Early or late intervention in high risk non ST elevation acute coronary syndromes

results of the ELISA-3 trial

Trial reg: ISRCTN39230163

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Disclosures

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☑ **I have the following potential conflicts of interest to report:** Consultancies Merck Sharp & Dohme, Sanofi-Aventis

Background

- Routine invasive strategy is treatment of choice in high risk patients with NSTE-ACS[1]
- Controversy about optimal timing of intervention
- Meta analysis[2]: early intervention modest benefit due to significant reduction recurrent ischemia
- Age in trials is lower than in NSTE-ACS patients in real life (68 y): generalizability questionable

[1]ESC guidelines NSTE-ACS . *Eur Heart J.* 2011;32:2999-3054
[2]Katritsis e.a *Eur Heart J.* 2011;32-40

Method

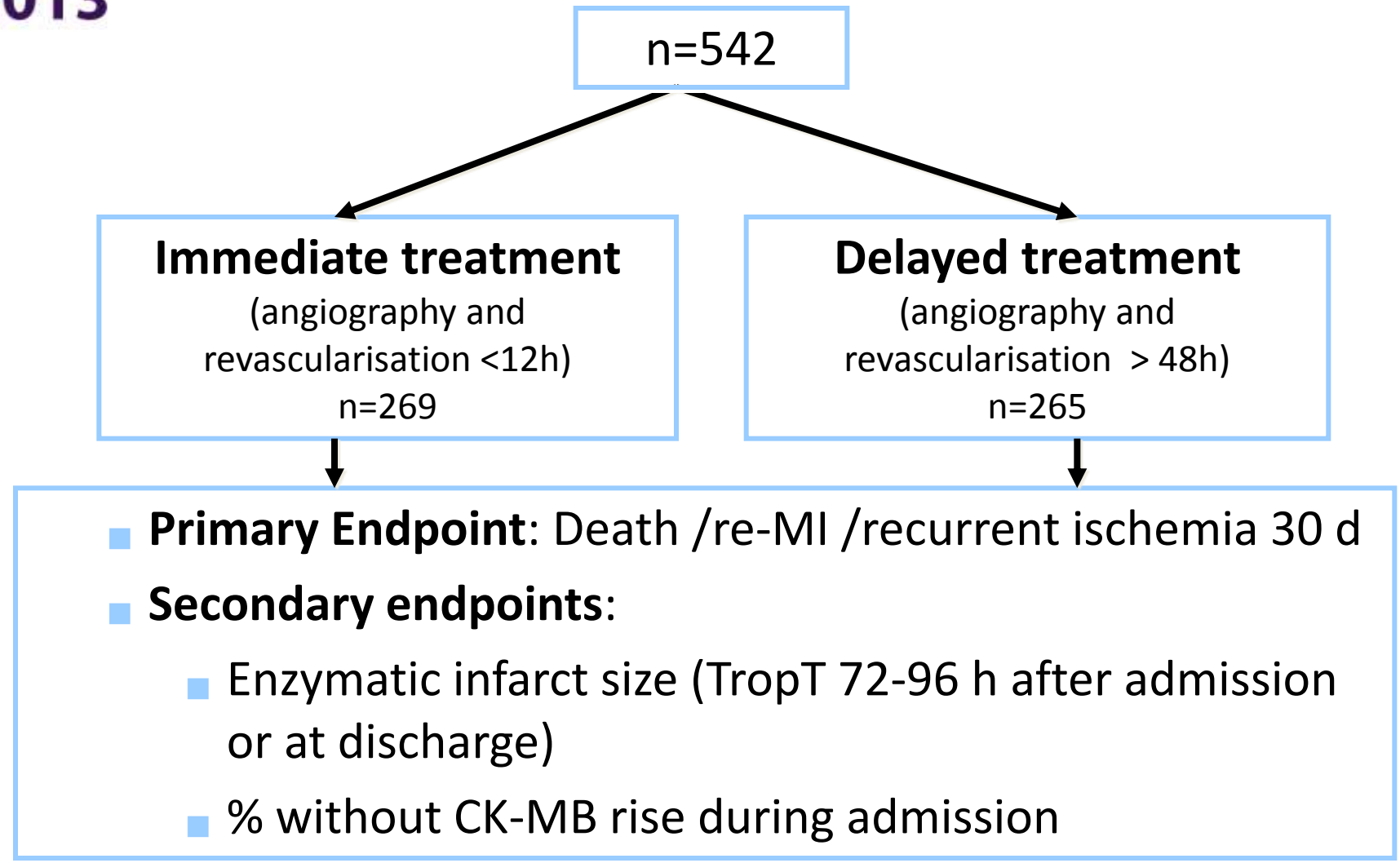
- Multicentre, randomized study in 1 PCI and 5 non-PCI centres
- Ischemic symptoms at rest < 24 h before randomisation plus at least 2 out of 3 high risk characteristics:
  - Extensive myocardial ischemia (> 5 mm cum. ST depression or temporary ST elevation < 30 min.)
  - Positive biomarkers (Troponin T > 10µg/l, Myoglobin > 150µg/l or CK-MB fraction > 6%)
  - Age > 65 years

