McMaster University

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Population Health Research Institute

Health Through Knowledge

PHRI

Effect of CV Adjudication in Trials conducted by Cardiologists

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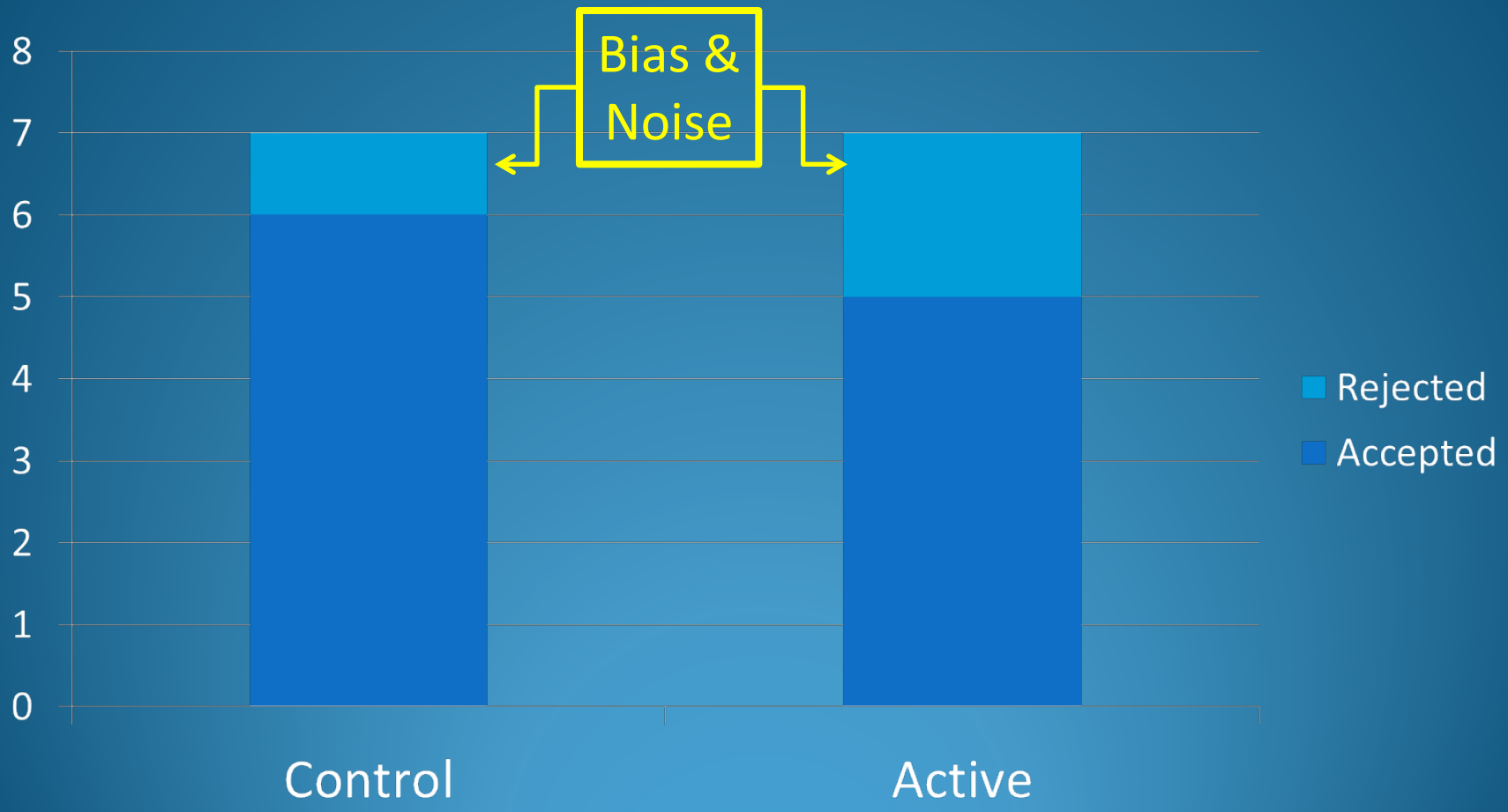
Idea of Adjudication



Adjudication alters Treatment Estimates(CV Outcomes)

