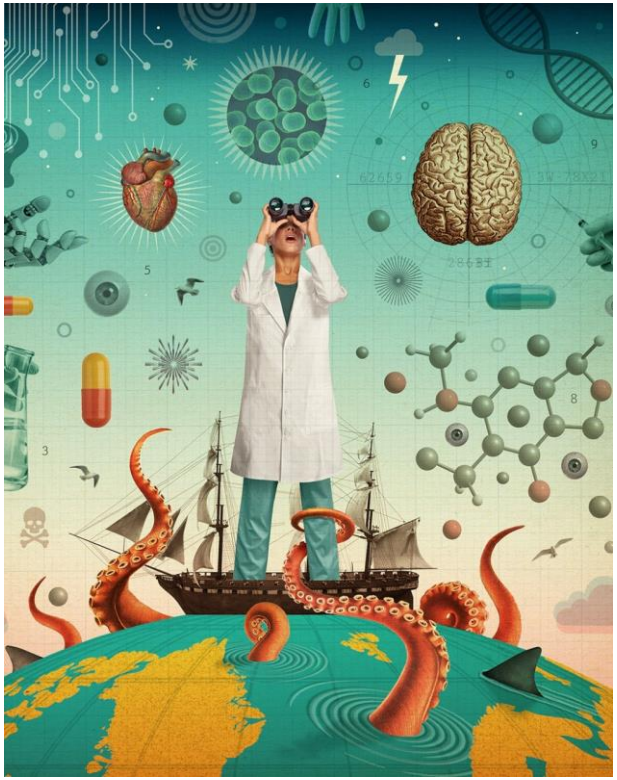
# Health Outcomes, Surrogate Endpoints, and Biomarkers

ibtn
international
behavioural
trials network



Cover of Stanford Medicine: Winter 2018

Robert M. Kaplan
Clinical Excellence Research Center
Stanford University School of Medicine

International Behavioural Trials Network

May 25, 2018

# Stanford Medical Grand Rounds: Last week and most other weeks

ibtn
international
behavioural
trials network

- The purpose of health care is to:
  - Increase length of life
  - Improve quality of life
- All other measures are only important if the are related to one of these two goals


# What Do Psychologists Prefer to Measure?

ibtn
international
behavioural
trials network

- Blood pressure
- Weight
- Glycosylated Hemoglobin
- Cortisol
- Avoid self report….

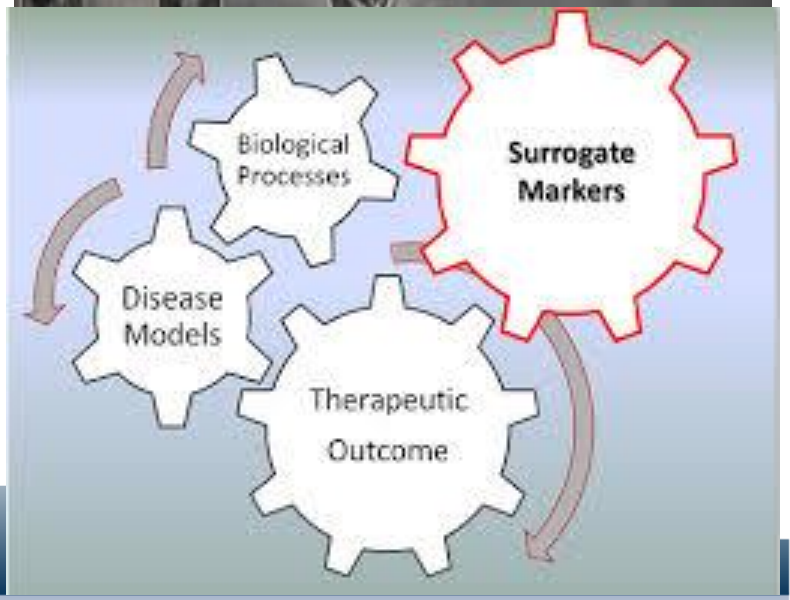
- Information is meaningful if it comes from your veins
- Not from your mouth

# The Surrogate Marker Problem:

ibtn
international
behavioural
trials network

Assumes the human body functions like a machine

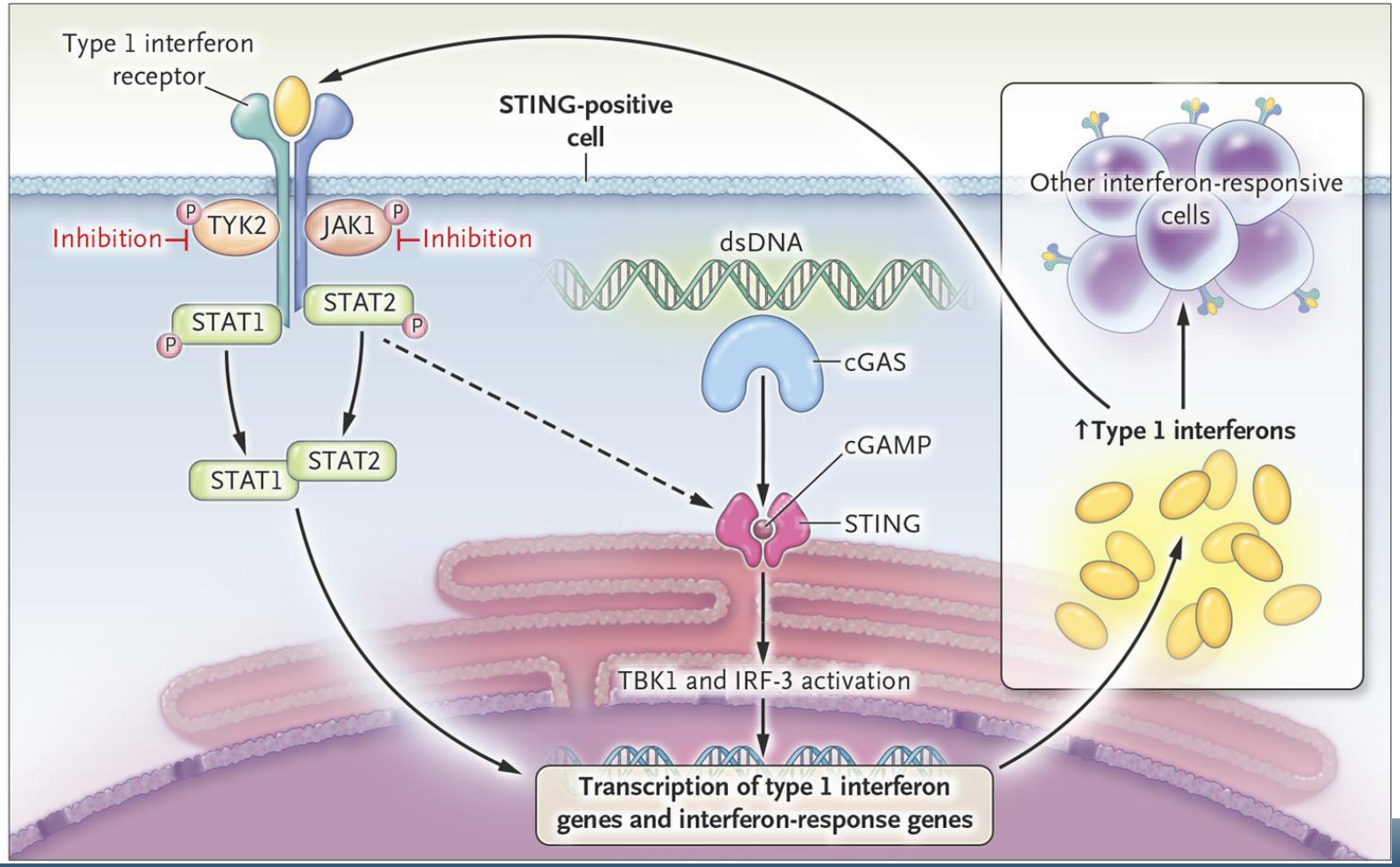
Surrogate Markers are assumed to be precise stand ins for health outcomes




USPSTF focuses on health outcomes rather than on intermediate markers

# The STING–Interferon-β Pathway.

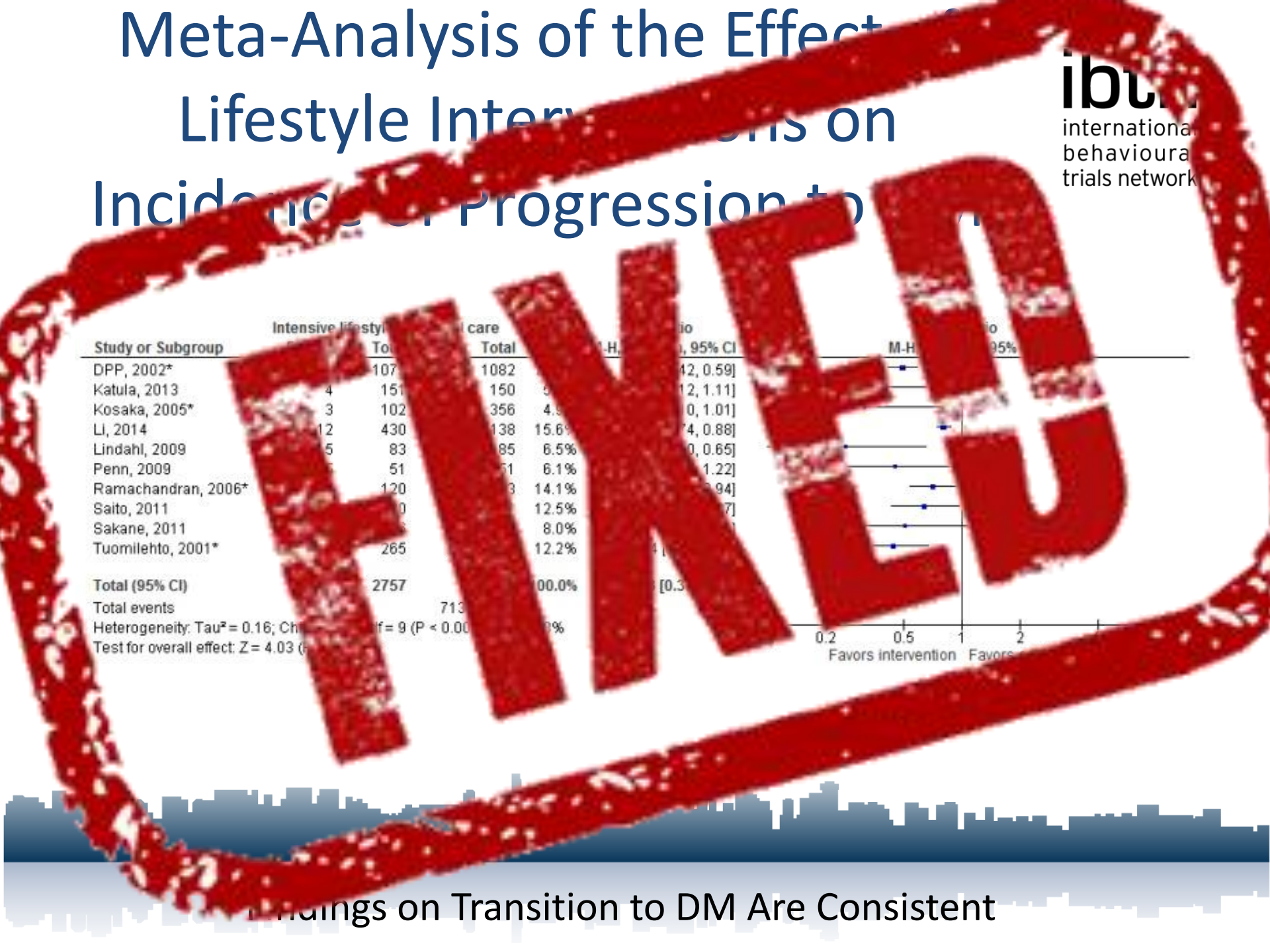
ibtn
international
behavioural
trials network




Liu Y et al. N Engl J Med 2014;371:507-518.

