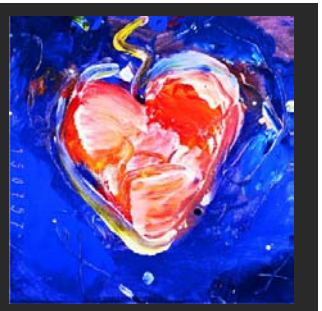
Cardiovascular Update
Rotterdam, June 11th, 2012



Revascularization in Patients with ACS without ST segment elevation

Robbert J de Winter MD PhD FESC

Professor Clinical Cardiology
Academic Medical Center
University of Amsterdam

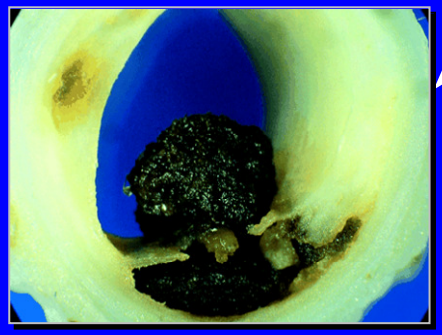
Hamm Lancet 358:1533,2001

Presentation

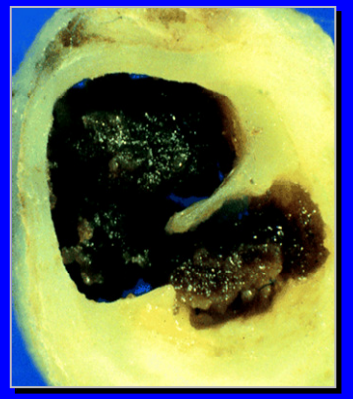
Ischemic Discomfort

Working Dx

Acute Coronary Syndrome



Davies MJ
Heart 83:361, 2000



ECG

No ST Elevation

NSTEMI

ST Elevation

Biochem. Marker

Myocardial Infarction

Final Dx

Unstable Angina **NQMI** **Qw MI**

Revascularization in STEMI / NSTEMI

- When there is a clinical diagnosis of thrombotic coronary artery occlusion, immediate angiography and mechanical reperfusion therapy is recommended and has been shown to reduce mortality

- For NSTEMI / UA this is less clear

Revascularization in nSTE-ACS 2012

- ♥ Revascularization to improve prognosis
- ♥ Revascularization to relieve symptoms
- ♥ Revascularization as part of a comprehensive strategy in nSTE-ACS

Revascularization in nSTE-ACS

Patients with nSTE-ACS represent a very heterogeneous population:

- **45-year old male, positive family history, new onset chest pain early morning, symmetrical negative T-waves anterior ECG leads, normal troponin**

- **80-year old lady with hypertension, diabetes, mitral regurgitation, paroxysmal atrial fibrillation, LBBB, progressive chest pain on exertion, presenting with elevated troponin**

Acute coronary syndromes

Non-ST-elevation ACS is often a combination of hemodynamically significant lesion, plaque rupture, thrombus formation, coronary spasm and increased oxygen demand, but with preserved flow

Medical treatment combination of anti-ischemic, vaso-dilator, anti-platelet and anti-coagulant drugs

Checklist of treatments when an ACS diagnosis appears likely

Aspirin	Initial dose of 150–300 mg non-enteric formulation followed by 75–100 mg/day (i.v. administration is acceptable)
$P2Y_{12}$ inhibitor	Loading dose of ticagrelor or clopidogrel[a]
Anticoagulation	Choice between different options depends on strategy: • Fondaparinux 2.5 mg/daily subcutaneously • Enoxaparin 1 mg/kg twice daily subcutaneously • UFH i.v. bolus 60–70 IU/kg (maximum 5000 IU) followed by infusion of 12–15 IU/kg/h (maximum 1000 IU/h) titrated to aPTT 1.5–2.5 × control • Bivalirudin is indicated only in patients with a planned invasive strategy
Oral ß-Blocker	If tachycardic or hypertensive without signs of heart failure

Decision-making algorithm in ACS

1. Clinical Evaluation	2. Diagnosis/Risk Assessment	3. Coronary angiography
Urgent coronary angiography (<2 h) is recommended in patients at very high ischaemic risk (refractory angina, with associated heart failure, life-threatening ventricular arrhythmias, or haemodynamic instability).		I C

Risk of ischemic events according to the GRACE risk score

Table 5 Mortality in hospital and at 6 months[50] in low, intermediate, and high risk categories in registry populations, according to the GRACE risk score

Risk category (tertile)	GRACE risk score	In-hospital death (%)
Low	≤108	<1
Intermediate	109–140	1–3
High	>140	>3
Risk category (tertile)	**GRACE risk score**	**Post-discharge to 6-month death (%)**
Low	≤88	<3
Intermediate	89–118	3-8
High	>118	>8

CRUSADE score of in-Hospital major bleeding

Predictor	Score
Baseline haematocrit, %	
<31	9
31–33.9	7
34–36.9	3
37–39.9	2
≥40	0
Creatinine clearance,[a] mL/min	
≤15	39
>15–30	35
>30–60	28
>60–90	17
>90–120	7
>120	0
Heart rate (b.p.m.)	
≤70	0
71–80	1
81–90	3
91–100	6
101–110	8
111–120	10
≥121	11

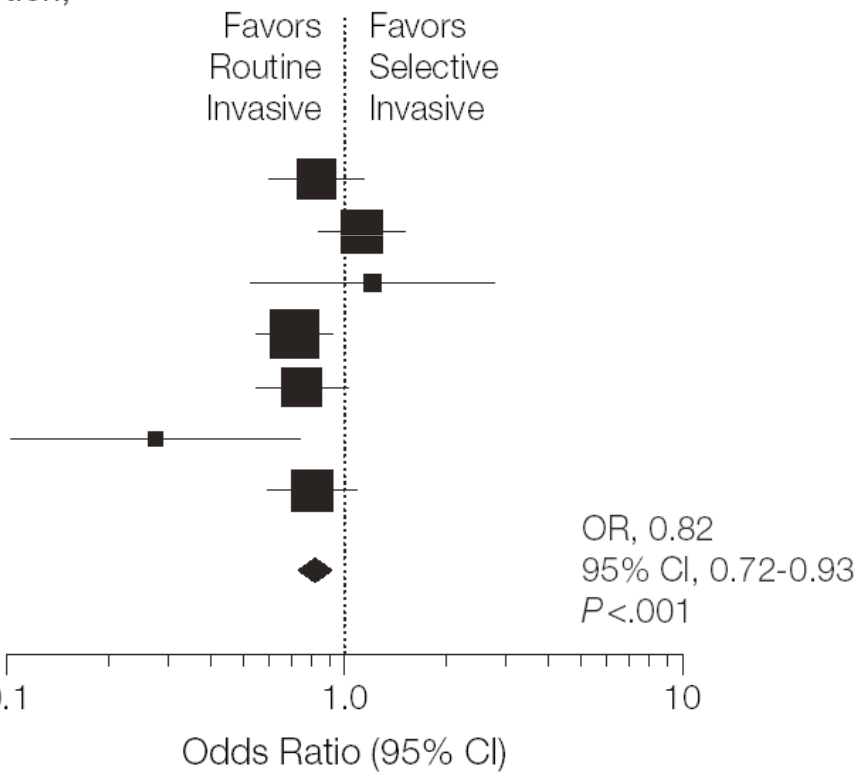
Predictor	Score
Sex	
Male	0
Female	8
Signs of CHF at presentation	
No	0
Yes	7
Prior vascular disease[b]	
No	0
Yes	6
Diabetes mellitus	
No	0
Yes	6
Systolic blood pressure, mmHg	
≤90	10
91–100	8
101–120	5
121–180	1
181–200	3
≥201	5

www.crusadebleedingscore.org

Meta-analysis non-STE-ACS

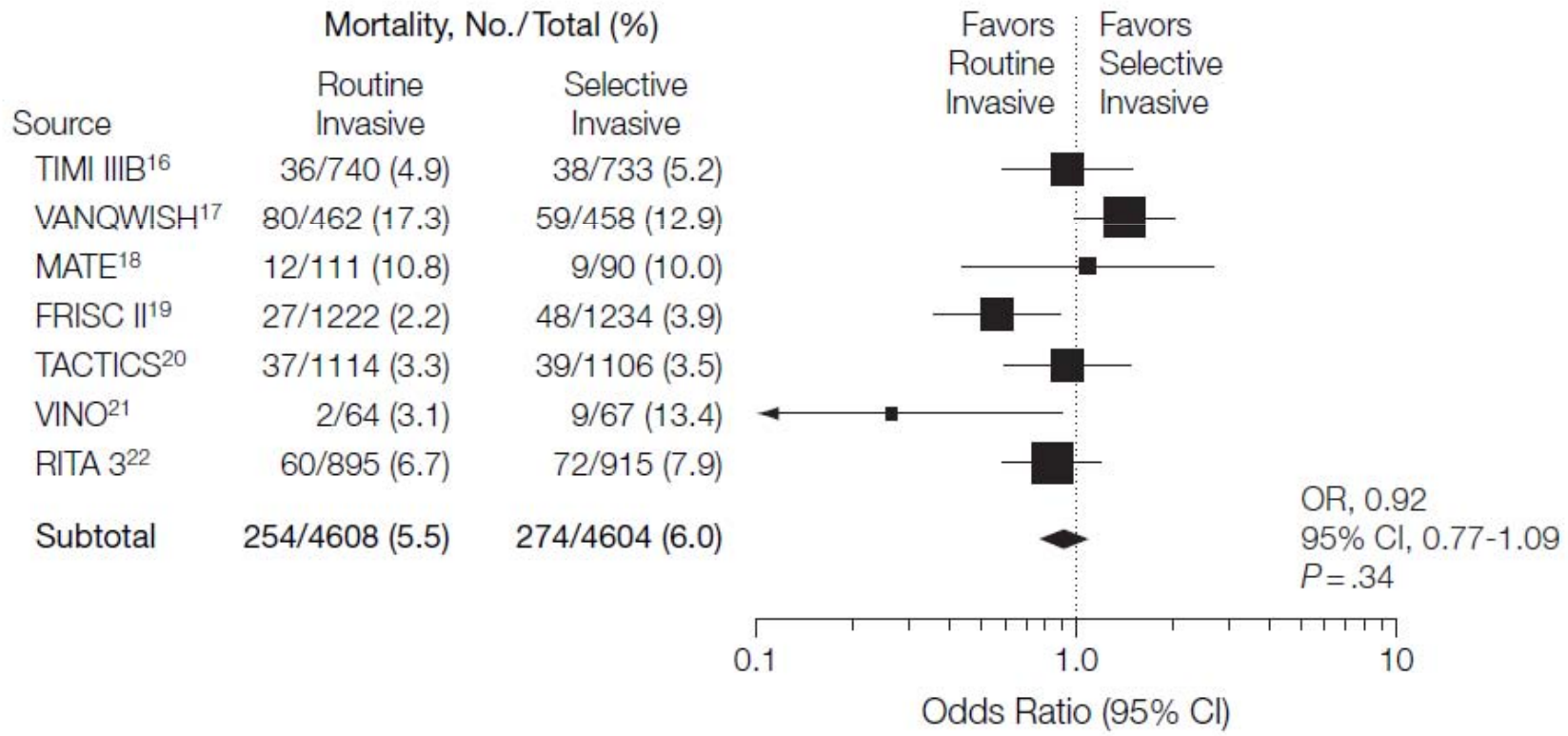
Composite of Death or Myocardial Infarction, No./Total (%)

Source	Routine Invasive	Selective Invasive
TIMI IIIB[16]	86/740 (11.6)	101/733 (13.8)
VANQWISH[17]	152/462 (32.9)	139/458 (30.3)
MATE[18]	16/111 (14.4)	11/90 (12.2)
FRISC II[19]	127/1222 (10.4)	174/1235 (14.1)
TACTICS[20]	81/1114 (7.3)	105/1106 (9.5)
VINO[21]	4/64 (6.3)	15/67 (22.4)
RITA 3[22]	95/895 (10.6)	118/915 (12.9)
Total	**561/4608 (12.2)**	**663/4604 (14.4)**



