How Do We Interpret Unexpected Findings From Large Clinical Trials?

Comparative Effectiveness Research Seminar

May 11, 2010

Some Theory and History

- Interventions are guided by understanding of disease.
  - Hippocrates (460-377 BC) described four basic temperaments in relation to physical characteristics known as "homors"
  - Galen (129-216 BC) believed that all disease was caused by imbalanced between the four humors
  - Galen did detailed studies in anatomy and physiology and employed 20 scribes to help document his findings

Reductionism and Linear Thinking: Are People Like Cars?

- Sir Isaac Newton --discrete components assumed to operate independently from one another.
- Ackoff - industrial revolution (18th Century England) initiated ways of thinking that dominated nearly all fields of science for several centuries. Core concepts:
  - reductionism,
  - analysis,
  - mechanism

Patient Education

- Typically very simple
- Emphasizes linear relationships

What Physiologists Tell Us

- The human body is complex
- Systems interact
- Linear model rarely fits
- Intervening on one system affects other systems

The Outcome Researcher Perspective

Disease: Shortens life or interferes with life quality now or in the future

We Look at Outcomes Differently

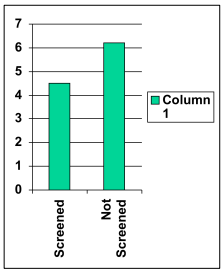
- There are only two outcomes of importance
  - Length of life
  - Quality of life
    - Patient reported outcomes
    - Functioning
    - Symptoms/problems
- Physiological measures are only important if they relate to length or quality of life
- Overall outcome represented as QALY

The total mortality problem

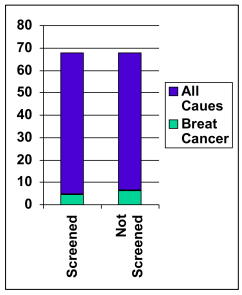
Is being dead from cancer worse than being dead from something else?

Cancer mortality in the Health Insurance Plan of New York

- 60,000 women assigned to mammography or usual care
- After 10 years 147 deaths in the mammography group and 192 deaths in usual care group
- 23% reduction in cancer deaths

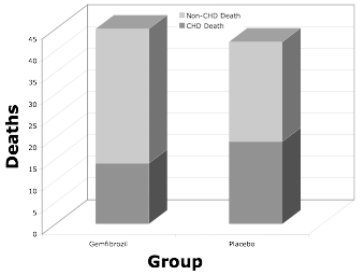


Cancer mortality in the Health Insurance Plan of New York



- Lower portion shows cancer deaths, upper shows non cancer deaths
- No difference is survival between screened and unscreened women

Sometimes Modifying Risk Factors Does Not Change Outcomes Helsinki Heart Study



Eight Examples From the Clinical Trial Literature

- Cardiac Arrymthia Suppression Trial (CAST)
- The Physicians Health Study (PHS)
- Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)
- Correction of Hemogloblin and Outcomes in Renal Insufficiency (CHOIR)
- COURAGE
- Woman's Health Initiative WHI
- Action to Control Cardiovascular Risk in Diabetes (ACCORD)
- Canadian National Breast Screening Study (CNBS)

Mayo Clinic on Preventing Diabetes Complications

- Aggressive care is the best care
- Make a commitment to managing your diabetes.
- Learn the basics of diabetes care and offer support and encouragement along the way.
- Keep your blood pressure and cholesterol under control.
  - Like diabetes, high blood pressure can damage your blood vessels. High cholesterol is a concern, too…

ADA Recommendations for Aggressive Management of Type 2 Diabetes Mellitus

Medscape® www.medscape.com

Targets for Glycemic Control

HbA_{1c}	< 7%
Fasting/preprandial glucose	80-120 mg/dL
Bedtime glucose	100-140 mg/dL

American Diabetes Association. Diabetes Care. 2000; 23(suppl 1):S32-S42.

University Group Diabetes Program (UGDP) *Diabetes 19*(1970) (supplement 2) 747-830.

- Twelve clinical centers,
- 823 patients were randomly assigned to one of five treatment groups (all got diet).
  - Insulin variable dosage
  - Insulin standard
  - Tolbutamide
  - Phenformin (discontinued early)
  - Placebo
- Followed for 8 years 10 months

UGDP Results

- Patients randomly assigned to receive tolbutamide had a significantly *increased probability of death due to* cardiovascular diseases in comparison to the placebo
- The two insulin groups did not differ significantly from the placebo group.
- The combination of tolbutamide and diet was less effective than diet alone

Reactions

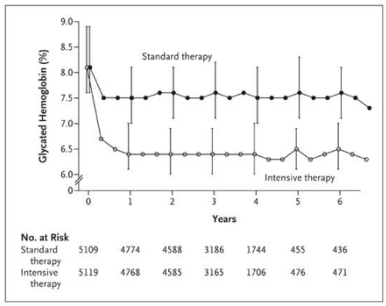
Feinstein

- Published a major attack on study and was called:
  - "drug-house horror,"
  - "snake-oil salesman,"
  - and was accused of engaging in activities which represented a "conflict of interest," "unbridled sensationalism," and "deliberate destruction"

Cornfield

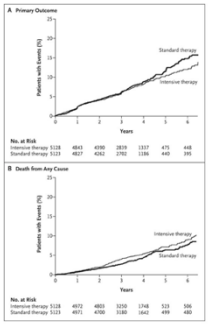
- It was suggested that there was poor randomization in the study, and that groups differed prior to treatment.
  - Yet, the groups did not differ on any of 17 baseline characteristics at the .05 significance level
- More Autopsies in tolbutamide group
- Too few deaths among women in placebo group
  - When reanalyzed, these issues could account for results

