The Medical-Industrial Complex

Kenneth Brummel-Smith, MD
Charlotte Edwards Maguire Professor of Geriatrics
Florida State University College of Medicine

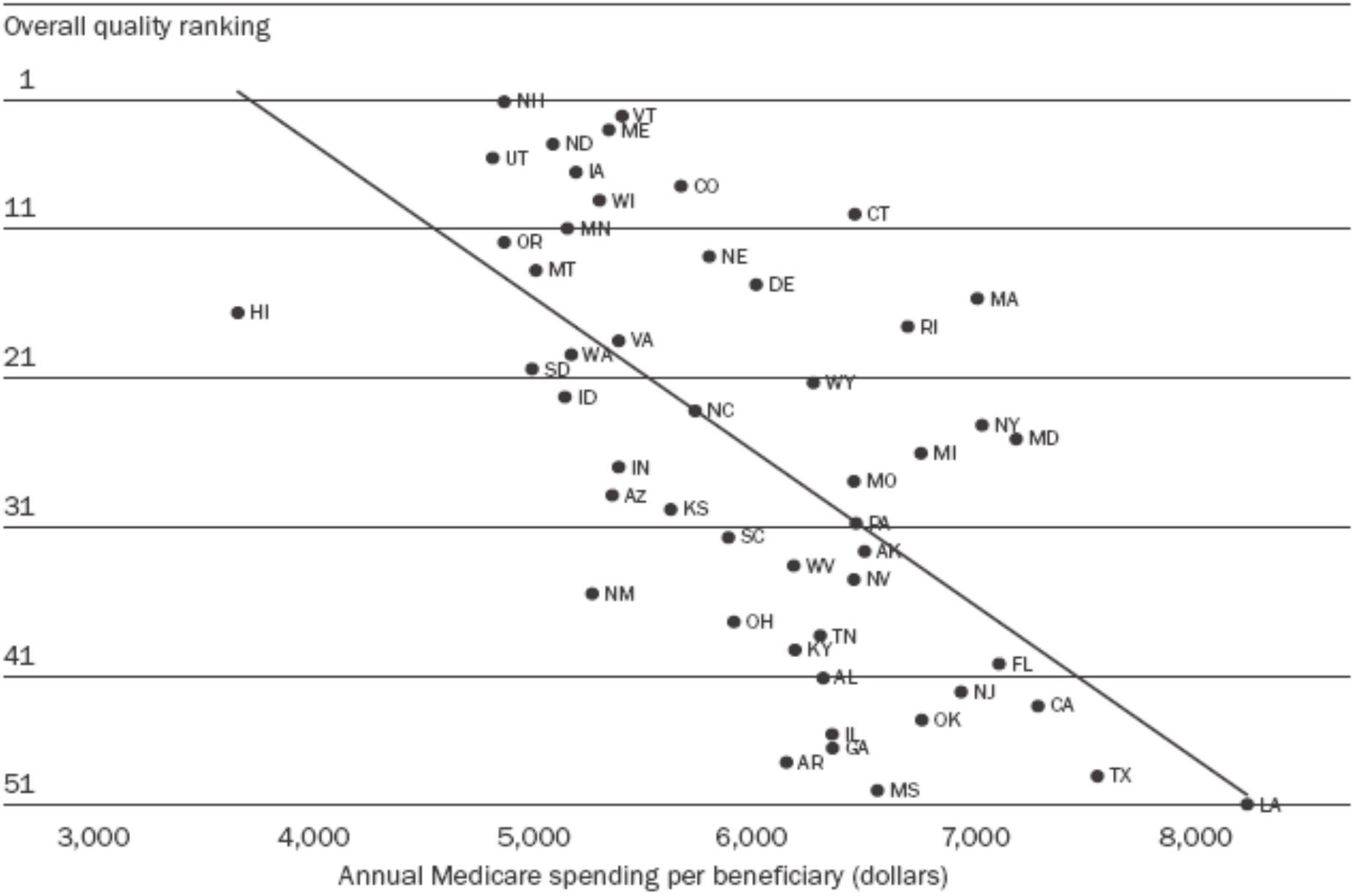
Special Thanks

- Marcia Angell
- John Abramson
- No Free Lunch

Delirium (R41.0):# Delirium (R41.0):

One person's drugs

Relationship Between Quality And Medicare Spending, As Expressed By Overall Quality Ranking, 2000–2001



Katherine Baicker and Amitabh Chandra. Medicare Spending, The Physician Workforce, And Beneficiaries' Quality Of Care
W E B E X C L U S I V E 07 April 2004


PRIMED
Pri-MedEast2004
Ride
the CREST™
at Booth #539
CRESTOR®
rosuvastatin calcium
AstraZeneca


Cialis
(tadalafil) tablets
PRIMED
Pri-MedEast 2004
Cialis
(tadalafil) tablets
PRIMED
Pri-MedEast 2004
Cialis
(tadalafil) tablets
Cialis
(tadalafil) tablets


PRESCRIBERS MED
400
300
200
PREVACID
LANSOPRAZOLE
actos
pioglitazone HCl
MERCK
SINGULAIR
ZOCOR
Zetia
ZETIA
Next
Fulfillment Area
WebMD
Works.
MASSACHUSETTS
MEDICAL SOCIETY
LifeExtension
Your Passport to the Future
www.lef.org
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BD
Cialis
Pfizer
ADVICOR
take
look


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RESTROOMS
this way
Pfizer
Visit us at Booth 715

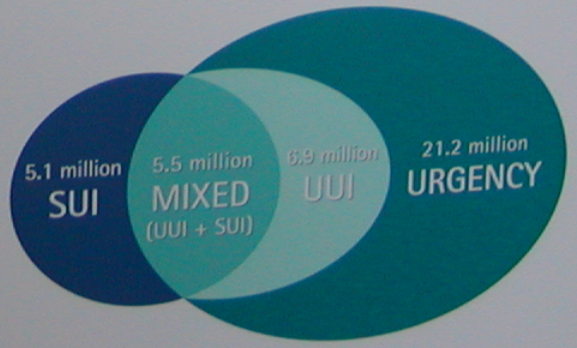

WOMEN

WOMEN

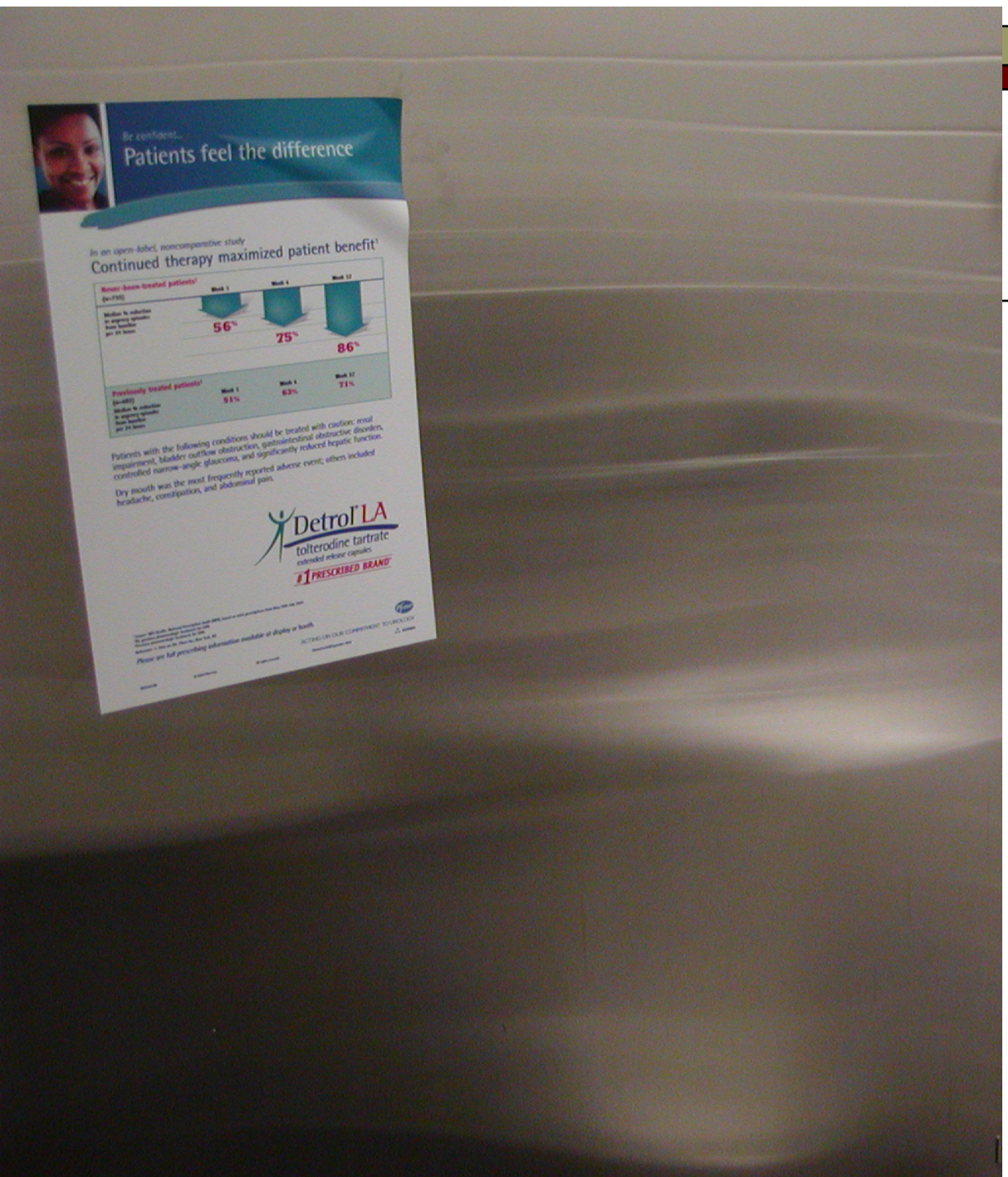
Trust DETROL LA–

The #1 prescribed OAB brand*

Millions of Americans† suffer from urinary incontinence and urgency[1]



SUI = Stress urinary incontinence; UUI = Urge urinary incontinence.


