ORIGINAL ARTICLE

# Clinical importance of early intensive medical treatment for improving prognosis in non-ST-elevation acute coronary syndrome

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**Received:**
14-8-2011

**Accepted:**
1-10-2011

**Conflict of interest:**
None

**Background and objective:** Current guidelines emphasize the importance of optimal medical treatment for improving the prognosis of patients diagnosed with acute coronary syndrome without persistent ST-segment elevation, although few studies have analyzed the importance of implementing prescribing guidelines on outcomes; our aim was to investigate this relationship.
**Methods:** Retrospective study of 1118 patients admitted to a coronary unit with non-ST-segment elevation acute coronary syndrome, analyzing baseline characteristics, treatment during admission, and prognostic variables during hospitalization.
**Results:** In-hospital mortality was lower (*P*<.001) in patients who were treated with at least 5 of 7 recommended drugs (acetylsalicylic acid, anticoagulants, glycoprotein IIb/IIIa inhibitors, clopidogrel, β-blockers, angiotensin-converting enzyme inhibitors, and statins) during emergency admission. Maximum in-hospital Killip score (*P*<.001) and the prevalence of a composite outcome (death, repeat myocardial infarct, Killip class 3 or 4) (*P*<.001) were also related to the number of drugs prescribed. In addition, our analysis revealed the prognostic relevance of degree of heart failure at admission and the severity of coronary disease.
**Conclusions:** These findings suggest that benefit derives from prescribing the largest possible number of currently recommended drugs when managing high-risk acute coronary syndrome without persistent ST-segment elevation. In this patient series, failing to administer more than 2 of the recommended drugs had a significant effect on outcome. Recommended drugs should be excluded only if strongly contraindicated. [Emergencias 2011;23:461-467]

**Key words:** Unstable angina. Myocardial infarction. Prognosis. Drug therapy. Non-ST-segment elevation acute coronary syndrome.

## Introduction

Non-ST-elevated acute coronary syndrome (NSTE ACS) is the most frequent form of ischemic heart disease, accounting for 56% of cases according to Spanish registries[1]. Average hospital mortality rate for NSTE ACS is 3.9%, lower than that of ACS with ST segment elevation (STE ACS), estimated at 7.6%. However, survival rates at six months of patients with STE and NSTE ACS are similar (90.3% and 88.2%, respectively, $p > 0.05$)[1,2]. Also, readmission-free survival rates at six months are 87.2% in NSTE ACS and 86.4% in the case of STE ACS ($p > 0.05$)[1,2], i.e., they are also similar. Regarding treatment at discharge, the latest data indicate a significant increase in medical drug prescription[1,3]. Similarly, there has been a significant increase in the rate of coronary revascularization in the past decade[3-6], which naturally affects the prognosis of patients diagnosed with NSTE ACS.

Although all current guidelines insist on the importance of careful and complete pharmacological treatment of patients in the context of NSTE ACS[7], studies have generally focused on particular drugs in isolation from each other. Therefore, the

clinical practice guidelines provide the strongest recommendations for individual drugs[8-12]. The relative clinical value resulting from adding a new drug to the treatment regime remains to be determined[13]. Although there are conclusive data to support the implementation of the guideline recommendations[8-12], tailored to the characteristics of each patient, few studies have analyzed the importance of joint pharmacological measures recommended by international documents in the context of NSTE ACS in Spain[14-16]. There is also little information about when to start with the maximum number of recommended drugs, and if early treatment in the emergency department (ED) or coronary care unit (CCU) has prognostic value in these patients.

This study evaluates the importance of complete, correct, early medication for the prognosis of patients diagnosed with NSTE ACS. The aim is to clarify whether the type of medical treatment, together with other variables, constitute an independent predictor of all-cause death.

