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Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes

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Aims An invasive approach is superior to medical management for the treatment of patients with acute coronary syndromes without ST-segment elevation (NSTE-ACS), but the optimal timing of coronary angiography and subsequent intervention, if indicated, has not been settled.

Methods and results We conducted a meta-analysis of randomized trials addressing the optimal timing (early vs. delayed) of coronary angiography in NSTE-ACS. Four trials with 4013 patients were eligible (ABOARD, ELISA, ISAR-COOL, TIMACS), and data for longer follow-up periods than those published became available for this meta-analysis by the ELISA and ISAR-COOL investigators. The median time from admission or randomization to coronary angiography ranged from 1.16 to 14 h in the early and 20.8–86 h in the delayed strategy group. No statistically significant difference of risk of death [random effects risk ratio (RR) 0.85, 95% confidence interval (CI) 0.64–1.11] or myocardial infarction (MI) (RR 0.94, 95% CI 0.61–1.45) was detected between the two strategies. Early intervention significantly reduced the risk for recurrent ischaemia (RR 0.59, 95% CI 0.38–0.92, $P = 0.02$) and the duration of hospital stay (by 28%, 95% CI 22–35%, $P < 0.001$). Furthermore, decreased major bleeding events (RR 0.78, 95% CI 0.57–1.07, $P = 0.13$), and less major events (death, MI, or stroke) (RR 0.91, 95% CI 0.82–1.01, $P = 0.09$) were observed with the early strategy but these differences were not nominally significant.

Conclusion Early coronary angiography and potential intervention reduces the risk of recurrent ischaemia, and shortens hospital stay in patients with NSTE-ACS.

Keywords NSTE-ACS • Angiography • Timing • Meta-analysis

Introduction

Acute coronary syndromes (ACS) without ST-elevation include unstable angina (UA) and non-ST-elevation myocardial infarction (NSTEMI) and represent a considerable burden of cardiac events that require hospitalization and advanced care.[1] An invasive approach is currently considered superior to medical management for the treatment of patients with non-ST-elevation ACS (NSTE-ACS).[2–5] However, the optimal timing of coronary angiography and subsequent intervention if indicated, i.e. immediately after admission or after pre-treatment with optimal medical therapy including potent antiplatelet agents, has not been settled. Randomized studies that have particularly addressed the issue of optimal timing for coronary angiography and potential intervention in patients with NSTE-ACS have produced inconclusive results.[6–9]

Thrombotic material in patients with UA may increase the risk of immediate coronary intervention. On the basis of evidence from randomized controlled trials[2,10,11] and a meta-analysis,[12] there is

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concern that adverse events such as myocardial infarction (MI) may be increased with routine early intervention. Thus, delayed catheterization to allow plaque passivation by pre-treatment with optimal antithrombotic medication, such as glycoprotein (GP) IIb/IIIa inhibitors, has been proposed,[13,14] despite a potentially increased risk of bleeding with this approach.[15] We have therefore conducted a meta-analysis of relevant randomized trials to address the question of optimal timing (early vs. delayed) of coronary angiography in patients who present with NSTE-ACS. The meta-analysis included both published data as well as additional information on outcomes from longer follow-up (up to 1 year) of two trials that had only published short-term information initially.

Methods

Detailed methods of literature search, selection of studies, data extraction, and statistical analysis were specified in a protocol that was elaborated in advance.

Definition of invasive strategies

For patients presenting with NSTE-ACS an 'early' intervention was defined as the performance of coronary angiography soon after admission and randomization. A 'delayed' invasive approach included pre-treatment with optimal medical therapy and subsequent catheterization in later stages after enrolment. The decision for subsequent therapy [percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), or conservative] was based on the angiographic findings and the physicians' clinical judgement.

Search strategy and inclusion of studies

Possibly eligible studies were identified through a MEDLINE literature search (until January 2010) using the keywords *acute coronary syndrome*, *unstable coronary syndrome*, *unstable angina*, *non-stemi*, *non-st-elevation*, *random**. Furthermore, we searched Google Scholar, the Clinical Trials Registry (www.clinicaltrials.gov), and the Current Controlled Trials Registry (www.controlled-trials.com) for unpublished studies, and the Web for relevant abstracts/presentations from major cardiology meetings. For each eligible published study, we also screened its references and its citations (ISI Web of Science).

Eligible studies for inclusion in this meta-analysis were randomized controlled trials comparing an early vs. a delayed invasive strategy in patients presenting with NSTE-ACS (UA or NSTEMI). We included studies in which patients were randomly allocated on admission to routine early or delayed diagnostic angiography. We excluded studies that compared invasive vs. conservative strategies (routine vs. selective intervention) for the management of NSTE-ACS, and studies where NSTE-ACS patients were randomized to early vs. late PCI following coronary angiography that had been previously performed in all patients.

