Acute Coronary Syndromes with non ST Segment Elevation

INVASIVE, CONSERVATIVE, ROUTINE INVASIVE, SELECTIVE, DELAYED, RAPID, ULTRA-RAPID MANAGEMENT

WHEN, WHO, HOW?

CRITICAL REVIEW OF "INVASIVE-CONSERVATIVE" STUDIES IN ACS WITH NON ST SEGMENT ELEVATION (NSTE)

TIMI III-B: Carried out between 1989 & 1992. Study without validity.

VANQWISH: Criticized for high surgical mortalitly. It does not use new drugs. It only included NSTEMI.

FRISC-2: Surgical mortality is so low that it seems impossible to reproduce.

TACTICS: All with tirofiban. Very low surgical mortality.

OASIS REGISTRY: Con: not randomized. Pro: it reflects the real world.

FRISC II: Fragmin and fast Revascularization during InStability in Coronary artery disease
- INVASIVE TREATMENT: TRIAL DESIGN cont. -

Patients
2457 (median age 66 years) entered invasive vs. non-invasive arm

Follow up and primary endpoint
Composite endpoint death or MI at 6 months

Treatment
- All patients: placebo-controlled dalteparin for 3 months
- Patients randomized to early invasive treatment:
    - coronary angiography
    - revascularization within 7 days if 70% obstruction of any artery supplying substantial part of myocardium
- Patients randomized to non-invasive treatment considered for invasive treatment on basis of exercise test and, during follow up, in setting of incapacitating symptoms, recurrence of instability or MI

FRISC II: Fragmin and fast Revascularization during InStability in Coronary artery disease
- INVASIVE TREATMENT: RESULTS cont. -

Death or MI at 6 months

	Invasive	Non-invasive	Risk ratio (95% CI)	P
Death, MI or both*	113 (9.4%)	148 (12.1%)	0.78 (0.62– 0.98)	0.031
MI	94 (7.8%)	124 (10.1%)	0.77 (0.60– 0.99)	0.045
Death	23 (1.9%)	36 (2.9%)	0.65 (0.39– 1.09)	0.10

* In invasive group, 6 (0.5%) events occurred before randomized revascularization
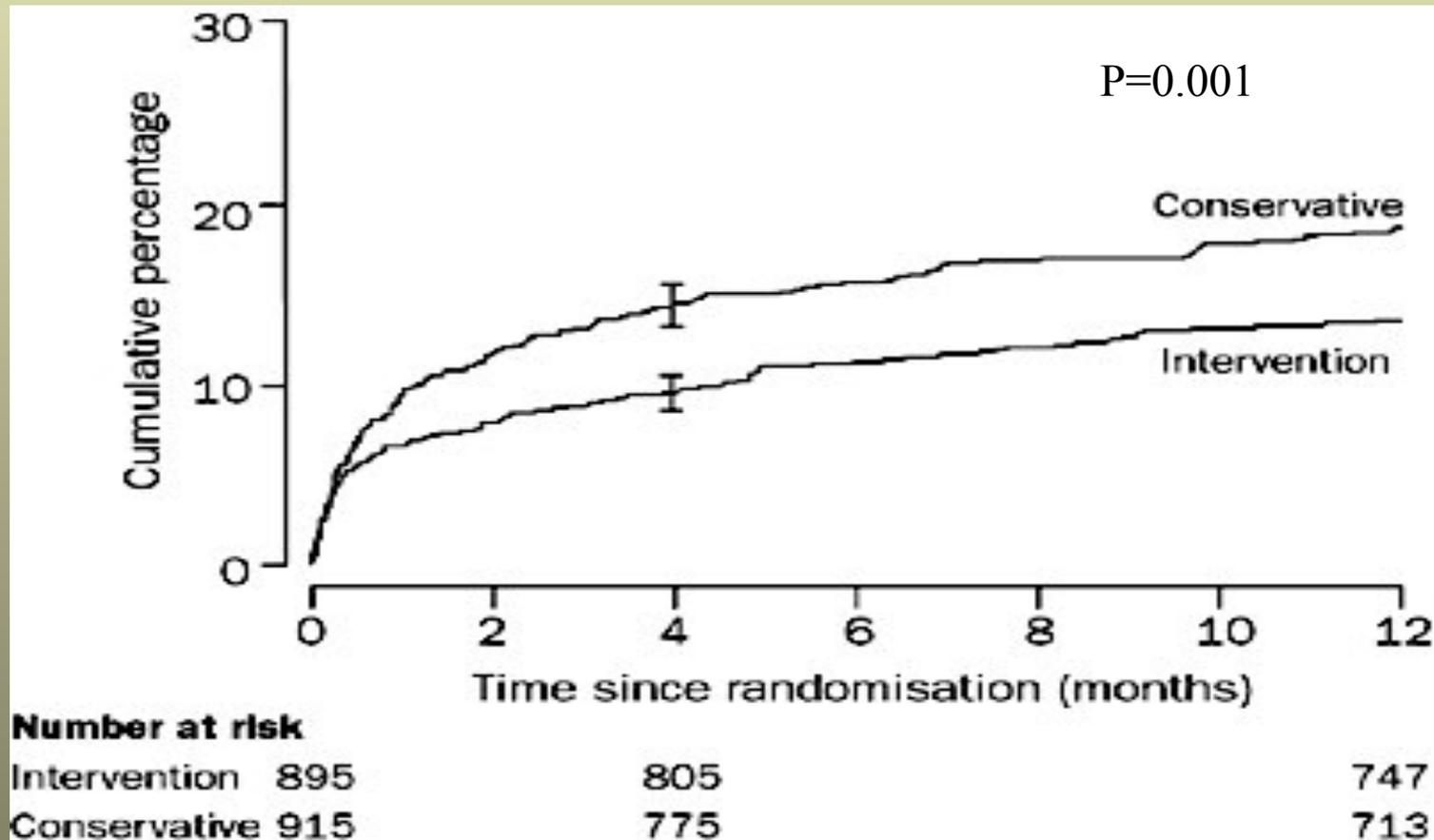
Invasive or conservative strategy
The RITA-3 study
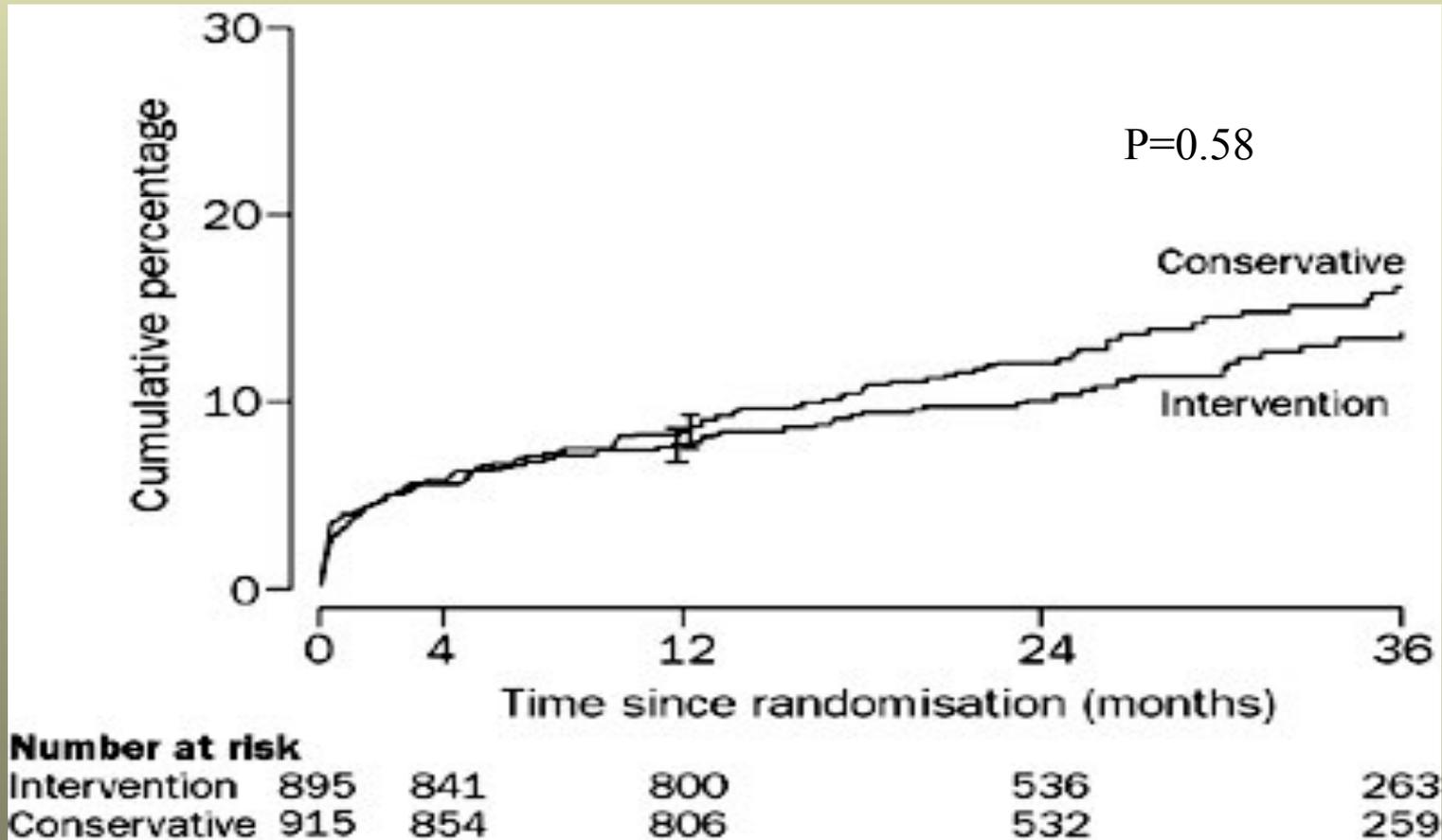# Time up to 1st revascularization
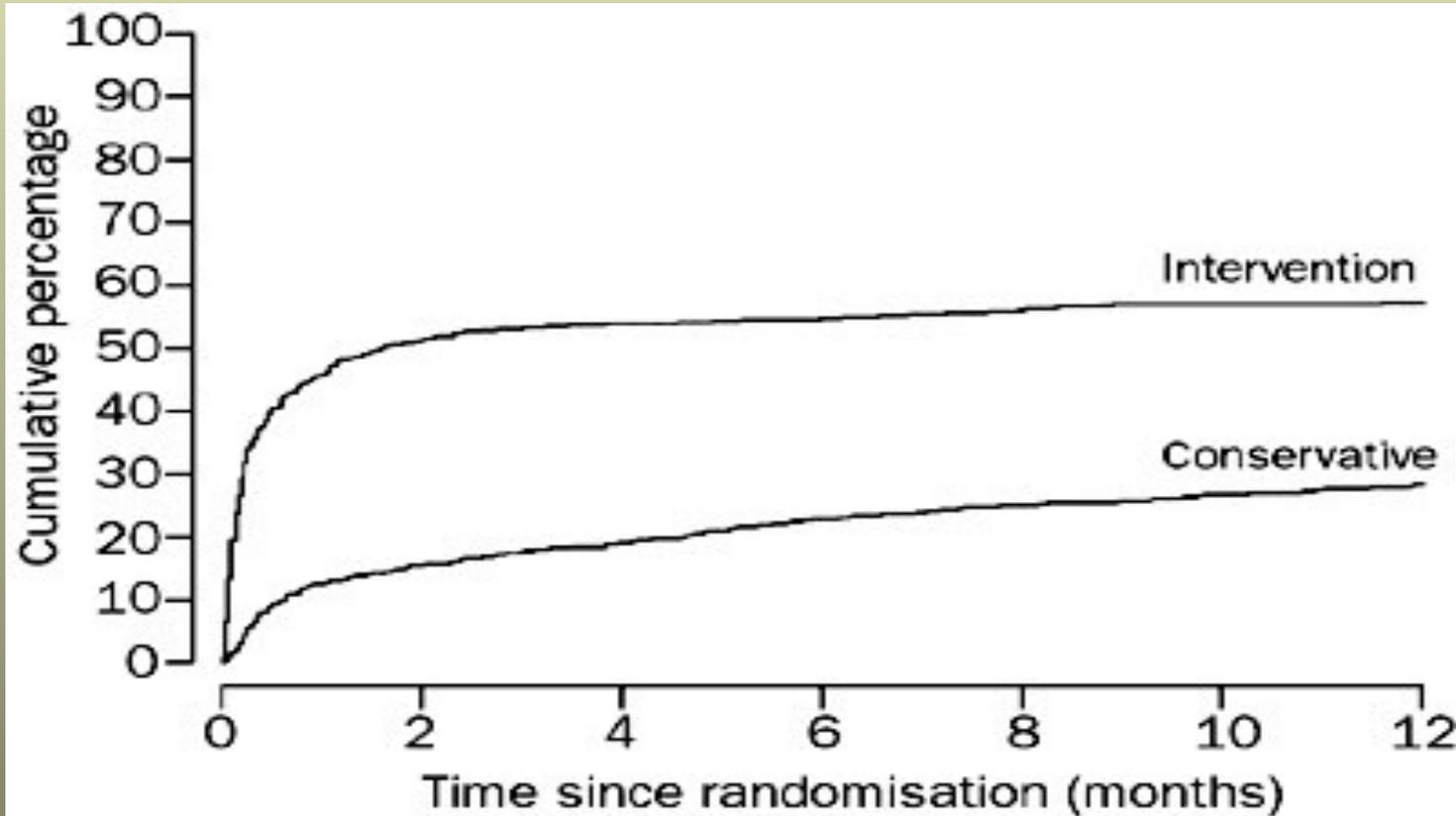
Invasive or conservative strategy
The RITA-3 study
Incidence of AMI, death, or refractory angina