# Meta-Analysis of the Effect of Lifestyle Interventions on Incidence of Progression to [illegible]

ibtn
international behavioural trials network




Intensive lifesty[illegible] care

| Study or Subgroup | Total | Total | M-H, [illegible], 95% CI |
|---|---|---|---|
| DPP, 2002* | 107 | 1082 | [illegible]42, 0.59] |
| Katula, 2013 | 4 151 | 150 | [illegible]12, 1.11] |
| Kosaka, 2005* | 3 102 | 356 | 4.9 [illegible]0, 1.01] |
| Li, 2014 | 12 430 | 138 | 15.6% [illegible]74, 0.88] |
| Lindahl, 2009 | 5 83 | 85 | 6.5% [illegible]0, 0.65] |
| Penn, 2009 | 51 | 51 | 6.1% [illegible]1.22] |
| Ramachandran, 2006* | 120 | 3 | 14.1% [illegible].94] |
| Saito, 2011 | 0 | | 12.5% [illegible]7] |
| Sakane, 2011 | | | 8.0% |
| Tuomilehto, 2001* | 265 | | 12.2% |
| Total (95% CI) | 2757 | | 100.0% [0.3 |
| Total events | 713 | | |
| Heterogeneity: Tau² = 0.16; Ch | | f = 9 (P < 0.00 | %) |
| Test for overall effect: Z = 4.03 ( | | | |

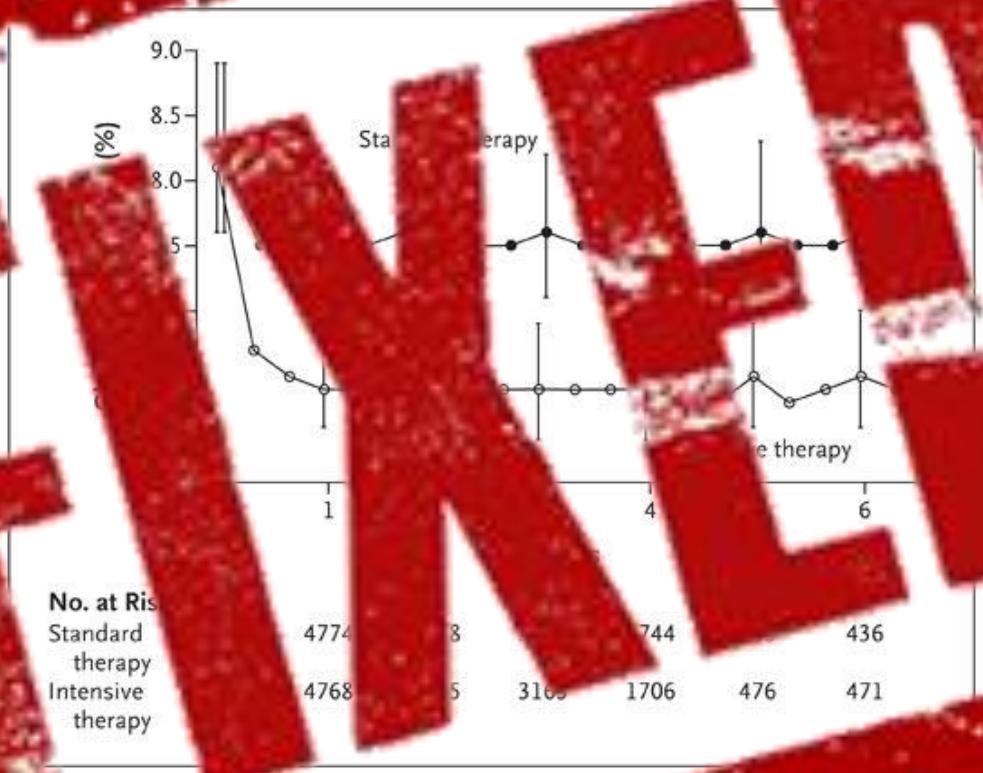
M-H, [illegible], 95%

0.2 0.5 1 2

Favors intervention Favors

[illegible]ndings on Transition to DM Are Consistent

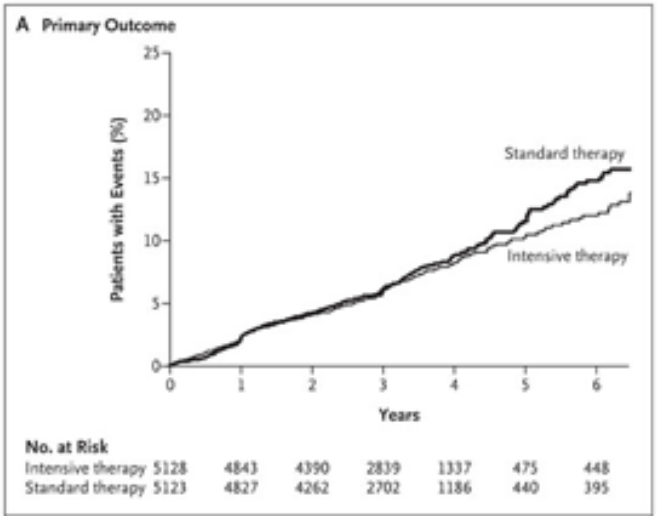
Median Glycated Hemoglobin Levels at Each
ACCORD Trial (NEJM, 35

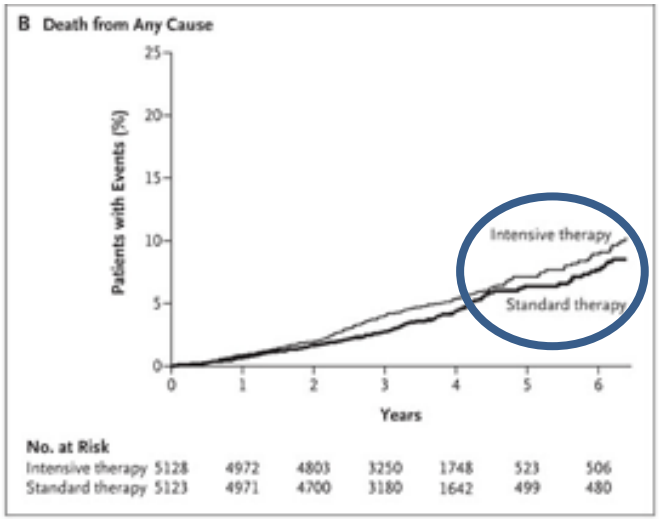



FIXED

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

ibtn
international
behavioural
trials network



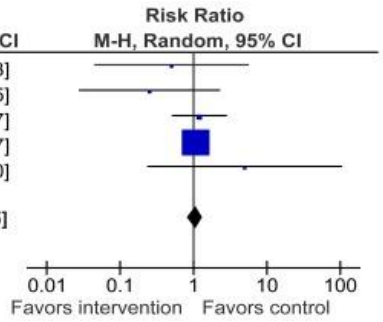

(NEJM, 358:2545-2559

# Meta Analysis of Glucose Lowering on CVD Mortality (Top) and All Cause Mortality (Bottom)

Cardiovascular Mortality

| Study or Subgroup | Intervention Events | Intervention Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Chiasson, 2002* | 1 | 682 | 2 | 686 | 1.0% | 0.50 [0.05, 5.53] |
| DPP, 2002* | 1 | 1073 | 4 | 1082 | 1.1% | 0.25 [0.03, 2.25] |
| DREAM, 2006* | 12 | 2635 | 10 | 2634 | 7.8% | 1.20 [0.52, 2.77] |
| NAVIGATOR, 2010 | 126 | 4645 | 118 | 4661 | 89.5% | 1.07 [0.84, 1.37] |
| Ramachandran, 2009 | 2 | 204 | 0 | 203 | 0.6% | 4.98 [0.24, 103.00] |
| **Total (95% CI)** | | **9239** | | **9266** | **100.0%** | **1.07 [0.84, 1.35]** |
| Total events | 142 | | 134 | | | |

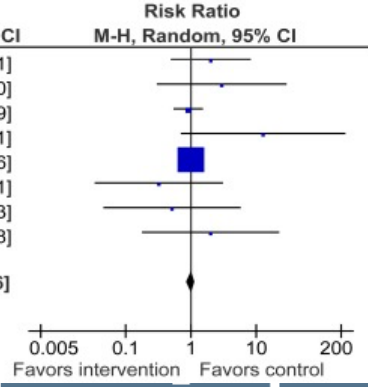
Heterogeneity: Tau² = 0.00; Chi² = 3.11, df = 4 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.60)




