Medical Reversal
Why 46% of What We Do Is Wrong

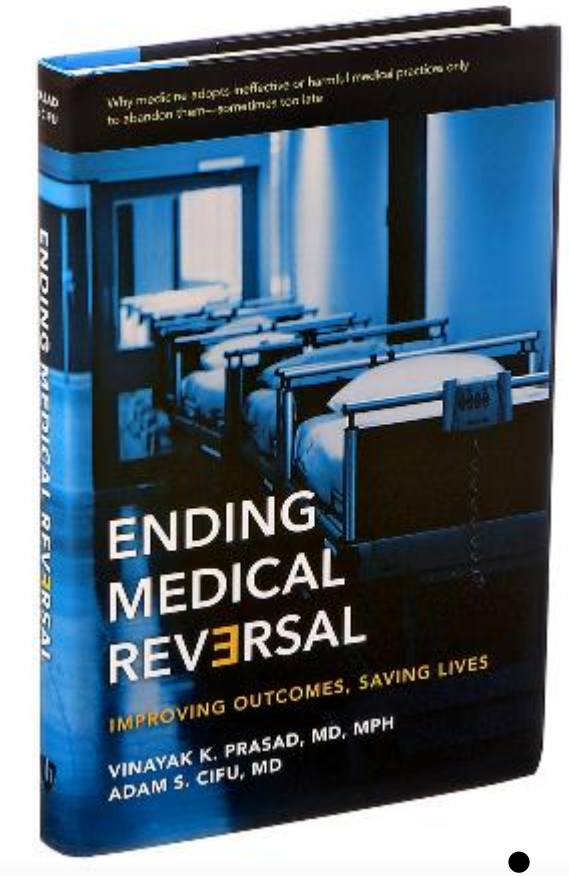
Vinay Prasad, MD MPH
Assistant Professor of Medicine

Division of Hematology-Oncology
Department of Public Health and Preventive Medicine
Senior Scholar in the Center for Ethics

Oregon Health & Science University

- @vinayprasad82

Disclosure



- @vinayprasad82

Disclosure

- Some of this talk is controversial.
- It is not my purpose to disparage any particular practice
- Broad patterns of medical progress/ innovation/ evidence (& hijacked) and missteps in medicine

- @vinayprasad82

What is Medical Reversal?

Often in medicine new practices replace older ones.

H2 -> PPI

MOMP -> MOPP -> ABVD

Streptokinase -> TPA -> PCA BM stent/-> drug eluting

What is Medical Reversal?

Many other times, something we had been doing is found to be no better or worse than a prior or lesser standard of care (incd. doing nothing)

Routine use of Swan Ganz for monitoring ICU patients

Routine HT for post-menopausal women

Routine PCA for stable angina

What is Medical Reversal?

Is much more like this….

Definition of Medical Reversal

A large, well done study; typically RCT (with better blinding/controls/ power/ endpoints aka less bias) contradicts current medical practice

VIEWPOINT

Reversals of Established Medical Practices

Evidence to Abandon Ship

Vinay Prasad, MD
Adam Cifu, MD
John P. A. Ioannidis, MD, DSc

Rarely, some investigators find the courage to test established "truths" with large, rigorous randomized trials. When this happens, empirical evidence suggests that "medical reversals" may be quite common. In an evaluation of 35 trials that were published in a major clinical journal in 2009 and that tested an established clinical practice, 16 (46%) re-

RESEARCH LETTER

The Frequency of Medical Reversal

We use the term *reversal* to signify the phenomenon of a new trial—superior to predecessors because of better design, increased power, or more appropriate controls—contradicting current clinical practice. In recent years, a number of such reversals have occurred. Use of hormone therapy,[1] the class 1C antiarrhythmic agents,[2] and the pulmonary artery catheter[3] have decreased when trials demonstrated that they are either less effective than previously thought or harmful.

Similar to other concepts

- No-value or low-value care
- De-adopt failed practices
- Contradicted or refuted practices
- Slow med

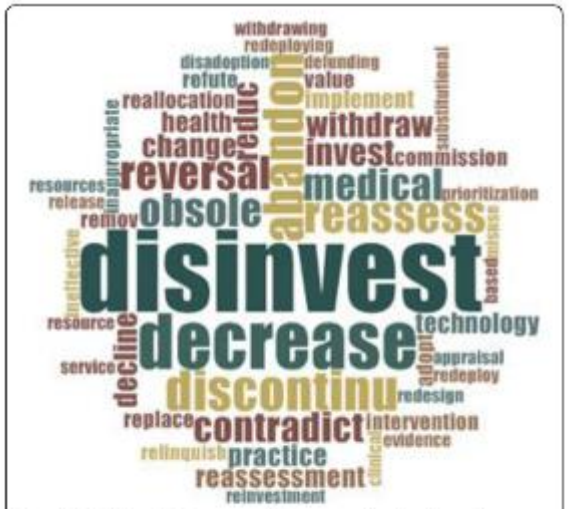


Fig. 1 Word cloud of frequency of terms used to label low-value care practices and policy processes, derived by entering the 43 terms identified by Nieven et al. [3] in nVivo software

Talk outline

- Select examples of reversal
- Frequency estimates
- Harms
- Origins
- Solutions
- Objections
- What will EBM look like in the age of recognition of Medical Reversal

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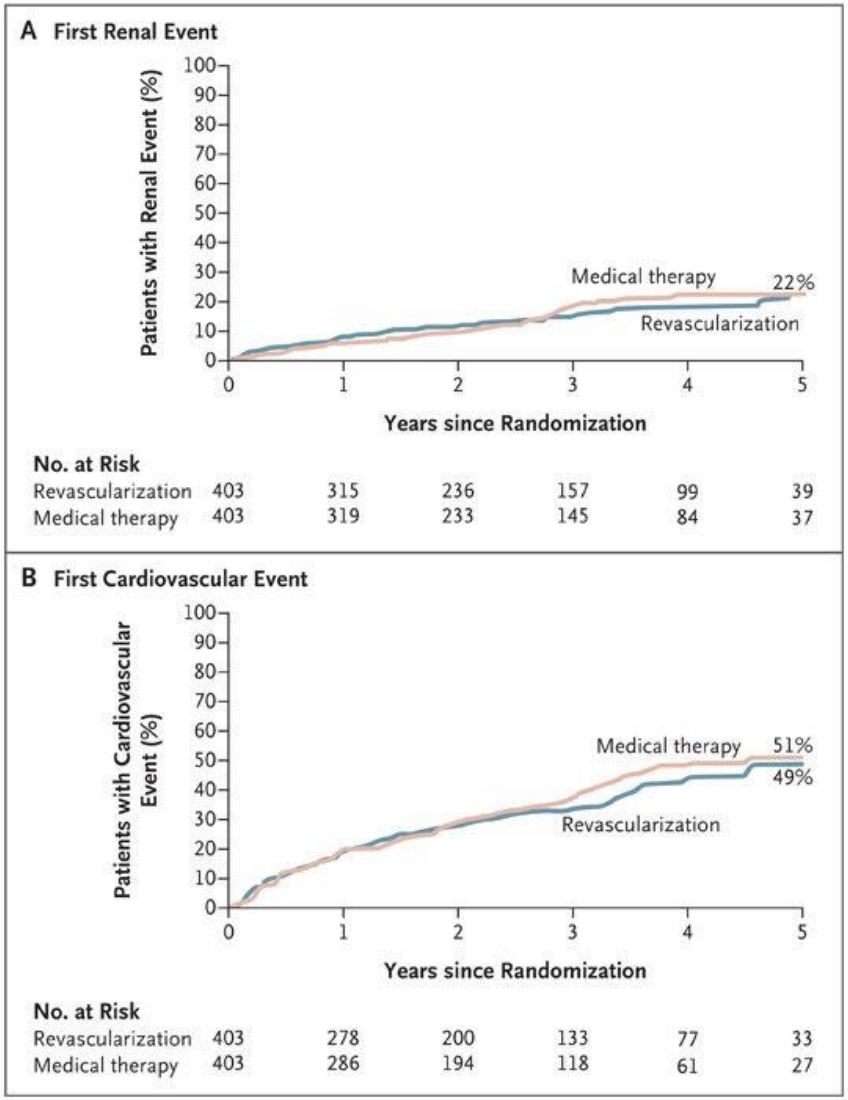
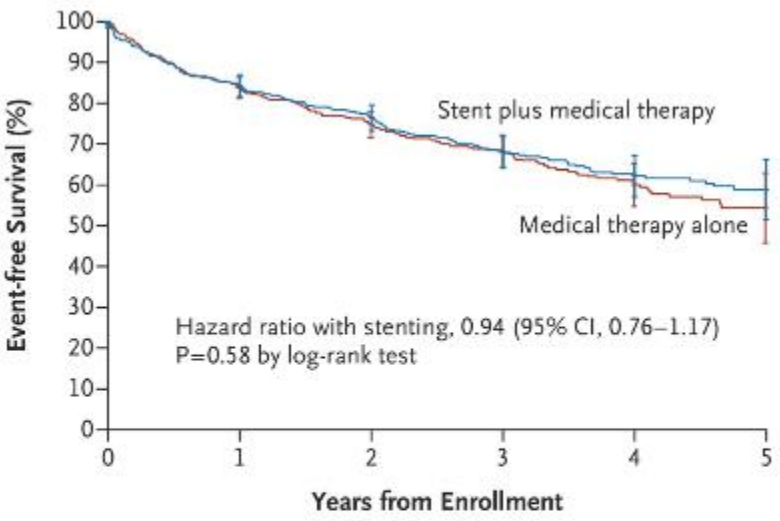
Revascularization versus Medical Therapy for Renal-Artery Stenosis

