Optimal Timing of Invasive Strategy in NSTEMI Patient : Immediate or Delayed?

Sang Yeub Lee, M.D., Ph.D.

Chungbuk National University, School of Medicine,

Chungbuk Regional Cardiovascular Center,

Chungbuk National University Hospital

Disclosure

- I have nothing to disclose in this issue.

Contents

- Guideline
- Key article in this issue
- Most recently published evidence
- Metaanalysis
- Conclusion

European guideline says

European Heart Journal (2016) **37**, 267–315
doi:10.1093/eurheartj/ehv320

ESC GUIDELINES

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

European Heart Journal (2016) 37, 267–315

Guideline says

- Risk criteria in patients with NSTEMI

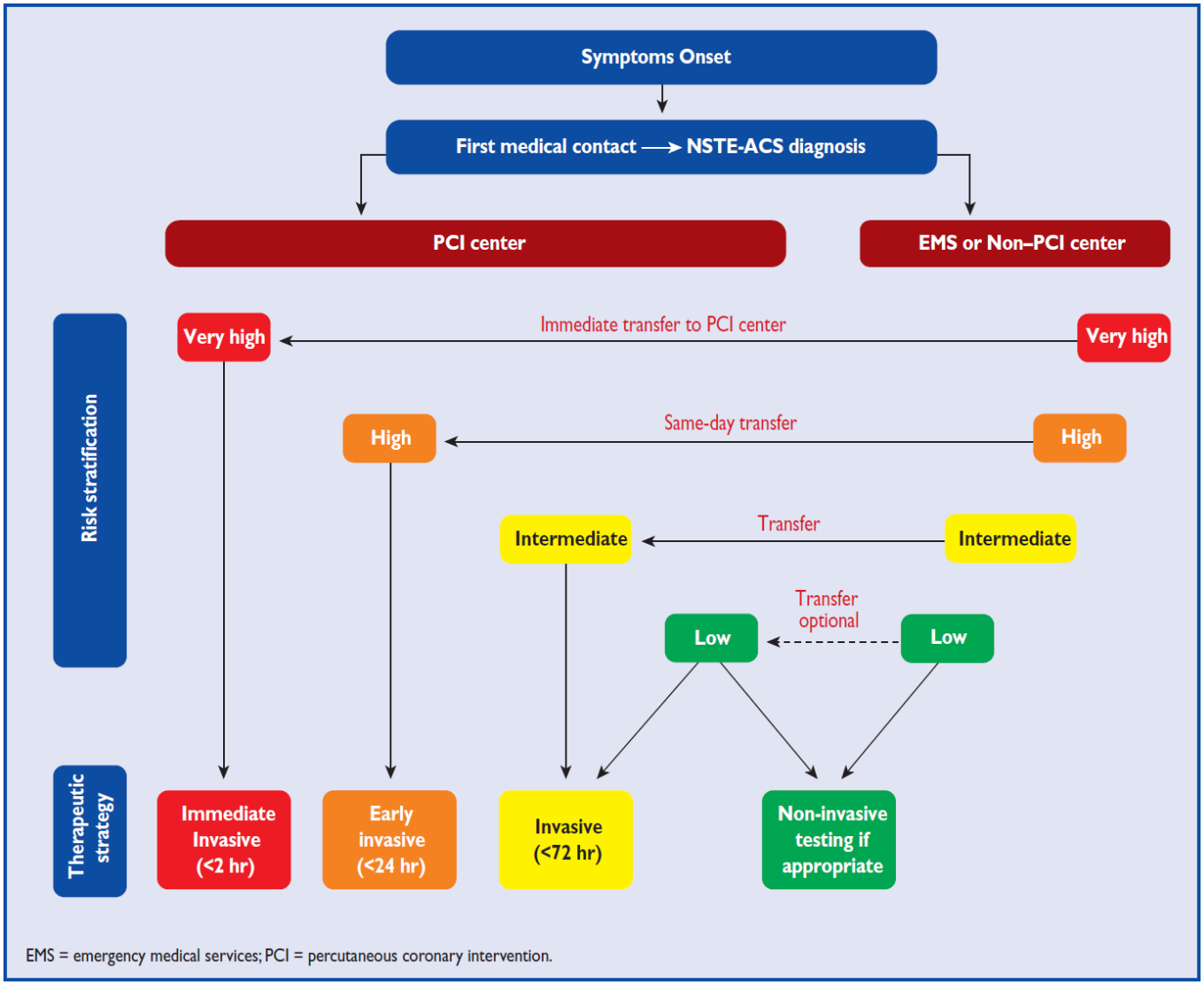
Table 13 Risk criteria mandating invasive strategy in NSTE-ACS

Very-high-risk criteria
• Haemodynamic instability or cardiogenic shock
• Recurrent or ongoing chest pain refractory to medical treatment
• Life-threatening arrhythmias or cardiac arrest
• Mechanical complications of MI
• Acute heart failure
• Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation
High-risk criteria
• Rise or fall in cardiac troponin compatible with MI
• Dynamic ST- or T-wave changes (symptomatic or silent)
• GRACE score >140
Intermediate-risk criteria
• Diabetes mellitus
• Renal insufficiency (eGFR <60 mL/min/1.73 m^2)
• LVEF <40% or congestive heart failure
• Early post-infarction angina
• Prior PCI
• Prior CABG
• GRACE risk score >109 and <140
Low-risk criteria
• Any characteristics not mentioned above

European Heart Journal (2016) 37, 267–315

Guideline says

- Selection of non-ST-elevation acute coronary syndrome (NSTE-ACS) treatment strategy and timing according to initial risk stratification.



European Heart Journal (2016) 37, 267–315

US Guideline says

- "It is reasonable to choose an early invasive strategy (within 24 h of admission) over a delayed invasive strategy (within 25 to 72 hours) for initially stabilized **high-risk patients** with NSTE-ACS. For patients **not at high/intermediate** risk, a delayed invasive approach is reasonable" (COR: II, LOE: B). : based on the results of the Intracoronary Stenting With Antithrombotic Regimen Cooling Off – ISAR-COLL
- Although the AHA/ACC recommend an early invasive strategy in patients at very high risk of ischemic events (COR: I, LOE: B), the ESC recommends **urgent angiography (<2 hours)** in these patients (COR: I, LOE: C).

Circulation 2014;130:2354-2394

Previous Key article : Cooling off Strategy, JAMA 2003

- early intervention : pretreatment less than 6hours
- Prolonged antithrombotic pretreatment : 3-5 days

528 Patients Assessed for Eligibility

Table 3. Incidence of Clinical Events During 30 Days

Event	No. (%) Prolonged Antithrombotic Pretreatment (n = 207)	No. (%) Early Intervention (n = 203)	RR (95% CI)	*P* Value
Death and nonfatal MI	24 (11.6)	12 (5.9)	1.96 (1.01-3.82)	.04
Death	3 (1.4)	0		.25
Nonfatal MI	21 (10.1)	12 (5.9)	1.72 (0.87-3.40)	.12
Q-wave	7 (3.4)	4 (2.0)	1.72 (0.51-5.77)	.54
Non–Q-wave	14 (6.8)	8 (3.9)	1.72 (0.74-4.00)	.21
Major bleeding event	8 (3.9)	6 (3.0)	1.31 (0.46-3.70)	.61
Nadir platelet count <20 × 10^3/μL	2 (1.0)	1 (0.5)	1.96 (0.18-21.5)	>.99

Abbreviations: CI, confidence interval; MI, myocardial infarction; RR, relative risk.

