Meta Analysis

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(10) 1–13

DOI: 10.1177/0300060520966500
journals.sagepub.com/home/imr
SAGE

Early invasive strategy for non-ST elevation acute coronary syndrome: a meta-analysis of randomized, controlled trials

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Abstract

Objective: Patients with non-ST elevation acute coronary syndrome (NSTE-ACS) benefit from coronary intervention, but the optimal timing for an invasive strategy is not well defined. This study aimed to determine whether an early invasive strategy (<12 hours) is superior to a delayed invasive strategy.

Methods: Twelve studies of nine randomized, controlled trials of 8586 patients were included.

Results: There were no significant differences in all-cause death (risk ratio [95% confidence interval]) (0.90, [0.77–1.06), re-myocardial infarction (re-MI) (0.95 [0.70–1.29]), major bleeding (0.97 [0.77–1.23]), and refractory ischemia (0.74 [0.53–1.05]) when we compared use of early and delayed invasive strategies. Furthermore, analysis of the effect of the chosen strategy on high-risk patients showed that the rate of composite death or re-MI was significantly decreased in patients with either a Global Registry of Acute Coronary Events (GRACE) risk score >140 or with elevated troponin levels (risk ratio 0.82 [0.72–0.92]; risk ratio 0.84 [0.76–0.93], respectively).

Conclusions: This meta-analysis shows that an early angiographic strategy does not improve clinical outcome in patients with NSTE-ACS. An early invasive strategy might reduce the rate of composite death or re-MI in high-risk patients with GRACE risk scores >140 or elevated cardiac markers.

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Keywords
Invasive strategy, non-ST elevation acute coronary syndrome, early intervention, coronary angiography, myocardial infarction, composite death

Date received: 24 February 2020; accepted: 24 September 2020

Introduction

Coronary revascularization improves clinical outcomes in patients with non-ST elevation acute coronary syndrome (NSTE-ACS). The American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines suggest that patients with NSTE-ACS should undergo coronary angiography within 2 hours when patients meet a high-risk condition. Coronary angiography should be performed within 24 hours in patients who are initially stabilized, especially in high- and intermediate-high-risk patients.[1] However, the optional timing of intervention for NSTE-ACS is controversial.

Several randomized, controlled trials (RCTs) and meta-analyses showed that an early invasive strategy (<24 hours) did not significantly improve the risk of all-cause death or recurrent myocardial infarction (re-MI).[2–4] In contrast, one meta-analysis reported that an early invasive strategy improved the clinical outcome.[5] In the TIMACS trial,[2] coronary interventions were performed either within 24 hours (median time after randomization: 14 hours) or 36 hours after randomization in patients with acute coronary syndrome (ACS). In this trial, the primary outcome (death, MI, or stroke) was similar between patients with early and delayed intervention, but a significant beneficial effect on the secondary endpoint of refractory ischemia (RI) was found in the early intervention group. However, whether this benefit was associated with the intervention time, which was conducted within 14 hours in patents with ACS, is unknown. Furthermore, recently, some investigators examined whether an early (<12 hours) intervention strategy is superior to a delayed invasive strategy in patients with NSTE-ACS. Deharo et al. found that high-risk patients (Global Registry of Acute Coronary Events [GRACE] risk score >140) with non-ST elevation myocardial infarction (NSTEMI) who underwent coronary angiography within 12 hours had a reduced risk of death and re-MI compared with patients who underwent intervention within 12 to 24 or >24 hours.[6]

To date, there is no definite conclusion regarding coronary angiography within 12 hours versus a delayed invasive strategy for NSTE-ACS. Regardless of admission time, the first 12 hours after admission allows most patients to be scheduled during the day, which could be more reasonable. Therefore, we conducted this meta-analysis to investigate whether coronary angiography performed within 12 hours post-MI improves clinical outcomes in high- to moderate-risk patients with NSTE-ACS.

Methods

Data sources and search parameters

We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for appropriate studies that were

performed from 1990 to 24 April 2019. The search terms included invasive strategy, invasive coronary angiography, early coronary intervention, delayed coronary intervention, acute coronary syndrome, non-ST elevation myocardial infarction, unstable angina, non-ST elevation acute coronary syndrome, NSTE-ACS, and NSTEMI. Review articles, editorials, and meta-analyses were also considered to assess potential information for this study. We did not include unpublished research. Data selection was performed by two investigators independently. There were no restrictions on language, study period, or sample size.