## Method

We included 1,118 consecutive patients admitted to our CCU, Hospital Clínico San Carlos, Madrid, with a diagnosis of NSTE ACS in the period January 2004 - December 2007. The diagnosis of NSTE ACS was based on criteria then accepted in the clinical practice guidelines of the European Society of Cardiology[17]. Patients were included in a retrospective cohort study. We rigorously reviewed the baseline epidemiological characteristics, treatment administered on admission and prognostic variables during their stay in the hospital. The drugs included in the study[18] were acetylsalicylic acid (ASA)[19], anticoagulants, clopidogrel[19-21], anti-IIbIIIa[22,23], angiotensin converting enzyme inhibitors (ACEI)[24], beta blockers[25] and statins[16,26,27], i.e. those drugs most highly recommended in all current treatment guidelines for NSTE ACS[8-12].

The main outcome variables were: all-cause hospital death, re-infarction, and maximum Killip class III or IV. Monitoring of patients continued until hospital discharge.

For statistical analyses, we used Windows SPSS v. 15 (Illinois, USA, 2006) and the software package Office 2007 (Microsoft Corp, USA, 2006).

Baseline characteristics of patients are expressed as mean ± standard deviation (SD) or median (interquartile range) for continuous variables and as absolute numbers (percentages) for categorical variables. Intergroup comparisons were performed using the chi-square test for categorical variables and ANOVA for quantitative variables of more than 2 groups. Multivariate analysis was performed using logistic regression test taking the value of $p \leq 0.05$ as the threshold for including a covariate in the multivariate model. Taking into account the results of univariate analysis and data from the existing literature, the following variables were considered in the models: diabetes, smoking, history of infarction, Killip 2 or higher on admission, 3-vessel disease, pharmacological drug treatment (5 to 7 drugs) and age. A two-sided $p$ value $< 0.05$ was considered statistically significant.

## Results

Baseline characteristics of patients are shown in Table 1. Patients treated with at least 5 of the 7 drugs made up 75.5% of the sample (845 patients). These patients were younger (66.5 vs 70.9 years, $p < 0.01$), had lower Killip class, both at admission (1.18 vs 1.42, $p < 0.01$) and compared with maximum Killip class (1.32 vs. 1.72, $p < 0.01$) and had greater extension of the infarction, as measured by creatine kinase (533.87 U/L vs 406.77 U/L, $p < 0.01$) and creatine kinase-MB (32.48 ng/mL vs 22.8 ng/mL, $p < 0.01$). The coronary lesions, stratified by group, are shown in Table 1.

Mean CCU stay was 2.01 and 1.87 days for patients in the two groups, without significant differences. No patient stayed for more than 5 days in this unit. Pharmacological treatment was initiated early in all patients, during ED stay or CCU stay i.e. in the first 48 hours for the majority of patients in the study.

All patients underwent coronary angiography within 72 hours of admission, during CCU stay. In total, 725 patients underwent revascularization, either percutaneously or surgically (64.85%), with no significant differences between the two groups. In patients receiving the most comprehensive drug treatment, the lesions were revascularized percutaneously mainly (60.59 vs 17.94, $p < 0.01$) and required less surgical revascularization in a second intervention as compared with those who received less than 5 of the 7 treatment drugs (10.29 vs 17.21, $p < 0.001$).

Regarding therapeutic results, the number of drugs that the patient received on admission was significantly associated with the variables all-cause hospital death, maximum Killip class III or IV on admission and the composite variable of in-hospital major adverse cardiac events (MACE), namely

