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Immediate versus deferred coronary angioplasty in non-ST-segment elevation acute coronary syndromes

R K Riezebos,[1] E Ronner,[1] E ter Bals,[1] T Slagboom,[1] P C Smits,[2] J M ten Berg,[3] F Kiemeneij,[1] G Amoroso,[1] M S Patterson,[1] M J Suttorp,[3] J G P Tijssen,[4] G J Laarman,[5] for the OPTIMA trial

[1] Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands; [2] Medisch Centrum Rijnmond-Zuid, Rotterdam, The Netherlands; [3] St Antonius Hospital, Nieuwegein, The Netherlands; [4] Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; [5] Kings College Hospital, London, UK

Correspondence to:
Dr R K Riezebos, Onze Lieve Vrouwe Gasthuis, Department of Interventional Cardiology, Postbus 95500, 1090 HM Amsterdam, The Netherlands; R.K.Riezebos@xs4all.nl

ABSTRACT

Background: The field of acute coronary syndromes is characterised by an increasing tendency towards early invasive catheter-based diagnostics and therapeutics—a practice based on observational and retrospective data.

Objective: To compare immediate versus deferred angioplasty in patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS)

Methods: A randomised, prospective multicentre trial was performed in patients admitted with NSTE-ACS, eligible for percutaneous coronary intervention (PCI). Interim analysis was performed after enrolment of 251 patients; PCI was appropriate in 142 patients. These patients were randomised to immediate PCI (n = 73) or deferred PCI (24–48 h) (n = 69). Patients received protocol-driven glycoprotein IIb/IIIa blockers, aspirin and clopidogrel. The primary end point was a composite of death, non-fatal myocardial infarction (MI) or unplanned revascularisation, at 30 days. After hospital discharge outpatient follow-up was performed at 30 days and 6 months.

Results: The incidence at 30 days of the primary end point was 60% in the group receiving immediate PCI and 39% in the group receiving deferred PCI (relative risk (RR) = 1.5, 95% CI 1.09 to 2.15; p = 0.004). No deaths occurred in either group. MI was significantly more common in the group receiving immediate PCI (60% vs 38%, RR = 1.6, 95% CI 1.12 to 2.28, p = 0.005). Unplanned revascularisation was similar in both groups. The observed difference was preserved over 6-months' follow-up.

Conclusions: Immediate PCI was associated with an increased rate of MI in comparison with a 24–48 h deferred strategy, despite aggressive antithrombotic treatment. The results suggest that PCI for high-risk patients with non-refractory NSTE-ACS should be delayed for at least 24 h after hospital admission.

Trial registration number: ISRCTN80874637

Current guidelines recommend an early invasive strategy for patients with high risk non-ST-segment elevation acute coronary syndromes (NSTE-ACS).[1 2] Routine invasive management reduces the occurrence of cardiac events as compared with a selective invasive management. However, the long-term benefits of routine invasive strategy are countered by an increased procedural risk when percutaneous coronary investigation (PCI) is performed in the very early phase of the ACS.[3] On the other hand, postponing PCI too long is associated with an increase in spontaneous cardiac events. The use of contemporary anticoagulant and antiplatelet therapies is known to reduce the early hazard of PCI.[4 5]

Two invasive strategies have emerged for managing patients with non-refractory high-risk NSTE-ACS. These are immediate or deferred angiography.[1] Recent, observational data suggest better outcome when coronary angiography is performed early after hospital admission.[6] However, the optimal timing of PCI in this early invasive strategy is unknown.

While immediate PCI may prevent spontaneous cardiac events, deferral of PCI might lead to fewer periprocedural complications. It has been suggested that very early intervention using triple antiplatelet therapy might reduce the occurrence of spontaneous cardiac events, outweighing a possible increase in periprocedural complications.[4 5 7]

This trial was designed to determine the influence of timing of PCI in patients with intermediate to high-risk NSTE-ACS. The hypothesis was that cardiac events are reduced by immediate PCI as compared with a deferred approach with PCI after 24–48 h, both under triple antiplatelet therapy protection.

