NSTE ACS

Timing of intervention

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Timing of intervention in NSTE-ACS

- What do the guidelines tell us?
- Any need for immediate invasive approach?
- No mortality benefit with an early invasive approach?
- Putting trials in perspective

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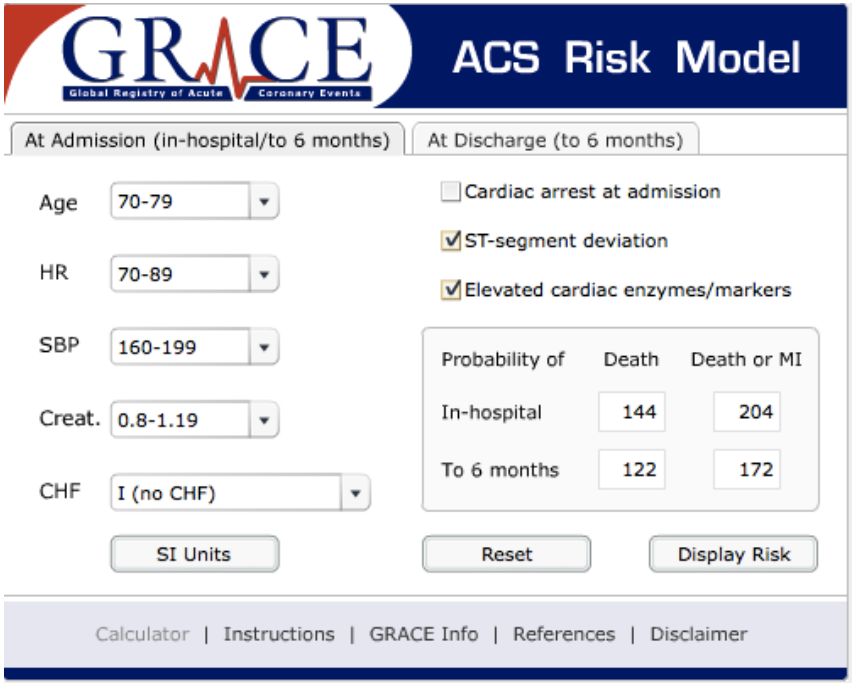
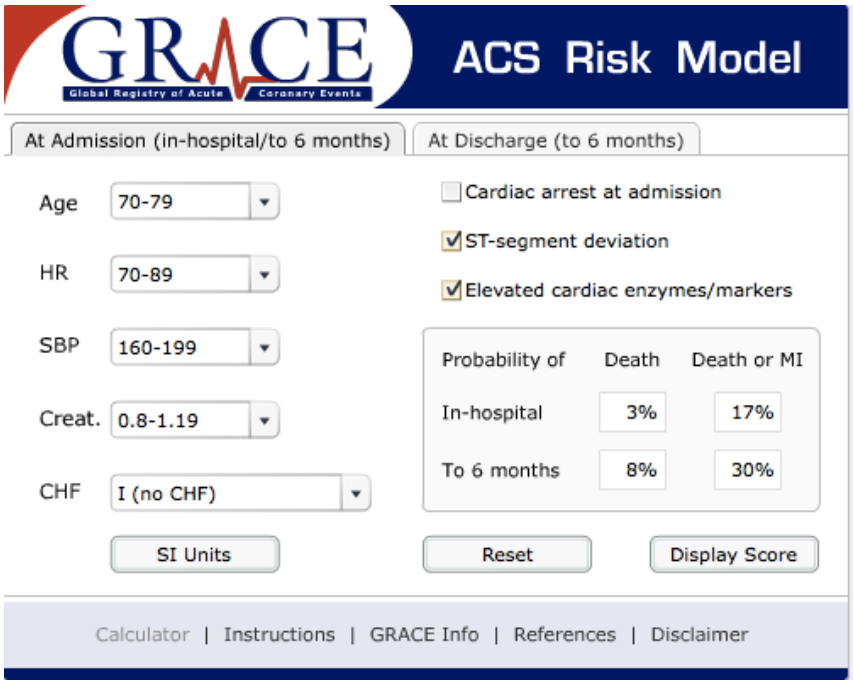
ESC guidelines: Risk stratify your ACS patients!





http://www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html

Recommendations for revascularization in NSTEMI

Specification Level	Class	Level
An invasive strategy is indicated in patients with: • GRACE score >140 or at least one high-risk criterion. • recurrent symptoms. • inducible ischaemia at stress test.	I	A
An early invasive strategy (<24 h) is indicated in patients with GRACE score >140 or multiple other high-risk criteria.	I	A
A late invasive strategy (within 72 h) is indicated in patients with GRACE score <140 or absence of multiple other high-risk criteria but with recurrent symptoms or stress-inducible ischaemia.	I	A
Patients at very high ischaemic risk (refractory angina, with associated heart failure, arrhythmias or haemodynamic instability) should be considered for emergent coronary angiography (<2 h).	IIa	C
An invasive strategy should not be performed in patients: • at low overall risk • at a particular high-risk for invasive diagnosis or intervention.	III	A

W Wijns & P Kohl et al.
ESC/EACTS revasc guidelines 2010

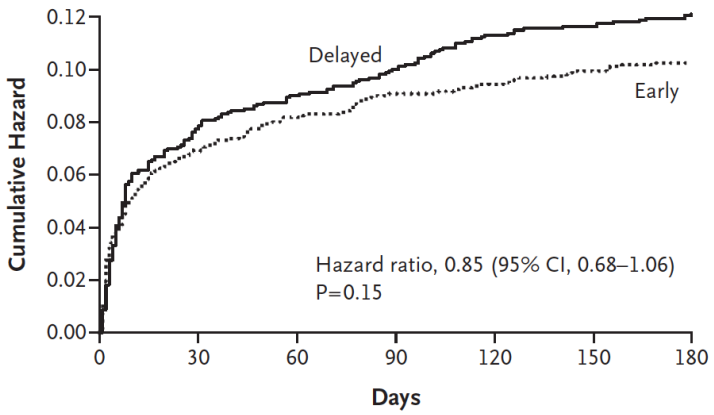
Randomized clinical trials comparing different invasive treatment strategies

