Timing of revascularisation for acute coronary syndrome

Acute coronary syndrome is predominantly caused by a luminal thrombus or a sudden plaque haemorrhage imposed on an atherosclerotic plaque with or without an accompanying vasospasm.[1] A luminal thrombus forms as a direct consequence of plaque rupture or erosion (if plaque rupture is not identifiable on intracoronary imaging).[2] Initial electrocardiography can be used to distinguish ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndrome (NSTE-ACS).

Patients with STEMI typically have a complete and persistent occlusion of a large epicardial coronary artery and are best managed with immediate primary percutaneous coronary intervention to restore flow and achieve reperfusion.[3] Primary percutaneous coronary intervention for STEMI is associated with a robust reduction in mortality compared with other reperfusion strategies.[4]

The best approach for patients with NSTE-ACS is more complex because such patients typically have a severe stenosis but flow is still present. In these patients, the initial decision is whether to proceed with a routine invasive or selective invasive strategy. European guidelines recommend a routine invasive strategy, consisting of angiography within 24–72 h, for patients with intermediate-to-high-risk characteristics (panel).[5] A selective invasive strategy is preferred for low-risk patients.[5] These patients undergo coronary angiography only in cases of refractory angina or inducible ischaemia by non-invasive stress testing. The second decision involves the optimal timing of angiography after pursuing the routine invasive approach. Different timings are defined as immediate, early (within 24 h), or delayed (after 24 h). The immediate, or STEMI-like, approach has been tested in several trials but has not been shown to be beneficial.[6–8] European guidelines recommend angiography within 24 h for high-risk patients, including transfer to a percutaneous coronary intervention centre.[5] This strategy during this timeframe is not without controversy: it is mainly supported by a subgroup analysis of the TIMACS study,[9] and few catheterisation laboratories are available and transferring patients uses resources including ambulances and personnel.

In *The Lancet*, Alexander Jobs and colleagues[10] present a meta-analysis of individual patient data from randomised trials that compared an early versus a delayed invasive approach in NSTE-ACS. They included more than 5000 patients from eight trials with a median follow-up of 180 days. In these patients, there was no significant difference in mortality between an early invasive and a delayed invasive strategy (hazard ratio [HR] 0·81, 95% CI 0·64–1·03). However, mortality was significantly lower in prespecified high-risk subgroups of patients with high concentrations of cardiac biomarkers (HR 0·76, 95% CI 0·58–1·00), diabetes (HR 0·67, 95% CI 0·45–0·99), a Global Registry of Acute Coronary Events (GRACE) risk score of more than 140 points (HR 0·70, 95% CI 0·52–0·95), or patients aged 75 years or older (HR 0·65, 95% CI 0·46–0·93). We congratulate the authors for putting together such a large database with individual patient data.

A few points deserve discussion in the interpretation of these results. This meta-analysis is timely, with more patients and longer follow-up than in the original publications, and given the fact that the individual studies did not show a reduction in mortality and were underpowered for this outcome. However, the effect of adding patients was small, the HR for mortality at 6 months in TIMACS was 0·81 (95% CI 0·60–1·11) and with the addition of 2000 patients in this meta-analysis

Panel: Criteria for determining risk in patients with non-ST-segment elevation acute coronary syndrome

High-risk criteria
- Rise or fall in cardiac troponin compatible with myocardial infarction
- Dynamic ST-wave or T-wave changes (symptomatic or silent)
- GRACE risk score >140 points

Intermediate-risk criteria
- Diabetes mellitus
- Renal insufficiency (estimated glomerular filtration rate <60 mL/min)
- Left ventricular ejection fraction <40% or congestive heart failure
- Previous percutaneous coronary intervention or coronary artery bypass graft
- Early post-infarction angina
- GRACE risk score >109 and ≤140 points

Low-risk criteria
- None of the above

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changed only slightly, to 0·81 (95% CI 0·64–1·03). The TIMACS and ELISA-3 trials[9,11] contributed 65% weight in the analysis and both were neutral with regards to mortality originally. Clearly, the mortality benefit in the subgroups can only be hypothesis-generating in an overall neutral study. The authors' pathophysiological explanation for this finding is a reduction in infarct size, comparable to the beneficial effect of early intervention in STEMI patients. However, data were not available on infarct size.

The general lack of a mortality benefit with earlier intervention lends support to the findings of an earlier meta-analysis of individual patient data comparing a routine invasive strategy with a selective invasive strategy.[12] However, the present results show no conclusive evidence of harm resulting from an early invasive approach in NSTE-ACS, and the lack of a difference in mortality between invasive strategies suggests that most patients with acute coronary syndrome can be treated safely with either early intervention or delayed intervention. The trials included in Jobs and colleagues' meta-analysis enrolled patients between 2000 and 2016, during which time pharmacotherapy and devices for diagnosis and treatment in patients with NSTE-ACS have changed substantially. Outcomes under current clinical practice, using high-sensitive cardiac troponins, powerful new P2Y12-receptor platelet aggregation inhibitors, and new drug-eluting stents may have changed greatly both with an early approach and a delayed approach.

Jobs and colleagues suggest that their findings in high-risk subgroups "might indicate the need for an early invasive strategy for older patients or patients with diabetes" and "strengthen guideline recommendations to use an early invasive approach in patients with elevated biomarkers compatible with myocardial infarction or in patients with a GRACE risk score of more than 140 points". The potential clinical and enormous logistic implications of these findings emphasise the need for an adequately powered randomised clinical trial comparing an early invasive strategy with a delayed or selective invasive strategy in patients with NSTE-ACS, using high-sensitive troponin measurements, the latest interventional modalities, and optimised pharmacological standards of care.

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1 Davies MJ. The pathophysiology of acute coronary syndromes. *Heart* 2000; **83:** 361–66.
2 Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res* 2014; **114:** 1852–66.
3 Steg PG, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012; **33:** 2569–619.
4 Keeley EC, Bour JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003; **36:** 13–20.
5 Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016; **37:** 267–315.
6 Riezebos RK, Ronner E, Ter Bals E, et al. Immediate versus deferred coronary angioplasty in non-ST-segment elevation acute coronary syndromes. *Heart* 2009; **95:** 807–12.
7 Thiele H, Rach J, Klein N, et al. Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: the Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI (LIPSIA-NSTEMI Trial). *Eur Heart J* 2012; **33:** 2035–43.
8 Montalescot G, Cayla G, Collet JP, et al. Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. *JAMA* 2009; **302:** 947–54.
9 Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 2009; **360:** 2165–75.
10 Jobs A, Mehta SR, Montalescot G, et al. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials. *Lancet* 2017; published online Aug 1. http://dx.doi.org/10.1016/S0140-6736(17)31490-3.
11 Badings EA, The SH, Dambrink JH, et al. Early or late intervention in high-risk non-ST-elevation acute coronary syndromes: results of the ELISA-3 trial. *EuroIntervention* 2013; **9:** 54–61.
12 Fox KA, Clayton TC, Damman P, et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. *J Am Coll Cardiol* 2010; **55:** 2435–45.

Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials

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Summary

Background A routine invasive strategy is recommended for patients with non-ST-elevation acute coronary syndromes (NSTE-ACS). However, optimal timing of invasive strategy is less clearly defined. Individual clinical trials were underpowered to detect a mortality benefit; we therefore did a meta-analysis to assess the effect of timing on mortality.