Median Glycated Hemoglobin Levels at Each Study Visit ACCORD Trial (NEJM, **358:2545-2559)**



Kaplan-Meier Curves for the Primary Outcome and Death from Any Cause

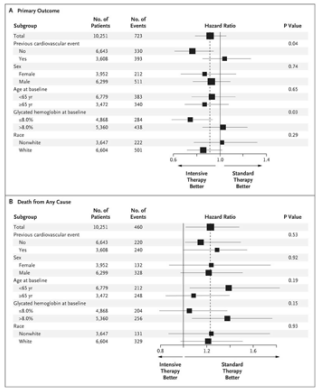
ACCORD Trial (NEJM, **358:2545-2559)**



ACCORD Effects on Primary Outcomes and on Mortality

NEJM June 12, 2008 vol. 358 no. 24

The Action to Control Cardiovascular Risk in Diabetes Study Group*



Veterans Affairs Diabetes Trial (VADT)

Duckworth et al NEJM 360:129-139

- 1791 military veterans
  - mean age, 60.4 years
  - mean number of years since the diagnosis of diabetes was 11.5,
  - 40% of the patients had already had a cardiovascular event.
- Randomly assigned
  - intensive-therapy group
  - standard-therapy group.
- Primary outcome time from randomization to the first occurrence of a major cardiovascular event, composite of
  - myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene.

VADT Results (NEJM, Jan 9, 2009

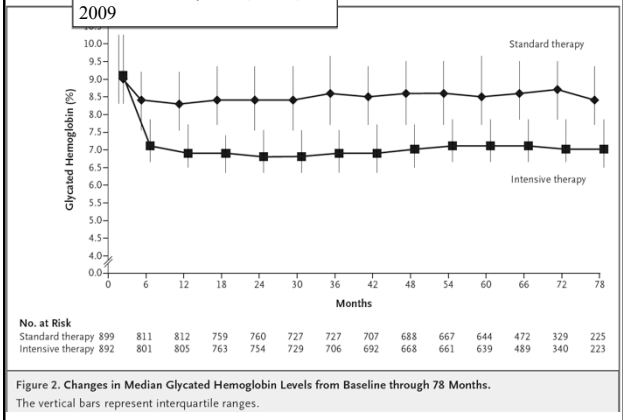


Figure 2. Changes in Median Glycated Hemoglobin Levels from Baseline through 78 Months.
The vertical bars represent interquartile ranges.

VADT Outcomes
(from NEJM 360;2 January 8, 2009)

Despite reductions in HbA1c, no noticeable benefit for any outcome. But, there was evidence of harm

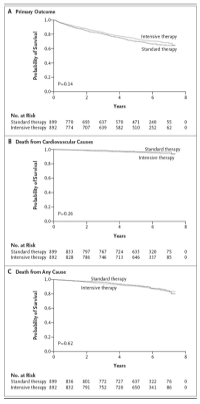
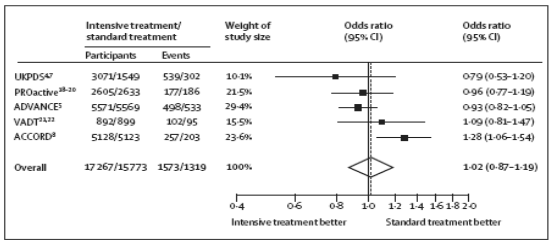


Table 2. **Hypoglycemic Episodes.***

Variable	Standard Therapy (N = 899)	Intensive Therapy (N = 892)
	no./100 patient-yr	
Episodes with impaired consciousness	3	9
Episodes with complete loss of consciousness	1	3
Nocturnal episodes	44	152
Total episodes		
With symptoms	383	1333
Without symptoms	49	233
Relieved by food or sugar intake	421	1516
Measurement of blood glucose during episode	348	1392
With documented blood glucose <50 mg/dl (2.8 mmol/liter)	52	203

* P<0.001 for all differences between the two groups.

It is not only the ACCORD Study (Ray: *Lancet* 2009, 373,1765)

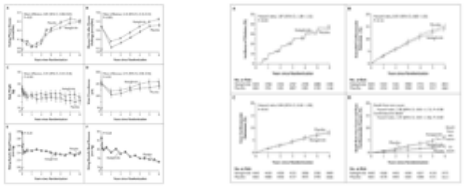


Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR)

NEJM **Volume 362:1463-1476 April 22, 2010**

- 9306 participants with impaired glucose tolerance and either cardiovascular disease or cardiovascular risk factors randomly assigned to receive
  - nateglinide (up to 60 mg three times daily) or placebo, in a 2-by-2 factorial design with
  - valsartan or placebo,
- Participants followed for a median of 5.0 years for incident diabetes (and a median of 6.5 years for vital status).