Be confident...
Patients feel the difference
In an open-label, noncomparative study
Continued therapy maximized patient benefit†
Never-been-treated patients†
Week 1
Week 4
Week 12
56%
75%
86%
Previously treated patients†
Week 1
51%
Week 4
63%
Week 12
71%
Patients with the following conditions should be treated with caution: renal impairment, bladder outflow obstruction, gastrointestinal obstructive disorders, controlled narrow-angle glaucoma, and significantly reduced hepatic function.
Dry mouth was the most frequently reported adverse event; others included headache, constipation, and abdominal pain.
Detrol LA
tolterodine tartrate
extended release capsules
#1 PRESCRIBED BRAND
Please see full prescribing information available at display or booth.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Detrol LA
tolterodine tartrate
extended release capsules
#1 PRESCRIBED BRAND
Please see full prescribing information available at display or booth.
ACTING ON OUR COMMITMENT TO UROLOGY
SLOAN

Prevalence of the Problem

- Medication errors each year:
  - 7000 deaths
  - 95,000 hospital admissions
  - 700,000 emergency visits
  - 3,000,000 office visits
- 30% more money spent on treating errors than on medications themselves
- 5th most common cause of death in US

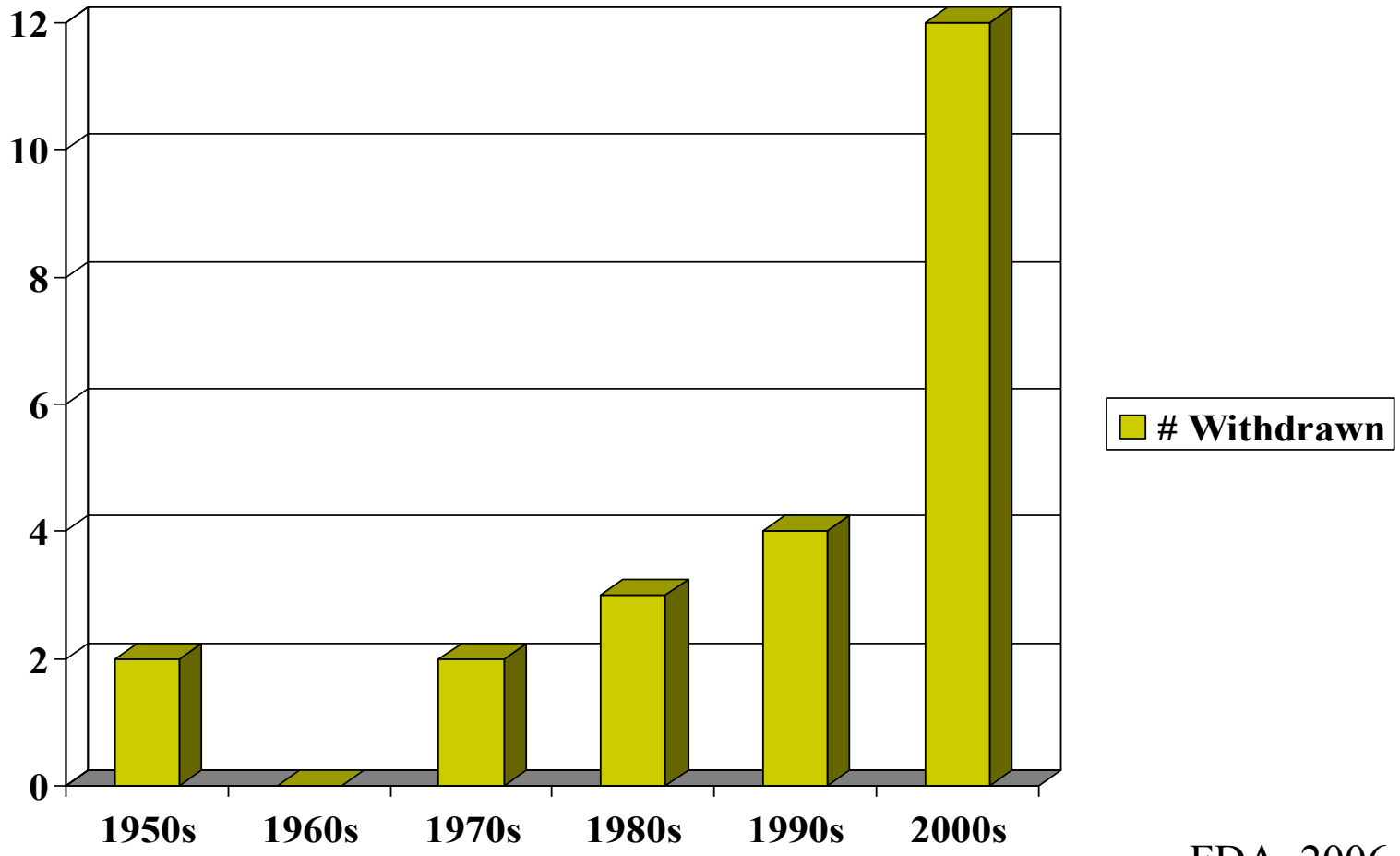
IOM, To Err is Human, 2000

Problem of New Drugs

- In last 10 years 16 name-brand drugs have been withdrawn for safety reasons
  - 50% of withdrawals happen in the first 2 years
- In 20 years, 2 generic drugs have been withdrawn for safety reasons
- Half of all "Black Box" warnings occur within 7 years of release of a new drug