Methods We identified randomised controlled trials comparing an early versus a delayed invasive strategy in patients presenting with NSTE-ACS by searching MEDLINE, Cochrane Central Register of Controlled Trials, and Embase. We included trials that reported all-cause mortality at least 30 days after in-hospital randomisation and for which the trial investigators agreed to collaborate (ie, providing individual patient data or standardised tabulated data). We pooled hazard ratios (HRs) using random-effects models. This meta-analysis is registered at PROSPERO (CRD42015018988).

Findings We included eight trials (n=5324 patients) with a median follow-up of 180 days (IQR 180–360). Overall, there was no significant mortality reduction in the early invasive group compared with the delayed invasive group HR 0·81, 95% CI 0·64–1·03; p=0·0879). In pre-specified analyses of high-risk patients, we found lower mortality with an early invasive strategy in patients with elevated cardiac biomarkers at baseline (HR 0·761, 95% CI 0·581–0·996), diabetes (0·67, 0·45–0·99), a GRACE risk score more than 140 (0·70, 0·52–0·95), and aged 75 years older (0·65, 0·46–0·93), although tests for interaction were inconclusive.

Interpretation An early invasive strategy does not reduce mortality compared with a delayed invasive strategy in all patients with NSTE-ACS. However, an early invasive strategy might reduce mortality in high-risk patients.

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Introduction

Guidelines for the management of patients with non-ST-elevation acute coronary syndromes (NSTE-ACS) recommend an invasive strategy in moderate to high-risk patients.[1,2] Recommendations for the timing of intervention in these patients depend on patient's baseline risk. Immediate coronary angiography within 2 h of presentation is recommended for all patients with a very high risk of in-hospital mortality (ie, those with haemodynamic instability, life-threatening arrhythmia, or recurrent or refractory angina); the recommendation is based on expert opinion without any evidence from clinical trials. Coronary angiography within 24 h is advised for patients not meeting these criteria but presenting with elevated troponin or ischaemic ST-wave or T-wave changes as well as patients with a Global Registry of Acute Coronary Events (GRACE) risk score of more than 140 points. The recommendation is primarily based on a pre-specified subgroup analysis of the TIMACS trial,[3] in which the early invasive strategy was superior to the delayed invasive strategy with regard to the composite endpoint of death, myocardial infarction, or stroke at 6 months in the highest GRACE risk score tertile. However, the effect of an early invasive strategy on individual clinical endpoints such as mortality or non-fatal myocardial infarction is unknown; individual trials were underpowered to detect an effect on these outcomes.

Moreover, previous meta-analyses pooling published data did not detect a difference on these outcomes. Only recurrent or refractory ischaemia and length of hospital stay have been shown to be improved by an early invasive strategy compared with a delayed invasive strategy.[4–8] Because of inconsistent trial reporting, no subgroup analyses of high-risk patients were possible in these meta-analyses.

To overcome shortcomings of conventional meta-analyses, we did a collaborative meta-analysis of randomised controlled trials investigating optimal timing of coronary angiography in patients with NSTE-ACS, based on individual patient or standardised tabulated data not previously published. We analysed all-cause mortality overall and in four pre-specified high-risk subgroups.

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Research in context

Evidence before this study

Guidelines for the timing of coronary angiography in non-ST-elevation acute coronary syndromes (NSTE-ACS) are based on results of individual randomised controlled trials and several meta-analyses. However, individual trials were underpowered to detect an effect on mortality. The meta-analyses were methodologically limited by their use of published data, which precluded subgroup analyses because of inconsistent trial reporting.

Added value of this study

We did a collaborative meta-analysis of published and unpublished trial data from studies of the timing of coronary angiography in NSTE-ACS. Our results accord with findings from previous meta-analyses that an early invasive strategy is not superior to a delayed invasive strategy in unselected patients with NSTE-ACS. Because our meta-analysis is based on individual patient data or standardised tabulated data, we were for the first time able to analyse high-risk subgroups. We found that an early invasive strategy might be associated with reduced mortality in high-risk patients (ie, patients with elevated cardiac biomarkers at baseline, diabetes, a GRACE risk score more than 140 points, or age ≥75 years).

Implications of all the available evidence

Our findings, particularly concerning high-risk patients, strengthen guideline recommendations to use an early invasive approach in patients with elevated biomarkers compatible with myocardial infarction or in patients with a GRACE risk score of more than 140 points. In addition, our results might indicate the need for an early invasive strategy for older patients or patients with diabetes.

Methods

Search strategy and selection criteria

We identified randomised controlled trials (RCTs) of potential interest by searching MEDLINE (up to Dec 20, 2016), Cochrane Central Register of Controlled Trials (up to Dec 21, 2016), and Embase (up to Jan 2, 2017), without language restrictions. We used three groups of search terms, of which at least one term in each was required to match: (1) "acute coronary syndrome", "unstable coronary syndrome", "unstable angina", "without persistent ST-segment elevation", "non-ST-elevation acute coronary syndrome", "non-ST-elevation myocardial infarction", "NSTE-ACS", and "NSTEMI"; (2) "angiography", "intervention", "invasive evaluation", and "invasive intervention"; (3) "timing", "early", "immediate", "late", and "delayed" (see appendix for specific search strategies).

See Online for appendix

We included randomised controlled trials comparing an early versus delayed coronary angiography in patients presenting with NSTE-ACS, reporting mortality at least 30 days after in-hospital randomisation, and for which the principal investigators agreed to provide data for patient characteristics (demographics, medical history, baseline risk evaluation, and procedural data) and outcomes as individual patient data or tabulated data on standardised table sheets in an ordinary spreadsheet format with uniform coding. In case of tabulated data, table sheets were prepared to ensure that the provided data facilitated pre-specified analyses. We excluded randomised controlled trials with pre-hospital randomisation and those comparing a routine invasive strategy with a selective invasive strategy or early versus delayed percutaneous coronary intervention.

Data analysis

After removal of duplicates, title and abstract of search items were screened and sequentially excluded according to the eligibility criteria (by AJ). Whenever uncertainty remained after screening title and abstract, full text articles were scrutinised independently by two investigators (SD and HT) and discrepancies resolved by consensus after discussion. Provided data were centrally checked for completeness, plausibility, and integrity before they were combined in a single database.

Two independent investigators assessed the risk of bias in the included trials (AJ and SD) according to the Cochrane Collaboration's tool[9] for assessing risk of bias using primarily original trial reports. Discrepancies were resolved by consensus after discussion. Principal investigators were contacted in case of missing information.

The primary outcome was all-cause mortality. To investigate a time-dependent effect of timing of invasive strategy, we divided the follow-up into distinct periods (ie, from randomisation to hospital discharge, and from hospital discharge to end of follow-up). Moreover, we analysed the effect of timing in four pre-defined high-risk subgroups (ie, patients with positive cardiac biomarkers at baseline, with diabetes, aged ≥75 years, or with a GRACE risk score >140 points). The secondary outcome was non-fatal myocardial infarction. The definitions of non-fatal myocardial infarction differed considerably between trials and each trial definition was used for the present meta-analysis (appendix).

