

The Role of NIH in Comparative Effectiveness Research

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October 12, 2011

Disclosures: None



A Short Time Ago...

Editorial

The New York Times

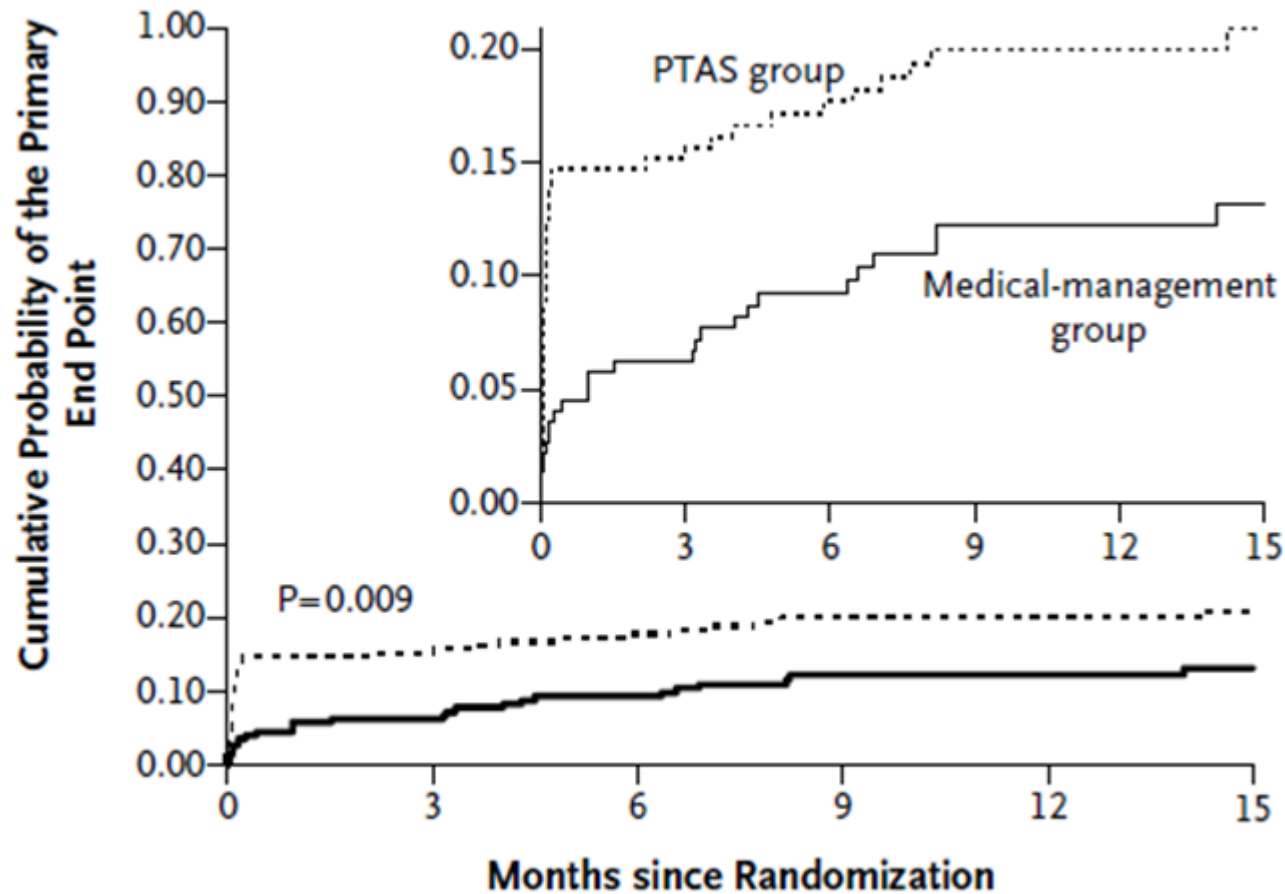
Damage From Brain Stents

Published: September 8, 2011

“.... The stents had been approved for humanitarian use by the FDA in 2005. That approval was based on a 45-person trial that lacked a control group. Optimistic surgeons have since inserted the devices in thousands of people.

Now [a] rigorous controlled [study](#) of some 450 patients has shown that those who simply had treatment with drugs and lifestyle changes fared better than those who got the stents as well. **This case...clearly shows the value of conducting rigorous controlled studies with enough patients to provide meaningful results. This is just the kind of ‘comparative effectiveness’ research that the national health care reforms seek to promote.**

The (NIH-Funded) Randomized CER Trial



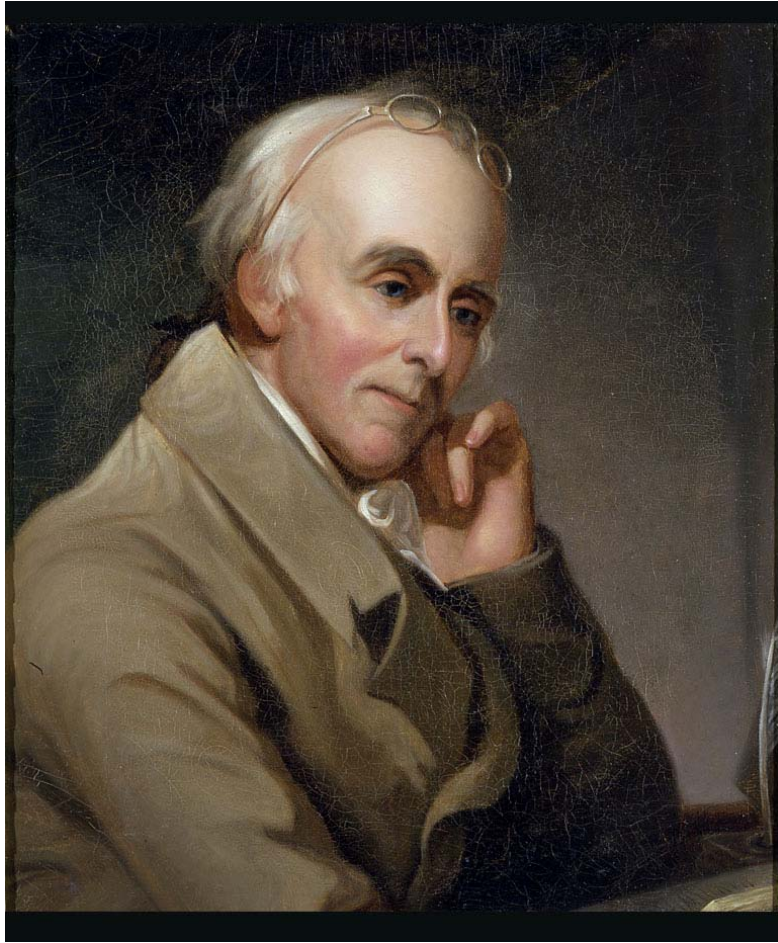
A Long Time Ago...

“Only a *limited amount of evidence is available* about which treatments work best for which patients...—yet current practice tends to adopt more-expensive treatments *even in the absence of rigorous assessments* of their impacts....”

