Liberating Clinical Trial Data: Pooling Data from Multiple Clinical Trials to answer Big Questions

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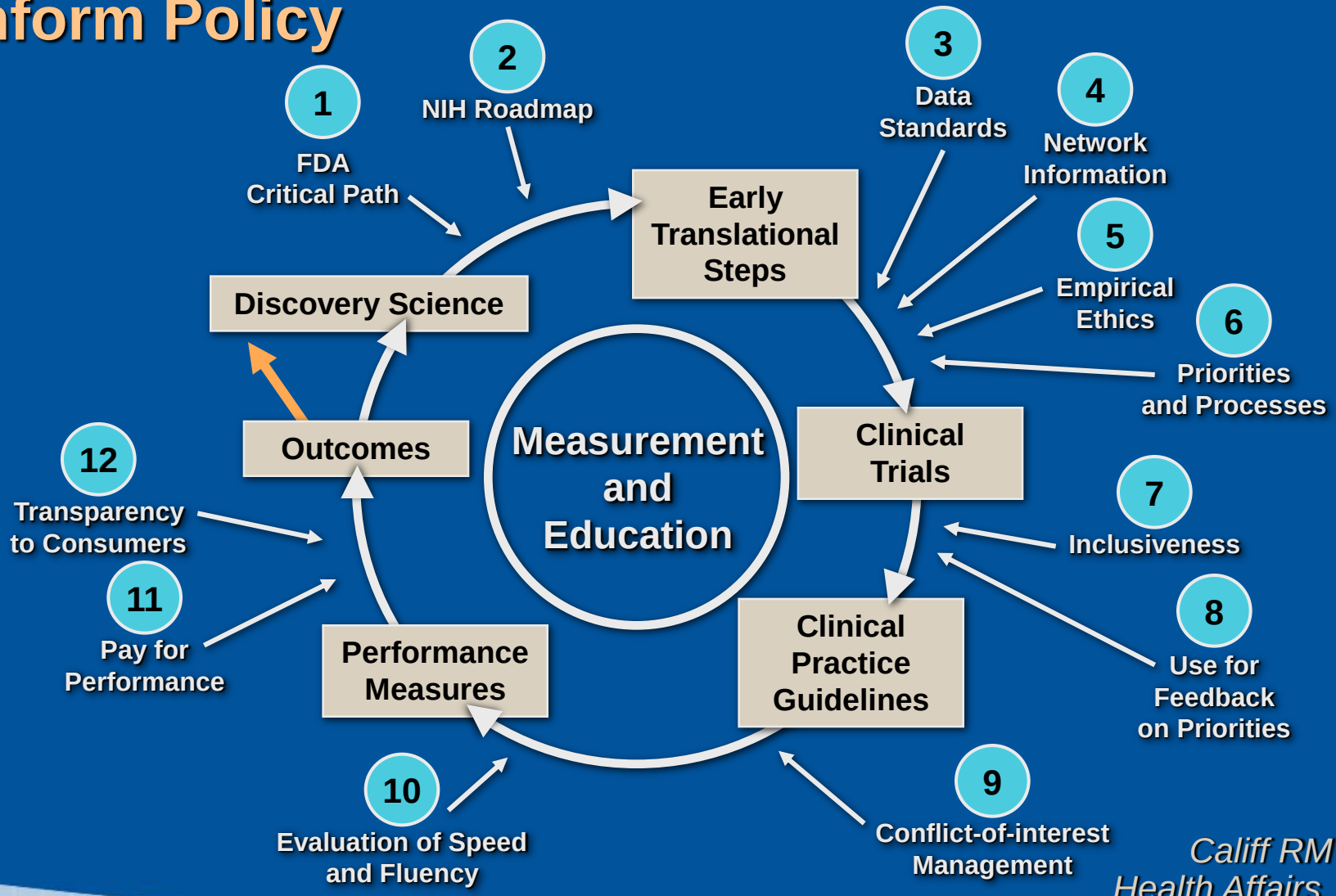
The Premise

- Trial participants give consent to be involved in a human experiment
- The basis for the experiment that enables ethics committees to approve it is the commitment to create generalizable knowledge
- First base: publishing the results
- Second base: sharing summary data
- Third base: confidentially sharing detailed clinical data
- Home run?: publicly sharing detailed clinical data
- Why?

3 Big Reasons to Share Data

- Trials often get results that seem conflicting
  - Demonstration of replication is a critical element of all science
  - When the results truly differ from trial to trial it can be chance or real
- The benefit/risk balance of treatment may vary as a function of patient characteristics
  - But most “subgroup differences” are random noise
  - Replication is critical: Harrell’s rule of trials: For every spurious trial result a clever scientist/doctor can come up with an obvious biological reason
- The cost effectiveness of treatment may vary as a function of patient characteristics

The Cycle of Quality: Generating Evidence to Inform Policy



Califf RM et al, Health Affairs, 2007

6 Medical Therapies Proven to Reduce Death

	Therapy	# pts	Reduction in deaths: Relative	Absolute	C/E
MI:	**Aspirin**	**18,773**	**23%**	**2.4%**	**+++++**
	Fibrinolytics	**58,000**	**18%**	**1.8%**	**++++**
	Beta blocker	**28,970**	**13%**	**1.3%**	**++++**
	ACE inhibitor	**101,000**	**6.5%**	**.6%**	**+**
2nd prev:	Aspirin	54,360	15%	1.2%	+++++
	Beta blocker	20,312	21%	2.1%	++++
	Statins	**17,617**	**23%**	**2.7%**	**++++**
	ACE inhibitor	9,297	17%	1.9%	++++
CHF:	ACE inhibitor	7,105	23%	6.1%	+++++
	Beta blocker	12,385	26%	4%	+++++
	Spironolactone	**1,663**	**30%**	**11%**	**+++++**

Goals for CRUSADE Registry

Improve Adherence to ACC/AHA Guidelines for Patients with Unstable Angina/Non-STEMI

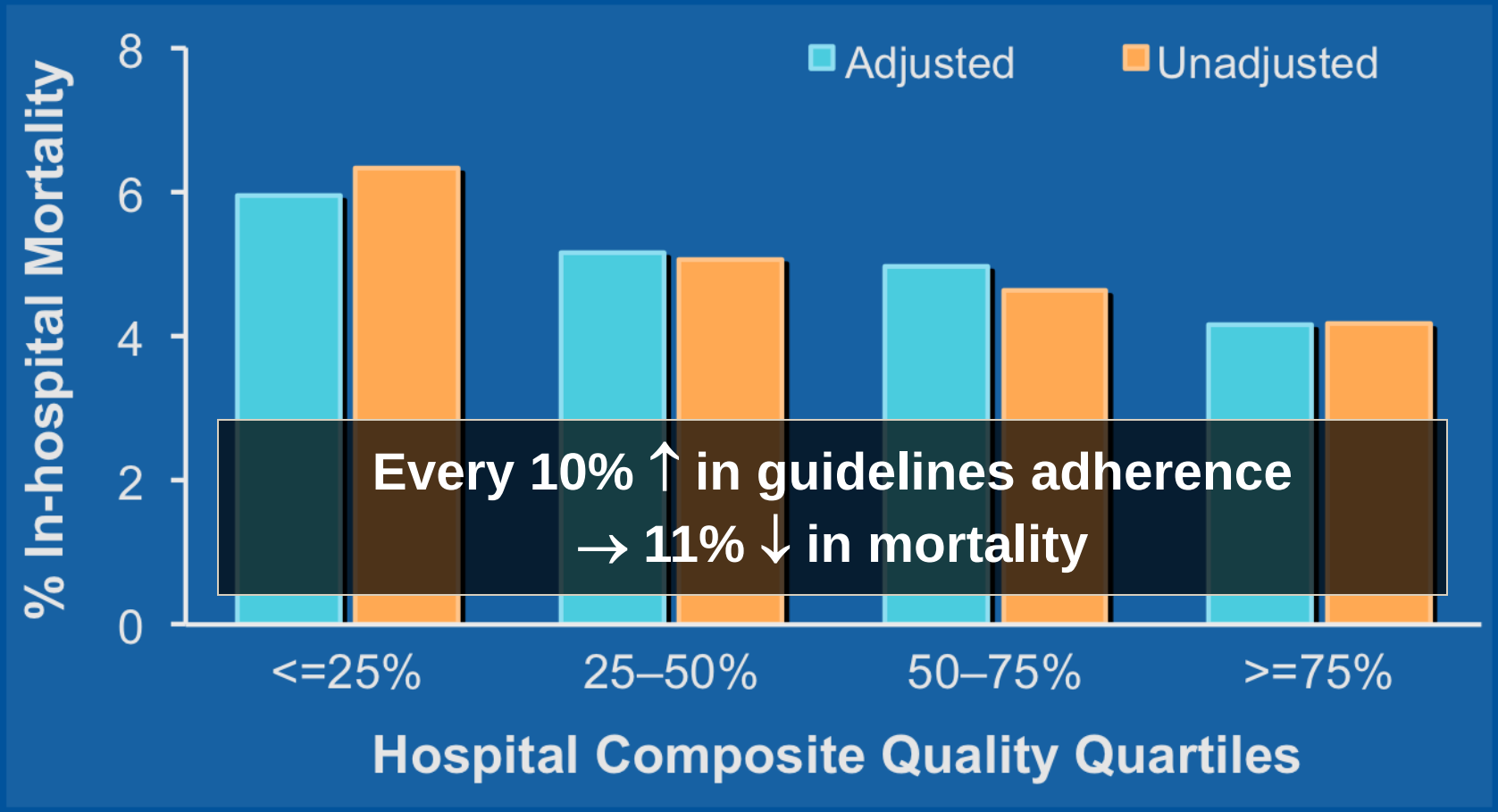
Acute Therapies **Discharge Therapies**

Evaluating the Process of Care

- An adherence score is applied to each patient. incorporating the components of process of care.
- The score from each patient then combined for all patients at each hospital.
  Typical scores ranged from 50 to 95%.
- All 400 hospital adherence scores then ranked in quartiles — best to worst.

Circulation, JACC 2002 — ACC/AHA Guidelines update

Link Between Overall ACC/AHA Guidelines Adherence and Mortality



Peterson et al, ACC 2004

Reduction in Acute Myocardial Infarction Mortality in the United States

Risk-Standardized Mortality Rates From 1995-2006

Results At the patient level, the odds of dying within 30 days of admission if treated at a hospital 1 SD above the national average relative to that if treated at a hospital 1 SD below the national average were 1.63 (95% CI, 1.60-1.65) in 1995 and 1.56 (95% CI, 1.53-1.60) in 2006. In terms of hospital-specific RSMRs, adecrease from 18.8% in 1995 to 15.8% in 2006 was observed (odds ratio, 0.76;95% CI, 0.75-0.77). A reduction in between-hospital heterogeneity in the RSMRs was also observed: the coefficient of variation decreased from 11.2% in 1995 to10.8%, the interquartile range from 2.8% to 2.1%, and the between-hospital variance from 4.4% to 2.9%.

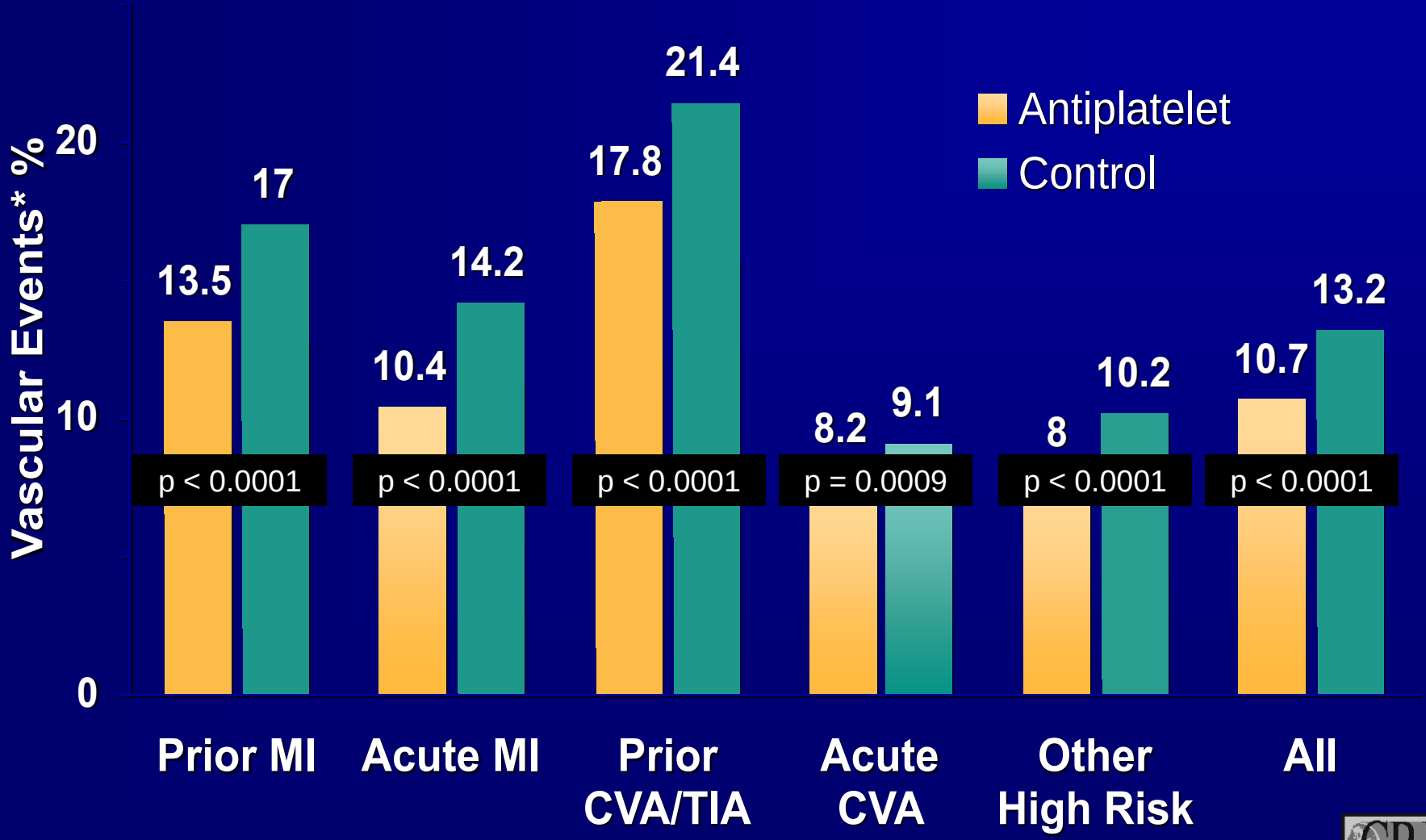
Harlan M. Krumholz, MD, SM et al; *JAMA.2009;302(7):767-773*

