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Early invasive strategy and outcomes of non-ST-elevation acute coronary syndrome patients: is time really the major determinant?

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Abstract In non-ST-elevation acute coronary syndromes (ACS), an early invasive strategy is recommended for middle/high-risk patients; however, the optimal timing for coronary angiography is still debated. The aim of this study was to evaluate the prognostic implications of the time of angiography in ACS patients treated in accord with an early invasive strategy. We analyzed the relationship between the time of angiography and outcomes at follow-up in 517 ACS patients, of whom 482 were revascularized with percutaneous coronary intervention (PCI) (86.9%) or coronary artery by-pass graft (13.1%). We also evaluated the influence of clinical, biohumoral and angiographic variables on the patients' outcomes at follow-up. Among patients submitted to angiography at different time intervals from both hospital admission and symptom onset, significant differences neither in mortality nor in cardiac ischemic events at follow-up were observed. At univariate analysis, complete versus partial revascularization, longer hospital stay, higher TIMI risk score, diabetes mellitus, higher discharge creatinine and admission anemia were associated with mortality and cardiac ischemic events at follow-up; a lower left ventricular ejection fraction was associated with mortality; higher peak troponin I and previous PCI were associated with cardiac ischemic events at follow-up. At multivariate analysis longer hospital stay, higher discharge creatinine levels, and previous PCI were independent predictors of cardiac ischemic events at follow-up. Our evaluation in ACS patients treated with an early invasive strategy does not support the concept that angiography should be performed as soon as possible after symptom onset or hospital admission. Rather, an unfavorable long-term outcome is influenced principally by the clinical complexity of patients.

Keywords Acute coronary syndromes · Early invasive strategy · Timing of angiography · Prognosis

Introduction

Current international guidelines on the management of non-ST elevation acute coronary syndromes (ACS) recommend, especially for high-risk patients, an early invasive strategy [1, 2], according to which patients quickly undergo coronary angiography, and, if necessary, early percutaneous coronary intervention (PCI) or surgical revascularization (CABG).

An early invasive strategy has been shown to improve long-term survival and reduce the risk of late myocardial infarction and rehospitalization [3–8] in comparison with a selectively invasive approach, according to which coronary angiography is performed only for recurrent ischemia or new-onset left ventricular dysfunction.

However, the optimal timing for coronary angiography in such patients is still unknown [8, 9], and in daily practice, there is a wide variation in interpreting the term "early". In some hospitals, ACS patients are rapidly transferred from the Emergency Department (ED) to the catheterization laboratory, whereas in others they may wait for coronary angiography up to a week, as suggested by FRISC II investigators [3].

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According to recommendations of the American and European Guidelines, in the past few years, an early invasive strategy has been adopted systematically in all patients admitted to our Institution for non-ST-elevation myocardial infarction (NSTEMI) or unstable angina (UA) judged at high or middle risk according to a TIMI risk score ≥ 3 [10].

The aim of the present study was to evaluate the prognostic implications of the time of angiography in patients with ACS, treated in accord with an early invasive strategy, during a median 13-month follow-up. Moreover, we analyzed the influence of some clinical, biohumoral, angiographic and procedural variables on patient's long-term outcome.

Methods

From January 2005 to December 2006, 554 ACS patients were consecutively admitted to the Cardiac Step Down Unit (CSDU) of the University of Florence: 346 (62.4%) were directly addressed to our CSDU from the ED, while 208 (37.5%) were referred to our Institution from other hospitals.

Patients were enrolled in the study if they had ischemic symptoms lasting $\geq$10 min within 24–48 h before admission to the CSDU, or cardiac troponin I (TnI) or CK-MB level elevation above the upper limits of normal, or transient ST segment shift on an electrocardiogram.

Patients with an urgent indication for coronary angiography, such as those with signs and symptoms of acute heart failure, hemodynamic instability, persistence of ischemic symptoms despite medical therapy or life-threatening arrhythmias, were excluded from the study.

Out of 554 patients, 517 (93.3%) underwent coronary angiography. In 37 patients, this invasive procedure was not performed because of major contraindications, serious comorbidities, or very recent surgery. In 482 ACS patients submitted to angiography, revascularization was performed with either PCI (86.9%) or CABG (13.1%). In the remaining 35 patients, revascularization was not performed because it was unnecessary, it was refused by the patients, or it was contraindicated because of comorbidities. All patients were discharged with optimal medical therapy, including antithrombotic agents, statins, beta-blockers, and angiotensin-converting enzyme inhibitors, unless individually contraindicated.

Coronary angiography and angioplasty were performed using standard techniques, usually by the femoral or radial approach. All patients received a 325-mg of acetyl-salicylic acid and 300 mg of clopidogrel loading dose at admission in CSDU or in the catheterization laboratory. Glycoprotein IIb–IIIa inhibitors were used at the operator's discretion in 72 patients (17.2%).

For each patient, the timing of angiography, clinical, biohumoral (creatinine and hemoglobin on admission and at discharge, glycemia and TnI on admission and at the peak), angiographic, and procedural data were collected. Two different times of angiography were considered: with respect to angiography, "timing of angiography" was defined as the time interval from admission to CSDU while "delay of angiography" was the time interval from symptoms onset. Data regarding the delay of angiography were available in 487/517 patients. Two physicians collected by phone the follow-up data in 509 out of 554 patients (93%) after a median follow-up period of 13 months (25^{th}–75th percentile: 8–21 months). Apart from mortality, the cardiovascular events reported by the patients themselves, or by their relatives were then verified, in a blinded manner, by means of hospital records.