	Early invasive / conservative						Early / late invasive				
Trials	**FRISC**	**TRUCS**	**TIMI18**	**VINO**	**RITA-3**	**ICTUS**	**ELISA**	**ISAR-COOL**	**OPTIMA**	**TIMACS**	**ABOARD**
Patients	2456	148	2220	131	1810	1199	220	410	142	3031	352
Enrolment period	1996–98	1997–98	1997–99	1998–2000	1997–2002	2001–03	2000–01	2000–02	2004–07	2003–08	2006–08
Time to angio (h)[a]	96/408	48/120	22/79	6.2/1464	48/1020	23/283	6/50	2.4/86	0.5/25	14/50	1.2/21
Mean age (year)	66	62	62	66	62	62	63	70	62	65	65
Women, %	30	27	34	39	38	27	30	33	32	35	28
Diabetes, %	12	29	28	25	13	14	14	29	20	27	27
Troponin ↑ at inclusion, %	55	NA	54	100	75	67	68	67	46	77	74
Invasive (%)[a,b]	78/45	100/61	64/45	73/39	57/28	79/54	74/77	78/72	100/99	74/69	91/81
PCI/CABG (%)[a,b]	30/27	43/16	36/19	50/27	26/17	51/10	54/15	68/8	99/0	57/28	63/2
Primary outcome	D/MI 6 months	D/MI/H	D/MI/A 6 months	D/MI 6 months	D/MI 12 months	D/MI/A 12 months	Infarct size LDH	D/MI 1 months	D/MI/UR 30 days	D/MI/S 6 months	Troponin release
Endpoint met	+	–	+	+	+	–	+	+	–	–	–

W Wijns & P Kohl et al.
ESC/EACTS revasc guidelines 2010

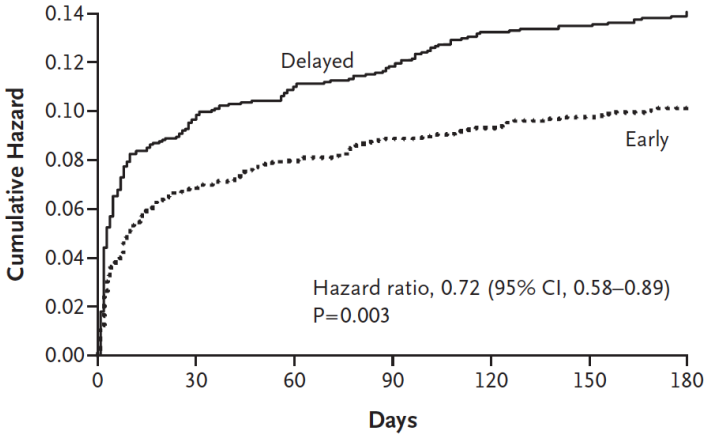
Early (≤24hrs) vs delayed (≥36hrs) coronary angiography in NSTEMI/UAP TIMACS trial

Death, MI, or stroke



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

Death, MI, or refractory ischemia



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

	Early Intervention (N=1593)	Delayed Intervention (N=1438)	P Value
Coronary angiography (%)	97.6	95.7	0.003
Median time (hr)	14	50	<0.001
Interquartile range (hr)	3–21	41–81	

SR Mehta et al.
N Engl J Med 2009;360:2165-75.

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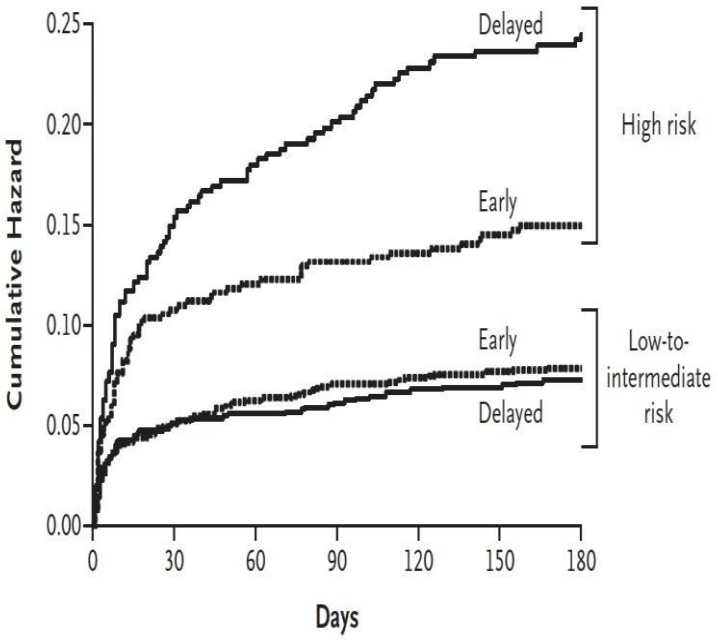
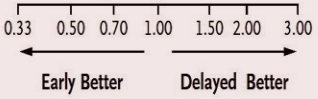
Early (≤24hrs) vs delayed (≥36hrs) coronary angiography in NSTEMI/Unstable AP - TIMACS trial

Death, MI, or stroke hazard in high (GRACE>140) vs low risk (GRACE ≤140) patients



Characteristic	No. of Patients	Early %	Delayed %	Hazard Ratio for Event (95% CI)	P Value for Interaction
Overall	3031	9.6	11.3	0.85 (0.68–1.06)	
Age					0.46
<65 yr	1293	6.4	6.4	0.98 (0.64–1.52)	
≥65 yr	1736	12.2	14.6	0.83 (0.64–1.07)	
Sex					0.53
Female	1052	9.6	12.3	0.77 (0.53–1.12)	
Male	1976	9.6	10.7	0.89 (0.68–1.18)	
ST-segment deviation					0.71
No	1523	7.5	8.5	0.88 (0.62–1.26)	
Yes	1508	11.6	14.2	0.81 (0.61–1.07)	
Elevated cardiac marker					0.43
No	668	10.4	10.4	1.00 (0.62–1.60)	
Yes	2363	9.4	11.5	0.81 (0.63–1.04)	
GRACE score					0.01
0–140	2070	7.6	6.7	1.12 (0.81–1.56)	
≥141	961	13.9	21.0	0.65 (0.48–0.89)	



SR Mehta et al.
N Engl J Med 2009;360:2165-75.

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High risk situations needing emergency coronary angiography

Ongoing or recurrent ischaemia.

Dynamic spontaneous ST changes (>0.1 mV depression or transient elevation).

Deep ST depression in anterior leads V2–V4 indicating ongoing posterior transmural ischaemia.

Haemodynamic instability.