The ASTRAL Investigators

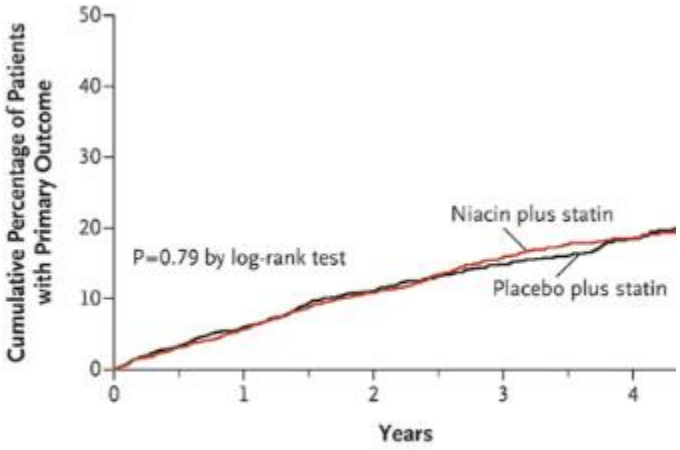


Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

Christopher J. Cooper, M.D., Timothy P. Murphy, M.D., Donald E. Cutlip, M.D., Kenneth Jamerson, M.D., William Henrich, M.D., Diane M. Reid, M.D., David J. Cohen, M.D., Alan H. Matsumoto, M.D., Michael Steffes, M.D., Michael R. Jaff, D.O., Martin R. Prince, M.D., Ph.D., Eldrin F. Lewis, M.D., Katherine R. Tuttle, M.D., Joseph I. Shapiro, M.D., M.P.H., John H. Rundback, M.D., Joseph M. Massaro, Ph.D., Ralph B. D'Agostino, Sr., Ph.D., and Lance D. Dworkin, M.D., for the CORAL Investigators*