Data extraction and assessment of risk of bias

For data extraction we scrutinized the main article, any accompanying supplemental material, and any published secondary analyses, if available. We systematically recorded study characteristics (number of patients randomized, enrolment period, length of follow-up), patient demographics, risk factors for coronary artery disease, previous cardiac history, and the number of patients with ischaemic electrocardiographic (ECG) changes and elevated cardiac biomarkers at baseline. We also recorded the medical therapy administered to patients on admission, the number of patients that eventually did not perform diagnostic angiography, the time needed from admission or randomization to angiography in each group, angiographic characteristics, and the type of treatment (PCI, CABG, medical/conservative). Finally, we extracted the number of events of the following outcomes: all-cause death, MI, major bleeding, recurrent ischaemia, repeat intervention, stroke; and the composite outcome of death or MI or stroke (first occurrence). Information on the duration of hospital stay was also recorded.

Data extraction was performed based on the intention-to-treat (ITT) principle. For all events we considered the longest available follow-up period. Two authors independently extracted the data using a pre-constructed form. Disagreements were resolved by consensus and arbitration by two other authors. The principal investigators of published eligible trials where the published data pertained to short-term follow-up (<6 months) were asked to provide data for outcomes on their patients followed-up for longer periods (up to 1 year), including information on outcomes not reported at all in the original publications.

We also assessed the risk of bias for each included trial. Specifically, we evaluated the mode of randomization, concealment of treatment allocation, description of losses to follow-up, whether outcomes were centrally adjudicated or site-reported, the blinding of outcome adjudicators, and whether analyses were performed according to ITT. Blinding of patients and/or health care providers is not applicable to trials where the intervention entails coronary angiography. We did not perform funnel plot asymmetry tests since they are inappropriate when only four trials are available.[16]

Statistical analysis

All categorical data are summarized as frequencies and percentages, whereas summary statistics for continuous variables are presented as means and standard deviations (SD) or medians and interquartile ranges (IQR). The risk ratio (RR) (the risk of an outcome among patients who were randomized to the early vs. delayed invasive strategy) was used as the metric of choice in meta-analyses of binary outcomes, while for hospital stay we calculated the relative difference. For length of hospital stay, given that the distribution of the data is skewed, we used logarithmic transformation and evaluated the SD based on the IQR, and the point estimate based on the logarithm of the median.[17] The Q-statistic based on the χ^2 test was used for evaluation of between-study heterogeneity and was considered statistically significant at a level of <0.10.[18] We also quantified the extent of heterogeneity across studies using the I^2 statistic [and its 95% confidence intervals (CIs)], which is independent of the number of studies and quantifies heterogeneity on a scale of 0–100% (>75% indicates very large between-study heterogeneity).[19,20] Data were combined across the included studies based on both fixed effects (FE, Mantel-Haenszel) and random effects (RE, DerSimonian and Laird) models. When there is no detectable between-study heterogeneity (between-study variance $\tau^2 = 0$), the two models give identical results. Otherwise, RE give wider CIs. Finally, FE meta-analyses were performed in subgroups to examine whether the overall results were different for patients who presented with ST-deviation; and for patients with elevated cardiac biomarkers above the upper limit of the normal range at baseline.

All statistical analyses were conducted in STATA 10.0 (STATA Corp). *P*-values are two-tailed. All presented CIs are calculated at the 95% level. The presentation of the meta-analysis complies with the PRISMA checklist.[21]

Results

Study selection and characteristics

The study selection process is presented in *Figure 1*. The electronic searches identified 4707 items, of which 4690 were excluded upon perusing the title and abstract. Seventeen potentially eligible