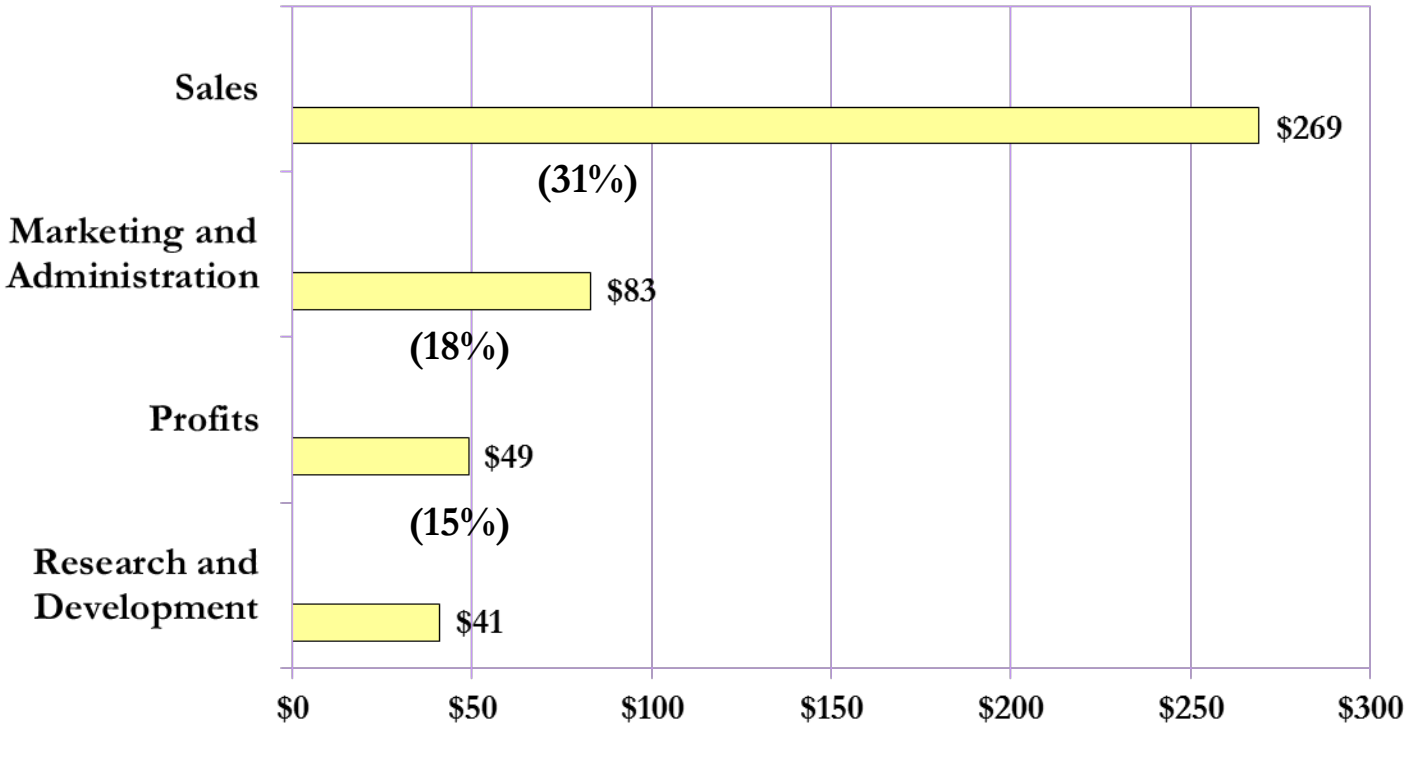
FDA Medwatch, 2006
Lasser KE, JAMA 2002

Drugs Withdrawn



FDA, 2006

*FORTUNE 500 U.S. DRUG COMPANIES 2008 SALES AND EXPENSES



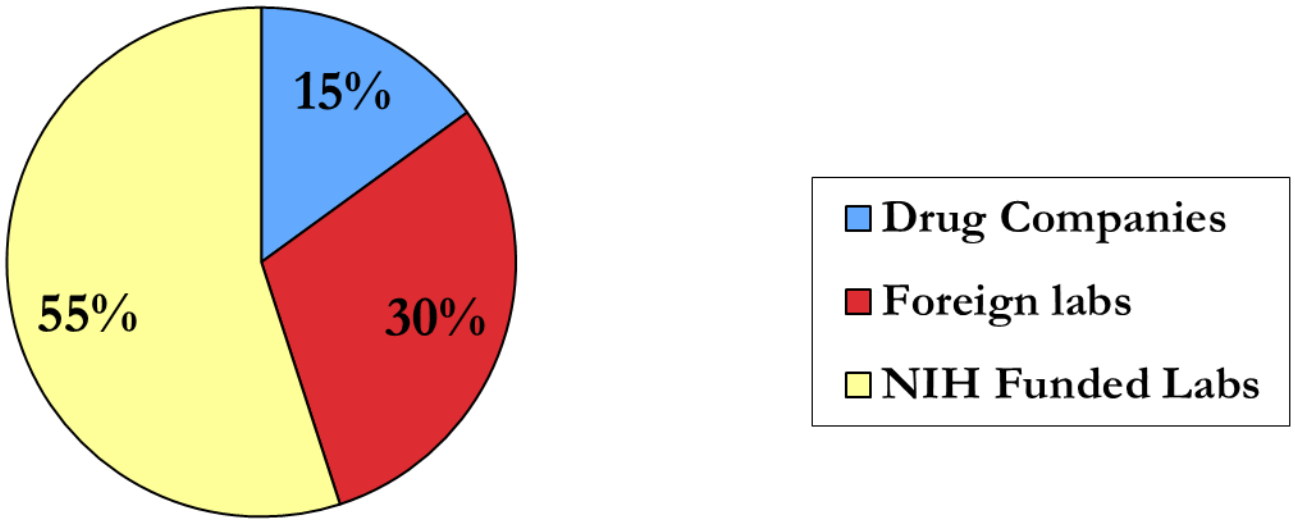
Average drug company profits 18% v. 0.9% for all Fortune 500 industries

***Johnson&Johnson, Pfizer, Abbott, Merck, Wyeth, Bristol-Myers Squibb, Lilly, Schering-Plough, Amgen, Gilead Sciences**

Source: *Fortune* 5/4/09; company annual reports

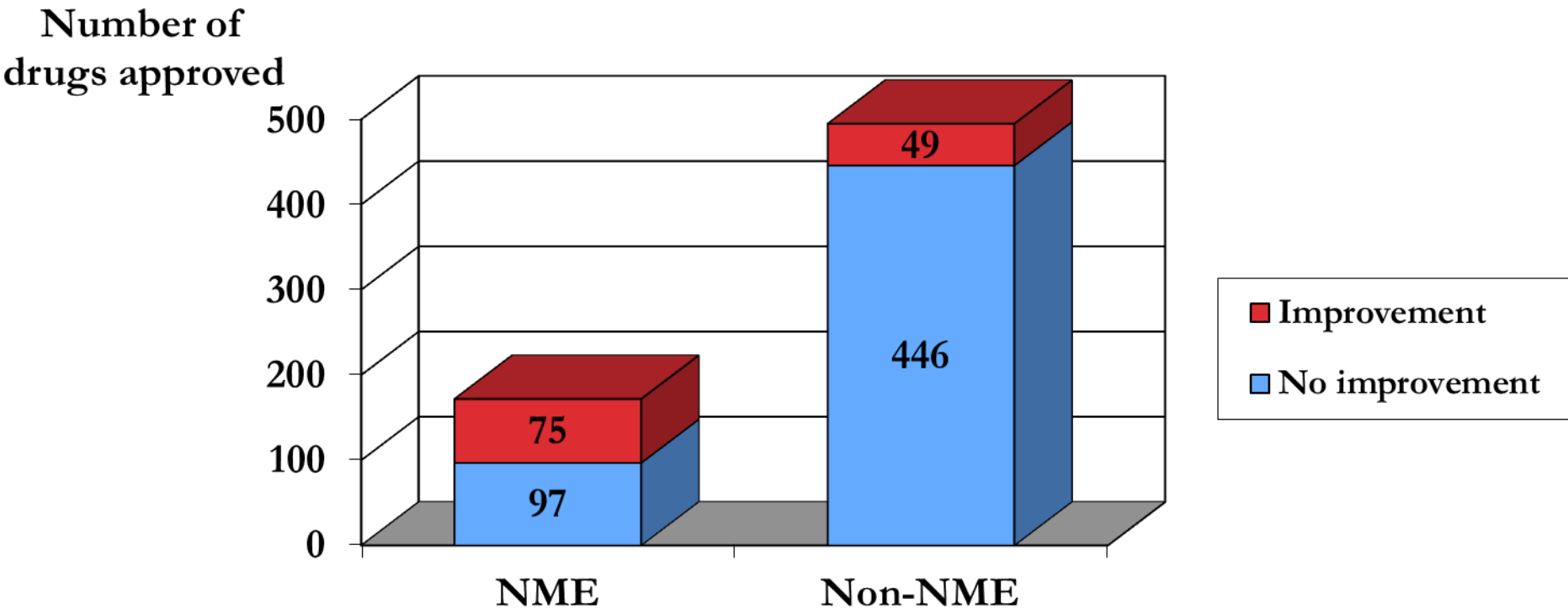
Innovation:

Published Research Leading to Drugs



Sources: Internal NIH document available from Public Citizen;
also Zinner, Health Affairs, Sept-Oct 2001; also Boston Globe 4/5/98

New Drug Approvals 2000-2007 (8 years)



667 new drug approvals

Only 75 (11%) were both Novel Medical Entities (NME) and improvements over existing drugs

Tricking Us With "New Drugs"

- Nexium (AstraZenica) – esomeprazole, for heartburn (GERD) – the "purple pill"
  - 2001 – came on market
  - Same time Prilosec (omeprazole) was going off patent
  - Not chemically different than omeprazole
  - Marketed it as better by comparing it to lower doses of omeprazole (40mg versus 20mg)

Other Tricks

- Clarinex and Claritin
  - Claritin (loratidine) – ($12 for 365 pills – OTC)
  - Clarinex (desloratidine) – ($233 for 30 pills)
- Prozac and Serafem
  - Prozac ($122 for 30 pills)
  - fluoxetine ($14 for 30 pills)
  - Sarafem ($67 for 7 pills) – “premenstrual dysphoric disorder”

95 of 170 contributors to DSM-IV had drug company ties – Cosgrove, Psychother Psychosom 2006:75:154-160

Antidepressant Tricks (SSRI)

- 74 FDA-registered studies
  - 31% were not published
- 37 studies with positive results were published
  - One positive study was not published
- 22 studies with negative results were not published
- 14 negative studies put a positive spin on it