Conclusion In patients with unstable coronary syndromes, deferral of intervention for prolonged antithrombotic pretreatment does not improve the outcome compared with immediate intervention accompanied by intense antiplatelet treatment.

Neumann FJ, et al. *JAMA* 2003;290:1593

Another previous Key article : TIMACS NEJM 2009

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 21, 2009 VOL. 360 NO. 21

Early versus Delayed Invasive Intervention in Acute Coronary Syndromes

Shamir R. Mehta, M.D., M.Sc., Christopher B. Granger, M.D., William E. Boden, M.D., Philippe Gabriel Steg, M.D., Jean-Pierre Bassand, M.D., David P. Faxon, M.D., Rizwan Afzal, M.Sc., Susan Chrolavicius, R.N., Sanjit S. Jolly, M.D., M.Sc., Petr Widimsky, M.D., Alvaro Avezum, M.D., Hans-Jurgen Rupprecht, M.D., Jun Zhu, M.D., Jacques Col, M.D., Madhu K. Natarajan, M.D., M.Sc., Craig Horsman, B.Sc., Keith A.A. Fox, M.B., Ch.B., and Salim Yusuf, M.B., B.S., D.Phil., for the TIMACS Investigators*

Mehta SR, et al. *NEJM* 2009;360:

Table 1. Baseline Characteristics of the Patients, Medications, and Interventions after Randomization.*

Variable	Early Intervention (N=1593)	Delayed Intervention (N=1438)	P Value
Demographic characteristic			
Age (yr)	65.0	65.7	0.28
Female sex (%)	34.8	34.6	0.92
Medical history (%)			
Diabetes	26.5	27.4	0.58
Previous myocardial infarction	19.7	20.9	0.41
Previous stroke	7.2	7.5	0.71
Ischemic changes on ECG	80.5	79.9	0.69
Elevated cardiac biomarker	77.2	76.9	0.84
Previous coronary procedure (%)			
PCI	13.9	14.2	0.81
CABG	7.0	7.3	0.73
In-hospital medication (%)			
Aspirin	98.0	98.1	0.90
Thienopyridine	87.2	86.7	0.66
Clopidogrel			
Loading dose of 300 mg before PCI	81.0	85.7	<0.001
Loading dose of 600 mg before PCI	9.8	6.9	0.009
Glycoprotein IIb/IIIa inhibitor	23.2	22.4	0.61
Thienopyridine or glycoprotein IIb/IIIa inhibitor	88.2	88.4	0.87
Anticoagulant†	97.0	97.0	1.00
Heparin			
Unfractionated	24.6	24.7	0.97
Low-molecular-weight	64.6	63.9	0.70
Fondaparinux	41.3	41.8	0.81
Bivalirudin	0.4	0.5	0.85
Beta-blocker	86.8	86.9	0.93
Statin	85.1	84.3	0.56
Angiotensin-converting–enzyme inhibitor	74.2	73.6	0.70
Extent of coronary disease			0.70
Left main artery	10.0	9.5	
No. of vessels involved			
1	31.6	31.1	
2	24.5	23.4	
3	17.1	15.8	
Interventions after randomization			
Coronary angiography (%)	97.6	95.7	0.003
Median time (hr)	14	50	<0.001
Interquartile range (hr)	3–21	41– 81	
PCI (%)	59.6	55.1	0.01
Median time (hr)	16	52	<0.001
Interquartile range (hr)	3–23	41–101	
CABG (%)	14.8	13.6	0.56
Median time (days)	7.7	10.8	<0.001
Interquartile range (days)	4.7–17.4	6.7–19.8	

: TIMACS NEJM 2009

- routine early intervention (coronary angiography ≤24 hours after randomization)
- delayed intervention (coronary angiography ≥36 hours after randomization)

Mehta SR, et al. *NEJM* 2009;360:

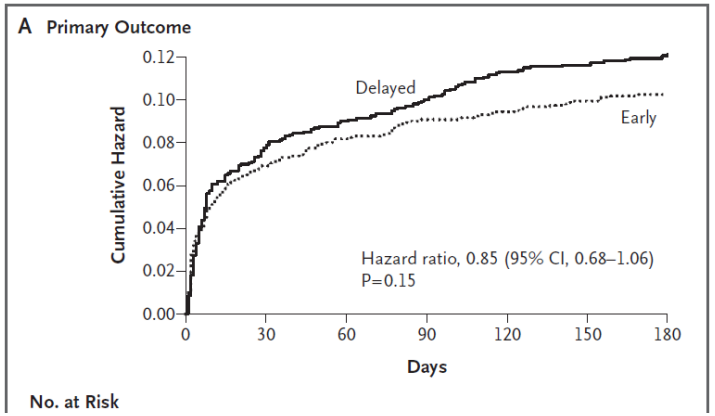
Another previous Key article : TIMACS NEJM 2009

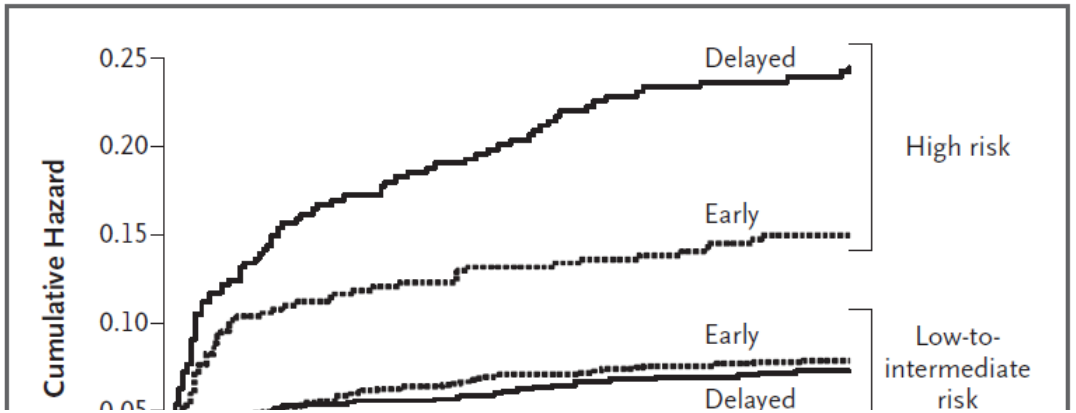
Table 2. Primary and Secondary Outcomes.*