PATIENTS AND METHODS

Study design

This study was a randomised, prospective, multicentre trial in patients admitted with NSTE-ACS eligible for PCI. Three high-volume centres with PCI facilities participated. The study protocol was approved by the review boards of the participating sites. The study was registered under current controlled trial number ISRCTN80874637.

Patients

Clinical inclusion criteria for participation in the study were age >21 years, typical anginal chest pain that had lasted for at least 10 min within the past 6 h and no contraindication to PCI. In addition, the patients had to meet at least one of the following four criteria: >1 mm of ST depression in two contiguous leads, a raised troponin T level (>0.01 ng/l), known coronary artery disease (CAD) or two or more risk factors for CAD.[1 2]

Clinical exclusion criteria for the study were chest pain suspected not to be caused by CAD, acute ST elevation myocardial infarction, thrombolytic therapy within 24 h, recent PCI (within14 days), any contraindication for the use of abciximab, participation in another study and an inability for follow-up.

All patients gave written informed consent before proceeding to the catheterisation laboratory.

Treatment strategy

At initial angiography, the operator assessed suitability of the coronary anatomy for PCI with stent implantation of the culprit lesion. Suitable anatomy was defined as the presence of coronary lesion(s) which would allow for safe and effective percutaneous treatment. The culprit lesion was identified by the operator, based on angiographic and electrocardiographic characteristics.

Patients were not randomised when angiography did not demonstrate significant coronary stenosis amenable for PCI, when coronary artery bypass grafting (CABG) was judged to be the preferred treatment, or when the culprit lesion was an in-stent restenosis or a chronic total occlusion. These patients were treated according to institutional practices and followed up in a registry.

Patients with suitable coronary anatomy were subsequently randomised to immediate PCI or deferred PCI (24–48 h after randomisation) using a computerised algorithm. Patients randomised to immediate PCI were treated with PCI directly after the diagnostic coronary angiography. The patients randomised to deferred PCI were transferred to the coronary care unit after the diagnostic procedure and stabilised medically. After 24–48 h the patients underwent PCI in an elective fashion.

PCI was performed according to the standard institutional practices. All patients were followed up from randomisation to hospital discharge. An outpatient visit was conducted at 30 days and 6 months after enrolment.

Biomarkers

Both troponin T and creatine kinase-MB (CK-MB) mass measurements were made on a Modular E chemiluminescence analyzer (Roche Diagnostics, Mannheim, Germany). Venous blood samples for CK, CK-MB mass and troponin T determination were obtained at admission and at 1, 6, 12, 18, 24 and 36 h after PCI. In the deferred group, sampling was also performed at 6 h intervals between randomisation and PCI. If ischaemia recurred, additional sampling at 0, 6 and 12 h was performed.

Medical treatment

At admission, a bolus dose of 500 mg aspirin intravenously and 300 mg clopidogrel by mouth was given followed by

Figure 1 Trial flow chart. No patients were lost to follow-up. The reasons for (late) angiographic exclusion (n = 109) were as follows: no significant coronary artery disease (n = 55), coronary artery bypass grafting (n = 27), in-stent restenosis (n = 9); clinically driven immediate percutaneous coronary intervention (PCI; n = 8), culprit lesion not amenable for PCI (n = 6), chronic total occlusion (n = 4).

respectively 80 mg and 75 mg by mouth daily. Aspirin was given indefinitely and clopidogrel for 12 months. In addition, patients were treated with low molecular weight heparin according to the current guidelines.[1]

The protocol required all interventional procedures to be performed with the use of abciximab that was given as a bolus of 0.25 mg/kg, followed by an infusion of 10 μg/min for 12 h. Unfractionated heparin was given before PCI as a weight-adjusted bolus of 100 IU/kg body weight. Other drugs were given at the discretion of the treating doctor.

End points

The primary end point was the composite of death, non-fatal myocardial infarction (MI) and unplanned revascularisation, at 30 days after enrolment. The secondary end points of the trial were the individual components of the composite end point, the size of MI during initial hospitalisation, any revascularisation, readmission to hospital because of CAD, major haemorrhage and length of in-hospital stay.

