Steroids In caRdiac Surgery (SIRS) Trial

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On behalf of the SIRS Investigators

Rationale

- Cardiopulmonary bypass results in an inflammatory response which is associated with adverse outcomes

- Prophylactic steroids attenuate this response, but clinical benefits are unclear

- Meta-analysis of small trials suggest clinical benefit of steroids

- DECS trial (n=4494) suggests clinical benefit in a prespecified subgroup of EuroSCORE ≥ 5

SIRS Hypotheses

- Methylprednisolone compared to placebo would reduce death and major morbidities at 30 days in high-risk patients undergoing cardiac surgery with the use of CPB

Trial Flow Diagram

Randomized (n = 7,507)

Steroid* (n = 3,755)

Placebo (n = 3,752)

Lost to follow-up (n = 1)

Lost to follow-up (n = 0)

Analyzed by intention-to-treat
(n = 3,755)

Analyzed by intention-to-treat
(n = 3,752)

*500 mg IV Methylprednisolone given intra-operatively

Patient Population (1)

Inclusions:

1) Age $\geq$ 18 years of age
2) Require CPB for <u>any</u> cardiac surgical procedure
3) EuroScore $\geq$ 6

   Note: For sites in China, Hong Kong and India, the following criteria applied:

   a) EuroScore $\geq$ 4 if undergoing a valve procedure

   b) EuroScore $\geq$ 6 if undergoing any other cardiac surgery procedure

4) Provide written informed consent

Patient Population (2)

Exclusions:

1) Planned use of perioperative systemic steroids
2) History of bacterial or fungal infection in the last 30 days
3) Allergy or intolerance to corticosteroids
4) Planned use of Aprotinin
5) Previous participation in this study

Primary Study Outcomes

1st Co-Primary Outcome:

- Total mortality within 30 days

2nd Co-Primary Outcome:

- Composite of total mortality, MI, stroke, renal failure, or respiratory failure within 30 days

2° Study Outcomes: Efficacy

- First 24 hours
  - Transfusions

- Length of ICU and hospital stay

- 30 days
  - Components of composite
  - Death or MI

2° Study Outcomes: Safety

- First 24 hours
  - Post-operative insulin use, peak blood glucose

- Day 3
  - Delirium

- 30 days
  - Infection, wound complication, GI hemorrhage/perforation

SIRS Early-MI Definition

	Activity Assay	Mass Assay
Isolated CABG Procedure	≥40 U/L	≥6 x ULN
Other Cardiac Surgery Procedure	≥120 U/L	≥15 x ULN

<u>NOTE</u>: In patients with elevated baseline CK-MB (greater than reported ULN) ➜ An absolute increase in CK-MB measurement as per the above definition is required

Baseline Characteristics

	Steroid (N=3,755)	Placebo (n=3,752)
Age (SD)	67.5 (±13.6)	67.3 (±13.8)
Male (%)	60.1	60.8
Previous MI (%)	26.2	24.7
Previous stroke (%)	8.1	8.4
Congestive heart failure (%)	26.8	27.2
Diabetes (%)	26.2	26.4
EuroSCORE (SD)	7.1 (±2.0)	7.1 (±2.0)
Procedure i. Any valve procedure (%) ii. Any CABG (%) iii. Isolated valve (%) iv. Isolated CABG (%)	2646 (70.4) 1838 (48.4) 1206 (32.1) 826 (22.0)	2723 (72.6) 1796 (47.9) 1228 (32.7) 762 (20.3)

Co-Primary Outcomes (30 days)

30-Day Outcome	Steroid (%) N=3755	Placebo (%) N=3752	RR (95% CI)	p-value
First Co-Primary - Death	155 (4.1)	176 (4.7)	0.88 (0.71-1.09)	0.23
Second Co-Primary - Composite death, MI, stroke, new renal failure, respiratory failure	908 (24.2)	869 (23.2)	1.04 (0.96-1.13)	0.30

Composite Components (30 days)