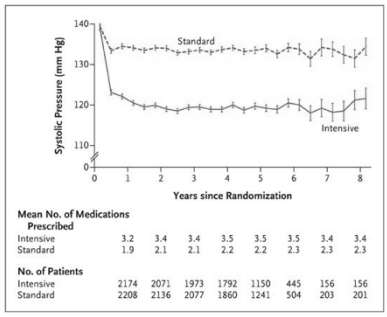
Navigator Results



The ACCORD Trial and Control of Blood Glucose Level in Type 2 Diabetes Mellitus: Time to Challenge Conventional Wisdom
Stephen Havas, MD, MPH, MS
Arch Intern Med. 2009;169(2):150-154

- Unlike blood glucose level, there is strong evidence that controlling high BP and high blood cholesterol levels significantly reduces both macrovascular and microvascular complications in persons with type 2 DM

Mean Systolic Blood-Pressure Levels at Each Study Visit

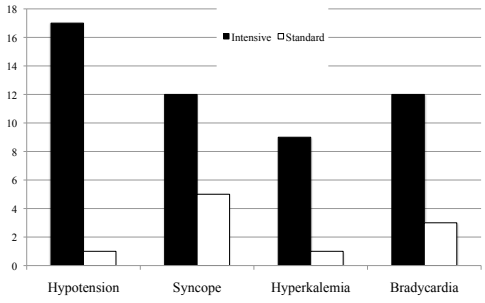


Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

The ACCORD Study Group. N Engl J Med 2010;10.1056/NEJMoa1001286

The NEW ENGLAND JOURNAL of MEDICINE

Adverse Events in Hypertension Component of ACCORD



Primary and Secondary Outcomes

Table 3. Primary and Secondary Outcomes.

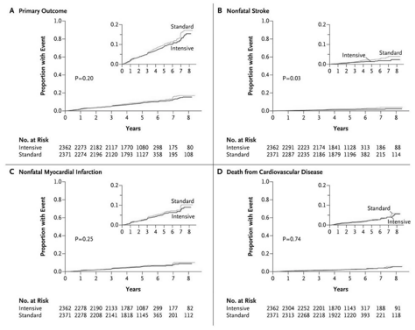
Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03
Death						
From any cause	150	1.28	144	1.19	1.07 (0.85–1.35)	0.55
From cardiovascular cause	60	0.52	58	0.49	1.06 (0.74–1.52)	0.74
Primary outcome plus revascularization or nonfatal heart failure	521	5.10	551	5.31	0.95 (0.84–1.07)	0.40
Major coronary disease event†	253	2.31	270	2.41	0.94 (0.79–1.12)	0.50
Fatal or nonfatal heart failure	83	0.73	90	0.78	0.94 (0.70–1.26)	0.67

* The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.
† Major coronary disease events, as defined in the protocol, included fatal coronary events, nonfatal myocardial infarction, and unstable angina.

The ACCORD Study Group. N Engl J Med 2010;10.1056/NEJMoa1001286

The NEW ENGLAND JOURNAL of MEDICINE

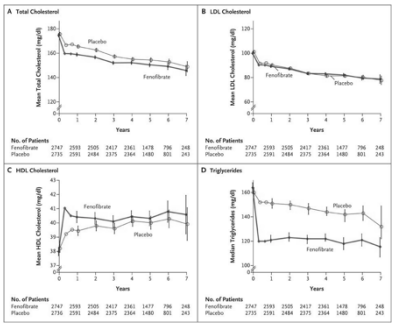
Kaplan-Meier Analyses of Selected Outcomes



The ACCORD Study Group. N Engl J Med 2010;10.1056/NEJMoa1001286

The NEW ENGLAND JOURNAL of MEDICINE

Lipid Values In ACCORD



The ACCORD Study Group. N Engl J Med 2010;10.1056/NEJMoa1001282

The NEW ENGLAND JOURNAL of MEDICINE

Prespecified Primary and Secondary Outcomes

Table 2. Prespecified Primary and Secondary Outcomes.

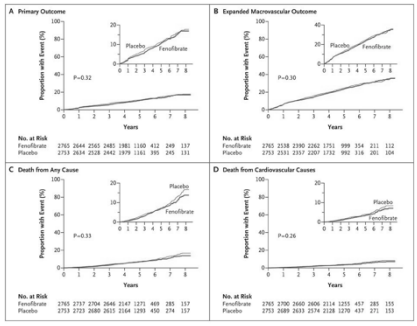
Outcome	Fenofibrate (N=2765)		Placebo (N=2753)		Hazard Ratio (95% CI)	P Value
	no. of events	rate/yr	no. of events	rate/yr		
Primary outcome (major fatal or nonfatal cardiovascular event)	291	2.24	310	2.41	0.92 (0.79–1.08)	0.32*
Secondary outcomes						
Primary outcome plus revascularization or hospitalization for congestive heart failure	641	5.35	667	5.64	0.94 (0.85–1.05)	0.30
Major coronary disease event†	332	2.58	353	2.79	0.92 (0.79–1.07)	0.26
Nonfatal myocardial infarction	173	1.32	186	1.44	0.91 (0.74–1.12)	0.39
Stroke						
Any	51	0.38	48	0.36	1.05 (0.71–1.56)	0.80
Nonfatal	47	0.35	40	0.30	1.17 (0.76–1.78)	0.48
Death						
From any cause	203	1.47	221	1.61	0.91 (0.75–1.10)	0.33*
From cardiovascular cause	99	0.72	114	0.83	0.86 (0.66–1.12)	0.26
Fatal or nonfatal congestive heart failure	120	0.90	143	1.09	0.82 (0.65–1.05)	0.10

* P values were adjusted for interim monitoring.
† A major coronary disease event was defined as a fatal coronary event, nonfatal myocardial infarction, or unstable angina.