All Cause Mortality

| Study or Subgroup | Intervention Events | Intervention Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Chiasson, 2002* | 6 | 682 | 3 | 686 | 1.1% | 2.01 [0.51, 8.01] |
| DeFronzo, 2011 | 3 | 303 | 1 | 299 | 0.4% | 2.96 [0.31, 28.30] |
| DREAM, 2006* | 30 | 2635 | 33 | 2634 | 8.5% | 0.91 [0.56, 1.49] |
| Kawamori, 2009 | 6 | 897 | 0 | 881 | 0.2% | 12.77 [0.72, 226.31] |
| NAVIGATOR, 2010 | 310 | 4645 | 312 | 4661 | 88.7% | 1.00 [0.86, 1.16] |
| Nijpels, 2008 | 1 | 60 | 3 | 58 | 0.4% | 0.32 [0.03, 3.01] |
| Ramachandran, 2006* | 1 | 262 | 2 | 269 | 0.4% | 0.51 [0.05, 5.63] |
| Ramachandran, 2009 | 2 | 203 | 1 | 203 | 0.4% | 2.00 [0.18, 21.88] |
| **Total (95% CI)** | | **9687** | | **9691** | **100.0%** | **1.00 [0.87, 1.16]** |
| Total events | 359 | | 355 | | | |

Heterogeneity: Tau² = 0.00; Chi² = 6.66, df = 7 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)



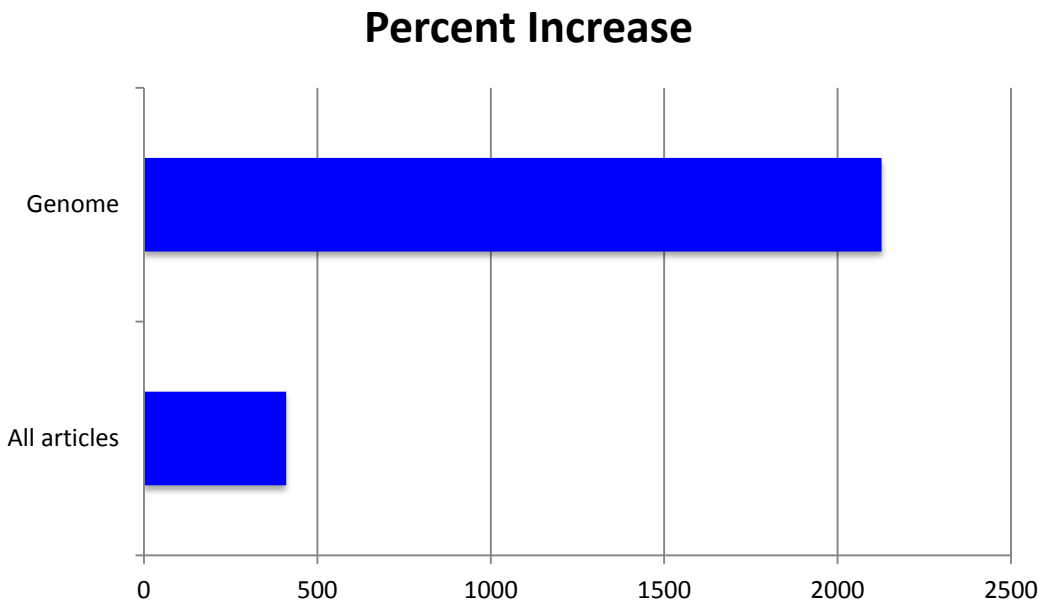
# Cancer Switched Off Here:
# U of T is Global Leader in Molecular Cancer Research

ibtn
international
behavioural
trials network


From *The Globe and Mail,* February 28, 2017

# Increase in the annual number of published articles indexed in PubMed between 1974 and 2014

ibtn international trials network




Based on Joyner et al, *JAMA*. Published online July 28, 2016.

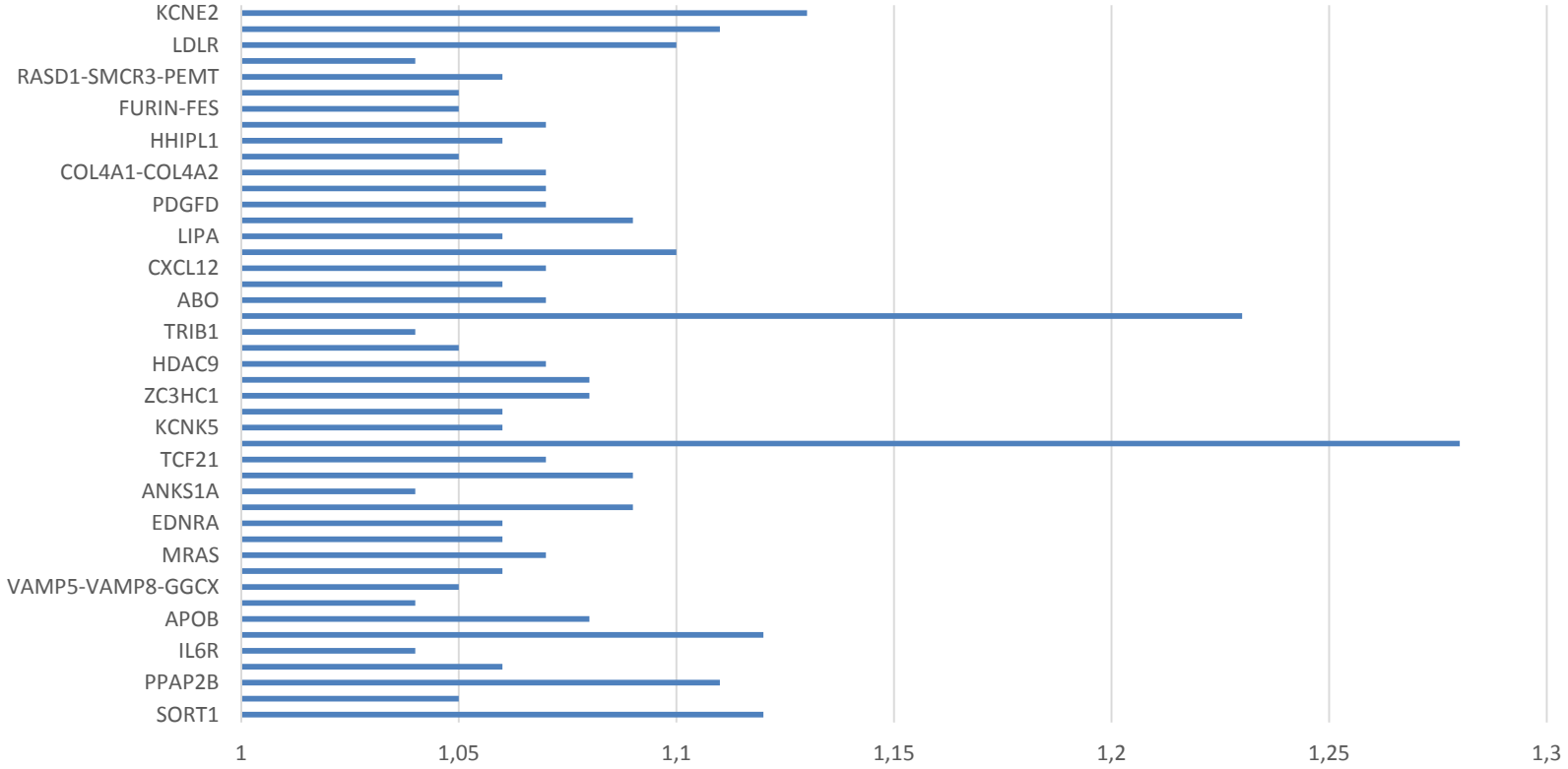
# Genetic: Sequencing vs One Simple question

ibtn
international
behavioural
trials network


Did your mother, father, or both parents die of heart disease? If so, at what age?

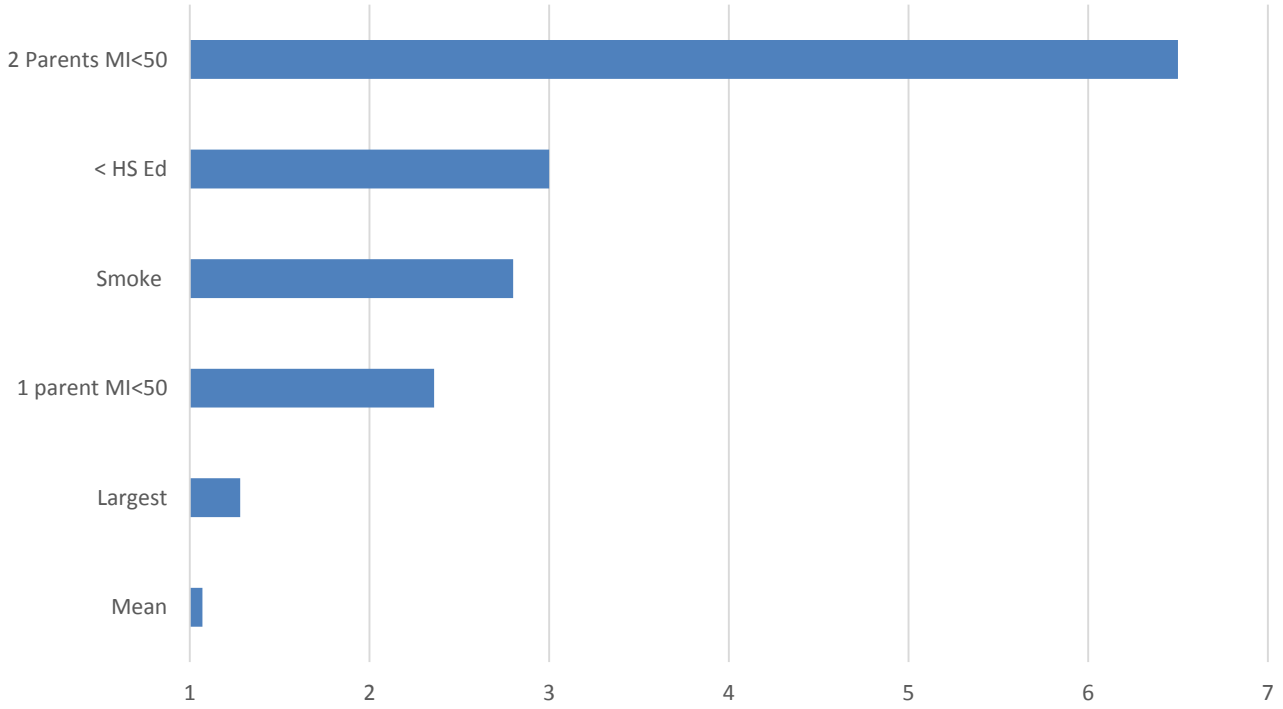
# Effect Size (OR) For All Significant SNPs Knows to Affect Coronary Artery Disease

ibtn
international
behavioural
trials network




Data from Circulation. 2017 March 7; 135(10): e146–e603.

