Optimal timing of intervention in non ST-elevation acute coronary syndromes without pretreatment with P2Y12-ADP receptor antagonists: the EARLY randomized trial.

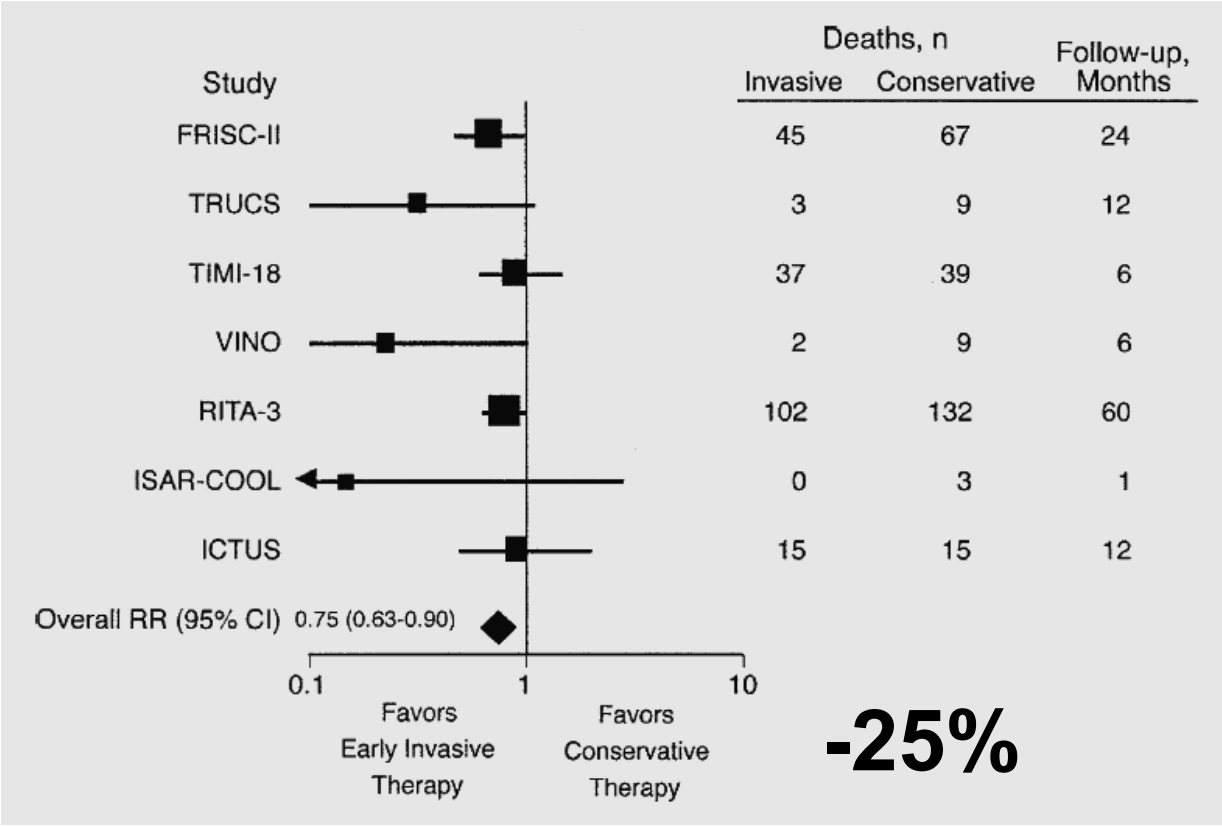
Gilles Lemesle MD, PhD; Marc Laine, MD; Mathieu Pankert, MD; Ziad Boueri, MD; Pascal Motreff, MD; PhD; Franck Paganelli, MD; Karine Baumstarck, MD, PhD; Antoine Roch, MD, PhD; François Kerbaul, MD, PhD; Etienne Puymirat, MD, PhD; Laurent Bonello, MD, PhD.