Invasive or conservative strategy
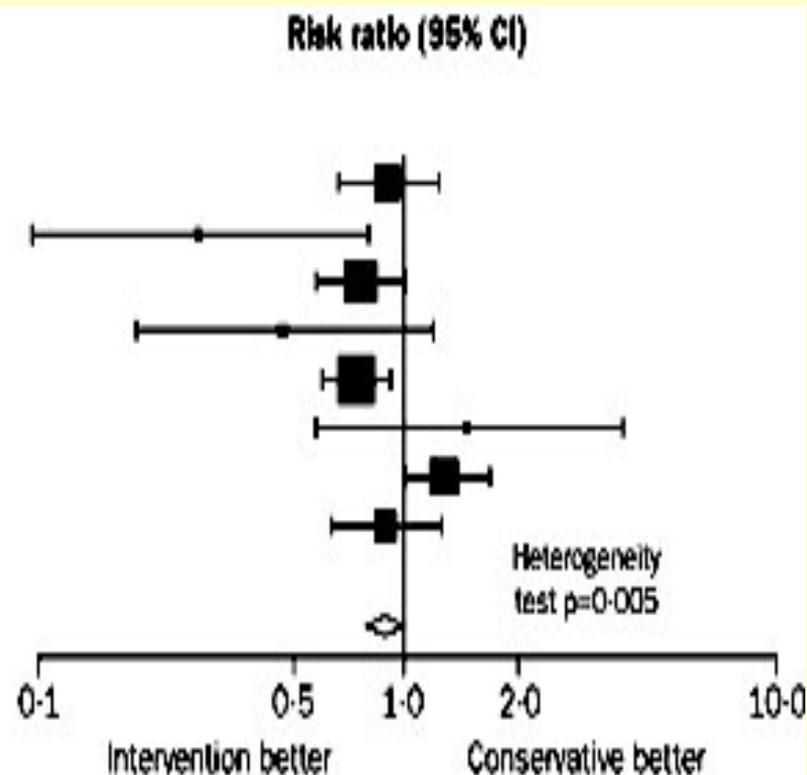# The RITA-3 study
Incidence of AMI or death