Turner EH, NEJM, 2008;358:252-260

Study Design Tricks

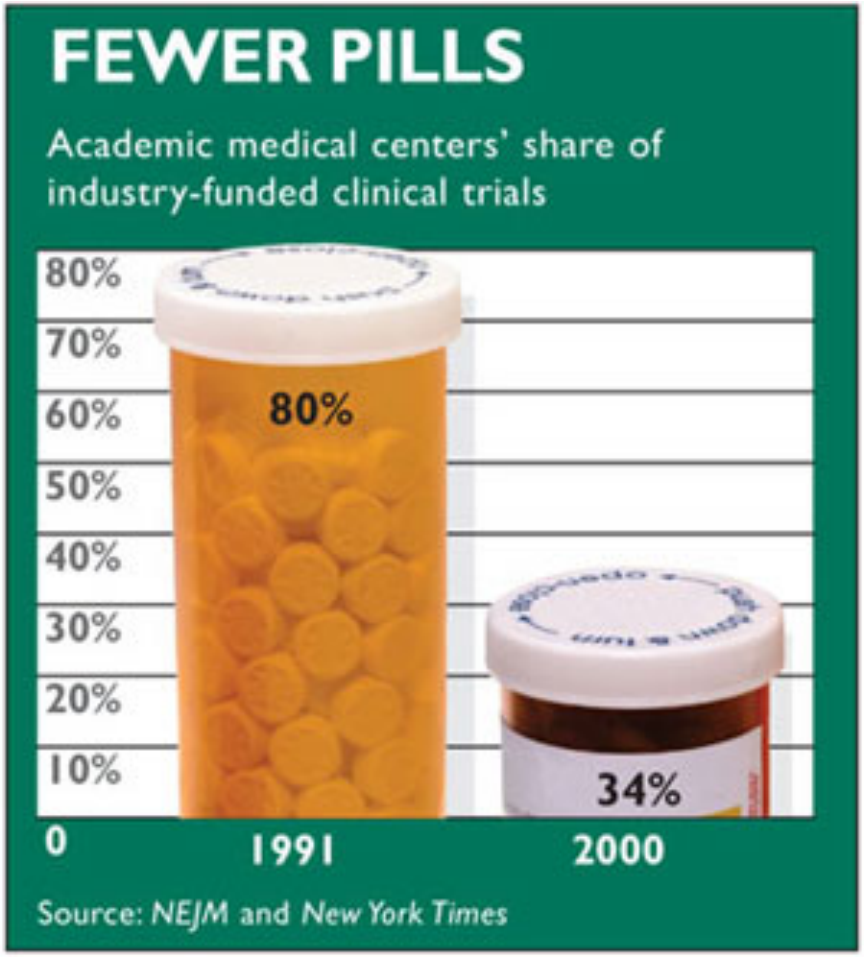
- Comparing the new drug to placebo when there are good drugs for the problem
  - Therefore, it is possible to get a drug approved by the FDA that is less effective (or more problematic) than existing drugs!
- Comparing new drug to an ineffective dose of the other drug

Contract Research Organizations

- Pharma designs the study, performs the analysis, writes the papers, and decides whether to publish
- PHARMA – "As owners of the study database, sponsors have discretion to determine who will have access to the database."

Steinbrook R. NEJM 2005;352:2160-2162

HARVARD
MAGAZINE



Craig Lambert, "Flasks of Cash: Doctored Research," November-December 2003

Academic Medicine Ties

- 2/3 hold equity interest in companies that sponsor research in their institution
- Faculty (and community physicians) are often paid consultants and on speakers bureaus
- Practice guidelines – 200 guidelines had more than 1/3 of the "experts" on the Pharma payroll

Taylor R, Nature 2005;437:1070-1071

JAMA

Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials

Comparison of Protocols to Published Articles

Results Overall, 50% of efficacy and 65% of harm outcomes per trial were incompletely reported…Eighty-six percent of survey responders (42/49) denied the existence of unreported outcomes despite clear evidence to the contrary.

Chan A-W, Hrobjartsson A, Haahr ME, et al, *JAMA. 2004;291:2457-2465*

JAMA

Empirical Evidence for Selective Reporting of Outcomes in Randomized Trials

Comparison of Protocols to Published Articles

Conclusions The reporting of trial outcomes is not only frequently incomplete but also biased and inconsistent with protocols. Published articles, as well as reviews that incorporate them, may therefore be unreliable and overestimate the benefits of an intervention.

Chan A-W, Hrobjartsson A, Haahr ME, et al, *JAMA. 2004;291:2457-2465*

JAMA

Association of Funding and Conclusions in Randomized Drug Trial

…trials funded by for-profit organizations were significantly more likely to recommend the experimental drug as treatment of choice (odds ratio, 5.3) compared with trials funded by nonprofit organizations.

Als-Neilsen B, Chen W, Gluud C, Kiaergard LL, *JAMA,* 2003; 290:921-928

JAMA

Association of Funding and Conclusions in Randomized Drug Trial

Conclusions in trials funded by for-profit organizations may be more positive due to biased interpretation of trial results. Readers should carefully evaluate whether conclusions in randomized trials are supported by data.

Als-Neilsen B, Chen W, Gluud C, Kiaergard LL, *JAMA,* 2003; 290:921-928

8 of 9 panel members had financial ties to the makers of statins

NCEP Report

Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines

- For moderately high-risk persons (2+ risk factors and 10-year risk 10% to 20%), the recommended LDL-C goal is <130 mg/dL; an LDL-C goal <100 mg/dL is a therapeutic option on the basis of available clinical trial evidence…

Third Report of the National Cholesterol Education Program (NCEP)

In recent trials, statin therapy reduced risk for CHD in…women, in those with or without heart disease…
(Table II.2–3)

Adapted from NCEP Report, 2001

Third Report of the National Cholesterol Education Program (NCEP)

Table II.2–3. CHD Risk Reduction (RR) in Cholesterol Trial Subgroups

CHD Risk Reduction in Cholesterol Trial Subgroups				
Trait	**Subgroup**	**N**	**Mean RR**	**Trials†**
Gender	Male	21651	32%	AFCAPS, POSCH, CARE, LIPID,
	Female	4147	34%	PLAC1, 4S, CCAIT

Adapted from NCEP Report, 2001

Third Report of the National Cholesterol Education Program (NCEP)

Table VIII.2–1. Special Considerations for Cholesterol Management in Women (Ages 45–75 years)

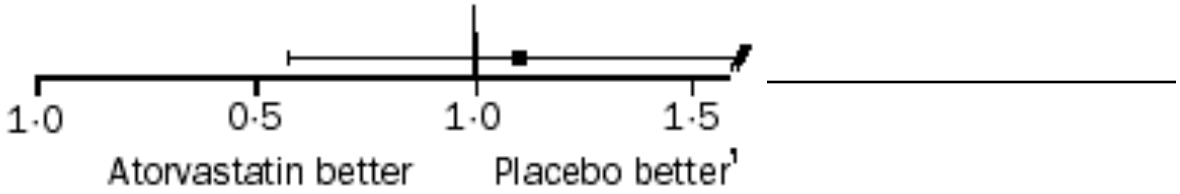
Risk Level	Special Considerations
Multiple (2+) risk factors 10-year risk 10–20% LDL goal <130 mg/dL	■ Clinical trials of LDL lowering generally are lacking for this risk category; rationale for therapy is based on extrapolation of benefit from men of similar risk

WOMEN

ASCOT

Subgroups

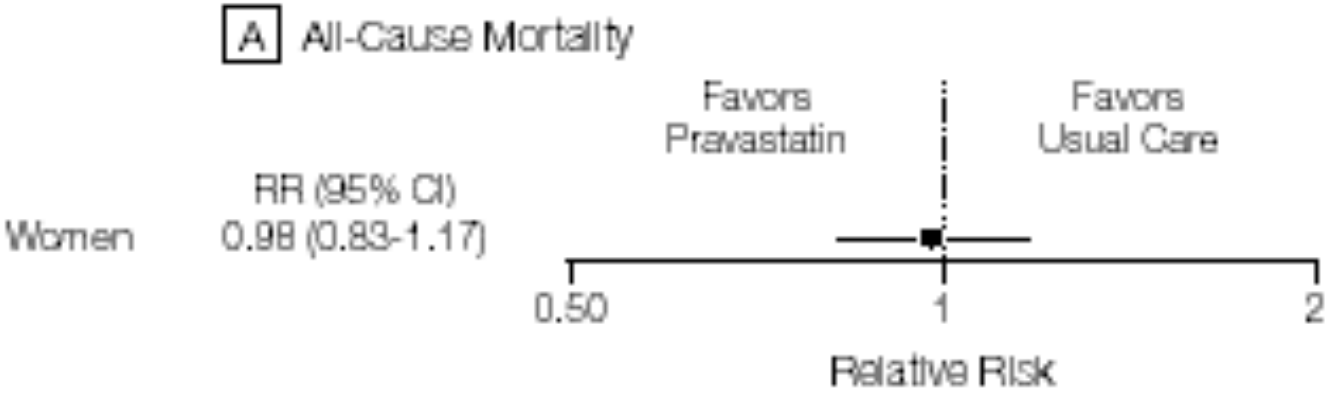
Female



PROSPER

	Placebo		Pravastatin		Hazard ratio (95% CI)
	Total number	Number with event (%)	Total number	Number with event (%)	
Sex					
Female	1505	194 (12·9)	1495	186 (12·4)	0·96 (0·79–1·18)
Male	1408	279 (19·8)	1396	222 (15·9)	0·77 (0·65–0·92)

ALLHAT-LLT



Third Report of the National Cholesterol Education Program (NCEP)

Selection of older persons for short-term, primary prevention

Approximately two-thirds of first major coronary events occur in persons ≥ 65 years…Recent clinical trials have revealed that aggressive LDL-lowering therapy is effective in reducing risk for CHD (see Table II.2–3).

Adapted from NCEP Report, 2001

Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines

Older Persons at High Risk Without Established CVD

The results of PROSPER…support the efficacy of statin therapy in older, high-risk persons without established CVD.

Articles

Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial

Incidence of Coronary Death, Non-Fatal MI,

Fatal and Non-Fatal Stroke

	Placebo		Pravastatin		Hazard ratio (95% CI)
	Total number	Number with event (%)	Total number	Number with event (%)	
Previous vascular disease†					
No					
Yes					

*p for interaction values for heterogeneity of treatment across subgroups. †Any of stable angina or intermittent claudication, or stroke, transient ischaemic attack, myocardial infarction, arterial surgery, or amputation for vascular disease more than 6 months before study entry.

