# Treatment modalities of non-ST-elevation acute coronary syndromes in the real world. Results of the prospective R.OS.A.I.-2 registry

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*Key words:*
**Acute coronary syndromes; Glycoprotein IIb/IIIa inhibitors.**

*Background.* **Despite advances in the treatment of non-ST-elevation acute coronary syndromes (ACS) based on randomized studies and published guidelines, the extent to which such treatments are applied in daily clinical practice remains elusive. The R.OS.A.I.-2 registry was undertaken to assess the modalities of the treatment of non-ST-elevation ACS, both in terms of the use of drugs, with particular attention to glycoprotein IIb/IIIa inhibitors and clopidogrel, as well as type of strategy, aggressive versus conservative, in a consecutive series of patients admitted to 76 coronary care units (CCU) in Italy.**

*Methods.* **The R.OS.A.I.-2 study group consisted of 76 hospitals in 7 regions of Northern and Central Italy: 38 centers had a CCU without cath lab facilities (type 1), whereas 38 type 2 centers had a CCU with an on-site interventional cath lab. Globally, 1581 patients with a diagnosis of non-ST-elevation ACS entered the registry during an 8-week period and had a 30-day follow-up. Patients were considered as being aggressively treated if they had coronary arteriography within 96 hours of admission, whereas all other patients were considered as being conservatively treated even if they underwent coronary arteriography after the first 96 hours of hospitalization.**

*Results.* **An aggressive approach was employed in 789 patients (50%), whereas of the 792 (50%) conservatively treated patients 363 had a late coronary arteriography at a mean of 10.5 ± 13 days after admission. Aggressively treated patients were younger ($p < 0.0001$), had less frequently ST-segment depression ($p = 0.04$), troponin positivity ($p = 0.02$), elevated creatine kinase (CK) and/or CK-MB levels within 24 hours of admission ($p = 0.01$), and had been more often admitted to type 2 hospitals ($p < 0.0001$) than those treated conservatively. Glycoprotein IIb/IIIa blockers (predominantly "small molecules") were more frequently used in younger patients ($p = 0.04$), in those treated aggressively ($p < 0.0001$), with ST-segment depression ($p = 0.01$), and in those with a high TIMI risk score ($p = 0.001$), whereas the use of clopidogrel did not differ in any patient subgroup except in patients < 70 years ($p = 0.01$) and in those treated aggressively ($p < 0.0001$). Percutaneous coronary interventions were performed in 656 patients (481 in the aggressively treated group and 175 in the conservatively treated group). At 30 days, the death rate was 3.4% and the myocardial infarction rate was 5.8%. Age, ST-segment depression, elevated CK and/or CK-MB levels within 24 hours of admission and a conservative approach were significant predictors of an unfavorable outcome.**

*Conclusions.* **The R.OS.A.I.-2 registry confirms that the population admitted to the CCU with non-ST-elevation ACS has a higher risk profile than that included in recent clinical trials. The aggressive approach is still more dependent on the cath lab availability than on a risk stratification process. Conservatively treated patients have worse clinical features and short-term prognosis. Applying an invasive approach to higher risk groups might further improve the global outcome of non-ST-elevation ACS.**

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## Introduction

Over recent years, a considerable series of studies have prompted impressive advances in the treatment of non-ST-elevation acute coronary syndromes (ACS). On one hand, medical therapy has been improved by the use of powerful antiplatelet drugs, such as the glycoprotein IIb/IIIa antagonists and clopidogrel, which have consistently reduced the occurrence of early and late coronary events[1-7]. On the other hand, refinements in technology and operator skill have so improved the results of invasive treatment that an aggressive strategy, based on early coronary arteriography followed by revascularization if feasible, has been shown to be superior to a conservative approach in recent comparative studies[8-11]. International guidelines have been recently released on the diagnosis, risk stratification and treatment of non-ST-elevation ACS[12,13]. However these guidelines are based on findings derived from randomized clinical trials, whose strict eligibility criteria raise questions about the applicability of those findings to the general population of patients[14].

The R.OS.A.I.-2 registry was prospectively designed to assess the current care of non-ST-elevation ACS, with particular reference to the rate of use of antiplatelet drugs, and type of strategy, aggressive versus conservative, in a population of consecutive patients admitted to coronary care units (CCU) in Italy.