The Magic Sequence

- Invent and develop a technology
- Do your trial
- Add your data to the cumulative database
- Generate new hypotheses
- Do more trials
- Continue to refine

Antithrombotic Trialists' Collaboration:

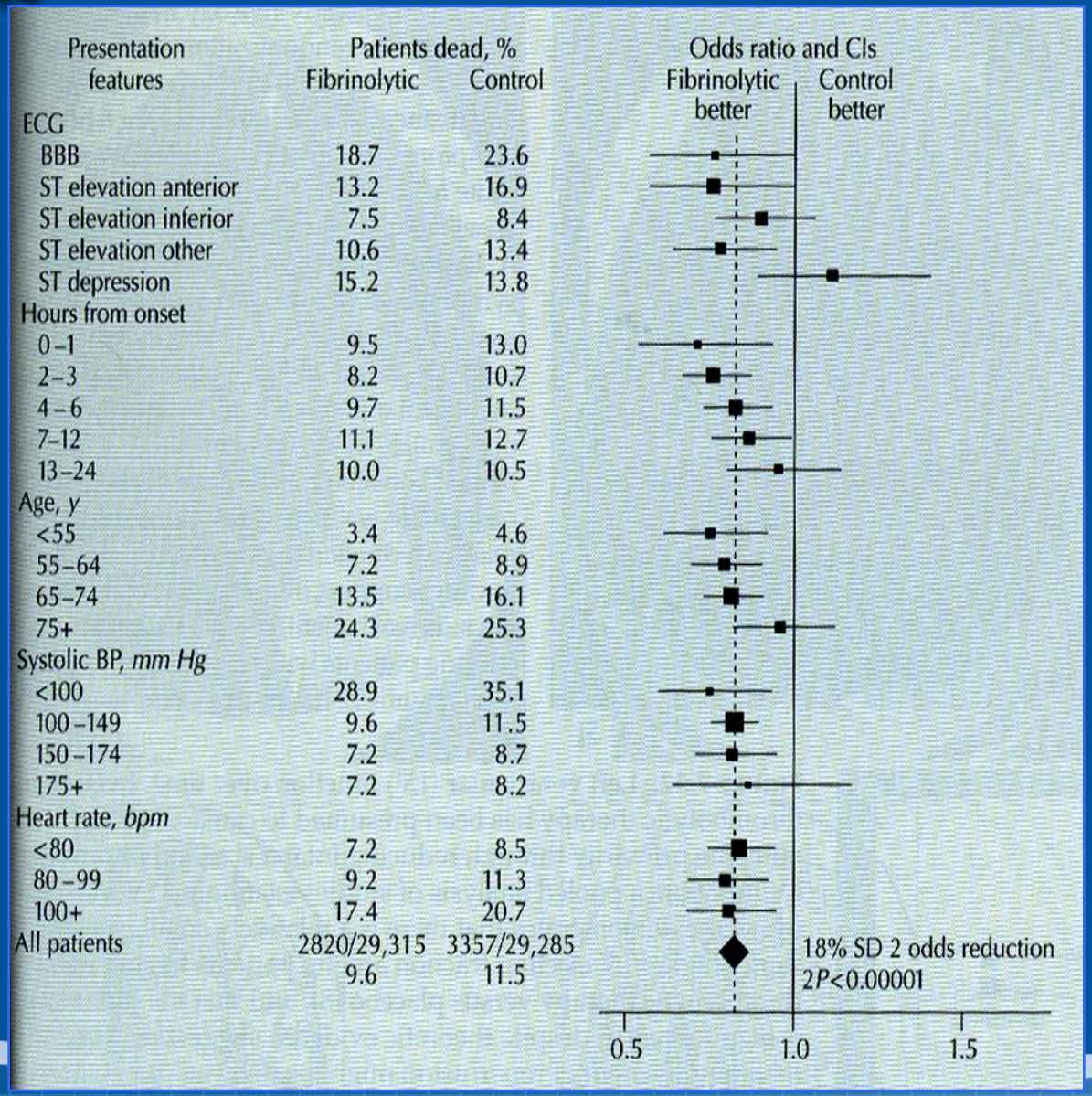
Trials Available through 09/97 (n=135,000, 287 RCTs)



*composite of MI, CVA, vascular deaths

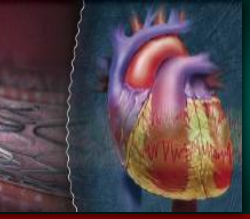
—*BMJ 2002;324:71-86*

FTT Overview



Presentation features	Patients dead, % Fibrinolytic	Control
ECG		
BBB	18.7	23.6
ST elevation anterior	13.2	16.9
ST elevation inferior	7.5	8.4
ST elevation other	10.6	13.4
ST depression	15.2	13.8
Hours from onset		
0–1	9.5	13.0
2–3	8.2	10.7
4–6	9.7	11.5
7–12	11.1	12.7
13–24	10.0	10.5
Age, *y*		
<55	3.4	4.6
55–64	7.2	8.9
65–74	13.5	16.1
75+	24.3	25.3
Systolic BP, *mm Hg*		
<100	28.9	35.1
100–149	9.6	11.5
150–174	7.2	8.7
175+	7.2	8.2
Heart rate, *bpm*		
<80	7.2	8.5
80–99	9.2	11.3
100+	17.4	20.7
All patients	2820/29,315	3357/29,285
	9.6	11.5

— Braunwald Atlas. Vol. VIII. Figure 7-9



Acute Coronary Syndromes
Clinical Spectrum and Presentation

Presentation

Emergency Department

In-hospital 6-24hrs

Ischemic Discomfort at Rest

No ST-segment Elevation

ST-segment Elevation

+

+

+

+

NSTEMI

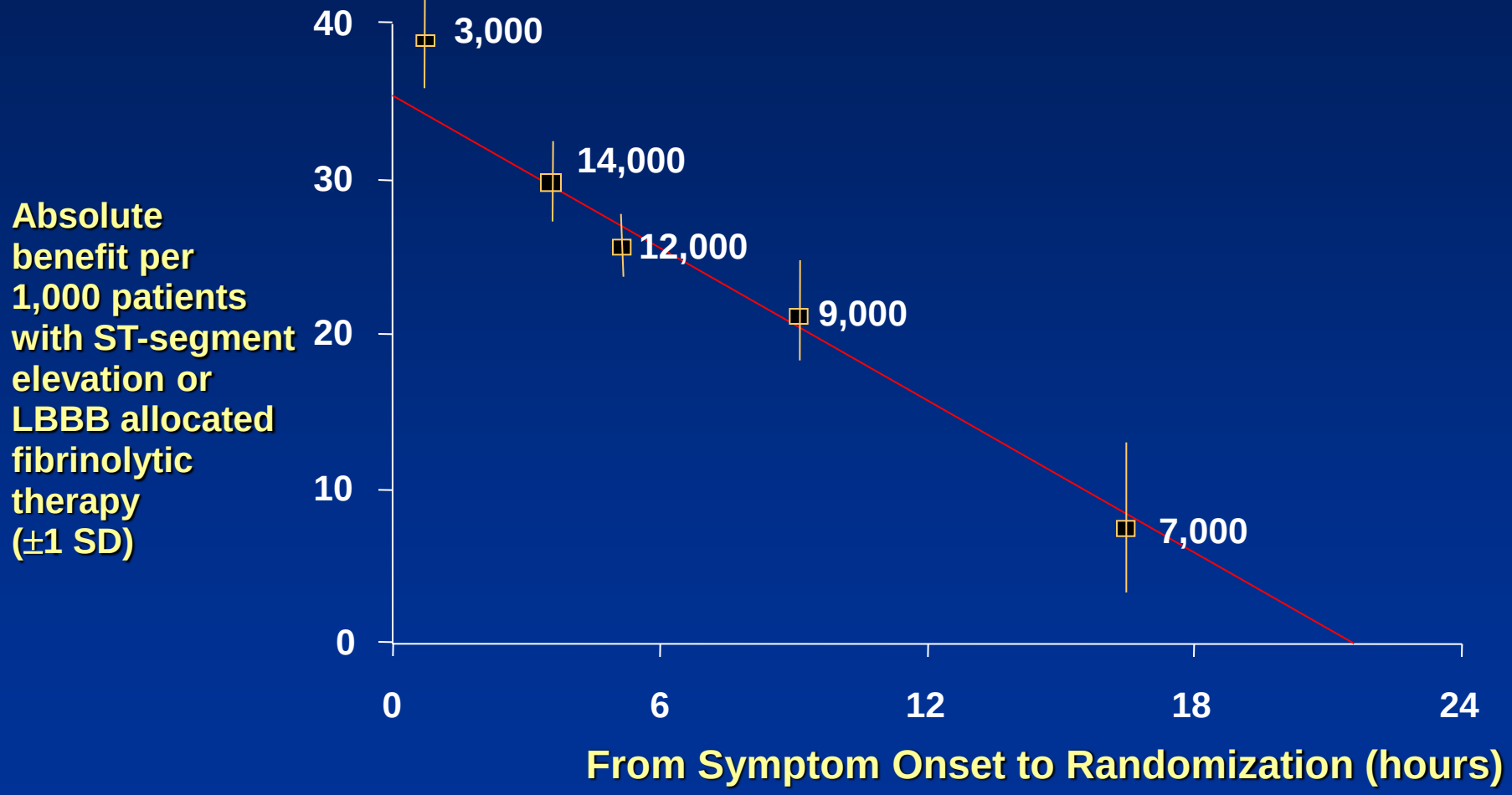
Unstable Angina

Non-Q-wave MI

Q-wave MI

(⊕ : positive cardiac biomarker)