Variable	Early Intervention (N = 1593)	Delayed Intervention (N = 1438)	Hazard Ratio (95% CI)	P Value
	percent			
At 6 mo				
Death, myocardial infarction, or stroke	9.6	11.3	0.85 (0.68–1.06)	0.15
Death, myocardial infarction, or refractory ischemia	9.5	12.9	0.72 (0.58–0.89)	0.003
Death, myocardial infarction, stroke, refractory ischemia, or repeat intervention	16.6	19.5	0.84 (0.71–0.99)	0.04
Death	4.8	5.9	0.81 (0.60–1.11)	0.19
Myocardial infarction	4.8	5.7	0.83 (0.61–1.14)	0.25
Stroke	1.3	1.4	0.90 (0.49–1.68)	0.74
Refractory ischemia	1.0	3.3	0.30 (0.17–0.54)	<0.001
Repeat intervention	8.7	8.5	1.04 (0.82–1.34)	0.73
At 30 days				
Death, myocardial infarction, or stroke	6.7	7.6	0.88 (0.67–1.15)	0.34
Death, myocardial infarction, or refractory ischemia	6.6	9.3	0.70 (0.54–0.90)	0.006
Death, myocardial infarction, stroke, refractory ischemia, or repeat intervention	12.0	13.0	0.91 (0.75–1.12)	0.37
Death	2.9	3.3	0.86 (0.58–1.29)	0.48
Myocardial infarction	3.6	4.1	0.87 (0.61–1.25)	0.46
Stroke	0.9	0.9	1.04 (0.50–2.19)	0.91
Refractory ischemia	1.0	3.1	0.30 (0.17–0.55)	<0.001
Repeat intervention	5.9	4.2	1.39 (1.01–1.93)	0.05

Mehta SR, et al. *NEJM* 2009;360:

Another previous Key article : TIMACS NEJM 2009





CONCLUSIONS

Early intervention did not differ greatly from delayed intervention in preventing the primary outcome, but it did reduce the rate of the composite secondary outcome of death, myocardial infarction, or refractory ischemia and was superior to delayed intervention in high-risk patients. (ClinicalTrials.gov number, NCT00552513.)

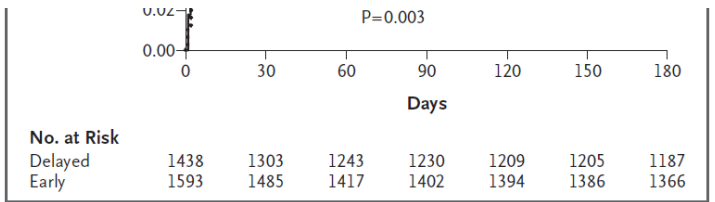


Figure 1. Kaplan–Meier Cumulative Risk of the Primary and Secondary Outcome at 6 Months.

Panel A shows the cumulative risk of the composite primary outcome of death, myocardial infarction, or stroke in the early-intervention group, as compared with the delayed-intervention group, with a nonsignificant between-group difference (P=0.15). Panel B shows the risk of the composite secondary outcome of death, myocardial infarction, or refractory ischemia, with a significant between-group difference (P=0.002).

Patients who had a risk score of more than 140 on the Global Registry of Acute Coronary Events (GRACE) scale (high risk) benefited more from early intervention than did patients with a score of 140 or less (low-to-intermediate risk) with respect to the composite primary outcome of death, myocardial infarction, or stroke.

Most recent evidence in this issue : RIDDLE JACC 2016

JACC: CARDIOVASCULAR INTERVENTIONS
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Immediate Versus Delayed Invasive Intervention for Non-STEMI Patients

The RIDDLE-NSTEMI Study

Aleksandra Milosevic, MD,[a,b] Zorana Vasiljevic-Pokrajcic, MD, PhD,[c] Dejan Milasinovic, MD,[a] Jelena Marinkovic, PhD,[b,d] Vladan Vukcevic, MD, PhD,[a,c] Branislav Stefanovic, MD, PhD,[a,b,c] Milika Asanin, MD, PhD,[a,b,c] Miodrag Dikic, MD,[a] Sanja Stankovic, PhD,[e] Goran Stankovic, MD, PhD[a,c]

J Am Coll Cardiol Intv 2016;9:541–9)

Most recent evidence in this issue

FIGURE 1 Study Flow Chart

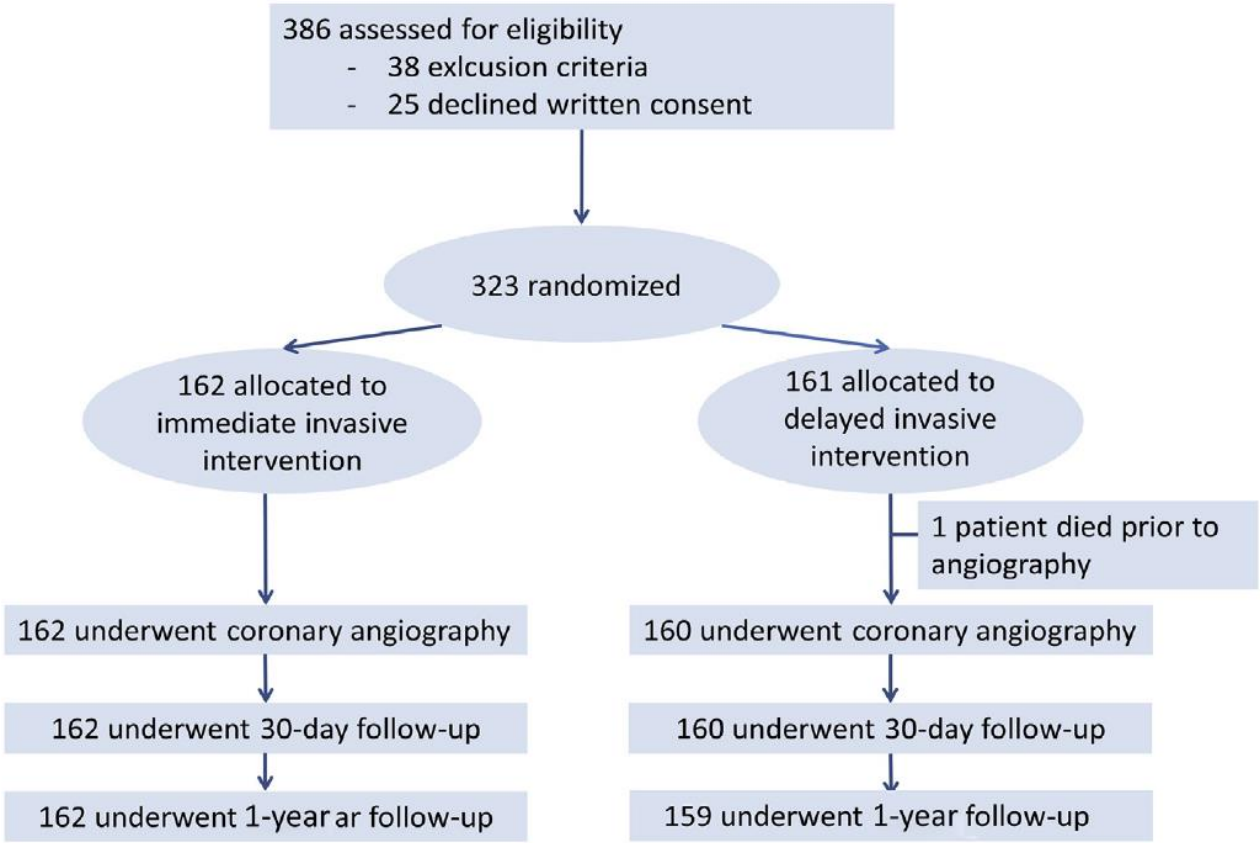

Diagram showing the flow of patients through each phase of the study. All randomized patients (n = 323) underwent 30-day follow-up for the primary endpoint.