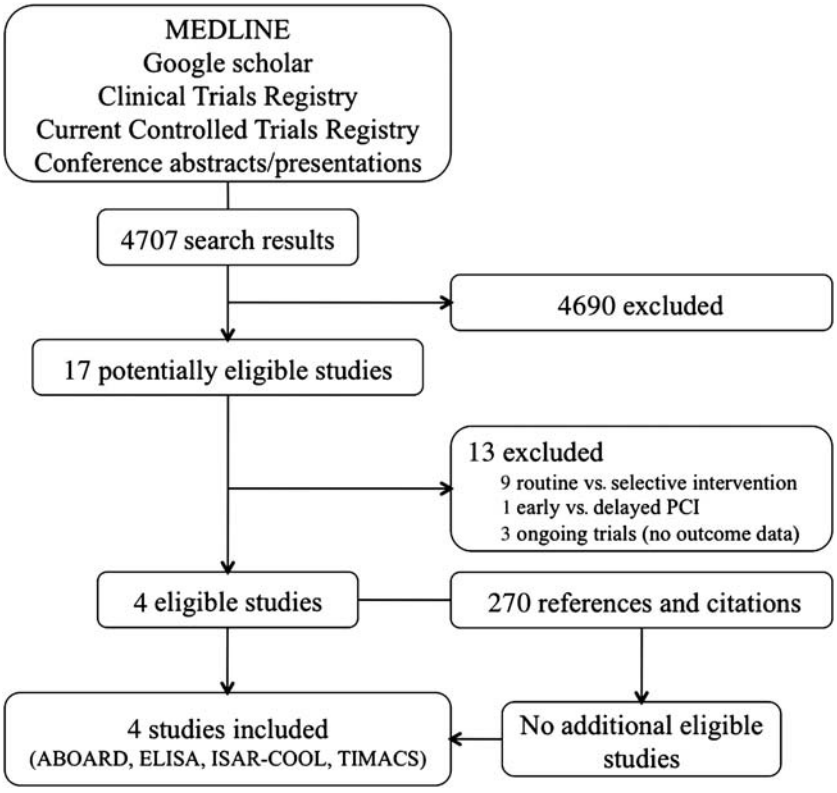

Figure 1 Selection of studies.

studies were scrutinized further. Nine were excluded because they compared a routine invasive vs. conservative (or selective invasive) strategy, and one was excluded because the enrolled patients were randomized to immediate or deferred PCI after coronary angiography was performed. Three possibly eligible studies were indentified in ClinicalTrials.gov and the Current Controlled Trials Registry (controlled-trials.com), but they were still in progress and had no outcome data to be included. Search of references and citations of the four eligible trials did not identify any additional studies. Finally, four randomized-controlled trials comparing early vs. delayed invasive strategies were suitable for inclusion in our meta-analysis. These were the Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate of Delayed Intervention (ABOARD),[6] Early or Late Intervention in Unstable Angina (ELISA),[7] Intracoronary Stenting With Antithrombotic Regimen Cooling-Off (ISAR-COOL),[8] and Timing of Intervention in Acute Coronary Syndromes (TIMACS)[9] trials.

The four eligible studies enrolled 4013 patients, of which 2080 were randomized to the early and 1933 to the delayed strategy. In the published reports, 6 month follow-up data were available in TIMACS and 1 month in the other three trials. Long-term follow-up (12 months) data were collected and included in the meta-analysis for ELISA and ISAR-COOL (*Table 1*). ELISA and ISAR-COOL also contributed information on recurrent ischaemia, repeat intervention, stroke, and the composite outcome for which no data at all had been published originally. We also communicated with the ABOARD investigators but they replied that no additional follow-up data were available.

Patients, medical treatment, procedural characteristics, and risk of bias

Baseline demographics of patients in each study are shown in *Table 1*. Women represented 34% of the total population (701 and 652 in the early and delayed strategy, respectively). Established risk factors for ischaemic heart disease (diabetes, hypertension, hyperlipidaemia, and smoking) were prevalent in the study populations and cardiac disease history was well-matched between the two treatment arms.

Table 2 presents procedural characteristics. In total, 39 (1.9%) and 64 (3.3%) patients did not eventually perform diagnostic angiography after randomization in the early and delayed strategy groups, respectively. The median time from randomization (or admission) to coronary angiography ranged from 1.16 to 14 h in the early strategy group and 20.8–86 h in the delayed catheterization group. Complete revascularization was achieved by PCI in 61.5 and 56.8% in the two arms and by CABG in 14.5 and 14.1%, respectively; 24% and 29.1%, respectively, were managed conservatively after diagnostic angiography.