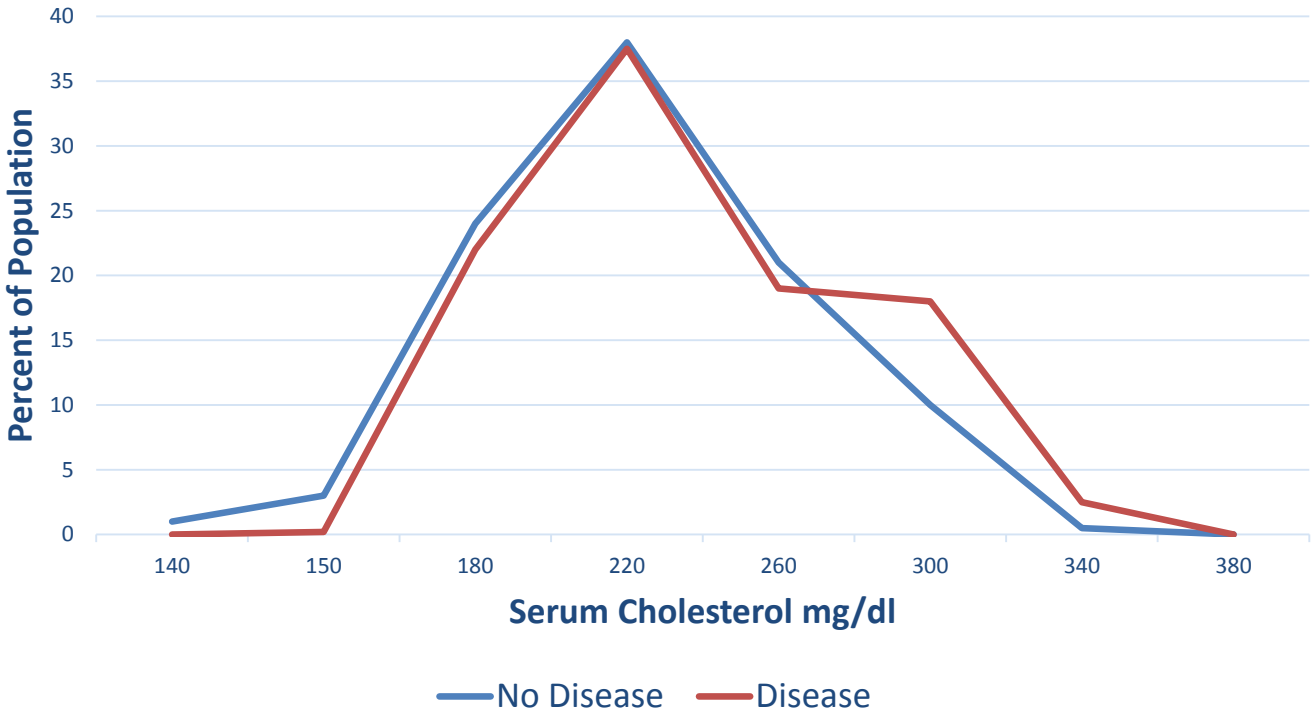
# Comparison of Gene Effects Versus Other Influences on CAD




Data from Circulation. 2017 March 7; 135(10): e146–e603.

# Serum Cholesterol for Framingham Heart Study Participants who developed or did not develop heart disease

ibtn international behavioural trials network



ibtn

Praluent®
(alirocumab) Injection 75mg/mL 150mg/mL
THE FALL OF HIGH CHOLESTEROL

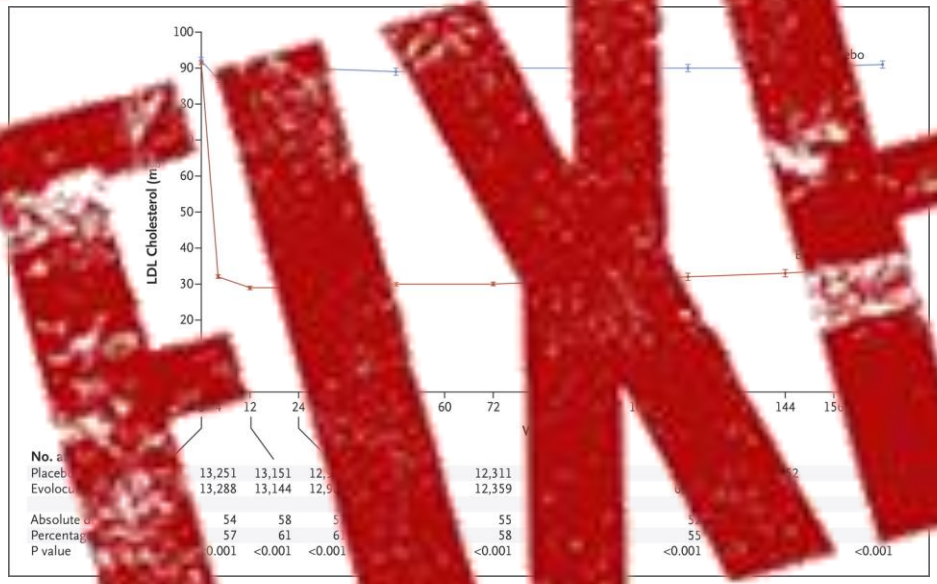
Patient Information | Prescribing Information | Healthcare Professionals Site | C

**Still struggling to lower your high cholesterol?**

When diet and the highest tolerated dose of a statin are not enough, adding PRALUENT® (alirocumab) could make your bad cholesterol **PLUNGE.**

# It's THE FALL OF HIGH CHOLESTEROL.

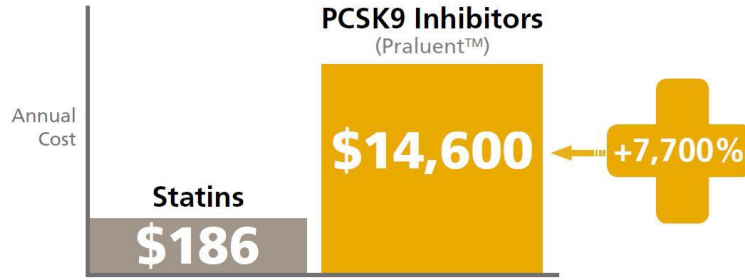
# Density Lipoprotein (LDL) Cholesterol Lev





## Average Annual Cost of Therapy

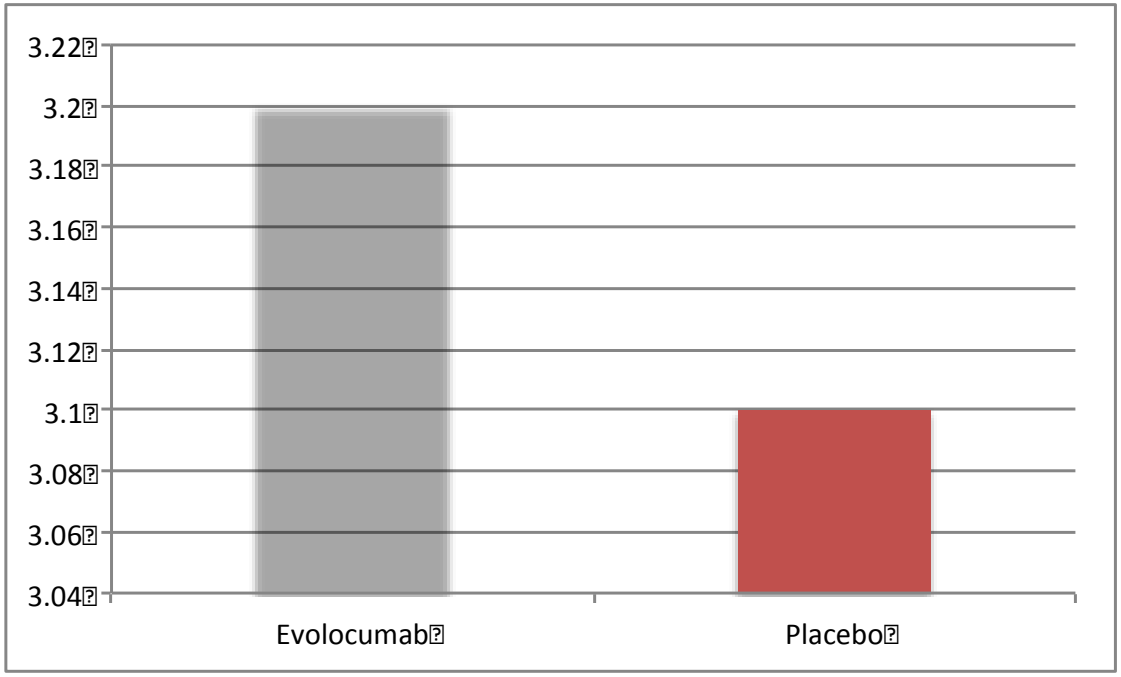
Costs could soar with widespread use of PCSK9 Inhibitor




Statin cost: WAC drug costs for atorvastatin. OptumRx Q2-2015 utilization data.
Reuters. New heart drugs come in more expensive than expected. Jul 27, 2015.

Sabatine MS et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1615664

# All Cause Mortality




Sabatine MS et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1615664

ibtn
national
ioural
twork

# Angioplasty with Stent Placement BI w


FIXED

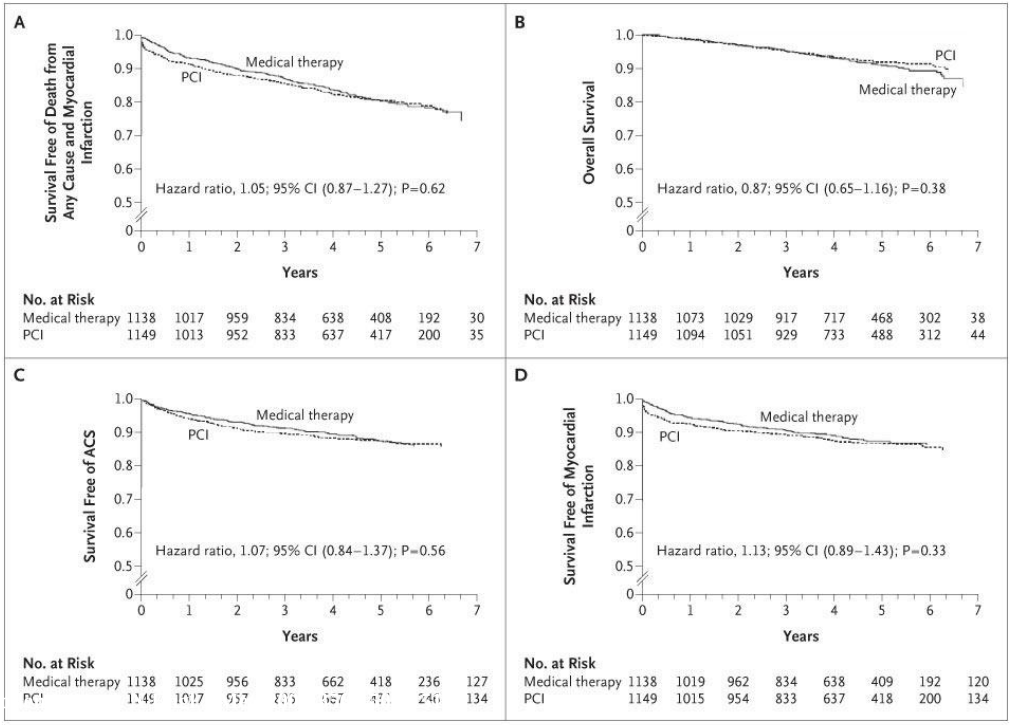
## Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Boden et al, NEJM 356:1503-1516

ibtn
international
behavioural
trials network

- 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)