Invasive or conservative strategy Comparison of 3 studies

	RITA-3	TACTICS	FRISC-2
N	1810	2220	2457
Term	1997-2001	1997-1999	1996-1998
Age	62	62	65
Depress. ST	37 %	39 %	46 %
+ markers	18 %	37 %	57 %
Death or AMI	7.9 %	8.4 %	12.2 %

Infarction or death at one year in studies of invasive vs conservative treatments

	Number of deaths or MIs within 1 year		**Risk ratio (95% CI)**
	Intervention	**Conservative**	
RITA 3	68/895 (7·6%)	76/915 (8·3%)	
VINO*	4/64 (6·3%)	15/67 (22·4%)	
TACTICS-TIMI 18	81/1114 (7·3%)	105/1106 (9·5%)	
TRUCS	6/76 (7·6%)	12/72 (16·7%)	
FRISC II	127/1219 (10·4%)	174/1234 (14·1%)	
MATE	11/111 (9·9%)	6/90 (6·7%)	
VANQWISH	111/462 (24·0%)	85/458 (18·6%)	
TIMI IIIB	52/484 (10·8%)	62/509 (12·2%)	

Combined risk ratio 0·88 (95% CI 0·78–0·99)

Heterogeneity test p=0·005

0·1   0·5   1·0   2·0   10·0

Intervention better   Conservative better

META-ANALYSIS OF ROUTINE VS SELECTIVE INVASIVE STRATEGY IN ACS WITH NSTE (N= 10648)
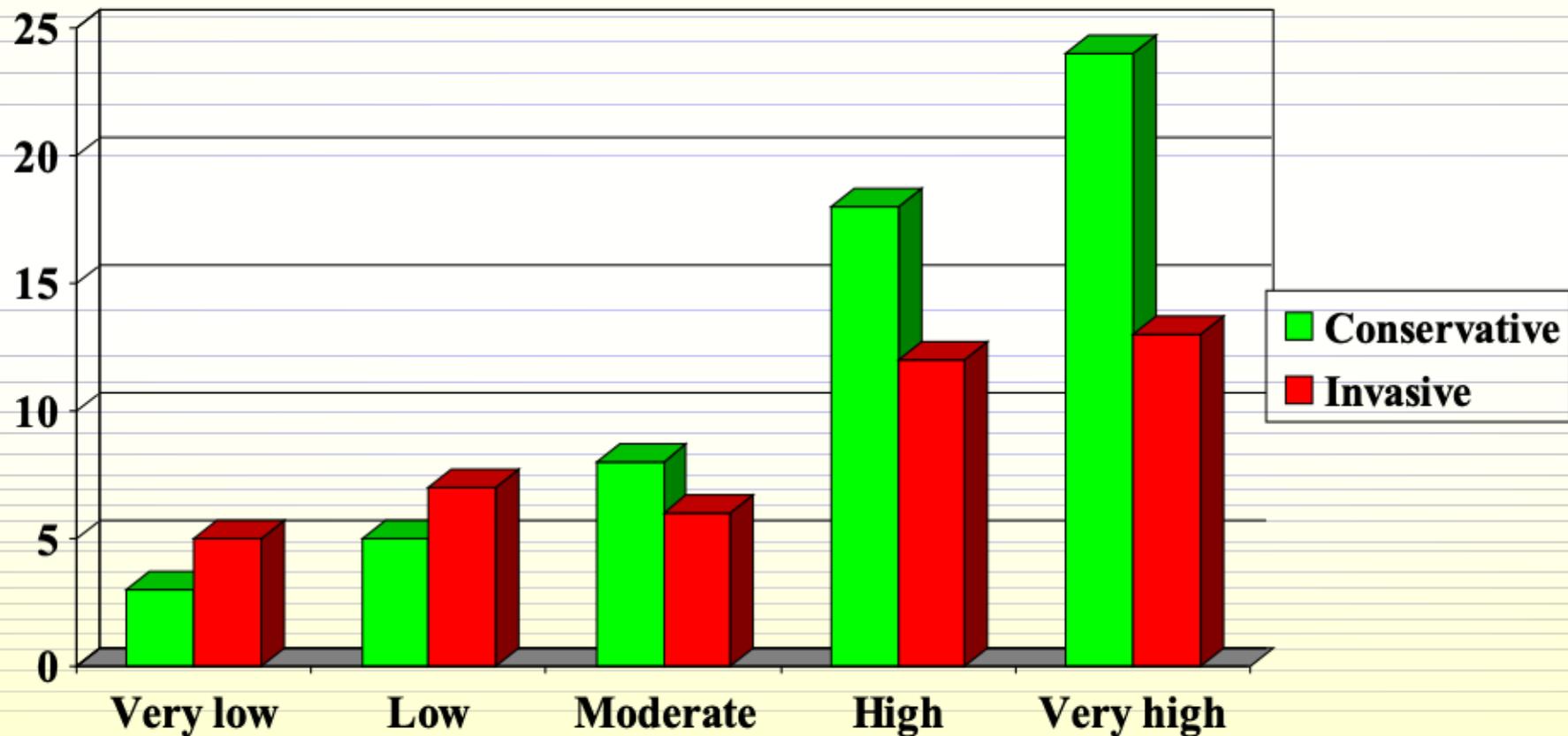
The evidence available is *heterogenous* and *insufficient* to compare routine and selective invasive strategies. So, in patients with NSTE-ACS you cannot state that a routine invasive strategy would reduce mortality or non-fatal infarction.

Quayyum et al; Ann Intern Med 2008; 148:186.

✓ **Routine invasive strategy produces an excess of infarction and death in the acute period (OR: 1.60) that disappears in the long term.**

✓ **It reduces the incidence of AMI in the long term.**

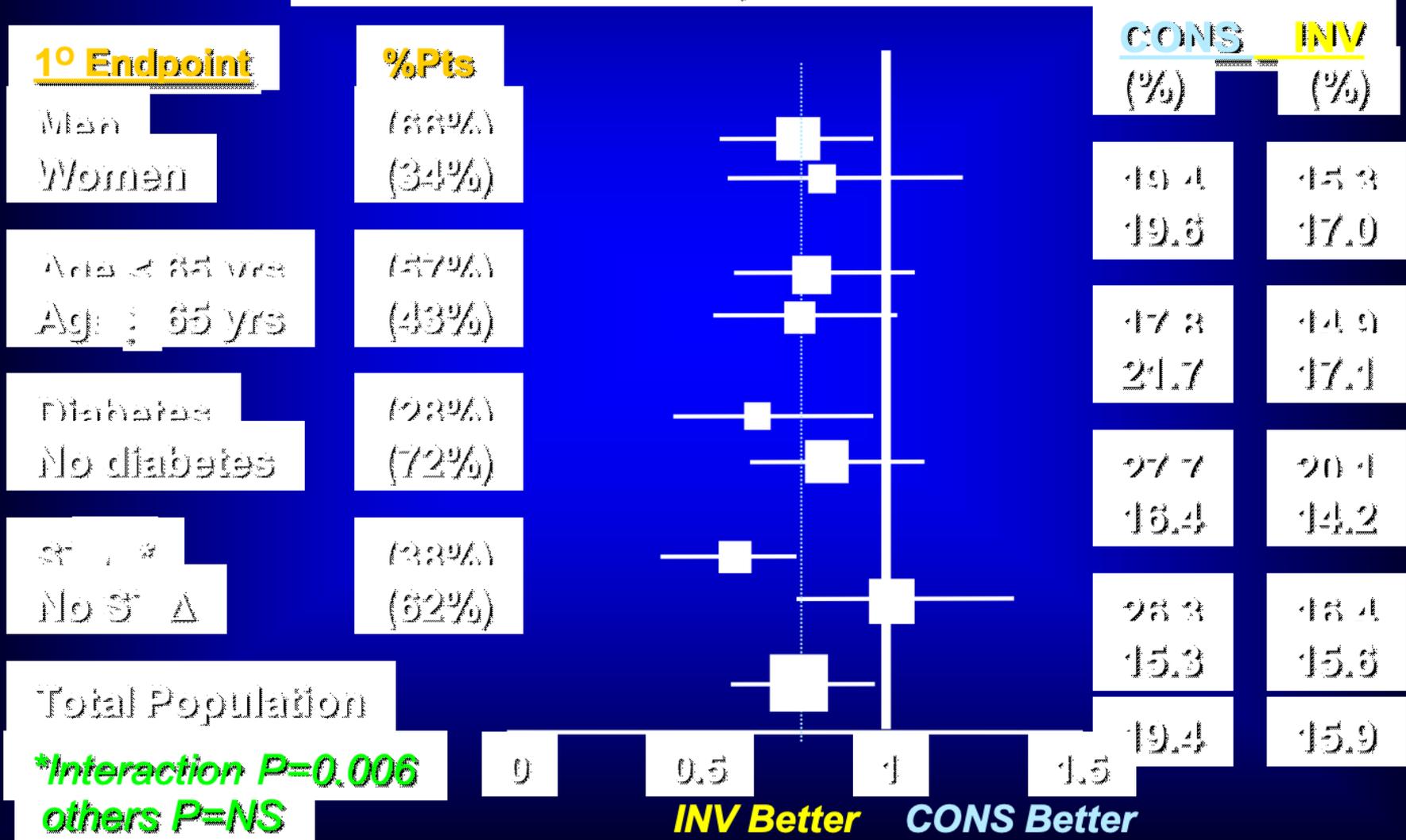✓ **It is also associated to an increase in the possibility of bleeding.**

