

# **OASIS-6 GIK results and the combined analyses of the OASIS-6 & CREATE/ECLA**

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# OASIS-6 GIK AND COMBINED CREATE/ECLA & OASIS-6 trials

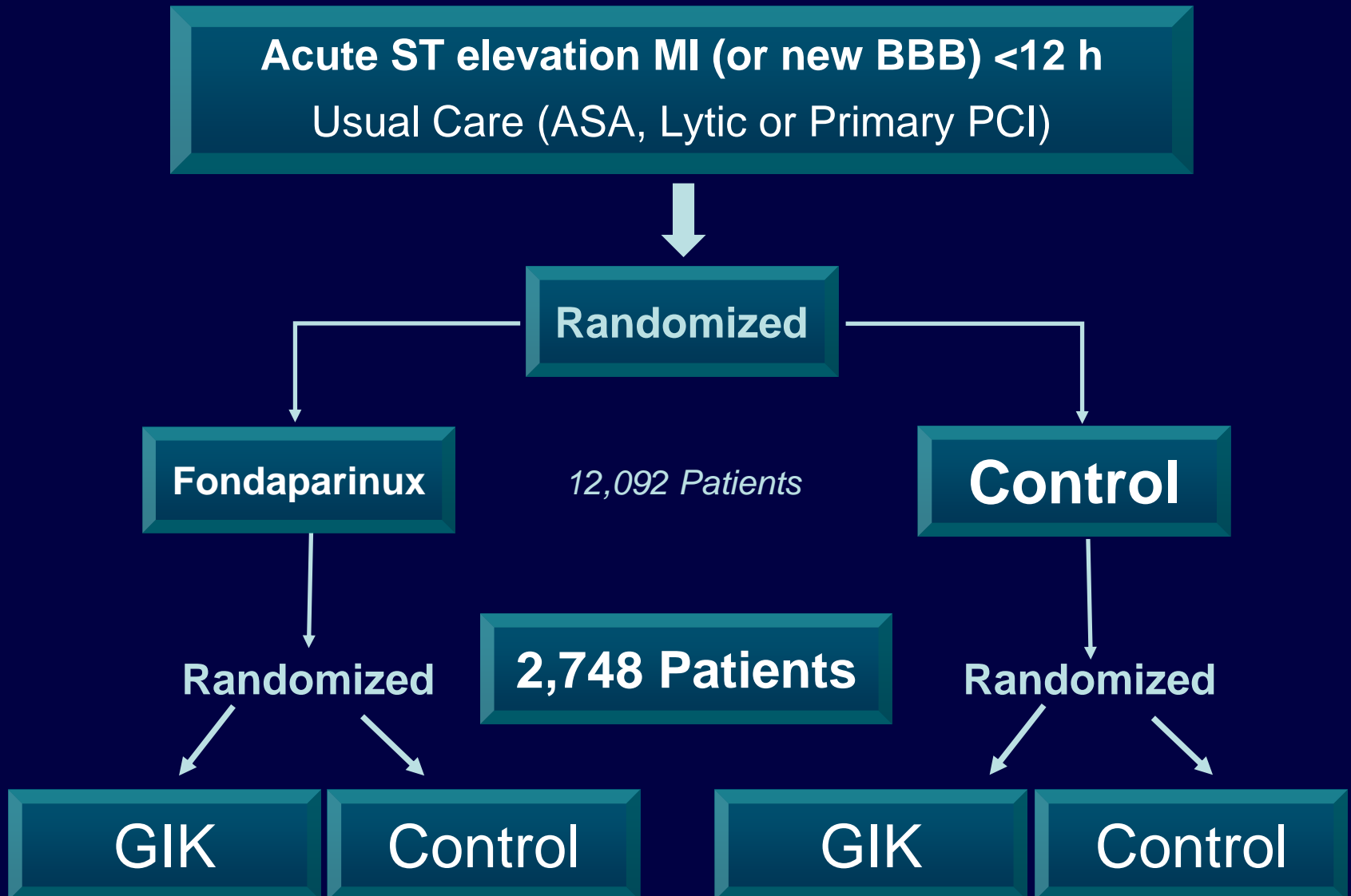
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## *Aims*

- Results of the GIK arm of the OASIS-6 trial
- Analyze the combined results of the GIK  
CREATE/ECLA & OASIS-6 trial

# OASIS-6 GIK TRIAL

## Study Design



# ***GIK OASIS-6 trial***

30 day outcomes

	<b>GIK</b> <i>(1,368)</i>	<b>CONTROL</b> <i>(1,377)</i>		
<b>OUTCOME</b>	<b>n/N (%)</b>	<b>n/N (%)</b>	<b>HR (95% CI)</b>	<b>p</b>
<b><i>DEATH</i></b>	104 (7.6)	92 (6.7)	1.14 (0.86 - 1.51)	0.36
<b><i>HEART FAILURE</i></b>	144 (10.6)	165 (12.2)	0.87 (0.70 - 1.09)	0.31
<b><i>DEATH/HF</i></b>	196 (14.3)	212 (15.4)	0.92 (0.76 - 1.12)	0.41

# GIK arm OASIS-6

## *Conclusion*

The GIK arm of OASIS-6 trial is consistent with the CREATE/ECLA trial and did not show beneficial effects with GIK

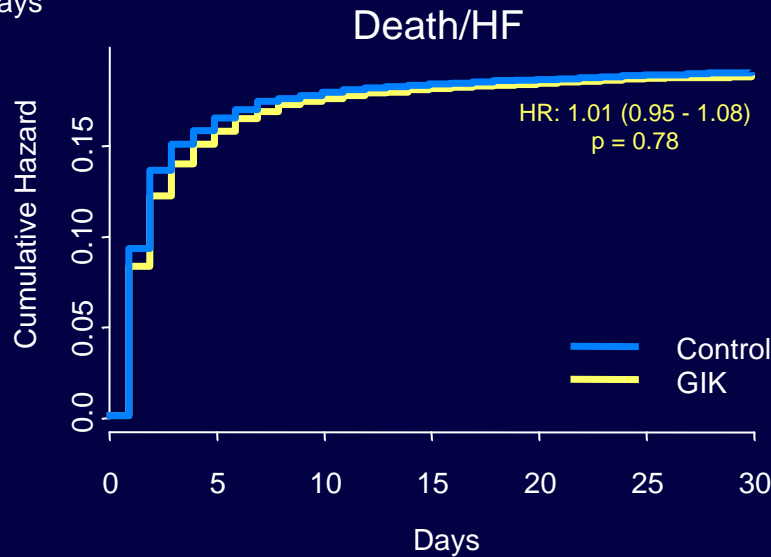
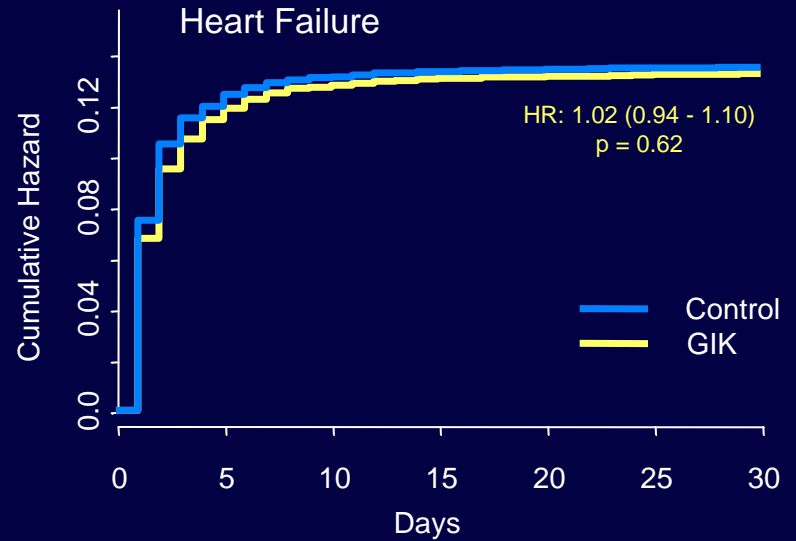
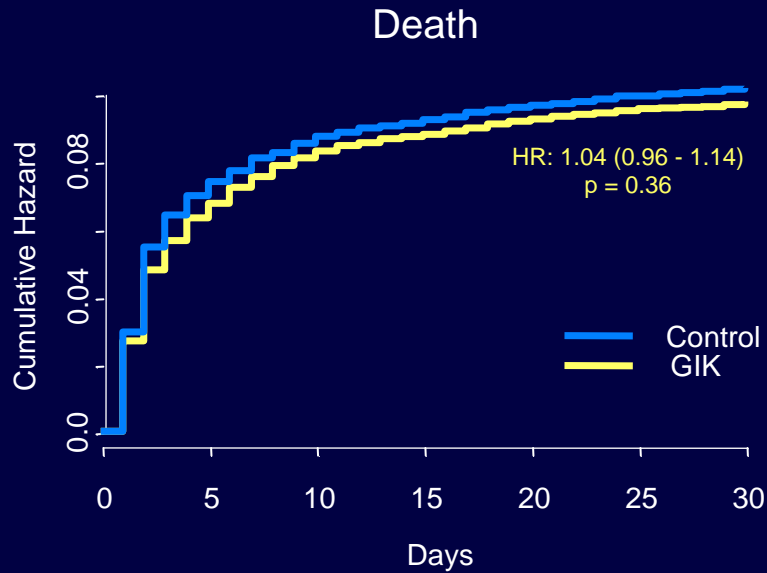
# OASIS-6 GIK ARM & CREATE/ECLA trials

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As both trials have been similarly designed will permit their combined analyses (23,000 patients, 2,200 deaths, 2,800 heart failures & 4,000 deaths/heart failure events) with the aim of clarifying the mechanisms by which GIK has neutral effects in the context of STEMI

# GIK OASIS-6 and CREATE trials

## KM cumulative event rate



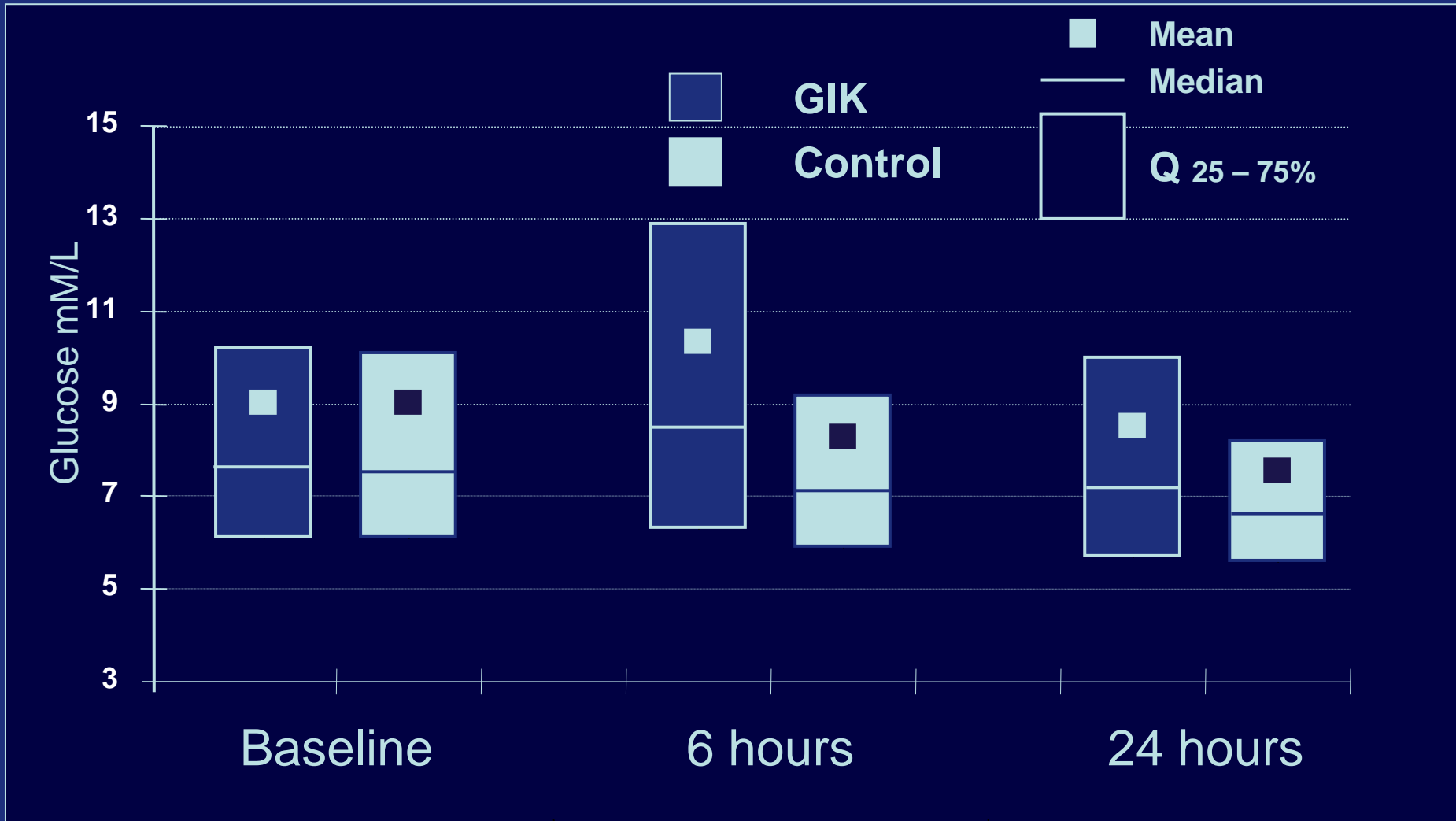
# Event rates estimated using Kaplan-Meier and Cox proportional hazard ratios. Day 3

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	<b>CONTROL</b> <b>N=11481</b>	<b>GIK</b> <b>N=11462</b>	<b>HR</b> <b>(95% CI)</b>	<b>p</b>
<b>Death</b>	632 (5.5%)	712 (6.2%)	1.13 (1.02- 1.26)	0.02
<b>Death/HF</b>	1485 (12.9%)	1591 (13.9%)	1.08 (1.00-1.16)	0.04
<b>Heart Failure</b>	1159 (10.1%)	1242 (10.8%)	1.08 (0.99- 1.17)	0.07