The study protocol was approved by the hospital ethics committee, and informed consent was obtained from each patient before enrolling in the study. Investigations were conducted in accordance with the Declaration of Helsinki.

UA and NSTEMI were diagnosed according to recent Guidelines [1, 11] (the normal value of TnI in our laboratory is <0.15 ng/ml).

Statistical analysis was performed using SPSS for Windows, version 11.5 (SPSS, Inc., Chicago, IL, USA). A P value < 0.05 was considered statistically significant. Data were expressed as frequencies and percentages, or median (25th–75th percentile). To evaluate differences in clinical, biohumoral and angiographic data, patients were divided into three groups of timing (<6, 6–24and >24 h) and delay (<24, 24–48 and >48 h) of angiography and χ^2 or Kruskal–Wallis tests were used for univariate analysis; post-tests (Z-score for discrete variables and Kruskal–Wallis, comparing one group with one another in turn, for continuous data) were performed when overall significance was less than 10%. Age (categorically divided into $\leq$75 and >75 years) and gender-adjusted Kaplan–Meier survival analyses were performed, as previously reported [12], to evaluate differences in mortality during follow-up in relation to both timing and delay of angiography within or beyond 24 h; these differences were assessed by means of a log-rank test. After assessment of risk proportionality, several univariate Cox regression analyses were performed to investigate relationships between clinical, biohumoral and procedural variables, and outcomes. To evaluate potential adjusted predictors of non-fatal cardiac ischemic events at follow-up, (angina or acute myocardial infarction), baseline variables, considered clinically relevant and showing a statistically significant association with outcome at univariate analysis, were entered into a multivariate Cox proportional regression analysis. Candidate variables were carefully chosen, considering the number of events, to ensure parsimony of the final model; both the timing and,

respectively, the delay of angiography were forced into the final models. Non-significant variables were dropped by means of backward selection.

Results

The study population consisted of 554 ACS patients, out of whom 391 were men, (70.8%), median age 73 years (25th-75th percentile 64–78).UA was diagnosed in 415 cases (74.9%) at admission, and in 250 cases (45.1%) at discharge. About 70% of the patients were hypertensive, and 43% of them were dyslipidemic.

The cardiovascular risk of our patients was estimated according to TIMI risk score: most of them (72.2%) were at intermediate risk (TIMI risk score 3–4), and 22.2% at high risk (TIMI risk score 5–7).

The distribution of ACS patients according to the timing and the delay of angiography was different in fact, considering the timing of angiography, 397 patients (76.8%) were submitted to angiography earlier than 24 h, and 120 (23.2%) later than 24 h from admission to the CSDU, while considering the delay of angiography, more than 60% of patients were submitted to angiography later than 24 h from symptom onset. Among the possible causes why patients were submitted to angiography later than 24 h from CSDU admission, the following were observed: arrival at our hospital during the night hours or during holidays ($n = 64$), presence of severe comorbidities ($n = 26$), pending arrival of relatives before giving consent ($n = 30$).

In Tables 1 and 2, data of ACS patients submitted to coronary angiography are reported in relation to the different timing of angiography (<6, 6–24 and >24 h) and delays of angiography (<24, 24–48 and >48 h). No significant difference in baseline characteristics was found in relation to the different timing and delays of angiography, except for a significantly lower percentage of patients with concomitant neoplasia and higher values of TnI at admission in the subgroup of those submitted to angiography earlier than 6 h from admission in the CSDU (Table 1), and for significantly higher values of TnI both at admission and at the peak in patients treated with a shorter delay from symptom onset (Table 2).

Tables 3 and 4 show angiographic and procedural data of patients submitted to coronary angiography, and treated with PCI according to the timing and delay of angiography.

No significant difference in angiographic and procedural variables was found in relation to the different timing and delays of angiography, except for a significantly higher percentage of patients in whom a complete revascularization was performed with a delay of angiography <24 h; moreover, in this group of patients, the culprit lesion was less frequently determined by a restenosis with respect to patients submitted to angiography later than 24 h from symptom onset (Table 4).

Moreover, no significant difference was observed in the pharmacological treatment in relation to the different timing and delays of angiography (data not shown).

The median follow-up length was 13.1 months (25th–75th percentile 8.4–21.0 months).

The in-hospital mortality as well as the mortality and the cardiac ischemic events at follow-up are summarized in Fig. 1.

No significant difference was observed in mortality during follow-up (Log Rank chi square 0.682; $P = 0.409$; Kaplan–Meier analysis adjusted for age and gender) (Fig. 2, Panel A) as well as in the incidence of angina and non-fatal myocardial infarction at follow-up (23.0 vs. 26.3%; $P = 0.545$) between patients submitted to angiography < or >24 h from admission in the CSDU (timing of angiography). Even when an earlier treatment (<6 h) was compared with a delayed one (>24 h), at logistic regression analysis, the timing of angiography was not a predictor of mortality (OR 1.69; 95% CI 0.54–5.23; $P = 0.365$). Similarly, at univariate analysis, the timing of angiography did not predict ischemic relapse at follow-up (OR 1.06; 95% CI 0.65–1.73; $P = 0.824$).