The ACCORD Study Group. N Engl J Med 2010;10.1056/NEJMoa1001282

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan-Meier Analyses of the Primary Outcome, Expanded Macrovascular Outcome, and Death



The ACCORD Study Group. N Engl J Med 2010;10.1056/NEJMoa1001282

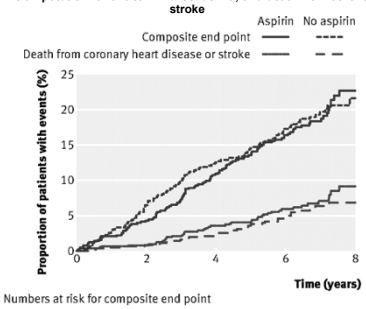
The NEW ENGLAND JOURNAL of MEDICINE

The prevention of progression of arterial disease and diabetes (POPADAD) trial

Published 16 October 2008, doi:10.1136/bmj.a1840

- Multicentre, randomized, double blind, 2x2 factorial, placebo controlled trial.
- 1276 adults aged 40 or more with type 1 or type 2 diabetes and an ankle brachial pressure index of 0.99 or less but no symptomatic cardiovascular disease.
- Daily, 1) 100 mg aspirin tablet plus antioxidant capsule (n=320), 2)maspirin tablet plus placebo capsule (n=318), 3) placebo tablet plus antioxidant capsule (n=320), or 4) placebo tablet plus placebo capsule (n=318).

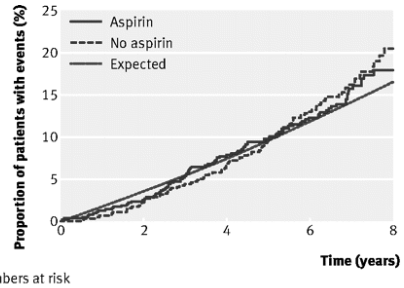
Fig 2 Kaplan-Meier estimates in aspirin and no aspirin groups of proportion of patients who experienced the composite end point of death from coronary heart disease or stroke, non-fatal myocardial infarction or stroke, or above ankle amputation for critical limb ischaemia; and death from coronary heart disease or stroke



Belch, J. et al. BMJ 2008;337:a1840

BMJ

Fig 3 Kaplan-Meier estimates for aspirin and no aspirin groups of proportion of patients who died from any cause, compared with proportion expected based on age and sex specific population rates for Scotland, 2002



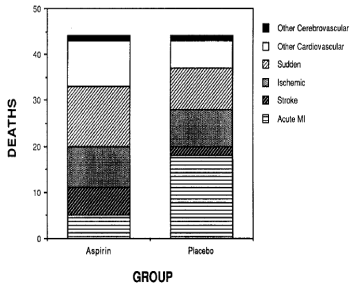
Belch, J. et al. BMJ 2008;337:a1840

BMJ

Post POPADAD Interpretation

- Aspirin is one of the top 10 causes of adverse drug events reported to the Commission on Human Medicines. Gastrointestinal bleeding is associated with general use of non-steroidal anti-inflammatory drugs in over 80% of reported cases, and 87% of that use is associated with aspirin, either alone or with other non-steroidal anti-inflammatory drugs.

Total mortality in the Aspirin component of the Physician's Health Study. Overall the number of physicians who died was identical (From Kaplan, NEJM 1989) in the Aspirin and the Placebo conditions



Internet Advice on Managing Anemia

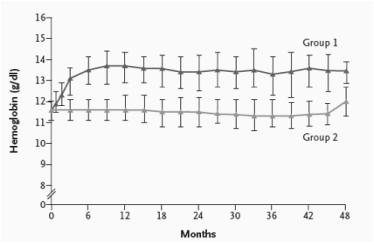
- When anemia is caused by decreased production of red blood cells, such as in cancer or severe kidney disease, a medication called epoetin alfa can be used. This medication mimics the action of erythropoietin, the natural hormone that causes the bone marrow to produce more red blood cells.

-

Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)

NEJM N Engl J Med 2006;355:2071-84.

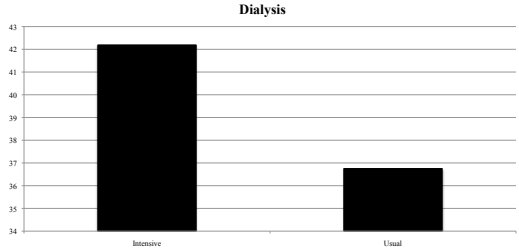
- 603 patients with an estimated glomerular filtration rate (GFR) of 15.0 to 35.0 ml per minute per 1.73 m2 of body-surface area and mild-to-moderate anemia (hemoglobin level, 11.0 to 12.5 g per deciliter) randomly assigned to
  - a target hemoglobin value in the normal range (13.0 to 15.0 g per deciliter, group 1) or the
  - subnormal range (10.5 to 11.5 g per deciliter, group 2). per deciliter --triggered treatment at 10.5 g (group 2).



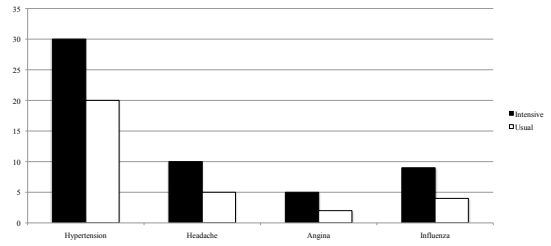
CREATE Median Hemoglobin Levels in the Intention-to-Treat Population during the Study.

Aggressive treatment effectively increases hemoglobin, but….