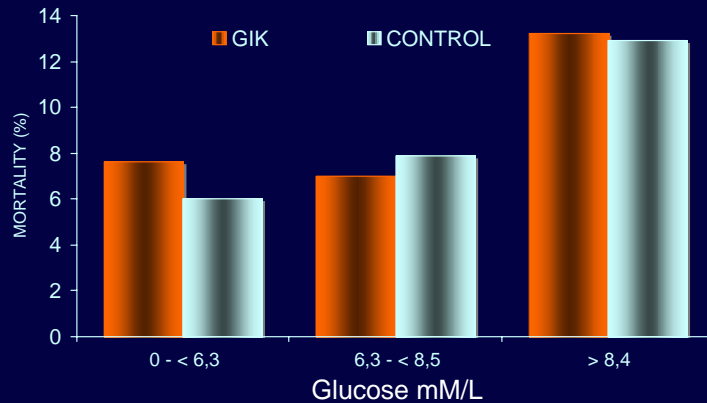
# OASIS-6 & CREATE/ECLA trials

## *Glucose levels*

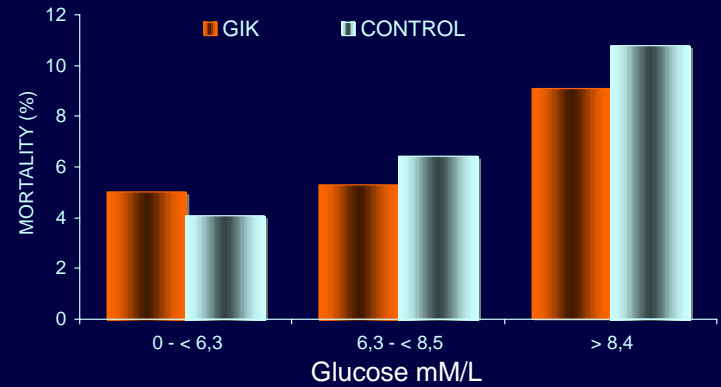


# GLUCOSE LEVELS & MORTALITY

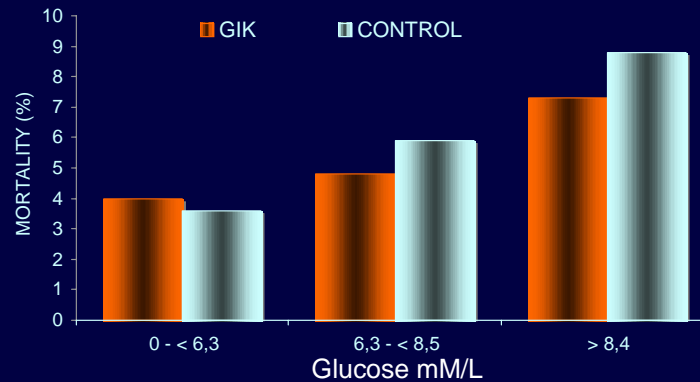
Baseline glucose & 30 day mortality



6 hours glucose & 30 day mortality

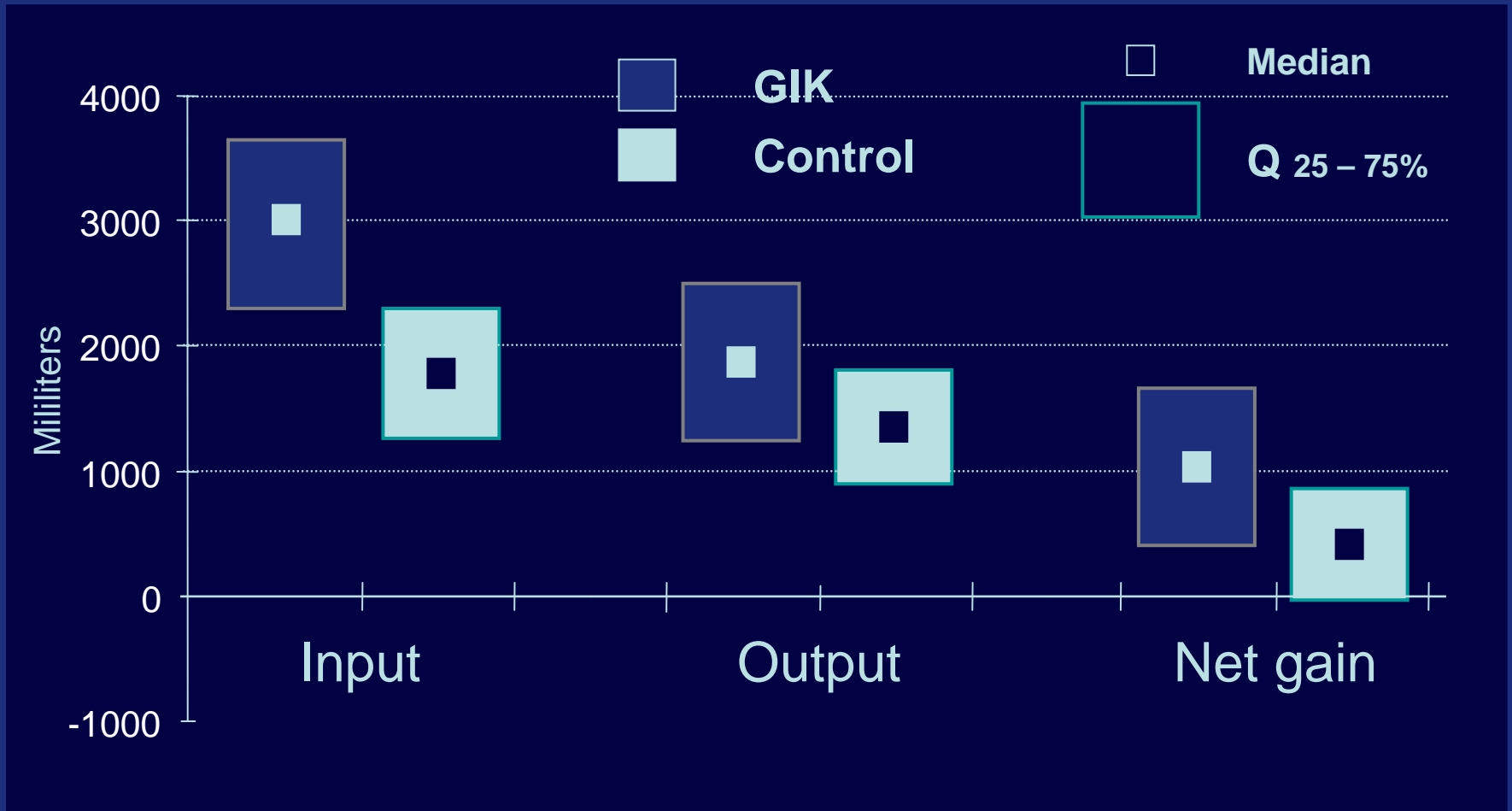


24 hours glucose & 30 day mortality



# OASIS-6 & CREATE/ECLA trials

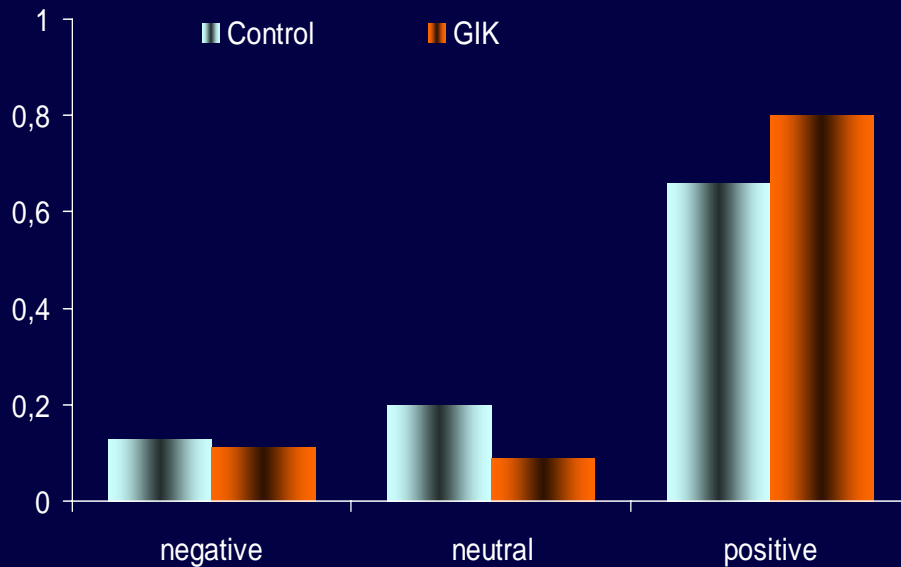
## *Fluid balance*



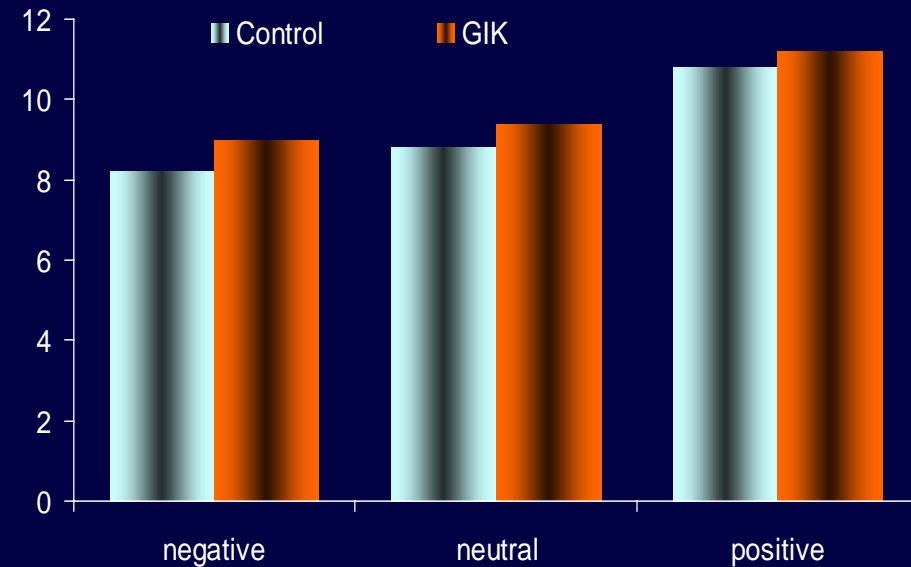
# CREATE/ECLA & OASIS-6 TRIALS

*Fluid Balance. Prevalence & Outcomes (Death/HF)*

Prevalence



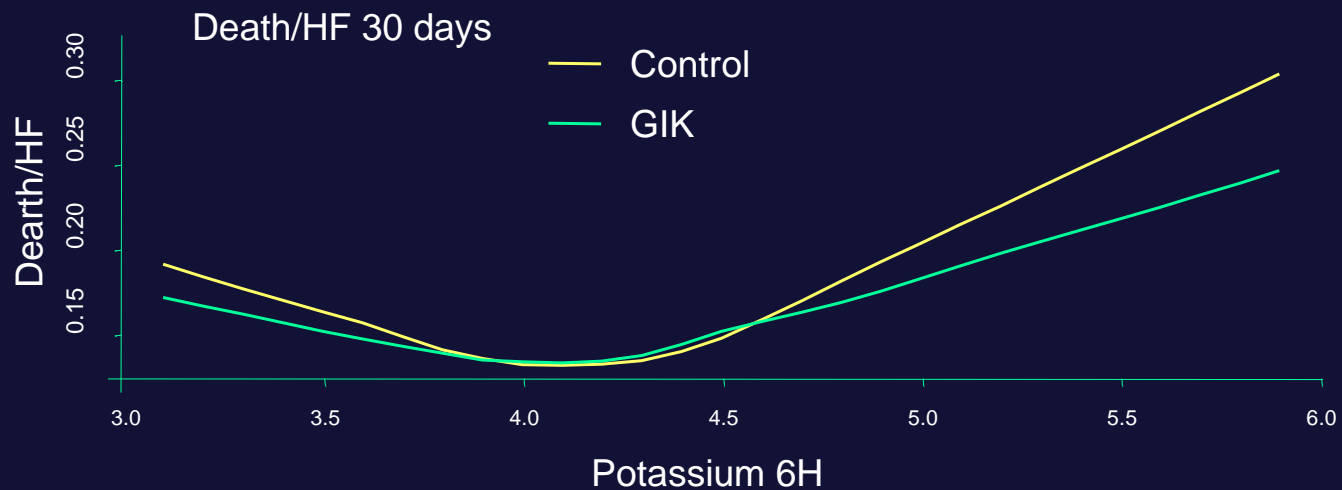
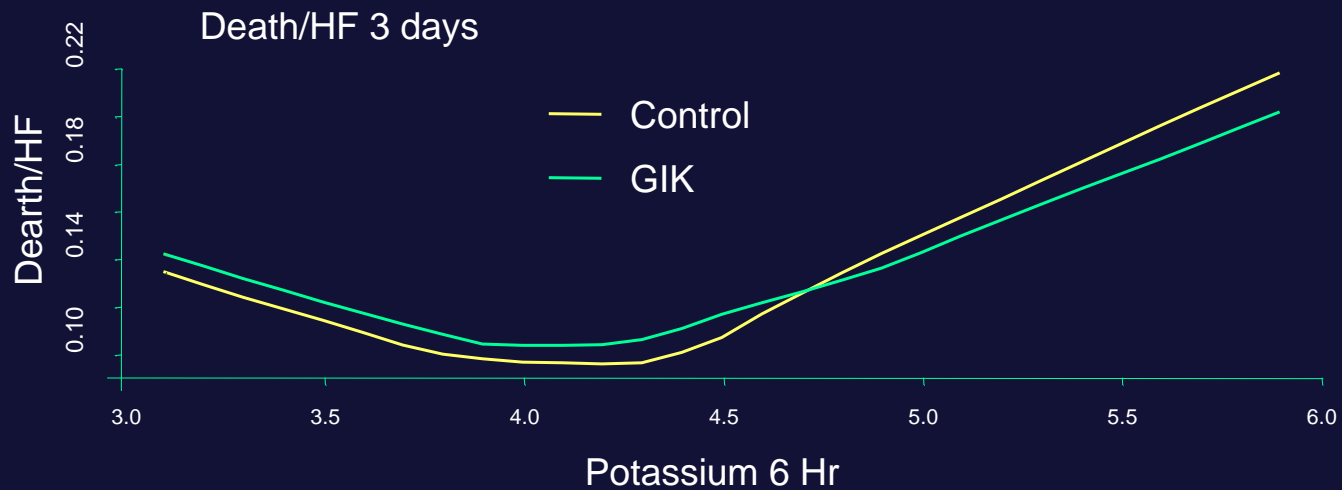
Death/HF



# OASIS-6 & CREATE/ECLA trials

*Relation between serum Potassium & Death/Heart Failure*

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# OASIS-6 GIK & CREATE/ECLA TRIAL