J Am Coll Cardiol Intv 2016;9:541–9

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TABLE 3 Clinical Outcomes Up to 1 Year

	Immediate Intervention (n = 162)	Delayed Intervention (n = 161)*	HR (95% CI)†	p Value
30 days				
Death or MI	4.3	13.0	0.32 (0.13-0.74)	0.008
Death, MI, or recurrent ischemia	6.8	26.7	0.23 (0.12-0.45)‡	<0.001
Death§	3.1	3.1	0.98 (0.28-3.37)	0.97
MI	2.5	9.9	0.24 (0.08-0.70)	0.01
Recurrent ischemia	3.7	15.5	0.24 (0.10-0.57)‡	0.001
Major bleeding	0.6	0.6	0.99 (0.06-15.89)	0.99
31 days to 1 yr				
Death or MI	2.6	6.5	0.39 (0.12-1.27)	0.12
Death, MI, or recurrent ischemia	9.3	9.3	0.99 (0.45-2.19)‡	0.71
Death§	1.9	2.6	0.74 (0.17-3.31)	0.69
MI	0.6	4.3	0.15 (0.02-1.22)	0.07
Recurrent ischemia	6.5	2.2	2.99 (0.82-10.85)‡	0.06
Major bleeding	0.0	2.6	0.01 (0.01-46.38)	0.30
1 yr				
Death or MI	6.8	18.8	0.34 (0.17-0.67)	0.002
Death, MI, or recurrent ischemia	15.4	33.1	0.28 (0.15-0.51)‡	<0.001
Death§	4.9	5.6	0.87 (0.34-2.26)	0.78
MI	3.1	13.8	0.21 (0.08-0.55)	0.002
Recurrent ischemia	9.9	16.9	0.28 (0.12-0.63)‡	0.002
Major bleeding	0.6	3.1	0.20 (0.02-1.68)	0.14

Values are % unless other indicated. *In the delayed intervention group, 1 patient was not available for 1-year follow-up. †From unadjusted Cox regression models. ‡From an extended Cox regression model with assignment to immediate versus delayed invasive treatment as time-dependent variable. §All deaths were due to a cardiovascular cause.

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction.

- New MI, recurrent ischemia

J Am Coll Cardiol Intv 2016;9:541–9

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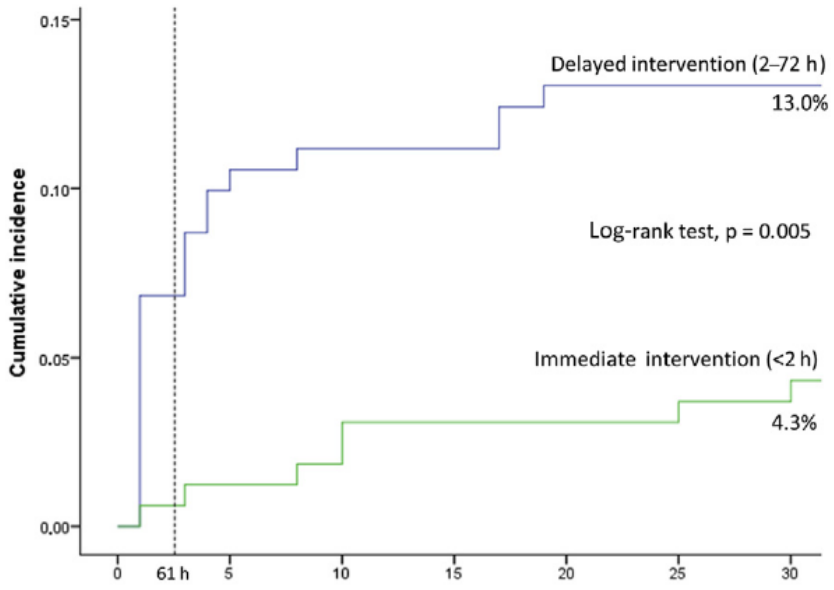
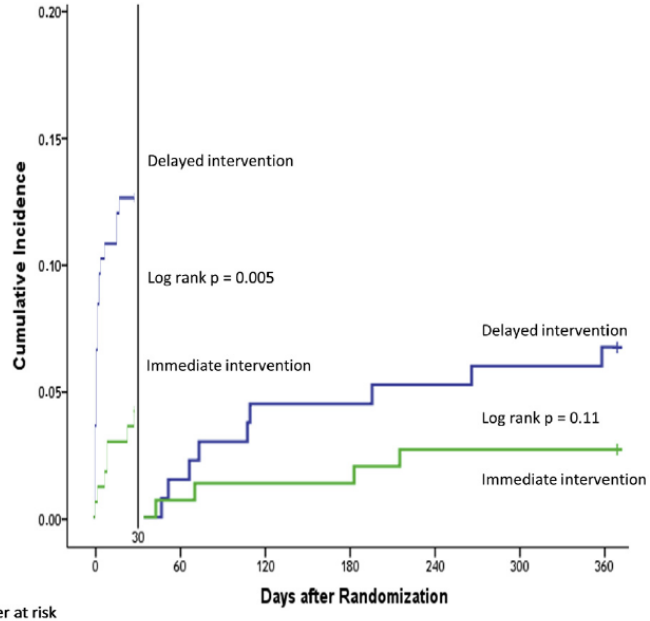
FIGURE 2 Cumulative Incidence of the Primary Endpoint



Number at risk							
Immediate intervention	162	160	159	157	157	157	155
Delayed intervention	161	145	143	143	140	140	140

FIGURE 3 Landmark Survival Analysis



Number at risk								
Immediate intervention	162	155	154	153	152	151	151	151
Delayed intervention	161	139	136	133	133	132	131	130

Cumulative incidence of the combined primary endpoint of death or new myocardial infarction at 30 days and thereafter for patients undergoing immediate versus delayed invasive inter-

CONCLUSIONS Immediate invasive strategy in NSTEMI patients is associated with lower rates of death or new MI compared with the delayed invasive strategy at early and midterm follow-up, mainly due to a decrease in the risk of new MI in the pre-catheterization period. (Immediate Versus Delayed Invasive Intervention for Non-STEMI Patients [RIDDLE-NSTEMI]; NCT02419833) (J Am Coll Cardiol Intv 2016;9:541–9) © 2016 by the American College of Cardiology Foundation.

J Am Coll Cardiol Intv 2016;9:541–9

Most recent evidence in this issue

- WHAT IS NEW? **An immediate invasive strategy** in NSTEMI patients is associated with **lower rates of death or MI at 30 days** compared with a delayed invasive strategy with a median time delay to intervention of 61 h. The observed difference is mainly due to **more frequent occurrence of new MI** in the period before catheterization of patients referred to delayed invasive intervention.
- WHAT IS NEXT? **Further large randomized studies with longer term** follow-up are needed to confirm these findings and to investigate whether the observed positive short-term effects of immediate invasive strategy in NSTEMI patients persist in the long term.

J Am Coll Cardiol Intv 2016;9:541–9

Most recent evidence in this issue : editorial

- Definition of " New MI"
- Most of event occurred within approximately the first 30 hrs.
- Much higher PCI in early group (78.4% vs. 65.0%, $p < 0.001$), a near doubling in the rate of CABG in the delayed group (12.3% vs. 23.8%, $p = 0.001$)

→ All observations could have led to increaesedrates of new MI in the delayed group and potentially influenced the results.