Similarly, no significant difference in ACS patients mortality was seen in relation to a delay of angiography < or > 24 h either in the acute phase (2.1 vs. 1.4%, respectively) or during follow-up (Log Rank chi square 0.584; $P = 0.445$; Kaplan–Meier analysis adjusted for age and gender) (Fig. 2, Panel B). Moreover, no significant difference was observed in the incidence of angina and myocardial infarction at follow-up among the two groups of patients (25.7 and 29.8% for patients treated with a delay of angiography < or > than 24 h, respectively).

Recurrence of cardiac ischemic events (angina or non-fatal myocardial infarction) at follow-up were significantly more frequent in patients with a previous PCI.

As far as the relationship between overall mortality and TnI is concerned, a positive trend between higher TnI levels at admission and an increased mortality was observed; moreover, increased mortality was also observed between patients with TnI at the peak >5.00 ng/mL versus those with normal values ($P < 0.05$).

Moreover, considering the relationship between other biohumoral data and mortality, serum creatinine and glucose values at admission were significantly higher in patients who died than in survivors [1.4 (95% CI 1.1–1.8) vs. 1.0 (95% CI 0.9–1.2) mg/dl; $P < 0.001$ and 1.21 (95% CI 1.00–1.62) vs. 1.04 (95% CI 0.91–1.27) g/dl; $P = 0.001$, respectively)]. Creatinine levels at discharge were significantly higher in dead patients than in survivors [1.3 mg/dl (95% CI 1.0–2.1) vs. 1.0 mg/dl (95% CI 0.9–1.2); ($P < 0.001$)]. Hemoglobin values were significantly

Table 1 Clinical and biohumoral characteristics of patients investigated in relation to timing of angiography

	<6 h (n = 352; 68.1%)	6–24 h (n = 45; 8.7%)	>24 h (n = 120; 23.2%)	P value (χ^2 or KW)
Age [years; median (IR)]	73 (63–78)	72 (64–78)	72 (63–78)	0.935
Males [% (95% CI)]	70.7 (66.0–75.5)	68.9 (55.4–82.4)	73.3 (65.4–81.2)	0.811
Body weight [kg; median (IR)]	74 (65–80)	75 (68–80)	75 (68–81)	0.971
Hypertension [% (95% CI)]	69.6 (64.8–74.4)	73.3 (60.4–86.3)	73.3 (65.4–81.2)	0.685
Diabetes mellitus [% (95% CI)]	28.7 (24.0–33.4)	15.6 (5.0–26.1)	29.2 (21.0–37.3)	0.164
Dyslipidemia [% (95% CI)]	41.2 (36.1–46.3)	44.4 (29.9–59.0)	48.3 (39.4–57.3)	0.388
Family history of CAD [% (95% CI)]	24.4 (19.9–28.9)	28.9 (15.6–42.1)	28.3 (20.3–36.4)	0.615
Smoking habit [% (95% CI)]	34.6 (29.7–39.6)	40.0 (25.7–54.3)	36.7 (28.0–45.3)	0.750
Chronic renal failure [% (95% CI)]	6.3 (3.7–8.8)	8.9 (0.6–17.2)	10.0 (4.6–15.4)	0.364
Neoplasia [% (95% CI)]	4.3 (2.2–6.4)	15.6 (5.0–26.1)*	5.8 (1.6–10.0)	0.008
Previous AMI [% (95% CI)]	33.5 (28.6–38.5)	40.0 (25.7–54.3)	30.0 (21.8–38.2)	0.471
Previous PCI [% (95% CI)]	31.3 (26.4–36.1)	37.8 (23.6–51.9)	43.3 (34.5–52.2)	0.052
TIMI Risk Score 1–2 [% (95% CI)]	4.0 (1.9–6.0)	6.7 (-0.6–14.0)	9.2 (4.0–14.3)	0.088
TIMI Risk Score 3–7 [% (95% CI)]	96.0 (94.0–98.1)	93.3 (86.0–100.6)	90.8 (85.7–96.0)	
Multivessel disease [% (95% CI)]	78.1 (73.8–82.4)	77.8 (65.6–89.9)	72.5 (64.5–80.5)	0.446
Admission LVEF [%;median (IR)]	55 (47–60)	53 (45–60)	55 (45–60)	0.891
Discharge LVEF [%;median (IR)]	55 (48–60)	53 (45–60)	55 (45–60)	0.761
Admission TnI [ng/ml; median (IR)]	0.12 (0.02 -1.33)†	0.14 (0.02–3.04)	0.04 (0.01–0.27)†	0.012
Peak TnI [ng/ml; median (IR)]	0.91 (0.17–6.32)	0.79 (0.14–5.18)	0.44 (0.10–1.92)	0.055
Admission creatinine [g/dl; median (IR)]	1.00 (0.90–1.20)	1.10 (0.90–1.25)	1.10 (0.90–1.30)	0.113
Discharge creatinine [g/dl; median (IR)]	1.00 (0.90–1.20)	1.00 (0.90–1.15)	1.00 (0.90–1.00)	0.796
Admission Hb [g/dl; median (IR)]	13.4 (11.9–14.4)§	12.7 (11.0–13.7)§	13.2 (12.0–14.2)	0.092
Discharge Hb [g/dl; median (IR)]	12.3 (11.0–13.4)	12.2 (10.7–13.1)	12.1 (11.0–13.1)	0.402
Admission glycemia [mg/dl; median (IR)]	104 (90–123)	110 (92–139)	106 (92–133)	0.273
Peak glycemia [mg/dl; median (IR)]	129 (110–166)	128 (108–160)	133 (109–165)	0.697
Discharge glycemia [mg/dl; median (IR)]	102 (92–130)	102 (91–124)	103 (91–124)	0.610

