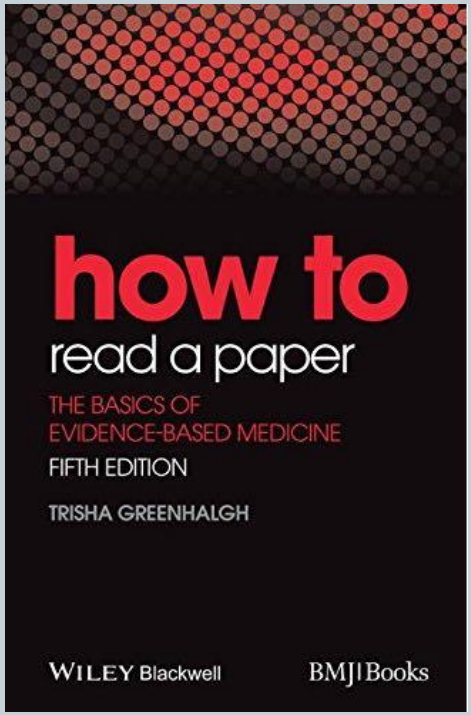
How To Analyse A Clinical Paper

CHRIS DAVIDSON
BRIGHTON UK

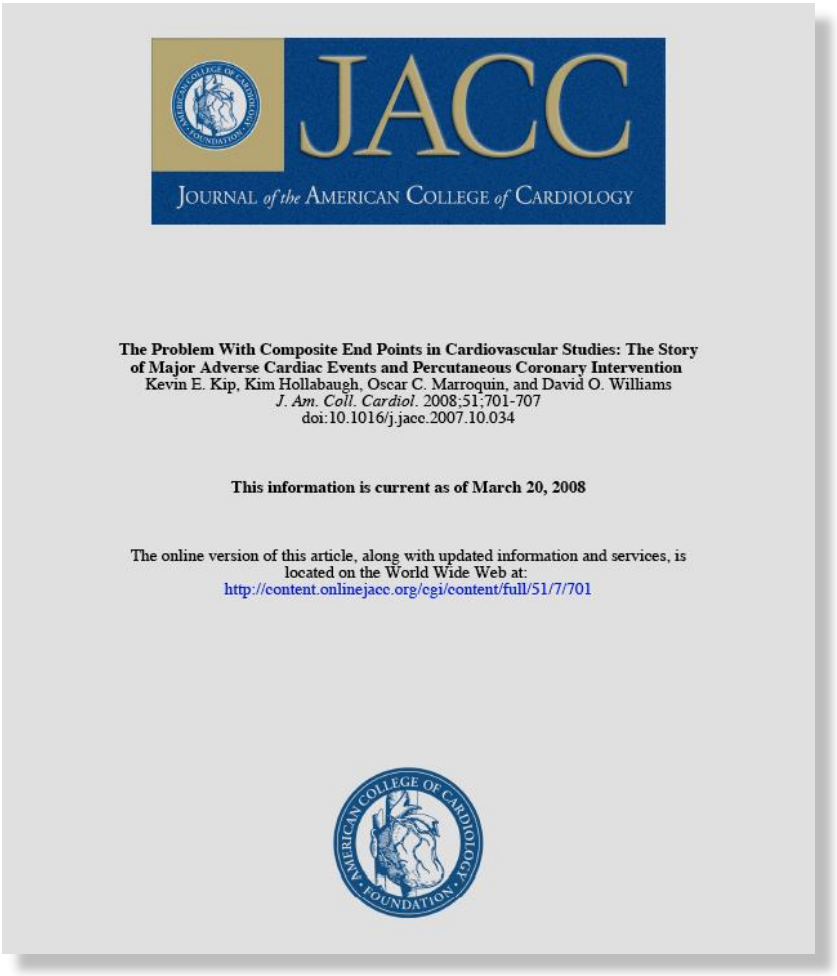
Why do we read original scientific papers?

- Inform clinical practice
- Investigate new drugs/procedures
- Find causes / risk factors for disease
- Part of a research project
- Pass examinations
- Get promotion!



REFERENCE: How to read a paper: The basis of Evidence-Based Medicine. Trisha Greenhalgh. Wiley-Blackwell 5th Edition 2014

How to read a Paper



JACC

JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY

The Problem With Composite End Points in Cardiovascular Studies: The Story of Major Adverse Cardiac Events and Percutaneous Coronary Intervention

Kevin E. Kip, Kim Hollabaugh, Oscar C. Marroquin, and David O. Williams

J. Am. Coll. Cardiol. 2008;51;701-707

doi:10.1016/j.jacc.2007.10.034

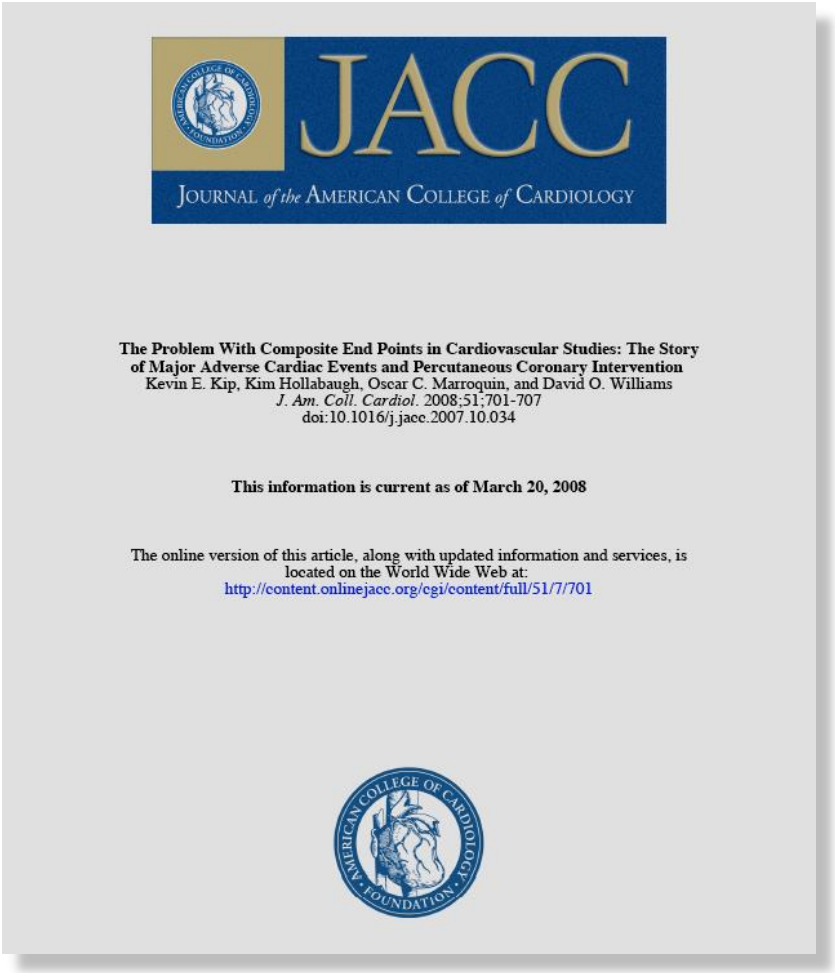
This information is current as of March 20, 2008

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://content.onlinejacc.org/cgi/content/full/51/7/701

- What was the Research Question?
  - Why was the Study needed?
- What was the Study Design?
  - Was the Design appropriate?

What was the Research Design?



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- Primary Studies
  - Experiments
  - Clinical Trials
  - Surveys
- Secondary Studies
  - Overviews (meta-analysis etc.)
  - Guidelines
  - Decision Analyses
  - Economic Analyses

Broad Fields of Research

- Therapy: Drugs or Procedures
  - Preferred Design: RCT
- Diagnosis: evaluation new test
  - Preferred Design: Cross-section Survey
- Screening
  - Preferred Design: Cross-section Survey
- Prognosis
  - Preferred Design: Longitudinal Survey
- Causation
  - Preferred Design: Cohort / Case-Control Study
- Psychometric studies
  - Preferred Design: Qualitative Study

REFERENCE: How to read a paper: The basis of Evidence-Based Medicine. Trisha Greenhalgh. Wiley-Blackwell 5th Edition 2014