Method

Exclusion criteria:

- Persistent ST-segment elevation
- Ongoing ischemic symptoms despite optimal medical therapy
- Contra-indication for angiography
- Active bleeding
- Cardiogenic shock
- Acute posterior infarction
- Life expectancy < 1 year

Method


n=542
Immediate treatment
(angiography and revascularisation <12h)
n=269
Delayed treatment
(angiography and revascularisation > 48h)
n=265
Primary Endpoint: Death /re-MI /recurrent ischemia 30 d
Secondary endpoints:
Enzymatic infarct size (TropT 72-96 h after admission or at discharge)
% without CK-MB rise during admission

Baseline and angiographic data

	Immediate (n=269)	Delayed (n=265)
Age (y;median, IQR)	72.1 (65.5-78.4)	71.8 (62.5-78.4)
Male (%)	69.5	65.7
Diabetes Mellitus (%)	23.8	20.4
Previous MI (%)	17.8	19.6
GRACE Risk Score (med, IQR)	136 (118-154)	133 (117-154)
Biomarker positive* (%)	78.4	79.2
Multivessel disease (%)	62.2	62.1
Time admission- randomisation (h; median, IQR)	2.0 (0.9 - 4.5)	2.1 (1.0 – 4.2)
Time randomisation -angio (h; median, IQR)	2.6 (1.2 – 6.2)	54.9 (44.2-74.5)

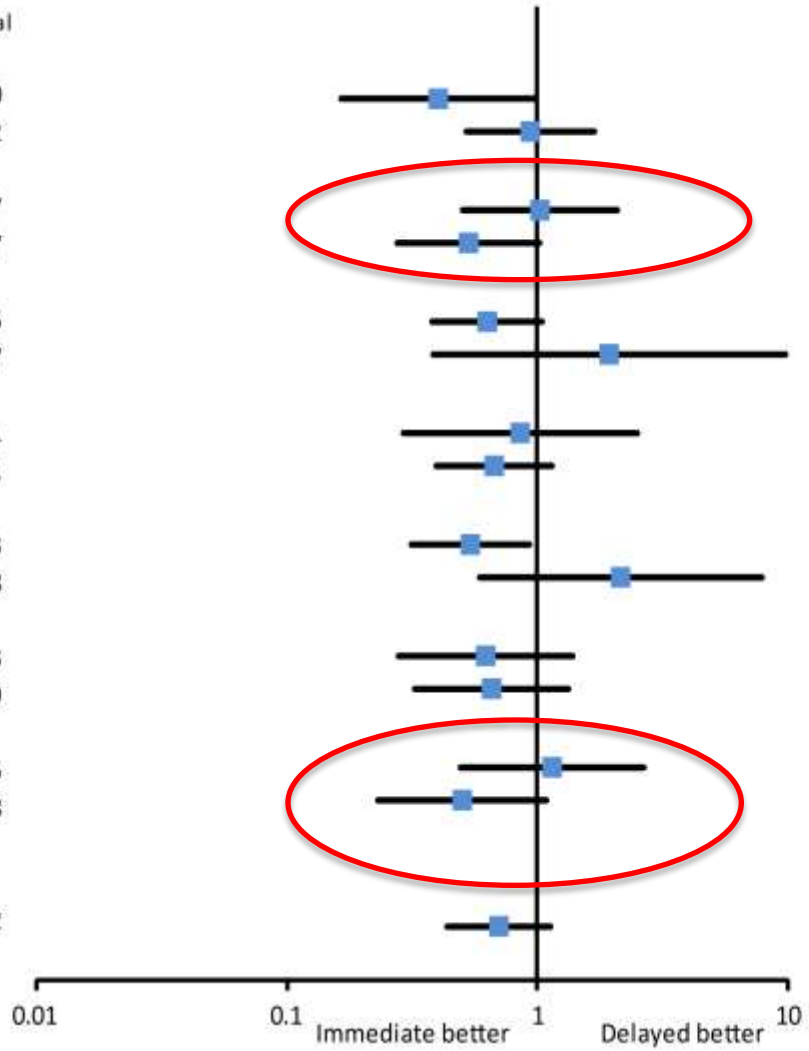
* Pos Trop (>0.10 µg/l), Myoglobin (>150 µg/l) or pos CK-mb (> 6%)