Myocardial infarction

MI during the initial hospitalisation was defined as any rise in CK-MB exceeding more than once the upper limit of normal (ULN). This non-standard definition was chosen to allow for a direct comparison of the amount of myocardial damage between the immediate and deferred treated group. The physiological delay in CK-MB rise after an event does often not permit differentiation between spontaneous and procedurally induced MI in patients immediately treated with PCI. Any infarction in the setting of NSTE-ACS was considered to be of clinical importance and hence should be noted.

At outpatient follow-up, MI was defined as at least two of the following: chest pain lasting for at least 20 min, new Q waves of at least 0.04 s in at least two contiguous leads or new ST-segment elevation of at least 1 mm in two contiguous leads, except for V1 and V2, in which the elevation should be at least 2 mm. In addition, MI was noted when there had been a readmission to hospital with a documented discharge diagnosis of MI.

Major bleeding

Major bleeding was defined using the TIMI criteria as the need for transfusion of ⩾2 units of whole blood or packed red blood cells, intracranial or retroperitoneal haemorrhage, a fall in haemoglobin >2.5 mmol/l (or 12% of haematocrit) without an identifiable bleeding site, spontaneous or non-spontaneous blood loss associated with >2 mmol/l decline of haemoglobin (or 10% of haematocrit) and vascular surgery for bleeding complications.

Statistical analyses

Descriptive statistics and patient data listings were used to summarise the data collected on the case report form. Continuous variables were summarised using means and standard deviations or medians with interquartile ranges, when appropriate. Categorical variables were described using frequencies and percentages.

Continuous variables were compared with the use of the Student t test or the Mann–Whitney U test for skewed data. Comparison between groups for categorical variables was performed using χ^2 or Fisher exact test, when appropriate.

In addition, regression analyses were performed using variables that correlated to the different end points. A survival
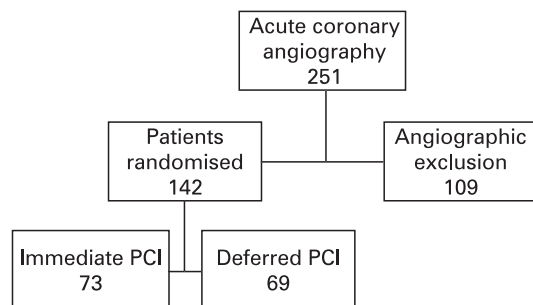
Table 1 Baseline and patient characteristics

Characteristics	Immediate PCI (n = 73)	Deferred PCI (n = 69)	p Value
Demographics			
Male sex	51 (70)	51 (74)	0.6
Age (years), mean (SD)	63 (12)	62 (12)	0.8
Risk factors			
Age >60 years	41 (56)	34 (49)	0.4
Known CAD	27 (37)	25 (36)	0.6
Diabetes mellitus	14 (19)	14 (20)	1.0
Hypertension	39 (53)	23 (33)	0.03
Smoking	28 (38)	27 (39)	0.8
Family history of IHD	32 (44)	29 (42)	0.8
Hyperlipidaemia	28 (38)	22 (32)	0.6
Peripheral artery disease	5 (7)	3 (4)	0.7
Cardiac history			
Previous MI	15 (21)	18 (26)	0.5
Previous PCI	20 (27)	13 (19)	0.2
Previous CABG	8 (11)	1 (1)	0.02
Previous CHF	1 (1)	1 (1)	0.3
ACS characteristics			
Time (h)			
Onset symptoms until admission, median (IQR)	3.0 (1.0–4.0)	3.0 (1.0–7.8)	0.6
Admission until randomisation, median (IQR)	2.0 (0.5–3.6)	1.8 (0.5–3.4)	0.4
Inclusion by			
ST depression >0.1 mV	38 (52)	36 (52)	1.0
Troponin at admission >0.01 ng/l	34 (47)	31 (45)	0.8
Clinical characteristics only	19 (26)	21 (30)	0.6
Braunwald classification			
1B	9 (12)	13 (19)	
2B	14 (19)	16 (23)	0.2
3B	49 (67)	38 (55)	
3C	1 (1)	2 (3)	
Coronary angiography characteristics			
Number of diseased vessels			
1	30 (41)	37 (54)	
2	33 (45)	22 (32)	0.3
3	10 (14)	9 (13)	
Target coronary artery			
LAD	27 (37)	33 (48)	
LM	1 (1)	0	
RCA	25 (34)	18 (26)	0.1
LCX	16 (22)	18 (26)	
SVG	4 (5)	0	
TIMI flow			
0–2	14 (19)	25 (36)	0.02
3	59 (81)	44 (64)	
Chest pain at time of CAG	10 (14)	10 (14)	0.7
PCI characteristics			
No PCI performed	0 (0)	1 (1)	
Culprit lesions PCI	73 (100)	68 (99)	0.5
More lesions treated	21 (29)	16 (23)	0.4
Drug-eluting stent	66 (90)	57 (83)	0.3
Number of stents placed			
0	4 (5)	4 (6)	
1	49 (67)	45 (65)	0.4
>2	20 (27)	20 (29)	