## Methods

The R.OS.A.I.-2 study group consisted of 76 CCU in 7 regions of Northern and Central Italy, including Lombardy, Veneto, Trentino-Alto Adige, Piedmont, Liguria, Emilia-Romagna and Tuscany. Selected hospitals within each region were identified in order to give a representative assessment of local practice patterns among two different hospital types: type 1 had a CCU but lacked a cath lab (38 hospitals); type 2 had a CCU with an interventional cath lab (38 hospitals). In order to make patient follow-up easier and more accurate, all selected type 1 hospitals had their referral center (type 2 hospital) also participating in the registry.

**Eligibility criteria.** During a 2-month period (May-June 2002) all patients admitted to CCU with a diagnosis of non-ST-elevation ACS associated with at least one of the following findings: 1) ischemic electrocardiographic changes consisting of new (or presumably new) ST-segment depression, transient (< 20 min) ST-segment elevation, T wave inversion; 2) elevated cardiac markers, including troponin T or I; 3) known coronary artery disease, as documented by a history of myocardial infarction, revascularization or previous coronary angiography, were enrolled in the registry. Consecutive enrolment was ensured by the investigators.

Patients were excluded if they had persistent ST-segment elevation on the initial electrocardiogram, had received thrombolytic therapy or a primary percutaneous coronary intervention (PCI) within the previous 24 hours, had been admitted with a diagnosis of chest pain of non-cardiac origin or had been transferred for planned revascularization. There were no exclusion criteria regarding age, gender, medical history or demographic characteristics.

A standard case record form was used to collect information on demographics, presenting symptoms, medical history, clinical and electrocardiographic features as well as laboratory data. The TIMI risk score was calculated for each patient at each local site[15]. In addition, the treatment characteristics and in-hospital and 30-day outcomes were recorded.

Quantitative troponin I or T levels were measured at each participating site. Levels exceeding the upper normal limit of each local laboratory were considered as increased. Elevated creatine kinase (CK) and/or CK-MB levels within 24 hours of admission were considered those values exceeding twice the upper normal limit of each local laboratory.

**Definitions and treatment strategies.** Patients were considered as having been aggressively treated if they had undergone coronary arteriography within 96 hours of hospital admission[8]. Among these patients, those who had had coronary arteriography within 48 hours[9] were considered to have had an early aggressive treatment. All other patients (including those undergoing coronary arteriography within the 30-day follow-up period, but later than 96 hours of admission) were considered as having been treated conservatively.

Coronary arteriography and PCI were performed in the various centers according to the local clinical practice and the experience of interventional cardiologists. All participating type 2 hospitals performed at least one measurement of cardiac enzymes (total CK and/or CK-MB) within 24 hours of the PCI (a prerequisite to participate in the registry).

Although the diagnosis of acute myocardial infarction was independently made at each participating center, to avoid heterogeneous criteria it was suggested that it be defined by the presence of either of the following: 1) an increase in CK serum levels, or of its MB isoform to at least twice the upper limit of the normal reference range (3 times the upper normal limit within 48 hours of a PCI, 5 times after coronary bypass surgery); 2) the development of new Q waves on the electrocardiogram in at least two contiguous leads.

The 30-day follow-up included for all patients clinical evaluation performed at that time.

**Statistical analysis.** All data analyses were carried out according to a pre-established plan. In general, proportions were compared using the $\chi^2$ test or the Fisher's exact test as appropriate, whilst continuous variables were compared using the Student's t-test. Multivariate analyses were conducted with logistic regression. The endpoints were the composite of death from cardiovascular causes, myocardial infarction, stroke and the composite of death from cardiovascular causes, myocardial infarction, stroke and urgent re-hospitalization. The covariates included in the multivariate models were: strategy (aggressive, conservative), age (≥ 70 and < 70 years), sex, TIMI risk score (≥ 5 and < 5), diabetes, ST-segment deviation, non-Q wave myocardial infarction at admission. The odds ratios and 95% confidence intervals were reported with their respective two-tailed probability values. A p value of ≤ 0.05 was considered as statistically significant. All statistical computations were performed using SAS version 8.2 procedures.