Major ventricular arrhythmia.

High risk situations needing emergency coronary angiography

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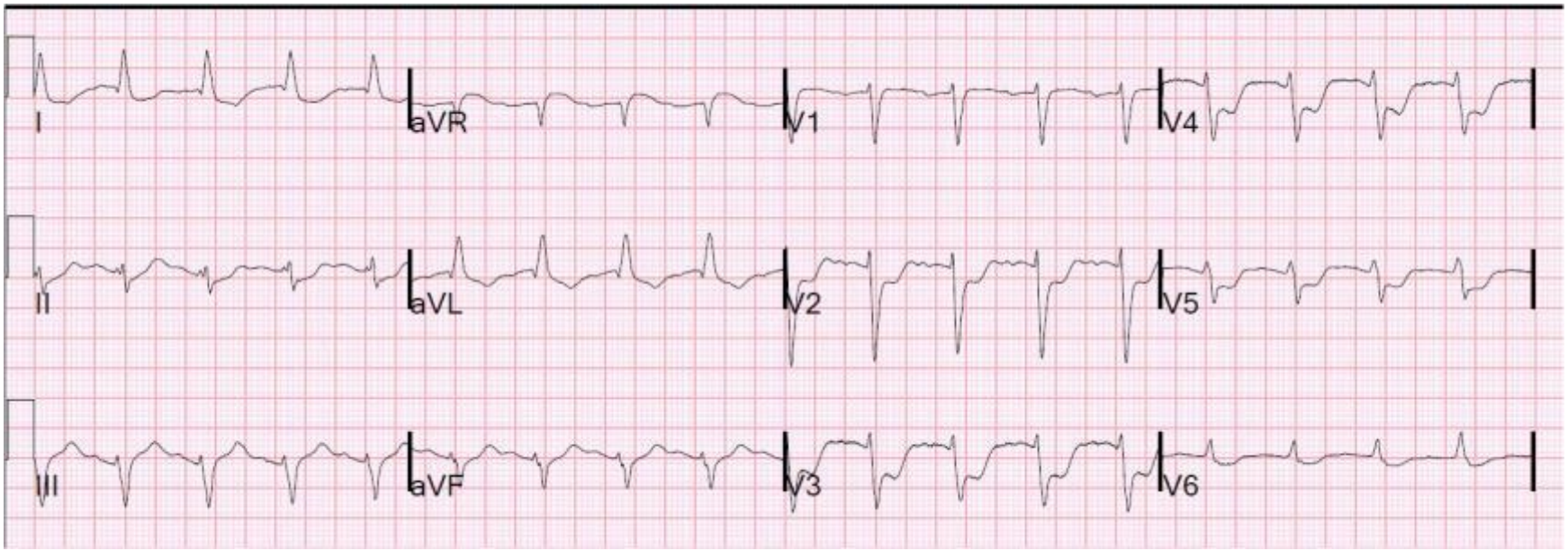
Major ventricular arrhythmia.

Do not miss a true posterior acute STEMI!



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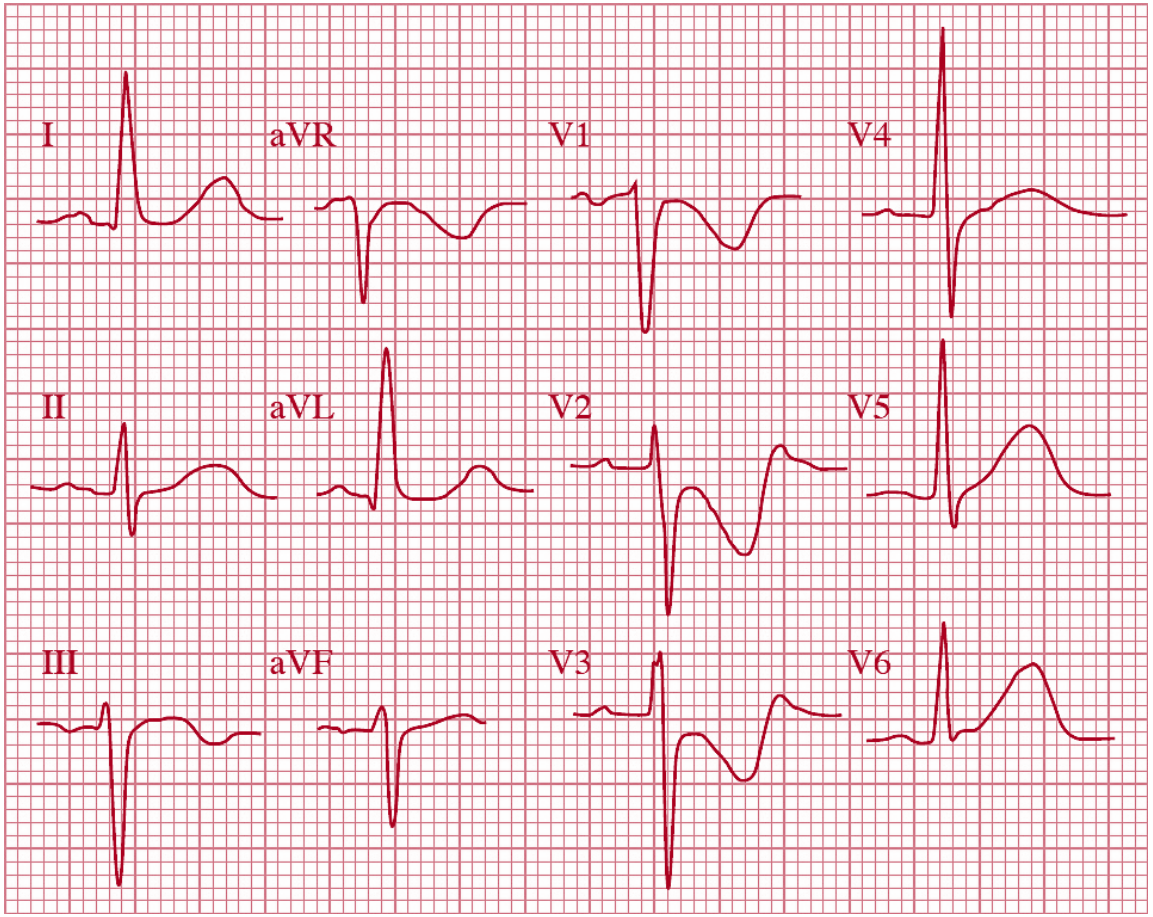