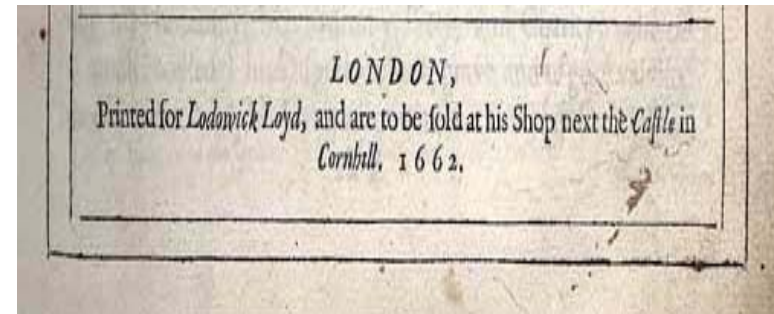
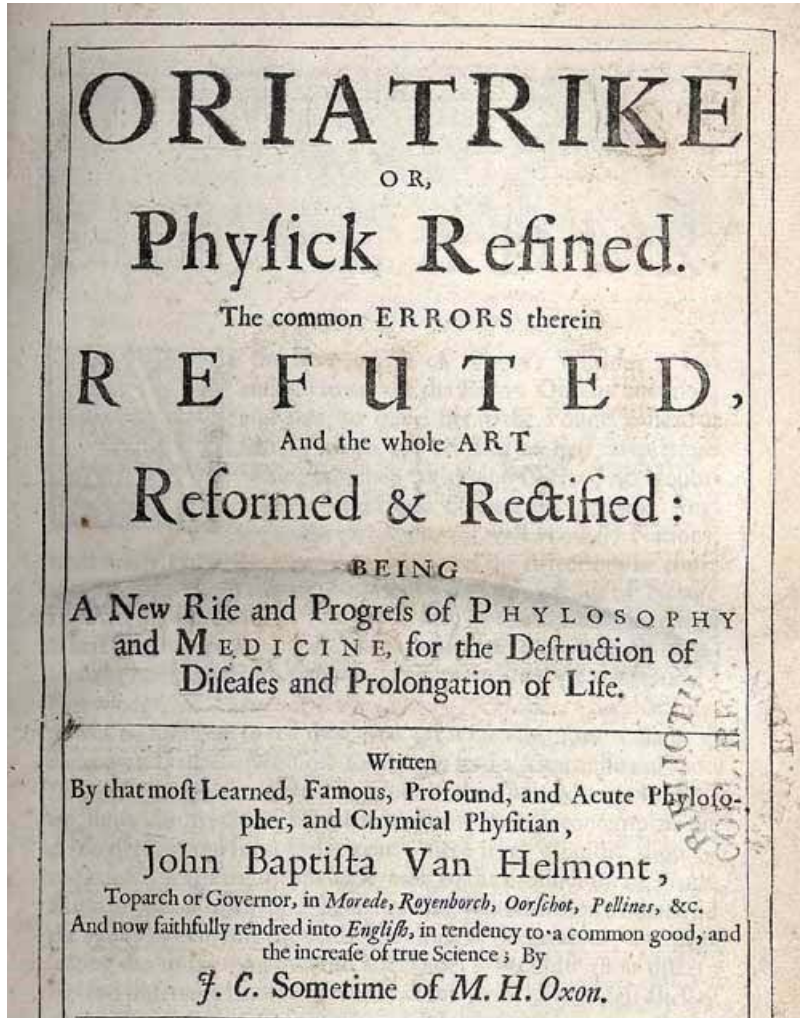


Peter Orszag

A Longer Time Ago...



A Real Long Time Ago...



A Call for a Comparative Effectiveness Trial

“Come down to the contest ye Humorists: Let us take out of the Hospitals or the camps or elsewhere, 200, or 500 poor People, that have Fevers etc. Let us divide them in Halfes, let us cast lots, that one half of them may fall to my share and the other to yours; I will cure them without bloodletting...; but do you do as ye know. We shall see how many Funerals both of us shall have: But let the reward of the contention or wager, be 300 Florens, deposited on both sides: Here your business is decided.”



Over 100 Years Later...



“During the last decades we have certainly bled too little.”

William Osler, MD

One NIH Role in Comparative Effectiveness

Vitamins to prevent cancer/CVD (failed)

Screening for ovarian cancer (over-diagnosis)

Anti-arrhythmic drugs (higher death rate)

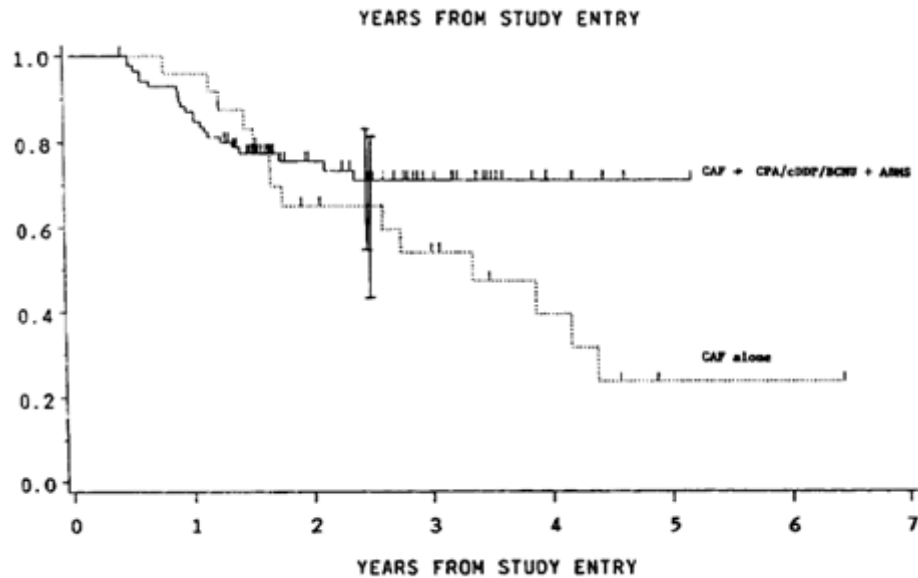
Hormone therapy (breast cancer, failed CHD)

Back surgery, kyphoplasty (little benefit)

Intracranial stents to prevent stroke (harm)

Bone marrow transplantation for breast cancer (higher death rate)

“Let Us Cast Lots...”



“...We believe that confirmation of these results in a prospective randomized trial is important before this therapy can be accepted for widespread use. Many new therapies, initially promising, fizzle. This treatment should only be offered at major centers...and, whenever possible, [into] randomized comparative trials...”

Troubles Getting It Done...

Bad Science and Breast Cancer

08.01.2002

For more than a decade, physicians convinced breast cancer patients that bone marrow transplants were their best hope of salvation. But the insurance companies who resisted paying for the procedures were right all along: It was experimental medicine and most women were a lot better off without it. How could so many oncologists ignore basic principles of science?

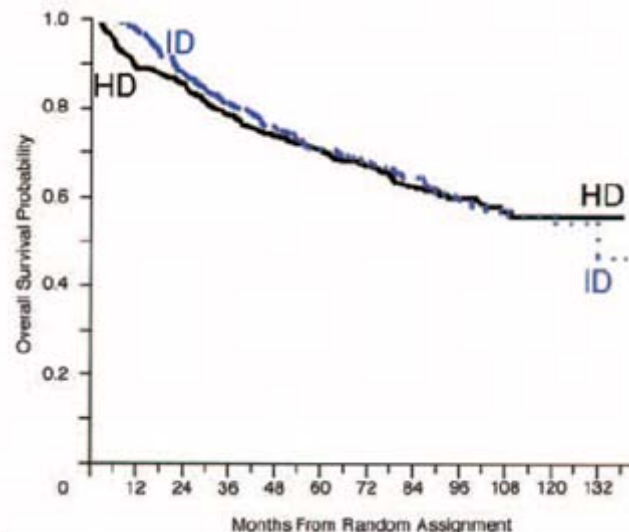
by Shannon Brownlee, Photography by Dan Winters

“... By the time Peters had organized his trial, few women wanted to participate...[It] meant running the risk of not getting high-dose chemo, and many had read newspaper accounts that convinced them that the treatment was their only chance for survival. **Their doctors often agreed.** One transplanter pulled out a copy of Peters' 1993 paper. ‘I don't see how it's even *ethical* to do a randomized trial,’ he said.”



They Finally Did Cast Lots...

“... From the moment Peters first administered high-dose chemotherapy until the first clinical trials were concluded, nearly 20 years passed. During that time, hundreds of physicians practiced the unproven treatment. An estimated 30,000 breast cancer patients suffered through high-dose chemotherapy, **only a fraction of them as part of a clinical trial**. All told, the nation spent around \$3 billion paying for it, while an estimated 4,000 to 9,000 women died not from their cancer but from the treatment...”