Study, Year (Reference)	Patients (RIS/SIS), n (n/n)	Patient Enrollment Criteria	Evaluation of Inducible Ischemia in SIS	MI Criteria† Non–Procedure-Related	MI Criteria† Procedure-Related
FRISC-II, 2006 (4)	2457 (1222/1235)	Within 48 h of symptoms of unstable angina with either ECG changes or elevated cardiac enzyme levels	Symptom-limited exercise stress test before discharge	CK-MB mass >ULN in 1 sample or CK, CK-B, or CK-MB activity >2× ULN in 1 sample or >ULN in 2 samples	CK-MB mass >1.5× ULN in 1 sample or CK, CK-B, or CK-MB activity >3× ULN in 1 sample or >1.5× ULN in 2 samples
ICTUS, 2007 (5)	1200 (604/596)	Within 24 h of the onset of symptoms of unstable angina with elevated cardiac enzyme levels and either ECG changes or history of CAD	Predischarge exercise stress test	Elevation in the CK-MB level above ULN	Elevation in the CK-MB level above ULN
MATE, 1998 (6)	201 (111/90)	Typical cardiac chest pain (with or without immediate enzymatic confirmation)	No mandated noninvasive tests scheduled in the conservative group	CK >230 U/L in men, CK >150 U/L in women, and an MB index >3% in both sexes	CK >230 U/L in men, CK >150 U/L in women, and an MB index >3% in both sexes
Eisenberg et al., 2005 (7)	88 (42/46)	Typical cardiac chest pain with ECG changes or elevated cardiac enzyme levels	Exercise stress test with nuclear imaging or echocardiography	Not reported	Not reported
RITA-3, 2005 (8)	1810 (895/915)	Typical cardiac chest pain at rest with ECG changes or history of angiographically proven CAD	No mandated noninvasive tests or schedules in the conservative group	Rise in concentration of ≥1 cardiac enzyme or marker 2× ULN	Rise in concentration of ≥1 cardiac enzyme or marker 2× ULN
TACTICS, 2001 (9)	2220 (1114/1106)	Unstable angina with either ECG changes or cardiac enzyme elevation or history of CAD	Exercise or pharmacologic stress test (mostly with nuclear perfusion imaging or echocardiography)	CK-MB >ULN and >50% over previous value	CK-MB >3× ULN and >50% over previous value
TIMI IIIB, 1995 (10)	1473 (740/733)	Typical chest discomfort at rest and either ECG changes or documented history of CAD within 24 h of enrollment	Abnormal predischarge modified Bruce protocol stress thallium exercise test	CK-MB >ULN or total CK >2× ULN	CK-MB >ULN or total CK >2× ULN
TRUCS, 2000 (11)	148 (76/72)	CCU patients with class IIIb and IIIc refractory unstable angina, despite "optimal" medical treatment for 48 h	No mandated noninvasive tests	CK-MB mass >ULN	CK-MB mass 1.5× ULN
VANQWISH, 1998 (12)	920 (462/458)	Evolving acute MI, cardiac enzyme elevation, and no new abnormal Q waves (or R waves) on serial ECGs	Symptom-limited treadmill exercise or pharmacologic stress test with nuclear imaging	CK >2× ULN or CK-MB >ULN	CK >2× ULN or CK-MB >ULN
VINO, 2002 (13)	131 (64/67)	Within 24 h of symptoms of unstable angina, ECG changes, and elevated cardiac enzyme levels	Symptom-limited exercise or pharmacologic stress test with nuclear imaging	CK-MB >1.5× ULN	Not diagnosed in first 72 h