Table 3: **Incidence of primary end point, according to subgroup**

Lancet 2002; **360:** 1623–30.

Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial

Incidence of Coronary Death, Non-Fatal MI,

Fatal and Non-Fatal Stroke

	Placebo		Pravastatin		Hazard ratio (95% CI)
	Total number	Number with event (%)	Total number	Number with event (%)	
Previous vascular disease†					
No	1654	200 (12·1)	1585	181 (11·4)	0·94 (0·77–1·15)
Yes	1259	273 (21·7)	1306	227 (17·4)	0·78 (0·66–0·93)

*p for interaction values for heterogeneity of treatment across subgroups. †Any of stable angina or intermittent claudication, or stroke, transient ischaemic attack, myocardial infarction, arterial surgery, or amputation for vascular disease more than 6 months before study entry.

Table 3: **Incidence of primary end point, according to subgroup**

Lancet 2002; **360:** 1623–30.

Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial

First New Cancer Diagnoses by Site and Year

Site	Treatment	Year				Hazard ratio (95% CI)	p
		1 (placebo n=2869, pravastatin n=2839)	2 (placebo n=2729, pravastatin n=2704)	3 (placebo n=2622, pravastatin n=2584)	4 (placebo n=804, pravastatin n=814)		
Total	Placebo	58	70	50	21		
	Pravastatin	65	79	69	32	1·25 (1·04–1·51)	0·020

Numbers=first new cancers, by site. Number of individuals at risk shown in table header are those at the midpoint of each year of study. Hazard ratio for effect of treatment adjusted for the covariates in table 1.

Table 4: **First new cancer diagnoses by site and year**

Articles

Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial

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Table 4: **First new cancer diagnoses by site and year**

Lancet 2002; **360:** 1623–30.

Cholesterol Levels and Age.

RESULTS: The relationship between total cholesterol level and all-cause mortality was positive at age 40 years, negative at age 80 years, and negligible at ages 50 to 70 years. The relationship with CHD mortality was significantly positive at ages 40, 50, and 60 years but attenuated with age until the relationship was positive, but not significant, at age 70 years and negative, but not significant, at age 80 years.

Framingham data

Kronmal RA, Cain KC, Ye Z, Omenn GS. *Arch Intern Med*. 1993 May 10;153(9):1065-73.

LDL Cholesterol and Mortality in Older People

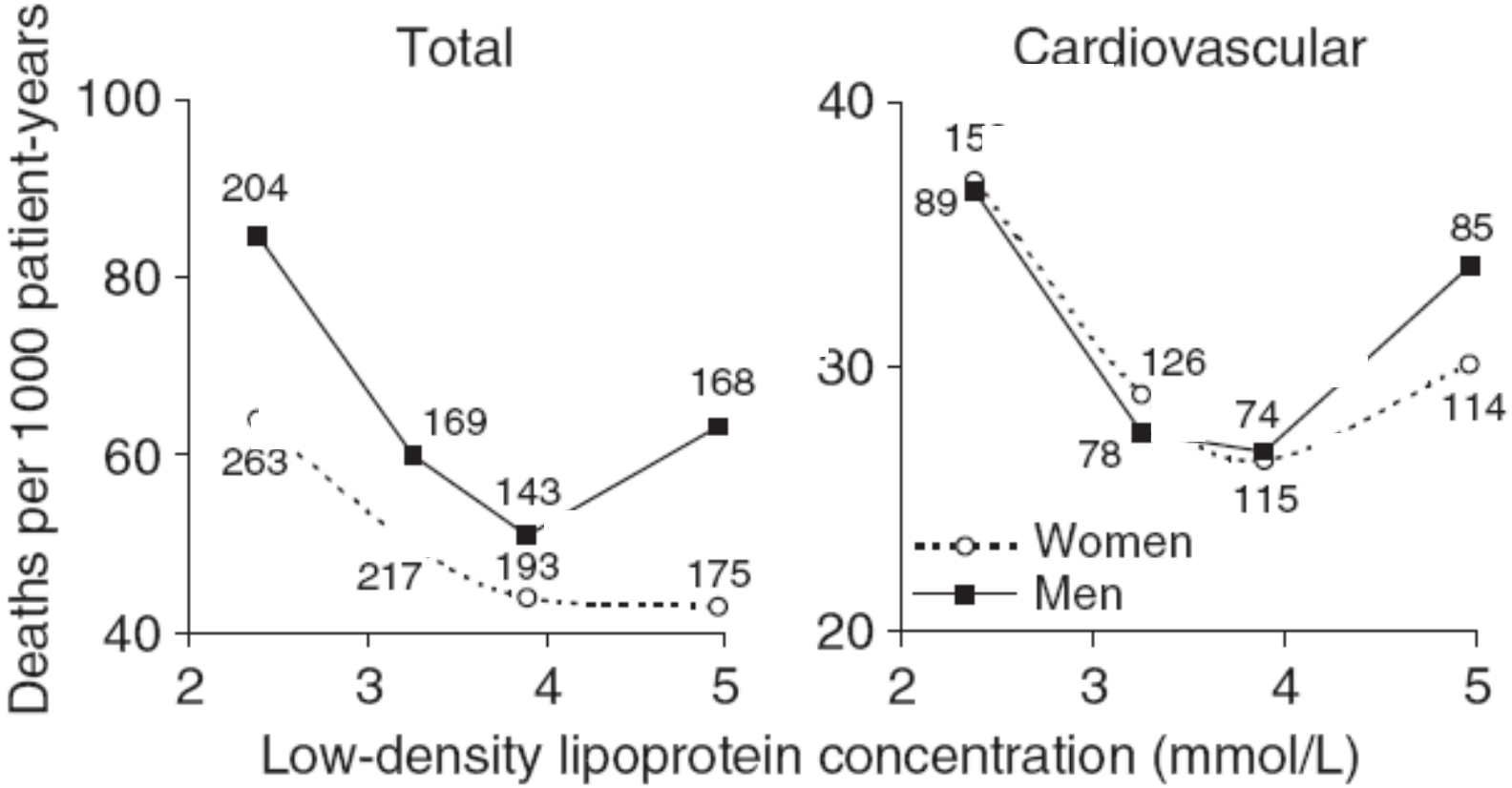


Figure 1. Sex-specific and age-adjusted rates of total and cardiovascular mortality by quartiles of serum low-density lipoprotein cholesterol at baseline. The number of deaths is given for each quartile. Conversion factor to conventional units is 38.6.

Journal of the American Geriatrics Society 53:2159–2164, 2005

JAMA

Statins and Cancer Risk

A Meta-analysis

Conclusions Statins have a neutral effect on cancer and cancer death risk in randomized controlled trials. We found that no type of cancer was affected by statin use and no subtype of statin affected the risk of cancer.

JAMA. 2006;295:74-80 www.jama.com

JAMA

Table 2. Subgroup Analysis

Outcome Measures	No. of Studies	No. of Events/ Total No. of Participants		Odds Ratio (95% Confidence Interval)	Q Statistic *P* Value
		Statin Group	Control Group		
Cancer type*					
Breast	5	81/16875	64/16901	1.33 (0.79-2.26)	.047
Prostate	3	305/10037	311/10026	0.98 (0.83-1.15)	.94
Gastrointestinal	6	400/23031	394/23032	1.01 (0.82-1.24)	.14
Colon	4	158/13984	162/13988	0.95 (0.73-1.25)	.24
Respiratory	7	409/30632	438/30641	0.94 (0.82-1.07)	.53
Melanoma	5	68/13168	80/13156	0.84 (0.57-1.25)	.30

