Social Value and Meaningful Outcomes

In Clinical Trials Research

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Stopping a Trial Early for Superiority

PARADIGM trial
LCZ696 vs enalapril in chronic heart failure
[NEJM online 30 Aug 2014]

intended 7980 patients
primary endpoint: CV death or heart failure hospitalisation
key secondary endpoint: CV death
event driven trial: require 2410 patients with primary event

interim analyses for efficacy after ⅓ ½ and ⅔ of events

stopping guideline for efficacy for both primary and secondary:
P<0.0001 at first interim analysis
P<0.001 at second and third

Third Interim Analysis: DMC meets 20 March 2014

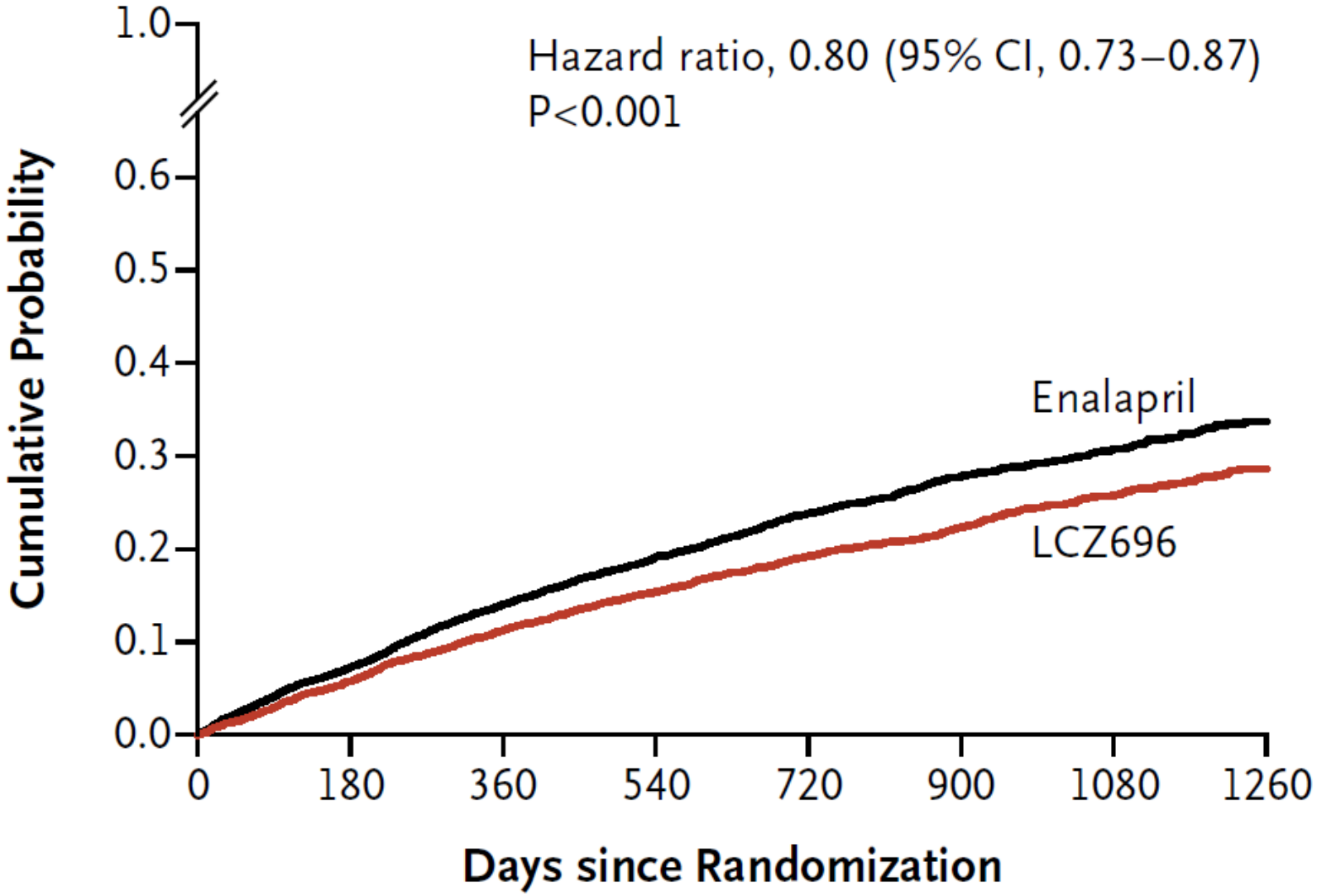
	LCZ696	enalapril	
N	4205	4231	
adjudicated events:			
primary	791	953	P=0.00002
CV death	463	564	P=0.0012
adjudicated + pending:			
CV death	517	628	P=0.001
all cause death	657	765	P=0.004

trial stopped early for superiority

Published Results on 30 August 2014 (median 27m f-up)

				hazard ratio
primary	914	1117	P<0.0000001	0.80
CV death	558	693	P<0.0001	0.80
all cause death	711	833	P<0.001	0.84

Primary End Point



No. at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

Issues re recommendation to stop early

statistical stopping guideline achieved

planned trial closure less than 1 year away

not all primary and secondary events adjusted

any serious safety concerns?
any issues re patient subgroups?
any other external evidence?

Implications for regulatory approval: a unique trial

risk that evidence changes in final report:
will “regression to the truth” occur?

IMPROVE-IT trial [AHA Nov 2014]