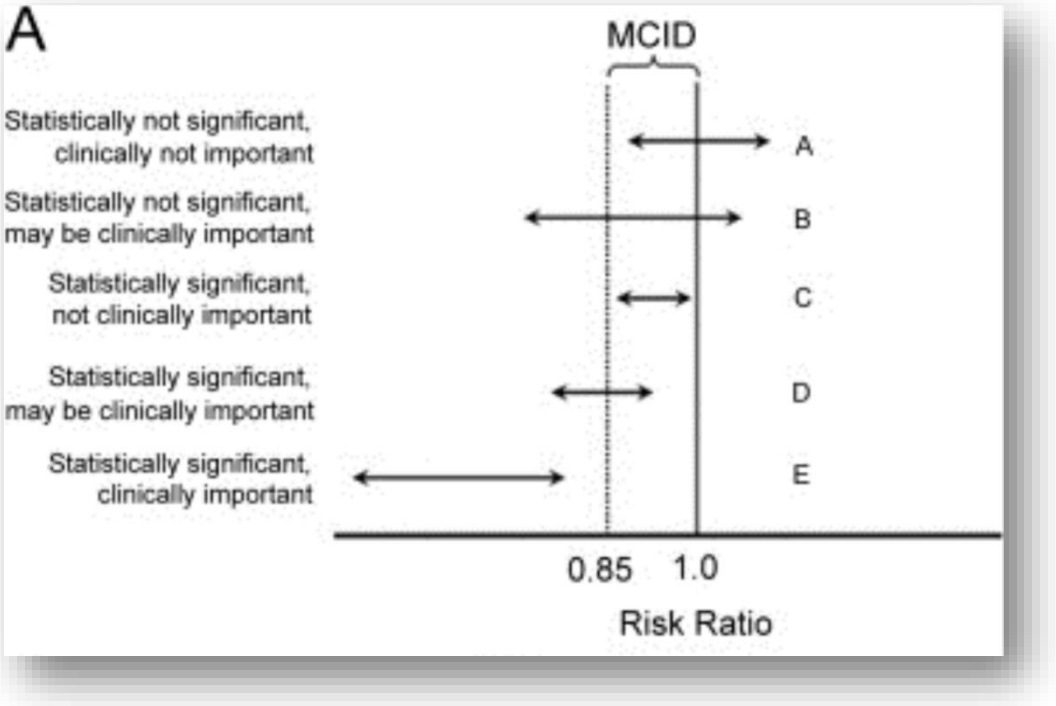
Why are Randomised Controlled Trials (RCTs) considered so important?

THEY MINIMISE THE EFFECT OF CONFOUNDING VARIABLES

RCTs : Statistics for the Amateur…

- Do the patients selected reflect the 'Real World' ?
  - Inclusion/exclusion criteria
- Are the studied groups comparable clinically?
  - Compare demography / Rx in each
- Are there significant numbers of 'drop-outs' or 'cross-over' patients?
  - Side-effects or patient/doctor preference
- Are the statistical tests appropriate?
  - Parametric vs non-Parametric data
  - Is the p-value appropriate with multiple tests ($p < 0.05$ can occur every 20 tests by chance)
- Is the difference seen clinically relevant?
  - RELATIVE and ABSOLUTE differences

Clinical Relevance of Trial results



From: Trial and Error: How to Avoid Commonly Encountered Limitations of Published Clinical Trials

J Am Coll Cardiol. 2010;55(5):415-427. doi:10.1016/j.jacc.2009.06.065

Invasive compared with non-invasive treatment in unstable coronary artery disease: FRISC II prospective randomised multicentre study

*FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators**

THE LANCET • Vol 354 • August 28, 1999

B a c k g r o u n d: In unstable coronary-artery disease early invasive procedures are common, despite lack of evidence for the superiority of this approach. W e compared an early invasive with a non-invasive treatment strategy in unstable coronary-artery disease .

I n t e r p r e t a t i o n: The early invasive approach should be the preferred strategy in most patients with unstable coronary artery disease who have signs of ischaemia on electrocardiography or raised biochemical markers of myocardial damage.