Study selection, data extraction, and quality assessment

We included RCTs that met the following criteria: (1) enrolled patients had NSTE-ACS; (2) each trial compared an early invasive strategy with a delayed invasive strategy, where an early invasive strategy was defined as coronary intervention performed within 12 hours after enrollment and a delayed invasive strategy was defined as intervention performed on the next working day after enrollment or at least 12 hours after hospitalization; and (3) clinical follow-up must have occurred at least 30 days after the intervention. For all clinical events, we used the longest available follow-up period for each trial. The quality of RCTs was assessed using the Cochrane Collaboration's tool for assessing the risk of bias for RCTs.[7]

Endpoints and definitions

The primary endpoint was all-cause death. Secondary endpoints were re-MI, recurrent or refractory ischemia (RI), and major bleeding. If the trials reported refractory angina (RA) instead of RI, RA was used for the secondary endpoint analysis.

Data synthesis and analysis

The included data were combined to estimate the pooled risk ratio (RR) of an early invasive strategy versus a delayed invasive strategy as the comparator treatment. Subgroup analyses were performed to evaluate 1) the rate of death and re-MI in the two invasive groups at 30 days and at long-term follow-up (>1 year), and 2) the rate of composite death or re-MI in the early and delayed invasive strategies for high-risk patients. Statistical analysis was performed using Stata software version 12.0 (Stata Corp, College Station, TX, USA). The RR with 95% confidence intervals (CIs) are shown as the summary statistic. We used Q and I^2 statistics to analyze heterogeneity among the included trials. The Q statistic indicated heterogeneity when P values were <0.10, whereas $I^2 \leq 50\%$ indicated that the magnitude of heterogeneity was moderate. If I^2 was $>50\%$ or P was <0.10, a random-effects model was adopted. We also performed a sensitivity analysis by sequentially excluding each study if I^2 was $>50\%$ or P was <0.10, and computed a meta-analysis. Results were considered statistically significant at $P \leq 0.05$.

Results

A total of 764 relevant trials were found using our search parameters. Finally, 12 studies of 9 trials that satisfied our selection criteria were included, involving a total of 8586 patients (Figure 1).[6,8–18] Three trials, namely, OPTIMA, ELISA-3, and RIDDLE-NSTEMI, were updated with long-term follow-up clinical outcomes at 5, 2, and 3 years, respectively.[11,12,14–17] Studies in which coronary intervention was performed 12 hours or later after hospitalization or there was randomization in the early invasive strategy were not included. Of those trials, there were 3907 patients

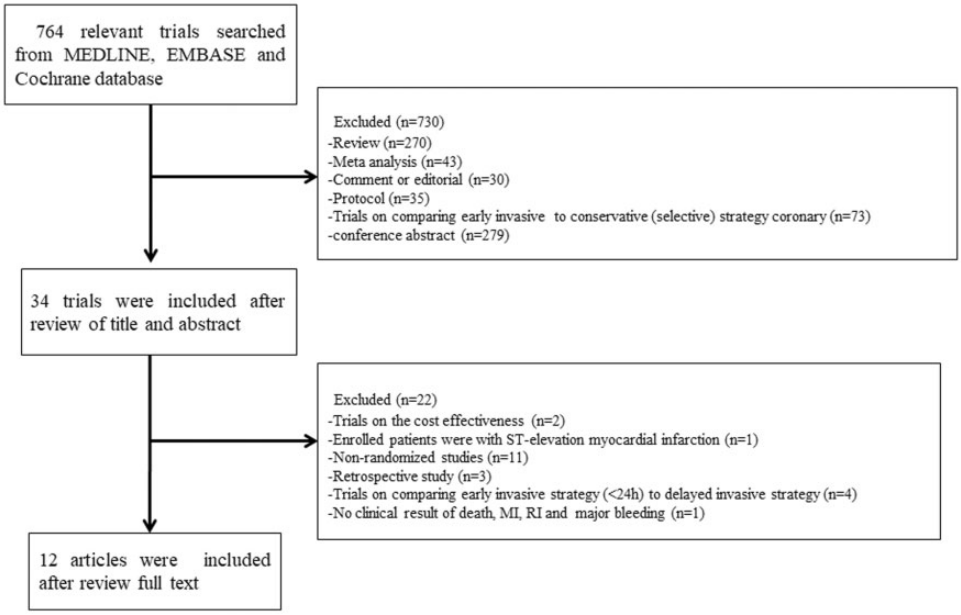

Figure 1. Study selection process.
MI, myocardial infarction; RI, refractory ischemia.