18,144 patients post ACS event on simvastatin 40 mg

ezetimibe vs placebo

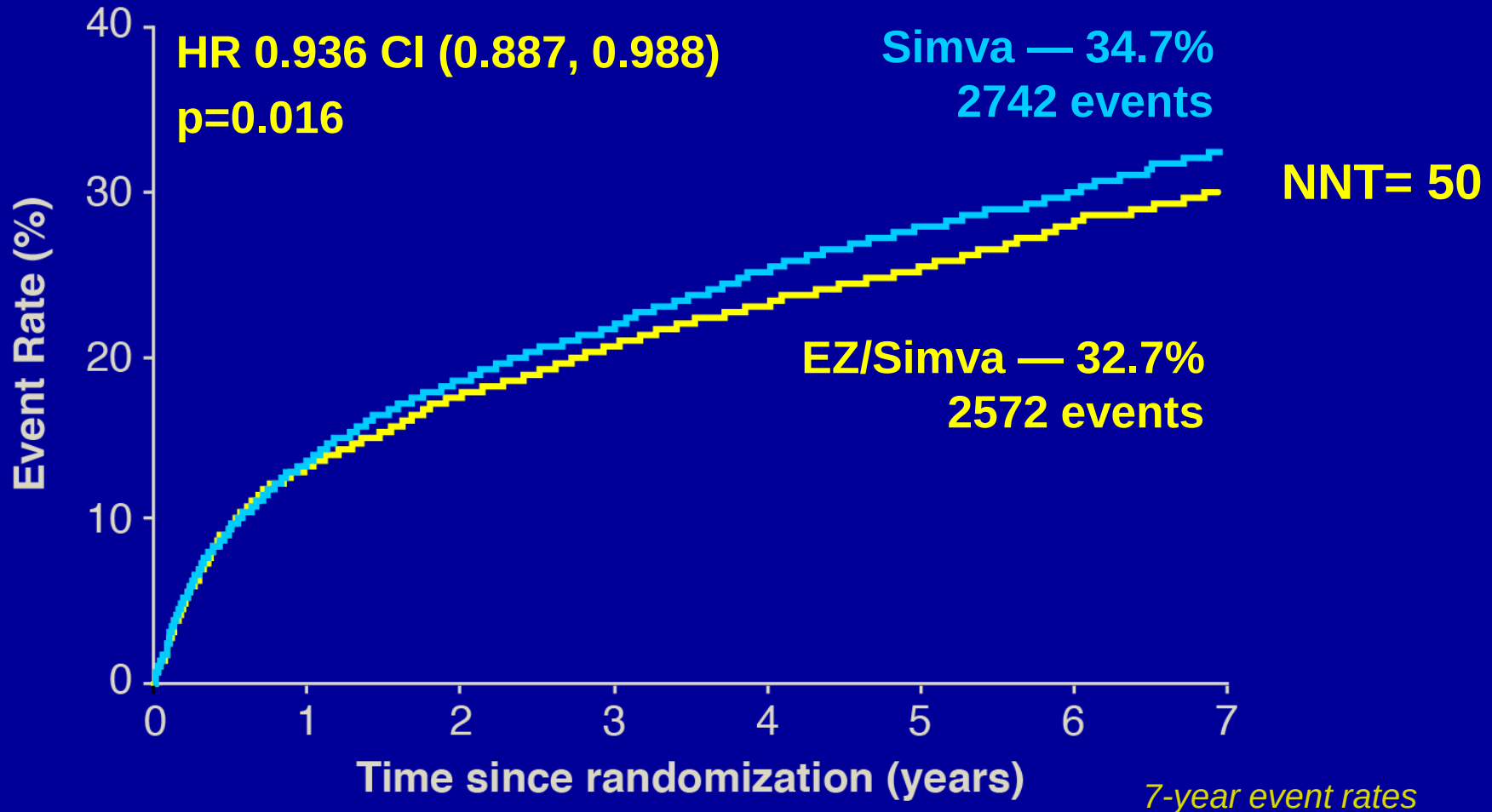
composite primary endpoint:
CV death, MI, stroke, unstable angina, coronary revasc.

5314 primary events over mean 5.4 years follow-up

the definitive study of ezetimibe?

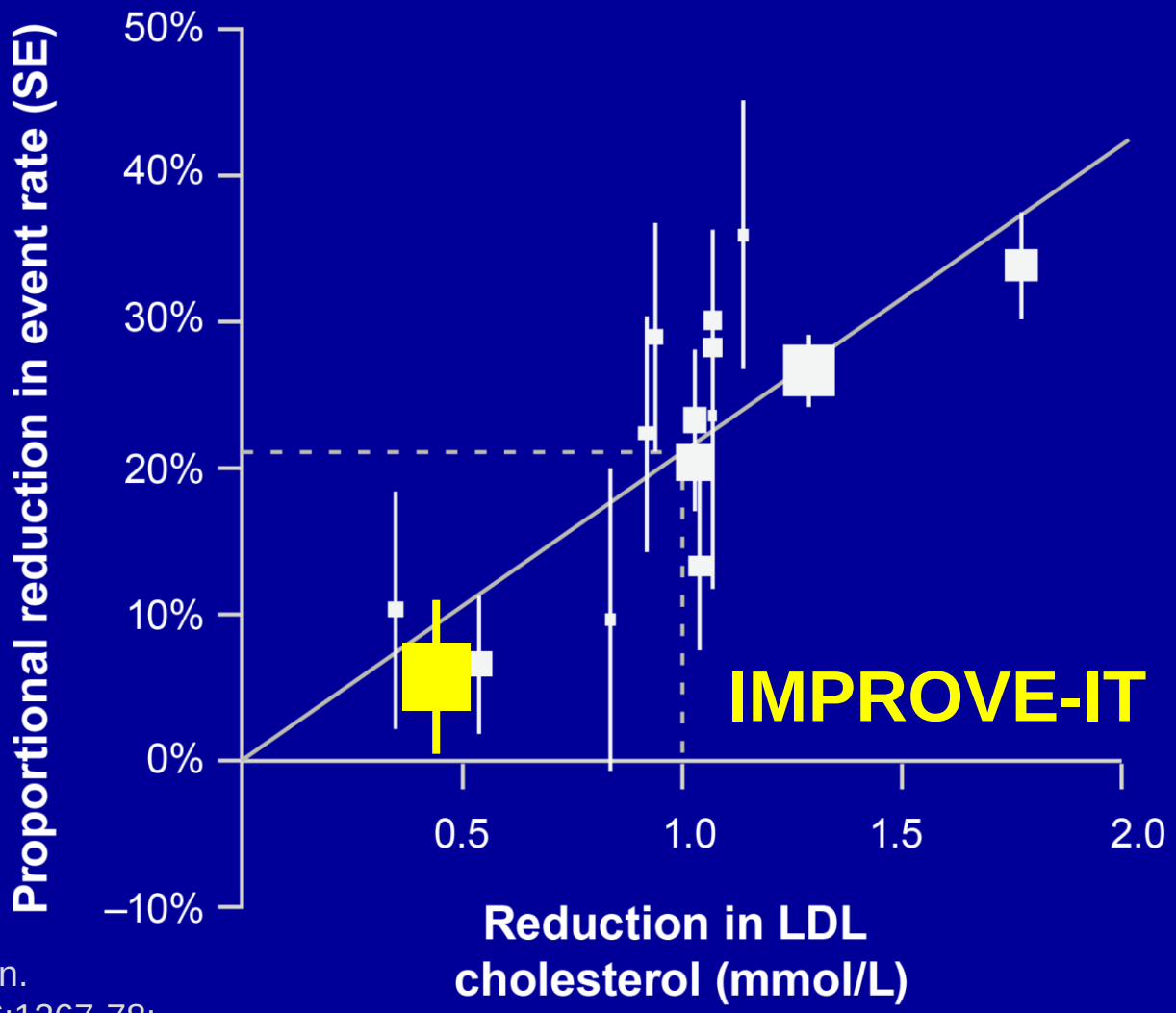
Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