FRISC II Trial - Patients

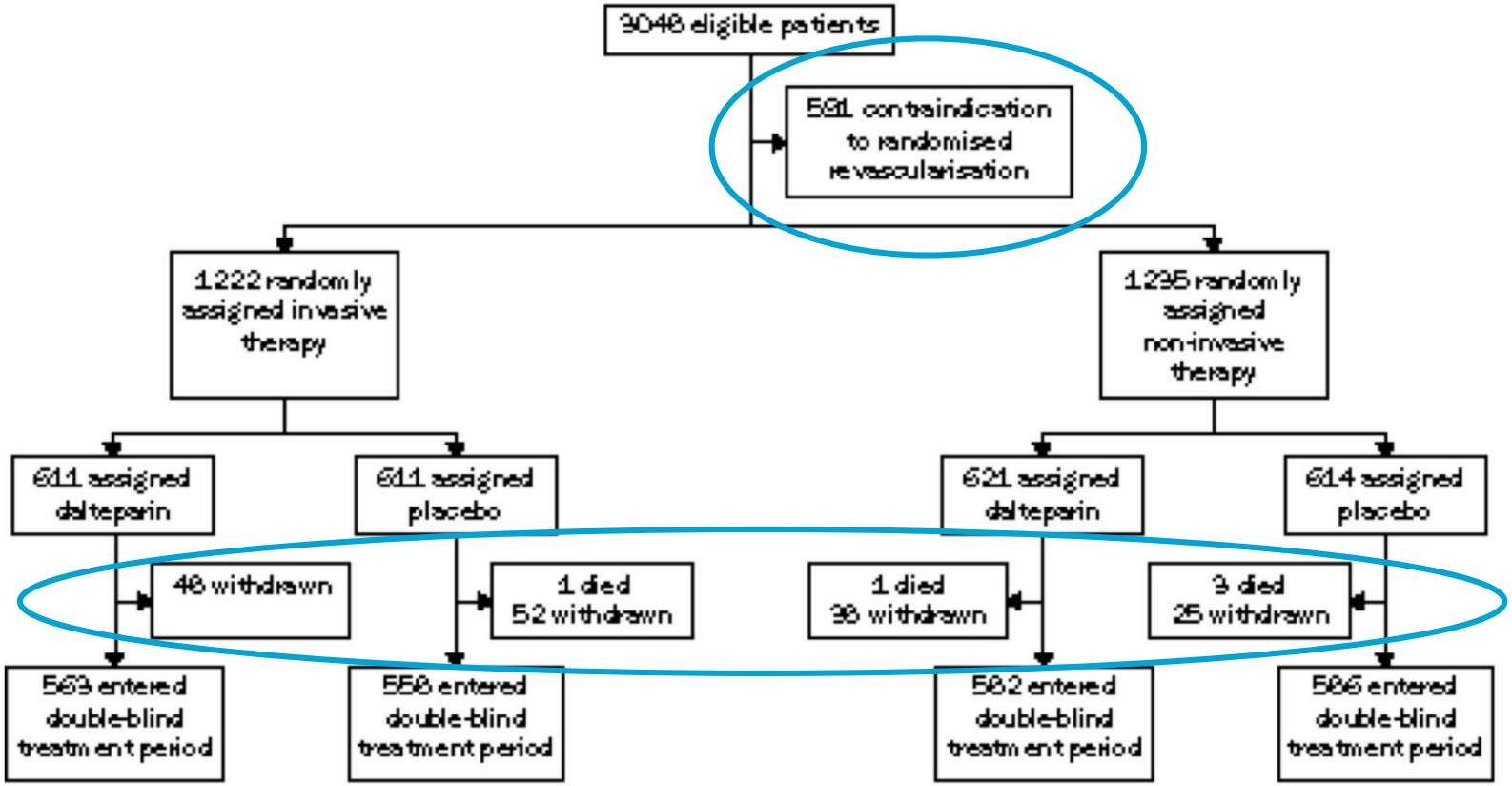


Figure 1: **Trial profile**

FRISC II Trial: Results

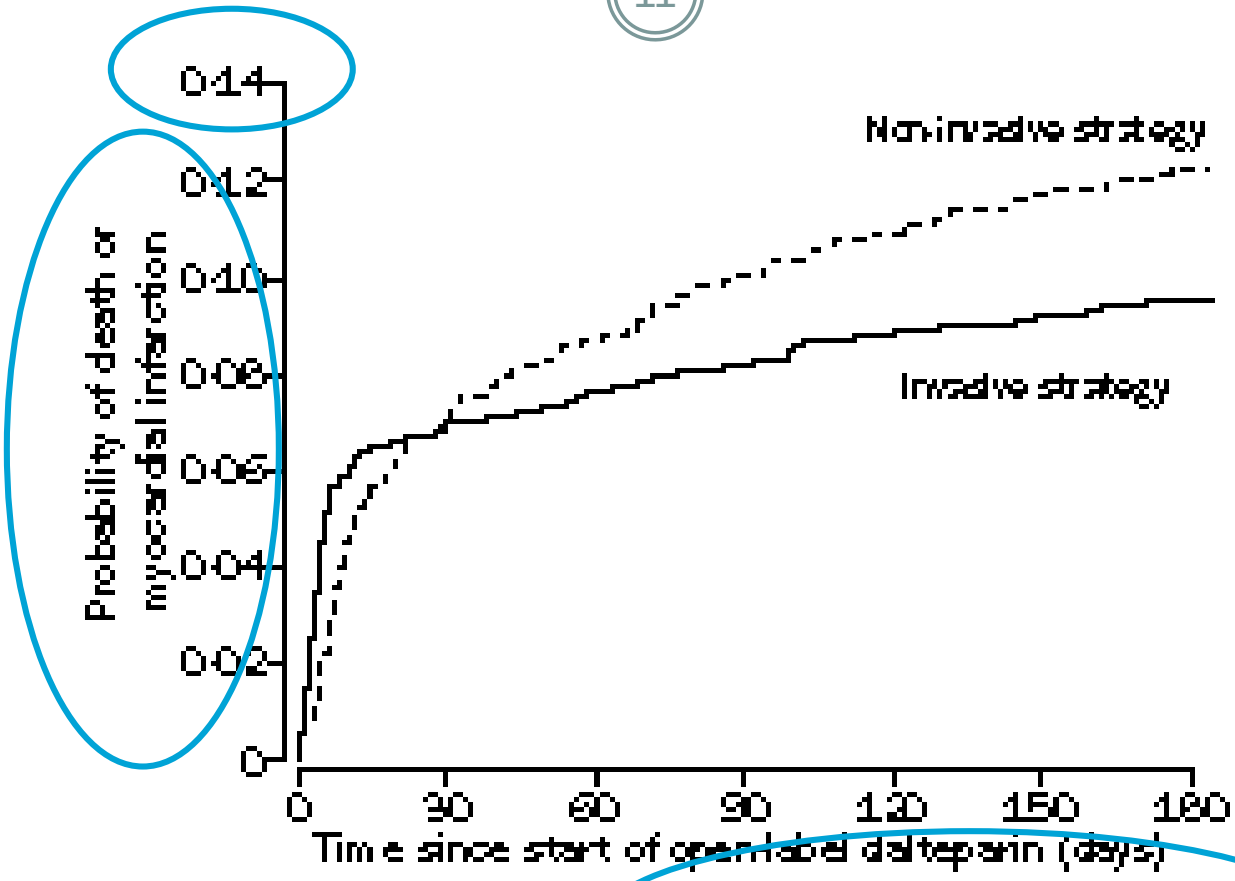
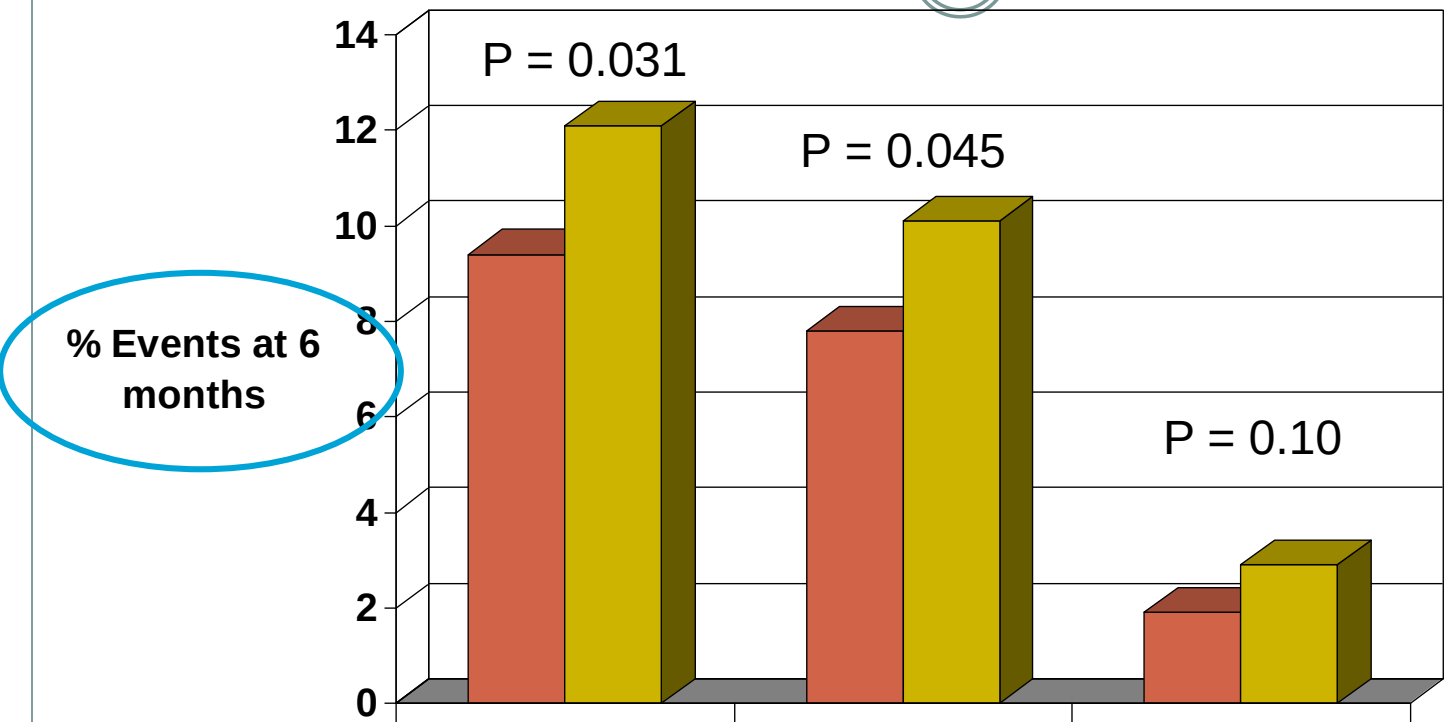


Figure 3: Probability of death or myocardial infarction in invasive and non-invasive groups