The Bloodletting Stories

Therapies were widely adopted

Scientists called for randomized CER trials

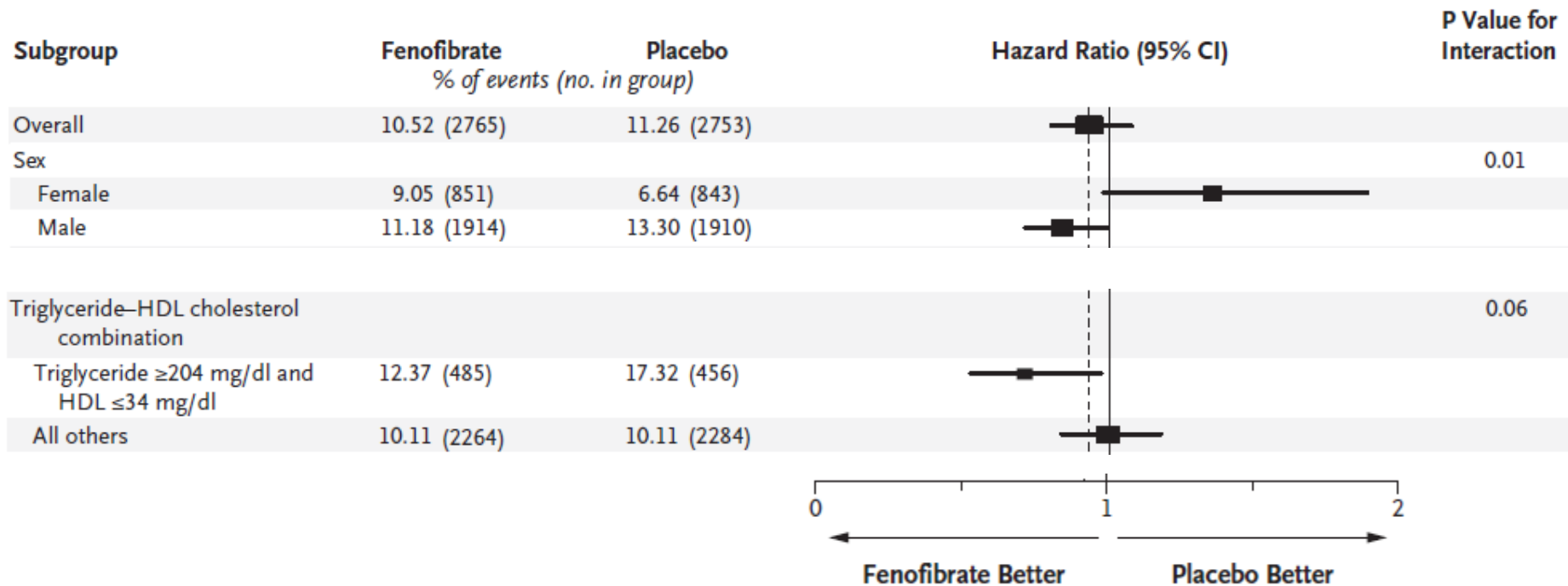
- Large numbers (“200, or 500 poor people”)
- Real world (“hospitals or camps or elsewhere”)
- Meaningful outcomes (“funerals”)
- Funding (300 florens) and business

It took a long time for trials to happen

The trials (in these cases) showed no value

CER findings may be slow to disseminate

Large Numbers: “200, or 500, Poor People”

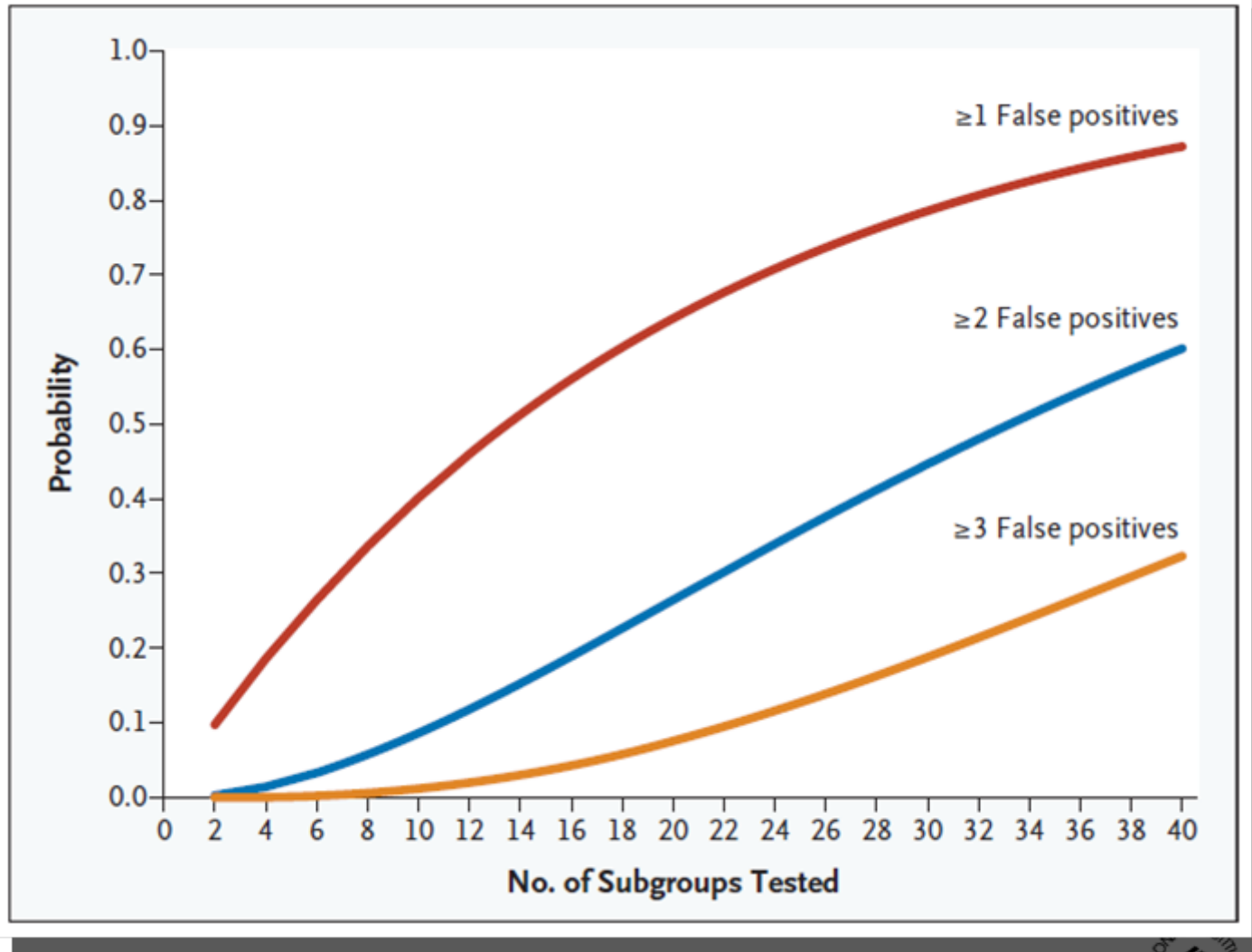


STATISTICS AND MEDICINE

The Challenge of Subgroup Analyses — Reporting without Distorting

Stephen W. Lagakos, Ph.D.

Don't We Need to Avoid "Average" Findings?



So How Do We Get Around This?

Fibrates in the Treatment of Dyslipidemias — Time for a Reassessment

Allison B. Goldfine, M.D., Sanjay Kaul, M.D., and William R. Hiatt, M.D.

“Accordingly, a properly designed trial is warranted to test the hypothesis that adding fenofibric acid to statin therapy significantly reduces the risk of cardiovascular events among high-risk patients who have reached their LDL cholesterol goal with a statin but have residual mixed dyslipidemia. This cohort ... is fairly large — about 7% of the U.S. population and 15% of U.S. patients with type 2 diabetes.”

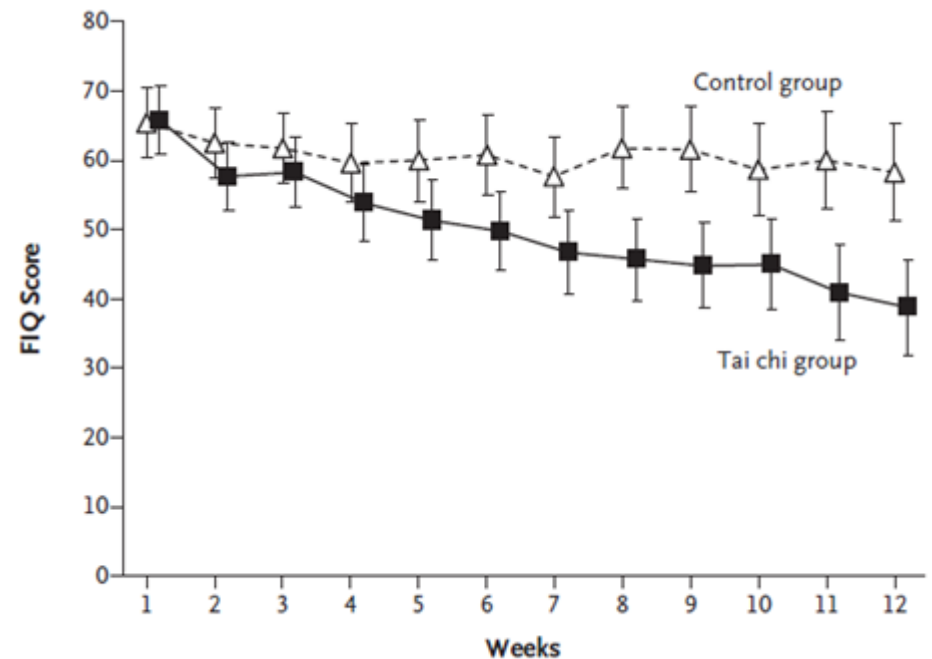
Bigger Numbers: Efficacy to Effectiveness

ORIGINAL ARTICLE

A Randomized Trial of Tai Chi for Fibromyalgia

Chenchen Wang, M.D., M.P.H., Christopher H. Schmid, Ph.D., Ramel Rones, B.S., Robert Kalish, M.D., Janeth Vinh, M.D., Don L. Goldenberg, M.D., Yoojin Lee, M.S., and Timothy McAlindon, M.D., M.P.H.