mars cardio
Mediterranean Academic Research and Studies in cardiology

AP HM

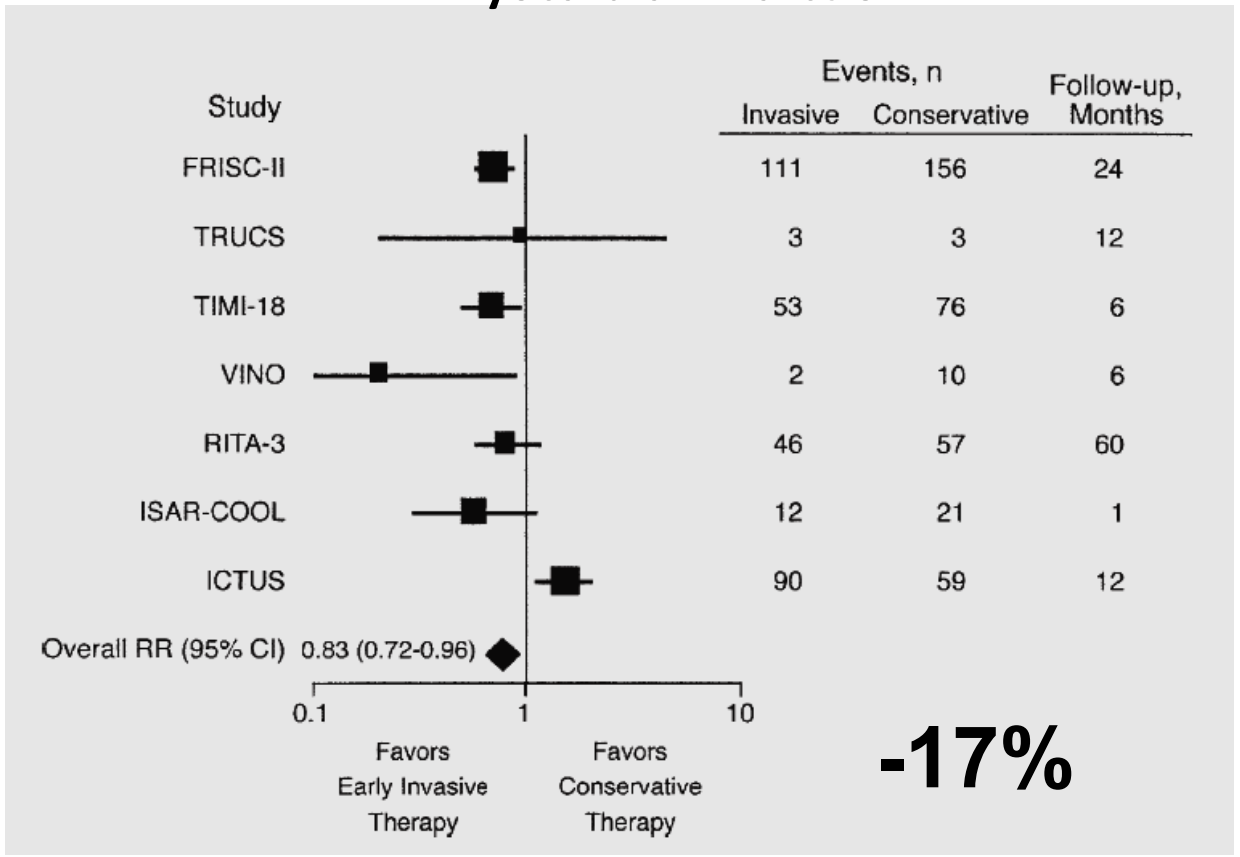
Benefit of an invasive strategy in NSTE-ACS

DEATH n= 8375



-25%

Myocardial infarction n= 8375



-17%

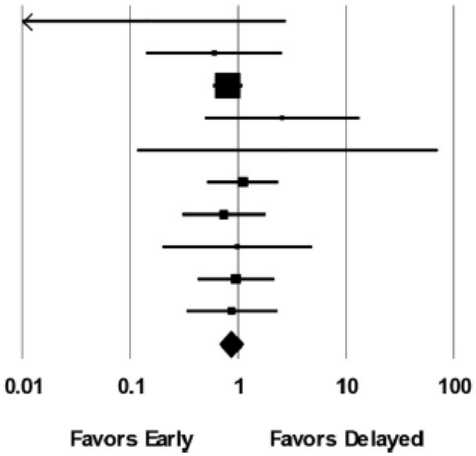
Bavry AA et al . JACC 2006

Optimal timing between early and delayed

- **No conclusive evidence**
- **Meta-analysis : no mortality difference, lower rates of recurent ischemic events**
- **All patients were pretreated**