FRISC II Results



	Combined	M. Infarct	Death
Intervention	9.4	7.8	1.9
Control	12.1	10.1	2.9

RELATIVE RISK REDUCTION

12.1 - 9.4 /12.1

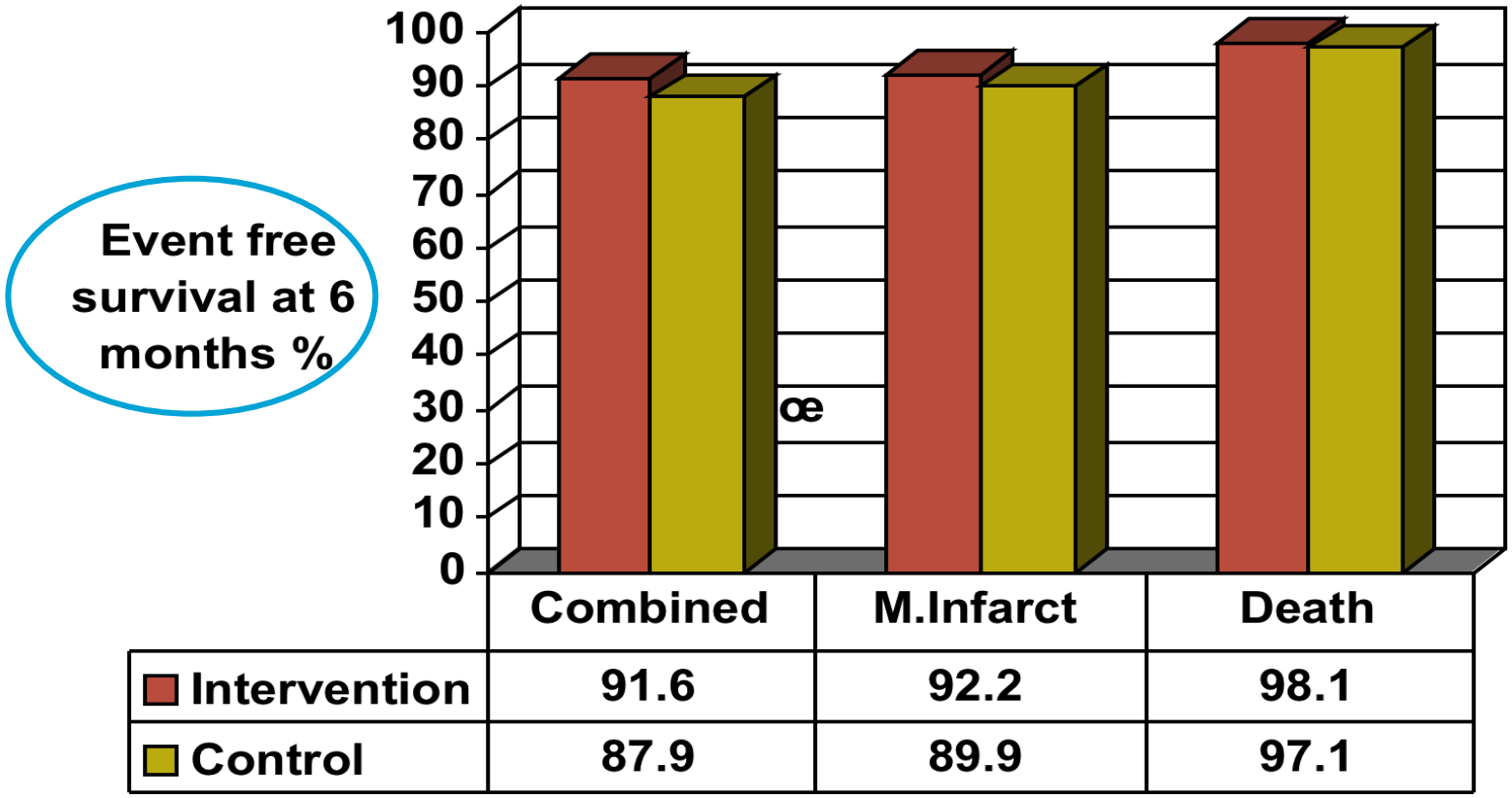
= 22.3 %

ABSOLUTE RISK REDUCTION

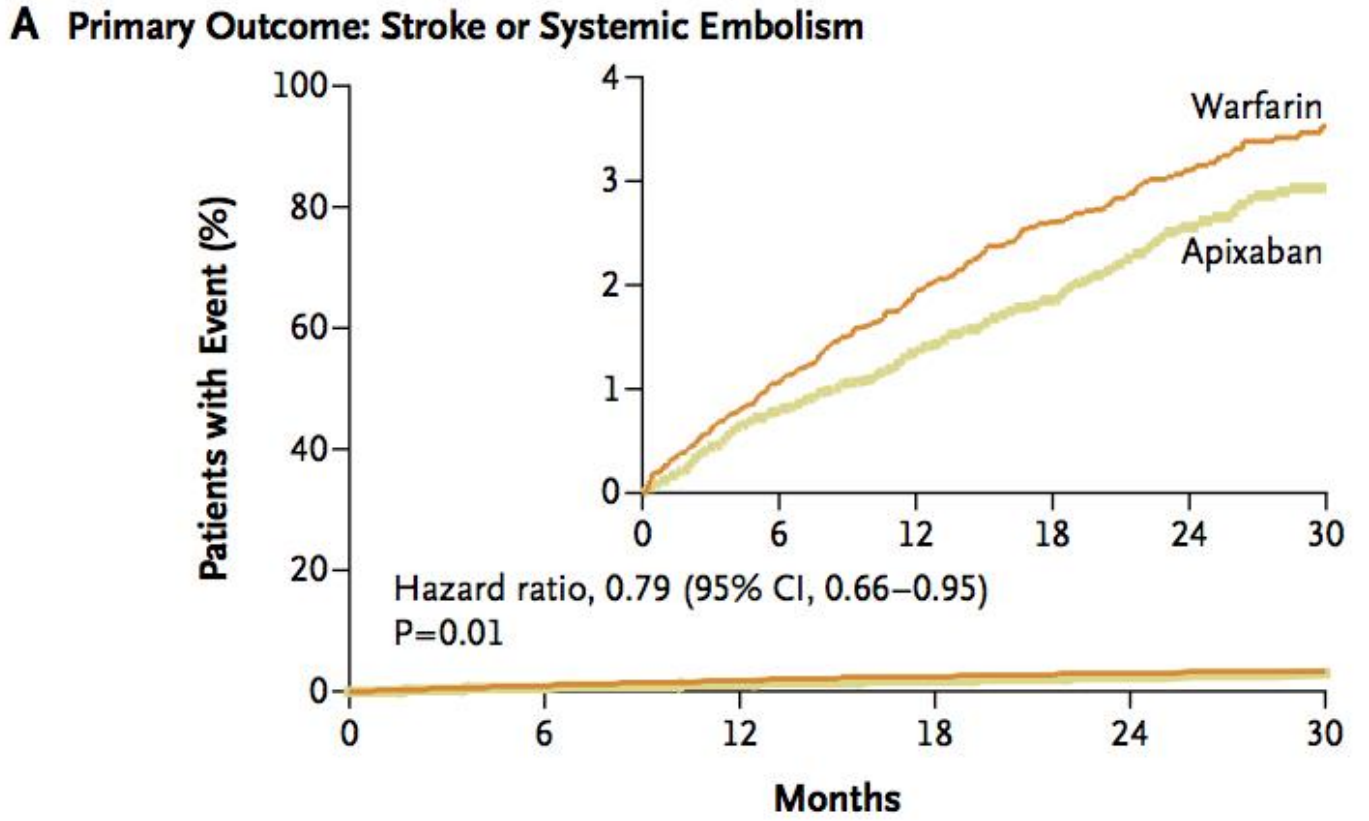
12.1 - 9.4

= 2.7 %

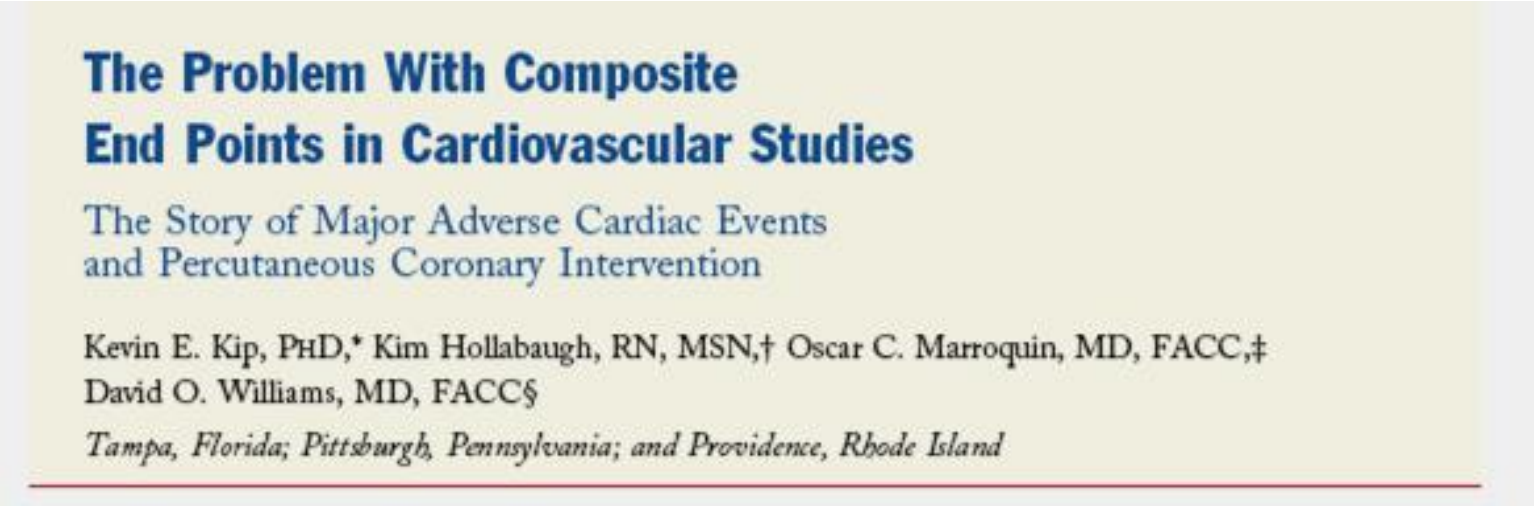
FRISC II Study



ARISTOTLE Trial: time course



No. at Risk						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768



The Problem With Composite End Points in Cardiovascular Studies

The Story of Major Adverse Cardiac Events and Percutaneous Coronary Intervention

Kevin E. Kip, PHD,* Kim Hollabaugh, RN, MSN,† Oscar C. Marroquin, MD, FACC,‡ David O. Williams, MD, FACC§

Tampa, Florida; Pittsburgh, Pennsylvania; and Providence, Rhode Island

- MACE
  - Death
  - Myocardial Infarction
  - Re-vascularisation

Used as a Quality standard for laboratories and published research in cardiac intervention