Wanger AD, et al. *J Clin Oncol* 2006;24:2903-9

Recent evidence in this issue : CAD 2016

Early versus delayed percutaneous coronary intervention in patients with non-ST elevation acute coronary syndromes

Matias B. Yudi[a,f], Andrew E. Ajani[b,c,f], Nick Andrianopoulos[c], Stephen J. Duffy[d], Omar Farouque[a,f], Jay Ramchand[a], Ronen Gurvitch[b], Jeffrey Lefkovits[b], Melanie Freeman[e], Angela Brennan[c], David J. Clark[a,f], Christopher Reid[c] and David Eccleston[b]; on behalf of the Melbourne Interventional Group

4307 patients with NSTEACS who underwent PCI
from the Melbourne Interventional Group registry.

Coronary Artery Disease 2016, 27:344–349

Recent evidence in this issue : CAD 2016

Table 1 Clinical characteristics, presentation, and angiographic characteristics

Table 4 Multivariate analysis (mortality at 12 months)

	Odds ratio	95% Confidence interval
Delayed PCI	0.95	0.68–1.32
eGFR <30 ml/min/1.73 m^2	9.34	5.74–15.22
eGFR 30–59 ml/min/1.73 m^2	3.17	2.18–4.61
Age	2.28	1.62–3.20
Positive cardiac biomarker	1.64	1.12–2.39
Previous CABG	1.33	0.86–2.05
Diabetes	1.31	0.93–1.83
Previous MI	1.22	0.83–1.79

CABG, coronary artery bypass graft surgery; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention.

MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

use

Coronary Artery Disease 2016, 27:344–349

Recent evidence in this issue : CAD 2016

Early versus delayed percutaneous coronary intervention in patients with non-ST elevation acute coronary syndromes

Matias B. Yudi[a,f], Andrew E. Ajani[b,c,f], Nick Andrianopoulos[c], Stephen J. Duffy[d], Omar Farouque[a,f], Jay Ramchand[a], Ronen Gurvitch[b], Jeffrey Lefkovits[b], Melanie Freeman[e], Angela Brennan[c], David J. Clark[a,f], Christopher Reid[c] and David Eccleston[b]; on behalf of the Melbourne Interventional Group

Conclusion

In patients with stable NSTEACS treated with PCI, delayed intervention was performed in those who were older and had higher risk features. However, there appears to be

no mortality hazard for these high-risk patients where PCI is delayed beyond the first 24 h after presentation and performed within the index admission.

Coronary Artery Disease 2016, 27:344–349

Meta-analysis 1 : JACC CV Interv 2016

CLINICAL RESEARCH

CORONARY

Timing of Coronary Invasive Strategy in Non–ST-Segment Elevation Acute Coronary Syndromes and Clinical Outcomes

An Updated Meta-Analysis

Laurent Bonello, MD, PhD,[a,b,c] Marc Laine, MD,[a,c] Etienne Puymirat, MD, PhD,[d,e] Gilles Lemesle, MD, PhD,[f] Franck Thuny, MD, PhD,[a,c] Franck Paganelli, MD,[a] Pierre Michelet, MD, PhD,[c,g] Antoine Roch, MD, PhD,[c,h] François Kerbaul, MD, PhD,[c,i] Laurent Boyer, MD, PhD[j]

J Am Coll Cardiol Intv 2016;9:2267–76

TABLE 1 Timing of Invasive Approach, Definitive Treatment, and Clinical Outcomes at Follow-Up for the 10 Randomized Controlled Trials Comparing Early and Delayed Strategies

First Author (Year) (Ref. #)	Trial Name	Median Time of Catheterization, h		Patients, n		Definitive Treatment, n (%)		Clinical Outcome
		Early	Late	Early	Late			
van't Hof et al. (2003) (12)	ELISA	6	50	109	111	PCI: 66 (60.5) CABG: 15 (13.8) Medical: 27 (24.7)	PCI: 64 (57.7) CABG: 21 (18.9) Medical: 25 (23.4)	Death, MI, major bleeding, re-PCI, RA
Neumann et al. (2003) (13)	ISAR-COOL	2.4	86	203	207	PCI: 143 (70.4) CABG: 16 (7.9) Medical: 44 (21.7)	PCI: 133 (64.3) CABG: 16 (7.7) Medical: 58 (28.0)	Death, MI, major bleeding, RI
Mehta et al. (2009) (5)	TIMACS	14	50	1,593	1,438	PCI: 954 (59.9) CABG: 225 (16.0) Medical: 384 (24.1)	PCI: 796 (55.4) CABG: 219 (15.2) Medical: 423 (29.4)	Death, MI, major bleeding, re-PCI, RA
Riezebos et al. (2009) (7)	OPTIMA	0.5	25	73	69	PCI: 73 (100.0)	PCI: 69 (100.0)	Death, MI, major bleeding, re-PCI
Montalescot et al. (2009) (14)	ABOARD	1.1	20.5	175	177	PCI: 117 (66.9) CABG: 16 (9.1) Medical: 42 (24.0)	PCI: 105 (59.3) CABG: 17 (9.6) Medical: 55 (31.1)	Death, MI, major bleeding, re-PCI, RI
Zhang et al. (2010) (9)		9.3	49.9	446	369	PCI: 314 (70.4) CABG: 41 (9.2) Medical: 91 (20.4)	PCI: 252 (68.3) CABG: 37 (10.1) Medical: 80 (21.6)	Death, MI, Major bleeding, re-PCI, RI
Thiele et al. (2012) (8)	LIPSIA-NSTEMI	1.1	18.3	200	200	PCI: 151 (75.5) CABG: 16 (8.0) Medical: 33 (16.5)	PCI: 141 (71.0) CABG: 25 (13.0) Medical: 34 (17.0)	Death, MI, RI, in-hospital bleeding
Badings et al. (2013) (10)	ELISA 3	2.6	54.9	269	265	PCI: 180 (66.7) CABG: 62 (23.2) Medical: 27 (10.1)	PCI: 164 (61.9) CABG: 68 (25.7) Medical: 33 (12.4)	Death, re-infarction RI, major bleeding
Reuter et al. (2014) (23)	SISCA	2.8	20.9	83	87	PCI: 45 (58.0) CABG: 8 (10.0) Medical: 25 (32.0)	PCI: 45 (59.0) CABG: 8 (11.0) Medical: 23 (30.0)	Death, myocardial infarction, urgent revascularization, major bleeding
Milosevic et al. (2016) (11)	RIDDLE-NSTEMI	1.4	61	162	161	PCI: 127 (78.4) CABG: 20 (12.3) Medical: 15 (9.3)	PCI: 105 (65.0) CABG: 38 (23.8) Medical: 18 (11.2)	Death, myocardial infarction, RI, major bleeding

Meta-analysis 1 : JACC CV Interv 2016

TABLE 2 Summary Odds Ratios or Standardized Mean Differences for Major Clinical Outcomes Comparing Early and Delayed Intervention at the Latest Follow-Up Available

Outcome	p Value (Q)	I^2	Random Effects (95% CI)	p Value
Death*	0.86	0.00	0.85 (0.67 to 1.09)	0.20
MI*	<0.01	77.54	0.88 (0.53 to 1.45)	0.62
RI*	0.21	28.34	0.55 (0.40 to 0.74)	<0.01
Major bleeding*	0.56	0.00	0.94 (0.73 to 1.22)	0.64
LOS†	<0.01	79.40	−0.40 (−0.59 to −0.21)	<0.01

*Odds ratio. †Standardized mean difference.