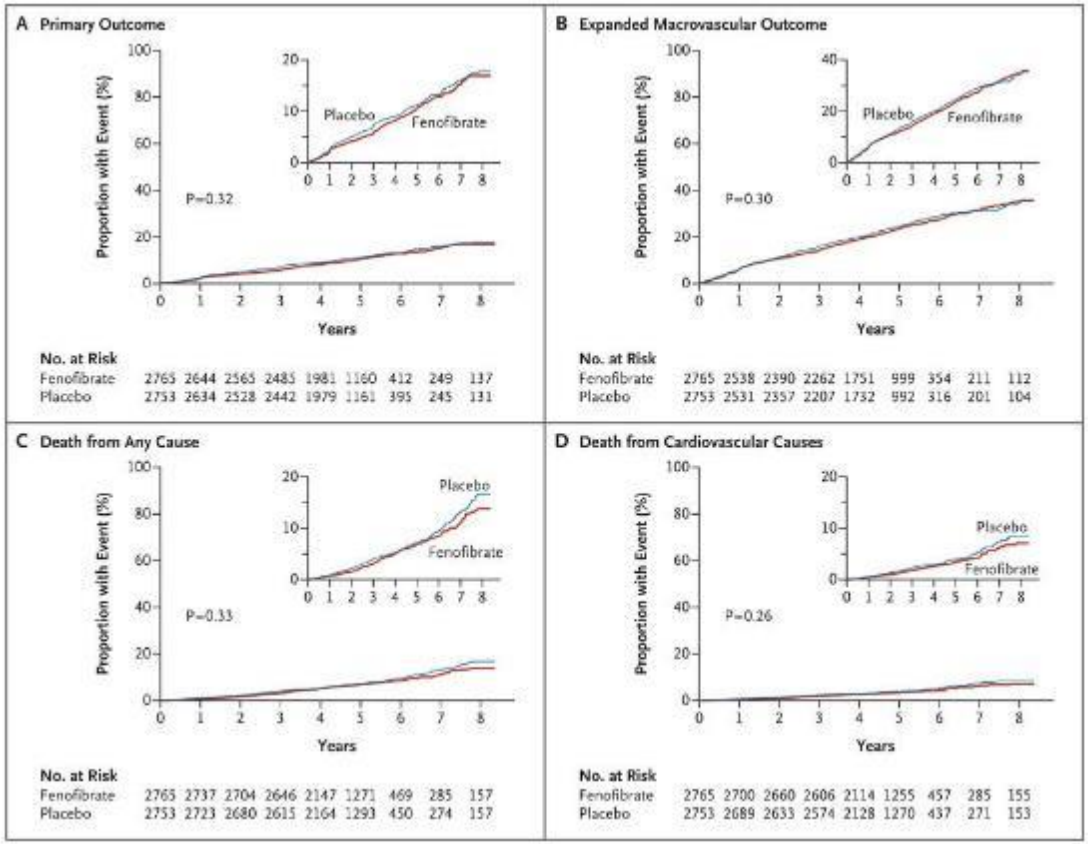


Niacin, Fenofibrate

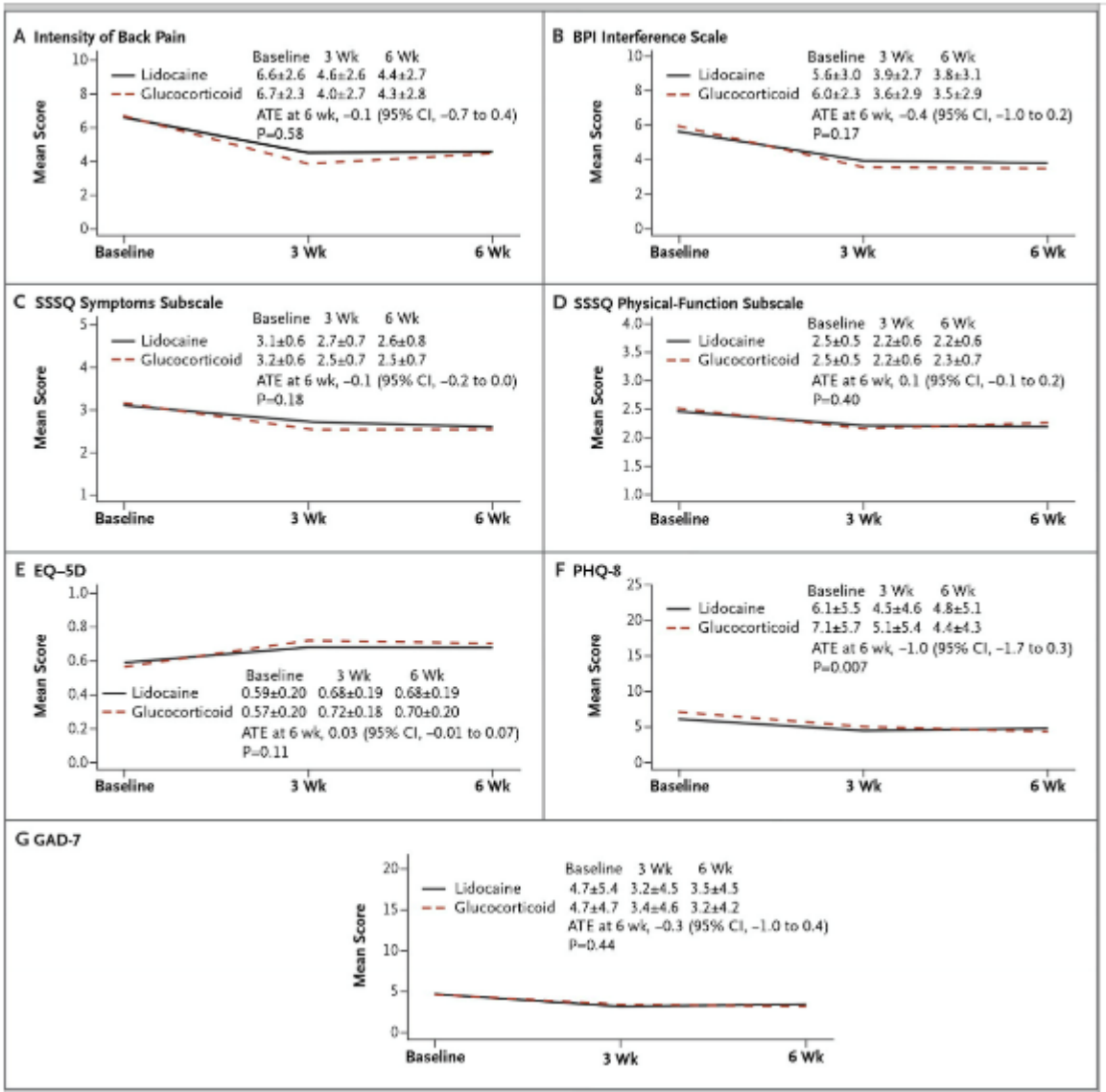


No. at Risk

Placebo plus statin	1696	1581	1381	910	436
Niacin plus statin	1718	1606	1366	903	428



Steroid injection for spinal stenosis



Talk outline

- Select examples of reversal
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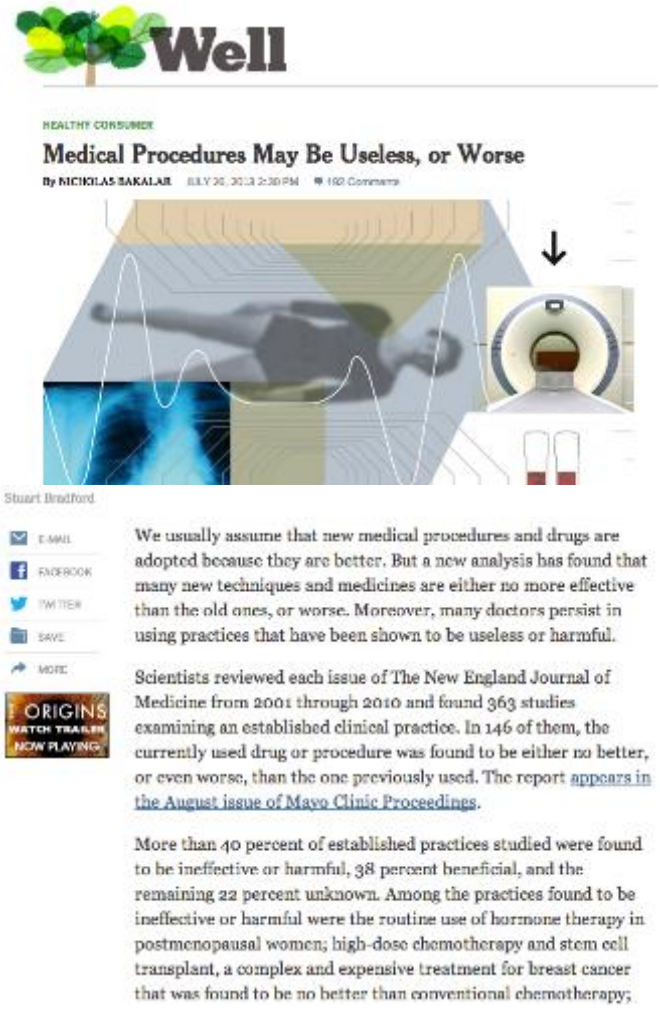
Our own estimate

A Decade of Reversal: An Analysis of 146 Contradicted Medical Practices

Vinay Prasad, MD; Andrae Vandross, MD; Caitlin Toomey, MD; Michael Cheung, MD; Jason Rho, MD; Steven Quinn, MD; Satish Jacob Chacko, MD; Durga Borkar, MD; Victor Gall, MD; Senthil Selvaraj, MD; Nancy Ho, MD; and Adam Cifu, MD

Abstract

Objective: To identify medical practices that offer no net benefits.
Methods: We reviewed all original articles published in 10 years (2001-2010) in one high-impact journal. Articles were classified on the basis of whether they addressed a medical practice, whether they tested a new or existing therapy, and whether results were positive or negative. Articles were then classified as 1 of 4 types: replacement, when a new practice surpasses standard of care; back to the drawing board, when a new practice is no better than current practice; reaffirmation, when an existing practice is found to be better than a lesser standard; and reversal, when an existing practice is found to be no better than a lesser therapy. This study was conducted from August 1, 2011, through October 31, 2012.
Results: We reviewed 2044 original articles, 1344 of which concerned a medical practice. Of these, 981 articles (73.0%) examined a new medical practice, whereas 363 (27.0%) tested an established practice. A total of 947 studies (70.5%) had positive findings, whereas 397 (29.5%) reached a negative conclusion. A total of 756 articles addressing a medical practice constituted replacement, 165 were back to the drawing board, 146 were medical reversals, 138 were reaffirmations, and 139 were inconclusive. Of the 363 articles testing standard of care, 146 (40.2%) reversed that practice, whereas 138 (38.0%) reaffirmed it.
Conclusion: The reversal of established medical practice is common and occurs across all classes of medical practice. This investigation sheds light on low-value practices and patterns of medical research.



Well

HEALTHY CONSUMER

Medical Procedures May Be Useless, or Worse

By NICHOLAS BAKALAR JULY 30, 2013 2:30 PM 192 Comments

Stuart Bradford

E-MAIL FACEBOOK TWITTER SAVE MORE

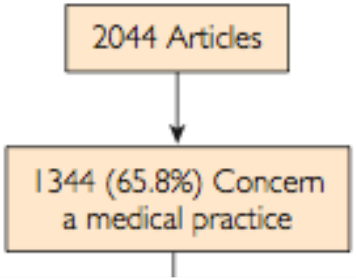
ORIGINS WATCH TRAILER NOW PLAYING

We usually assume that new medical procedures and drugs are adopted because they are better. But a new analysis has found that many new techniques and medicines are either no more effective than the old ones, or worse. Moreover, many doctors persist in using practices that have been shown to be useless or harmful.

Scientists reviewed each issue of The New England Journal of Medicine from 2001 through 2010 and found 363 studies examining an established clinical practice. In 146 of them, the currently used drug or procedure was found to be either no better, or even worse, than the one previously used. The report appears in the August issue of Mayo Clinic Proceedings.

More than 40 percent of established practices studied were found to be ineffective or harmful, 38 percent beneficial, and the remaining 22 percent unknown. Among the practices found to be ineffective or harmful were the routine use of hormone therapy in postmenopausal women; high-dose chemotherapy and stem cell transplant, a complex and expensive treatment for breast cancer that was found to be no better than conventional chemotherapy;

How often does it happen?



How often does it happen?