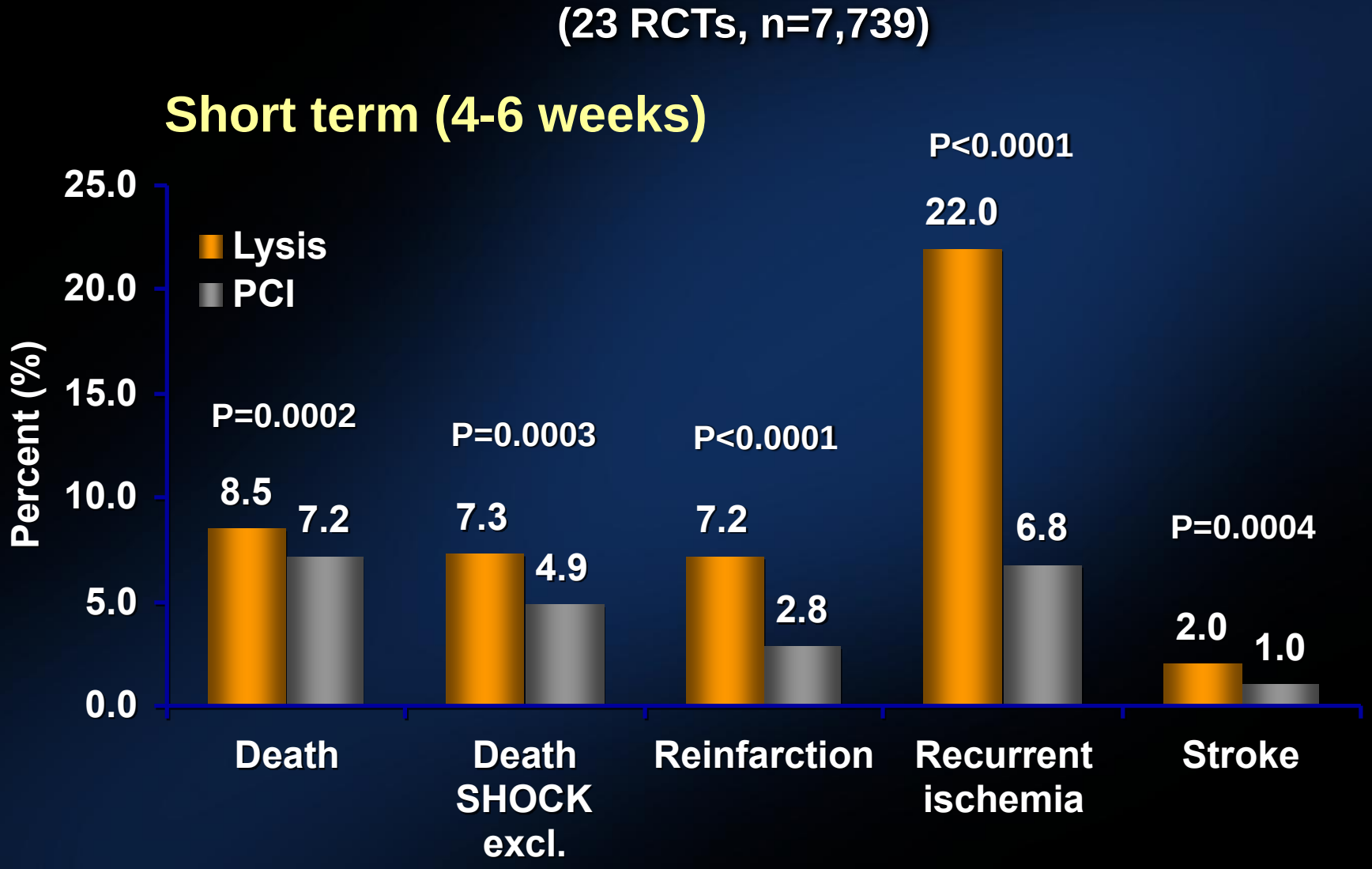
Absolute Reduction in 35-Day Mortality Versus Delay From Symptom Onset to Randomization in Patients With ST-Segment Elevation or LBBB



Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet.* 1994;343:311-322.

PCI versus Fibrinolysis Systematic Overview

(23 RCTs, n=7,739)



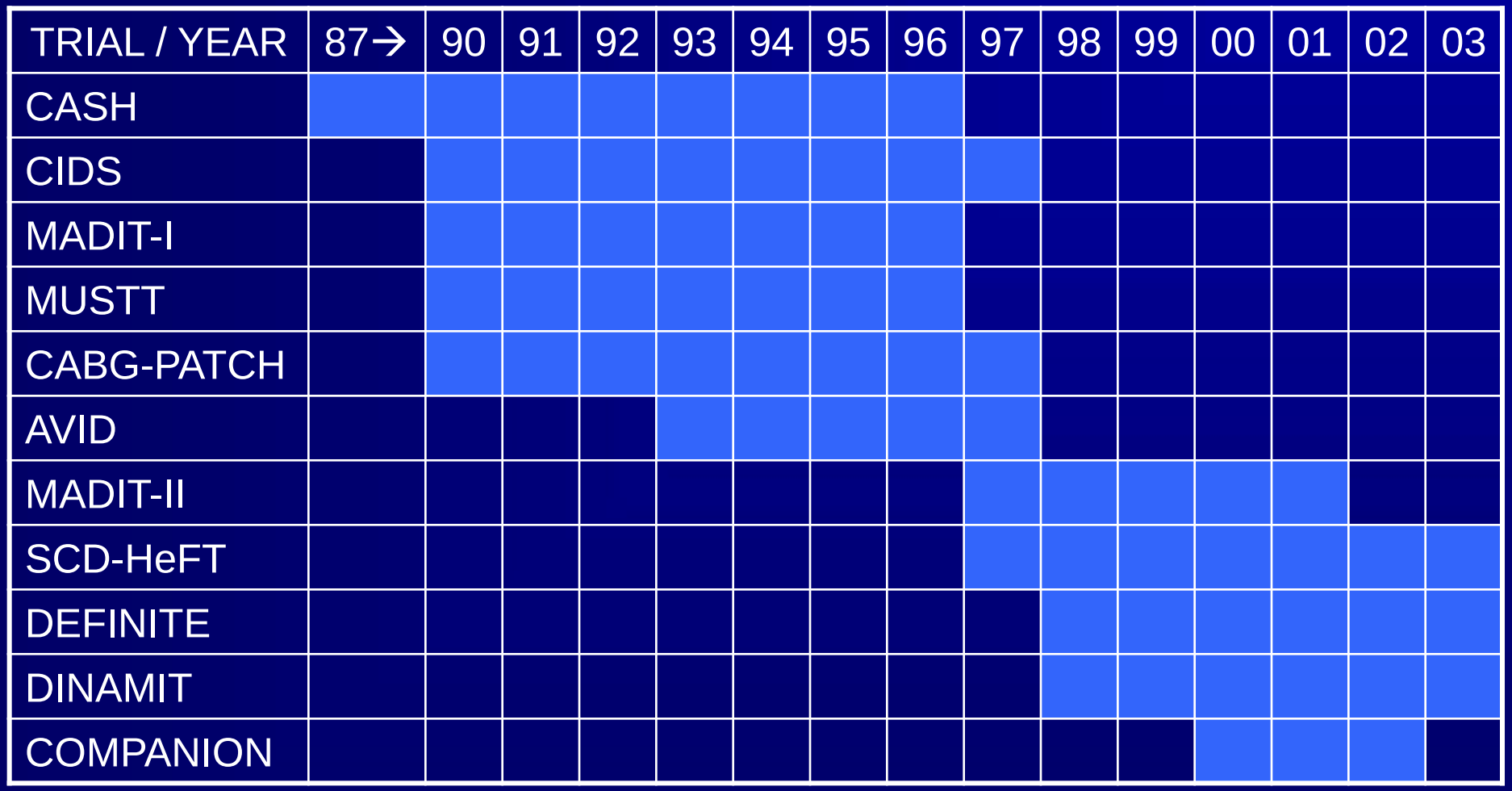
Keeley EC, Boura JA, Grines CL. *Lancet.* 2003.

ST Elevation MI

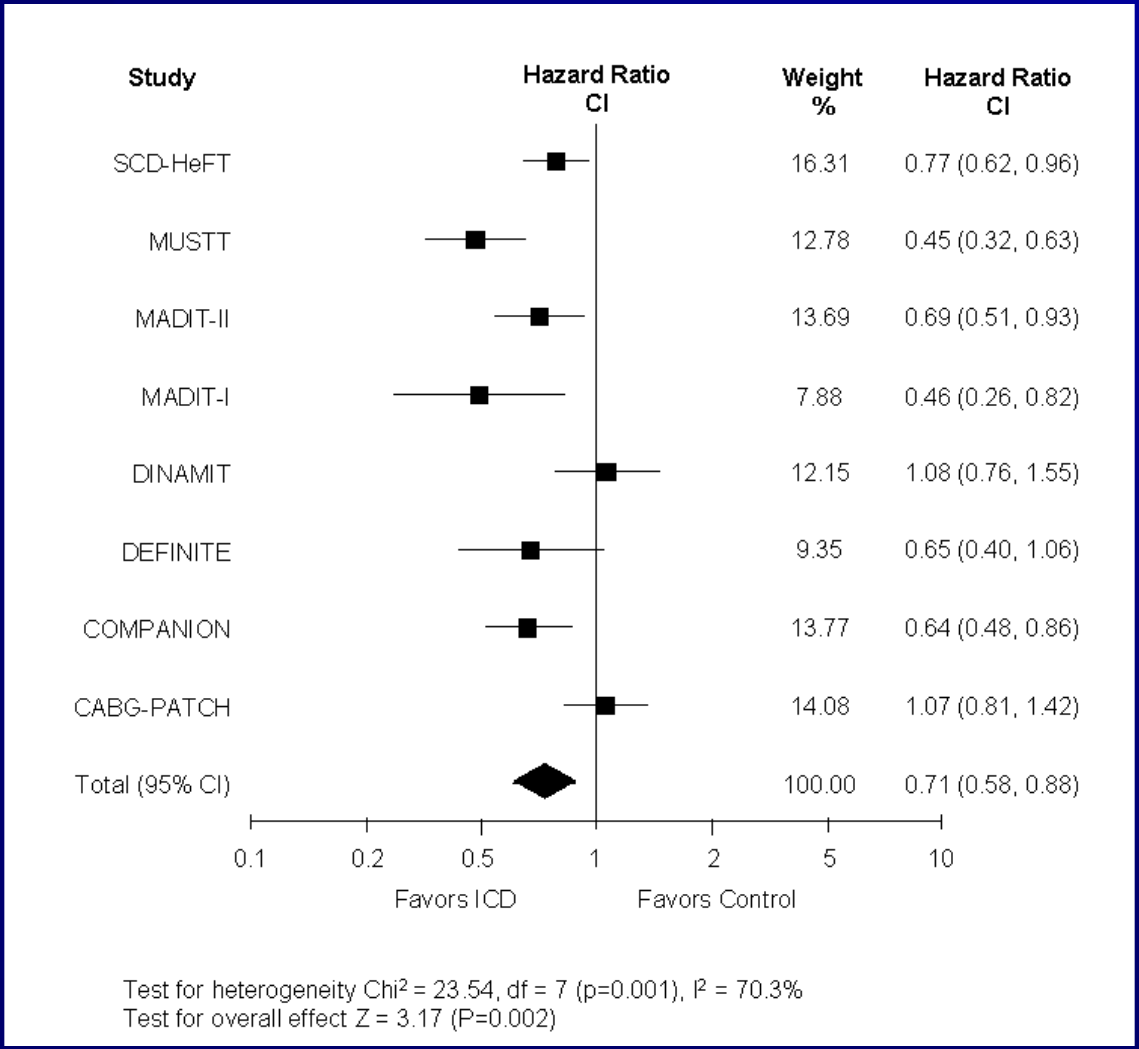
- Dramatic reduction in MI
- Key steps
  - Invent new therapies
  - Do the right trials
  - Combine the data
  - Invent more new therapies and do more trials
- The “valley of death” is there for a good reason
  - The path from biology to marketing is full of monsters and hazards
  - Liberated data is critical to knowing whether the path was traversed fairly or the monsters were bypassed
- WE NEED INTELLIGENT GUIDES TO TRAVERSE THE VALLEY OF DEATH