Longer-term studies involving larger clinical samples are warranted to assess the generalizability of our findings and to deepen our understanding of this promising therapeutic approach.



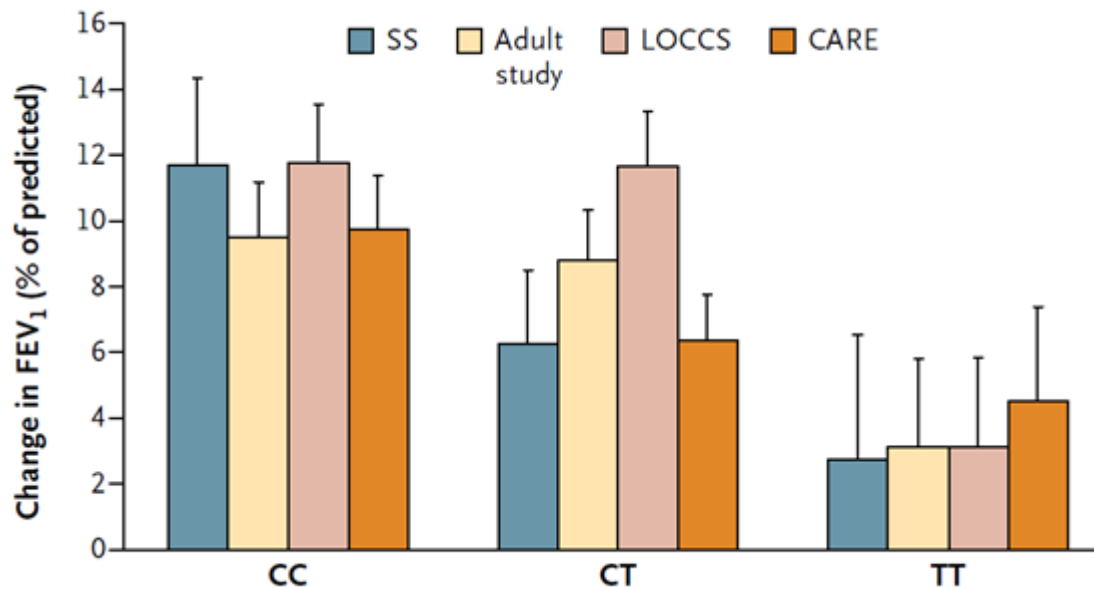
“The fact that treatment was delivered by a single tai chi master at a single center also potentially limits the generalizability of our results...Longer-term studies involving **larger clinical samples** are warranted to assess generalizability...and to deepen our understanding of this promising therapeutic approach.”

Big Numbers: Path to Personalized Medicine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genomewide Association between *GLCC11* and Response to Glucocorticoid Therapy in Asthma



Screening Trial: N = 118

First replication: N = 264

Second: N = 385

Third: N = 185

Fourth: N = 101

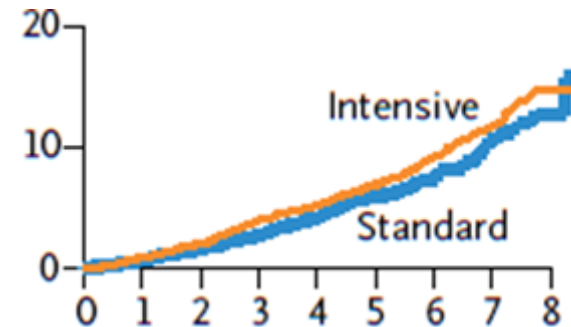
Real World: “Hospitals, Camps or Elsewhere”

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Effects of Intensive Glucose Lowering on Cardiovascular Outcomes