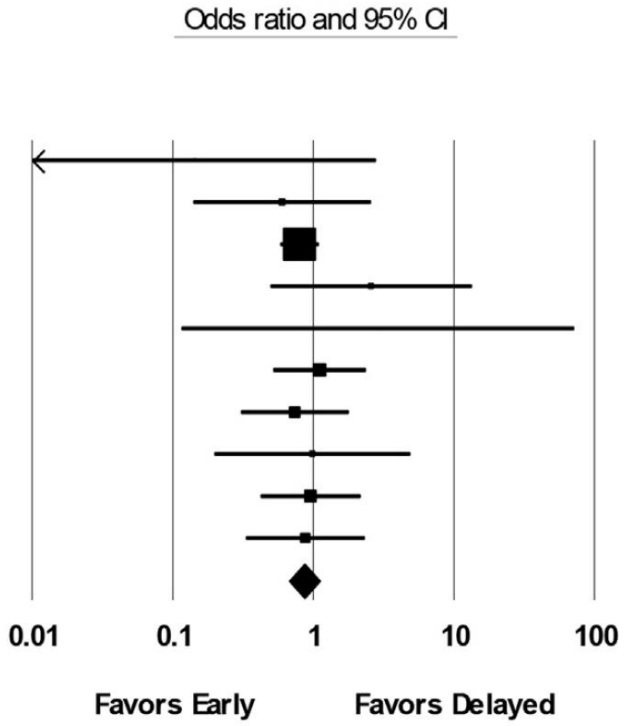
CI = confidence interval; MI = myocardial infarction; RI = recurrent ischemia; Q = Cochran Q test.

J Am Coll Cardiol Intv 2016;9:2267–76

Meta-analysis 1 : JACC CV Interv 2016

FIGURE 1 Individual and Summary Odds Ratios for Mortality in Randomized Trials Comparing Early and Delayed Invasive Strategies

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	



CI = confidence interval; other abbreviations as in Table 1.

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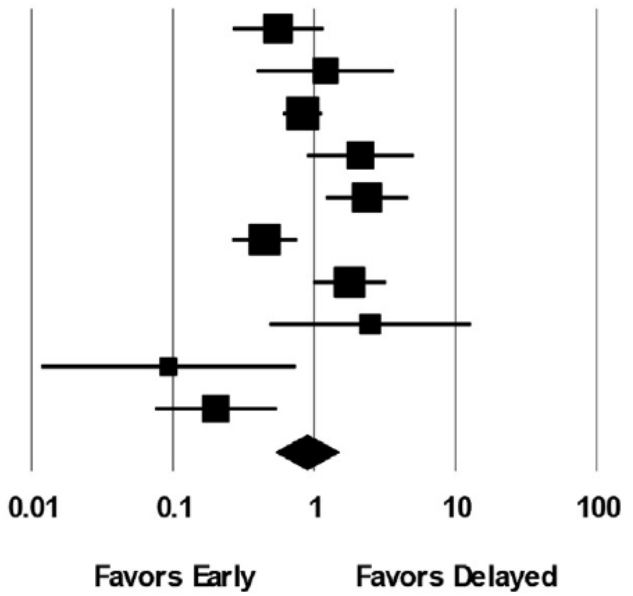
FIGURE 2 Individual and Summary Odds Ratios for Myocardial Infarction in randomized Trials Comparing Early and Delayed Invasive Strategies

Study name	Events / Total		Statistics for each study				
	Early strategy	Delayed strategy	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
ISAR-COOL	12 / 203	21 / 207	0.56	0.27	1.16	0.12	11.3
ELISA	7 / 109	6 / 111	1.20	0.39	3.70	0.75	8.5
TIMACS	76 / 1593	82 / 1438	0.83	0.60	1.14	0.25	14.0
ABOARD	16 / 175	8 / 177	2.13	0.89	5.10	0.09	10.2
OPTIMA	44 / 73	27 / 69	2.36	1.20	4.63	0.01	11.7
Zhang et al, 2010	23 / 446	40 / 369	0.45	0.26	0.76	0.00	12.7
LIPSIA-NSTEMI	33 / 200	20 / 200	1.78	0.98	3.22	0.06	12.3
ELISA 3	5 / 269	2 / 265	2.49	0.48	12.95	0.28	5.7
SISCA	1 / 83	10 / 86	0.09	0.01	0.74	0.02	4.2
RIDDLE-NSTEMI	5 / 162	22 / 161	0.20	0.07	0.55	0.00	9.4
			0.88	0.53	1.45	0.62	



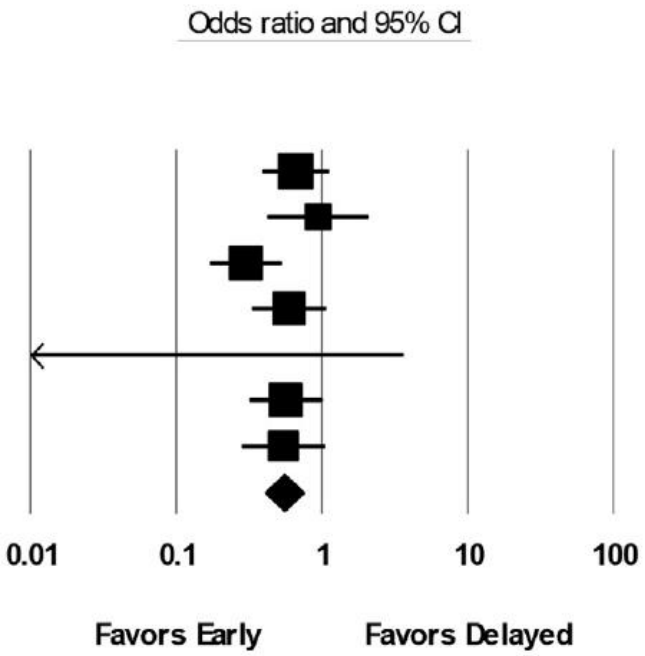
CI = confidence interval; other abbreviations as in Table 1.

J Am Coll Cardiol Intv 2016;9:2267–76

Meta-analysis 1 : JACC CV Interv 2016

FIGURE 3 Individual and Summary Odds Ratios for Recurrent Ischemia or Refractory Angina in Randomized Trials Comparing Early and Delayed Invasive Strategies

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	



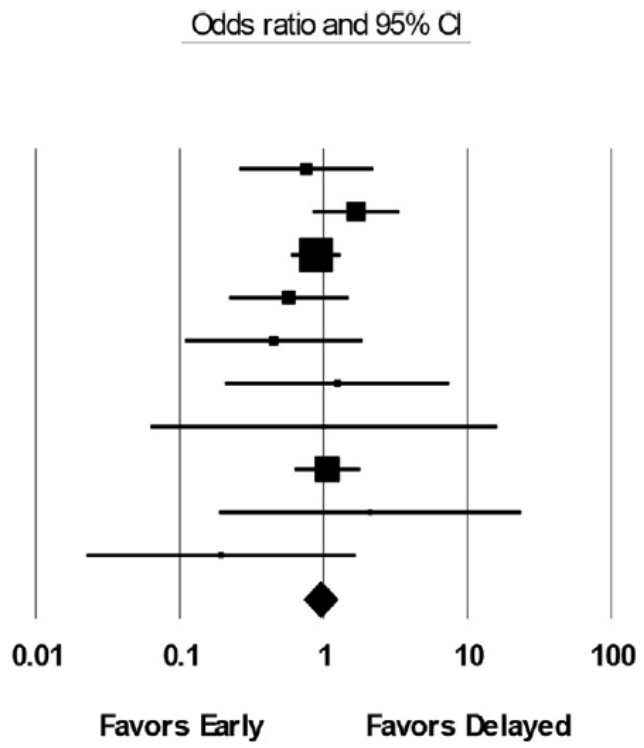
CI = confidence interval; other abbreviations as in Table 1.