We analysed data by the intention-to-treat principle. We summarised baseline characteristics by treatment group as mean and SD, or if skewed, as median and IQR. We used frequencies and percentages to summarise categorical variables. Under the assumption that hazard rates are constant over time, HRs are more reliable for pooling data of trials with different durations of follow-up.[10] Therefore, we used HRs with 95% CIs for both outcomes. Clinical events were considered as in-hospital events when they occurred between randomisation and

	Early invasive group	Delayed invasive group	Major inclusion criteria	Biomarker positive	Biomarker positivity as inclusion criteria	GRACE risk score
ABOARD (IPD)[12]	Immediate invasive strategy	Invasive strategy scheduled on the next working day (ie, 8–60 h) after enrolment	At least two of: symptoms of myocardial ischaemia; ST-segment abnormalities on ECG; elevated troponin I	Troponin I >ULN	Not mandatory	Not available
ELISA (IPD)[13]	Angiography within 12 h without tirofiban pre-treatment	Pre-treatment with tirofiban for ≥12 h	At least two of: symptoms of myocardial ischaemia; ST-segment abnormalities on ECG; elevated troponin T	Troponin I >0·05 ng/mL	Not mandatory	Not available
ELISA-3 (IPD)[14]	Angiography within 12 h after randomisation	Angiography ≥48 h after randomisation	Symptoms of myocardial ischaemia plus at least two of: evidence of extensive myocardial ischaemia on ECG (ie, new cumulative ST depression >5 mm or temporary ST-segment elevation in two contiguous leads <30 min); elevated troponin T, myoglobin, or CK-MB fraction; age >65 years	Troponin T >0·1 µg/L, myoglobin >150 µg/L, CK-MB fraction >6% of total CK	Not mandatory	Available
ISAR-COOL (IPD)[15]	Angiography within 6 h with anti-thrombotic pre-treatment	Angiography ≥72 h with antithrombotic pre-treatment	Symptoms of myocardial ischaemia plus at least one of: ST-segment abnormalities on ECG; elevated troponin T value, myoglobin, or CK-MB fraction	Troponin T ≥0·03 mg/L	Not mandatory	Not available
LIPSIA-NSTEMI (IPD)[16]	Angiography within 2 h after randomisation	Angiography on the next working day (ie, 10–48 h) after randomisation	Symptoms of myocardial ischaemia plus elevated troponin T	Troponin T ≥0·1 ng/mL	Mandatory	Available
RIDDLE-NSTEMI (IPD)[18]	Angiography within 2 h after randomisation	Angiography within 72 h after randomisation	Symptoms of myocardial ischaemia; elevated troponin I; ST-segment abnormalities or T-wave inversion on ECG	Troponin I >ULN	Mandatory	Available
Sciahbasi and colleagues (IPD)[17]	Angiography within 6 h after hospital admission	Angiography within 72 h after hospital admission	Symptoms of myocardial ischaemia plus at least one of: ST-segment abnormalities on ECG; elevated troponin T or CK-MB fraction	Troponin T >2 × ULN, CK-MB >2 × ULN	Not mandatory	Not available
TIMACS (ATD)[3]	Angiography within 24 h after randomisation	Angiography ≥36 h after randomisation	Symptoms of myocardial ischaemia plus at least two of: ST-segment abnormalities on ECG; elevated troponin T, myoglobin, or CK-MB fraction; age ≥60 years	Cardiac biomarkers >ULN	Not mandatory	Available

ATD=trial provided additional tabulated data. CK-MB=creatine kinase–myocardial band. ECG=electrocardiograph. GRACE=Global Registry of Acute Coronary Events. IPD=trial provided individual patient data. ULN=upper limit of normal.

Table 1: **Key features of includes trials**

hospital discharge or as post-discharge events if they occurred between hospital discharge and the end of follow-up. Analysis of post-discharge events excludes patients who died before discharge. Trials without clinical events or only few events resulting in infinite HRs were weighted with zero. We used a two-step approach for the meta-analysis to preserve clustering of patients in trials.[11] All trials were analysed separately and respective principal investigators were asked to confirm the results. Discrepancies were resolved by discussion. We obtained individual patient data for ABOARD,[12] ELISA,[13] ELISA-3,[14] ISAR-COOL,[15] LIPSIA-NSTEMI,[16] Sciahbasi et al,[17] and RIDDLE-NSTEMI,[18] which we analysed centrally. Because of legal issues, TIMACS[3] provided standardised tabulated data compatible with the pre-specified central analysis of other trials. For each outcome, we pooled HRs using inverse variance weighting and calculated DerSimonian and Laird random-effects models since all trials were done independently and we assumed that clinical heterogeneity will be present even despite a negative Cochrane's *Q* statistic. We assessed heterogeneity between trials using τ^2 as measure of between-study variance and Higgins' and Thompson's I^2. We evaluated interactions in subgroups by random-effects models (combined from the final results). We did post-hoc meta-regression to assess the relationship

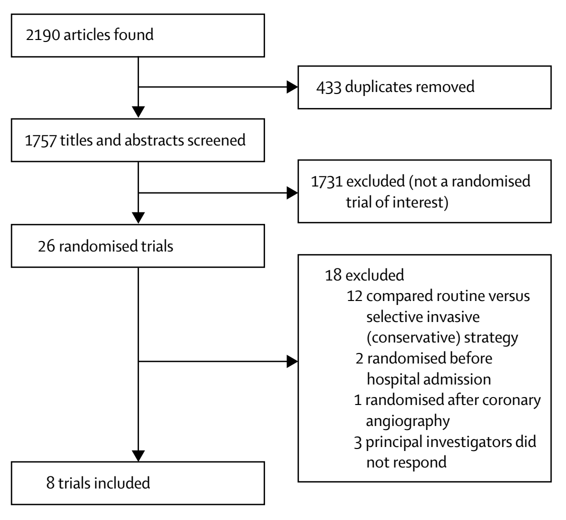

Figure 1: **Trial selection**

between the median difference in time to angiography and outcomes. All analyses were pre-specified unless otherwise stated. All p values were two-sided and judged as significant if less than 0·05. We used R (version 3.1.0) and its package meta (version 4.3.2) for all statistical analyses.

