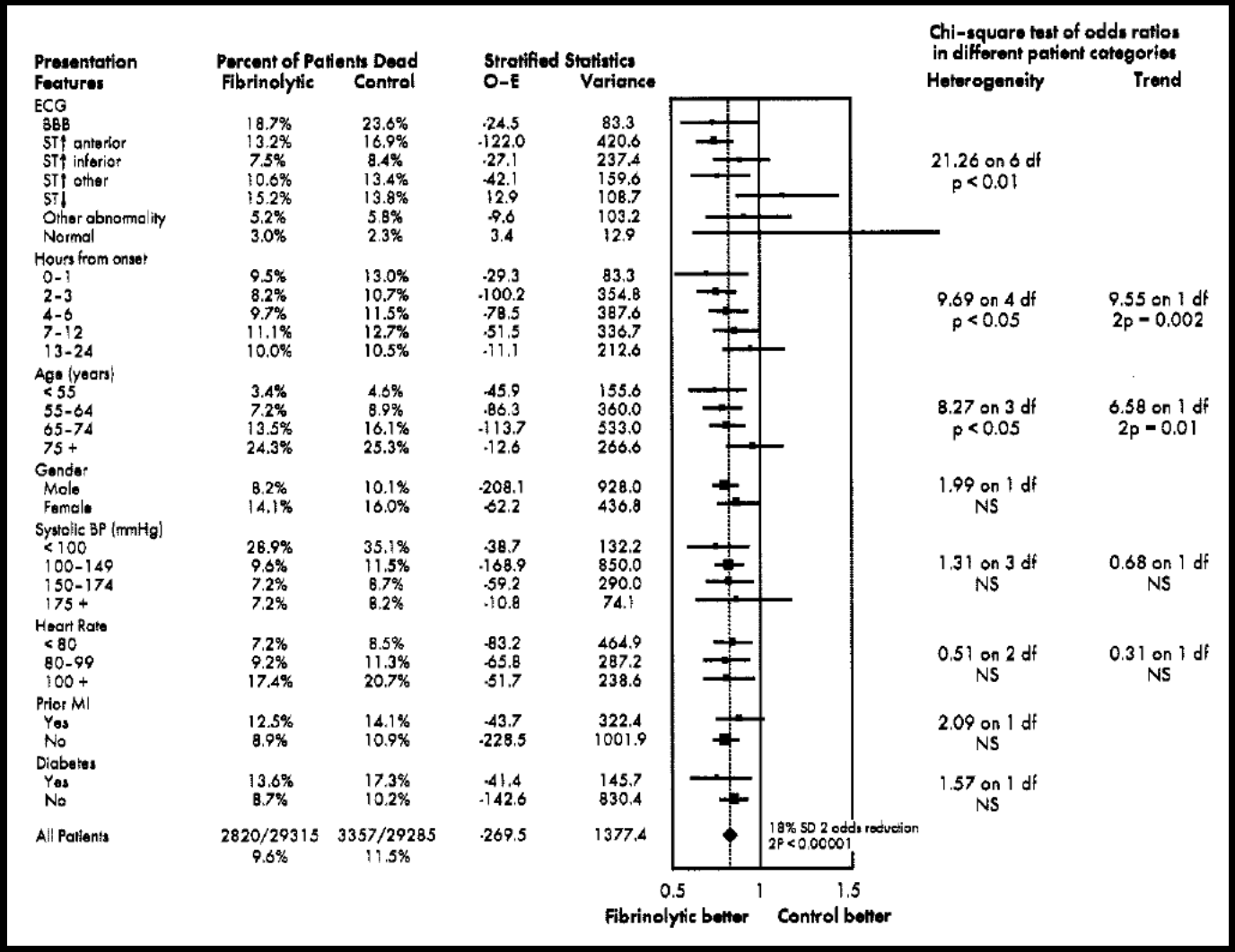


Figure 2. Overview of treatment effect of fibrinolytic therapy in myocardial infarction. This figure demonstrates several key points: the treatment effects are modest; the only qualitative interaction is a reversal of the treatment benefit seen in all other subgroups in patients with ST-segment depression;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