7-year event rates

IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit



CTT Collaboration.
Lancet 2005; 366:1267-78;
Lancet 2010;376:1670-81.

My Conclusions

on top of simvastatin, ezetimibe had a modest mean reduction in LDL-C (16.7 mg/dl)

modest impact on cardiovascular primary events:

relative risk reduction 6.4% (95% CI 2.2% to 11.3%)

absolute risk reduction 2.0%

somewhat less than equivalent LDL-C reduction using a statin?

Renal Denervation for Resistant Hypertension

SYMPLICITY HTN-3 [NEJM March 2014]

renal denervation vs sham procedure
[N=364] [N=171]

primary outcome: 6 month change in systolic BP

no evidence of a treatment effect

contradicts previous uncontrolled and unblinded trials

Symplicity 1 Uncontrolled Trial [Lancet 2009]

86 patients received renal denervation

mean SBP decrease 22 mmHg after 6 months

Symplicity 2 Randomised Unblinded Trial [Lancet 2010]

	renal denervation	vs control	
N	49	51	
mean SBP decrease	32 mmHg	1 mmHg	after 6 months

Symplicity 3 Randomised Single Blinded Trial [NEJM 2014]

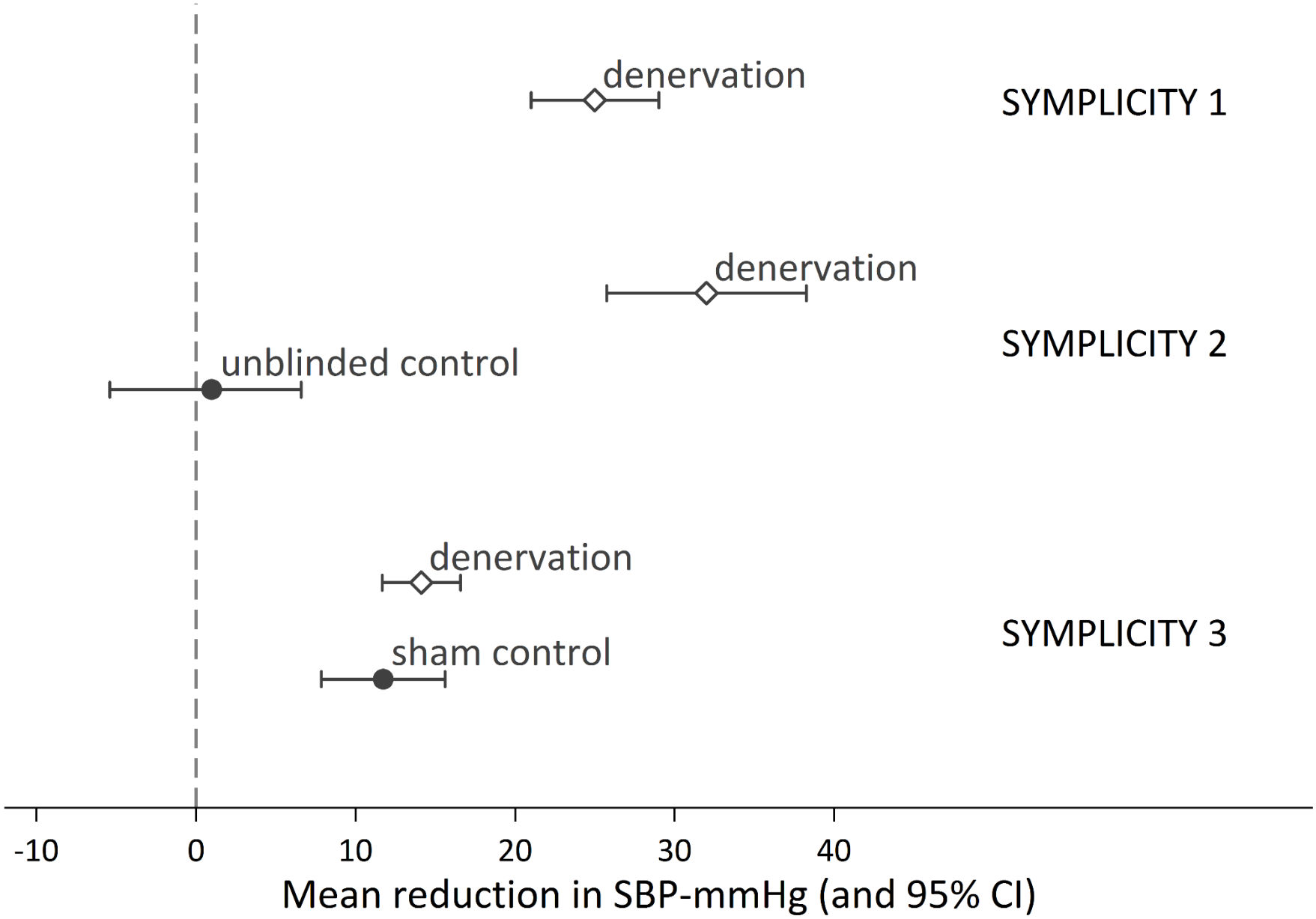
	renal denervation	vs sham procedure	
N	364	171	
mean SBP decrease	14 mmHg	12 mmHg	after 6 months

explanation: placebo effect, ie device ineffective

counter arguments: patient selection, drug use

poor operators

Changes in SBP at 6 months in three renal denervation trials



Trials of Medical Devices in Europe

CE Mark: device can be marketed in EU

typically requires uncontrolled study, not an RCT
procedure via Notified Bodies

eg. Stents, TAVIs, renal denervation readily approved
much faster than FDA (CDRH) who require RCTs

speed in Europe vs thoroughness in US

⇓ ⇓

good if all is well necessary to establish efficacy and safety

need for radical improvement in Europe

HORIZONS trial: 3602 STEMI patients undergoing primary PCI [Lancet 2009]

co-primary 1 year endpoints	**heparin + GPI**	**bivalirudin alone**	
major bleed	9.2%	5.8%	P<.0001
net adverse clinical events	18.3%	15.6%	P=.02