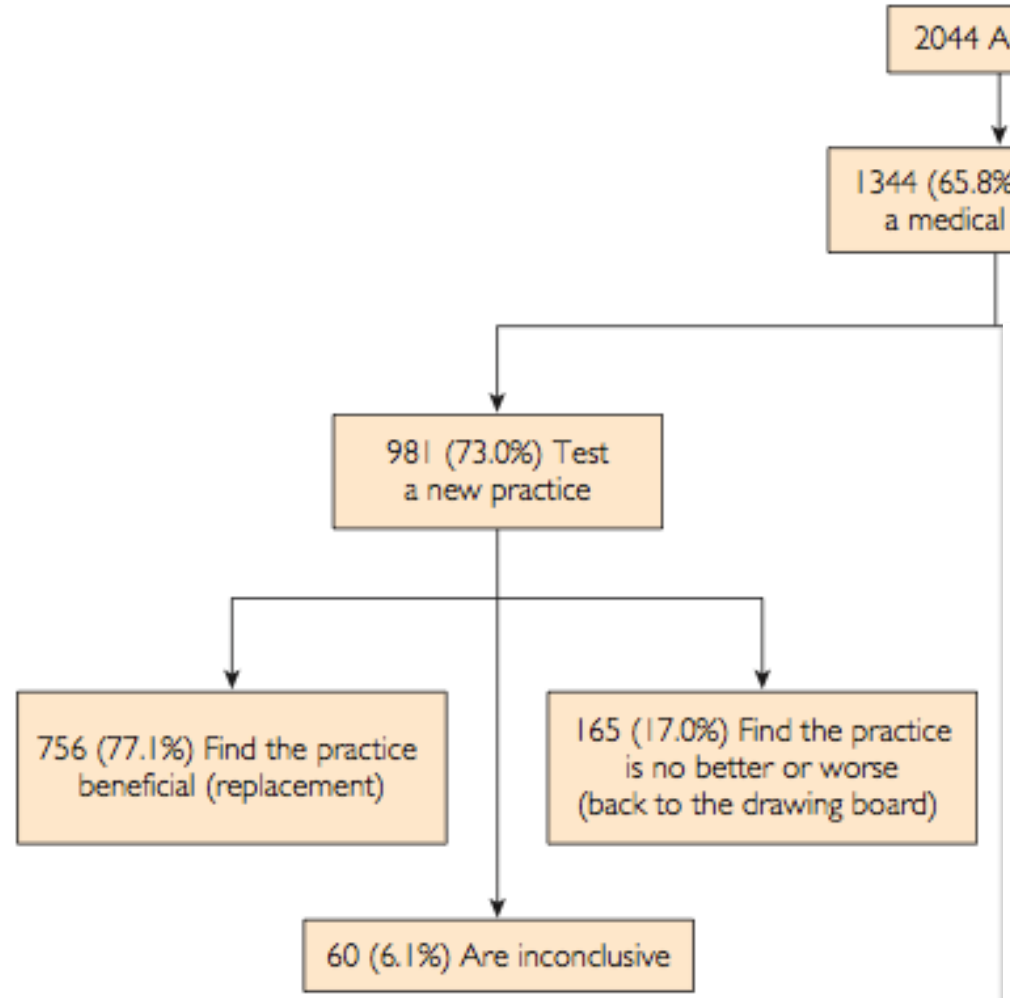


FIGURE 1. A breakdown of articles concerning a medical practice.

How often does it happen?

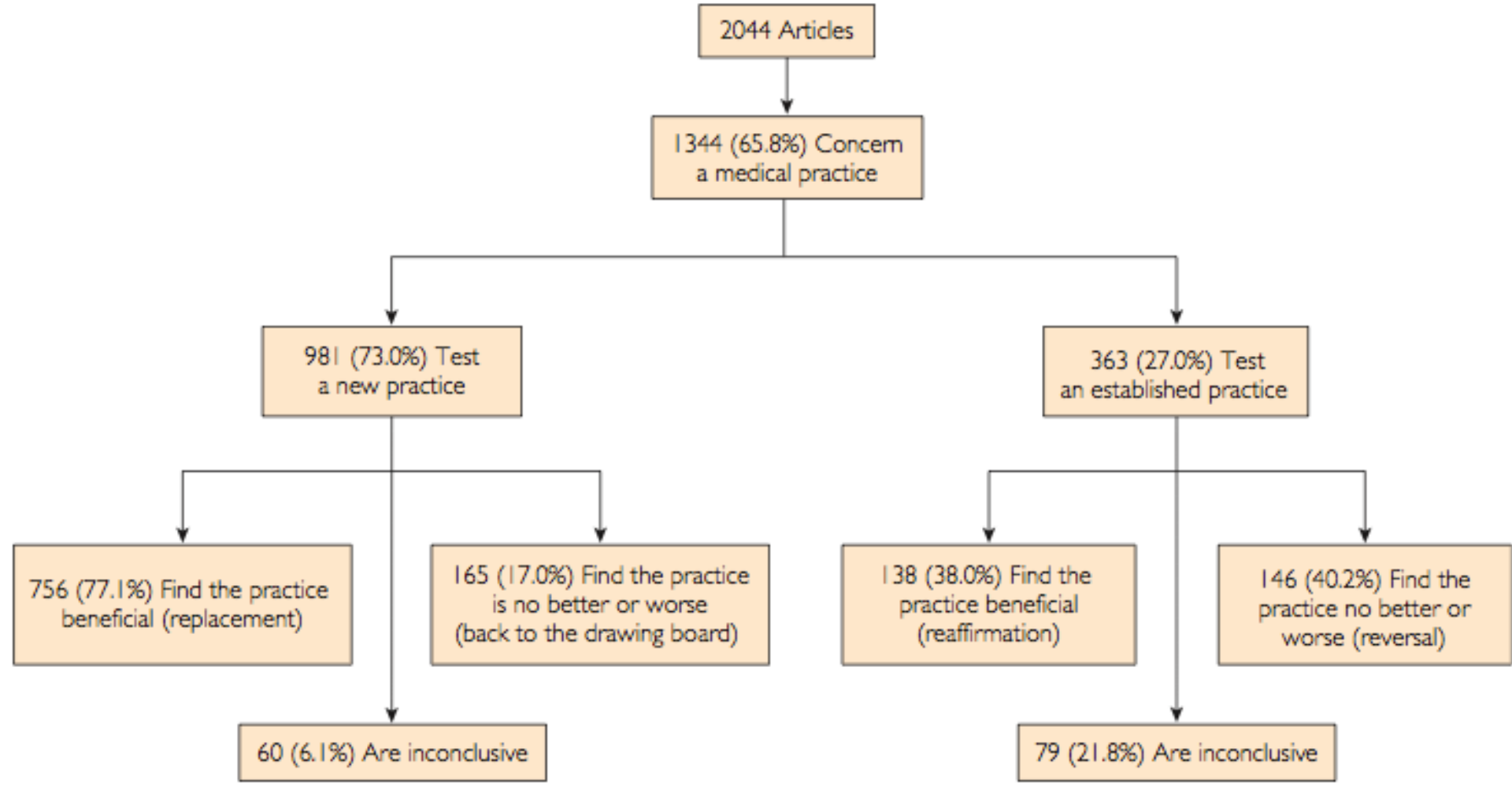


FIGURE 1. A breakdown of articles concerning a medical practice.