Table 1 Continued

Characteristics	Immediate PCI (n = 73)	Deferred PCI (n = 69)	p Value
TIMI flow after PCI			
0–2	4 (5)	4 (6)	1.0
3	69 (95)	64 (93)	
Complete revascularisation	51 (70)	54 (78)	0.3
Medication at admission			
Aspirin	36 (49)	32 (46)	0.7
Clopidogrel	5 (7)	4 (6)	0.8
ACE inhibitors	13 (18)	15 (22)	0.5
ATII blockers	11 (15)	7 (10)	0.4
β Blockers	34 (47)	29 (42)	0.5
Calcium channel antagonists	18 (25)	8 (12)	0.08
Nitrates	17 (23)	11 (16)	0.3
Statins	33 (45)	25 (36)	0.2
Medication first 48 h			
Aspirin	73 (100)	67 (97)	0.1
Clopidogrel	73 (100)	68 (99)	0.3
ACE inhibitors	25 (34)	29 (42)	0.3
ATII blockers	11 (15)	4 (6)	0.08
β Blockers	70 (96)	66 (96)	0.3
Calcium channel antagonists	21 (29)	14 (20)	0.2
Nitrates	58 (79)	59 (86)	0.3
Statins	71 (97)	66 (96)	0.6
UFH during PCI	73 (100)	69 (100)	1.0
Heparin (LMWH)	69 (95)	65 (94)	0.9
GP IIb/IIIa inhibition	71 (97)	64 (93)	0.2
Abciximab	70 (96)	63 (91)	
Tirofiban	1 (1)	1 (1)	

Data are expressed as number (%) unless stated otherwise.
ACS, acute coronary syndrome; ATII, angiotensin II; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CAG, coronary angiography; CHF, congestive heart failure; GP, glycoprotein; IHD, ischaemic heart disease; LAD, left anterior descending; LCX, left circumflex; LM, left main; LMWH, low molecular weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SVG, saphenous vein graft; TIMI, thrombolysis in myocardial infarction; UFH, unfractionated heparin.
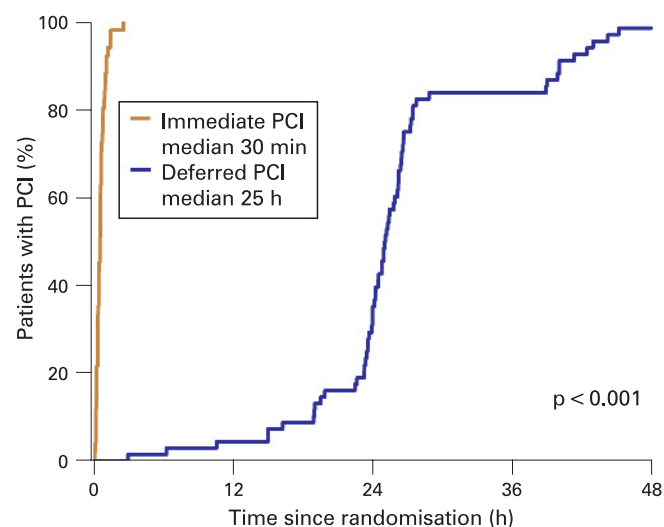
Figure 2 Time from randomisation to percutaneous coronary intervention (PCI).