Rate of infarction or death at 42 days according to risk category (Solomon et al)
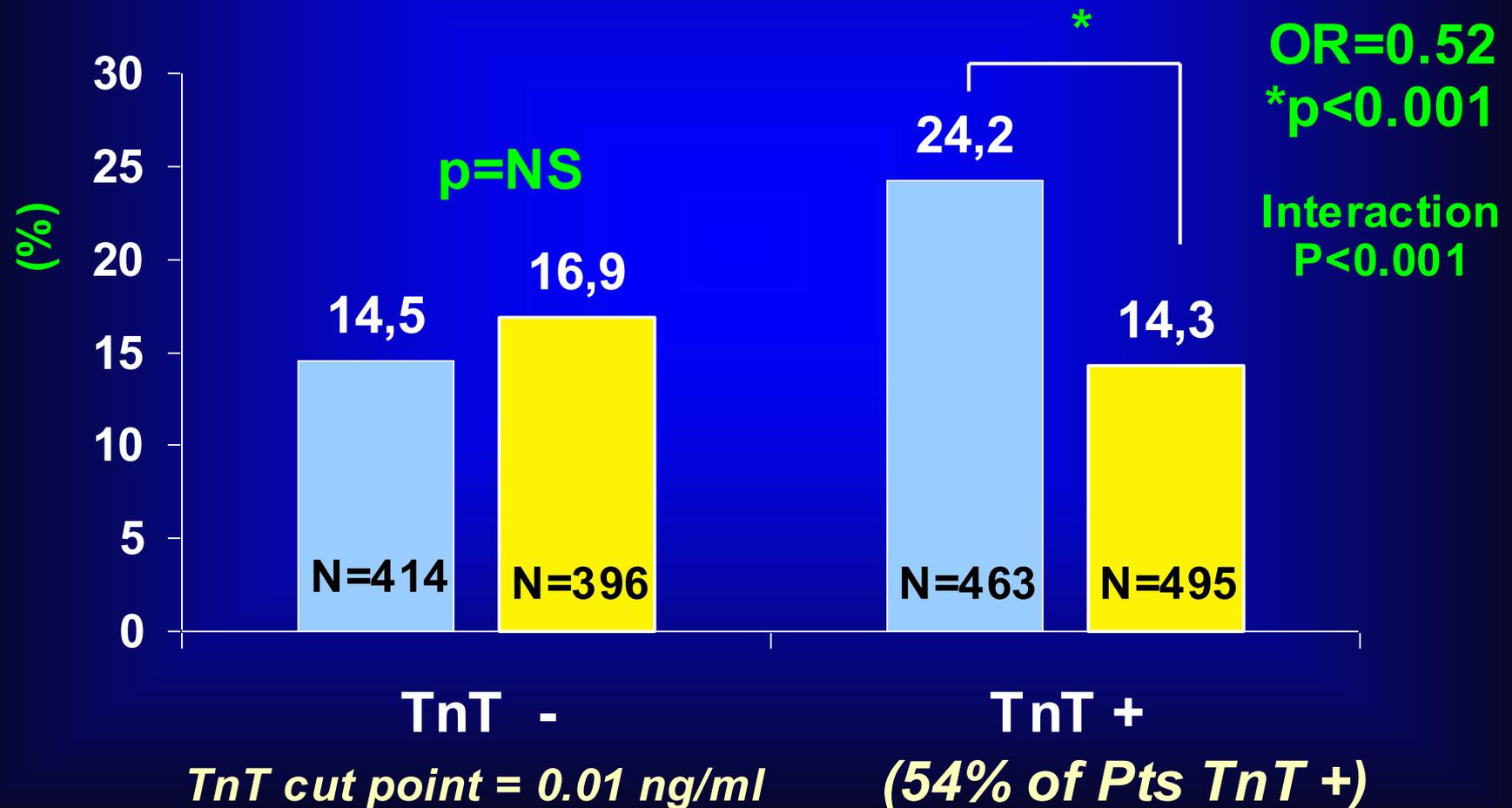
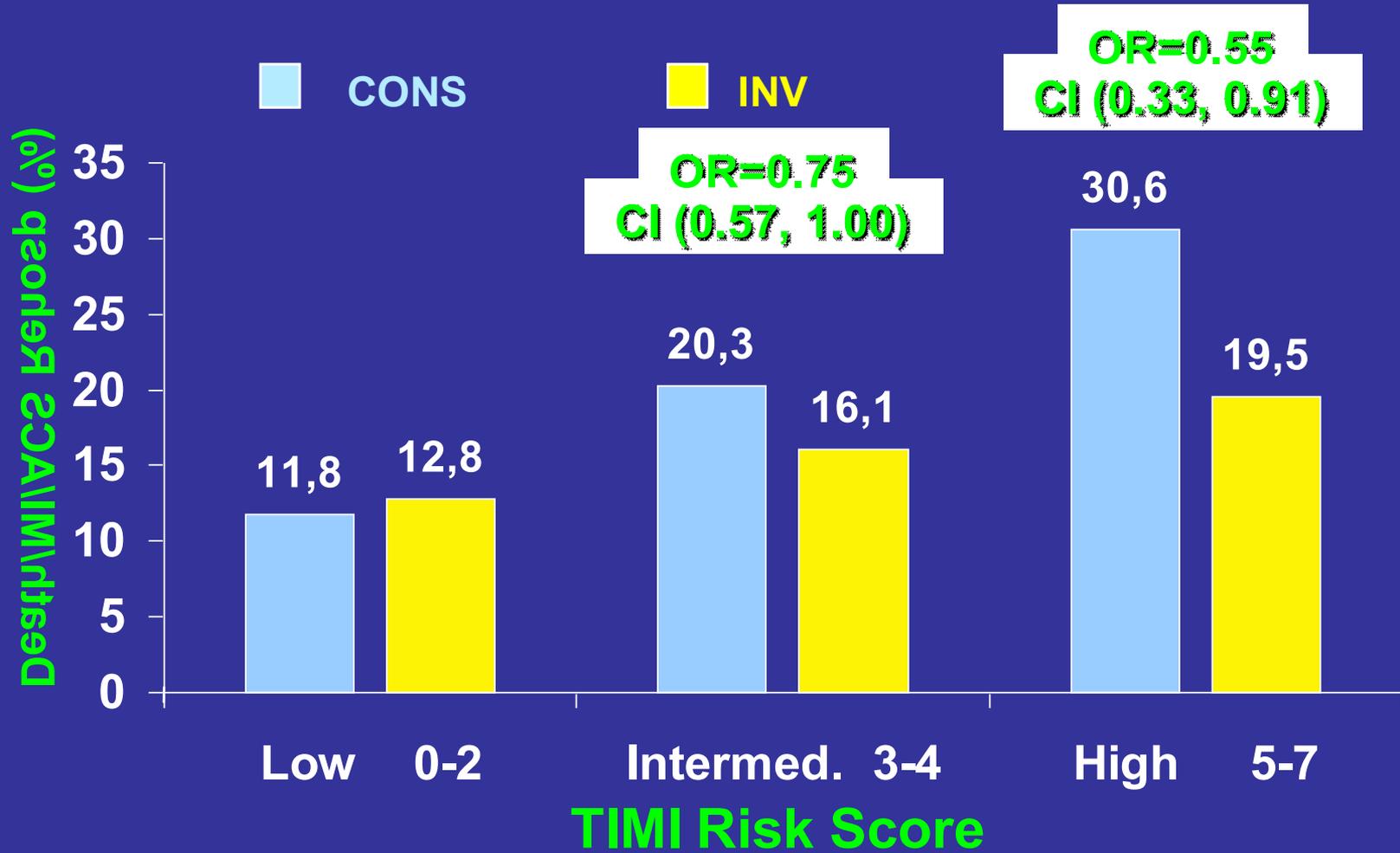# TACTICS: Subgroups: Primary Endpoint

Death, MI, Rehosp ACS at 6 Months

1° Endpoint	%Pts		CONS (%)	INV (%)
Men	(66%)		19.4	15.3
Women	(34%)		19.6	17.0
Age < 65 yrs	(57%)		17.8	14.9
Age ≥ 65 yrs	(43%)		21.7	17.1
Diabetes	(28%)		27.7	20.1
No diabetes	(72%)		16.4	14.2
ST ↑ *	(38%)		26.3	16.4
No ST Δ	(62%)		15.3	15.6
Total Population			19.4	15.9

0   0.5   1   1.5

INV Better   CONS Better

*Interaction P=0.006
others P=NS

FRISC II: Death or infarction at 12 months according to ECG and troponin

Variable	n	Invasive (%)	Non invasive (%)	p
Non ST & TnT < 0.03	431	6.2	8.8	NS
↓ST & TnT < 0.03	301	9.2	8.1	NS
Non ST & TnT ≥ 0.03	799	10.2	11.3	NS
↓ST & TnT ≥ 0.03	753	13.2	22.1	0.001

EARLY INVASIVE VS SELECTIVE INVASIVE ICTUS STUDY

- 1200 patients with angina over the last 24 hs and *high* troponin T.
- Randomized to:
- A) Early invasive strategy: CAG in 24-48 hs and PTCA in less than 48 hs or CABG as soon as possible.
- B) Selective invasive strategy: medical stabilization and CAG/CABG in case of refractory angina and ischemia in pre-discharge test.
- Primary end point: death, AMI, or rehospitalization by ACS at 1 year.
- Medical management: ASA, LMWH, BBs, nitrates, clopidogrel, and statins. Abciximab in PTCA.

European Congress of Cardiology 2004

ICTUS: End points at one year

| End point	Early invasive (%)	Selective invasive (%)	Relative risk	p
Primary end point (composite)	21.7	20.4	1.06	0.59
Death	2.2	2.0	1.07	0.86
New or recurrent AMI	14.6	9.4	1.55	0.006
Rehosp by ACS	7.0	10.9	0.63	0.017