Percent of Patients Requiring Dialysis in CREATE Study by Group



Percent Adverse Reactions (selected) by Group in CREATE

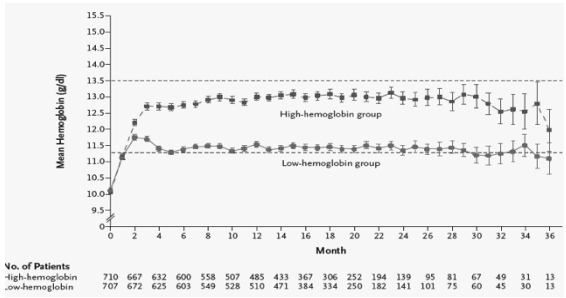


Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)

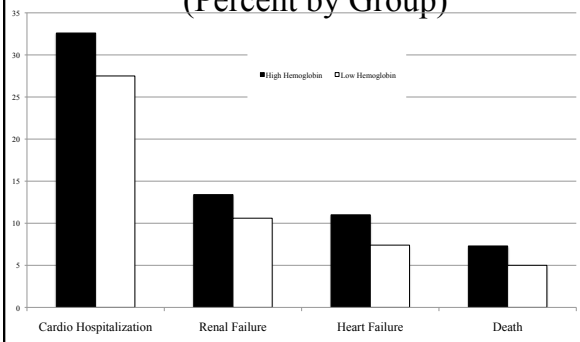
N Engl J Med 2006;355:2085-98

- 1432 patients with chronic kidney disease randomly assigned to
  - receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 13.5 g per deciliter (N=715)
  - Receive a dose targeted to achieve a level of 11.3 g per deciliter (N=717).
- The primary end point was a composite of death, myocardial infarction,hospitalization for congestive heart failure (without renal replacement therapy)

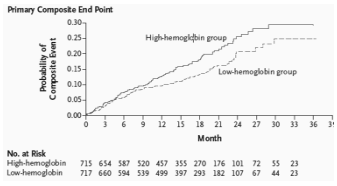
Hemoglobin in CHIOR trial



Outcomes in CHIOR Trial (Percent by Group)



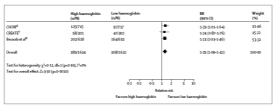
Outcomes in CHIOR Trial



Editorial on Erythropoiesis

Strippoli et al. Lancet, Vol 369 February 3, 2007

Studies are consistent in meta analysis



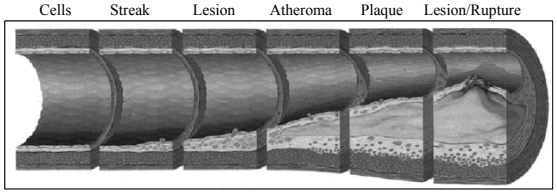
Editorial

- "A serious reconsideration of the rationale and of the relevance of ongoing studies is necessary, because the effects of erythropoiesis-stimulating agents are not fully understood. Not only do they increase haemoglobin concentrations, but they also might act through alternative dose-dependent pathways that could be harmful" p 349.

Atherosclerosis Timeline

Endothelial Dysfunction

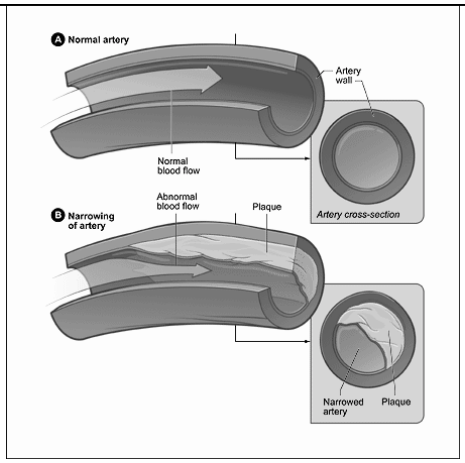
Foam Cells | Fatty Streak | Intermediate Lesion | Atheroma | Fibrous Plaque | Complicated Lesion/Rupture



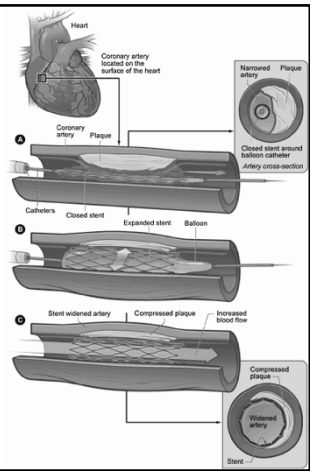
From first decade	From third decade	From fourth decade

Growth mainly by lipid accumulation	Smooth muscle and collagen	Thrombosis, hematoma

Stary et al. *Circulation.* 1995;92:1355-1374.



Angioplasty with Stent Placement NHLBI website

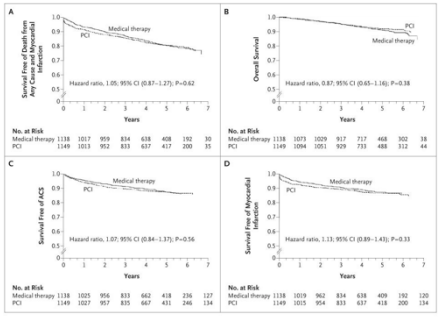


Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE)
Boden et al, NEJM 356:1503-1516

- 2287 patients who had objective evidence of myocardial ischemia and significant coronary artery disease randomly assigned to patients to undergo
  - PCI with optimal medical therapy (PCI group)
  - optimal medical therapy alone (medical-therapy group).
- Primary outcome was death from any cause and nonfatal myocardial infarction during a follow-up period of 2.5 to 7.0 years (median, 4.6)