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Timing of intervention in NSTE-ACS

- What do the guidelines tell us?
- **Any need for immediate invasive approach?**
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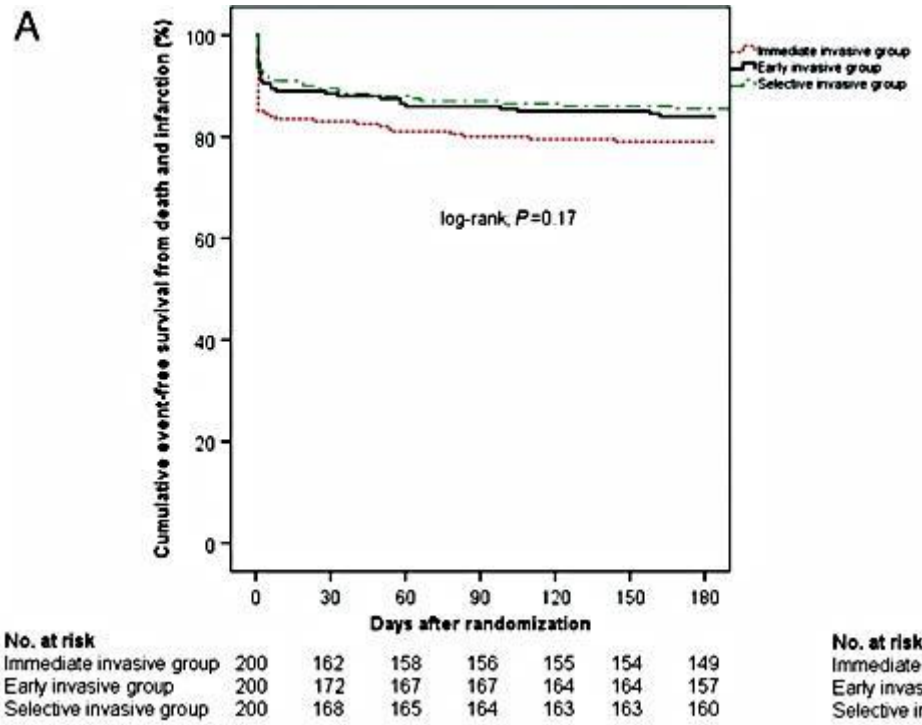
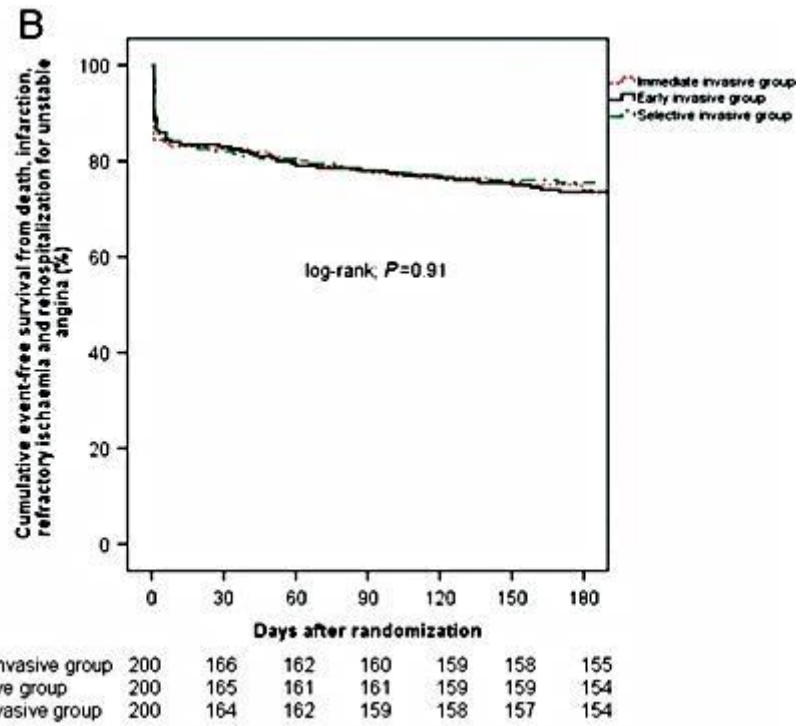
- Putting trials in perspective

Immediate (<2 hrs) vs. early (10-48 hrs) vs. selective invasive approach (LIPSIA-NSTEMI Trial)

death and non-fatal MI



death, non-fatal MI, & refractory ischaemia



H Thiele et al.
Eur Heart J (2012) 33, 2035–2043

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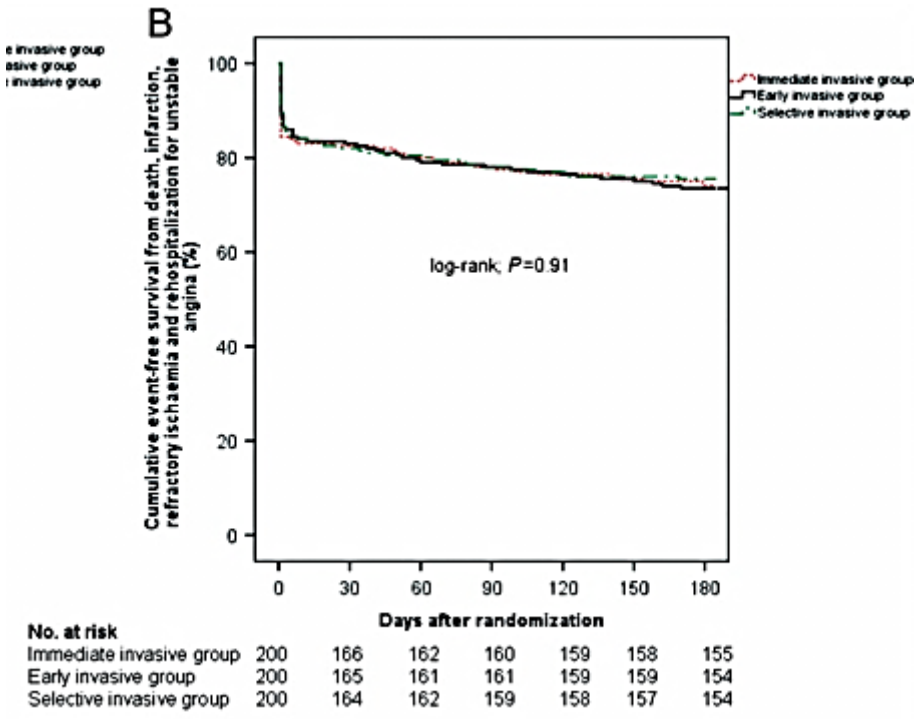