in the early invasive treatment group and 4679 patients in the delayed group. Details of the trials are summarized in Tables 1 and 2. LIPSIA-NSTEMI,[13] RIDDLE-NSTEMI[16,17] and TAO[6] included patients with NSTEMI, and the other six trials included NSTE-ACS. The median time of intervention (2.48 hours in the early invasive strategy and 47.19 hours in the delayed invasive strategy) was available in all trials, except in TAO.[6] The clinical follow-up period ranged from 30 days to 5 years. However, most trials with long-term clinical follow-up reported only rates of death and re-MI.

Risk of bias

Risks of bias were similar in all enrolled RCTs (Table 3). All studies were conducted in accordance with the intention-to-treat principle. Clinical follow-up was performed for almost all patients and patients lost to follow-up were rare. In the OPTIMA trial,[11] methods for random-sequence generation, allocation concealment, and blinding of outcome assessment were unclear.

Primary endpoint

All studies described the rate of death. The rate of total death was similar between the early and delayed invasive strategies (RR 0.90 [0.77–1.06]; $P = 0.197$; Figure 2a).

Secondary endpoints

The incidence of re-MI was recorded in all studies. The incidence of re-MI was similar between the early and delayed invasive strategies (RR 0.95 [0.70–1.29]; $P = 0.733$; Figure 2b). All studies included the number of major bleeding episodes as a clinical outcome. The rate of major bleeding was similar between the two strategies (RR 0.97 [0.77–1.23]; $P = 0.799$; Figure 2c). The occurrence of RI was reported in all

Table 1. Demographic data and medical history of the included studies.

Trial name (year)	No. of patients	Average age (years)	Follow-up (months)	Medical history, %						
				DM	Hypertension	Hyperlipidemia	Smoking	Prior MI	Prior PCI	Prior CABG
ELISA (2003)	109/111	63/65	1	15/14	45/38.7	38.5/37.8	36.7/32.4	17.4/12.6	14.7/14.4	11/7.2
ISAR-COOL (2003)	203/207	70/70	12	31.4/26.1	85.7/87	64.5/71.5	24.1/18.4	21.7/25.1	20.7/23.2	9.9/13.5
ABOARD (2009)	175/177	65/65	1	22/32	66/61	NR	32/33.9	16.6/18.6	24.6/30.5	5.1/6.8
OPTIMA (2009, 2016)	73/69	63/62	60	19/20	61/33	57.6/32	33.9/39	21/26	27/19	11/1
LIPSIA-NSTEMI (2012)	200/200	68/70	6	39/43	82/82	40/42	29/25	18/24	16/16	5/8
ELISA-3 (2013, 2017)	269/265	72.1/71.8	24	23.8/20.4	54.3/58.1	NR	21.2/26.4	17.8/19.6	18.2/20.8	13.8/12.1
RIDDLE-NSTEMI (2016, 2018)	162/161	60.5/63	36	21.6/32.3	65.4/72	74.7/73.9	51.9/38.5	19.1/21.1	10.5/9.3	4.9/7.5
TAO (2017)	1648/1003	70.7/70.5	6	34/31.2	80.1/78.7	52.7/57.2	19.7/20.2	22.5/23/4	100/100	9.5/10.5
VERDICT (2018)	1075/1072	63.6/63.6	51.6	14.7/16.1	50.5/53.9	NR	31.8/30.1	17.3/17/4	14/15.2	5.3/5.3

Data are reported for early invasive/delayed invasive strategies.

DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; NR, not reported.

Table 2. Clinical characteristics of the included studies.