ICD and Sudden Death

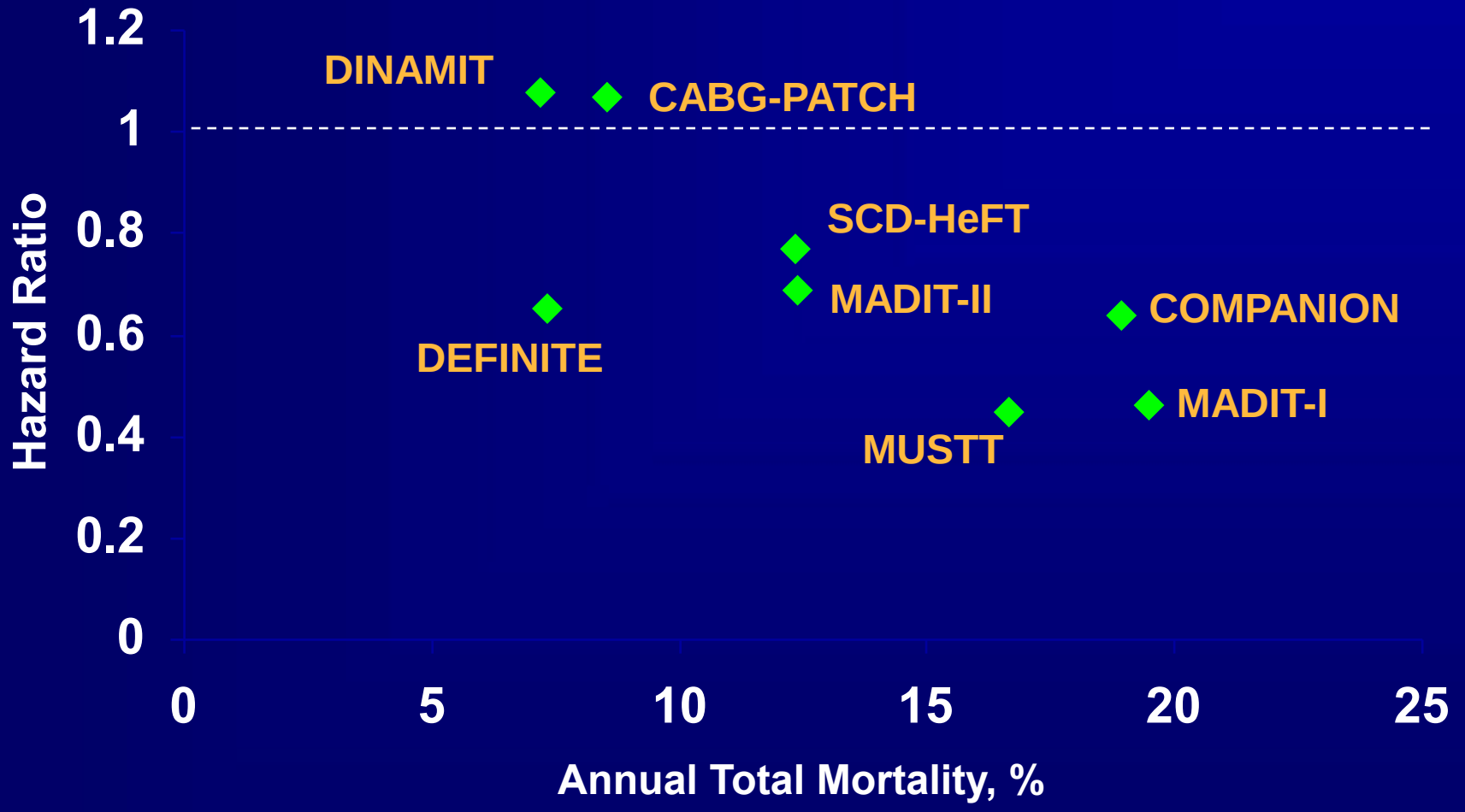
Timing of Clinical Trials



Efficacy of ICD



Hazard Ratios versus Total Mortality



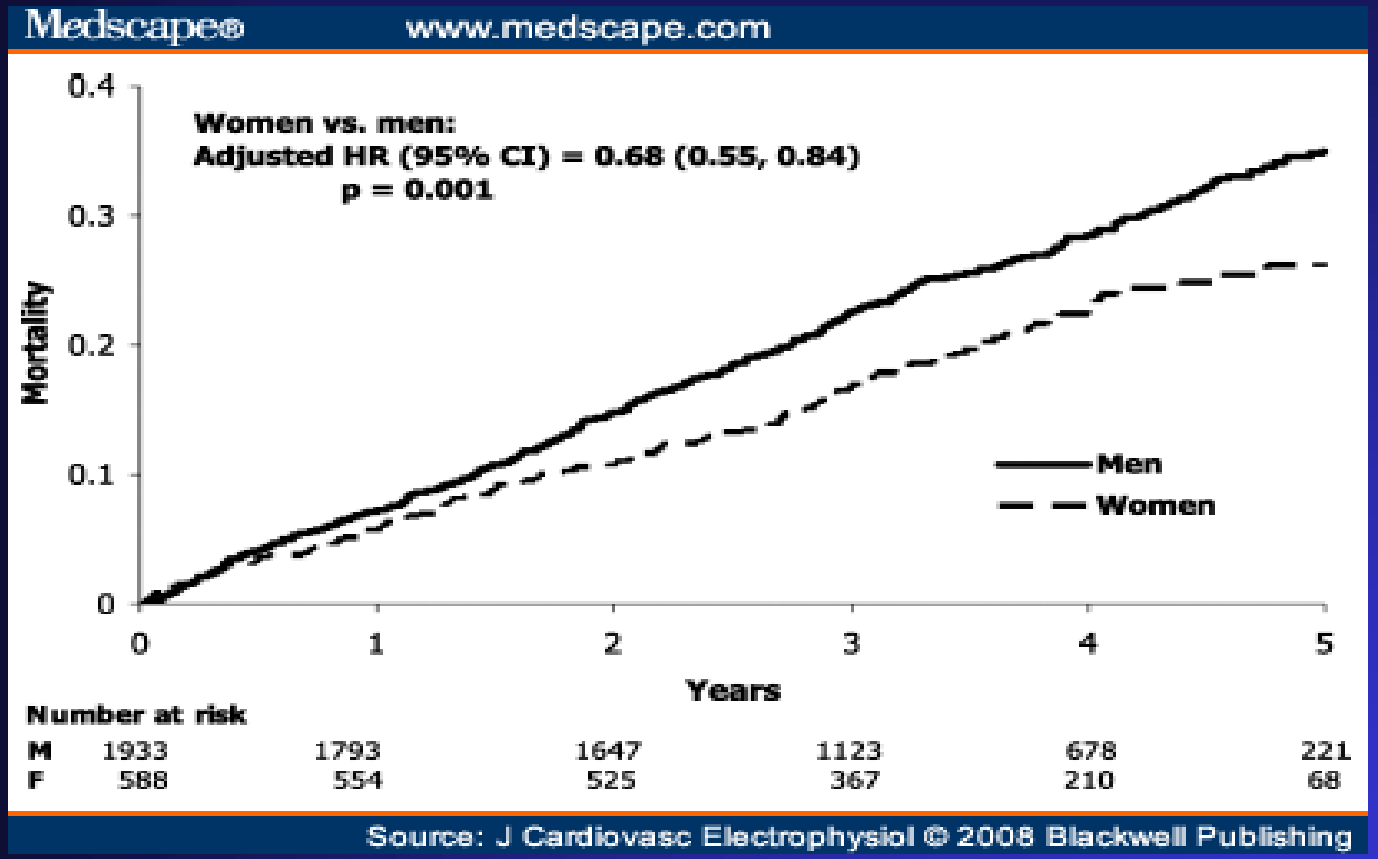
Influence of Gender on Outcome of ICD Therapy in MADIT-II (n=192)

	Men	Women
Adjusted HR (95% CI) for ICD effectiveness	0.66 (0.48, 0.91)	0.57 (0.28, 1.18)

→ *Women had similar ICD effectiveness and survival to men. Women were less likely to have appropriate ICD therapy for VT/VF. Big limitation is the small sample size.*

Zareba W et al. JCE 2005;16:1265-70

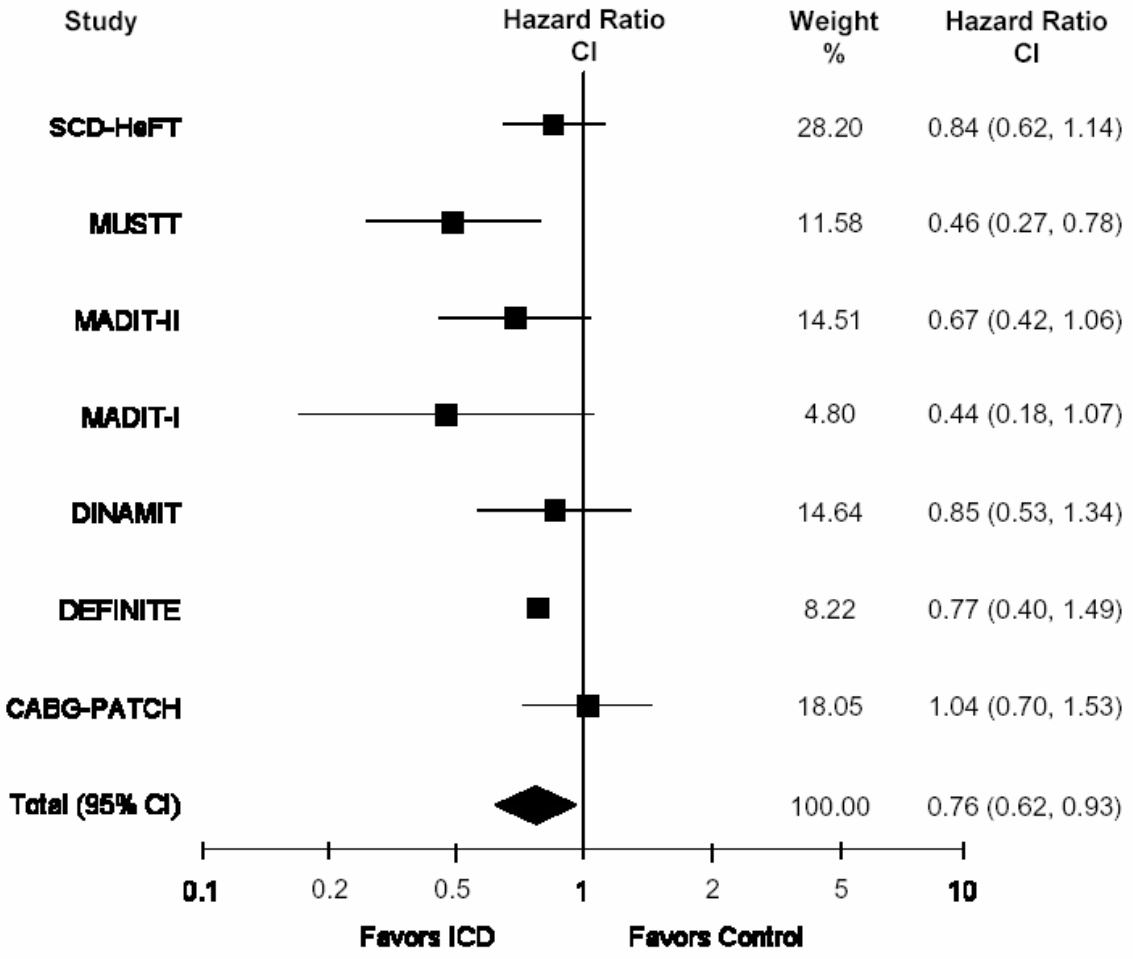
Influence of Gender on Outcome of ICD Therapy in SCD-HeFT (n=588)