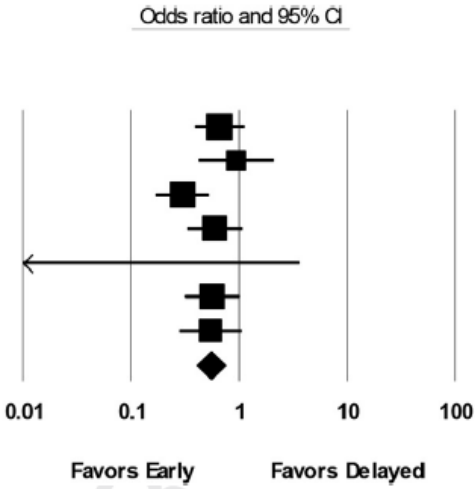
Death

Study name	Events / Total		Statistics for each study				
	Early strategy	Delayed strategy	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
ISAR-COOL	0 / 203	3 / 207	0.14	0.01	2.80	0.20	0.7
ELISA	3 / 109	5 / 111	0.60	0.14	2.57	0.49	2.8
TIMACS	76 / 1593	85 / 1438	0.80	0.58	1.10	0.16	58.7
ABOARD	5 / 175	2 / 177	2.57	0.49	13.45	0.26	2.2
OPTIMA	1 / 73	0 / 69	2.88	0.12	71.80	0.52	0.6
Zhang et al, 2010	16 / 446	12 / 369	1.11	0.52	2.37	0.79	10.2
LIPSIA-NSTEMI	9 / 200	12 / 200	0.74	0.30	1.79	0.50	7.5
ELISA 3	3 / 269	3 / 265	0.98	0.20	4.92	0.99	2.3
SISCA	13 / 83	14 / 86	0.96	0.42	2.18	0.91	8.8
RIDDLE-NSTEMI	8 / 162	9 / 161	0.88	0.33	2.33	0.79	6.2
			0.85	0.67	1.09	0.20	