J Am Coll Cardiol Intv 2016;9:2267–76

Meta-analysis 1 : JACC CV Interv 2016

FIGURE 4 Individual and Summary Odds Ratios for Major Bleeding in Randomized Trials Comparing Early and Delayed Invasive Strategies

Study name	Events / Total		Statistics for each study				
	Early strategy	Delayed strategy	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
ISAR-COOL	6 / 203	8 / 207	0.76	0.26	2.22	0.61	5.7
ELISA	24 / 109	16 / 111	1.68	0.84	3.37	0.15	13.6
TIMACS	49 / 1593	50 / 1438	0.88	0.59	1.32	0.54	41.2
ABOARD	7 / 175	12 / 177	0.57	0.22	1.49	0.25	7.2
OPTIMA	3 / 73	6 / 69	0.45	0.11	1.87	0.27	3.2
Zhang et al, 2010	3 / 446	2 / 369	1.24	0.21	7.48	0.81	2.1
LIPSIA-NSTEMI	1 / 200	1 / 200	1.00	0.06	16.10	1.00	0.9
ELISA 3	32 / 269	30 / 265	1.06	0.62	1.80	0.84	23.6
SISCA	2 / 83	1 / 86	2.10	0.19	23.59	0.55	1.1
RIDDLE-NSTEMI	1 / 162	5 / 161	0.19	0.02	1.68	0.14	1.4
			0.94	0.73	1.22	0.64	



CI = confidence interval; other abbreviations as in Table 1.

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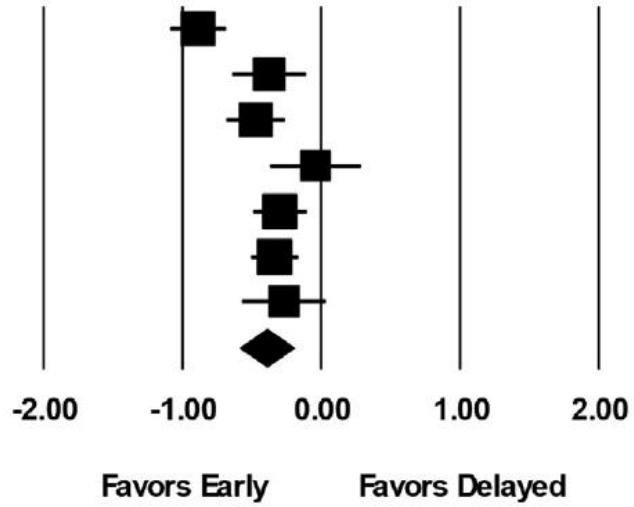
Meta-analysis 1 : JACC CV Interv 2016

FIGURE 5 Individual and Summary Standardized Mean Difference for In-Hospital Length of Stay in Randomized Trials Comparing Early and Delayed Invasive Strategies

Study name	Std diff in means	Standard error	Lower limit	Upper limit	p-Value	Relative weight
ISAR-COOL	-0.89	0.10	-1.09	-0.68	0.00	15.3
ELISA	-0.38	0.14	-0.64	-0.11	0.01	13.6
ABOARD	-0.47	0.11	-0.68	-0.26	0.00	15.1
OPTIMA	-0.04	0.17	-0.37	0.29	0.81	11.9
LIPSIA-NSTEMI	-0.30	0.10	-0.49	-0.10	0.00	15.4
ELISA 3	-0.34	0.09	-0.51	-0.16	0.00	16.1
SISCA	-0.27	0.15	-0.57	0.03	0.08	12.6
	-0.40	0.10	-0.59	-0.21	0.00	



CI = confidence interval; Std diff in means = standardized mean difference; other abbreviations as in Table 1.

J Am Coll Cardiol Intv 2016;9:2267–76

Meta-analysis 1 : JACC CV Interv 2016

The present updated meta-analysis suggests that there is **no difference in death or MI** between early and delayed invasive strategies in patients with NSTE-ACS. However, an **early strategy is safe and reduces both the rates of RI or RA and in-hospital LOS**.

Meta-analysis 2 : Atherosclerosis 2016

Atherosclerosis 241 (2015) 48–54

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Timing of invasive strategy in NSTE-ACS patients and effect on clinical outcomes: A systematic review and meta-analysis of randomized controlled trials

Dejan Milasinovic [a], Aleksandra Milosevic [a, d], Jelena Marinkovic [b, c], Vladan Vukcevic [a, b], Arsen Ristic [a, b], Milika Asanin [a, b, d], Goran Stankovic [a, b, *]

[a] *Department of Cardiology, Clinical Center of Serbia, Belgrade, Serbia*
[b] *Faculty of Medicine, University of Belgrade, Belgrade, Serbia*
[c] *Institute for Medical Statistics and Informatics, Belgrade, Serbia*
[d] *Emergency Department, Department of Cardiology, Clinical Center of Serbia, Belgrade, Serbia*

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Meta-analysis 2 : Atherosclerosis 2016

Table 1
Main study characteristics.

Study	TIMACS		ELISA		ISAR-COOL		OPTIMA		ABOARD		LIPSIA-NSTEMI		ELISA-3		Tekin et al.		Sciahbasi et al.		Zhang et al.	
	Early	Delayed	Early	Late	Early	Delayed	Immed.	Defer.	Immed.	Delayed	Immed.	Early	Early	Delayed	Early	Delayed	Immed.	Early	Early	Delayed
No. of patients	1593	1438	109	111	203	207	73	69	175	177	200	200	269	265	69	62	27	27	446	369
Median time to angio (h)	14.0	50.0	6.0	50.0	2.4	86.0	0.5	25.0[c]	1.1	20.5	1.1	18.3	2.6	54.9	<24	24–72	5	24	9.3	49.9
Median (mean) age	65.0	65.7	63.0	65.0	70.0	70.0	63.0	62.0	65.0	65.0	68.0	70.0	72.1	71.8	58.1	55.6	58.8	59.7	67.0	66.1
Female (%)	34.8	34.6	28.0	32.0	34.0	32.4	30.0	26.0	27.4	29.4	34.0	30.0	30.5	34.3	40.6	28.8	18.5	11.1	33.9	32.2
Diabetes (%)	26.5	27.4	15.0	14.0	26.1	31.4	19.0	20.0	21.7	32.2	39.0	43.0	23.8	20.4	31.9	45.2	26.0	18.5	23.5	22.5
NSTEMI at baseline (%)	77.2	76.9	78.0	71.0	66.0	67.6	47.0	45.0	75.4	72.9	100	100	nr		100	100	nr		79.1	77.8
PCI rate (%)	59.6	55.1	61	58	70.4	64.3	n/a[c]		66.9[e]	59.3[e]	76.0	71.0	66.7	61.9	100	100	100	100	70.4	68.3
Primary end point	9.6	11.3[a]	629	432[b]	5.9	11.6[b]	60.0	39.0[b]	2.1	1.7[a]	0.94	0.78[a]	9.9	14.2[a]	59.3 8.7	54.1[d] 30.6	26	69[d]	9.0	14.6[b]
	death, new MI or stroke at 6 months (%)		area under the curve of 48-h LDH release		death or non-fatal MI at 30 days (%)		death, non-fatal MI or unplanned revasc. at 30 days (%)		In-hospital peak Troponin I (ng/ml)		In-hospital peak CK-MB activity (μkat/L)		Death, reinfarction or recurrent ischemia at 30 days (%)		LVEF/Death, re-MI or rehosp., at 3 months (%)		Peak CK-MB (ng/ml)		Death, MI or stroke at 6 months (%)	