EUROMAX trial: 2218 STEMI patients undergoing primary PCI [NEJM 2012]

	heparin + GPI	**bivalirudin alone**	
death + major bleed (primary 30 day endpoint)	6.0%	2.6%	P<.0001
re-infarction	0.9%	1.7%	P=.08

bivalirudin alone looks superior to heparin **+GPI**

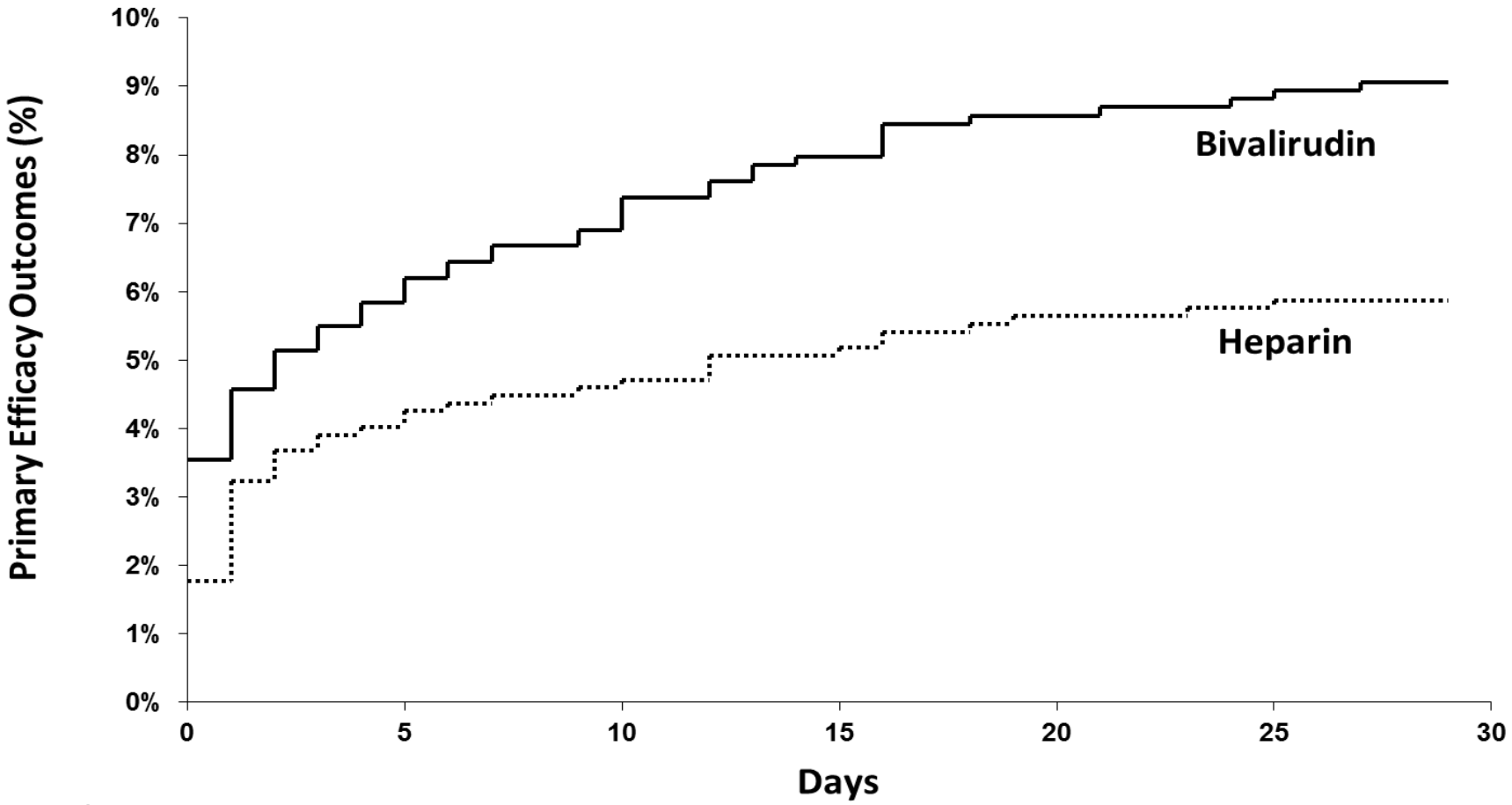
HEAT PPCI trial [ACC March 2014]

anti thrombotic therapy with selective use of GPI

	heparin vs	**bivalirudin**	
N	914	915	
MACE (primary)	**52**	**79**	**P=0.01**
Death	39	46	
Stroke	11	15	
Reinfarction	8	24	
TLR	6	24	
Stent thrombosis	6	24	P=0.001
Major bleed	28	32	P=0.59

Heparin more efficacious and equally safe?

Timing of First MACE Event



No. at risk

Heparin	907	871	866	862	857	856
Bivalirudin	905	853	844	835	830	828

Event curve shows first event experienced

HORIZONS, EUROMAX

funded, conducted by industry

GPI added to standard (cheap) comparator heparin

HEAT PPCI

single centre trial (Liverpool) with mostly public funds

head-to-head comparison (heparin v bivalirudin)

randomised all eligible patients

multi-center heparin v bivalirudin trial needed

De Mets and Califf [JAMA 2011:305 p 713]

A Historical Perspective on Clinical Trials Innovation and Leadership:

Where have the Academics Gone?