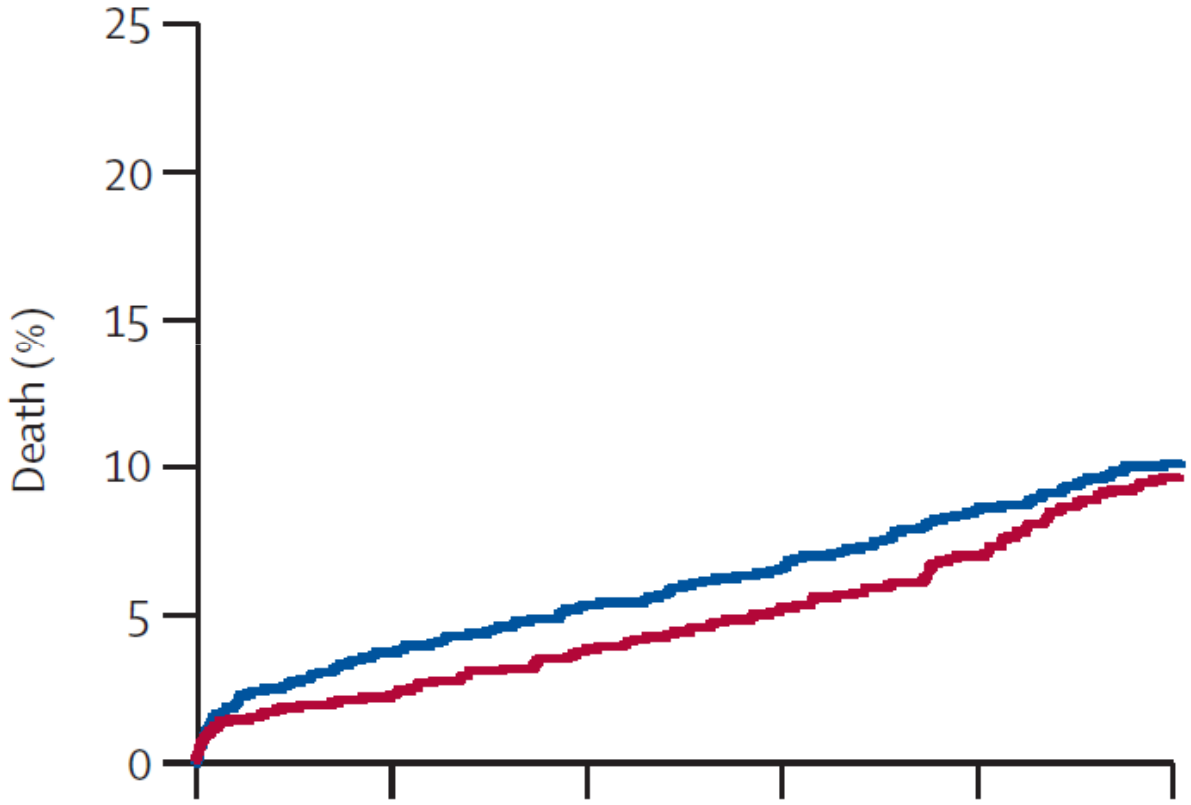
Mehta et al. JAMA 2005;293:2908-17

Meta-analysis non-STE-ACS



Mehta et al. JAMA 2005;293:2908-17

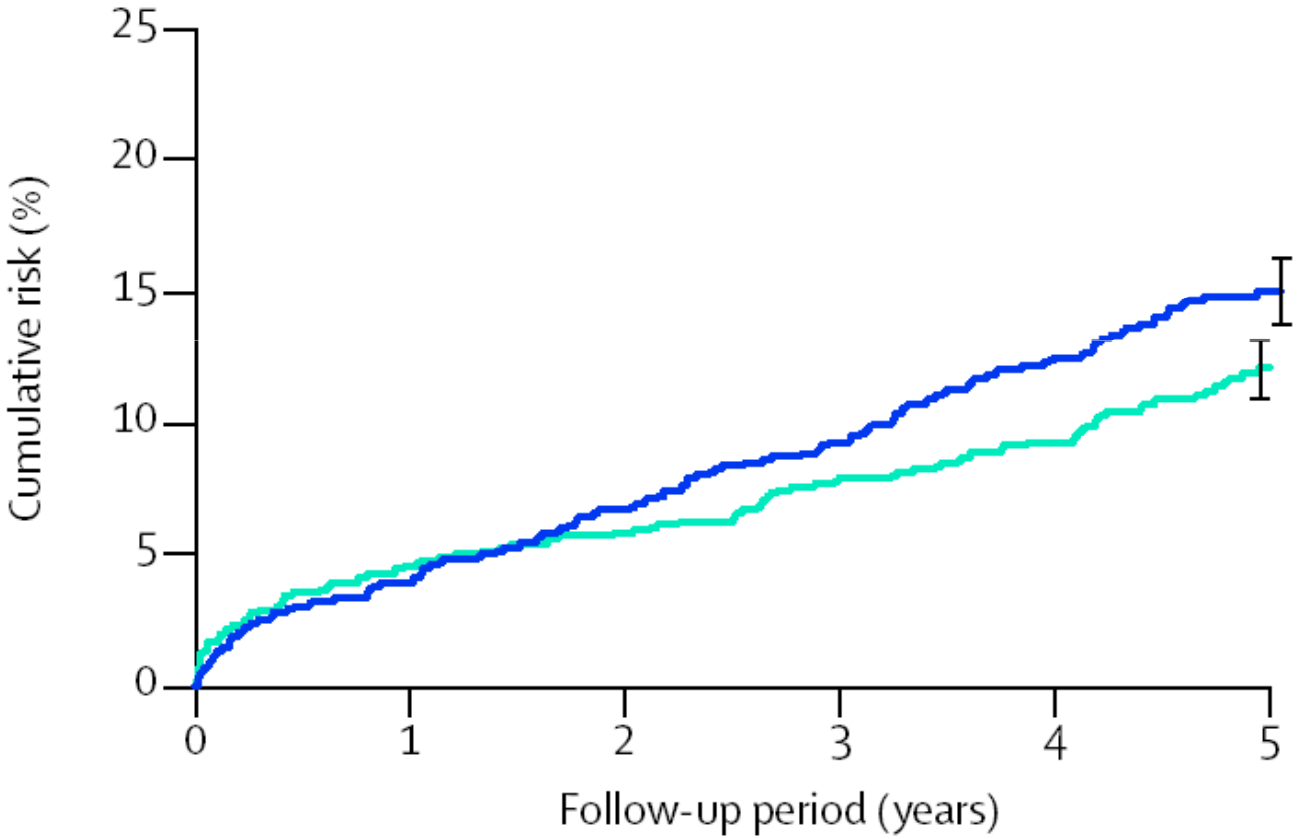
FRISC II: 5-year mortality



Numbers at risk

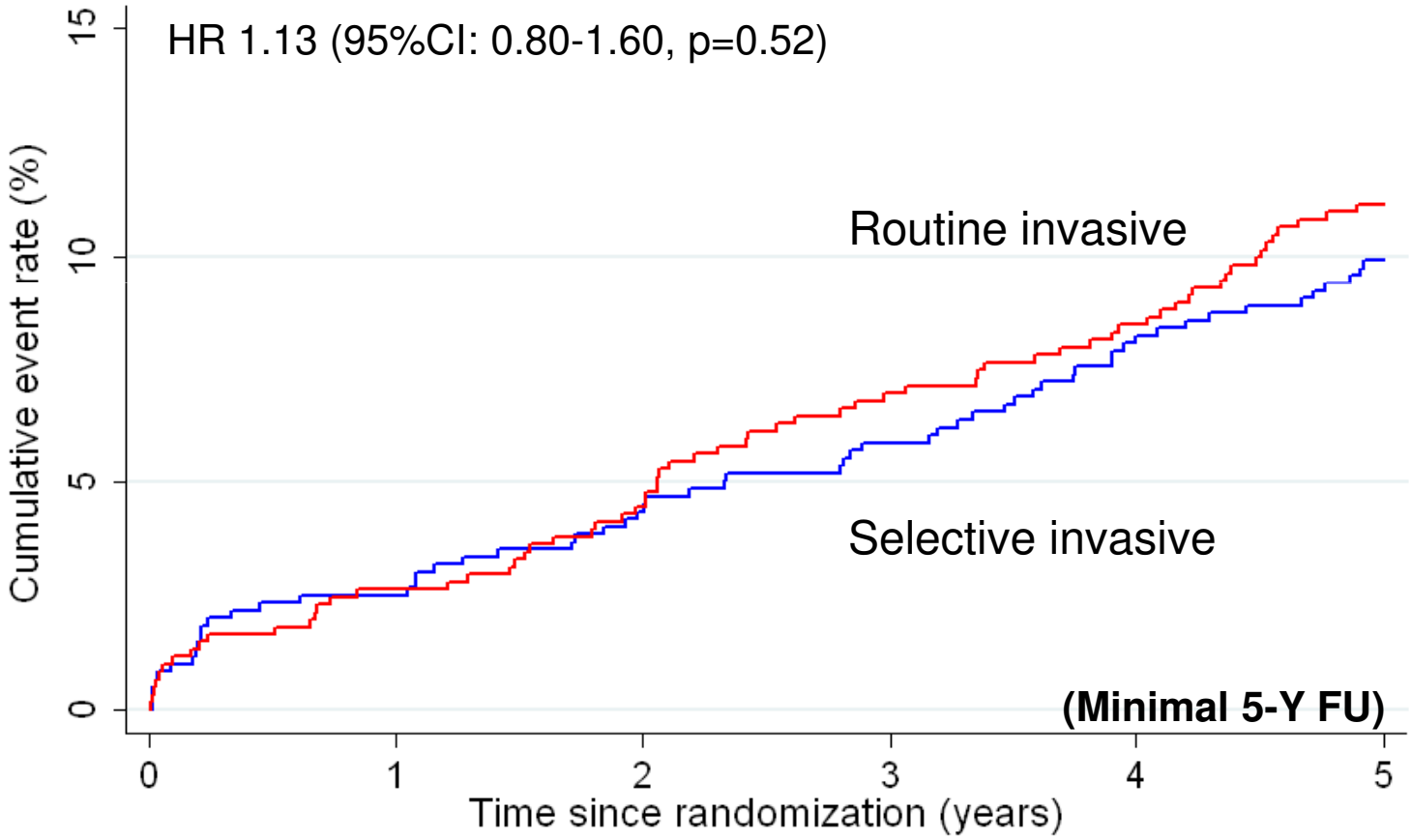
Invasive	1222	1189	1168	1137	1126	1094
Non-invasive	1235	1170	1116	1079	1118	1099

RITA-3: 5-year mortality



Numbers at risk						
Intervention	895	854	842	822	743	470
Conservative	915	878	853	828	729	463

ICTUS: 5-year mortality



Damman P. et al.

Long-Term Outcome of a Routine versus Selective Invasive Strategy in Patients with non-ST elevation ACS

Keith AA Fox, Tim C Clayton, Peter Damman, Stuart J Pocock, Robbert J de Winter, Jan GP Tijssen, Bo Lagerqvist, Lars Wallentin

FIR collaboration: FRISC ICTUS RITA

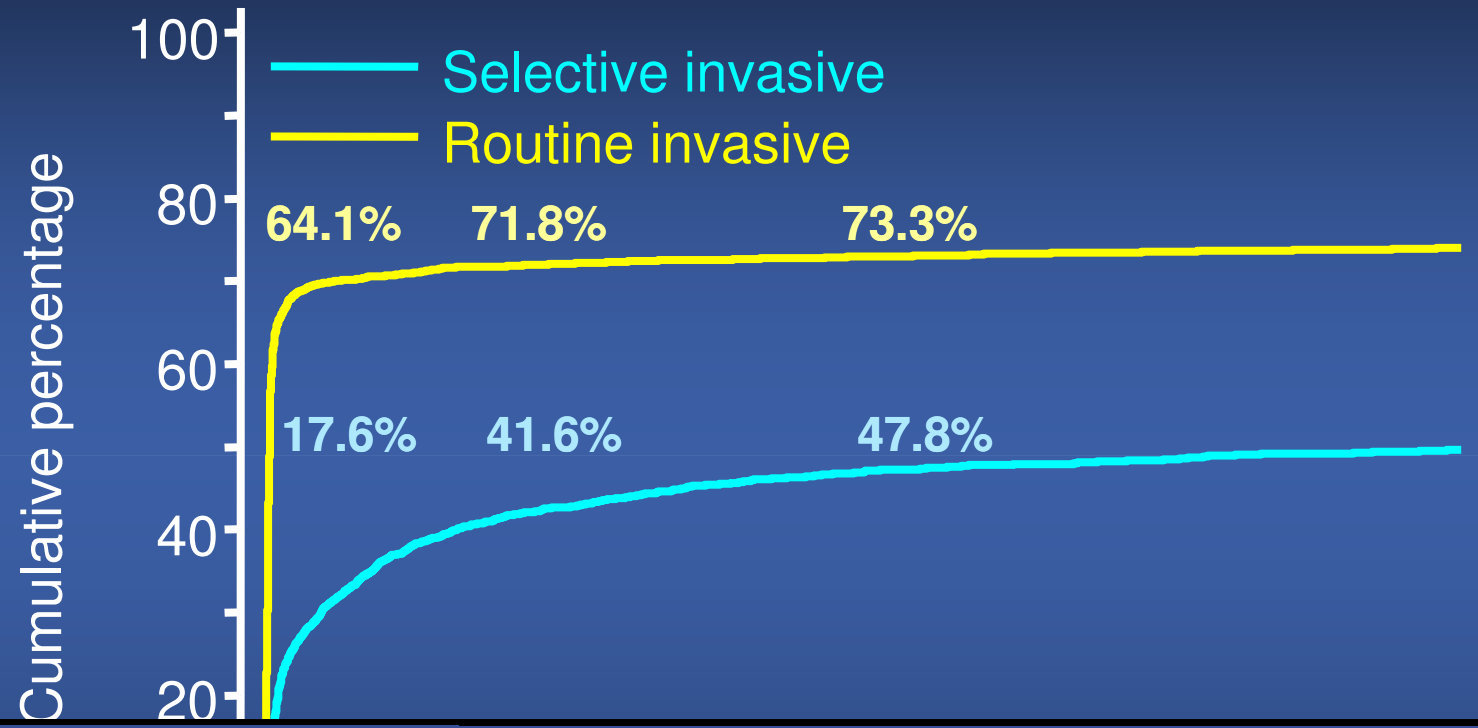
FIR patient-pooled database

- Core variables:
  - Demographics
  - Clinical history
  - Risk factors for CAD
  - Baseline ECG characteristics
  - Baseline laboratory results
  - 5-year clinical outcomes

- 5467 patients with nSTE-ACS included

FIR collaboration: FRISC ICTUS RITA

Timing of first coronary revascularization



Revasc at 1yr %	Routine invasive	Selective invasive
ICTUS	79	54
FRISC II	78	44
RITA-3	57	28

Primary outcomes at 5 years

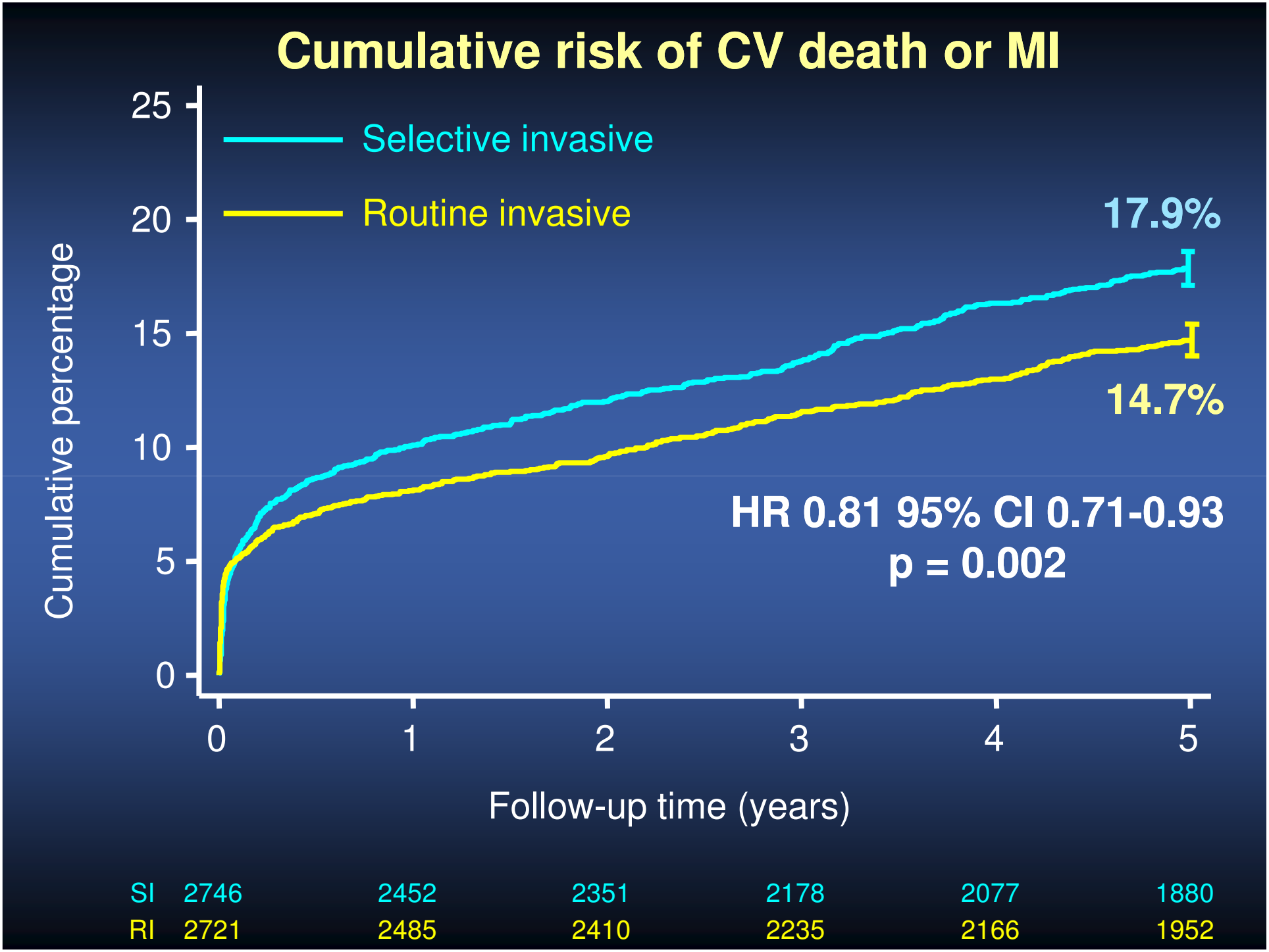
Table 2: Outcomes by study and treatment

	Combined dataset		Hazard ratio	p-value
	Selective invasive n = 2746	Routine invasive n = 2721	(95% CI)	
MI	338 12.9%	260 10.0%	0.77 (0.65 - 0.90)	0.001
CV death	218 8.1%	181 6.8%	0.83 (0.68 - 1.01)	0.068
CV death/MI	475 17.9%	389 14.7%	0.81 (0.71 -0.93)	0.002

Outcomes at 5 years

Table 2: Outcomes by study and treatment

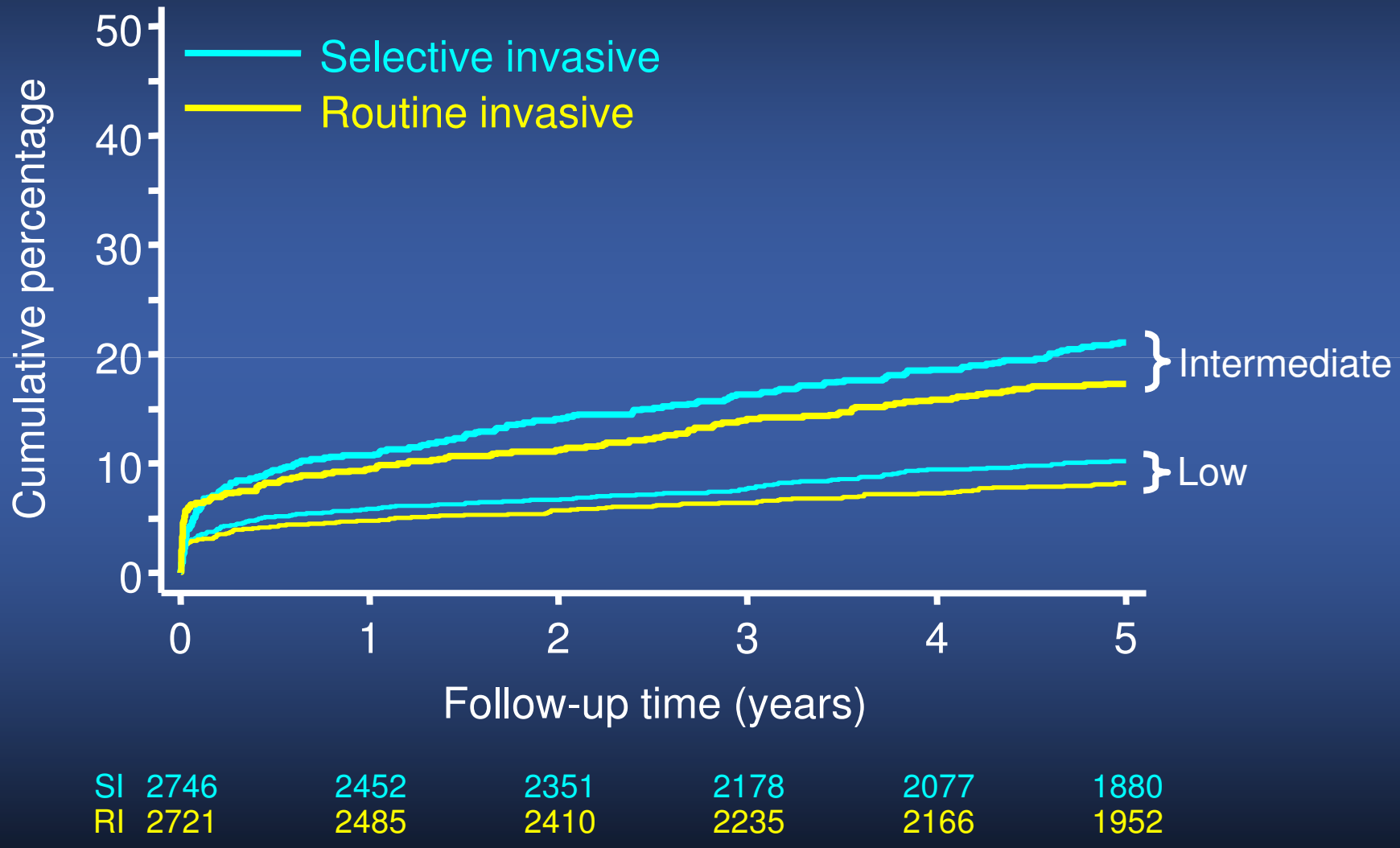
	Combined dataset		Hazard ratio	p-value
	Selective invasive	Routine invasive	(95% CI)	
All-cause death	321 11.7%	288 10.6%	0.90 (0.77 -1.05)	0.19
All-cause death/MI	560 20.9%	480 18.1%	0.85 (0.75 - 0.96)	0.008


Cumulative risk of CV death or MI
Selective invasive
Routine invasive
17.9%
14.7%
HR 0.81 95% CI 0.71-0.93
p = 0.002
Cumulative percentage
25
20
15
10
5
0
0
1
2
3
4
5
Follow-up time (years)
SI 2746 2452 2351 2178 2077 1880
RI 2721 2485 2410 2235 2166 1952

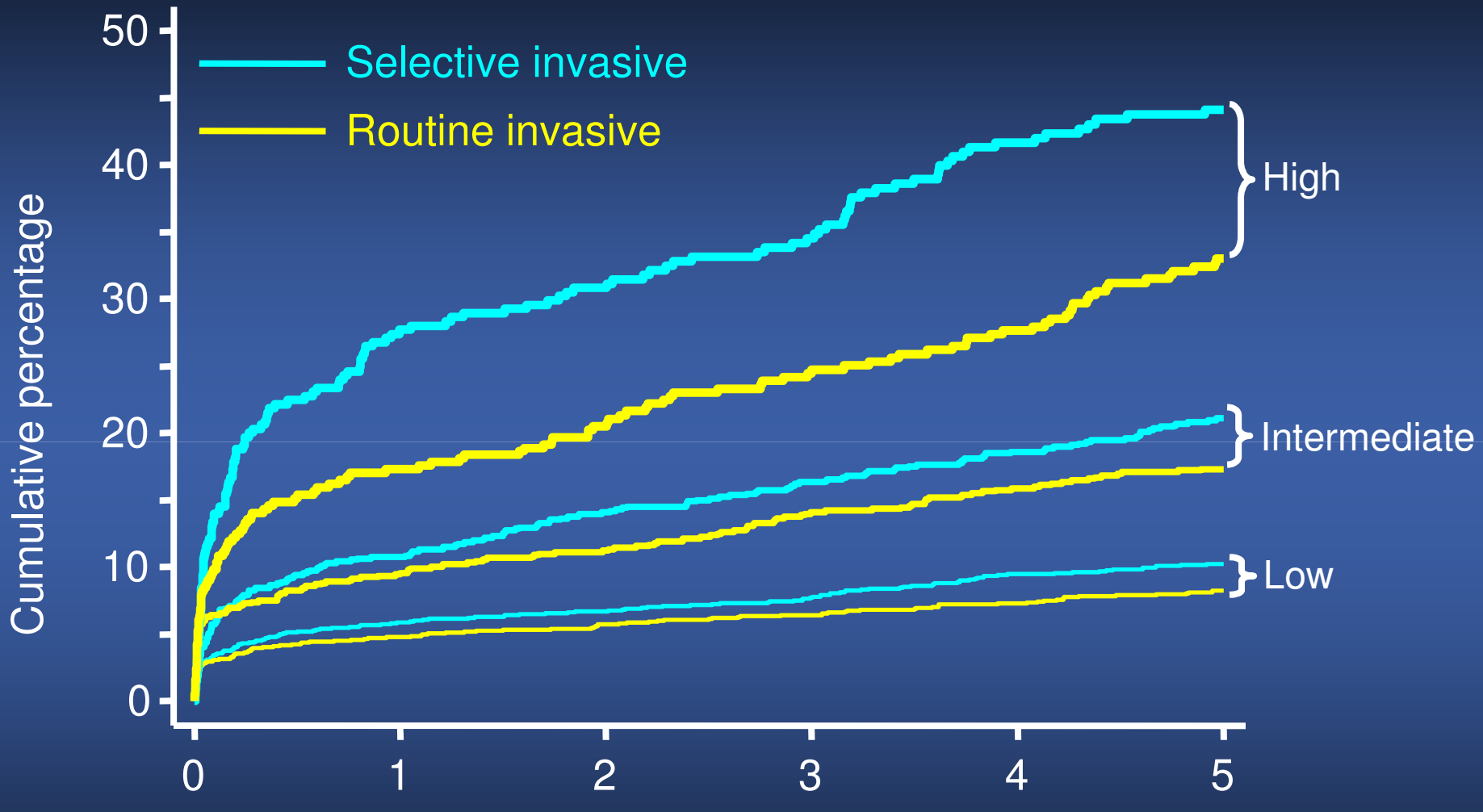
Are the results influenced by the baseline risk of the patients?