Results

	Immediate	delayed	P-value
Primary endpoint (incid of death/ MI / rec. isch. 30d)	9.9 %	14.2 %	0.135
Death	1.1 %	1.1 %	> 0.99
MI (%)	1.9 %	0.8 %	0.450
Recurrent ischemia (%)	7.6 %	12.6 %	0.058
Secondary endpoints			
Enzymatic infarct size (TropT 72-96 h (median,IQR)	0.31 µg/l (0.12-0.68)	0.31 µg/l (0.10-0.99)	0.983
% without CK-MB rise	35.4 %	36.5 %	0.801
Safety			
Any Bleeding	22.9 %	19.9 %	0.407
Major Bleed	11.8 %	11.1 %	0.796
Hospital stay (d, median IQR)	4.0 (2.0-10.0)	6.0 (4.0-12.0)	<0.001

Subgroup analysis

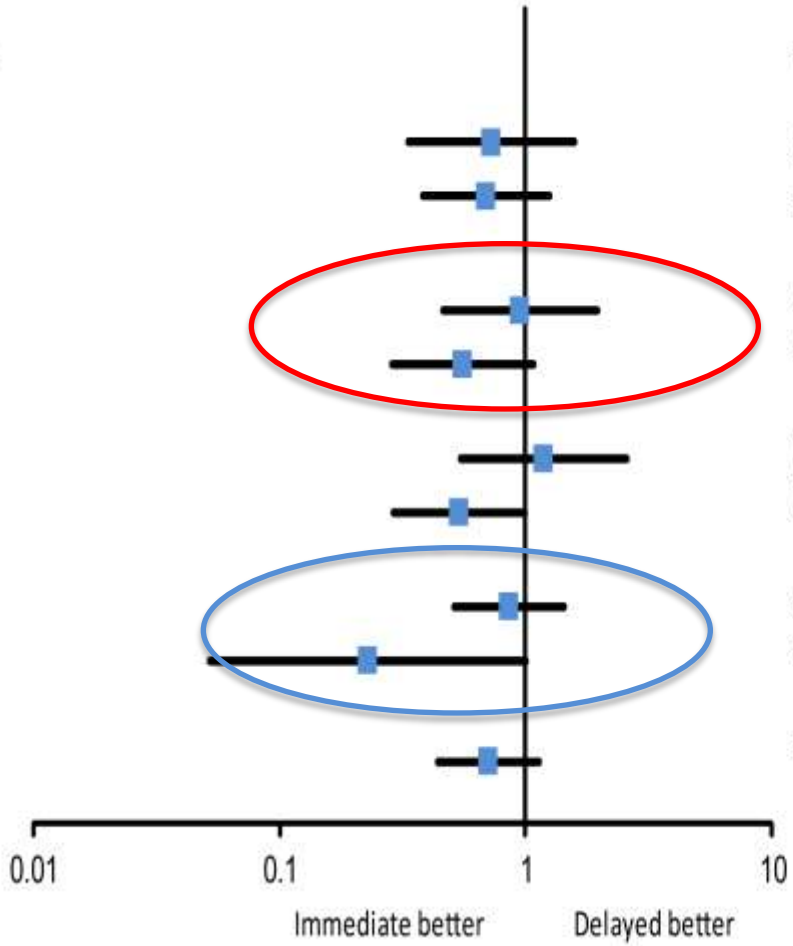
	Delayed Number (%)	Total	Immediate Number (%)	Total	Relative risk (95% CI)	P value interaction
Female	17 (18.7%)	91	6 (7.5%)	80	0.401 (0.166 - 0.969)	0.111
Male	20 (11.8%)	170	20 (11.0%)	182	0.934 (0.521 - 1.674)	
ST depr < 5 mm	14 (9.3%)	150	14 (9.5%)	147	1.02 (0.504 - 2.065)	0.163
St depr ≥ 5 mm	22 (21.2%)	104	12 (11.2%)	107	0.53 (0.277 - 1.015)	
Ischemic chest pain	35 (14.9%)	235	22 (9.4%)	235	0.629 (0.381 - 1.038)	0.188
Dyspnoe/aspecific symptoms	2 (7.7%)	26	4 (14.8%)	27	1.926 (0.385 - 9.63)	
Diabetes	6 (11.5%)	52	6 (9.8%)	61	0.852 (0.293 - 2.484)	0.686
No diabetes	31 (14.8%)	209	20 (10.0%)	201	0.671 (0.396 - 1.137)	
Heart rate < 100 bpm	34 (15.7%)	217	18 (8.5%)	213	0.539 (0.315 - 0.925)	0.050
Heart rate >= 100 bpm	3 (6.8%)	44	7 (14.6%)	48	2.139 (0.589 - 7.764)	
pro-BNP on admission < median	14 (12.8%)	109	9 (8.0%)	113	0.62 (0.28 - 1.373)	0.936
pro-BNP on admission >= median	16 (15.4%)	104	12 (10.1%)	119	0.655 (0.325 - 1.321)	
tropT on admission < median	9 (9.2%)	98	11 (10.5%)	105	1.141 (0.494 - 2.634)	0.149
tropT on admission >= median	16 (16.7%)	96	9 (8.3%)	108	0.5 (0.232 - 1.079)	
All	37 (14.2%)	261	26 (9.9%)	262	0.7 (0.437 - 1.122)	