“a better balance between commercial interests and public health is critically needed”

many key trials of drugs have no commercial value

public funding is insufficient, difficult to get

example: required trials of beta-blockers

Perioperative beta-blocker use in non-cardiac surgery

DECREASE trial of bisoprolol [NEJM 1999;341 p 1789-]

	bisoprolol	control		
N	59	53		"too good to be true"?
death	2	9	P=0.02	**scientific misconduct**
myocardial infarction	0	9	P<0.001	

POISE trial of metoprolol [Lancet 2008;371 p 1839-]

	metropolol	placebo	
N	4174	4177	
death	129	97	P=0.03
myocardial infarction	176	239	P<0.002

Beta blocker in non-cardiac surgery

ESC/ESA Guidelines 2014: evidence inconclusive

2 past key trials favouring beta-blocker declared invalid
ESC Guidance recently re-written, evidence inconclusive
largest trial shows excess mortality

new large placebo controlled trial needed in high-risk patients:
which beta-blocker, when to give it, which patients,
primary outcome, over what period, how many patients?

how to fund this trial?

Effects of Long-Term Use of Cardiovascular Drugs

Julian and Pocock, Lancet Letter Jan 24, 2015

effectiveness and safety of drugs change with age

concern particularly relevant to beta-blockers

Desmond Julian experienced two potentially fatal events:

1) Hypotension on exercise: skiing in Davos!

2) Extreme bradycardia due to sinoatrial block

both abnormalities ceased when beta-blocker stopped

Proposed Randomised Trial of Withdrawal of Beta-blocker

patients with stable coronary disease take several drugs

eg aspirin, beta-blocker, statin, ACE inhibitor
maybe anti-hypertensive, anti-diabetic, others

industry-sponsored placebo-controlled trials geared to adding new drugs

but when can a drug be withdrawn, either because it becomes ineffective or actually harmful, especially in elderly

which patients? which drug? which outcomes?

PCI for stable CHD, already on beta-blocker

at post-procedure follow-up visit
randomise to withdrawal or continuation of beta-blocker

primary endpoint: death, MI or CHF over 1 year

large, simple trial

When to stop dual antiplatelets after drug-eluting stent

DAPT Trial [NEJM online Nov 2014]

9961 patients received drug-eluting stent
and on 12 months aspirin + clopidogrel or prasugrel

randomised to clopidogrel/prasugrel or placebo on top of aspirin
ie CONTINUE out to 30 months or STOP

co-primary efficacy endpoints:
- stent thrombosis
- composite of death, MI, stroke

primary safety endpoint:
- moderate or severe bleeding (GUSTO criteria)

Key Results of DAPT Trial

	Continue	Stop	difference	
N	5020	4941		
Stent Thrombosis	0.4%	1.4%	-1.0%	P<0.001
Death, MI, stroke	4.3%	5.9%	-1.6%	P<0.001
Death	2.0%	1.5%	+0.5%	P=0.05
Myocardial Infarction	2.1%	4.1%	-2.0%	P<0.001
Stroke	0.8%	0.9%	-0.1%	P=0.32
Bleed (severe or moderate)	2.5%	1.6%	+1.0%	P=0.001
Bleed (BARC2, 3 or 5)	5.6%	2.9%	+2.6%	P<0.001

trade-off: less stent thrombosis and MI
more bleeds (and increased mortality?)

trade-off between efficacy and safety is patient-specific

do these findings apply to all patients?

subgroup analysis, i.e. data dredging!

DES type and risk of myocardial infarction

	N	hazard ratio (95% CI)
sirolimus	1118	
zotarolimus	1264	0.35 (0.24, 0.49)
paclitaxel	2666	
everolimus	4703	0.63 (0.44, 0.91)

post hoc interaction P=0.019

Meta-analysis: RCTs of Differing Dual Antiplatelet Duration

[Giustino et al JACC 2015 in press]

Trial Acronym	Shorter DAPT	Longer DAPT	N
OPTIMIZE	3 m	12 m	3119
RESET	3 m	12 m	2117
ISAR-SAFE	6 m	12 m	4000
ITALIC	6 m	12 m	1822
SECURITY	6 m	12 m	1399
EXCELLENT	6 m	12 m	1443
PRODIGY	6 m	24 m	1970
ARCTIC	12 m	18-30 m	1259
DAPT	12 m	30 m	9961
DES-LATE	12 m	48 m	5045

Stopping DAPT: risks versus benefits

	Stent Thrombosis		Clinically Sig. Bleed	
	Shorter DAPT	Longer DAPT	Shorter DAPT	Longer DAPT
OPTIMIZE	13	12	10	14
RESET	2	3	5	10
ISAR-SAFE	5	4	6	13
ITALIC	3	0	5	7
SECURITY	2	3	4	8
EXCELLENT	6	1	2	4
PRODIGY	15	13	15	27
ARCTIC	3	0	1	7
DAPT	69	31	84	124
DES-LATE	25	13	63	99
Combined	**143**	**80**	**195**	**313**

Trade Off: Excess of Stent Thromboses, Fewer Bleeds

Combined Results: Shorter vs Longer DAPT

Ratio Scale	Odds Ratio	(95% CI)
Stent Thrombosis	1.71	(1.26, 2.32)
Clinically Significant Bleed	0.63	(0.52, 0.75