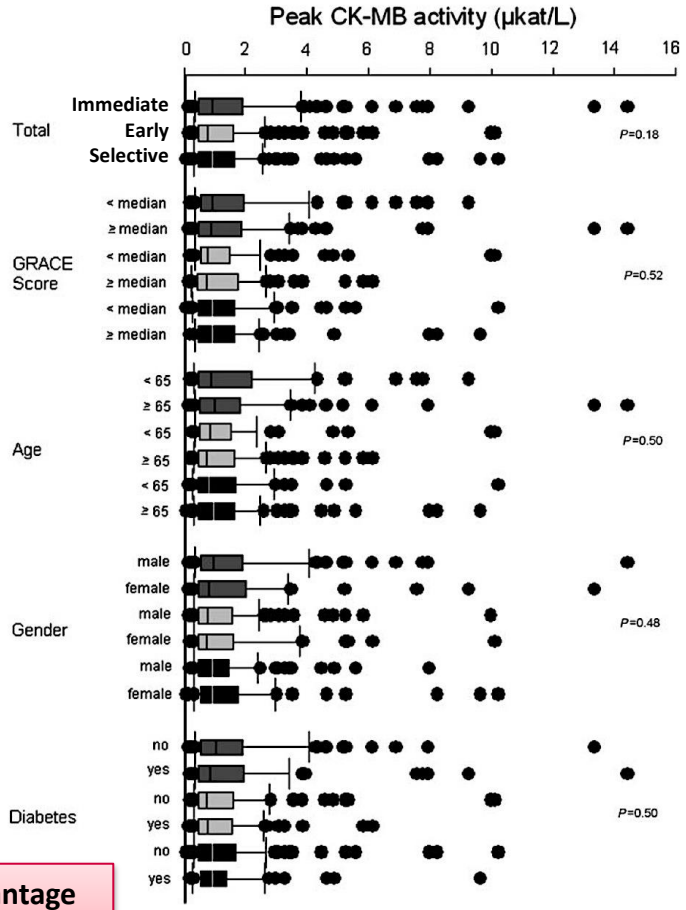

In NSTEMI patients, an immediate invasive approach does not offer an advantage over an early or a selective invasive approach with respect to large MI's as defined by peak CK-MB levels, which is supported by similar clinical outcomes.

H Thiele et al.
Eur Heart J (2012) 33, 2035–2043

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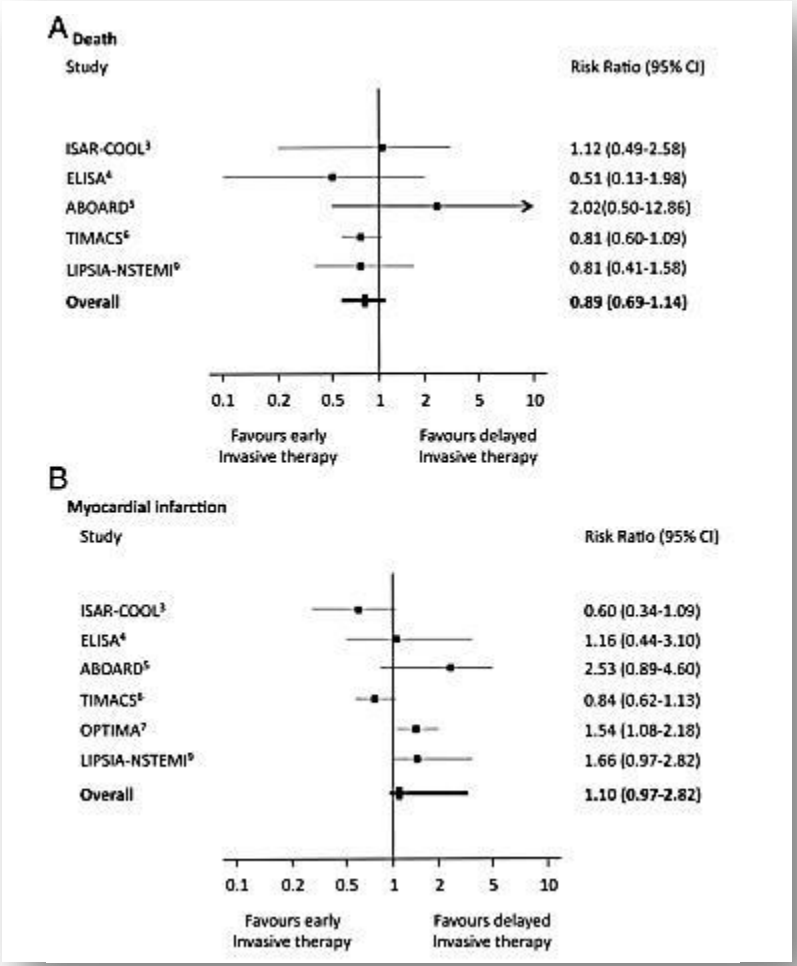
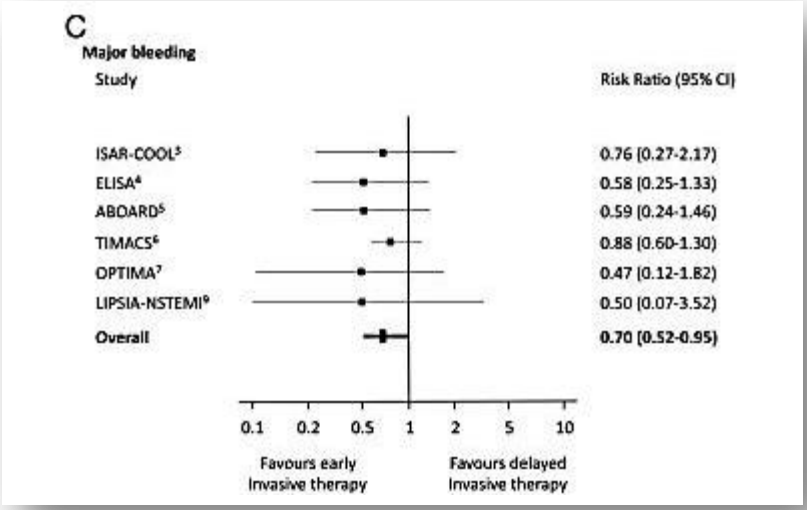
Catheterization laboratories open 24 hours a day, every day: does stable NSTE ACS need the offer?