Trial investigators prescribed optimal medical antithrombotic treatment peri- and post-PCI in the majority of patients, as shown in *Table 2*. Use of GP IIb/IIIa inhibitors was similar between study arms, except for ELISA, where no such agent was

Table 1 Baseline characteristics of the included studies

Characteristic	ABOARD		ELISA		ISAR-COOL		TIMACS	
	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed
No. of patients	175	177	109	111	203	207	1593	1438
Enrolment period	2006–08		2000–01		2000–02		2003–08	
Follow-up (months)	1		12		12		6	
Demographics								
Age (yrs), mean (SD)	65 (12)	65 (12)	63 (10.7)	65 (11.4)	68 (12)	69 (11)	65 (ND)	65.7 (ND)
Male, No. (%)	127 (73.6)	125 (70.6)	79 (72.5)	76 (68.5)	134 (66.0)	140 (67.6)	1039 (65.2)	940 (65.4)
Medical history, No. (%)								
Diabetes mellitus	38 (21.7)	57 (32.2)	16 (14.7)	16 (14.4)	53 (26.1)	65 (31.4)	422 (26.5)	394 (27.4)
SH	115 (65.7)	108 (61.0)	49 (45.0)	43 (38.7)	174 (85.7)	180 (87.0)	ND	
Hyperlipidaemia	100 (57.1)	102 (57.6)	42 (38.5)	42 (37.8)	131 (64.5)	148 (71.5)	ND	
Smoking	56 (32.0)	60 (33.9)	40 (36.7)	36 (32.4)	49 (24.1)	38 (18.4)	ND	
Prior MI	29 (16.6)	33 (18.6)	19 (17.4)	14 (12.6)	44 (21.7)	52 (25.1)	314 (19.7)	301 (20.9)
Prior PCI	43 (24.6)	54 (30.5)	16 (14.7)	16 (14.4)	42 (20.7)	48 (23.2)	221 (13.9)	204 (14.2)
Prior CABG	9 (5.1)	12 (6.8)	12 (11.0)	8 (7.2)	20 (9.9)	28 (13.5)	112 (7.0)	105 (7.3)
Baseline risk variables, No. (%)								
Ischaemic ECG changes	122 (69.7)	136 (76.8)	ND		133 (65.5)	134 (64.7)	1282 (80.5)	1149 (79.9)
Elevated cardiac biomarkers[a]	132 (75.4)	129 (72.9)	80 (73.4)	72 (64.9)	134 (66.0)	140 (67.6)	1230 (77.2)	1106 (76.9)

No., number; yrs, years; SD, standard deviation; SH, systematic hypertension; ND, no data; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ECG, electrocardiographic.
[a]Troponin I (ABOARD); Troponin T (ELISA, ISAR-COOL); Creatine kinase MB and Troponin (TIMACS).

prescribed in the early strategy group. Of note, different types of GP IIb/IIIa inhibitors were administered across the trials.

In all trials, proper mode of randomization, allocation concealment, and the extent of losses to follow-up were reported. Outcomes were adjudicated by blinded central committees in the three multicenter trials (ABOARD, ISAR-COOL, TIMACS). Also, a blinded committee adjudicated outcomes in ELISA which was a single-centre trial. Analyses were performed according to ITT in all trials.

Outcome events and synthesis of data

The summary of events of the selected outcomes across the studies is presented in *Table 3* and the definitions of outcomes across studies are listed in Supplementary material online, Table. Across all four trials 95 (4.6%) and 103 (5.3%) patients died, and 116 (5.6%) and 124 (6.4%) suffered a MI in the early and delayed strategy groups, respectively. A total of 154 major bleeding events were recorded (3.4 and 4.3% of patients in the early and delayed strategy, respectively) and recurrent ischaemia was observed in 77 (3.7%) patients of the early strategy group and 133 (6.9%) patients of the delayed strategy group. Repeat intervention was necessary in 172 and 160 patients, respectively (8.3% in each group). Forty-seven strokes were recorded across the three trials with such data available.

In the synthesis of data (*Table 4* and *Figure 2*), RE showed no statistically significant difference of risk between the early and delayed strategy for death (RR 0.85, 95% CI 0.64–1.11, $P = 0.24$) and MI (RR 0.94, 95% CI 0.61–1.45, $P = 0.79$). As for major bleeding, the summary point estimates suggested increased bleeding risk with the delayed strategy, but this association did not reach the level of formal statistical significance (RE RR 0.78, 95% CI 0.57–1.07, $P = 0.13$). In addition, the summary estimates showed no statistically significant differences between the two strategies regarding the need for repeat intervention (RR 0.96, $P = 0.84$) and stroke (RR 0.84, $P = 0.55$). Fixed and RE summary estimates were similar for all the aforementioned outcomes, since the between-study heterogeneity was not nominally statistically significant. Conversely, for the outcome of recurrent ischaemia statistically significant heterogeneity (estimated $I^2 = 61\%$) was detected among studies. The fixed and RE estimates were 0.57 (95% CI 0.44–0.74, $P < 0.001$) and 0.59 (95% CI 0.38–0.92, $P = 0.02$), respectively, demonstrating a more than 40% reduction in the relative risk of recurrent ischaemia with the early strategy. The composite outcome could be evaluated only in the three trials with long-term follow-up data (excluding ABOARD). The estimate suggested less major events (death, MI, or stroke) with early performed coronary angiography (RE RR 0.91, 95% CI 0.82–1.01; *Figure 2*, last panel), but the association was not nominally significant ($P = 0.09$).