Occurrence of primary endpoint in pre-specified subgroups

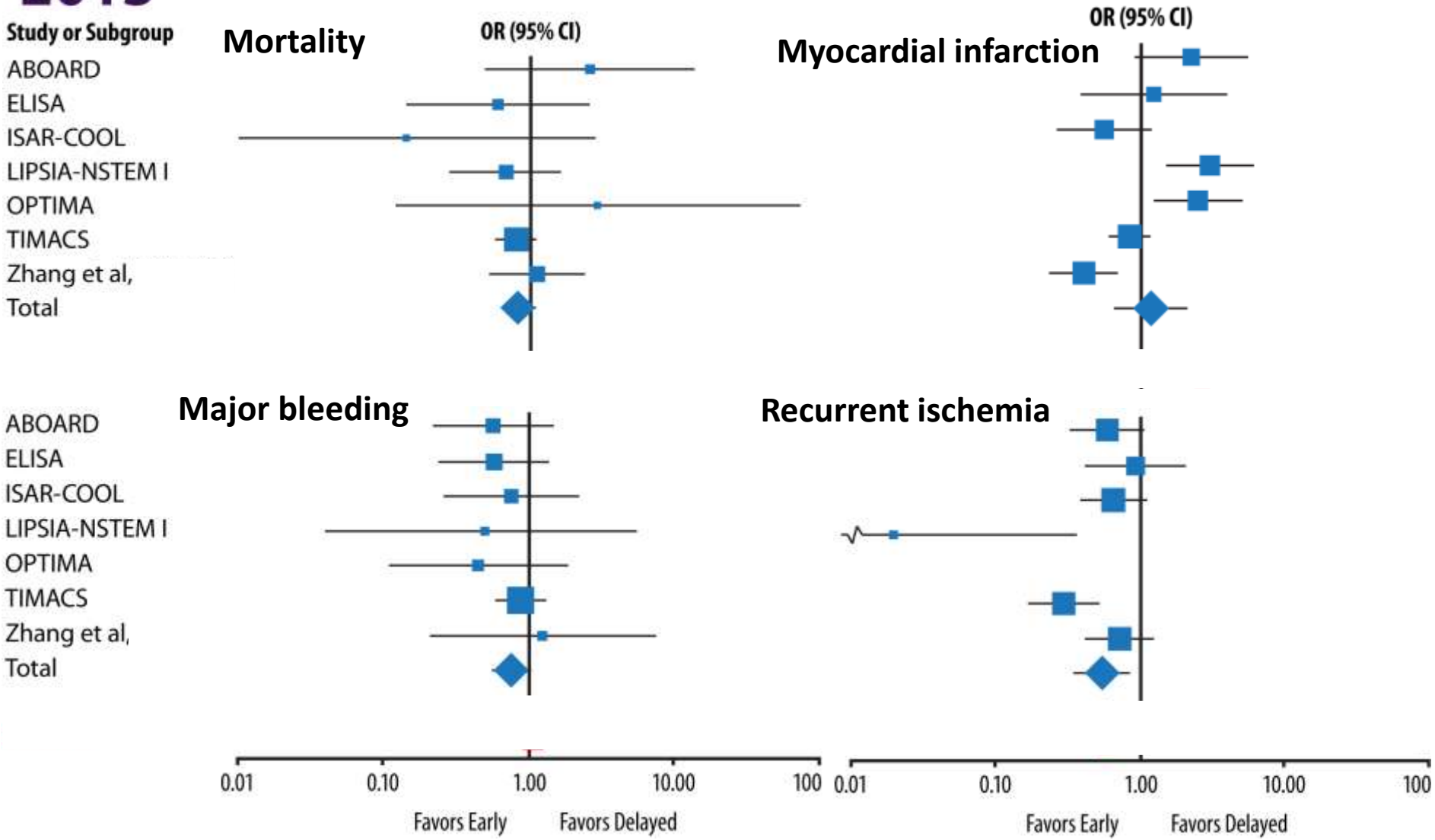
Subgroup analysis

	Delayed Number (%)	Total	Immediate Number (%)	Total	Relative risk (95% CI)	P value interaction
Age < median	14 (10.7%)	131	10 (7.7%)	130	0.72 (0.332 - 1.561)	0.884
Age >= median	23 (17.7%)	130	16 (12.1%)	132	0.685 (0.38 - 1.236)	
Grace ≤ 140	14 (9.5%)	147	13 (9.0%)	145	0.941 (0.459 - 1.932)	0.262
Grace > 140	21 (19.1%)	110	12 (10.5%)	114	0.551 (0.285 - 1.066)	
ST depr < 5 mm and no temp ST elev.	11 (9.6%)	115	12 (11.2%)	107	1.172 (0.54 - 2.544)	0.112
ST depr ≥ 5 mm or temporary ST elev.	25 (17.9%)	140	14 (9.5%)	147	0.533 (0.289 - 0.983)	
PCI center	28 (12.9%)	217	24 (11.0%)	219	0.849 (0.509 - 1.417)	0.089
Non-PCI center	9 (20.5%)	44	2 (4.7%)	43	0.227 (0.052 - 0.992)	
All	37 (14.2%)	261	26 (9.9%)	262	0.7 (0.437 - 1.122)	