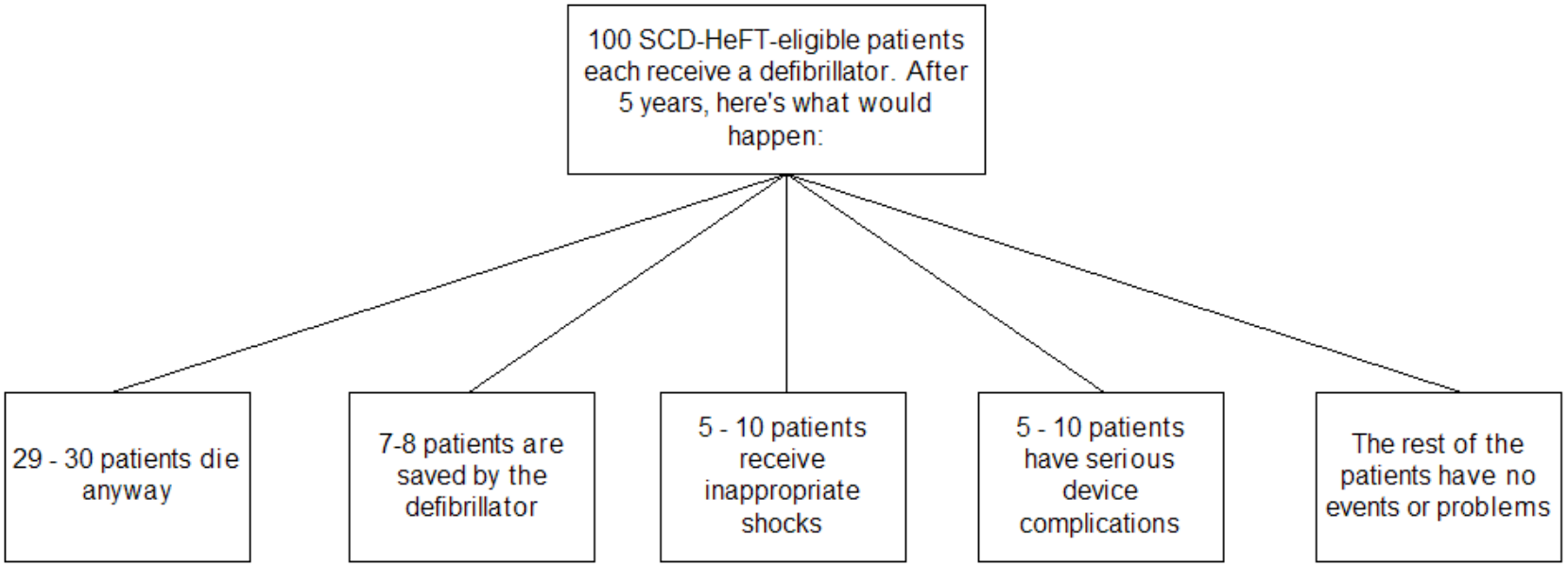
1. Recommendations for Permanent Pacing in Sinus Node Dysfunction
2. Recommendations for Acquired Atrioventricular Block in Adults
3. Recommendations for Permanent Pacing in Chronic Bifascicular Block
4. Recommendations for Permanent Pacing After the Acute Phase of Myocardial Infarction
5. Recommendations 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)

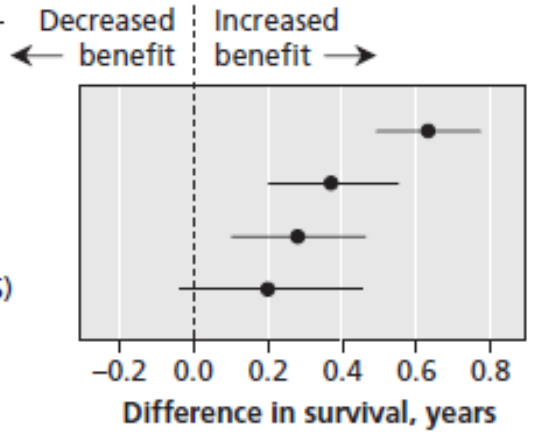


Figure 1: The maximum potential benefit of preventing sudden death with the use of implantable defibrillators among patients admitted to hospital because of heart failure. The values shown represent the difference between the observed survival after each hospital admission and the hypothetical survival 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