the heart.org
CARDIOLOGY ONLINE

Prevalence of risk groups according to Solomon's score

ACP
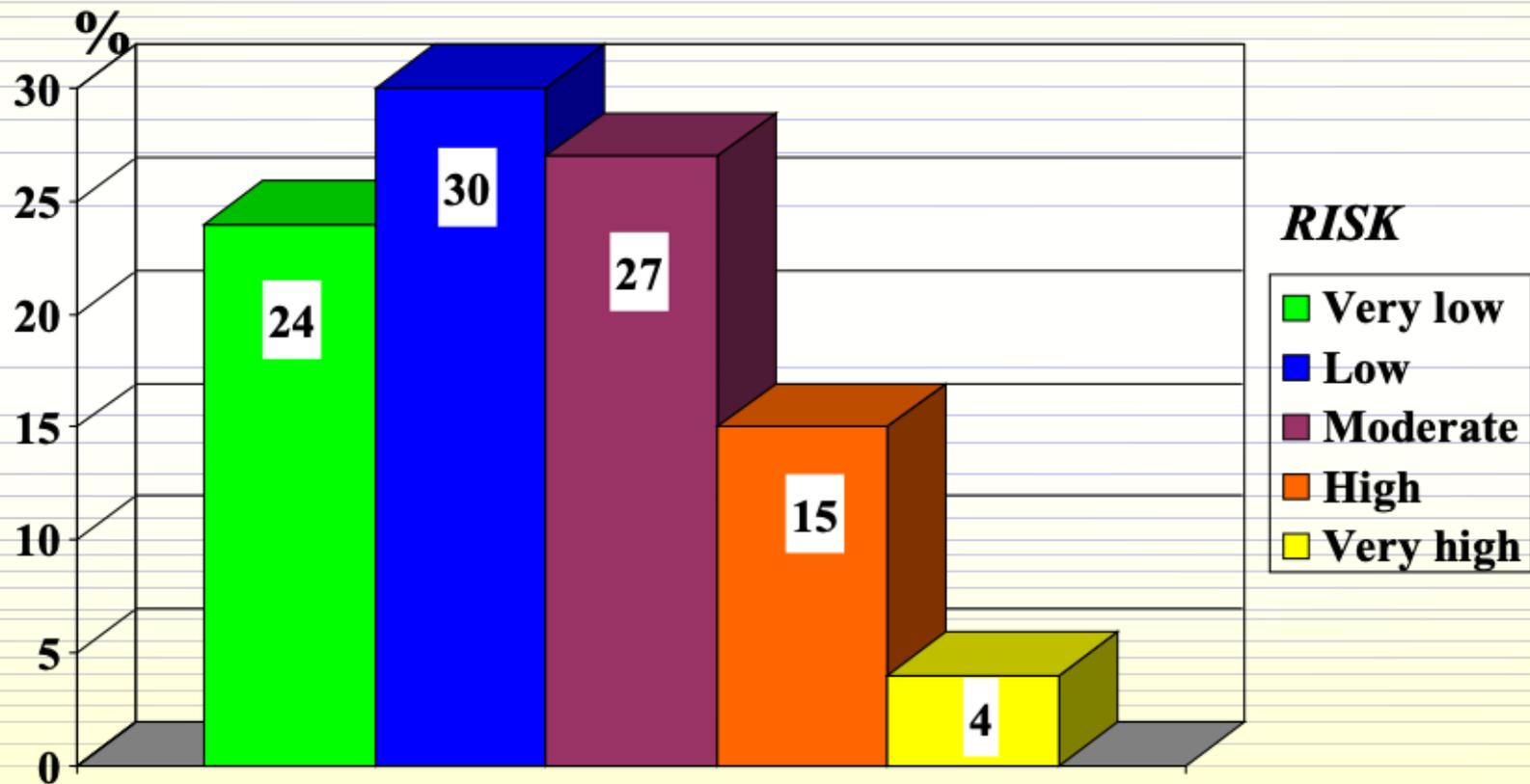
DISTRIBUTION OF RISK GROUPS IN VALIDATION PHASE (red) AND TOTAL POPULATION (green) D.I.C. SCORE
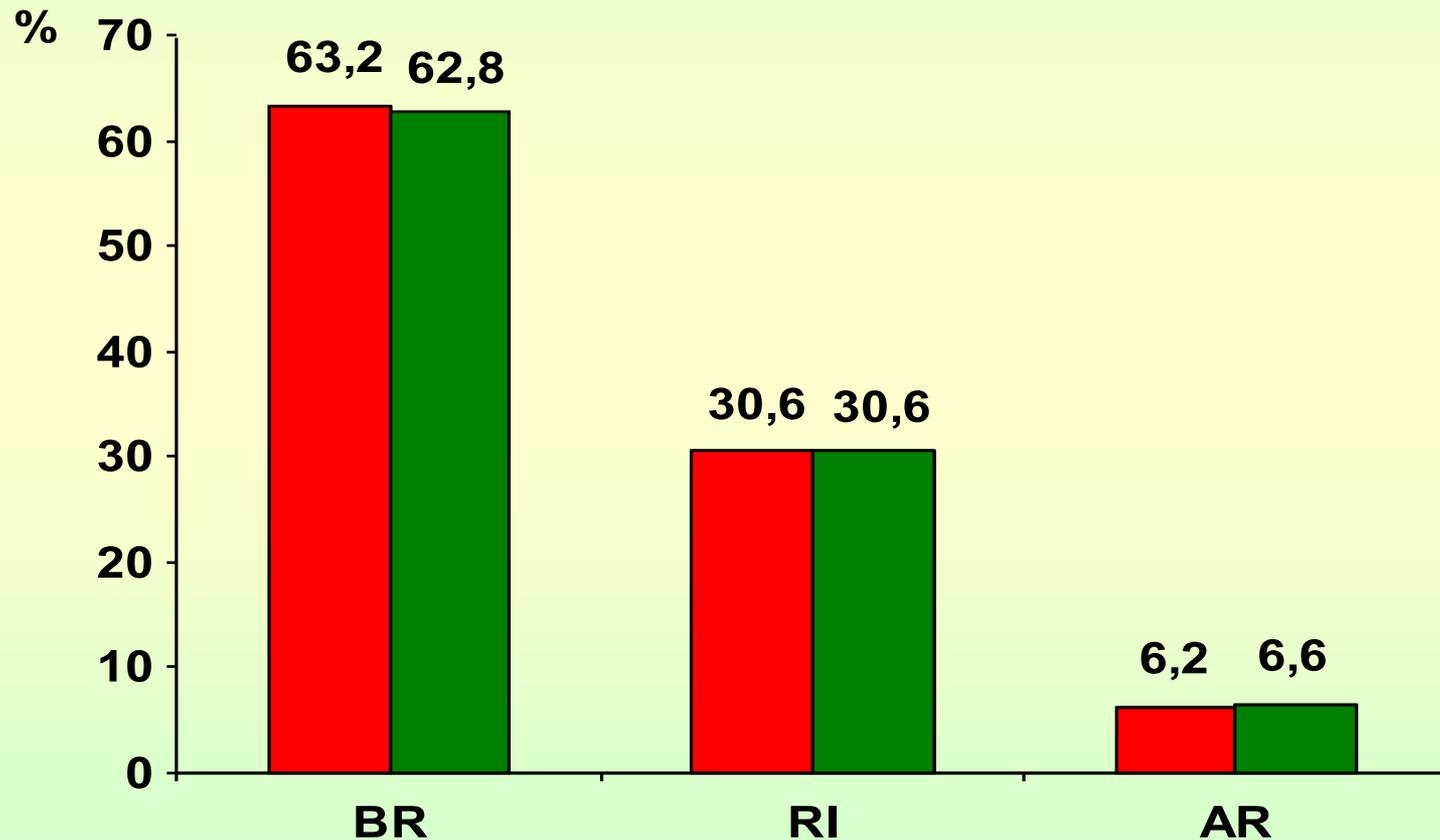
INCIDENCE OF TRIPLE (blue) AND DOUBLE (orange) END POINT IN THE TOTAL POPULATION D.I.C. SCORE
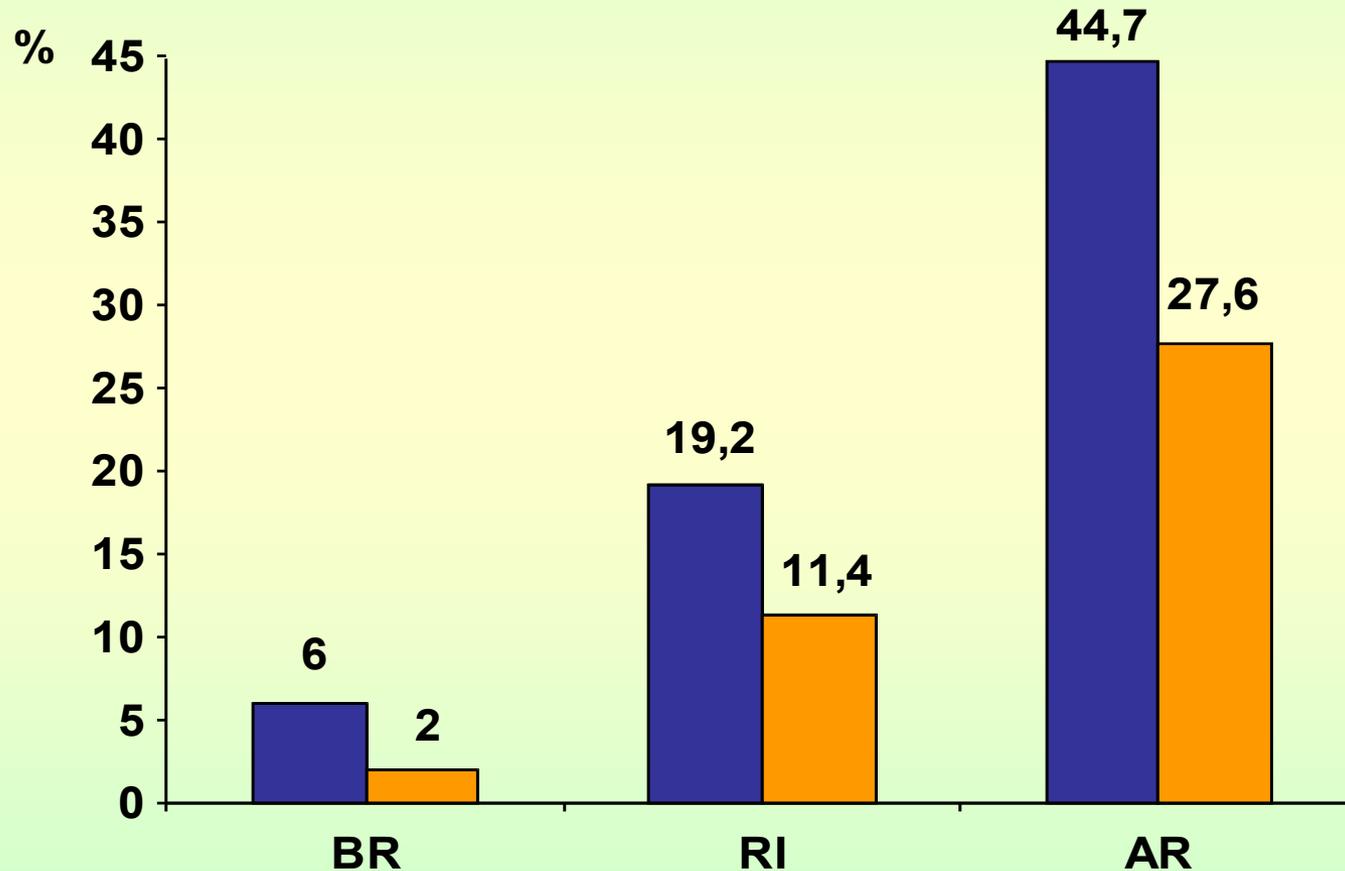
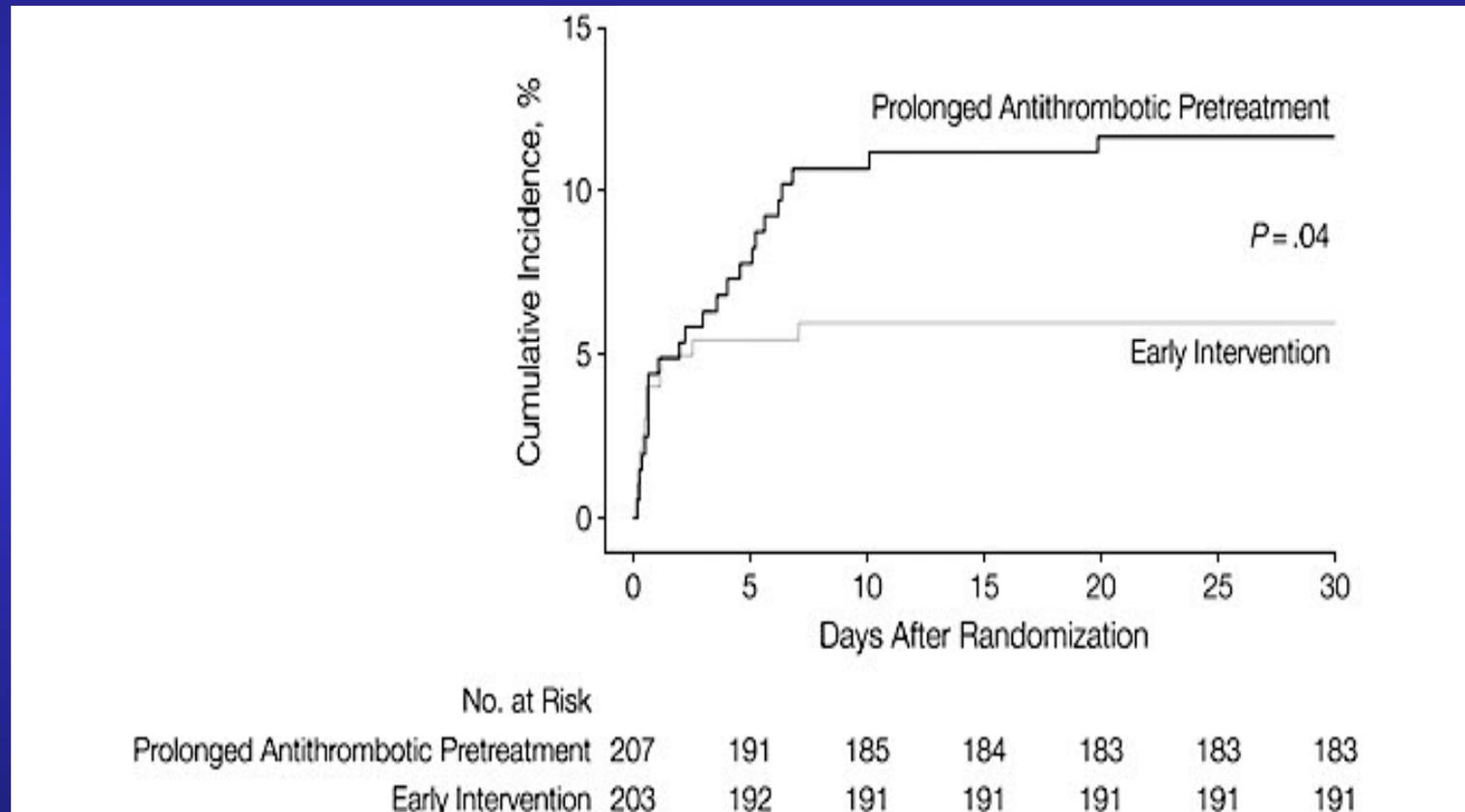# IMMEDIATE (<24hs) or DELAYED (3-5 days) INTERVENTION in UNSTABLE CORONARY SYNDROMES ISAR-COOL STUDY