## *Conclusion*

- OASIS-6 GIK did not show any beneficial effect
- The combined analyses of OASIS-6 and the CREATE/ECLA trial showed an increased event rate at 3 days and a neutral effect at 30 days
- This is likely due to an “Early Hazard” phenomenon (increased mortality & HF with GIK) which may be counterbalance by a “Late Benefit” effect
- The “Early Hazard” appears to be related to increases in glucose levels and fluid overload with the GIK infusion

# OASIS-6 GIK & CREATE/ECLA TRIAL

## *Limitations*

- Early Hazard is possible; Late Benefit (post-randomization) requires prospective confirmation

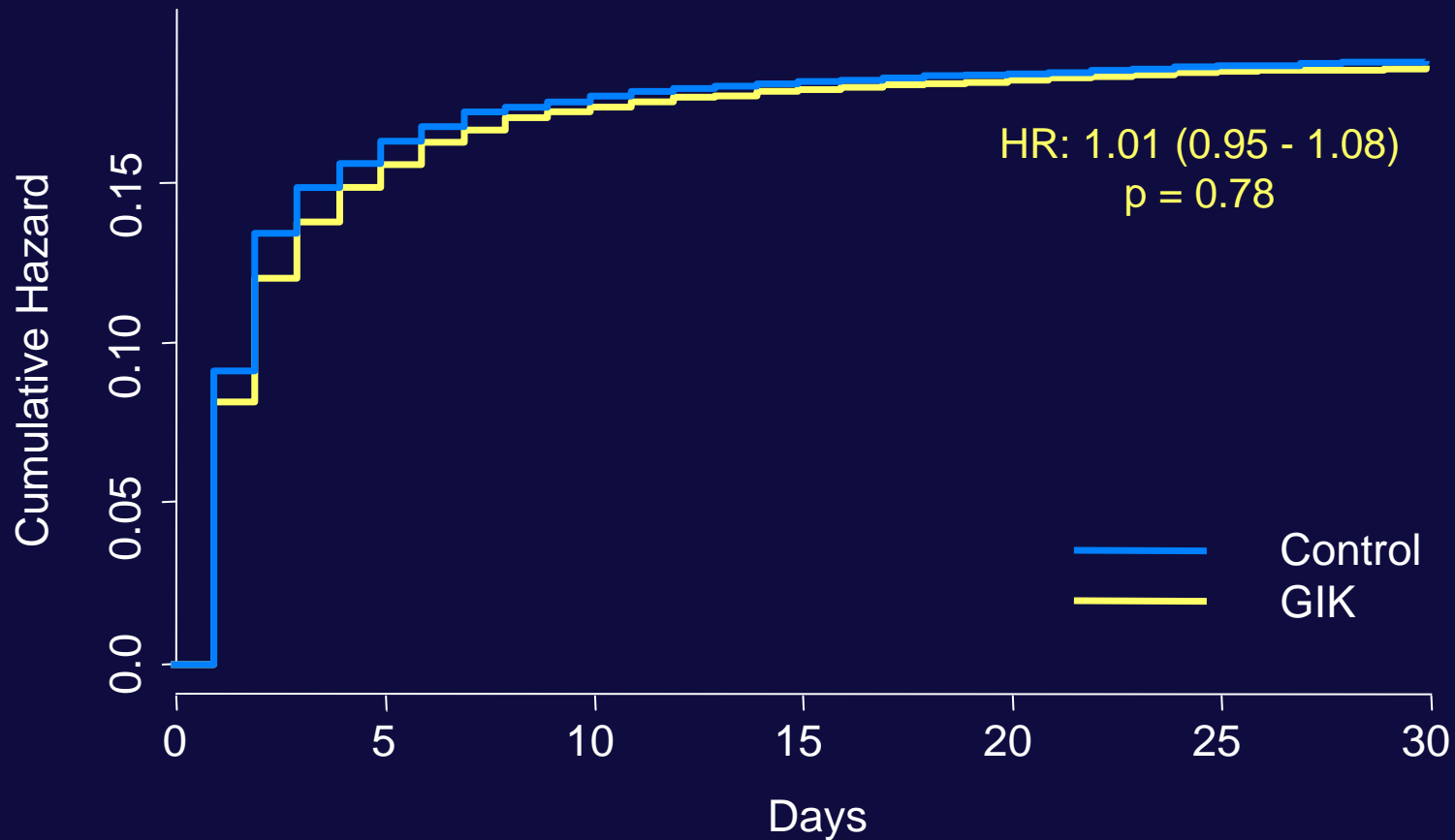
## *Implications*

- Will lowering glucose levels without increasing fluids may reduce both early and late mortality?
- This hypothesis requires prospective evaluation

# GIK OASIS-6 and CREATE trials

KM cumulative death/heart failure rate

## Death/Heart Failure



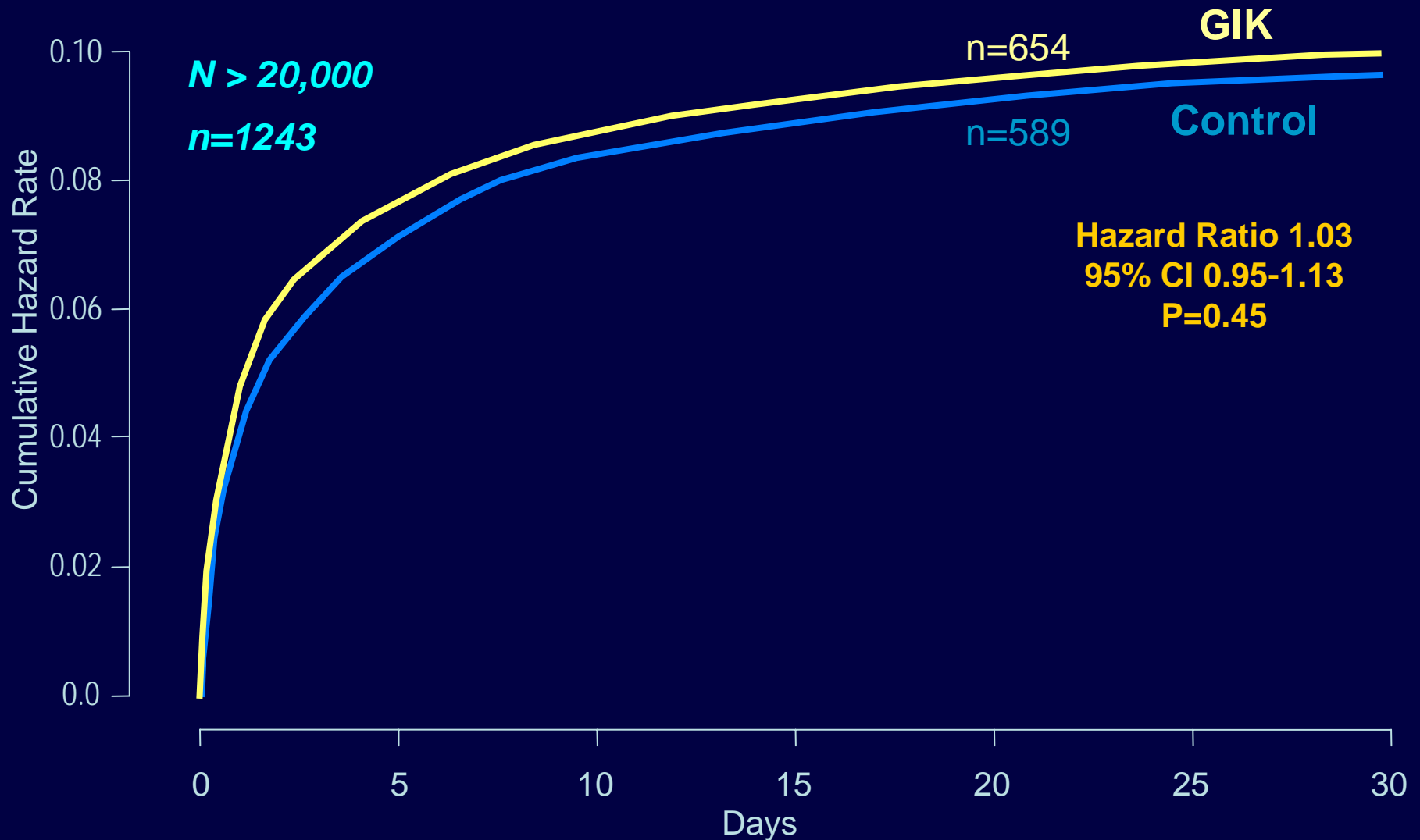
# Could the “Early Hazard” observation be related to the infusion or its components

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- High dose glucose administration
- Large volume infused
- High dose potassium administration

# CREATE/ECLA trial

## Mortality at 30 Days



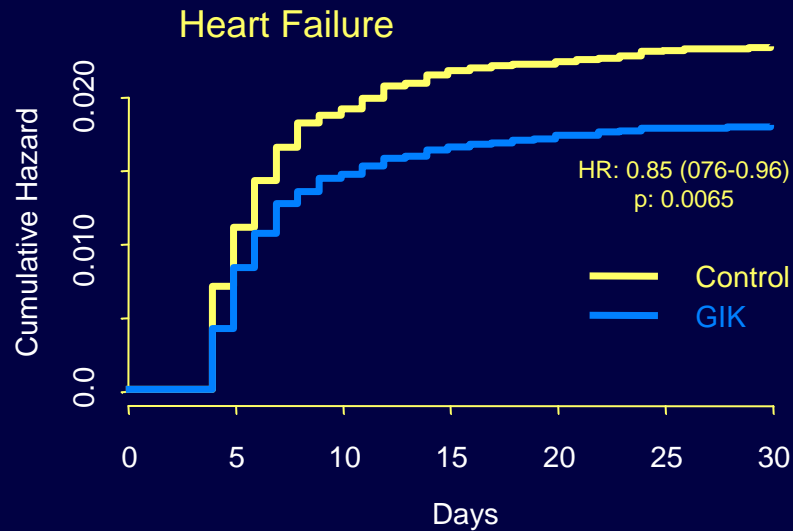
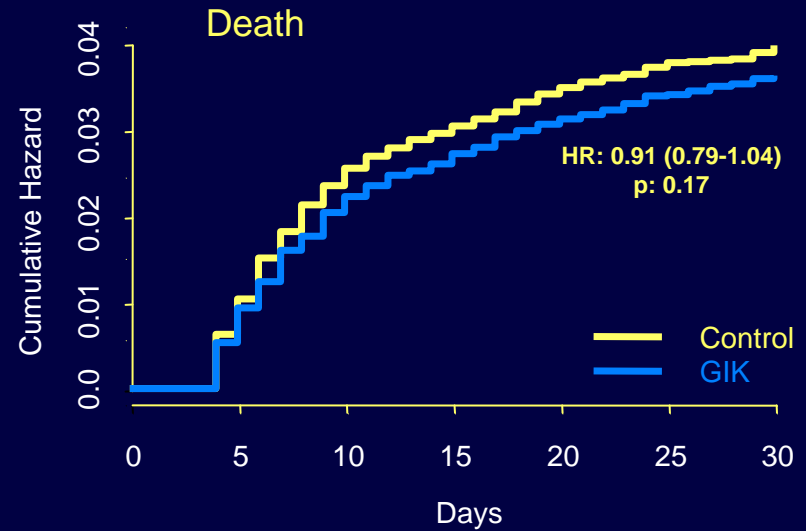
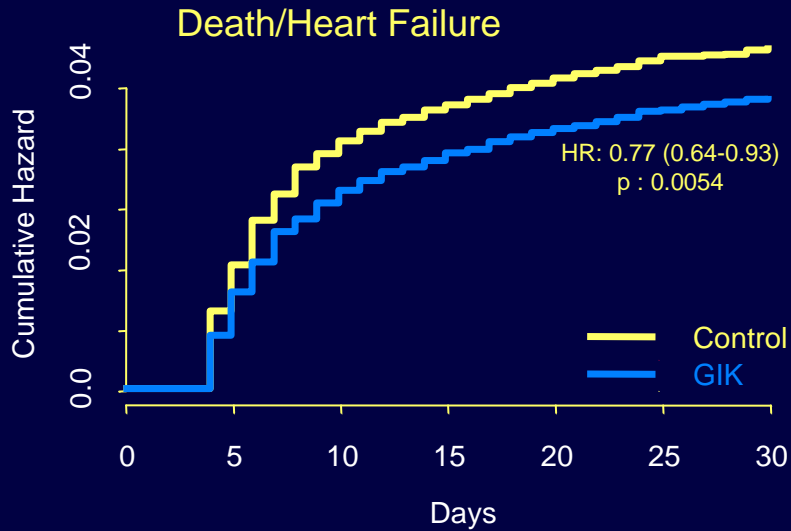
# OASIS-6 & CREATE/ECLA TRIALS

*30 days Outcomes*

	GIK (11,462)	CONTROL (11,481)	HR	95 % CI	p
Death	1,108 (9.7)	1,068 (9.3)	1.04	(0.96 - 1.13)	0.33
Heart Failure	1,441 (12.6)	1,418 (12.4)	1.02	(0.95 - 1.10)	0.57
Death/HF	1,973 (17.2)	1,963 (17.1)	1.01	(0.95 - 1.08)	0.72