## Results

**Clinical and electrocardiographic findings.** Data regarding 1581 patients with a confirmed diagnosis of non-ST-elevation ACS were collected. Of these patients, 634 were admitted to type 1 hospitals, and 947 to type 2. The patients admitted to type 1 hospitals were older

and more frequently presented with ischemic electrocardiographic changes and CK/CK-MB elevations (Tables I and II) compared to those admitted to type 2 hospitals. Troponin levels (troponin I in 847 cases and troponin T in 242 cases) were measured in 75% of the patients admitted to type 1 hospitals and in 83% of those admitted to type 2 hospitals and were higher than the upper reference limit in about 60% of cases in both types of centers. The great majority of patients had a TIMI risk score of 3-4, suggesting a moderate risk, with about one fourth of patients having a high-risk profile.

**Treatment strategies.** An aggressive approach was followed in 789 patients (50%), of whom 507 had coronary arteriography within 48 hours of admission, whereas 792 patients (50%) were treated conservatively. Tables III and IV show the clinical and electrocardiographic characteristics of the two groups of patients. The patients treated aggressively were younger, more frequently male, with more prior angina and prior PCI. Among the electrocardiographic characteristics at presentation, a transient ST-segment elevation was associated with an aggressive strategy, whereas ST-segment depression was more frequently observed in patients treated conservatively. Likewise, an elevation in the CK/CK-MB or troponin levels on admission was more frequently observed in patients treated conservatively. A high TIMI risk score was similar in the two groups. An aggressive strategy was more frequently adopted in patients admitted to hospitals with cath lab facilities (72.9%) than among those admitted to hospitals without cath lab facilities (27.1%, $p < 0.0001$).

**Table I.** Clinical characteristics of patients according to hospital type.

| | Type 1 hospital (n = 634) | Type 2 hospital (n = 947) | p |
|---|---|---|---|
| Age (years) | 70 ± 11 | 67 ± 11 | 0.005 |
| Female sex | 221 (34.9%) | 293 (30.9%) | 0.10 |
| Type 1 diabetes | 24 (3.8%) | 24 (2.5%) | 0.15 |
| Type 2 diabetes | 126 (19.9%) | 192 (20.3%) | 0.84 |
| Family history | 117 (18.5%) | 217 (22.9%) | 0.03 |
| Hypertension | 370 (58.4%) | 628 (66.3%) | 0.001 |
| Hyperlipidemia | 325 (51.2%) | 495 (52.3%) | 0.43 |
| Smoking | 177 (27.9%) | 274 (28.9%) | 0.51 |
| Obesity | 99 (15.6%) | 142 (15%) | 0.82 |
| Prior angina | 81 (12.8%) | 158 (16.7%) | 0.03 |
| Prior myocardial infarction | 203 (32%) | 325 (34.3%) | 0.34 |
| Prior coronary bypass surgery | 52 (8.2%) | 89 (9.4%) | 0.41 |
| Prior PCI (< 6 months) | 40 (6.3%) | 72 (7.6%) | 0.32 |
| Prior PCI (> 6 months) | 59 (9.3%) | 116 (2.2%) | 0.06 |
| Prior use of statins | 142 (22.4%) | 251 (26.5%) | 0.06 |
| Prior use of aspirin | 262 (41.3%) | 416 (43.9%) | 0.30 |
| Killip class III-IV | 30 (4.7%) | 41 (4.3%) | 0.72 |
| Chest pain > 30 min | 420 (66.2%) | 535 (56.5%) | < 0.0001 |
| Chest pain within 24 hours of admission | 411 (64.8%) | 555 (58.6%) | 0.01 |
| ≥ 2 chest pain within 24 hours of admission | 183 (28.9%) | 245 (25.9%) | 0.18 |

PCI = percutaneous coronary intervention.