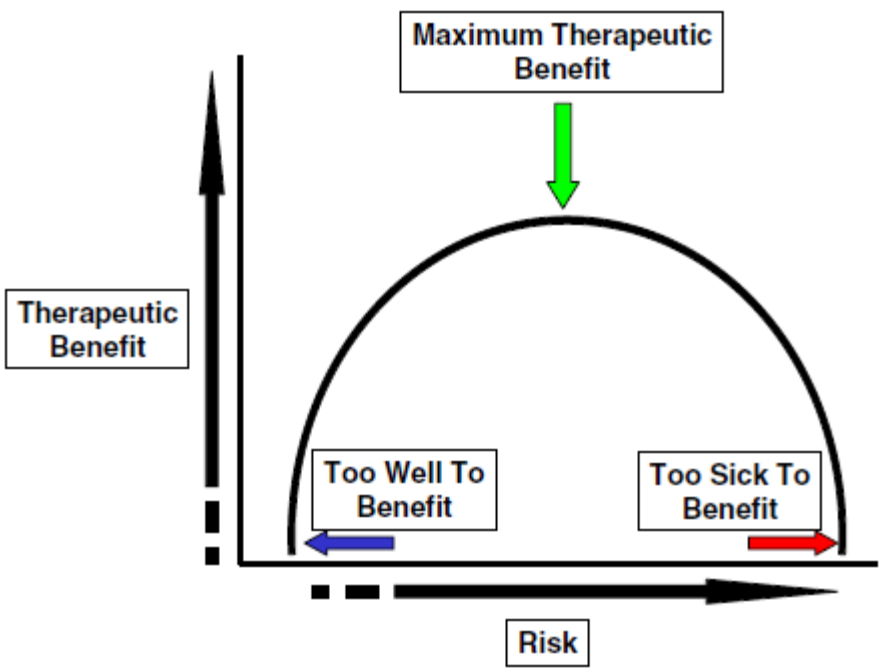


Figure 1 The Goldilocks Effect

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.

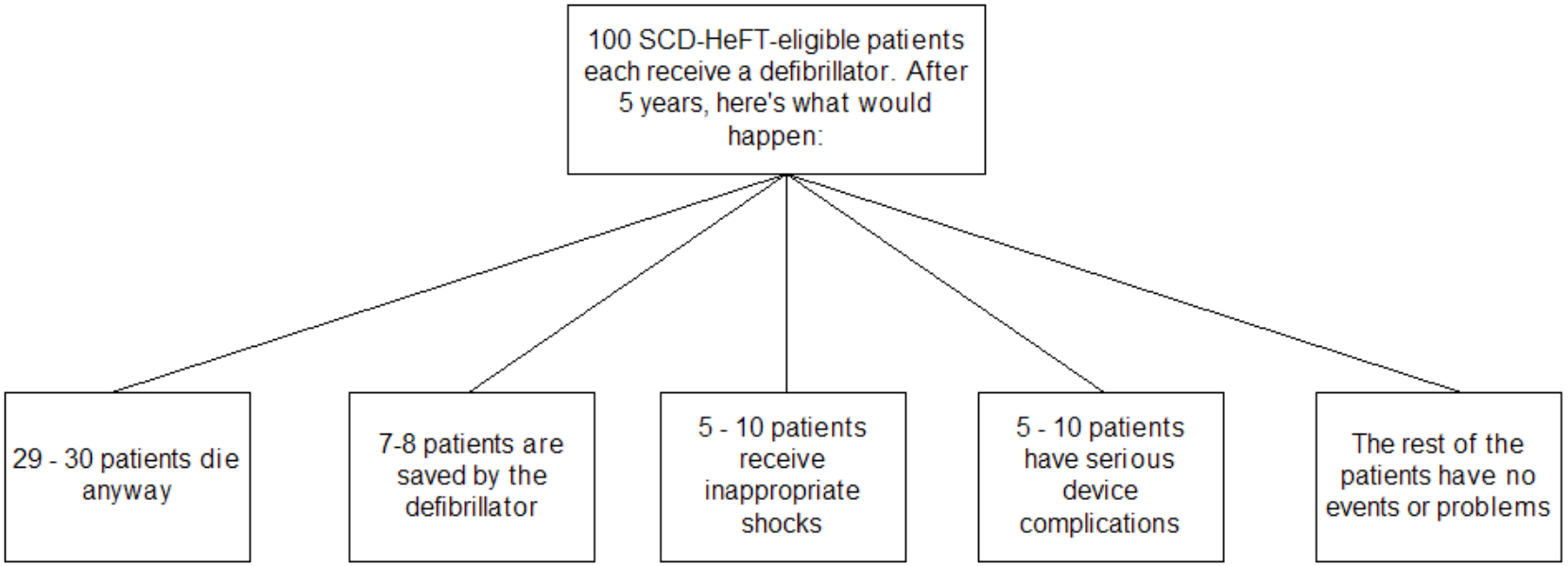
JACC 2009;53:608–11.