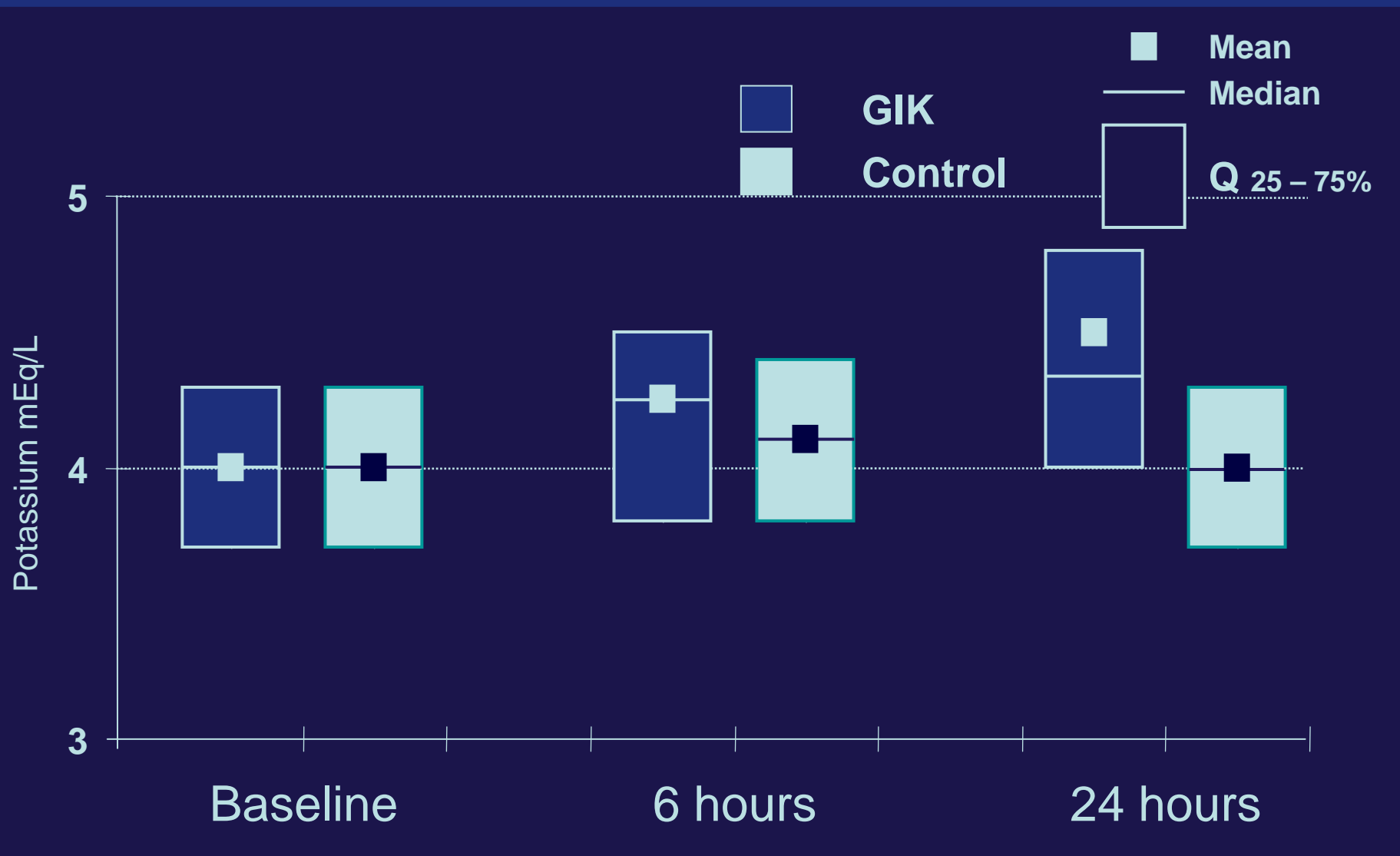
# OASIS-6 & CREATE/ECLA trials

## KM cumulative event rate after day 3



# OASIS-6 & CREATE/ECLA trials

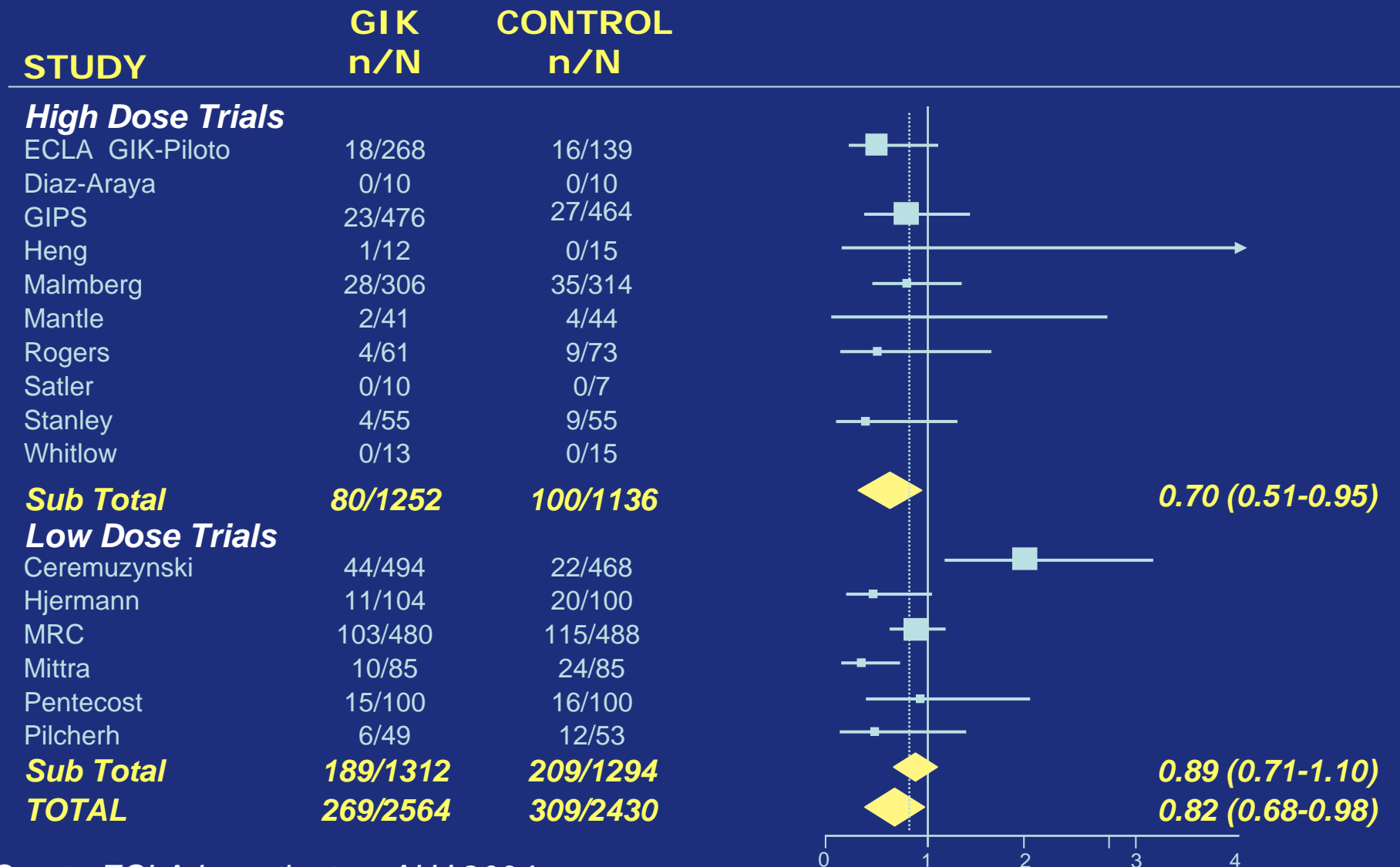
## *Serum Potassium*



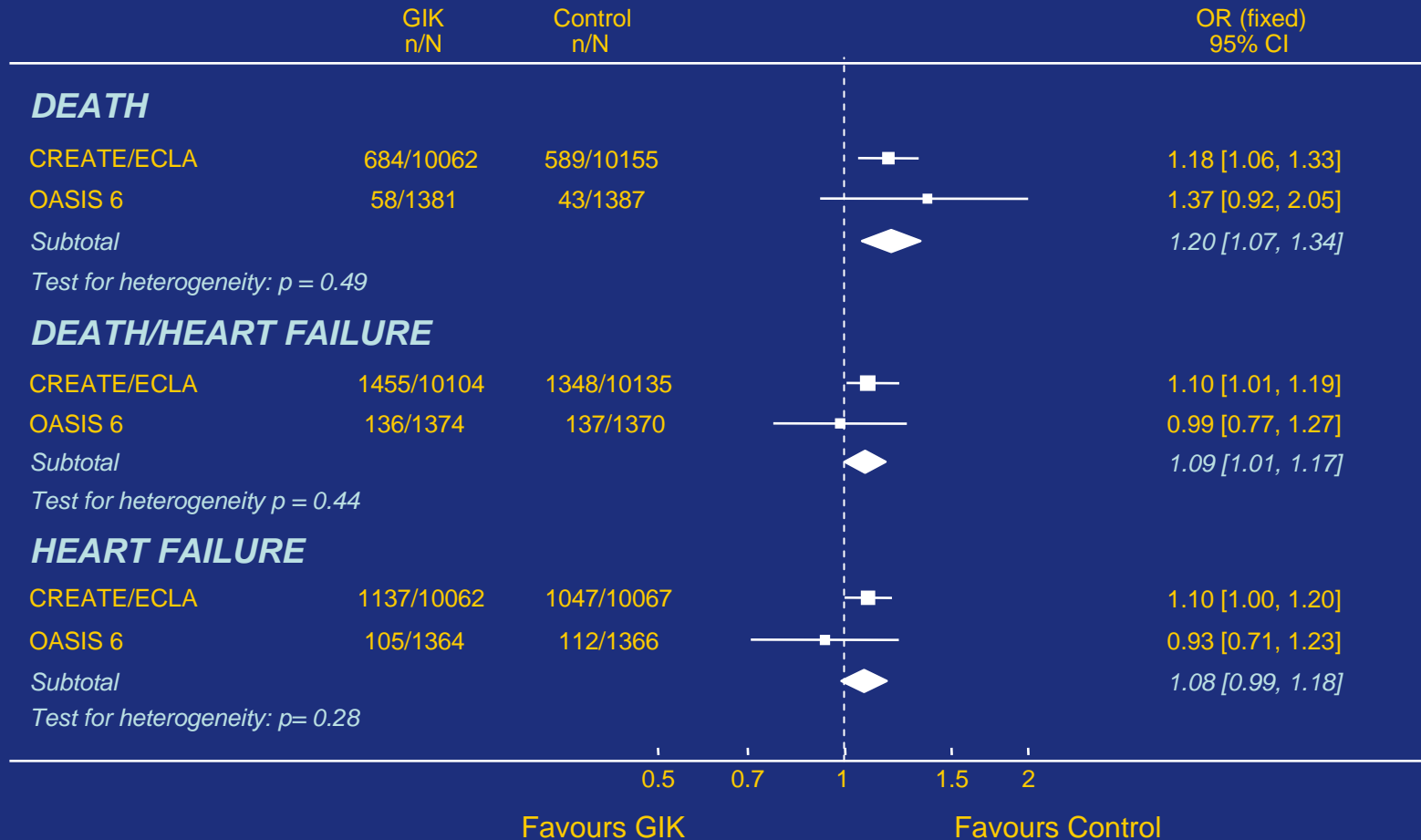
# Event rates estimated using Kaplan-Meier and Cox proportional hazard ratios. Day 0-3 and 4-30

	<b>CONTROL N=11481</b>	<b>GIK N=11462</b>	<b>HR (95% CI)</b>	<b>p</b>	<b>Heter. test</b>
<b>Death (day 0-3)</b>	632 (5.5%)	712 (6.2%)	1.13 (1.02- 1.26)	0.02	p=0.01
<b>Death (day 4-30)</b>	436 (3.9%)	396 (3.3%)	0.91 (0.79-1.04)	0.17	
<b>Death/HF (day 0-3)</b>	1485 (12.9%)	1591 (13.9%)	1.08 (1.00-1.16)	0.037	p=0.0009
<b>Death/HF (day 4-30)</b>	618 (5.5%)	526 (4.7%)	0.85 (0.76-0.96)	0.006	
<b>Heart Failure (day 0-3)</b>	1159 (10.1%)	1242 (10.8%)	1.08 (0.99- 1.17)	0.070	p=0.0005
<b>Heart Failure (day 4-30)</b>	259 (2.3%)	199 (1.8%)	0.77 (0.64-0.93)	0.005	