Al-Khatib

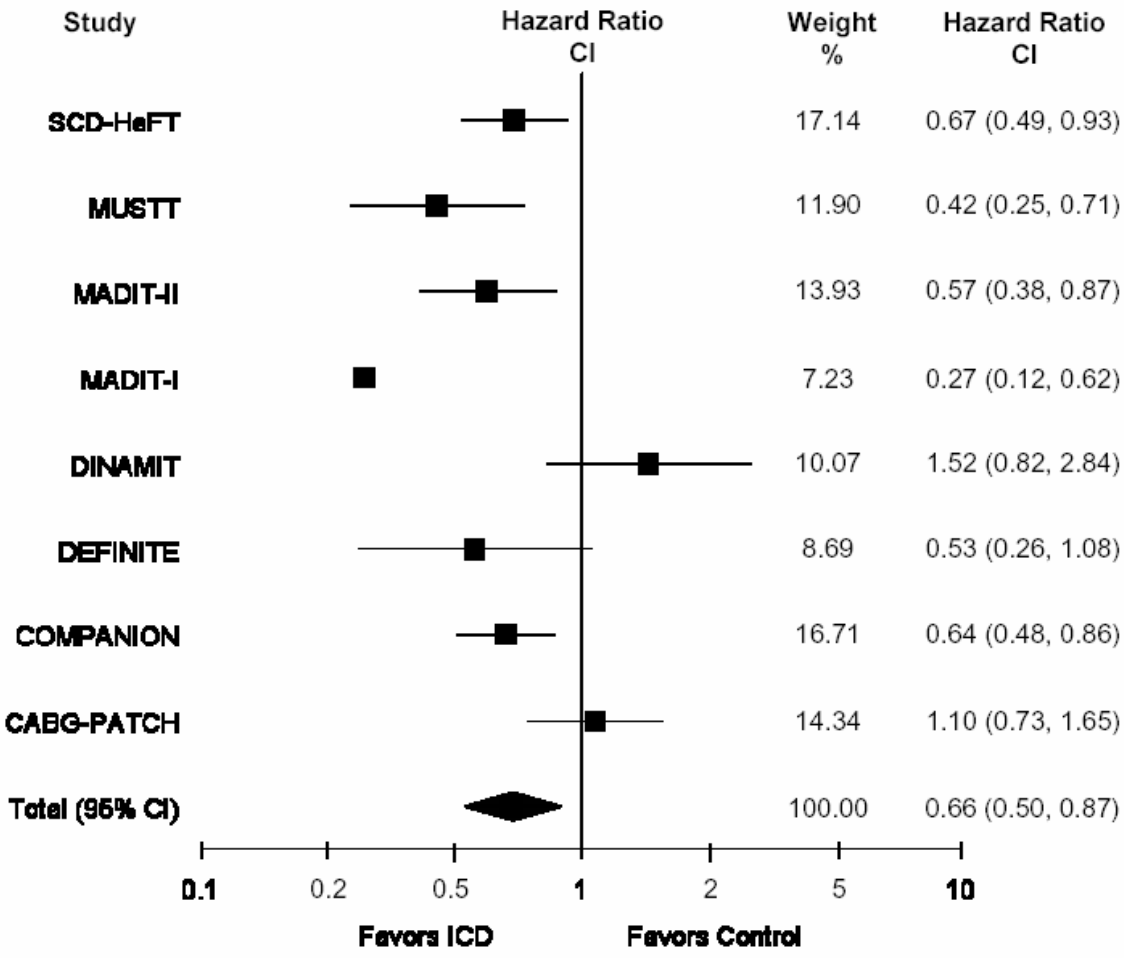
Russo AM et al. JCE 2008;19:720-724

ICD versus Control
Total Mortality
QRS < 120ms



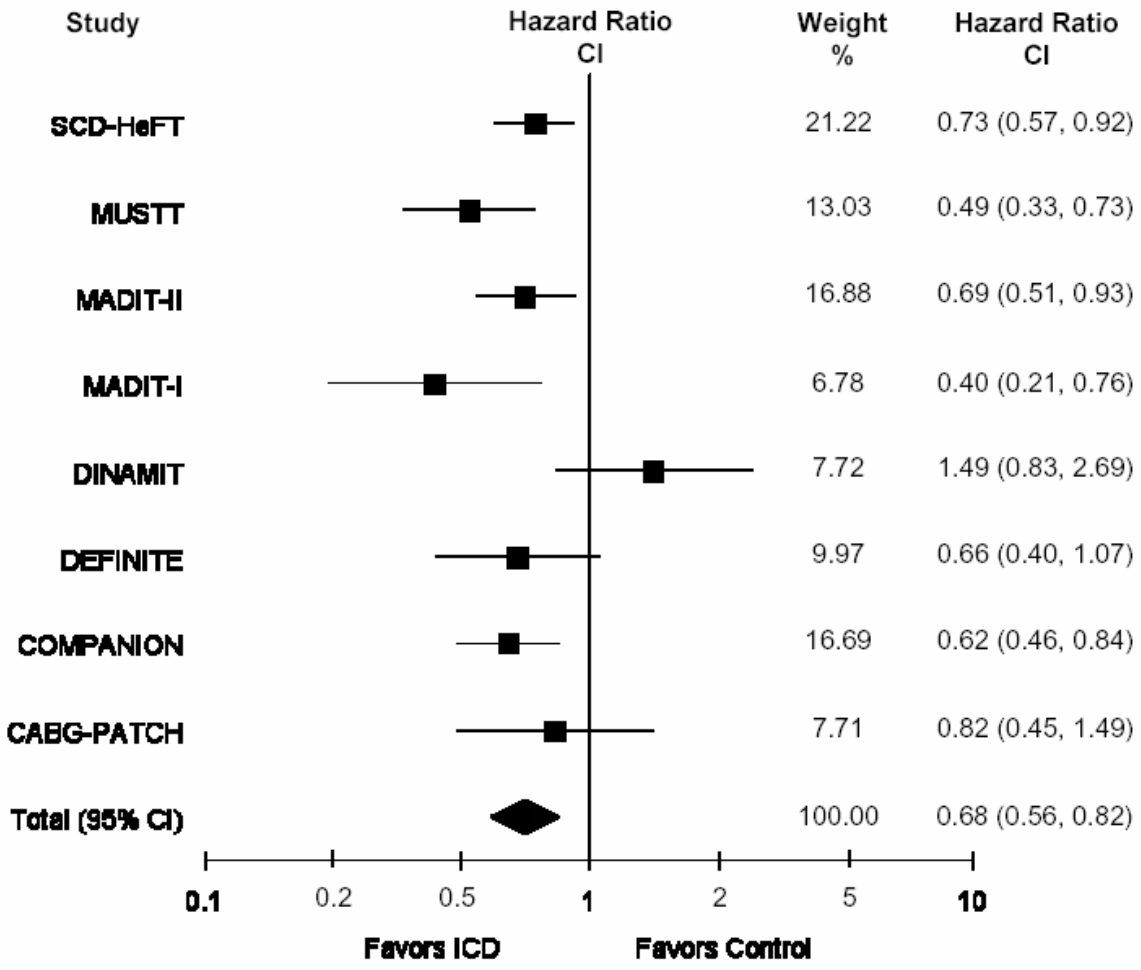
Test for heterogeneity Chi^2 =8.26, df = 6 (p=0.22), I^2 = 27.3%
Test for overall effect Z = 2.65 (P=0.008)

ICD versus Control
Total Mortality
QRS ≥ 120ms



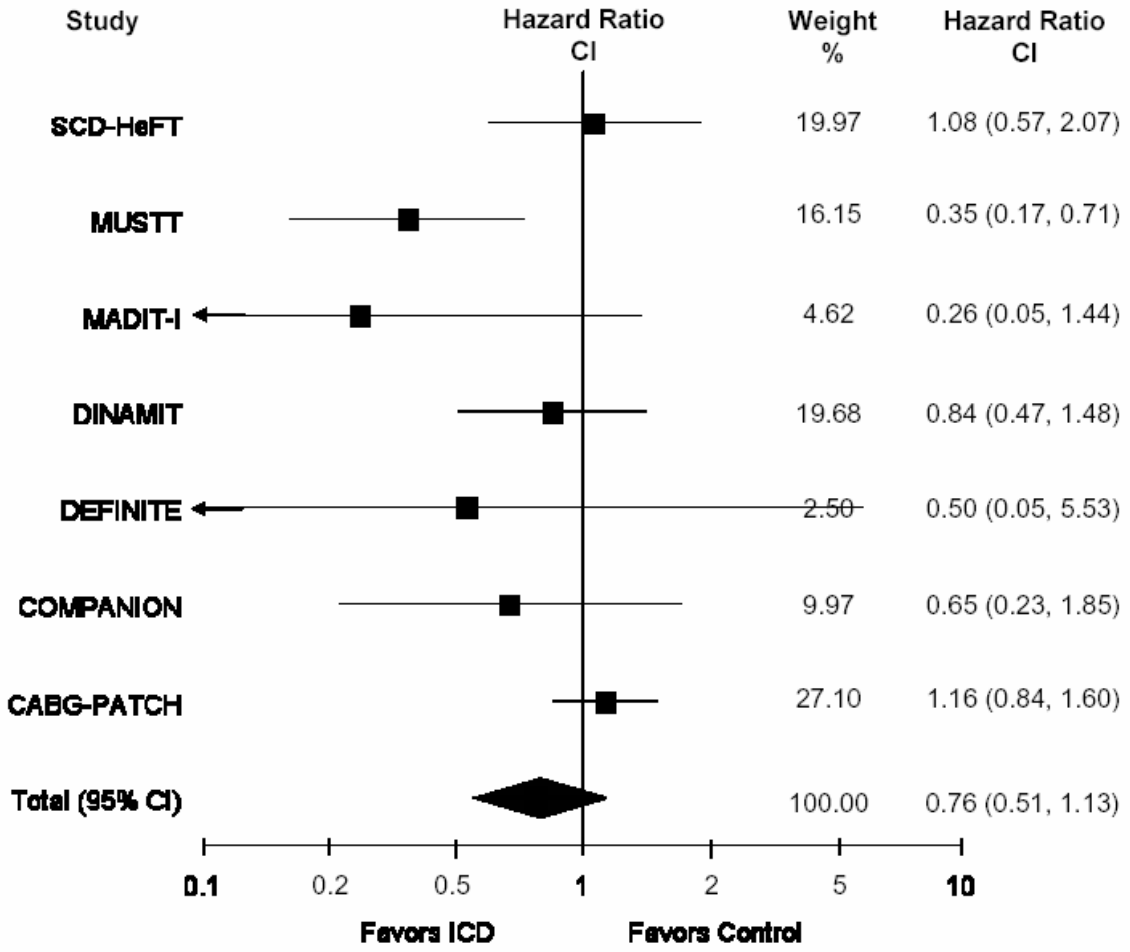
Test for heterogeneity $Chi^2 = 21.12$, df = 7 (p=0.004), $I^2 = 66.9\%$
Test for overall effect Z = 2.96 (P=0.003)

ICD versus Control
Total Mortality
EF ≤ 30%



Test for heterogeneity $Chi^2 = 13.21$, df = 7 (p=0.07), $I^2 = 47.0\%$
Test for overall effect Z = 4.00 (P<0.0001)

ICD versus Control
Total Mortality
EF > 30%



Test for heterogeneity $Chi^2 = 12.43$, df = 6 (p=0.05), $I^2 = 51.7\%$
Test for overall effect Z = 1.34 (P=0.18)

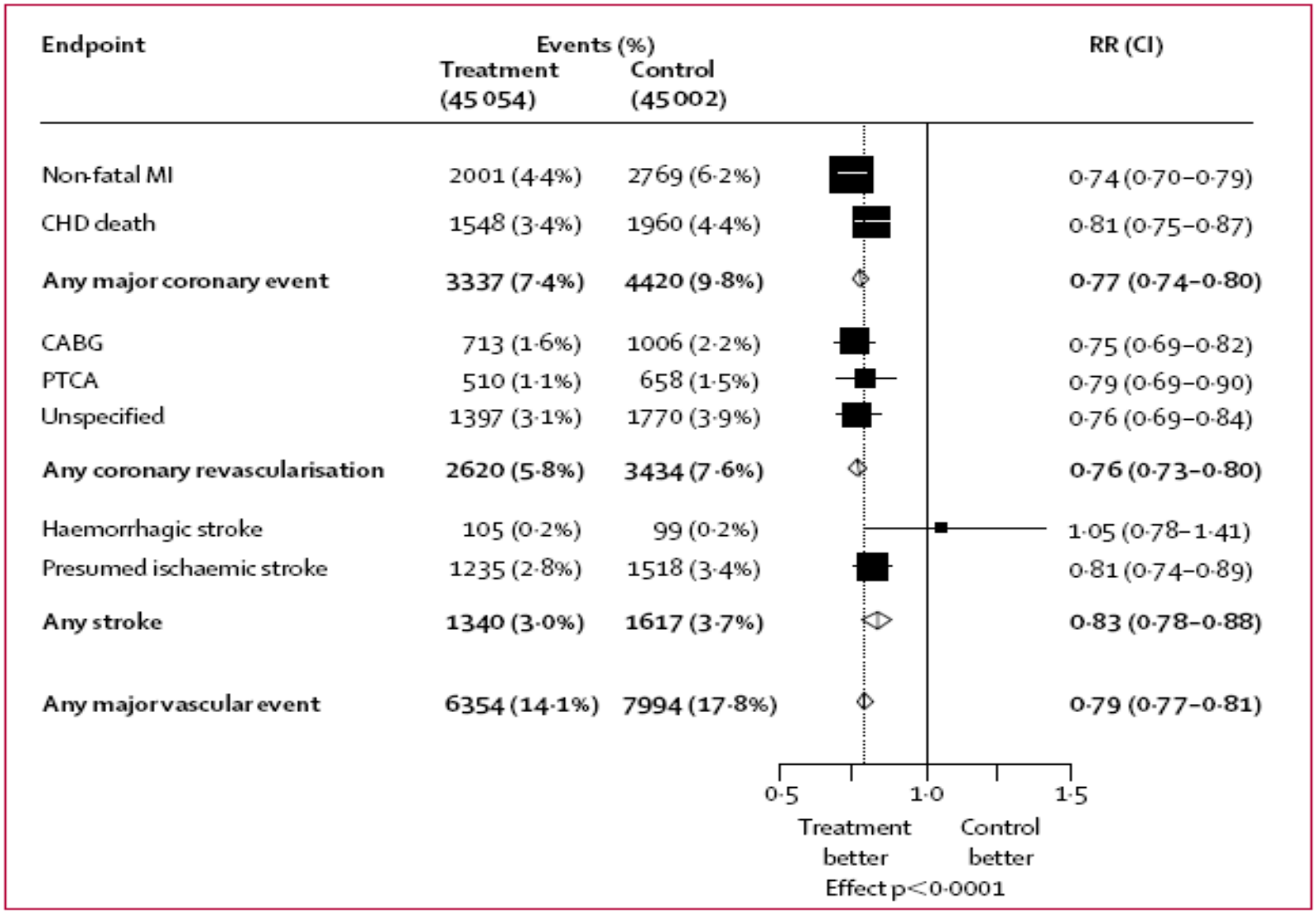


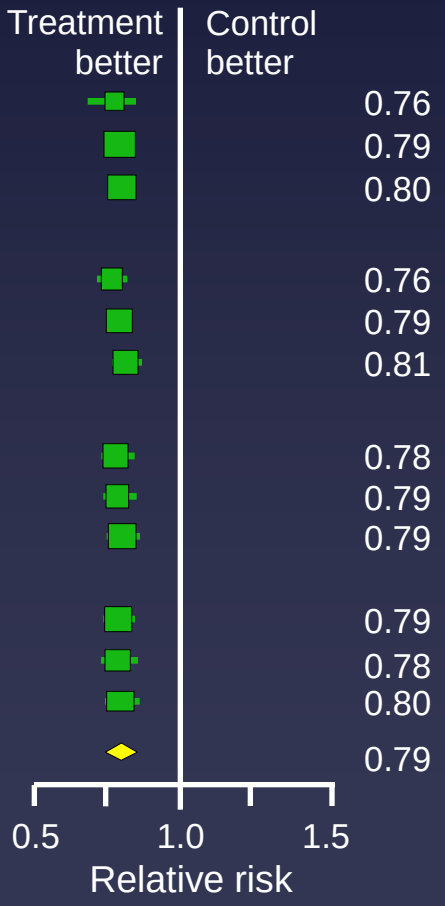
Figure 2: **Proportional effects on major vascular events per mmol/L LDL cholesterol reduction**

-Lancet 2005

Statin benefit independent of baseline lipids: Meta-analysis of 14 trials

Cholesterol Treatment Trialists' Collaboration

Groups	Events (%)		
	Treatment (45,054)	Control (45,002)	
Total-C (mg/dL)			
≤201	13.5	16.6	0.76
>201–251	13.9	17.4	0.79
>251	15.2	19.7	0.80
LDL-C (mg/dL)			
≤135	13.4	16.7	0.76
>135–174	14.2	17.6	0.79
>174	15.8	20.4	0.81
HDL-C (mg/dL)			
≤35	18.2	22.7	0.78
>35–43	14.3	18.2	0.79
>43	11.4	14.2	0.79
TG (mg/dL)			
≤124	13.4	16.8	0.79
>124–177	13.8	18.0	0.78
>177	15.3	18.8	0.80
Overall	14.1	17.8	0.79



CHD death, MI, stroke, coronary revascularization

CTT Collaborators. *Lancet*. 2005;366:1267-78.