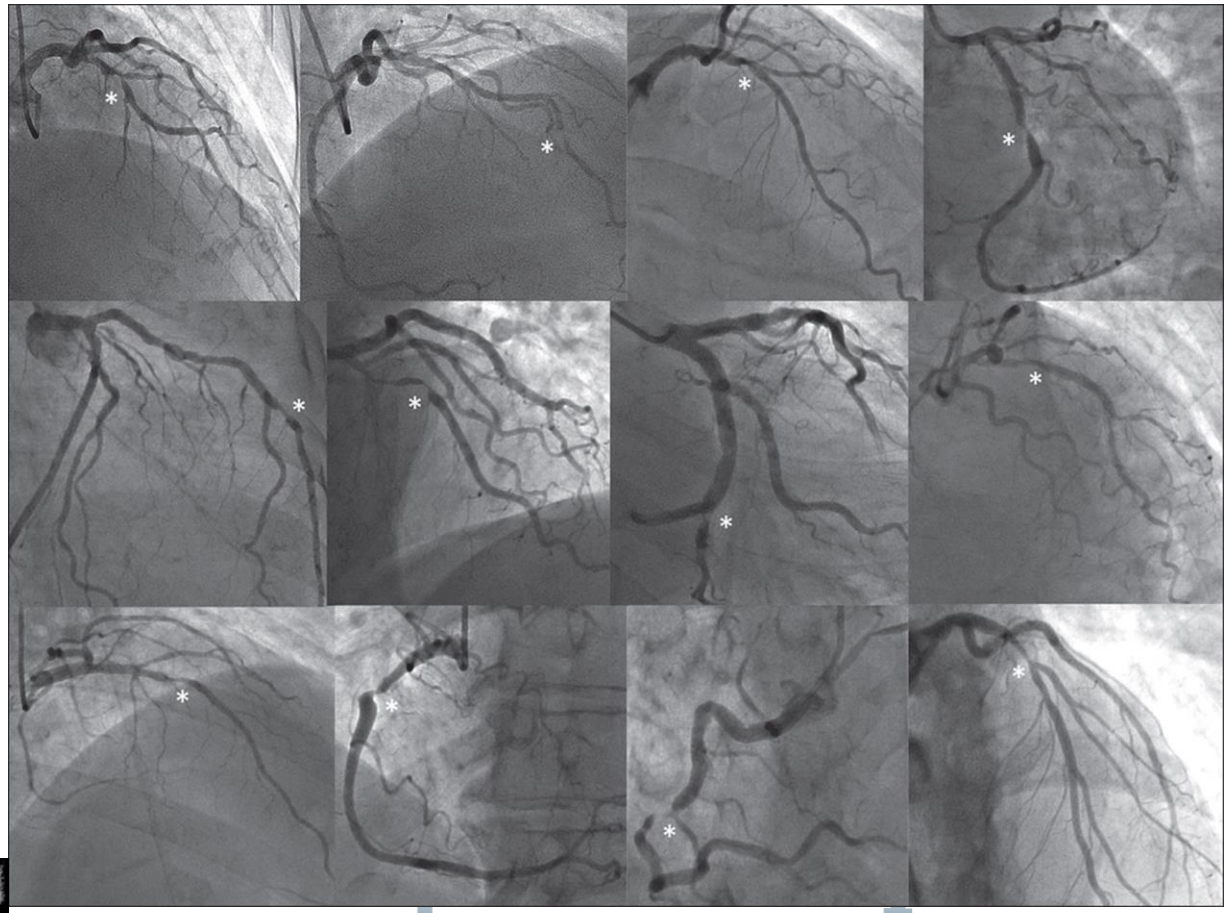
# COURAGE TRIAL

Kaplan-Meier Survival Curves




The NEW ENGLAND JOURNAL of MEDICINE

# ORBITA: Coronary angiograms of the first 12 consecutively randomized patients



*The Lancet* 2018 391, 31-40DOI: (10.1016/S0140-6736(17)32714-9)

# Effects of PCI on Primary and Secondary Outcomes in ORBITA

| | PCI | Placebo |
|---|---|---|
| **Exercise time (s)** | | |
| Patients assessed | 104 | 90 |
| Pre-randomisation | 528·0 (178·7) | 490·0 (195·0) |
| Follow-up | 556·3 (178·7) | 501·8 (190·9) |
| Increment (pre-randomisation to follow-up) | 28·4 (95% CI 11·6 to 45·1) | 11·8 (95% CI −7·8 to 31·3) |
| Difference in increment between groups | 16·6 (95% CI −8·9 to 42·0) | .. |
| p value | 0·200 | .. |
| **Time to 1 mm ST depression (s)** | | |
| Pre-randomisation | 479·7 (141·4) | 471·1 (128·7) |
| Patients assessed | 27 | 18 |
| Follow-up | 472·7 (129·1) | 470·1 (176·0) |
| Patients assessed | 23 | 21 |
| p value between groups | 0·164 | .. |
| **Peak oxygen uptake (mL/min)** | | |
| Patients assessed | 99 | 89 |
| Pre-randomisation | 1715·0 (638·1) | 1707·4 (567·0) |
| Follow-up | 1713·0 (583·7) | 1718·3 (550·4) |
| Increment (pre-randomisation to follow-up) | −2·0 (95% CI −54·1 to 50·1) | 10·9 (95% CI −47·2 to 69·0) |
| Difference in increment between groups | −12·9 (95% CI −90·2 to 64·3) | .. |
| p value | 0·741 | .. |
| **SAQ-physical limitation** | | |
| Patients assessed | 100 | 88 |
| Pre-randomisation | 71·3 (22·5) | 69·1 (24·7) |
| Follow-up | 78·6 (24·0) | 74·1 (24·7) |
| Increment (pre-randomisation to follow-up) | 7·4 (19·7; 95% CI 3·5 to 11·3) | 5·0 (21·2; 95% CI 0·5 to 9·5) |
| Difference in increment between groups | 2·4 (95% CI −3·5 to 8·3) | .. |
| p value | 0·420 | .. |
| **SAQ-angina frequency** | | |
| Patients assessed | 103 | 90 |
| Pre-randomisation | 63·2 (20·4) | 60·0 (25·1) |
| Follow-up | 74·4 (21·4) | 67·7 (22·1) |
| Increment (prerandomisation to follow-up) | 11·2 (20·3; 95% CI 7·2 to 15·1) | 7·7 (22·7; 95% CI 2·9 to 12·4) |
| Difference in increment between groups | 3·5 (95% CI −2·6 to 9·6) | .. |
| p value | 0·260 | .. |
| **SAQ-angina stability** | | |
| Patients assessed | 102 | 89 |
| Pre-randomisation | 64·7 (25·5) | 68·5 (24·3) |
| Follow-up | 60·5 (23·7) | 63·5 (25·6) |
| Increment (Pre-randomisation to follow-up) | −4·2 (33·4; 95% CI −10·7 to 2·4) | −5·1 (31·6; 95% CI −11·7 to 1·6) |
| Difference in increment between groups | 0·9 (95% CI −8·4 to 10·2) | .. |
| p value | 0·851 | .. |
| **EQ-5D-5L QoL** | | |
| Patients assessed | 103 | 89 |
| Pre-randomisation | 0·80 (0·21) | 0·79 (0·22) |
| Follow-up | 0·83 (0·21) | 0·82 (0·20) |
| Increment (pre-randomisation to follow-up) | 0·03 (0·14; 95% CI 0·00 to 0·06) | 0·03 (0·17; 95% CI 0·00 to 0·07) |
| Difference in increment between groups | 0·00 (95% CI −0·04 to 0·04) | .. |
| p value | 0·994 | .. |
| **Peak stress wall motion index score** | | |
| Patients assessed | 91 | 70 |
| Pre-randomisation | 1·08 (0·12) | 1·07 (0·11) |
| Follow-up | 1·02 (0·05) | 1·09 (0·14) |
| Increment (pre-randomisation to follow-up) | −0·05 (0·12; 95% CI −0·08 to −0·03) | 0·02 (0·10; 95% CI −0·01 to 0·04) |
| Difference in increment between groups | −0·07 (95% CI −0·11 to −0·04) | .. |
| p value | <0·0001 | .. |
| **Duke treadmill score** | | |
| Patients assessed | 104 | 90 |
| Pre-randomisation | 4·24 (4·82) | 4·18 (4·65) |
| Follow-up | 5·46 (4·79) | 4·28 (4·98) |
| Increment (pre-randomisation to follow-up) | 1·22 (4·36; 95% CI 0·37 to 2·07) | 0·10 (5·70; 95% CI −0·99 to 1·19) |
| Difference in increment between groups | 1·12 (95% CI −0·21 to 2·45) | .. |
| p value | 0·101 | .. |

- No effect for primary outcome (Exercise time)
- No effect for 7 of 8 secondary outcome measures
- Effect for wall motion significant

# Logic

ibtn
international
behavioural
trials network

- Heart disease is the leading cause of death
- High cholesterol predicts death from heart disease
- Dietary habits contribute to high serum cholesterol
- National programs to modify diet will reduce deaths from heart disease

## Harcomb et al, 2015
## 2467 males participated in six dietary trials: five secondary prevention studies and one including healthy participants

ibtn
international
behavioural
trials network

- 2467 males participated in six dietary trials: five secondary prevention studies and one including healthy participants.
- All cause mortality: The risk ratio (RR) from meta-analysis was 0.996 (95% CI 0.865 to 1.147).
- CHD Mortality: 207 and 216 deaths in the intervention and control groups, respectively. The RR was 0.989 (95% CI 0.784 to 1.247).