Trial	Reported		Adjudicated	
	HR	p	HR	p
EPIC	0.73	0.120	0.65	0.008
IMPACT II	0.71	0.018	0.79	0.063
GUSTO IIB	0.88	0.016	0.89	0.058
PURSUIT	0.81	0.001	0.91	0.04
CHARM-Preserved	0.85	0.028	0.89	0.12
TRITON	0.89	0.059	0.81	<0.001
TRIM (OR & 95% CI)	1.83	(0.95-3.54)	5.02	(1.19-21.2)

(Naslund EHJ 1999; Granger CT 2008; Serebruany 2010)

A Systematic Comparison

CLINICAL TRIALS ARTICLE

Clinical Trials 2009; 6: 239–251

Evaluating the benefit of event adjudication of cardiovascular outcomes in large simple RCTs

Janice Pogue[a], *Stephen D Walter*[b] *and Salim Yusuf*[a]

Has adjudication changed our treatment estimates?

Methods:

- All Cardiovascular Outcomes Trials at Population Health Research Institute (PHRI) of McMaster University from 1993 to 2006
- 10 trials with 95,038 participants randomized and 9,152 primary outcomes
- Blinded therapy: OASIS-2, HOPE, HOPE-2, CURE, OASIS-5, OASIS-6, CREATE
- Open therapy: OASIS-1, ACTIVE-W, WAVE

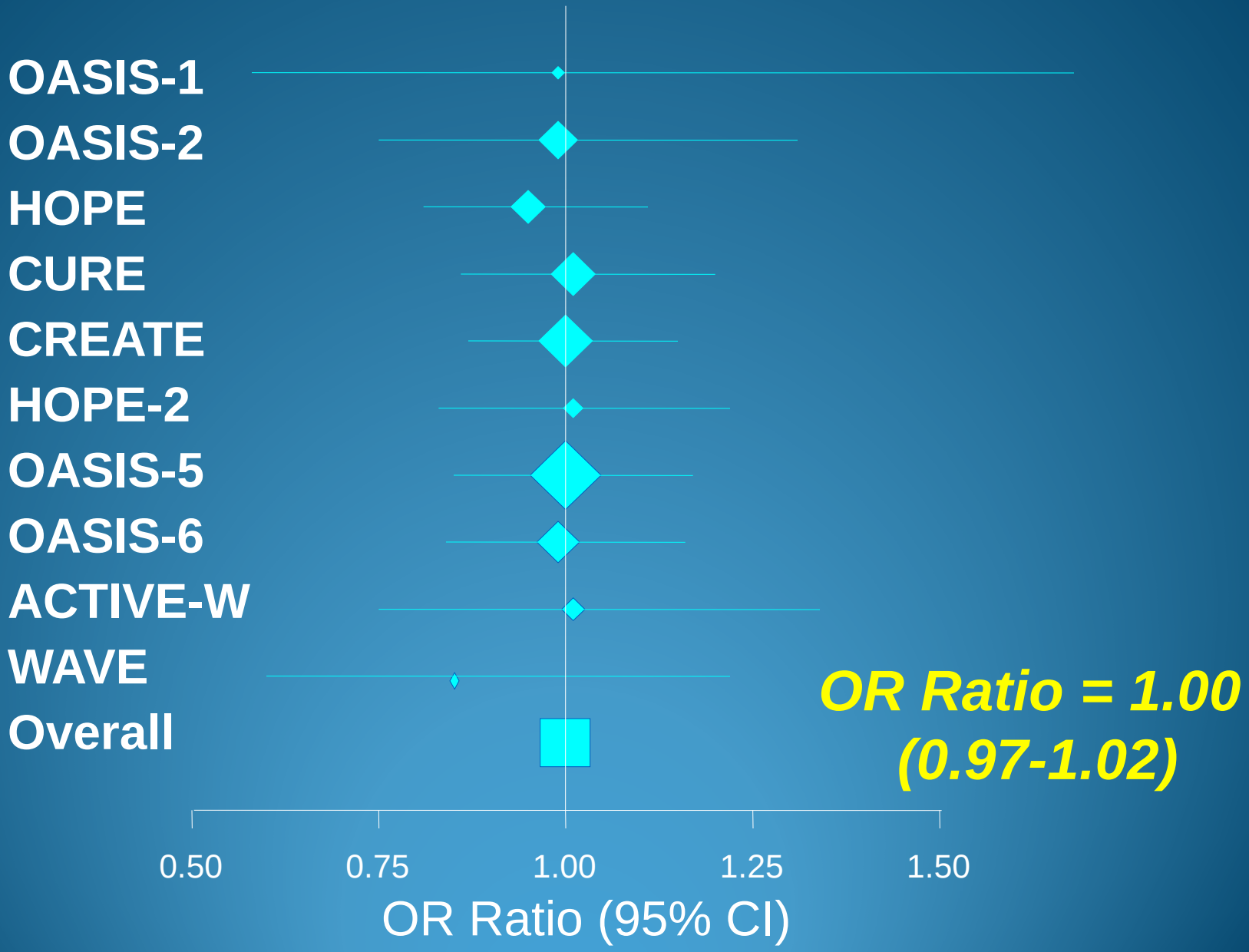
The Trials:

Trial	N	Population	Therapies	Primary Outcome
OASIS-2	10141	ACS	Hirudin vs. Heparin	CVD, MI, Refractory Isch
HOPE	9541	CV risk	Ramipril vs. Placebo	CVD, MI, Stroke
HOPE-2	5522	CV risk	Folate vs. Placebo	CVD, MI, Stroke
CURE	12562	ACS	Clopidogrel/ASA vs. ASA	CVD, MI, Stroke
OASIS-5	20078	ACS	Fondaparinux vs. Enoxaparin	Death, MI
OASIS-6	12092	AMI	Fondaparinux vs. Control	Death, MI
CREATE	15570	AMI	Reviparin vs. Placebo	Death, MI, Stroke
OASIS-1	909	ACS	Hirudin vs. Heparin	CVD, MI, Sev Angina
WAVE	2161	PAD	OAC/ASA vs. ASA	CVD, MI, Stroke
ACTIVE-W	6706	AF	Clopidogrel vs. OAC	Vas D, MI, Stroke, Non-SEE

Statistical Methods

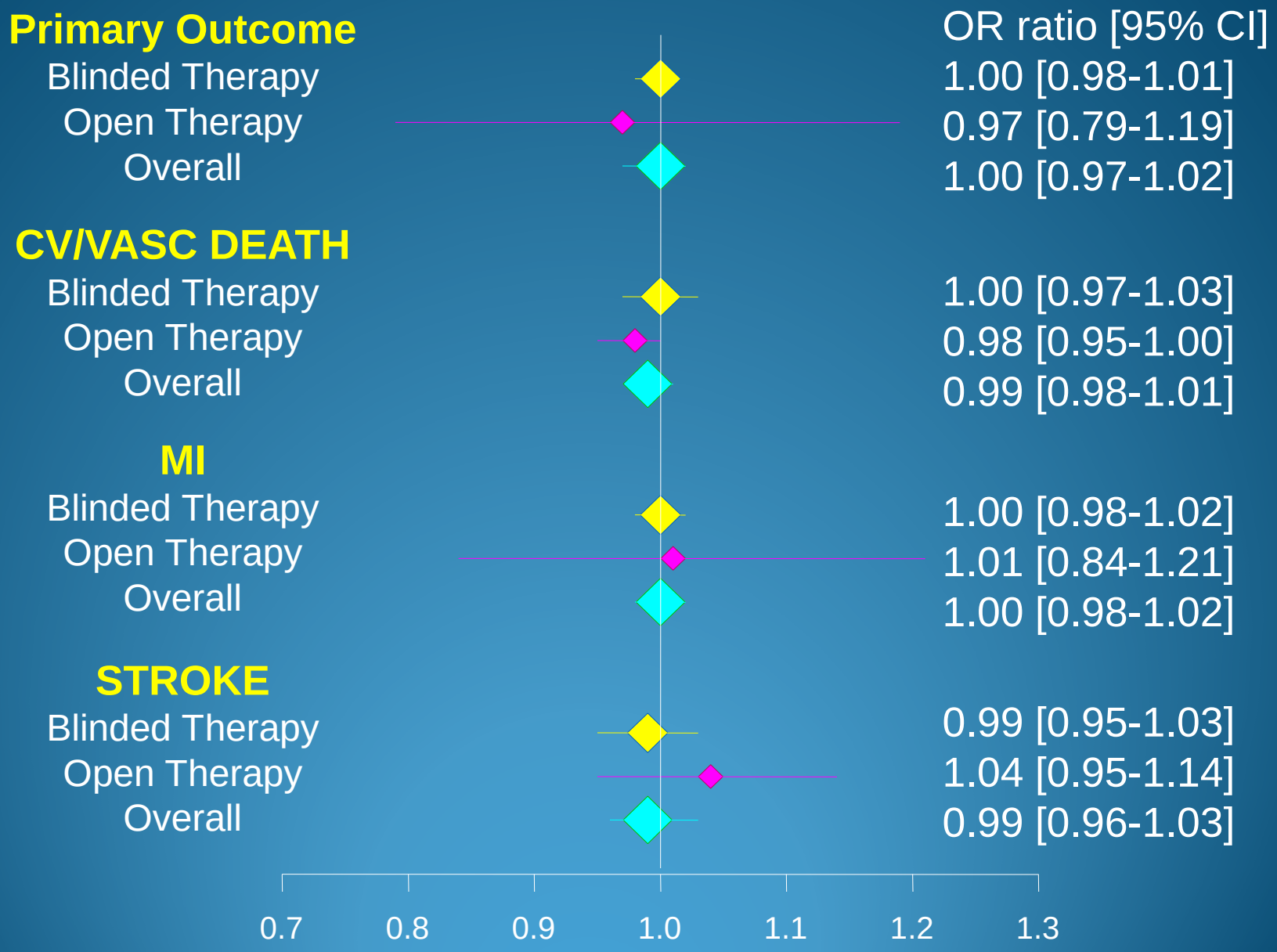
- Empirical Evidence of Bias due to a lack of adjudication = Different treatment estimates without it
- Linear random effects model, weighted by trial size on Log $OR_{adjudicated}$ – Log $OR_{reported}$
- Exponentiated to represent effect of adjudication as a ratio of ORs
- Ratio of OR = 1 indicated no evidence of an effect (< 1= adjudication increased treatment effect)