Comparison of ezetimibe plus simvastatin versus simvastatin monotherapy on atherosclerosis progression in familial hypercholesterolemia: Design and rationale of the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial

John J. P. Kastelein, MD, PhD,[a] Philip T. Sager, MD,[b] Eric de Groot, MD, PhD,[a] and Enrico Veltri, MD[b] *Amsterdam, The Netherlands, and Kenilworth, NJ*

Background Lipid lowering through statin therapy significantly reduces the risk of cardiovascular events. The ENHANCE study is an international 2-year, randomized, double-blind, controlled trial designed to test the hypothesis that treatment of hypercholesterolemia by use of 2 complementary agents, ezetimibe (a specific cholesterol absorption inhibitor) and simvastatin (a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor), will result in larger beneficial effects on carotid artery intima-media thickness (CA IMT) than simvastatin monotherapy.

Methods The study will recruit 725 men and women with heterozygous familial hypercholesterolemia. After a placebo washout period, participants are randomized to receive daily administration of either simvastatin 80 mg and ezetimibe 10 mg or simvastatin 80 mg and placebo. The ENHANCE trial uses novel state-of-the-art single-frame digital image acquisition and rigorous quality assurance and control.

Results The primary end point is mean change from baseline to 2 years in CA IMT, using composite measures from the right and left far wall common carotid artery, carotid bulb, and internal carotid artery. Secondary end points include (1) the proportion of participants who exhibit reductions in CA IMT, (2) the change in maximum far wall IMT, (3) the proportion of participants who develop new carotid artery plaques, and (4) the changes in carotid plus common femoral artery IMT.

-Am Heart J 149; 2005

Study Design

Amendment 2

IMPROVE-IT

Patients stabilized post Acute Coronary Syndrome < 10 days
LDL ≤ 125*mg/dL (or ≤ 100**mg/dL if prior lipid-lowering Rx)

Double-blind

ASA + Standard Medical Therapy

N>18,000

Simvastatin 40 mg

Eze/Simva 10/40 mg

Follow-Up Visit Day 30, Every 4 Months

*3.2mM
**2.6mM

Duration: Minimum 2 1/2 year follow-up (>5250 events)

Primary Endpoint: CV Death, MI, Hospital Admission for UA, revascularization (> 30 days after randomization), or Stroke

SEAS – Safety
Cancer risk findings

About a 50% relative excess incidence of any cancer was observed during about 4 years of follow-up among the 944 patients randomly allocated ezetimibe 10mg plus simvastatin 40mg daily compared with the 929 allocated placebo.

102 (10.8%) versus 67 (7.2%) 95% CI 1.1 to 2.1; 2p=0.01

Cancer deaths - (39 vs 23) 2p=0.051

Other cases of cancer - (63 vs 44)

SEAS – Meta-analysis using ongoing Simva-EZ data

Hypothesis testing meta-analysis performed by Sir Richard Peto. The generated hypothesis of increased cancer risk should be confirmed by ongoing trial data

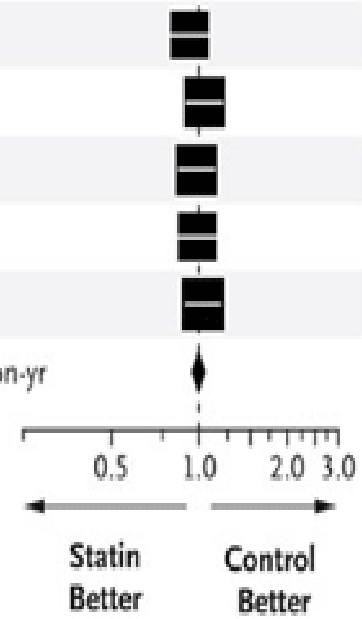
Trials analyzed: (about 4 times more cancers than SEAS)

SHARP – This trial is comparing ezetimibe 10mg plus simvastatin 20mg daily vs double placebo in subjects with chronic kidney disease. Data included 9,264 subjects with unblinded follow-up data available for a median of 2.7 years

IMPROVE-IT 11353 subjects with unblinded median f/u 1 year

Statins and Cancer

Year of Onset	No. with Cancer Onset in Trials		Risk Ratio for Statin vs. Control (confidence interval)
	Statin (N=45,054)	Control (N=45,002)	
0–1	488	535	
>1–2	616	588	
>2–3	582	588	
>3–4	511	503	
>4	613	590	
All	2810/199,063 person-yr (1.4% per yr)	2804/197,680 person-yr (1.4% per yr)	



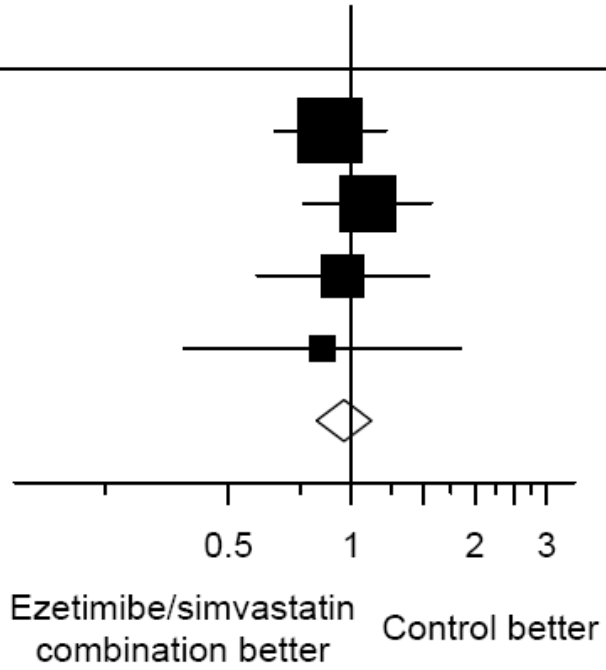
SEAS –Cancer incidence SHARP and IMPROVE IT

ANY SITE, 10th ICD C00–C99

Years	Events (%) Ezetimibe/ simvastatin	Control	RR (CI)
0–1 year	128 (1.2%)	144 (1.4%)	0.89 (0.65 – 1.21)
1–2 years	109 (1.5%)	99 (1.4%)	1.09 (0.77 – 1.56)
2–3 years	56 (1.5%)	59 (1.6%)	0.95 (0.59 – 1.54)
3+ years	20 (1.1%)	24 (1.3%)	0.85 (0.39 – 1.84)
All years	313 (3.0%)	326 (3.2%)	0.96 (0.82 – 1.12)

Trend test: χ^2_1=0.04 (NS)

99% or 95% limits



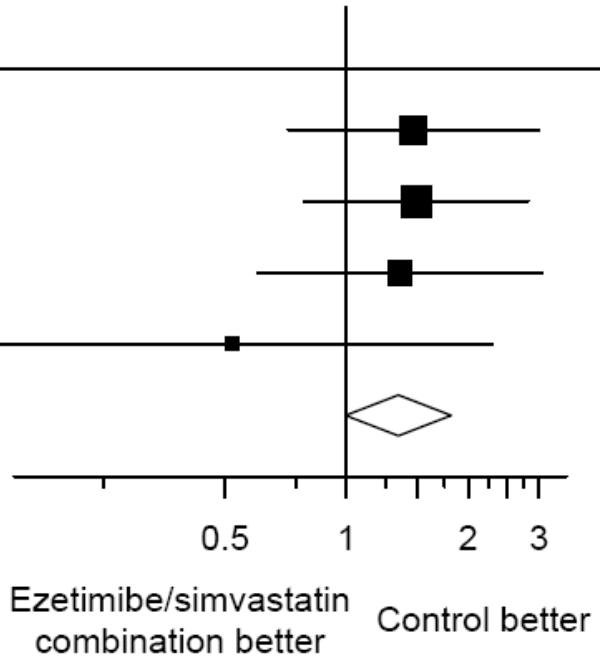
SEAS – Cancer death in SHARP and IMPROVE IT

ANY SITE, 10th ICD C00–C99

Years	Events (%) Ezetimibe/ simvastatin	Control	RR (CI)
0–1 year	31 (0.3%)	21 (0.2%)	1.46 (0.72 – 2.99)
1–2 years	39 (0.5%)	26 (0.4%)	1.49 (0.78 – 2.82)
2–3 years	23 (0.6%)	17 (0.4%)	1.35 (0.60 – 3.06)
3+ years	4 (0.2%)	8 (0.4%)	0.52 (0.12 – 2.30)
All years	97 (0.9%)	72 (0.7%)	1.34 (0.99 – 1.82)

Trend test: χ^2_1=1.30 (NS)

99% or 95% limits



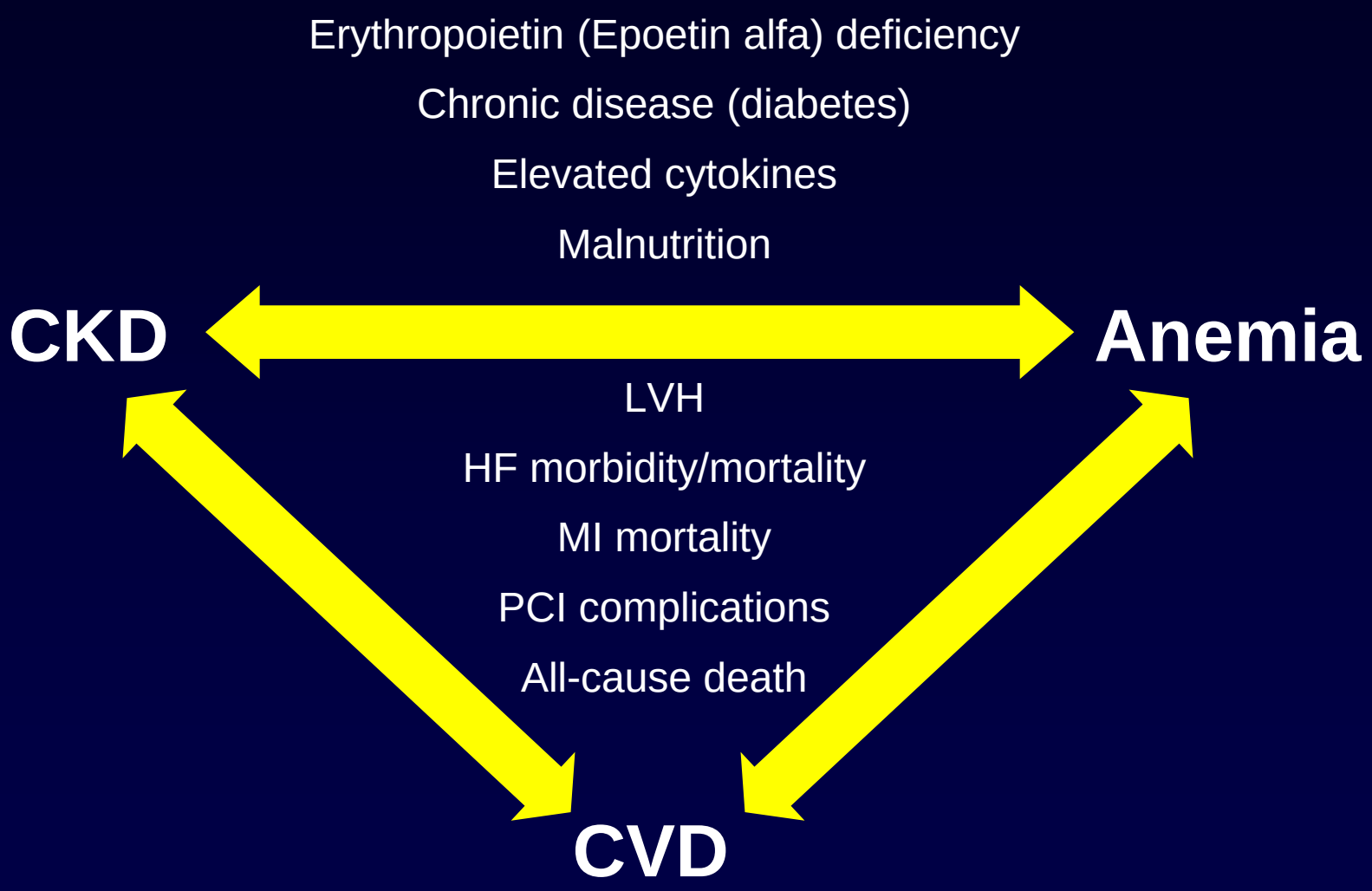
SEAS – Conclusions

Aggressive lipid lowering with simva and EZ does not effect progression of AS in those with mild to moderate disease at baseline