Table 2 Results at 30 days and 6 months

Results	30 Days			6 Months		
	Immediate PCI (n = 73)	Deferred PCI (n = 69)	p Value	Immediate PCI (n = 73)	Deferred PCI (n = 69)	p Value
Composite end point	44 (60)	27 (39)	0.004	48 (66)	30 (43)	0.008
Death	0	0		1 (1)	0	0.5
Unplanned revascularisation	2 (3)	3 (4)	0.6	7 (10)	9 (13)	0.5
Myocardial infarction (≥1 ×ULN)	44 (60)	26 (38)	0.005	44 (60)	27 (39)	0.01
Other clinical end points						
Rehospitalisation CAD	6 (8)	5 (7)	0.7	18 (25)	14 (20)	0.5
Recurrent MI	1 (1)	1 (1)	1.0	2 (3)	3 (4)	0.6
Any revascularisation	4 (5)	3 (4)	1.0	9 (12)	9 (13)	0.9
Major bleeding	3 (4)	6 (9)	0.1			

Data are expressed as number (%).
CAD, coronary artery disease; MI, myocardial infarction; ULN, upper limit of normal.

analysis was performed using Kaplan–Meier models. A p value of 0.05 (two sided) was used to indicate significance.

Power analysis
The sample size of the study was calculated using an estimated control event rate of 30% and an underlying relative benefit of 35% for the immediate strategy at 30 days' follow-up. With a two-sided α level of 0.05, the number of randomised patients needed to compare immediate versus early PCI was 283 in both treatment arms.

Premature trial termination
On April 2007, the funding agency discontinued further support for the study because of slow patient recruitment. Subsequently, the steering committee discontinued patient enrolment. All 251 enrolled patients were followed up clinically until 1 year after inclusion. The most important cause for the slow inclusion rate was probably the strict logistics of the study protocol. On top of a regular PCI programme there were difficulties in logistics and in staff availability. This implied that patients were only included during regular office hours and from Mondays to Thursdays. Thus, although patients were not included consecutively, selection bias could be avoided.
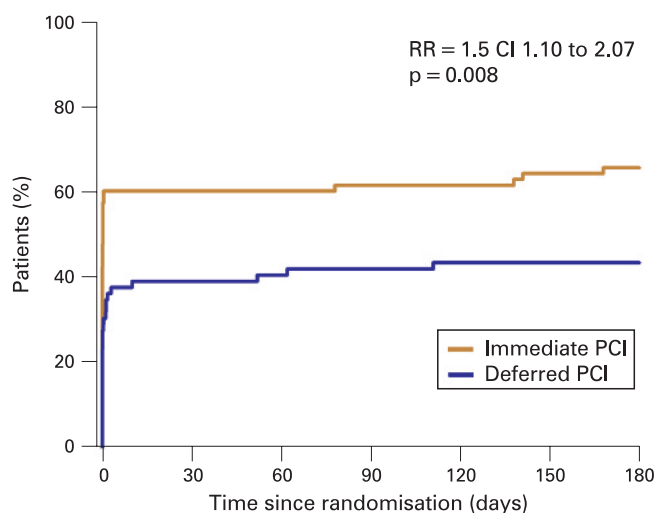

Figure 3 Occurrence of the primary composite end point at 6 months. No patients were lost to follow-up.

The current analysis focuses on the 30-day follow-up of all randomised patients, which was the primary end point of the original study protocol.

RESULTS
Patients
From March 2004 to April 2007 251 patients fulfilling the clinical inclusion and exclusion criteria were enrolled and underwent immediate coronary angiography (fig 1). In 142 patients a culprit lesion amenable to PCI could be identified. These patients were subsequently randomised to immediate PCI (73) or to deferred PCI (69). Table 1 shows the baseline characteristics. Baseline characteristics were similar for the two groups, except for previous CABG (11% vs 1%, p = 0.02) and hypertension (53% vs 33%, p = 0.03).

Fifty-two per cent of the patients in each group presented with ST-segment depression and about half of the patients showed raised troponin T levels at presentation (table 1). Patients (immediate PCI group: 26%; deferred PCI group: 30%, NS) who had neither troponin rise or ECG changes were included owing to typical chest pain at rest, a high-risk clinical profile and the presence of a high-grade coronary artery stenosis. The median time from onset of symptoms to admission was 3 h in both groups. The time from admission until randomisation was 2.4 h for the immediate group versus 1.8 h for the deferred group (NS).