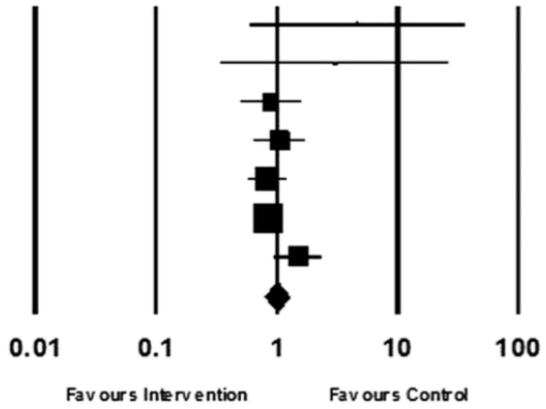
Harcombe Z,Baker JS, Cooper SM, et al. Evidence from randomised controlled trials did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review and meta-analysis. Open Heart 2015;2:e000196. doi:10.1136/openhrt-2014- 000196

# Harcombe et al (2015). Trials on dietary guidelines and heart disease deaths

ibtn
international
behavioural
trials network

## Dietary Intervention & Heart Deaths

| Study name | Risk ratio | Lower limit | Upper limit | Heart Deaths / Total: Intervention | Heart Deaths / Total: Control |
|---|---|---|---|---|---|
| Rose Corn Oil (1965) | 4.643 | 0.580 | 37.149 | 5 / 28 | 1 / 26 |
| Rose Olive Oil (1965) | 3.000 | 0.333 | 26.992 | 3 / 26 | 1 / 26 |
| Research Committee Low-Fat (1965) | 0.891 | 0.490 | 1.620 | 17 / 123 | 20 / 129 |
| MRC Soybean Oil (1968) | 1.053 | 0.634 | 1.748 | 27 / 199 | 25 / 194 |
| LA Veterans Dayton (1969) | 0.816 | 0.552 | 1.206 | 41 / 424 | 50 / 422 |
| Leren, Oslo heart study (1970) | 0.840 | 0.669 | 1.056 | 79 / 206 | 94 / 206 |
| Woodhill, Sydney heart study (1978) | 1.501 | 0.930 | 2.425 | 35 / 221 | 25 / 237 |
| | 0.989 | 0.784 | 1.247 | | |




Harcombe Z,Baker JS, Cooper SM, et al. Evidence from randomised controlled trials did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review and meta-analysis. Open Heart 2015;2:e000196. doi:10.1136/openhrt-2014- 000196

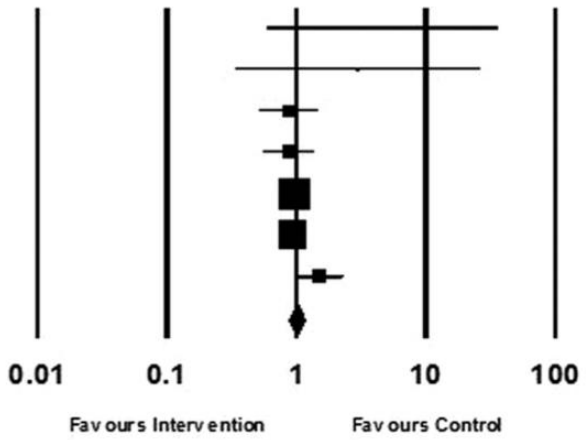
# Harcombe et al (2015). Trials on dietary guidelines and all cause deaths

ibtn
international
behavioural
trials network

## Dietary Intervention & All Deaths

| Study name | Risk ratio | Lower limit | Upper limit | All Deaths / Total: Intervention | All Deaths / Total: Control |
|---|---|---|---|---|---|
| Rose Corn Oil (1965) | 4.643 | 0.580 | 37.149 | 5 / 28 | 1 / 26 |
| Rose Olive Oil (1965) | 3.000 | 0.333 | 26.992 | 3 / 26 | 1 / 26 |
| Research Committee Low-Fat (1965) | 0.874 | 0.510 | 1.499 | 20 / 123 | 24 / 129 |
| MRC Soybean Oil (1968) | 0.881 | 0.550 | 1.411 | 28 / 199 | 31 / 194 |
| LA Veterans Dayton (1969) | 0.978 | 0.834 | 1.148 | 174 / 424 | 177 / 422 |
| Leren, Oslo heart study (1970) | 0.935 | 0.773 | 1.131 | 101 / 206 | 108 / 206 |
| Woodhill, Sydney heart study (1978) | 1.494 | 0.953 | 2.342 | 39 / 221 | 28 / 237 |
| | 0.996 | 0.865 | 1.147 | | |

Risk ratio and 95% CI




Harcombe Z,Baker JS, Cooper SM, et al. Evidence from randomised controlled trials did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review and meta-analysis. Open Heart 2015;2:e000196. doi:10.1136/openhrt-2014- 000196

# Today's NEJM

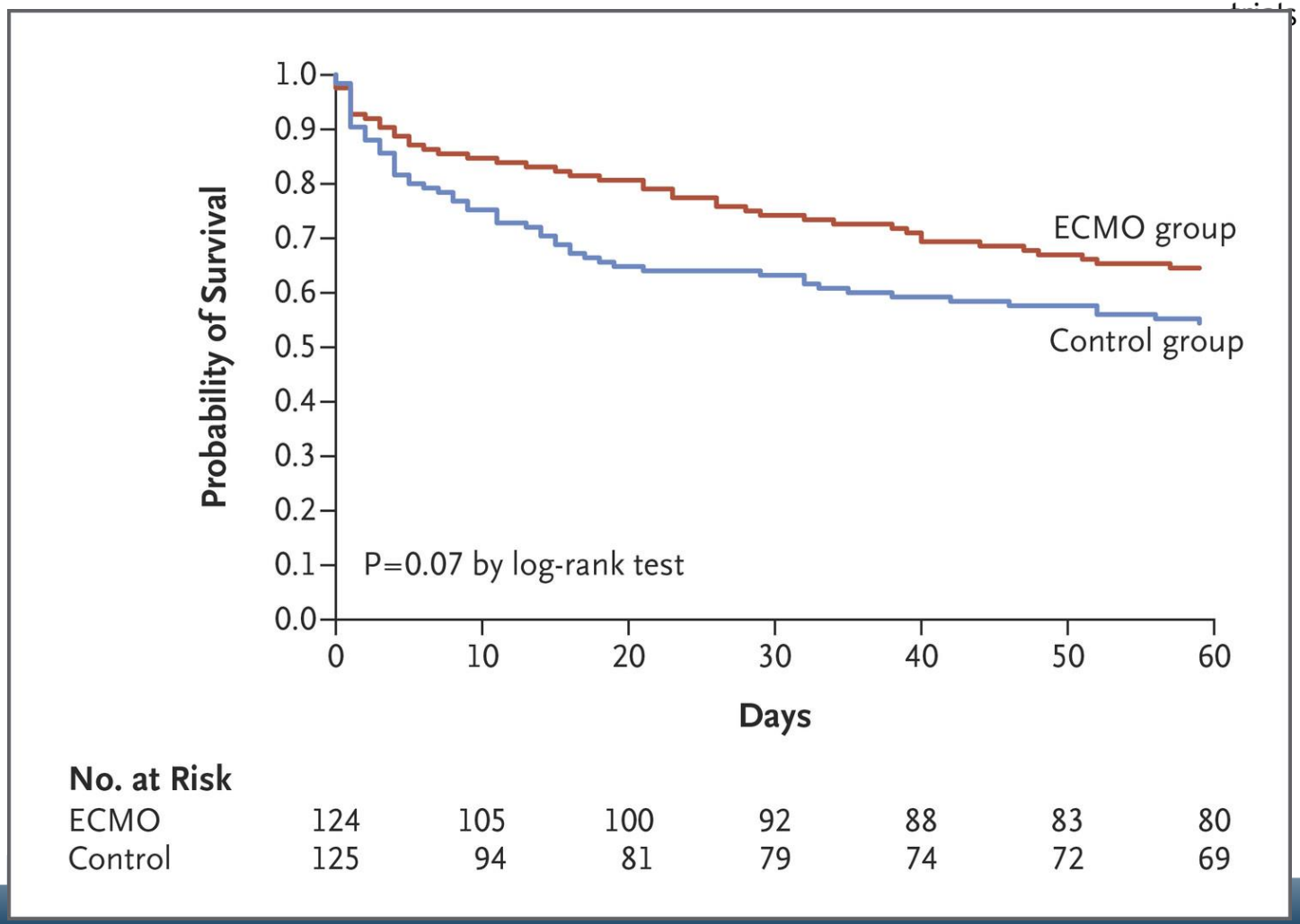
ibtn
international
behavioural
trials network

- International clinical trial randomly assigned patients with very severe ARDS to
  - receive immediate venovenous ECMO (ECMO group) or
  - continued conventional treatment (control group)
  - The primary end point was mortality at 60 days

Combess et al N Engl J Med 2018; 378:1965-1975

# Today's NEJM : Kaplan–Meier Survival Estimates in the Intention-to-Treat Population during the First 60 Days of the Trial.