Data on the effects of the two strategies on the duration of hospital stay were reported in three trials (ABOARD, ELISA, ISAR-COOL). Quantitative synthesis of the available data showed a need for shorter hospitalization (by 28%, 95% CI 22–35%, $P < 0.001$; $I^2 = 0\%$) of patients who were randomized to the early strategy compared with those randomized to the delayed strategy.

Table 2 Timing of intervention, angiographic characteristics, and definitive treatment

Characteristic	ABOARD		ELISA		ISAR-COOL		TIMACS	
	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed
Coronary angiography not performed	0	1 (1)	1 (0.9)	1 (0.9)	0	0	38 (2.4)	62 (4.3)
Time to angiography (hrs), median (IQR)	1.16 (0.85–2.1)[a]	20.8 (17.5–24.6)[a]	5.9 (3.6–15.0)[b]	50.2 (42.3–73.0)[b]	2.4 (1–4.3)[a]	86 (78.2–106.7)[a]	14 (3–21)[a]	50 (41–81)[a]
Diseased vessels								
One	63 (36.0)	51 (28.8)	36 (33.0)	37 (33.3)	39 (19.2)	40 (19.3)	503 (31.6)	447 (31.1)
Two	48 (27.4)	54 (30.5)	29 (26.6)	25 (22.5)	49 (24.1)	50 (24.2)	390 (24.5)	336 (23.4)
Three	32 (18.3)	44 (24.9)	31 (28.4)	33 (29.7)	94 (46.3)	92 (44.4)	272 (17.1)	227 (15.8)
Definitive treatment								
PCI	117 (66.9)	105 (59.3)	66 (60.6)	64 (57.7)	143 (70.4)	133 (64.3)	954 (59.9)	796 (55.4)
Use of DES[c]	56 (47.9)	58 (55.2)	40 (36.7)	43 (38.7)	0	0	473 (53.6)	422 (56.9)
CABG	16 (9.1)	17 (9.6)	15 (13.5)	21 (18.9)	16 (7.9)	16 (7.7)	255 (16.0)	219 (15.2)
Conservative	42 (24.0)	55 (31.1)	27 (24.8)	25 (22.5)	44 (21.7)	58 (28.0)	384 (24.1)	423 (29.4)
Antiplatelet drugs								
Aspirin	173 (99.4)[d]	177 (100)	98 (89.9)	94 (84.7)	203 (100)	207 (100)	1561 (98.0)	1411 (98.1)
Clopidogrel	168 (96.6)[d]	175 (98.9)	48 (44.0)	55 (49.5)	203 (100)	207 (100)	1389 (87.2)	1247 (86.7)
GP IIb/IIIa inhibitor	114 (65.1)	101 (57.4)[d]	4 (3.7)	60 (54.1)	203 (100)	207 (100)	370 (23.2)	322 (22.4)
Abciximab	114 (65.1)	101 (57.4)[d]	0	0	0	0	ND	
Tirofiban	0	0	4 (3.7)	60 (54.1)	203 (100)	207 (100)	ND	
Anticoagulants								
Bivalirudin	ND		ND		0	0	6 (0.4)	7 (0.5)
Fondaparinux	ND		ND		0	0	658 (41.3)	601 (41.8)
UFH only	9 (5.1)[d]	6 (3.4)	ND		203 (100)	207 (100)	392 (24.6)	355 (24.7)
LMWH only	120 (68.6)[d]	119 (67.2)	ND		0	0	1029 (64.6)	919 (63.9)

hrs, hours; IQR, interquartile range; PCI, percutaneous coronary intervention; DES, drug eluting stent; CABG, coronary artery bypass graft; GP, glycoprotein; ND, no data; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin.
Values are presented as No. (%), unless otherwise indicated.
[a]Randomization to angiography.
[b]Admission to angiography.
[c]Shown are the percentages of patients receiving at least one stent among those treated with PCI.
[d]Missing value for one patient.

Subgroup analyses did not indicate any significant difference of the effect of early intervention on the composite outcome (data available from TIMACS and ISAR-COOL). For patients with baseline ST-deviation the calculated effect was 0.84 (95% CI 0.65–1.08) while it was 0.81 (95% CI 0.58–1.14) for those with no ST-deviation (*P*-for-interaction = 0.87). Similarly, the benefit did not differ between patients with elevated biomarkers (0.83, 95% 0.66–1.05) and those with normal values at baseline (0.86, 95% 0.56–1.32; *P*-for-interaction = 0.89).