**Table II.** Electrocardiographic features and risk variables of patients according to hospital type.

| | Type 1 hospital (n = 634) | Type 2 hospital (n = 947) | p |
|---|---|---|---|
| Abnormal ECG | 563 (88.8%) | 797 (84.2%) | 0.009 |
| ST-segment depression | 323 (50.9%) | 415 (43.8%) | 0.005 |
| Transient ST-segment elevation | 41 (6.5%) | 87 (9.2%) | 0.05 |
| Negative T waves | 213 (33.6%) | 257 (27.1%) | 0.005 |
| Raised troponin levels | 383 (60.4%)* | 596 (62.9%)** | 0.06 |
| Elevated CK/CK-MB† | 177 (27.9%) | 211 (22.3%) | 0.01 |
| TIMI risk score | | | |
| 0-2 | 108 (17%)§ | 163 (17.2%)§§ | |
| 3-4 | 352 (55.5%) | 470 (49.6%) | 0.09 |
| 5-7 | 158 (24.9%) | 275 (29%) | |

CK = creatine kinase. * not measured in 159 patients (25.1%); ** not measured in 164 patients (17.3%); § not calculated in 16 patients (2.5%); §§ not calculated in 39 patients (4.1%); † twice the laboratory upper normal limit within 24 hours of admission.

**Table III.** Clinical characteristics of patients according to treatment strategy.

| | Conservative strategy (n = 792) | Aggressive strategy (n = 789) | p |
|---|---|---|---|
| Age (years) | 70.8 ± 11 | 65.8 ± 11 | < 0.0001 |
| Female sex | 281 (35.5%) | 233 (29.5%) | 0.01 |
| Type 1 diabetes | 25 (3.2%) | 23 (2.9%) | 0.77 |
| Type 2 diabetes | 173 (21.8%) | 145 (18.4%) | 0.08 |
| Hypertension | 511 (64.5%) | 487 (61.7%) | 0.24 |
| Family history | 130 (16.4%) | 204 (25.9%) | 0.01 |
| Smoking | 196 (24.7%) | 255 (32.3%) | 0.01 |
| Obesity | 132 (16.7%) | 109 (13.8%) | 0.03 |
| Hyperlipidemia | 421 (53%) | 399 (50%) | 0.22 |
| Prior angina | 102 (12.9%) | 137 (17.4%) | 0.01 |
| Prior myocardial infarction | 273 (34.5%) | 255 (32.3%) | 0.36 |
| Prior coronary bypass surgery | 77 (9.7%) | 64 (8.1%) | 0.26 |
| Prior PCI (< 6 months) | 45 (5.7%) | 67 (8.5%) | 0.03 |
| Prior PCI (> 6 months) | 67 (8.5%) | 108 (13.7%) | < 0.0001 |
| Type 1 hospitals | 420 (66.2%) | 214 (33.8%) | < 0.0001 |
| Type 2 hospitals | 372 (39.2%) | 575 (60.8%) | |
| Killip class III-IV | 33 (4.2%) | 38 (4.8%) | 0.56 |
| Prior use of aspirin | 336 (42.4%) | 342 (43.3%) | 0.71 |
| Chest pain > 30 min | 485 (61.2%) | 470 (59.6%) | 0.49 |
| Chest pain within 24 hours of admission | 481 (60.7%) | 485 (61.5%) | 0.76 |
| ≥ 2 chest pain within 24 hours of admission | 190 (24%) | 238 (30.2%) | 0.005 |

PCI = percutaneous coronary intervention.

**Table IV.** Electrocardiographic features and risk variables of patients according to treatment strategy.

| | Conservative strategy (n = 792) | Aggressive strategy (n = 789) | p |
|---|---|---|---|
| Abnormal ECG | 690 (87.1%) | 670 (84.9%) | 0.20 |
| ST-segment depression | 390 (49.2%) | 348 (44.1%) | 0.04 |
| Transient ST-segment elevation | 44 (5.6%) | 84 (10.6%) | < 0.0001 |
| Negative T waves | 225 (28.4%) | 245 (31.1%) | 0.25 |
| Raised troponin levels | 513 (64.8%)* | 466 (59.1%)** | 0.02 |
| Elevated CK/CK-MB† | 213 (26.9%) | 175 (22.2%) | 0.01 |
| TIMI risk score | | | |
| 0-2 | 120 (15.2%)§ | 151 (19.1%)§§ | |
| 3-4 | 421 (53.2%) | 401 (50.8%) | 0.10 |
| 5-7 | 224 (28.3%) | 209 (26.5%) | |

CK = creatine kinase. * not measured in 154 patients (19.4%); ** not measured in 169 patients (21.4%); § not calculated in 27 patients (3.4%); §§ not calculated in 28 patients (3.5%); † twice the laboratory upper normal limit within 24 hours of admission.