**Table 1.** Baseline characteristics of the population (n = 1.118)

| | Tr. yes N = 845 | Tr. no N = 273 | p |
|---|---|---|---|
| Age (years) | 66.54 | 70.96 | NS |
| Males (%) | 71.83 | 68.49 | NS |
| History of diabetes (%) | 33.01 | 31.13 | NS |
| History of dyslipidemia (%) | 55.02 | 45.05 | < 0.001 |
| History of hypertension (%) | 64.61 | 67.03 | NS |
| History of AMI (%) | 29.58 | 29.3 | NS |
| History of smoking (%) | 32.3 | 32.23 | NS |
| Stay in CCU (days) | 2.01 | 1.87 | NS |
| Killip on admission (mean) | 1.18 | 1.42 | < 0.001 |
| Killip maximum (mean) | 1.32 | 1.72 | < 0.001 |
| Necrosis markers (mean) | | | – |
| Peak Tropi (normal < 0.05 ng/mL) | 17.2 | 12.88 | NS |
| Peak CK (normal 1-190 U/L) | 533.87 | 406.77 | < 0.01 |
| Peak CK-MB (normal 0.1 to 5 ng/mL) | 32.48 | 22.8 | 0.01 |
| Location of coronary lesion (%) | | | – |
| LCA | 8.63 | 7.69 | NS |
| ADCA/Diagonal | 50.17 | 34.06 | < 0.001 |
| RCA/PL | 43.66 | 29.3 | < 0.001 |
| CX/OM | 43.19 | 35.16 | NS |
| Trunk/three vessels | 26.15 | 27.1 | NS |
| Type of revascularization (%) | | | – |
| Stenting | 60.59 | 17.94 | < 0.001 |
| Surgery second intervention | 10.29 | 17.21 | < 0.05 |

Tr. yes: Treatment with at least 5 of the 7 drugs recommended. Tr. no: Treatment with fewer than 5 of the 7 drugs recommended. AMI: acute myocardial infarction. Tropi: troponin I. CK: creatine kinase. CK-MB: creatine kinase MB isoform. LCA: left coronary artery. ADCA: anterior descending coronary artery CD: right coronary artery. PL: posterolateral. CX: Circumflex. OM: obtuse marginal.

death + re-infarction +maximum Killip class III or IV, with a clear linear association ($p < 0.01$) (Figure 1). As shown in the graphs, for all outcome variables studied, the determinant cutoff was compliance with treatment involving 5 of the 7 drugs recommended in clinical guidelines (ASA, anticoagulants, anti-IIbIIIa, clopidogrel, beta blockers, ACEI and statins). When the results were stratified according to the dichotomous variable revascularization yes/no (by thrombolysis, percutaneous or surgical) we observed that in both situations, compliance with treatment involving 5 of the 7 treatments continued to correspond with a lower percentage of adverse events ($p < 0.05$).

The composite variable MACE was studied as a function of the factors listed in Table 2. After univariate analysis, we observed that the presence of classical cardiovascular risk factors and the severity of coronary disease were related with a greater number of major adverse events during hospital stay, while the use of anti-IIbIIIa, beta blockers, clopidogrel, statins and treatment with at least 5 of the 7 recommended drugs correlated with a smaller number of major adverse events on. As for all-cause death during hospitalization, univariate analysis (Table 3) also showed that treatment with at least 5 of the 7 recommended drugs acted a protective factor ($p < 0.001$).

In the multivariate analysis, all-cause in-hospital death was again used as the outcome variable. Independent risk factors were Killip class >II at the time of admission, coronary artery disease and three vessel disease. As suggested by previous analysis, treatment with 5 of the 7 recommended drugs during CCU stay acted as a significant protective factor ($p < 0.001$) against MACE (Table 4). Diabetes mellitus, smoking, history of previous myocardial infarction or age were not independent risk factors.

## Discussion

As is clear from the latest data in Spanish registries, NSTE ACS is a common form of ischemic heart disease, associated with significant complications and a non-negligible rate of death. Optimal patient management is essential, and this involves urgent application (in the ED itself, if possible) of all measures that have proven useful, especially correct drug treatment.