- Univariable and multivariable predictors of outcome derived (Cox regression). $p<0.01$ for inclusion in multivariable model (Wald test)
- Simplified integer score derived:
  - **Age, diabetes, prior MI, ST depression, hypertension, BMI**

Cumulative risk of CV death or MI by risk group



Cumulative risk of CV death or MI by risk group



SI	2746	2452	2351	2178	2077	1880
RI	2721	2485	2410	2235	2166	1952

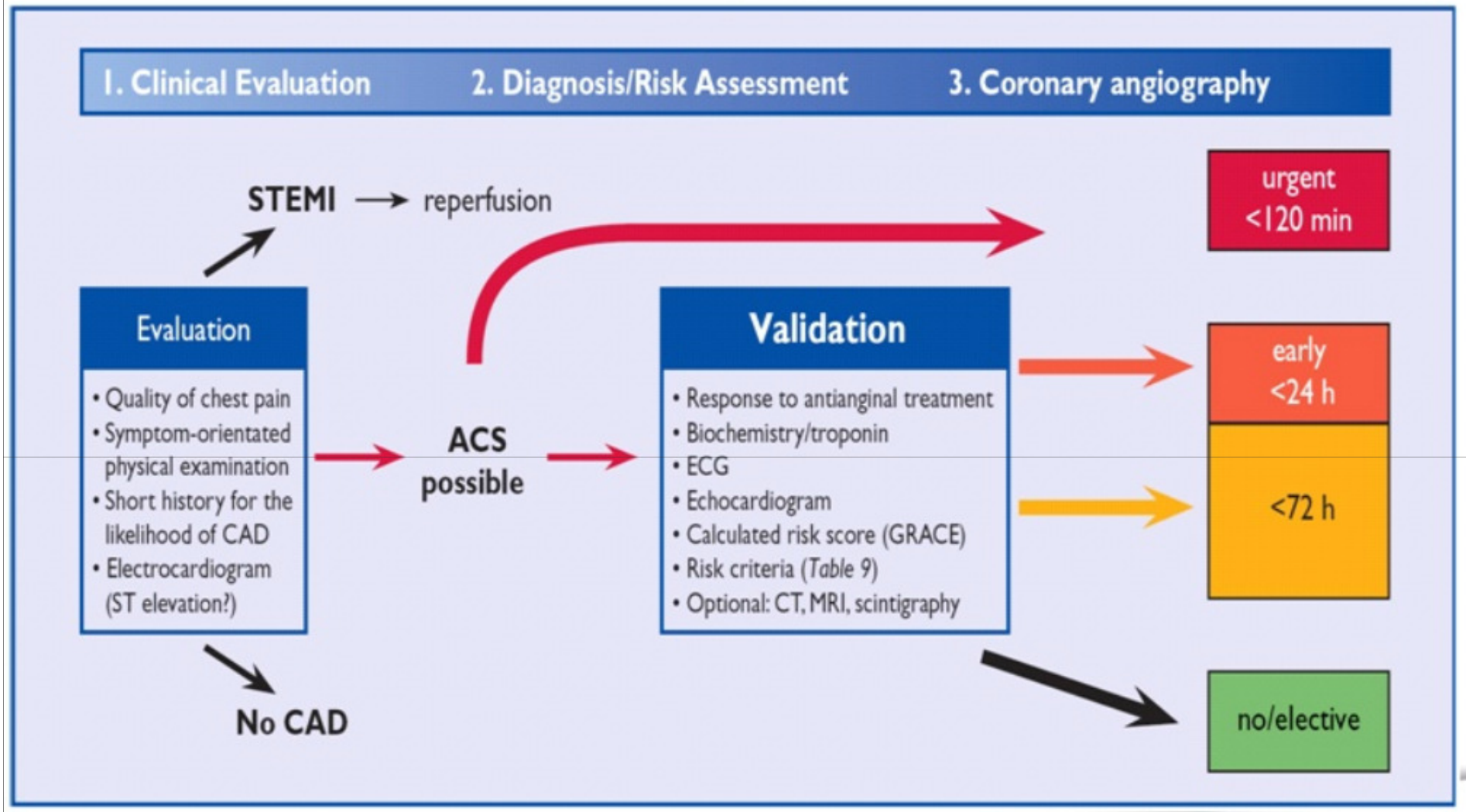
Summary

- The routine invasive strategy reduced cardiovascular death or MI at long-term follow-up
  - 3.2% absolute risk reduction in CV death/MI
  - 19% relative risk reduction
  - No statistically significant reduction in mortality
- Risk stratification identifies the patient group with the greatest absolute benefits
  - 11.1% absolute risk reduction in highest risk patients

KAA Fox, TC Clayton, P Damman, SJ Pocock, RJ de Winter, JGP Tijssen, B Lagerqvist, L Wallentin (FIR collaboration) JACC 2010;55:2435-45

JACC

Decision-making algorithm in ACS



EUROPEAN SOCIETY OF CARDIOLOGY®

Recommendations	Class [a]	Level [b]
An invasive strategy (within 72 h after first presentation) is indicated in patients with: • at least one high-risk criterion (*Table 9*); • recurrent symptoms.	I	A
Urgent coronary angiography (<2 h) is recommended in patients at very high ischaemic risk (refractory angina, with associated heart failure, life-threatening ventricular arrhythmias, or haemodynamic instability).	I	C
An **early** invasive strategy (<24 h) is recommended in patients with a GRACE score >140 or with at least one primary high-risk criterion.	I	A
Non-invasive documentation of inducible ischaemia is recommended in low-risk patients without recurrent symptoms before deciding for invasive evaluation.	I	A

< 72 hrs

< 24 hrs

Criteria for high risk with indication for invasive management

Primary	
• Relevant rise or fall in troponin[a] • Dynamic ST- or T-wave changes (symptomatic or silent)	< 24 hrs
Secondary	
• Diabetes mellitus • Renal insufficiency (eGFR <60 mL/min/1.73 m^2) • Reduced LV function (ejection fraction <40%) • Early post infarction angina • Recent PCI • Prior CABG • Intermediate to high GRACE risk score (*Table 5*)	< 72 hrs

TIMACS

Timing of Intervention in patients with Acute Coronary Syndromes

An International Randomized Trial of Early Versus Delayed Invasive Strategies in Patients with Non-ST Segment Elevation Acute Coronary Syndromes

Preliminary Results

Funded by Canadian Institutes of Health Research
Additional support from GSK and Sanofi-Aventis

Interventions and Timing

	Early N=1,593	Delayed N=1,438
Coronary Angiography (%)	97.6	95.5
Median time (h ± iqr)	14 (3-21)	50 (41-81)
PCI (%)	59.6	55.0
Median time (h ± iqr)	16 (3-23)	52 (41-101)
CABG (%)	14.7	13.6
Median time (d ± iqr)	7.7 (4.7-17.4)	10.8 (6.7-19.8)

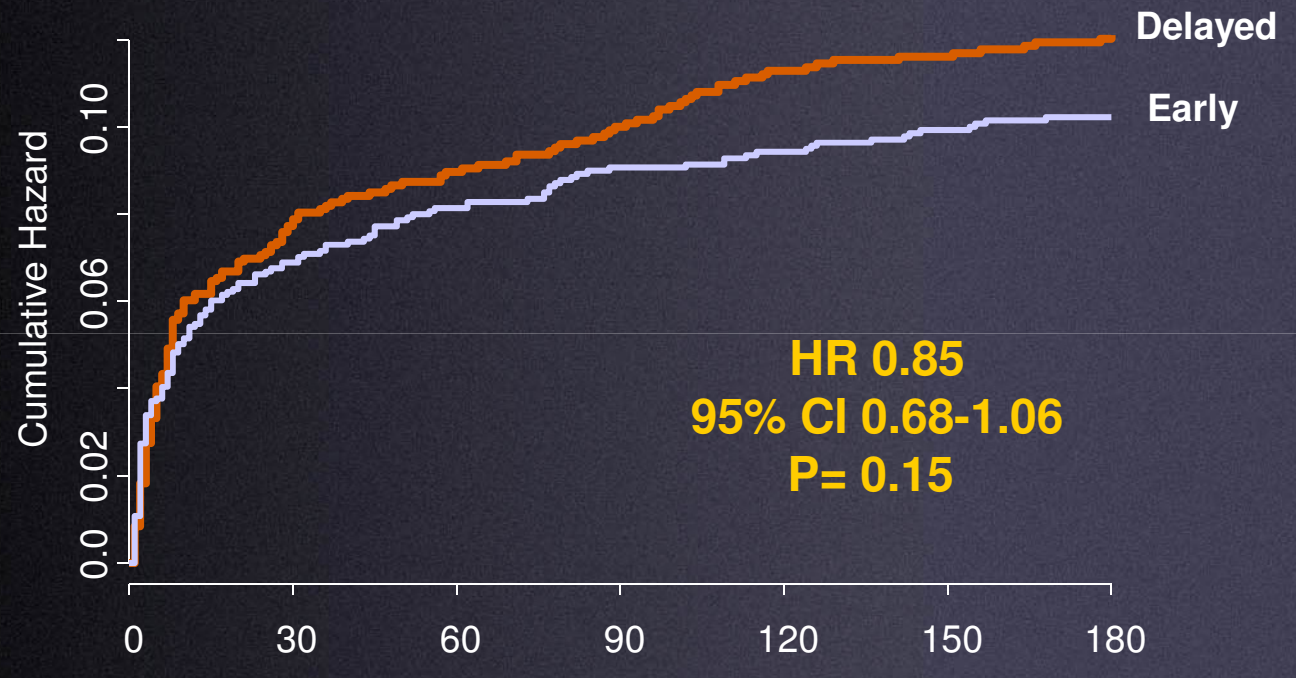
iqr=interquartile range

Preliminary Results as of Nov 7, 2008

Primary Outcome
Death, MI, or Stroke

TIMACS

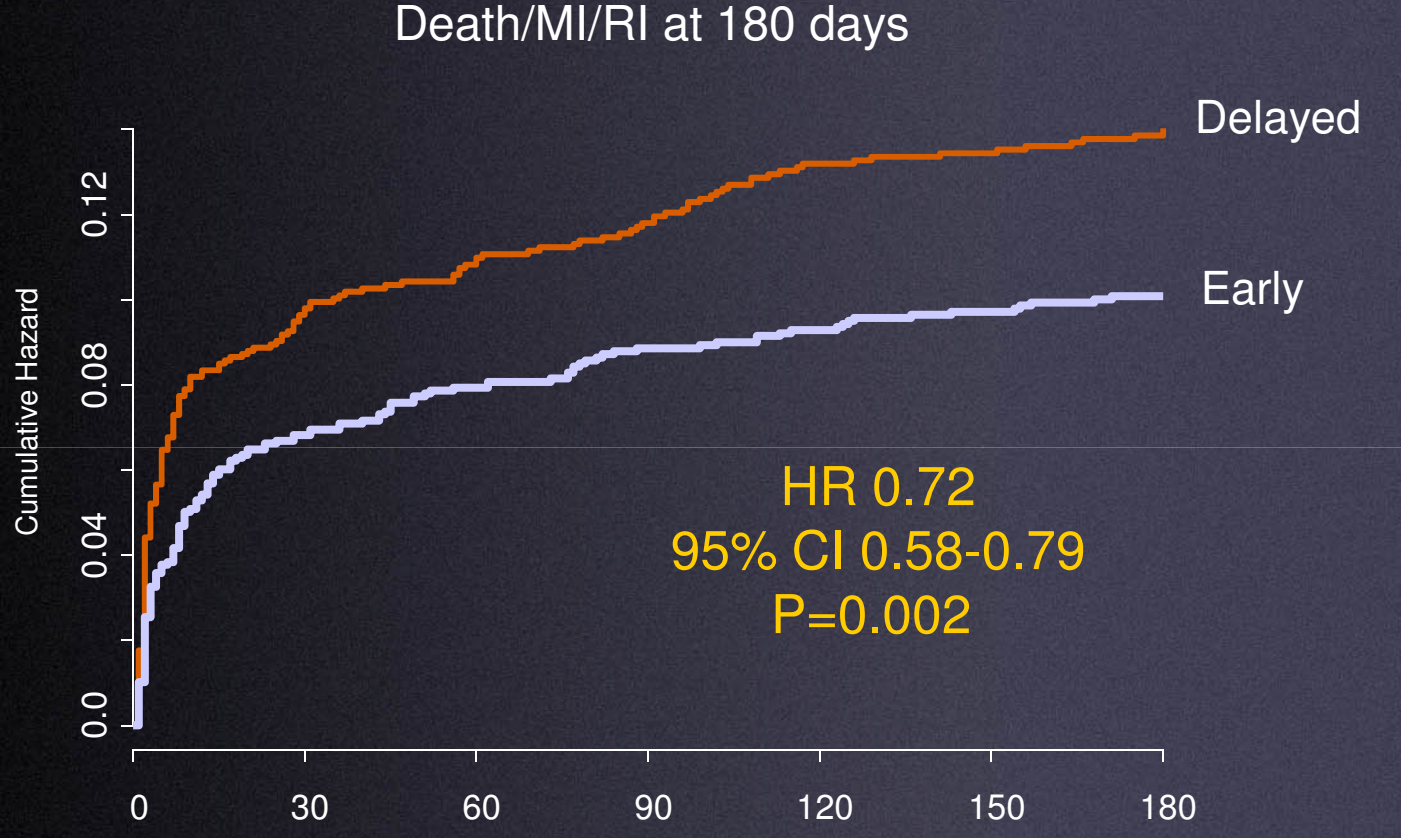
Death/MI/Stroke at 180 days



No. at Risk							
Delayed	1438	1328	1269	1254	1234	1229	1211
Early	1593	1484	1413	1398	1391	1382	1363

Preliminary Results as of Nov 7, 2008

Secondary Outcome
Death, MI, or Refractory Ischemia

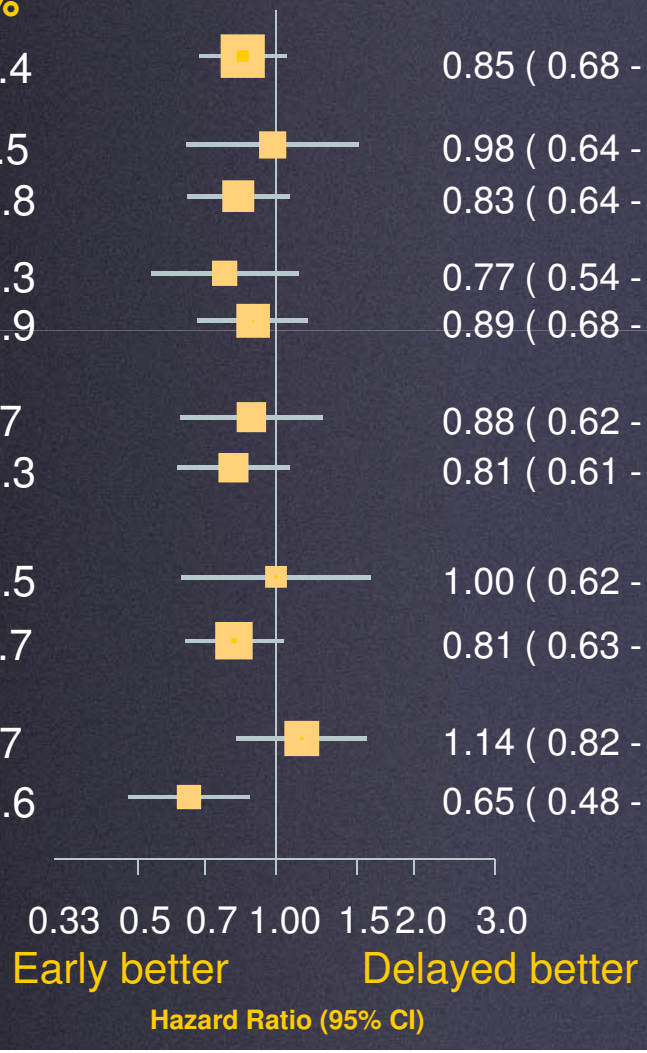


No. at Risk							
Delayed	1438	1303	1243	1230	1209	1205	1187
Early	1593	1485	1417	1402	1394	1386	1366