KW Kruskal–Wallis, *IR* interquartile range, *AMI* acute myocardial infarction, *PCI* percutaneous coronary intervention, *LVEF* left ventricle ejection fraction, *Tn* troponin, *Hb* hemoglobin

* Z-score 2.82, $P < 0.01$ versus timing <6 and >24 h

§ $P < 0.05$ timing <6 versus 6–24 h

† $P < 0.05$ timing <6 versus >24 h

lower in patients who die than in survivors both on admission and at discharge (11.8 vs. 13.1 g/dl; $P = 0.023$ and 11.0 vs. 12.2 g/dl; $P = 0.013$, respectively).

At univariate analysis, the following variables were unadjusted predictors of mortality and cardiac ischemic events at follow-up: length of CSDU stay (1 day increase), TIMI Risk Score (1 unit increase), diabetes mellitus, discharge creatinine (1 mg/dl increase), admission anemia, complete versus partial revascularization (Fig. 3). Moreover, a lower admission left ventricular ejection fraction (LVEF) was associated with mortality at follow-up, and a previous PCI and increased peak TnI were associated with cardiac ischemic events at follow-up. Both the timing of angiography (>24 vs. <24 h), and the delay of angiography (>24 vs. <24 h) were not significantly associated with either mortality or cardiac ischemic events at follow-up (Fig. 3).

At multivariate analysis, 12 variables, whose association with cardiac ischemic events at follow-up was clinically relevant or statistically significant, were found on two backward stepwise Cox regression analyses: in this model, the timing and delay of angiography were forced as covariates. The length of CSDU stay (1 day increase; HR 1.19, 95% CI 1.10–1.29, $P < 0.001$), the creatinine level at discharge (1 mg/dl increase; HR 1.61, 95% CI 1.02–2.55, $P = 0.043$), and a previous PCI (HR 1.91, 95% CI 1.32–2.75, $P < 0.001$) were independent predictors of cardiac ischemic events at follow-up when adjusted for the timing of angiography (>24 vs. <24 h; HR 0.74, 95% CI 0.41–1.22, $P = 0.259$). Similarly, length of CSDU stay (1 day increase; HR 1.19, 95% CI 1.10–1.29, $P < 0.001$), creatinine level at discharge (1 mg/dl increase; HR 1.77, 95% CI 1.07–2.92, $P = 0.026$), and a previous PCI (HR 1.95, 95% CI 1.34–2.82, $P < 0.001$) were also independent

Table 2 Clinical and biohumoral characteristics of patients investigated in relation to delay of angiography

	<24 h (n = 167; 34.3%)	24–48 h (n = 66; 13.6%)	>48 h (n = 254; 52.2%)	P value (χ^2 or KW)
Age [years; median (IR)]	70 (60–78)	72 (62–78)	73 (65–78)	0.242
Males [% (95% CI)]	72.5 (65.7–79.2)	66.7 (55.3–78.0)	72.4 (66.9–77.9)	0.625
Body weight [kg; median (IR)]	75 (67–82)	75 (65–80)	73 (67–81)	0.584
Hypertension [% (95% CI)]	71.9 (65.0–78.0)	69.7 (58.6–80.8)	70.1 (64.4–75.7)	0.911
Diabetes mellitus [% (95% CI)]	26.9 (20.2–36.7)	25.8 (15.2–36.6)	28.3 (22.8–33.9)	0.897
Dyslipidemia [% (95% CI)]	39.5 (32.1–46.9)	45.5 (33.4–57.5)	44.1 (38.0–50.2)	0.578
Family history of CAD [% (95% CI)]	28.1 (21.3–35.0)	24.2 (13.9–34.6)	24.4 (19.1–29.7)	0.664
Smoking habit [% (95% CI)]	35.3 (28.1–42.6)	30.3 (19.2–41.4)	37.8 (31.8–43.8)	0.517
Chronic renal failure [% (95% CI)]	7.8 (3.7–11.8)	3.0 (-1.1–7.2)	7.9 (4.6–11.2)	0.372
Neoplasia [% (95% CI)]	7.2 (3.3–11.1)	4.5 (-0.5–9.6)	3.1 (1.0–5.3)	0.161
Previous AMI [% (95% CI)]	29.9 (23.0–36.9)	30.3 (19.2–41.4)	35.4 (29.6–41.3)	0.449
Previous PCI [% (95% CI)]	31.7 (24.7–38.8)	47.0 (34.9–59.0)	33.9 (28.0–39.7)	0.079
TIMI Risk Score 1–2 [% (95% CI)]	3.6 (0.8–6.4)	4.5 (-0.5–9.6)	7.1 (3.9–10.2)	0.287
TIMI Risk Score 3–7 [% (95% CI)]	96.4 (93.6–99.2)	95.5 (90.4–100.5)	92.9 (89.8–96.1)	
Multivessel disease [% (95% CI)]	73.1 (66.3–79.8)	74.2 (63.7–84.8)	80.3 (75.4–85.2)	0.189
Admission LVEF [%;median (IR)]	55 (46–60)	55 (42–60)	55 (47–60)	0.716
Discharge LVEF [%;median (IR)]	55 (48–60)	55 (44–60)	55 (50–60)	0.797
Admission TnI [ng/ml; median (IR)]	0.37 (0.03–3.76)[§]	0.22 (0.03–1.83)[†]	0.05 (0.01–0.26)[§, †]	<0.001
Peak TnI [ng/ml; median (IR)]	1.30 (0.20–9.31)[§]	1.25 (0.26–5.66)[†]	0.44 (0.12–2.26)[§, †]	<0.001
Admission creatinine [g/dl; median (IR)]	1.00 (0.90–1.20)	1.00 (0.90–1.20)	1.00 (0.90–1.30)	0.898
Discharge creatinine [g/dl; median (IR)]	1.00 (0.90–1.20)	1.00 (0.90–1.15)	1.00 (0.90–1.20)	0.990
Admission Hb [g/dl; median (IR)]	13.4 (12.0–14.4)[§]	13.0 (11.9–14.4)§	13.3 (11.8–14.3)	0.786
Discharge Hb [g/dl; median (IR)]	12.3 (11.2–13.2)	11.8 (11.2–13.3)	12.3 (11.0–13.4)	0.705
Admission glycemia [mg/dl; median (IR)]	108 (93–126)	103 (89–126)	103 (90–126)	0.309
Peak glycemia [mg/dl; median (IR)]	130 (111–162)	128 (108–174)	132 (110–166)	0.984
Discharge glycemia [mg/dl; median (IR)]	104 (93–127)	100 (93–133)	102 (91–125)	0.875