	ABOARD[12]		ELISA[13]		ELISA-3[14]		ISAR-COOL[15]		LIPSIA-NSTEMI[16]		RIDDLE-NSTEMI[18]		Sciahbasi and colleagues[17]		TIMACS[3]	
	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed
Patients (n)	175	177	109	111	269	265	203	207	200	200	162	161	27	27	1593	1438
Median follow-up (days)	30	30	373	371	732	732	360	360	180	180	365	365	365	365	184	184
Age (mean, SD, or median IQR; years)	65 (12)	65 (12)	63 (11)	65 (11)	71 (10)	70 (11)	68 (12)	69 (11)	66 (12)	68 (13)	60 (11)	62 (10)	57 (54–64)	59 (51–68)	65 (11)	66 (11)
Age ≥75 years	48 (27%)	44 (25%)	16 (15%)	29 (26%)	105 (39%)	105 (40%)	65 (32%)	72 (35%)	52 (26%)	62 (31%)	19 (12%)	21 (13%)	1 (4%)	2 (7%)	328 (21%)	313 (22%)
Men	127 (73%)	125 (71%)	79 (72%)	76 (68%)	187 (70%)	174 (66%)	134 (66%)	140 (68%)	132 (66%)	139 (70%)	114 (70%)	106 (66%)	22 (81%)	24 (89%)	1038 (65%)	940 (65%)
Hypertension (n/N; %)	115/175 (66%)	108/177 (61%)	49/107 (46%)	43/110 (39%)	146/269 (54%)	154/265 (58%)	174 /203 (86%)	180/207 (87%)	163/199 (82%)	165/200 (82%)	106/162 (65%)	116/161 (72%)	13/27 (48%)	18/27 (67%)	1084/1593 (68%)	996/1438 (69%)
Diabetes	38 (22%)	57 (32%)	16 (15%)	16 (14%)	64 (24%)	54 (20%)	53 (26%)	65 (31%)	77 (39%)	86 (43%)	35 (22%)	52 (32%)	7 (26%)	5 (19%)	422 (27%)	394 (27%)
Smoking (n/N; %)	56/175 (32%)	60/177 (34%)	40/109 (37%)	36/110 (33%)	57/269 (21%)	70/265 (26%)	49/203 (24%)	38/207 (18%)	57/200 (28%)	50/198 (25%)	84/162 (52%)	62/161 (39%)	16/27 (59%)	12/27 (44%)	441/1593 (28%)	394/1438 (27%)
Previous stroke (n/N; %)	9/174 (5%)	8/177 (5%)	3/109 (3%)	4/111 (4%)	9/269 (3%)	12/265 (5%)	NA	NA	9/200 (4%)	11/200 (6%)	9/162 (6%)	16/161 (10%)	0/27 (0%)	0/27 (0%)	114/1593 (7%)	108/1593 (8%)
Previous myocardial infarction	29 (17%)	33 (19%)	19 (17%)	14 (13%)	48 (18%)	52 (20%)	44 (22%)	52 (25%)	36 (18%)	47 (24%)	31 (19%)	34 (21%)	0 (0%)	0 (0%)	313 (20%)	300 (21%)
Previous PCI	43 (25%)	54 (31%)	16 (15%)	16 (14%)	49 (18%)	55 (21%)	42 (21%)	48 (23%)	33 (17%)	32 (16%)	17 (10%)	15 (9%)	0 (0%)	0 (0%)	221 (14%)	204 (14%)
Previous CABG	9 (5%)	12 (7%)	12 (11%)	8 (7%)	37 (14%)	32 (12%)	20 (10%)	28 (14%)	10 (5%)	15 (8%)	8 (5%)	12 (7%)	0 (0%)	0 (0%)	111 (7%)	105 (7%)
Biomarker elevation	132 (75%)	129 (73%)	66 (61%)	55 (50%)	211 (78%)	210 (79%)	134 (66%)	140 (68%)	200 (100%)	200 (100%)	162 (100%)	161 (100%)	19 (70%)	22 (81%)	1245 (78%)	1120 (78%)
ST-T segment changes	122 (70%)	136 (77%)	NA	NA	196 (73%)	182 (69%)	134 (66%)	134 (65%)	158 (79%)	163 (82%)	159 (98%)	160 (99%)	19 (70%)	20 (74%)	1282 (81%)	1149 (80%)
Median GRACE risk score (IQR)	NA	NA	NA	NA	136 (118–154)	133 (117–154)	NA	NA	133 (115–154)	137 (112–160)	131 (115–144)	129 (115–150)	NA	NA	129 (109–148)	129 (111–147)
GRACE risk score >140 (n/N, %)	NA	NA	NA	NA	119/266 (45%)	112/261 (43%)	NA	NA	85/200 (42%)	96/200 (48%)	56/162 (35%)	67/161 (42%)	NA	NA	520/1593 (33%)	464/1438 (32%)
Median time to randomisation (IQR; h)	2·0 (0·8–5·6)	2·5 (1·1–5·4)	2·3 (1·1–3·9)	2·0 (1·1–4·3)	2·0 (0·9–4·5)	2·1 (1·0–4·1)	NA	NA	2·1 (1·0–3·8)	2·5 (1·6–4·1)	NA	NA	8·0 (4·0–10·0)	8·0 (5·5–12·0)	NA	NA
Median time to angiography (IQR; h)	1·2 (0·8–2·0)	20·7 (17·4–24·6)	3·3 (1·0–11·2)	48·0 (39·4–68·9)	2·6 (1·2–6·1)	54·9 (44·3–74·2)	2·4 (1·0–4·3)	87·4 (78·2–106·7)	1·1 (0·8–1·5)	18·3 (14·0–21·2)	1·4 (1·0–2·4)	61·0 (37·2–85·0)	5·0 (2·0–6·0)	24·0 (13·0–33·0)	14 (3–21)	50 (41–80)
Number of diseased vessels																
0	32 (18%)	28 (16%)	11 (10%)*	14 (13%)	26 (10%)†	28 (11%)†	21 (10%)	25 (12%)	19 (10%)	17 (8%)‡	5 (3%)	4 (2%)‡	0 (0%)	0 (0%)	427 (27%)	427 (30%)
1	63 (36%)	51 (29%)	36 (33%)*	37 (33%)	74 (28%)†	67 (26%)†	39 (19%)	40 (19%)	63 (32%)	53 (27%)‡	48 (30%)	37 (23%)‡	17 (63%)	17 (63%)	504 (32%)	447 (31%)
2	48 (27%)	54 (31%)	29 (27%)*	25 (23%)	77 (29%)†	93 (36%)†	49 (24%)	50 (24%)	59 (30%)	65 (33%)‡	52 (32%)	54 (34%)‡	9 (33%)	8 (30%)	390 (25%)	337 (23%)
3	32 (18%)	44 (25%)	32 (30%)*	35 (32%)	87 (33%)†	69 (27%)†	94 (46%)	92 (44%)	59 (30%)	65 (33%)‡	57 (35%)	65 (41%)‡	1 (4%)	2 (7%)	272 (17%)	227 (16%)

(Table 2 continues on next page)

	ABOARD		ELISA		ELISA-3		ISAR-COOL		LIPSIA-NSTEMI		RIDDLE-NSTEMI		Sciahbasi and colleagues		TIMACS	
	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed
(Continued from previous page)																
Mode of revascularisation																
Conservative	46 (26%)	55 (31%)	27 (25%)*	26 (26%)	27 (10%)	33 (12%)	44 (22%)	58 (28%)	33 (16%)	34 (17%)	15 (9%)	18 (11%)‡	0 (0%)	0 (0%)	409 (26%)	449 (31%)
PCI	113 (65%)	105 (59%)	66 (61%)*	64 (58%)	179 (67%)	164 (62%)	143 (70%)	133 (64%)	151 (76%)	141 (70%)	127 (78%)	104 (65%)‡	27 (100%)	27 (100%)	949 (60%)	792 (55%)
CABG	16 (9%)	17 (10%)	15 (14%)*	21 (19%)	63 (23%)	68 (26%)	16 (8%)	16 (8%)	16 (8%)	25 (12%)	20 (12%)	38 (24%)‡	0 (0%)	0 (0%)	235 (15%)	197 (14%)

Data are n (%) unless stated otherwise. CABG=coronary artery bypass graft. GRACE=Global Registry of Acute Coronary Events. NA=not available. PCI=percutaneous coronary intervention. *Coronary angiography was not done in one patient. †Coronary angiography was not done in five patients in the early invasive group and eight in the delayed invasive group. ‡One patient died before coronary angiography.

***Table 2*: Patient and treatment characteristics of included trials**

This meta-analysis is registered with PROSPERO (CRD42015018988).

Role of the funding source

There was no funding source for this meta-analysis. The first author and the corresponding author had full access to all data (standardised tabulated data for TIMACS and individual patient data for all other trials). The corresponding author had final responsibility for the decision to submit for publication.