	Immediate N: 203	Delayed N: 207	p
Death or AMI (%)	5.9	11.6	0.04
Death (%)	0	1.4	0.25
AMI (%)	5.9	10.1	0.12
Bleeding > (%)	3	3.9	0.61

IMMEDIATE OR DELAYED INTERVENTION IN UNSTABLE CORONARY SYNDROMES
AMI OR DEATH AT 30 DAYS

Neumann et al; JAMA 290; 2003

TIMACS STUDY
Immediate (<24 hs) vs delayed (>36 hs) invasive treatment in acute ischemic syndrome with NSTE

- Median randomization-CAG "immediate" arm: **1.4** hs
- Median randomización-CAG "delayed" arm: **50** hs
- N= 3031 ps
- 2 out of 3: age >60; troponin or CKMB ↑; ECG changes
- Primary end point: death, infarction, or stroke at 6 months
- Secondary end point: infarction, death, stroke, refractory ischemia, or coronary re-intervention

Primary and secondary end points in the TIMACS study. Early vs delayed strategy

End point	HR (IC 95%)	p
Death, AMI, stroke	0.85 (0.68–1.06)	0.15
Death, AMI; refractory ischemia	0.72 (0.58–0.89)	0.002
Death, AMI, stroke, refractory ischemia, reintervention	0.84 (0.71–0.99)	0.039
Refractory ischemia	0.30 (0.17–0.53)	<0.001

TIMACS study. Death, AMI, or stroke at six months according to the risk level according to the GRACE score (<> 140)

Risk	Early (%)	Delayed (%)	HR (CI 95%)	p
Low/ intermediary (n=2070)	7.7	6.7	1.14 (0.82–1.58)	0.43
High (n=961)	14.1	21.6	0.65 (0.48–0.88)	0.005

Mehta SR et al. American Heart Association 2008 Scientific Sessions; November 10, 2008; New Orleans, LA.