COURAGE TRIAL

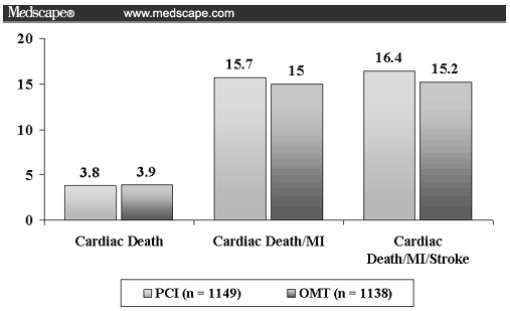
Kaplan-Meier Survival Curves



Boden W et al. N Engl J Med 2007;356:1503-1516

The NEW ENGLAND JOURNAL of MEDICINE

COURAGE Results



Meta Analysis of PCI Trials

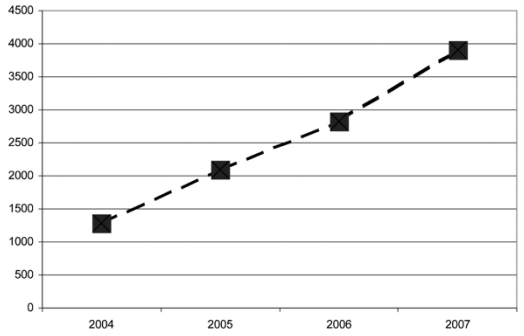
Katritsis, NEJM 2007, 357:414-418

Table 1. **Update of Meta-Analysis of PCI, as Compared with Medical Treatment, for Stable Coronary Artery Disease.***

Outcome	PCI	Medical Treatment	Summary Risk Ratio (95% CI)	P Value	Q Statistic
	no.				
Death from any cause	195	219	0.90 (0.75–1.08)	0.25	5.93
Myocardial infarction or death from cardiac causes	321	313	1.01 (0.88–1.17)	0.87	10.35
Nonfatal myocardial infarction	242	221	1.07 (0.90–1.28)	0.43	8.75

* The updated meta-analysis includes 13 studies involving 5442 patients. The original meta-analysis[2] included data from 11 trials. The updated meta-analysis includes data from the COURAGE trial and the Adenosine Sestamibi SPECT Post-Infarction Evaluation (INSPIRE) trial and updated long-term follow-up data from the Medicine, Angioplasty, or Surgery Study II (MASS II). Summary risk ratios by fixed and random effects were practically identical in the two groups, since there was no between-study heterogeneity for any of the three outcomes ($I^2=0$). PCI denotes percutaneous coronary intervention.

The number of cases utilising coronary pressure wire in UK interventional practice 2004–8.15.



Curzen N P Heart 2010;96:103-105

HEART

Post-Hoc Discussion of COURAGE

- Rationale has never been completely clear
- Infarcts do not necessarily occur at the narrowest point in the artery
- Medical therapy stabilizes plaque
- And …..

Schwartz et al results

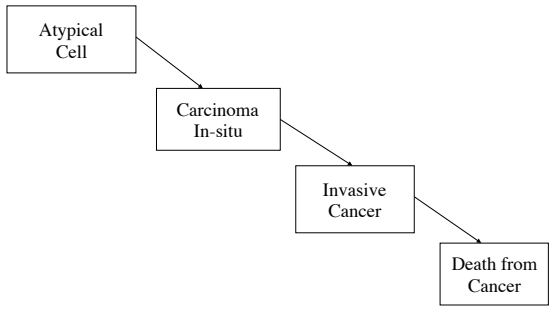
- Cancer screening is almost always a good idea -- 87%
- Finding cancer early saves lives--74%
- An 80 year old woman who decides not to get a mammogram is irresponsible --41%
- Had a false positive, but still glad I was tested -- 98%

Cancer Screening and Public Policy

- President Obama on cancer screening. From address to joint session of congress, September 9, 2009

Cancer Progress

Welch, 2003



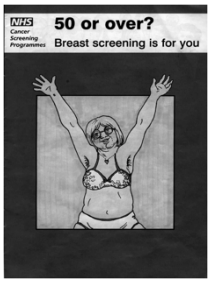
The simple description of breast cancer…..

Cost-Effectiveness of Pap Smear (from David Meltzer, 2010)

Frequency	Increase in life expectancy	Increase in cost	Average cost per life year gained	Marginal increase in LE	Marginal increase in cost	Marginal cost/life year saved
3 Years	70 days	$500	$2600/ YL	70 days	$500	$2600/LY
2 Years	71 days	$750	$3900/ LY	1 day	$250	$91000/ LY
1 Year	71 days, 8 hours	$1500	$7300/ LY	8 hours	$750	$830000/ LY

American Cancer Society On Women Who Question Screening

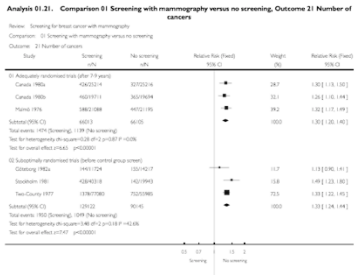
British National Health Service: "Informational Campaign"



Canadian National Breast Screening Study (Miller et al,

- 50,472 women aged 40-49 years individually randomized
  - an annual mammography and clinical examination, or
  - examined at the first visit and were taught self-examination thereafter
- Followed 13 years
- Comparable study for women 50-59

Cancers detected: Cochrane Review October 2006 Gotzsche & Nielsen



Results of Randomized, Controlled Trials of Mammography among Women 39 to 74 Years of Age

Table 4. **Results of Randomized, Controlled Trials of Mammography among Women 39 to 74 Years of Age***