Coronary angiography showed one- or two-vessel disease in most cases. A lower TIMI flow was seen in the patient group randomised to deferred PCI (TIMI 0–2: 19% vs 36%, p = 0.02) (table 1).

Treatment
Immediate PCI of the culprit lesion could be performed in all patients randomised to immediate PCI. One patient randomised to deferred PCI was not treated with PCI because the initial complaints of chest pain appeared to be caused by cholelithiasis. (table 1). Only three patients randomised to deferred PCI underwent earlier PCI than planned because of recurrent ischaemia. The median time from randomisation to PCI was 30 min in the immediate group compared with 25 h in the deferred group (fig 2).

Seventy-four (52%) of all 142 patients showed multivessel disease. Of these, 26% underwent treatment of two or more lesions leading to complete revascularisation in 74% of the total number of patients. Treatment characteristics were equally

Table 3 Characteristics of the myocardial infarction at the index hospitalisation

Characteristics	Immediate PCI (n = 73)	Deferred PCI (n = 69)	p Value
Raised CK-MB			
At randomisation	16 (22)	12 (17)	0.5
After randomisation	28 (38)	14 (20)	0.03
Peak CK-MB			
≥1×ULN	44 (60)	25 (36)	0.004
≥3×ULN	24 (33)	17 (25)	0.3
≥5×ULN	16 (22)	10 (14)	0.3
≥10×ULN	11 (15)	6 (9)	0.2
Biomarkers, median (IQR)			
Peak CK-MB (ng/l)	9.8 (4.9–34.5)	4.9 (2.8–24)	0.008
Peak troponin (ng/l)	0.23 (0.07–1.34)	0.1 (0.01–0.67)	0.049
CK-MB AUC ((ng/l)×h)*	186 (74–512)	75 (44–345)	0.008

Data are expressed as number (%) unless stated otherwise.
*CK-MB AUC was calculated using five serial infarct-related samples at 6 h intervals using a linear trapezoid method.
AUC, area under the curve; CK, creatine kinase; PCI, percutaneous coronary intervention; ULN, upper limit of normal.

distributed between the groups. (table 1). Pharmacological treatment regimens were similar in both groups with over 95% aspirin, clopidogrel and glycoprotein IIb/IIIa inhibitor use. Furthermore, the use of β-blocking agents and statins was high, indicating optimal medical treatment (table 1).

Composite end point

The primary end point of the study, a composite of death, unplanned revascularisation and non-fatal MI, at 30 days occurred in 60% of patients in the immediate PCI group and in 39% of the patients in the deferred PCI group (p = 0.004) (table 2). This difference was due almost entirely driven by a significant difference in the rate of MI. There were no deaths, and unplanned revascularisation rates were similar at 30 days.

This difference was preserved over a 6-month follow-up period. At 6 months the incidence of the primary end point in the immediate group was 66% as compared with 43% in the deferred treated group (p = 0.008). During follow-up one patient died in the immediate group (table 2). Figure 3 shows Kaplan–Meier curves for the composite end point up to 6 months.

Multivariate analyses of the composite end point were performed. Adjustment for baseline characteristics such as previous CABG, culprit lesion localisation and hypertension yielded the same results as the unadjusted analysis.

Myocardial infarction

Table 3 shows categories of infarct size according to peak CK-MB level. Most of the difference between the groups was due to an increase in infarctions with a peak CK-MB level of one to three times the ULN. Most myocardial infarctions occurred within hours after randomisation. The median peak CK-MB levels and the median peak troponin T levels were higher with immediate PCI than with deferred PCI (table 3).

To adjust for a possible bias by an early wash-out phenomenon for CK-MB levels in the immediate PCI group, an area under the curve analysis was performed using a number of five serial infarct-related CK-MB samples with 6 h intervals using linear interpolation. (table 3) This comparison did not alter the strength of the observed difference in infarction between the groups.

Other secondary end points

The incidence of unplanned repeat revascularisation was low and did not differ between the groups (table 2). The rate of rehospitalisation was similar. One patient treated with deferred PCI had acute stent thrombosis at 3 days after PCI. There was no acute stent thrombosis in the group treated with immediate PCI.