Trial name (year)	Invasive strategy		Median time to angiogram (hours)	Troponin positive, %	GRACE risk score >140, %	Clinical outcome
	Early	Delayed				
ELISA (2003)	Within 12 hours	24–48 hours after	6/50	61/50	NR	Death, MI, major bleeding, re-PCI, RI
ISAR-COOL (2003)	Within 6 hours	72 hours after	2.4/86	66/68	NR	Death, MI, major bleeding, RI
ABOARD (2009)	Immediate	Next working day	1.2/21	75.4/72.9	NR	Peak troponin I levels, death, MI, or UR
OPTIMA (2009, 2016)	Immediate	24–48 hours after	0.5/25	47/45	NR	Death, MI, major bleeding, re-PCI
LIPSIA-NSTEMI (2012)	Immediate	Next working day	1.1/18.3	100/100	42/48	Peak CK-MB activity, death, MI, RI,
ELISA-3 (2013, 2017)	Within 12 hours	No sooner than 48 hours	2.6/54.9	78/79	40.5/43.0	Death, MI, RI, major bleeding
RIDDLE-NSTEMI (2016, 2018)	No later than 2 hours	Within 72 hours	1.4/61	100/100	34.6/41.6	Death, MI, RI, major bleeding
TAO (2017)	First ECG <12 hours	First ECG ≥24 hours	NR	90.2/90	100/100	Death, MI, ST, unplanned revascularization
VERDICT (2018)	Within 12 hours	Within 48–72 hours	4.7/61.6	81.2/79.2	49.3/48.7	Death, MI, RI, repeat coronary revascularization, CA, bleeding, stroke

Data are reported for early invasive/delayed invasive strategies.

GRACE, Global Registry of Acute Coronary Events; NR, not reported; MI, myocardial infarction; PCI, percutaneous coronary intervention; RI, recurrent or refractory ischemia; UR, urgent revascularization; CK-MB, creatinine kinase-MB; ECG, electrocardiogram; ST, stent thrombosis; CA, cardiac arrest.

Table 3. Risk of bias assessment.

Trial name	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data and selective reporting
ELISA (2003)	+	+	+	+	+
ISAR-COOL (2003)	+	+	+	+	+
ABOARD (2009)	+	+	+	+	+
OPTIMA (2009, 2016)	?	?	+	?	+
LIPSIA-NSTEMI (2012)	+	+	+	+	+
ELISA-3 (2013, 2017)	+	+	+	+	+
RIDDLE-NSTEMI (2016, 2018)	+	+	+	+	+
TAO (2017)	+	+	+	+	+
VERDICT (2018)	+	+	+	+	+

+, Low risk; ?, unclear risk.

trials, except in OPTIMA[11] and TAO.[6] ELISA reported RA rather than RI. There was no significant difference between the early and delayed invasive strategies for RI (RR 0.74 [0.53–1.05]; $P = 0.088$; Figure 2d).

Subgroup analyses

We investigated the risk of composite death or re-MI in patients with a GRACE risk score >140 and elevated troponin levels. Additionally, we compared the risk of death and re-MI as subgroup analyses between the early and delayed invasive strategy groups at 30 days and at a long-term follow-up (>1 year).

Four studies included patients with GRACE risk scores >140[6,14–18] and five studies included patients with elevated serum troponin levels.[6,13–18] The risks of composite death or re-MI in the early intervention group were significantly decreased in patients with GRACE risk scores >140 (RR 0.82 [0.72–0.92]; $P = 0.001$) and in those with elevated troponin levels (RR 0.84 [0.76–0.93]; $P = 0.001$; Figure 3) compared with those in the delayed invasive strategy group.

Seven studies reported 30 days of clinical outcome,[6,8–11,14,16] and only four studies reported long-term clinical follow-up,[12,15,17,18] with a median follow-up of 3.5 years. The rate of death or re-MI was similar in the two groups, regardless of whether there was a short- or long-term follow-up (death: RR 0.97 [0.71–1.33]; $P = 0.858$, RR 0.93 [0.76–1.13]; re-MI: RR 0.87 [0.54–1.39]; $P = 0.547$, RR 0.87 [0.49–1.54], respectively; Figure 4). Sensitivity analysis showed no difference when compared with the results of the main analysis.