…there is again a **trend** for an early invasive strategy **to reduce mortality**.

In contrast, as for **MI**, the analysis suggests **increased risk with the early strategy**, which can be explained by the periprocedural elevation of cardiac damage biomarkers, but this association did not reach the level of formal statistical significance.

Finally, **major bleeding** is, for the first time, shown to be **significantly reduced by early intervention**, suggesting that patients at high risk of bleeding may benefit from an early angiography.

Thus, we have yet to start to **open our catheterization laboratory 24 h a day, every day, for 'stable' NST-ACS** in order specifically to target fragile patients.

P.L. Sanchez & F. Fernandez-Aviles
Eur Heart J (2012) 33, 1992–1995

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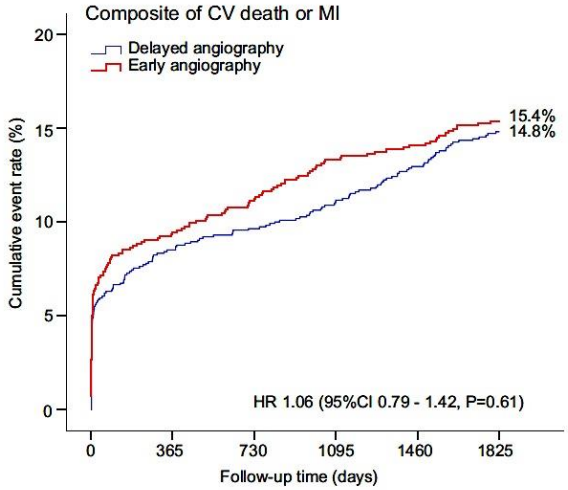
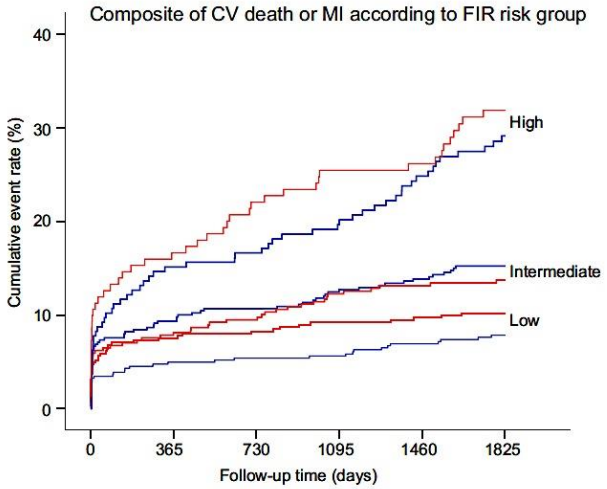
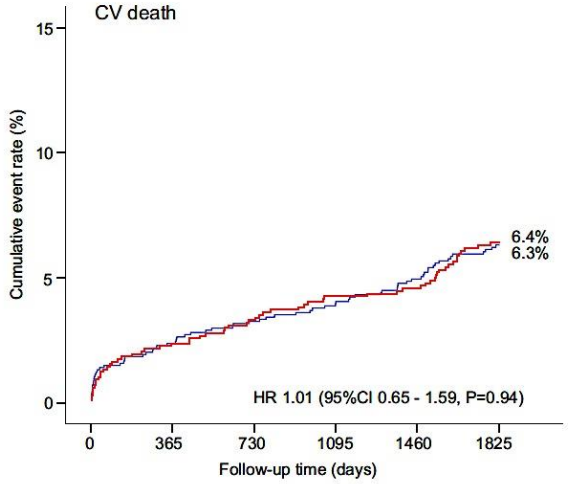
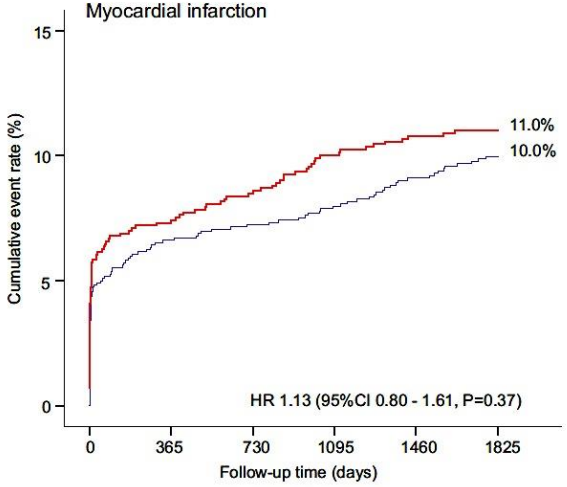
early (≤ 2 days) vs. delayed (3 to 5 days) angiography post hoc analysis FRISC-II + ICTUS + RITA-3









In patients presenting with NSTE-ACS, early angiography within 48 h does not reduce the incidence of 5-year death or MI, when compared with delayed angiography within 48 to 120 h.

P Damman et al.
J Am Coll Cardiol Intv 2012;5:191–9

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Optimal Timing of Invasive Strategy in NSTE-ACS

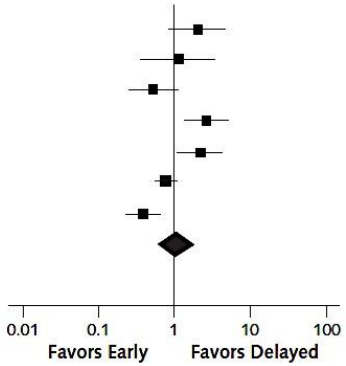
ORs for MI early vs. a delayed invasive strategy

Randomized Trials

Study or Subgroup	Early Strategy		Delayed Strategy		Weight, %	OR D-L, Random (95% CI)
	Events, *n*	Total Patients, *n*	Events, *n*	Total Patients, *n*		
ABOARD	16	175	8	177	12.8	2.13 (0.89–5.10)
ELISA	7	109	6	111	10.6	1.20 (0.39–3.70)
ISAR-COOL	12	203	21	207	14.0	0.56 (0.27–1.16)
LIPSIA-NSTEMI	33	200	13	200	14.6	2.84 (1.45–5.58)
OPTIMA	44	73	27	69	14.6	2.36 (1.20–4.63)
TIMACS	76	1593	82	1438	17.5	0.83 (0.60–1.14)
Zhang et al, 2010 (16)	23	446	40	369	15.9	0.41 (0.24–0.69)
Total (95% CI)	211	2799	197	2541	100	1.15 (0.65–2.01)