**Use of drugs.** The pharmacological treatment in the CCU according to the type of hospitals where patients were admitted is described in table V. Of note, low molecular weight heparin was more frequently used than unfractionated heparin in both hospital types, but its use, as well as that of ACE-inhibitors, was more frequent in type 1 hospitals. On the contrary, glycoprotein IIb/IIIa blockers (predominantly, the "small molecules" tirofiban and eptifibatide) were more frequently used in type 2 hospital patients (p = 0.001). Clopidogrel was administered to about one fourth of patients, with a slightly higher prevalence in hospitals with cath lab facilities. Analysis of the use of small molecule glycoprotein IIb/IIIa blockers as "upstream" treatment and of clopidogrel according to the clinical characteristics and risk variables (Figs. 1 and 2) showed that glycoprotein IIb/IIIa antagonists were more frequently used in patients < 70 years (p = 0.04), in those with ST-segment depression (p = 0.01), in those with a high TIMI risk score (p = 0.001), as well as in those who were aggressively treated (p < 0.0001), whereas the use of clopidogrel did not differ in any patient subgroup, except in patients < 70 years (p = 0.01) and in those treated aggressively (p < 0.0001).

**Coronary arteriography.** Coronary arteriography was performed in the 789 aggressively treated patients at a mean time of 45 hours after admission. Among the 792 conservatively treated patients, 363 had a late coronary arteriography after a mean time of 10 ± 13 days after

**Table V.** Use of drugs in the coronary care unit according to hospital type.

| | Type 1 hospital (n = 634) | Type 2 hospital (n = 947) | p |
|---|---|---|---|
| Low molecular weight heparin | 419 (66.1%) | 494 (52.2%) | 0.001 |
| Unfractionated heparin | 185 (29.2%) | 340 (35.9%) | 0.005 |
| Aspirin | 601 (94.8%) | 902 (95.2%) | 0.78 |
| Beta-blockers | 396 (62.5%) | 608 (64.2%) | 0.48 |
| Calcium antagonists | 123 (19.4%) | 219 (23.1%) | 0.07 |
| Statins | 317 (50%) | 479 (50.6%) | 0.82 |
| ACE-inhibitors | 363 (57.3%) | 462 (48.83%) | 0.001 |
| GP IIb/IIIa blockers (small molecules) | 73 (11.5%) | 232 (24.5%) | 0.001 |
| GP IIb/IIIa blockers (abciximab) | 4 (0.6%) | 25 (2.6%) | < 0.0001 |
| Clopidogrel | 146 (23%) | 260 (27.5%) | 0.048 |
| Ticlopidine | 165 (26%) | 329 (34.7%) | 0.005 |

GP = glycoprotein.

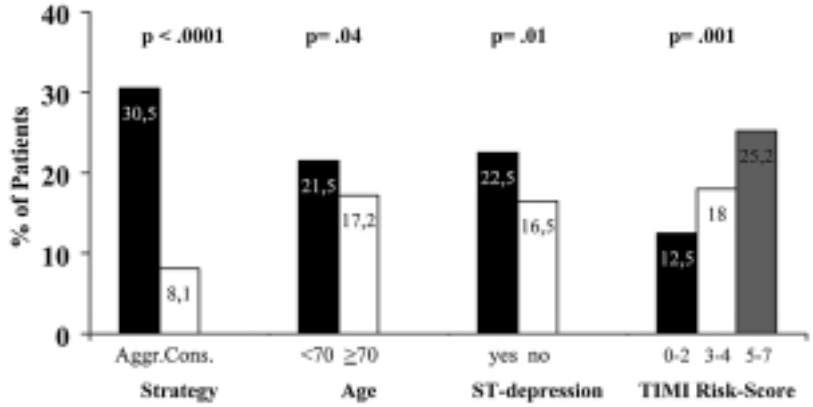


**Figure 1.** *Use of small molecule glycoprotein IIb/IIIa inhibitors in relation to the type of strategy, conservative versus aggressive, age, presence of ST-segment depression, and TIMI risk score.*