KW Kruskal–Wallis, *IR* interquartile range, *AMI* acute myocardial infarction, *PCI* percutaneous coronary intervention, *LVEF* left ventricle ejection fraction, *Tn* troponin, *Hb* hemoglobin

[§] $P < 0.05$ delay <24 versus >48 h

[†] $P < 0.05$ delay 24–48 versus >48 h

predictors of cardiac ischemic events at follow-up when adjusted for a delay of angiography (>24 vs. <24 h; HR 1.11, 95% CI 0.74–1.66, $P = 0.630$).

Discussion

The main finding of the present study is that, considering the time to angiography from CSDU admission or the delay from the onset of symptoms, early coronary angiography does not affect either short-term or long-term outcome in these patients. Moreover, several clinical and biohumoral variables, indicative of each patient's risk, as well as the type of revascularization, are associated with both mortality and cardiac ischemic events during follow-up.

Our analysis in ACS patients does not support the need to perform coronary angiography as soon as possible after symptom onset or hospital admission, different from those patients presenting with an ST elevation myocardial infarction. Such finding can be explained, at least in part, by the pathogenesis of non-ST elevation ACS [1, 13–15] being generally due to a partially occlusive thrombus causing distal microembolization or, less frequently, to an occlusive thrombus in the presence of an extensive collateral blood supply. Both conditions allow the maintenance of some degree of myocardial perfusion, thus preventing extensive necrosis. The angiographic findings in our patients confirmed this explanation; in fact, only 8.4% of our patients showed a TIMI flow 0 in the culprit vessel.

Our results are in agreement with the primary end-point of the recently published TIMACS study [16], even though we used a different scoring system for patients' risk stratification, and different time intervals were used to consider an invasive strategy "delayed". The TIMACS study shows,

Table 3 Angiographic and procedural characteristics in relation to timing of angiography

	<6 h (n = 288; 68.7%)	6–24 h (n = 32; 7.6%)	>24 h (n = 99; 23.6%)	P value
Coronary artery disease				0.387
One vessel	20.2 (15.5–24.8)	25.0 (10.0–40.0)	28.3 (19.4–37.2)	
Two vessels	31.9 (26.6–37.3)	28.1 (12.5–43.7)	20.2 (12.3–28.1)	
Three vessels	38.9 (33.3–44.5)	40.6 (23.6–57.6)	41.4 (31.7–51.1)	
Left main	9.0 (5.7–12.3)	6.3 (-2.1–14.6)	10.1 (4.2–16.0)	
Pre-procedural TIMI flow				0.451
III	1.4 (0.0–2.7%)	3.1 (-2.9–9.2)	2.0 (-0.8–4.8)	
II	37.5 (31.9–43.1)	31.2 (15.2–47.3)	38.4 (28.8–48.0)	
I	54.5 (48.8–60.3)	56.3 (39.1–73.4)	46.5 (36.6–56.3)	
0	6.6 (3.7–9.5)	9.4 (-0.7–19.5)	13.1 (6.5–19.8)	
Coronary angioplasty				0.865
1 vessel	60.8 (55.1–66.4)	65.6 (49.2–82.1)	57.6 (47.8–67.3)	
2 vessels	24.7 (19.7–29.6)	28.1 (12.5–43.7)	30.3 (21.3–39.4)	
>2 vessels	14.5 (10.5–18.7)	6.3 (-2.1–14.6)	12.1 (5.7–18.6)	
Culprit vessel				0.212
LAD culprit	48.6 (42.8–54.4)	46.9 (29.6–64.2)	44.4 (34.7–54.2)	
Circumflex artery culprit	21.3 (16.5–25.9)	28.1 (12.5–43.7)	17.2 (9.7–24.6)	
RCA culprit	19.7 (15.2–24.4)	18.8 (5.2–32.3)	27.3 (18.5–36.0)	
Graft culprit	3.1 (1.1–5.1)	3.1 (-2.9–9.2)	8.1 (2.7–13.4)	
Left main culprit	7.3 (4.3–10.3)	3.1 (-2.9–9.2)	3.0 (-0.3–6.4)	
Restenosis	18.1 (13.6–22.5)	12.5 (1.0–24.0)	20.2 (12.3–28.1)	0.202
De novo lesions	79.5 (74.9–84.2)	81.3 (67.7–94.8)	72.7 (64.0–81.5)	
Undetermined	2.4 (0.7–4.2)	6.3 (-2.1–14.6)	7.1 (2.0–12.1)	
Treated vessels (n)	452	45	154	N/A
Complete revascularization	22.6 (17.7–27.4)	40.6 (23.6–57.6)	27.3 (18.5–36.0)	0.069
Vessels treated with:				0.475
BMS	21.9 (17.1–26.6)	12.5 (1.0–24.0)	17.2 (9.7–24.6)	
DES	67.0 (61.6–71.4%)	78.1 (63.8–92.4)	67.6 (58.5–76.9)	
Balloon	11.1 (7.5–14.7)	9.4 (-0.7–19.5)	15.2 (8.1–22.2)	
Both BMS and DES	5.9 (3.2–8.6%)	3.1 (-2.9–9.2)	5.1 (0.7–9.4)	0.788
Post-procedural TIMI flow				N/A
III	96.9 (94.9–98.9)	96.9 (90.8–102.9)	100 (100.0–100.0)	
II	0.7 (-0.3–1.7)	0	0	
I	0	0	0	
0	2.4 (0.7–4.2)	3.1 (-2.9–9.2)	0	
PCI failure	3.1 (1.1–5.1)	3.1 (-2.9–9.2)	0	0.205