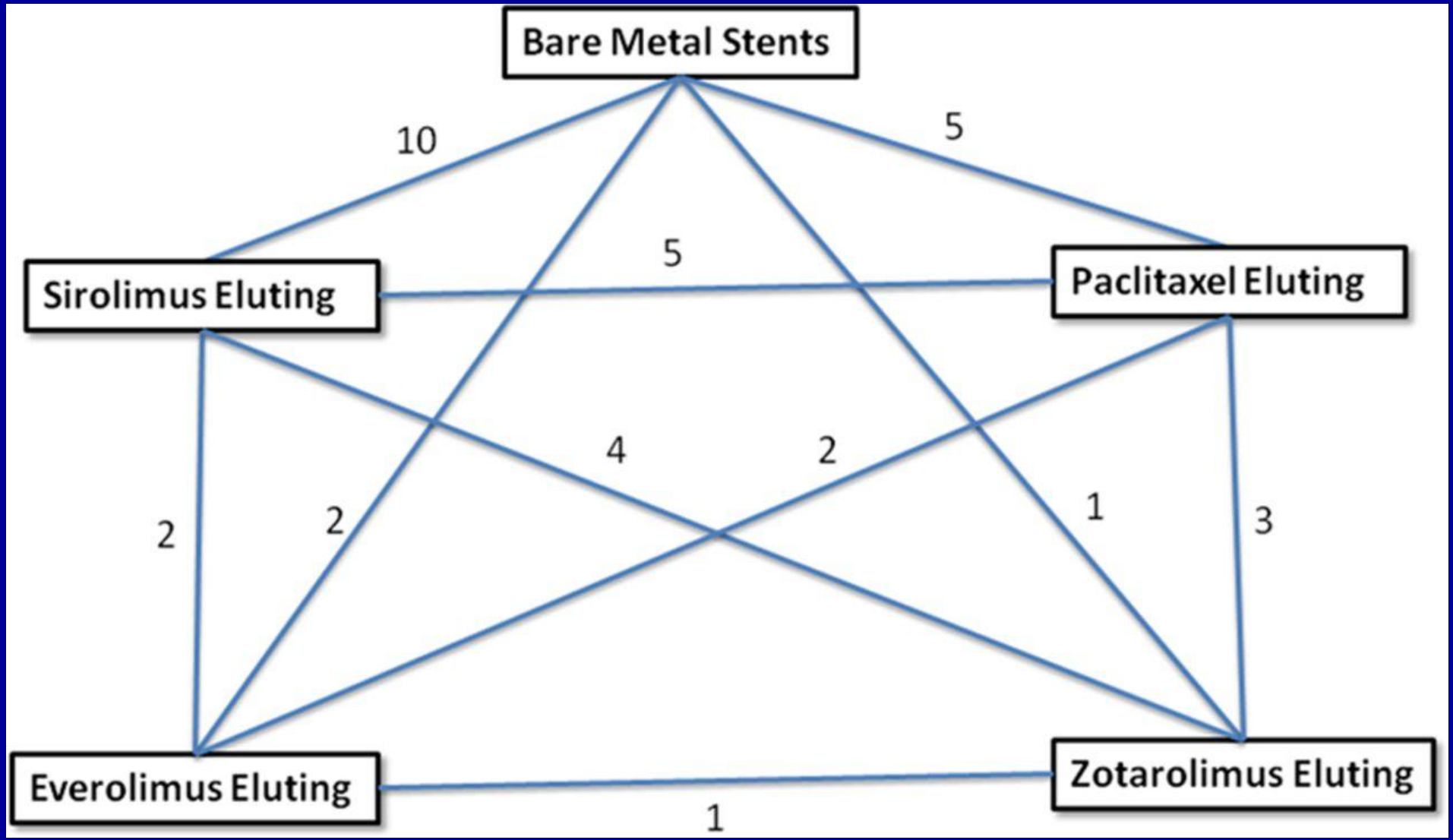
Absolute Scale	**Incidence Rate Difference** (95% CI) per 100 patient years	
Stent Thrombosis	+0.21	(+0.11, +0.31)
Clinically Significant Bleed	-0.51	(-0.68, -0.33)

for every ST caused, around 2.4 CSB events prevented

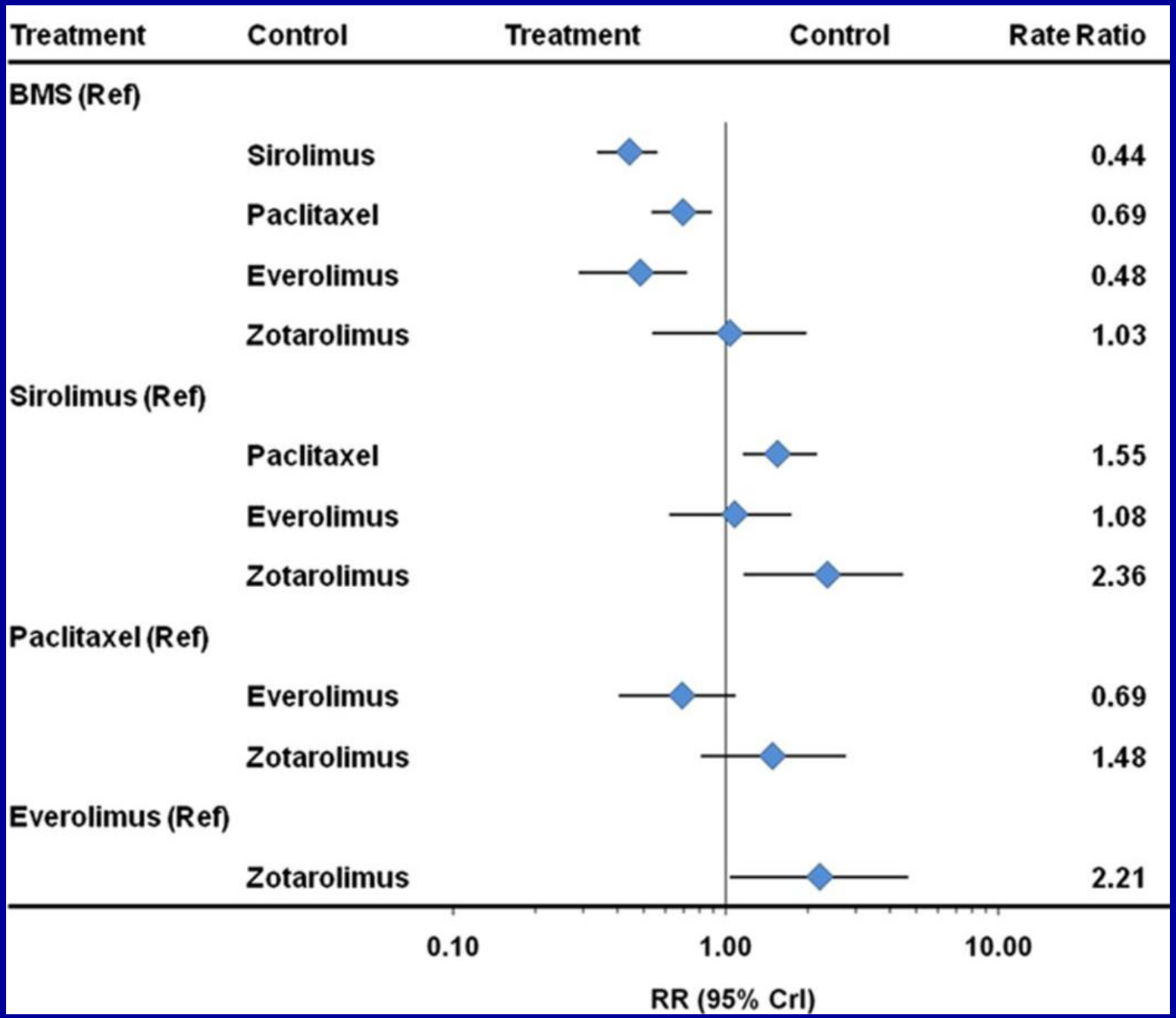
Comparison of Stents in STEMI patients

[Bangalore et al Circ Cardiov Interv 2013; 6 p 378-]