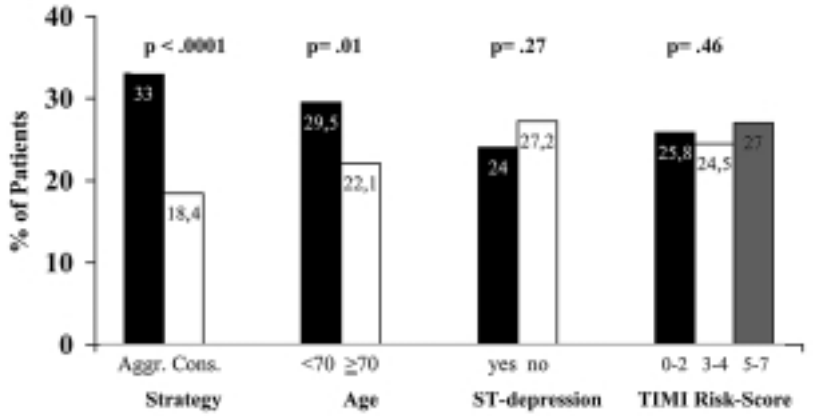


**Figure 2.** *Use of clopidogrel in relation to the type of strategy, aggressive versus conservative, age, presence of ST-segment depression, and TIMI risk score.*

admission. Globally, single-vessel disease was found in 366 patients (32%), two-vessel disease in 303 patients (26%) and three-vessel disease in 340 patients (29.5%), whereas 143 patients (12.5%) had no significant coronary artery disease. A left main disease was also found in 82 patients (7%). The ejection fraction was measured in 881 patients. Among these, 295 patients (33.5%) had a value < 50%.

**Coronary revascularization procedures.** Globally, PCI were completed in 656 patients, 481 in the aggressive group (in 327 they were performed within 48 hours

of admission), and 175 in the conservative group: 218 patients had been admitted to type 1 hospitals (34% of the population admitted to these hospitals) and 438 had been admitted to type 2 hospitals (46% of the population admitted to these hospitals).

Stents were implanted in 559 patients (85%): 1 stent was implanted in 388 patients, while > 1 stent was implanted in 171 patients. In the cath lab, abciximab was used in 61 patients (9.3% of those who underwent a PCI) whereas small molecules were used in 31 patients (4.7%). Clinical complications occurred in 32 patients (5%): 4 patients (0.6%) died, 24 patients (3.7%) had an acute myocardial infarction, 4 patients required an urgent revascularization procedure (3 were submitted to a new PCI and 1 was submitted to coronary bypass surgery).

Coronary bypass surgery was performed in 135 of the aggressively treated patients (17%) and in 78 of the conservatively treated patients (9.8%): 81 had been admitted to type 1 hospitals (12.7% of the population admitted to these hospitals) and 132 had been admitted to type 2 hospitals (12.7% of the population admitted to these hospitals). The interventions were accomplished within 48 hours of coronary arteriography in 78 patients (49 in the aggressive group and 29 in the conservative group).

**In-hospital and 30-day outcome.** The rates of cardiovascular events are reported in table VI and the multivariate predictors of the composite endpoint of death, acute myocardial infarction and stroke are shown in table VII: age, ST-segment depression, type of strategy and elevated CK/CK-MB levels within 24 hours of admission were significantly associated with the 30-day outcome, while diabetes had a borderline significance. When the composite endpoint included urgent re-hospitalization, the analysis did not change substantially, although the TIMI risk score attained a borderline significance (p = 0.07). When the analysis was restricted to the 1089 patients in whom troponin was measured, this variable did not give any additional prognostic information (p = 0.37) whereas the type of strategy (p = 0.002), age (p = 0.01) diabetes (p = 0.02) and elevated CK/CK-MB levels within 24 hours of admission (p = 0.001) retained their statistical significance.