Values reported are percentages and 95% confidence intervals when not otherwise specified

N/A not applicable, *TIMI* Thrombolysis in myocardial infarction, *LAD* left anterior descending, *RCA* right coronary artery, *BMS* bare metal stent, *DES* drug eluting stent

in patients treated with an early invasive strategy, a lower rate of refractory ischemia, an end-point not considered in our study.

Moreover, the results of our study also are in accord with those of a recent metanalysis in which no significant difference in mortality and occurrence of myocardial infarction was observed between ACS patients treated with a delayed versus an early invasive approach [17].

However, our findings do not agree with those reported by Tricoci et al. who found, in a larger number of patients, a decreased risk in the combined end-point mortality or myocardial infarction at 1-month follow-up in patients treated with an early invasive strategy [9]. Our results are also different from those reported by the ISAR-COOL investigators who found that a "very early" invasive strategy was associated with a significantly better outcome

Table 4 Angiographic and procedural characteristics in relation to delay of angiography

	<24 h (n = 130; 31.5%)	24–48 h (n = 56; 13.6%)	>48 h (n = 227; 54.9%)	P value
Coronary artery disease				0.476
One vessel	27.7 (20.0–35.4)	23.2 (12.2–34.3)	19.4 (14.2–24.5)	
Two vessels	27.7 (20.0–35.4)	25.0 (13.7–36.3)	30.8 (24.8–36.8)	
Three vessels	38.5 (30.1–46.8)	42.9 (29.9–55.8)	38.8 (32.4–45.1)	
Left main	6.1 (2.0–10.3)	8.9 (1.5–16.4)	11.0 (6.9–15.1)	
Pre-procedural TIMI flow				0.460
III	1.5 (-0.6–3.7)	1.8 (-1.7–5.3)	1.8 (0.1–3.5)	
II	34.6 (26.4–42.8)	32.2 (19.9–44.4)	40.1 (33.7–46.5)	
I	58.5 (50.0–66.9)	58.9 (46.0–71.8)	48.0 (41.5–54.5)	
0	5.4 (1.5–9.3)	7.1 (0.4–13.9)	10.1 (6.2–14.1)	
Coronary angioplasty				0.252
1 vessel	66.9 (58.8–75.0)	57.1 (44.2–70.1)	56.8 (50.4–63.3)	
2 vessels	24.6 (17.2–32.0)	26.8 (15.2–38.4)	27.3 (21.5–33.1)	
>2 vessels	8.5 (3.7–13.2)	16.1 (6.5–25.7)	15.9 (11.1–20.6)	
Culprit vessel				0.070
LAD culprit	49.2 (40.6–57.8)	48.3 (35.1–61.3)	46.3 (39.8–52.7)	
Circumflex artery culprit	23.9 (16.5–31.2)	26.8 (15.2–38.4)	15.0 (10.3–19.6)	
RCA culprit	20.0 (13.1–26.9)	10.7 (2.6–18.8)	27.3 (21.5–33.1)	
Graft culprit	2.3 (-0.3–4.9)	7.1 (0.4–13.9)	4.8 (2.1–7.6)	
Left main culprit	4.6 (1.0–8.2)	7.1 (0.4–13.9)	6.6 (3.4–9.8)	
Restenosis	13.8 (7.9–19.8)	16.1 (6.5–25.7)	21.6 (16.2–26.9)	0.007
De novo lesions	83.1 (76.6–89.5)	73.2 (61.6–84.8)	76.7 (71.1–82.2)	
Undetermined	2.4 (1.5–9.3)	6.3 (-1.3–8.4)	7.1 (0.8–5.3)	
Treated vessels (n)	184	92	368	N/A
Complete revascularization	33.1 (25.0–41.2)	25.0 (13.7–36.3)	21.1 (15.8–26.5)	0.045
Vessels treated with:				0.152
BMS	15.4 (9.2–21.6)	12.5 (3.8–21.2)	15.0 (10.3–19.6)	
DES	78.4 (71.4–85.5)	76.8 (65.7–87.8)	70.0 (64.1–76.0)	
Balloon	6.2 (54.8–71.4)	10.7 (2.6–18.8)	15.0 (10.3–19.6)	
Both BMS and DES	5.4 (1.5–9.3)	10.7 (2.6–18.8)	4.4 (1.7–7.1)	0.182
Post-procedural TIMI flow				N/A
III	98.5 (96.3–100.6)	94.6 (88.7–100.5)	98.2 (96.5–99.9)	
II	0	0	0.9 (-0.3–2.1)	
I	0	0	0	
0	1.5 (-0.6–3.7)	5.4 (-0.5–11.3)	0.9 (-0.3–2.1)	
PCI failure	1.5 (-0.6–3.7)	5.4 (-0.5–11.3)	1.8 (0.1–3.5)	0.213