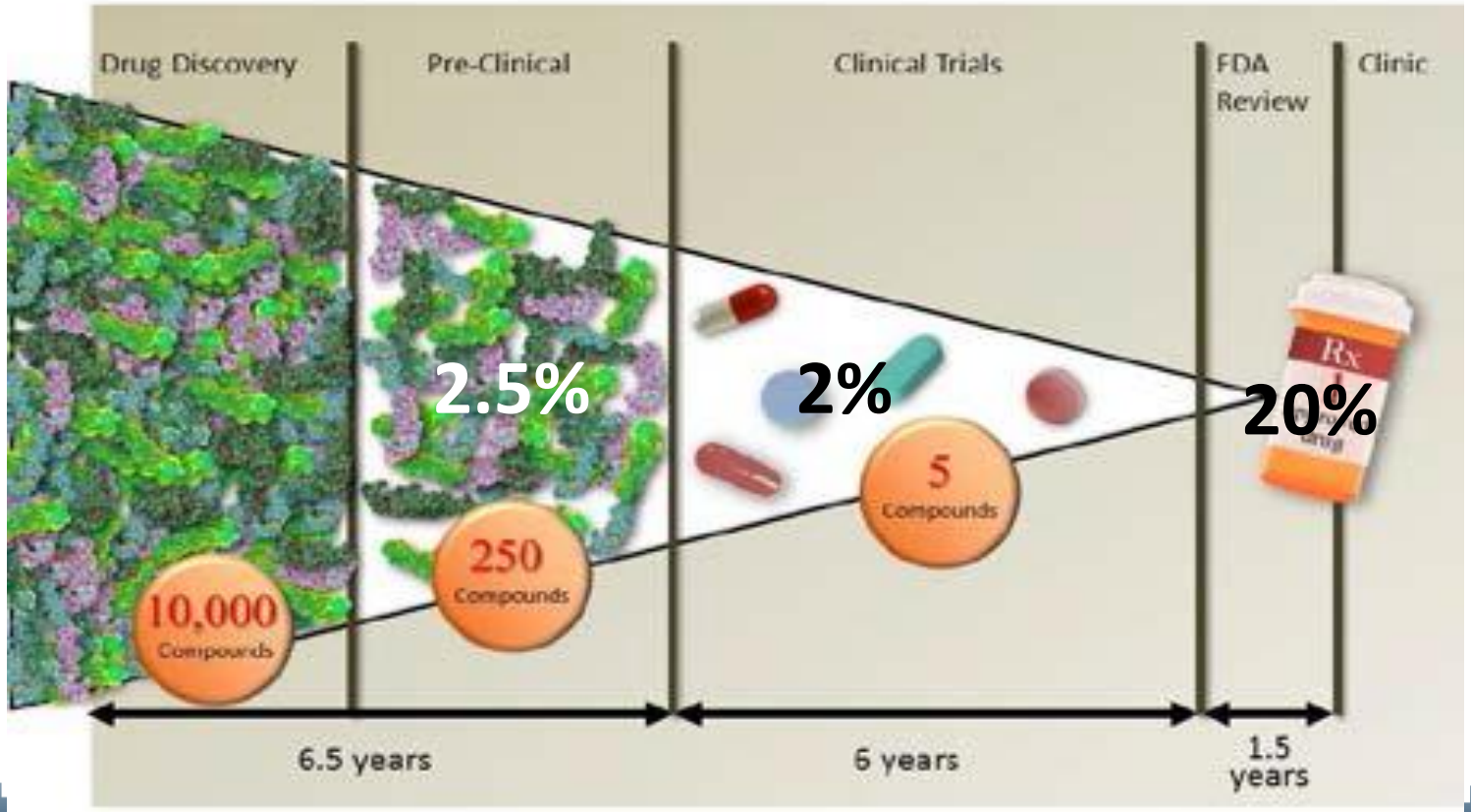
ibtn international behavioural trials network



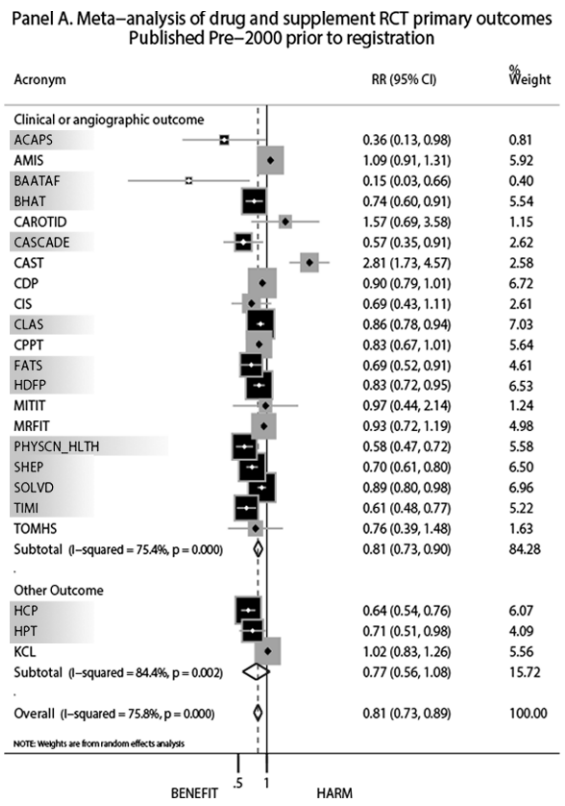

A Combes et al. N Engl J Med 2018;378:1965-1975.

ibtn
international
ioural
etwork

# Therapeutic Development Pipeline



# How often are trials null for primary outcomes?: Since 2000, most of the time

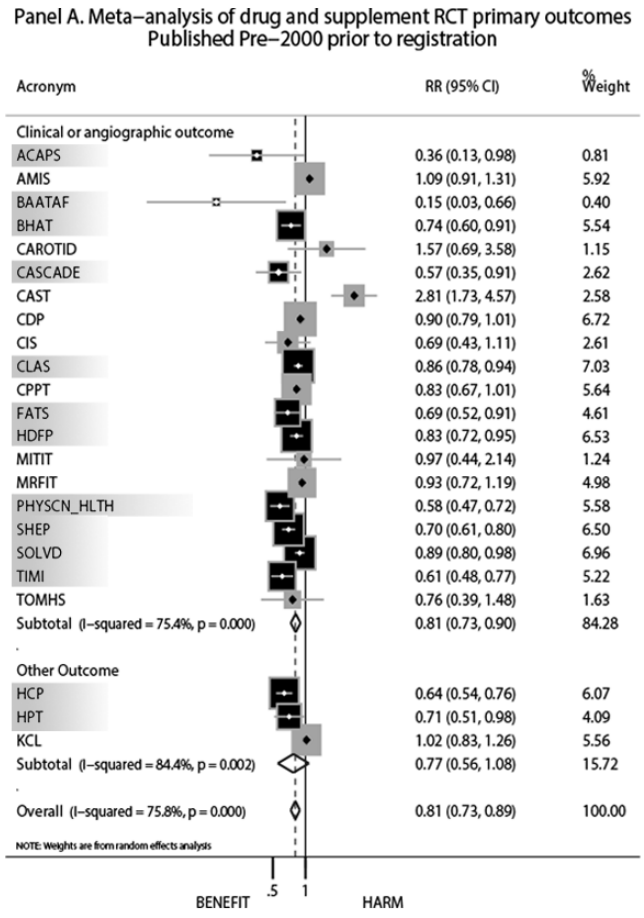


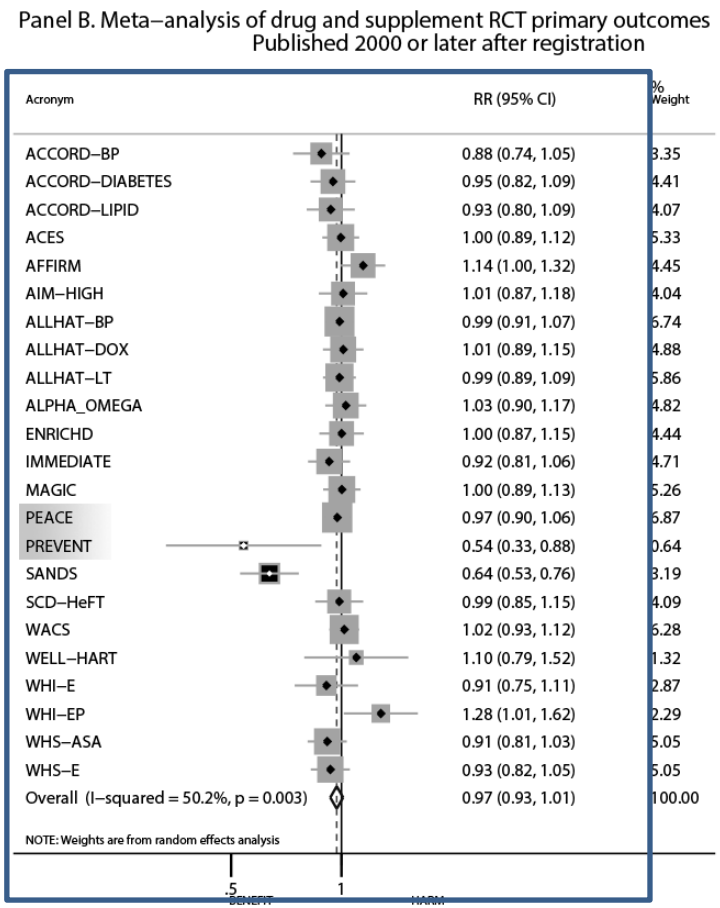

- FDA Modernization ACT of 1997
- Created high transparency reporting standards
- Initiated Clinical Trials.gov
- NHLBI required all clinical trials grantees to register by 2000

(Kaplan & Irvine PLOS One Aug 5, 2015)

# How often are trials null for primary outcomes?: Since 2000, most of the time

ibtn international behavioural trials network




(Kaplan & Irvine PLOS One Aug 5, 2015)

# Sweeping plan to revamp biomedical innovation: The 21st Century Cures Act

ibtn
international
behavioural
trials network

- A U.S. House of Representatives panel today released a widely anticipated proposal for speeding, the development of new medical treatments. The massive, 393-page document, dubbed the 21st Century Cures Act….


# Sweeping plan to revamp biomedical innovation: The 21st Century Cures Act includes controversial ideas for NIH

ibtn
international
behavioural
trials network


- Focus on Surrogate endpoints
  - Speeds up process
- Dormant Therapies Act, takes aim at drugs for complex diseases, such as Alzheimer's, that are particularly time-consuming to develop and test.

kids
FOR THE
CURE®

# Public Policy: Zuckerman reviewed all recent FDA cancer drug approvals.

ibtn
international
behavioural
trials network

- Among 54 new drug licenses for cancer therapuetics, 36 had been approved on the basis of surrogate markers. Typically tumor shrinkage was used as a surrogate for prolonging life
- Among the 36 drugs approved on the basis of surrogates,
  - For 31 of 36 there was no evidence of improved life expectancy.
  - 15 of the 18 drugs did not improve quality of life and the remaining two drugs actually made quality-of-life worse
  - One of the drugs that reduces quality of life and does not increase life expectancy is sold for approximately $170,000 per person per year.

Zuckerman, D et al JAMA Internal Med 2016

# How are surrogate endpoints treated in public policy?

ibtn
international
behavioural
trials network

- USPSTF requires evidence relevant to outcomes rather than surrogate markers
- Very few papers in the behavioral medicine literature report health outcomes, most use surrogate markers
- FDA was trending toward requiring health outcomes, but 21st Century Cures Act will allow a return to approvals based on surrogate markers
- Trump administration argues that relaxing FDA standards will lower drug prices.

# Final Teaser

ibtn
international
behavioural
trials network

- Is a cancer diagnosis a health outcome?