**Table VII.** Multivariate analysis. Composite endpoint: death, myocardial infarction, stroke.

| | OR | 95% CI | p |
|---|---|---|---|
| Age | 1.98 | 1.34-2.95 | 0.0007 |
| Sex | 0.99 | 0.68-1.44 | 0.97 |
| Conservative strategy | 1.62 | 1.12-2.34 | 0.01 |
| TIMI risk score | 1.25 | 0.85-1.85 | 0.25 |
| Diabetes | 1.44 | 0.97-2.12 | 0.06 |
| Elevated CK/CK-MB* | 2.33 | 1.63-3.35 | < 0.0001 |
| ST-segment depression | 1.46 | 1.01-2.12 | 0.04 |

CI = confidence interval; CK = creatine kinase; OR = odds ratio. * twice the laboratory upper normal limit within 24 hours of admission.

## Discussion

The results of this registry offer a unique picture of the current modalities of treatment of patients with non-ST-elevation ACS in the light of the recent developments in this field. Potent antiplatelet drugs such as glycoprotein IIb/IIIa blockers and clopidogrel have greatly improved our pharmacological armamentarium by providing consistent benefit in such patients. Clinical trials comparing aggressive and conservative strategies, such as the FRISC II[8], TACTICS-TIMI 18[9] and RITA 3 trials[10], have shown the superiority of an approach based on early coronary arteriography followed by revascularization, if feasible, over a conservative approach.

The population included in the R.OS.A.I.-2 registry was mostly composed of patients with moderate to high-risk features. Approximately 50% of patients were > 70 years, ST-segment changes were recorded in 56% of patients, a raised troponin level was found in 77% of the patients in whom it was measured and 28% of patients had a high TIMI risk score. In comparison, patients enrolled in the FRISC II[8], TACTICS-TIMI 18[9] and the RITA 3 studies[10] were younger and less frequently had ST-segment changes and elevated troponin levels. The 30-day mortality was 3.4% in the current registry, 2.2% in the TACTICS-TIMI 18 trial[9] and 1.9% in the FRISC II trial[8], whereas in the RITA 3 study, the 4-month mortality was 2.7%[10]. These data highlight the difference between the "real world" population admit-

**Table VI.** Clinical outcome at 30 days according to hospital type at admission and adopted strategy.

| | Total events | Type 1 hospital (n = 634) | Type 2 hospital (n = 947) | Conservative strategy (n = 792) | Aggressive strategy (n = 789) |
|---|---|---|---|---|---|
| Death | 53 (3.4%) | 21 (3.3%) | 32 (3.4%) | 38 (4.8%) | 15 (1.9%) |
| Myocardial infarction | 91 (5.8%) | 35 (5.5%) | 56 (5.9%) | 55 (6.9%) | 36 (4.6%) |
| Stroke | 12 (0.7%) | 7 (1.1%) | 5 (0.5%) | 8 (1.1%) | 4 (0.5%) |
| Re-hospitalization for CP recurrence | 46 (2.9%) | 24 (3.8%) | 22 (2.3%) | 26 (3.3%) | 20 (2.5%) |
| Combined endpoint | 194 (12.3%) | 85 (13.4%) | 109 (11.5%) | 122 (15.4%) | 72 (9.1%) |

CP = chest pain.

ted to CCU for non-ST-elevation ACS and that selected for inclusion in randomized clinical trials. In the R.OS.A.I.-2 registry, patients admitted to hospitals without cath lab facilities were older and more frequently had ST-segment depression and elevated CK/CK-MB levels within 24 hours of admission. Since our protocol excluded those patients transferred from community to tertiary centers for planned revascularization, these differences may be due to the fact that the 38 hospitals with a cath lab included in the registry had to deal with a larger patient population than the 39 hospitals without this facility and that age was probably a selection criterion for CCU admission. However, other risk factors, such as troponin positivity and the TIMI risk score, were similarly distributed in the patient population admitted to the two hospital types.

Globally, coronary arteriography was performed in 73% of the patients included in this registry and revascularization procedures (either PCI or coronary bypass surgery) were accomplished in about half of the total population. These figures are higher than those reported in previous registries[16-18]. In the ENACT study[16] 41% of patients underwent coronary arteriography and 23% underwent PCI procedures, whereas in the Euro Heart Survey ACS[17] 52% of patients had coronary angiography and 30.8% had coronary revascularization procedures. However, in those registries there was a wide variability in the use of these procedures between participating countries. It is also interesting to compare the R.OS.A.I.-2 data with those of the EARISA registry[19] (39% of patients undergoing coronary arteriography and 13% undergoing revascularization procedures), involving 287 Italian hospitals in 1996. Although the higher incidence of procedures certainly reflects a growing tendency toward invasive treatment modalities, it should be noted that our population was mainly composed of moderate to high-risk patients admitted to the CCU, whereas the EARISA registry also included patients admitted to cardiology wards.