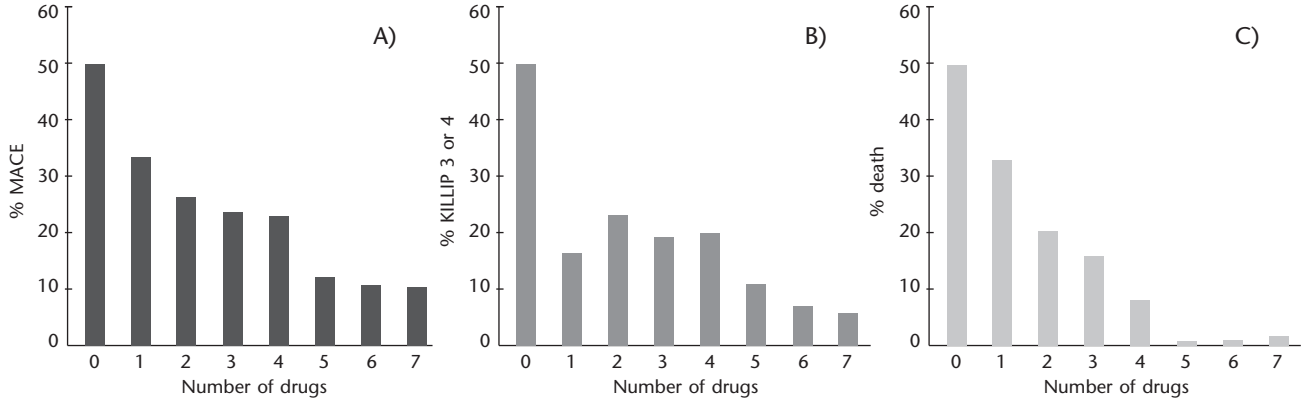


**Figure 1.** Percentage of major adverse cardiac events (MACE) including death, re-infarction, Killip III or IV shown in (A). Killip III or IV shown in (B) and death shown in (C) during hospitalization according to the number of drugs that the patient received.

**Table 2.** Univariate analysis for the composite outcome variable "death-re-infarction-Killlip 3 or 4" (MACE) during hospitalization

| Variable studied | N | MACE N | MACE % | *p* |
|---|---|---|---|---|
| Male sex | 794 | 110 | 13.9 | 0.30 |
| Diabetes mellitus | 364 | 88 | 24.2 | < 0.001 |
| Smoking | 361 | 31 | 8.6 | < 0.001 |
| Dyslipidemia | 588 | 96 | 16.3 | 0.09 |
| Hypertension | 729 | 122 | 16.7 | 0.01 |
| AMI | 330 | 78 | 23.6 | < 0.001 |
| Admission Killip II | 209 | 98 | 46.9 | < 0.001 |
| Two-vessel disease | 255 | 42 | 16.5 | < 0.001 |
| Three-vessel disease | 295 | 78 | 26.4 | 0.01 |
| Main stem & 3 vessel CAD | 295 | 78 | 26.4 | < 0.001 |
| Use of beta blockers | 774 | 82 | 10.6 | < 0.001 |
| Use of ACEI | 664 | 105 | 15.8 | 0.17 |
| Use of statins | 931 | 116 | 12.5 | < 0.001 |
| Use of anti-IIbIIa | 670 | 80 | 11.9 | < 0.001 |
| Use of anticoagulants | 1094 | 157 | 14.4 | 0.14 |
| Use of ASA | 1066 | 154 | 14.4 | 0.55 |
| Use of clopidogrel | 699 | 84 | 12 | < 0.001 |
| Percutaneous revascularization | 604 | 69 | 11.4 | < 0.001 |
| Surgery in 2nd intervention | 134 | 36 | 23.9 | < 0.001 |
| Revascularization yes | 725 | 101 | 13.9 | 0.42 |
| Treatment with at least 5 of the 7 drugs | 845 | 96 | 11.4 | < 0.001 |

Showing the number of patients for each variable studied (N), % of major adverse cardiac events (MACE) and p value compared with other patients without the variable studied. AMI: acute myocardial infarction, ASA: acetylsalicylic acid, ACEI: angiotensin converting enzyme inhibitors.