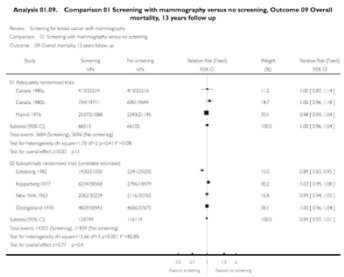
Study (Reference)	Age	Median Follow-up	Breast Cancer Deaths/Total Women		Breast Cancer Death Rate per 1000 Women		Relative Risk for Death from Breast Cancer (95% CI)	Absolute Risk Reduction per 1000 Women	Number Needed To Invite to Screening†
			Screened Group	Control Group	Screened Group	Control Group			
	y		n/n						
Mammography alone									
Stockholm (23)	40–64	13.8	82/39 139	50/20 978	2.10	2.38	0.91 (0.65–1.27)	0.288	3468
Gothenburg (23)	39–59	12.8	62/20 724	113/29 200	2.99	3.87	0.76 (0.56–1.04)	0.878	1139
Malmö (23)	45–70	17.1	161/21 088	198/21 195	7.63	9.35	0.82 (0.67–1.00)	1.712	584
Swedish Two-County Trial (26)	40–74	17	319/77 080	333/55 985	4.14	5.95	0.68 (0.59–0.80)	1.809	553
Mammography plus CBE									
CNBSS-1 (22)	40–49	13	105/25 214	108/25 216	4.16	4.28	0.97 (0.74–1.27)	0.12	–
CNBSS-2 (20)	50–59	13	107/19 711	105/19 694	5.43	5.33	1.02 (0.78–1.33)	−0.097	–
HIP (19)	40–64	16	232/30 239	281/30 256	5.46	6.89	0.79	1.438	883
Edinburgh (18)	45–64	13	156/22 926	167/21 342	6.80	7.82	0.79 (0.60–1.02)	1.020	980

* CBE = clinical breast examination; CNBSS = Canadian National Breast Screening Study; HIP = Health Insurance Plan of Greater New York.
† Number needed to invite to screening to prevent one death from breast cancer 13–20 years after randomization.

Humphrey, L. L. et. al. Ann Intern Med 2002;137:34760-3

Annals of Internal Medicine

Cochrane Review October 2006 Gotzsche & Nielsen

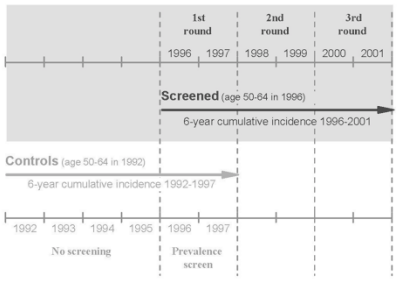


Do We Understand The Natural History of Breast Cancer?

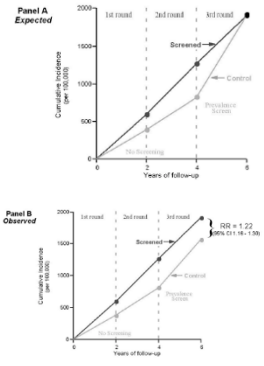
The Problem of Pseudodisease

Natural History of Breast Cancer

Zahl et al Archives of Int Med Nov 24, 2008



Repeated Screening Vs Prevalence Screening among Norwegian Women Age 40-64. (From Zahl, Maehlen, & Welch, Archives of Int Med, Nov 2008)



Is there any evidence for spontaneous regression of advanced cancer?

- Metastatic melanoma (Printz JNCI, 2001)
- Metastatic renal cell (Gleave et al NEJM, 1998)
- National Polyp Study (Int J. Cancer, 2004)
- Pre-cancerous cervical lesions (Moscicki et al, Lancet, 2004)

Alternative Explanations

Were the samples comparable?

No differences between groups on any variable

	Screened Group (age 50-64 in 1996)	Control Group (age 50-64 in 1992)
N (start of observation period)	119,472	109,784
Starting age (mean)	56.8	57.4
Educational level (%)		
some high school	69.5%	74.0%
completed high school	10.8%	10.0%
some college	11.7%	10.4%
completed college	8.0%	5.7%
Family income* (mean)	266,000Kr ($41,900)	239,000Kr ($37,600)
Reproductive history		
Nulliparous (%)	15.6%	16.3%
Age at first birth (mean)	24.5	25.0
Number of births (mean)	2.17	2.20
Attendance at screening at the end of observation period (3rd round screened group, prevalence screen control group)	78.3%	79.5%

Evidence from Trials

- Malmo study estimated that there was 19% higher rate of diagnosis in the screened group 10 years after the trial ended (both groups got screened at exit)
- Canadian trials screen all women at end. Four years later cumulative rates remained 7% higher in the screened group

Evidence from simulation studies

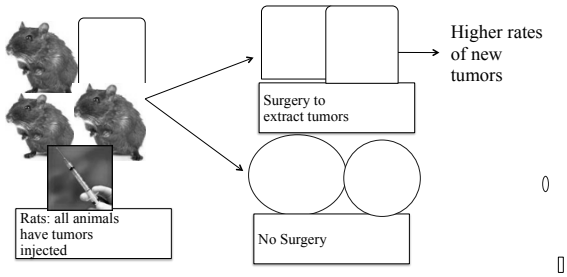
- Wisconsin Breast Cancer Epidemiology Simulation Model (Fryback et al JNCI 2007)
  - Stochastic simulation to replicate breast cancer incidence and mortality in the US 1975-2000
  - Postulated that 40% in initiated breast cancers were of "limited malignant potential"
  - "progress to a maximum of 1-cm, dwell at this size for 2 years, and then regress if untreated"

Could it be temporal change in incidence of cancer?

- Unlikely. No evidence for an epidemic of breast cancer in Norway at that time.