# Meta-analysis of RCT's of GIK vs Control in AMI

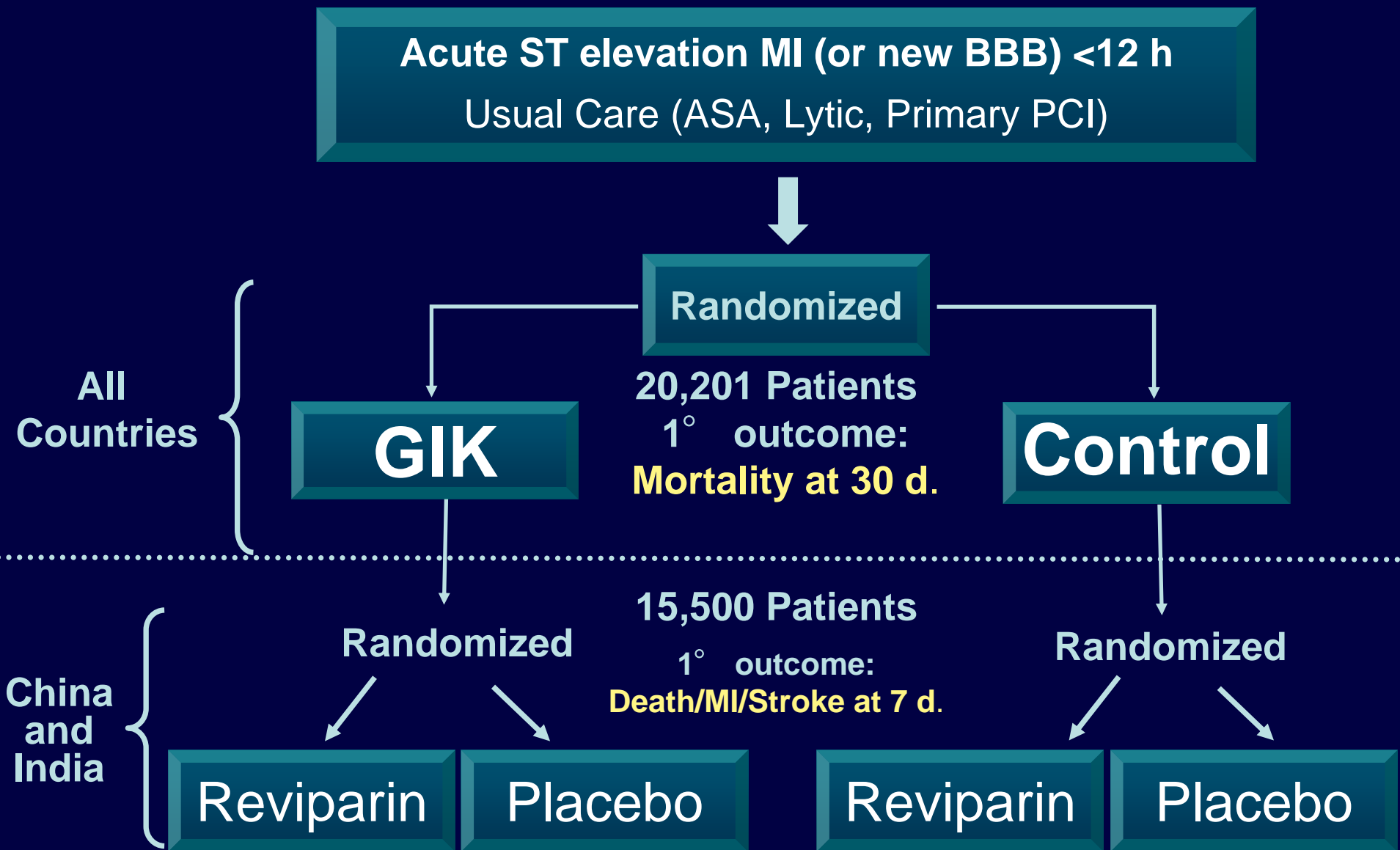


# Death, Heart Failure & Death/Heart Failure at day 3 in OASIS-6 & CREATE/ECLA trials



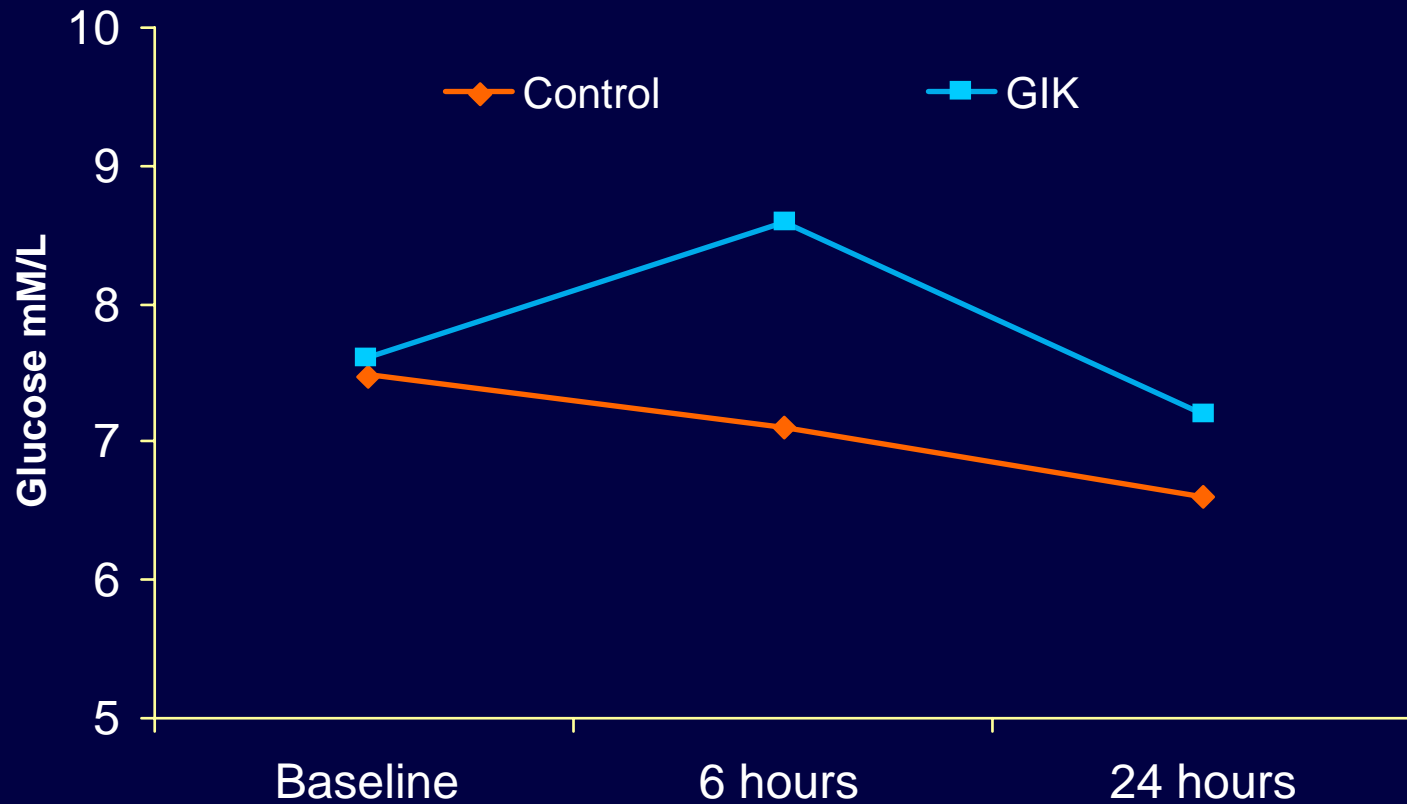
# CREATE/ECLA GIK TRIAL

## Study Design



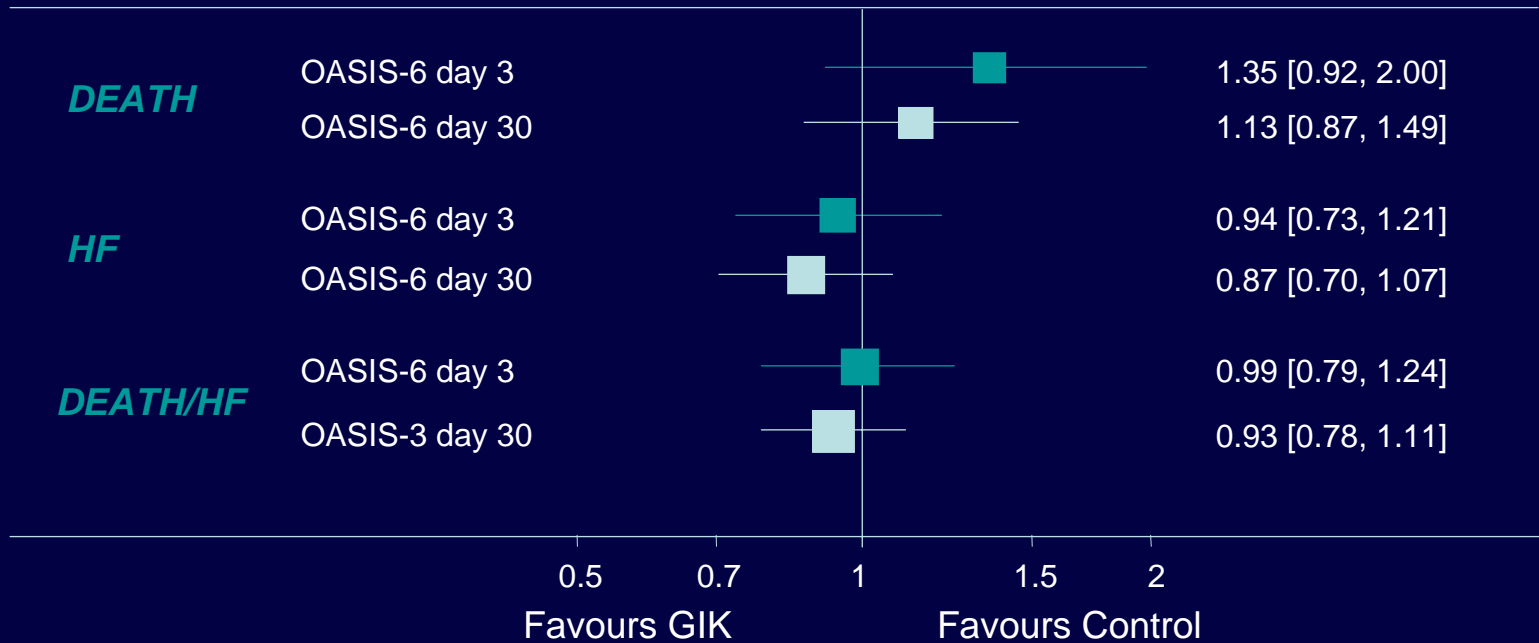
# GIK OASIS-6 & CREATE/ECLA TRIALS

*Glucose behaviour (N=22,716)*

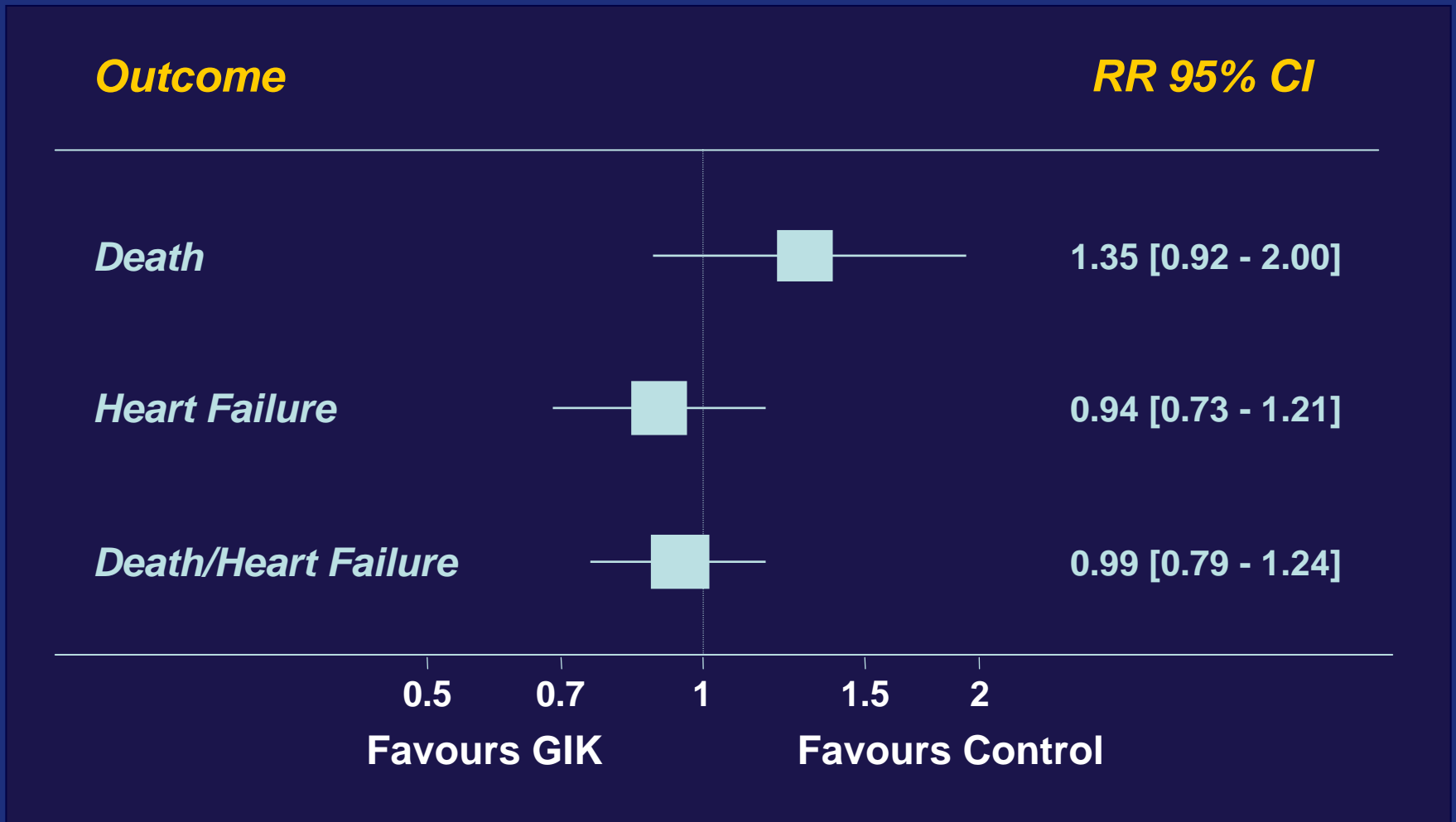


# GIK OASIS-6 trial

## 3 & 30 day outcomes

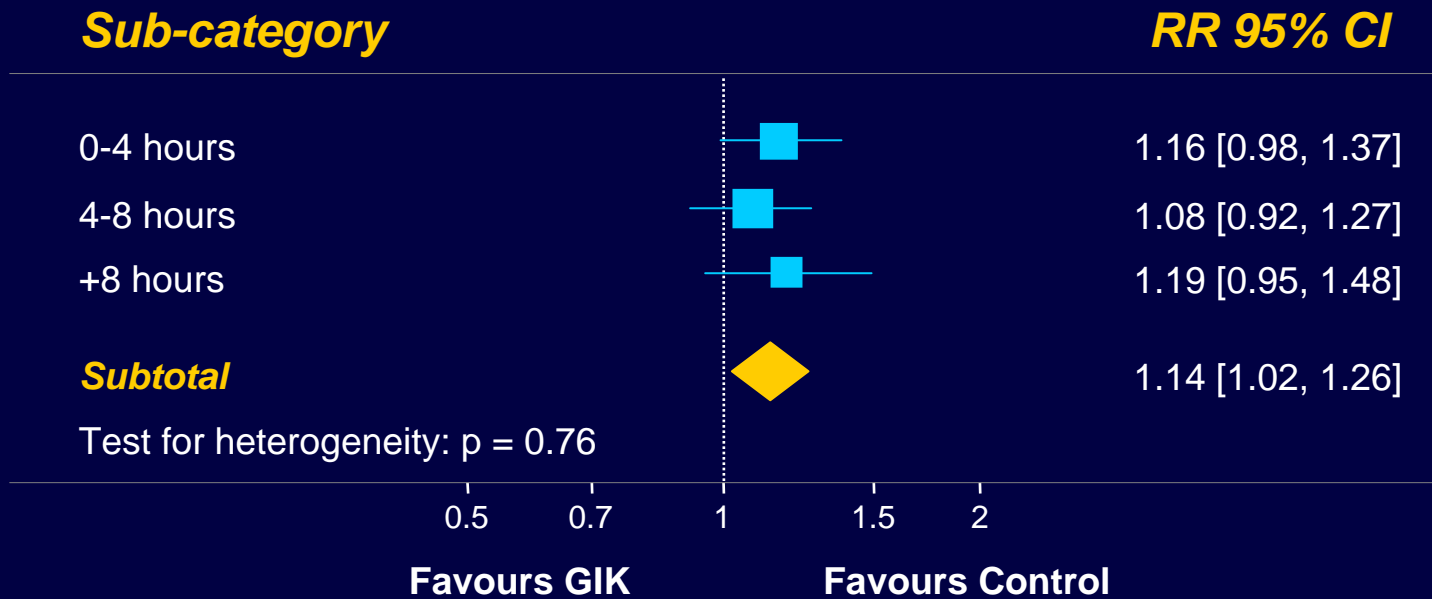


# Death, Heart Failure & Death/Heart Failure at day 3 in OASIS-6 trial



# OASIS-6 & CREATE/ECLA trials.

## Death at day 3. Time to randomization subgroup analyses



# Death, Heart Failure & Death/Heart Failure at day 3 in OASIS-6 & CREATE/ECLA trials

## Sub-category

RR 95% CI

### Death/Heart Failure

CREATE/ECLA

1.08 [1.01, 1.16]

OASIS 6

0.99 [0.79, 1.24]

### Total

1.07 [1.01, 1.15]