Results

Our search retrieved 2190 items, of which 433 were duplicates. After screening titles and abstracts, 26 reports of randomised controlled trials remained and were evaluated in detail. Of these, we excluded 12 trials because they compared routine versus selective invasive strategy, two trials[19,20] because patients were randomised before hospital admission, one trial[21] because patients were randomised after coronary angiography, and three trials because their principal investigators did not respond to our request.[22–24] Eight trials involving 5324 patients met the eligibility criteria and were included in the meta-analysis (table 1, figure 1).

All included trials had a low risk of bias overall (appendix). Table 2 shows key design features of the included trials; table 2 shows baseline and procedural characteristics. With the exception of LIPSA-NSTEMI, all trials assigned patients to two groups. In LIPSIA-NSTEMI, patients were assigned to either an immediate, early, or selective invasive strategy. We excluded patients assigned to the selective invasive group. Median follow-up was 180 days (IQR 180–360), ranging from 30 days in ABOARD to 732 days in ELISA-3. The maximum follow-up varied in ELISA and ELISA-3, depending on the time of inclusion; other trials had a fixed end of follow-up for each patient. This meta-analysis included longer follow-up than in the original reports of three trials: ELISA (372 days *vs* 30 days), ELISA-3 (732 days *vs* 30 days), and ISAR-COOL (360 days *vs* 30 days). During the extended follow-up period two deaths and no non-fatal myocardial infarctions occurred in ELISA, 33 deaths and 24 non-fatal myocardial infarctions occurred in ELISA-3, and 18 deaths and ten non-fatal myocardial infarctions occurred in ISAR-COOL. LIPSIA-NSTEMI and RIDDLE-NSTEMI only enrolled patients with positive cardiac biomarkers (ie, NSTEMI rather than NSTE-ACS).

Three trials used a strategy of immediate (primary) percutaneous coronary intervention for the early invasive group (ABOARD, LIPSIA-NSTEMI, and RIDDLE-NSTEMI), whereas for the others, the timing in the early invasive group differed by several hours, up to 24 h. The heterogeneity in timing is even more obvious for the delayed invasive group. Trials such as ABOARD and LIPSIA-NSTEMI, which tested primary percutaneous coronary intervention for NSTEMI, had control groups with the fastest procedural times. Thus, there was

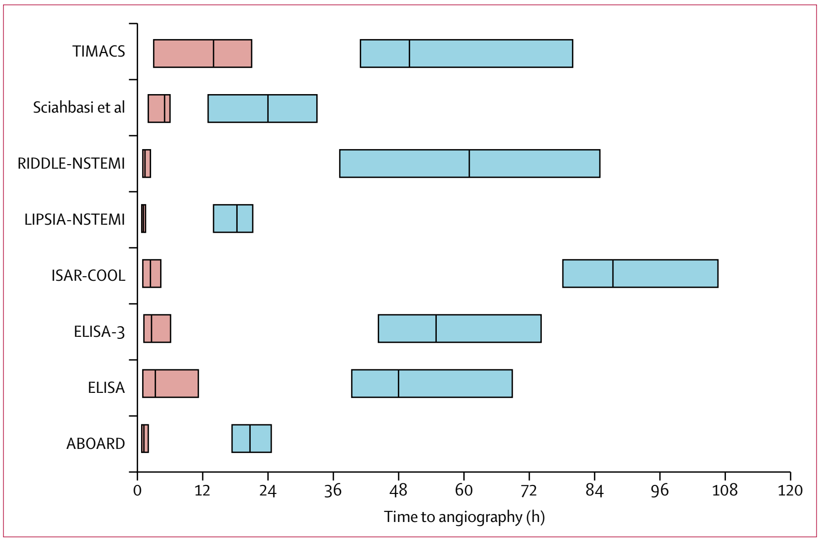

***Figure 2:* Time to coronary angiography in the early invasive and delayed invasive group of included trials**
Bars depict IQR and median time from randomisation to coronary angiography in the early invasive group (red) and delayed invasive group (blue).

considerable overlap between the fast procedural times in the delayed invasive groups of these trials and the early invasive strategy of other trials (figure 2). The remaining baseline characteristics were well-balanced between included trials and therefore allowed pooling for meta-analysis.

Data for all-cause mortality and non-fatal myocardial infarction were complete for all patients. In total, 277 (5%) of 5324 patients died during the entire follow-up period. Of these, 121 (44%) deaths occurred during in-hospital treatment and 156 (56%) occurred after hospital discharge. The assigned treatment strategy did not have a significant effect on all-cause mortality when analysing the total population (HR 0·81, 95% CI 0·64–1·03; p=0·0879; figure 3). Treatment strategy did not have a significant effect when follow-up was divided into periods from randomisation to hospital discharge and from hospital discharge to end of follow-up (appendix). There was no evidence of heterogeneity in the outcome of mortality (I^2=0% and p>0·5 for heterogeneity for each period; figure 3, appendix).

Overall, 338 (6%) of 5324 patients had a non-fatal myocardial infarction. We detected no significant difference for non-fatal myocardial infarction between an early and delayed invasive strategy during any follow-up period (HR for overall follow-up period 0·91, 95% CI 0·57–1·46; p=0·7014; appendix). Heterogeneity was high in all analyses of non-fatal myocardial infarction (I^2 >50%, and p<0·05 for heterogeneity for each period; figure 3, appendix).

We detected no association between mortality and difference in time to angiography between the early invasive and delayed invasive group in post-hoc meta-regression analysis. We detected no significant effect among trials in which coronary angiography was done in most patients in the delayed invasive group within 24 h after randomisation; nor did we detect an effect among trials in which most patients in the delayed invasive group had coronary angiography later than 24 h after randomisation (appendix). However, we did observe a significant association in post-hoc meta-regression with regard to non-fatal myocardial infarction (appendix).

Patients with elevated cardiac biomarkers at baseline (4206 [79·0%] of 5324) had 219 (79·1%) of the 277 recorded deaths; patients with diabetes (1441 [27·1%] of 5324) had 105 (37·9%) of the 277 deaths, and patients aged 75 years or older (1282 [24·1%] of 5324) had 136 (49·1%) of the 277 deaths. Although there was no significant mortality reduction for the entire patient cohort, an early invasive strategy might be associated with lower mortality in these pre-specified high-risk subgroups compared with a delayed invasive strategy (for patients with elevated biomarkers, HR 0·761; 95% CI 0·581–0·996; for diabetes, HR 0·67, 95% CI 0·45–0·99; for age ≥75 years, HR 0·65, 95% CI 0·46–0·93; figure 4). GRACE risk score was determined prospectively in four trials (ELISA-3, LIPSIA-NSTEMI, RIDDLE-NSTEMI, and TIMACS). These trials included 4288 (80·5%) of the 5324 patients and 239 (86·3%) of the 277 deaths. Patients with a GRACE risk score of more than 140 points (1519 of 4288 patients with 173 of 239 deaths) might also benefit from an early invasive strategy compared with a delayed invasive strategy (HR 0·70, 95% CI 0·52–0·95; figure 4). However, the test for interaction was not significant in any subgroup analysis (figure 4).

Discussion

This collaborative meta-analysis is the largest and first studying the optimal timing of coronary angiography with regard to deaths in high-risk subgroups of patients with NSTE-ACS. For the entire NSTE-ACS patient cohort there was no significant mortality benefit with an early invasive strategy compared with a delayed invasive strategy. However, pre-defined subgroup analyses suggested lower mortality in four high-risk subgroups: those with elevated cardiac biomarkers at baseline, diabetes, GRACE risk score more than 140 points, and age 75 years or older, although tests for risk–treatment interactions were not statistically significant.