Discussion

Although in the setting of NSTE-ACS the benefit of an invasive strategy compared with conservative medical therapy has been demonstrated in previous trials[2–4] and meta-analyses,[5,12] clinicians have not been left with a clear guide as to when to intervene. Current guidelines[22] suggest that in high-risk, unstable patients, intervention within 24 h is preferred while either an early or a delayed approach may be adopted in other patients.

Our analysis indicates that early intervention can be safely adopted without increased risk and with significant benefits. Early intervention was found to be protective against recurrent ischaemia events, although the observed heterogeneity among the trials dictates a cautious interpretation of this difference. Of note, TIMACS[9] reported a limited number of recurrent ischaemia events, because only events that required additional intervention were considered as episodes of recurrent (i.e. refractory) ischaemia. The need for additional intervention was not a prerequisite for the definition in the other trials. Regardless, one should not overlook even a small comparative benefit with early intervention, since recurrent ischaemia can be a cause of prolonged hospital stay, re-admissions, and repeat interventions. Our analysis also detected reduced major bleeding with an early invasive approach that avoids prolonged anticoagulation, although this was not a nominally significant finding. Periprocedural bleeding is an

Table 3 Summary of major clinical outcomes

Outcomes	ABOARD		ELISA		ISAR-COOL		TIMACS	
	Early	Delayed	Early	Delayed	Early	Delayed	Early	Delayed
Death	5 (2.9)	2 (1.1)	3 (2.8)	6 (5.4)	11 (5.4)	10 (4.8)	76 (4.8)	85 (5.9)
MI	16 (9.1)	8 (4.5)	8 (7.3)	7 (6.3)	16 (7.9)	27 (13)	76 (4.8)	82 (5.7)
Major bleeding	7 (4.0)	12 (6.8)	8 (7.3)	14 (12.6)	6 (3.0)	8 (3.9)	49 (3.1)	50 (3.5)
Recurrent ischaemia	21 (12.0)	33 (18.6)	13 (11.9)	14 (12.6)	27 (13.3)	39 (18.8)	16 (1.0)	47 (3.3)
Repeat intervention	6 (3.4)	10 (5.6)	12 (11.0)	6 (5.4)	15 (7.4)	22 (10.6)	139 (8.7)	122 (8.5)
Stroke	ND		0 (0)	2 (1.8)	1 (0.5)	3 (1.4)	21 (1.3)	20 (1.4)
Death, MI, or stroke	ND		11 (10.1)	12 (10.8)	25 (12.3)	33 (15.9)	153 (9.6)	162 (11.3)
Hospital stay (hrs), median (IQR)	55 (30–98)	77 (49–145)	96 (48–192)	120 (72–312)	120 (72–168)	168 (144–264)	ND	

MI, myocardial infarction; ND, no data; hrs, hours; IQR, interquartile range.
Values are presented as No. (%), unless otherwise indicated.

Table 4 Summary risk ratios for major clinical outcomes

Outcomes	Random effects (95% CI)	*P* (RE)	*P* (Q)	I^2 (95% CI)	Fixed effects (95% CI)	*P* (FE)
Death	0.85 (0.64–1.11)	0.24	0.42	0 (0–85)	0.85 (0.65–1.12)	0.25
MI	0.94 (0.61–1.45)	0.79	0.12	49 (0–83)	0.88 (0.69–1.12)	0.31
Major bleeding	0.78 (0.57–1.07)	0.13	0.74	0 (0–85)	0.78 (0.57–1.07)	0.13
Recurrent ischaemia	0.59 (0.38–0.92)	0.02	0.05	61 (0–87)	0.57 (0.44–0.74)	<0.001
Repeat intervention	0.96 (0.67–1.38)	0.84	0.21	33 (0–76)	1.00 (0.81–1.22)	0.97
Stroke	0.84 (0.47–1.49)	0.55	0.44	0 (0–90)	0.81 (0.46–1.43)	0.47
Death, MI, or stroke	0.91 (0.82–1.01)	0.09	0.89	0 (0–90)	0.91 (0.82–1.01)	0.09

CI, confidence interval; RE, random effects; FE, fixed effects; MI, myocardial infarction.

established factor of ominous prognosis. It affects both short- and long-term outcomes, including mortality, regardless of how exactly major bleeding is defined.[23,24]

We could not detect any significant difference in MI between the two strategies and the 95% CIs exclude any substantial increase in death risk with the early strategy. On the contrary, an analysis limited to the three trials with long-term follow-up showed that early intervention most likely improves the composite of major clinical endpoints (death, MI, or stroke). This finding is consistent with previous reports[2,10–12] that suggested short-term hazards and long-term benefits with routine early intervention, particularly when combined with optimum antiplatelet therapy.[25] However, we should mention that these trials compared routine early vs. selective intervention, and early intervention was performed later compared with the trials of this meta-analysis.