The ACCORD Study Group*



The NEW ENGLAND JOURNAL of MEDICINE

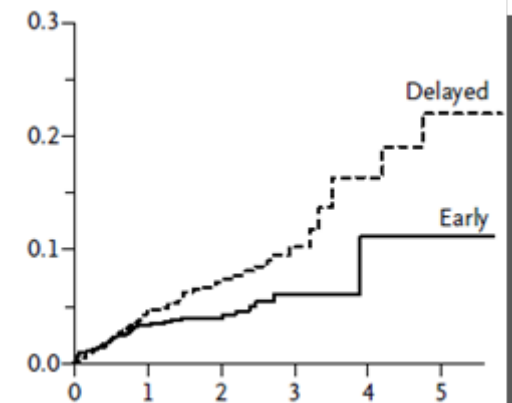
ESTABLISHED IN 1812

AUGUST 11, 2011

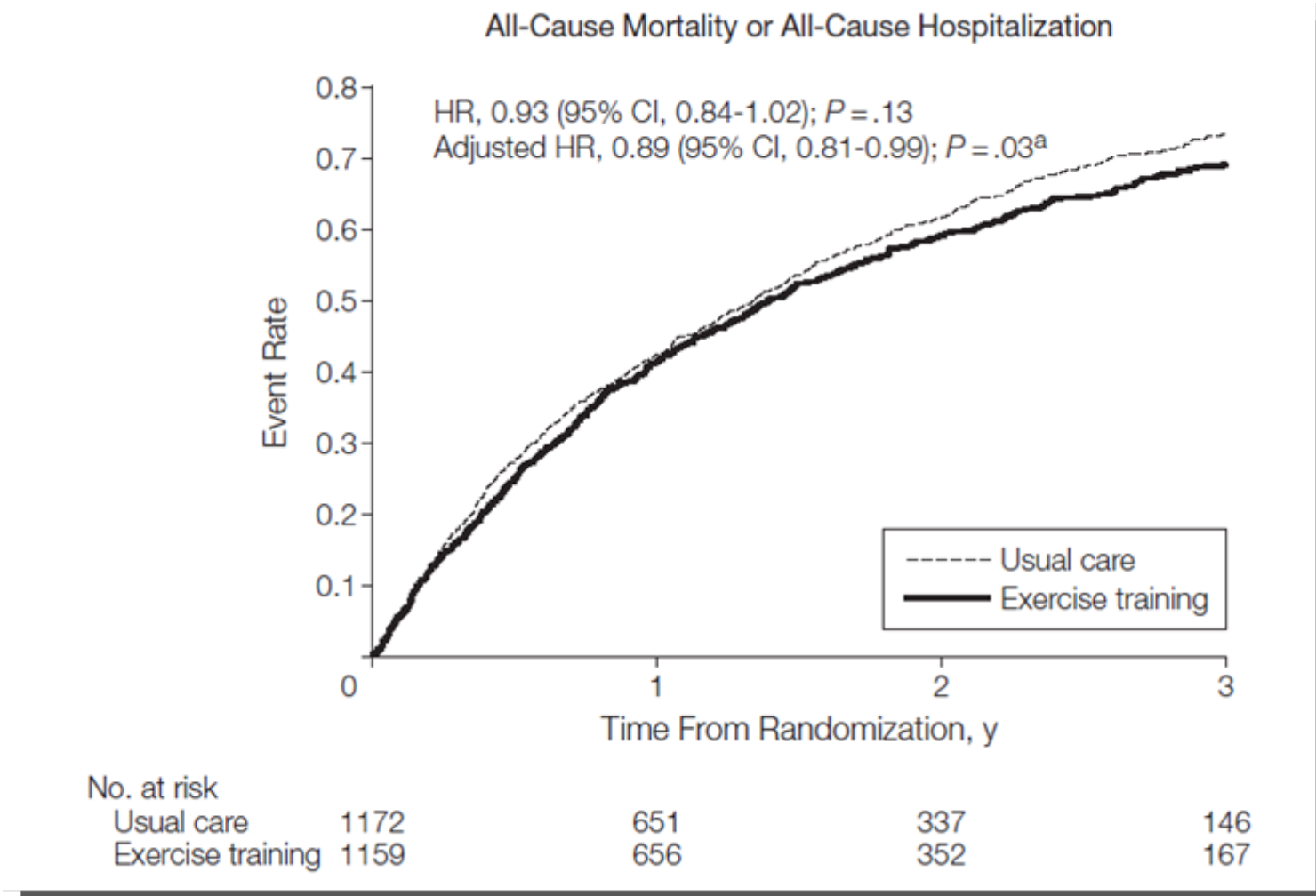
VOL. 365 NO. 6

Prevention of HIV-1 Infection with Early Antiretroviral Therapy

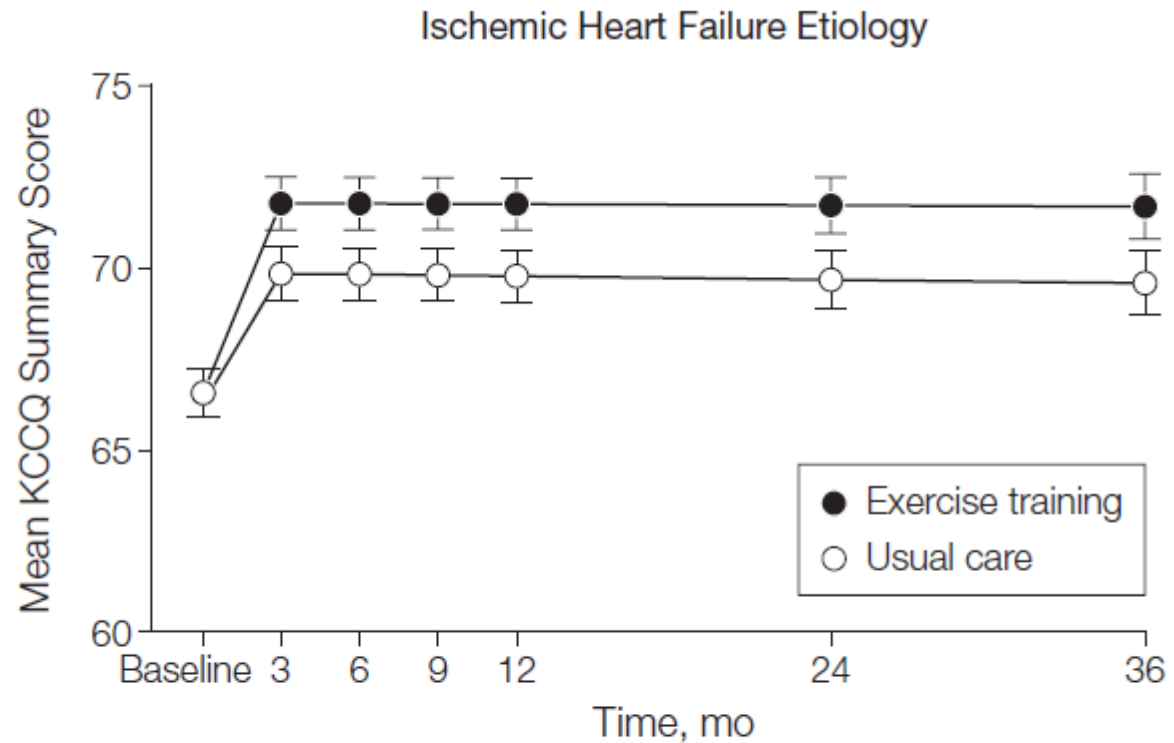
Myron S. Cohen, M.D., Ying Q. Chen, Ph.D., Marybeth McCauley, M.P.H., Theresa Gamble, Ph.D.,



Outcomes: Heart Failure “Funerals”

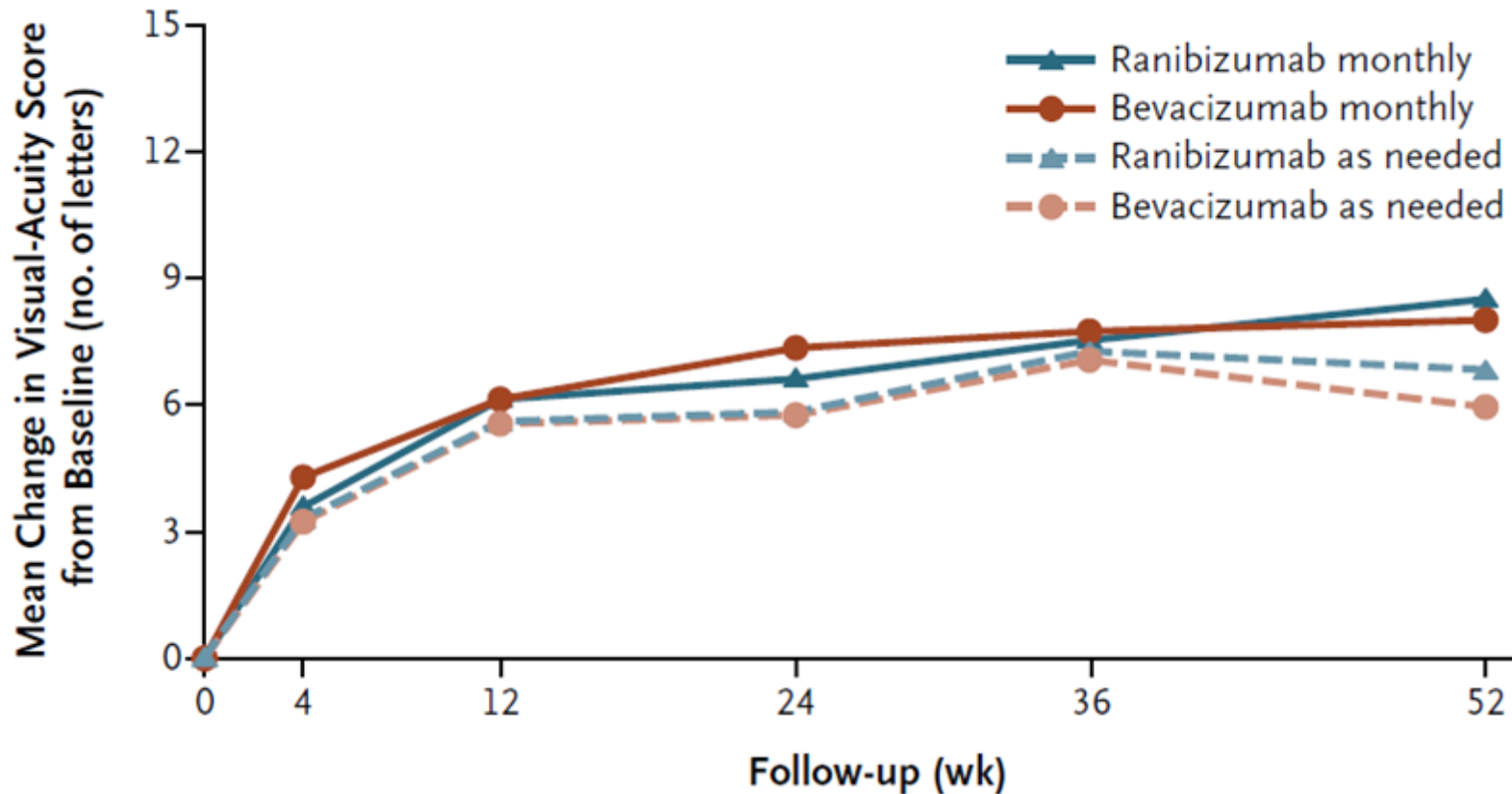


Other Meaningful Outcomes...




No. of participants	Baseline	3	6	9	12	24	36
Exercise training	598	547	511	472	470	277	131
Usual care	599	514	481	471	431	285	151

Another Outcome: Ability to See



Trials Can Be Affordable... “300 Florens”




VITAL

THE VITAMIN D AND OMEGA-3 TRIAL (VITAL)

Welcome to the VITAL Study

Welcome to the Web site of the VITamin D and Omega-3 Trial (VITAL) at Brigham and Women's Hospital and Harvard Medical School in Boston, Massachusetts. VITAL is a research study in 20,000 men and women across the U.S. investigating whether taking daily dietary supplements of vitamin D3 (2000 IU) or omega-3 fatty acids (Omacor® fish oil, 1 gram) reduces the risk for developing cancer, heart disease, and stroke in people who do not have a prior history of these illnesses. Recruitment for the study began in January 2010 and is continuing through 2011. Please click on [Study Q&A](#) to learn more about participating in this important research endeavor.