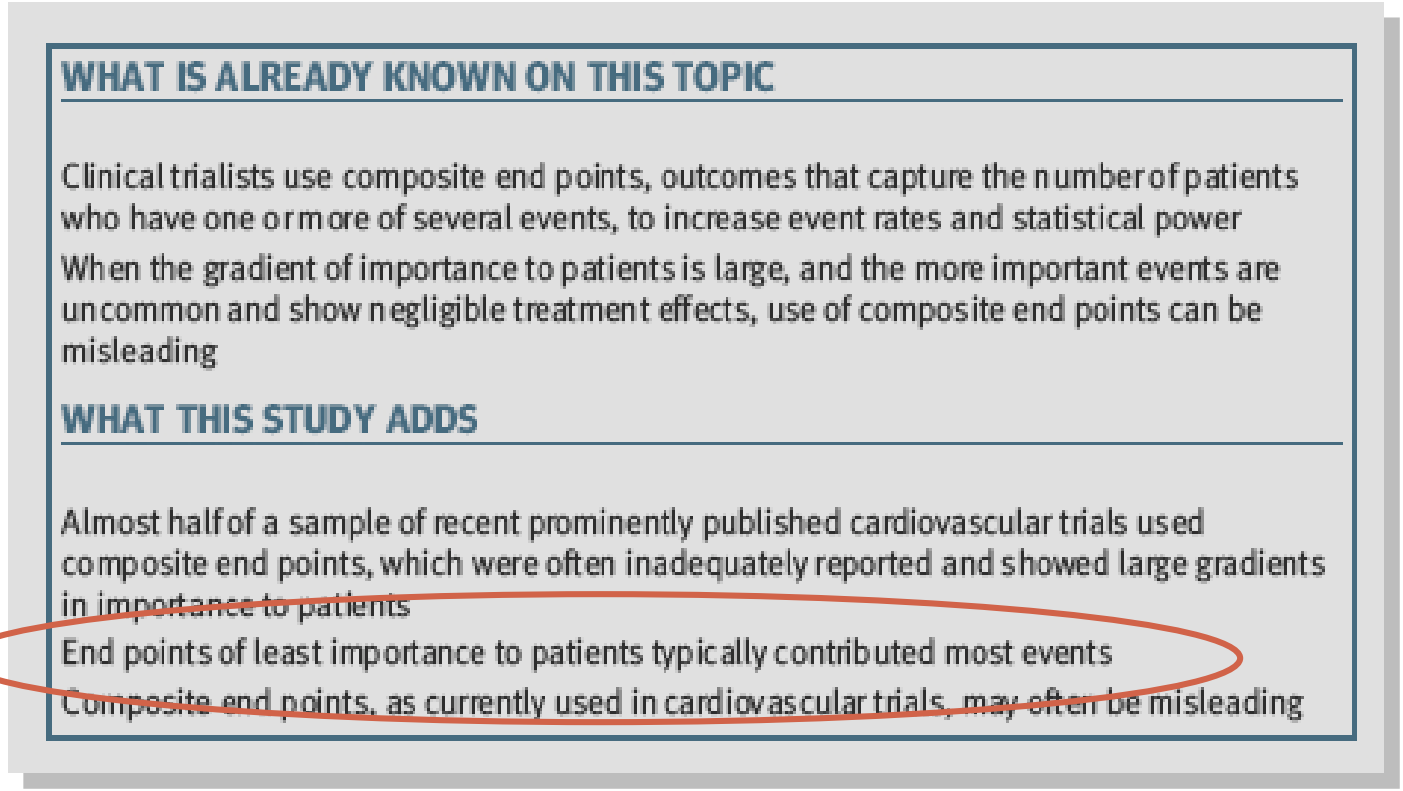
***J. Am. Coll. Cardiol.* 2008;51;701-707**

Table 2 Use of the Term MACE as an Outcome in the *Journal* (2006)

Reference	Trial Name/Description	Composite Name	Death	Cardiac Death	MI	Q-Wave MI	ST	TLR	TVR	CABG (Emergent)	CABG	Stroke	Other
Alfonso et al. (30)	RESS-II	Any major event	✓		✓				✓				
Ali et al. (31)	AMI rheolytic thrombectomy/PCI/infarct size	MACE, S	✓			✓	✓	✓		✓		✓	
Beyar et al. (32)	Remote-Control PCI	MACE	✓		✓								Urgent revascularization
Cosgrave et al. (33)	Drug-eluting stent: restenosis	MACE, S			✓				✓				
Eliot et al. (34)	Cost analysis: SES versus PES	MACE	✓		✓						✓		PCI or CABG
Engelmann et al. (35)	Stem cell mobilization after MI	MACE			✓ Repeat						✓		ACS
Gupta et al. (36)	Hemodynamic depression after carotid stenting	MACE	✓		✓							✓	
Hochholzer et al. (37)	EXCELSIOR Platelet inhibition and clopidogrel and coronary stent	MACE, F	✓		✓				✓ Urgent				
Hoye et al. (38)	Long-term DES outcomes with crush	MACE	✓		✓ AMI				✓				
Kandzari et al. (39)	ENDEAVOR III Comparison of ZES versus SES	MACE, S	✓		✓			✓					
Kelbaek et al. (23)	SCANDSTENT	MACE, S	✓		✓			✓					
Kereiakes et al. (40)	Overlapping SES	MACE	✓		✓			✓					
Kim et al. (41)	RCT–Korea Abciximab-coated versus BMS	MACE, F		✓	✓			✓					
Knopf et al. (42)	Summit PROGRESS-AMS trial	MACE		✓	✓			✓					
Lee et al. (43)	Comparison of CABG with PCI with DES	MACE & CVA events	✓		✓				✓			✓	
Lilliaro et al. (44)	TRUE registry; effect/safety of SES for in-stent restenosis	MACE	✓		✓			✓					
McClearn et al. (45)	Vascular disease HTN and prevention	MACE	✓		✓								
Montalescot et al. (46)	ALBION RCT high clopidogrel dose in NST ACS	MACE, S	✓		✓								Ischemia-driven hospitalization PCI or CABG
Nunes et al. (47)	DES in intermediate lesions; pooled analysis	MACE		✓	✓		✓		✓				Restenosis on angiography
Ong et al. (48)	RESEARCH registry, 2-year follow-up	MACE	✓		✓				✓				
Price et al. (49)	Angiographic follow-up in SES	MACE	✓		✓		✓	✓					
Rodriguez et al. (50)	ORAR II study; oral rapamycin after BMS	MACE, S	✓		✓				✓			✓	
Sala et al. (51)	REAL registry PES versus SES	MACE, F	✓		✓				✓				
Sato et al. (52)	Serum tenascin-C as predictor of LV remodeling	MACE		✓	✓ AMI								CHF hospitalization
Valgimigli et al. (53)	Distal LM disease RESEARCH/T-SEARCH registries	MACE, F	✓		✓				✓				
Vermeersch et al. (29)	RRISC	MACE, S	✓		✓				✓				
Weisz et al. (54)	SIRUS 2-year outcomes	MACE F & S	✓S	✓F	✓F			✓S	✓F		✓F ✓S		

ACS = acute coronary syndromes; AMI = acute myocardial infarction; AMI = A Prospective, Randomized, Controlled Trial of Thrombectomy With the Angiolet in Acute Myocardial Infarction; ALBION = Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation, and Ongoing Necrosis; CHF = congestive heart failure; ENDEAVOR III = Randomized Comparison of Zotarolimus-Eluting and Sirolimus-Eluting Stents in Patients With Coronary Artery Disease; EXCELSIOR = Impact of Extent of Clopidogrel-Induced Platelet Inhibition During Elective Stent Implantation on Clinical Event Rates; HTN = hypertension; LM = left main coronary artery; LV = left ventricular; NST = non-ST-segment-elevation acute coronary syndrome; ORAR II = Oral Treatment of Restenosis; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; PROGRESS-AMS = Clinical Performance and Angiographic Results in Absorbable Metal Stents; RCT = randomized clinical trial; REAL = REgistro regionale AngioPlastiche dell'Emilia-Romagna; RESEARCH = Registro e-Eluting Stent Evaluated at Rotterdam Cardiology Hospital; RRISC = Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting; SES = sirolimus-eluting stent; TRUE = Tuscany Registry of Sirolimus for Unselected In-Stent Restenosis; T-SEARCH = Taxus-Stent Evaluated At Rotterdam Cardiology Hospital; ZES = zotarolimus-eluting stent; other abbreviations as in Table 1.

Composite End-Points



WHAT IS ALREADY KNOWN ON THIS TOPIC

Clinical trialists use composite end points, outcomes that capture the number of patients who have one or more of several events, to increase event rates and statistical power

When the gradient of importance to patients is large, and the more important events are uncommon and show negligible treatment effects, use of composite end points can be misleading

WHAT THIS STUDY ADDS

Almost half of a sample of recent prominently published cardiovascular trials used composite end points, which were often inadequately reported and showed large gradients in importance to patients

End points of least importance to patients typically contributed most events

Composite end points, as currently used in cardiovascular trials, may often be misleading

Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials Ferreira-Gonzalez et al BMJ 2007 334; 786

SPRINT Trial

Wright JT, Williamson PK, Snyder JK, et al. *N Engl J Med* 2015; DOI:10.1056

ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

ABSTRACT

CONCLUSIONS

Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT01206062.)