Occurrence of primary endpoint in post-hoc defined subgroups

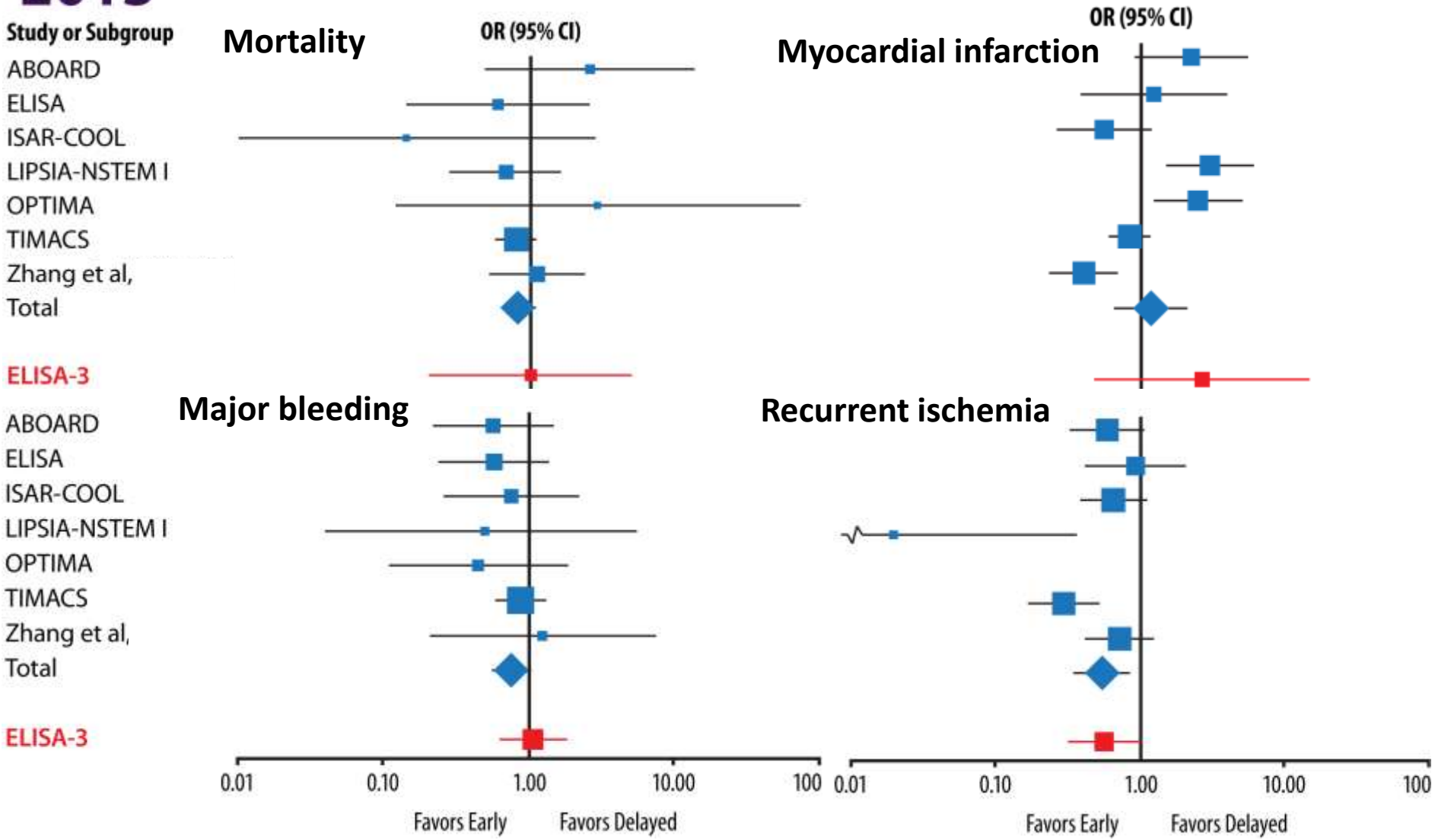
Comparison with meta analysis



Navarese e.a. *Ann Intern Med.* 2013

Katritsis *e.a.Eur Heart J* 2011

Comparison with meta analysis



Navarese e.a. *Ann Intern Med.* 2013

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Limitations

- Incidence of primary end point lower than expected (study underpowered)
- Accurate assessment of periprocedural MI's is difficult in patients with elevated biomarkers

Conclusions

- In this group of relatively old, high risk patients with NSTE-ACS early angiography and revascularisation was not superior to a delayed invasive strategy