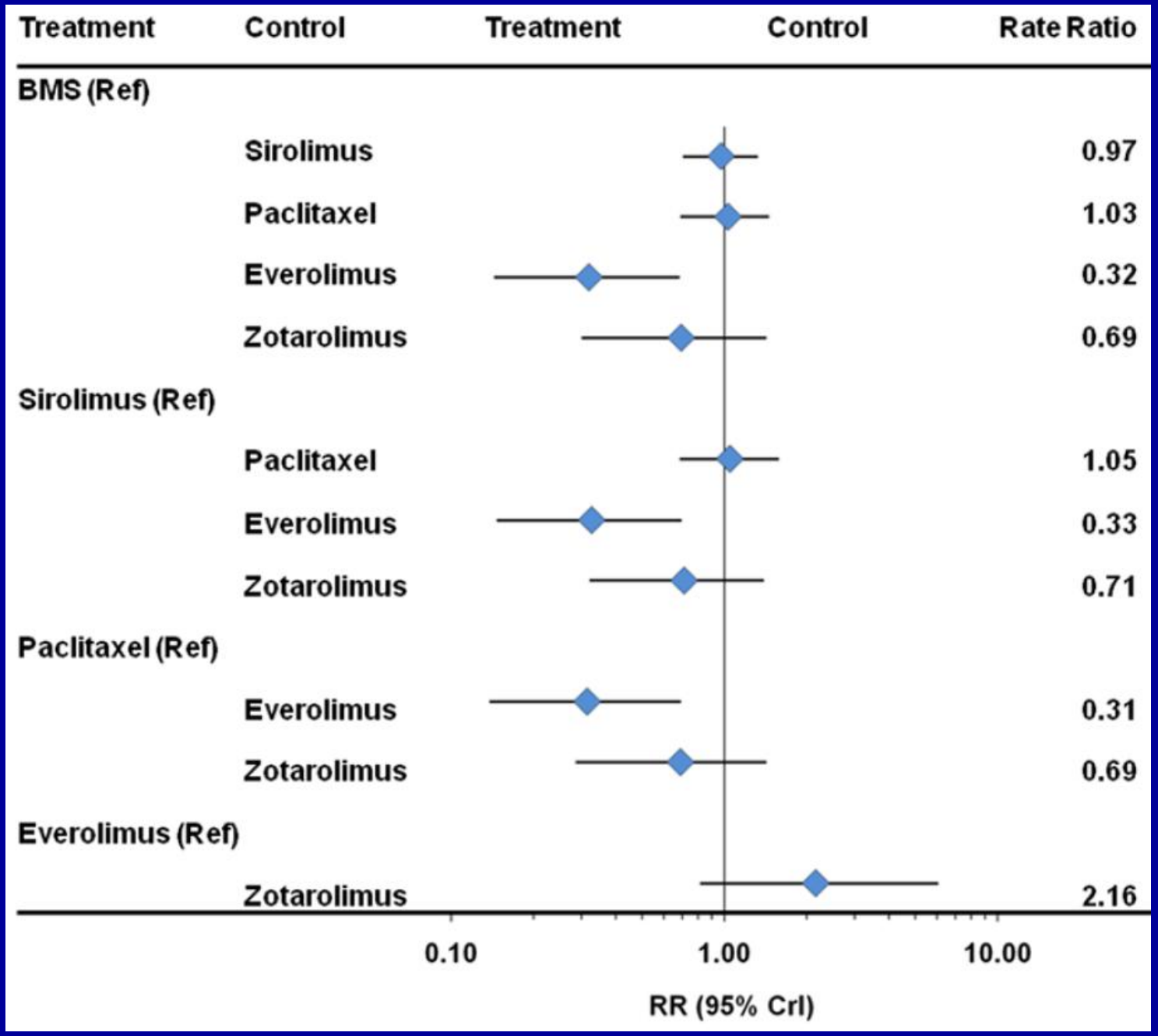
A **Network Meta-analysis** of 28 RCTs



Target Vessel Revascularisation



Stent Thrombosis



Network Meta-analysis

arouse suspicion amongst non-specialists

combine direct and indirect treatment comparisons

need to separate their contributions

they make strong assumptions

need a “solid” network of “similar” trials

FDA Guidance for Industry (Dec 2008)

Cardiovascular Risk in New Antidiabetic Therapies

Non-inferiority CV safety trial of new drug vs placebo

Primary endpoint: CV death, myocardial infarction, stroke

1) **to get approval**, need trial evidence
to rule out unacceptable (80%) excess CV risk

2) **post-approval**, need longer, larger trial to establish CV safety more clearly (ie rule out 30% excess risk)

3) evidence of CV benefit would be a bonus

SAVOR-TIMI 53 trial [NEJM 2013; 369 p 1317-]

Saxagliptin vs Placebo in 16,492 high risk type II diabetics

788 sites in 26 countries, median 2.1 years follow-up

	saxagliptin [N=8280]	**placebo** [N=8212]	**hazard ratio (95% CI)**
primary endpoint (CV death, MI, stroke)	613	609	1.00 (0.89 to **1.12**)
heart failure hosp^{n}.	289	228	1.27 (1.07 to 1.51) ⇓ P=.007

primary endpoint: non-inferiority established, but no benefit

heart failure: given multiple testing, a false positive?