The 20% reduction in new CV events associated with the Simva/EZ treatment arm is about what would be expected for a primary prevention population

The available results do not provide credible evidence of any adverse effect of combination therapy with Simva/EZ on cancer

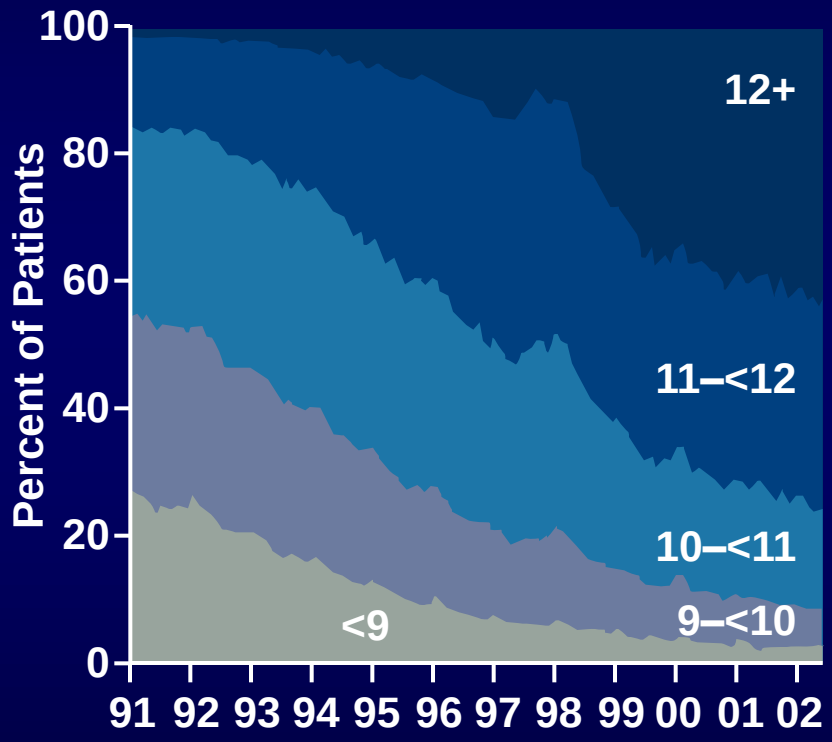
Deadly Triangle



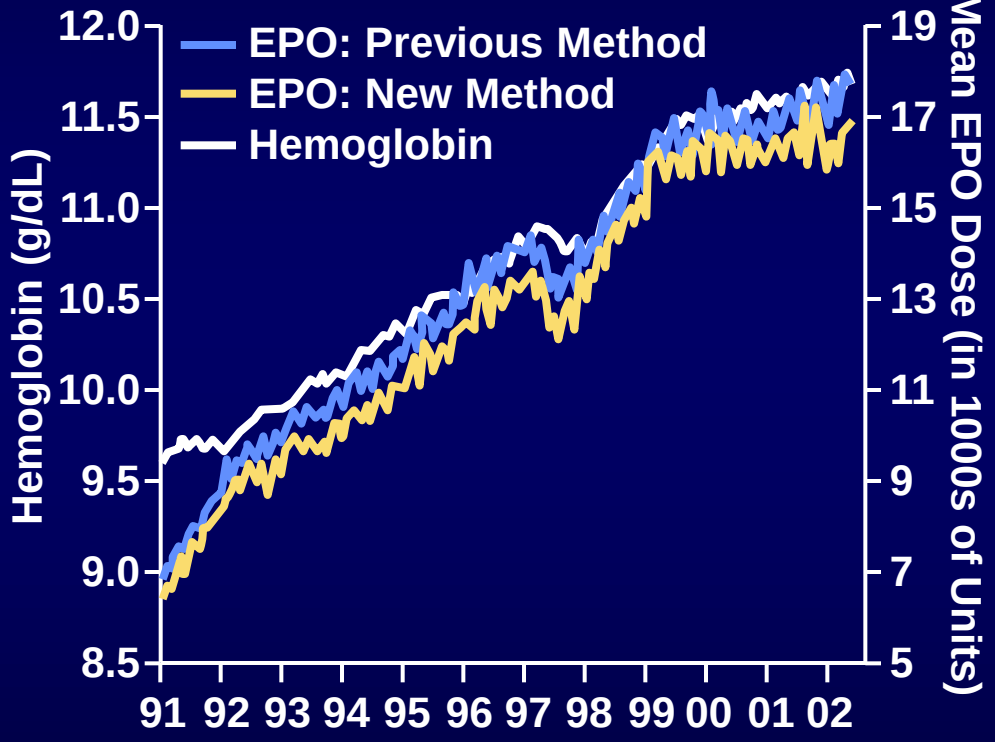
McCullough PA, Lepor NE. The deadly triangle of anemia, renal insufficiency, and cardiovascular disease: implications for prognosis and treatment. Rev Cardiovasc Med. 2005 Winter;6(1):1-10. NLM CIT. ID: 15741920

ESRD Anemia Treatment

Patient Distribution, by Mean Monthly Hemoglobin (g/dL)

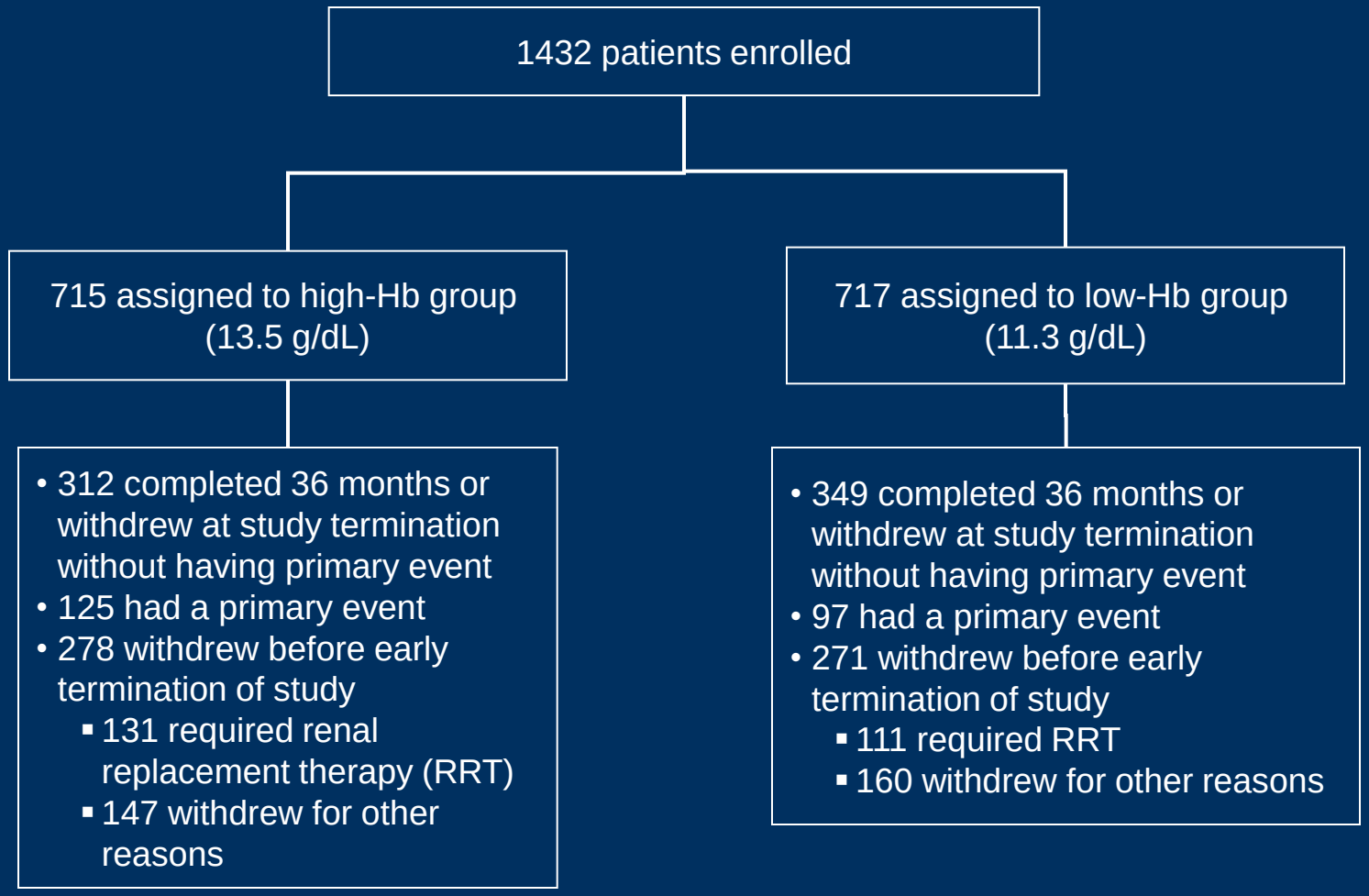


Mean Monthly Hemoglobin (g/dL) and Mean EPO Dose per Week



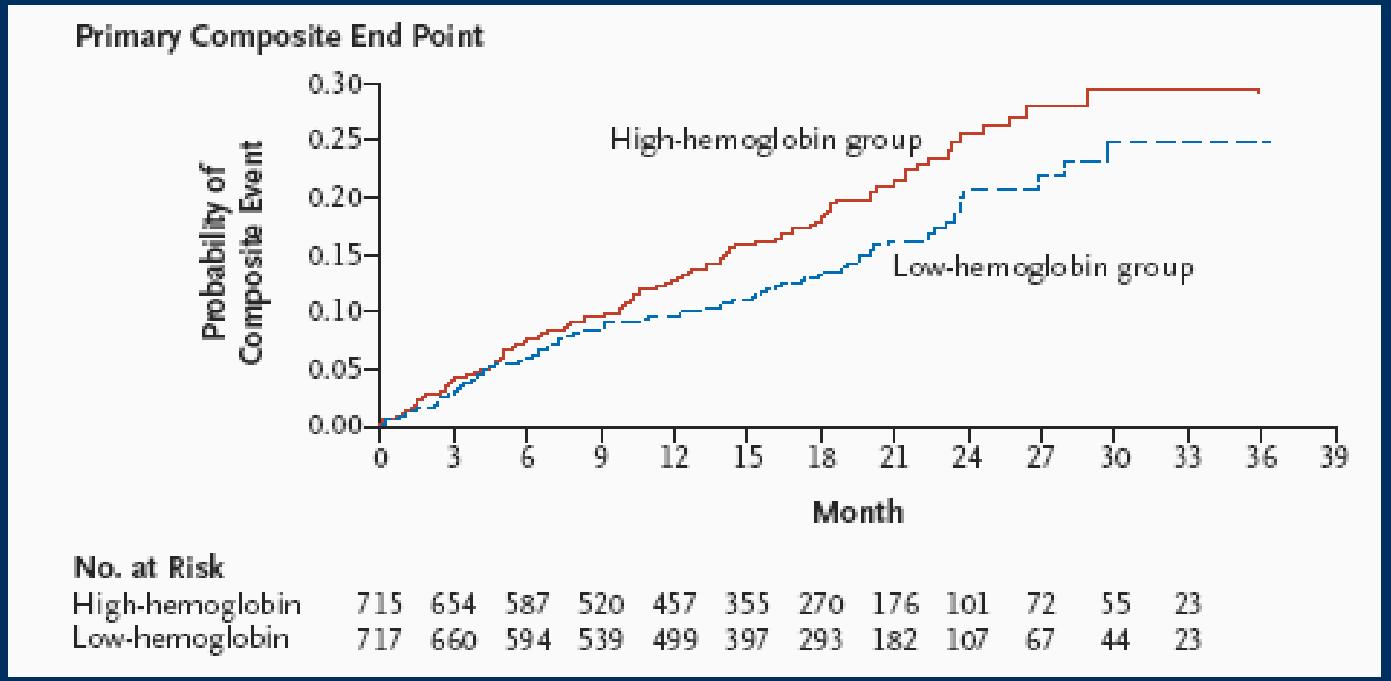
USRDS. 2003.

CHOIR Trial



Singh AK, et al. *N Engl J Med*. 2006;355:2085-98.