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.

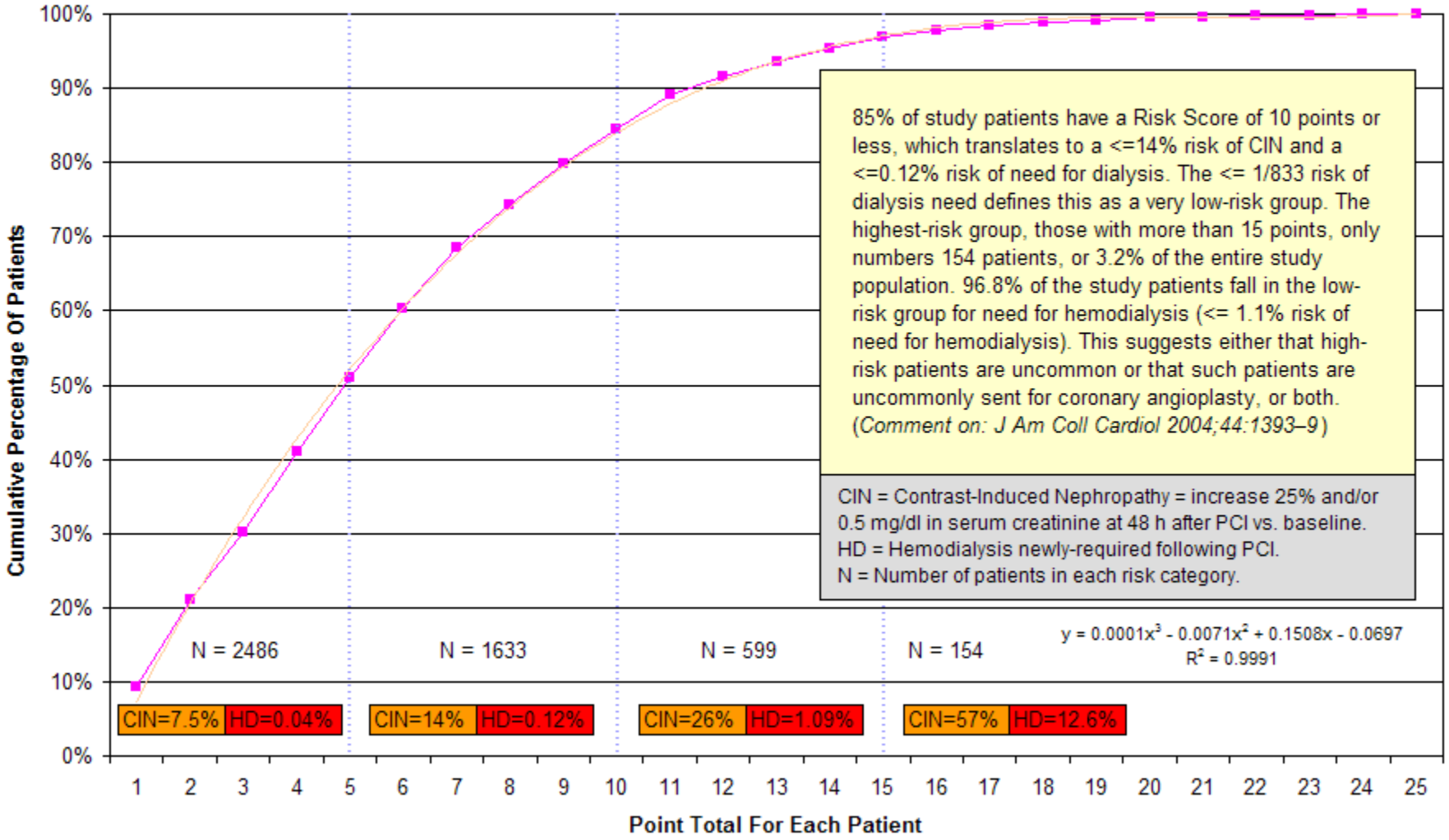


When this information is presented to CHF patients, 1/3 want an ICD, 1/3 don't want an ICD, 1/3 want to think it over.