JoAnn Manson, MD

During the course of the study, this website will be updated regularly to keep participants informed about the study's progress, as well as health topics that we

Recruit a pal
We will be recruiting participants for VITAL throughout 2011. Please spread the word to friends and family (men aged 50 or older or women aged 55 or older with no history of cancer, heart attack, or stroke) about this important research— you can refer those who are interested to our website, or ask them to call us toll-free at 1-800-388-3963.

Numbers to Know For Your Heart's Health
[Click here](#) to download an article about the 11

About the VITAL Study

News
National Vitamin D Guidelines Highlight the Need for the VITAL Trial

From Sun & Sea: New Study Puts Vitamin D and Omega-3s to the Test

Ancillary Studies

Study Q&A

VITAL Signs
Download issues of our newsletter

Contact Us

Brigham and Women's

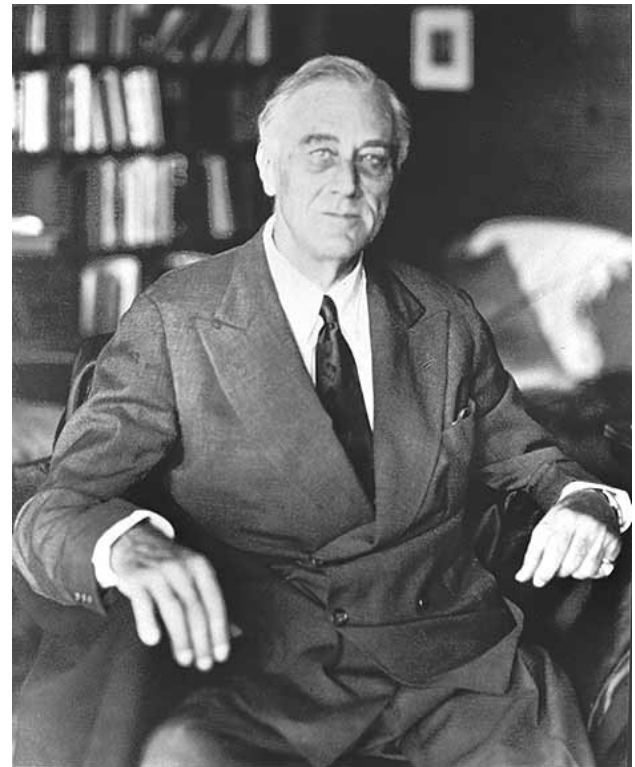
Making Trials Affordable (...Again...)

Department of Health and Human Services

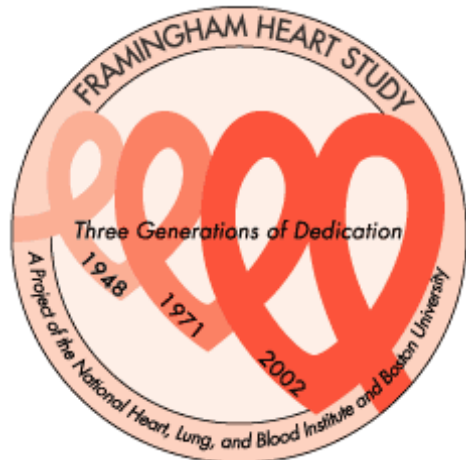
Part 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	National Heart, Lung, and Blood Institute (NHLBI)
Funding Opportunity Title	Pilot Studies to Develop and Test Novel, Low- Cost Methods for the Conduct of Clinical Trials (R01)
Activity Code	R01 Research Project Grant
Announcement Type	New
Related Notices	<ul style="list-style-type: none">• June 10, 2011 - See Notice NOT-HL-12-150 NHLBI announces correction to the eligibility criteria.
Funding Opportunity Announcement (FOA) Number	RFA-HL-12-019

How to Do It Right



Engage Stakeholders (People, Communities)



Observations: Appropriate Caution

Factors of Risk in the Development of Coronary Heart Disease—
Six-Year Follow-up Experience

The Framingham Study

WILLIAM B. KANNEL, M.D., THOMAS R. DAWBER, M.D., F.A.C.P.,
ABRAHAM KAGAN, M.D., F.A.C.P., NICHOLAS REVOTSKIE, M.D.,
AND JOSEPH STOKES, III, M.D.
Framingham, Massachusetts

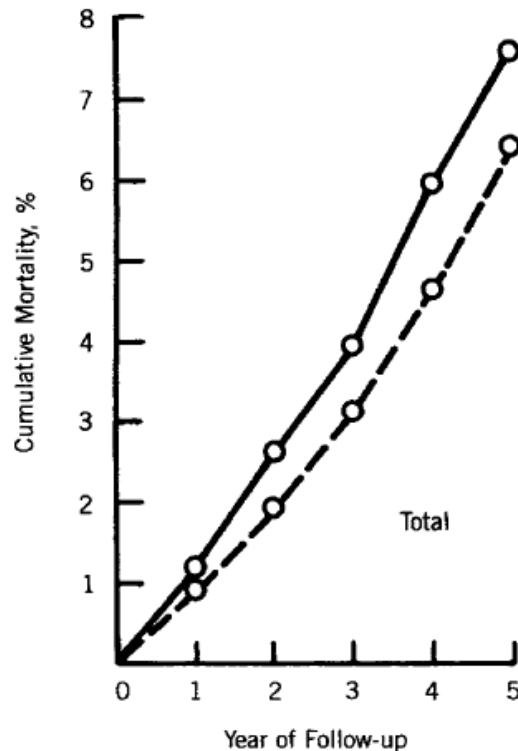
INCREASINGLY RELIABLE ESTIMATES of the prevalence and incidence of coronary atherosclerosis is present for m



“Whether or not the correction of these abnormalities once they are discovered will favorably alter the risk of development of disease, while reasonable to contemplate and perhaps attempt, remains to be demonstrated...”

Pivotal Trials

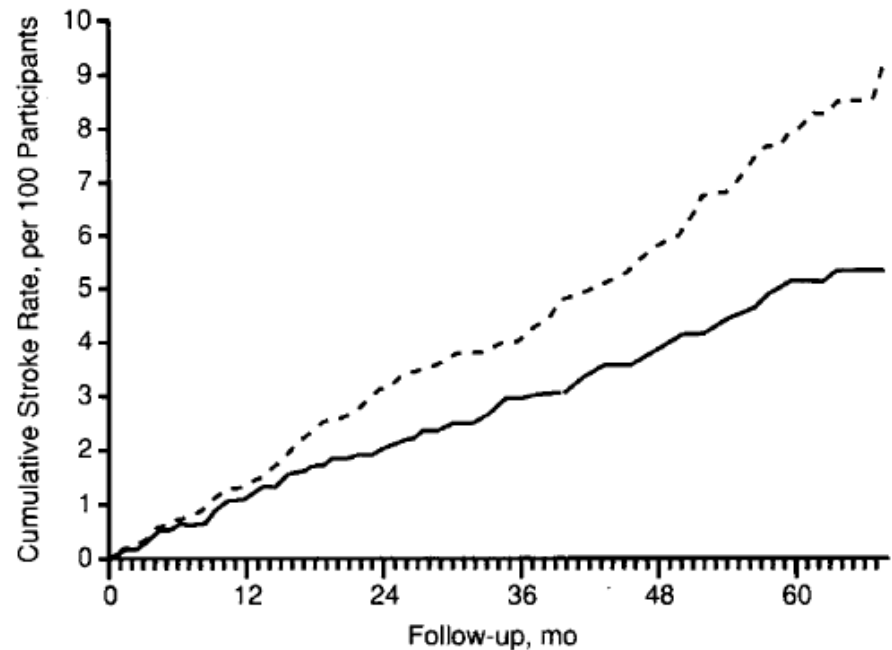
Five-Year Findings of the Hypertension Detection and Follow-up Program



Original Contributions

Prevention of Stroke by Antihypertensive Drug Treatment in Older Persons With Isolated Systolic Hypertension

Final Results of the Systolic Hypertension in the Elderly Program (SHEP)