Preliminary Results as of Nov 7, 2008

Pre-specified Subgroups

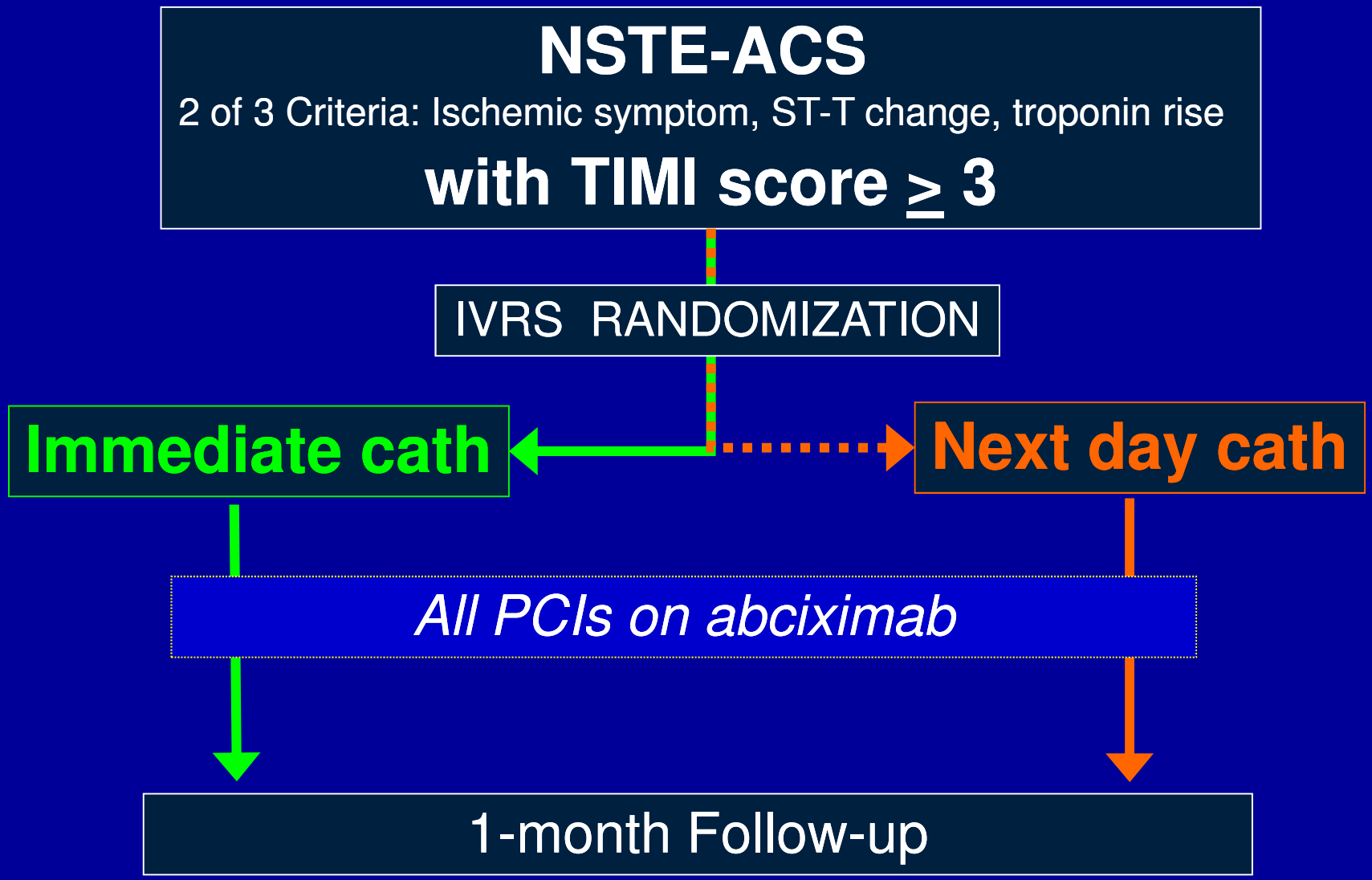
Characteristic	N	Early %	Delayed %	HR (95% CI)	Interaction p-Value
Overall	3031	9.7	11.4	0.85 (0.68 - 1.06)	
Age < 65	1293	6.5	6.5	0.98 (0.64 - 1.52)	
>=65	1736	12.3	14.8	0.83 (0.64 - 1.07)	0.463
Female	1052	9.7	12.3	0.77 (0.54 - 1.12)	
Male	1976	9.8	10.9	0.89 (0.68 - 1.18)	0.540
No ST deviation	1523	7.6	8.7	0.88 (0.62 - 1.26)	
ST deviation	1508	11.7	14.3	0.81 (0.61 - 1.07)	0.722
No elevated marker	668	10.5	10.5	1.00 (0.62 - 1.60)	
Elevated marker	2363	9.5	11.7	0.81 (0.63 - 1.04)	0.423
GRACE 0-140	2070	7.7	6.7	1.14 (0.82 - 1.58)	
GRACE >=141	961	14.1	21.6	0.65 (0.48 - 0.88)	**0.0097**



Conclusions

1. Overall, we found no significant difference between an early and a delayed invasive strategy for prevention of death, MI or stroke (primary outcome).
2. In the subgroup at highest risk (GRACE score > 140), an early invasive strategy appears to be superior to a delayed invasive strategy for prevention of death, MI or stroke.
3. The early invasive strategy had a large impact on reducing the rate of refractory ischemia by 70%.
4. There were no significant differences in major bleeding or other safety concerns between the two strategies.

ABOARD study design



Preliminary Results

Outcomes

- Primary
  - MI: defined as the peak of troponin I during hospitalization
- Secondary
  1. Death (any), new MI (CK-MB) or urgent revascularization (PCI or CABG)
  2. Death, new MI, urgent revascularization or recurrent ischemia
  3. Individual parameters

Preliminary Results

Index ACS event

Entry criteria, (%)	Immediate (N=175)	Delayed (N=177)
Ischemic symptom	98.2	97.7
ST-T segment changes	69.7	76.8
Elevated Troponin I	75.4	72.9
TIMI score, (%)		
≥ 3	95.4	95.5
≥ 5	22.9	30.5

Preliminary Results

In-hospital medications

	Immediate (N=175)	Delayed (N=177)
Aspirin, (%)	99.4	100
Clopidogrel, (%)	96.6	98.9
Loading dose, mean ± sd, mg	660 ± 268	663 ± 267
Maintenance dose, mean ± sd, mg	111 ± 40	111 ± 39
Abciximab, (%)	65.1	57.4
Unfractionated heparin only, (%)	5.1	3.4
Low Molecular Weight Heparin only, (%)	68.6	67.2
Both UFH and LMWH, (%)	22.9	28.8
Neither UFH nor LMWH, (%)	2.9	0.6
Beta-blocker, (%)	87.4	85.3
Statin, (%)	94.3	95.5
ACE inhibitor or ARB, (%)	84.5	80.2

Preliminary Results

Time to catheterization (hrs)

	IMMEDIATE	DELAYED
FRISC 2 (1999)	96	408
TRUCS (2000)	48	120
TIMI-18 (2001)	22	79
VINO (2002)	6	1464
RITA 3 (2002)	48	1020
ELISA (2003)	6	50
ISAR-COOL (2003)	3	86
ICTUS (2005)	23	283
TIME-ACS (2008)	14	50
ABOARD (2009) median (IQR), hr.min	**1.10** (0.51-2.03)	**20.48** (17.30-24.36)

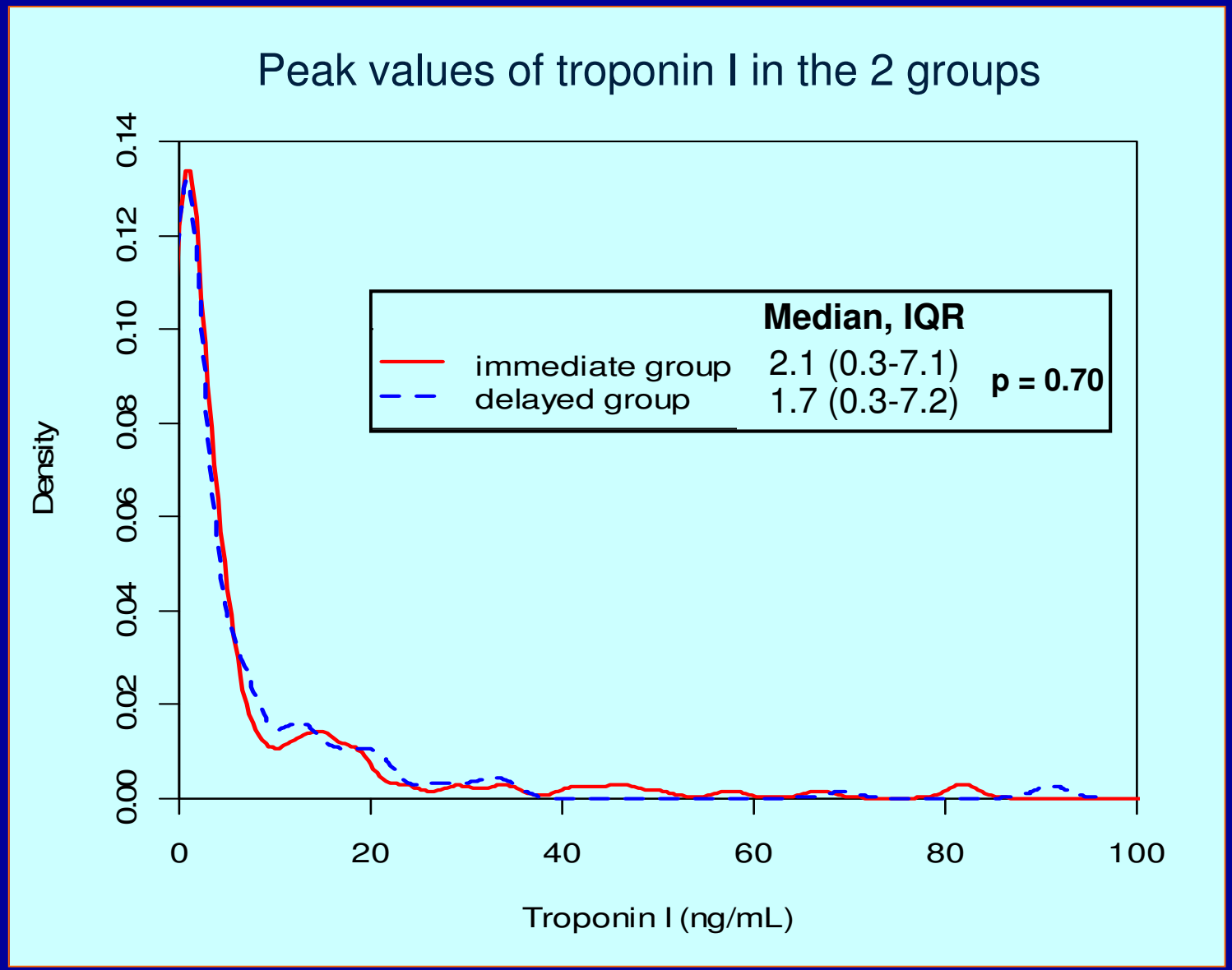
Preliminary Results

Interventions

	IMMEDIATE	DELAYED
Radial access (%)	**87.4**	**81.8**
Culprit artery		
Left main trunk, (%)	**4.1**	**7.3**
Left anterior descending artery, (%)	**48.6**	**45.0**
Circumflex artery, (%)	**24.7**	**29.1**
Right coronary artery, (%)	**24.7**	**25.2**
Coronary bypass graft, (%)	**2.1**	**2.0**
Percutaneous Coronary Intervention, (%)	**80.1**	**69.5**
Stent (at least one), (% of PCI)	**94.0**	**96.2**
DES (at least one), (% of PCI)	**47.9**	**55.2**
Number of stents/patient, mean±sd	**1.2 ± 0.9**	**1.2 ± 1.0**
CABG surgery, (%)	**11.0**	**11.3**

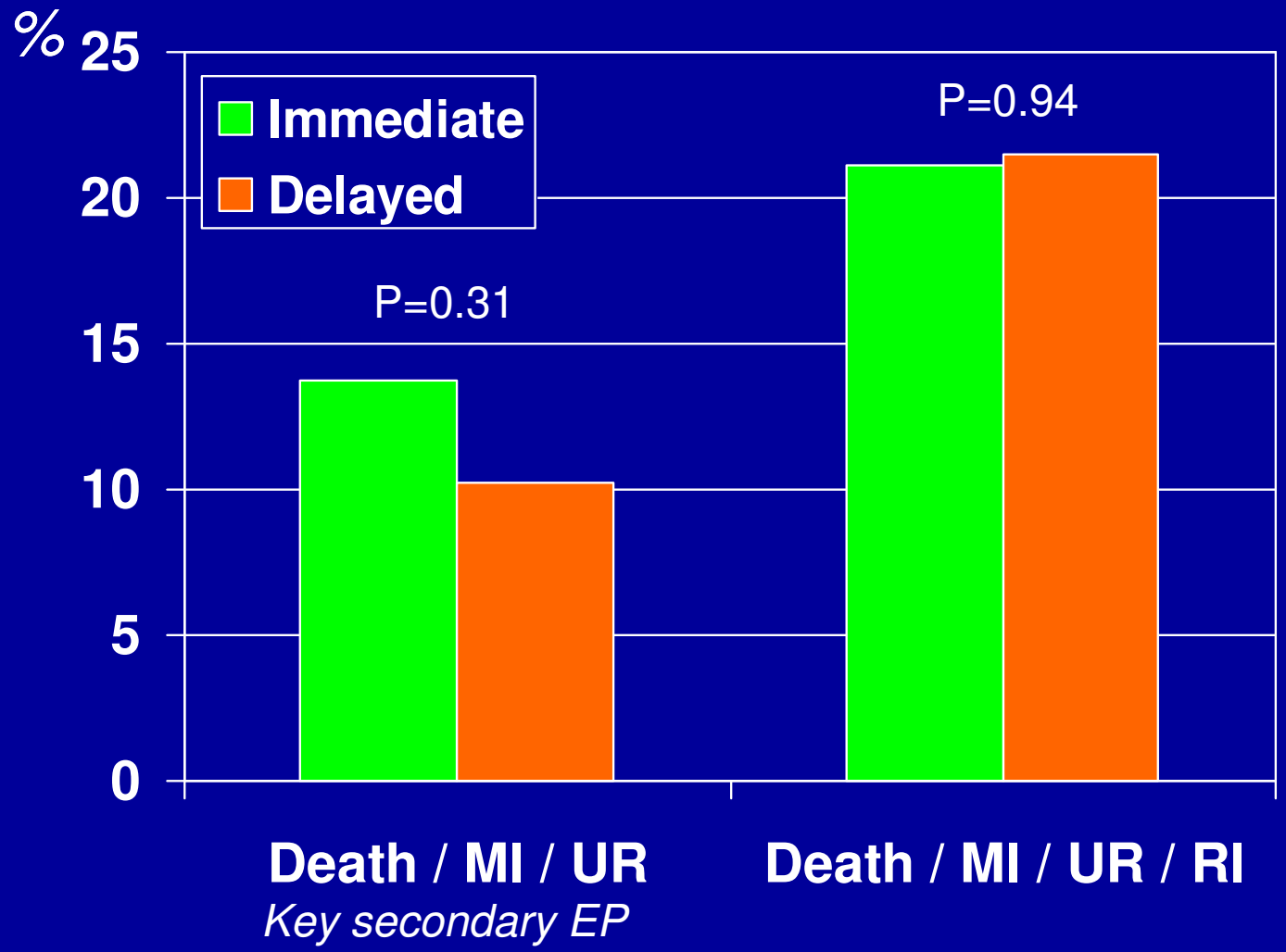
Preliminary Results

Primary EP (peak of troponin I)