SPRINT Trial

Wright JT, Williamson PK, Snyder JK, et al. *N Engl J Med* 2015; DOI:10.1056

ORIGINAL ARTICLE

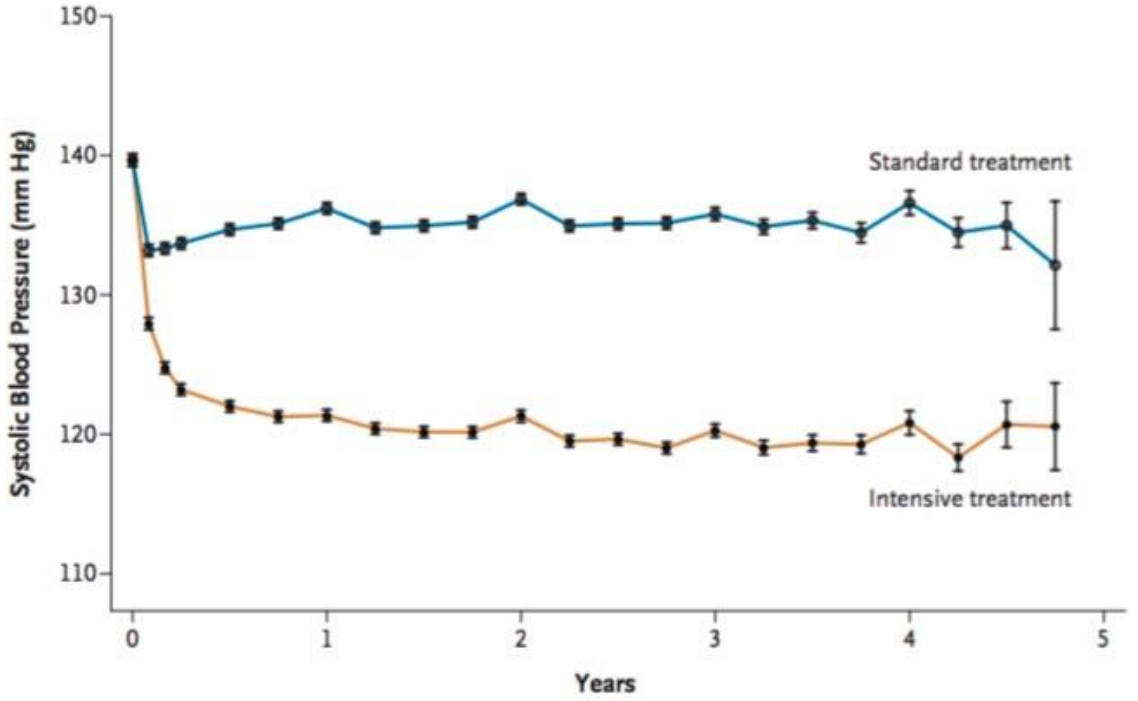
A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

ABSTRACT

METHODS

We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.



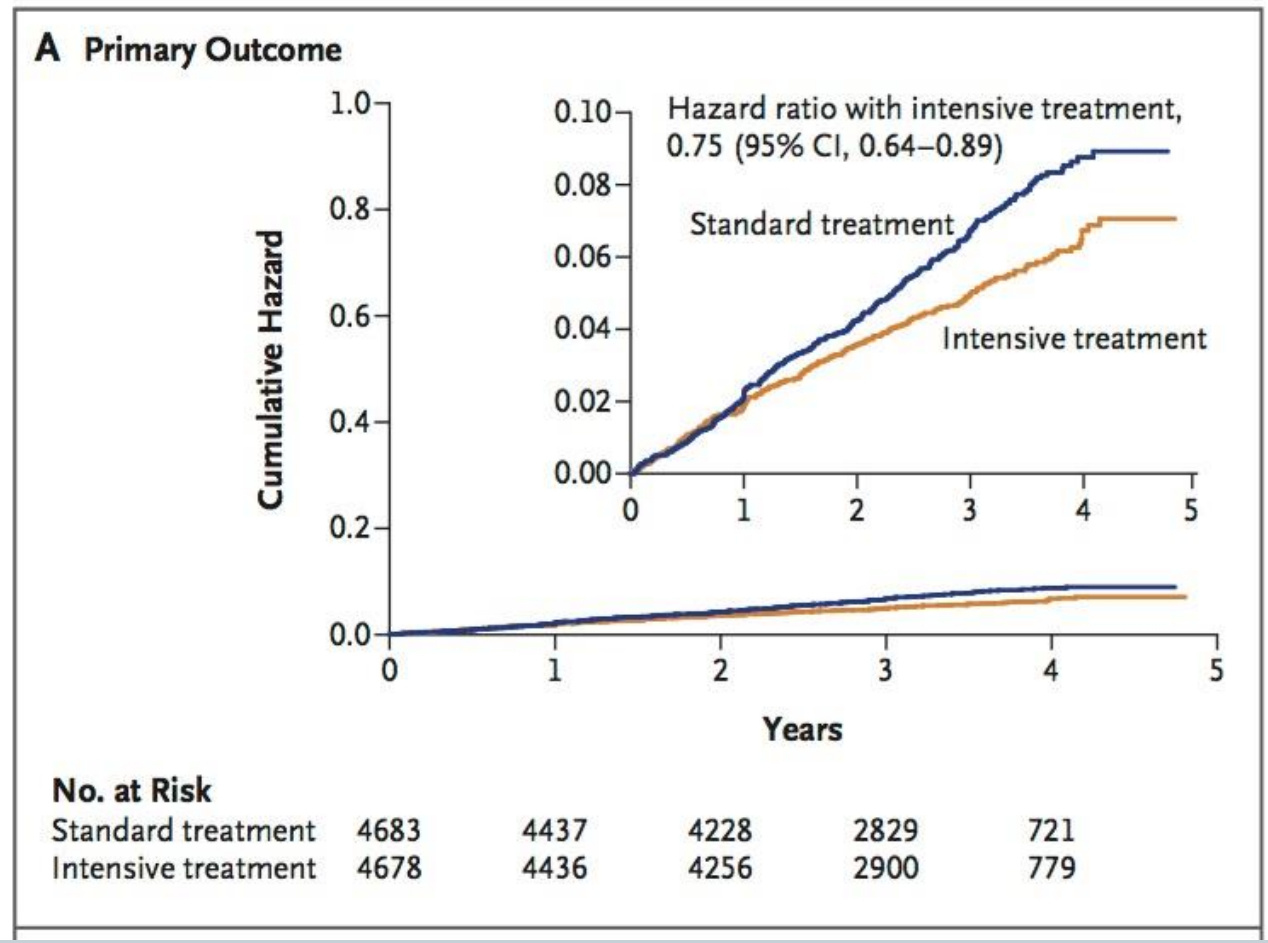
No. with Data										
Standard treatment	4683	4345	4222	4092	3997	3904	3115	1974	1000	274
Intensive treatment	4678	4375	4231	4091	4029	3920	3204	2035	1048	286
Mean No. of Medications										
Standard treatment	1.9	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9
Intensive treatment	2.3	2.7	2.8	2.8	2.8	2.8	2.8	2.8	2.8	3.0

Figure 2. Systolic Blood Pressure in the Two Treatment Groups over the Course of the Trial.

The systolic blood-pressure target in the intensive-treatment group was less than 120 mm Hg, and the target in the standard-treatment group was less than 140 mm Hg. The mean number of medications is the number of blood-pressure medications administered at the exit of each visit. I bars represent 95% confidence intervals.

SPRINT Trial

Wright JT, Williamson PK, Snyder JK, et al. *N Engl J Med* 2015; DOI:10.1056



SPRINT Trial

Wright JT, Williamson PK, Snyder JK, et al. *N Engl J Med* 2015; DOI:10.1056

Table 2. Primary and Secondary Outcomes and Renal Outcomes.*

Outcome	Intensive Treatment		Standard Treatment		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*% per year*	*no. of patients (%)*	*% per year*		
All participants	**(N=4678)**		**(N=4683)**			
Primary outcome†	243 (5.2)	1.65	319 (6.8)	2.19	0.75 (0.64–0.89)	<0.001
Secondary outcomes						
Myocardial infarction	97 (2.1)	0.65	116 (2.5)	0.78	0.83 (0.64–1.09)	0.19
Acute coronary syndrome	40 (0.9)	0.27	40 (0.9)	0.27	1.00 (0.64–1.55)	0.99
Stroke	62 (1.3)	0.41	70 (1.5)	0.47	0.89 (0.63–1.25)	0.50
Heart failure	62 (1.3)	0.41	100 (2.1)	0.67	0.62 (0.45–0.84)	0.002
Death from cardiovascular causes	37 (0.8)	0.25	65 (1.4)	0.43	0.57 (0.38–0.85)	0.005
Death from any cause	155 (3.3)	1.03	210 (4.5)	1.40	0.73 (0.60–0.90)	0.003
Primary outcome or death	332 (7.1)	2.25	423 (9.0)	2.90	0.78 (0.67–0.90)	<0.001

SPRINT Trial

Wright JT, Williamson PK, Snyder JK, et al. *N Engl J Med* 2015; DOI:10.1056

ORIGINAL ARTICLE

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Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT01206062.)