Test for heterogeneity: P = 0.46

### Heart Failure

CREATE/ECLA

1.09 [1.00, 1.18]

OASIS 6

0.94 [0.73, 1.21]

### Total

1.07 [0.99, 1.16]

Test for heterogeneity: P = 0.28

### Death

CREATE/ECLA

1.12 [1.01, 1.25]

OASIS 6

1.35 [0.92, 2.00]

### Total

1.14 [1.02, 1.26]

Test for heterogeneity: P = 0.36

0.5

0.7

1

1.5

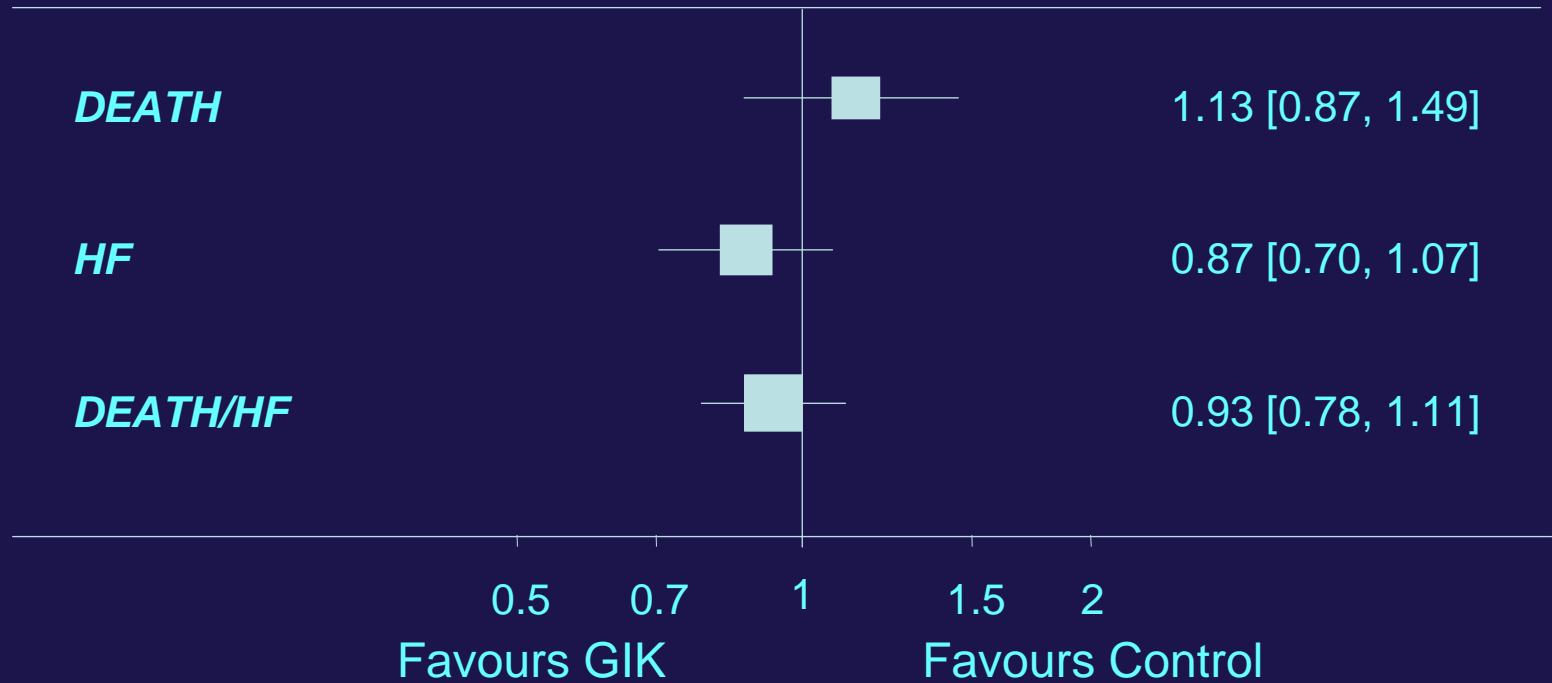
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Favours GIK

Favours Control

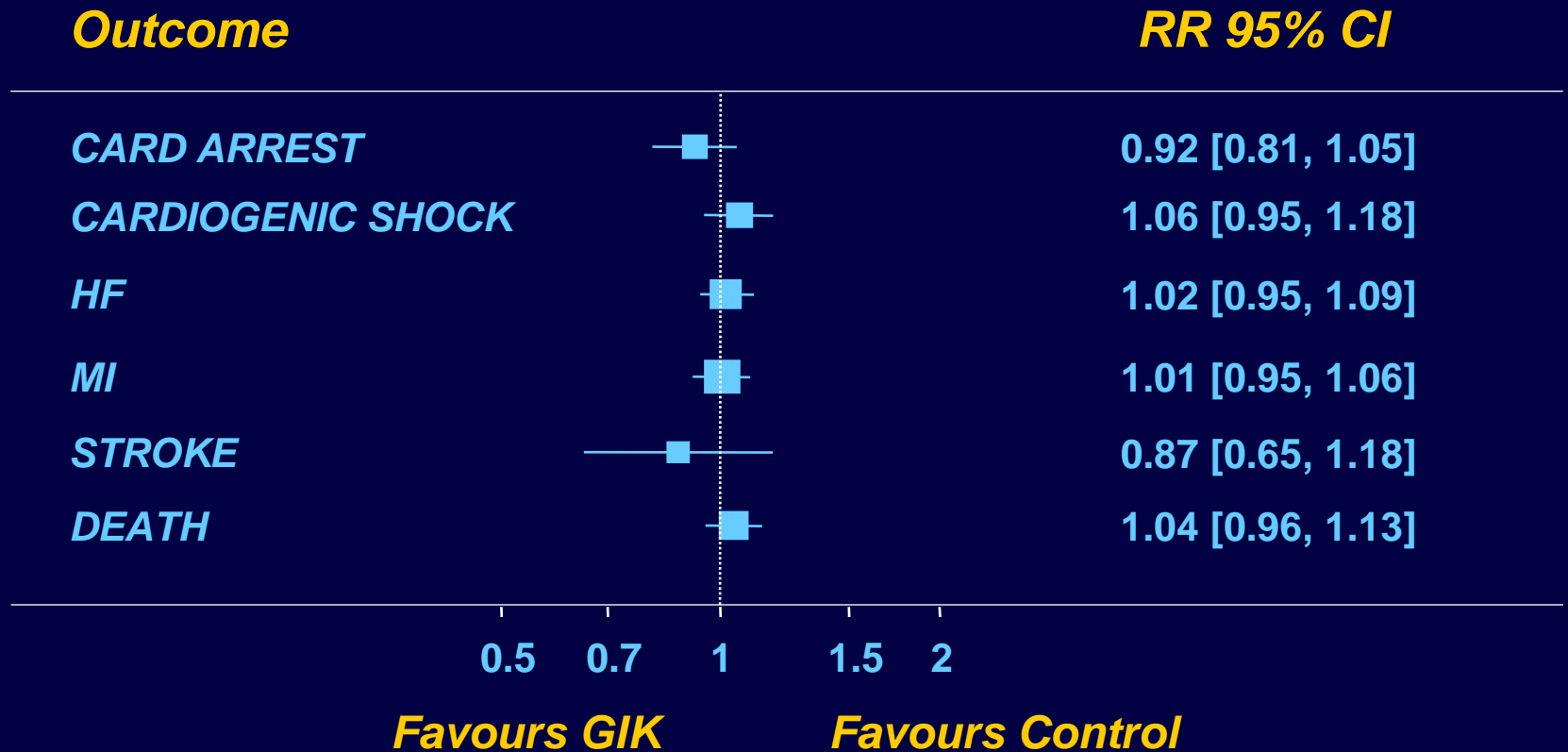
# ***GIK OASIS-6 trial***

30 day outcomes



# OASIS-6 & CREATE/ECLA trials

## Secondary 30 days Outcomes



# CREATE/ECLA & OASIS-6 trials

## *In-hospital treatments*

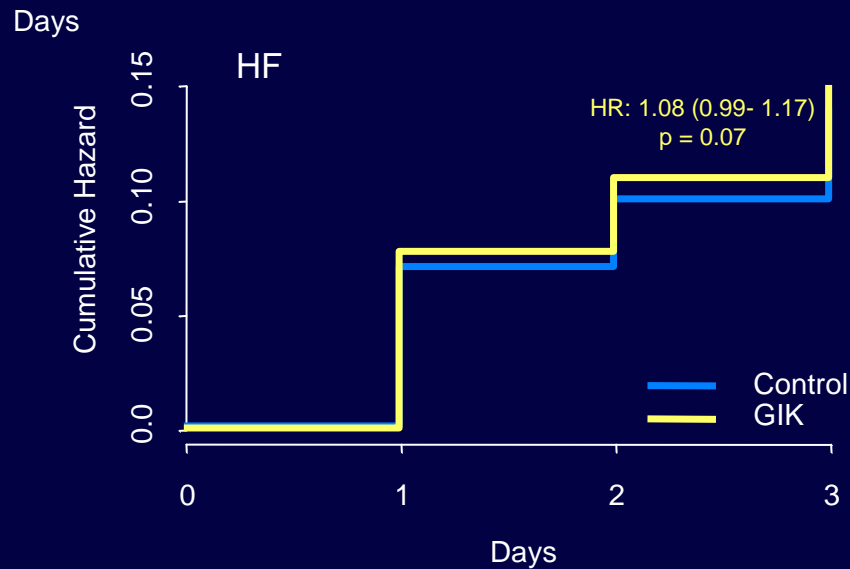
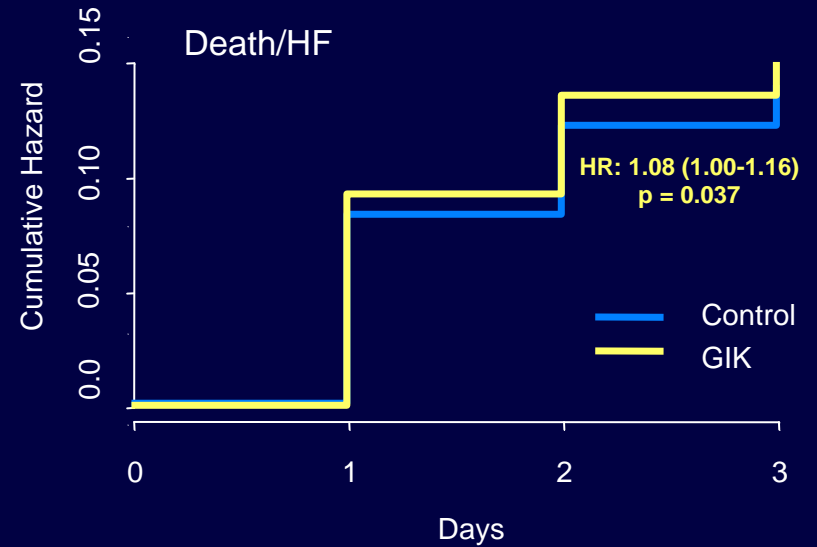
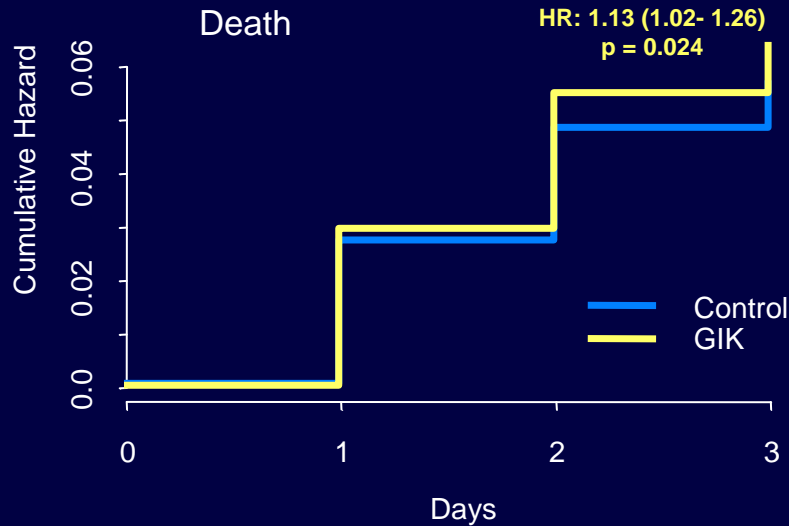
	CREATE/ECLA TRIAL		OASIS-6 TRIAL	
	Usual Care Only n = 10 107 n (%)	GIK Infusion n = 10 088 n (%)	Usual Care Only n = 1 374 n (%)	GIK Infusion n = 1 374 n (%)
Aspirin	9818 (97.1)	9826 (97.4)	1335 (97.2)	1310 (95.4)
Clopidogrel/ticlopidine	4920 (48.7)	4891 (48.5)	805 (58.6)	808 (58.9)
B-blocker	7074 (70.0)	7063 (70.0)	1168 (85.0)	1177 (85.7)
ACEI	7235 (72.5)	7287 (72.2)	1073 (78.1)	1075 (78.3)
Lipid-lowering drug	5646 (68.8)	5456 (66.6)	1012 (73.6)	1012 (73.7)
Intravenous nitroglycerine	7482 (74.0)	7365 (73.0)	1028 (74.8)	999 (72.8)
Glycoprotein IIb/IIIa inhibitor	279 (2.8)	277 (2.7)	240 (17.5)	241 (17.6)
Diuretic Any	2343 (23.2)	2411 (23.9)	557 (40.5)	536 (38.0)
Diuretic Oral	602 (7.3)	537 (6.6)	129 (9.4)	116 (8.4)
Diuretic Intravenous	1296 (15.8)	1458 (17.8)	428 (31.1)	420 (30.6)
Streptokinase	5185 (51.3)	5211 (51.7)	187 (13.6)	189 (13.8)
Urokinase	1832 (18.1)	1762 (17.5)	1 (0.1)	6 (0.4)
Alteplase	371 (3.7)	371 (3.7)	22 (1.6)	15 (1.1)
Primary PCI	906 (9.0)	925 (9.2)	527 (38.4)	555 (40.4)