Preliminary Results

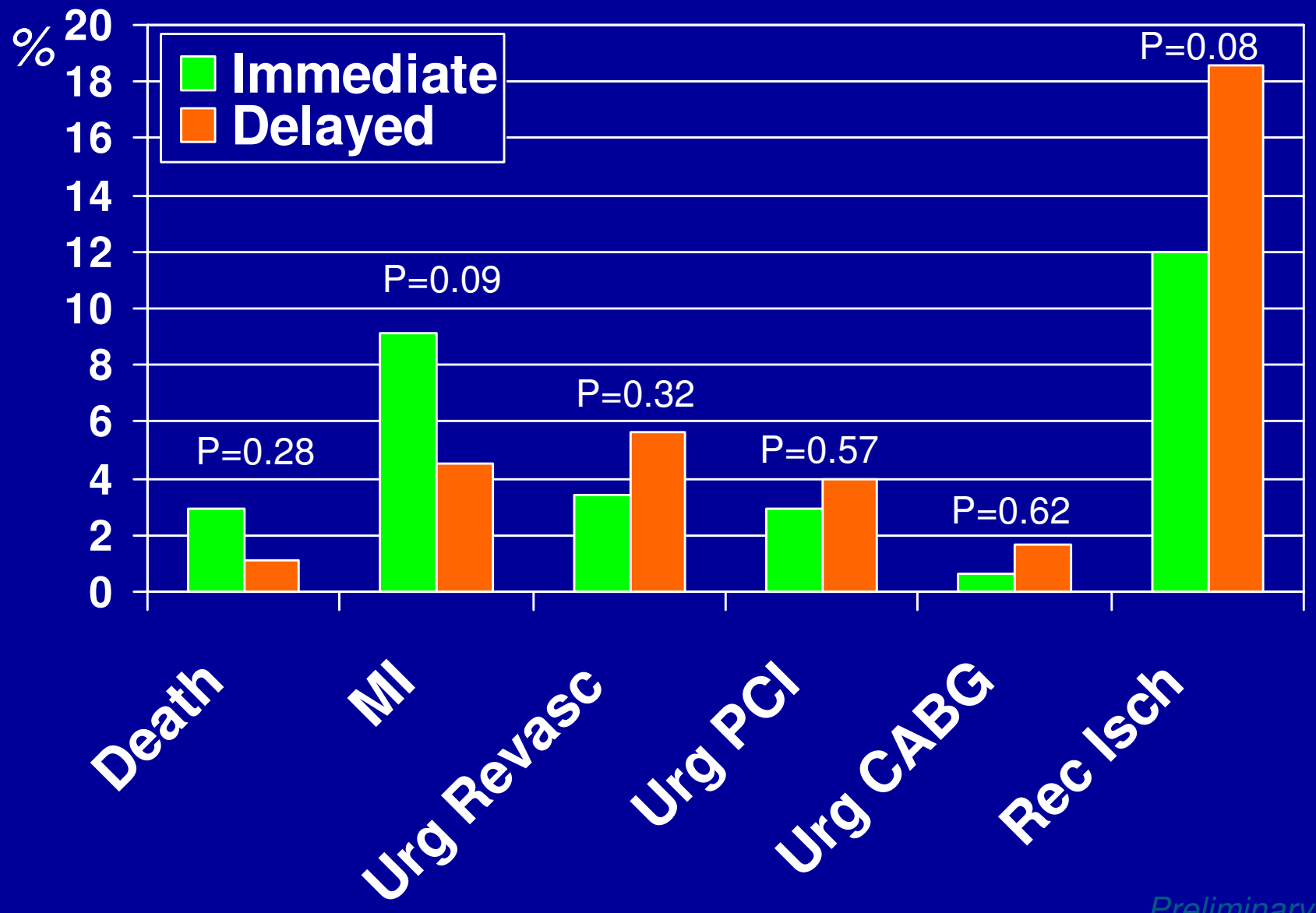
Composite Ischemic Endpoints at 1 month



Key secondary EP

Preliminary Results

Individual Ischemic Endpoints at 1 month



Preliminary Results

Safety outcomes at 1 month

	Immediate	Delayed	*P*
Major bleeding at 1 month, (%)	**4.0**	**6.8**	*0.25*
Non-CABG related major bleeding,	2.3	5.1	*0.26*
CABG-related major bleeding	1.7	1.7	*1.00*
Transfusion ≥ 2 units	3.4	5.6	*0.32*
Transfusion ≥ 5 units	1.1	1.1	*1.00*
Thrombocytopenia at 1 month, (%)	**2.9**	**4.5**	*0.41*
Non-CABG thrombocytopenia, (%)	2.3	4.0	*0.54*
Post-CABG thrombocytopenia, (%)	0.6	0.6	*1.00*

Preliminary Results

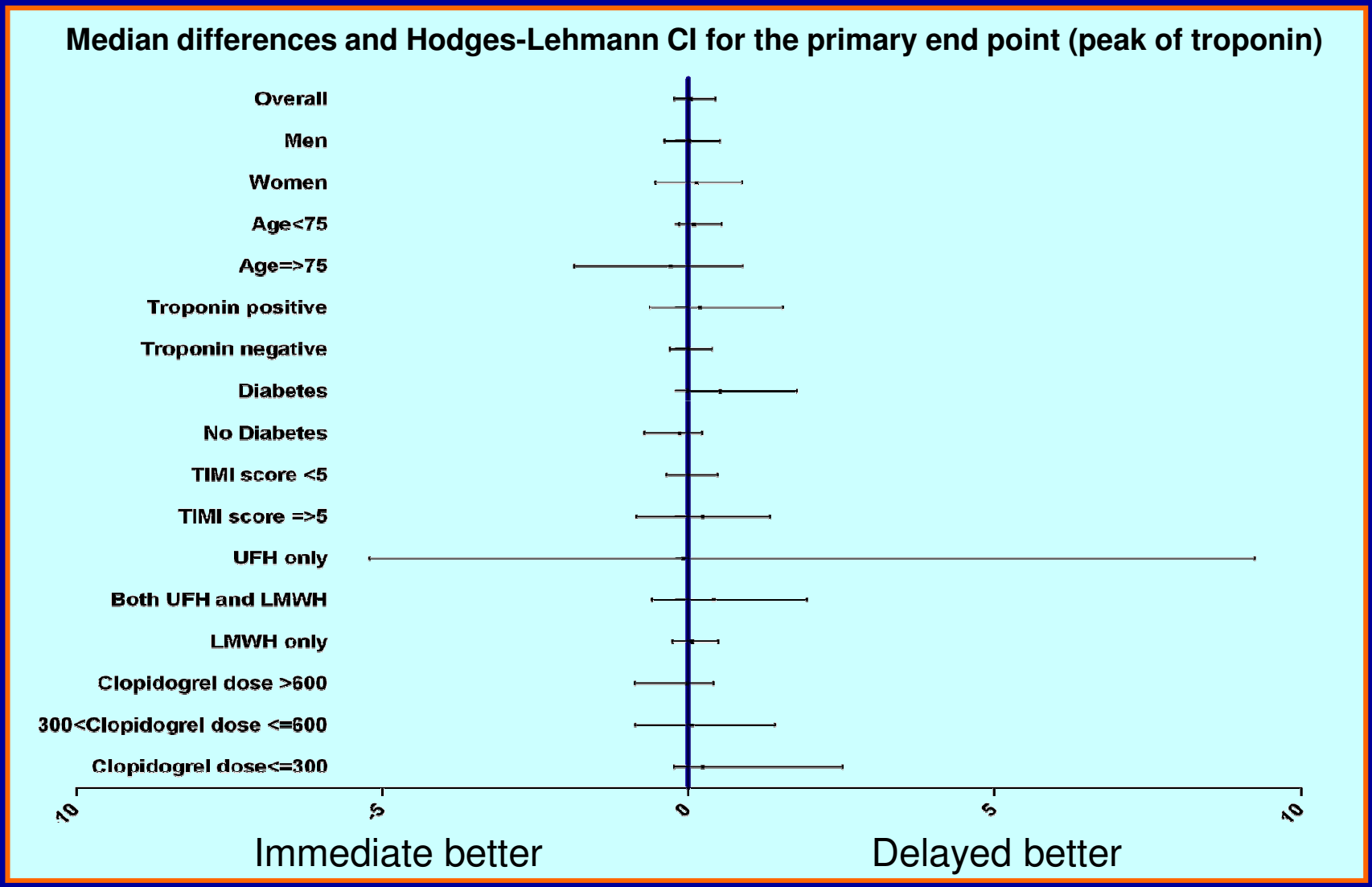
Sites of Major Bleedings

	n
1- Gastro-Intestinal	4
2- Puncture-related	4
3- Hemopericardium	2
4- Intracranial	1
5- Epistaxis	1
6- Hematoma (not puncture-related)	1
unknown	7

One patient had 2 bleeding events

Preliminary Results

Subgroup analysis (primary EP)



Preliminary Results

Hospital stay

Immediate Median, IQR, hrs	**55** (30; 98)
Delayed Median, IQR, hrs	**77** (49; 145)

P<0.001

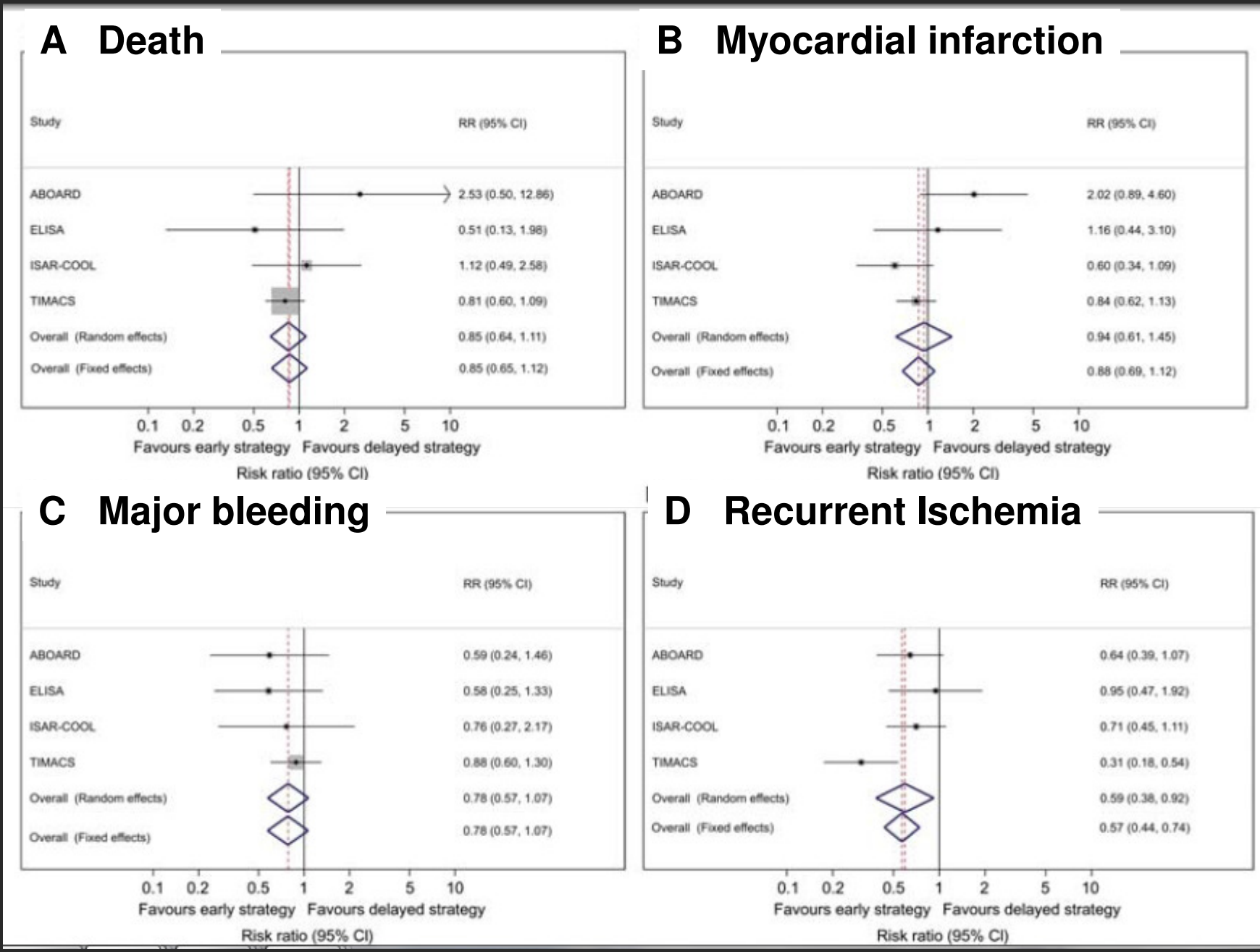
Preliminary Results

Conclusions

A « primary PCI strategy » in NSTE-ACS (compared with a rapid intervention on the next day):

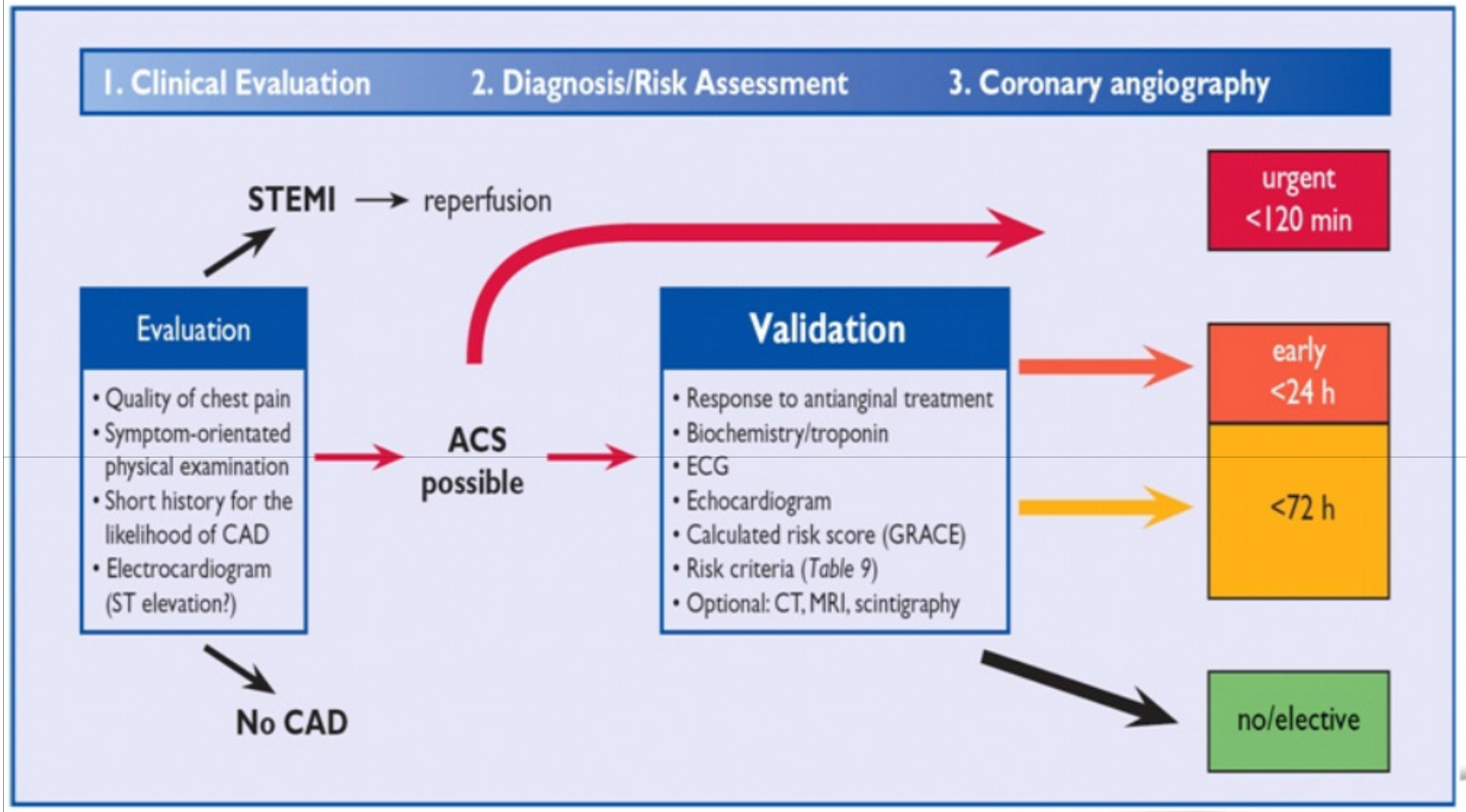
- is feasible, but does not reduce the risk of MI (primary outcome)
- is not associated with significant differences in other efficacy or safety outcomes
- does not benefit to a particular subgroup of patients
- shortens significantly hospital stay

Preliminary Results



Katritsis et al. EurHJ 2011;32:32-40

Decision-making algorithm in ACS



EUROPEAN SOCIETY OF CARDIOLOGY®

Medical management vs Revascularization

Table 4 Predictors of subsequent conservative management of NSTE-ACS patients with angiographically documented significant coronary artery disease (adapted from SYNERGY data [37])

Predictors of conservative management	Odds ratio (95% CI)
More likely (revascularization less likely)	
Prior history of CABG	1.44 (1.25–1.64)
Weight (per 10 kg decrease)	1.10 (1.05–1.14)
Three-vessel disease	1.33 (1.17–1.50)
History of heart failure	1.48 (1.24–1.77)
Killip class II–IV	1.33 (1.13–1.56)
Diabetes mellitus	1.15 (1.03–1.29)
Less likely (revascularization more likely)	
MI after admission but before catheterization	0.21 (0.11–0.42)