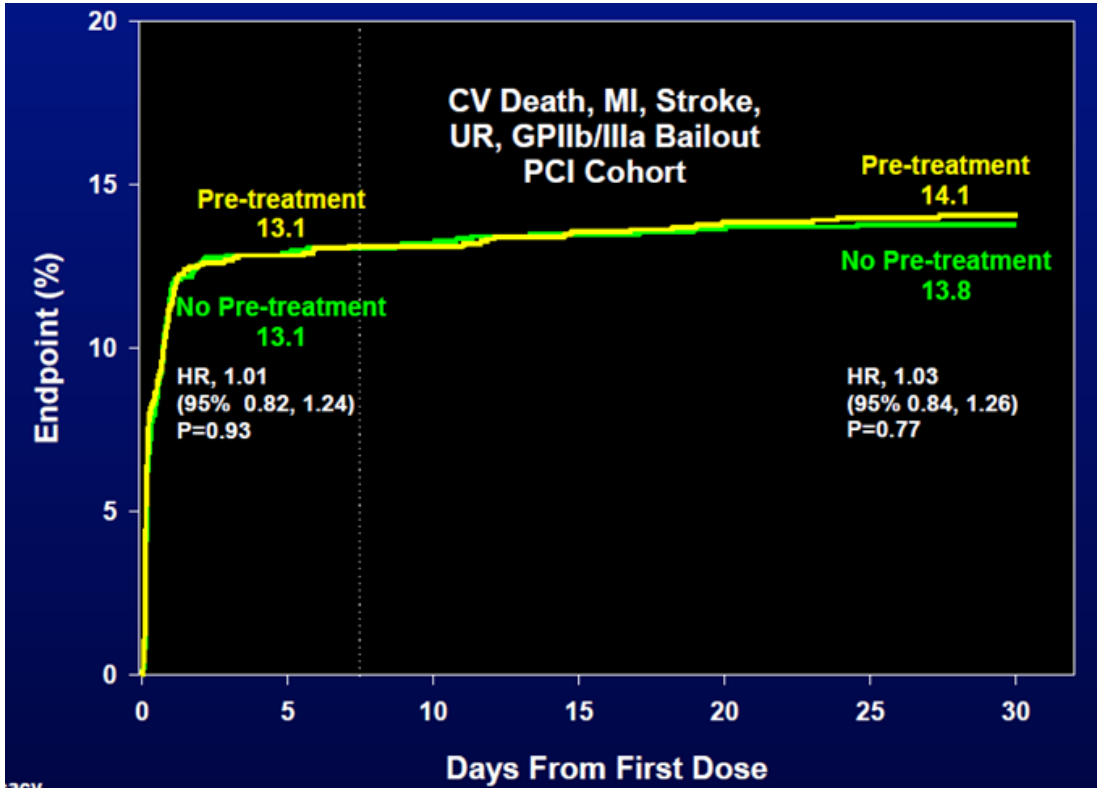
RI

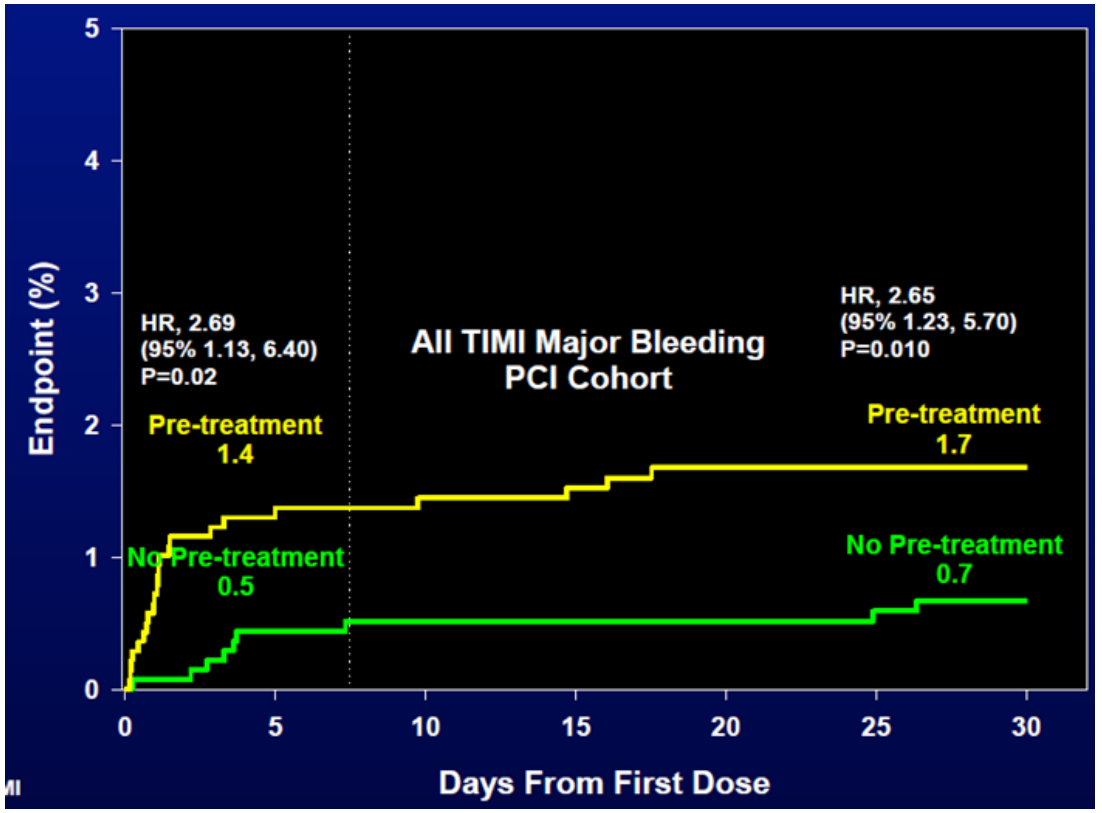
Study name	Events / Total		Statistics for each study				
	Early strategy	Delayed strategy	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
ISAR-COOL	27 / 203	39 / 207	0.66	0.39	1.13	0.13	20.0
ELISA	13 / 109	14 / 111	0.94	0.42	2.10	0.88	11.2
TIMACS	16 / 1593	47 / 1438	0.30	0.17	0.53	0.00	18.3
ABOARD	21 / 175	33 / 177	0.60	0.33	1.08	0.09	17.5
LIPSIA-NSTEMI	0 / 200	13 / 200	0.01	0.00	3.64	0.12	0.2
ELISA 3	20 / 269	33 / 265	0.56	0.32	1.01	0.05	17.8
RIDDLE-NSTEMI	16 / 162	27 / 161	0.54	0.28	1.05	0.07	15.0
			0.55	0.40	0.74	0.00	



Bonello L et al. JACC Interv. 2016

Controversy surrounding pretreatment





- **In the ACCOAST trial pretreatment with prasugrel in NSTE ACS resulted in a bleeding harm**

Montalescot et al. NEJM 2013

Gap in evidence

- A significant proportion of NSTE ACS patients are not pretreated before a scheduled invasive strategy
- The current guidelines on the optimal timing are based on secondary endpoints of overall negatives trials
- No RCT available on the specific group of NSTE ACS patients not pretreated for the timing of the invasive strategy

Aim of the EARLY trial

Compare 2 invasive strategies:

- **Very Early (< 2 hours)**
- **Delayed (12-72 hours)**

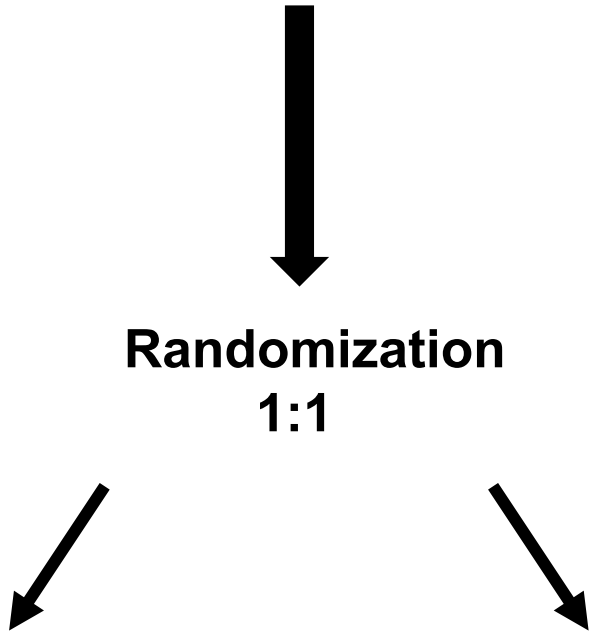
in intermediate and high-risk NSTE ACS not pretreated

regarding MACE (CV death, recurrent ischemic events) at 1 month

ClinicalTrial.gov identifier: NCT02750579

DESIGN

Intermediate or high risk NSTE ACS scheduled for an invasive strategy



Randomization 1:1

Delayed group 12-72 hours

Very early group (2< hours)

- **13 centers in France**
- **Cath lab 24/24 7/7**
- **Sept, 2016- March 2018**
- **<u>No P2Y12</u> ADP receptor anatgonist pretreatment allowed**

- **Following CA:**
  - **Medical therapy**
  - **PCI**
  - **CABG**

→ **<u>Real life</u>**

Lemesle G et al. Clin Cardiol. 2018

Primary end-point at 30 day

- **CV death**
- **Recurrent ischemic events**:

occurrence of ≥1 of the following events requiring an emergent CA:

- symptoms of ischemia

- ventricular arrhythmias

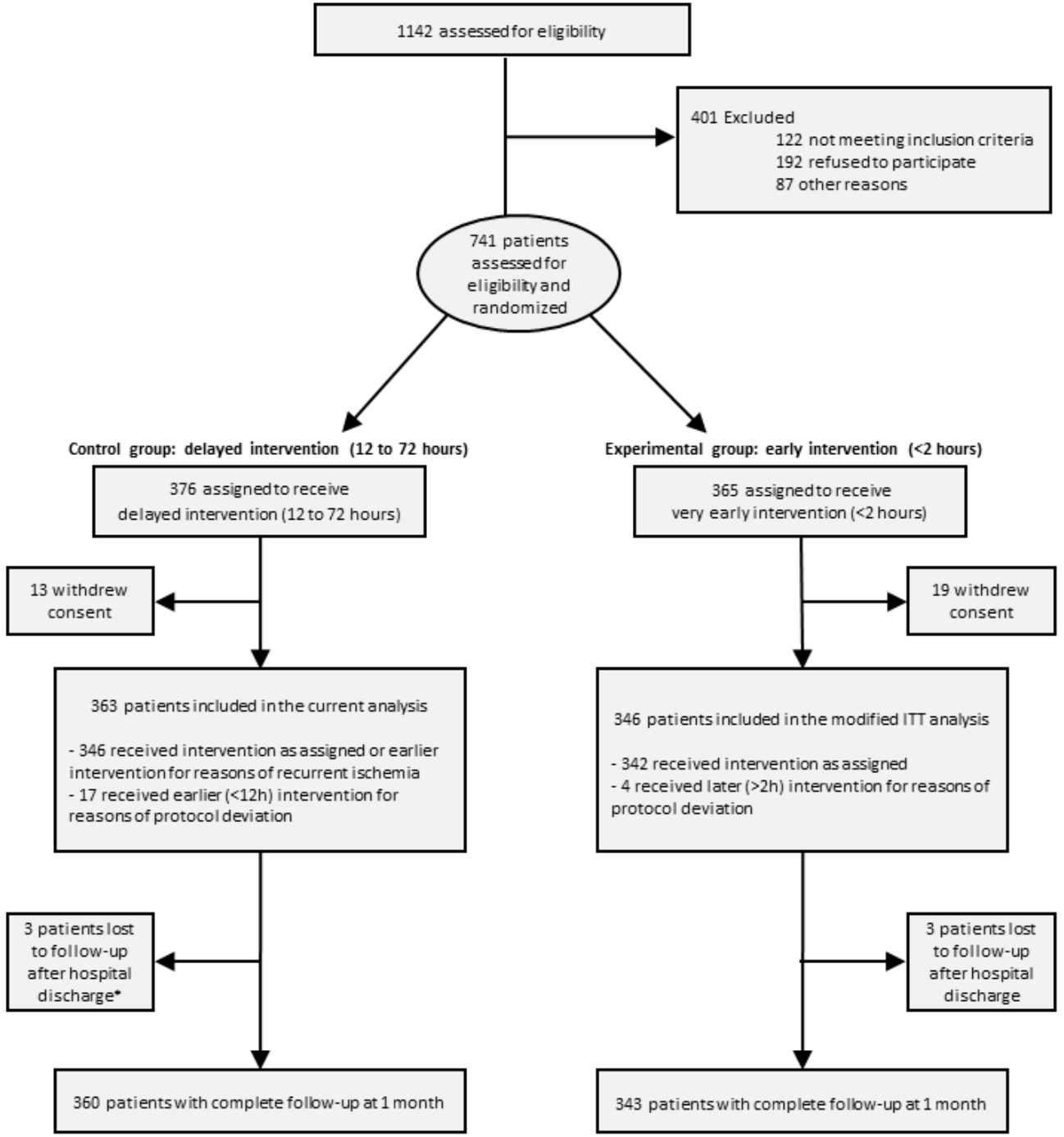
- acute pulmonary edema

- cardiogenic shock

Resulting in urgent revascularization
CEC adjudicated / Medically-motivated

RESULTS

	Delayed group (n=363)	Very early group (n=346)
Age, mean (SD), years	65.5 (13.0)	65.0 (12.4)
Sex Men, N (%)	252 (69.4)	250 (72.3)
CV risk factors and medical history		
Diabetes, N (%)	127 (35.0)	98 (28.3)
History of MI, N (%)	92 (25.4)	89 (25.8)
History of PCI, N (%)	115 (31.7)	107 (31.0)
Antithrombotic treatments at inclusion		
Aspirin, N (%)	158 (44.3)	145 (43.2)
$P2Y_{12}$-ADP-receptor antagonist, N (%)	69 (19.3)	76 (22.6)
Clopidogrel, N (%)	49 (13.7)	53 (15.8)
Ticagrelor, N (%)	18 (5.0)	18 (5.4)
Prasugrel, N (%)	3 (0.8)	5 (1.5)