Discussion

Several meta-analyses have shown that a routine invasive strategy reduces ischemic events (death or MI) compared with a selective invasive strategy in patients with NSTE-ACS, regardless of a short- or long-term follow-up.[19,20] However, results of several conflicting studies and meta-analyses have shown that an early invasive strategy was not superior to a delayed or routine strategy. Therefore, we performed

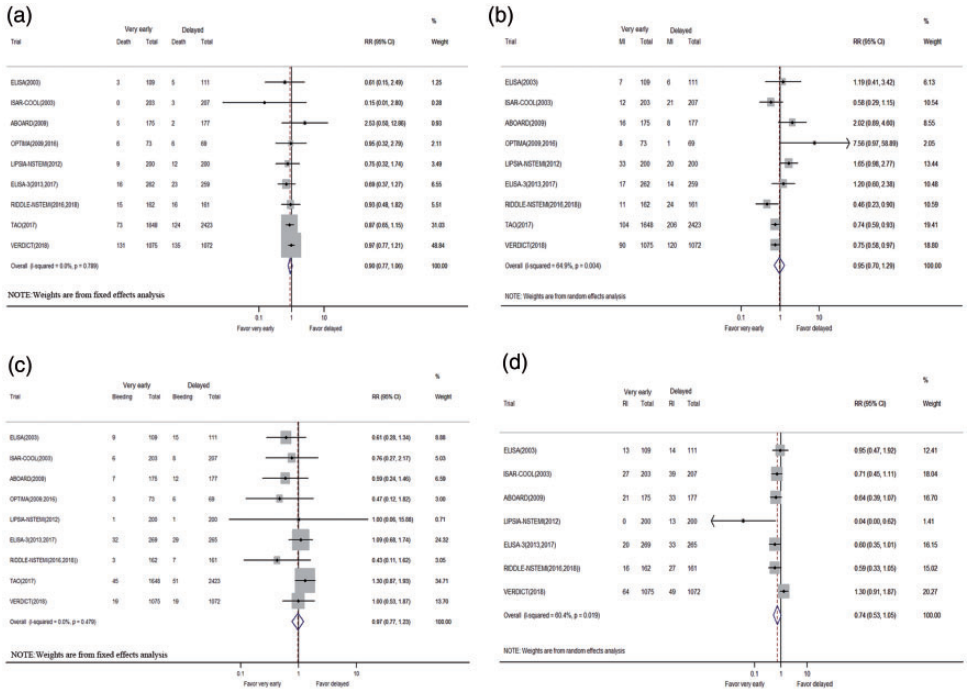

Figure 2. Forest plots showing (a) all cause death; (b) recurrent MI; (c) major bleeding; and (d) recurrent or RI.
MI, myocardial infarction; RI, refractory ischemia; RR, risk ratio; CI, confidence interval.

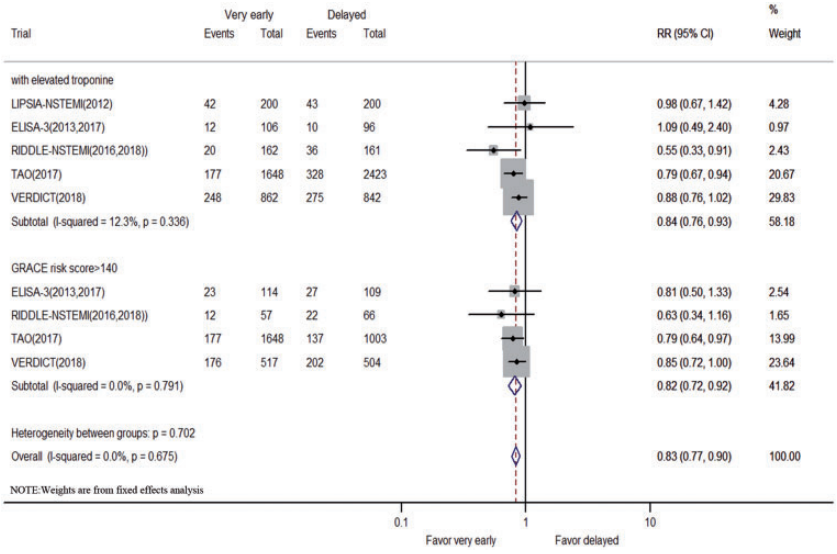

Figure 3. Forest plot showing composite all-cause death or recurrent myocardial infarction in high-risk patients.
GRACE, Global Registry of Acute Coronary Events; RR, risk ratio; CI, confidence interval.