Effect of Adjudication on Primary Outcome



OR Ratio = 1.00 (0.97-1.02)

All Outcomes – OR Ratios



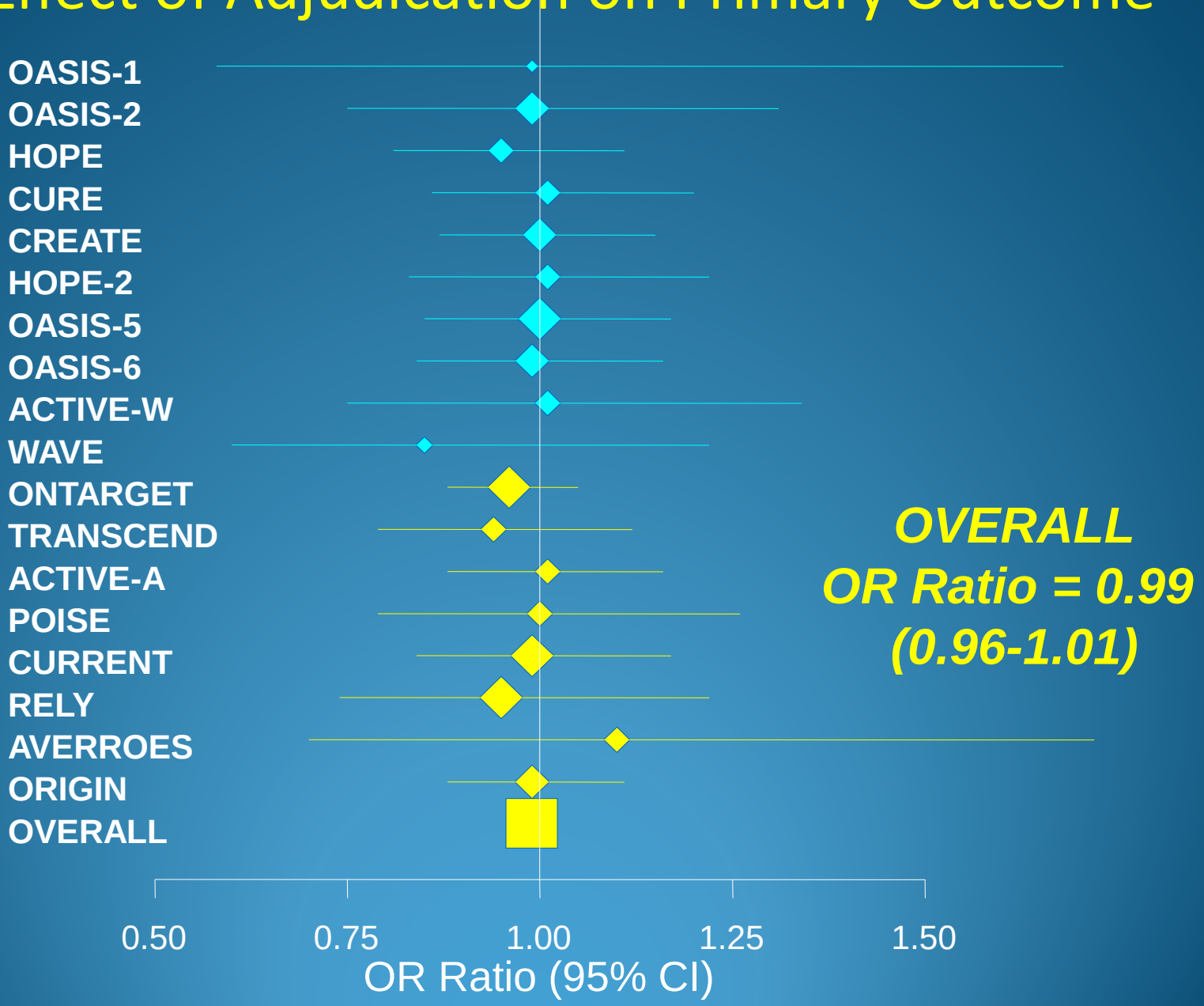
Updated Analysis:

- Added 8 major Cardiovascular Outcomes Trials at PHRI from 2007 to 2012
- 18 trials with 204,037 participants randomized and 21,456 outcomes
- 13 Blinded therapy and 5 Open therapy
- Presented at SCT 2013

The New Trials:

Trial	N	Population	Therapies	Primary Outcome
ONTARGET	25630	CV risk	Telmisartan+Rampril vs. Ramipril	CVD, MI,Stroke
TRANSCEND	5926	CV risk	Telmisartan vs. Placebo	CVD, MI,Stroke, HF Hosp
ACTIVE-A	7554	AF	Clopidogrel/ASA vs. ASA	CVD, MI,Stroke, HF Hosp
POISE	8351	CV risk	Beta-Blockers vs. Placebo	CVD, MI,Stroke
CURRENT	25086	ACS	Clopidogrel High vs. Low Dose	CVD, MI,Card Arrest
RELY	18113	AF	Dabigatran vs. Warfarin	CVD, MI,Stroke
AVERROES	5599	AF	Apixaban vs. ASA	Stroke, Non-SEE
ORIGIN	12750	DM/IGT	Insulin Glargine vs. Standard Care	Stroke, Non-SEE

Effect of Adjudication on Primary Outcome

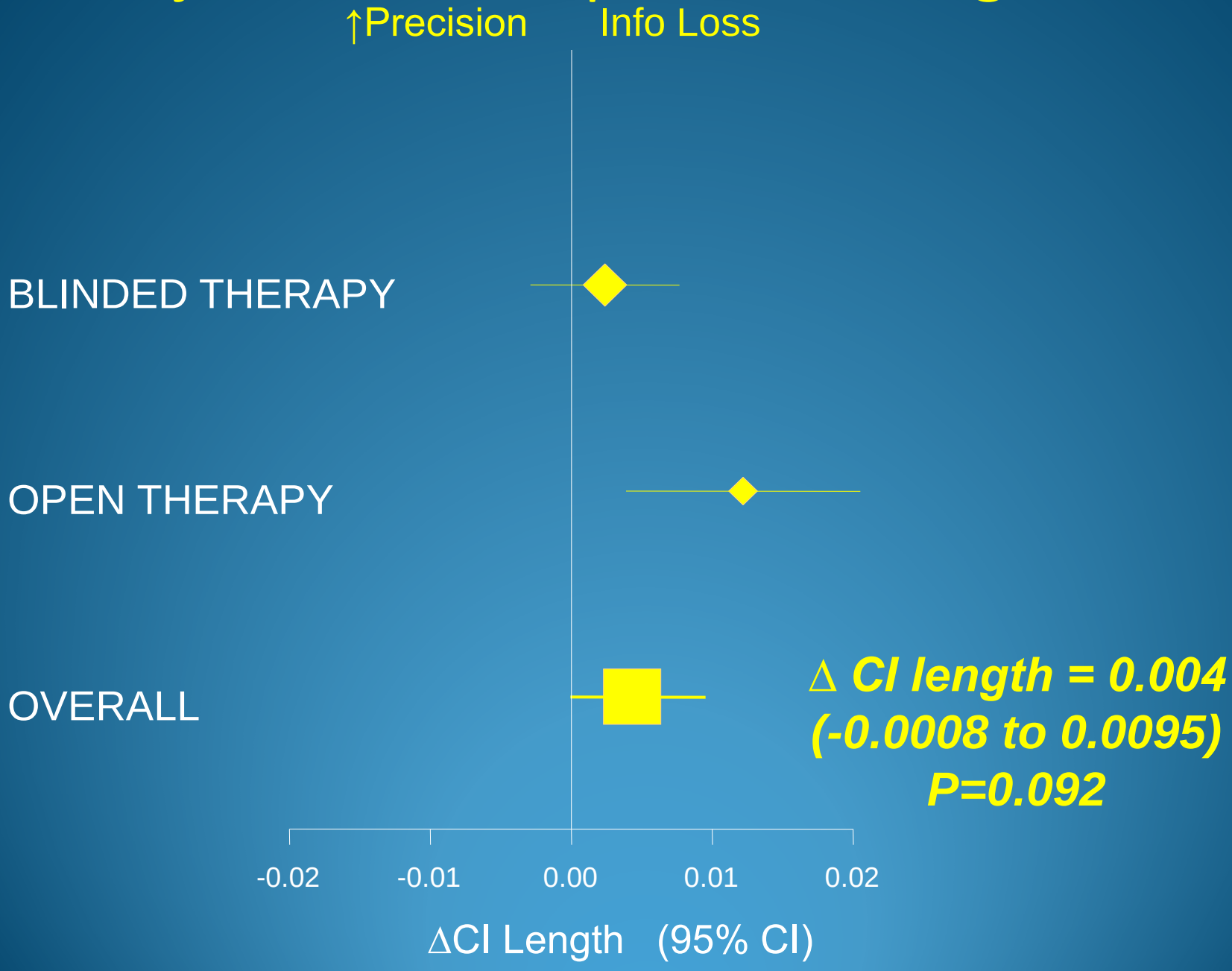


OVERALL
OR Ratio = 0.99
(0.96-1.01)

What about Precision?

- Does Adjudication reduce Confidence Interval Length?
- < CI Length = increased precision
- >CI Length = information loss
- CI Length = Log Upper CI – Log Lower CI
- $\text{CI Length}_{\text{adjudicated}} - \text{CI Length}_{\text{reported}}$
- Linear random effects model, weighted by trial size on difference in CI length

Adjudicated – Reported CI Length



Δ CI length = 0.004
(-0.0008 to 0.0095)
P=0.092

Why have some trials found an Effect of Adjudication?

3 Possible Reasons

1. Publication Bias

- Chance findings for a process that has no effect
- Publication effect only if one is observed