RESULTS

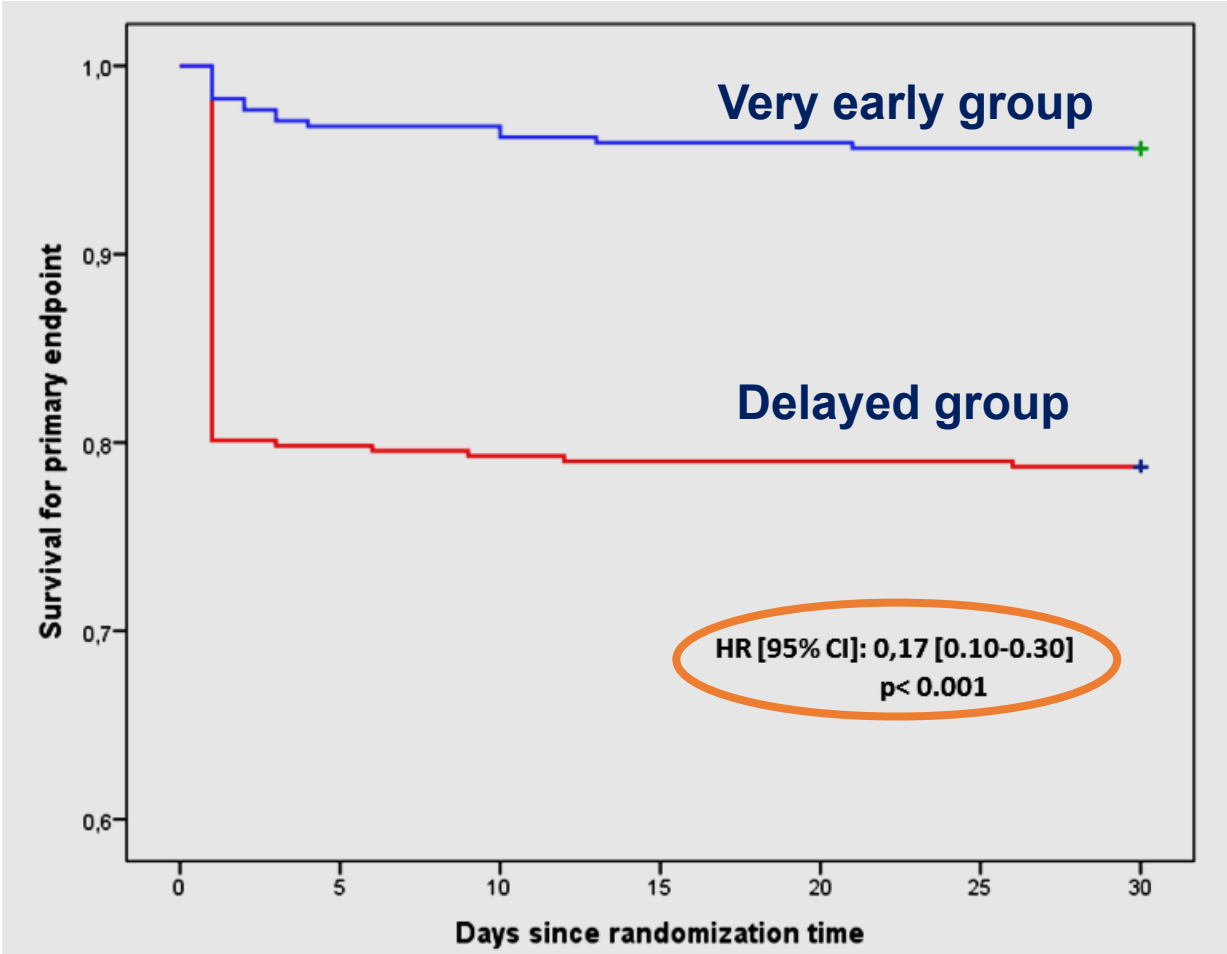
Clinical presentation n (%)	Delayed group	Very early group
NSTEMI	244 (68.0)	238 (69.0)
High-risk NSTE ACS	320 (92.5)	307 (93.0)
Intermediate-risk NSTE ACS	26 (7.5)	23 (7.0)
GRACE score, mean (SD)	123.4 (35.1)	121.2 (31.9)

Coronary angiography n (%)	Delayed group	Very early group
Delay between randomization and CA, median [IQR], hours	18 [12-23]	0 [0-1]
Diffusion of CAD (n° of vessels)		
0 vessel	63 (17.4)	74 (21.4)
1 vessel	124 (34.2)	105 (30.3)
2 vessels	93 (25.6)	88 (25.4)
3 vessels	83 (22.9)	79 (22.8)
Therapeutic strategy after CA		
PCI	262 (78.0)	230 (71.7)
CABG	10 (3.0)	9 (2.8)
Medical therapy	64 (19.0)	82 (25.5)
PCI procedures		
Number of treated lesions		
1	176 (67.4)	150 (65.5)
2	71 (27.2)	58 (25.3)
≥3	14 (5.4)	21 (9.2)
Total stent length (per patient), mean (SD), mm	32.8 (19.1)	34.0 (20.2)

Primary end-point at 30-day

n (%)	Delayed group (n=362)	Very early group (n=346)	p-value
CV death or recurrent ischemic event	77 (21.3)	15 (4.4)	<0.001