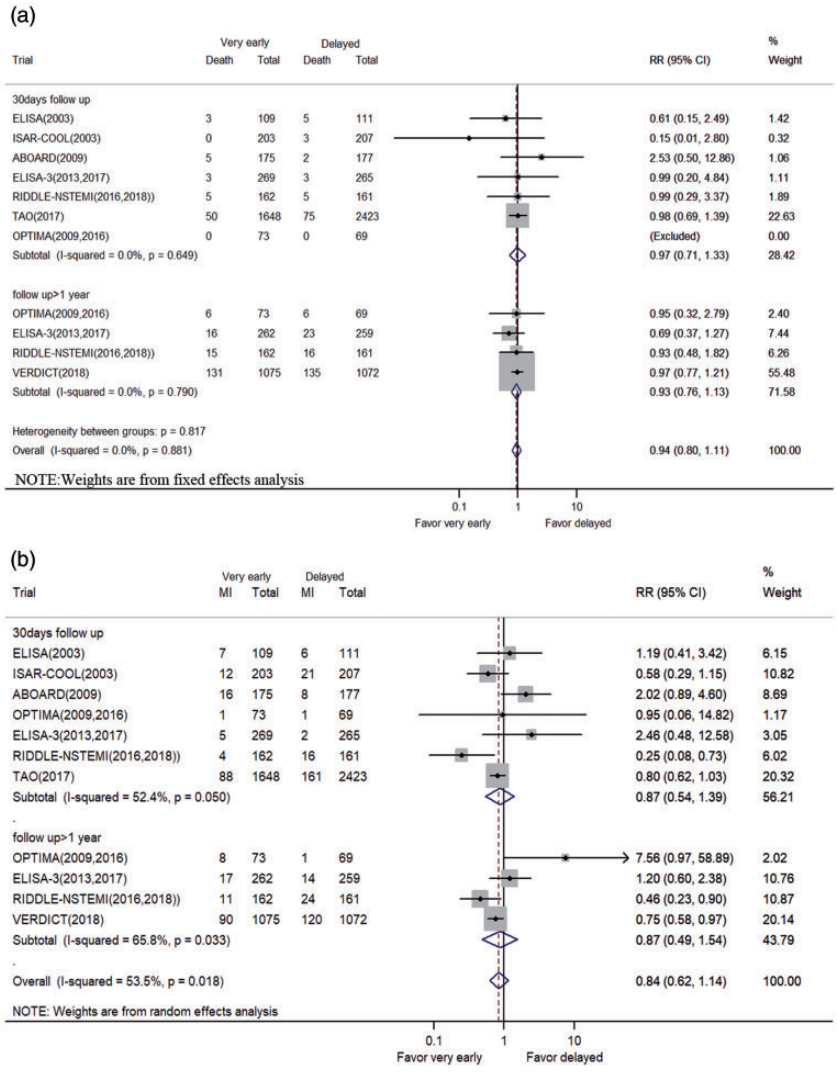

Figure 4. Forest plots for 30 days and long-term follow-up. a) All-cause death and b) recurrent MI MI, myocardial infarction; RR, risk ratio; CI, confidence interval.

this meta-analysis to investigate whether coronary angiography performed within 12 hours could improve clinical outcomes. Our meta-analysis showed that an early invasive strategy did not reduce the risk of death, re-MI, RI, or major bleeding. Furthermore, this strategy significantly reduced the risk of composite death or re-MI in patients with high-risk factors, such as a GRACE risk score >140 or elevated troponin levels.

An early invasive strategy is not superior to a delayed invasive strategy

The rates of all-cause death, re-MI, and major bleeding were similar between the two invasive strategies, as well as

long-term mortality, in our meta-analysis. Patients with acute coronary syndrome are at risk of death because of persistent coronary occlusion caused by acute thrombosis. Therefore, stabilization of the culprit lesion to prevent growth of thrombus and its complications are major therapeutic strategies in these patients.[21] Coronary intervention significantly reduces clinical outcomes of mortality and MI compared with a conservative management strategy.[22,23] However, we did not find that an early intervention reduced the mortality rate in patients with NSTE-ACS.