Previous meta-analyses showed a benefit of a routine invasive strategy over a selective invasive (or conservative) strategy in patients with NSTE-ACS with regards to a composite endpoint of death or myocardial infarction.[26,27] However, optimal timing of coronary angiography is less clearly defined. Guidelines recommend an immediate invasive strategy for all unstable very high-risk patients. For all other patients, an invasive strategy within 24–72 h is recommended depending on their risk level. An early invasive strategy within 24 h is recommended for high-risk patients with positive cardiac biomarkers, dynamic ST-T changes, or a GRACE risk score more than 140 points.[1,2] Previous meta-analyses[4–7] on the timing of coronary angiography in patients with NSTE-ACS consistently showed that an early invasive strategy is superior to a delayed invasive strategy on soft outcomes of refractory or recurrent ischaemia and length of hospital stay without an increase in adverse outcomes (ie, all-cause mortality, myocardial infarction, stroke, or bleeding).

Overall, neither treatment strategy was superior in reducing all-cause mortality or non-fatal myocardial infarction in our meta-analysis. In contrast to previous meta-analyses,[4–8] we were able to categorise follow-up into distinct periods (ie, from randomisation to hospital discharge and from hospital discharge to end of follow-up). No significant effect was apparent for either outcome in any follow-up period.

Our collaborative approach using individual patient data and standardised tabulated data enabled us to explore treatment effects in pre-specified high-risk subgroups. Biomarker positive patients represented the largest subgroup, containing 79% of all patients. However, individual trials were underpowered to detect a significant effect of an early invasive strategy compared with a delayed invasive strategy on all-cause mortality in such patients. Moreover, because of inconsistent trial reporting, previous meta-analyses[4–8] based on published data were unable to detect such an effect. Hence, our collaborative meta-analysis is the first to suggest a mortality benefit of an early invasive strategy compared with a delayed invasive strategy in patients with NSTEMI at baseline. In line with this, two meta-analyses including trials comparing a routine versus a selective invasive strategy showed the superiority of a routine invasive strategy with regard to composite endpoints (ie, death or myocardial infarction[25] and death, myocardial infarction, or readmission to hospital[27]) in patients with positive biomarkers at baseline.

The guidelines recommendation of performing coronary angiography within 24 h in patients with GRACE scores of more than 140 points is based on a pre-specified subgroup analysis of the TIMACS trial. Only patients in the highest GRACE score tertile benefited from an early invasive strategy compared with a delayed invasive strategy regarding the composite endpoint of death, myocardial infarction, or stroke.[3] Four of eight trials included in our meta-analysis prospectively calculated the GRACE risk score. Under these caveats, an early invasive strategy might be associated with lower mortality than a delayed invasive strategy in this high-risk group.

11·5% of patients in the ACOS registry[28] and 25·0% in the Euroheart acute coronary syndrome survey were older than 75 years.[29] Compared to these registries, patients older than 75 years were well represented in our meta-analysis (1282 [24·1%] of 5325 patients) and accounted for almost half of deaths. Coronary angiography was less often done in older patients in different registries[28,30,31] but registry data suggest that a routine invasive strategy is also beneficial in these patients.[29,32] Our meta-analysis

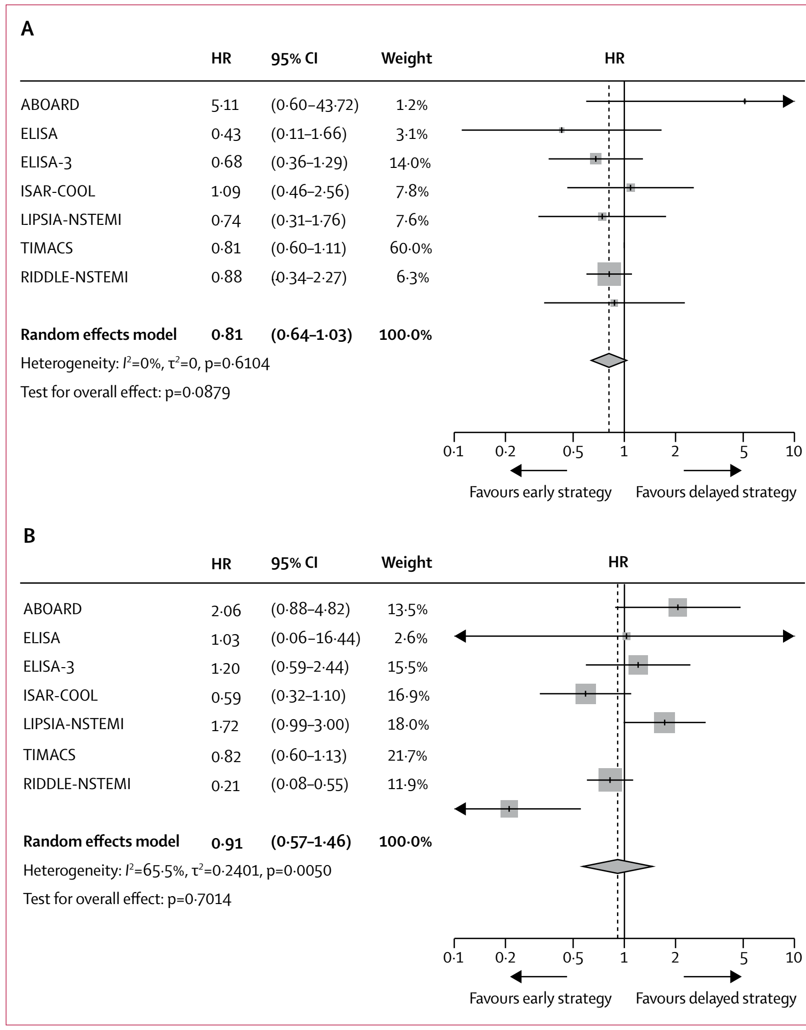

Figure 3: **Outcomes after an early invasive strategy versus a delayed invasive strategy**
(A) All-cause mortality from randomisation to end of follow-up, (B) non-fatal myocardial infarction from randomisation to end of follow-up. Size of data markers indicates weight of study in the pooled analysis. HR=hazard ratio.

supports this observation, suggesting that patients aged older than 75 years assigned to the early invasive group might have lower mortality. No direct information in this population was available regarding fragility, which is strongly and independently associated with in-hospital mortality and 30-day mortality.[33]

In a pooled analysis of the TIMI study group trials, 3457 (28·8%) of 12 002 patients with NSTE-ACS had diabetes. These patients had an increased risk for mortality at 30 days and at 1 year.[34] Patients with diabetes and pre-diabetes were also at increased risk of death in other studies;[35,36] therefore, the presence of diabetes identifies a high-risk subgroup of patients with NSTE-ACS. The proportion of patients in our meta-analysis who had diabetes (27·1%) is close to that of the pooled TIMI trial analysis. Even though guidelines do not recommend basing the timing of coronary angiography on diabetes status and diabetes status is not a parameter