A large benefit of an early invasive strategy



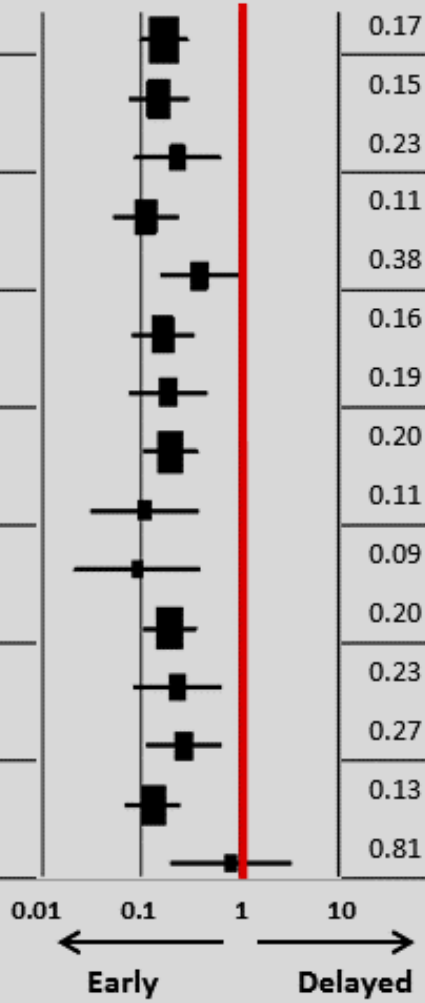
Secondary endpoints

At 30 days

n (%)	Delayed	Very early	p-value
All cause death, N (%)	4 (1.1)	2 (0.6)	0.69
CV death, N (%)	4 (1.1)	2 (0.6)	0.69
Recurrent ischemic events	75 (20.7)	14 (4.1)	<0.001
Symptoms of ischemia	71	13	
Ventricular arrhythmias	2	0	
Acute pulmonary edema	1	1	
Cardiogenic shock	1	0	
Myocardial infarction	3 (0.8)	4 (1.2)	0.72
BARC bleeding ≥3	3 (0.8)	1 (0.3)	0.62
Peak troponin (x UNL), median [IQR]	14 [1-76]	14 [2-81]	0,42
Length of stay in hospital, mean (SD), days	3.8 (5.8)	3.6 (7.5)	0,046

Pre-specified sub-groups analyses

	Subgroup	No. of patients	No. events Delayed group	No. events Early group	HR [95%CI]	p	Interaction p-value
All		705	77	15	0.17 [0.09-0.30]	<0.001	
Age	<=75 y	531	56	10	0.15 [0.08-0.30]	<0.001	0.490
	>75 y	174	21	5	0.23 [0.08-0.65]	0.003	
Sex	Men	499	58	8	0.11 [0.05-0.24]	<0.001	**0.041**
	Women	206	19	7	0.38 [0.15-0.96]	0.036	
Diabete	No	481	44	9	0.16 [0.08-0.35]	<0.001	0.828
	Yes	224	33	6	0.19 [0.08-0.47]	<0.001	
$P2Y_{12}$-ADP-recept. antag.	No	544	57	12	0.20 [0.10-0.38]	<0.001	0.407
	Yes	145	19	3	0.11 [0.03-0.39]	<0.001	
NSTEMI	No	220	20	2	0.09 [0.02-0.40]	<0.001	0.347
	Yes	480	56	13	0.20 [0.10-0,37]	<0.001	
GRACE score	]109-140]	245	18	5	0.23 [0.08-0.65]	0.003	0.826
	>140	183	27	7	0.27 [0.11-0.66]	0.003	
Therapeutic strategy	PCI	490	73	11	0.13 [0.07-0.25]	<0.001	**0.022**
	Others	164	4	4	0.81 [0.20-3.37]	1.00	



CONCLUSION

- 1st trial on the optimal timing of invasive strategy in intermediate and high-risk NSTE-ACS without P2Y12-ADP antagonist pretreatment
- Large benefit of a very early strategy (<2 hours) on recurrent ischemic events resulting in urgent revascularizations
- Homogenous in all sub-groups but for patients not receiving PCI

Thank you

- **Investigators:**

Centre hospitalier Marseille Timone: Pr Thomas Cuisset
Hôpital Européen Marseille : Dr Sébastien Armero
Hôpital de Toulon Saint Musse : Dr Gonzalo Quaino
Hôpital Saint Anne Toulon : Dr Raphael Poyet
Hôpital de Cannes : Dr Laurent Bali
Clinique Axium, Aix-En-Provence : Dr Luc Maillard
Centre Hospitalier d'Aix-en-Provence : Dr Bernard Jouve
Centre Hospitalier d'Avignon : Dr Barnay, Dr Pansieri, Dr Matthieu Pankert
Centre Hospitalier Universitaire de Nîmes : Pr Guillaume Cayla
Centre Hospitalier Universitaire de Lille : Pr Gilles Lemesle
Hôpital Européen Georges Pompidou,:Dr Etienne Puymirat
Hôpital Universitaire de Clermont Ferrand, Pr Motreff
Centre Hospitalier de Bastia: Dr Ziad Boueri

- **CEC :**

Clement Delmas, Centre Hospitalier Universitaire de Toulouse, France; Jean-Guillaume Dillinger, Hôpital Bichat, Assistance Publique des Hôpitaux de Paris, Paris, France; Axel De Labriolle, Clinique de Montauban, Montauban, France,

- **Research nurses**

Caroline Gouarne, Pauline Armangaud, Floriane Robin