TABLE 2. Key Reversals, 2001-2010

Reference, year	Description
Antimicrobial treatment in diabetic women with asymptomatic bacteriuria (Harding et al,[48] 2002)	In contrast to European societies, several groups[49,50] in the United States recommended screening and treating for asymptomatic bacteriuria in women with diabetes. This randomized trial found that although this practice leads to more antibiotic use, it did not reduce complications or improve the time to symptomatic infection
Conventional adjuvant chemotherapy with or without high-dose chemotherapy and autologous stem-cell transplantation in high-risk breast cancer (T et al,[51] 2003)	Multiple studies have claimed that high-dose chemotherapy with stem cell transplantation improves disease-free survival at 3 years to 65%-70%, an improvement of 20%-30% beyond standard adjuvant chemotherapy.[52,53] High-dose chemotherapy and autologous stem cell transplantation became a common, costly, and controversial practice for more than a decade. This trial randomized patients with primary breast cancer with involvement of at least 10 ipsilateral axillary lymph nodes to standard adjuvant chemotherapy vs adjuvant chemotherapy followed by high-dose chemotherapy and stem cell transplant. The study arm was found to
Control of exposu allergen and alle impermeable be adults with asthma (Woodcock et al,[54] 2003)	st of all preventive idelines recommend d, placebo-controlled trial of >1100 patients found no benefit on any clinical or physiologic outcome for this practice
Methylprednisolone, valacyclovir, or the combination for vestibular neuritis (Strupp et al,[58] 2004)	The cause of vestibular neuritis is presumed to be a viral infection,[59] and yet it is unknown whether corticosteroids, an antiviral medication, or a combination of both have any benefit in treating this disease. At the time of this publication, physicians prescribed either or both. A prospective, randomized, double-blind, 2-by-2 factorial trial was performed assessing whether placebo, methylprednisolone, valacyclovir, or a combination of the 2 would improve symptoms. Only the corticosteroids, and not the antiviral, improved the recovery of patients with vestibular neuritis
Mild intraoperative hypothermia during surgery for intracranial aneurysm (Todd et al,[60] 2005)	Hypothermia was found to be helpful as a neurosurgical adjunct in 1955, especially for ischemic and traumatic insults. At the time of this publication, the practice was used in nearly 50% of aneurysm surgeries.[61] This large randomized study, the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST), found no improvement in neurologic outcomes with hypothermia, while noting an increase in bacterial infections with the intervention
Optimal medical therapy with or without PCI for stable coronary disease (Boden et al,[35] 2007)	Although treatment guidelines recommended an initial approach of intensive medical therapy, reduction of risk factors, and lifestyle modification (optimal medical therapy) for patients with stable coronary artery disease, percutaneous coronary intervention (PCI) was still a common initial treatment strategy for patients with stable coronary artery disease at the time this study was performed.[62,63] The authors found that PCI added to optimal medical therapy did not reduce the risk of death, myocardial infarction, or other major cardiovascular events

We detail all 146 Reversals in the Supplementary Appendix

Reversals include

- Medications/ Procedures/ Devices/ Surgeries/ Screening tests/ OTC medications/ Vitamins/ Supplements/ Treatment algorithms (P2y12 testing)/ Diagnostic instruments (Swan Ganz)/ Systems interventions/ Quality and performance measures

- In short, every corner of health care

Talk outline

- Select examples of reversal
- Frequency estimates
- **Harms**
- Origins
- Solutions
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- What will EBM look like in the age of recognition of Medical Reversal

What are the harms of reversal

- Harms are threefold:
- People who undergo the practice during the years it fell in favor
- People who undergo the practice during the lag time before it falls out of favor
  Ten years of inertia
- Loss of trust in medical system

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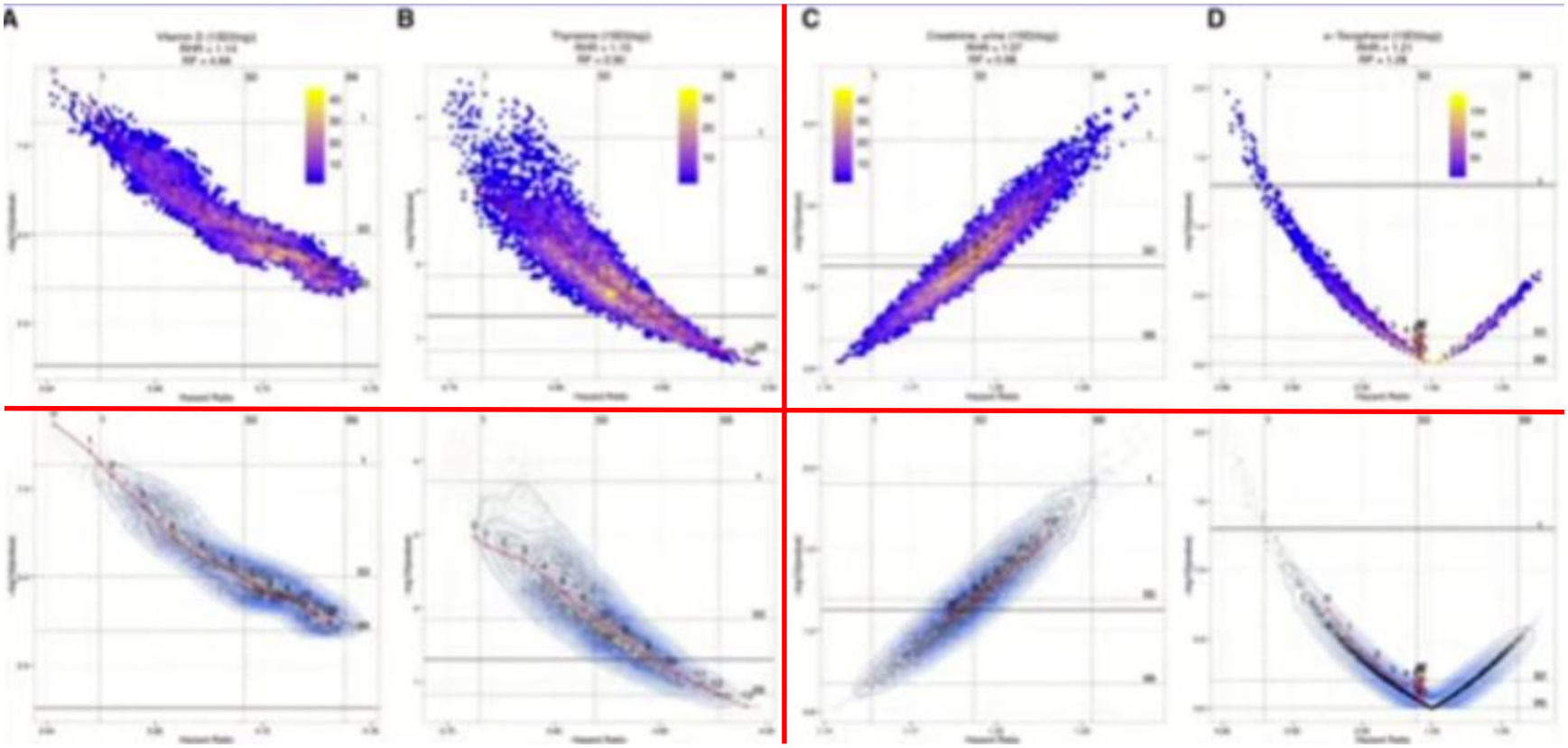
Why does Reversal happen?

- We adopted something based on inadequate & biased studies (w/o definitive trials ongoing or forthcoming)
  - Pathophysiology alone
  - Pathophysiology plus anecdotal evidence
  - Epidemiological evidence (with residual confounding)
  - Historical controlled evidence
  - Randomized trials
    - Inappropriate controls (too young/ non representative)
    - Inappropriate dosing/ comparators/ concom. medications
    - Single center
    - Drug run periods
    - Inappropriate endpoints (surrogates)
    - Early termination
    - Selective reporting/ publication bias

    } Pragmatic
  - Meta-analysis – based on caliber of included studies & completeness