ABOARD STUDY
## Immediate vs delayed invasive treatment in acute ischemic syndrome NSTE

- Median randomization-CAG "immediate" arm: **1.2** hs
- Median randomization-CAG "next day" arm: **20.5** hs
- N= 352 ps; TIMI score >=3 (no low risk)
- 84 % radial access
- 52 % stent with drugs
- Primary end point: peak level of troponin I
- Secondary end point: infarction, death, or emergency reintervention at one month

ABOARD: primary end point (n=352; TIMI score ≥ 3)

End point	Immediate arm	"Next day" arm	p
Median peak of troponin I	2.0 (0.3–7.16)	1.7 (0.3–7.2)	0.70

Montalescot G. American College of Cardiology 2009 Scientific Sessions.
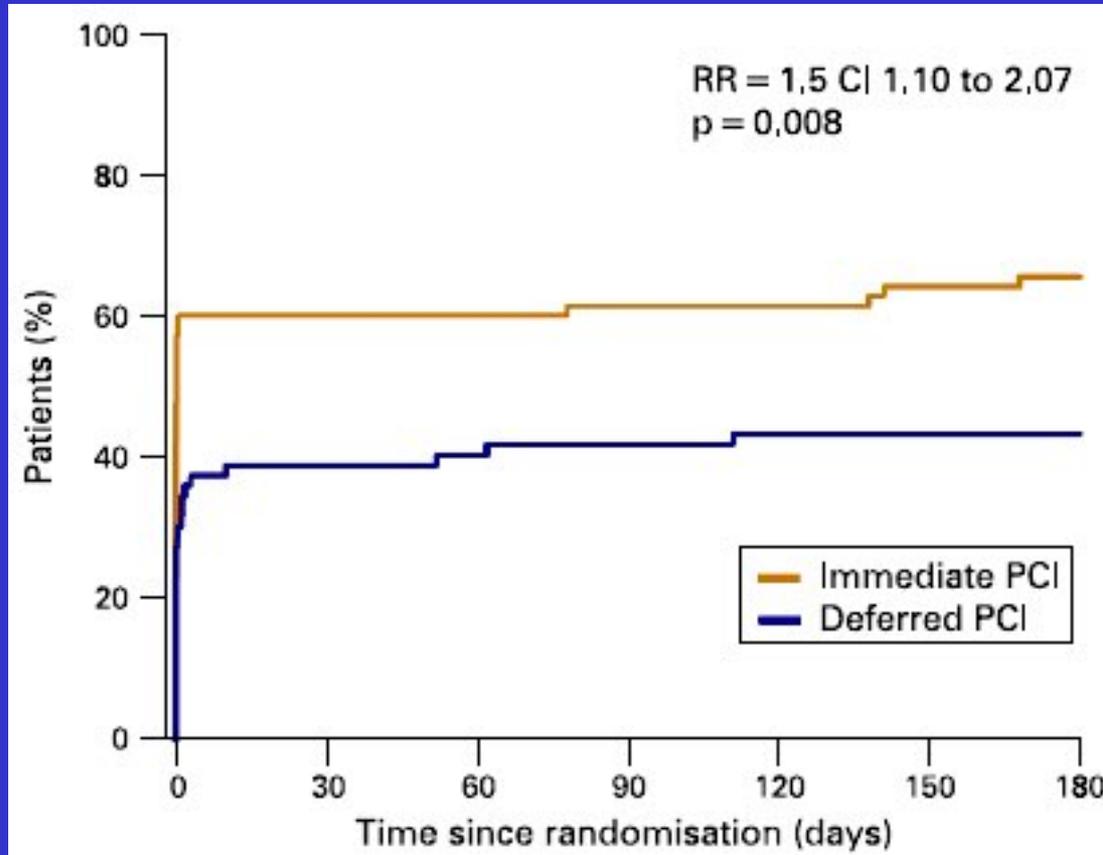
OPTIMA STUDY
RANDOMIZATION-ANGIOPLASTY TIME
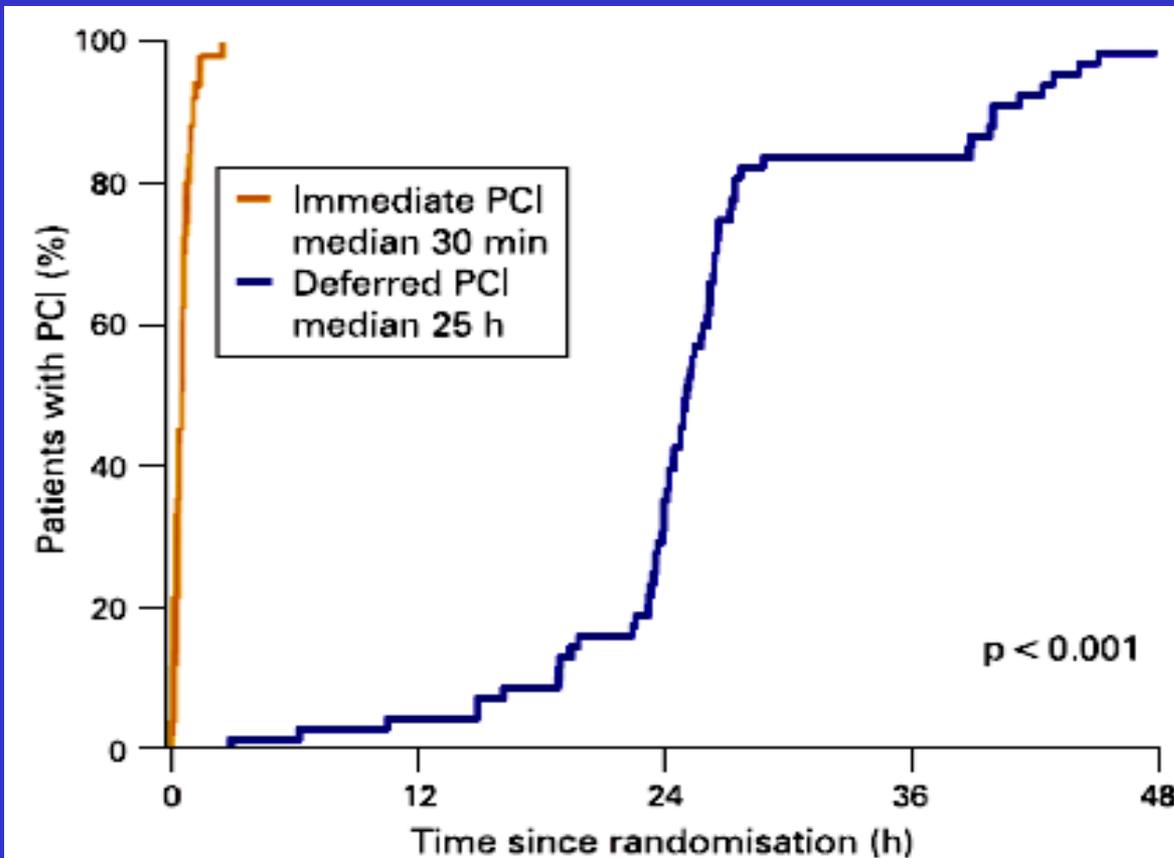
n=142

Riezebos et al; Heart, Mayo 2009

OPTIMA STUDY
PRIMARY END POINT AT 6 MONTHS
AMI, DEATH, OR REVASCULARIZATION

n=142

Riezebos et al; Heart, Mayo 2009

ROUTINE VS SELECTIVE INVASIVE STRATEGY
CONCLUSIONS

- Overall results are not very different.
- The results are different *according to the arms in which they are applied.*
- In low-risk patients *(majority)* the selective invasive strategy (conservative) should be preferred.
- In high-risk patient the routine invasive strategy should be preferred.
- The "ultra-rapid" invasive strategy does not seem to be better than the classical one (24-48 hs).

THANK YOU FOR YOUR ATTENTION