# Baseline Characteristics of the CREATE/ECLA and OASIS-6 population

<b>Baseline Characteristics</b>	<b>CREATE/ECLA TRIAL</b>		<b>OASIS-6 TRIAL</b>	
	<b>Usual Care Only (n = 10,107)</b>	<b>GIK Infusion (n = 10,088)</b>	<b>Usual Care Only (n = 1,374)</b>	<b>GIK Infusion (n = 1374)</b>
Age, mean (SD), years	58.6 (12.5)	58.6 (12.2)	62.1 (12.5)	61.5 (12.1)
Female sex (%)	2267 (22.4)	2255 (22.4)	389 (28.3)	366 (26.7)
Type 2 diabetes (%)	1802 (17.8)	1780 (17.6)	193 (14.0)	204 (14.9)
Known hypertension (%)	3755 (37.2)	3739 (37.1)	763 (55.5)	783 (57.0)
Congestive heart failure (%)	137 (1.7)	135 (1.6)	188 (13.7)	183 (13.3)
Stroke (%)	453 (5.5)	426 (5.2)	78 (5.7)	73 (5.3)
Weight, mean (SD), Kg	67.8 (12.8)	67.5 (12.8)	76.9 (14.5)	77.1 (14.0)
SBP mean (SD), mm/Hg	128.8(26.4)	129.1 (26.6)	134.6 (23.2)	134.4 (22.5)
DBP mean (SD), mm/Hg	81.5 (16.2)	81.6 (16.1)	81.3 (14.6)	80.6 (14.3)
Heart rate, mean (SD), beats/min	79.7 (18.5)	79.5 (18.4)	75.7 (14.6)	75.3 (14.5)

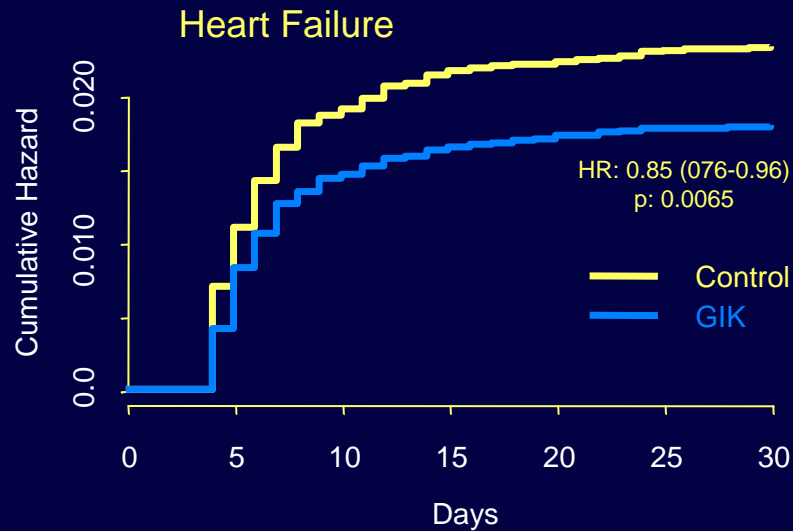
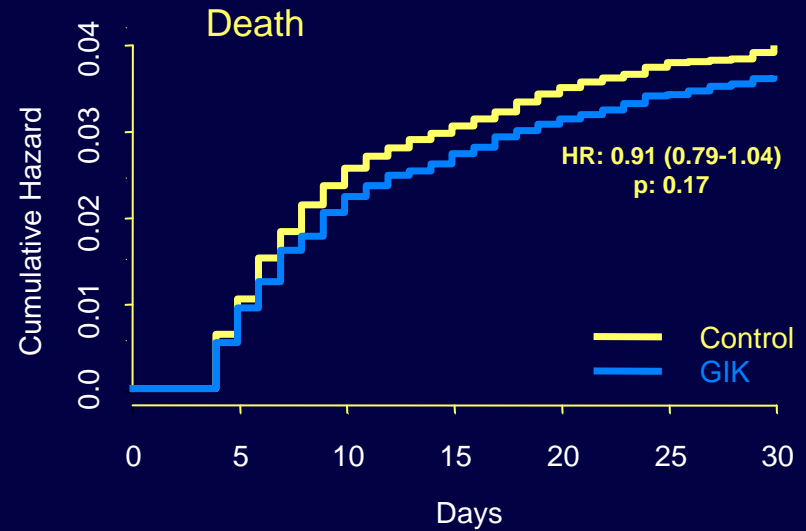
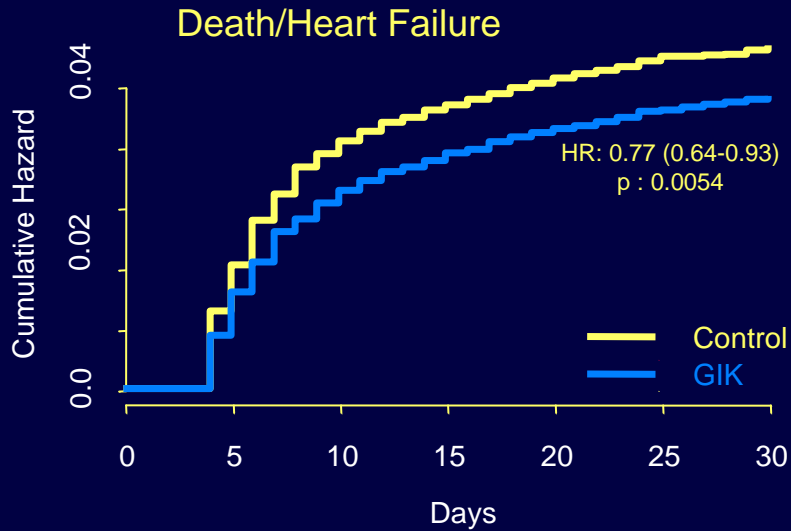
# GIK OASIS-6 and CREATE trials

*KM cumulative event rate. Day 0 - 3*



# OASIS-6 & CREATE/ECLA trials

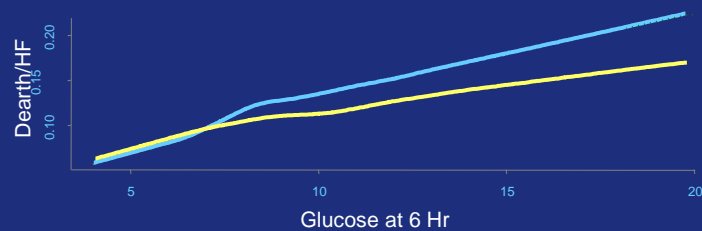
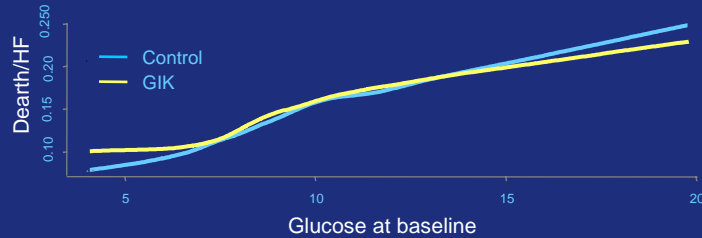
## KM cumulative event rate after day 3



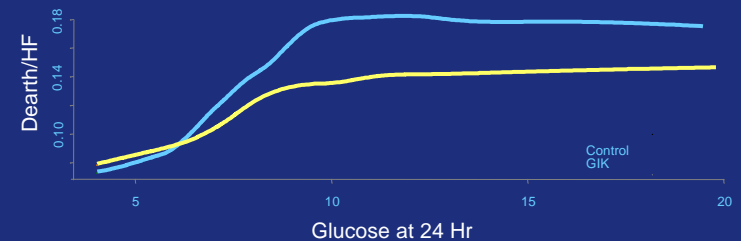
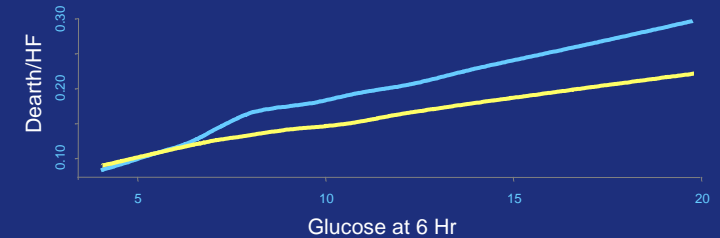
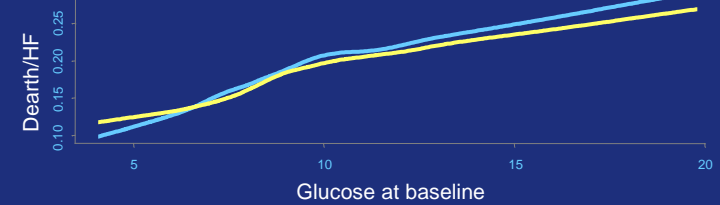
# GIK OASIS-6 & CREATE/ECLA trials

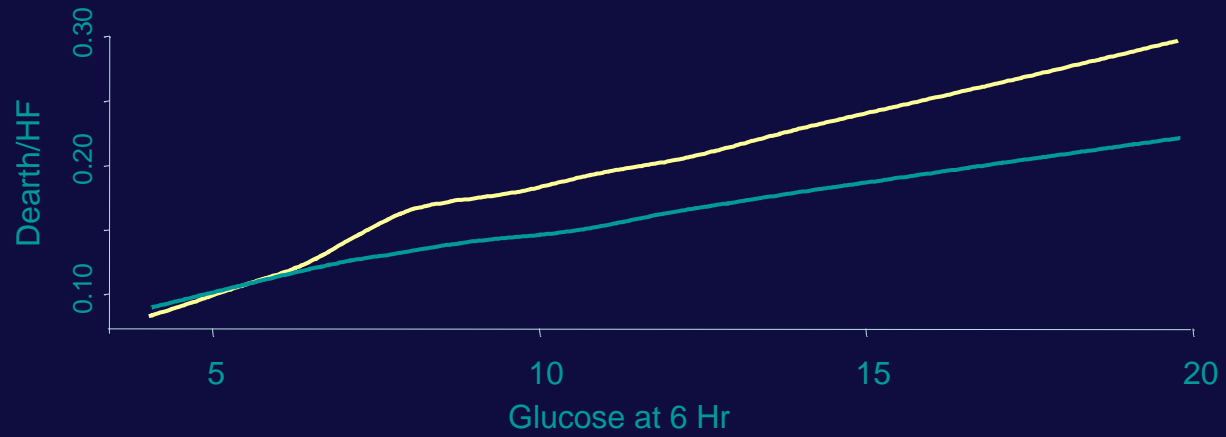
Relation between baseline, 6 & 24 hours glucose & Death/HF at 3 & 30 days

## 3 days outcomes



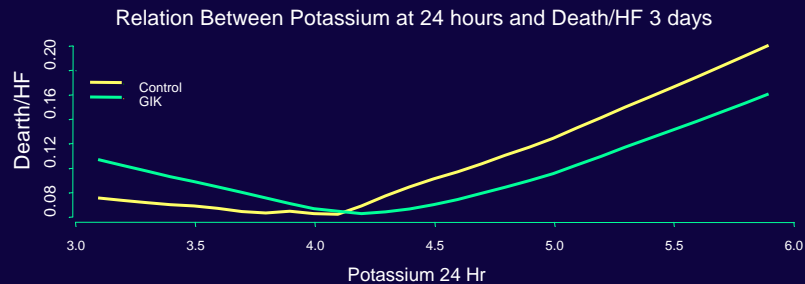
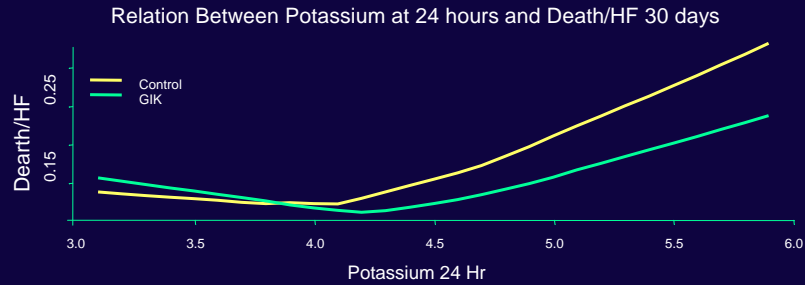
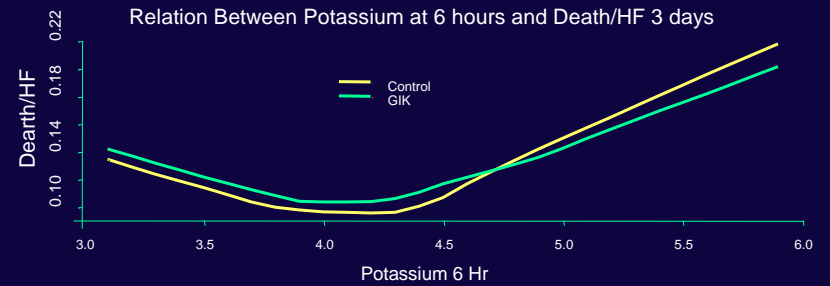
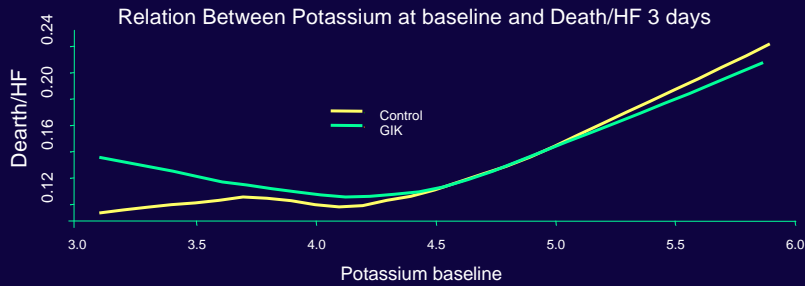
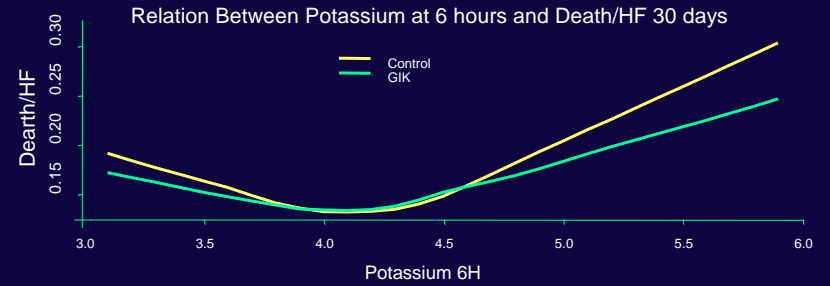
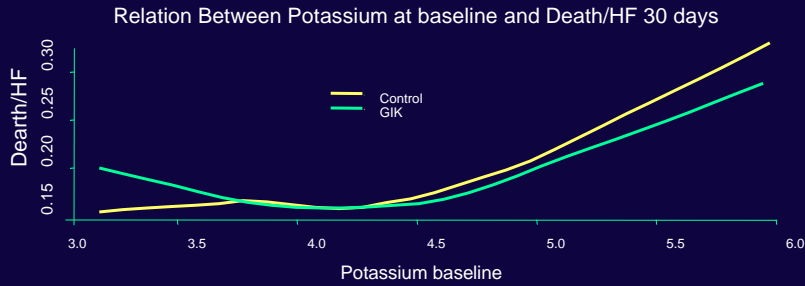
## 30 days outcomes