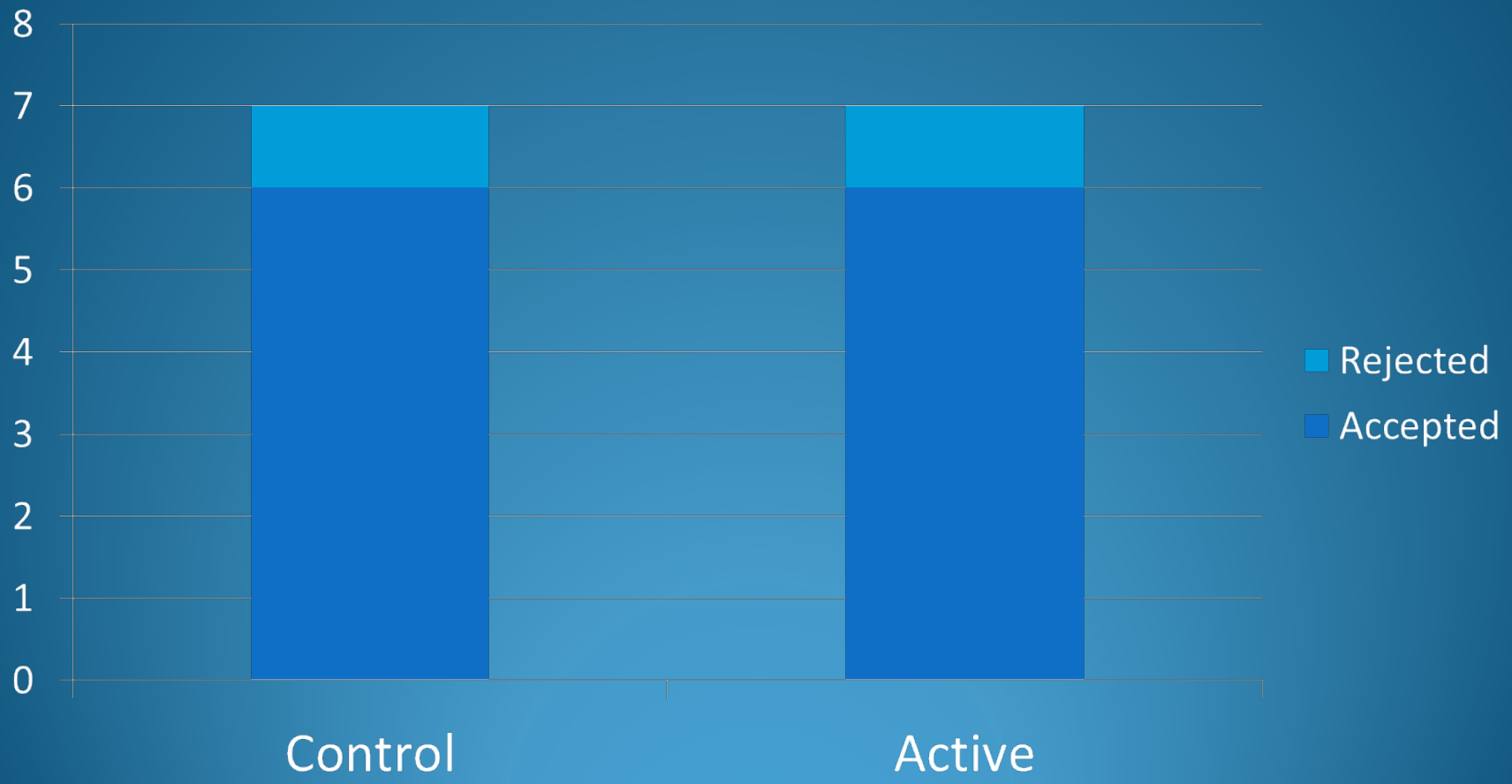
2. Reported ≠ Reported Outcomes

- CV Outcomes collected from SAE database (e.g. TRIM)
- No one has asked the Site PI if event met study definition
- Outcome definitions within a study are not equivalent to a coded SAE term
- Site input is not sought
- **Effect of Adjudication = effect of at least one physician reviewing an outcome, compared to none**

3. Adjudication: Bundled vs. Á la Carte

- Bundled: Adjudication contains two processes:
  1. Reviewing reported outcomes
  2. Searching for unreported outcome that are then adjudicated (e.g. PURSUIT) ↑events
- Á la Carte: Adjudication involved only the review of reported outcomes. Finding Unreported Outcomes is handled through Data Management and Monitoring ↓=events
- **Different Processes can have different Effects**

Reality of Adjudication?



Cost of Adjudication

$ Supporting Documents, Masking, Translation, Shipment, Web apps, Adjudicators

β Lower event rates, Reduced Power, Increased Sample Size

Adjudication Time at Trial End, Longer Trial Time

Our Conclusions

- We failed to find an adjudication effect in our large cardiovascular trials
  - No bias without it
  - No increased precision
- Plausible reasons why some other trials have found differences
- Need to understand adjudication and systematically determine when it is necessary for different types of outcomes and trials