JAMA

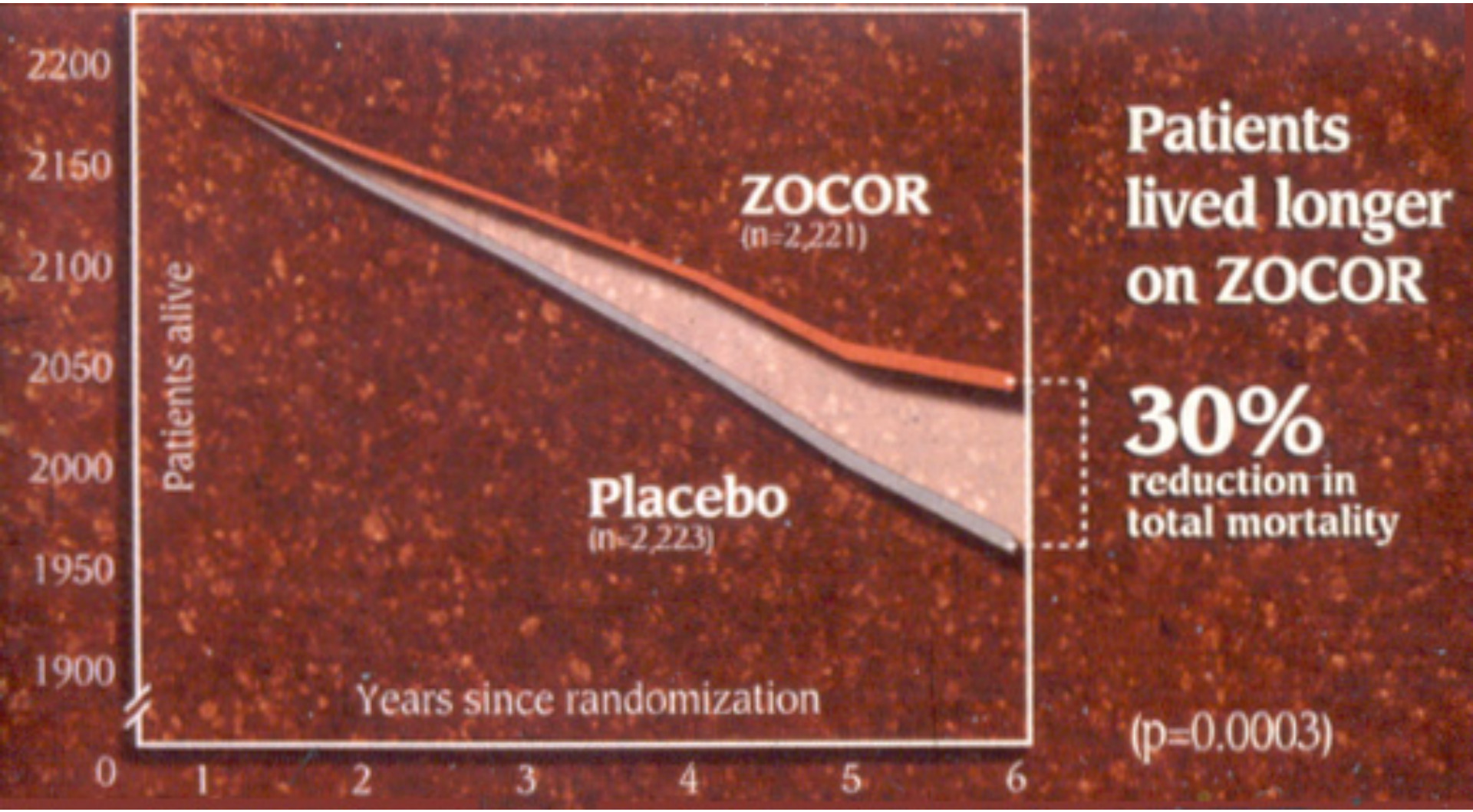
Expanding Statin Use to Help More At-Risk Patients Is Causing Financial Heartburn

[Medical News & Perspectives]

Country	Percentage of Eligible Patients Taking Statins
United States	56%
United Kingdom	23%
Germany	26%
Netherlands	36%
Italy	17%
Switzerland	29%

Mitka, Mike Volume 290(17) 5 November 2003 p 2243–2245

Selling “Evidence” to Drs


2200
2150
2100
2050
2000
1950
1900
Patients alive
ZOCOR
(n=2,221)
Placebo
(n=2,223)
Years since randomization
0
1
2
3
4
5
6
Patients lived longer on ZOCOR
30%
reduction in total mortality
(p=0.0003)

	Dead	Alive
Therapy	8	92
Placebo	12	88

Risk (Rx) = 8/100 = 8%

Risk (Pl) = 12/100 =12%

	Dead	Alive
Therapy	8	92
Placebo	12	88

Relative Risk(RR) = Risk (Rx)/ Risk (Pl) = .08/.12 = .67
Relative Risk Reduction (RRR) = 1 - RR = 1- .67 = .33 or 33%

	Dead	Alive
Therapy	8	92
Placebo	12	88

Absolute Risk Reduction (ARR) = Risk (Pl) - Risk (Rx) = .12 - .08 = .04 or 4%

Causes of death	No (%) of patients		
	Placebo (n=2223)	Simvastatin (n=2221)	Relative risk (95% CI)
Definite acute MI	63	30	
Probable acute MI	5	5	
Acute MI not confirmed			
Instantaneous death	39	29	
Death within 1 h*	24	8	
Death within 1–24 h	15	9	
Death >24 h after onset of event	11	10	
Non-witnessed death†	23	13	
Intervention-associated‡	9	7	
All coronary	189 *(8·5)*	111 *(5·0)*	0·58 (0·46–0·73)
Cerebrovascular	12	14	
Other cardiovascular	6	11	
All cardiovascular	207 *(9·3)*	136 *(6·1)*	0·65 (0·52–0·80)
Cancer	35	33	
Suicide	4	5	
Trauma	3	1	
Other	7	7	
All noncardiovascular	49 *(2·2)*	46 *(2·1)*	
All deaths	256 *(11·5)*	182 *(8·2)*	0·70 (0·58–0·85)

Relative risk, calculated by Cox regression analysis. MI=myocardial infarction.
*Following acute chest pain, syncope, pulmonary oedema, or cardiogenic shock.
†With no likely non-coronary cause. ‡Coronary death within 28 days of any invasive procedure.

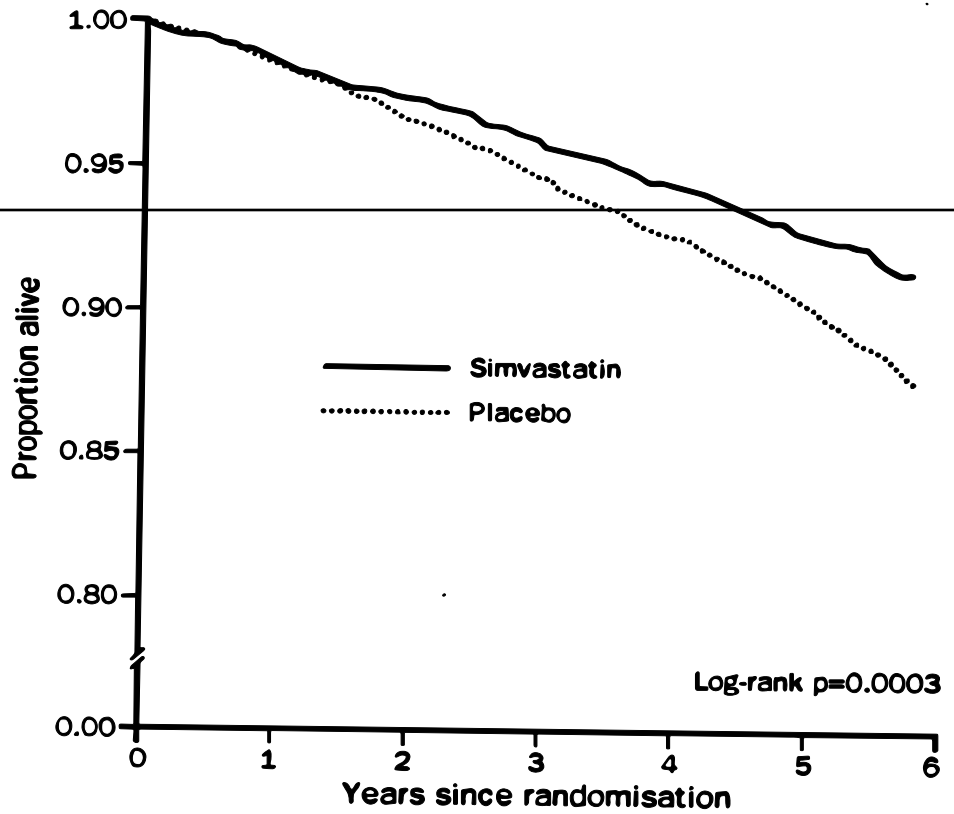
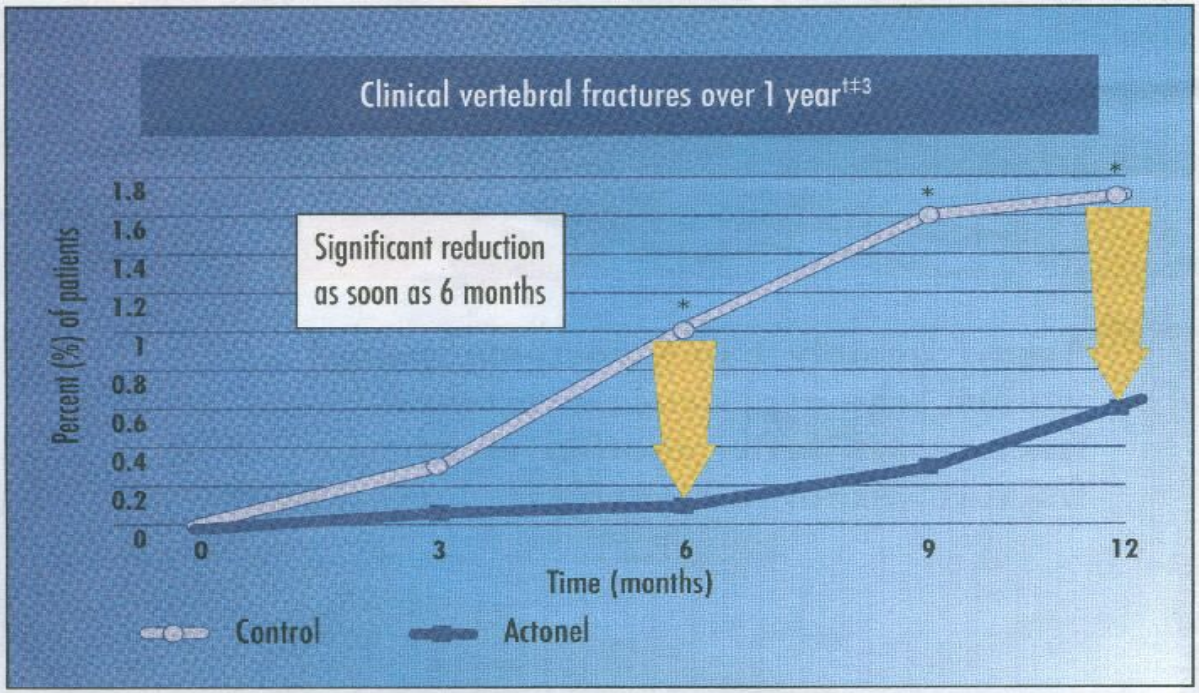