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.

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

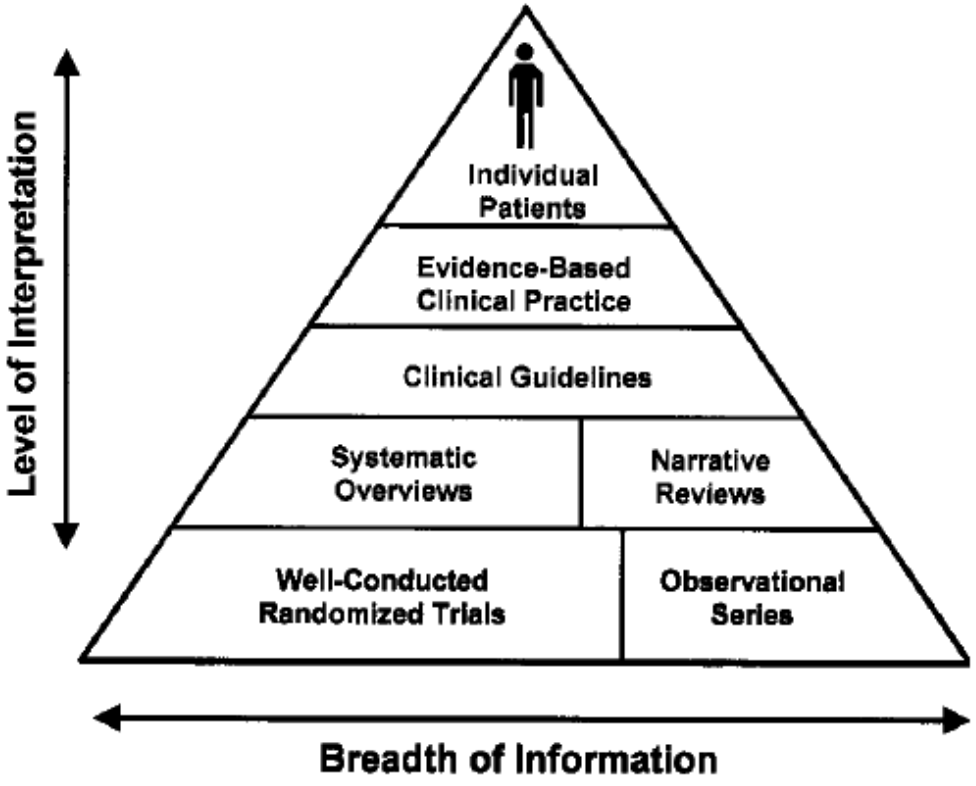


Figure 2. The pyramid of clinical evidence. In a rational, quantitative world, the recommendation for the individual patient would emanate from evidence built along the left-hand side of the pyramid. By integrating clinical trial outcome data into systematic overviews and guidelines, evidence-based clinical 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.

Califf's Principles

Principle 4: Applying the Results of Clinical Trials Is Beneficial

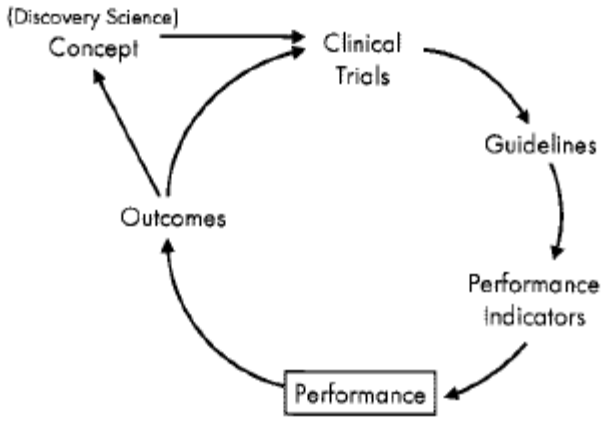


Figure 3. The quantitative cycle of quality can be envisioned as driven by discovery science (both physical and behavioral), which leads to inventions that may lead to medical therapy or technology that can be evaluated in clinical trials. If the clinical trials are adequately designed and performed 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.