- Results consistent with trials and meta-analyses: early invasive strategy:
  - Trend towards more benefit in higher risk patients
  - Hospital stay significantly shorter
- Patients included in non-PCI centres seem to benefit more from early intervention: further investigation needed

ELISA – 3

CLINICAL RESEARCH

EuroIntervention 2013;9:0-0

Early or late intervention in high-risk non-ST-elevation acute coronary syndromes: results of the ELISA-3 trial

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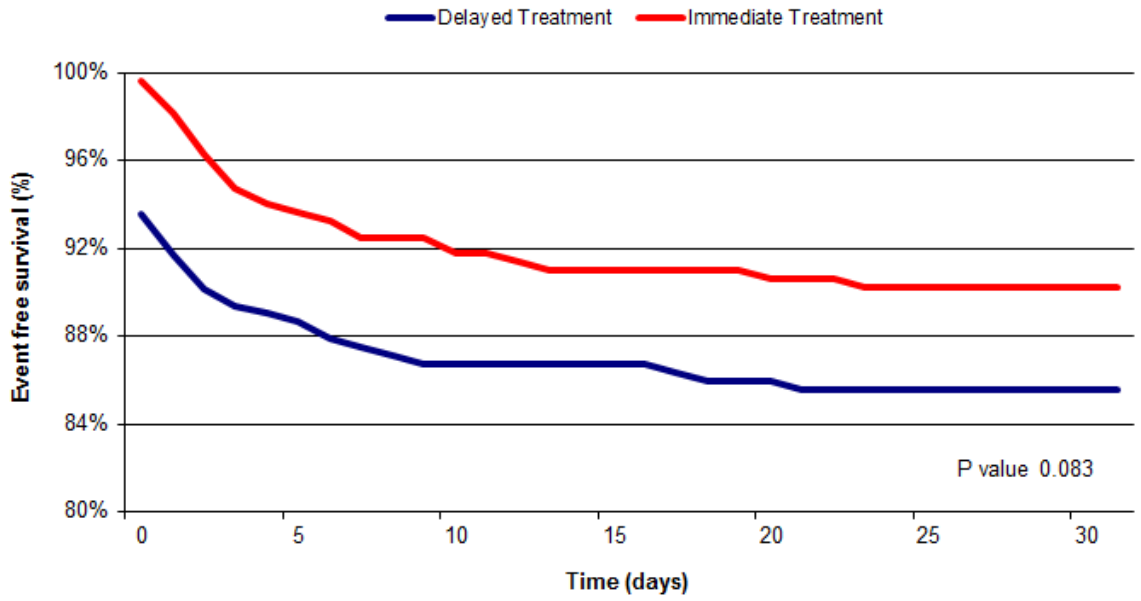
euro PCR 2013