Heterogeneity: $\tau^2 = 0.44$; chi-square = 32.98; $P < 0.001$; $I^2 = 82\%$

Test for overall effect: $Z = 0.48$ ($P = 0.63$)

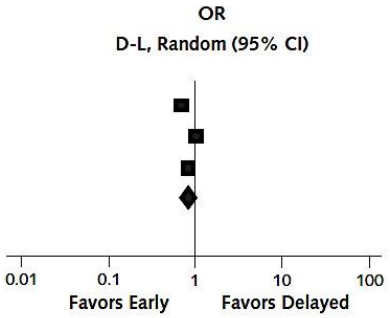


Observational Studies

Study or Subgroup	Early Strategy		Delayed Strategy		Weight, %	OR D-L, Random (95% CI)
	Events, *n*	Total Patients, *n*	Events, *n*	Total Patients, *n*		
ACUITY	382	4937	301	2812	32.4	0.70 (0.60–0.82)
CRUSADE	1366	45 548	313	10 804	34.5	1.04 (0.91–1.17)
SYNERGY	404	3326	416	3026	33.1	0.87 (0.75–1.00)
Total (95% CI)	2152	53 611	1030	16 642	100	0.86 (0.69–1.08)

Heterogeneity: $\tau^2 = 0.03$; chi-square = 14.66; $P < 0.001$; $I^2 = 86\%$

Test for overall effect: $Z = 1.32$ ($P = 0.190$)



EP Navarese et al.
Ann Intern Med. 2013;158(4):261-270

Optimal Timing of Invasive Strategy in NSTE-ACS

To definitively answer the question of a potential survival benefit with early compared with later intervention:

an RCT would require approximately 7807 patients per group (a total of 15 614 patients) to have 80% statistical power

and approximately 10 450 per group (a total of 20 900 patients) to have 90% statistical power

to detect the 30-day mortality decrease estimated in this analysis (OR, 0.80, translating into a 1% absolute difference in favor of early intervention, assuming the absolute mortality rate of 4.7% seen in the late intervention trial groups) with ⟨ 2-sided of 0.05.

EP Navarese et al.
Ann Intern Med. 2013;158(4):261-270

Timing of intervention in NSTE-ACS

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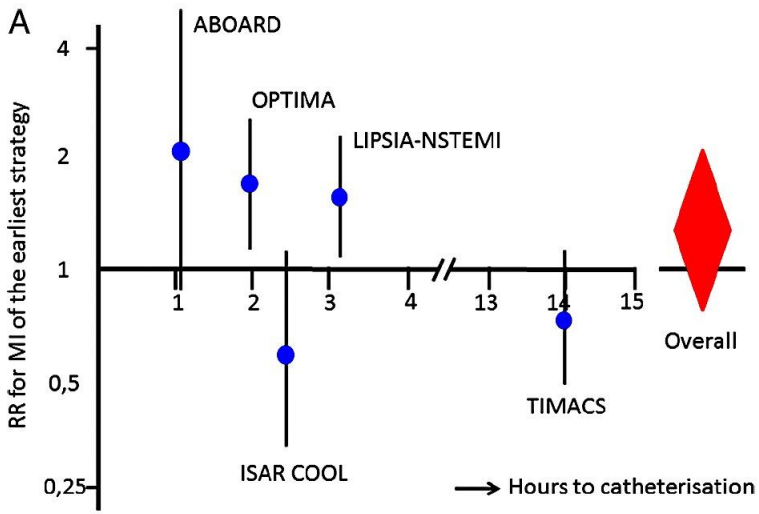
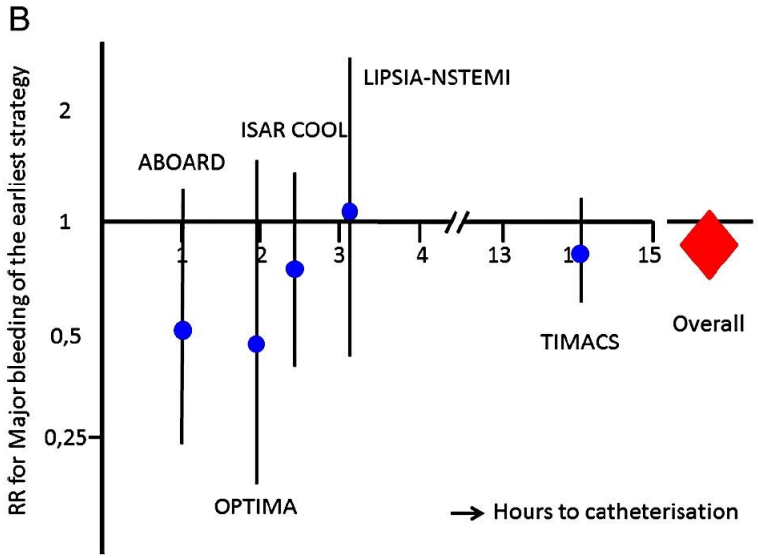
Timing of angiography in NSTEMI and risk of complications