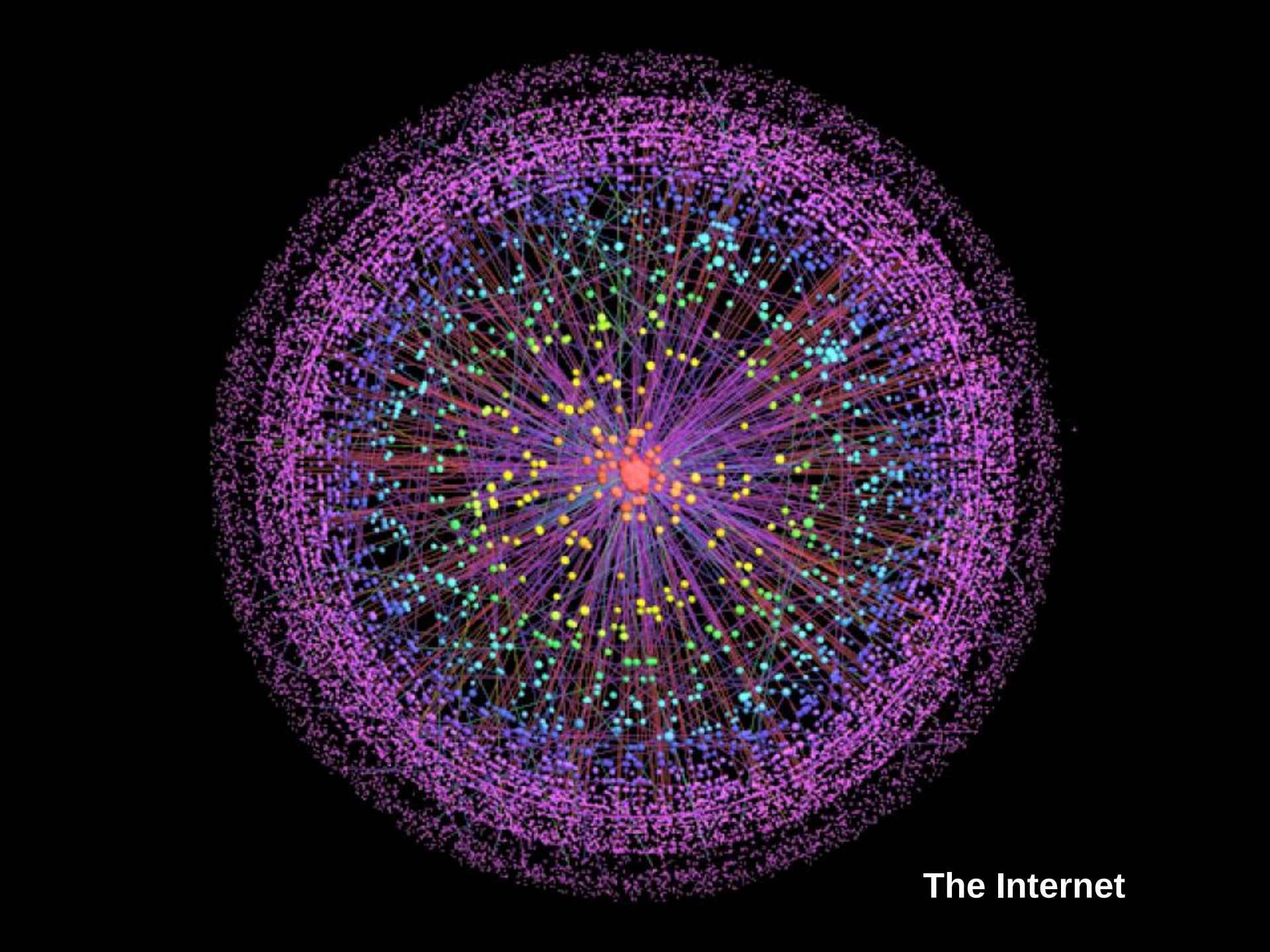
Califf RM , DeMets DL. *Circulation* 2002;106;1015-1021, 1172-1175.

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.


THANK YOU


The Internet