30-Day Outcome	Steroid (%) N=3755	Placebo (%) N=3752	RR (95% CI)	p-value
Components of Composite				
MI	500 (13.3)	408 (10.9)	1.22 (1.08-1.38)	0.001
Stroke	72 (1.9)	80 (2.1)	0.90 (0.66-1.23)	0.51
New Renal Failure	105 (2.8)	114 (3.0)	0.92 (0.71-1.20)	0.53
Respiratory Failure	343 (9.1)	375 (10.0)	0.91 (0.79-1.05)	0.21

Secondary Outcomes: Efficacy

Outcomes	Steroid N=3755	Placebo N=3752	RR (95% CI)	p-value
Death or MI (%)	620 (16.5)	536 (14.3)	1.16(1.04-1.29)	0.008
New atrial fibrillation (%)	821 (21.9)	846 (22.5)	0.97(0.89-1.06)	0.53
Any transfusion (%)	1832 (48.8)	1865 (49.7)	0.98 (0.94-1.03)	0.43
Length of ICU stay (hrs)	46.0 (23.0-90.0)	47.0 (24.0-91.0)		0.05
Length of hospital stay (days)	9.0 (7.0-13.0)	9.0 (7.0-13.0)		0.06

Secondary Outcomes: Safety

Outcomes	Steroid N=3755	Placebo N=3752	RR (95% CI)	p-value
Infection (%)	464 (12.4)	494 (13.2)	0.94 (0.83-1.06)	0.29
Delirium (%)	295 (8.4)	290 (8.3)	1.01 (0.87-1.19)	0.84
Surgical site infection (%)	150 (4.0)	150 (4.0)	1.00(0.80-1.25)	0.99
GI perforation or hemorrhage (%)	55 (1.5)	46 (1.2)	1.19 (0.81-1.76)	0.37
Peak blood glucose (mmol/L)	12.7 ($\pm$7.2)	12.1 ($\pm$18.7)		0.04
Post-operative Insulin (u)	50.3 ($\pm$66.3)	32.6 ($\pm$52.9)		<0.00001