Values reported are percentages and 95% confidence intervals when not otherwise specified

N/A not applicable, *TIMI* Thrombolysis in myocardial infarction, *LAD* left anterior descending, *RCA* right coronary artery, *BMS* bare metal stent, *DES* drug eluting stent

at 30 days [18]. The different end-points considered in our study (mortality and ischemic events at long term follow-up) may explain, at least in part, these different results.

The supposed advantages of very early angiography and intervention are (1) a faster identification of the culprit lesion that allows a rapid resolution of ischemia with revascularization [19, 20]; (2) for patients suitable for PCI, an early intervention may be less frequently associated with a more organized intracoronary thrombus, that results in a higher incidence of distal microembolization [8] or coronary dissection.

On the other hand, the supposed advantages of angiography deferred more than 24 h from hospital admission are (1) a better assessment of patients' general clinical status and comorbidities; (2) a more appropriate pre-interventional medical management able to reduce the thrombotic burden, distal microembolization, and renal complications.

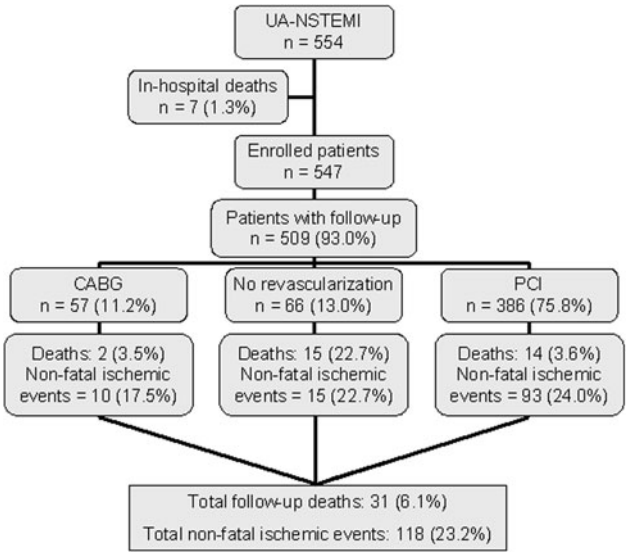

Fig. 1 Follow-up data of study population. *UA* unstable angina, *NSTEMI* Non-ST-elevation myocardial infarction, *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention

Our analysis of ACS patients treated with an early invasive strategy confirms that the relationship between TnI levels and outcome is maintained even in patients undergoing early revascularization [1, 21–27], in agreement with FRISC II and GUSTO IV trials [3, 28]. However, in our population, TnI levels were not independently associated with mortality and cardiac ischemic events at long-term follow-up.

Our data confirm also the negative influence on ACS patients' outcome of high serum creatinine [29–32], glucose levels [33–36] and low hemoglobin concentration at admission [37–39], suggesting that an accurate assessment of comorbidities is very important for ACS patients' care, especially when an early invasive strategy is preferred.

The results of our study suggest that complete revascularization is beneficial on long-term outcome, which is at variance with previous reports [40, 41].

Moreover, in our study, a higher TIMI risk score and a longer hospital stay are associated with a worse outcome. A longer hospitalization is generally due to patients' comorbidities or post-procedural complications, and can be considered an indirect index of clinical complexity.

Our study has some limitations. First, it is an observational, single-center real-world study, and, although it faithfully reflects our daily practice, a larger number of patients should have been enrolled to detect a significant difference in mortality and cardiac ischemic events with a higher statistical power. Second, our patients were not randomized to two different times of angiography, even though no significant difference in clinical, biohumoral and angiographic characteristics were observed in the subgroups of patients according to different timing and delays of angiography.