**Table 3.** Univariate analysis for the outcome variable "death during hospitalization"

| Variable studied | N | Death N | Death % | *p* |
|---|---|---|---|---|
| Male sex | 794 | 32 | 4 | 0.42 |
| Diabetes mellitus | 364 | 28 | 7.7 | < 0.001 |
| Smoking | 361 | 9 | 4.4 | < 0.05 |
| Dyslipidemia | 588 | 25 | 4.3 | 0.884 |
| Hypertension | 729 | 36 | 4.9 | < 0.28 |
| AMI | 330 | 22 | 6.7 | < 0.05 |
| Admission Killip II | 209 | 32 | 15.3 | < 0.001 |
| Two-vessel disease | 255 | 5 | 2 | < 0.001 |
| Three-vessel disease | 295 | 30 | 10.2 | < 0.001 |
| Main stem & 3 vessel CAD | 295 | 30 | 10.2 | < 0.001 |
| Use of beta blockers | 774 | 15 | 1.9 | < 0.001 |
| Use of ACEI | 664 | 19 | 2.9 | < 0.01 |
| Use of statins | 931 | 21 | 2.3 | < 0.001 |
| Use of anti-IIbIIa | 670 | 20 | 3 | < 0.01 |
| Use of anticoagulants | 1.094 | 44 | 4 | < 0.01 |
| Use of ASA | 1.066 | 43 | 4 | 0.0023 |
| Use of clopidogrel | 699 | 17 | 2.4 | < 0.001 |
| Percutaneous revascularization | 604 | 17 | 2.8 | < 0.01 |
| Surgery in 2nd intervention | 134 | 11 | 8.2 | < 0.05 |
| Revascularization yes | 725 | 27 | 3.7 | 0.17 |
| Treatment with at least 5 of the 7 drugs | 845 | 12 | 1.4 | < 0.001 |

Showing the number of patients for each variable studied (N), percentage (%) of in-hospital deaths and p value compared with other patients without the variable studied. AMI: acute myocardial infarction, CAD: coronary artery disease, ACEI: angiotensin converting enzyme inhibitors, ASA: acetylsalicylic acid.

This study highlights the benefit of appropriate, combined early administration of drugs recommended for the management of NSTE ACS in clinical practice guidelines. On reviewing the literature, it is easy to find data supporting the importance of complete drug treatment for the prognosis of patients with NSTE ACS[4,16,29]. However, few studies have focused on an evaluation of the drug treatment itself, adjusting for other factors that influence the prognosis of NSTE ACS. Especially relevant is the bias that could result from intergroup differences in the rate of revascularization. Previous studies have shown that revascularization (either percutaneous or surgical) is the factor that relates with a greater increase in survival rates in the short and medium term (up to six months) in patients diagnosed with NSTE ACS[16,30-33]. In 2006, Heras et al.[4] demonstrated the negative impact of incomplete drug treatment on survival of these patients. However, that study was based on a Spanish population sample of patients diagnosed with NSTE ACS (DESCARTES registry[2]) where less than a third of the patients underwent coronary artery revascularization (percutaneous or surgical), despite their diagnoses and high-risk data in many cases. Furthermore, only 18% of patients underwent coronary angiography within 48 hours. Similar data are provided by other contemporary registries, such as CRUSADE[3-5] or GRACE[6], in which only 28% of NSTE ACS patients underwent percutaneous coronary intervention. These data contrast with the percentage of coronary artery bypass patients in the present study, which was 64.85%. Given the importance of new revascularization strategies (more aggressive) for the prognosis of NSTE ACS patients[16,30-33], the present study provides updated information on the beneficial effect of complete drug treatment, and it also reflects the significant increase in revascularization rates of of patients with ACS in recent years.

Regarding the drugs recommended by the latest clinical practice guidelines[8-12], it is important they be studied not only jointly but also one by one, to avoid possible bias from drug interactions[34-35] and the synergic effect observed in previous studies.

It is not the purpose of this paper to discern

**Table 4.** Multivariate analysis (logistic regression) of all-cause in-hospital mortality

| Mortality | OR | 95% CI | *p* |
|---|---|---|---|
| Treatment with 5-7 drugs | 0.097 | (0.047-0.202) | < 0.001 |
| Main stem 3 vessel CAD | 3.91 | (2.00-7.63) | < 0.001 |
| Killip 2 or higher on admission | 4.71 | (2.40-9.23) | < 0.001 |

Showing only those variables that were statistically significant ($P < 0.05$) and remained in the model. OR: odds ratio; CI: confidence interval, *p* = statistical significance value. CAD: coronary artery disease.

which specific drugs are associated with greater reduction in the number of in-hospital deaths[16], but to determine whether the application of complete drug therapy has a real impact on mortality in these patients. The usefulness of these results is that they address the issue of drugs currently recommended in all therapeutic guidelines on NSTE ACS[8-12] both individually and jointly: ASA, clopidogrel, anticoagulants, anti-IIbIIIa, statins, beta blockers and ACEI.