Duration of hospitalization was considerably shorter with the early strategy, as shown in the present analysis. Having decided an invasive approach, delay of the procedure may result in unnecessary waste of resources, drugs, and physician and nursing time, by prolonging the hospital stay. It would be useful to study whether new diagnostic tools such as triple-rule-out computed tomographic angiography may help in this respect.[26]

It should be noted that the question asked in this meta-analysis is early vs. delayed angiography, not early vs. delayed PCI. Percutaneous coronary intervention was not performed in all patients recruited in all four eligible trials. Patients who were not suitable for PCI (~40% of the patients in the studies) had medical therapy or CABG. Thus, studies such as the OPTIMA trial that investigated the effect of timing of PCI, were not deemed eligible for our analysis.[27] This particular trial detected an increased number of MI with early (30 min) compared with delayed (24–48 h) intervention that was mainly driven by an increase in mostly small infarcts with minimal enzyme rise. In this trial, however, patients were randomized after coronary angiography and only if their vessels were considered suitable for intervention.

Some limitations should be acknowledged. First, only four completed trials have addressed the clinical question of early vs. delayed intervention in NSTE-ACS and TIMACS is larger than the other trials. Availability of data from ongoing, potentially eligible trials (LIPSIA-NSTEMI, ELISA-3, IDEAL NSTEMI) may help clarify whether observed trends (e.g. for major bleeding) reach formal statistical significance. Second, data are overall limited to perform subgroup analyses to identify whether any specific populations may have excess benefits or harms with either of the two invasive strategies. Our assessment of two trials with available