CHOIR Results – Primary Endpoint Composite Events

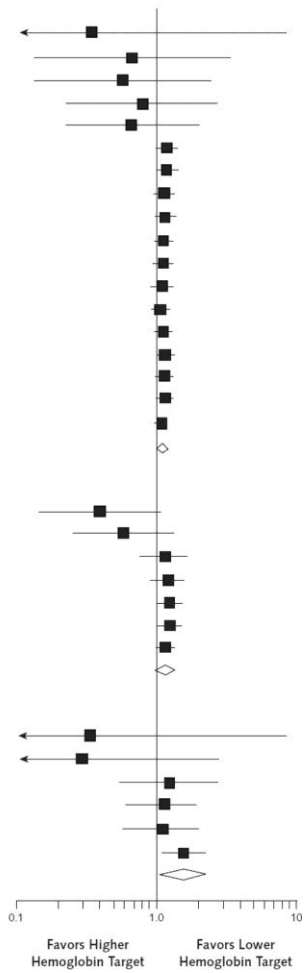


- 222 composite events (death, MI, hospitalization for CHF, stroke)
  - High Hb (13.5 g/dL): 125 events (18%)
  - Low Hb (11/3 g/dL): 97 events (14%)
  - Hazard ratio = 1.34; 95% CI, 1.03 to 1.74 (*P* = 0.03)

Singh AK, et al. *N Engl J Med*. 2006;355:2085-2098.

Cumulative meta-analysis of randomized trials comparing higher versus lower hemoglobin targets on clinical outcomes in patients with chronic kidney disease.ACORD = Anemia Correction in Diabetes; EPO = erythropoietin; CHOIR = Correction of Hemoglobin and Out...

Study, Year (Reference)	Cumulative Events, *n/N*		Cumulative Relative Risk (95% CI)	Cumulative *P* Value
	Higher Hemoglobin Target	Lower Hemoglobin Target		
All-cause mortality				
Canadian EPO Study Group, 1990 (7)	0/38	1/40	0.35 (0.01–8.35)	0.52
Bahlmann et al, 1991 (8)	2/91	3/86	0.68 (0.13–3.52)	0.65
Revicki et al, 1995 (14)	2/134	4/126	0.58 (0.13–2.48)	0.46
Nissenson et al, 1995 (13)	4/212	5/200	0.80 (0.23–2.77)	0.72
Kuriyama et al, 1997 (11)	5/254	7/231	0.67 (0.22–2.03)	0.48
Besarab et al (NHS), 1998 (22)	188/872	157/846	1.19 (1.00–1.43)	0.06
Foley et al, 2000 (30)	192/945	160/919	1.20 (1.00–1.43)	0.05
Furuland et al, 2003 (31)	216/1125	186/1083	1.15 (0.97–1.36)	0.11
Roger et al, 2004 (36)	216/1199	186/1161	1.15 (0.97–1.36)	0.11
Gouva et al, 2004 (32)	219/1244	190/1204	1.14 (0.97–1.35)	0.12
Levin et al, 2005 (33)	220/1318	193/1282	1.14 (0.96–1.34)	0.14
Parfrey et al, 2005 (24)	233/1614	213/1582	1.10 (0.93–1.30)	0.25
Rossert et al, 2006 (37)	234/1809	219/1777	1.09 (0.92–1.28)	0.31
Drüeke et al (CREATE), 2006 (29)	265/2110	240/2079	1.12 (0.96–1.31)	0.16
Singh et al (CHOIR), 2006 (23)	317/2825	276/2796	1.15 (1.00–1.34)	0.05
Macdougall et al, 2007 (34)	318/2890	282/2928	1.15 (0.99–1.33)	0.06
Cianciaruso et al, 2008 (27)	319/2939	282/2974	1.15 (0.99–1.33)	0.06
Pfeffer et al (TREAT), 2009 (18)	731/4951	677/5000	1.09 (0.99–1.20)	0.07
Cumulative total	731/4951	677/5000	1.09 (0.99–1.20)	0.07
Serious cardiovascular events				
Bahlmann et al, 1991 (8)	5/53	11/46	0.39 (0.14–1.07)	0.07
Foley et al, 2000 (30)	9/126	14/119	0.58 (0.25–1.33)	0.20
Rossert et al, 2006 (37)	57/321	49/314	1.14 (0.77–1.67)	0.52
Drüeke et al (CREATE), 2006 (29)	115/622	96/616	1.18 (0.90–1.57)	0.24
Singh et al (CHOIR), 2006 (23)	240/1337	193/1333	1.23 (1.00–1.51)	0.05
Ritz et al (ACORD), 2007 (35)	246/1426	198/1416	1.23 (1.00–1.51)	0.05
Pfeffer et al (TREAT), 2009 (18)	878/3438	800/3442	1.15 (0.98–1.33)	0.08
Cumulative total	878/3438	800/3442	1.15 (0.98–1.33)	0.08
Stroke				
Bahlmann et al, 1991 (8)	0/53	1/53	0.33 (0.01–8.18)	0.50
Kuriyama et al, 1997 (11)	0/95	2/84	0.29 (0.03–2.75)	0.28
Besarab et al (NHS), 1998 (22)	14/713	11/699	1.22 (0.53–2.85)	0.64
Singh et al (CHOIR), 2006 (23)	26/1428	23/1416	1.11 (0.61–2.04)	0.73
Ritz et al (ACORD), 2007 (35)	26/1517	24/1499	1.06 (0.59–1.93)	0.84
Pfeffer et al (TREAT), 2009 (18)	127/3529	77/3525	1.51 (1.03–2.21)	0.04
Cumulative total	127/3529	77/3525	1.51 (1.03–2.21)	0.04



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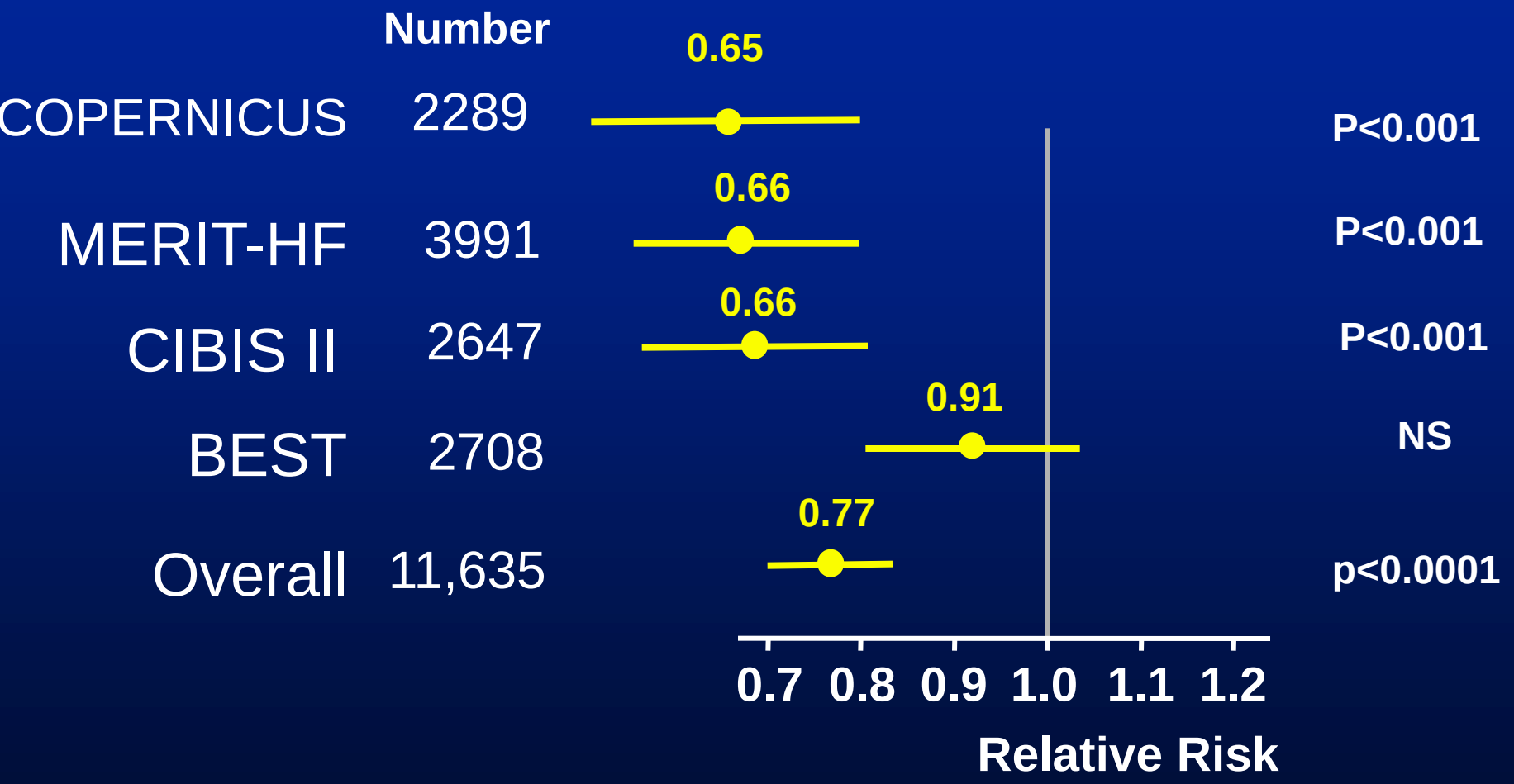
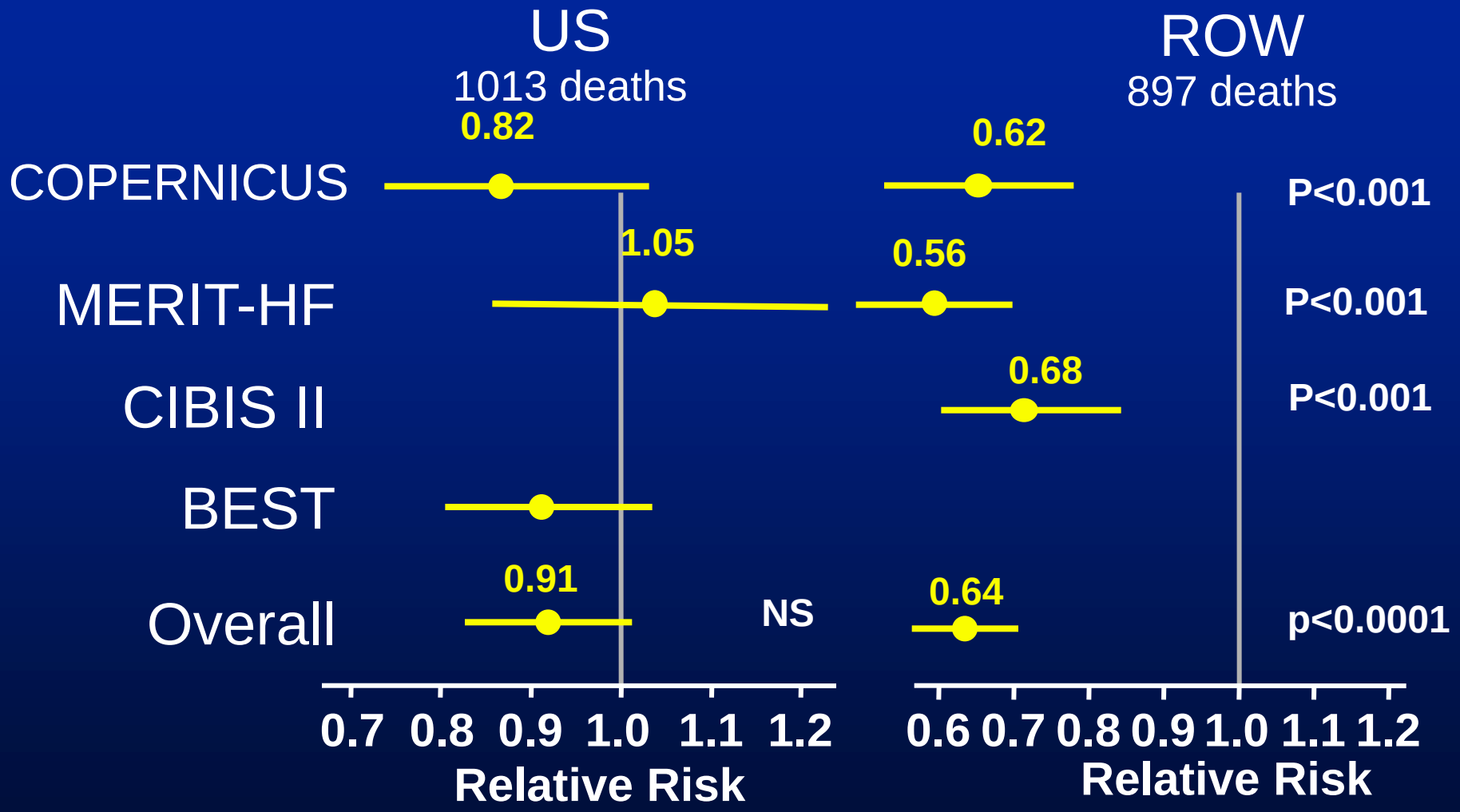
Annals of Internal Medicine

Beta-blockers in heart failure
Landmark outcome trials



Modified from O'Connor et al ACC 2009

Beta-blocker trials
US vs. ROW



Modified from O'Connor et al ACC 2009

LIBERATING DATA ACROSS TRIALS FOR BIG CONCLUSIONS

- Ethically sound
- Clarifies findings for policy recommendations
- Often raises new questions
- When the “evidence step” is skipped, there is a significant hazard to the public health
- One element of the “evidence step” should be sharing patient level data across trials
- Many details to work out!