Chan et al. JACC Int 2008;1:369-78

Medical management vs Revascularization

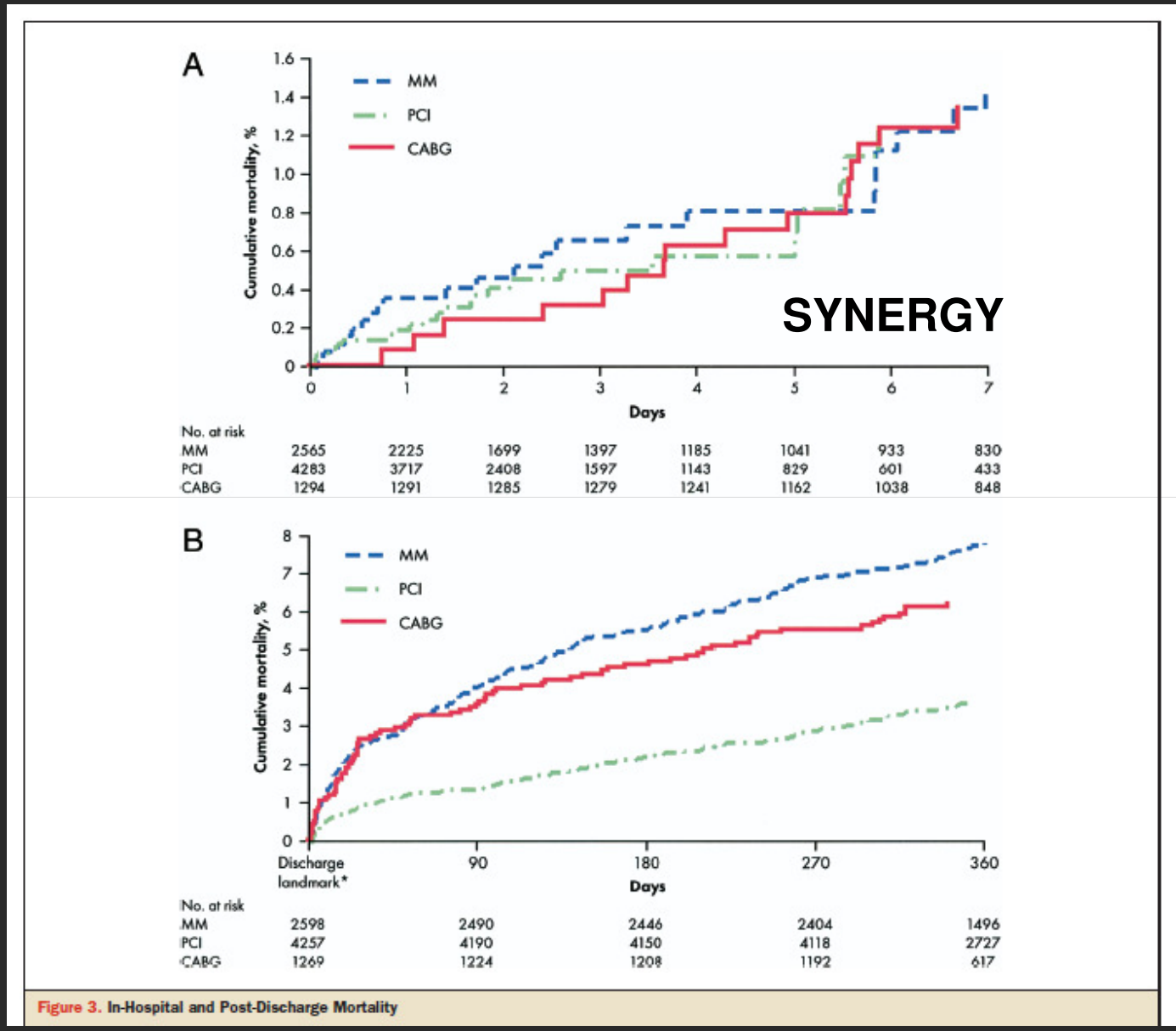


Figure 3. In-Hospital and Post-Discharge Mortality

Chan et al. JACC Int 2008;1:369-78

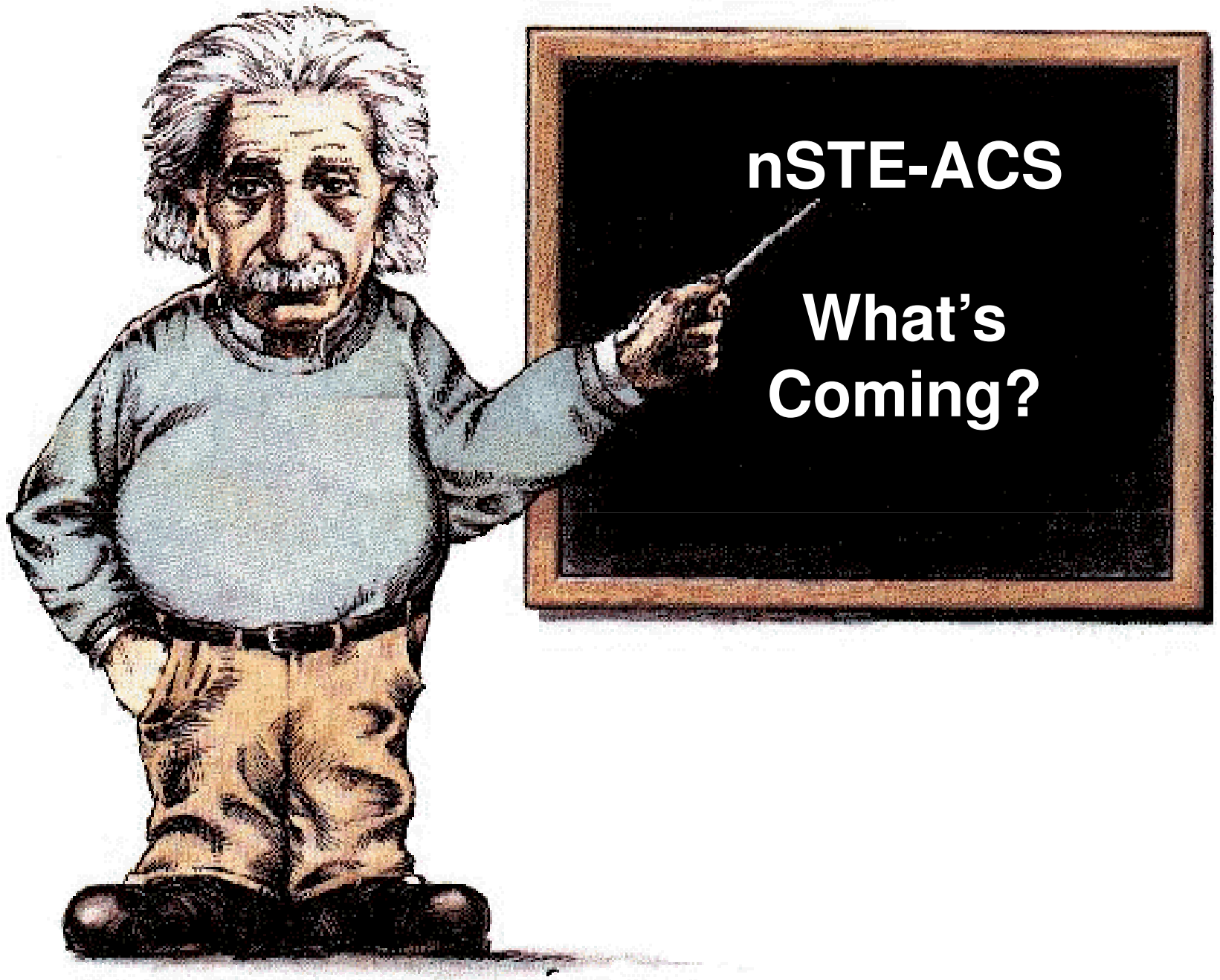
Predictors of early invasive management

Predictors of early invasive management **CRUSADE**	Odds ratio (95% CI)	*P* value
More likely		
Cardiology care	2.21 (2.06–2.37)	<0.001
ST segment depression	1.26 (1.16–1.36)	<0.001
Positive cardiac markers	1.51 (1.36–1.67)	<0.001
Hospital angioplasty capabilities	1.41 (1.12–1.76)	<0.001
Prior PCI	1.35 (1.24–1.47)	<0.001
Less likely		
Age (per 10 year increase)	0.80 (0.77–0.82)	<0.001
Prior congestive heart failure	0.49 (0.44–0.55)	<0.001
Female gender	0.86 (0.80–0.92)	<0.001
Renal insufficiency (creatinine >2.0 mg/dL or CrCl <30 mL/min)	0.51 (0.46–0.58)	<0.001
Off-hour presentation	0.80 (0.75–0.85)	<0.001
Diabetes	0.93 (0.86–1.00)	0.04
Prior CABG	0.83 (0.76–0.91)	<0.001

Bhat DL et al. JAMA 2004;292:2096

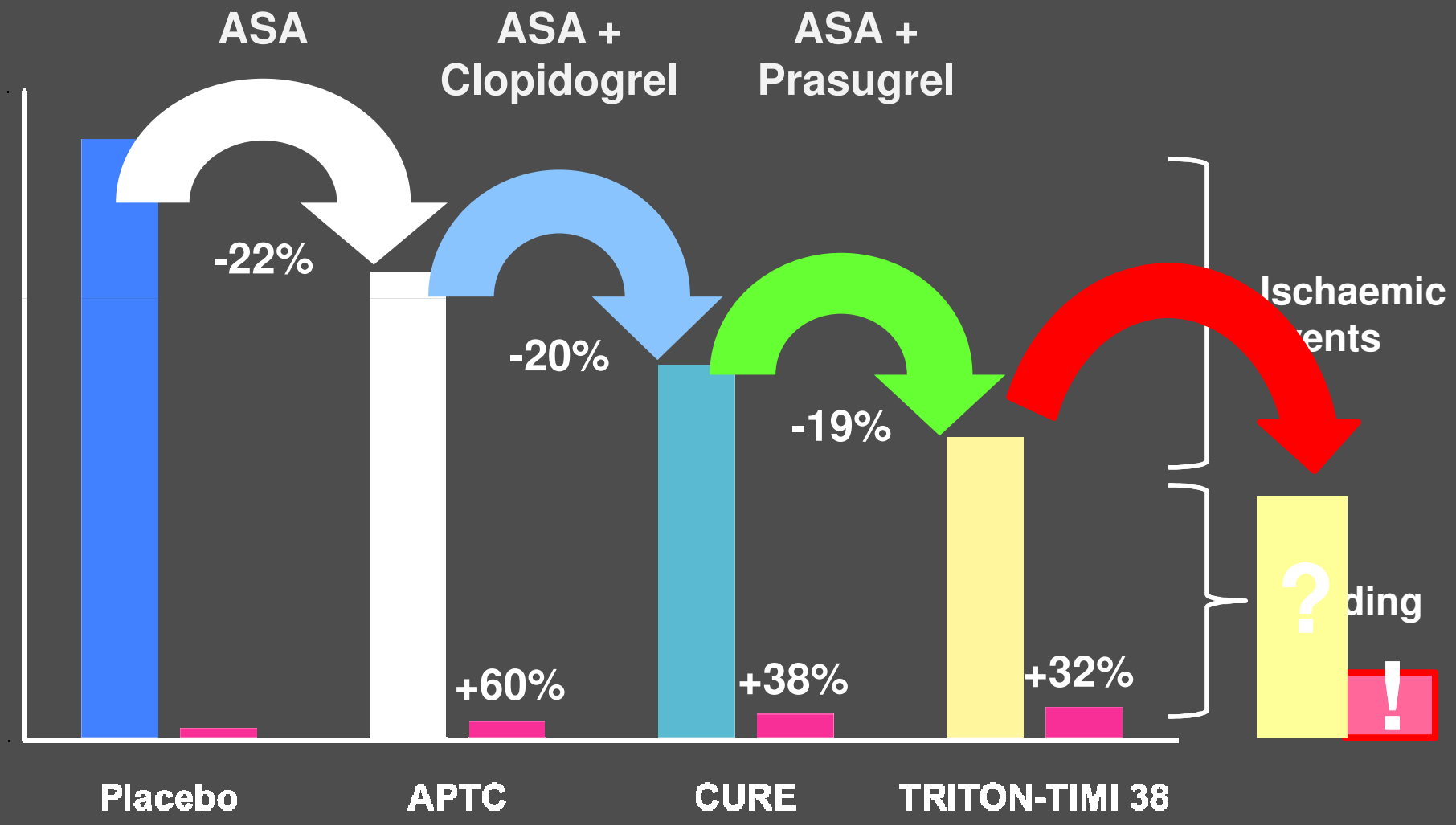
Medical management vs Revascularization

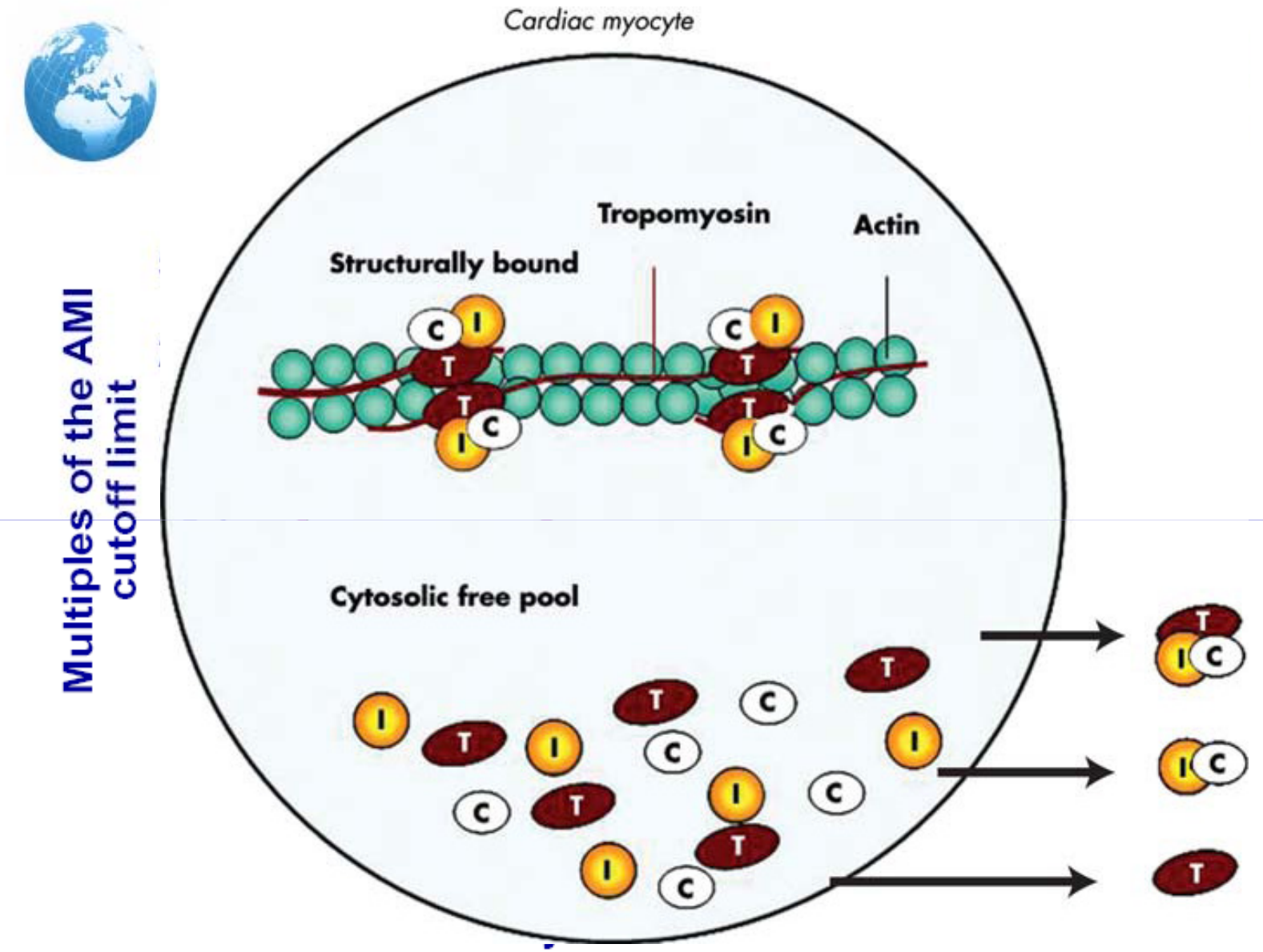
- Post hoc analyses SYNERGY / CRUSADE
- Patients magaged medically after angiography constitute a particularly high risk group of patients
- We need better strategies to improve outcome in these patients



"The secret to creativity is knowing how to hide your sources."

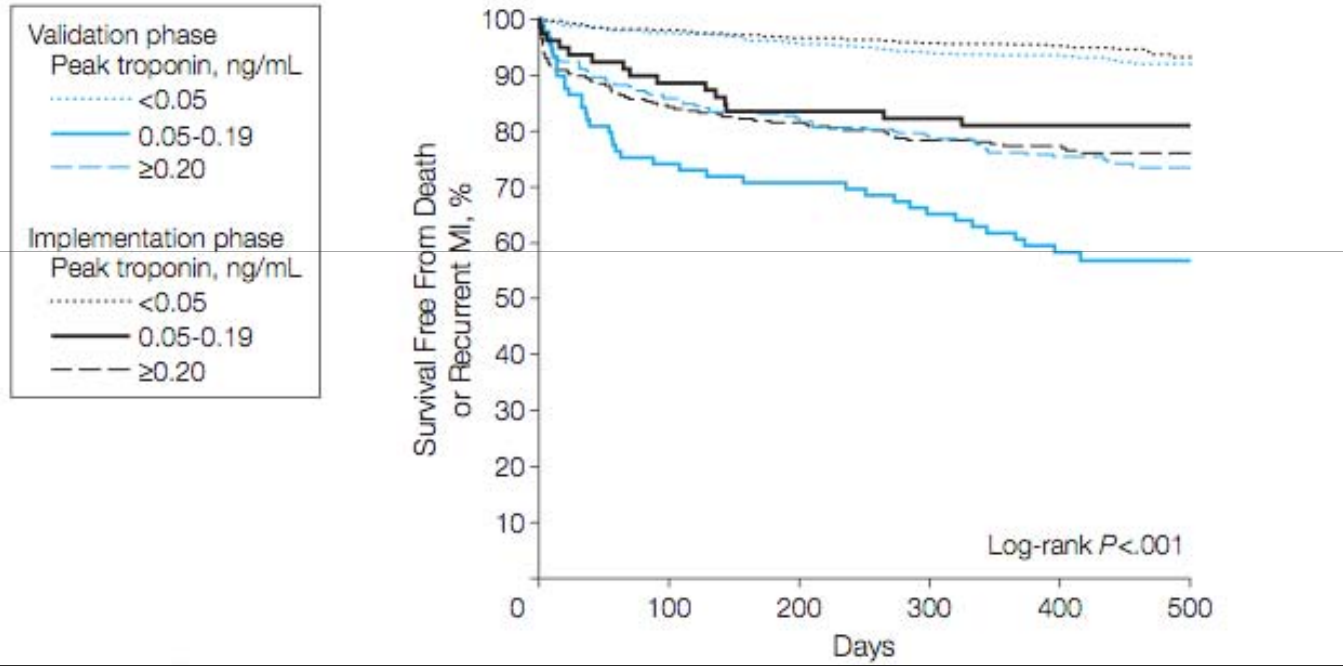
Antiplatelet therapy in ACS
The risk of bleeding