Back-up slides

PCI vs. non-PCI centres

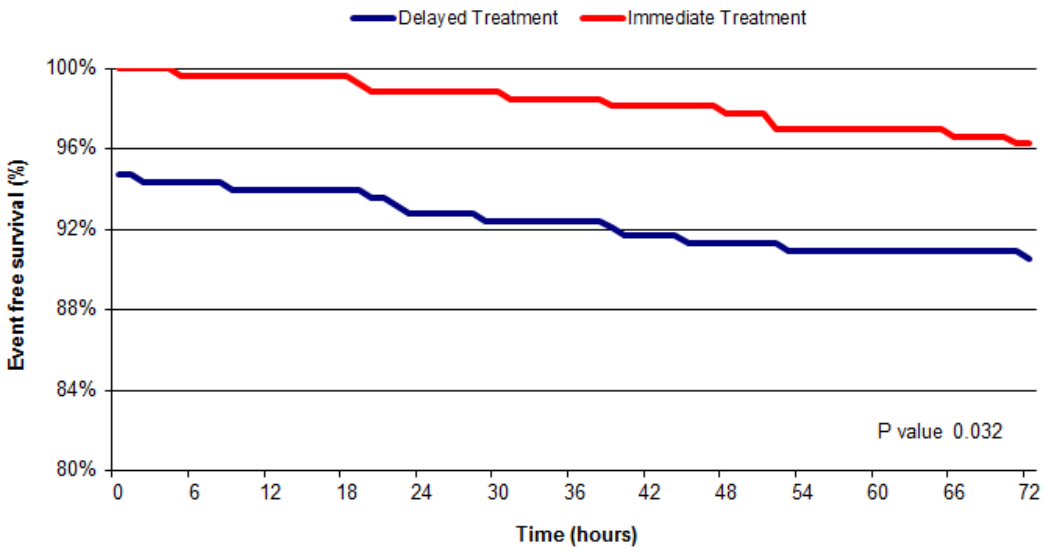
	PCI centre n= 444		Non-PCI centres n=90	
	Immediate	Delayed	Immediate	Delayed
Age (y, median)	71.2	70.8	73.8	73.0
GRACE Risk Score (med)	136	135	136	130
Biomarker positive (%)	81.7	82.3	62.2	64.4
Multivessel disease (%)	63.6	61.2	54.5	66.7
Time admission-randomisation (h;median, IQR)	2.0 (1.1-4.2)	2.2 (1.2-3.9)	2.8 (0.5-5.8)	1.9 (0.5-9.1)
Time randomisation – angio (h;median, IQR)	2.6 (1.1-6.7)	53.1 (43.5-71.9)	3.0 (2.2-4.0)	70.1 (50.6-112.6)
Time angio – revascularisation (h;median, IQR)	0.40 (0.21-24.8)	0.53 (.25-48.5)	0.71 (0.29-63.7	146 (82.0-297)
% of patients treated with PCI	59.8	55.5	52.3	41.9

Back-up slides



Numbers at risk							
Delayed treatment	265	234	227	227	225	222	210
Immediate treatment	269	249	243	239	239	235	221

Death, MI, recurrent ischemia event free survival



Numbers at risk							
Delayed treatment	265	248	245	244	241	240	240
Immediate treatment	269	267	265	263	262	259	257

Recurrent ischemia event free survival