In conclusion, even though our study shows an adherence of our Institution to an early invasive strategy as suggested by Guidelines, it does not support the concept that in ACS patients angiography should be performed as soon as possible after symptom onset or hospital admission. In fact, in our study a longer time to angiography does not produce a higher mortality or an increased incidence of cardiac ischemic events during follow-up. Instead, an unfavorable long-term outcome is influenced by the clinical complexity of patients, indirectly expressed by a higher

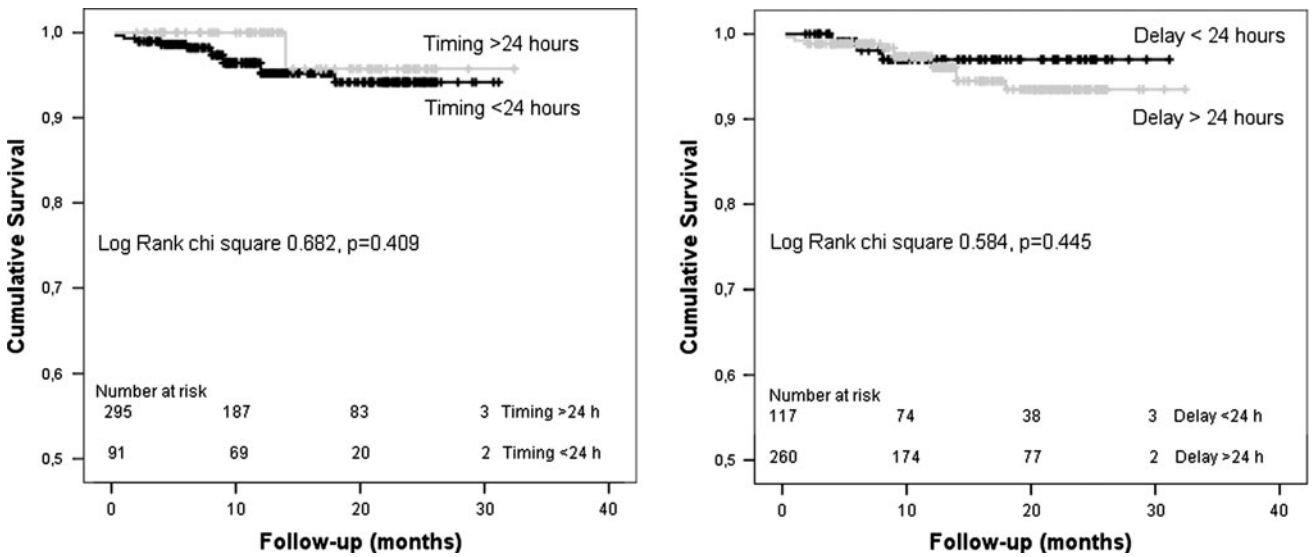

Fig. 2 Kaplan–Meier survival curves in relation to timing and delay of angiography (> vs. <24 h)

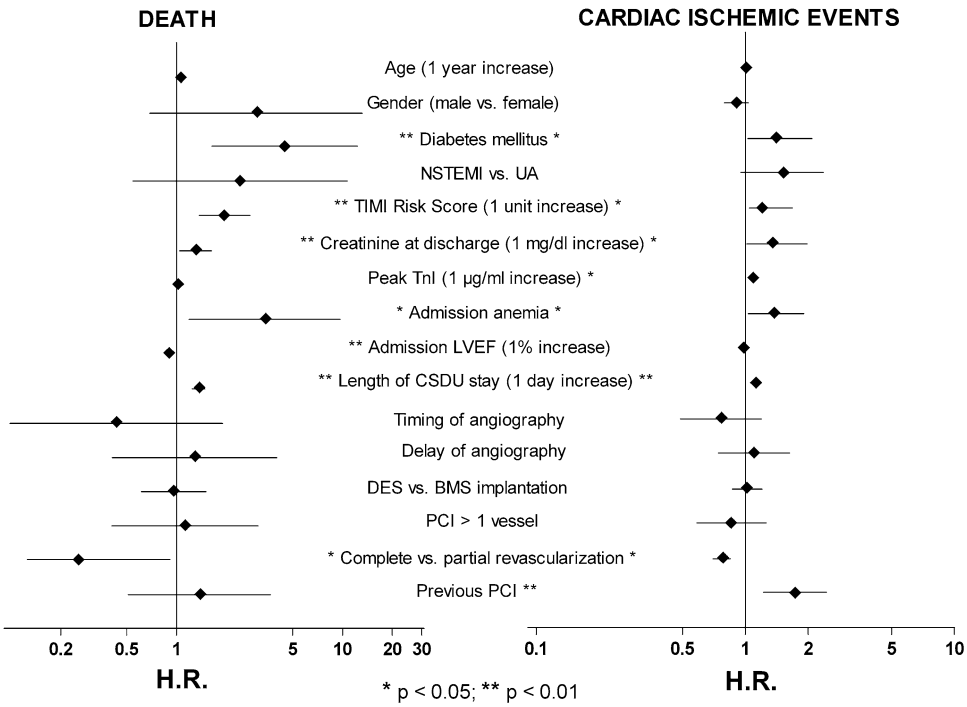

Fig. 3 Unadjusted hazard ratios and 95% CI's for death and cardiac ischemic events at follow-up. *NSTEMI* Non-ST-elevation myocardial infarction, *UA* unstable angina, *TIMI* thrombolysis in myocardial infarction, *TnI* troponin I, *LVEF* left ventricular ejection fraction, *CSDU* Cardiac step down unit, *DES* drug eluting stent, *BMS* bare metal stent, *PCI* percutaneous coronary intervention

TIMI risk score, a longer hospital stay, high serum creatinine concentrations, low hemoglobin levels, left ventricular dysfunction, diabetes mellitus, or a positive history for a previous PCI.

Conflict of interest None.

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