ACCORD Trial

N Engl J Med 2010;362:1575-85

ORIGINAL ARTICLE

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

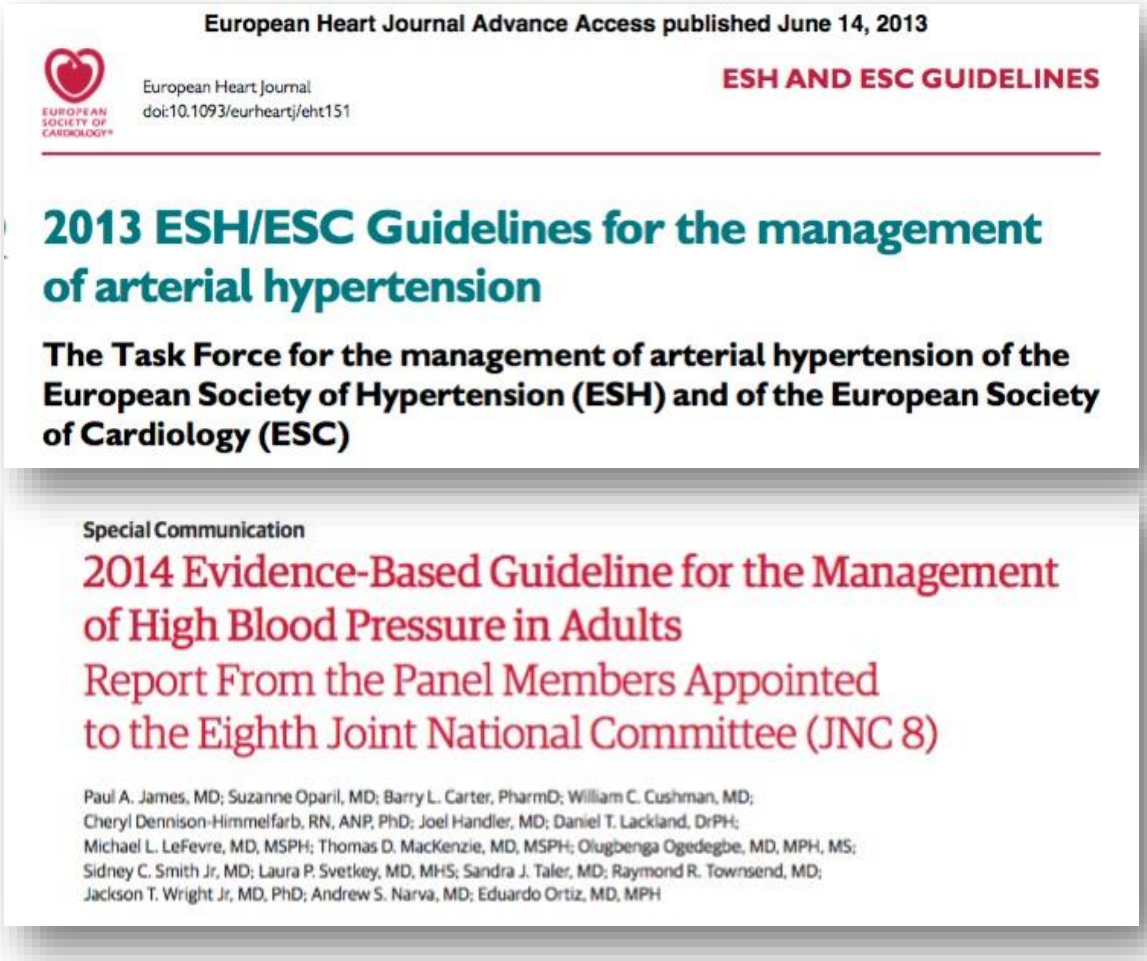
The ACCORD Study Group*

ABSTRACT

CONCLUSIONS

In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events. (ClinicalTrials.gov number, NCT00000620.)

HT Guidelines and SPRINT Trial



European Heart Journal Advance Access published June 14, 2013

European Heart Journal
doi:10.1093/eurheartj/eht151

ESH AND ESC GUIDELINES

2013 ESH/ESC Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

Special Communication

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults
Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD; Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH; Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS; Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD; Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH

'Relaxed' Evidence-based targets for BP control (2013) now challenged by SPRINT Trial (2015)

SPRINT Trial: Discussion Groups

- Group A: Trial Design and Oversight
- Group B: Characteristics of study population
- Group C: Drug Treatment
- Group D: Adverse events
- Group E: End point definitions