The incidence of major bleeding did not differ significantly between the groups. At 30 days, three (4%) patients treated with immediate PCI and six (9%) patients treated with deferred PCI had a major haemorrhage.

Although the mean (SD) length of stay in the coronary care unit was shorter for the patients in the group randomised to immediate PCI (1.7 (0.9) vs 2.2 (1.1) days, p = 0.002), the total duration of hospital stay was similar in both groups (3.9 (3.1) vs 4.0 (1.6) days, NS).

DISCUSSION

This prospective, randomised trial unexpectedly showed a higher incidence of MI in patients who were treated with immediate PCI than in patients treated with PCI after 24–48 h. Although TIMI flow before PCI was better in the immediate group, the difference in MI was evident and largely driven by an increase in mostly small, procedurally inflicted events. The excess MI seen in the patients randomised to immediate PCI probably reflects the vascular and thrombotic vulnerability in the acute setting. Most PCI-related infarcts were small and probably resulted from micro emboli from the atherosclerotic plaque, thrombus particles disrupted or formed during angioplasty or thrombotic side branch occlusions.[8]

Differentiation between spontaneous (type 1, CK-MB >1× ULN) and PCI-related (type 4a, CK-MB >3× ULN) MI[9] is largely impossible in patients with ACS treated with immediate PCI. Therefore, we counted any rise in CK-MB above the ULN as an MI regardless of treatment strategy. This approach was chosen because it best reflects the total amount of myocardial damage present before the intervention and that inflicted by the intervention. Accordingly, the amount of myocardial damage in both groups could be compared in a more valid way. This is important, as there is convincing evidence that the adverse prognostic implications of periprocedural myocardial necrosis should be considered similar to the adverse consequences of spontaneous myocardial necrosis.[10]

The main benefit of an early invasive strategy is the prevention of cardiac events over the longer term. Unfortunately, this treatment is associated with an increase in periprocedural events. The use of glycoprotein IIb/IIIa inhibitors as well as clopidogrel is thought to reduce the iatrogenic induced myocardial damage.[4–5 11–13] However, this study showed that intensive antiplatelet therapy does not provide sufficient plaque passivation at the time of immediate intervention relative to deferred PCI. The clopidogrel loading dose used in this study may have been too low. Indeed, recently updated ESC guidelines recommend a 600 mg loading dose when rapid onset of action is wanted.[2]

The ISAR-COOL trial showed contrasting results.[7] This study randomised patients with suspected NSTE-ACS to an early (within 24 h after anginal complaints) or a 3–5-day deferred invasive diagnostic strategy. In this study, the early invasive strategy led to better outcomes than the deferred strategy. However, both the early and deferred strategies consisted of heterogeneous treatments given at different times. The timing of intervention under the early strategy in the ISAR-COOL study was in between that of our immediate and deferred treatment strategy. Because of this substantial difference in

timing of diagnostic catheterisation, treatment modalities and treatment timings, the ISAR-COOL results cannot be compared with ours.

The time–event relationship in patients with NSTE-ACS in the early invasive strategy could be that of a "U" shaped curve: sufficient time is needed to allow pharmacological stabilisation, but postponement of intervention may lead to an increase of new spontaneous events.[4 7] The early hazard seen in the early invasive strategy in older studies appeared still valid and could not be adequately prevented by the use of extensive pharmacological antithrombotic and antiplatelet regimens.[14 15] Conceivably, medical pretreatment for at least 24 h might decrease the risk of intervention considerably. Future trials are awaited to provide answers on the optimal delay to PCI in the high-risk patient group.

Study limitations

Owing to the premature termination of the study, the intended number of included patients could not be achieved. Although the results show a significant difference in the primary end point, the possibility of chance cannot be fully eliminated, especially with study results that are opposite to those of the initial hypothesis.

CONCLUSIONS

This study showed an increased rate of periprocedural MI in patients treated with immediate PCI as compared with patients with a 24–48 h deferred PCI. The results suggest that PCI for high-risk, non-refractory NSTE-ACS should be delayed for at least 24 h after hospital admission.

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