Observational/ Epidemiology studies can say anything

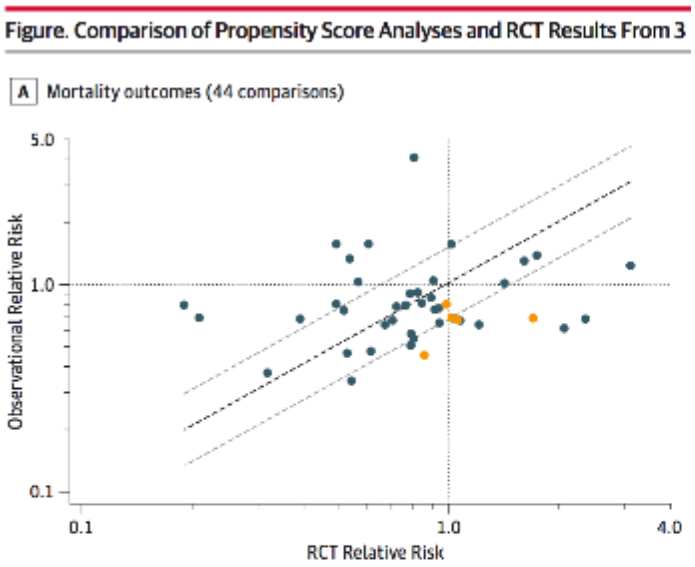


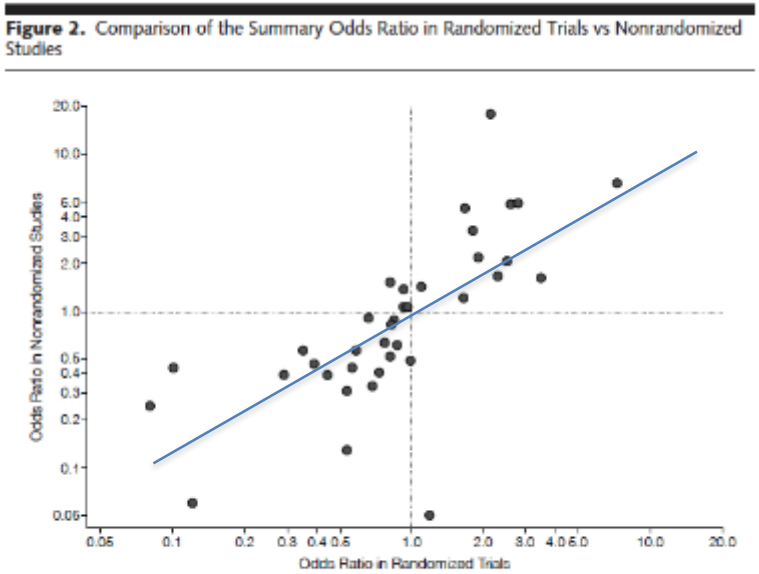
Significance

Hazard Ratio

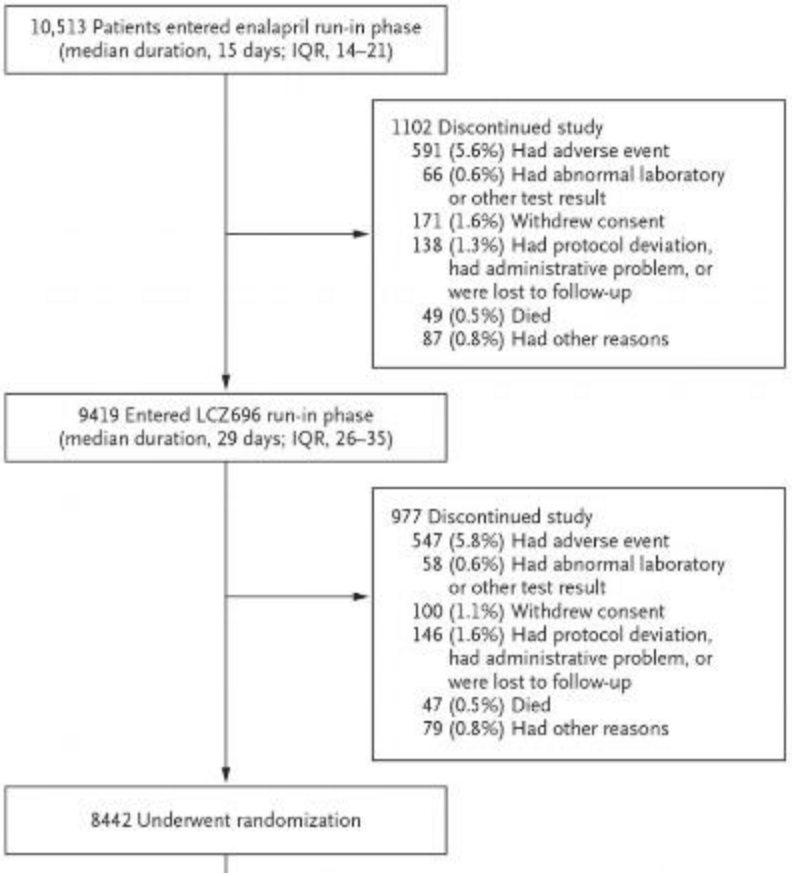
Propensity score is not better

- Literature on concordance of RCT & Obs on same Q (a select set)





Drug run in periods



September 1st, 2014

Let's Take a Close Look at PARADIGM-HF

Vinay Prasad, MD MPH

- Test a different question: whether it is better to stay on Entresso or switch to enalapril after exposure to both agents for unequal time

Sham controls needed for subjective endpoints

- Meniscectomy for knee OA
- Debridement for knee OA
- RV pacing for HOCM
- Vertebroplasty
- Lumbar steroid injections
- PCA for stable angina (IMA ligation, Cobb)

PERSPECTIVE

SHAM CONTROLS IN MEDICAL DEVICE TRIALS

Sham Controls in Medical Device Trials

Rita F. Redberg, M.D.

Talk outline

- Select examples of reversal
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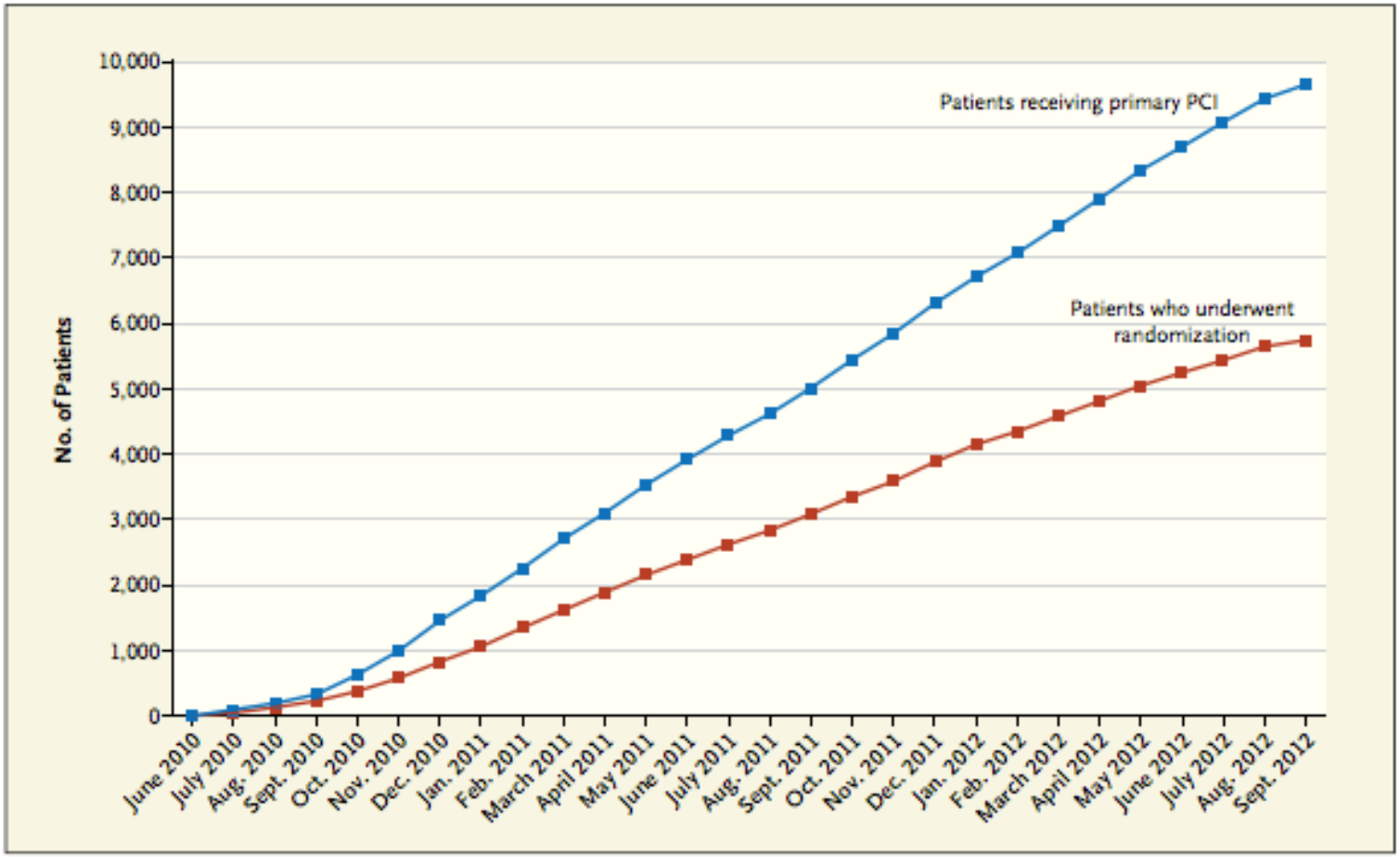
The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.