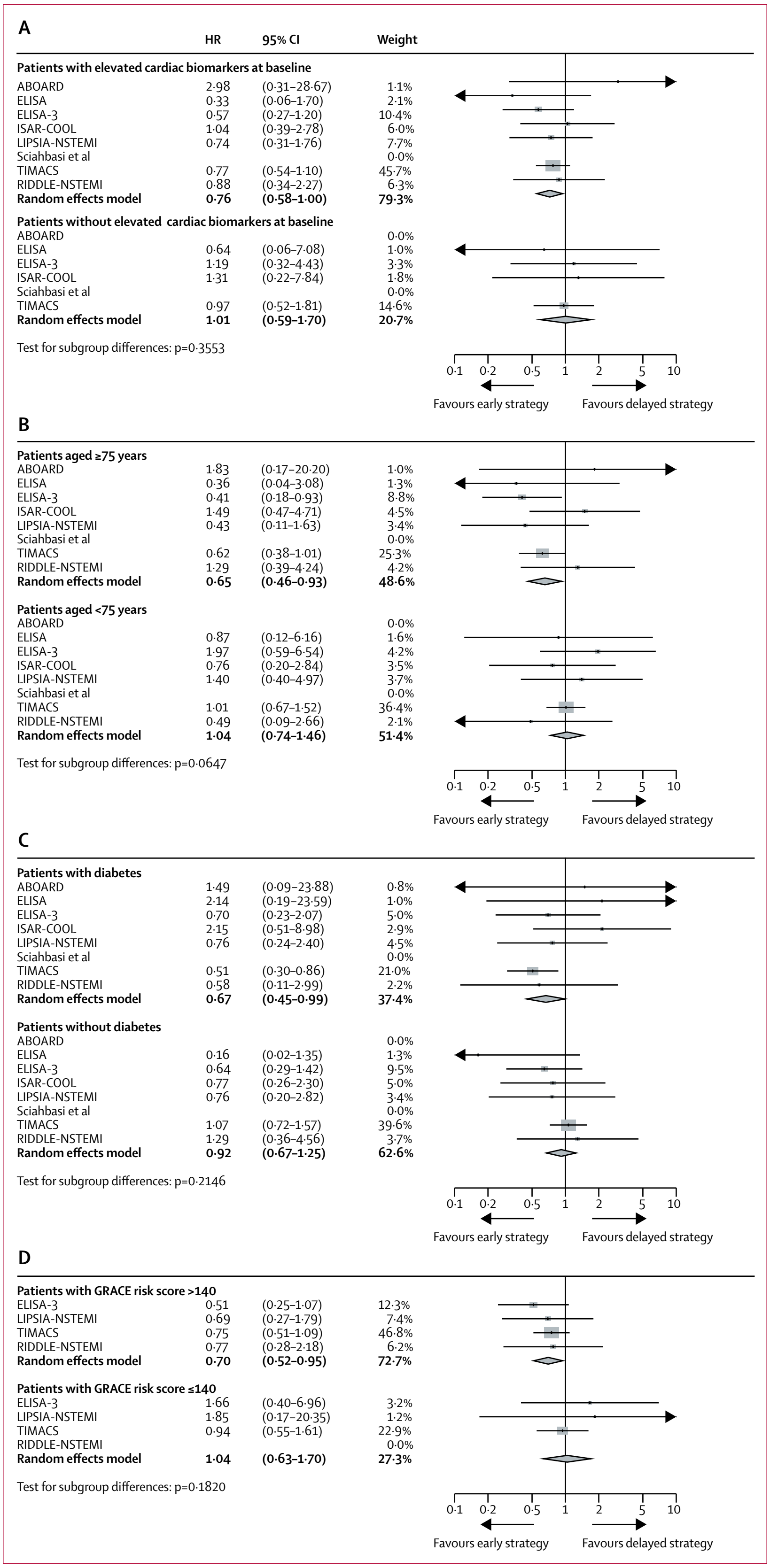

Figure 4: **Mortality after an early invasive strategy versus a delayed invasive strategy in different subgroups**

(A) Patients with or without elevated cardiac biomarkers at baseline, (B) patients aged <75 years or ≥75 years, (C) patients with or without diabetes, (D) patients with GRACE risk score ≤140 or >140. Size of data markers indicates weight of study in the pooled analysis. HR=hazard ratio.

of the GRACE risk score, an early invasive strategy might be associated with lower mortality than a delayed invasive strategy in patients with diabetes.

Although the timing of coronary angiography might reduce mortality, a routine invasive strategy compared with a selective invasive strategy did not.[25,27] However, a routine invasive strategy reduced the composite endpoint of all-cause mortality or non-fatal myocardial infarction, predominantly in high-risk patients.[25,26] High-risk characteristics were more common in the present analysis than in previous reports (eg, elevated biomarkers at baseline 79% *vs* 55%;[27] diabetes 24% *vs* 18%[37]). Accumulation of these risk factors might shift patients to benefit from routine invasive or early invasive strategy for NSTE-ACS.[37] From a pathophysiological point of view, an early invasive strategy might limit infarct size, as in ST-elevation myocardial infarction, and reduce inflammation and other systemic stress responses. This might explain the suggested mortality benefit in high-risk subgroups in our meta-analysis.

The following limitations should be acknowledged. First, TIMACS contributed 56·9% of patients and 58·8% of deaths to our meta-analysis. Therefore, the statistical weight to the calculated models of TIMACS ranged between 43% and 84% for all mortality analyses. However, TIMACS alone was underpowered to detect differences in mortality. Second, timing of coronary angiography for the early invasive and delayed invasive groups varied between included studies. Although median time to angiography in the early invasive group was less than 3 h for most trials, it was 14 h for TIMACS. Moreover, the difference between early invasive and delayed invasive group was more than 24 h for all trials besides ABOARD and LIPSIA-NSTEMI. Our meta-regression analysis did not reveal a significant association with mortality for the difference in time to coronary angiography in the early invasive and delayed invasive groups although such an effect was detected on non-fatal myocardial infarction. Third, coronary angiography was almost always performed within 24 h of randomisation in all trials, which could have masked detection of myocardial re-infarction due to already elevated cardiac biomarkers. Therefore, this outcome might be underdiagnosed. Fourth, tests for interaction were negative in all subgroup analyses. The significant HR within these high-risk strata should therefore be interpreted as exploratory and hypothesis-generating. Fifth, different biomarkers and assays were used to define biomarker positivity and most trials were done before high-sensitivity troponin assays became clinical

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standard in Europe.[38] These assays shift some patients with NSTE-ACS from unstable angina to NSTEMI.[39] Use of high-sensitive troponin assays does not much change risk prediction by GRACE score.[40] Therefore, it is highly probable that results of our meta-analysis will also apply in the high-sensitive troponin era. In general, biomarker positive patients are a high-risk subgroup vulnerable to cardiovascular events.[25] Sixth, three eligible trials were not included since the respective principal investigators did not respond to our request. However, these trials were only small and their quality difficult to assess.

In conclusion, an early invasive strategy was not associated with a significant mortality reduction compared with a delayed invasive strategy in the overall NSTE-ACS population. However, an early invasive strategy might be beneficial in four pre-defined high-risk subgroups. Since this finding is exploratory in nature, a pragmatic large-scale confirmatory trial would be needed to obtain definitive evidence of whether an early invasive strategy is beneficial compared with a delayed invasive strategy in these high-risk subgroups.

Contributors

AJ had the idea for and designed the study, did the systematic review, collected and analysed data, and wrote the Article. SRM, GM, EV, AWJvH, EAB, F-JN, AK, and AS designed the study, extracted data, and revised the Article. P-GR and FL revised the Article. AM, GS, and DM extracted data and revised the Article. RV designed the study and revised the Article. SD collected and analysed data, and revised the Article. HT collected and analysed data, and wrote the Article.

Declaration of interests

We declare no competing interests.

References

1 Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; **64:** e139–228.