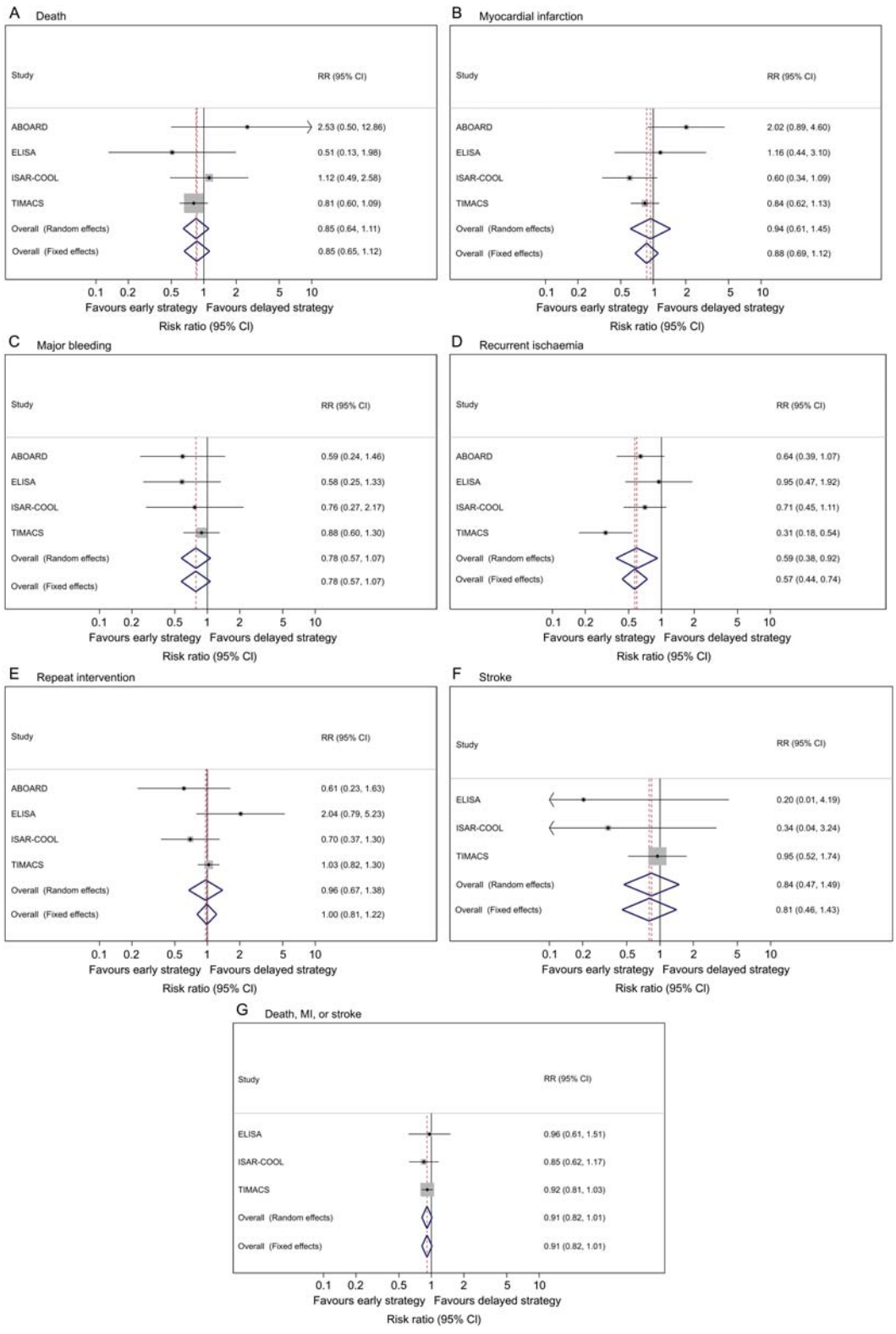

Figure 2 Meta-analysis of early vs. delayed invasive strategy for non-ST-elevation acute coronary syndromes for (*A*) Death, (*B*) Myocardial infarction, (*C*) Major bleeding, (*D*) Recurrent ischaemia, (*E*) Repeat intervention, (*F*) Stroke, and (*G*) Death, myocardial infarction, or stroke during follow-up. Each study is presented by name with point estimate of risk ratio and respective 95% confidence intervals (CIs). The overall risk ratios and 95% CIs are shown according to random effects model using the DerSimonian and Laird method and fixed effects model.

subgroup data for baseline ST-deviation and elevated cardiac biomarkers could not identify any substantial differences, but this might be due to lack of power of the specific analyses. However, evaluation of the TIMACS[9] data in a pre-specified subgroup analysis suggested that for the composite outcome of death, MI, or stroke, the early strategy fared better than the delayed strategy specifically for patients with high-risk GRACE[28] score (>140). Information was not available on the risk factors necessary to compute GRACE in the other trials. Third, some of the analyses had notable between-trial heterogeneity. This may be due to differences in definition of outcomes, or follow-up or other unidentified reasons, but heterogeneity does not negate the credibility of the meta-analysis estimates.[29]

In summary, early catheterization and intended coronary intervention within the first day of admittance is superior to a strategy of preceding anticoagulation and subsequent intervention in patients with NSTE-ACS. It reduces residual ischaemia and the duration of hospital stay and may also reduce complications, such as bleeding, and major events (death, MI, or stroke).

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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CARDIOVASCULAR FLASHLIGHT

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Cardiac metastasis of bladder cancer presented as mimicking ST-segment elevation myocardial infarction

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A 63-year-old man, who diagnosed as bladder cancer 3 years previously, presented to the emergency department complaining of chest discomfort. An electrocardiogram (ECG) revealed marked ST-segment elevations in leads V1–4 (*Panel A*). The level of cardiac enzymes (CK-MB 6.87 ng/mL, Troponin-I 0.19 ng/mL) was found to be elevated. Under the impression of acute myocardial infarction (AMI), we initially performed the coronary angiogram. However, there was no significant coronary artery lesion (*Panel B*).

Transthoracic echocardiography from a modified parasternal long-axis view showed hypokinetic apico-anteroseptal wall of left ventricle (LV) associated with the mural mass lesion (arrows, *Panel C*). To differentiate the cardiac mass, we performed cardiac magnetic resonance imaging, and a T2-weighted black-blood acquisition imaging without contrast medium administration showed a 37 × 31 mm sized well enhanced mass with central haemorrhagic necrosis in the apico-anteroseptal wall of LV (arrows, *Panel D*). An additional F-18 fluoro-fluorodeoxyglucose whole body positron emission tomography–computed tomography scan revealed multiple metastases to bones, lymph nodes, muscles, and myocardium (*Panel E*). Although intensive chemotherapy was initiated, the patient's condition gradually worsened and he eventually died.

We described unique ECG changes due to myocardial metastasis, initially misdiagnosed as AMI. The leads with ST-segment elevations seemed to match to the location of the LV mass. These ECG changes might be due to focal myocardial ischaemia or mass effect related to the invasion of the tumour mass.