Rapid Randomization in the TASTE Trial, with Enrollment of Most Patients Receiving Primary Percutaneous Coronary Intervention (PCI).

Adapted from the Institute of Medicine (www.iom.edu/~/media/Files/Activity%20Files/Quality/VSRT/LST%20Workshop/Presentations/Granger.pdf). The incremental cost of the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial was $300,000, or $50 for each participant who underwent randomization.

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What about RCTs of parachutes

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.
Design Systematic review of randomised controlled trials.
Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.
Study selection: Studies showing the effects of using a parachute during free fall.
Main outcome measure Death or major trauma, defined as an injury severity score >15.
Results We were unable to identify any randomised controlled trials of parachute intervention.
Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

What about RCTs of parachutes

- Two limits of the analogy
- 1. A single clear etiology (BCR-ABL)
  - Trauma –
- 2. A huge effect size

Prior “parachutes” were no such thing

BMJ 2012;344:e2156 doi: 10.1136/bmj.e2156 (Published 5 April 2012)

RESEARCH

Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials

OPEN ACCESS

Results Four randomised controlled trials with a total of 900 patients (470 antibiotic treatment, 430 appendicectomy) met the inclusion criteria. Antibiotic treatment was associated with a 63% (277/438) success rate at one year. Meta-analysis of complications showed a relative risk reduction of 31% for antibiotic treatment compared with appendicectomy (risk ratio (Mantel-Haenszel, fixed) 0.69 (95% confidence interval 0.54 to 0.89); I^2=0%; P=0.004). A secondary analysis, excluding the study with crossover of patients between the two interventions after randomisation, showed a significant relative risk reduction of 39% for antibiotic therapy (risk ratio 0.61 (0.40 to 0.92); I^2=0%; P=0.02). Of the 65 (20%) patients who had appendicectomy after readmission, nine had perforated appendicitis and four had gangrenous appendicitis. No significant differences were seen for treatment efficacy, length of stay, or risk of developing complicated appendicitis.

Conclusion Antibiotics are both effective and safe as primary treatment for patients with uncomplicated acute appendicitis. Initial antibiotic treatment merits consideration as a primary treatment option for early uncomplicated appendicitis.

Most medical practices don't have large treatment effects

ORIGINAL CONTRIBUTION

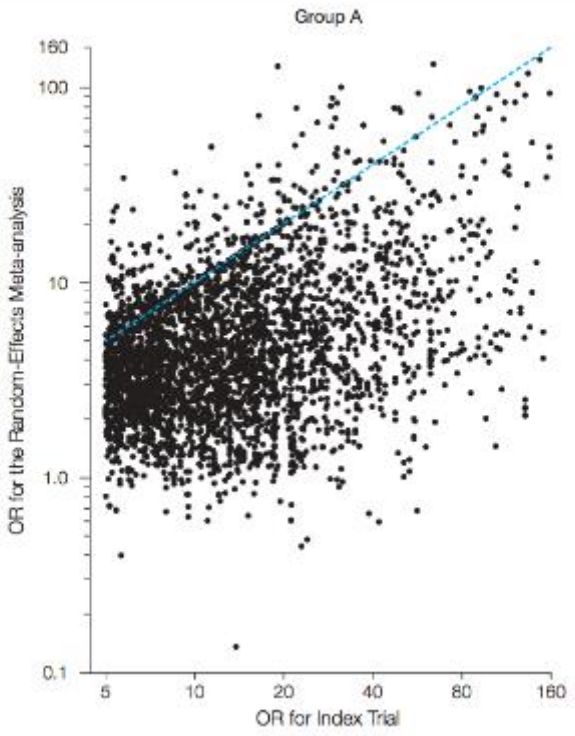
Empirical Evaluation of Very Large Treatment Effects of Medical Interventions

Tiago V. Pereira, PhD
Ralph I. Horwitz, MD
John P. A. Ioannidis, MD, DSc

Context Most medical interventions have modest effects, but occasionally some cli
cal trials may find very large effects for benefits or harms.

Objective To evaluate the frequency and features of very large effects in medici

Figure 2. Treatment Effects in Index Trials vs the Meta-analysis of All Trials



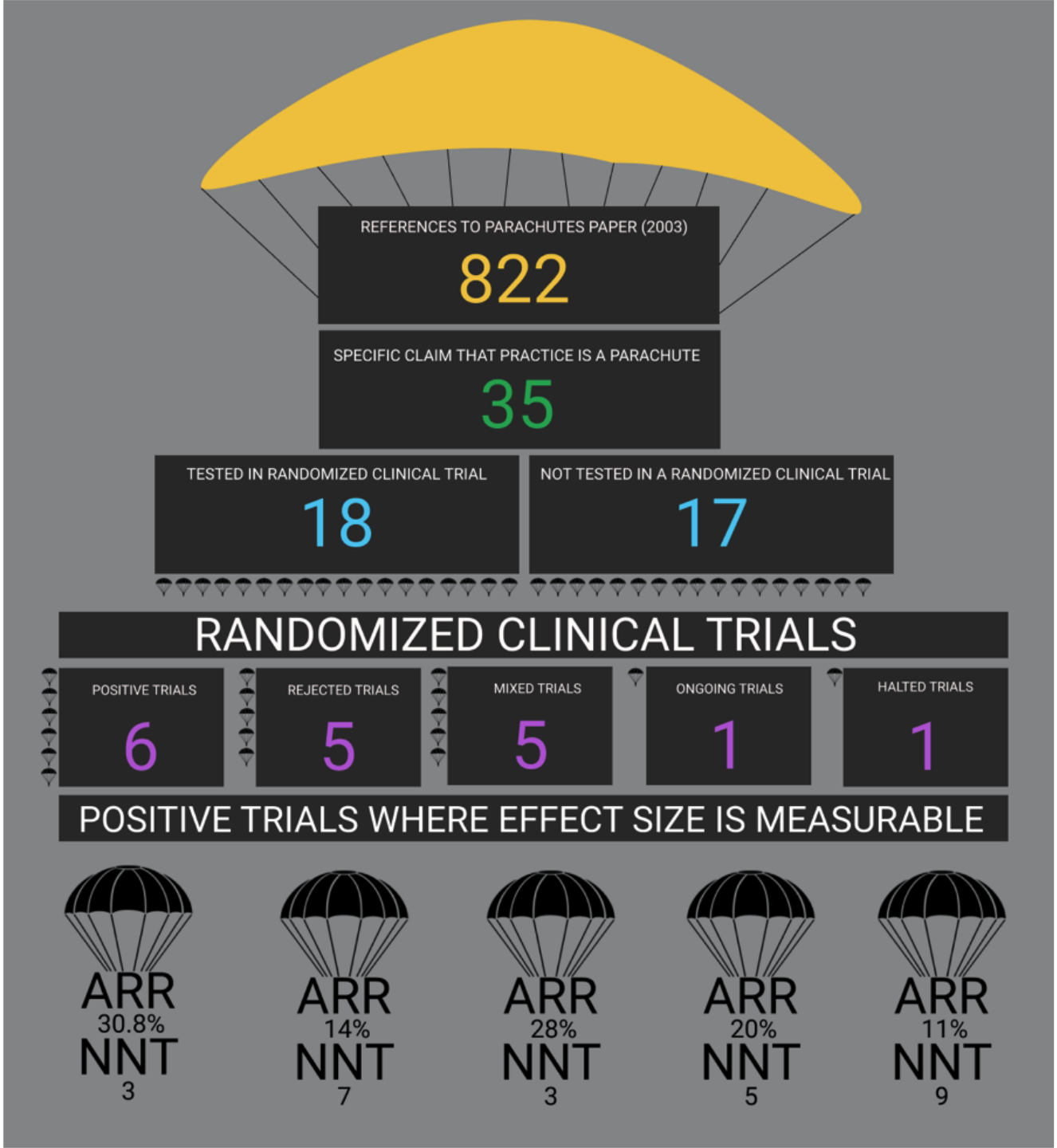
Some advances have been tested without RCT