We would highlight the reduction in early in-hospital mortality achieved by administering at least five of the seven recommended drugs, even after adjusting the model for revascularization of coronary lesions, which itself is associated with a significant reduction in mortality (OR 0.58 in the latest studies[16]). Therefore, these drugs should be part of the generic treatment for all patients with NSTE ACS[8-12], provided there are no formal contraindications for any one of them.

As a limitation of the study, we would mention that it was a retrospective observational study, thus precluding any inference of causal relationships, which would require a prospective experimental study. In addition, follow-up was limited to the length of hospital stay in the CCU. However, the results achieved statistical significance required to propose hypotheses that should be confirmed by studies with longer-term follow-up.

We believe that a longer-term follow-up could yield results with greater intergroup differences, as already noted in other studies16,36,37, including 6-month survival and re-admission-free time which are currently similar in NSTE ACS and STE ACS at six months after the event1. The design and analysis of the present study did not allow us to clearly separate ED from CCU performance in our hospital. For practical purposes, thy were considered the same chain of care. In general, by protocol, stay time in the ED was short, barely hours, and antithrombotic treatment usually began there as soon as the suspected diagnosis was made. Based on our results and those of previous studies, we would strongly recommend that patients with NSTE ACS start treatment with the highest number of recommended drugs in the ED itself, individualizing the treatment in accordance with current clinical practice guidelines. This approach is associated with a reduction in the prevalence of adverse events and the number of in-hospital deaths in the short term.

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## Relevancia clínica del tratamiento farmacológico completo precoz en el pronóstico del síndrome coronario agudo sin elevación del ST

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**Objetivo:** Las guías actuales insisten en la relevancia de un tratamiento farmacológico optimizado para mejorar el pronóstico de los pacientes diagnosticados de síndrome coronario agudo sin elevación del segmento ST (SCASEST), pero son pocos los estudios que analizan sus resultados. El presente estudio analiza este aspecto.
**Método:** Se incluyeron en una cohorte retrospectiva 1.118 pacientes ingresados en la unidad coronaria con el diagnóstico de SCASEST, y se analizaron sus características epidemiológicas basales, el tratamiento llevado a cabo durante el ingreso y las variables pronósticas durante su estancia hospitalaria.
**Resultados:** Instaurar durante el ingreso en urgencias/unidad coronaria un tratamiento farmacológico con al menos cinco de los siete fármacos recomendados (ácido acetilsalicílico, anticoagulantes, anti-IIbIIIa, clopidogrel, betabloqueantes, inhibidores de la ECA y estatinas) se asocia a una reducción en el número de fallecimientos hospitalarios ($p < 0,001$), la clase Killip máxima alcanzada durante el infarto ($p < 0,001$) y la prevalencia del evento combinado muerte-reinfarto-Killip 3 ó 4 ($p < 0,001$). Destaca asimismo la relevancia que adquiere el grado de insuficiencia cardiaca al ingreso y la severidad de la enfermedad coronaria en el pronóstico de estos pacientes.
**Conclusiones:** Nuestros datos apoyan el efecto beneficioso de la administración del mayor número posible de los fármacos actualmente recomendados en el tratamiento del SCASEST de alto riesgo. En nuestra serie, la no administración de más de dos de estos fármacos tiene una repercusión significativa, por lo que se deben limitar las exclusiones sólo a las contraindicaciones muy justificadas. [Emergencias 2011;23:461-467]

**Palabras clave:** Angina inestable. Infarto de miocardio. Pronóstico. Fármacos. SCASEST.