The patients in the R.OS.A.I.-2 registry were also classified according to whether they had been treated aggressively or conservatively. Recent randomized trials have compared modern revascularization techniques with current medical therapy. Both the FRISC II[8] and TACTICS-TIMI 18[9] studies showed the superiority of an invasive approach, consisting of early systematic coronary arteriography followed by revascularization, over a conservative strategy. We considered that patients who had coronary arteriography within 4 days of admission had been treated aggressively, whereas continuous medical treatment or later coronary angiography was part of a conservative approach. We thought that 4 days was a reasonable time for hospitals without cath lab facilities to stratify their patients and to transfer those needing coronary angiography to the referral center. Moreover, 4 days was the mean time interval within which coronary angiography and PCI were performed in the invasive arm of the FRISC II trial[8]. Furthermore, 64% of the patients had coronary angiography performed within 48 hours of admission, as in the TACTICS-TIMI 18 trial[9], whereas the 363 patients who had coronary angiography in the conservatively treated cohort (45% of the whole group) had that exam performed at a mean of 10.5 days after hospital admission. Aggressively treated patients were more frequently admitted to hospitals with cath lab facilities and had a lower risk profile, since they were younger than conservatively treated patients with a lower incidence of ST-segment depression, troponin positivity and elevated CK/CK-MB levels within 24 hours of admission. In the multivariate analysis however, taking into account these differences in risk profile, an invasive strategy was associated with a better 30-day outcome. Other significant prognostic indicators were age, ST-segment depression, and elevated CK/CK-MB levels within 24 hours of admission. This latter finding is in keeping with a recently reported analysis of the GUSTO-IIb trial, showing that CK elevation has an independent prognostic value in patients with non-ST-elevation ACS[20]. Interestingly, in our study troponin positivity was not correlated with the 30-day outcome. Since the majority of our patients had increased troponin levels, a quantitative rather than a simply qualitative analysis would have improved the value of this marker of myocardial necrosis as a prognostic indicator[21,22]. This quantitative analysis, however, could not be accomplished because the troponin measurements were not centralized and the various participating centers used different methods of troponin detection.

Glycoprotein IIb/IIIa blockers were globally used in 29% of patients with a prevalence of small molecules (tirofiban or eptifibatide) in the CCU and abciximab in the cath lab, in association with PCI. The proportion of patients who received these drugs was somewhat higher than that reported for Europe in the GRACE study[23], which was performed in 1999, and than that reported in the Euro Heart Survey ACS which collected data in the year 2000[17]. Such an increase in the use of these agents may be secondary to the implementation of more recent guidelines that recommend the use of glycoprotein IIb/IIIa blockers for patients with high-risk features, such as those with increased troponin concentrations, ST-segment depression, and recurrent ischemia. Indeed, we found that patients treated with these drugs had a greater incidence of chest pain within 24 hours of admission, ST-segment depression, elevated CK/CK-MB levels within 24 hours of admission, a high TIMI risk score and underwent more frequently aggressive treatment. There was therefore a tendency to use these drugs in patients with a higher risk profile. This is in keeping with the recent guidelines of the Task Force of the American Heart Association/American College of Cardiology and of the European Society of Cardiology[12,13]. Treatment with clopidogrel was also more frequent in aggressively treated patients, but, in keeping

with the results of the CURE trial[24], its use was not influenced by the risk profile of the patients.

In conclusion, the present registry confirms that the population admitted to CCU with non-ST-elevation ACS has a higher risk profile than that included in recent randomized clinical trials. The aggressive approach, although undertaken in a sizable proportion of patients, is related more to the cath lab availability than to the risk stratification of patients. However, although the invasive strategy was more frequently adopted in lower risk patients, multivariate analysis showed that an aggressive treatment was associated with better 30-day outcome. Applying a more aggressive approach to higher risk groups may further improve the global outcome of non-ST-elevation ACS.

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## Appendix

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