When are randomised trials unnecessary? Picking signal from noise

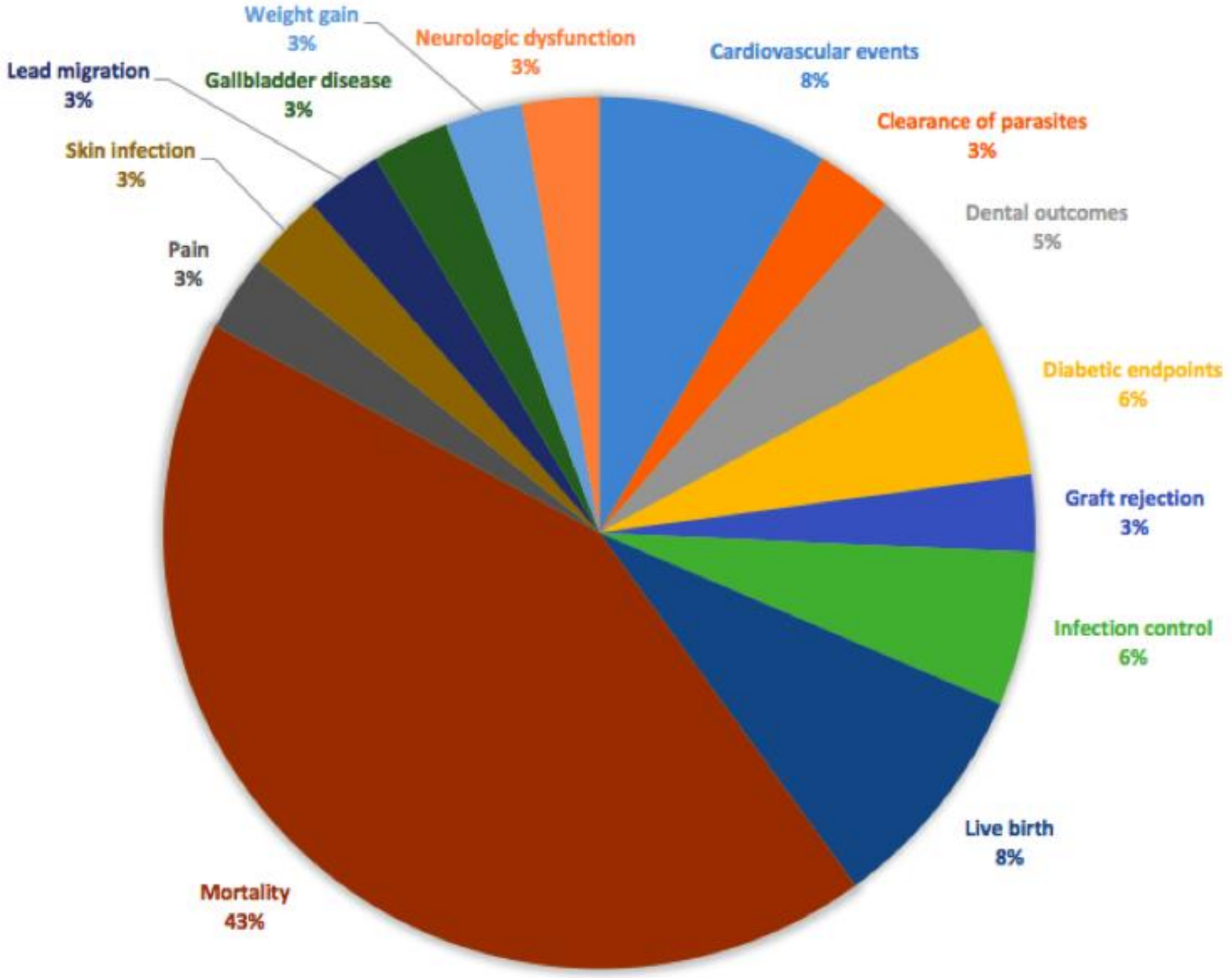
The relation between a treatment and its effect is sometimes so dramatic that bias can be ruled out as an explanation. **Paul Glasziou and colleagues** suggest how to determine when observations speak for themselves

Some historical examples of treatments with dramatic effects

- Insulin for diabetes[w1]
- Blood transfusion for severe haemorrhagic shock[w2]
- Sulphanilimide for puerperal sepsis[w3]
- Streptomycin for tuberculous meningitis[w4]
- Defibrillation for ventricular fibrillation[w5]
- Closed reduction and splinting for fracture of long bones with displacement
- Salicin for acute rheumatism[w6]
- Neostigmine for myasthenia gravis[w7]
- Tracheostomy for tracheal obstruction[w8]
- Suturing for repairing large wounds
- Drainage for pain associated with abscesses
- Pressure or suturing for arresting haemorrhage
- Ether for anaesthesia
- One way valve or underwater seal drainage for pneumothorax and haemothorax[w9]
- Phototherapy for skin tuberculosis[w10]
- Combination chemotherapy with cisplatin, vinblastine, and bleomycin for disseminated testicular cancer


REFERENCES TO PARACHUTES PAPER (2003)
822
SPECIFIC CLAIM THAT PRACTICE IS A PARACHUTE
35
TESTED IN RANDOMIZED CLINICAL TRIAL
18
NOT TESTED IN A RANDOMIZED CLINICAL TRIAL
17
RANDOMIZED CLINICAL TRIALS
POSITIVE TRIALS
6
REJECTED TRIALS
5
MIXED TRIALS
5
ONGOING TRIALS
1
HALTED TRIALS
1
POSITIVE TRIALS WHERE EFFECT SIZE IS MEASURABLE
ARR
30.8%
NNT
3
ARR
14%
NNT
7
ARR
28%
NNT
3
ARR
20%
NNT
5
ARR
11%
NNT
9

ULTIMATE ENDPOINTS OF PARACHUTE PRACTICES



The arc of medicine

- History has taught us that the arc of medicine bends towards higher standards of evidence

Acknowledgements

Dr. Adam Cifu
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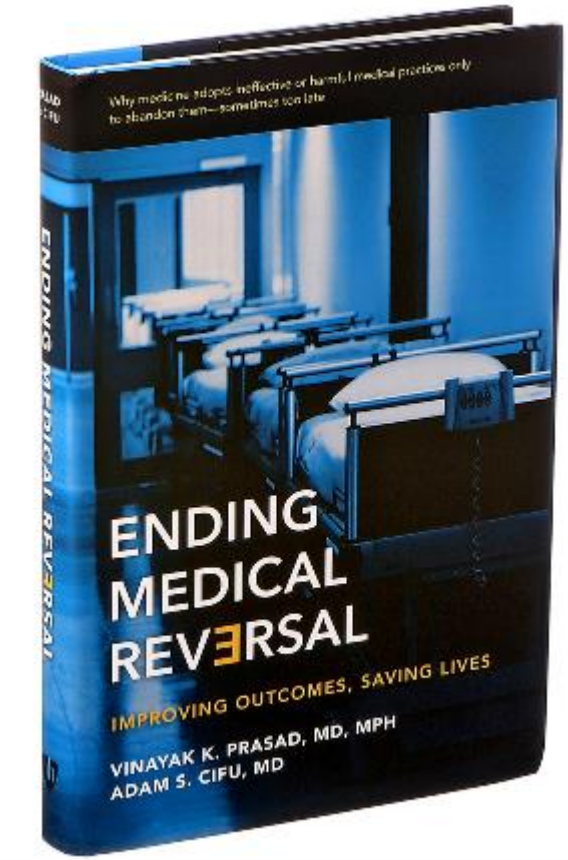
Dr. Nancy Ho
Dr. Joel Jorgenson
Dr. Jacob Chacko
Dr. Steven Quinn
Dr. Michael Cheung
Dr. Sham Mailankody
Dr. Chul Kim
Dr. Mauricio Burotto
Mr. Matt Abola
Dr. Usama Bilal

Purpose of this talk is not to litigate any *particular* practice

But to speak broadly about patterns of medical progress and missteps.

If you liked the talk, check out the book

Questions



@vinayprasad82