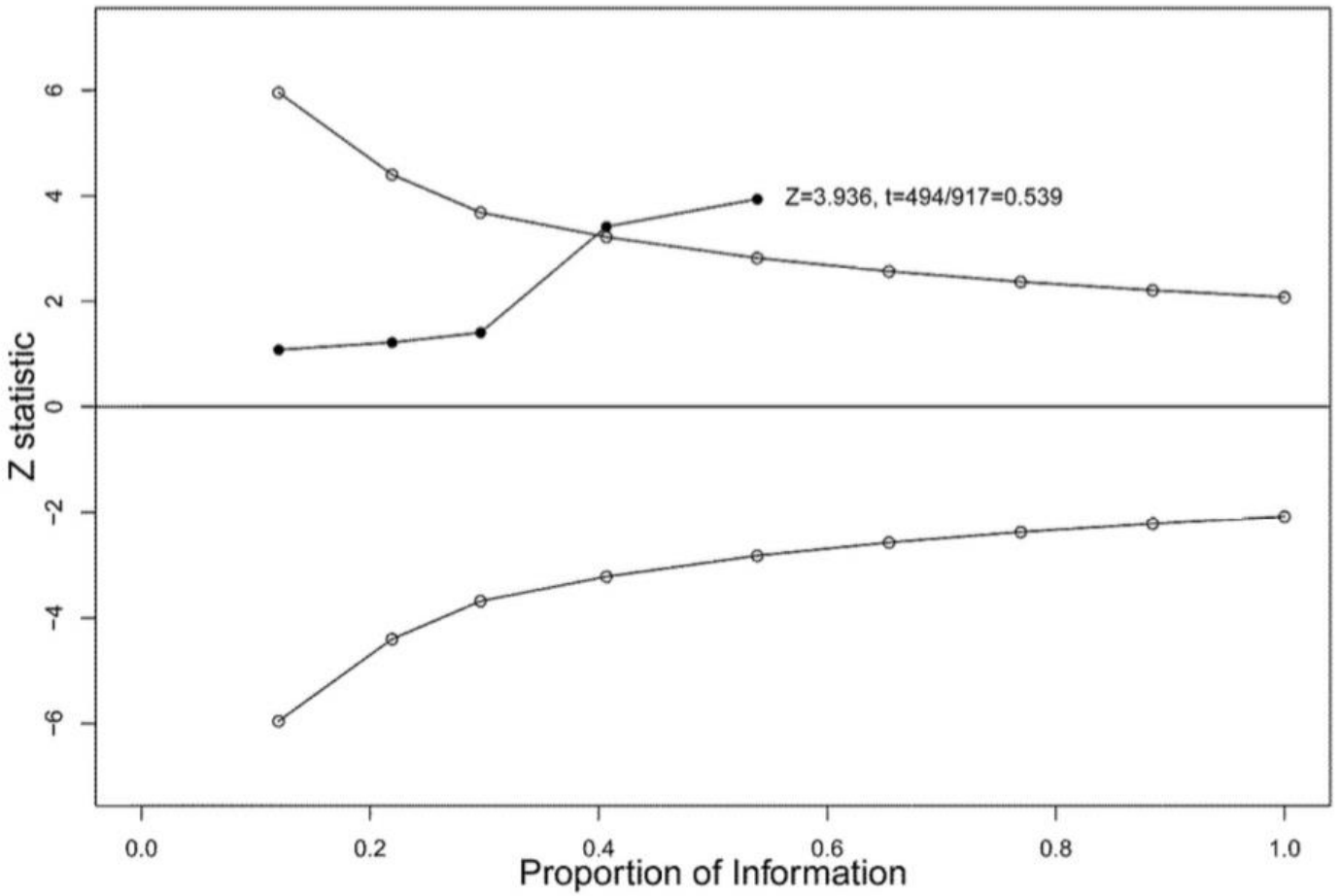
SPRINT Trial

DISCUSSION

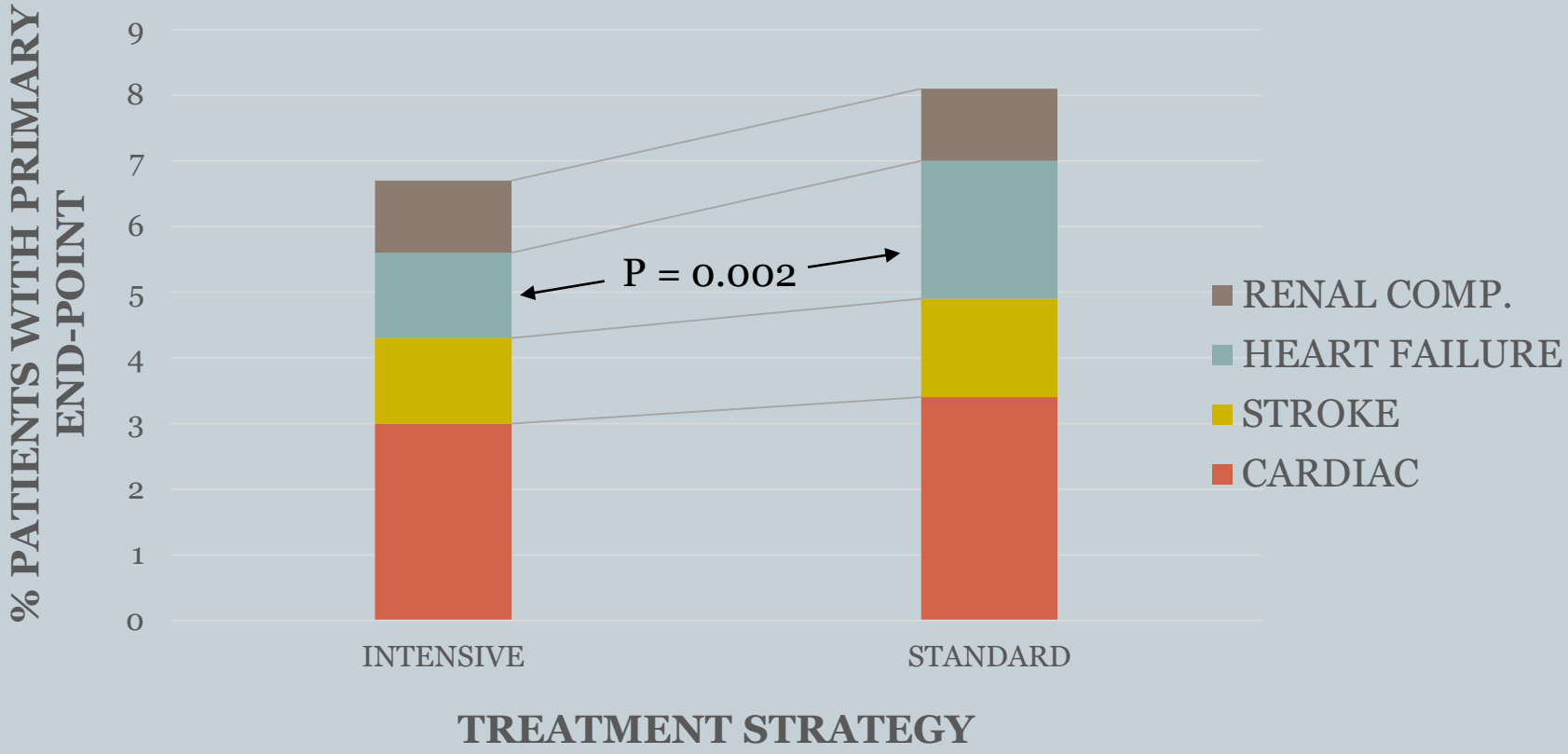
SPRINT Trial: Conclusions

- Significant benefit from Intensive vs standard therapy in primary composite end-point
  - Significant reduction in heart failure
  - Significant reduction in total and CV mortality
- Trial terminated early when significant threshold reached
  - Insufficient renal end-points
  - Study of dementia abandoned
- Some increase in adverse events
  - Hypotension, electrolyte abnormalities, renal impairment
  - Frequency no greater in elderly (>75 yrs)

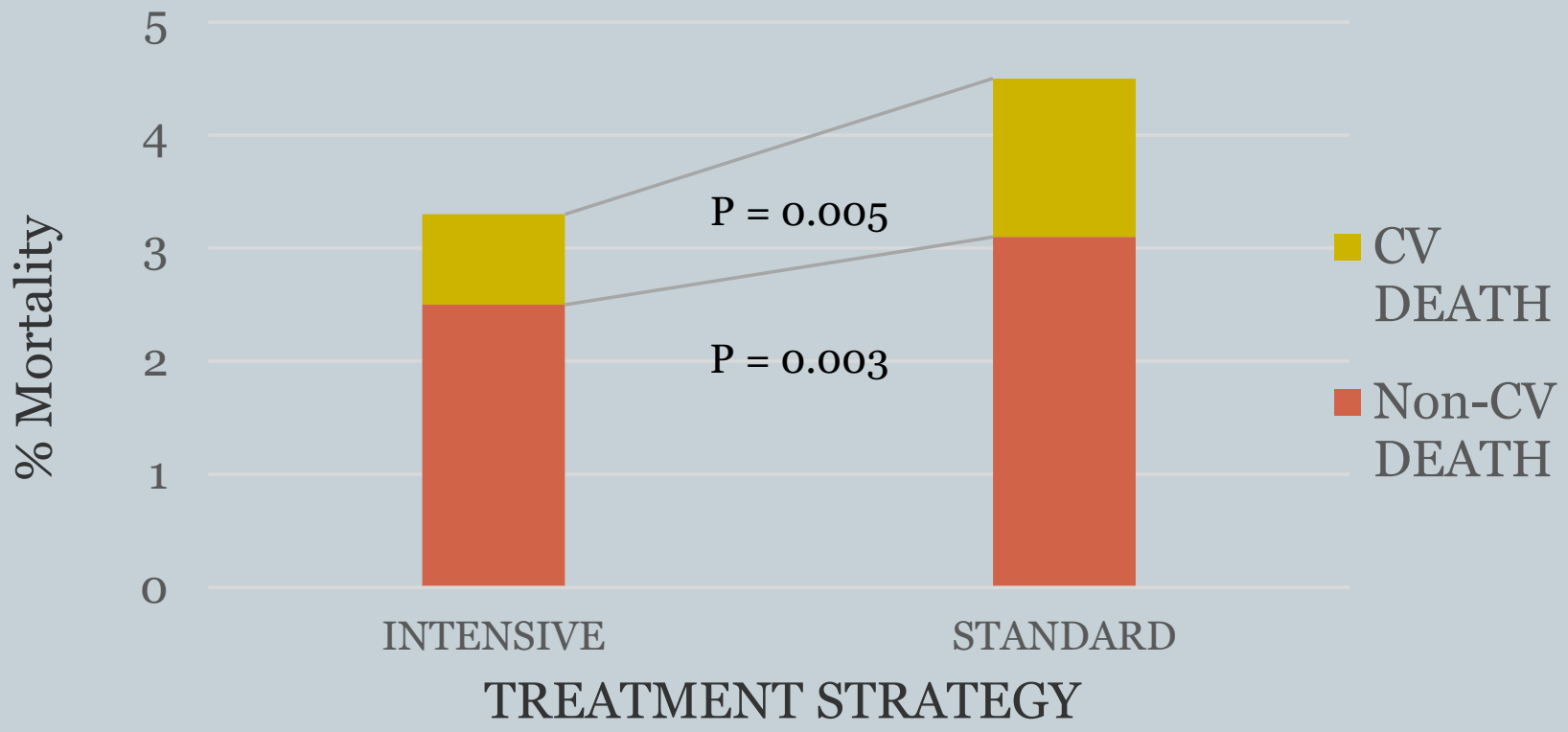
SPRINT Termination by Data Monitoring Committee



SPRINT TRIAL: Primary Outcomes



SPRINT TRIAL: Mortality



SPRINT Study

Will this trial change guidelines and clinical practice?

Appraisal Tools

- Critical Appraisal Skills Programme
  - http://www.casp-uk.net/homepage/
- Evidence based medicine: Tool kit University of Alberta
  - http://www.ebm.med.ualberta.ca/

CASP website: http://www.casp-uk.net