Subgroup Analysis

- Co-primary and MI results were consistent across 6 subgroups of:
  - Gender
  - Diabetic status
  - Age
  - EuroSCORE
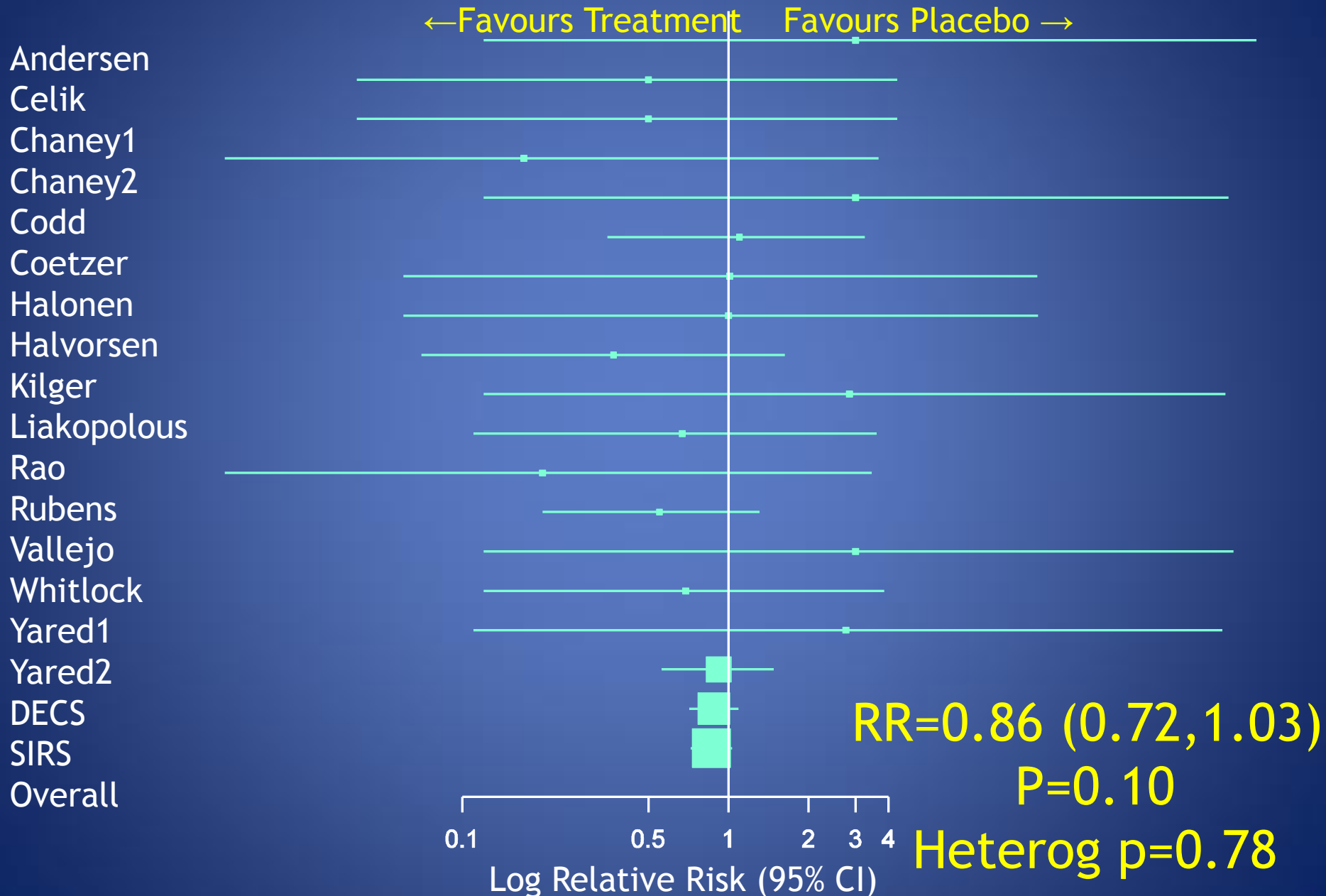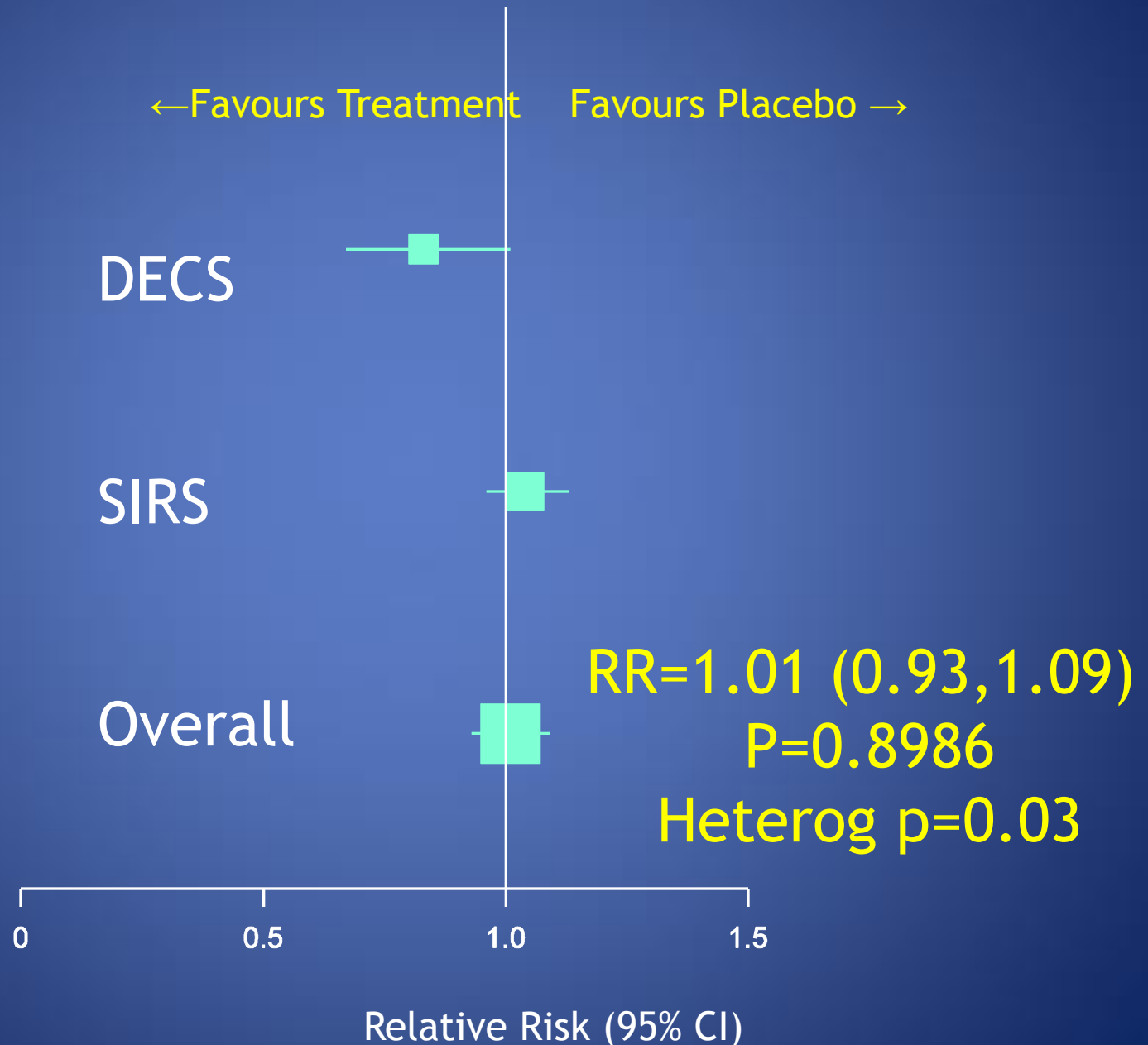 - Surgery type
  - CPB duration