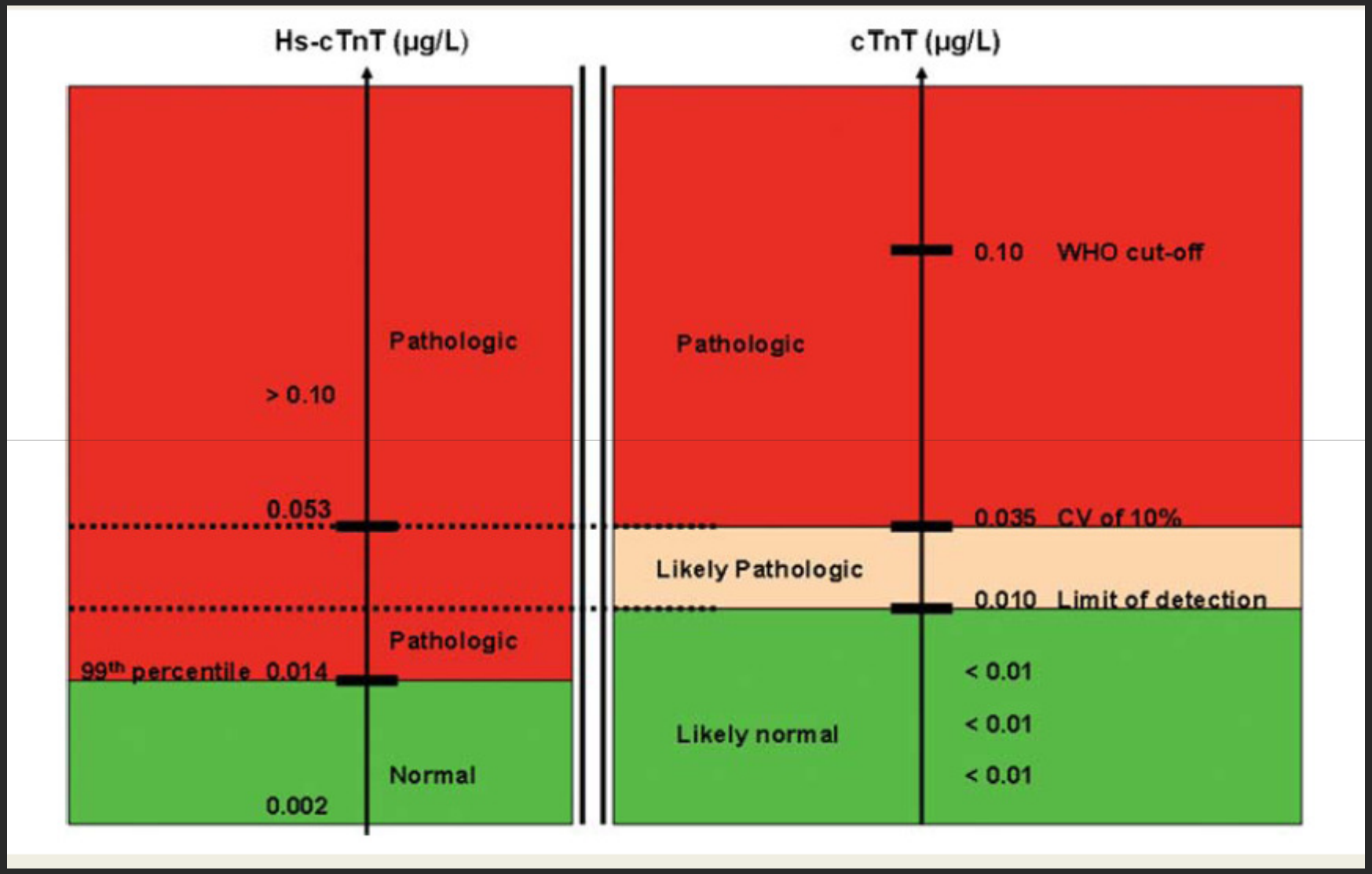

Cardiac myocyte
Tropomyosin
Actin
Structurally bound
C
I
T
Cytosolic free pool
Multiples of the AMI cutoff limit

hsTnT

Figure. Survival Free From Death or Recurrent MI in Patients With Suspected Acute Coronary Syndrome Before (Validation Phase) and After (Implementation Phase) the Introduction of a Sensitive Troponin Assay



Mills et al, JAMA 2011

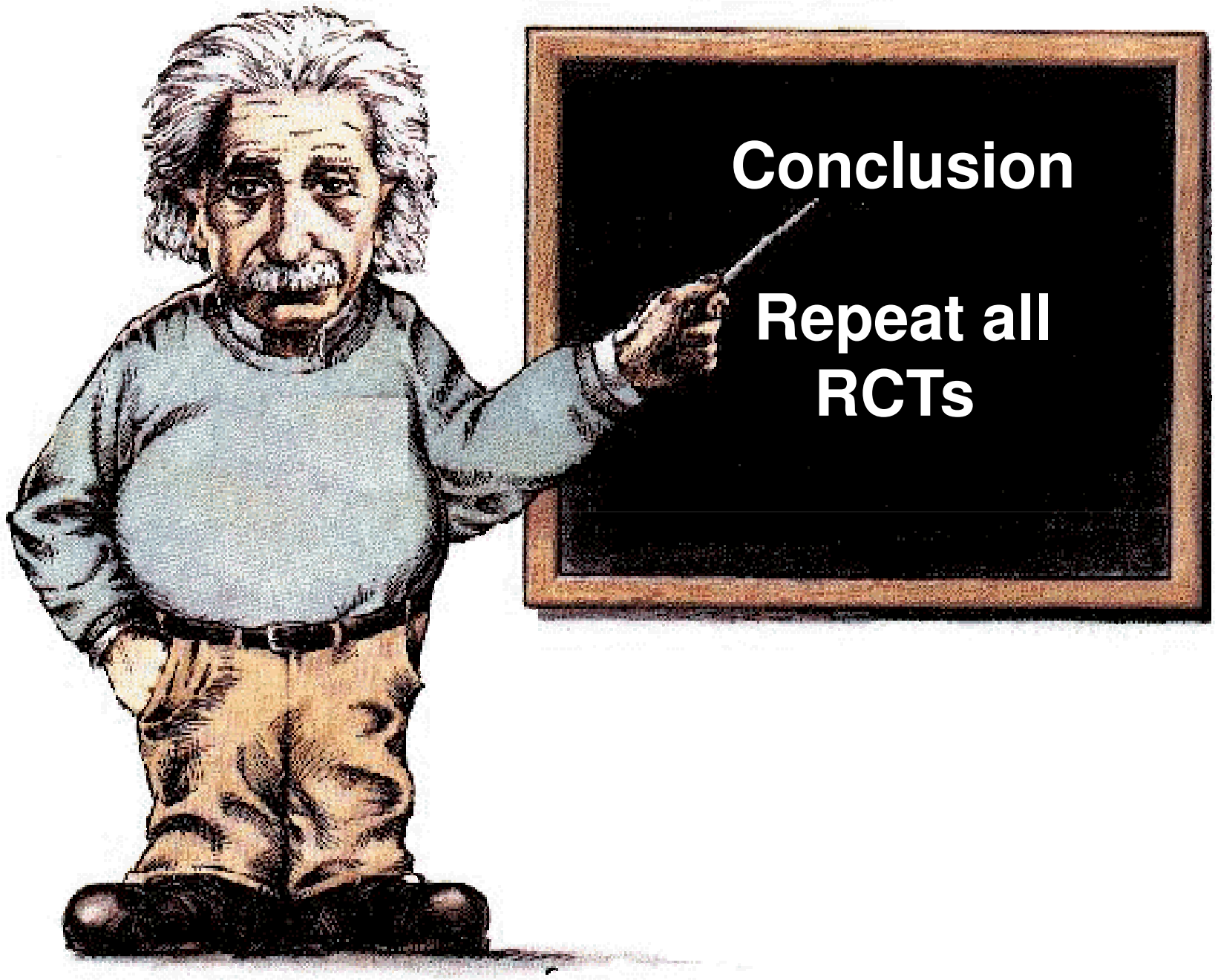


Twerenbold et al, Eur H J 2012

Criteria for high risk with indication for invasive management

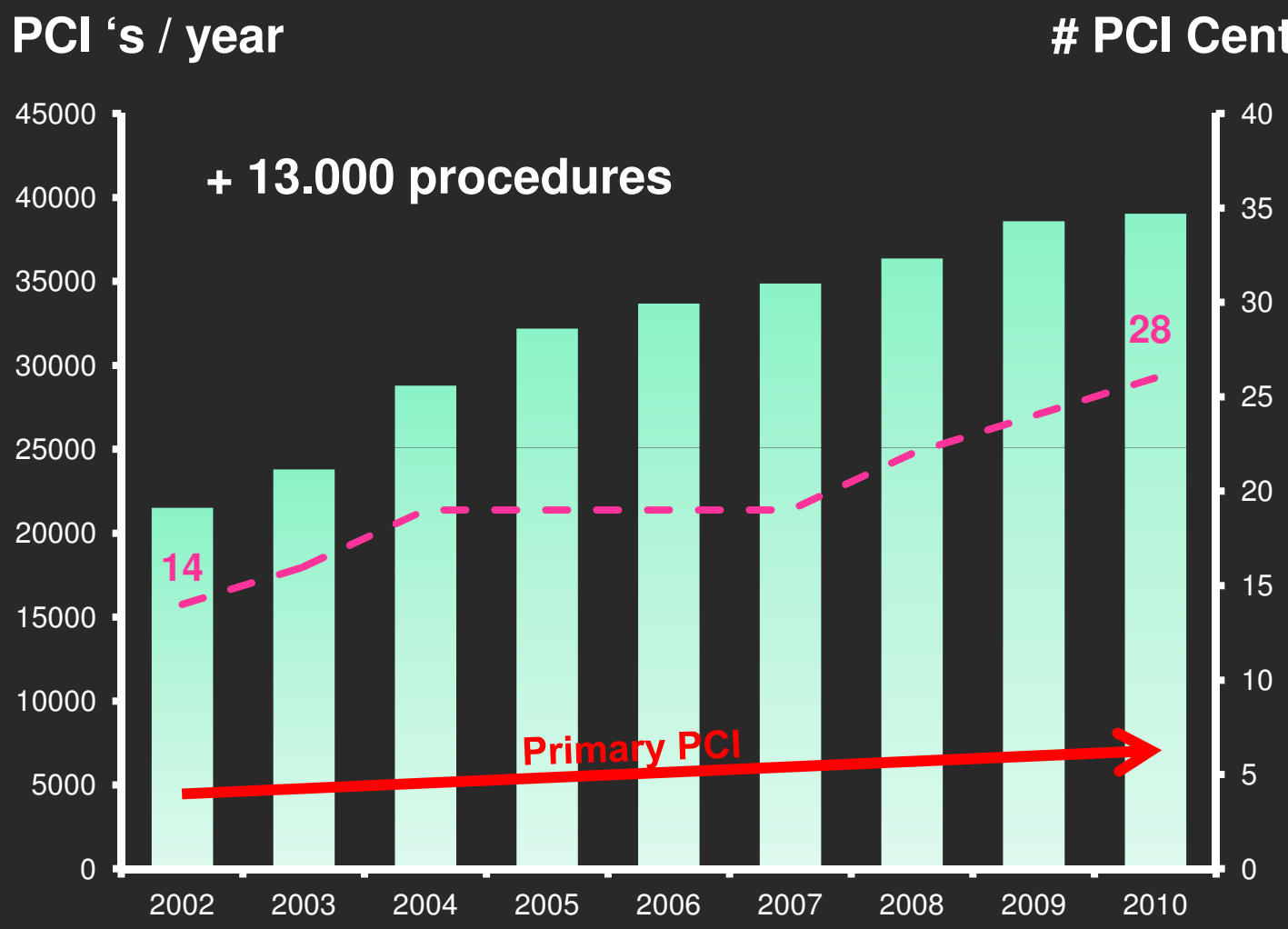
Primary	
• Relevant rise or fall in troponin[a] • Dynamic ST- or T-wave changes (symptomatic or silent)	< 24 hrs
Secondary	
• Diabetes mellitus • Renal insufficiency (eGFR <60 mL/min/1.73 m²) • Reduced LV function (ejection fraction <40%) • Early post infarction angina • Recent PCI • Prior CABG • Intermediate to high GRACE risk score (*Table 5*)	< 72 hrs

"The only thing that interferes with my learning is my education."



"The only thing that interferes with my learning is my education."

Number of PCI's procedures and PCI-centers in the Netherlands



Source: BHN Nederland

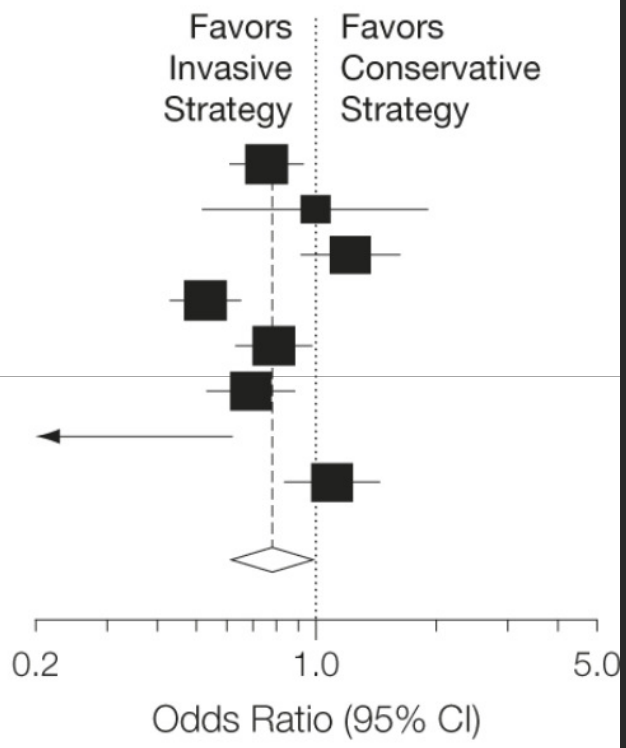
Revascularization in nSTE-ACS 2012

- **Invasive strategy after risk stratification**
  - √ most patients
- **Reduction in death or MI**
  - √ mortality reduction modest
- **Reduction length of stay**
- **Improvements in pharmacology & stents & hs-Troponins**
  - √ has not been tested


Academisch Medisch Centrum
Thank You

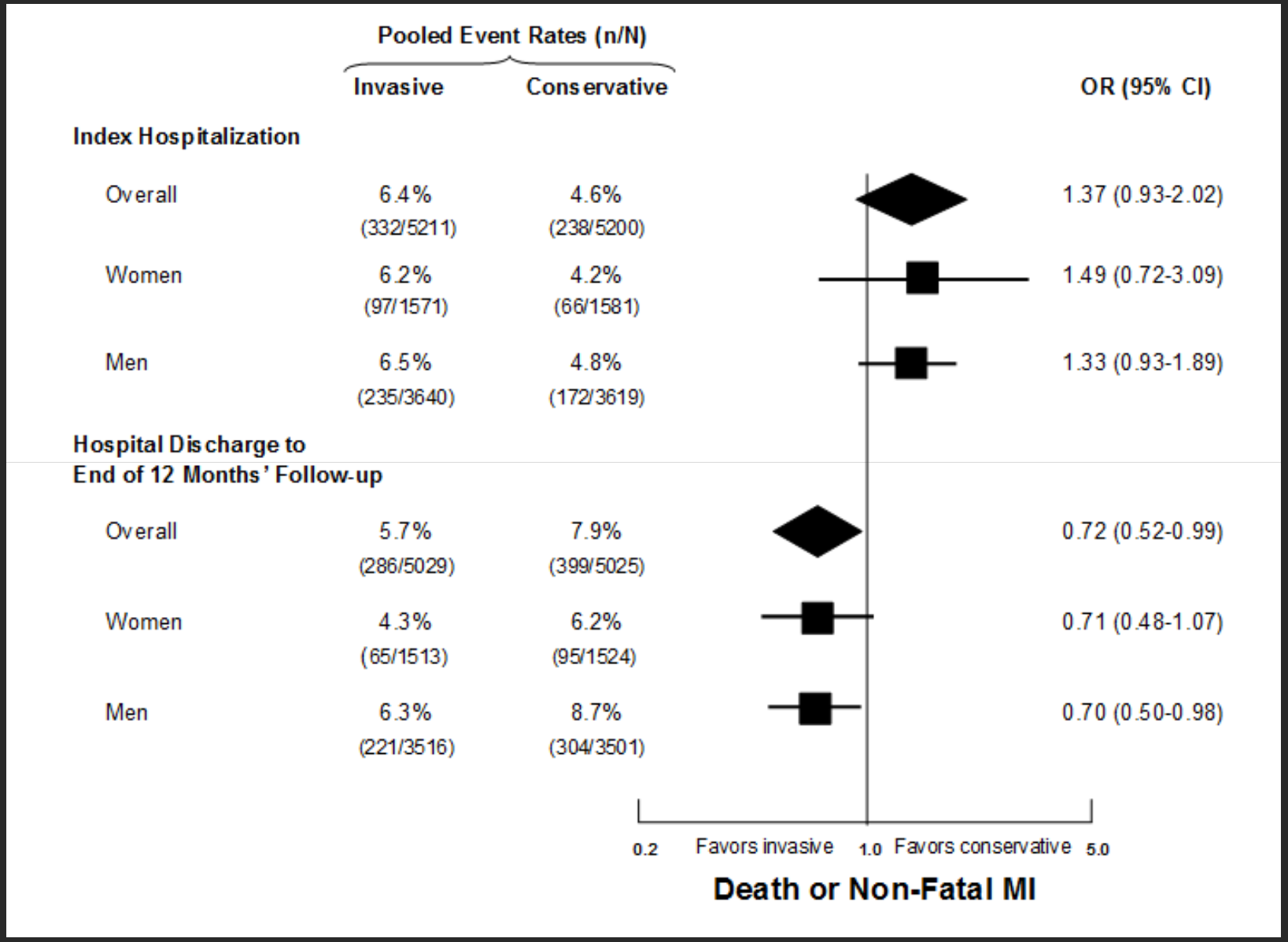
Gender and revascularization in nSTE-ACS

All Patients	Rates of Death, MI, or Rehospitalization With ACS, No./Total No. (%)		Odds Ratio (95% CI)
	Invasive Strategy	Conservative Strategy	
TIMI IIIB[10]	122/895 (13.6)	171/915 (18.7)	0.75 (0.61-0.93)
MATE[11]	27/111 (24.3)	22/90 (24.4)	0.99 (0.52-1.90)
VANQWISH[18]	148/462 (32.0)	124/458 (27.7)	1.22 (0.92-1.61)
FRISC II[1]	196/1093 (17.9)	322/1102 (29.2)	0.53 (0.43-0.65)
TACTICS-TIMI 18[7]	177/1114 (15.9)	215/1106 (19.4)	0.78 (0.63-0.97)
RITA 3[2]	122/895 (13.6)	171/915 (18.7)	0.69 (0.53-0.88)
VINO[20]	5/64 (7.8)	19/67 (28.4)	0.21 (0.07-0.62)
ICTUS[8]	137/604 (22.7)	126/596 (21.1)	1.09 (0.83-1.44)
Overall	1075/5083 (21.1)	1313/5067 (25.9)	0.78 (0.61-0.98)