In this meta-analysis, the rate of RI was not significantly reduced with the early invasive strategy, which is different from the finding of a previous study.[3] One possible reason for this difference between studies is that the inclusion criteria were different. In this meta-analysis, we evaluated coronary angiography performed within 12 hours as the early invasive strategy and intervention that was performed on the next working day after enrollment or at least 12 hours after hospitalization was the delayed strategy. In contrast, the above-mentioned study investigated the effectiveness of early (<24 hours) and delayed (>24 hours) invasive strategies. In this previous meta-analysis, TIMACS was included,[2] which produced a significant reduction of the risk of RI with the early strategy (1% versus 3.27%, P<0.001). Overall, we suggest that an early invasive strategy within 12 hours does not significantly improve the risk of mortality.

An early invasive strategy might be beneficial to high-risk patients

ACC/AHA and ESC guidelines suggest that patients with high-risk factors should have revascularization performed within 24 hours (class I). In TIMACS,[2] the risk of composite death, MI, or RI at 6 months was significantly decreased using an early invasive strategy for patients with GRACE risk scores >140, elevated cardiac markers, or ST-segment deviation. A collaborative meta-analysis showed that for predefined subgroup analyses, patients with elevated cardiac biomarkers at baseline, diabetes, a GRACE risk score >140 points, or age >75 years could benefit from early intervention.[4] Therefore, in our meta-analysis, we investigated the effect of an early invasive strategy within 12 hours in patients with a GRACE risk score >140 or elevated cardiac troponin levels. Three trials (ELISA-3, RIDDLE-NSTEMI, and VERDICT) reported these variables. TAO included patients with NSTEMI with GRACE risk scores >140. Therefore, we included this definition for the subgroup analysis. We did not analyze the effect of age and ST-T deviation because of the lack of data provided by the studies. We found that the incidence of composite death or re-MI was significantly reduced in patients with GRACE risk scores >140 who received angiography within 12 hours. Recently, the MINAP trial[24] showed that an invasive coronary strategy improved survival for intermediate- and high-risk patients with NSTEMI. In the clinical setting, physicians use the GRACE risk score to estimate the ischemic risk for NSTEMI and define patients as high risk when this score is >140. High-risk patients should undergo coronary intervention within 24 hours according to this guideline. However, in TAO, undergoing coronary angiography within 12 hours in high-risk patients with NSTEMI reduced ischemic clinical outcomes compared with intervention performed at 12 to 24 hours or >24 hours, which is supported by our meta-analysis. Additionally, this study showed that patients with elevated cardiac biomarkers benefited from an early invasive strategy (RR 0.84 [0.76–0.93]; $P = 0.001$). An elevated cardiac biomarker is a parameter of the GRACE risk score, indicating

the presence of necrosis of myocytes due to coronary occlusion, and myocardial ischemia of an extended duration can promote necrosis. Therefore, an early invasive strategy could shorten the ischemic duration and reduce necrosis of myocytes, resulting in an improved clinical outcome.

This meta-analysis has several limitations. First, the time to angiography varied in the early and delayed invasive strategies. The time to angiography ranged from 0.5 to 12.2 hours in the early invasive group and from 6.0 to 106.7 hours in the delayed group. TAO did not report the time to angiography and OPTIMA only reported the median time of intervention from randomization. Second, the sample size was small, especially in our subgroup analysis. Only three trials (ELISA-3, RIDDLE-NSTEMI, and VERDICT) reported risk factors for subgroup analysis and four trials (OPTIMA, ELISA-3, RIDDLE-NSTEMI, and VERDICT) investigated long-term clinical outcomes. In pre-specified analysis, VERDICT enrolled 2147 patients, which accounted for 71.5% of the total number of high-risk patients and contributed to 68.5% of the total number of long-term follow-up patients. However, the design of this trial was strict, and this produced high-quality data from VERDICT. Finally, ACC/AHA and ESC guidelines consider dynamic ST- or T-wave changes as a high-risk criterion. Because of limited data, we did not examine the influence of an early invasive strategy on this parameter.

Conclusions

This meta-analysis shows that an early angiographic strategy within 12 hours does not reduce the risk of death, re-MI, major bleeding, or RI in patients with NSTE-ACS. Furthermore, an early invasive strategy might reduce the rate of composite death or re-MI in high-risk patients, such as those with GRACE risk scores >140 or elevated cardiac markers. More studies are required to investigate an early invasive angiographic strategy within 12 hours.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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