nr – not reported; NSTEMI – non-ST-segment elevation myocardial infarction; LVEF – left ventricular ejection fraction; CK-MB – creatine kinase MB isoenzyme.
[a] Not statistically significant ($p > 0.05$).
[b] Statistically significant ($p < 0.05$).
[c] All patients underwent early coronary angiography and were then randomized into immediate versus deferred PCI group.
[d] No primary end-point was formally defined in the manuscript.
[e] PCI rate in the overall study population.

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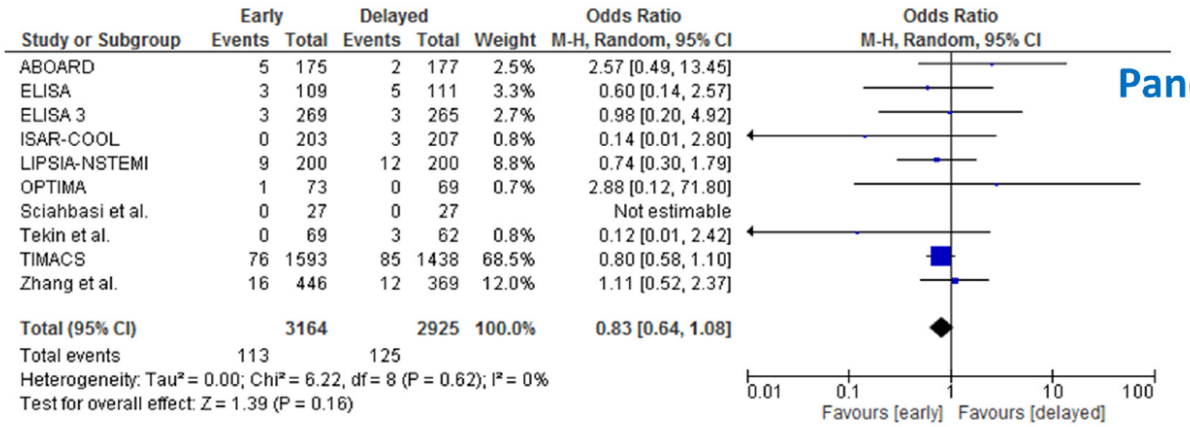

Study or Subgroup	Early Events	Early Total	Delayed Events	Delayed Total	Weight	Odds Ratio M-H, Random, 95% CI
ABOARD	5	175	2	177	2.5%	2.57 [0.49, 13.45]
ELISA	3	109	5	111	3.3%	0.60 [0.14, 2.57]
ELISA 3	3	269	3	265	2.7%	0.98 [0.20, 4.92]
ISAR-COOL	0	203	3	207	0.8%	0.14 [0.01, 2.80]
LIPSIA-NSTEMI	9	200	12	200	8.8%	0.74 [0.30, 1.79]
OPTIMA	1	73	0	69	0.7%	2.88 [0.12, 71.80]
Sciahbasi et al.	0	27	0	27		Not estimable
Tekin et al.	0	69	3	62	0.8%	0.12 [0.01, 2.42]
TIMACS	76	1593	85	1438	68.5%	0.80 [0.58, 1.10]
Zhang et al.	16	446	12	369	12.0%	1.11 [0.52, 2.37]
Total (95% CI)		**3164**		**2925**	**100.0%**	**0.83 [0.64, 1.08]**
Total events	113		125			

Heterogeneity: Tau² = 0.00; Chi² = 6.22, df = 8 (P = 0.62); I² = 0%
Test for overall effect: Z = 1.39 (P = 0.16)

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours [early] Favours [delayed]

Panel A Death

Study or Subgroup	Early Events	Early Total	Delayed Events	Delayed Total	Weight	Odds Ratio M-H, Random, 95% CI
ABOARD	16	175	8	177	10.9%	2.13 [0.89, 5.10]
ELISA	7	109	6	111	8.8%	1.20 [0.39, 3.70]
ELISA 3	5	269	2	265	5.6%	2.49 [0.48, 12.95]
ISAR-COOL	12	203	21	207	12.2%	0.56 [0.27, 1.16]
LIPSIA-NSTEMI	33	200	20	200	13.6%	1.78 [0.98, 3.22]
OPTIMA	44	73	27	69	12.8%	2.36 [1.20, 4.63]
Tekin et al.	2	69	9	62	6.0%	0.18 [0.04, 0.85]
TIMACS	76	1593	82	1438	16.0%	0.83 [0.60, 1.14]
Zhang et al.	23	446	40	369	14.2%	0.45 [0.26, 0.76]
Total (95% CI)		**3137**		**2898**	**100.0%**	**1.02 [0.63, 1.64]**
Total events	218		215			

Heterogeneity: Tau² = 0.34; Chi² = 30.83, df = 8 (P = 0.0002); I² = 74%
Test for overall effect: Z = 0.08 (P = 0.94)

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours [early] Favours [delayed]

Panel B MI

Study or Subgroup	Early Events	Early Total	Delayed Events	Delayed Total	Weight	Odds Ratio M-H, Random, 95% CI
ABOARD	21	175	33	177	16.6%	0.60 [0.33, 1.08]
ELISA	13	109	14	111	11.8%	0.94 [0.42, 2.10]
ELISA 3	20	269	33	265	16.9%	0.56 [0.32, 1.01]
ISAR-COOL	27	203	39	207	18.3%	0.66 [0.39, 1.13]
LIPSIA-NSTEMI	0	200	13	200	1.4%	0.03 [0.00, 0.59]
TIMACS	16	1593	47	1438	17.2%	0.30 [0.17, 0.53]
Zhang et al.	26	446	29	369	17.9%	0.73 [0.42, 1.26]
Total (95% CI)		**2995**		**2767**	**100.0%**	**0.56 [0.40, 0.79]**
Total events	123		208			

Heterogeneity: Tau² = 0.10; Chi² = 11.38, df = 6 (P = 0.08); I² = 47%
Test for overall effect: Z = 3.26 (P = 0.001)

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours [early] Favours [delayed]

Panel C recurrent ischemia

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Conclusion

- There is **no mortality difference** between an early and a delayed invasive strategy in patients with **NSTE-ACS**. An early invasive strategy **reduces RI and in-hospital LOS**.

- Future trials should determine whether the results are different depending on **subgroups of patients on the basis of their risk profiles**. In addition, whether
- these results are valid for patients without pre-treatment with P2Y12 ADP receptor antagonists should be evaluated.

- We are waiting the results of **NONSTEMI trial** (Acute Versus Subacute Angioplasty in Patients With NON-ST-Elevation Myocardial Infarction).

Thank You For Your Attention