Comparison with trials of other DPP-4 inhibitors

EXAMINE trial of alogliptin [NEJM 2013:369 p 1327-]

Incidence of heart failure hospitalisations

	alogliptin	**placebo**	**hazard ratio (95% CI)**
EXAMINE	3.1%	2.9%	1.07 (0.79, 1.46)
	saxagliptin	placebo	
SAVOR-TIMI	3.5%	2.8%	1.27 (1.07, 1.51)

interaction test not sig, indirect comparison

secondary hypothesis, data inconclusive

await TECOS trial of sitagliptin

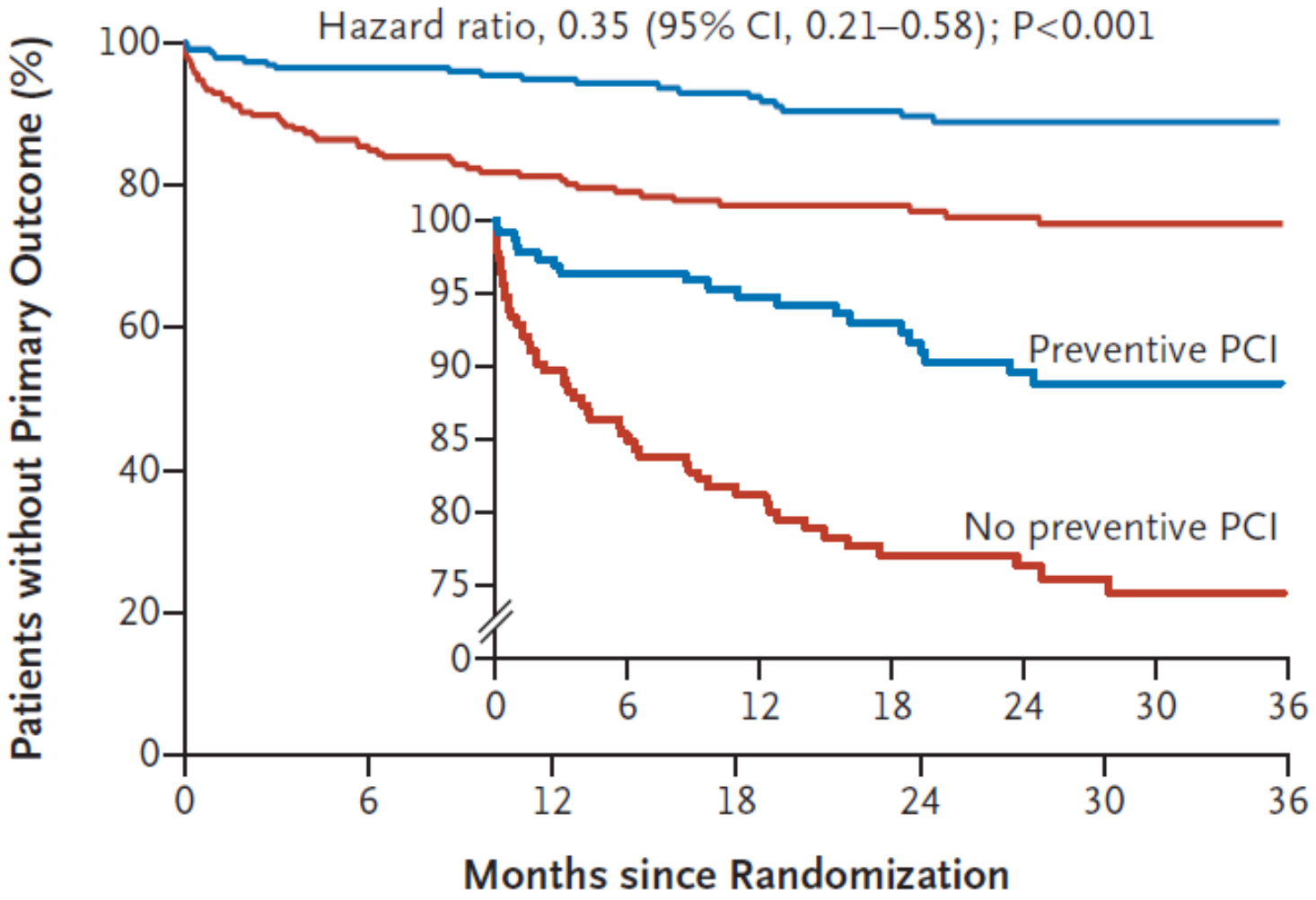
PRAMI trial: Preventive Angioplasty in Myocardial Infarction
[NEJM Sept 2013]

treat culprit lesion only OR other narrowed arteries as well

trial stopped early (mean 23 months follow-up)

	Preventive Angioplasty NO (N=231)	YES (N=234)	hazard ratio (95% CI)	
primary endpoint	**53**	**21**	**0.35(0.21,0.58)**	**P<.001**
refractory angina	30	12	0.35(0.18,0.69)	P=.002
nonfatal MI	20	7	0.32(0.13,0.75)	P=.009
cardiac death	10	4	0.34(0.11,1.08)	P=.07

Kaplan Meier Curves for the Primary Outcome



No. at Risk							
Preventive PCI	234	196	166	146	118	89	67
No preventive PCI	231	168	144	122	96	74	50

Issues to consider

a huge treatment difference: too good to be true?

trial stopped early: tendency to exaggerate efficacy

smallish trial with rather few events

trial not blinded, potential for bias

“hypothesis generating”, rather than changing practice?

another larger trial (COMPLETE) in progress
staged procedures during same hospitalisation

Pragmatic Trials of Alternative Treatment Strategies

Tackle key issues in patient management

Strategies often fundamentally different:

eg **ISCHEMIA trial**

Routine Invasive vs Conservative Strategy in stable IHD patients with ischemia

Compared to drug vs drug or drug vs placebo trials:

answers make a bigger impact on practice

more difficult to conduct

more difficult to recruit sufficient patients

“Do current clinical trials meet Society’s needs:

a critical review of recent evidence

Pocock & Gersh JACC 2014:64 p 1615-

What Society Needs from Clinical Trials

1) **Trials of Importance to Public Health**
balancing commercial interests and benefit to patients

2) **Asking the Right Question**
which treatments, patients and outcomes?

3) **Delivering Unbiased Answers**
randomisation, blinding, quality

4) **Efficient and Ethical Trial Conduct**
avoiding excess bureaucracy, role of DMCs

5) **Trials Conclusive and Representative**
large sample size, pragmatic "real world" trials

6) **Trial Publications that Tell the Whole Story**
balancing efficacy and safety, personalized medicine

7) **Trial Evidence ⇒ Guidelines ⇒ Best Patient Care**
totality of evidence, systematic reviews, impact on routine practice