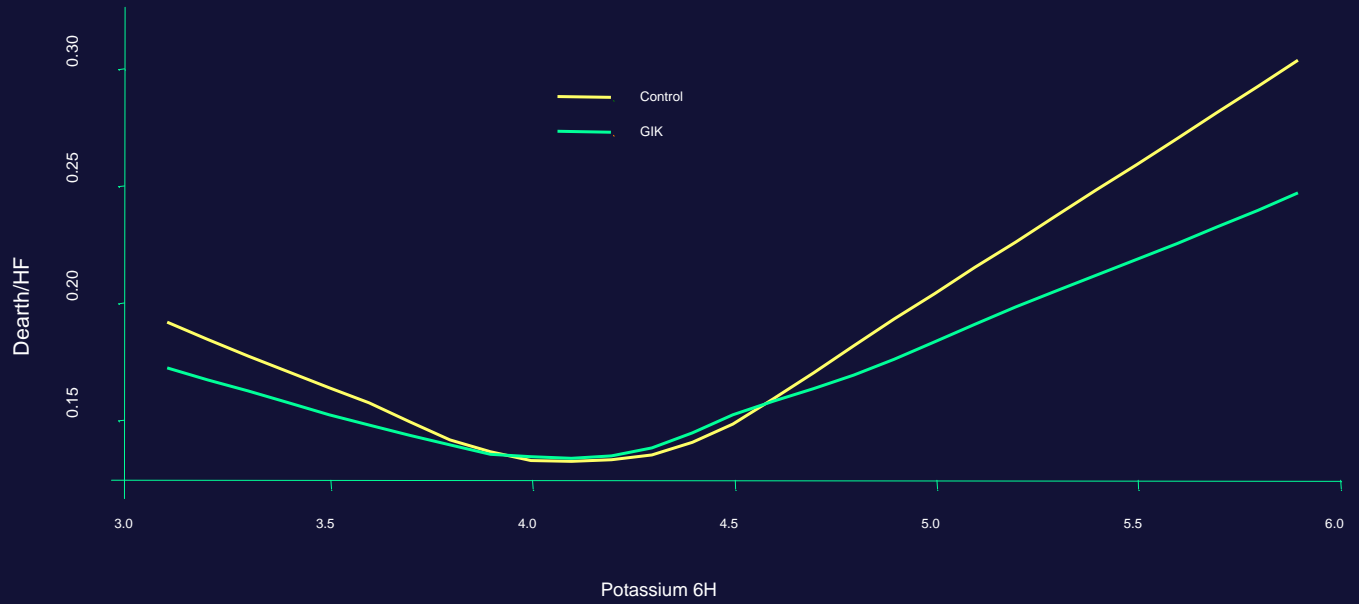


# OASIS-6 & CREATE/ECLA trials

## Relation between serum Potassium & Death/Heart Failure



Relation Between Potassium at 6 hours and Death/HF 30 days



Relation Between Potassium at 6 hours and Death/HF 3 days

# Baseline Characteristics of the OASIS-6 population

<b>Baseline Characteristics</b>	<b>OASIS-6 TRIAL</b>	
	<b>Usual Care Only (n = 1,374)</b>	<b>GIK Infusion (n = 1374)</b>
Age, mean (SD), years	62.1 (12.5)	61.5 (12.1)
Female sex (%)	389 (28.3)	366 (26.7)
Type 2 diabetes (%)	193 (14.0)	204 (14.9)
Known hypertension (%)	763 (55.5)	783 (57.0)
Congestive heart failure (%)	188 (13.7)	183 (13.3)
SBP mean (SD), mm/Hg	134.6 (23.2)	134.4 (22.5)
Heart rate, mean (SD), beats/min	75.7 (14.6)	75.3 (14.5)

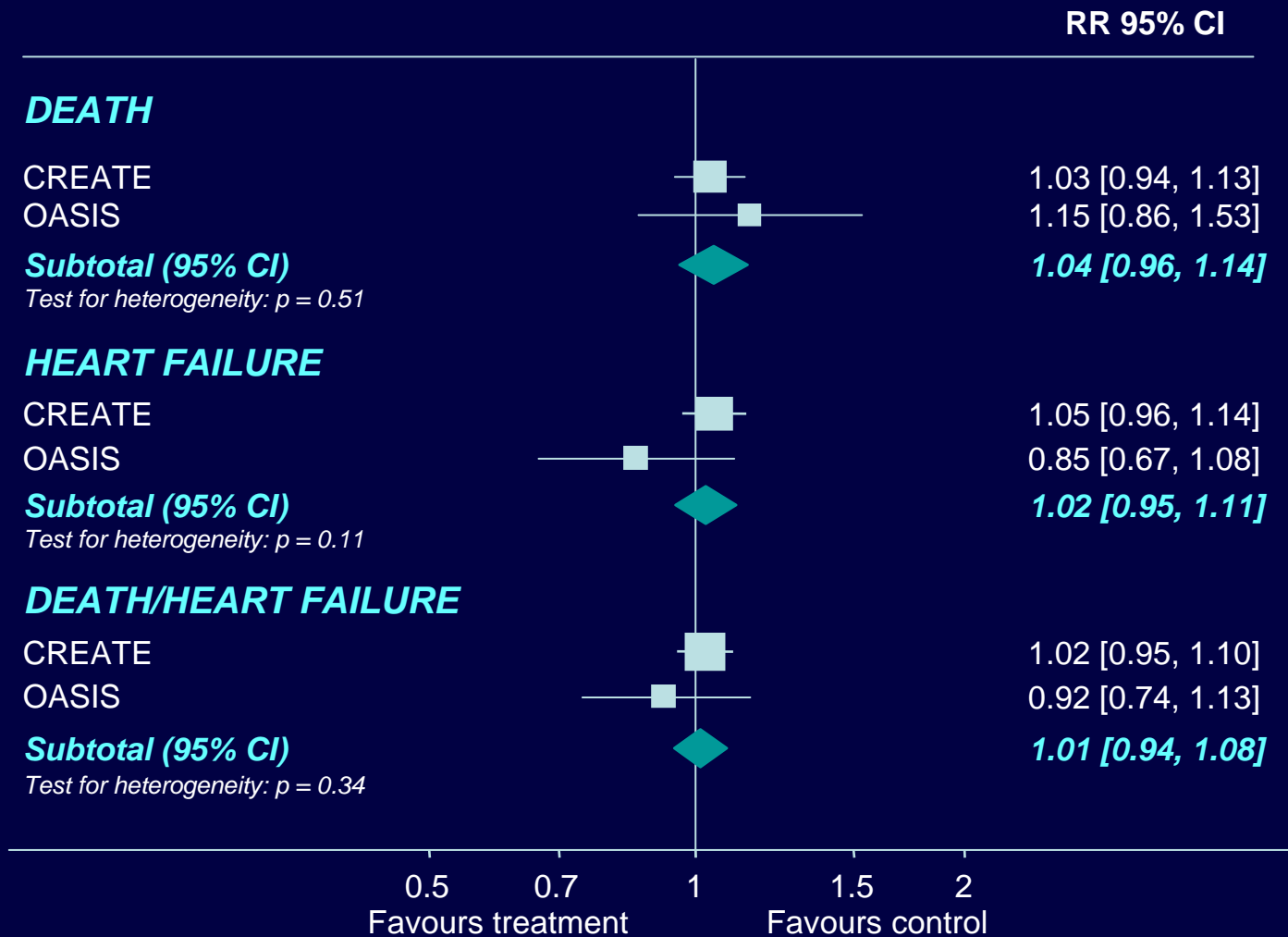
# CREATE/ECLA & OASIS-6 trials

## *In-hospital treatments*

	OASIS-6 TRIAL	
	Usual Care Only n = 1 374 n (%)	GIK Infusion n = 1 374 n (%)
Aspirin	1335 (97.2)	1310 (95.4)
Clopidogrel/ticlopidine	805 (58.6)	808 (58.9)
B-blocker	1168 (85.0)	1177 (85.7)
ACEI	1073 (78.1)	1075 (78.3)
Lipid-lowering drug	1012 (73.6)	1012 (73.7)
Glycoprotein IIb/IIIa inhibitor	240 (17.5)	241 (17.6)
Diuretic Any	557 (40.5)	536 (38.0)
Reperfusion strategy	737 (53.7)	765 (53.3)
Primary PCI	527 (38.4)	555 (40.4)

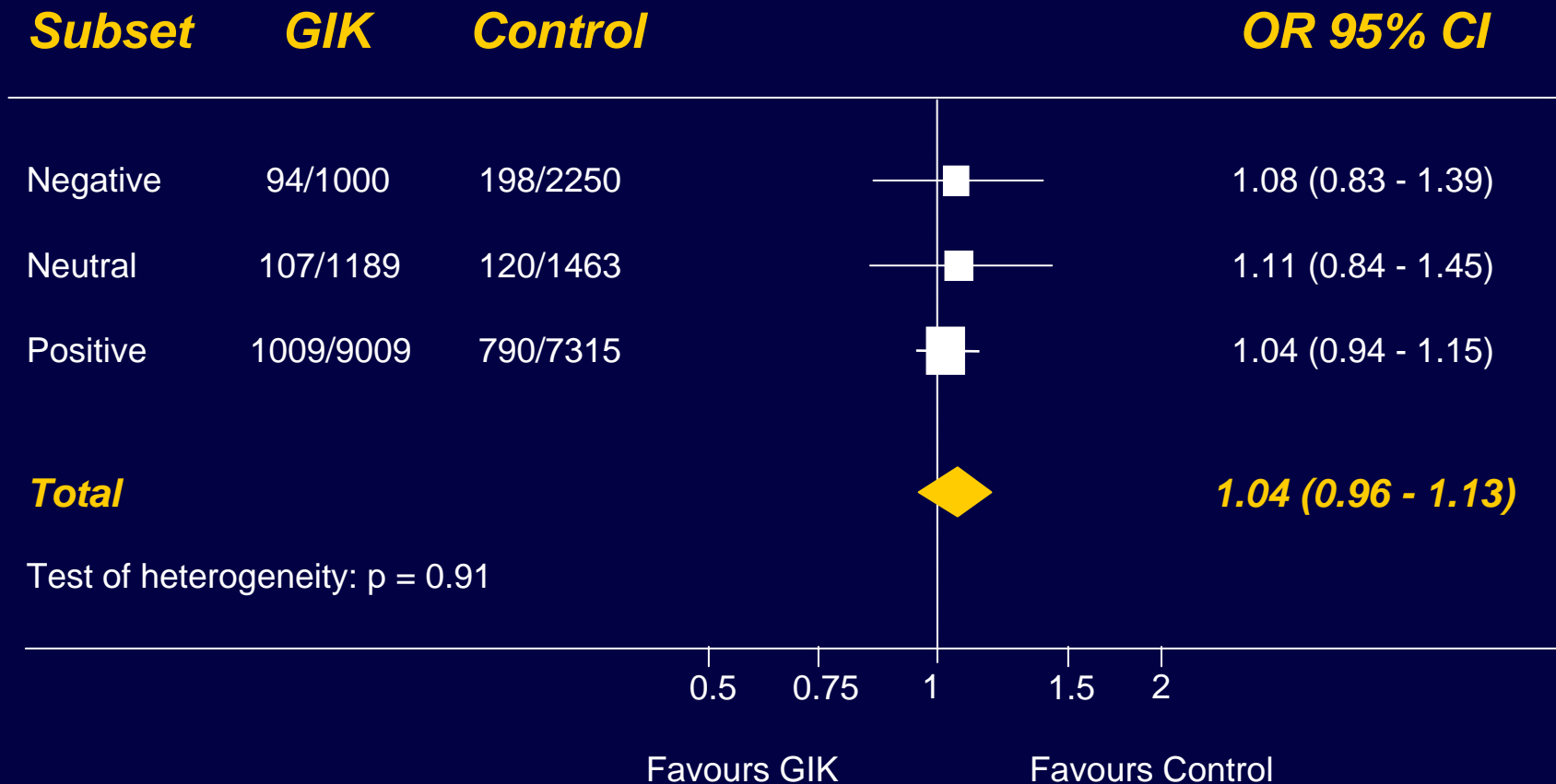
# CREATE/ECLA & GIK OASIS-6 trial

## 30 days outcomes by trial



# CREATE/ECLA & OASIS-6 TRIALS

## Fluid Balance & 30 days Death



# GIK Infusion in AMI. Suggested Mechanisms

## Glucose

- increases substrate for glycolysis thereby preventing myocyte death during ischemia (ie, anaerobic conditions)

## Insulin

- decreases circulating FFA, which are toxic to the ischemic myocardium
- facilitates anaerobic glycolysis

## Potassium

- myocyte K becomes depleted during ischemia. Exogenous K increases myocyte uptake of K and prevents ventricular arrhythmias

# OASIS-6 & CREATE/ECLA TRIALS

## *Secondary 30 days Outcomes*

	<i>Control</i> (11,481)	<i>GIK</i> (11,462)	<i>HR</i>	<i>95 % CI</i>	<i>p</i>
<i>Myocardial Infarction</i>	2094 (18.5)	2097 (18.6)	1.01	0.95 - 1.07	0.85
<i>Cardiac Arrest</i>	439 (3.8)	397 (3.5)	0.91	0.79 - 1.04	0.15
<i>Cardiogenic Shock</i>	586 (5.1)	613 (5.4)	1.05	0.94 - 1.17	0.40
<i>Stroke</i>	91 (0.8)	80 (0.7)	0.88	0.65 - 1.19	0.41

# ***GIK OASIS-6 trial***

## Secondary 30 days outcomes

	<i><b>GIK</b></i>	<i><b>CONTROL</b></i>	<i><b>HR 95% CI</b></i>	<i><b>p</b></i>
<i><b>CARDIOGENIC SHOCK</b></i>	55 (4.0)	63 (4.6)	0.87 (0.61 - 1.26)	0.46
<i><b>MI</b></i>	47 (3.6)	43 (3.2)	1.10 (0.73 - 1.67)	0.64
<i><b>CARDIAC ARREST</b></i>	60 (4.4)	65 (4.8)	0.93 (0.65 - 1.32)	0.67
<i><b>STROKE</b></i>	6 (0.5)	15 (1.1)	0.40 (0.16 - 1.04)	0.059

# GIK OASIS-6 and CREATE trials

## KM cumulative death rate