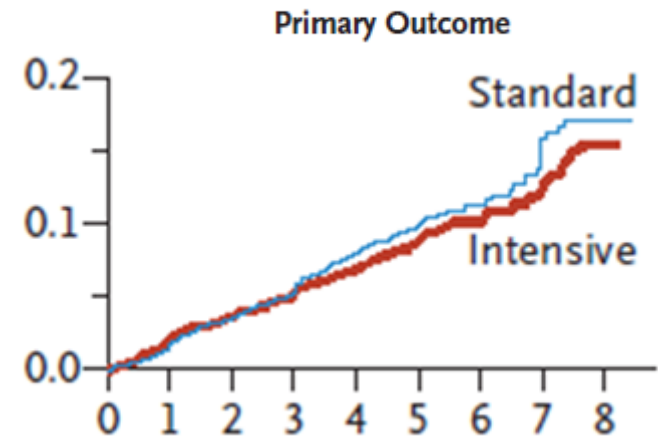
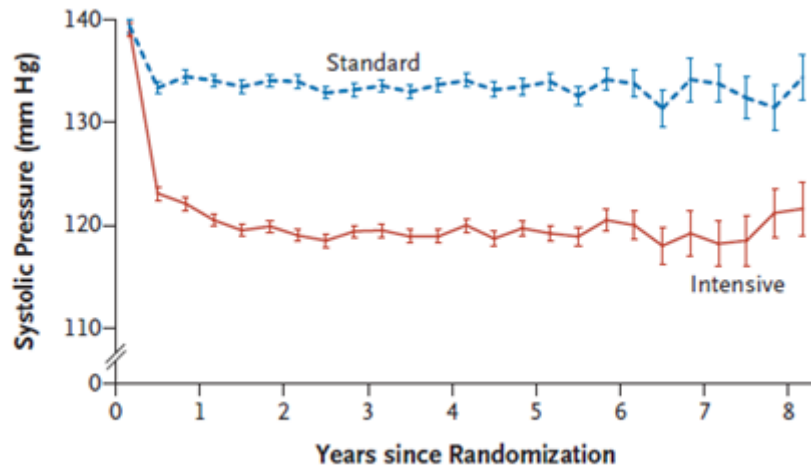


An Ongoing Story...

ORIGINAL ARTICLE

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*



Doing it Right: Another Story



A Bruising Battle Over Lung Scans

Doctors and researchers are sharply divided over the merits of screening smokers and others at high risk of lung cancer with costly CT scans; a \$200 million clinical trial has become a

Sheila Ross is known as a "two-time survivor" at the advocacy group where she works. Doctors found cancer in her lung. low-dose spiral CT scanning should find tumors when they

spoken skeptic Peter Bach, a lung-cancer specialist at the Memorial Sloan-Kettering Cancer Center in New York City.

CANCER SCREENING

The Promise and Pitfalls of a Cancer Breakthrough

Cancer research got some good news last week: A landmark clinical trial reported that screening for small tumors with advanced x-ray imaging led to a significant drop in lung cancer deaths (20% fewer) among smokers and ex-smokers, compared with screening with standard chest x-rays. Such positive

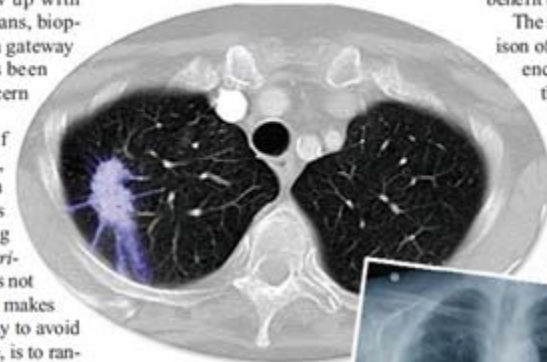
Harold Varms said in a teleconference on 4 November that he saw "a potential for saving many lives," presumably through early detection and treatment. The study, called the National Lung Screening Trial (NLST), enrolled 53,454 smokers and ex-smokers between ages 55 and 74; 354 died of lung

studies, said Lowy. According to NCI, about 96% to 98% are false positives.

In NLST, about 25% of those screened with CT got a positive result requiring follow-up. Some researchers have seen higher rates. Radiologist Stephen Swensen of the Mayo Clinic in Rochester, Minnesota, says that a

How up with y scans, biop- is a gateway has been concern

s of ach, olin thers ening Amerit- it is not This makes t way to avoid rgue, is to range a CT scan or : of who dies. rial results can example, by se illusion that for extending the patient has : called "length rise from the " Too little is



Resolving power. Although new imaging techniques (above) offer more information than the chest x-ray (right), they also deliver more false-positive signals.

describe this byproduct of screening. He and his Dartmouth colleague, clinical epidemiologist H. Gilbert Welch,



benefit be." The study by Bach an ison of a validated mod ence with data on three CT screeni evidence" that s risk of death fi period of al screening dr medical wor found that biop fold above the d

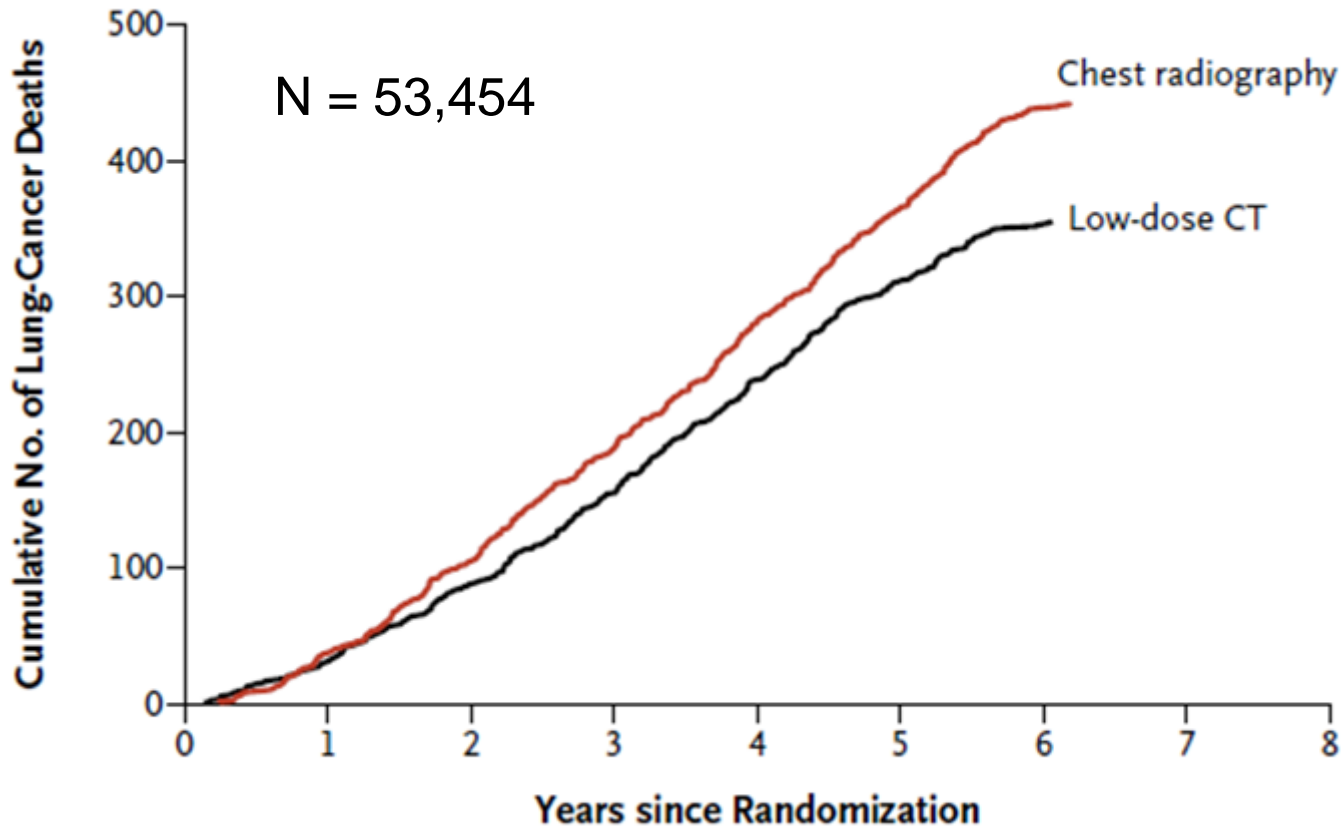
January 31, 2011
from www.sciencemag.org