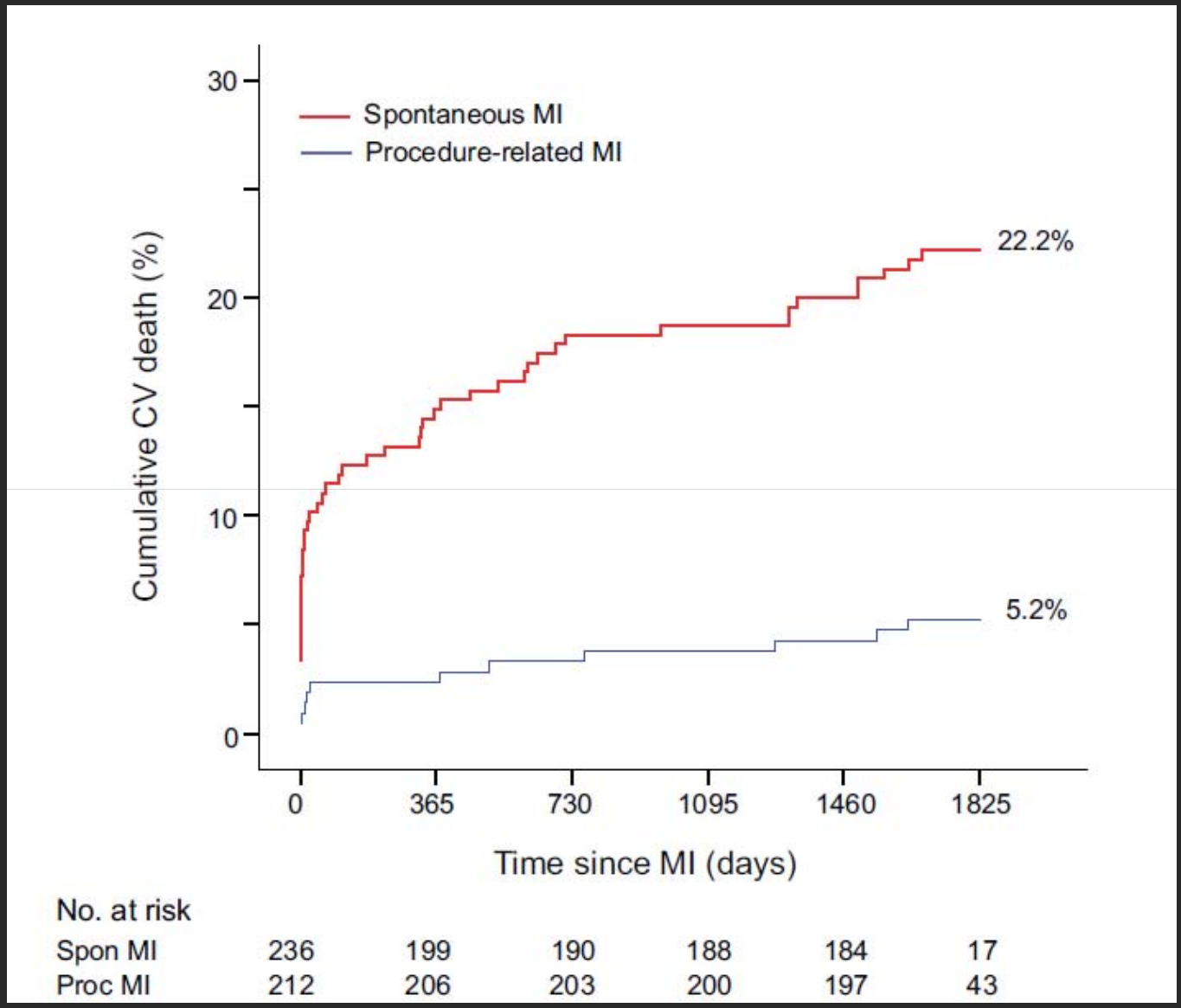
O'Donoghue et al. JAMA. 2008 Jul 2;300(1):71-80

Gender and revascularization in nSTE-ACS



O'Donoghue et al. JAMA. 2008 Jul 2;300(1):71-80

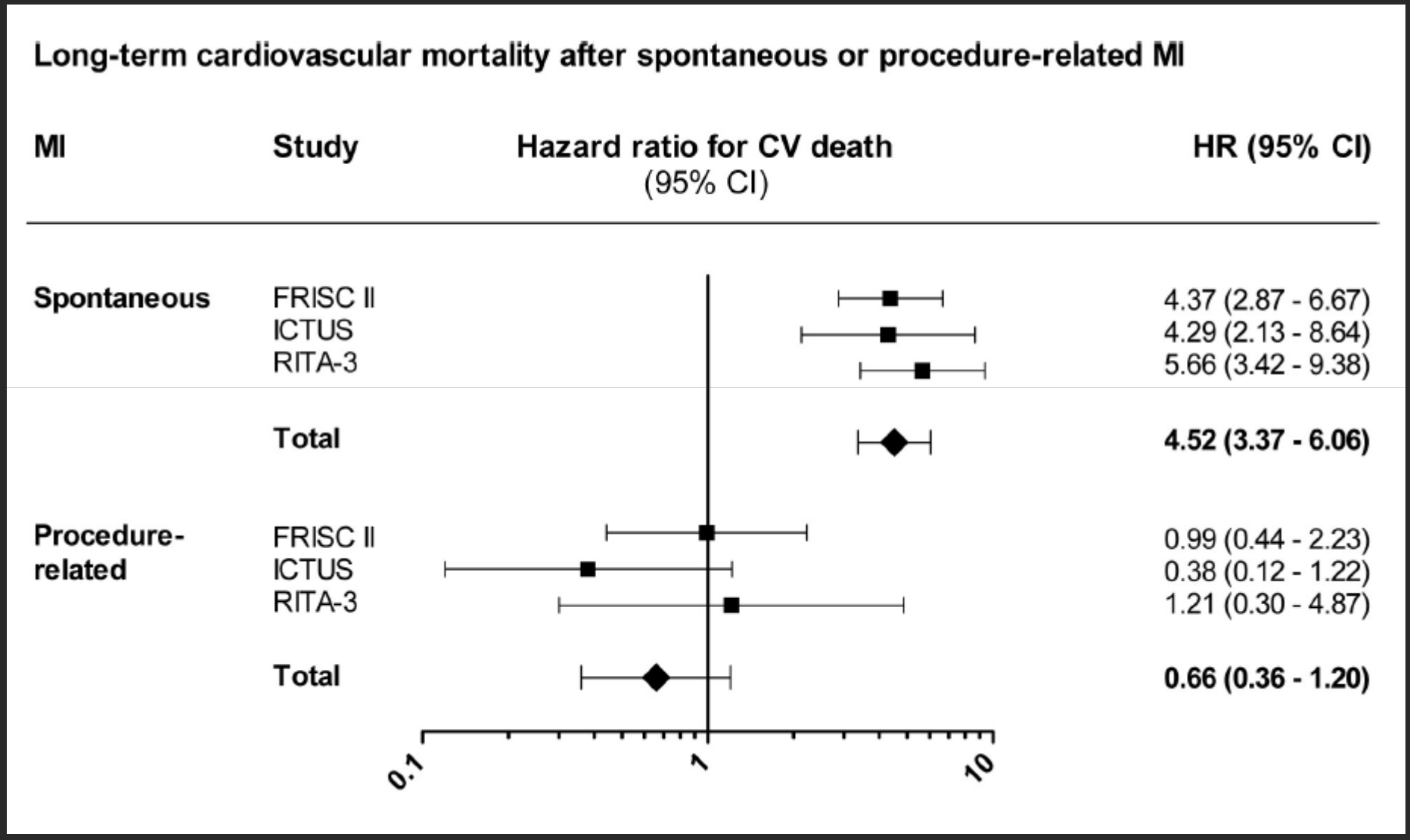
Prognosis after procedure related MI



Damman et al. *Circulation.* 2012;125:568-576

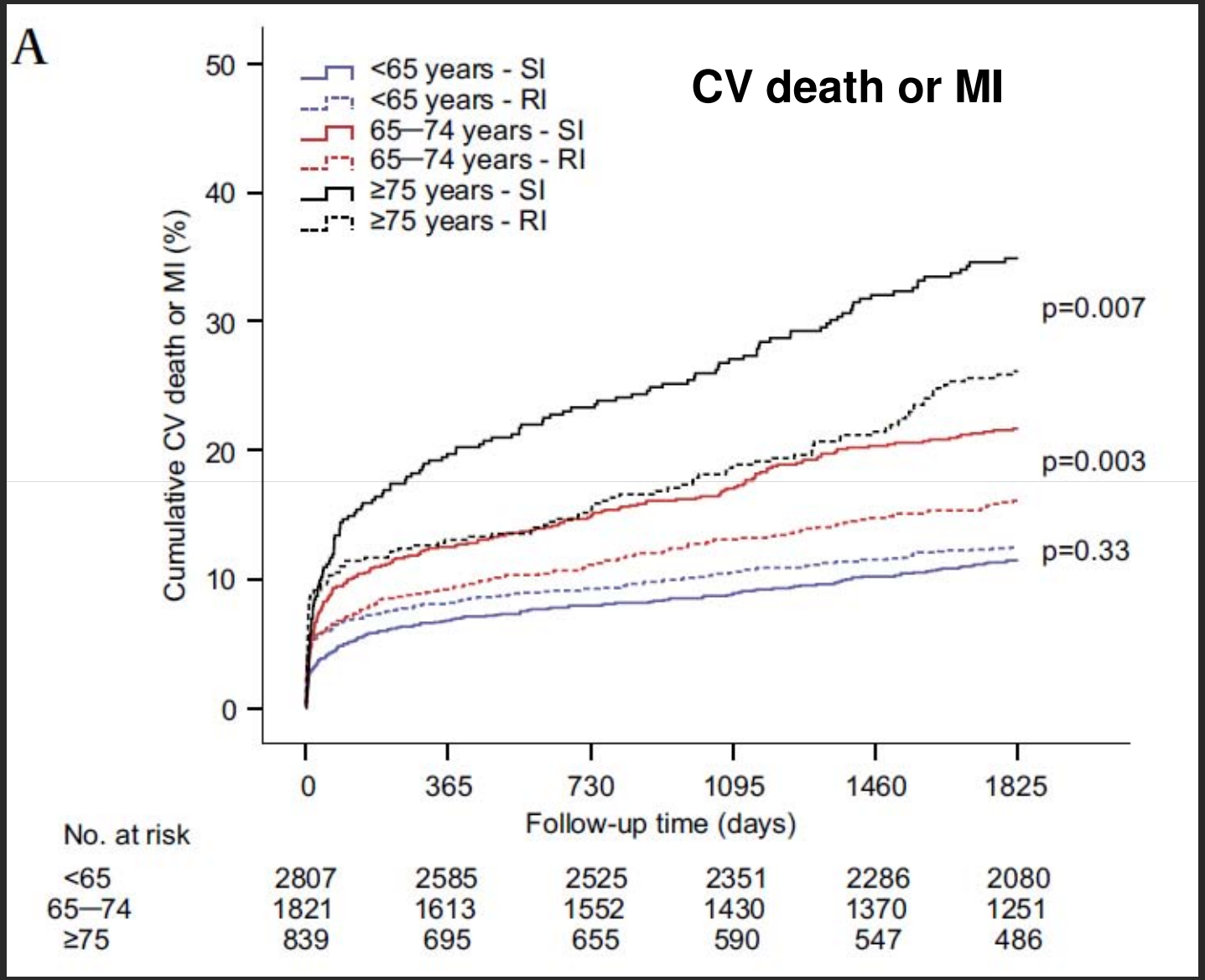
Prognosis after procedure related MI

Long-term cardiovascular mortality after spontaneous or procedure-related MI



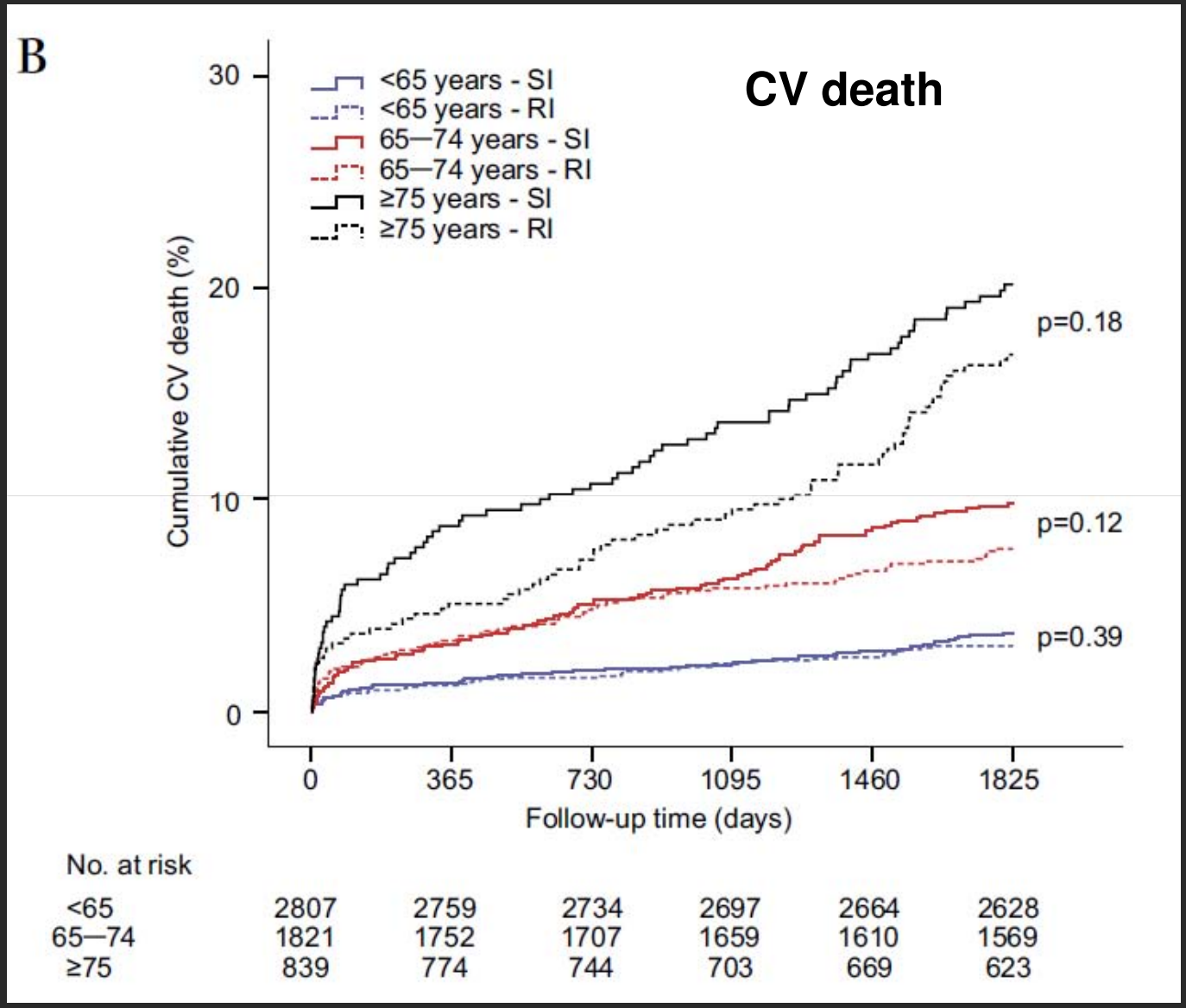
Damman et al. *Circulation.* 2012;125:568-576

Age and revascularization in nSTE-ACS



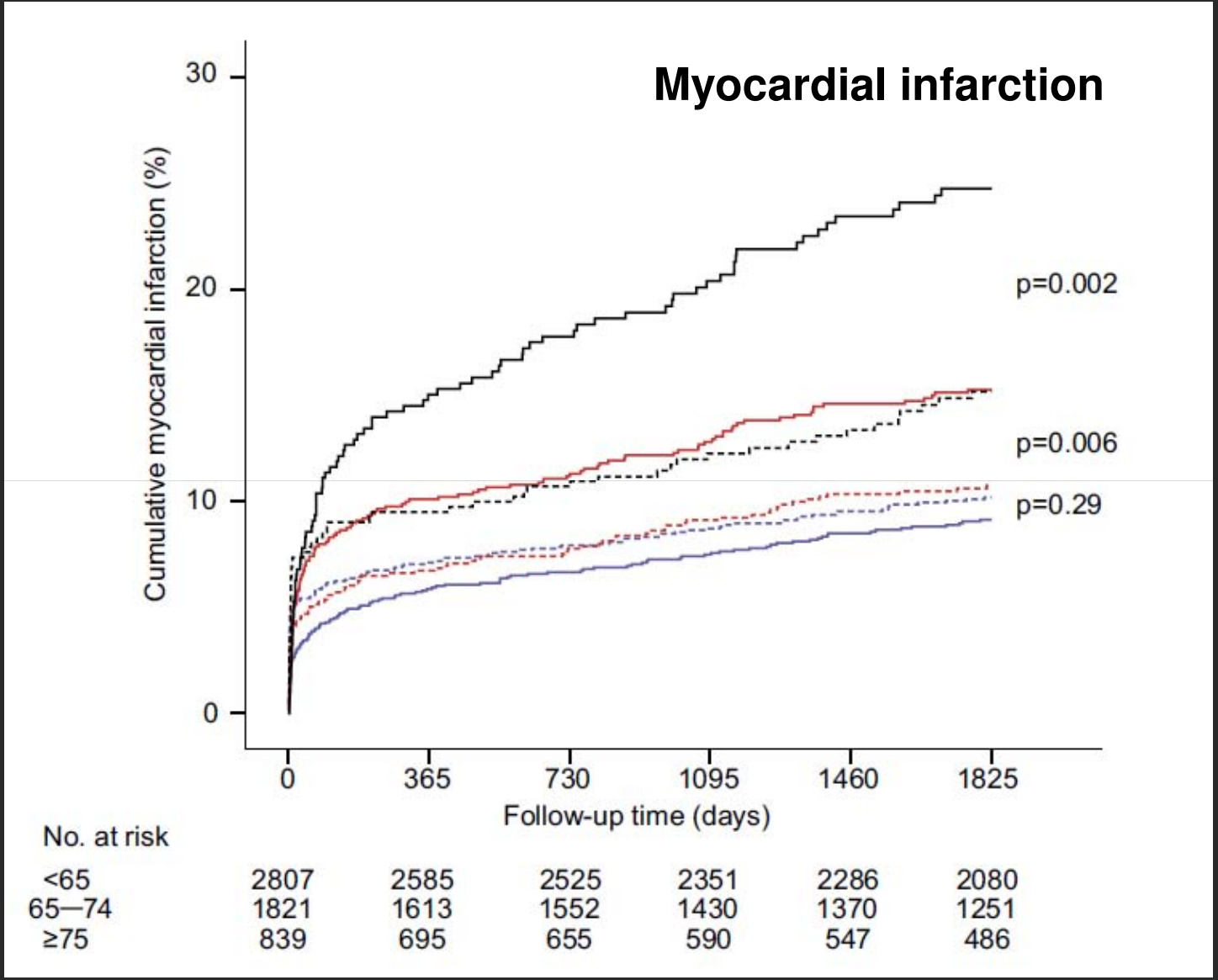
Damman et al. Heart 2012;98:207-213

Age and revascularization in nSTE-ACS



Damman et al. Heart 2012;98:207-213

Age and revascularization in nSTE-ACS



Damman et al. Heart 2012;98:207-213