Figure 1: Kaplan-Meier curves for all-cause mortality
Number of patients at risk at the beginning of each year is shown below the horizontal axis.

lowering drugs, either because serum cholesterol rose above the protocol-specified limit of 9·0 mmol/L (16 patients) or because such therapy was initiated by non-study physicians (19 patients).

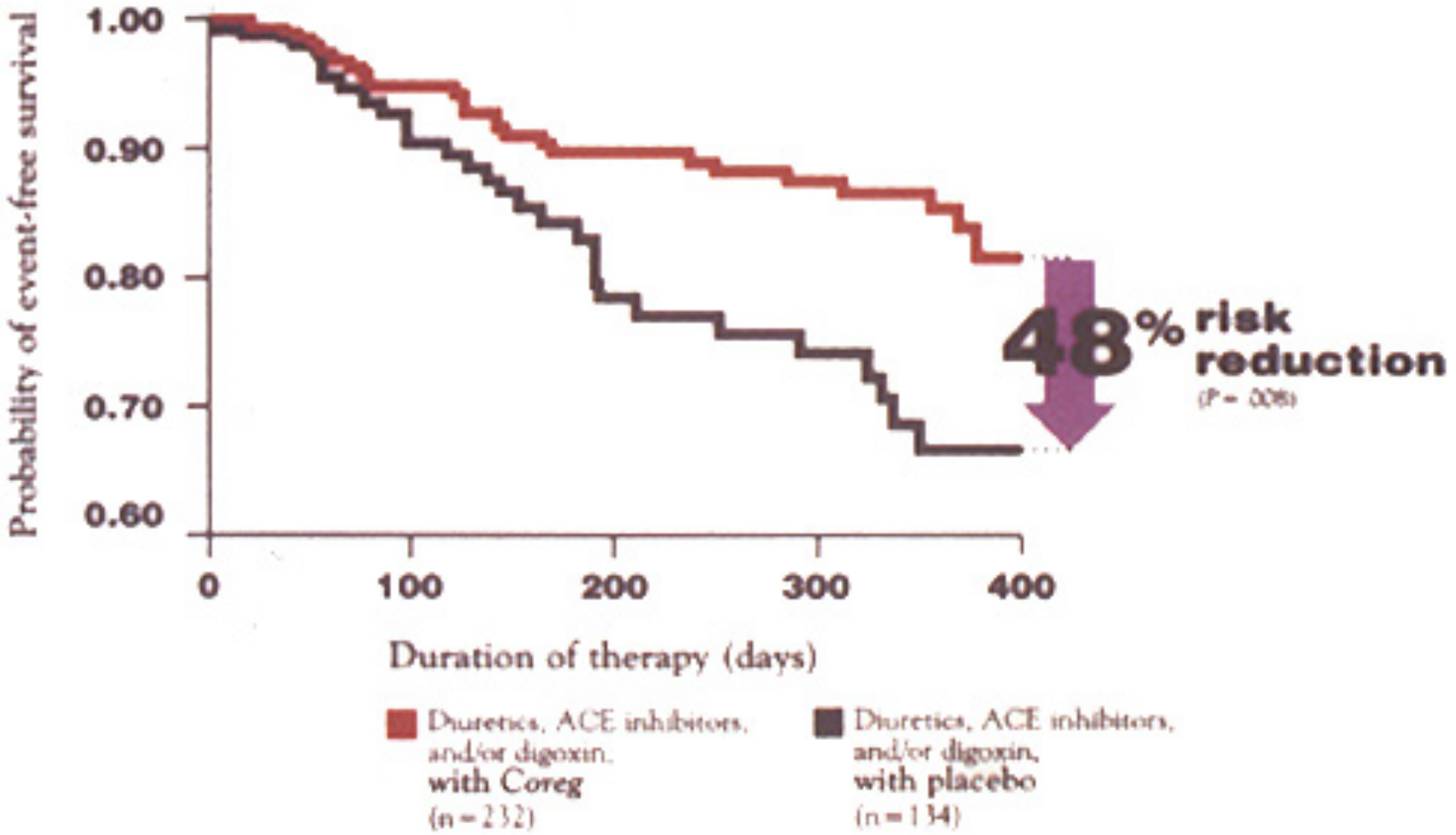
Mortality

- Actonel is the only therapy proven to significantly reduce vertebral fractures in just 1 year[2]
- Actonel is proven to significantly reduce clinical vertebral fractures by 69% in 1 year[3] (absolute risk reduction 1.1%)
- A significant reduction was seen ***as early as 6 months***[3]

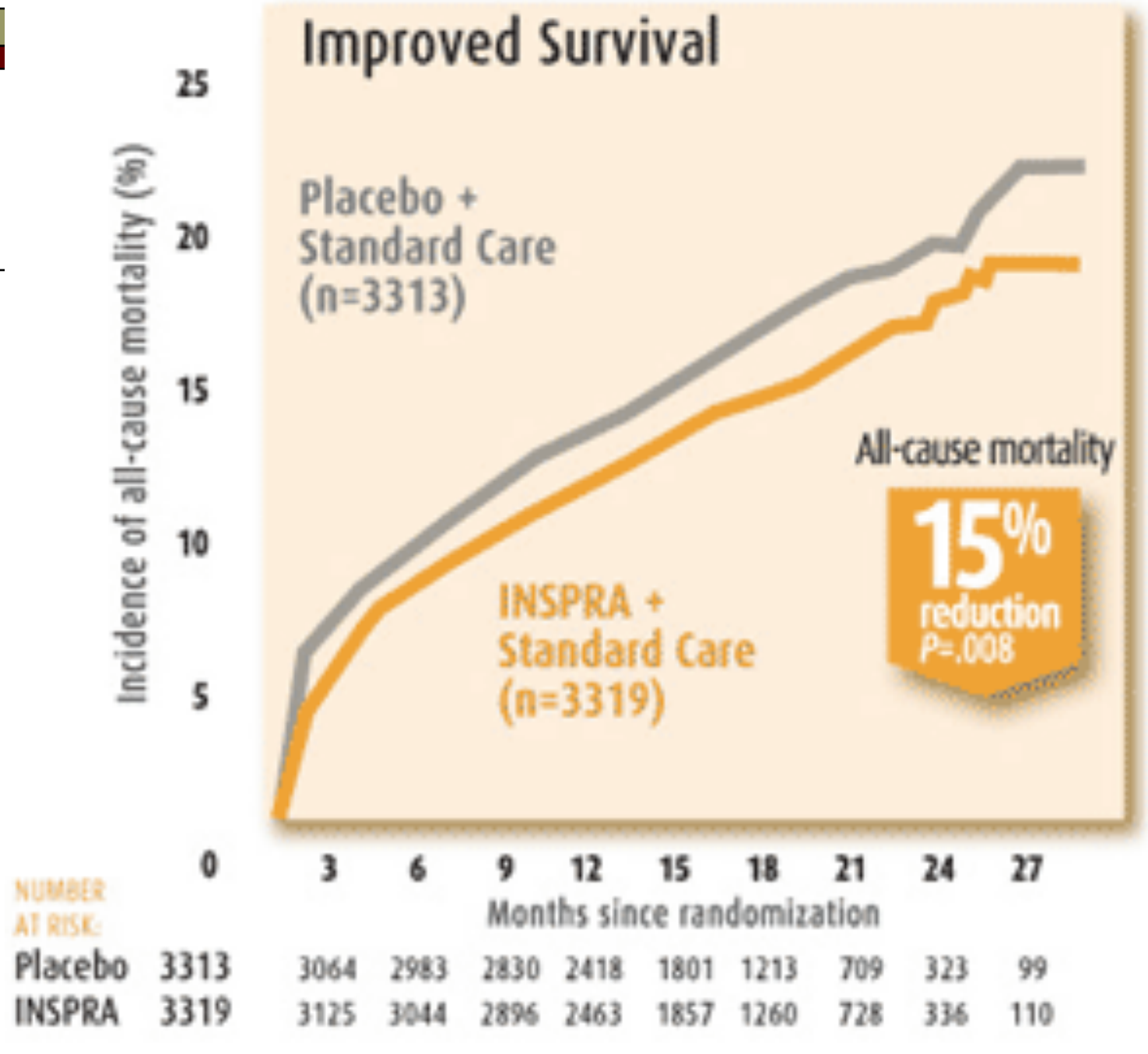


*P< 0.01 vs control.
†Combined analysis of 2 studies in 2442 postmenopausal women. All patients received 1000 mg/d calcium and, if baseline levels were low, 500 IU/d vitamin D.
‡Clinical vertebral fractures were reported as adverse events and all were confirmed radiographically.