# American Cancer Society On Women Who Question Screening

ibtn
international
behavioural
trials network

## Crazy not to be screened

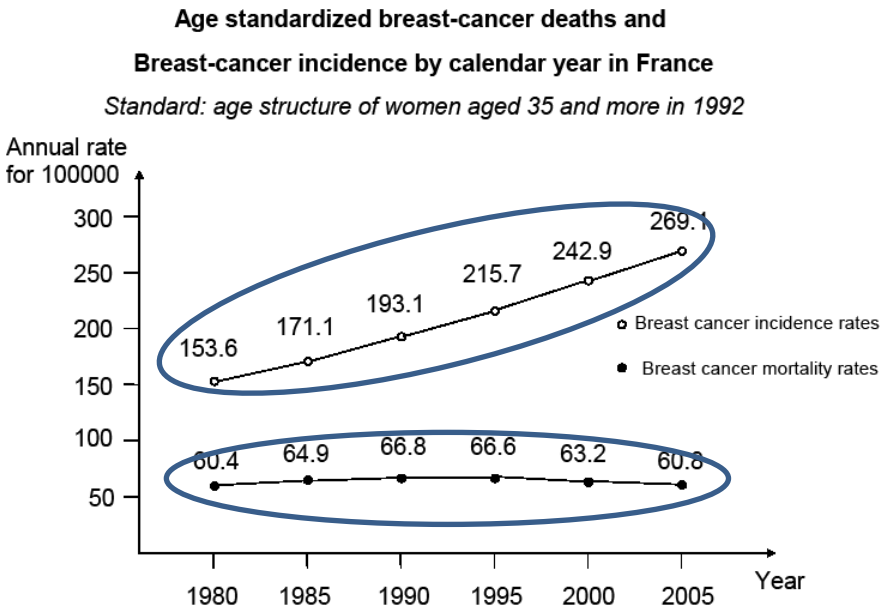

## National Poll Results

- 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%

# The French Story (Junod, Kaplan, Olsen, Greenland, 2010)

ibtn
international
behavioural
trials network

- Screening increases the number of cases detected.
- But, screening has not effect on number of deaths.
- Adjusted for population size, there has been no change in death rates for more than 50 years.

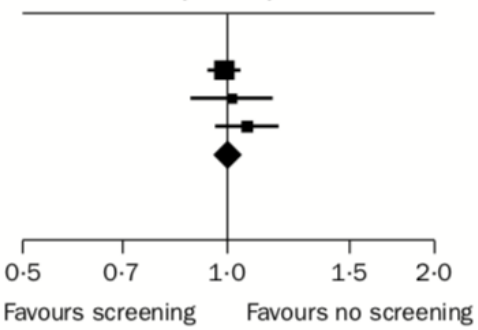


# Cochrane Review of Mammography Trials for All Cause Mortality

ibtn
international
behavioural
trials network

| Study | Screened<br>Number of deaths/ number of women | Not screened<br>Number of deaths/ number of women | Relative risk* (95% CI) | Weight (%) | Relative risk* (95% CI) |
|---|---|---|---|---|---|
| Malmö 1976 | 2537/21 088 | 2593/21 195 | | 70·08 | 0·98 (0·93–1·04) |
| Canada 1980a | 418/25 214 | 414/25 216 | | 11·22 | 1·01 (0·88–1·16) |
| Canada 1980b | 734/19 711 | 690/19 694 | | 18·70 | 1·06 (0·96–1·18) |
| Subtotal | 3689/66 013 | 3697/66 105 | | 100·00 | 1·00 (0·96–1·05) |

Test for heterogeneity: $\chi^2$=1·80, df=2 (p=0·41)
Test for overall effect: z=0·05 (p=0·96)

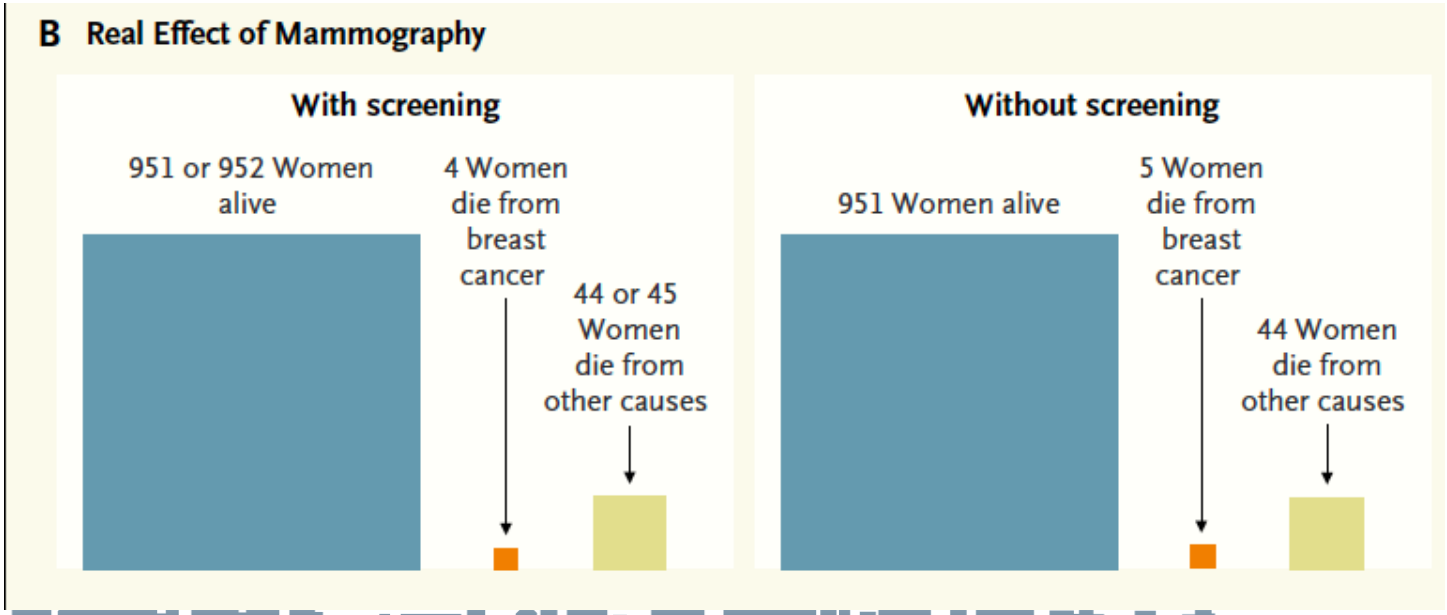



**All-cause mortality in medium-quality screening trials after 13 years**

*Fixed-effects model.

# Cancer Screening: A View from the Swiss Medical Board

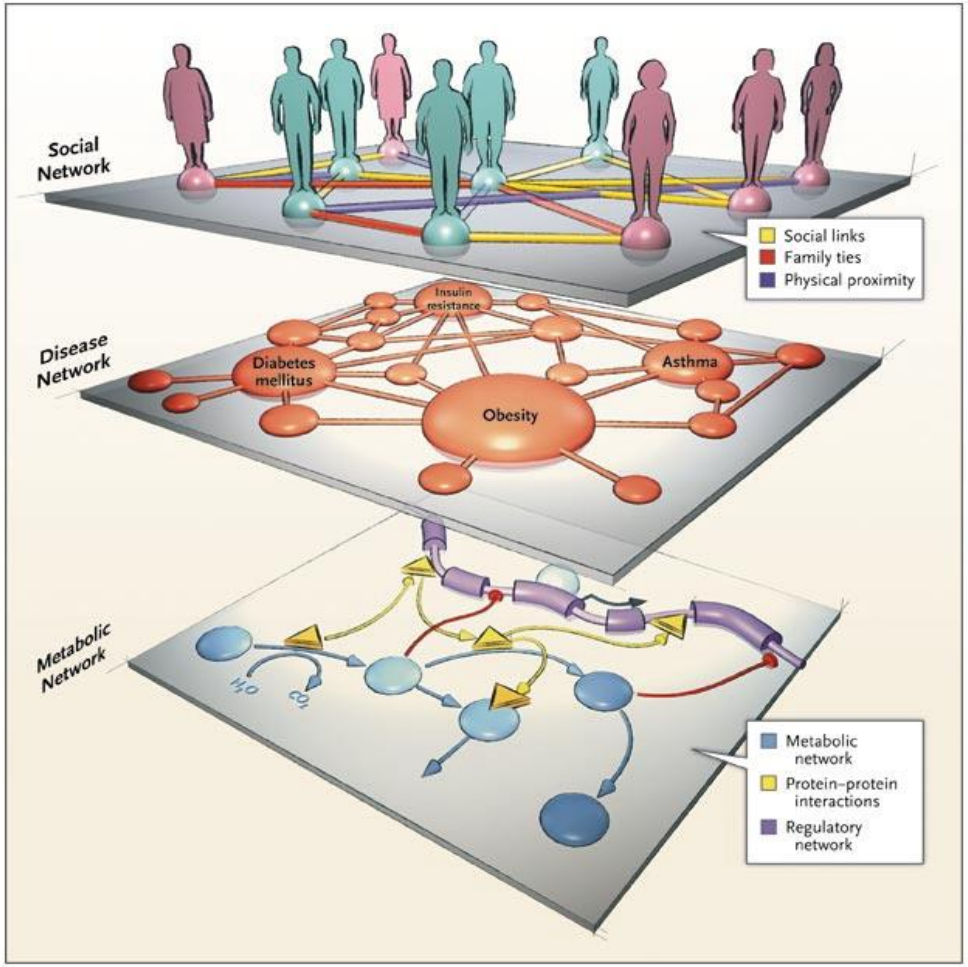
The actual effect of mammography screening on breast-cancer deaths, with numbers calculated from breast-cancer mortality data for 2008 from the National Cancer Institute and U.S. mortality statistics for 2008, assuming a relative risk reduction of 20% for breast-cancer mortality in women invited to undergo screening




Biller-Andorno &r Jüni . NEJM April 16, 2014.

# Complex Networks of Direct Relevance to Network Medicine

ibtn
international
behavioural
trials network




Barabási A. N Engl J Med 2007;357:404-407.

The NEW ENGLAND JOURNAL of MEDICINE

# Conclusions

ibtn
international
behavioural
trials network

- There are only two important outcomes in health care
  - Length of Life
  - Quality of life
- Blood pressure, cholesterol, cortisol, CRP…. are not outcomes, they are surrogate endpoints
- Surrogate end points are meaningful only when shown to be associated with outcomes
- Behavioral medicine needs to shift focus of attention away from surrogate markers and toward outcomes.

# What Went Wrong?

ibtn
international
behavioural
trials network

- Goal of health care is to increase length of life and quality of life
- Human bodies rarely work like precise machines
- Medications typically do not have just one biological effect
  - They often create cascades of compensatory reactions
  - Measuring single surrogate measures often offers an incomplete picture