Conclusions

1. Methylprednisolone does not reduce death or major morbidity at 30 days for high-risk patients undergoing cardiac surgery with the use of cardiopulmonary bypass.

2. Methylprednisolone increases the risk of early post-operative myocardial infarction

3. Methylprednisolone should not be administered prophylactically to high-risk patients undergoing cardiac surgery with the use of cardiopulmonary bypass.

Additional slides

Meta Analysis - Death

←Favours Treatment   Favours Placebo →
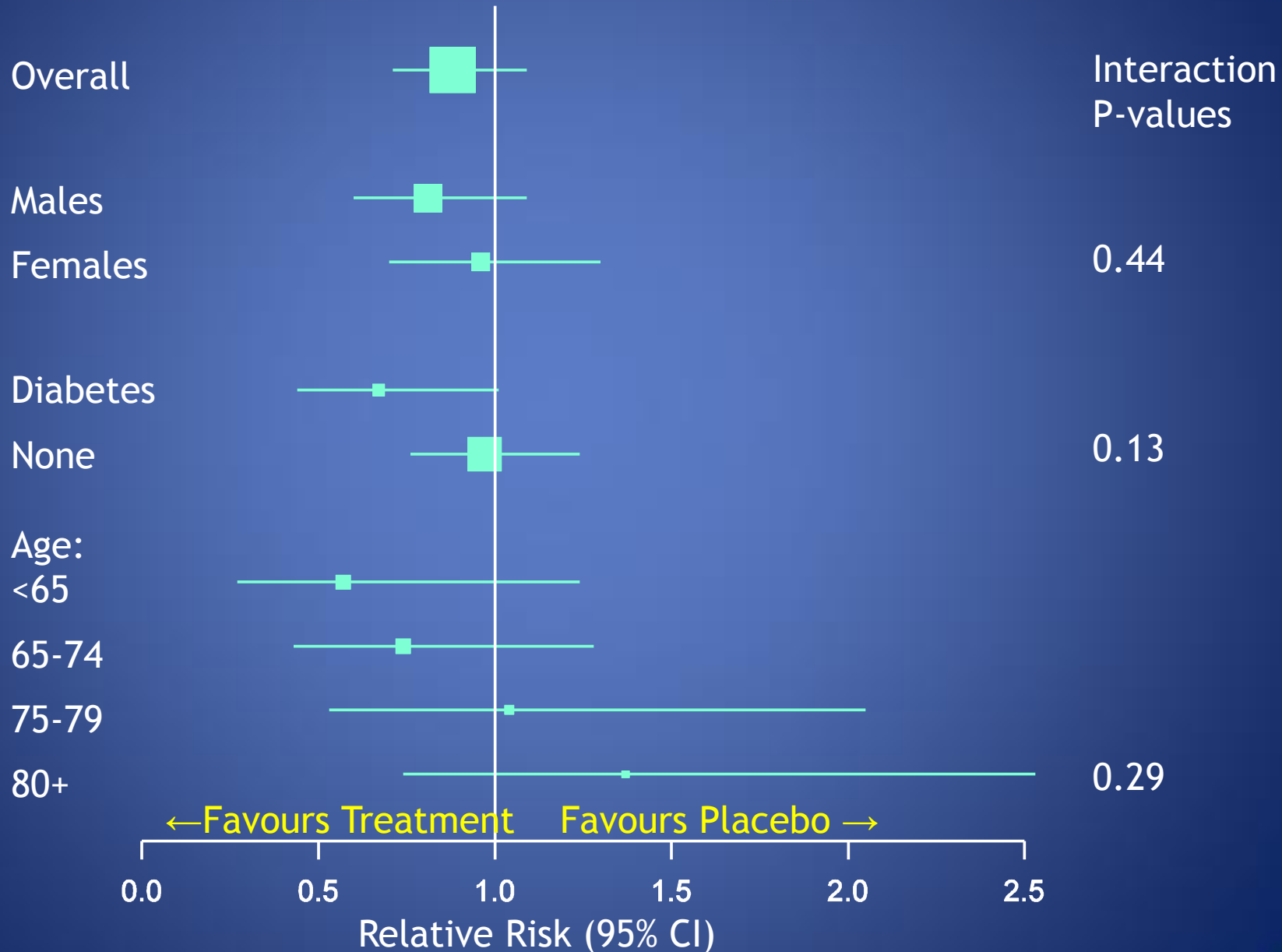
Andersen
Celik
Chaney1
Chaney2
Codd
Coetzer
Halonen
Halvorsen
Kilger
Liakopolous
Rao
Rubens
Vallejo
Whitlock
Yared1
Yared2
DECS
SIRS
Overall

RR=0.86 (0.72,1.03)
P=0.10
Heterog p=0.78

0.1   0.5   1   2   3 4
Log Relative Risk (95% CI)

Meta Analysis – Co Primary

←Favours Treatment   Favours Placebo →

DECS

SIRS

Overall

RR=1.01 (0.93,1.09)
P=0.8986
Heterog p=0.03

0   0.5   1.0   1.5

Relative Risk (95% CI)

Types of MI

	Steroid (%) N=3755	Placebo (%) N=3752	RR (95% CI)	P-value
Any MI	13.3	10.9	1.22 (1.07-1.37)	0.001
MI ≤72 hours	13.3	10.8	1.23 (1.09-1.39)	0.001
Q-wave	0.6	0.6	0.87 (0.49-1.57)	0.65
Non Q-wave	12.7	10.2	1.25 (1.10-1.42)	<0.001
CK-MB 5-10 x ULN	3.1	2.6	1.19 (0.92-1.56)	0.19
CK-MB >10 x ULN	7.7	6.1	1.26 (1.07-1.49)	0.006

Mortality CK-MB Thresholds by Treatment

	Above Threshold		Below Threshold		Above vs. Below	
	N	Death (%)	N	Death (%)	RR (95% CI)	P-value
Steroid	537	37 (6.9)	3218	118 (3.7)	1.88 (1.31-2.69)	<0.0001
Placebo	430	47 (10.9)	3322	129 (3.9)	2.81 (2.05-3.87)	<0.0001
All	967	84 (8.7)	6540	247 (3.8)	2.30 (1.81-2.92)	<0.0001

Subgroups 1 – Death at Day 30