Risk periprocedural MI



Risk major bleeding



RK Riezebos & FWA Verheugt
Heart 2013, in press

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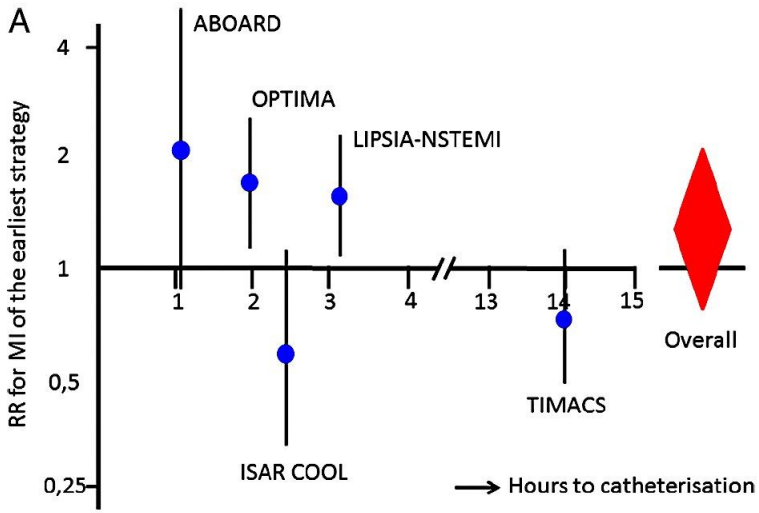
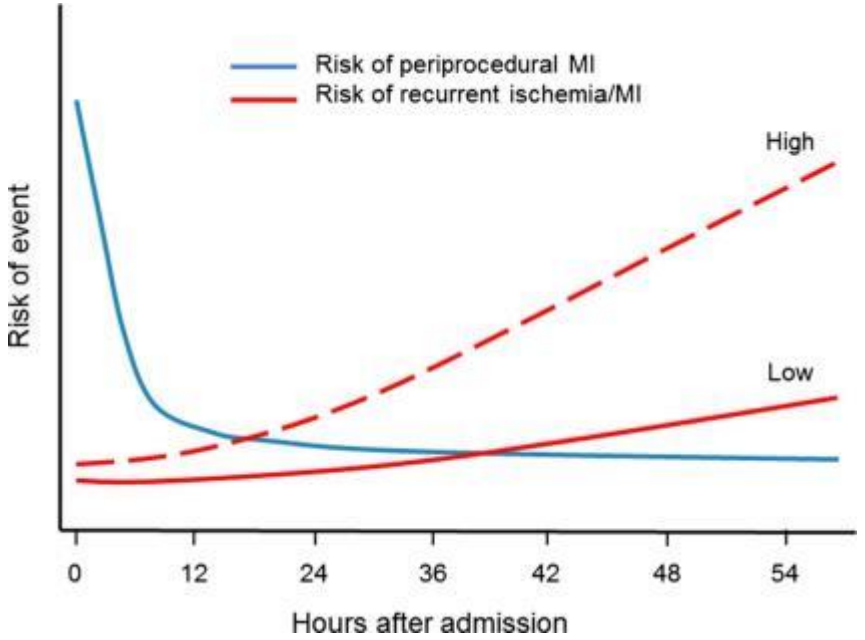
Timing of angiography in NSTEMI and risk of complications

Risk periprocedural MI



Risk recurrent ischemia/MI



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Heart 2013, in press

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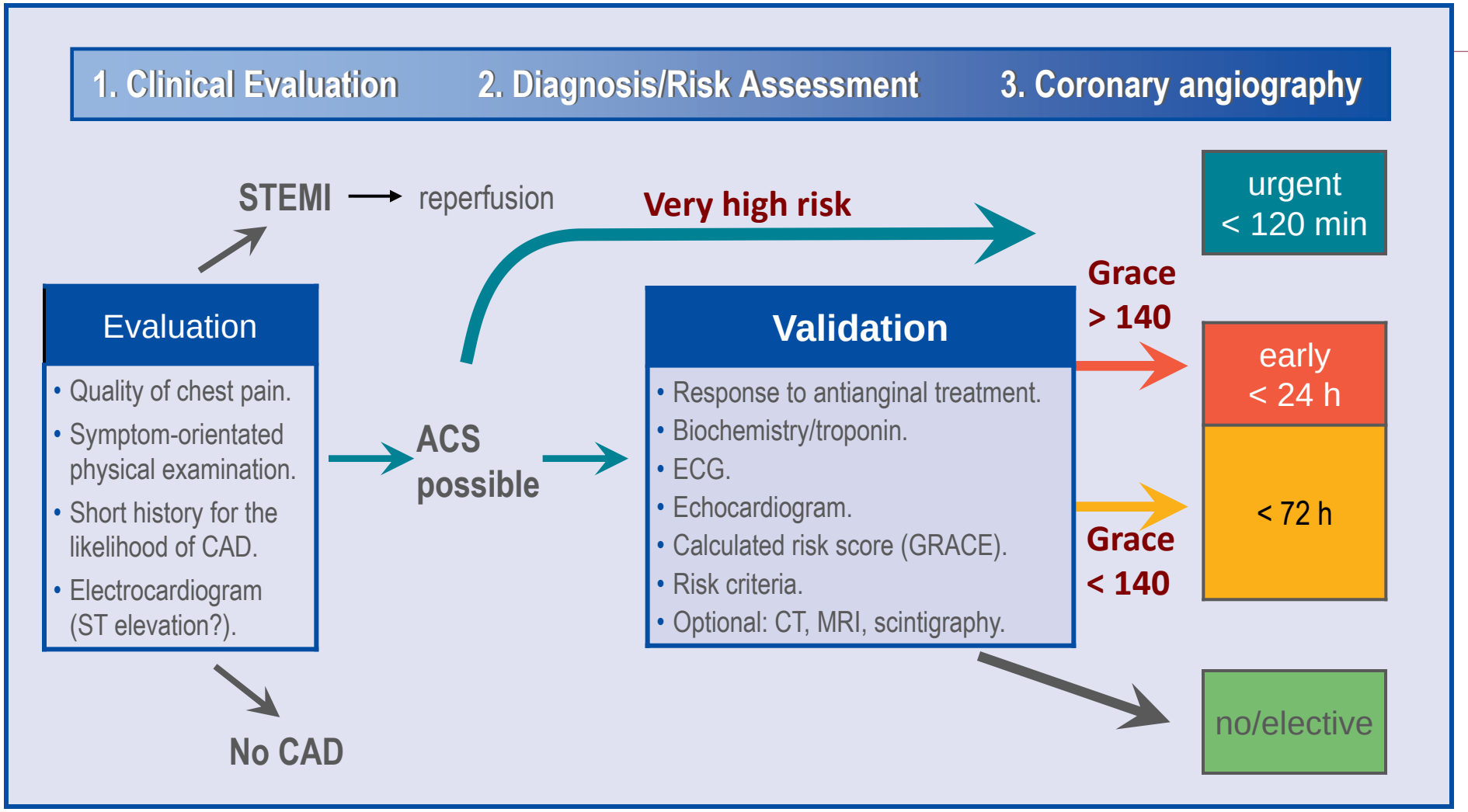
Conclusion: Let‘s stick to the guidelines!



Eur Heart Journal (2011) 32:2999–3054
doi:10.1093/eurheartj/ehr236

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