Reduced combined risk* of morbidity and mortality[3]



*Evaluated by combined endpoint of CHF death or hospitalization or need for sustained increase in CHF medications.


Improved Survival
Placebo + Standard Care (n=3313)
INSPRA + Standard Care (n=3319)
All-cause mortality
15% reduction
P=.008
Incidence of all-cause mortality (%)
25
20
15
10
5
0
3
6
9
12
15
18
21
24
27
Months since randomization
NUMBER AT RISK:
Placebo 3313 3064 2983 2830 2418 1801 1213 709 323 99
INSPRA 3319 3125 3044 2896 2463 1857 1260 728 336 110

The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V)

- **"Because diuretics and β-blockers have been shown to reduce cardiovascular morbidity and mortality in controlled clinical trials, these two classes of drugs are preferred for initial drug therapy."**

Medication	1995 Rank	1995 Volume	1992 Rank	1992 Volume	Change, %
Nifedipine	1	23 723	1	21 060	+13
Enalapril	2	19 250	4	17 987	+7
Diltiazem	3	19 096	5	17 740	+8
Lisinopril	4	17 316	7	11 756	+47
Verapamil	5	14 021	3	18 454	−24
Metoprolol	6	11 685	9	9492	+23
Amlodipine	7	9980	23	72	+13 761
Captopril	8	8425	8	10 530	−20
Terazosin	9	8150	12	4069	+100
Hydrochlorothiazide-triamterene	10	8039	2	19 816	−59

*Includes all formulations, strengths, and brands combined for each of the drugs.

How Did This Happen?

- Calcium channel blockers were the most detailed anti-hypertensives in the 1990s.
- **Norvasc™ (amlodipine - a calcium channel blocker) was the most prescribed anti-hypertensive in 1998.**
  - **Higher rate of heart failure than diuretics**
  - **Higher death rate than diuretics**

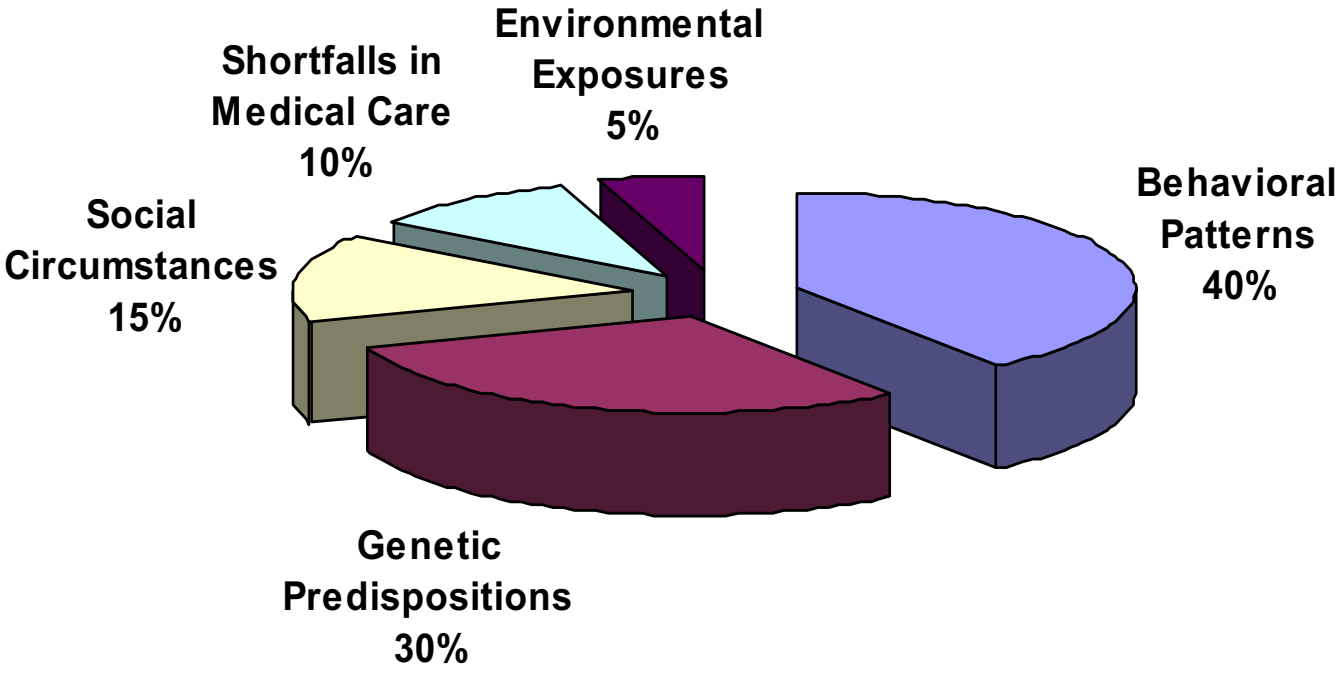
INSTITUTE OF MEDICINE

Shaping the Future for Health

THE FUTURE OF THE PUBLIC'S HEALTH IN THE 21ST CENTURY

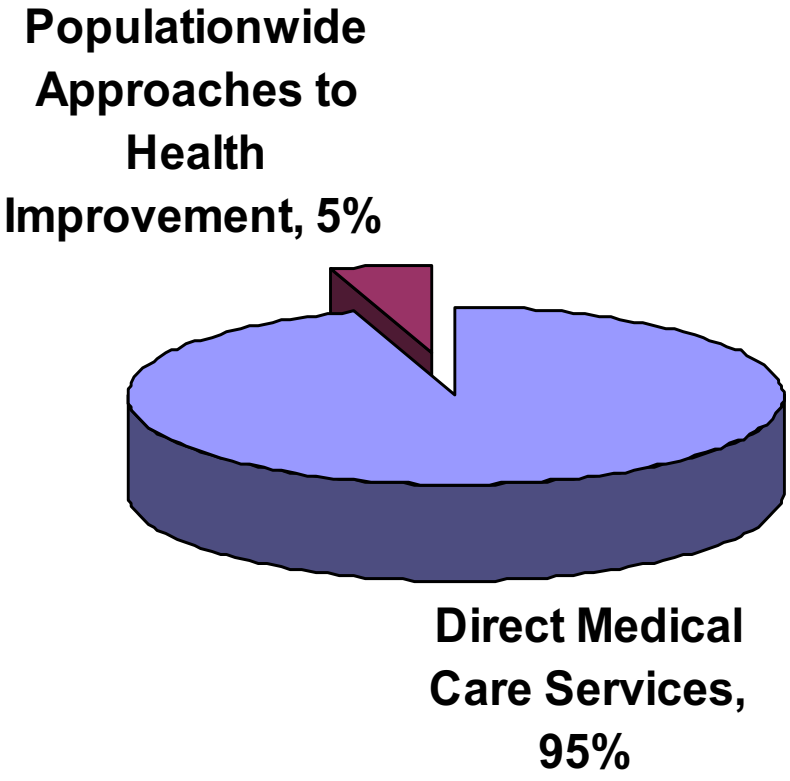
There is strong evidence that behavior and environment are responsible for over 70 percent of avoidable mortality, and health care is just one of several determinants of health.

Determinants of Health in the U.S.



McGinnis JM, Williams-Russo P, Knickman JR. The case for more active policy attention to health promotion. Health Affairs. 2002;21(2):78-93.

Allocation of Health Care Resources in the U. S.



McGinnis JM, Williams-Russo P, Knickman JR. The case for more active policy attention to health promotion. Health Affairs. 2002;21(2):78-93.

What You Can Do

- Keep a list of your drugs – show it every visit
- Use only one pharmacy
- Don't ask for any drug that is advertised on TV or in magazines
- Ask how long the drug has been on the market
  - Don't take any drug until it's been out for at least 2 years
- Ask if there are other things besides taking a drug you can do
- Ask if you should stop any current drugs
- Look for signs of drug company influence

What Society Can Do

- Free standing, nongovernmental drug effectiveness center (like the IOM) (Abramson)
- NIH Institute for Prescription Drug Trials (Angell)
- Demand doctors no longer accept gifts, serve on speaker bureaus, or publish articles written by industry

Great Books

- The Truth About The Drug Companies, Marcia Angell, MD, Random House, 2004
- Overdosed America, John Abramson, MD, Harper Collins, 2004
- Worst Pills, Best Pills, Sidney Wolfe, MD, Pocket Books, 2005

Helpful Sites

- Therapeutics Education
- Therapeutics Initiative: Evidence Based Drug Therapy
  - **www.ti.ubc.ca**
- OHSU Drug Effectiveness Review Project
  - **www.ohsu.edu/drugeffectiveness**
- **Worst Pills**
- Drs Drug Money