What Harm Is Done?

100 years of animal experimentation (after Baum and Retsky, 2008)



Cardiac Arrhythmia Suppression Trial (CAST)

- Designed to test the hypothesis that suppression of ventricular ectopy after a myocardial infarction reduces the incidence of sudden death,
- Patients in whom ventricular ectopy randomly assigned to receive
  - active drug (encainide N= 432) and flecainide N=323)
  - or placebo (425 encainide placebo, 318 flecainide placebo)
- After a mean follow-up of 10 months,
  - 43 arrhythmia deaths in active drug group
  - 16 arrhythmia deaths in placebogroup; P = 0.0004),
  - Almost all cardiac deaths not due to arrhythmia were attributed to acute myocardial infarction with shock (11 patients receiving drug and 3 receiving placebo) or to chronic congestive heart failure (4 receiving drug and 2 receiving placebo). unknown.

Women's Health Initiative (WHI)

JAMA. 2002;288:321-333

- Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which
- 16608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.
- Participants randomly assigned to
  - conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n = 8506) or
  - placebo (n = 8102)
- Primary outcome coronary heart disease (CHD)
  - (nonfatal myocardial infarction and CHD death),
  - invasive breast cancer ---primary adverse outcome.
  - A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

WHI Results
JAMA 2002;288:321-333

Table 2. Clinical Outcomes by Randomization Assignment[a]

Outcomes	No. of Patients (Annualized %) Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	Hazard Ratio	Nominal 95% CI	Adjusted 95% CI
Follow-up time, mean (SD), mo	62.2 (16.1)	61.2 (15.0)	NA	NA	NA
Cardiovascular disease†					
CHD	164 (0.37)	122 (0.30)	1.29	1.00-1.63	0.85-1.97
CHD death	33 (0.07)	26 (0.06)	1.18	0.70-1.97	0.47-2.98
Nonfatal MI	133 (0.30)	96 (0.23)	1.32	1.02-1.72	0.82-2.13
CABG/PTCA	183 (0.42)	171 (0.41)	1.04	0.84-1.28	0.71-1.51
Stroke	127 (0.29)	85 (0.21)	1.41	1.07-1.85	0.86-2.31
Fatal	16 (0.04)	13 (0.03)	1.20	0.58-2.50	0.32-4.49
Nonfatal	94 (0.21)	59 (0.14)	1.50	1.08-2.08	0.83-2.70
Venous thromboembolic disease	151 (0.34)	67 (0.16)	2.11	1.58-2.82	1.39-3.55
Deep vein thrombosis	115 (0.26)	52 (0.13)	2.07	1.49-2.87	1.14-3.74
Pulmonary embolism	70 (0.16)	31 (0.08)	2.13	1.39-3.25	0.99-4.56
Total cardiovascular disease	694 (1.57)	546 (1.32)	1.22	1.09-1.36	1.00-1.49
Cancer					
Invasive breast	166 (0.38)	124 (0.30)	1.26	1.00-1.59	0.83-1.92
Endometrial	22 (0.05)	25 (0.06)	0.83	0.47-1.47	0.39-2.32
Colorectal	45 (0.10)	67 (0.16)	0.63	0.43-0.92	0.32-1.24
Total	502 (1.14)	458 (1.11)	1.03	0.90-1.17	0.86-1.22
Fractures					
Hip	44 (0.10)	62 (0.15)	0.66	0.45-0.98	0.33-1.33
Vertebral	41 (0.09)	60 (0.15)	0.66	0.44-0.98	0.32-1.34
Other osteoporotic‡	579 (1.31)	701 (1.73)	0.77	0.69-0.86	0.63-0.94
Total	650 (1.47)	788 (1.91)	0.76	0.69-0.85	0.63-0.92
Death					
Due to other causes	165 (0.37)	166 (0.40)	0.92	0.74-1.14	0.62-1.35
Total	231 (0.52)	218 (0.53)	0.98	0.82-1.18	0.70-1.37
Global index§	751 (1.70)	623 (1.51)	1.15	1.03-1.28	0.95-1.39

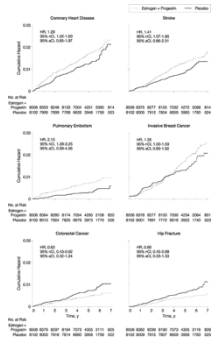
*CI indicates confidence interval; NA, not applicable; CHD, coronary heart disease; MI, myocardial infarction; CABG, coronary artery bypass grafting; and PTCA, percutaneous transluminal coronary angioplasty.

†CHD includes acute MI requiring hospitalization, silent MI determined from serial electrocardiograms, and coronary death. There were 8 silent MIs. Total cardiovascular disease is the first event for each participant from among the following types: CHD, stroke, pulmonary embolism, breast cancer, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

‡Other osteoporotic fractures include all fractures other than cranial/facial, hands, toes, and cervical vertebrae, as well as hip and vertebral fractures reported sepa- rately.

§The global index represents the first event for each participant from among the following types: CHD, stroke, pulmonary embolism, breast cancer, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Kaplan-Meier Estimates of Cumulative Hazards for Selected Clinical Outcomes



Writing Group for the Women's Health Initiative Investigators, JAMA 2002;288:321-333.

JAMA

Conclusions

- Interventions are often guided by mental models of disease
  - These models of often linear
  - Disease is often non linear
- Outcomes researchers focus on different aspects of the data
  - Total mortality
  - Quality of Life
- Aggressive care is not always the best care
- There is still a place for large RCTs

"Make everything as simple as possible…but not simpler"

Albert Einstein