2 Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016; **37:** 267–315.

3 Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med* 2009; **360:** 2165–75.

4 Katritsis DG, Siontis GC, Kastrati A, et al. Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. *Eur Heart J* 2011; **32:** 32–40.

5 Navarese EP, Gurbel PA, Andreotti F, et al. Optimal timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes: a systematic review and meta-analysis. *Ann Intern Med* 2013; **158:** 261–70.

6 Rajpurohit N, Garg N, Garg R, et al. Early versus delayed percutaneous coronary intervention for patients with non-ST segment elevation acute coronary syndrome: a meta-analysis of randomized controlled clinical trials. *Catheter Cardiovasc Interv* 2013; **81:** 223–31.

7 Milasinovic D, Milosevic A, Marinkovic J, et al. Timing of invasive strategy in NSTE-ACS patients and effect on clinical outcomes: a systematic review and meta-analysis of randomized controlled trials. *Atherosclerosis* 2015; **241:** 48–54.

8 Bonello L, Laine M, Puymirat E, et al. Timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes and clinical outcomes: an updated meta-analysis. *JACC Cardiovasc Interv* 2016; **9:** 2267–76.

9 Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343:** d5928.

10 Duchateau L, Pignon JP, Bijnens L, Bertin S, Bourhis J, Sylvester R. Individual patient-versus literature-based meta-analysis of survival data: time to event and event rate at a particular time can make a difference, an example based on head and neck cancer. *Control Clin Trials* 2001; **22:** 538–47.

11 Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010; **340:** c221.

12 Montalescot G, Cayla G, Collet JP, et al. Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. *JAMA* 2009; **302:** 947–54.

13 van 't Hof AW, de Vries ST, Dambrink JH, et al. A comparison of two invasive strategies in patients with non-ST elevation acute coronary syndromes: results of the Early or Late Intervention in unStable Angina (ELISA) pilot study. 2b/3a upstream therapy and acute coronary syndromes. *Eur Heart J* 2003; **24:** 1401–05.

14 Badings EA, The SH, Dambrink JH, et al. Early or late intervention in high-risk non-ST-elevation acute coronary syndromes: results of the ELISA-3 trial. *EuroIntervention* 2013; **9:** 54–61.

15 Neumann FJ, Kastrati A, Pogatsa-Murray G, et al. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA* 2003; **290:** 1593–99.

16 Thiele H, Rach J, Klein N, et al. Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: the Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI (LIPSIA-NSTEMI Trial). *Eur Heart J* 2012; **33:** 2035–43.

17 Sciahbasi A, Madonna M, De Vita M, et al. Comparison of immediate vs early invasive strategy in patients with first acute non-ST-elevation myocardial infarction. *Clin Cardiol* 2010; **33:** 650–55.

18 Milosevic A, Vasiljevic-Pokrajcic Z, Milasinovic D, et al. Immediate versus delayed invasive intervention for non-STEMI patients: the RIDDLE-NSTEMI study. *JACC Cardiovasc Interv* 2016; **9:** 541–49.

19 Reuter PG, Rouchy C, Cattan S, et al. Early invasive strategy in high-risk acute coronary syndrome without ST-segment elevation. The Sisca randomized trial. *Int J Cardiol* 2015; **182:** 414–18.

20 Stengaard C, Sorensen JT, Rasmussen MB, et al. Acute versus subacute angiography in patients with non-ST-elevation myocardial infarction - the NONSTEMI trial phase I. *Eur Heart J Acute Cardiovasc Care* 2016; published online May 6. DOI:10.1177/2048872616648468.

21 Riezebos RK, Ronner E, Ter Bals E, et al. Immediate versus deferred coronary angioplasty in non-ST-segment elevation acute coronary syndromes. *Heart* 2009; **95:** 807–12.

22 Shen W, Zhang R, Shen Y, et al. Optimal timing of coronary stenting in unstable angina patients. *Chin Med J (Engl)* 2001; **114:** 59–61.

23 Tekin K, Cagliyan CE, Tanboga IH, et al. Influence of the timing of percutaneous coronary intervention on clinical outcomes in non-ST-elevation myocardial infarction. *Korean Circ J* 2013; **43:** 725–30.

24 Zhang J, Qiao SB, Zhu J, Chinese Cooperative Group of the Timing of Intervention in Acute Coronary S. Outcome of patients with non-ST segment elevation acute coronary syndrome undergoing early or delayed intervention. *Zhonghua Xin Xue Guan Bing Za Zhi* 2010; **38:** 865–69 (in Chinese).

25 Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA* 2005; **293:** 2908–17.

26 Fox KA, Clayton TC, Damman P, et al. Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. *J Am Coll Cardiol* 2010; **55:** 2435–45.

27 O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive *vs* conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2008; **300:** 71–80.

28 Bauer T, Koeth O, Junger C, et al. Effect of an invasive strategy on in-hospital outcome in elderly patients with non-ST-elevation myocardial infarction. *Eur Heart J* 2007; **28:** 2873–78.

29 Rosengren A, Wallentin L, Simoons M, et al. Age, clinical presentation, and outcome of acute coronary syndromes in the Euroheart acute coronary syndrome survey. *Eur Heart J* 2006; **27:** 789–95.

30 Devlin G, Gore JM, Elliott J, et al. Management and 6-month outcomes in elderly and very elderly patients with high-risk non-ST-elevation acute coronary syndromes: the Global Registry of Acute Coronary Events. *Eur Heart J* 2008; **29:** 1275–82.

31 Malkin CJ, Prakash R, Chew DP. The impact of increased age on outcome from a strategy of early invasive management and revascularisation in patients with acute coronary syndromes: retrospective analysis study from the ACACIA registry. *BMJ Open* 2012; **2:** e000540.

32 Bach RG, Cannon CP, Weintraub WS, et al. The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. *Ann Intern Med* 2004; **141:** 186–95.

33 Ekerstad N, Swahn E, Janzon M, et al. Frailty is independently associated with short-term outcomes for elderly patients with non-ST-segment elevation myocardial infarction. *Circulation* 2011; **124:** 2397–404.

34 Donahoe SM, Stewart GC, McCabe CH, et al. Diabetes and mortality following acute coronary syndromes. *JAMA* 2007; **298:** 765–75.

35 Norhammar A, Tenerz A, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* 2002; **359:** 2140–44.

36 Giraldez RR, Clare RM, Lopes RD, et al. Prevalence and clinical outcomes of undiagnosed diabetes mellitus and prediabetes among patients with high-risk non-ST-segment elevation acute coronary syndrome. *Am Heart J* 2013; **165:** 918–25.e2.

37 O'Donoghue ML, Vaidya A, Afsal R, et al. An invasive or conservative strategy in patients with diabetes mellitus and non-ST-segment elevation acute coronary syndromes: a collaborative meta-analysis of randomized trials. *J Am Coll Cardiol* 2012; **60:** 106–11.

38 Apple FS, Collinson PO, IFCC Task Force on Clinical Applications of Cardiac Bio-Markers. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clin Chem* 2012; **58:** 54–61.

39 Brush JE Jr, Kaul S, Krumholz HM. Troponin testing for clinicians. *J Am Coll Cardiol* 2016; **68:** 2365–75.

40 Meune C, Drexler B, Haaf P, et al. The GRACE score's performance in predicting in-hospital and 1-year outcome in the era of high-sensitivity cardiac troponin assays and B-type natriuretic peptide. *Heart* 2011; **97:** 1479–83.