Downloaded from www.sc

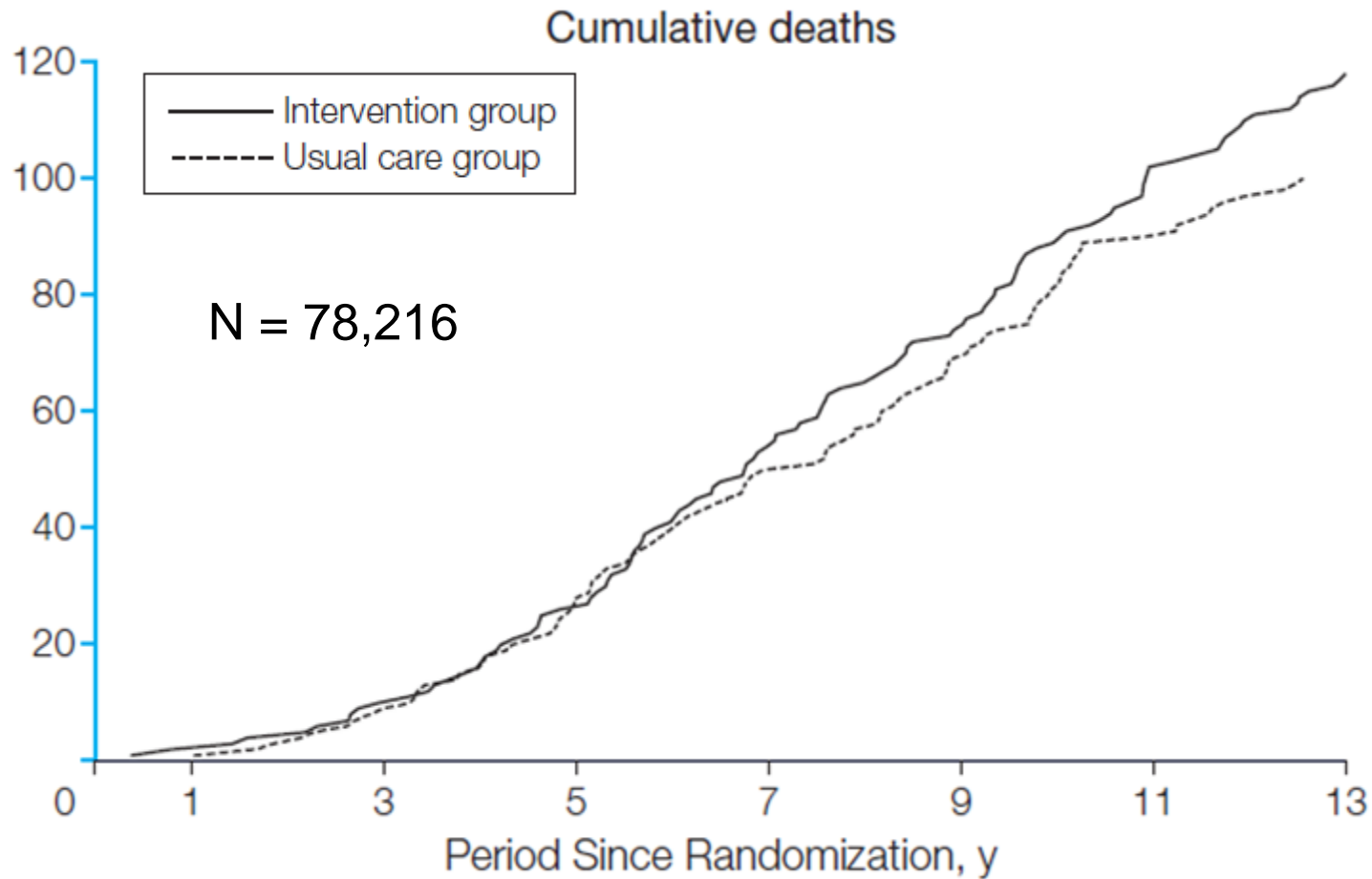


This Diagnostic Test Works...

B Death from Lung Cancer



This One Does Not...



The Best Way: Marfan



“The National Marfan Foundation **does not recommend switching** from a beta blocker to losartan as a way to manage Marfan syndrome **until the trial is completed**. This is because **we do not know** whether losartan is clearly better than atenolol for taking care of people with Marfan syndrome.”

<http://www.marfan.org/marfan/2408/Atenolol-vs.-Losartan-Clinical-Trial>



Contemporary Challenges...

Criteria for priorities

- Public health
- Scientific opportunity
- Stakeholder interests: may collide

How will do affordable pragmatic trials?

When can we trust observational data?

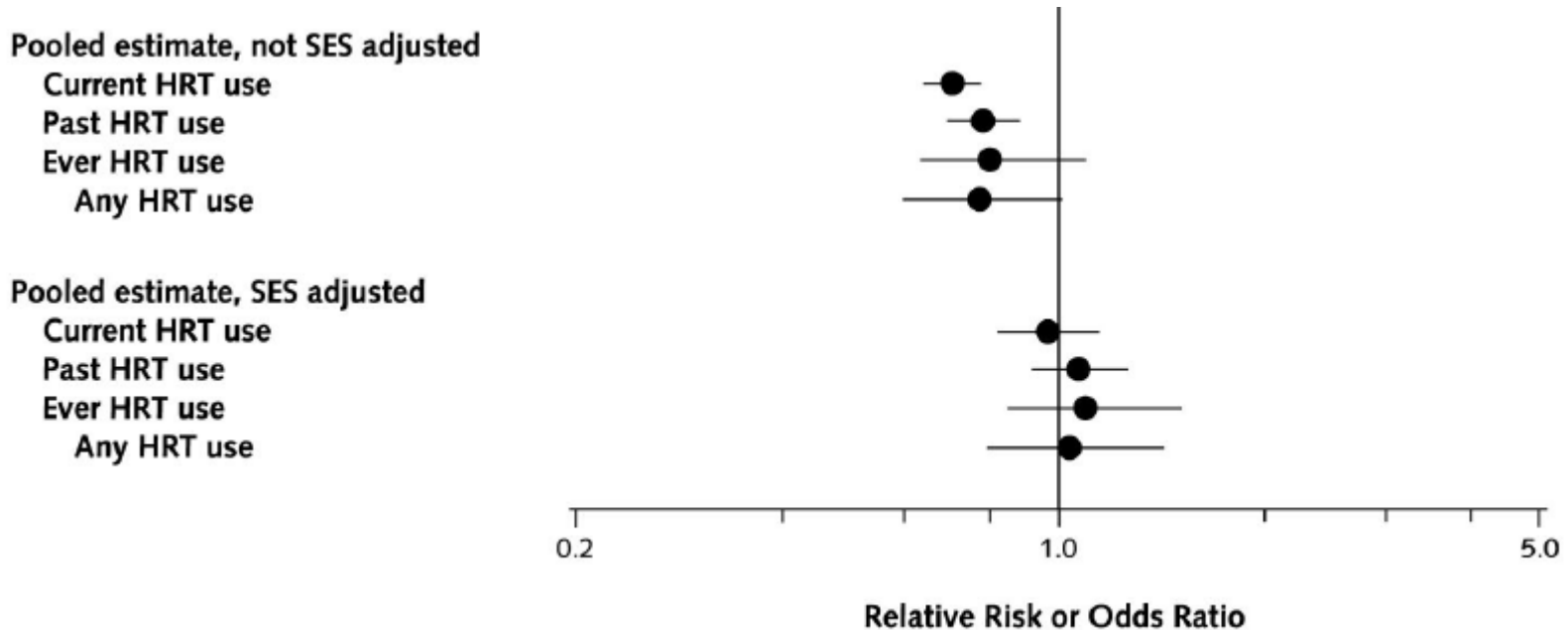
Implementation: Will knowledge help?

What about personalized medicine?



Why We Must (Almost Always) Randomize

Failure to account for unmeasured (or improperly measured) confounders



Failure to abide by the intent-to-treat principle

“If you do not ask the right questions, you do not get the right answer.”

-- Edward Hodnett

Really: Must We Always Randomize?

Hazardous journeys

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

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.



Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

Role of NIH in CER

“Evidence-free” medicine (long history)

- Intracranial stents, high-dose chemotherapy
- Diagnostic screening tests for cancer
- Bevacizumab for macular degeneration

Observational and basic findings for health

- Treatment of hypertension
- Personalized treatment of asthma
- Losartan for Marfan syndrome

Harness the power of randomization

What It's All About (Van Helmont con't)

“Oh ye Magistrates, unto whom the health of the People is dear! It shall be contested for a publique good, for the knowledge of truth, for your Life, and Soul, for the health of your Sons, Widows, Orphans, and the health of your whole People.”